Evaluation of HLB values in drug delivery systems

PhD thesis

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INTRODUCTION

Most active ingredients possess poor water soluble properties and thus, unfavourable bioavailability properties. Therefore, formulating the appropriate drug carrier system for such active ingredients poses a challenge in pharmaceutical technology. Recently, more and more attention is paid to lipid based drug delivery systems and other modern drug systems, such as active ingredient-cyclodextrin complexes or freeze-dried emulsions carrying nanoparticles.

Interest in traditional drug delivery systems grew side by side with research on modified release drug delivery systems and bioavailability studies. The development of homogenization techniques and tools facilitated the production of emulsions with higher dispersion levels, such as micro and nanoemulsions. The properties of these emulsions are more favourable than those of traditional emulsions, and the range of excipients available for their formulation is also increasing.

Surface active substances are often components of dispersed systems. Their dual structural qualities are characterized by a numeral, namely the hydrophile–lipophile balance, or HLB value. HLB value describes the ratio of hydrophilic and lipophilic groups within a surface active molecule. This concept was introduced about 70 years ago by American chemist William C. Griffin. The obtainability of HLB values is beneficial in providing further information about excipients, therefore, an emulgent with the most suitable qualities may be selected for formulating emulsion systems. Griffin's HLB system is widely used even today, despite the fact that it disregards several formulation parameters, such as the concentration of surface active substances, or the most desirable ratio of oil and water in emulsions, or optimal manufacturing temperature. The HLB system raises several issues, especially in determining the HLB values of substances in research. Furthermore, it is controversial that in some emulsion systems there seems to be no connection between HLB value and type of emulsion, and stability.

AIMS

My PhD research was conducted with the following aims:

1. To scrutinize HLB values in emulsion systems:

- Determining the HLB value of paraffin oil, an oil widely known in the literature and chosen as standard. The HLB value of paraffin oil was determined in oil-in-water (O/W) emulsions with Tween® 80 or Gelucire® 44/14 hydrophilic and Span® 80 lipophilic emulgents.
- Analysis of the emulsifying processes of paraffin oil in O/W emulsions formed in a high-pressure homogenizer with emulgents Gelucire® 44/14 and Span® 80, as well as a comparison of the effects of laboratory versus high-pressure homogenizers on HLB value.
- Determining the required HLB value of lemon oil in O/W emulsion systems based on droplet size analysis and turbidimetry measurements.
- Determining the required HLB value of olive oil.

2. Formulation of dry emulsion tablets

- Formulation of dry emulsion tablets with olive oil via lyophilization and compression using various excipients.
- Analysis of reconstituted emulsion systems from dry emulsion tablets through droplet size analysis, turbidimentry measurements and physical tests of tablets.

METHODS

O/W emulsions with paraffin, lemon or olive oil were either produced in a laboratory homogenizer (Miccra D-8, ART Labortechnik, Germany), or a high-pressure homogenizer (EmulsiFlex®-B15, Avestin Inc., Canada). Dry emulsion tablets were produced through lyophillization and compression. Excipients were selected based on viscosity (Kinexus pro rheometer, Malvern Instruments Ltd, UK) and contact angle measurements.

During the process of freeze drying suspension emulsion samples were frozen at -40 °C in a ScanVac CoolSafe™ (100-9 PRO, LaboGene™, Denmark) freeze dryer in 2 hours, and then the temperature of the trays was gradually raised (1 hour: at 15 °C, 1 hour: at 20 °C, 10 hours: at 30 °C, and 10 hours: at 40 °C) to +40 °C to lyophilise the samples in 24 hours.

During the process of compression I compressed 1 gramm tablets in an excenter tablet press (Diaf TM 20, Denmark) loaded manually after adequate homogenizing. Pressure was adjusted to produce 30 N breaking strength biconvex tablets 12 mm in diameter, with an even surface without a score mark.

Required HLB values were determined with droplet size analysis and turbidimetry measurements, in accordance with Orafidiya and Oladimeji's research.

Droplet size analysis

The droplet size of emulsion systems was measured directly after formulating, whereas for reconstituted emulsions it was measured 10 minutes following the dissolving of tablets. Measurements were taken with Mastersizer 2000™ (Malvern Instruments Ltd, UK), and results were evaluated with the Mastersizer 2000 E v. 5.60 software. Apart from cumulative distribution curves (droplet size distribution and cumulative distribution curves), d_{10}, d_{50} and d_{90} values were also evaluated, which suggest that 10, 50 or 90% of particles within a given system are smaller in size than the size determined. Span value, characteristic of distribution width, was also employed, and was calculated using the formula:

$$\text{span-value} = \frac{d_{90} - d_{10}}{d_{50}} \quad (1)$$

Turbidimetry measurements

The following formula was used in evaluating turbidimetry measurements:

$$\text{Turbidity} = 100 - T(\%) \quad (2)$$

Following a period of a week's storage, emulsions split into a clearly distinguishable upper and lower part. Samples from the lower parts of emulsions as well as the cloudiness (T(%)) in the separated lower parts of reconstituted emulsions (24 hours) was measured with UV spectrophotometry (UV2, Unicam Ltd, UK) at 600 nanometres.

The reconstitution of dry emulsion tablets

Both lyophilized and compressed dry emulsion tablets were dissolved and dispersed in 30 mL demineralized water constantly stirred, and of a temperature of 37 ± 2 °C. Reconstitution is a process through which tablets are dispersed in water directly before application, thus, during this process a dispersed emulsion system is formed, or reconstituted. Unlike in the case of lyophilized systems, there is no original emulsion in the case of compressed tablets. Reconstituted emulsions were compared to the olive oil emulsion preceding lyophilization.

Physical tests of tablets

The mass (Sartorius LA 230S, Sartorius AG, Germany) and disintegration (Pharma Test PTZ 3H Tablet Disintegration Tester, Germany) of tablets were measured as well as friability (Erweka TAP, one glass cylinder) and hardness (Erweka TBH 200, Erweka GmbH, Germany) of compressed tablets, whereas in the case of lyophilized tablets moisture balance (Scaltec SMO 01, Scaltec Instruments GmbH, Germany) and texture analysis (Brookfield CT3-4500 Texture Analyser, Brookfield Eng. Labs., Inc., USA) were also performed.

The morphological analysis of dry emulsion tablets was performed with a scanning electron microscope (Inspect™ S50, FEI™, USA).

RESULTS

1. Determining HLB values in emulstion systems

- O/W paraffin oil emulsions were formulated with Tween® 80 - Span® 80, and Gelucire® 44/14 - Span® 80 emulgents, whose droplet size distribution and turbidity were measured. Knowing that the most stable emulsion is characterized with the smallest droplet size and the greatest cloudiness, the results indicated that the required HLB value of paraffin oil in O/W emulsions is HLB=10.

- It was supported by droplet size distribution and turbidity measurements that the required HLB value of paraffin oil is within the threshold limit values set in the literature (HLB=11 ± 1) in the emulgent concentrations examined.
- In comparing O/W emulsions formulated with paraffin oil with different equipments (laboratory and high-pressure homogenizers), it was found that emulsions produced with the laboratory homogenizer were more suitable for required HLB value analysis. Based on the findings it can be concluded that apart from the energy invested in the production of emulsions, the equipment used also greatly influences the required HLB value of the oil.
- With regard to droplet size analysis, based on the HLB value curves it was concluded that the required HLB value of lemon oil in O/W emulsions is HLB=12 ± 1, and the required HLB value of olive oil is HLB=6 ± 1.
- In accordance with the preliminary examination of excipients, it was found that 0.5% concentrations of XG mucilage, 1.5% concentration of emulgents and HLB=6 were the most suitable for formulating dry emulsion tablets. Based on viscosity measurements, a 0.5% XG mucilage, a 22.5% concentration of gum arabic, a 0.7% concentration of hydroxyethyl cellulose and a 12% concentration of hydroxypropyl cellulose were chosen as excipients.

2. Formulating dry emulsion tablets

- Dry emulsion drug delivery systems containing olive oil were produced by lyophilizing O/W emulsions and by compression of a combination of excipients. It was found that compression is a suitable alternative to freeze drying in the manufacturing of dry emulsion tablets. Due to the pressure applied, the size of oil droplets decreased as compared to the original compound.
- Comparisons of structure-forming excipients (mannitol, erythritol and lactose) indicated in both instances that tablets prepared with mannitol possessed the best physical properties.
- Following the dissolution of tablets in water, it was found that the droplet size distribution of emulsions was almost identical to that of the original emulsion, thus, it was concluded that the emulsion was reconstituted or formed from the tablets produced with the two methods mentioned above.

- Based on reconstitution analysis tablets lyophilized with mannitol was found to be the most adequate carrier system for olive oil.

CONCLUSIONS

Most active ingredients have poor water solubility properties during pharmaco-technological use. Therefore, emulsion carrier systems presently have a vital role in increasing the bioavailability of non-water-soluble active ingredients.

During the first phase of my doctoral research I focused on formulating O/W emulsion systems to examine the HLB values of surface active agents and the HLB values of various oils. I found that through an understanding and correct application of the HLB system advantageous characteristics can be incorporated into drug carrier systems. One of the aims of my research was to identify the HLB values of two oils: lemon oil and olive oil. Liquid paraffin was chosen as a reference oil, since its required HLB value is well-known in the literature. Two research methods were employed as the bases of comparison: droplet size analysis of emulsions and turbidimetry measurements for separated systems, since earlier research has proven that the required HLB value of the oil is equal to the derivative HLB value of the emulgents in the system, which is the minimum point of the droplet size distribution versus HLB curve and the maximum point of the turbidity versus HLB curve. I found that the required HLB value of lemon oil in O/W emulsion systems is 12 ± 1 and the required HLB value of olive oil is 6 ± 1.

Due to the instability of emulsions I focused on dry emulsion systems which can help avoid stability issues, since one of the advantages of these dry carrier systems is that the emulsion itself is only formed right before and at the place of its application. Lyophilisation is a well-known and established method for producing such systems. During my research I produced dry emulsions with yet another method, by compression. Mannitol proved to be suitable in producing olive oil containing tablets with both methods. During the reconstitution of emulsions, that is, following the dispersion of tablets in water, the droplet size of olive oil in reconstituted emulsions retained their original droplet sizes, whereas in emulsions from compressed tablets

droplet size decreased. Therefore, apart from lyophilisation, compression might also be an adequate method for producing dry emulsion systems.

LIST OF PUBLICTIONS

1. **Niczinger NA**, Hajdú M, Budai L, Dredán J, Antal I. (2011) Importance of the HLB-value in the drug-technology. Acta Pharm Hung, 81: 151-163.

2. **Niczinger NA**, Kállai-Szabó N, Dredán J, Budai L, Hajdú M, Antal I. (2015) Application of droplet size analysis for the determination of the required HLB of lemon oil in O/W emulsion. Curr Pharm Anal, 11:11-15.

3. **Niczinger NA**, Kállai-Szabó B, Lengyel M, Gordon P, Klebovich I, Anal I. (2017) Physicochemical analysis in the evaluation of reconstituted dry emulsion tablets. J Pharm Biomed Anal, 134:86-93.