Investigation, development and evaluation of orally disintegrating tablets

PhD thesis

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Introduction

Tablet is one of the most common pharmaceutical dosage forms, it is able to deliver the appropriate amount of the active pharmaceutical ingredient (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 and many illnesses may be associated with this condition. The orally disintegrating tablet (ODT), or, alternatively the 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 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; however, it is possible to promote drug absorption through local oromucosal tissues, and through pre-gastric, gastric and post-gastric parts of the gastrointestinal tract.

ODT products have several advantages over liquid dosage forms, which are useful in the case of swallowing difficulties, but manufacturing of ODTs is more difficult process compared to conventional tablets due to their special properties. There are several manufacturing methods to produce ODTs, but the method has its drawbacks in all cases. Tablets need to have an acceptable taste due to the bitter taste most of the drugs and very short disintegration time in the

mouth in addition to the pharmacopoeial requirements. 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 availability of superdisintegrant excipients made the production of various kinds of ODT products possible using conventional tableting methods. These unique polymeric materials are cross-linked forms of hygroscopic polymers, which are able to absorb large amounts of water and swell to a remarkable degree after contact with saliva.

Valuable *in vitro* characterisation of these products plays also an important role during the development of the formulations in addition to the technological considerations.

Aims

The purposes of my work were the followings:

- 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.

Methods

Different superdisintegrant powders were stored at different humidity conditions for given periods in small containers to absorb water. Nine samples of different water contents from five commercial excipients were prepared for water content and FTIR measurements, thus 45 samples were involved in the investigation. Initial water content of the superdisintegrants was determined by the loss on drying method. The amount of absorbed water was calculated based on weight changes of the samples and measured with analytical balance. At the end of the conditioning of the superdisintegrants, the weights of the samples were measured, then spectral measurements were carried out. ATR-FTIR spectra were collected using a Jasco FT/IR-4200 spectrophotometer with an ATR PRO470-H single reflection accessory (Jasco). 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 on the ATR accessory and the AUC values of spectra between 3700 and 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. Calibration lines were calculated based on these ratios and the measured water contents using linear regression.

Tablets were prepared for screening the efficacy of superdisintegrants. Directly compressible mannitol was used as filler and the applied superdisintegrants were as follows: crospovidone, croscarmellose sodium and sodium starch glycolate. Tablets contained the superdisintegrants at three levels,

i.e. they contained 3, 5, and 7% w/w superdisintegrant. 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. Wetting times of tablets were measured by placing them on the surface of a slice of six-layered paper immersed in 4 ml methylene blue solution using a small glass vessel. Wetting was complete, when water was observable on the whole surface 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. *In vitro* disintegration times of tablets were measured by dropping them into a glass vessel filled with 20 ml water. Complete disintegration took place when no coherent solid portion of the tablet remained.

Tablets were prepared by exploiting the swelling of crospovidone and the phase transition of xylitol. All formulation contained mannitol as filler, milled anhydrous citric acid as flavouring agent, xylitol as melting component and sodium stearyl fumarate as lubricant. Some formulation contained additional fillers. Superdisintegrants were crospovidones, the sodium starch glycolate and the croscarmellose sodium. Different formulation series were successively prepared and compared. 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. Each series was treated using the same procedure. The prepared tablets were stored over saturated NaCl solution in a desiccator in order to absorb water. Tablets were subjected to a temperature of 93 °C for 12 minutes in a drying chamber, which caused partial melting of the xylitol component. *In*

vivo disintegration times of the tablets were determined by a healthy volunteer in a blind randomized order. Complete disintegration was achieved when there was no perceptible solid particle in the mouth.

Tablets were prepared for the *in vitro* determination of disintegration times of ODTs. Excipients for tablet preparations were spray-dried mannitol as filler, sodium stearyl fumarate 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, croscarmellose sodium, and sodium starch glycolate. The first five types of 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. A CT3 texture analyzer (Brookfield Engineering Laboratories) was used for the measurements. Tablets were attached to a cylindrical probe head. The device where disintegration took place consisted of a miniature stainless steel test sieve 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. The volume of the medium was sufficient to create a homogenous fluid layer over the surface of the mesh of the sieve. After starting the measurement, the tablet was moved towards the surface of the disintegration medium. The instrument started to record the load-displacement points (curves) (100 points/mm) with its software (TexturePro CT, Brookfield Engineering Laboratories) as the tablet reached the mesh of the sieve. The endpoint (where the probe got into contact with the mesh) was detectable based on the shape of the load-displacement curves. *In vivo* disintegration times of the tablets were determined by a healthy volunteer in a blind randomized order. Complete disintegration was achieved when there was no perceptible solid

particle in the mouth. In the case of each texture analysis measurement the area under curve (AUC) values were calculated based on the recorded load–displacement curves. 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*. The *k* correction factor was calculated from these angles using the Eq. (1):

$$k = \frac{angle}{105°} \tag{1}$$

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

$$in\ vitro\ DT = \frac{AUC^{n_1}}{k^{n_2}} \cdot c \tag{2}$$

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:

$$c = \frac{in\ vivo\ DT \cdot k^{n_2}}{AUC^{n_1}} \tag{3}$$

A c value belongs to each AUC, *k*, n_1, and n_2 combination in the case of each calibration tablet based on Eq. (3). 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. (3). The *in vivo* DT value of all tablets (T1 - T9) was predicted by Eq. (2) using c_{av} in place of the c value after the determination of the optimum circumstances at the evaluation procedure. After determination of regression equations for the AUC 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. (2) and (3) by changing the independent parameters of the texture analysis method via a mathematical procedure and 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:

$$SSR = \sum_{i=1}^{5}(in\ vivo\ DT_i - in\ vitro\ DT_i)^2 \quad (4)$$

where i was the number of the tablet. The resulted sum of squared residuals function (SSR) was minimized during the optimization procedure since the closer the *in vitro* and *in vivo* disintegration times were, the smaller the SSR became. All nine types of tablets were measured with the texture analyzer using the obtained, optimized settings and the *in vitro* DT values were compared to their *in vivo* values in order to evaluate the efficiency of the optimization.

Hydrogen-bonded polymer complexes were prepared to mask the bitter taste of desloratadine. Desloratadine salt was dissolved in purified water and the pH of the solution was adjusted to 3.6 using 1M HCl solution. Then crospovidone was added to the solution and thick, paste-like suspension was prepared in a metallic bowl using a pestle. Carbopol® solution was prepared

separately with water and their concentrations were set to 0.8% w/w. The suspension was drawn into syringe and it was pumped into the intensively stirred Carbopol® solution using a syringe pump through a silicone tube. The homogenizer was stopped after the addition of the suspension, and the precipitated complex was floated on the solution. The precipitate was dried in a vacuum chamber (60 °C, 150 mbar, 24 h). The dried pieces were milled and the obtained granules were fractionated using a vibratory sieve shaker into the following particle size fractions: <90 μm, 90-180 μm, 180-355 μm, 355-500 μm. The dissolution tests of the hydrogen-bonded polymer complexes were performed in phosphate-citrate buffers according the USP method 2. The released drug was determined spectrophotometrically. The pH-dependency of the release rate of complexes was measured with dissolution tests performed in Erlenmeyer flasks using the 355-500 μm sieve fractions.

Results

- 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 - 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. The dried and milled complex particles had unique pH-dependent dissolution characteristics.

Conclusion

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. 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. Superdisintegrants, one of the most important components of ODT formulations, were characterised in terms of both physico-chemical features and efficiency.

List of original publications

Papers connected to the Ph.D. thesis

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.

Other publications

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