INVESTIGATION, DEVELOPMENT AND EVALUATION OF ORALLY DISINTEGRATING TABLETS

PhD thesis

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2. List of abbreviations

$t_{n-2}^{5\%}$ - two tail critical value of the t-distribution

t_{max} - the time after the administration of a drug when maximum plasma concentration reached

API   - active pharmaceutical ingredient

ATR   - attenuated total reflection

AUC   - area under curve

AUC_{BC} - Box-Cox transformed AUC values

c   - a multiplier calculated based on the *in vivo* disintegration times

C=O str   - streching vibration of carbonyl group

c_{av} - averaged c value

c_{max} - maximum plasma concentration

CCS   - croscarmellose sodium

CDER   - Center for Drug Evaluation and Research

CI   - confidence interval

COO^- str as   - asymmetric stretching vibration of carboxylate anion

COO^- str sy   - symmetric stretching vibration of carboxylate anion

CrosP   - crospovidone

d   - diameter

Da   - Dalton

d_p - penetration depth of the infrared beam

DSC   - differential scanning calorimetry

DT   - disintegration time (s)

EFF   - effervescent agent content of the tablet (% w/w)

EM   - electromagnetic

FDT   - fast disintegrating tablet

FTIR   - Fourier-transform infrared

gly   - glycerol concentration of the medium in coded values

h   - hour / hours

HBIC   - hydrogen-bonded interpolymer complex

HLB   - hydrophilic-lipophilic balance

IR	- infrared
IVIVC	- *in vitro-in vivo* correlation
k	- correction factor
MC	- methylcellulose
MCC	- microcrystalline cellulose
min	- minute / minutes
M_w	- molecular weight
N	- new oral disintegration time (s)
n	- number of the observations in the sample
n_c	- refractive index of the ATR crystal
n_s	- refractive index of the sample
O	- *in vivo* disintegration time (s)
ODT	- orally disintegrating tablet
OROS[®]	- osmotic-controlled release oral delivery system
PAA	- poly(acrylic acid)
PCA	- principal component analysis
PEG	- poly(ethylene glycol)
PEO	- poly(ethylene oxide)
Ph. Eur.	- European Pharmacopoeia
PPI	- proton pump inhibitor
pts	- pre-test speed of the texture analysis measurements in coded values
PVP 25	- PVP (Kollidon[®] 25) concentration of the medium in coded values
PVP	- polyvinylpyrrolidone
PXRD	- powder X-ray diffraction
RH	- relative humidity
s	- second / seconds
S.D.	- standard deviation
$scCO_2$	- supercritical CO_2
SD	- superdisintegrant content of the tablet (% w/w)
SEM	- scanning electron microscopy
SSG	- sodium starch glycolate
SSR	- sum of squared residuals

T	- temperature (°C)
T_g	- glass transition temperature (°C)
ts	- test speed of the texture analysis measurements in coded values
USP-NF	- The United States Pharmacopeia and The National Formulary
x_1	- coded values of test speed
x_2	- coded values of the glycerol concentration
x_c	- the value of x_i for which the confidence interval calculations are made
x_i	- a particular $AUC_{polymer \times water} : AUC_{polymer}$ ratio value
x_p	- the value of x_i for which the prediction interval calculations are made
Y	- predicted value of the correction factor k
y_i	- a particular water content (g) / 100 g dry excipient value
θ_i	- angle of incidence of the infrared beam
λ	- wavelength
λ_{BC}	- λ value of the Box-Cox transformations

3. Introduction

Along with the development of the pharmaceutical sciences, there are many advances in administering, delivering and releasing drug molecules. It is possible to improve a therapy by chemically modifying an active pharmaceutical ingredient (API) in order to achieve a better safety profile and eliminate certain side effects or by changing the pharmaceutical formulation in order to improve the rate and location of the drug release as well as the bioavailability. A well-known example is the OROS® technology (osmotic-controlled release oral delivery system) used by many modern medicaments, e.g. Adalat OROS® (Bayer®) which contains nifedipine, which is an antianginal and antihypertensive calcium channel blocker. The use of short acting formulations of nifedipine was often associated with dangerous tachycardia due to the temporary high level of the drug, but changing the release profile of the drug to extended release by OROS® technology allowed the smooth reduction of the blood pressure without sympathetic simulation (Lundy et al., 2009).

Another important aspect of the pharmaceutical manufacturing is to provide convenient products to a wide range of patients. The tablet is one of the most common pharmaceutical dosage forms and it is very versatile to deliver the appropriate amount of the API at the appropriate site of the gastrointestinal tract with the appropriate release rate. Nevertheless, patients suffering from swallowing difficulties may be unable to use this type of medicine due to its solid nature. Dysphagia, i.e. swallowing difficulties is a common problem among elderly and paediatric patients. On the other hand, many illnesses may be associated with dysphagia, e.g. stroke, Parkinson's disease, gastro-esophageal reflux, head and neck injuries, cerebral palsy, etc. (Sandri et al., 2006).

The orally disintegrating tablet (ODT), or, alternatively, the fast disintegrating tablet (FDT) or orodispersible tablet dosage form is specifically developed to disintegrate in the mouth in a short period even if there is only a low amount of saliva present. Once the tablet has disintegrated in the mouth, the resultant suspension is easy to swallow compared to the original structure.

The European Pharmacopoeia (Ph. Eur. 8.0) uses the term 'orodispersible tablets' for ODTs with the following definition: "Orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being

swallowed." The United States Pharmacopeia (USP 36) uses the term 'orally disintegrating tablets' and its definition is: "Orally disintegrating tablets are intended to disintegrate rapidly within the mouth to provide a fine dispersion before the patient swallows the resulting suspension where the API is intended for gastrointestinal delivery and/or absorption." The USP mentions that further details can be found in a guidance issued by the Center for Drug Evaluation and Research (Guidance for Industry, Orally Disintegrating Tablets, FDA, CDER, 2008).

3.1. Clinical aspects of orally disintegrating tablets

ODTs are preferred for people suffering from dysphagia, nausea, vomiting or motion sickness and for hospitalized patients suffering from mental disorders, stroke, thyroid disorder, Parkinson's disease, multiple sclerosis and cerebral palsy (Badgujar and Mundada, 2011). Apart from the swallowing difficulties, this dosage form is appropriate for travelling people as well, since they can take their tablets even if they have no access to water.

These products/tablets are distinguished from conventional sublingual or buccal tablets where disintegration requires several minutes. ODTs have the ability to release the API at different locations of the gastrointestinal tract (GIT). Using this technology, it is possible to promote drug absorption through local oromucosal tissues, and through pre-gastric, gastric and post-gastric parts of the GIT (Pfister and Ghosh, 2005). Dissolution of the portion of the drug in the saliva allows pre-gastric absorption, which causes faster onset of action and reduces first pass metabolism. The absorption through the buccal and the pharyngeal regions may have benefits in the case of drugs undergo high first-pass metabolism. Safety profiles could be also improved in the case of drugs producing toxic metabolites by hepatic or gastric biotransformation (Hirani et al., 2009). Dissolved and swallowed fraction of drug can be absorbed in the conventional way. However, the non-swallowed fraction can enter into epithelium, which is not keratinized in the soft palate, the sublingual, and the buccal regions endowing them with good permeability. Smaller molecules can get into the circulation directly while larger

molecules get into the lymphatic system from the epithelium first (Dévay and Antal, 2009; Shojaei, 1998).

The administration of an ODT may not result inevitably in faster onset of the therapeutic effect, but it has several advantages over conventional tablets and could possess beneficial clinical, medical, technical, and marketing features. Usually ODTs are formulated as bioequivalent line extensions of existing products. In this case, it is necessary to provide drug absorption that is similar to the absorption of the drug of the conventional tablets. It causes financial difficulties for the manufacturer if an ODT fails bioequivalence tests due to the varying degrees of pre-gastric absorption for example. The characteristics of the API greatly determine its sensitivity to the formulation. If it can be absorbed pre-gastric and is subject to high first-pass metabolism then the dissolved fraction from an ODT formulation may cause pharmacokinetic changes (Pfister and Ghosh).

3.1.1. Biopharmaceutical aspects of ODTs

Several clinical studies were conducted using ODT formulations due to the high versatility, patient compliance and convenience of the dosage form.

Proton pump inhibitors (PPIs) act through the long-lasting reduction of gastric acid production and are widely used in the treatment of several gastro-intestinal diseases, such as dyspepsia, gastroesophageal reflux and esophagitis. There is a great need to provide a convenient dosage form for patients suffering from excessive acid secretion due to the obvious swelling difficulties caused by these diseases. Lansoprazole was the first PPI formulated as orally disintegrating tablets. It was made up of enteric-coated microgranules of the drug and was compressed using a rapidly dispersing matrix. Bioavailability studies showed that the formulation was comparable to lansoprazole capsules of 15 and 30 mg doses (Baldi and Malfertheiner, 2003).

In an another study, bioavailability of two dosing regimens of lansoprazole ODT was compared, i.e. administration of the tablet per os without water or dispersed in water and administered via nasogastric tube. There was no clinically significant difference between the two methods, because dispersing the tablet in water and administering via a nasogastric tube did not resulted in drastic pharmacokinetic

changes. In conclusion, the formulation was stable with respect to the *in vivo* efficacy, which enables an important additional dosing option for the drug (Freston et al., 2004).

Selegiline is an irreversible inhibitor of the MAO-B enzyme. It has several beneficial clinical effects as an adjuvant to levodopa in the treatment of Parkinson's disease, e.g. reduction of the motor performance deterioration (Riederer and Lachenmayer, 2003). It was possible to avoid largely the gut and first-pass metabolism of the drug by the use of an ODT formulation, which enabled transbuccal absorption. This formula allowed higher bioavailability and lowered the plasma concentration of harmful metabolites, such as the amphetamine (Lew, 2005; Clarke and Jankovic, 2006).

Ondansetron is an effective and well-tolerated antiemetic agent, which is useful for the prevention of the chemotherapy and radiotherapy induced emesis and nausea. The use of ODTs is highly recommended in the case of such conditions. Freeze-dried ondansetron tablets were prepared and evaluated in two doses (8 and 16 mg). The preparations dispersed rapidly on the tongue without water and were effective to treat emesis and nausea in a placebo controlled clinical trial (LeBourgeois et al., 1999).

The onset of antidepressant efficacy of mirtazapine and sertraline were compared in a multinational, randomized, double-blind study. Mirtazapine was formulated as orally disintegrating tablet. The study was conducted for 8 weeks and mirtazapine was more effective after the first 2 weeks. After this time, there was no significant difference between the efficacies of the two medicaments. It was concluded, that the mirtazapine ODT had faster onset of action than sertraline and it was superior in convenience and compliance due to its modern dosage form (Behnke et al., 2003).

It is considered that the food has no effect on the bioavailability of the atypical antipsychotic drug clozapine. Bioavailability and pharmacokinetics of clozapine ODTs were investigated by healthy subjects in fasted and fed conditions in a clinical study. Pharmacokinetic results demonstrated significant differences between fasted and fed conditions for both clozapine and the metabolite desmethylclozapine at various time points. The lower limits of the 90% confidence intervals (CI) for the geometric mean fed-to-fasted maximum plasma concentration (c_{max}) ratios were below the bioequivalence lower limit, 0.80. The mean c_{max} of both clozapine and the metabolite was decreased approximately by 20% when the formulations were administered after a high-fat/calorie breakfast. However, the 90% CIs for the fed-to-fasted ratios of the

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geometric means of the AUC values from time zero to infinity ($AUC_{0-\infty}$) were within the bioequivalence boundaries of 0.80-1.25. In conclusion, the coadministration of food was shown to decrease the rate of clozapine absorption but had no effect on the extent of clozapine absorption, therefore clozapine ODTs should be administered at least 1 hour before meals or after a light meal (Disanto and Golden, 2009).

Considering these examples, it can be seen that ODTs offer new opportunities for physicians and patients and their benefits include convenience but serious clinical possibilities, as well. Bioavailability studies are important in the field of this technology because the fast disintegration increase the number of the possible interactions between our system and the drug molecule.

3.2. Orally disintegrating tablets

ODT products have several advantages over liquid dosage forms (e.g. good chemical stability, more accurate dosing, small package size, etc.), but the manufacturing of an orally disintegrating tablet is more difficult compared to a traditional tablet due to the special requirements (Sandri et al., 2006). There are several different manufacturing methods to produce ODTs, but the method has its drawbacks in all cases. Tablets need to have an acceptable taste and very short disintegration time in the mouth in addition to the pharmacopoeial requirements. Tablet friability is one of the most challenging requirements (max. 1.0% according to the Ph. Eur. 8.0 and the USP 36) since ODT products cannot be too compact in order to provide fast water absorption but the oral disintegration time is usually in positive correlation with the mechanical strength of the tablets. Some commercially available examples are listed in Table 1.

Table 1 Commercially available ODT products

Commercial name	Drug	Pharmacological information
Zyprexa® Zydis®	olanzapine	atypical antipsychotic for schizophrenia and bipolar disorder
Remeron® SolTab	mirtazapine	noradrenergic and specific serotonergic antidepressant
Parcopa®	carbidopa, levodopa	carbidopa inhibits peripheral metabolism of levodopa in Parkinson's disease
Niravam®	alprazolam	short-acting anxiolytic benzodiazepine
Rybix® ODT	tramadol	centrally acting opioid analgesic to treat moderate or moderately severe pain.
Zomig-ZMT®	zolmitriptan	selective serotonin receptor agonist to treat migraine attacks
Zofran® Zydis®	ondansetron	serotonin 5-HT$_3$ receptor antagonist to prevent of nausea and vomiting
Metozolv® ODT	metoclopramide	antiemetic and gastroprokinetic drug
Claritin® RediTabs®	loratadine	second-generation H$_1$ histamine antagonist to treat allergies
Clarinex® RediTabs®	desloratadine	second-generation H$_1$ histamine antagonist to treat allergies
Orapred ODT®	prednisolone	glucocorticoid to treat a variety of inflammatory and auto-immune conditions
Paralyoc®	acetaminophen	analgesic and antipyretic drug
Feldene® Flash	piroxicam	non-steroidal anti-inflammatory drug

3.2.1. Orally disintegrating tablet technologies

Orally disintegrating tablets need to have proper mechanical strength, their packages need to protect them from water absorption and harmful mechanical impacts and tablets should disintegrate or dissolve in the mouth in short period of time in the presence of

salivary fluid. Since the drug molecule is surrounded by aqueous medium after disintegration, it is possible that the API starts to dissolve and causes a bitter taste due to the interaction with the taste buds. Therefore, manufacturers also have to ensure satisfactory taste masking of the API, because most drug molecules have an unpleasant taste.

Fast disintegration is generally achieved by a special tablet structure characterised by loosely compacted or lyophilised porous structure, highly swelling excipients, effervescent components or other special features. The lyophilised orally disintegrating tablet technology (e.g. the patented Zydis®) was one the first to provide tablets with these unique features (Sastry et al., 2000). The development of superdisintegrant excipients made the production of various kinds of ODT products possible, manufactured by conventional tableting methods. These unique polymeric materials are cross-linked forms of hydrophilic and hygroscopic polymers, which are able to absorb large amounts of water and swell to a remarkable degree, but they do not dissolve, nor do they create a viscous solution that would otherwise slow down the disintegration process. Since then there are hundreds of patents dealing with ODT technology and many original and generic pharmaceutical companies have their own technique to manufacture ODT products.

3.2.1.1. Lyophilisation

Tablets of very short oral disintegration times can be prepared using the freeze-drying or lyophilisation technique, since the final formula has low density and high porosity. Water can quickly enter the tablet due to capillary effect, and the dissolution of the water-soluble excipients causes tablet disintegration within a few seconds. The freeze-drying process often results in a glassy amorphous structure of excipients and drugs, which also accelerates the dissolution (Sandri et al., 2006).

One of the most known lyophilisation ODT technologies is the Zydis®, which consists of three main steps:

1. Preparation of the aqueous drug solution or suspension and its subsequent filling into pre-formed blisters, which will form the shape of the tablets.

2. Passing the filled blisters through a cryogenic freezing process, which controls the ultimate size of the ice crystals; these frozen units are then transferred to the freeze dryers for the sublimation process, where the majority of the remaining moisture is removed from the tablets.

3. Sealing the open blisters in order to ensure the stability and the protection of the product from varying environmental conditions and water vapour absorption (Shukla et al., 2009a).

The optimum excipient matrix is the most important feature of the tablets from technological viewpoint. The matrix typically consists of amorphous polymers that provide structural strength to tablets (e.g. gelatine or alginates), saccharides that provide hardness and elegance (e.g. mannitol or sorbitol) and taste-masking agents such as sweeteners, furthermore flavourings, pH-adjusting substances, preservatives, etc. (Sastry et al., 2000).

Lyoc$^®$ is also a freeze-drying technology to prepare ODTs for drugs with poor solubility in water. The API is in nano-particulate form coated by adsorbed surface stabilizers (e.g. surfactants, natural polymers or phospholipids). The decreased particle size, increased surface area and solubilisation of the drug are ideal to provide fast, systemic absorption and high bioavailability after ingestion. The tablet matrix may consist of sugars, polysaccharides, gums, or synthetic polymers. The formulation may also contain binding agents, filling agents, suspending agents and must include effervescent agents (Sandri et al., 2006).

Lyophilisation is the method to prepare ODTs with shortest disintegration time (McLaughlin et al., 2009). There is no lag time in the disintegration of tablets prepared by this method and tablets disintegrate even in the case of severe xerostomia (dry mouth). It is also possible to formulate sensitive pharmaceuticals like peptides and proteins with this technique. However, the technology also has its drawbacks. Taste masking is a critical parameter of this type of ODT products because the freeze-dried structure disintegrates and dissolves very rapidly, which also enhances the drug dissolution in the lack of proper preventive technology. On the other hand, the method is relatively extensive; tablets need special blister packaging therefore the product costs may be higher in comparison with other ODT products.

3.2.1.2. Cotton-candy technology

The cotton-candy process to produce sugar flosses is a heat moulding process. The heat melts the selected sugars or polysaccharides, and centrifugal force (e.g. a spinning disc) shapes them into solidified amorphous sugar flosses. The obtained matrix is cured, partially recrystallized to gain bulk matter with good flow properties and compressibility. Tablets with short disintegration times can be prepared from the candy flosses after milling and blending with other excipients and with the API. The patented FlashDose® fast disintegrating tablet technology uses this approach. Flosses consist of water-soluble sugars with a very high surface area and may have a partially amorphous structure; therefore, they can act as a binder in the tablets and they have good dissolution properties. The prepared tablets undergo a further curing process at elevated temperature and humidity when the amorphous components crystallize, therefore the physical stability and mechanical hardness of tablets increase (Sandri et al., 2006).

3.2.1.3. Compaction technologies

The conventional tableting process is also feasible to produce fast disintegrating tablets due to the different technologies and special excipients. Special sensation can be achieved by using effervescent agents (e.g. combination of citric acid and sodium bicarbonate), where the presence of water elicits reaction between the organic acid and the bicarbonate and the originating CO_2 gas cause tablet disintegration. One of the most important components of many ODT products are the so-called superdisintegrants, whose best known representatives are the crospovidone, the sodium starch glycolate and the croscarmellose sodium (Thibert and Hancock, 1996; Zhang et al., 2010). Each excipient is cross-linked hydrophilic polymer with high affinity to water. These excipients swell to a considerable degree in contact with aqueous fluids or high relative humidity, therefore they are able to cause fast tablet disintegration generating strain force inside the tablet matrix. They rapidly absorb water (water wicking) due to their hydrophilic nature and create a capillary system if they are homogeneously dispersed inside the tablet.

Filler is another important factor concerning compacted ODT products. Most manufacturer prefer fillers of high water solubility, especially sugar alcohols (like mannitol), since they are naturally occurring, low caloric, non-cariogenic, sweet molecules, often causing cooling sensation in the mouth (Hancock and Shamblin, 1998; Cammenga et al., 1996). They rapidly dissolve after tablet disintegration without causing a gritty feeling compared to insoluble tablet fillers used in ODT technology (such as calcium phosphate).

Tablets are prepared at low pressures with direct compression using the patented OraSolv® technology. The active ingredient is in the form of taste-masked micro-particles, the effervescent agents (20-25% of the tablet weight) help the fast disintegration. Since tablets manufactured by the OraSolv® technology are soft and fragile, they need to be packed into a special package. The DuraSolv® technology provides harder tablets than the OraSolv® technology; therefore, special packaging is not necessary. The technology is based on conventional, non-direct compression fillers (e.g. mannitol or lactose) in the form of fine particles that do not cause a gritty feeling after tablet disintegration, and wicking agents that facilitate fast water absorption. Effervescent and swelling agents are present only in small amounts or not used at all (Sandri et al., 2006).

Lubricant type, concentration and method of lubrication influence many of the tablet parameters, such as hardness, friability, disintegration time and dissolution of the API (Wang et al., 2010). External lubrication has many advantages in the case of ODTs when compared to conventional internal lubrication. In this case, lubricant is not mixed with the excipients and can only be found on the surface of the tablets. It is possible to avoid some of the drawbacks of lubrication using this technique, since in the case of conventional lubrication, lubricants tend to coat the excipient particles, and such coating decreases the mechanical strength of tablets due to the reduced bonding between the particles. On the other hand, the lubricant coating is more or less hydrophobic; therefore, water wicking and wetting of the tablet matrix is prolonged, which also makes the oral disintegration time longer (Yamamura et al., 2009).

AdvaTab® is an innovative ODT technology based on direct compression using external lubrication in order to avoid problems deriving from internal lubrication. The prepared tablets are 30-40% stronger than the conventional ones and are characterised

by short disintegration times due to the lack of water insensitive cohesive bonds that would otherwise hinder water penetration and tablet disintegration (Sandri et al., 2006).

3.2.1.4. ODT technologies employing sugars and sugar alcohols

Sugars and especially sugar alcohols are widely used for ODT production due to their excellent physiological, chemical and technological properties. Sugar alcohols are usually non-toxic, chemically inert, sweet and thermostable compounds, and many of them are available in the form of directly compressible granules. Researchers have developed many interesting technologies for the production of fast disintegrating tablets employing the special properties of sugars and sugar alcohols. Mizumoto et al. (2005) investigated sugars and sugar alcohols based on their tableting and disintegrating properties and divided the compounds into two groups. Compacts prepared from saccharides of the first group were characterised by poor mechanical strength but fast disintegration while compacts prepared from saccharides of the second group were characterised by good mechanical strength but slow disintegration. Mannitol, lactose, glucose and xylitol are examples of the first group (weakly compressible saccharides) and trehalose and maltose belong to the second group (well-compressible saccharides). Correlation was found between the compressibility characteristics of the saccharides and the polar component of their surface free energies, i.e. saccharides with more polar components yielded stronger compacts. Special granules were prepared exploiting these findings using the combination of the two types of saccharides. Mannitol and other excipients were granulated with maltose solution (15% w/w), using a fluidized-bed granulator and the granules were compressed into tablets after lubrication with magnesium stearate. Maltose was in the amorphous state on the surface of mannitol particles after the granulation but a conditioning step (25 °C, 70% RH) caused its recrystallization. Tablet hardness significantly increased using the conditioning process due to the new crystalline bonds between particles but tablets maintained their fast disintegrating properties due to the high mannitol content (Mizumoto et al., 2005).

Crystallisable amorphous materials possess a higher energy level compared to their crystalline state (Antal and Zelkó, 2009). Their disordered structure is characterised by microscopic voids where water molecules can be absorbed. These

molecules are able to induce the amorphous-crystalline transition. Such a transition creates new solid crystalline bridges between the particles inside a tablet that in turn increase the tablet hardness significantly. Sugimoto et al. (2006) prepared fast disintegrating tablets utilizing the amorphous-crystalline transition phenomena of sucrose. The researchers prepared high porosity rapidly disintegrating tablets by fluidized bed granulating of mannitol with sucrose solution (5% w/w final concentration) and tableting the prepared granules. Tablet hardness was significantly increased by a curing process at elevated humidity conditions (51% RH). In earlier experiments, amorphous sucrose was prepared by the freeze-drying method (Sugimoto et al., 2001; Sugimoto et al., 2005). However, it was demonstrated by powder X-ray diffraction (PXRD) technique that sucrose (contrary to mannitol) remained in the amorphous state after correctly devised fluidized bed granulation. The main advantage of this technique is that loosely compressed tablets retain their high porosity after the curing process, which is essential for fast disintegration, but they become hard enough to be suitable for commercial production (Sugimoto et al., 2006).

Kuno et al. (2005) prepared a new fast disintegrating formulation where the low melting point sugar alcohol component is heated and partially melted. Erythritol (melting point: 122 °C) was fluidized-bed granulated with xylitol (melting point: 93-95 °C) solution. Granules were loosely compressed into tablets and the tablets were placed into a drying oven to heat them at 93 °C for 15 minutes. Tablets containing 5% w/w xylitol or more were sensitive to the heating process, i.e. the hardness of initially fragile tablets significantly increased along with the oral disintegration times. This was due to the partial melting of the xylitol component, which re-solidified after cooling and created new solid bridges between the particles. Tablets containing 5% w/w xylitol have good disintegrating properties and satisfactory mechanical strength. The median pore size of the tablets increased to 5.03 μm from 2.37 μm due to the heating process that is also favourable for water wicking and the subsequent disintegration processes (Kuno et al., 2005).

3.2.1.4. Miscellaneous ODT technologies

In addition to the commercialized and patented ODT technologies, there are hundreds of papers dealing with the development, preparation, and evaluation of fast disintegrating tablets. For example, doxylamine succinate containing taste masked, fast disintegrating tablets was prepared by the combination of ion exchange resin and a superdisintegrant (Puttewar et al., 2010). Ion exchange resins were able to retain the dissolution of the API; therefore, they have a taste masking effect and they facilitated tablet disintegration due to their swelling properties as well (Jeong et al., 2008). Effervescent agents are often used in ODT technology, since their effect can enhance mouthfeel and trigger saliva production. Using mannitol-based effervescent tablets, it was shown that superdisintegrant content significantly reduced the disintegration time, which can be high without superdisintegrants (Nagendrakumar et al., 2009). Therefore, it can be stated that the two excipients acted synergistically. In another example, four amino acids (L-lysine·HCl, L-alanine, glycine and L-tyrosine) were investigated for their suitability for fast disintegrating tablet production. Tablets of similar hardness were prepared by different compression forces in the case of the four compositions. Wetting times and oral disintegration times were measured. It was found that when the polar component of the surface free energy of an amino acid was large and the dispersion component was small, the wetting process was faster. However, it seemed that the higher dispersion component contributed to the disintegration process, which emphasized the underlying thermodynamic events of tablet disintegration (Fukami et al., 2005). Chitosan, a swellable, biodegradable polymer was also combined with glycine to produce orodispersible tablets both with wet granulation and with the direct compression technique (Goel et al., 2009).

3.2.2. In vitro evaluation of orally disintegrating tablets

There are many requirements (pharmacopoeial and conventional) that an ODT product should meet. In addition to the common requirements concerning weight uniformity, drug content, friability, stability, dissolution, etc, these products also need to have an acceptable taste and fast disintegration. An orodispersible tablet / ODT should

disintegrate within 3 min according to the Ph. Eur. 8.0 and within 30 sec according to the guidance of the FDA (Guidance for Industry, Orally Disintegrating Tablets, FDA, CDER, 2008). Since *in vitro* evaluation methods are usually preferable over *in vivo* methods due to safety and economic reasons, therefore researchers have developed *in vitro* techniques to characterise ODTs in terms of taste and disintegration.

3.2.2.1. In vitro evaluation of the oral disintegration time

An *in vitro* method, which intends to provide information about the *in vivo* disintegration time (DT), usually attempts to mimic conditions of the mouth where oral disintegration takes place. The European (Ph. Eur. 8.0) and the United States Pharmacopoeias (USP 36) specify the use of conventional tablet disintegration apparatus for orodispersible (Ph. Eur.) / orally disintegrating (USP) tablets. The disintegration takes place in a 1000 ml beaker filled with water and using intense agitation (29-32 cycles/min) at 37 ± 2 °C, which does not mimic the oral conditions; therefore, the correlation between the *in vitro* and the *in vivo* DT values is usually poor (Shukla et al., 2009b). Que et al. (2006) proposed an alternative method where tablets were placed in a cylindrical metal sinker with a mesh size of 1.98 mm (Fig. 1). The sinker was fixed to the side of a dissolution vessel, filled by 900 ml water of 37 °C. The medium was stirred at 50 rpm. The disintegration time was defined as the time at which tablets completely disintegrated and the particles passed through the screen of the sinker. The measured *in vitro* disintegration times were similar to the *in vivo* ones.
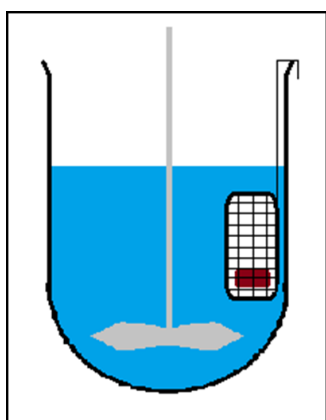
Figure 1 Scheme of the determination of disintegration time of ODT products (Que et al., 2006)

Morita et al. (2002) investigated the reduction of the surface of ODTs placed into the hollow of a metal grid The grid along with the tablets was immersed into stirred and thermostated (37 °C) water and the surface reduction of tablets caused by disintegration was followed by a CCD camera. The rate of the surface reduction was in correlation with the oral disintegration times, however the method was only able to compare tablets of similar composition in terms of DT. The comparability of different tablets was poor. One of the most effective methods for oral disintegration time prediction of fast disintegrating tablets is the texture analysis method. Texture analysers are widely used instruments in the food and pharmaceutical industries because they are able to measure various parameters of solid, semi-solid, and viscous liquid products such as hardness, stickiness, fracturability, compaction, viscosity, etc. These instruments either apply constant force on materials and record the displacement of the probe head as a function of time, or move the probe head at a constant speed and record the force necessary to maintain the predetermined speed value. Dor and Fix (2000) developed a texture analysis-based method to predict the oral disintegration time of tablets. A small amount of water was dropped onto a Petri dish and tablets under a constant force were immersed in the water drop using the instrument (Fig. 2). As tablets started to disintegrate, the probe head moved to the surface of the dish. Time-distance curves were recorded, which were characteristic of the disintegrating properties of the tablets. Good correlation was found between the *in vitro* DT values calculated from the curves and the *in vivo* disintegration times. This method was investigated in detail by El-Arini and Clas (2002) using commercial ODT products. Abdelbary et al. (2005) developed a special accessory for texture analyser-based investigations of fast disintegrating tablets in order to mimic the *in vivo* disintegration processes better. Tablets were placed onto a perforated grid, which was on a movable platform connected to the base by an elastic spring. The system was immersed into the disintegrating medium, only the tablet and the surface of the perforated grid remained above the medium's surface. When the texture analyser exerted pressure to the tablet, it got into contact with the medium and started to disintegrate. Displacement-time curves were recorded, from which the disintegration times were determined. The authors found very good correlation between the *in vitro* results and the *in vivo* disintegration times.
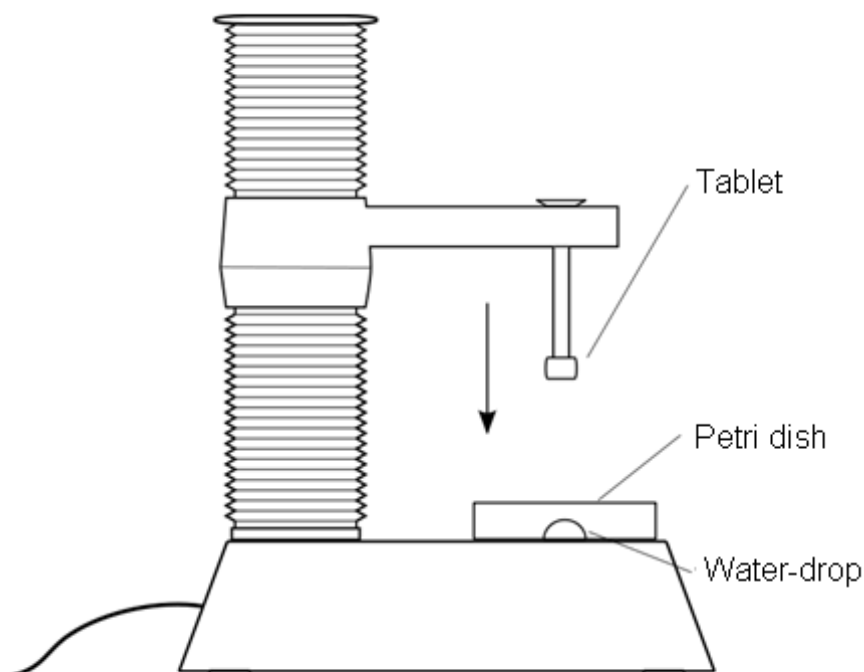
Figure 2 Texture analysis instrument for measuring of tablet softening under constant pressure as a function of time

3.2.2.2. In vitro evaluation of the taste of pharmaceutical products

It is also necessary to evaluate the taste of a final ODT formulation due to the bitter taste of many drugs that are clinically used. Similarly, in this case the *in vitro* method is preferable to the *in vivo* method because the dissolved drug molecules are easily absorbed through the buccal epithelium and may produce systemic effects and side effects, which complicates such measurements. Taste masking can be effectively achieved by preventing the dissolution of the API in the mouth. Most of the taste masking technologies uses this approach. Therefore, the effectiveness of one technology can be evaluated based on dissolution tests if the bitterness threshold value is available for the investigated API. It is possible to predict the bitterness of a product by comparing the concentration of the released drug to the threshold value. The composition, amount and pH of the dissolution medium and the testing time have to be chosen carefully in order to gain relevant information about the *in vivo* bitterness of the

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product (Shukla et al., 2009b). Instrumental methods based on electrochemical measurements are also available for taste evaluation of pharmaceutical products. The most widely used methods are based on potentiometry (Woertz et al., 2011a) and are called electronic tongues since they act analogously to the receptors of human taste buds. At present, two taste-evaluating systems are available on the market, the TS-5000Z system by the Japanese company Insent and the Astree electronic tongue by Alpha MOS, a French company. Both systems are based on potentiometry but characteristics of the sensors and the data processing differ to some extent (Woertz et al., 2011b).

The taste sensors of the TS-5000Z instrument are based on special membranes whose most important constituents are various artificial lipids and plasticisers. These lipids contain both hydrophilic and hydrophobic groups, and they are able to get into contact with chemical entities through electrostatic and hydrophobic interactions. These membranes respond differently to materials belonging to one of the main taste groups (salty, sour, sweet, bitter and umami) changing their membrane potential that can be exploited to gain information about the taste of a single or a complex material (Kobayashi et al., 2010).

The sensors of the TS-5000Z instrument are more or less specific to a given taste. The main component of the instrument is a complex potentiometric system where each sensor is calibrated to detect a specific taste (Woertz et al., 2011b).

Sensors of the Astree instrument are cross selective, i.e. each sensor responds to materials of any taste with different intensity. Therefore, it is not possible to gain direct information about the taste of a material based on potential changes until statistical data processing such as principal component analysis has been performed (PCA) (Woetz et al., 2011b).

The sensors of the Astree are based on the chemically modified field effect transistor technology (ChemFET), which is similar to the ion selective FET (ISFET) technology, but the sensors are coated with specific materials. The ChemFET sensors consist of two high-conductivity semiconductor regions, an insulator region and the sensor membranes on the insulator region (Woetz et al., 2011b).

The method of artificial taste evaluation has its limitations. However, much research was performed using these instruments. Different marketed ibuprofen

suspensions were investigated using the TS-5000Z instrument. Taste changes were detected between the formulations mainly due to the sodium salt, sweetener and preservative components (Woertz et al., 2011c). The taste masking efficiency of microencapsulation of roxithromycin and ibuprofen was evaluated using a laboratory built taste sensor system and principal components analysis. Similar changes were observed on the PCA plots in the case of the two drugs due to the microencapsulation, and the presented method was able to detect the taste changing (Jańczyk et al., 2010). Taste masking possibilities of liquid quinine formulation were investigated using an electronic tongue due to the very bitter characteristic of the substance. Different taste masking agents were used, such as sweeteners (sodium saccharin, sucrose, sucralose, monoammonium glycyrrhizinate, etc.), ion exchange resins and cyclodextrines, and they were evaluated by the PCA method. Authors also presented a schematic, stepwise approach to serve as protocol for the development of taste-masked formulations (Woertz et al., 2010).

3.3. Taste masking of orally disintegrating tablets

Taste masking of bitter drugs can be achieved in various ways, such as screening the taste of bitter materials by sweeteners and flavouring agents or reducing the sensitivity of taste buds, however the most widely used method is the inhibition of the drug's dissolution in the mouth. This method is often combined with the addition of various sweeteners and flavouring agents to the formulation, since many drug molecules have an extremely bitter taste and complete taste masking would create formulation difficulties (e.g. too thick taste masking layer around drug particles). The inhibition of the drug dissolution can be achieved by complex formation between the drug and special molecules or by forming a protective layer around the drug particles. One can also combine the two methods in order to gain better result.

3.3.1. Reduction or screening of the taste of bitter substances

Sweeteners, flavouring agents and effervescent agents have taste reducing effects in the case of moderately bitter substances. Artificial sweeteners are able to suppress different

taste sensations even at very low concentration. On the other hand, many useful excipients for tableting have naturally sweet taste (e.g. sugar, sugar alcohols, some amino acids). Sugar alcohols are especially useful for this purpose because many of them are available in directly compressible form; they have cooling effect in the mouth and are non-cariogenic, non-toxic compounds. Effervescent agents (usually sodium bicarbonate and citric acid) have some taste masking effect in addition to their disintegration and buccal absorption promoting effects (Sohi et al., 2004).

Flavouring agents could be natural or synthetic compounds. Some useful natural compounds are menthol, borneol, or eucalyptus oil. These components are used mainly at liquid formulations and mostly in combination with other ingredients, since they only change the taste of the formulations and are ineffective to mask a bitter taste (Sohi et al., 2004).

3.3.2. The reduction of the sensitivity of the taste buds

This alternative method can only be regarded as an auxiliary method because it is obviously unsuitable to be effective by itself. Materials with local anaesthetic effects can reduce the intensity of tastes in the mouth. Clove oil has mild anaesthetic and taste masking effects (Pandya et Callahan, 1998). Zinc salts can reduce the bitter taste of certain compounds while encountering particular proteins of the taste buds, as well as reducing the taste of sweet molecules. The fact that they do not reduce the bitter taste of other compounds indicates the perception of the bitter taste involves different mechanisms and is a complex process (Keast and Breslin, 2005).

If the taste-masked system contains lipophilic components with low melting point, it reduces the sensitivity of taste buds by partially covering them and increasing the viscosity in the mouth (Sohi et al., 2004). It can be stated that many pharmaceutical excipients could bear more or less taste masking effect.

3.3.3. Inhibition of the dissolution of drug molecules in the mouth

The most common method to eliminate the bitter taste of dosage form is to prevent the dissolution of the drug molecule in the mouth. This task can be achieved by various

ways. Forming a complex with the drug molecule is usually a reversible process that may be slow enough to avoid significant drug release before complete swallowing of the disintegrated product. Physical barrier formation could eliminate any drug release in the mouth, however limitations of these formulations should be given consideration, since the bioavailability of the product should not be modified with the taste masking technology.

3.3.3.1. Complex forming methods

The most widely used complex forming agents for taste masking are the cyclodextrins and ion-exchange resins. Cyclodextrins can form non-covalent complexes with various drug molecules due to their special structures. They are often used to increase the solubility and the bioavailability of compounds with poor water-solubility. Cyclodextrins have the shape of a shallow truncated cone. The non-polar cyclodextrin cavity is occupied by water molecules in aqueous solutions, which can be substituted by drug molecules of lower polarity than water. The main driving forces of the inclusion complexation could be hydrophobic, van der Waals, electrostatic, and hydrogen-bonding interactions (García-Río et al., 2010). Despite the solubility-increasing effect of cyclodextrins, they are useful compounds for taste masking applications. The reason is that the concentration of the free soluble form of the drug is low in the case of the formation of high stability complexes, and the inclusion complex does not interact significantly with the receptors of the taste buds (Szejtli and Szente, 2005).

There are various methods for the preparation of taste-masked formulations using cyclodextrins, such as wet granulation, co-crystallization, spray-drying. The API does not have to be in a complex form in a formulation for effective taste masking in the case of the *in vivo* complex formation. Unpleasant taste does not necessarily occur if both the API and the cyclodextrin components start to dissolve after tablet disintegration, the formed cyclodextrin complex has high stability constant and the free API concentration is low enough. However, in most cases, the physical mixture is inappropriate for successful taste masking and additional procedures are needed. Retarding the drug dissolution by e.g. a polymer coating and accelerating the

cyclodextrin dissolution by reducing the particle size or amorphization may be an effective combination (Friesen et al., 2008).

Ion-exchange resins are also useful materials for taste masking complex formation. Cation-exchange resins form complexes with basic drugs while anion-exchange resins with acidic drugs. Non-complete drug release may raise problems in the case of highly cross-linked gel type resins while in other cases the partial taste masking causes difficulties. Therefore, a coating is applied around the complex particles in most cases. Drug molecules gradually release into the stomach or the small intestines after ingestion due to the presence of ions (Jeong et al., 2006).

The complex formation between the API and the ion-exchange resin is an equilibrium reaction, which involves a diffusion process. The reaction time depends on the particle size of the resin and the degree of cross-linking among other parameters that determine the drug release rate, as well (Jeong and Park, 2008).

Drug molecules can be easily loaded to the resins by stirring the water-insoluble resins in the solution of the drug. In the course of the reaction, drug molecules are absorbed to the resins while ions are released into the solution until equilibrium. The reaction can be completed by changing the solvent periodically to ion-free new drug solution. After the procedure the loaded resins are filtered, washed with distilled water and dried for further processing (Jeong et al., 2006).

3.3.3.2. Protective layer forming methods

Using a physical barrier, a coating around drug particles is a reasonable method to mask the bitter taste of the drug since only dissolved molecules can come into contact with the receptors of the taste buds. This method separates drug molecules from the solvent (salivary fluid) but in a technological point of view, this technique poses certain difficulties, e.g. an imperfect coat may lead to unsuccessful formulation. Considering fast disintegrating tablets, the size of the coated drug particles should not exceed 300 μm because otherwise a gritty feeling can occur in the mouth. Polymers are used for taste masking protective coating formation in most cases, and their physico-chemical parameters can be chosen according to the actual formulation requirements. It is possible to formulate coated particles with retarded dissolution in the mouth but fast

dissolution in the stomach using appropriate polymer due to the pH differences in the gastro-intestinal tract. The pH of the salivary fluid is usually between 6 and 7 (Humphrey and Williamson, 2001). Many commercialized polymer-based products used for taste masking applications have pH-dependent dissolution or swelling (e.g. Eudragit® E 100 or Kollicoat® MAE 30 DP).

A multiparticulate dosage form arises from coated drug particles with the advantage that the tablets can be splitted without impairing the release profile or the bioavailability of the drug since the polymer coat is not damaged at all or only at the splitting surface of the tablet.

There are many pharmaceutical methods suitable for drug particle coating, e.g. spray drying, hot melt extrusion, freeze-drying, microencapsulation. Fexofenadine HCl particles were coated with Eudragit® E 100 by fluidized bed granulation. Eudragit® E 100 is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate. It is soluble in the gastric fluid up to pH 5 and swellable and permeable above pH 5, therefore the drug release is ensured over a wide pH range (Chenevier and Marechal, 2009). Eudragit® E 100 was used for the taste masking of pirenzepine HCl and oxybutinine HCl model drugs. The drugs were mixed with the copolymer and ethanol was added to the mixture in order to obtain a gel. Granules were produced from the gel using extrusion followed by a drying and a milling step. Fast disintegrating tablets were prepared from the granules using cellulose, hydroxypropyl cellulose (L-HPC) excipients and a lubricant (Ishikawa et al., 1999). The hot melt extrusion technique is also suitable for taste masking purposes using low melting point lipoid excipients. These materials form a water-insoluble layer around drug particles; therefore only minimal drug release takes place in the mouth. Compritol® 888 ATO (glyceryl dibehenate) and Dynasan® 116 (glyceryl tripalmitate) are useful excipients to this task. They were mixed with the API and 1% colloidal silica and then the partially melted mixture was extruded with a twin-screw extruder. This method was successfully used for the taste masking of enrofloxacin and prasiquantel (Kinikanti et al., 2010). Freeze-drying is also suitable for API processing in addition to the fast disintegrating tablet preparation. Taste masked granules of piroxicam were produced using this method. Since the drug is practically insoluble in water, therefore it was incorporated into β-cyclodextrin complex, which had bitter taste. A taste-masked

formulation was prepared using dextrose as filler, a citric acid - pectin combination as taste masking agent and water to create a gel from the excipients. The drug-containing complex was homogenised with the gel after that the solvent was removed with freeze-drying procedure (Plouvier et al., 2005).

Basically, microencapsulation could be performed in three ways, i.e. solvent extraction, phase separation (coacervation) and spray drying. The solvent extraction method has the advantage that it could be used also in the case of heat sensitive materials and it does not yield high amounts of remaining solvent or coacervation agent in the microcapsules. Using this method, organic solution of the API and a matrix-forming agent is emulsified in an aqueous phase and the drops of the organic phase solidified due to the extraction of the organic solvent from the droplets by diffusion or evaporation (Freitas et al., 2005). Microcapsules containing Ibuprofen were prepared using either Eudragit® RS 100 or Eudragit® RL 100 polymers by the solvent extraction method. The organic phase contained the API, ethanol and the Eudragit® polymer while emulsifier suspended in water was the aqueous phase. The alcoholic phase dispersed into droplets after the addition to the aqueous phase under stirring and solidified as small spheres. The RS 100 type Eudragit® was able to sustain the release of the drug to a greater extent due to its lower content of quaternary ammonium group, which reduced its permeability (Perumal et al., 1999).

3.4. Incorporation of the API into hydrogen-bonded polymer complexes

Association of polymers in solution via hydrogen bonds may result in the so-called hydrogen-bonded interpolymer complexes (HBICs). The hydrogen donor molecule is usually a poly(carboxylic acid), mainly poly(acrylic acid) (e.g. Carbopol®), the hydrogen acceptor molecule may be a wide variety of non-ionic polymers, such as polyvinylpyrrolidone, poly(ethylene oxide), poly(vinyl alcohol), hydroxypropyl methylcellulose (Khutoryanskiy, 2007). The two interacting polymers are usually soluble in water or ethanol, but during mixing of the two polymer solutions, turbidity can be observed, because hydrogen bonds are developing between the two polymers, therefore water molecules are expelled from the functional groups of the polymers. The resulting interpolymer complexes have lower solubility than the corresponding

polymers, and the precipitated complex causes the turbidity. Complexes in a granular form can be obtained for further use after evaporating the solvent. If an API is also present in the system, it can be bound into the complex via hydrogen bonds (Ozeki et al., 1998, 2000). This method is viable in the case of both water-soluble and water-insoluble drugs. In the case of an API of high water solubility, the complex releases the drug in a controlled manner. On the other hand, in the case of an API of low water solubility its release rate could be higher than the corresponding crystal form, because the drug could be in the form of amorphous solid dispersion stabilized by hydrogen bonds (Mooter, 2012).

The driving force of the polymer association is the high number of consecutive (ladder type) hydrogen bonds. The formed structure usually begins compacting after the formation in order to reduce the surface contact with solvent molecules (Khutoryanskiy, 2007). Changes in the external conditions (e.g. temperature, pH, ionic strength) can trigger the formation of interpolymer complexes through the altered molecular interactions. The complexation of the polymers occurs only under a critical pH value in aqueous solutions in the case of poly(acrylic acid) (PAA) and a hydrogen acceptor molecule, in the case of required protonation of PAA molecules. Hydrogen bonds and hydrophobic interactions contribute to the complex formation. Hydrophobic interactions promote HBIC formation and alter the temperature dependence of the process. The chemical nature of the polymers and the solvents and the temperature determine the main thermodynamical parameters of the reaction, e.g. the ratio of the enthalpy and the entropy part of the Gibbs free energy (Sudre et al., 2012; Bian and Liu, 2003).

Hydrogen bonded interpolymer complexes have many possible useful applications in the drug delivery field. Their special features could be exploited in *in situ* gelling parenteral formulations (Haglund et al., 1996), in ophthalmic formulations due to the increased residence time (Lin and Sung, 2000), in the development of various mucoadhesive dosage forms (Satoh et al., 1989; Gupta et al., 1994; Dubolazov et al., 2006), and in similar innovative solutions, as well (Khutoryanskiy, 2007).

Drug release modification is one of the possible applications of HBICs. Poly(ethylene oxide) (PEO) was complexed with Carbopol® polymers of various cross-linking densities and phenacetin was used as model drug. Crystalline peaks of PEO and phenacetin disappeared in the X-ray diffraction patterns of the complexes indicating the

amorphous state of the components. The function of the release rate of phenacetin versus the molecular weight of the Carbopol® showed a U-shaped curve and Carbopol® 971P provided the slowest release rate, which was characterised by intermediate cross-linking degree and molecular weight (Ozeki et al., 2000). The release rate of phenacetin was also modified by a methylcellulose (MC) - Carbopol® complex. The complex composition was prepared by the solvent evaporation method using 1:1 (v/v) water/ethanol mixture. Release rate of phenacetin varied depending on the MC/Carbopol ratio of the complex and the molecular weight of the MC. The release rate was the slowest at a MC/Carbopol ratio of 50:50 and it decreased by the molecular weight of the MC reaching a plateau at ≥180 kDa (Ozeki et al., 2006).

The use of supercritical CO_2 (scCO$_2$) could be an alternative method for drug processing, which is a "greener" alternative of the conventional solvent-based approaches. CO_2 is a non-toxic material and it is easily removed from the product. Supercritical CO_2 has the ability to plasticise polymers and solubilise drug molecules, therefore it may promote solid dispersion formation (Kazarian and Martirosyan, 2002; Gong et al, 2006). Ibuprofen loaded poly(ethylene glycol) (PEG, M_w = 400) - polyvinylpyrrolidone (PVP) complexes were prepared from ethanol cast solutions and in supercritical CO_2, as well. It was shown by differential scanning calorimetry, infrared spectroscopy and X-ray diffraction methods, that the drug was molecularly incorporated into the complex and ibuprofen was mainly bonded to the carbonyl groups of PVP (Labuschagne et al., 2011).

3.5. The role of water content of the excipients in pharmaceutical technology

Water undoubtedly plays a significant role in pharmaceutical technology and specifically in tableting technology, too. It can be bound to pharmaceutical excipients in at least three states according to differential scanning calorimetriy (DSC) measurements. These states are: 1, free water that undergoes similar phase transitions than bulk water; 2, freezeable bound water that undergoes phase transitions at different temperatures than bulk water due to hydrophilic interactions with the surrounding molecules; 3, non-freezeable bound water that does not undergo phase transitions during DSC experiments (heating or cooling). Non-freezeable bound water is in direct

contact with the polar groups of surrounding molecules, therefore it cannot be crystallized (Hodge et al., 1996). This water may be associated with the so-called monolayer adsorbed water measured by water sorption experiments. For example, it was shown that the stability of dried proteins decreased as their water content exceeded this monolayer values due to the increased molecular flexibility (Constantino et al., 1997; Chang et al., 2005).

Amorphous hydrophilic excipients, usually water-soluble polymers are amongst the most moisture-sensitive pharmaceutical materials. Unlike crystalline solids, amorphous materials have only a short-range molecular order without long-range order of molecular packing (Yu, 2001). The molecules or clusters of molecules are randomly arranged; therefore, they occupy a larger volume compared to their crystalline equivalent. The excess volume (called free volume) available for molecular rotational and translational motions is the reason for the different physico-chemical behaviours of amorphous materials (Abiad et al., 2009).

One of the most important parameters of an amorphous material is its glass transition temperature (T_g). An amorphous solid is in the glassy state under this temperature value where molecular rotational or translational motions are restricted and only vibration is possible (Jadhav et al., 2009). Over the glass transition temperature large scale molecular movements are allowed and the glassy-to-rubbery transition (glass transition) occurs. The material has a liquid-like structure with very high viscosity in this state (Hancock and Zografi, 1997).

Polymers mainly exist in the amorphous state due to their special structure, while other molecules, e.g. sugars, sugar alcohols, and many drug molecules easily crystallise under non-controlled conditions. (Haque et Roos, 2005; Columbano et al., 2002). Cooling melts of crystalline solids fast enough to prevent crystal formation leads to the formation of the rubbery state, a supercooled liquid of relative high viscosity and a solid-like glassy state is achieved by further cooling the system below its T_g value (Ottenhof et al., 2003). The differences between glassy and crystalline solids are as follows: molecular motions (Jadhav et al., 2009), enhanced chemical reactivity (Yoshioka and Aso, 2007), dissolution rate (Sun et al., 2012), susceptibility to water absorption (Ottenhof et al., 2003), etc. The difference between polymers and small molecules is that the rubbery state of the latter is kinetically very unstable and the large-

scale molecular movements induce crystallisation compared to most macromolecules where crystallization might not be possible.

The number of different techniques capable of detecting the glass transition demonstrates the importance of the physic-chemical changes of materials around their glass transition temperatures well. These techniques among others are differential scanning calorimetry, thermomechanical analysis, dynamic mechanical analysis, nuclear magnetic resonance, positron annihilation lifetime spectroscopy, inverse gas chromatography and scanning probe microscopy (Abiad et al., 2009).

Water has special role in regards to amorphous materials since water absorption proportionally lowers their T_g value and once the T_g value of an amorphous material decreases below the environmental temperature, glass transition occurs which significantly increase the crystallization rate of the material (Craig et al., 1999). This T_g lowering effect of water is called plasticisation, that effect has many important technological implications. This phenomenon has been exploited to produce fast disintegrating tablets containing amorphous sucrose (see 3.1.1.4.; Sugimoto et al., 2006).

3.5.1. The role of water content of superdisintegrants

Since superdisintegrants are components of many ODT formulations and due to their highly hygroscopic nature, water absorption and water content are of special importance in the case of these pharmaceutical excipients. Hahm devoted a complete doctoral thesis to this topic of the title of "Effect of Sorbed Water on the Efficiency of Super Disintegrants: Physical and Mechanistic Considerations" (Hahm, 2002).

The three most important superdisintegrants are crospovidone (CrosP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG). These excipients are water-insoluble cross-linked hydrophilic polymers. Crospovidone is the cross-linked homopolymer of N-vinyl-2-pyrrolidone (Fig. 3); sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch or of a cross-linked carboxymethyl ether of starch (Fig. 4); croscarmellose sodium is the sodium salt of a cross-linked, partly O-carboxymethylated cellulose (Fig. 5).
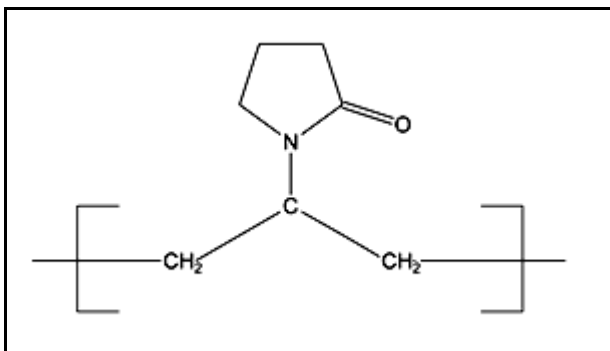
Figure 3 Chemical structure of crospovidone
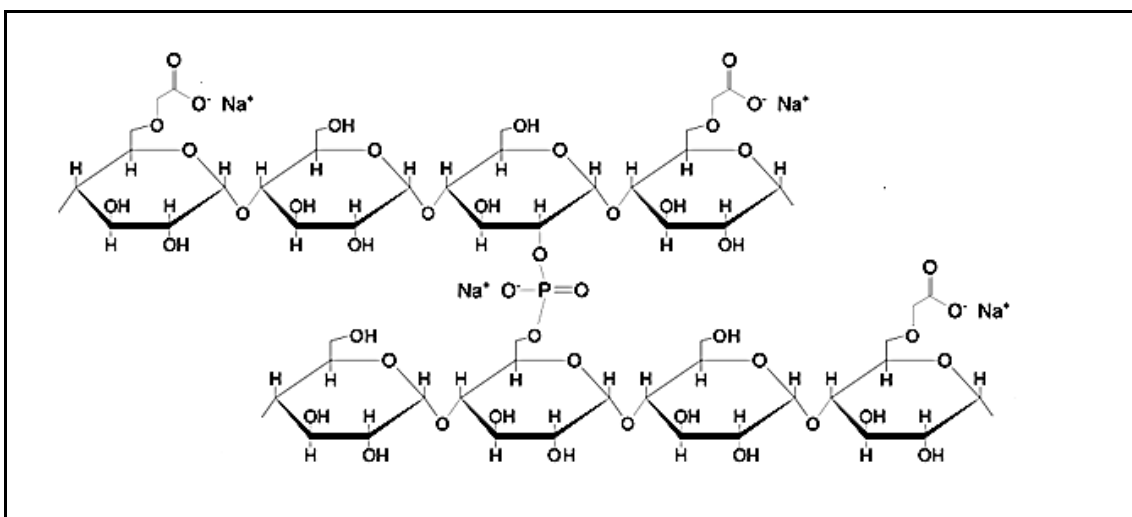
Figure 4 Chemical structure of sodium starch glycolate
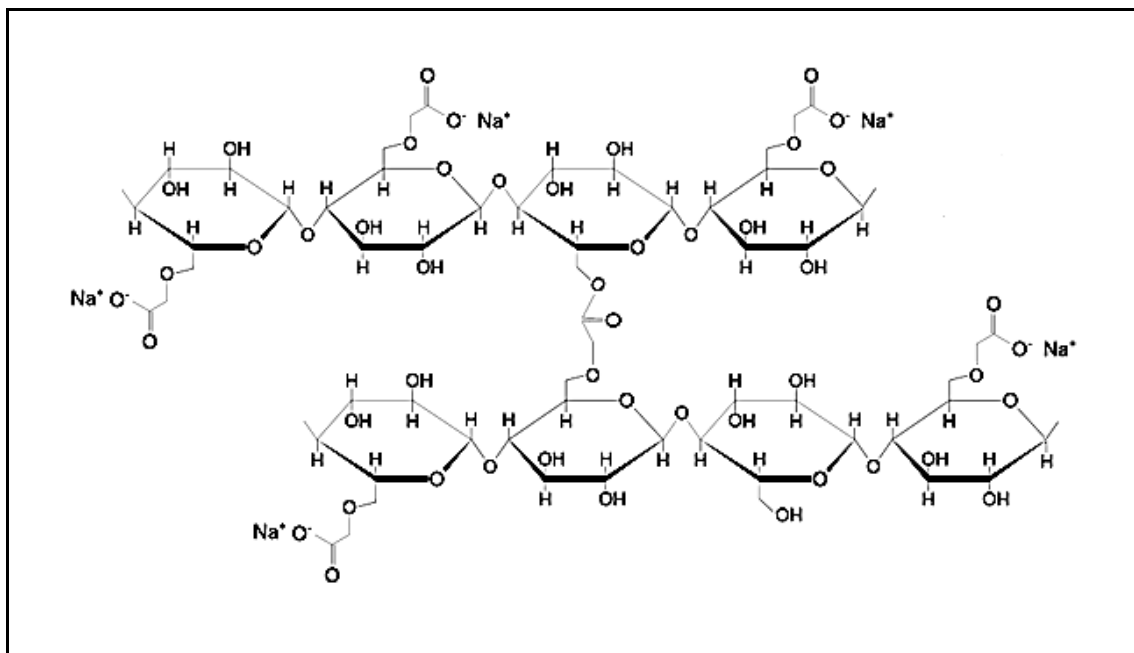
Figure 5 Chemical structure of croscarmellose sodium

Their mechanisms of action are water wicking and the subsequent immediate swelling, which causes fast destruction of the integrity of the tablets. These excipients were investigated using an environmental scanning electron microscope, which enabled their structural investigation at different humidity conditions. Particles of croscarmellose sodium showed considerable twisting and expansion upon exposure to high relative humidity (RH) detected in real time. The particles did not regain their original shape upon the decrease of the RH value. Swelling and deformation were observed in the case of sodium starch glycolate particles at high RH. The fusion of the particles was also observed (Fig. 6). Some shrinkage of the fused particles was detectable during dehydration. Crospovidone particles resemble crumpled pieces of paper. They did not show significant signs of swelling even at high RH (80%) in spite of the considerable water absorption. These materials absorbed water vapour between 48 and 62% w/w at 90% RH in dynamic water sorption experiments (Thibert and Hancock, 1996).
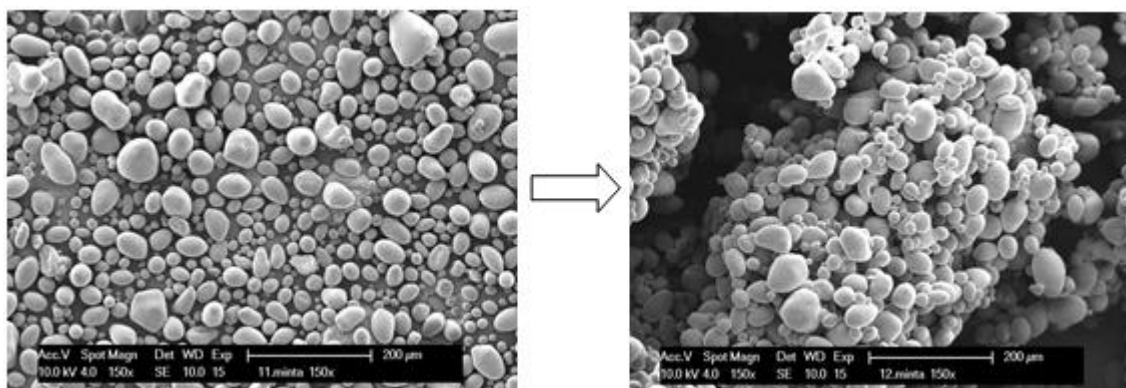
Figure 6 SEM pictures of sodium starch glycolate (Explotab[®]) particles before and after exposure to 75% relative humidity; magnification 150× (unpublished result of the author)

Particles size changes due to water absorption were measured with laser diffraction technique and, interestingly, the results showed no particle size increase in the case of croscarmellose sodium and sodium starch glycolate but showed increase in the case of crospovidone in contrast with the results of the environmental scanning electron microscope experiments (Hahm, 2002).

Water absorption affects the physical properties of the superdisintegrants. Water acts as plasticizer, induce particle size changes and deformations and high water content can also induce changes of the parameters of other excipients present in a tablet, especially if amorphous components are included. Water sorption did not seem to have an adverse effect on the swelling ability of the superdisintegrants. However, the high relative humidity caused aggregation in the case of CrosP and SSG. X-ray diffraction studies revealed that the moisture sorption of SSG led to irreversible structural changes. It was also shown that the performance of the superdisintegrants might decrease due to water sorption, especially above 15% w/w moisture content. High amounts of absorbed moisture delays the disintegration processes. CrosP was the most sensitive superdisintegrant using insoluble filler, while SSG was the most sensitive in the case of a partially soluble matrix (Hahm, 2002).

It can be stated that superdisintegants are moisture sensitive materials and they can gradually absorb water from the environment under improper storage conditions, but their performance usually is not affected by small amounts of absorbed water.

3.6. Principles of the ATR-FTIR spectroscopy

The infrared spectral region can be divided into three subdivisions: the far-infrared (400 - 10 cm^{-1}), the mid-infrared (further this region will be called "infrared") (4000 - 400 cm^{-1}) and the near-infrared (13000 - 4000 cm^{-1}) region, where the electromagnetic (EM) wave of a higher energy is associated with a higher wavenumber (Bunaciu et al., 2010). All polyatomic organic molecules have infrared bands in the mid-infrared region between 400 and 4000 cm^{-1} and this region is used by the conventional Fourier-transform infrared (FTIR) spectrophotometers for qualitative and quantitative measurements. The energies of an infrared (IR) radiation are unable to cause electron transitions of molecules but the stretching and bending of bonds between atoms and the rotation of the whole molecule are exited. Energy of the EM wave is transferred from the radiant beam to the molecule if the wave is passing through a substance. A measure of this energy transfer, relative to wavenumber, is the infrared absorption spectrum. One of the advantages of this technique is that there are no two identical spectra for two different molecules (Carol, 1961). However, the infrared spectrum of a compound depends on its structure (i.e. amorphous or crystalline) and IR spectroscopy is a valuable tool for the identification of drug polymorphism as well (Kalinkova, 1999). IR spectroscopy obeys a law that is similar to the Beer-Lambert's law; therefore, it enables quantitative measurements (Bunaciu et al., 2010).

When using transmission measurement, the infrared beam illuminates the sample, and a detector is placed behind the sample to record the fraction of the transmitted light. Transparent sample is a prerequisite of this technique; therefore, most materials have to be diluted in a non-absorbing matrix (usually potassium bromide) and pressed into transparent thin discs (Bunaciu et al., 2010).

The sample preparation method of potassium bromide disc formation is not applicable in all cases because many materials cannot be effectively pulverised (e.g. rubbers, biological tissues), or transparent film formation is not possible. The attenuated total reflection technique (ATR) makes the investigation of such samples (both of the liquid and the solid phase) without any sample preparation possible. Using this technique, the sample is pressed with a head to the ATR crystal with high pressure to ensure intimate contact with the crystal and only the few micrometres of the connected

part of the sample is brought into contact with the IR beam. ATR crystals are made of materials with high refractive indices (usually zinc selenide, diamond or germanium), therefore the samples have usually lower refractive indices. The angle of inclination of the incident IR beam is chosen to that the IR beam shows total reflection at the ATR crystal - sample interface (according to Snell's law) and only an evanescent wave penetrates the sample with an amplitude that exponentially decays with distance (Fig. 7) (Vitali, 2001). This evanescent wave interacts with the absorbing material, resulting in the spectrum.
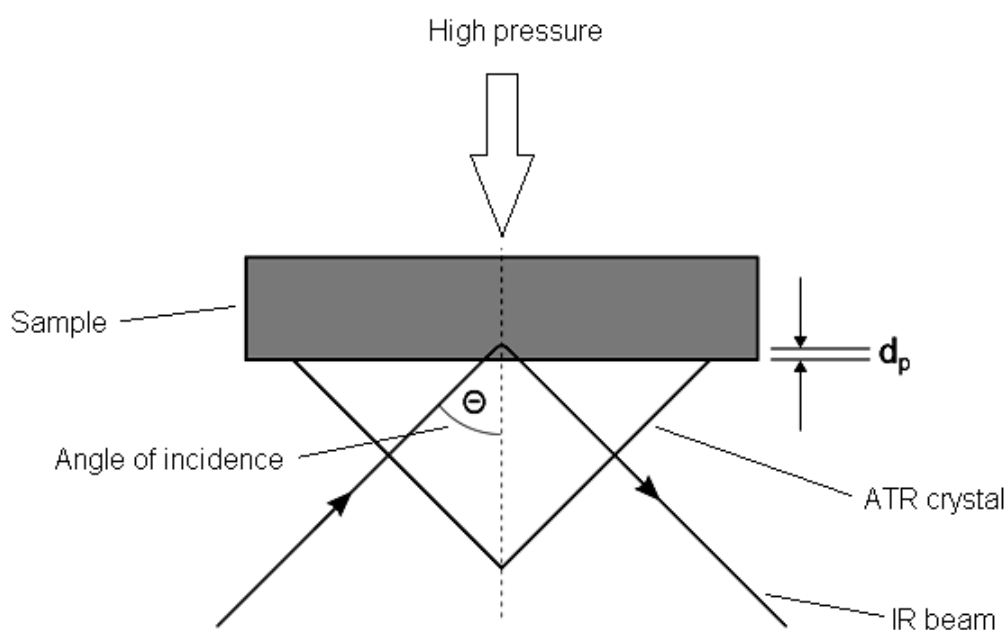
Figure 7 Schematic of the ATR accessory; d_p is the penetration depth of the evanescent IR beam

The penetration depth (d_p) of the evanescent wave is only a few microns, therefore quantitative information may only be obtained from this surface region about the whole material. Therefore, homogenously distributed chemical composition of the bulk material is prerequisite for analytical work. There is a linear relationship between the penetration depth of the evanescent wave and the wavelength (λ) of the IR beam according to Eq. (1), where n_c and n_s are the refractive indices of the ATR crystal and the sample, respectively, and θ_i is the angle of incidence of the IR beam (Buffeteau et al., 1996).

$$d_p = \frac{\lambda}{2\pi n_c \sqrt{(sin\,\theta_i)^2 - \left(\frac{n_c}{n_s}\right)^2}} \qquad\qquad (1)$$

It can be seen from this equation that the penetration depth depends on the wavelength of the IR beam; consequently, spectral intensities will also depend on the wavelength in addition to the chemical composition of the material. On the other hand, the refractive index of an absorbing material is also wavelength dependent, and it changes drastically around an absorption band. This phenomenon is called anomalous dispersion or refractive index dispersion (Luthra et al., 2007). These spectral differences can be easily observed on the IR spectra of water measured by the transmission and the ATR technique (Gradadolnik, 2002). Uncorrected ATR spectra can be used despite of these spectral differences. Max et al. (2001) showed that the spectral intensity of aqueous salt solutions followed the Beer-Lambert's law during ATR-FTIR measurements.

3.6.1. Water content determination of amorphous pharmaceutical polymers by ATR-FTIR spectroscopy

Amorphous hydrophilic polymers can absorb a large amount of water into their bulk structure at high humidity environments. This water absorption is not restricted to the surface of the materials unlike crystalline structures but water molecules penetrate the whole material due to its porous structure (Hancock and Shamblin, 1998). This more or less homogenous water absorption enables the water content measurement of amorphous or partially amorphous polymers (e.g. superdisintegrants) using ATR-FTIR spectroscopy. Liquid water has strong absorption around 1640 cm^{-1} due to its bending vibration and very strong absorption between 3700 and 2800 cm^{-1} due to its stretching vibrations, while in the 1510 - 1050 cm^{-1} spectral region has only week absorption due to combination absorption bands (Max and Chapados, 2001). The stretching vibrations of hydrogen-bonded water molecules overlap with the stretching vibrations of hydroxyl and amino groups, constituents of most pharmaceutical polymers. However, the increase of the spectral intensities in the 3700 - 2800 cm^{-1} spectral region is indicative of the water absorption of the polymer, since only the water content changes, therefore

spectral intensity changes of this region can be transformed into quantitative information. Another attribute that should be considered for the ATR-FTIR spectroscopic measurement of the water content of polymeric materials is spectral intensities, which, unlike the transmission method, do not depend on the thickness of the sample (since the penetration depth is only a few microns anyway), but they depend on the amount of the molecules the evanescent wave penetrates. In the lack of an ordered crystalline structure of amorphous materials, their structure (e.g. density of the polymer chains) on the ATR crystal will depend on the applied pressure of the ATR accessory and the water content. It is a well-known phenomenon that water has plasticising effect on hydrophilic polymers, i.e. their free volume, porosity, compactability depends on their water content. The chain arrangement of a polymer with high water content is denser on the ATR crystal compared to its dried state using the same pressure. This denser chain arrangement is due to the increased molecular mobility caused by the absorbed water molecules (Abiad et al., 2009). In conclusion, it is obvious that spectral intensities depend on the water content of the polymer due to the different degree of compaction of the polymer chains on the ATR crystal. On the other hand, as water molecules are expected to be homogenously distributed in the polymeric chains, their contribution to the absorption also depends on the degree of compaction of the chains. It is necessary to separate the contribution of the amount of the water molecules from the contribution of the polymer compaction to a particular absorption spectrum in order to gain quantitative information. The spectral region of 1510 - 1050 cm^{-1} is useful to investigate polymer compaction on the ATR crystal, since water molecules have only weak absorption in this region, but polymer molecules usually have strong absorption bands. ATR-FTIR spectroscopy may be a new method for water content determination of amorphous solid materials (Szakonyi and Zelkó, 2012).

4. Objectives

The general aim of the thesis was to investigate the various technologies applied to ODT formulations and the additional pharmaceutical considerations including excipient selection and characterisation, tablet evaluation, theoretical backgrounds. The direct compression technology using superdisintegrants and/or effervescent agents as disintegration promoting materials was selected for the formulations.

Superdisintegrants were key components of the formulations and they were the most sensitive materials among the selected excipients in terms of relative humidity, therefore one of the aims of the presented work was their detailed investigations based on infrared spectroscopic measurements and the construction of a quantitative method to measure their water content using the ATR-FTIR technique.

Another purpose was to prepare different fast disintegrating tablets by various technologies and to investigate their disintegration characteristics. Tablet preparation was also applied to select the best superdisintegrant using mannitol, a highly water soluble sugar alcohol, as filler.

Due to the fact that the existing *in vitro* tablet disintegration testing methods usually give poor *in vitro-in vivo* correlation (IVIVC), it was important to develop an optimized *in vitro* disintegration test, which can provide good IVIVC of the investigated different tablets. The latter is of decisive impact since it is the most important functionality-related characteristic of ODTs.

Taste masking of the API is a critical step of the formulation processes. Due to the large variety of patented and experimental techniques, a novel method, hydrogen-bonded polymer complex formation, was investigated in order to broaden the possibilities of taste masking.

The aims of the dissertation were as follows:

- Water content determination of pharmaceutical superdisintegrants by ATR-FTIR spectroscopy,
- Tablet preparation for the screening of the efficiency of different pharmaceutical superdisintegrants,

- Tablet preparation by exploiting of the swelling of crospovidone and the phase transition of xylitol,
- Development of a method for the *in vitro* determination of the disintegration times of different ODTs,
- Formation of hydrogen-bonded polymer complexes to sustain the release of a water soluble API.

5. Materials and Methods

5.1. Materials

5.1.1. Materials for the water content determination of pharmaceutical superdisintegrants

The investigated superdisintegrants were the crospovidone (Polyplasdone$^®$ XL, ISP; Polyplasdone XL-10, ISP; and Kollidon CL-SF, BASF), the sodium starch glycolate (Explotab$^®$, JRS Pharma), and the croscarmellose sodium (Vivasol$^®$, JRS Pharma). All superdisintegrants were in powdered form. The particle sizes of Polyplasdone$^®$ XL, Polyplasdone$^®$ XL-10 and Kollidon$^®$ CL-SF were 100-130 μm, 30-50 μm and 10-30 μm, respectively based on the manufacturers' data.

5.1.2. Materials for tablet preparations

5.1.2.1. Tablet preparation for superdisintegrant screening

Directly compressible mannitol (Pearlitol$^®$ 200 SD, Roquette) was used as filler. The applied superdisintegrants were as follows: crospovidone (Kollidon® CL-SF, BASF), croscarmellose sodium (Vivasol$^®$, JRS Pharma) and sodium starch glycolate (Explotab$^®$, JRS Pharma). Tablets contained the superdisintegrants at three levels, i.e. they contained 3, 5, and 7% w/w superdisintegrant. Sodium stearyl fumarate (Pruv$^®$, JRS Pharma) was used as lubricant. 2% w/w lubricant was used in the case of the tablets containing crospovidone and 1.5% w/w in the case of the tablets containing the other two superdisintegrants.

5.1.2.2. Tablet preparation by exploiting the swelling of crospovidone and the phase transition of xylitol

All formulation contained mannitol (Mannogem$^®$ EZ, SPI Pharma) as filler, milled anhydrous citric acid as flavouring agent, xylitol (Xylisorb$^®$, Roquette) as melting

component and sodium stearyl fumarate (Pruv®, JRS Pharma) as lubricant. Vivapur® 112 (microcrystalline cellulose, JRS Pharma), Prosolv® EASYtab (microcrystalline cellulose based composite excipient, JRS Pharma) and Ludiflash® (mannitol-based composite excipient, BASF) were additional fillers. Finely ground xylitol was prepared by grinding Xylisorb® for a few minutes using a mortar and pestle. Superdisintegrants were crospovidones (Kollidon® CL-SF, BASF and Polyplasdone® XL-10, Ashland), the sodium starch glycolate (Explotab®, JRS Pharma), and the croscarmellose sodium (Vivasol®, JRS Pharma).

5.1.2.3. Tablet preparation for the in vitro determination of disintegration times of ODTs

Excipients for tablet preparations were spray-dried mannitol (Mannogem® EZ, SPI Pharma) as filler, sodium stearyl fumarate (Pruv®, JRS Pharma) as lubricant, milled anhydrous citric acid and sodium bicarbonate in 1:1 mass ratio as effervescent agent, and milled anhydrous citric acid as flavouring agent. Superdisintegrants were crospovidon (Polyplasdone® XL, Ashland), croscarmellose sodium (Vivasol®, JRS Pharma), and sodium starch glycolate (Explotab®, JRS Pharma).

5.1.3. Materials for the disintegration medium of the in vitro disintegration time determination method

The disintegration medium consisted of glycerol with 99.5% purity, distilled water and optionally polyvinypyrrolidone (Kollidon® 25, BASF).

5.1.4. Materials for the formation of hydrogen-bonded polymer complexes

Desloratadine-hemisulphate (Gedeon Richter Plc., Hungary) was used as water soluble model compound. Water insoluble crospovidones (Polyplasdone XL-10 and Polyplasdone XL, Ashland) were used as the hydrogen acceptor polymers, and intermediate cross-linked poly(acrilic acid) (Carbopol® 971P, Lubrizol) was used as the hydrogen donor polymer. Polysorbate 80 (Tween 80) was used as surfactant in the case

of the Tween 80-containing samples. The dissolution tests were performed in phosphate-citrate buffers, while the dissolutions in the Erlenmeyer flask were performed in citrate buffers and hydrochloric acid solution.

5.2. Sample preparations

5.2.1. Samples for the water content determination of superdisintegrants

The superdisintegrants were stored at different humidity conditions for given periods of time in small plastic open containers to absorb water. In the case of crospovidones, dried samples (95 °C, 0.5 h) were also prepared. The maximum water content of crospovidones was reached by the storage at 75% RH for 48 h, and in the case of sodium starch glycolate and croscarmellose sodium at 100% RH for 48 h. Nine samples of different water contents from each of the five excipients were prepared for the calibrations, thus 45 samples were involved in the investigation.

5.2.2. Conditions of the tablet preparations

All tablets were prepared by direct compression after gentle homogenization of the ingredients with a pestle. Round tablets of 8 mm in diameter were prepared with a single-punch tableting machine (Diaf, Denmark).

5.2.2.1. Tablet preparation for superdisintegrant screening

Two tableting pressures were applied to tablet preparation by using different penetration distances of the upper punch into the die. The pressure levels were adjusted to obtain significantly different tablets in terms of hardness and disintegration for each formulation.

5.2.2.2. Tablet preparation by exploiting the swelling of crospovidone and phase transition of xylitol

Different formulation series were successively prepared and compared. The compositions of the prepared and compared series (1 - 5) are listed in Table 2 - 6. In the case of each series, there were few differences between the formulations in order to examine the effects of the components or the preparation methods. Formulation 4/B was prepared using external lubrication when the lubricant was carried up to the surface of the punches with a brush. Each series was treated using the same procedure (Table 7).

Table 2 Composition of tablets of series 1

Components (% w/w)	1/A	1/B	1/C	1/D
Mannogem® EZ	73.2	73.2	73.2	73.2
citric acid	2.0	2.0	2.0	2.0
Kollidon® CL-SF	3.0	3.0	3.0	3.0
Xylisorb®	20.0	15.0	10.0	5.0
ground Xylisorb®	0	5.0	10.0	15.0
Pruv®	1.8	1.8	1.8	1.8

Table 3 Composition of tablets of series 2

Components (% w/w)	2/A	2/B	2/C	2/D
Mannogem® EZ	73.2	53.2	53.2	53.2
Ludiflash®	0	20.0	0	0
Prosolv® EASYtab	0	0	20.0	0
Vivapur® 112	0	0	0	20.0
citric acid	2.0	2.0	2.0	2.0
Kollidon® CL-SF	3.0	3.0	3.0	3.0
Xylisorb®	5.0	5.0	5.0	5.0
ground Xylisorb®	15.0	15.0	15.0	15.0
Pruv®	1.8	1.8	1.8	1.8

Table 4 Composition of tablets of series 3

Components (% w/w)	3/A	3/B	3/C	3/D
Mannogem® EZ	73.2	73.2	73.2	73.2
citric acid	2.0	2.0	2.0	2.0
Kollidon® CL-SF	3.0	0	0	0
Vivasol®	0	3.0	0	0
Polyplasdone® XL-10	0	0	3.0	0
Explotab®	0	0	0	3.0
Xylisorb®	5.0	5.0	5.0	5.0
ground Xylisorb®	15.0	15.0	15.0	15.0
Pruv®	1.8	1.8	1.8	1.8

Table 5 Composition of tablets of series 4

Components (% w/w)	4/A	4/B
Mannogem® EZ	73.2	73.2
citric acid	2.0	2.0
Kollidon® CL-SF	3.0	3.0
Xylisorb®	5.0	5.0
ground Xylisorb®	15.0	15.0
Pruv®	1.8	only external

Table 6 Compositon of tablets of series 5

Components (% w/w)	5/A	5/B
Mannogem® EZ	64.2	54.2
citric acid	2.0	2.0
Kollidon® CL-SF	2.0	2.0
Xylisorb®	20.0	26.7
ground Xylisorb®	10.0	13.3
Pruv®	1.8	1.8

Table 7 Conditions of the storage of the series in the desiccator

Series number	Storage RH (%)	Storage T (°C)	Storage time (h)
1	71 - 75	25 - 27	48
2	70 - 75	24 - 25.5	48
3	71 - 74	24 - 25	48
4	70 - 73	28.5 - 29.5	48
5	73 - 76	28 - 30	72

The prepared tablets were stored over saturated NaCl solution in a desiccator in order to absorb water. The conditions of the desiccator were followed by a temperature and humidity data logger (DL-120 TH, Voltcraft).

Tablets were subjected to a temperature of 93 °C for 12 minutes in a drying chamber. Immediate transfer of the tablets was carried out after the heat treatment into tightly closed plastic containers in order to avoid water absorption. Properties of tablets were measured after 7 - 8 days of storage.

5.2.2.3. Tablet preparations for the in vitro disintegration time determination of ODTs

Names and compositions of tablets are listed in Table 8. In addition to the filler and the disintegrating agent(s), each tablet contained 2% w/w sodium stearyl fumarate (SSF) and 2% w/w milled anhydrous citric acid. Filler was spray-dried mannitol. The first five tablets (T1-T5, called calibration tablets) were used to determine the optimum conditions of the texture analysis method. The other tablets (T6-T9) were used to evaluate the optimized method. Tablets T6 and T7 were called interpolation tablets, since they were characterized by similar oral disintegration time as the calibration tablets. Tablets T8 and T9 were called extrapolation tablets, since they were characterized by the lowest oral disintegration times and mechanical hardness.

Table 8 Disintegrating agent components of the prepared tablets for *in vitro* disintegration time determinations

Tablet code	Varying components (% w/w)
T1	Vivasol®, 3%
T2	Vivasol®, 3%; Polyplasdone® XL, 1%
T3	Explotab®, 3%; Polyplasdone® XL, 1%
T4	Polyplasdone® XL, 3%; effervescent agent, 2%
T5	Polyplasdone® XL, 1%; effervescent agent, 4%
T6	Explotab®, 3%; Vivasol®, 1%
T7	Explotab®, 3%; effervescent agent, 6%
T8	Vivasol®, 3%; Explotab®, 2%
T9	Vivasol®, 3%; effervescent, 6%

5.2.3. Hydrogen-bonded polymer complex formation

4 g desloratadine salt was dissolved in purified water and the pH of the solution was adjusted to 3.6 using 1M HCl solution. The solution was made up to 24 g with water (original samples). 1.6 g Tween 80 was added to the same desloratadine solution to prepare the Tween 80-containing samples under stirring. Then 5.6 g crospovidone (Polyplasdone XL-10 in the case of the normal samples and Polyplasdone XL in the case of the Tween 80-containing samples) was added to the solutions and thick, paste-like suspensions were prepared in a metallic bowl using a pestle. 600 - 600 g Carbopol® solutions were prepared separately with water and their concentrations were set to 0.8% w/w. The suspensions were drawn into syringe (BD Plastic 50 ml, BD) and they were pumped separately into the stirred Carbopol® solutions using a syringe pump (Legato 100, KD Scientific) through a silicone tube of diameter of 2 mm. The Carbopol® solutions were intensively agitated using a high-speed homogenizer (Ultra Turrax T25, IKA) in a beaker glass of diameter of 10 cm. The end of the tube was located under the head of the homogenizer, the distance between the head and the tube was set to 35 mm (Fig 8).
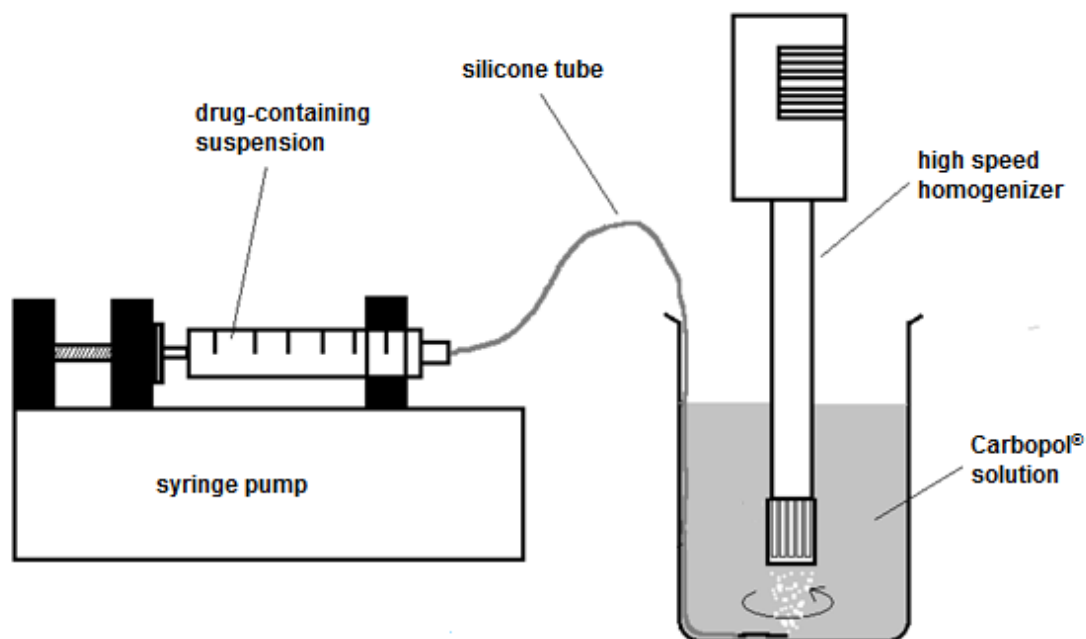
Figure 8 Tool for the preparation of the drug-containing polymer complexes

The homogenizer was stopped after the addition of the suspensions, and the precipitated complexes were floated on the solutions. The complexes were washed with purified water four times then most of its moisture content was removed using filter papers. The precipitates were divided into small pieces of 1 - 2 cm diameter and were dried in a vacuum chamber (60 °C, 150 mbar, 24 h). The dried pieces were milled in a comminutor (Fitzmill L1A, Fitzpartick,) using the knife-edged configuration of the blade profile and a screen of diameter of 2.7 mm at 4000 rpm (Fitzmill, 2013). The obtained granules were further milled using a screen of diameter of 0.8 mm at 3000 rpm. The granules were fractionated using a vibratory sieve shaker (Analysette 3 PRO, Fritsch) into the following particle size fractions: <90 μm, 90-180 μm, 180-355 μm, 355-500 μm.

5.3. Experimental set-up

5.3.1. Texture analysis method for the determination of the disintegration times of ODTs

CT3 texture analyzer (4500 g maximum load, Brookfield Engineering Laboratories) was used for the measurements. Tablets were attached with a small amount of semi-solid glue to an acrylic cylindrical probe of 25.4 mm diameter (TA11/1000, Brookfield Engineering Laboratories). The disintegration device consisted of a miniature stainless steel test sieve (diameter 38 mm, aperture 1.25 mm, Endecotts) which was placed on an extruded polystyrene (XPS) plate and the disintegration medium was poured into the space between the XPS plate and the sieve with pipette (Biohit Proline 1-5 ml). The XPS plate prevented the medium from flowing off the sieve. The volume of the medium was 5.40 ml which was sufficient to create a homogenous fluid layer over the surface of the mesh of the sieve. The temperature of the stock disintegration medium was maintained at 24 ± 0.5 °C.

After starting the measurement, the tablet that was glued to the probe was moved towards the surface of the disintegration medium with a predetermined constant speed (pre-test speed). As the tablet reached the mesh and the generated load increased to 20 g (trigger load), the instrument changed the speed to the predetermined test speed value and started to record the load-displacement points (curves) (100 points/mm) with its software (TexturePro CT, Brookfield Engineering Laboratories). The endpoint (where the probe got into contact with the mesh) was detectable based on the

shape of the load-displacement curves. The initial setup of the experiment and disintegration device is depicted in Fig. 9.
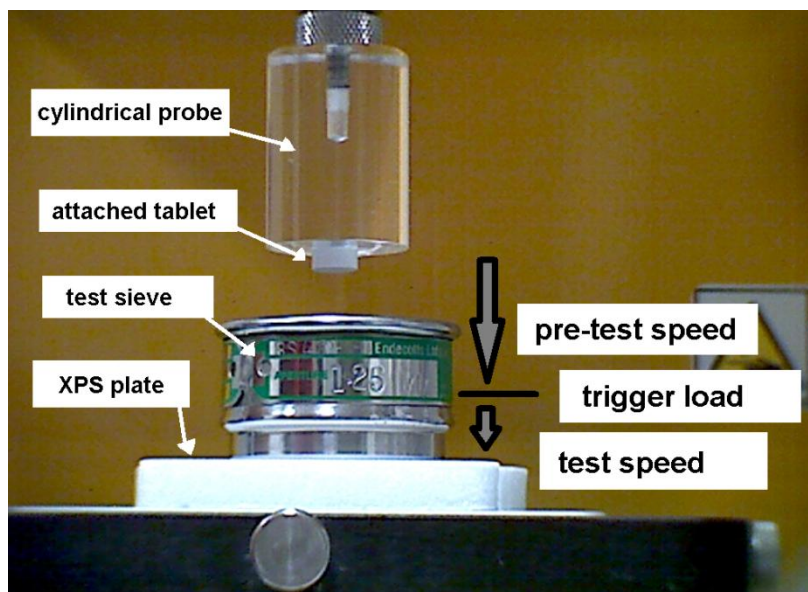
Figure 9 Experimental set-up of the texture analysis-based disintegration time determination method

5.4. Measurements

5.4.1. Water content determination of superdisintegrants

5.4.1.1. Actual water content measurements

Initial water content of the superdisintegrants was determined by the loss on drying method using 1 - 2 g samples. Crospovidones were dried at 105 °C for 2 h, sodium starch glycolate at 130 °C for 1.5 h and croscarmellose sodium at 105 °C for 6 h based on the USP 34-NF 29.

The amount of absorbed or desorbed water was calculated based on weight changes of the samples and measured with analytical balance (BP 110 S, Sartorius) with 0.1 mg accuracy.

5.4.1.2. ATR-FTIR measurements

At the end of the conditioning of the superdisintegrants, the weights of the samples were measured, then samples were transferred to closed glass vials to avoid changes in their

water content and the spectral measurements were carried out. ATR-FTIR spectra were collected using a Jasco FT/IR-4200 spectrophotometer between 4000 and 300 cm^{-1} with an ATR PRO470-H single reflection accessory (Jasco) equipped with flat pressure tip. The spectral measurements were performed at the maximum 1700 kg/cm^2 pressure on the diamond ATR crystal in absorbance mode. To obtain a homogenous and reproducible sample layer over the ATR crystal, each sample was pressed twice with the flat pressure tip at maximum pressure (i.e. after the first press with the ATR accessory some material was put on the formed compact layer and after this a second press was carried out). 16 scans at a resolution of 4 cm^{-1} were co-added by the FT-IR software (Spectra Manager-II, Jasco). Eight parallel spectral measurements were carried out in the case of each sample.

5.4.2. Determination of the parameters of the tablets

5.4.2.1. Tablet weights, dimensions and hardness

Weights of tablets were measured with laboratory balance of 1 mg accuracy (XB 160M, Precisa). Tablet dimensions (diameter and thickness) and hardness values were determined by a tablet hardness tester (8 M, Dr. Schleuniger Pharmatron).

5.4.2.2. Determination of the wetting time

Wetting times of tablets were measured by placing them on the surface of a slice of six-layered paper immersed in 4 ml blue solution (~0.01% methylene blue) using a small glass vessel. Wetting was complete, when water (and the accompanying swelling) was observable on the whole surface of the tablets (Fig. 10).
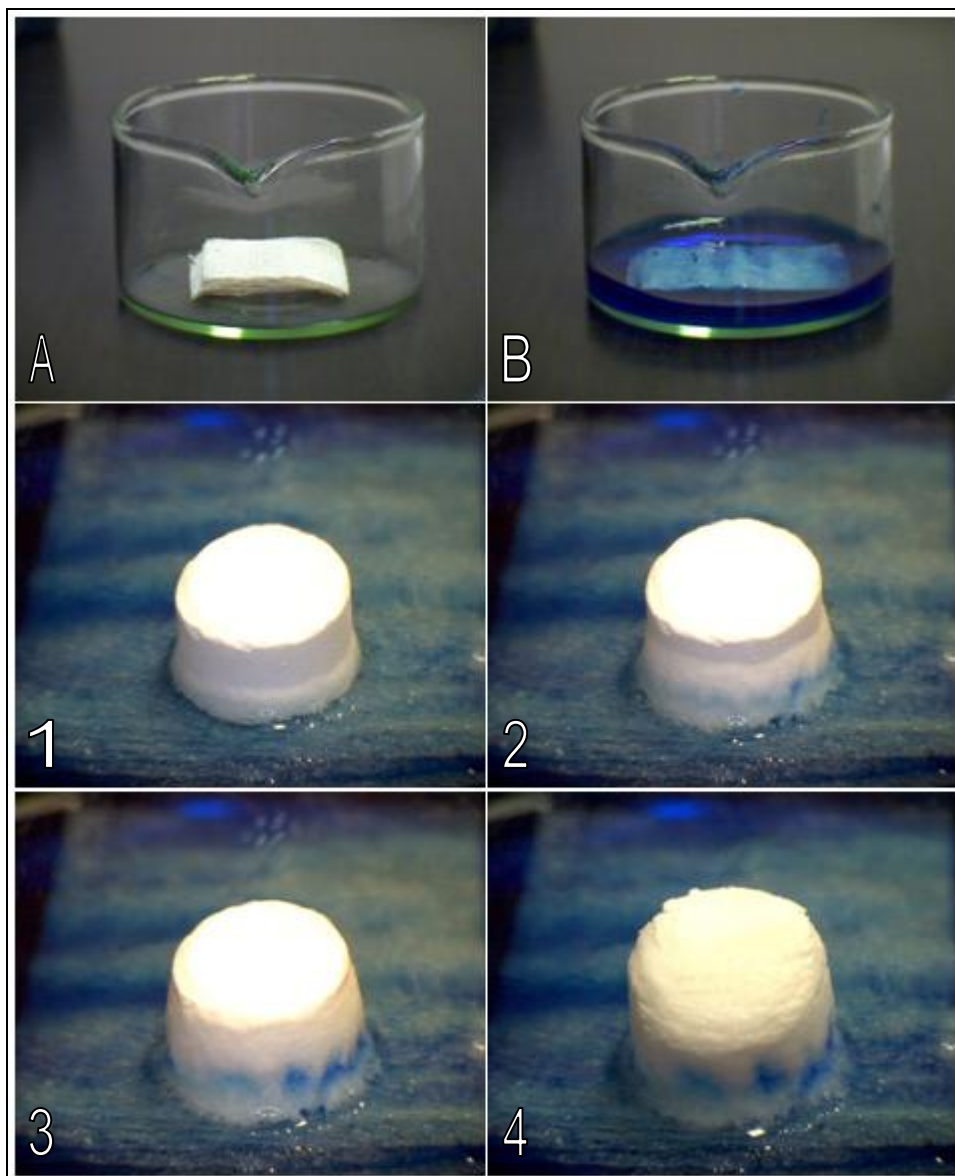
Figure 10 Accessory for wetting time determinations. A: the glass vessel with a six-layered paper in the middle; B: the same arrangement after the addition of the 4 ml solution; 1 - 4: steps of the wetting of the tablets

Consistency of the wetted tablets was measured immediately after the complete wetting in the case of tablets. The hardness of the wetted tablets was estimated by a manual measurement, i.e. the investigator pressed carefully the wetted tablet by finger and rated the consistency of the tablet on a scale with a number between 1 and 10. Value of 1 indicated a very soft consistency, while value of 10 a completely dense structure. This value was called as consistency index.

5.4.2.2. Determination of the in vitro disintegration time

In vitro disintegration times of tablets were measured by dropping them into a glass vessel filled with 20 ml water. The vessel was the same that was used for the determination of the wetting times. Complete disintegration took place when no coherent solid portion of the tablet remained.

5.4.2.3. Determination of the oral disintegration time

In vivo disintegration times of the tablets were determined by a healthy volunteer in a blind randomized order. The volunteer placed a tablet on his tongue and started a chronometer. Complete disintegration was achieved when there was no perceptible solid particle in the mouth. During the measurement, it was allowed to move the tablet gently with the tongue, but not chewing. After each measurement, the tester rinsed out his mouth with water.

5.5. Dissolution tests

The dissolution tests of the original hydrogen-bonded polymer complexes were performed in phosphate-citrate buffers according the USP method 2. Volume of the dissolution medium was 500 ml, stirring rate was 50 rpm, temperature of the medium was 37 ± 0.5 °C. The released drug was determined spectrophotometrically at 280 nm in the case of pH 3.0 and 3.5 and at 276 nm in the case of pH 4.5 and due to the pH dependence of the UV spectrum of desloratadine (Popović et al., 2009). Three paralell measurements were performed in the case of each pH and of each sieve fraction.

The pH-dependency of the release rate of both complexes (original and Tween 80-containing) was measured with dissolution tests performed in Erlenmeyer flasks at laboratory temperature using the 355-500 μm sieve fractions. Definite amounts of milled polymer complexes were placed into the flasks, then 200 g citrate buffers of pH 2.5, 3.0, 3.5, 4.0, 4.5 were added into the corresponding flasks. Samples were agitated with magnetic stirrers, and the dissolved fractions were measured after half an hour spectrophotometrically at 280 nm in the case of pH 2.5, 3.0, 3.5 and 4.0 and at 276 nm

in the case of pH 4.5. Additional dissolutions were performed in pH 1.1 hydrochloride acid solution and in pH 6.0 citrate buffer in the case of the Tween 80-containing samples for FTIR measurements.

5.6. Data processing, calculations and statistical evaluations

5.6.1. Data processing during the water content determination of superdisintegrants

5.6.1.1. Spectral transformations and corrections; calculation of the regression lines

Eight parallel ATR-FTIR spectra of each sample were averaged using the data accumulation function of the FT-IR software to obtain a common spectra representative for a sample of given water content. Along with the decrease of the water content of samples, the baselines of their spectra increased, which distorted the calculation of the area under the curve values. Therefore, for each excipient, the baselines of their spectra were corrected to be equal at 4000 and 1900 cm^{-1} to the baseline of the sample of maximum water content, thus receiving overlapping spectra in the non-absorbing regions (between 4000 and 3700 cm^{-1} and 2700 and 1800 cm^{-1}). The area under curve values (AUC) of spectra between 1510 and 1050 cm^{-1} were called $AUC_{polymer}$, since this region was characteristic to the degree of the polymer compaction and the AUC values of spectra of different samples in the 3700 - 2800 cm^{-1} region were called $AUC_{polymer \times water}$, since this value depended on both the water content and the polymer compaction. The ratio of $AUC_{polymer \times water}$: $AUC_{polymer}$ was proportional to the amount of the absorbed water per dry polymer weight. These ratios were calculated from the averaged (n=8) and baseline corrected spectra in the case of all 45 samples (5 excipients of 9 water content levels) and the calibration lines were calculated based on the ratios and the measured water contents using linear regression.

5.6.1.2. Confidence and prediction intervals of the regression lines

The 95% confidence and prediction intervals of the regression lines were calculated using Eq. (2) and (3) respectively.

confidence interval: $\left[y_c \ \pm \ t_{n-2}^{5\%} \cdot s_e \sqrt{\dfrac{1}{n} + \dfrac{(x_c - \bar{x})^2}{\sum(x_i - \bar{x})^2}} \right]$ (2)

prediction interval: $\left[y_p \ \pm \ t_{n-2}^{5\%} \cdot s_e \sqrt{1 + \dfrac{1}{n} + \dfrac{(x_p - \bar{x})^2}{\sum(x_i - \bar{x})^2}} \right]$ (3)

where $s_e \ = \ \sqrt{\sum e_i^2 / n - 2}$, $t_{n-2}^{5\%}$ is the two tail critical value of the t-distribution; n is the number of the observations in the sample; $\sum e_i^2$ is the error sum of squares $(\sum (y_i - \bar{y})^2)$; i = 1,..,n; x_c and x_p are the value of x_i for which the confidence interval and the prediction interval calculations are made, respectively; y_c and y_p are calculated based on the regression equations at x_c and x_p, respectively.

5.6.2. Data processing of the in vitro disintegration time determination of ODTs

5.6.2.1. Data processing and calculation of the in vitro disintegration times

In the case of each texture analysis measurement the area under curve (AUC) values were calculated based on the recorded load–displacement curves with Microsoft Excel® using the rectangle integration method. The AUC values (AUC) were determined between the start point and the 70% of the full displacement. Lines were laid on short sections (0.1 - 0.2 mm) of each recorded curve before and after the endpoints and their angles were calculated in order to gain the correction factor called *k*. Since the two axes (load and displacement) of the curves had their own, independent scale, a reference line of a slope of 2000 g/mm was determined in order to calculate the angle values. A 45◦ angle of inclination was assigned to the reference line. It was possible to calculate the angles between the fitted lines at the endpoints after the determination of this reference line (Fig. 11), and the *k* correction factor was calculated from these angles using the Eq. (4).

$k = \dfrac{angle}{105°}$ (4)

where 105° was the angle between the fitted lines in experiments performed without tablet on the probe.
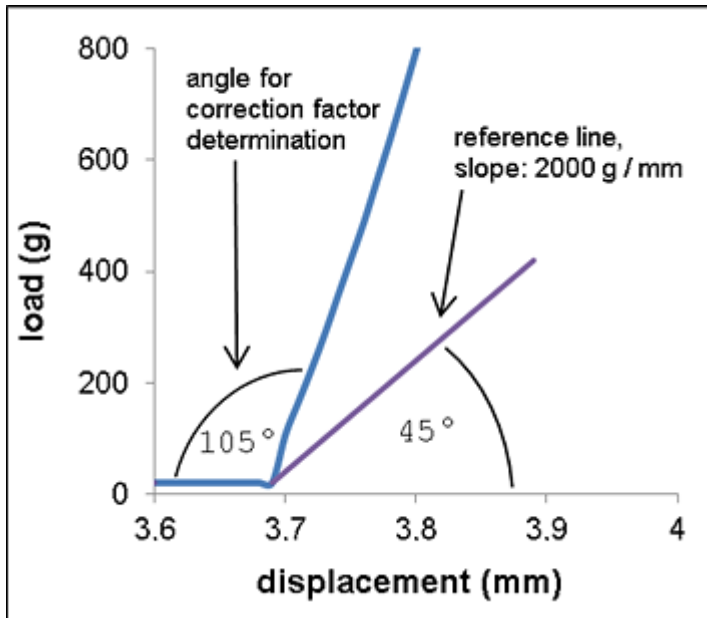
Figure 11 Angle of fitted lines in the case of a measurement recorded without tablet and the arbitrarily chosen reference line (fitted lines are not illustrated since they are almost identical to the represented curve sections)

Based on the AUC and *k* values an empirical function was constructed to predict the oral disintegration times:

$$in\ vitro\ DT = \frac{AUC^{n_1}}{k^{n_2}} \cdot c \tag{5}$$

where n_1 and n_2 are exponents of the AUC values and *k* correction factor, respectively while c was a multiplier calculated from the in vivo disintegration times:

$$c = \frac{in\ vivo\ DT \cdot k^{n_2}}{AUC^{n_1}} \tag{6}$$

A c value belongs to each AUC, k, n_1, and n_2 combination in the case of each calibration tablet (T1 - T5) based on Eq. (6). Under optimum circumstances, these c values are nearly identical, and their average (c_{av}) is characteristic to the whole system including the tablets, their *in vivo* disintegration times and the parameters of the texture analysis method. The *in vitro* DT values of the calibration tablets will be close to their *in vivo* DT values using this averaged c value (c_{av}) in Eq. (5). The *in vivo* DT value of all tablets (T1 - T9) was predicted by Eq. (5) using c_{av} in place of the c value after the determination of the optimum circumstances at the evaluation procedure.

5.6.2.2. Regression equations of the AUC and the k values and Box-Cox transformation

The dependence of the AUC values and correction factors k on the parameters of the method was investigated by full factorial experiments in the case each calibration tablet (T1 - T5), where the independent variables were the pre-test speed, glycerol concentration of the medium and test speed in the first experiment (2^3) and glycerol and PVP concentration of the medium in the second experiment (2^2). Three parallel measurements (n = 3) were performed in randomized order at each factorial setting. Independent variables of the factorial experiments and their levels are summarized in Table 9.

Table 9 Coded and original values of the variables in the factorial experiments

Coded values	-1	0	+1
1. Experiment (2^3)			
Pre-test speed (mm/s)	0.3		0.5
Glycerol concentration (% w/w)	25		30
Test speed (mm/s)	0.04		0.05
2. Experiment (2^2)			
Glycerol concentration (% w/w)	15	18.75	22.5
PVP concentration (% w/w)	2.25	3.375	4.5

The regression equations of AUC and k for the five tablets were determined using the R statistical program (R Core Team, 2012). In order to check the adequacy of the

regression model, residual plots were constructed using the program. Analysis of the residual plots indicated a non-constant variance (heteroscedasticity) in the case of the 2^3 experiment investigating the AUC values. Box-Cox transformations were carried out on the AUC values at the 2^3 factorial experiments in order to gain a first order model with constant variance (Box et al., 1978). λ_{BC} values for each regression equation were determined using the MASS R package (Venables and Ripley, 2002) and the transformed AUC values (AUC_{BC}) were calculated by Eq. (7) in order to remove heteroscedasticity from the regression model:

$$AUC_{BC} = \frac{AUC^{\lambda_{BC}} - 1}{\lambda_{BC}} \qquad (7)$$

The regression equations for the calibration tablets in the 2^3 experiment were constructed using these transformed AUC (AUC_{BC}) values.

5.6.2.3. Computational optimization of the parameters of the texture analysis method

After the determination of the regression equations of the AUC_{BC} values and the *k* correction factors for each calibration tablet, it was possible to collectively investigate the *in vitro* DT functions and the c values of the calibration tablets using Eqs. (5) and (6) by changing the independent parameters of the method via a mathematical procedure and, through the corresponding regression equations, to find a combination of the independent variables where the c values were similar in the case of the five calibration tablets. Using their average (c_{av}) the *in vitro* DT values were calculated and compared with their *in vivo* DT values with the SSR function:

$$SSR = \sum_{i=1}^{5}(in\ vivo\ DT_i - in\ vitro\ DT_i)^2 \qquad (8)$$

where i was the number of the tablet. The resulted sum of squared residuals function (SSR) was minimized (Kemmer and Keller, 2010) during the optimization procedure using an optimization software (Solver®, Microsoft Excel® add-in), since the closer the *in vitro* and *in vivo* disintegration times were, the smaller the SSR became. The

computer program optimized the parameters of the method (test speed, glycerol concentration, pre-test speed) and the exponents of Eqs. (5) and (6) (n_1, n_2) in the first experiment and the exponents (n_1, n_2) in the second experiment using the generalized reduced gradient method. During the optimization, initial conditions in coded values were equal to 0 for the independent variables of the method and were equal to 1 for the exponents. All nine types of tablets were measured with the texture analyzer (n = 3) using the obtained settings after the parameter optimization and the *in vitro* DT values were compared to their *in vivo* values in order to evaluate the efficiency of the optimization. Since the *in vitro* DT function uses the AUC values instead of the AUC_{BC} values, the AUC_{BC} values were retransformed into the AUC values during the computer calculations.

6. Results

6.1. Water content determination of pharmaceutical superdisintegrants by ATR-FTIR spectroscopy

Water content changes of superdisintegrants were followed by ATR-FTIR spectroscopy exploiting the strong absorption of water molecules between 3700 and 2800 cm^{-1}, while different extent of compaction of the samples on the ATR crystal was followed by the spectral intensities between 1510 and 1050 cm^{-1}.

Samples of five excipients were prepared at nine water content levels in order to gain a correlation between the ATR-FTIR spectra of the samples and the water content values. The 3700 - 2800 cm^{-1} infrared region (region A) was useful to follow the increase of the water contents of the samples. On the other hand, the 1510 - 1050 cm^{-1} region (region B) was indicative for the compaction of the powdered samples on the ATR crystal (Fig. 12). Materials of higher water contents had higher absorption in this region compared to their dried state which phenomena could be explained based on the plasticizing effect of water. It can be seen in the figure that the increase of the infrared absorption in region A was accompanied by the absorption increase of region B except in the case of crospovidone. The absorption in region B is indicative to the polymer chain density on the ATR crystal since only the polymers have noticeable absorption in this region but not water. The spectral differences between the dried and the wetted states of the excipients can be explained by the plasticizing effect of water. According to the spectra of crospovidone, water had low plasticizing effect in the case of this excipient that can be explained by its different chemical structure.
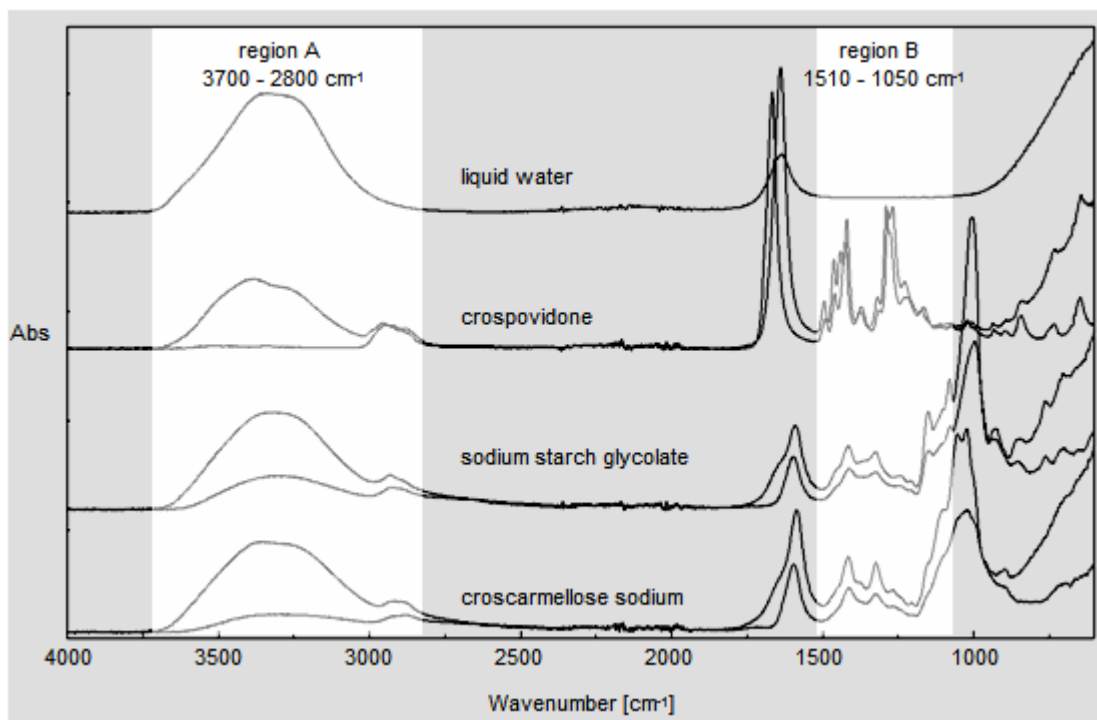
Figure 12 Spectra of liquid water and the superdisintegrants in their dried and wetted state (Szakonyi and Zelkó, 2012; reproduced with permission)

Water content of the samples can be quantitatively characterised by the AUC values of the two regions. The AUC value of region A depends both on the actual water content of the sample and the polymer chain density, therefore it was called $AUC_{polymer \times water}$. The AUC value of region B depends mainly on the density of the polymer chains on the ATR crystal, consequently it was called $AUC_{polymer}$. A good linear correlation was found between the ratios of the AUC values in the region A and B ($AUC_{polymer \times water}$: $AUC_{polymer}$ ratio) and the water contents for each excipient, which indicated that the approach based on the AUC values of the two selected region is suitable for quantitative water content measurements.

Another characteristic of the recorded spectra was the progressive base line shift, which increased with decreasing water content (Fig. 13). If the particle size is commensurable to the wavelength, the electromagnetic radiation scatters thus considerably increasing the baseline. The baseline shifts can also be explained with the plasticizing effect of water. With increasing water content, the high pressure ATR-accessory was able to form a more homogeneous smooth surface on the ATR crystal, consequently the scattering of the infrared radiation decreased. The applied baseline

corrections improved the correlation coefficients in all cases except for croscarmellose sodium, may be due to its irregular rod-like particle shape and special scattering property, therefore the uncorrected raw spectral data were used for the calculations.
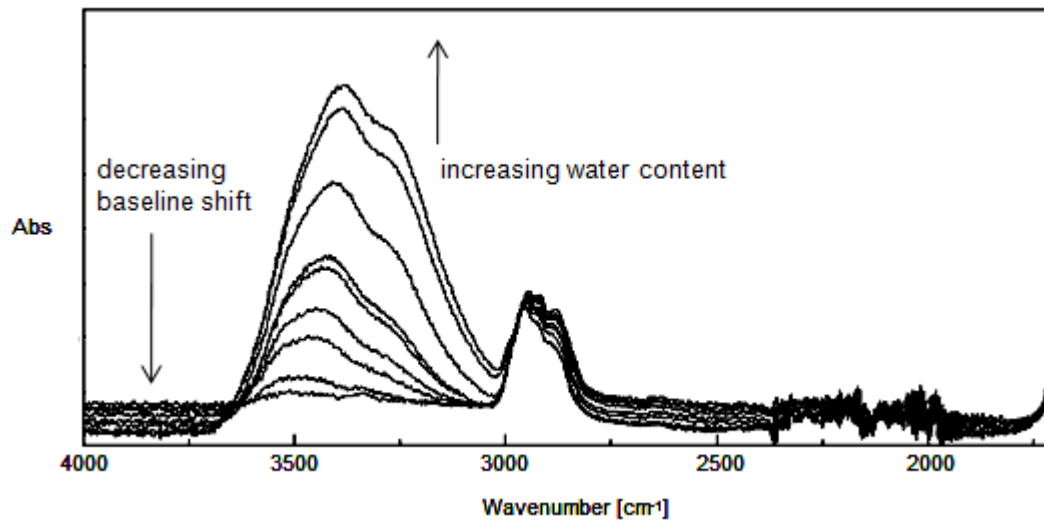
Figure 13 Based line shifts in the case of spectra of Polyplasdone® XL (Szakonyi and Zelkó, 2012; reproduced with permission)

Regression lines were constructed after the baseline corrections based on the AUC values. The regression lines of the two Polyplasdone® excipients did not differ from each other significantly (Fig. 14), therefore a common regression line was determined for them.
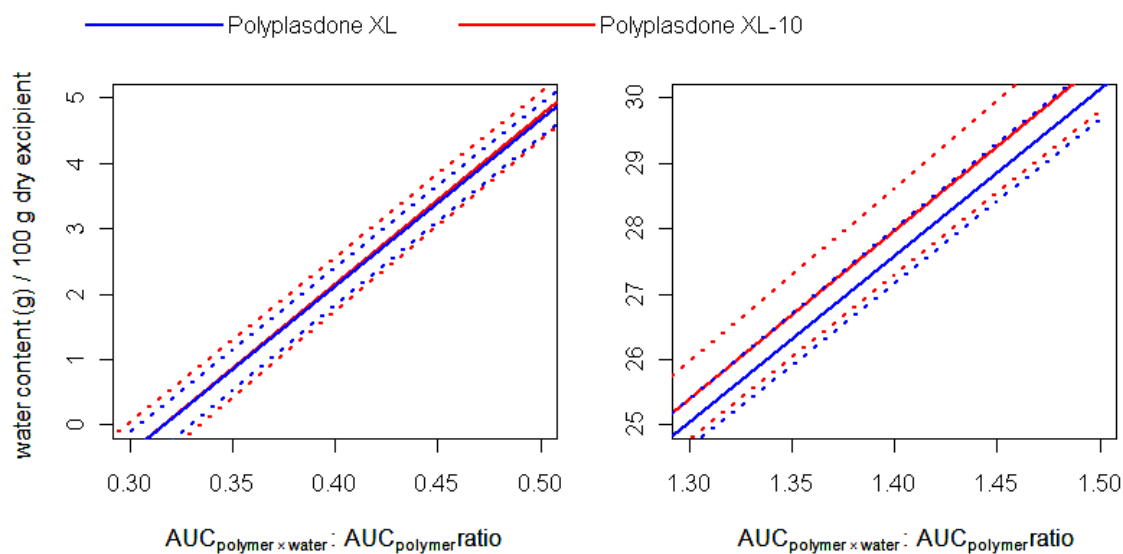
Figure 14 End sections of the regression lines for the two Polyplasdone[®] excipients with the prediction intervals of the lines (dotted lines) (Szakonyi and Zelkó, 2012; reproduced with permission)

In the case of Kollidon[®] CL-SF (crospovidone from a different manufacturer), the slope of the regression line was slightly different, which may be explained by its very light structure and low particle size.

The regression lines were constructed in the form of water content (g) / 100 g dry excipient versus the $AUC_{polymer \times water}$: $AUC_{polymer}$ ratio (Fig. 15). Some parameters of the investigated excipients can be seen in Table 10.
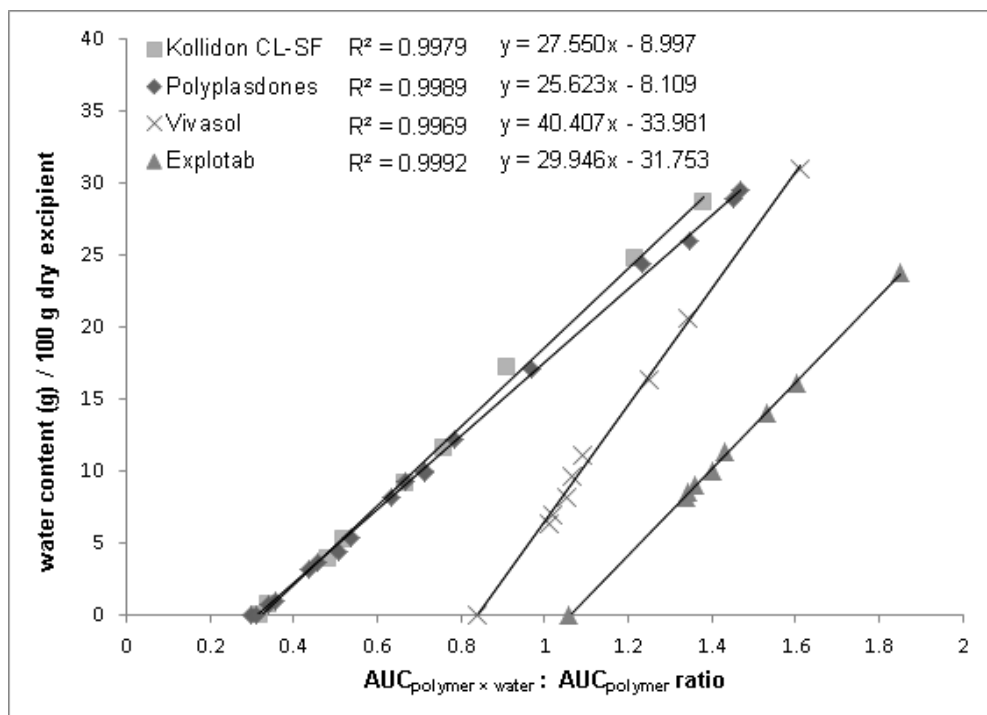
Figure 15 Regression lines for the water content determination of pharmaceutical superdisintegrants (Szakonyi and Zelkó, 2012; reproduced with permission)

Table 10 Parameters of the investigated excipients

	Kollidon® CL-SF	Polyplasdone® XL	Polyplasdone® XL-10	Explotab®	Vivasol®
Max. acc. water cont.[a]	5	5	5	10	10
Max. inv. water cont.[b]	22	22	23	19	24
Water by drying[c]	3.68 (0.02)	3.50 (0.01)	3.02 (0.01)	7.56 (0.09)	5.92 (0.05)
Water by ATR-FTIR[d]	4.11	3.54	2.95	7.65	6.39

a, Maximum acceptable water content of excipients by the pharmacopoeias (% w/w)

b, Maximum experimentally investigated water content of excipients (% w/w)

c, Initial water content of excipients with standard deviation (n = 3) determined by the loss on drying test of pharmacopeia (% w/w)

d, Calculated initial water content of excipients based on the calibration lines (% w/w)

6.2. Tablet preparation for the screening of the efficiency of different superdisintegrants

Mannitol based orally disintegrating tablets were prepared using three levels of superdisintegrants (3, 5, 7% w/w) in order to compare the efficiency of crospovidone, croscarmellose sodium and sodium starch glycolate. Similar tableting fill volumes were used, which improved the comparability of the formulations. Two tableting pressures were applied to tablets, since the tablet porosity and the degree of compaction could influence the behaviour of the superdisintegrants (Goel et al., 2010).

Table 11 Physical characteristics of various tablets containing different superdisintegrants[a]

	Crospovidone			Sodium starch glycolate			Croscarmellose sodium		
SD conc.[b] pres. lev.[c]	3% (L/H)	5% (L/H)	7% (L/H)	3% (L/H)	5% (L/H)	7% (L/H)	3% (L/H)	5% (L/H)	7% (L/H)
weight (mg)	239 240	238 238	218 217	262 262	262 265	264 265	268 267	260 262	263 262
hardness (N)	20 55	23 59	23 51	55 103	53 108	57 107	51 99	35 92	33 80
in vitro DT (s)	19 19	17 18	21 21	37 55	35 54	42 48	18 21	21 30	20 35
wetting time (s)	34 42	36 44	29 31	64 102	57 87	62 82	44 36	74 33	64 39
cons. index[d]	6.8 3.6	8.6 4.6	9.4 7.2	2.8 1.8	3.0 2.2	2.0 3.0	3.6 1.6	4.2 4.2	6.0 7.8

a, all data are the mean of six measurements (n = 6)

b, superdisintegrant concentration (% w/w)

c, pressure level (low / high)

d, consistency index

Tablet hardness, wetting time and *in vitro* disintegration time are *in vitro* parameters of tablets, which are often used for the characterisation of ODTs (Shukla et al., 2009b). These parameters are useful for comparing the superdisintegrants and they can provide information about the best superdisintegrant, its amount and the optimum tablet hardness. Parameters of different formulations can be seen in Table 11. Two tableting pressure level, high (H) and low (L) were applied in the case of each formulation, and the superdisintegrant content also varied. Friability values of the tablets were below the 1% level in all cases.

Crospovidone (CrosP) was the Kollidon® CL-SF type, which decreased the bulk density of the powder mixture, therefore mechanical hardness and the weight of the tablets were lower in the case of these formulations. Hardness of the tablets decreased using higher levels of croscarmellose sodium (CCS) at the low pressure level, but tablet hardness was not influenced using sodium starch glycolate (SSG). It can be concluded that SSG had smaller influence on the characteristic of the powder mixture and did not affect negatively the bonds between the excipient particles and was able to provide the most robust formulation from a technological point of view.

The *in vitro* disintegration time of tablets was influenced by neither the CrosP concentration nor the applied pressure level. Crospovidones are characterised by high specific surface area and low bulk density (Nakanishi et al., 2011) and the Kollidon® CL-SF (Fig. 16) is an especially "light" powder. Presumably, it created a superdisintegrant network around the particles and allowed the fast wetting of the tablet. On the other hand, it might prevent the strong cohesive bonds between the filler particles due to its high specific surface area, therefore the wetted tablet disintegrated fast irrespective of the actual hardness value.
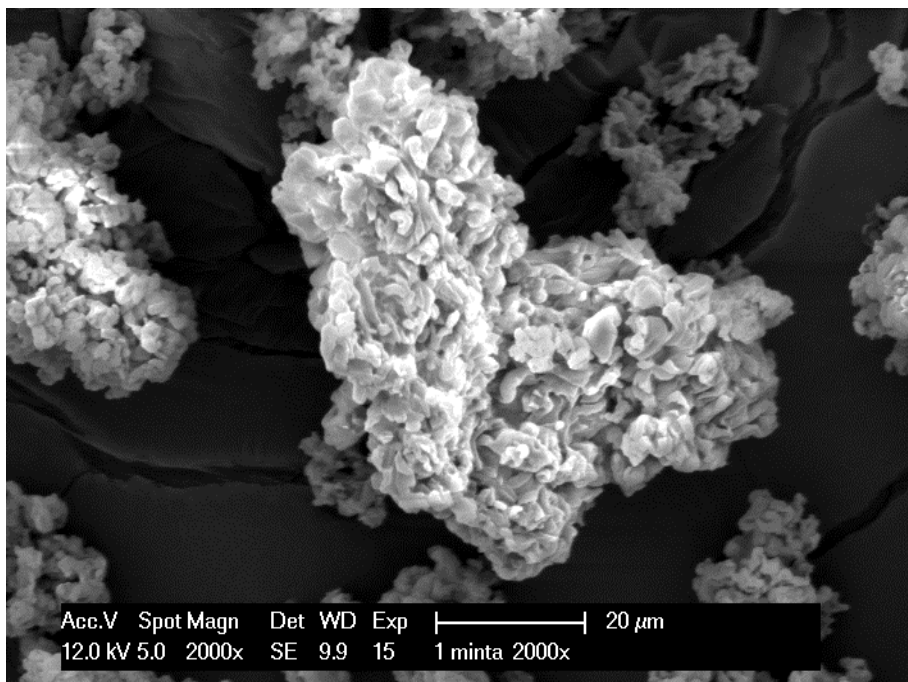
Figure 16 SEM picture of crospovidone (Kollidon® CL-SF) at magnification of 2000×

There was a correlation between the tablet hardness and the disintegration time in the case of formulations that contained SSG (Fig. 17). There was a trend of lower wetting and disintegration times using higher levels of the excipient in spite of the similar mechanical strengths, which indicated that a higher amount of this excipient was necessary for effective disintegration.
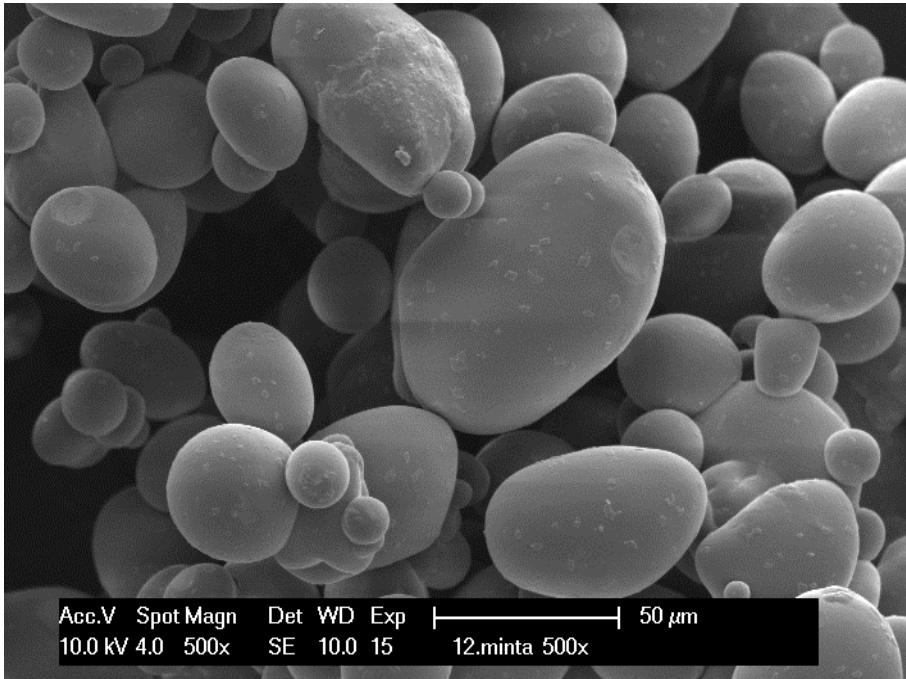
Figure 17 SEM picture of sodium starch glycolate (Explotab®) at magnification of 500×

Disintegration and wetting times were the lowest at 3% w/w of CCS (Fig. 18) and significantly faster wetting was achieved using the higher pressure level, which could be surprising at the first glance. Considering that one of the main disintegrating effects of CCS is particle twisting (Thibert and Hancock, 1996), it is obvious that this excipient works better in a low porosity environment. Wetting times were also smaller in the case of tablets prepared with high pressure, which indicated that primarily CCS particles being in close contact could cause the water wicking not the tablet porosity itself.
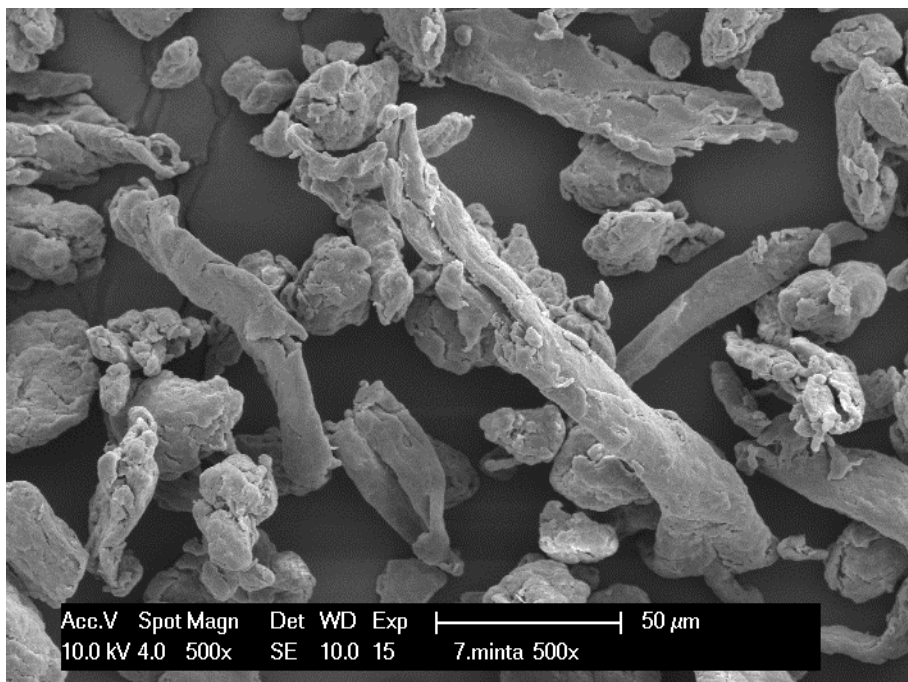
Figure 18 SEM picture of croscarmellose sodium (Vivasol®) at magnification of 500×

Consistency index is a numerical value between 1 and 10, which refers to the solidity of the tablet mass after complete wetting (Fig. 10/4). Wetting time is only meaningful if this value is also supplied, since a wetted but hardly disintegrated tablet cannot disintegrate fast in the mouth. It can be seen that tablets that contained CrosP and were prepared with high pressure had lower consistency index in all cases, which can be associated with the higher wetting times and the mechanism of effect of CrosP. Tablets containing 7% CrosP had the lowest wetting time but the highest consistency index, which might be due to the good water binding and poor swelling ability of the excipient (Thibert and Hancock, 1996). The net of the CrosP particles imbibed significant amounts of water but the mannitol matrix did not wetted properly, therefore the filler matrix did not dissolve to cause disintegration. The consistency indices of tablets containing SSG were low but this effect was not associated with the good disintegration action of the excipient rather with the slow wetting that enabled the dissolution of the mannitol particles. On the other hand, SSG has also good swelling properties (Thibert and Hancock, 1996), which could also contribute to the mechanical weakening effect of this excipient. CCS was the best superdisintegrant with water soluble filler. It provided fast wetting and low consistency index using the high pressure level, i.e. it had both good water wicking and disintegrating effect. It was more effective at lower

concentrations *in vitro*, which might indicate that above a threshold value the excipient had inhibiting effect on the disintegration. Since these excipients are water insoluble cross-linked polymers, they could form viscous suspension at higher concentrations which could be the explanation of their concentration dependent disintegration effects.

6.3. Tablet preparation based on the swelling of crospovidone and the phase transition of xylitol

Loosely compacted tablet matrices are ideal solutions for ODT production. Tablets of such characteristic have fast disintegrating properties, since the particles of the excipient are in contact with a relatively lower surface compared to that of the highly compressed tablets. On the other hand, tablet porosity is very high, which enhances the penetration of water into the matrix. The main problem with these high porosity tablets is the low mechanical strength, and consequently, they do not necessarily meet the requirements of pharmaceutical manufacturing. The tablet hardness increasing method, developed by Kuno et al. (2005), may solve this problem, since the low initial hardness of the tablets is increased to an acceptable value due to the partial melting of one of the excipients that creates new solid bridges between the particles while maintaining the high tablet porosity. However these tablets were very vulnerable before the heating process, which might cause problems during the pharmaceutical manufacturing processes, e.g. during collection, conveying, transfer, etc.

A new tablet preparation method was developed based on the special properties of superfine grade crospovidone (Kollidon® CL-SF). As demonstrated in chapter 6.2., Kollidon® CL-SF lowered the bulk density of the tablet powder mixture and prevented the formation of tablets of high mechanical hardness. The characteristics of tablets prepared using this superdisintegrant were also affected to a lesser extent by the level of the compression force. Kollidon® CL-SF is a crospovidone of a special type, similar to talc or colloidal silica with low bulk density; its specific surface area is between that of microcrystalline cellulose and talc (Zhang, 2011; Vehovec et al., 2012; Ribet et al., 2003). Presumably, a crospovidone layer is created around the filler particles, thus forming a loosely structure and the water vapour absorption could increase the distance between the particles in the course of crospovidone swelling.

Tablets containing Kollidon® CL-SF and prepared using moderate compression force were able to absorb water vapour in high humidity environment, which caused the significant increase of their volume without the disruption of the tablet structure (Fig. 19). It was possible to increase of the mechanical hardness of these tablets after the storage using a sugar alcohol component of low melting point. Partial melting of this sugar alcohol (xylitol) component created new solid bridges between the detached filler particles, which ensured appropriate mechanical strength for the tablets. The difference between the original invention (Kuno et al., 2005) and this approach is the porosity of the initial formula. The tablet porosity must be high using the original technique, while in the case of tablets containing Kollidon® CL-SF, high porosity develops under the storage. On the other hand, the use of high amounts melting component is not possible in the case of the original method, since tablet disintegration time significantly increases (Kuno et al., 2005). However, in the case of the crospovidone containing tablets, the distance between the xylitol particles is far enough to prevent their fusing during the melting process even at higher concentrations.
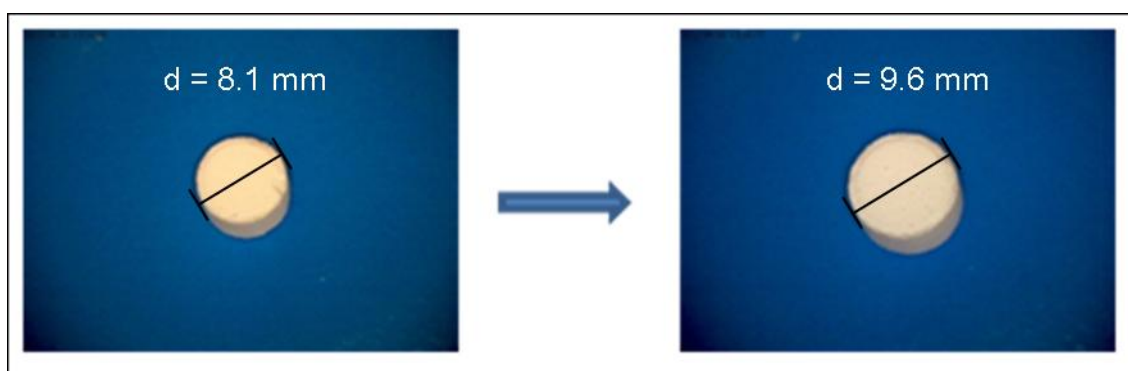
Figure 19 Volume increase of a tablet containing 3% w/w Kollidon® CL-SF after storage at 75% RH (using the same magnification)

Formulations of different compositions were prepared in order to investigate the critical parameters of the method. Five series of formulations were prepared and one important formulation parameter was changed in the case of each series.

Formulations of series 1 contained the ground and the original form of xylitol in different ratios. It was shown, that melting of the ground form of the sugar alcohol component could result in different tablet parameters (Kuno et al., 2008), which could

be explained by the formation of solid bridges of a different structure. Formulations contained increasing amounts of ground xylitol (from 1/A to 1/D). The weight of tablets of similar final volumes progressively decreased with increasing ground xylitol content, which referred to the porosity increase caused by the fine particles. There was a hardness decrease and friability increase above 5% ground xylitol content, while comparing formulation 1/C (10% ground xylitol) with 1/D (15% ground xylitol), the *in vivo* DT significantly decreased in spite of similar friability and hardness values (Fig. 20). The latter indicated that the higher amounts of ground xylitol could be effective for maintaining high porosity and low *in vivo* DT values. Comparison of formulation 1/C and 1/D may also suggest that the ground xylitol is able to provide a net of solid bridges, which was advantageous for fast disintegration.
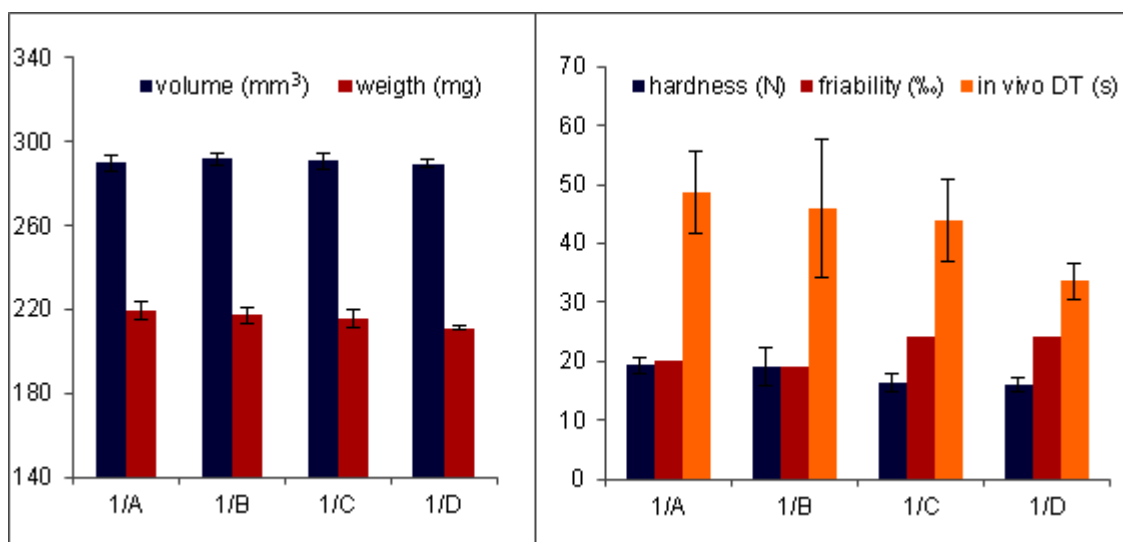
Figure 20 Physical characteristics of tablets of series 1

Formulations of series 2 contained different filler excipients at an amount of 20% in addition to mannitol except formulation 2/A (reference tablet). There were drastic changes between the parameters of tablets contained mannitol-based excipient (Ludiflash® (2/B)) and microcrystalline cellulose (MCC)-based excipients (Vivapur® 112 (2/C), Prosolv® EASYtab (2/D)). When tablets contained MCC, there was no measureable tablet strength (hardness values were about or less than 5 N), and the tablets were very friable (~20%). Using the Ludiflash® and in the case of the reference

tablet, hardness and friability values were more acceptable, but the *in vivo* DT values were high (Fig. 21).
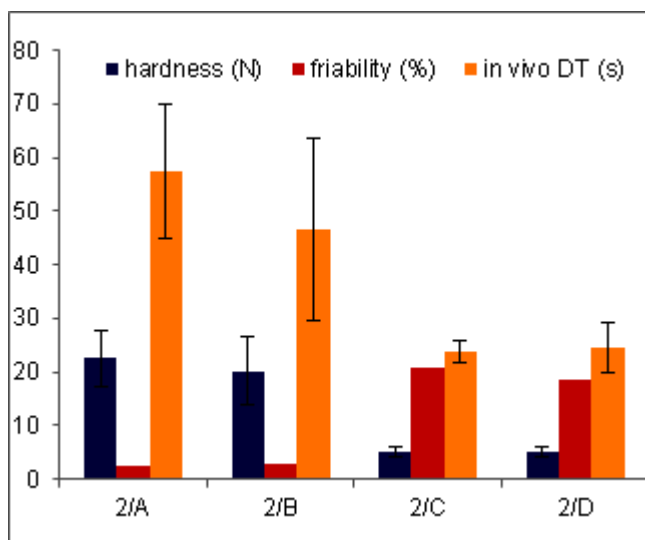
Figure 21 Physical characteristics of tablets of series 2

Since tableting parameters were similar, the chemical nature of the excipients was the important factor. The different behaviour of the tablets can be explained with the mechanism of the formation of solid bridges. There could be two mechanisms for the explanation of the phenomenon of post tablet hardening. One possible mechanism is the melting of the xylitol component, which covers the particles and creates a crystalline net after solidification. In the second mechanism, the xylitol does not cover the filler particles, it can only adhere to the surface of the adjacent particles, binding them together. In the case of the second mechanism, it is very important that the molten xylitol component has to adhere to the filler. According to the *in vitro* parameters of the tablets, molten xylitol is unable to adhere to the MCC-based fillers and 20% of these additional fillers were able to prevent the formation of a cohesive solid network. Ludiflash® composite particles consist of 90% mannitol, 5% crospovidone and 5% poly(vinyl acetate) as binder. They reduced the disintegration time by 10 s, but the friability value slightly increased compared the control formulation.

Formulations of series 3 contained different types of superdisintegrants at an amount of 3%. Both Kollidon® CL-SF (3/A) and Polyplasdone® XL-10 (3/C) were

crospovidones, but their manufacturer and particle sizes were different. Similar fill volumes were used, but tablet weights and final volumes were greatly influenced by the type of the applied superdisintegrant. Tablets contained Explotab® (3/D) experienced the largest volume increase (23%), while volume increase was between 14 - 16% in the case of the other tablets. Only tablets contained Kollidon® CL-SF provided short disintegration time, but the tablets' hardness and friability were not acceptable. Tablets contained Vivasol® (3/B) gave intermediate results.
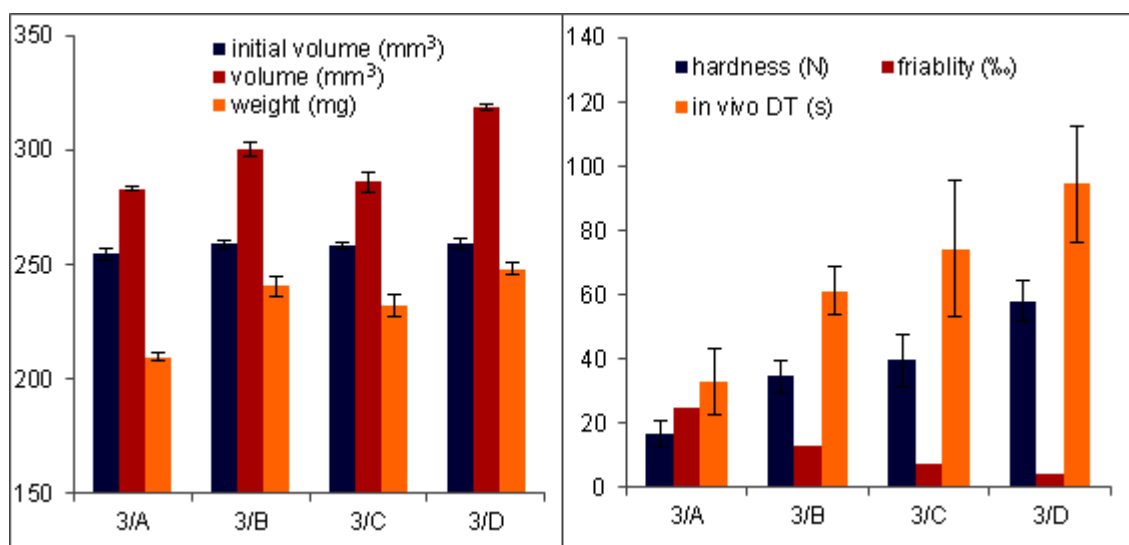
Figure 22 Physical characteristics of tablets series 3

As tablet hardness values increased, friability values were reduced and the *in vivo* disintegration times increased (Fig. 22). It means that, at first glance, the disintegration time was mainly affected by the parameters of the tablets and not by the type of the superdisintegrants. The results indicated that each superdisintegrant was able to cause the increase of the tablet volume without the destruction of the matrix and comparison of the superdisintegrants would only be possible in the case of tablets characterised by similar parameters.

Compositions of the two formulations of series 4 were identical except the amount of the lubricant, since the second formula did not contain lubricant and only external lubrication was performed. Volume increase of the tablets was high in both cases (36 - 37%), therefore the final tablets were very porous and tablet hardness values were acceptable. Lubricant can slow the disintegration of the tablet and the dissolution

of the filler particles due to its hydrophobic nature and it can reduce the hardness values (Wang et al., 2010), as well. The initial density of the tablet prepared by external lubrication was lower (0.879 g/cm^3) compared to the conventional tablet (0.914 g/cm^3) which might be associated with a slightly lower hardness value, but the absence of the lubricant must have also had an effect on the mechanical strength. Friability was much higher in the case of external lubrication (Fig. 23), but it might be associated to the roughness of the external lubrication method, since it was observed that only the surface of the tablets abraded during the friability testing and the remaining tablet portion was stronger. The explanation can be that the relatively high amount of lubricant on the punches was incorporated into the surface of the tablets, which prevented the suitable adhesion of the filler particles. On the other hand, *in vivo* disintegration was very fast in the case of tablet prepared by external lubrication despite the normal mechanical strength, which might indicate the disintegration hindering effect of the incorporated lubricant and the superiority of the external lubrication.
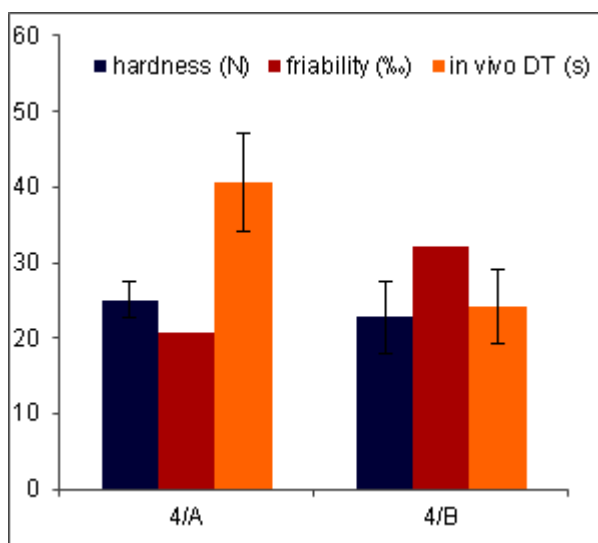
Figure 23 Physical characteristics of tablets of series 4

The effect of the amount of xylitol and tablet height was investigated by the formulations of series 5.
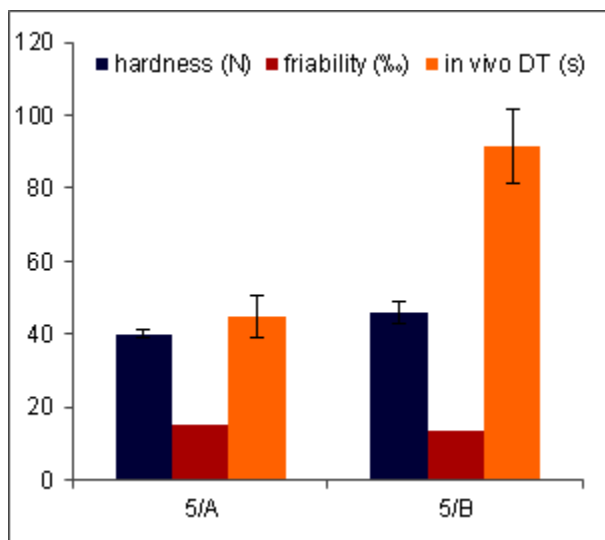
Figure 24 Physical characteristics of tablets of series 5

Formulation 5/A contained 30% xylitol, while 5/B contained 40% xylitol; Kollidon[®] CL-SF content was reduced to 2% and storage time was increased to 72 hours. Formulation had a low effect on the hardness values and a minimal effect on friability but *in vivo* disintegration times were greatly influenced (Fig. 24). The disintegration times of tablets containing 40% xylitol were greatly increased and crystalline knots were observed in the tablets during the *in vivo* disintegration. It indicated that using more than 30% xylitol may cause excipient aggregation during the melting process and did not improve the parameters of the tablets further.

6.4. In vitro determination of the disintegration times of different mannitol based ODTs

The *in vitro* prediction of oral disintegration times of ODT products is of great importance, since human investigations involving circuitous and expensive procedures and testing of highly toxic materials can be dangerous because the dissolved drug portion is easily absorbed. On the other hand, the established *in vitro* methods usually lack the good *in vivo* predictability in case of a wide range of tablets. A method based on texture analysis was developed which could be optimised to gain good *in vitro-in vivo* correlation in the case of tablets disintegrating by different mechanisms.

Texture analysis is a useful method to follow the softening of tablets during the disintegration process. The instrument exerts pressure on the sample that is fixed on the probe head and as the tablet reaches the disintegration medium, it starts to disintegrate. Since tablets reach the bottom of the equipment in a short time, force is generated between the tablet and the probe head. The instrument applies increasing load values on tablets in order to maintain the constant movement speed of the probe head at the initial stage of the disintegration and decreasing load values after the complete wetting of tablets (Fig. 25). The applied load values reach a minimum value, when only a paste-like structure remains, but afterwards, the load values increase again due to the resistance of the thick layer formed from the undissolved tablet excipients that was located between the probe head and the bottom of the equipment.
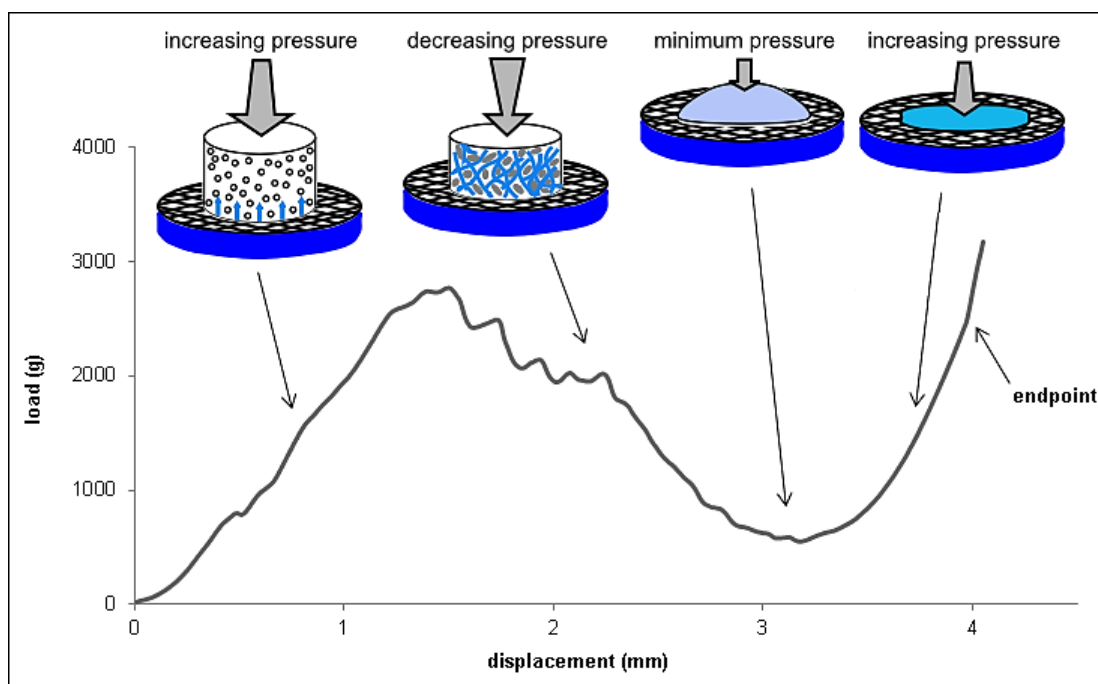
Figure 25 Process of tablet disintegration during the measurements and the corresponding load–displacement curve (Szakonyi and Zelkó, 2013; reproduced with permission)

Tablets of different compositions, hardness values and oral disintegration times were prepared in order to cover the behaviour of the large variety of the marketed products. Main parameters of the tablets are listed in Table 12.

Table 12 Oral disintegration times (n=10), weights, and hardness values (n=6) of tablets involved in the investigations

Tablet code	*In vivo* DT (s) ± S.D.	Weight (mg)	Hardness (N) ± S.D.
T1	27.3 ± 3.4	227-231	64.0 ± 6.1
T2	25.8 ± 3.2	230-236	59.7 ± 5.0
T3	39.0 ± 5.8	235-239	64.7 ± 4.2
T4	27.8 ± 4.0	225-229	47.7 ± 3.1
T5	59.8 ± 3.8	234-238	55.7 ± 2.9
T6	29.3 ± 2.4	261-266	32.3 ± 0.6
T7	52.0 ± 1.8	268-272	33.3 ± 2.1
T8	22.5 ± 2.6	223-227	14.7 ± 0.6
T9	21.5 ± 1.6	231-235	23.3 ± 4.9

There was some correlation between the *in vitro* disintegration of tablets and the gained AUC values and the oral disintegration times, as can be seen in Fig. 26, however the ratios of the AUC values and the oral DT values were not identical. The idea was to optimize the parameters of the measurements in order to gain a setting, which is able to provide AUC values for the different tablets in the same ratios as the oral disintegration times. In this case, only one factor is necessary to divide the AUC values in order to obtain the DT values. The first five tablets (T1 - T5) were used to find the optimum settings of the parameters of the method and the last four tablets (T6 - T9) were used to evaluate the method in the case of independent tablets. The tablets contained superdisintegrants alone or were combined with effervescent agent in order to model the high variability of the marketed products.
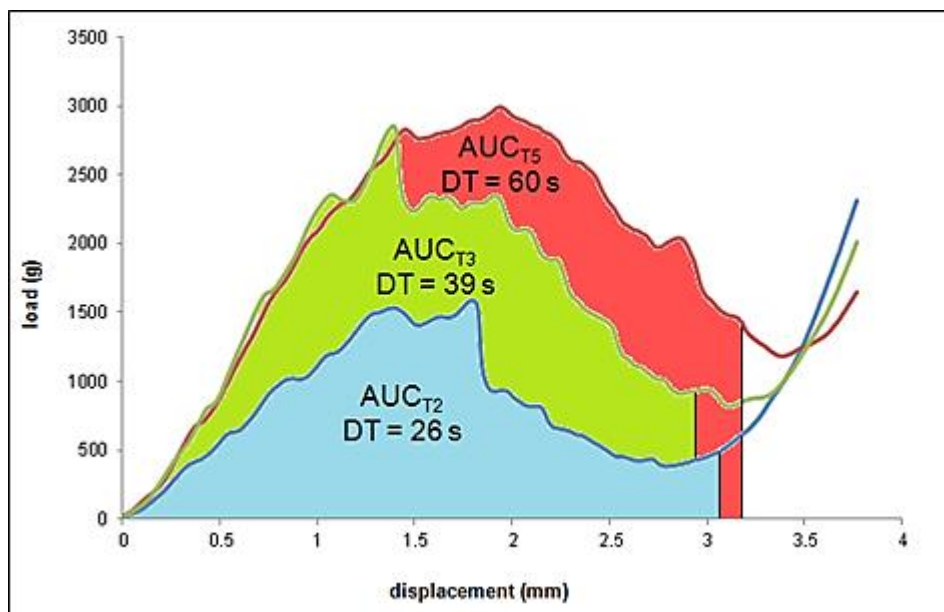
Figure 26 Load displacement curves of tablets T2, T3 and T5 and the corresponding oral disintegration times

The dependence of the AUC values of the different tablets on the parameters of the method was determined by full factorial experiments and the optimum setting was calculated from the obtained regression equations using computational optimization.

The independent variables were the pre-test speed, glycerol concentration of the medium and test speed during the first experiment (2^3 full factorial). Each parameter had an influence on the AUC values but to different extents in the case of the various formulations. The *in vitro* behaviour of tablets contained effervescent agent (T4, T5) was markedly different from those ones lacking such agents (T1, T2, T3). The AUC values expected based on the *in vivo* disintegration times were always smaller in the case of tablets that contained effervescent agent and there was no setting combination when the ratios of the AUC values were similar to the ratios of the oral disintegration times. Based on the load-displacement curves it was evident that these tablets softened very fast *in vitro* and they did not form a thick mass after the complete disintegration (Fig. 27). Since the effervescent agent had no pronounced effect *in vivo*, a correction was performed based on the slopes of the recorded curves located in the vicinity of the endpoints. Endpoints that appeared at lower load values indicated a very soft consistency of the disintegrated tablets, which was associated with the effect of the effervescent agent. A *k* correction factor was introduced in order to gain good IVIVC,

based on the angles of the lines near the endpoints and an *in vitro* DT value was determined based on the *in vivo* DT, the AUC and the *k* values according to Eq (5). (Szakonyi and Zelkó, 2013).
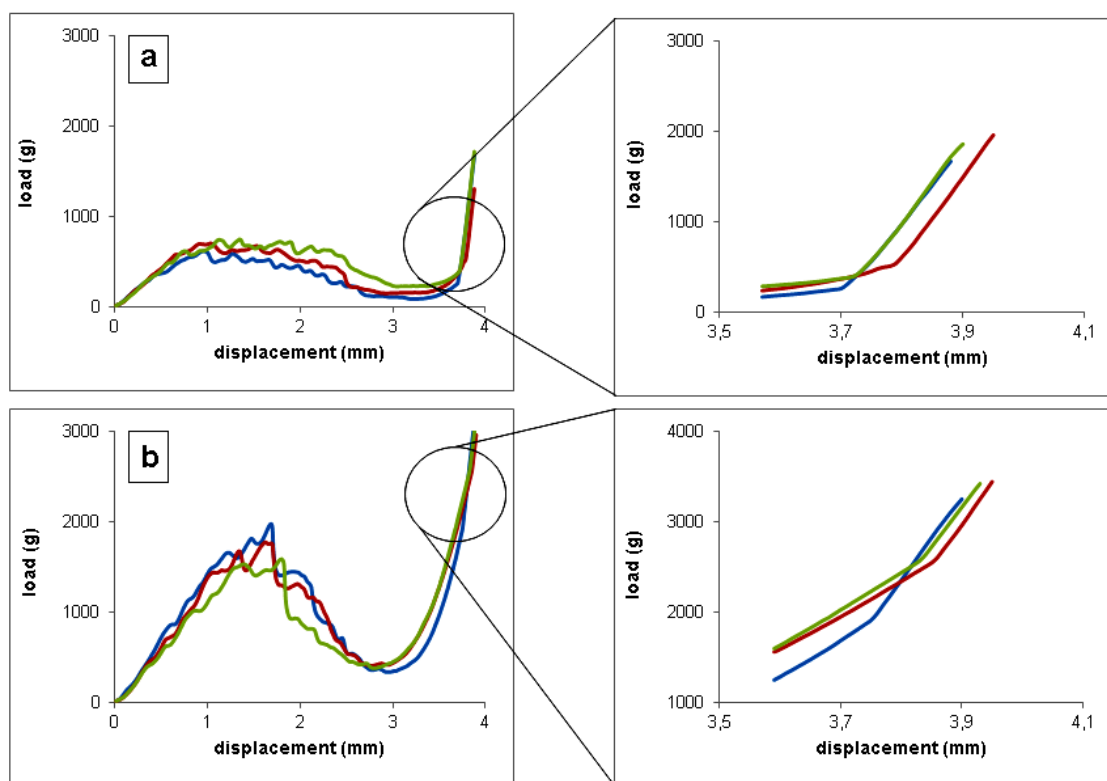
Figure 27 Behaviour of tablets containing effervescent agent (a) and containing no effervescent agent (b) and the slopes of the recorded curves in the vicinity of the endpoints (3 parallel measurements) (Szakonyi and Zelkó, 2013; reproduced with permission)

6.4.1. First (preliminary) experiment

The 2^3 full factorial experiment was statistically evaluated where AUC values and *k* correction factors were investigated as a function of the independent parameters. After the calculation of the regression equations for AUC and checking of the residual plots, non-constant variance (heteroscedasticity) was observed. Therefore, the regression equations were determined with the Box-Cox transformed AUC values (AUC_{BC}), as

well (see Eq. (7)). The λ_{BC} values and the coefficients of the equations for tablets T1 - T5 are listed in Table 13.

Table 13 Significant coefficients of the regression equations of the AUC values after the Box-Cox transformation (AUC_{BC})

	T1	T2	T3	T4	T5
λ_{BC}	0.141	0.505	-0.020	-0.182	-0.343
b_0	12.45	74.18	7.44	3.62	2.74
b_1 (ts)	0.772	12.43	0.146	0.128	0.0116
b_2 (gly)	0.697	11.77	0.174	0.170	0.0075
b_3 (pts)	0.292	7.07	0.040	0.136	0.0048
b_{23} (gly:pts)			-0.043	-0.039	
adjR^2	0.843	0.903	0.895	0.951	0.759

λ_{BC}: λ value used at the Box-Cox transformations; ts: test speed; gly: glycerol concentration; pts: pre-test speed; gly:pts: glycerol - pre-test speed interaction

In the case of the regression equations of the correction factors (k), the accuracy of the predictions was relatively low and the effect of the test speed and the glycerol concentration were the significant factors in almost all cases. Therefore, the following regression equations were used for the tablets:

$$Y = b_0 + b_1 x_1 + b_2 x_2 \tag{9}$$

where Y was the predicted value of the correction factor k, b_0, b_1, b_2 were the coefficients of the equation, x_1, x_2 were the coded values of test speed and glycerol concentration, respectively (Table 14)

Table 14 Coefficients of the regression equations of the k values

	T1	T2	T3	T4	T5
b_0	1.524	1.533	1.575	1.124	1.332
b_1 (ts)	0.022	0.007	0.007	0.013	0.024
b_2 (gly)	0.019	0.010	0.010	0.015	0.025

ts: test speed; gly: glycerol concentration

It was possible to optimize the independent parameters of the method after obtaining the regression equations based on the comparison of the *in vivo* DT and the *in vitro* DT values using the SSR function (Eq. (8)) and the optimization program, which calculated the ts, gly, and pts parameters in coded values and the two exponents (Table 15).

The optimization procedure included the following steps:

1. The program altered the independent variables which changed the AUC_{BC} and the *k* values trough the regression equations

2. The AUC_{BC} values were retransformed to AUC values and the AUC^{n_1}/k^{n_2} values were calculated

3. The c values were calculated based on the *in vivo* DT values and the AUC^{n_1}/k^{n_2} values

4. The *in vitro* DT values were calculated using the averaged c values (c_{av})

5. The *in vivo* and the *in vitro* DT values were compared and summarized

6. The program determined an optimal factor combination, where the SSR value was minimal (Table 16)

Table 15 Initial settings of the independent variables before optimization and the corresponding calculated values of the functions

factors	actual values	steps of the optimization	T1	T2	T3	T4	T5
ts	0.000	AUC_{BC}	12.45	74.18	7.44	3.62	2.74
gly	0.000	AUC	1326	1376	3136	366	3333
pts	0.000	*k*	1.524	1.533	1.575	1.124	1.332
n_1	1.000	AUC^{n1}/k^{n2}	870	898	1991	326	2502
n_2	1.000	*in vivo* DT	**27.2**	**25.5**	**38.1**	**26.9**	**59.7**
		c	31.98	35.20	52.26	12.11	41.92
		c_{av}	34.69				
		in vitro DT	**25.1**	**25.9**	**57.4**	**9.4**	**72.1**
		(*in vivo* DT - *in vitro* DT)^2	4.5	0.1	372.2	306.6	154.6
		SSR	**838.1**				

Table 16 Settings of the independent variables after the optimization and the corresponding calculated values of the functions

factors	actual values	steps of the optimization	T1	T2	T3	T4	T5
ts	-0.801	AUC_{BC}	11.39	56.02	7.21	3.38	2.72
gly	-0.522	AUC	890	802	2406	190	2656
pts	-0.292	k	1.496	1.510	1.565	1.106	1.300
n_1	0.437	AUC^{n1}/k^{n2}	8	8	11	8	18
n_2	2.189	*in vivo* DT	**27.2**	**25.5**	**38.1**	**26.9**	**59.7**
		c	0.30	0.30	0.30	0.30	0.30
		c_{av}	0.30				
		in vitro DT	**27.2**	**25.5**	**38.1**	**26.9**	**59.7**
		(*in vivo* DT - *in vitro* DT)^2	0.0	0.0	0.0	0.0	0.0
		SSR	**0.0**				

It is important to mention that the calculated AUC and *k* values under the optimal parameters are only valid if the prediction ability of the regression equations is good. On the other hand, the optimum values for the test speed (0.041 mm/s) and the pre-test speed (0.37 mm/s) parameters were not practically feasible, since the resolution of the instrument was 0.01 mm/s at the test speed and 0.1 mm/s at the pre-test speed parameters. Therefore, different feasible combinations were evaluated using the optimization program (Table 17).

Table 17 Values of the optimized parameters at different test speed and pre-test speed combinations

setting-combination	variables in coded values	gly	n_1	n_2	c_{av}	SSR
1	ts = -1; pts = -1	-0.17	0.42	2.28	0.25	0.4
2	ts = -1; pts = 0	-0.65	0.43	2.10	0.29	0.0
3	ts = -1; pts = 1	-1.21	0.45	1.89	0.37	1.0
4	ts = 1; pts = -1	-0.27	0.51	2.62	0.49	0.6
5	ts = 1; pts = 0	-0.90	0.51	2.35	0.56	1.5
6	ts = 1; pts = 1	-2.96	0.44	1.82	0.36	0.4

ts: test speed; pts: pre-test speed; gly: glycerol concentration of the medium

Since the prediction of the *k* values based on their regression equations was affected by relatively large error, it was advisable to use the smallest possible exponent n_2 value in order to minimize the error of the calculated *in vitro* DT values. The calculated SSR values were small in all cases, and the exponent n_2 values were the smallest at combinations 3 and 6. However, in the case of combination 6, the glycerol concentration was far from the investigated region, therefore, combination 3 was used for the checking procedure. Each nine type of tablets (T1 - T9) were measured (n = 3) with the texture analyzer using this parameter combination, and then the *in vitro* disintegration times were determined based on the measured AUC and *k* values and the n_1, n_2, c_{av} values obtained at setting combination 3. The *in vivo* disintegration times and the calculated *in vitro* DT values were compared (Fig. 28).
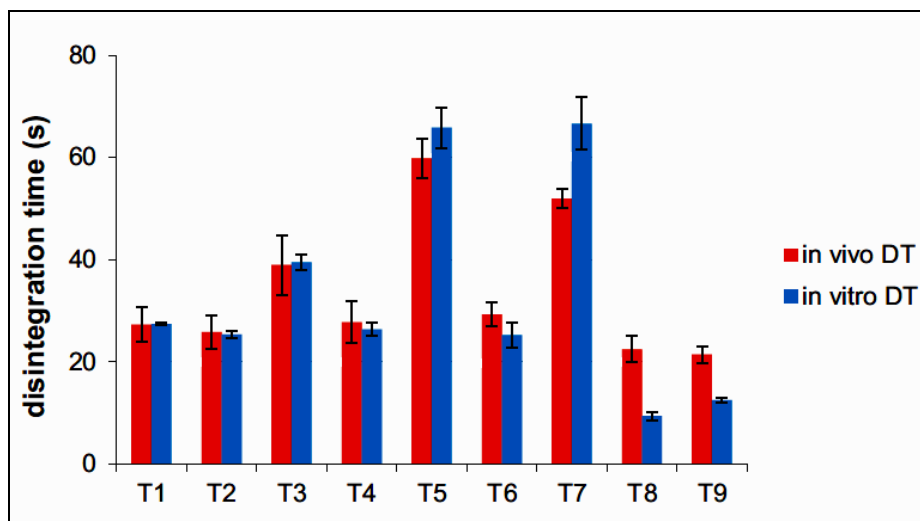
Figure 28 Comparison of the disintegration times of the different tablets after the determination of the optimal settings and parameters (Szakonyi and Zelkó, 2013; reproduced with permission)

Satisfactory results were obtained in the case of the five calibration tablets and the first interpolation tablet (T6), but in the case of the second interpolation tablet (T7), a remarkable overestimation of the disintegration time was noticed. In addition to, the two extrapolation tablets (T8, T9) gave very small *in vitro* DT values compared to their *in vivo* disintegration times, therefore the method was inadequate to predict the *in vivo* disintegration time of tablets characterised by low mechanical hardness (Szakonyi and Zelkó, 2013).

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### 6.4.2. Second experiment (effect of the composition of the medium)

It can be seen from Table 14 that, according to the SSR values, the method was not sensitive to the pre-test speed and the test speed values, therefore the composition of the medium was changed in a factorial experiment. The test speed was fixed at a low value (0.02 mm/s) in order to better mimic the *in vivo* circumstances, and the pre-test speed was fixed at the centre point value (0.4 mm/s). The medium contained PVP in addition to glycerol. Both materials increased the viscosity of the solution, but they acted differently to the thermodynamical parameters of the system. After the construction of the regression equations based on the 2^2 factorial experiments, the validity of the first order relationship between the independent variables and the AUC values was checked using the centre point values. Since there was a great difference between the estimated and the measured centre points in the case of each tablet, the first order relationship had to be rejected. This discrepancy was presumably due to the large difference in the applied PVP concentration at the high and the low level, therefore a second order term should be also implemented into the regression equations, e.g. with expanding the experiment to a central composite design. However, the performed measurements enabled the optimization procedure using the four setting combinations. Therefore, only the values of the exponents (n_1, n_2) were optimized by minimizing the SSR function. The results are listed in Table 18.

Table 18 Values of the optimized parameters at the measured glycerol and PVP concentrations

setting-combinations	variables in coded values	n_1	n_2	c_{av}	SSR
1	gly = -1; PVP 25 = -1	0.29	1.80	0.094	6.3
2	gly = +1; PVP 25 = -1	0.34	2.10	0.158	16.8
3	gly = -1; PVP 25 = +1	0.47	2.18	0.450	5.8
4	gly = +1; PVP 25 = +1	0.97	2.09	33.9	210

gly: glycerol concentration of the medium; PVP 25: PVP (Kollidon[®] 25) concentration of the medium

It is evident from combination 4 that at high glycerol and high PVP concentration levels, the method was unable to mimic the *in vivo* conditions (due to the high maximum load on tablets and the very slow wetting). Consequently, the prediction at this setting combination was very poor (SSR = 210). However, at setting combination 1 both the SSR and the n_2 values were satisfactory, therefore the remaining tablets (T6 - T9) were also measured with the texture analyzer at this "mildest" condition (lowest maximum load on tablets) and the corresponding *in vitro* DT values were calculated by Eq. (5) The results can be seen in Figure 29.
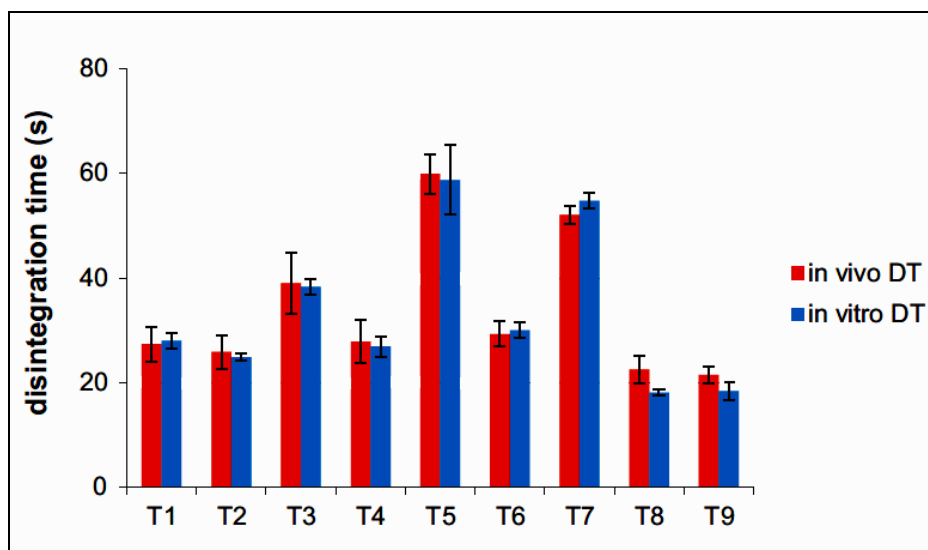
Figure 29 Comparison of the disintegration times of the different tablets after the determination of the optimal settings and parameters (Szakonyi and Zelkó, 2013; reproduced with permission)

The *in vitro* disintegration times were in good agreement with the *in vivo* ones in the case of all calibration tablets (T1 - T5) and the interpolation tablets (T6, T7), too. In the case of the extrapolation tablets (T8, T9) the predicted *in vivo* disintegration times were smaller than the measured ones, however the differences were less pronounced compared to the results of the first experiment. This finding enabled the measuring of tablets of acceptable hardness.

Although both PVP and glycerol content of the disintegration medium increased the viscosity of the solution and hindered the *in vitro* disintegration processes, but the

nature of their effect was different. There were several factors during the disintegration procedures, which were affected differently by the two compounds, such as the moistening of the tablets, the effervescent effect, the dissolution of the filler, etc. Nevertheless it would be difficult to list all types of interactions between tablets and the disintegration medium (Szakonyi and Zelkó, 2013).

6.4.3. Evaluation of the method using theoretically changed conditions

Since there was a good correlation between the *in vitro* results and the *in vivo* disintegration times after the optimization of the method where the medium contained both glycerol and PVP, it was important to show what would happen if other volunteers determined the *in vivo* disintegration times. It can be assumed that the oral disintegration times of tablets would change in the case of patients suffering from xerostomia (dry mouth), but not with the same extent. Therefore, the prediction efficiency of the method was evaluated using a theoretical patient group characterized by mild xerostomia (reduced saliva production), using a new *in vivo* disintegration time for each tablet (T1 - T9) calculated by the following arbitrary formula:

$$N = O(1 + 0.05 \cdot SD + 0.03 \cdot EFF) \tag{10}$$

where N is the new oral disintegration time (s), O is the original *in vivo* disintegration time (s), SD is the superdisintegrant content of the tablet (% w/w) and EFF is the effervescent agent content of the tablet (% w/w) (Table 19).

The idea behind this formula is that the reduced saliva production increases the oral disintegration times due to the reduced superdisintegrant and the reduced effervescent effects. The instrumental parameters were the same as in the optimized second experiment (both PVP and glycerol concentration were at the level -1), only the exponents (n_1, n_2) were recalculated using the optimization program, and the new values were: $n_1 = 0.27$, $n_2 = 1.75$, $c_{av} = 0.074$. Figure 30 shows the comparison of the new *in vivo* disintegration times with the calculated *in vitro* results.

Table 19 New oral disintegration times in the case of a theoretical patient group calculated by Eq 10.

Tablet code	T1	T2	T3	T4	T5	T6	T7	T8	T9
original *in vivo* DT (s)	27.3	25.8	39.0	27.8	59.8	29.3	52.0	22.5	21.5
new *in vivo* DT (s)	31.4	31.0	46.8	33.6	70.0	35.2	69.2	28.1	28.6
increase (%)	15	20	20	21	17	20	33	25	33

original *in vivo* DT: oral disintegration time of tablets measured by one healthy person; new *in vivo* DT: in vivo disintegration time of tablets in the case of a theoretical patient group
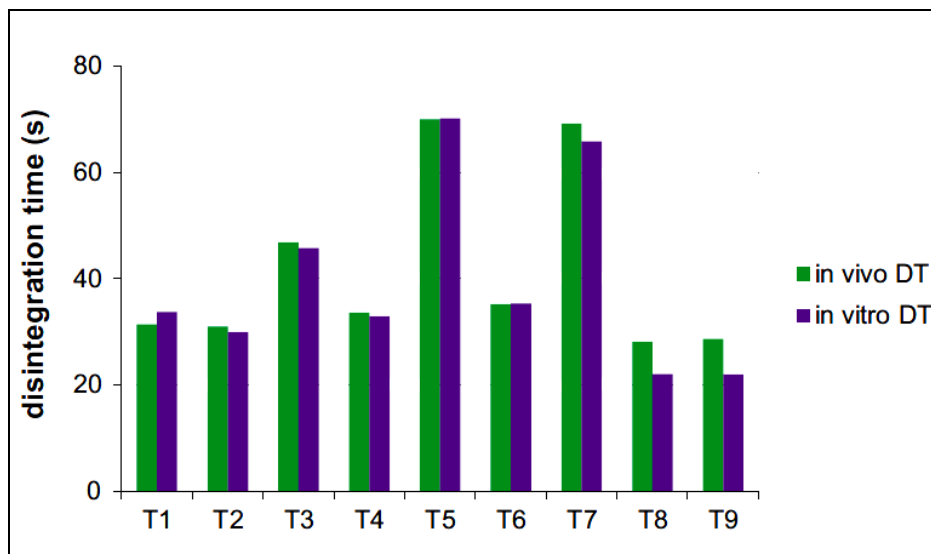
Figure 30 Comparison of the new *in vivo* disintegration times and the corresponding *in vitro* disintegration times calculated by the empirical equation after optimization (Szakonyi and Zelkó, 2013; reproduced with permission)

The method was able to predict the new *in vitro* values in this theoretical case in spite of the non-identical increments of the original disintegration times. Only the extrapolation tablets gave unsatisfactory results, but that was expected because the optimization was

performed using tablets of relatively high mechanical hardness. The method can be further extended if the results are not satisfactory, using more calibration tablets and by changing the composition of the medium and/or changing other parameters of the method, e.g. mesh size of sieve, volume of the medium (Szakonyi and Zelkó, 2013).

6.5. Formation of hydrogen-bonded polymer complexes to sustain the release of a water soluble API

Formulation of the API originates new challenges steadily, because of the continuously changing nature of the drug molecules. Many approaches use the direct processing of the API (such as microencapsulation or solid dispersion) instead of the use of a conventional method (such as granulation and tableting) in order to provide good stability, dissolution profile and bioavailability. The preparation of hydrogen-bonded interpolymer complexes creates an environment for the drug molecule that is similar to the case of solid dispersions. It is able to stabilize the drug molecules in the amorphous form through hydrogen bonds and to alter the dissolution profile of the molecule. Ozeki et al. (2000) reported the controlled release of phenacetin prepared using poly(ethylene oxide) and Carbopol®, while Tan et al. (2001) investigated the complex formation of polyvinylpyrrolidone with Carbopol®.

Drug containing polymer complexes were prepared based on the strong association of the poly(carboxylic acid) Carbopol® and the cross-linked PVP (crospovidone). Water soluble salt of desloratadine (desloratadine hemisulphate) was incorporated into hydrogen bonded polymer complexes using Carbopol® 971P and crospovidone (Polyplasdone® XL-10) (Fig. 31).

Crospovidone is a well-known polymer, which is able to keep a wide variety of drugs in the amorphous form. The dissolution of the desloratadine salt was retarded (at higher pH values) using Carbopol®, since the complex of the two polymers showed a pH-dependent drug release, while the dissolution of the drug is not or less pH-dependent using only crospovidone due to the chemical nature of PVP. The obtained precipitated material differed from both Carbopol® and crospovidone in its all physical attributes. It was suspected, that the polar groups of the polymers interacted and the hydrophobic polymer backbones came into contact with the solvent molecules,

therefore insoluble complex formed, which separated from the aqueous phase by precipitation and aggregation.
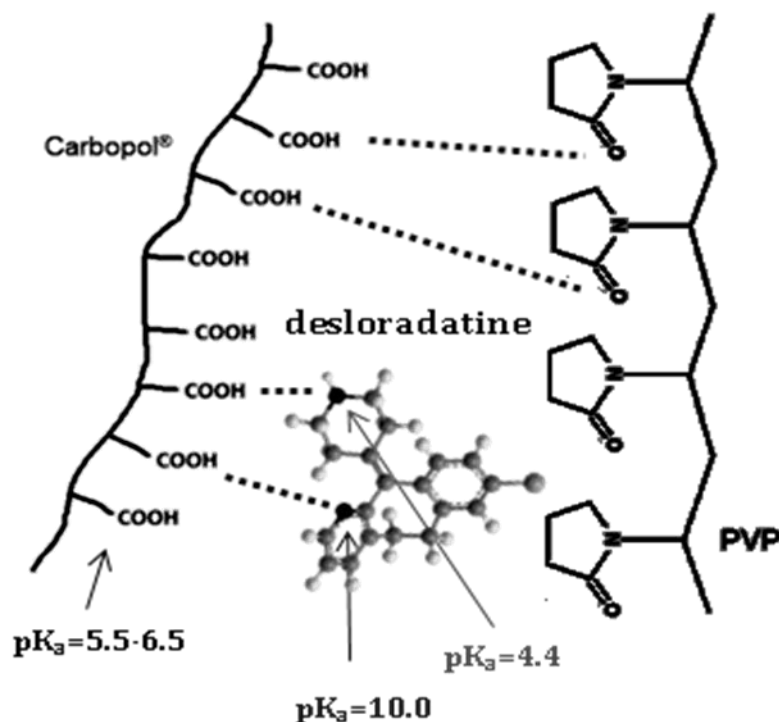

Figure 31 Possible interactions of the components of the complex through hydrogen bonds

The dried complex was milled into particles of different sizes in order to investigate the effect of the particle size on the release rate. The desloratadine model drug was highly water soluble in the investigated pH region (pH 1 - pH 6), since it has a secondary amine group with a pK_a value of 10.0 and a pyridine nitrogen atom with a pK_a value of 4.4 (Popović et al., 2009). The pH of the desloratadine solution was set at 3.6 during the complex preparation, since the complex formation was only possible with protonated Carbopol® molecules, therefore the pH value of both the crospovidone - drug suspension and the Carbopol® solution had to be lower than a certain value.

Dissolution curves of the powdered complexes were measured in order to investigate the influence of the pH of the medium and the particle size of the complexes on the drug release rate. Immediate dissolution occurred in 0.1M HCl solution, while strongly retarded dissolution was observed in water (data not shown). Detailed

dissolution tests were performed in order to investigate the pH-dependency of the dissolution process at an intermediate pH region (pH 3.0 - pH 4.5).

The release rate of the drug was dependent on both the pH value and the particle size of the complex. The release rate was high using a medium of pH 3.0 and complete drug release was achieved within 60 min in each cases, except in the case of sample with the smallest particles (<90 μm) (Fig. 32). The release of the API was highly retarded using the medium of pH 4.5, less than 30 percent of the drug was dissolved within 3.5 hours (Fig. 34). It is hard to estimate whether a complete disintegration would take place after a longer investigation time. Possibly, the dissolution profile has a zero order kinetic after the first 90 min. The dissolution had an intermediate rate at pH 3.5 and its dependence on the particle size was well appreciable (Fig. 33)
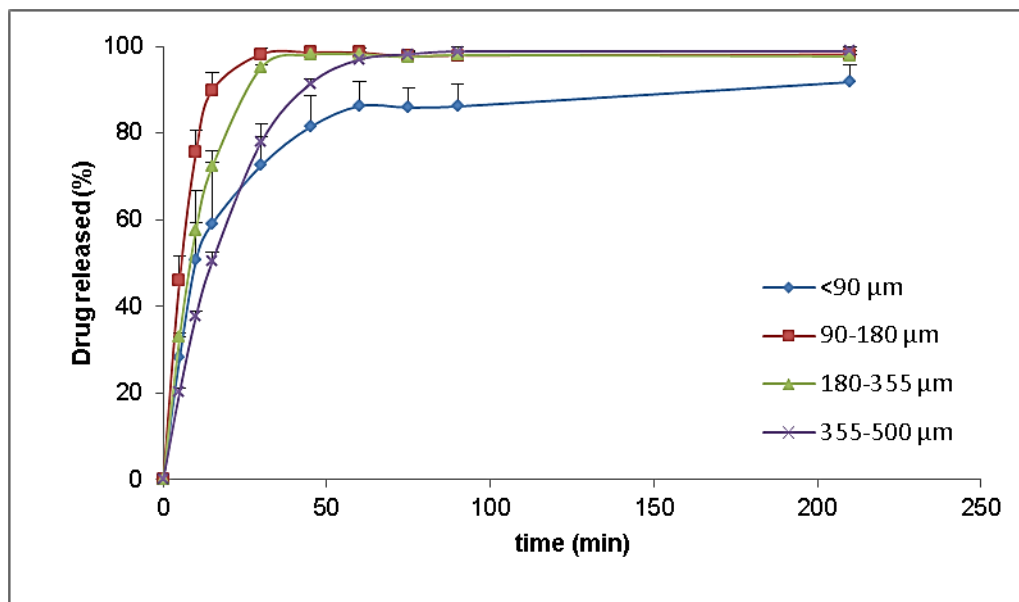
Figure 32 Dissolution of the drug at buffer pH 3.0 as a function of time and particle size
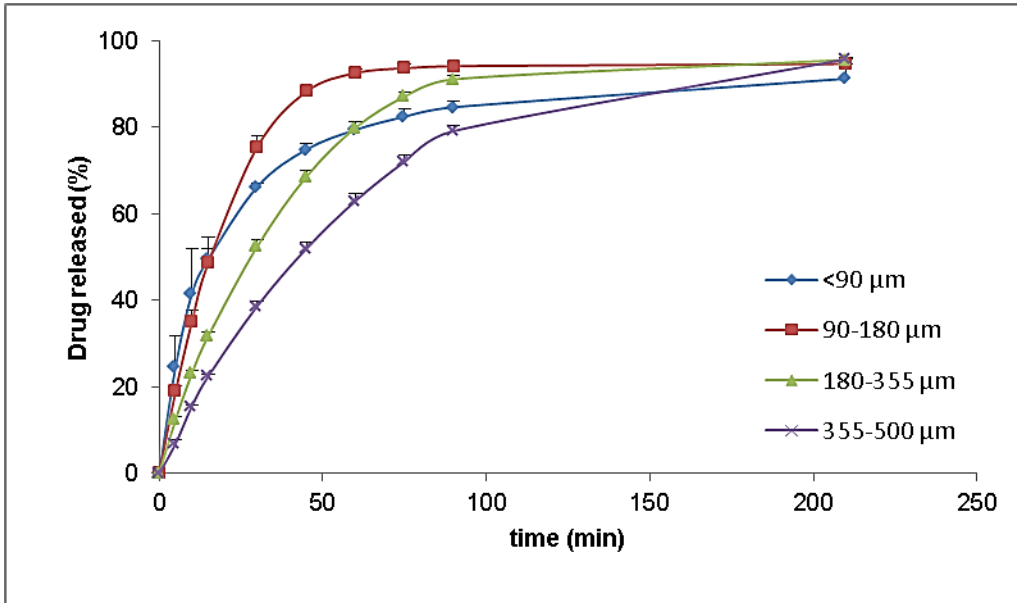
Figure 33 Dissolution of the drug at buffer pH 3.5 as a function of time and particle size
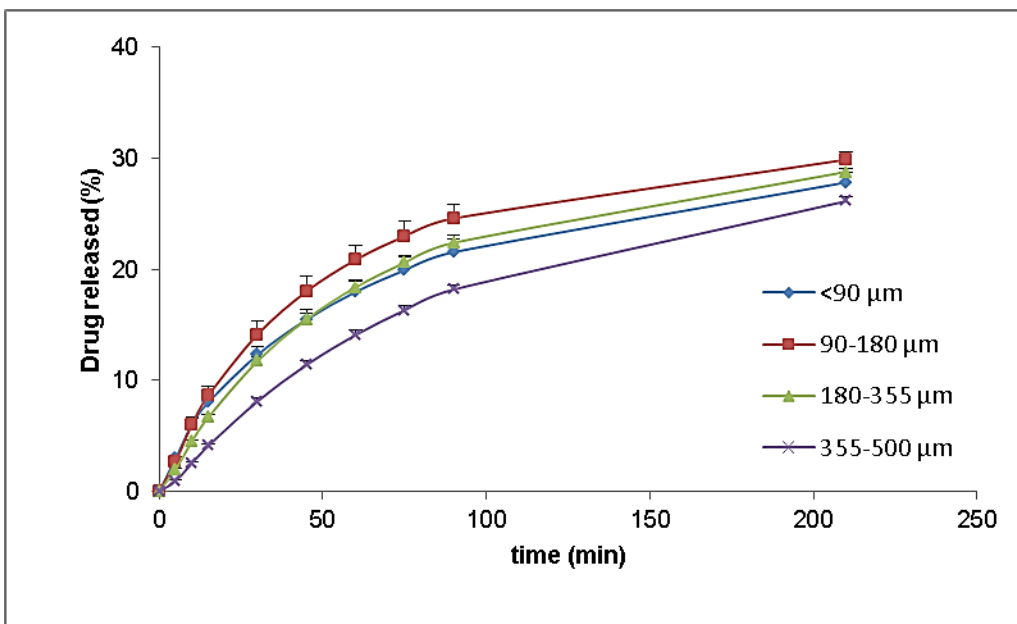
Figure 34 Dissolution of the drug at buffer pH 4.5 as a function of time and particle size

The particle size dependence of the dissolution was evident in the case of each pH, but the smallest particles had a deviant dissolution profile. On the one hand, there was no burst release effect using the smallest sieve fraction, which could indicate that the drug

molecules were molecularly attached to the polymer chains; otherwise, the milling procedure should disrupt the release-retarding coat around the drug crystals. On the other hand, inspecting the microscopic picture of the particles with different sizes, inhomogeneous particle size distribution can be observed in the case of the smallest fraction (Fig. 35). The sample was composed of particles of size around 90 μm, however much smaller particles are also detectable. This particle size distribution can explain the biphasic drug release, i.e. the release rate was similar to the release rate of the sample with the second smallest particles (90-180 μm) in the first 10 minutes, while the release profile deviated after the first 10 minutes compared to the other samples, and its slower dissolution was maintained during the investigation time. The explanation could be, that the very small particles created an interconnected aggregate in the dissolution vessel, therefore the diffusion layer was larger in this case compared to the other particles, where particles did not formed such an aggregate. The high initial release rate was due to the fast release of the drug from the surface of the aggregate, while the larger diffusion barrier dominated in the later stages of the dissolution.

Particles showed neither swelling nor disintegration during the dissolution tests, which was in accordance with the observation of Tan et al., (2001), who had shown that Carbopol® - PVP polymer complexes did not dissolve in acidic environment, only at higher pH levels.
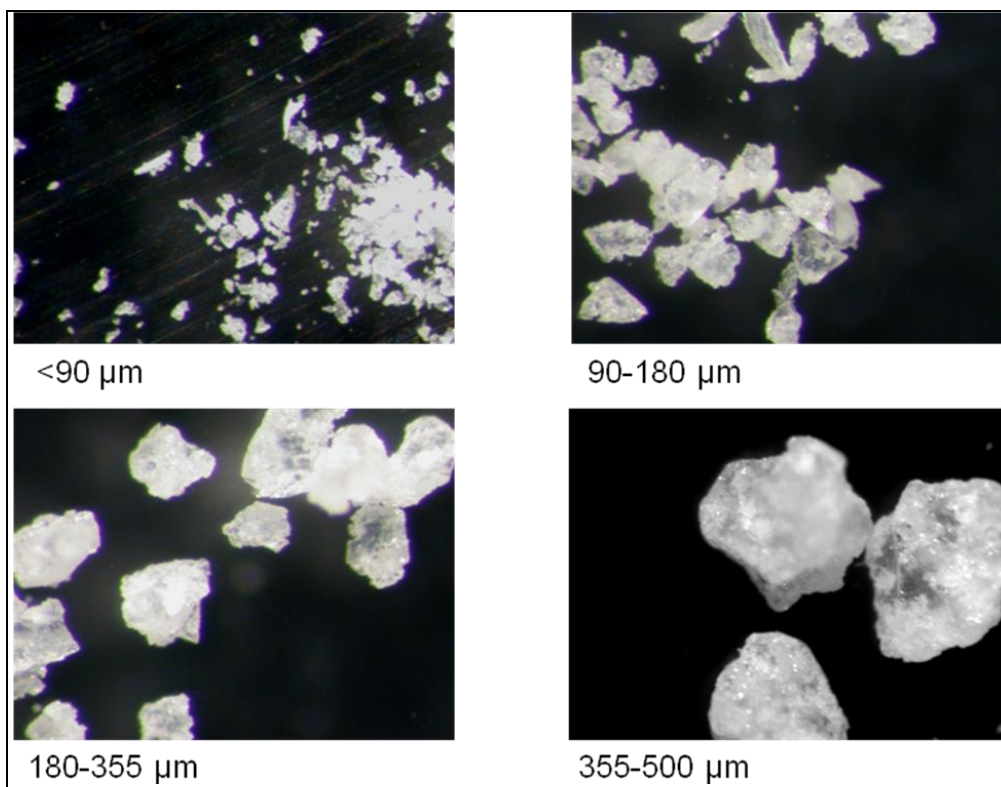
Figure 35 Microscopic pictures of the dried and milled polymer complex particles of different particle size distributions (magnification of 60×)

Taste masking was successfully achieved using this formula, since the dissolution of the drug was negligible in water during a short period of time. However, it would be advisable to change the molecular structure of the hydrogen-bonded polymer complexes in order to alter the drug release rate and the pH dependence of the release rate.

Polysorbate 80 (Tween 80), a non-ionic surfactant and emulsifier with high HLB-value, was added to the crospovidone - drug suspension in order to plasticise the polymer complex and to alter the structure of the hydrogen bonds. On the other hand, a crospovidone with higher particle size (Polyplasdone XL) was chosen, since the Carbopol® - crospovidone reaction occurs at the surface of the crospovidone particles due to its insoluble nature. Therefore, the specific surface area of crospovidone might influence strength of the complex formation. Specific surface area of the XL-10 type of Polyplasdone is 0.94 g/m^2 and it is only 0.69 g/m^2 in the case of the XL type (Nakanishi et al., 2011).

The new formula was compared with the original one in terms of drug dissolution. The dissolved drug fraction was measured after half an hour and plotted as

a function of the pH of the dissolution medium. The original and the modified, Tween 80-containing samples were investigated with a dissolution test performed in Erlenmeyer flask using the sieve fraction of 355-500 μm of the complexes in both cases (Fig. 36). The dissolution behaviour of the two samples was almost identical in spite of the large differences in their physical appearance. The original formula formed a white, nearly homogenous rubber-like precipitates after preparation (before the drying step), while the new formula with the Polyplasdone XL had not such a homogenous appearance and it easily disaggregated into smaller granules. It can be concluded that the pH-dependency of the release rate of the system is quite stable irrespective of the physical characteristics of the system, which can also indicate the molecularly dispersed state of the drug.
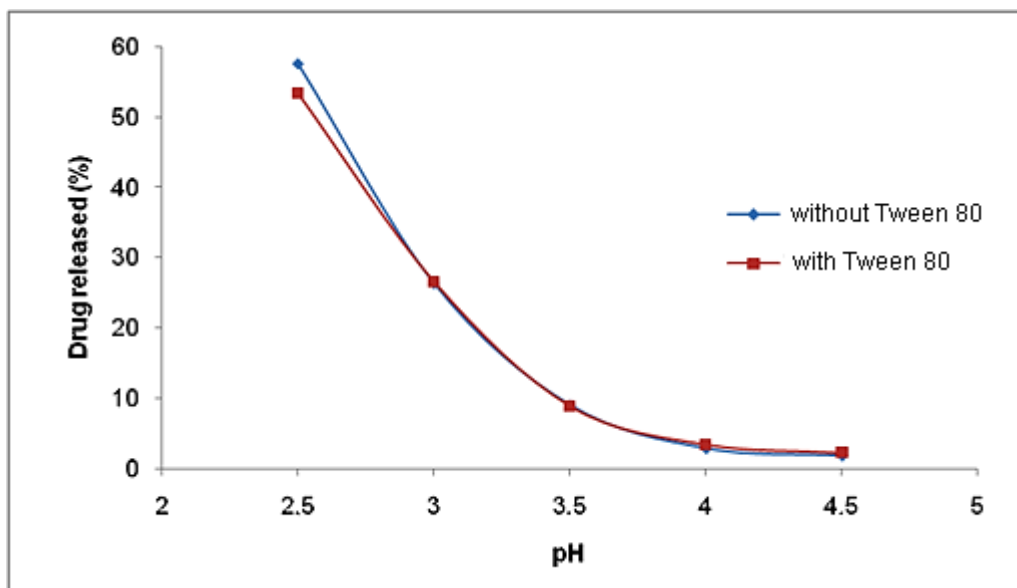
Figure 36 The amount of the drug released after half an hour as a function of pH

The dissolved fraction after half an hour at pH 6.0 was also measured in the case of the Tween 80-containing sample and ATR-FTIR spectra of the dried residues of the dissolution tests were recorded using the solid residues of the tests performed at pH 1.1, pH 3.0, pH 4.5 and pH 6.0.

Only the peaks of the two polymers were detectable in the spectra of the complexes, characteristic peaks of desloratadine did not appear due to its low concentration in the samples.

Most important infrared absorption peak of crospovidone was associated with the carbonyl stretching vibration (C=O str) around 1650 cm^{-1} (Fig. 37). This band is usually strong and appears between 1740 - 1630 cm^{-1} in amide compounds (Pretsch et al., 2009). The band gradually shifts to lower wavenumbers due to the formation of hydrogen bonds; therefore its position indicates the extent and strength of hydrogen bonding. Since the molecule does not partake in acid-base reactions and has no hydrogen-donor group; therefore only his C=O str band can provide information about its state in the complex without more complex investigations.
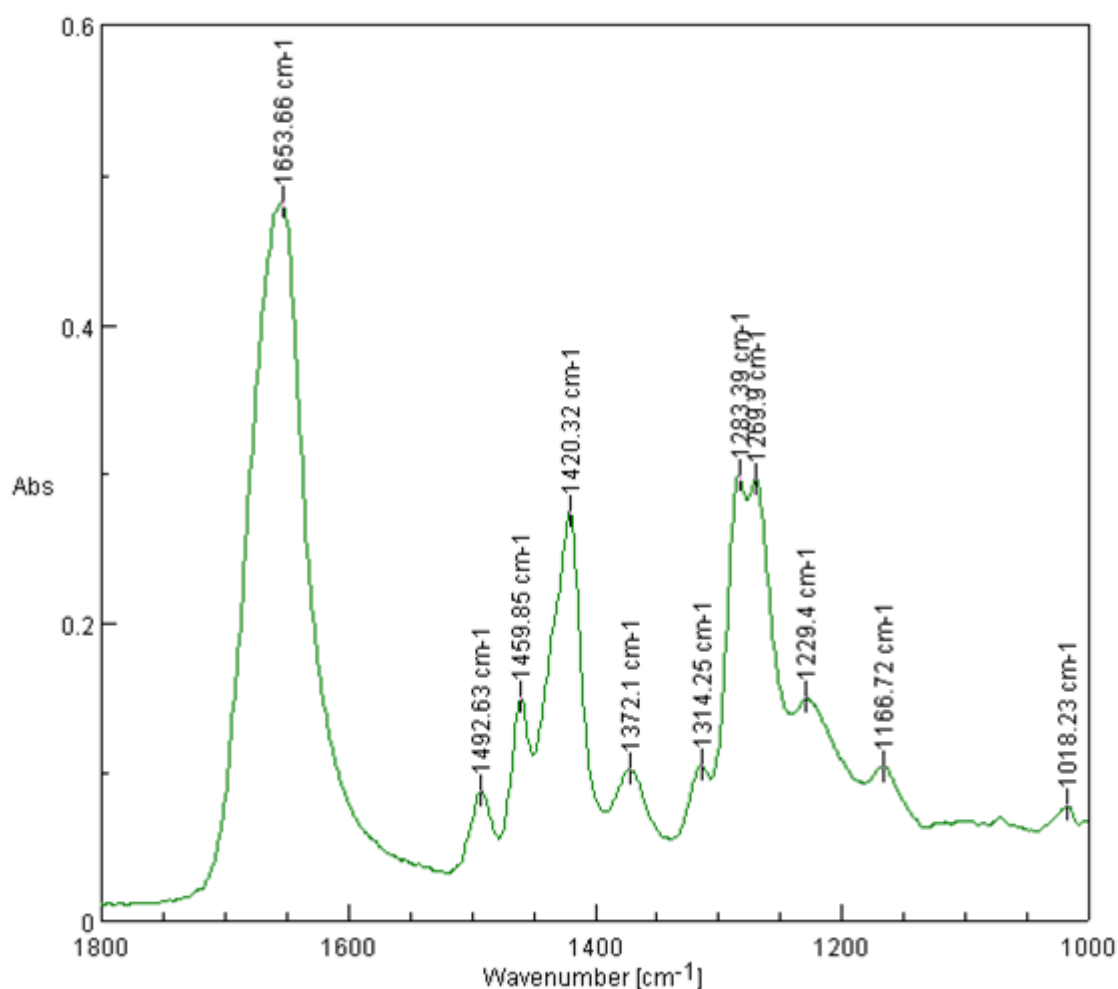
Figure 37 ATR-FTIR spectrum of crospovidone (Polyplasdone XL)

Carbopol$^{®}$ has three characteristic peaks on IR spectra between 1800 - 600 cm^{-1}. Its C=O str band appears around 1695 cm^{-1}, which corresponds to the free state of the carbonyl group (Fig. 38). The hydrogen bonded C=O str band appears at lower

wavenumbers, usually as a shoulder of the free C=O str band. The deprotonated carboxyl (COO⁻) group has absorption bands around 1560 cm^{-1} and 1410 cm^{-1} due to its asymmetric (COO⁻ str as) and symmetric stretching (COO⁻ str sy), respectively, but only the asymmetric stretching has practical significance (Pretsch et al., 2009).
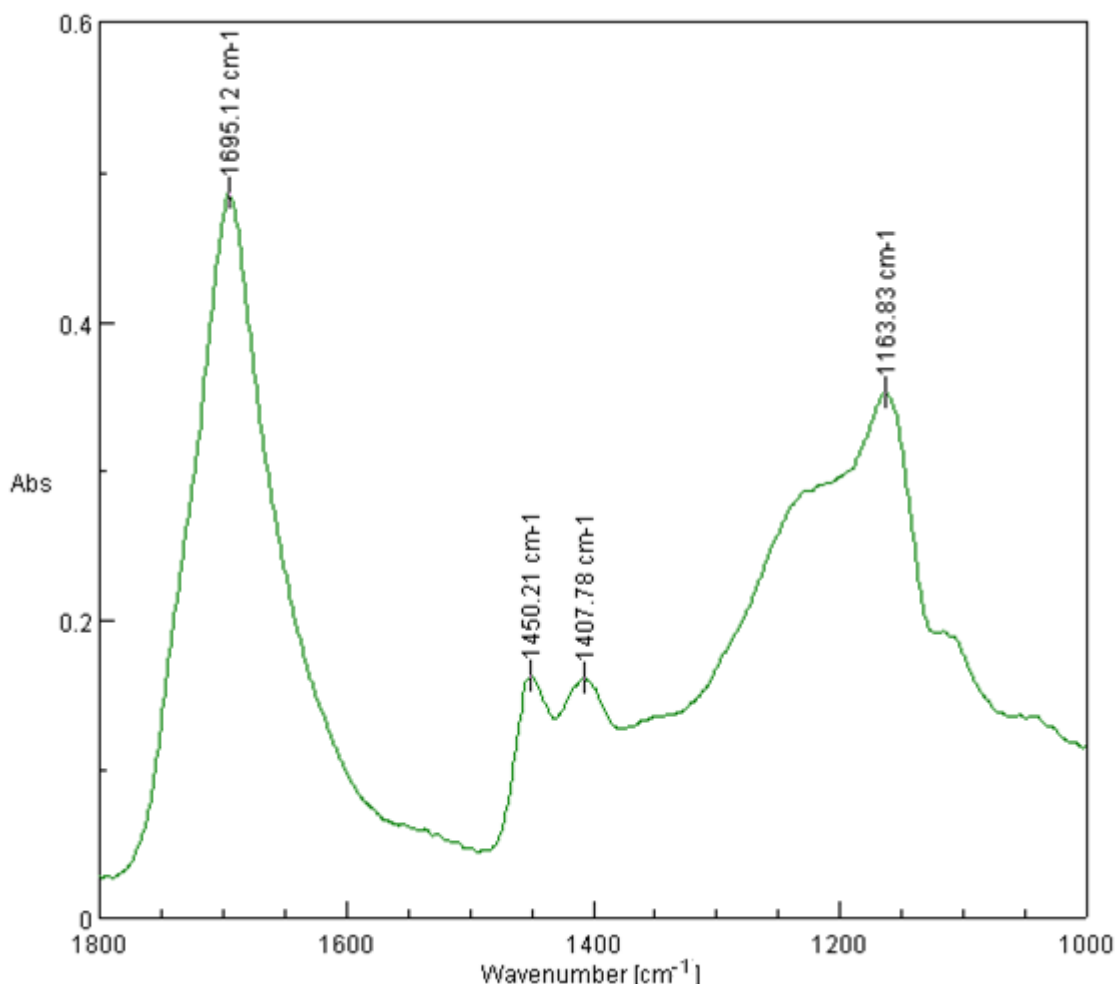
Figure 38 ATR-FTIR spectrum of Carbopol®

Investigation of Carbopol® cast films prepared using different solutions (0.5% w/w Carbopol 971P; pH 2 HCl solution for acidic, water for neutral, pH 11 NaOH solution for basic samples) could help in the interpretation of the IR spectra of the complexes. Fig. 39 shows IR spectra of the Carbopol® films, which correspond to the differently protonated state of the molecule. It can be seen from the increase of the intensity of the COO⁻ stretching bands at higher pH levels, that IR spectroscopy is able to detect the increase of the amount of the deprotonated carboxylic groups. On the other hand, the

asymmetric COO⁻ stretching band shifted significantly to the higher wavenumbers at basic conditions, which indicated changes in the chemical environment of the group. These changes can be associated with the uncoiling of the polymer chains due to the electrostatic repulsion between the groups. Nevertheless, the development of the adjacent negatively charged carboxyl groups should be a more important factor.
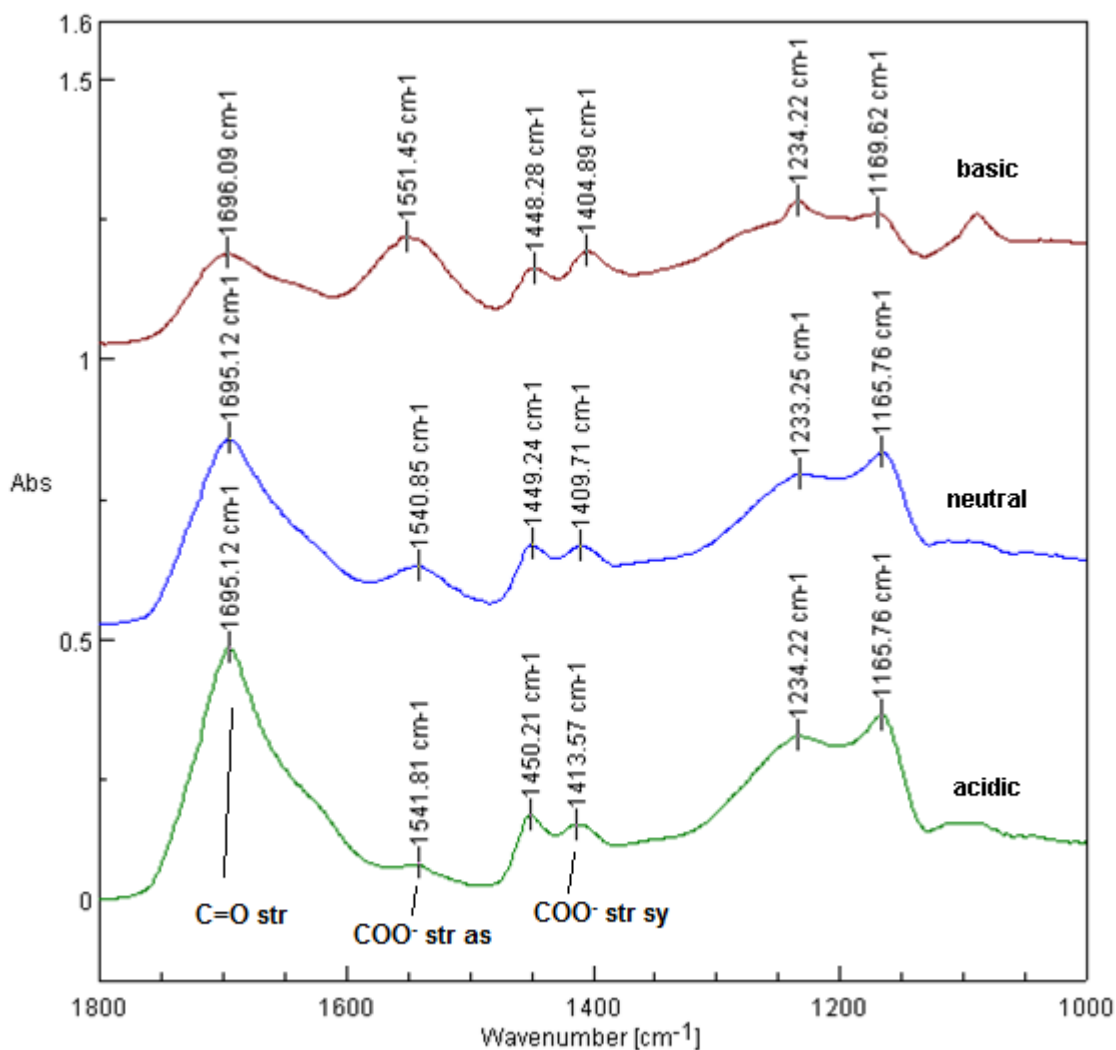
Figure 39 ATR-FTIR spectra of Carbopol® films, casted from aqueous solutions of different acid-base conditions

Peaks of crospovidone dominated on the IR-spectra of the polymer complexes. Peaks of Carbopol® were either covered by the absorption of crospovidone or mixed with the crospovidone peaks. C=O stretching band of Carbopol® was easily detectable at pH 1.1

(1699 cm^{-1}) and asymmetric COO^{-} stretching of Carbopol$^{®}$ at pH 6.0 (1557 cm^{-1}) (Fig. 40). The progressive decrease of C=O stretching and the increase of asymmertic COO^{-} stretching as a function of pH indicated that the complex responded to the changes of the pH during the dissolution, and that the deprotonation of Carbopol$^{®}$ molecules should contribute to the large changes in the dissolution rates at various pH values in addition to the state of the desloratadine. On the other hand, the relative stable position of the C=O stretching band of crospovidone (1645 cm^{-1}) indicated that the strength of hydrogen bonds of crospovidone did not changed significantly. It is important to note, that the released portion of the drug was the lowest at pH 4.5 (about 2 %) and it increased to about 13% using buffer pH 6.0. Some swelling of the complex particles was also observed at this pH, and the IR spectrum confirmed the presence of the large number of carboxylate anion groups at pH 6.0 with absorption of relatively high wavenumber (1557 cm^{-1}). It is suspected that the complex would dissociate at higher pH values due to the electrostatic repulsion of Carbopol$^{®}$ molecules and hydrogen bond breaking, which is in accordance with the observation of Tan et al. (2001). The largely different protonation of the pyridine nitrogen atom of desloratadine possibly also plays an important role in the drug release.
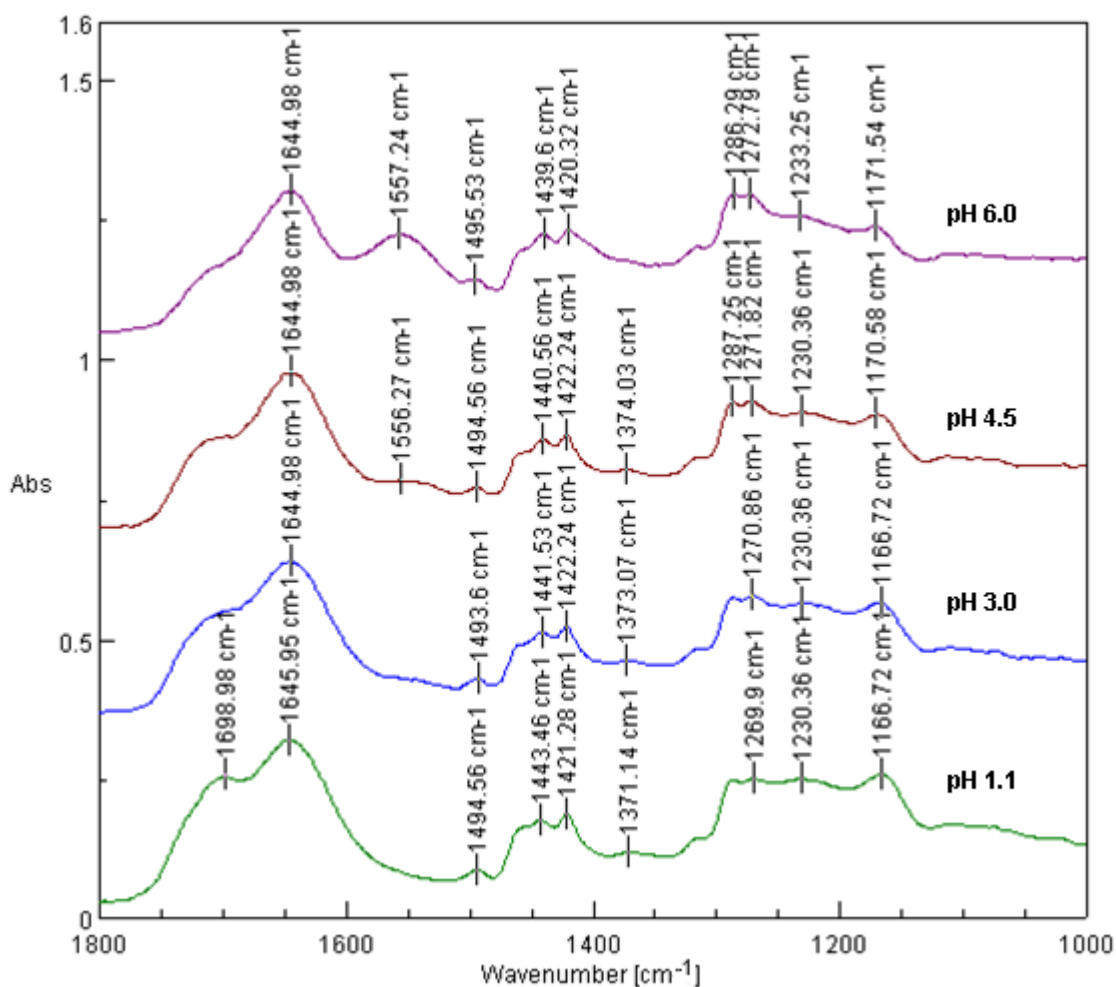
Figure 40 ATR-FTIR spectra of the dried residues after dissolution at various pH values

It can be concluded, that desloratadine release from the complex should involve different molecular interactions, such as hydrogen bonding between the two polymers, hydrogen bonding between desloratadine and the polymers, electrostatic interaction between the monoprotonated desloratadine and Carbopol®, electrostatic interaction between the doubly protonated desloratadine and Carbopol®, etc., therefore more detailed interpretation of the dissolution curves would require additional investigations.

7. Discussion

7.1. Water content determination of pharmaceutical superdisintegrants by ATR-FTIR spectroscopy

Loss on drying method was prescribed in the pharmacopoeias for the water content determination of the three common superdisintegrants. This method requires a relatively high amount of samples and time-consuming measurements. The ATR-FTIR measurements give results of very good reproducibility based on the spectra of an inert, non-hygroscopic material (mannitol). FTIR spectroscopy is a sensitive technique to measure water content changes of materials due to the strong infrared absorption of water molecules. Water binds easily to the polar functional groups of polymers in the case of amorphous materials that can be tracked by the FTIR spectra. The ATR technique allows the direct measurement of powdered materials without any sample preparation that enables the rapid determination of any changes in the actual water content. The variance of the measurements can be derived not only from the instrument but from the local water content inhomogeneity of the samples frequently occuring in the case of pharmaceutical technology since the surface of a hygroscopic material stored in a container absorb more moisture than the bottom layers. Pharmacopoeias determine a water content limit, which is high enough to safely detect by ATR-FTIR method. Superdisintegrants are good example of moisture sensitive pharmaceutical excipients, however the method has no limitations in terms of chemical composition, therefore it could be a useful mean for the water content determination of any hygroscopic amorphous or partially amorphous powdered material (Szakonyi and Zelkó, 2012).

7.2. Tablet preparation for the screening of the efficiency of different superdisintegrants

Mannitol based orally disintegrating tablets were prepared by direct compression and with a different levels of superdisintegrant content in order to compare their efficiencies, to determine their optimal concentrations and the effect of the hardness of the tablets. The effects of superdisintegrants comprise different mechanisms, and these

effects depend on the nature of the tablet matrix (e.g. solubility of the matrix), therefore superdisintegrant screening is advisable after the determination of the component of the formulation. The superdisintegrants behaved differently in the different *in vitro* tests and only their collective investigation was able to provide an insight of their actions. CrosP provided the tablets of the weakest mechanical strength, their wetting and *in vitro* disintegration times were low, but the wetted tablets did not softened in the required extent. Tablets containing SSG softened after complete wetting, but their wetting and *in vitro* disintegration times were high, which indicated the poor capillary effect of superdisintegrants. Tablets containing CCS in low amounts and prepared by the high level of compression force gave the best results, therefore it can be suspected that both its capillary and disintegrating action is pronounced using this tablet composition and tableting parameters. The superiority of croscarmellose sodium was also demonstrated by tablets containing dicalcium phosphate, a water-insoluble filler (Zhao and Augsburger, 2005).

The proposed screening method could be useful for the evaluation of the marketed superdisintegrants and various extensions of the range of the investigations are possible (e.g. physical stability testing of the formulations, *in vivo* disintegration tests).

7.3. Tablet preparation using the swelling of crospovidone and the phase transition of xylitol

The development of novel, innovative ODT formulations is an interesting topic in the recent scientific works, since hundreds of papers deal with novel solutions in this field. The combination of two molecular phenomena was exploited for the purpose of ODT preparation, i.e. the swelling of crospovidone due to moisture absorption and the melting and resolidification of xylitol. Different experiments were performed that helped to clarify the mechanisms of solid bridge formation, the role of the superdisintegrants in the volume increase of tablets, the effect of the lubricant on the disintegration time, etc. It was found that the partially melted xylitol bound the filler particles together instead of forming a solid network, but they presumable formed large aggregates at higher concentrations. Each investigated superdisintegrant was able to

cause tablet increase after moisture sorption maintaining the integrity of the tablets, but their final hardness and *in vivo* disintegration times markedly differed. One of the most important finding was, that external lubrication could be very effective to reduce the oral disintegration time. It was reported that this solution could increase the hardness of the tablets without prolonging its disintegration because of the very low amount of lubricant in the formulations (Takeuchi et al., 2005; Yamamura et al., 2009). Main problems of the formulation were associated with the high friability and the low mechanical hardness, however it was suspected that these problems might be partially overcome by the use of modern external lubrication system.

7.4. In vitro determination of the disintegration times of different mannitol based ODTs

The developed disintegration time prediction procedure can be divided into three main steps:

1. Determination of the *in vivo* disintegration times of different ODT preparations;
2. Construction of a design of experiment which is able to provide an equation which shows the dependence of the measured values as a function of the parameters of the method (e.g. glycerol concentration, test speed);
3. Optimization of the parameters by a computational procedure in order to gain the best IVIVC.

It was possible to predict the *in vivo* disintegration times of fast disintegrating tablets based on the load-displacement curves of texture analysis measurements by using an empirical equation. Tablets characterized by different disintegration mechanisms and hardness were included in the investigation. Since the oral disintegration times can greatly depend on the target group of patients, it was necessary to indicate that it is possible to optimize the method even if the *in vivo* disintegration times have changed. It seems possible to gain satisfactory, optimized conditions by using mathematical methods in all cases, although there are many variables that influence the *in vitro* disintegration times. When using patient groups, the parameters of the method would be different, however the presented method enabled the optimization. It seems that the

composition of the disintegrating medium is of great importance. Since the *in vitro* disintegration process can be characterized thermodynamically, a better understanding of the role of the excipients and the circumstances along with the development of reliable theories may improve the obtained *in vitro-in vivo* correlation of pharmaceutical test methods (Szakonyi and Zelkó, 2013).

7.5. Formation of hydrogen-bonded polymer complexes to sustain the release of a water soluble API

Water soluble desloratadine salt was successfully incorporated into a complex matrix with special drug releasing behaviour. The release rate was an exponential function of the pH, which is dissimilar to the well-known drug releasing behaviour of methacrylic acid/methyl methacrylate copolymer (Eudragit® L 100) film coats for example, where drug release occurs only above a certain pH value, i.e. the release rate - pH function has a breakpoint. The drug release is fast at lower pH values and the polymer complex would disintegrate at higher pH values presumable; however the dissolution was retarded in water and at pH values between 3.5 and 6.0. The release mechanism of the drug is not clear, it would be important to investigate other molecules with different pK_a values, in order to separate of the role of the electrostatic interactions form the role of the hydrogen bonds. Carbopol® responded to the changes of the pH values based on the IR data, and there were changes in the protonation of desloratadine in the investigated pH region according to its pK_a values, as well.

8. Conclusions

The development of orally disintegrating tablets is a complex process, where different requirements should be met therefore it is advisable to study all aspects of the formulations. Superdisintegrants, one of the most important components of ODT formulations, were characterised in terms of both physico-chemical features and efficiency.

- A novel method was developed for fast water content determination of superdisintegrants, which is useful as an evaluation tool, as well.

- The observation of water sorption could be very easily recorded with the ATR-FTIR spectra of superdisintegrants (or other similar excipient), and the constructed regression lines are able to give information about its extent, as well.

- The comparison of the three most frequently applied superdisintegrants helped to gain information about the *in vitro* behaviour of these compounds. Croscarmellose sodium was selected as the most promising excipient in small amounts and after direct compression with mannitol, its disintegration was the best *in vitro* which was also confirmed *in vivo*.

- A novel method - preparation of fast disintegrating tablets by phase transition of sugar alcohols, developed by Kuno et al. (2005) - was modified and further evaluated. Some of the influencing parameters were investigated and it was concluded that the adhesion of the melted sugar alcohol component to the filler is critical considering the hardness of the tablets. It was also shown, that there is an upper limit of the amount of the melting component and the external lubrication could be more advantageous for this type of formulation considering the disintegration times.

- Due to the lack of a widespread and useful *in vitro* disintegration time determination process, an optimised method was developed based on texture analysis measurements. The method was able to predict the oral disintegration times of different tablets prepared by direct compression with or without effervescent components with high accuracy.

- Hydrogen bonded polymer complexes were prepared as a carrier for a water soluble model drug, desloratadine hemisulphate in order to mask its unpleasant

taste. A new method was developed which enabled the mixing of the water insoluble crospovidone with the Carbopol® solution, since the conventional techniques usually use polymer solutions for the complex preparations (Rolfes et al., 2001; Kumar, 2002). The developed method allowed the use of concentrated, drug-containing suspension, where the crospovidone content is advantageous for maintaining the drug in the amorphous form (Shibata et al., 2007). The dried and milled complex particles had unique pH-dependent dissolution characteristics, which showed inverse pH-dependency than that of the complex formation.

9. Summary

Various technologies were evaluated, which can facilitate the development of orally disintegrating tablets. It was shown that the combinations of different methods in the research phase of the development could be useful for the promotion of the further phases of technological development. It was possible to introduce new methods and to improve existing techniques, as well.

The water content determination of superdisintegrants using ATR-FTIR spectroscopy enabled to check the actual water content of the excipients, which was necessary for the reproducible quality of the samples. The developed method is a useful mean for the characterisation of other hygroscopic excipients in terms of water content, as well.

Superdisintegrants were characterised in terms of their *in vitro* performance and novel ODT formulations were developed using them, and their *in vivo* disintegration times were determined, as well.

Based on the *in vivo* data, an *in vitro* disintegration time determination method was evaluated using a texture analyser. A computational optimization method was constructed in order to provide an *in vitro* method, which is able to reliably predict the disintegration time of large range of products. The computational approach enabled the simple tailoring of the method according to the actual characteristics of the formulations and the consumer group.

The final ODT formula should have acceptable taste, mechanical hardness, stability; therefore, the taste masking possibilities of a bitter drug, desloratadine, were also investigated. Since there are large variety of taste masking techniques, a relatively novel approach was investigated, the formation of hydrogen-bonded interpolymer complexes. The drug release from the prepared complexes was retarded using a dissolution medium of higher pH; therefore the preparation had a good taste masking properties supposedly.

9. Összefoglalás

Különféle technológiák kiértékelését végeztem el, melyek megkönnyíthetik szájban széteső tabletták kifejlesztését. A fejlesztés kutatási fázisában a különféle módszerek kombinálása hasznos lehet a technológiai fejlesztés további fázisainak elősegítésére. Lehetséges volt új módszerek bevezetése, valamint a meglévő technológiák fejlesztése is.

Szuperdezintegránsok víztartalmának meghatározása ATR-FTIR spektroszkópiával lehetővé tette a segédanyagok aktuális víztartalmának ellenőrzését, mely szükséges többek között a jól reprodukálható mintákhoz. A kifejlesztett módszer hasznos lehet egyéb higroszkópos segédanyagok neminvazív víztartalom meghatározására.

A szuperdezintegránsokat az *in vitro* tulajdonságok tekintetében is jellemeztem, valamint egy új ODT formulációt fejlesztettem és értékeltem ki felhasználásukkal, amelyeknek az *in vivo* szétesési idő értékeit is meghatároztam.

In vivo szétesési idő adatok alapján egy *in vitro* szétesési idő meghatározási módszert dolgoztam ki állományelemző felhasználásával. Alapja egy számítógépes optimalizálási módszer, ahol cél volt, hogy egy olyan *in vitro* módszert kapjunk, mely megbízhatóan képes előre jelezni a szétesési időket különböző összetételű termékek esetén. A számítógépes módszer lehetővé tette a módszer beállítását a formulációk aktuális jellemzőihez és speciális betegcsoportokhoz.

Mivel egy végleges ODT formulációnak elfogadható ízűnek, mechanikai szilárdságúnak és stabilitásúnak kell lennie, ezért egy keserű hatóanyag, a dezloratadin, ízfedési lehetőségeinek vizsgálatát is elvégeztem. Az ízfedési módszerek nagy száma miatt egy relatív új megközelítési módot vizsgáltam, a hidrogén kötött polimer komplexek formulálását. Az elkészült komplexekből a hatóanyag felszabadulás lassított volt enyhén savas vagy semlegeshez közeli pH értékű kioldóközegben, amely a készítménynek feltehetően jó ízfedési tulajdonságot biztosít.

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11. List of publications

11.1. Publications relevant to the dissertation

1. Szakonyi G, Zelkó R. (2012) Water content determination of superdisintegrants by means of ATR-FTIR spectroscopy. J Pharm Biomed Anal, 63: 106-111.

2. Szakonyi G, Zelkó R. (2012) Ízfedési lehetőségek szilárd gyógyszerformák esetén. [Taste-masking possibilities in solid dosage forms.] Acta Pharm Hung, 82: 81-90.

3. Szakonyi G, Zelkó R. (2012) The effect of water on the solid state characteristics of pharmaceutical excipients: Molecular mechanisms, measurement techniques, and quality aspects of final dosage form. Int J Pharma Investig, 2:18-25.

4. Szakonyi G, Zelkó R. (2013) Prediction of oral disintegration time of fast disintegrating tablets using texture analyzer and computational optimization. Int J Pharm, 448: 346-353.

11.2. Other publications

1. Szakonyi G, Zelkó R. (2010) Különböző gyógyszerformákkal kapcsolatos gyógyszerészi tanácsadás. Acta Pharm Hung, 80**:** 121-127.

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