Drug release stability of polymer matrices

Ph.D. thesis

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Introduction

The rate and the kinetic profile of drug release are determined by the physical and chemical attributes of the formulation and also by the physiological media. The drug release of the delivery system can be designed by the application of suitable inactive ingredients and dosage form, and the chosen manufacturing process. Based on these an appropriate pharmaceutical formulation can be produced for the attributes of API and the therapeutic target.

Polymers are widely used as excipients and delivery and also packaging material of dosage forms in the modern pharmaceutical technology. Application of such materials in drug products requires long-term stability. However, the most frequently used polymers are in a non-equilibral state, certain transformations may occur as a result of the environmental effects that can cause structural changes in the material. The changes of the stability of excipients may influence the stability of the formulation and consequently the rate and the kinetic profile of drug release. Therefore the bioavailability of the product can also be altered.

Examination of the functional attributes of polymeric excipients can be performed by long-term storage experiments and by applying the combination of certain physical-chemical methods. Recently not enough attention is being dedicated by the Pharmacopoeias (Ph.Eur., Ph.Hg.VIII. and USP) to such investigations. The chemical stability of the API and the physical changes of the formula are generally monitored during stability studies. In case of polymer based delivery systems the monitoring of the physical-chemical interactions between the polymer and the API is of great importance. Besides the primary chemical interactions the secondary bonds can also be studied during the preformulation of the API-polymer system in order to predict the alteration of API's diffusion of the dosage form.

Aims

The aim of my work was:

- Selection of polymer excipients for modified release formula,
- Preparation of modified release tablet formulations,

- Examination of the physical ageing of the polymer formulation during stress storage conditions,
- Performing dissolution test of stored matrices and comparison of *in vitro* dissolution curves,
- Find relation between the supramolecular changes and the alteration of drug release kinetics of various matrices.

Questions during my work:

- How does the physical stability of the API-polymer system change under stressed storage conditions,
- How does the alteration depend on the physical-chemical attributes of the API and the polymer,
- How does the alteration depend on the secondary bonds formed between API and the polymer,
- How does the micro structural alteration influence the stability of drug release?

Methods

Metronidazole (Unichem Laboratories Ltd.) and famotidine (Gedeon Richter) were used as model drugs. Carbopol 71G (Noveon), a granulated form of carbomer in use of direct compression formulations, two kinds of vinylpyrrolidone-type polymers: Povidone (Hungaropharma) and Kollidon SR (BASF Chem Trade GmbH), which is a spray dried physical mixture of polymers polyvinyl acetate and povidone in the ratio of 8:2 were used as hydrophilic matrix forming agent, Avicel 101 (FMC) as an inert crystalline ingredients and magnesium stearate (Hungaropharma Ltd., Budapest, Hungary), as a lubricant for the formulation of matrix tablets.

Matrix tablets were prepared, each containing 30 mg API (metronidazole or famotidine) 30 mg Kollidon or Povidone or Carbopol, 119.2 mg Avicel and 1.8 mg Magnesium Stearate (1 %) as a lubricant. After weighing and homogenizing the components, tablets were directly compressed with a Diaf type (Denmark) single punch press.

1:1 physical mixtures of the API and hydrophilic polymers were used for the FT-IR and PALS analysis.

Samples of the tablets and powder mixtures were stored in closed containers at 40 ± 2 °C and 75 ± 5 % relative humidity for 1, 2 and 4 weeks.

Dissolution tests of the tablets were carried out in a Hanson SR8-Plus (Hanson Research, USA) type dissolution tester. The temperature of the dissolution fluid was 37 ± 1°C and the rotation speed was 75 rpm, using rotating paddles. The tests were made with two different dissolution mediums: 900 ml of a buffer of pH1.2 and 900 ml of a buffer of pH6.8. Samples were taken at predetermined time points with AutoPlus Maximizer system and an Auto Plus MultiFill type collector (Hanson Research, USA). The sample volume was 10 ml, which was replaced each time with the equivalent amount of the dissolution medium. The active content of the samples was determined with an Auto Plus On-Line UV/VIS Autosamples spectrophotometer at 277 nm (pH1.2) and 320 nm (pH6.8) in case of metronidazole, and at 266 nm (pH1.2) and 274 nm (pH6.8) in case of famotidine.

The drug release characteristics of the examined formulations were evaluated using the following models. For this, Solver function of Microsoft Excel 2002 was used.

- Zero order model

The drug release from the dosage form follows a 'steady-state release', running at a constant rate:

$$M_t/M_\infty = kt \qquad (1)$$

where M_t is the amount of drug released at time t, M_∞ is the maximal amount of the released drug at infinite time, k is the rate constant of drug release.

- First order model

The drug activity within the reservoir is assumed to decline exponentially and the release rate is proportional to the residual activity:

$$M_t/M_\infty = 1 - \exp(-kt) \qquad (2)$$

- Semi empirical model proposed by Ritger and Peppas

$$M_t/M_\infty = K\,t^n \qquad (3)$$

where M_t/M_∞ is the fraction of drug release at time t, K is a constant incorporating the structural and geometric characteristics of the release device, and n is the release exponent indicating the type of the drug release mechanism. If n approaches 0.5, the

release mechanism can be considered Fickean, while if n is close to l, the release mechanism can be zero order. n values between 0.5 and 1 indicate non-Fickean processes.

- Higuchi square root time model

The most widely used model to describe drug release from matrices, derived from Higuchi for a planar matrix, however, it is applicable for systems of different shapes, too:

$$M_t/M_\infty = K\, t^{1/2} \qquad (4)$$

Mathematical comparison of the drug release profiles before and after storage was carried out by calculating the difference (f_1) and similarity (f_2) factors:

$$f_1 = \{[\Sigma_{t=1}^{n} | R_t - T_t |]/[\Sigma_{t=1}^{n} R_t]\} \times 100 \qquad (5)$$

$$f_2 = 50 \times \log \{[1+(1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0,5} \times 100\} \qquad (6)$$

where n is the number of time points, R is the dissolution value of the reference sample at time t (here the sample before storage), and T is the dissolution value of the test sample at time t (here the sample stored for 4 weeks). For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values up to 15 (0–15) and f_2 values greater than 50 (50–100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference samples.

The physical mixtures and the pure substances were diluted with crystalline potassium bromide (sample:KBr=1:200) and compressed at 7 t for 2 min on KBr press and the spectra scanned over wavenumber range of 4000-400 cm^{-1} in transmission mode using a JASCO FT/IR-4200 (Jasco, Japan) spectrometer. 16 scans were performed at a resolution of 4 cm^{-1}.

The computer capacity was not enough to consider very large polymer molecules. Thus, each polymer was represented by a small segment of the polymeric chain, i.e., by a two-monomer unit. As Kollidon SR is not a pure polyvinylpyrrolidone, the polyvinyl acetate segments of the polymer were also studied. The GAUSSIAN computer code was used for the calculation. The DFT method and the basis set of 6-

31G** were used to determine optimum geometries and energies. All of the calculations were performed for the vacuum-states of molecules. Therefore the calculations give only a hint (however strong) for the circumstances in an aqueous solution.

A positron source made of carrier-free ^{22}NaCl was used for positron annihilation lifetime spectroscopy (PALS) measurements of famotidine containing samples. The activity of source was around 10^5 Bq and the active material was sealed between two very thin Kapton foils. Lifetime spectra were measured with a fast-fast coincidence system based on BaF_2 detectors and Ortec electronics. The time resolution of the system was about 200 ps. The spectra were first evaluated by the RESOLUTION computer code. However, the discrete evaluation has revealed only minor changes. Thus, a variation of the MELT code was used to extract lifetime distributions from the spectra.

For Doppler-broadening measurement, a high purity germanium detector was used with Canberra electronics. The annihilation photo peak contained about 10^6 counts in each case. The energy resolution of the system was around 1.1 keV at 511 keV.

Results

- Non-invasive microstructural examination methods and *in silico* methods were combined to evaluate the alteration of drug release (metronidazole and famotidine) from hydrophilic polymer matrices.
- The changes of the drug release profiles were tracked by the alteration of the supramolecular structures.
- Based on the calculations, the metronidazole molecule was able to form strong hydrogen bonds with the Carbopol chains. Due to the interaction between the polymer and the drug, the drug embedded in the polymeric matrix hindered the polymer expansion, thus the erosion provided immediate drug release. In acidic medium the swelling of Carbopol was incomplete which resulted in prompt release. The interaction between metronidazole and povidone or Kollidon SR polymers is much weaker thus the rate of drug release was not changed during storage time. The adsorbed water did not remarkably influence the drug-polymer interaction as well.
- In the case of famotidine tablets the drug release of Carbopol base matrices can be considered stable in the course of storage, which was confirmed by PALS

and FT-IR examinations and *ab initio* calculations, as well. The latter can be explained by the low binding energy of the H-bonds between famotidine and Carbopol, thus the water uptake did not cause any structural changes associated with breaking the secondary bonds. Based on the *ab initio* calculations the famotidine can form extremely strong H-bonds with Kollidon SR polymer. However, the formed bonds had no effect on the swelling of polymer, thus sustained drug release was obtained and possibly complex formation occurred, which further delayed the drug release.

Conclusion

1. In order to predict the drug-release stability from polymer deliveries the examination of hydration of API and polymer and the study of binding energy of the formed H-bonds is suggested.

2. The *ab initio* calculation of the formed secondary bonds between API and water; polymer and water and also between API and polymer can provide information about drug release from polymer matrices in aqueous medium.

3. The changes in the supramolecular structure of polymeric delivery systems during storage can be investigated by positron annihilation lifetime spectroscopy.

4. The combination of *in vitro* drug release studies with *ab initio* calculations and supramolecular examinations could predict the possible structural changes caused by the generated secondary bonds. These can provide information already during short term stability tests on the consistency of the API's diffusion of the dosage form.

Practical use:

- Alteration of the kinetics of processes based on diffusion (solution, crystallization, water uptake and swelling) can be predicted by tracking the changes in the supramolecular structure of active delivery systems. These processes are crucial to the functionality of modified release dosage systems.
- In the development phase, during the stability studies of hydrophilic polymer-containing delivery systems, not only the amount of API released in one sampling point, and which is determined in the planned drug product specification, is informative, but recording the entire dissolution profile may be necessary as well, which facilitates the understanding of the possible change in the supramolecular structure of the system. If the basis of the comparison of samples stored under different conditions is only the amounts of API dissolved in the certain sampling point, then no change can be observed in the systems containing small amount of polymer, however, the kinetic change can be detected by recording the entire dissolution profile.
- The composition can be optimized by sorting out the inactive ingredients that underwent anomalistic structural alterations.

List of original publications

Publications connected to the Ph.D. thesis

1. **Szente V**, Süvegh K, Marek T, Zelkó R. (2009) Prediction of the stability of polymeric matrix tablets containing famotidine from the positron annihilation lifetime distributions of their physical mixtures. J Pharm Biomed Anal, 49: 711–714.

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10. Zelkó R, **Szente V**. Characterization of novel polymeric materials from the point of their physical ageing. In: Hincal A, Çelebi N, Yüksel N. (Ed.) New Progresses and Challenges in Pharmaceutical Sciences. Part 4: Biotechnology, Delivery of Biologics and Vaccination. 3rd BBBB International Conference on Pharmaceutical Sciences, Antalya, 2009: 208-216. ISBN 978-975-01193-1-6

11. Zelkó R, **Szente V**. (2009) Characterization of novel polymeric materials from the point of their physical ageing. Eur. J. Pharm. Sci. 38: 38.