# Prediction of the stability of polymeric matrix tablets containing famotidine from the positron annihilation lifetime distributions of their physical mixtures

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## ARTICLE INFO

## ABSTRACT

The aim of the present work was to elucidate the impact of the structural changes of polymeric excipients during the course of storage on the drug release stability of tablets containing different polymers. Matrix tablets were formulated with famotidine as a model drug, using polyvinylpyrrolidone and carbopol matrix. Dissolution tests were carried out before and after storing the tablets under stress conditions for different time intervals. Parameters characterizing the release kinetics of matrix tablets, just as difference and similarity factors, were calculated to compare the release profiles as a function of storage time. Positron annihilation lifetime measurements were carried out to track the structural changes of the physical mixtures containing polymers during the course of storage. The changes in the positron lifetime distribution curves of the famotidine-polymer mixtures were in good correlation with the significant changes of release parameters of tablets. Thus the method would be a valuable tool for the screening of possible destabilizing interactions in the preformulation phase.

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## 1. Introduction

Polymers are widely used in pharmaceutical technology for a diversity of purposes. They are applied as fillers, binders, matrix-forming and film-forming excipients in solid dosage forms and most of the gelling agent of semisolid preparations and solutions are polymers, too.

Although the chemical structures and compositions of polymers applied vary enormously, their physical state is usually similar, as most of them are amorphous or partly amorphous. Such materials might undergo serious physical ageing, which is usually accompanied by volume and enthalpy relaxation and, thus, might result in severe structural changes in the polymer. The enhanced molecular mobility, caused by the plasticization effect of absorbed water, has been proposed to be the major underlying factor in chemical and physical instability of amorphous pharmaceutical materials [1,2]. As amorphous or partly amorphous polymers are not in equilibrium below their glass transition temperature, they usually undergo spontaneous, however slow transformations towards

low-energy equilibrium states [3]. Sometimes common gases (as $CO_2$) or the natural humidity of air can initiate these processes and the plasticization effects of these materials are enough to change the crystallinity or the $T_g$ of the polymer significantly [4]. Structural changes, i.e. a transition from glassy to rubbery state could be observed even after a short storage time (4 weeks), which highlights the importance of further investigations of the effects of physical ageing on the properties of dosage forms containing amorphous polymers. Studies have shown that polymers used in solid dispersions (like povidone) can inhibit the crystallization of drugs resulting in an amorphous form of the drug in the solid dispersions [5,6]. The mechanism of crystallization inhibition by povidone is often due to specific interactions, especially hydrogen-bonding between the drug and the polymer. The effect of physical ageing on the drug release behaviour of several polymers and lipids was studied and can be found in the literature [7–11].

The purpose of the present study was to illustrate the effect of the absorbed water on the free volume distribution of the physical mixtures of amorphous polymers and famotidine during storage. Another aim was to compare the free volume changes of the physical mixtures tracked by positron annihilation lifetime measurements with the drug release parameters of matrix tablets containing the same polymeric excipients.

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## 2. Materials and methods

### 2.1. Materials

Famotidine al. op. from Richter Gedeon Plc. (batch number: K37050N) was used as an active ingredient. Avicel PH101 from FMC (batch number: G312C), Carbopol 71G NF from Noveon (batch number: TW56GA 5066), Kollidon SR from BASF Chem Trade GmbH (batch number: 530206) and magnesium stearate from Hungaropharma (batch number: 0705 1207) were used as excipients in the formulation of the tablets.

### 2.2. Methods

#### 2.2.1. Sample preparation

Two kinds of tablets (formulation 1 and 2) were prepared from the following compositions:

- Composition 1: 30 mg famotidine, 30 mg Carbopol 71G NF, 119.2 mg Avicel PH101, 1.8 mg magnesium stearate.
- Composition 2: 30 mg famotidine, 30 mg Kollidon SR, 119.2 mg Avicel PH101, 1.8 mg magnesium stearate.

After weighing and homogenizing the components thoroughly in a mortar, tablets of 8 mm in diameter were directly compressed with a Diaf type (Denmark) single punch press at constant compression force. Avicel PH101 a crystalline powder was selected for the formulation due to its good compressibility and structural stability.

#### 2.2.2. Storage condition

Samples of the two kinds of tablets were stored at $40 \pm 2\,^{\circ}\mathrm{C}$ and $75 \pm 5\%$ relative humidity for 1, 2 and 4 weeks. Dissolution tests were carried out directly after the storage intervals had expired.

#### 2.2.3. Dissolution tests

Dissolution tests of the tablets were carried out in a Hanson SR8-Plus (Hanson Research, Chatsorth, USA) dissolution tester. The temperature of the dissolution fluid was $37 \pm 1\,^{\circ}\mathrm{C}$ and the speed rotation was 75 rpm, using rotating paddles. The tests were made with two different dissolution mediums: 900 ml of buffer pH 1.2 (0.1 N HCl) and 900 ml of buffer pH 6.8 (34 g $KH_2PO_4$ and 4.7 g NaOH in 5000 ml). Samples were taken at predetermined time points with AutoPlus Maximizer system and an Auto Plus MultiFill collector (Hanson Research, Chatsorth, USA). The sample volume was 10 ml, which was replaced each time with the equivalent of dissolution medium. The active content of the samples was determined with an Auto Plus On-LineUV/VIS Autosamples spectrophotometer at 266 nm (pH 1.2) and 272 nm (pH 6.8) on the basis of a calibration curve recorded earlier. The relationship between the absorbance and concentration of the active material was found to be linear between 3 and 30 µg/ml with a correlation coefficient of 0.9996.

#### 2.2.4. Data analysis
##### 2.2.4.1. Model independent evaluation.
In order to see whether the dissolution curves of the matrices stored for different time intervals could be considered similar, difference $(f_1)$ and similarity $(f_2)$ factors proposed by Moore and Flanner [12] and implemented by FDA CDER were calculated according to the following equations:

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100 \tag{1}$$

$$f_2 = 50 \times \log \left\{ \left[ 1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \tag{2}$$

where $n$ is the number of time points, $R$ is the dissolution value of the reference (prechange) batch (here the sample before storage) at time $t$, and $T$ is the dissolution value of the test (postchange) batch at time $t$. 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 equivalence of the two curves and, thus, that of the performance of the test (postchange) and reference (prechange) products (FDA CDER, 1997).

##### 2.2.4.2. Positron lifetime measurements.
This method measures the size distribution of free volumes in polymers.

For that, it applies positrons. The positron source applied for the measurements was made of carrier free $^{22}$NaCl of the activity of 105 Bq. The active sodium chloride was sealed between two very thin (2 µm) kapton foils. The source was then placed between two pieces of polymeric mixture treated identically before. Positron lifetime spectra were recorded by a conventional fast–fast coincidence system. The system was constructed from standard ORTEC electronic units and the detectors from $BaF_2$ scintillator crystals and XP2020Q photomultipliers. The time resolution of the system was about 200 ps. The spectra were first evaluated by the RESO-LUTION [13] computer code. Four lifetime components could be found in each case among which the two longest were identified as positronium lifetimes.

However, the discrete evaluation has revealed only minor changes. Thus, a variation of the MELT [14] code was used to extract lifetime distributions from the spectra. This latter kind of evaluation gave a more detailed view of the changes, so, it was used to characterize the size distribution of free volume holes in the samples using o-Ps lifetimes.

## 3. Results and discussion

Fig. 1 represents the drug release profile of famotidine tablets containing Carbopol as a function of storage time under different pH values. As it was expected, the pH value of the dissolution medium influenced the kinetic profile of famotidine release. The fast first order release at pH 1.2 indicates that the drug release is determined by the intrinsic dissolution of famotidine in acidic medium, while at pH 6.8 the extent and rate of drug release is influenced by the diffusion of the drug through the polymeric matrix.

In the case of Carbopol 71G NF the original polymeric structure remained intact during the storage, although the o-Ps lifetime distributions shifted towards the shorter lifetime values, indicating a smaller and smaller free volume as the ageing process went on (Fig. 2). However, the change in the free volume did not influence the viscoelastic behaviour of the polymer and the drug release stability of tablets (Table 1). Note that the lifetime distribution might not reveal the real free volume distribution in this case. The system is quite complex: a mixture of two materials having lifetime distributions with peaks close to each other. However, the slow shifting
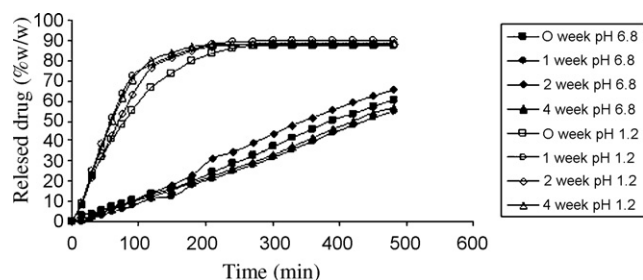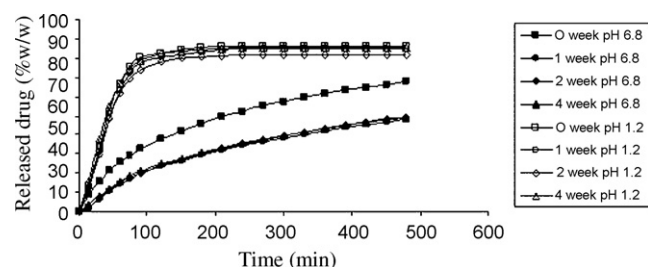


**Fig. 1.** Drug release profiles of famotidine matrix tablets containing Carbopol 71G NF.

**Table 1**
Difference ($f_1$) and similarity ($f_2$) factors of the two compositions.

| Composition | Factors | pH | Compared dissolution after different storage intervals (weeks) | | |
|---|---|---|---|---|---|
| | | | 0–1 | 0–2 | 0–4 |
| 1 | $f_1$ | 1.2 | 8.65 | 3.64 | 6.72 |
| | | 6.8 | 14.41 | 13.19 | 8.37 |
| | $f_2$ | 1.2 | 61.38 | 74.95 | 62.85 |
| | | 6.8 | 72.36 | 72.09 | 81.75 |
| 2 | $f_1$ | 1.2 | 3.03 | 5.70 | 0.28 |
| | | 6.8 | 34.70 | 33.15 | 32.63 |
| | $f_2$ | 1.2 | 84.23 | 71.05 | 93.86 |
| | | 6.8 | 45.43 | 46.30 | 41.60 |

towards shorter lifetimes (i.e. smaller free volume holes) is a real effect.

The picture is quite different in the case of Kollidon as applied as a carrier for famotidine (Figs. 3 and 4). For this carrier, it is clearly visible from Fig. 4 that the *o*-Ps lifetime distribution is continuously changing due course of storage. At the beginning, a completely disordered structure forms, indicated by the wide peaks of the lifetime distribution curve. However, the peaks become narrower, as the ageing process develops. This can be attributed to the water absorption properties of Kollidon. The pyrrolidone rings of the Kollidon SR macromolecule are able to move closer to each other in a hydrated solid state of, allowing the water molecule to use



**Fig. 3.** Drug release profiles of famotidine matrix tablets containing Kollidon SR.
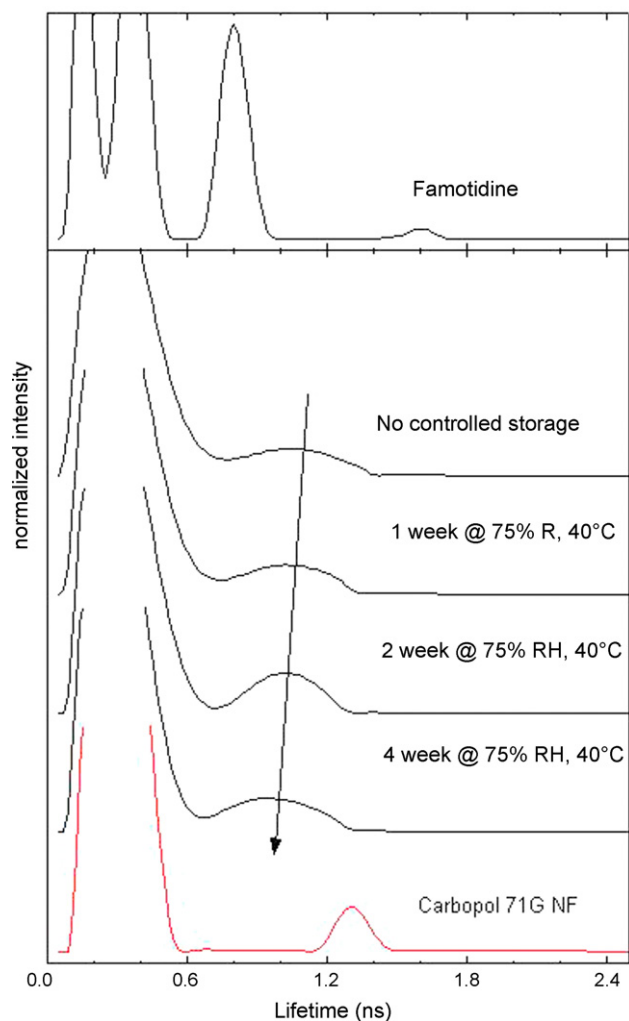


**Fig. 2.** The effect of storage conditions on the positron lifetime distribution in famotidine:Carbopol 71G NF 1:1 physical mixture.
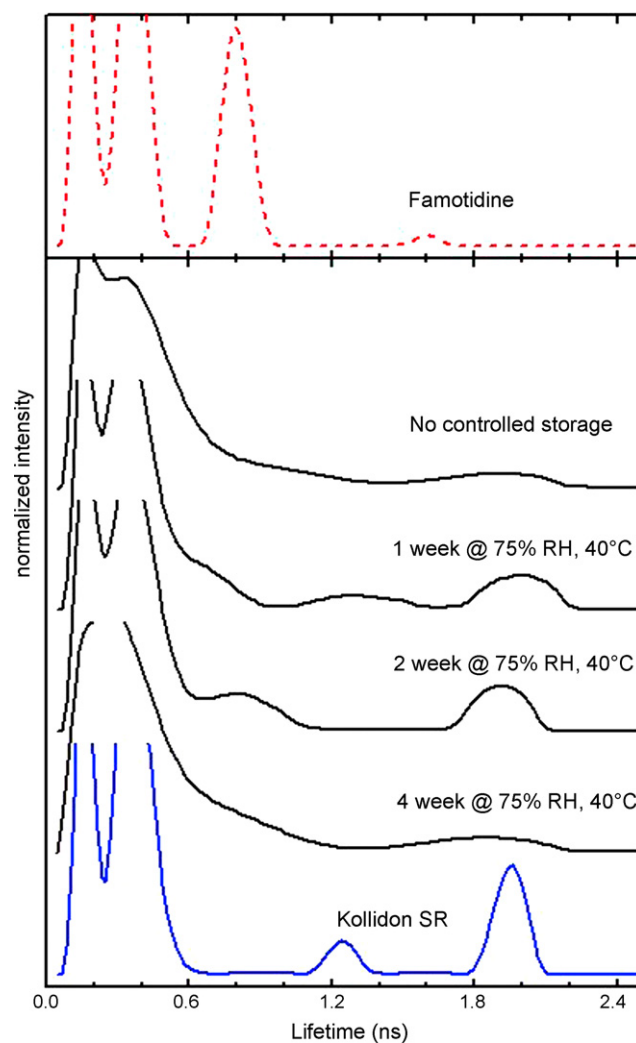


**Fig. 4.** The effect of storage conditions on the positron lifetime distribution in famotidine:Kollidon SR 1:1 physical mixture.

both its proton-donating vacancies to form two hydrogen bonds simultaneously with neighboring Kollidon SR repeat unit [15]. The formation of such intermolecular hydrogen bonds becomes only possible at relatively large degrees of hydration. As the chains of Kollidon SR becomes "networked" by water molecules, the structure becomes more ordered and, so, free volume holes more uniform (Fig. 4, 2 weeks). However, the formed water bridges fix the distance between polymeric chains only temporarily. A longer exposure of Kollidon SR to water leads to different structures with a less ordered structure. The widening of the lifetime distribution after a 4 weeks storage period suggests that a large fraction of "crosslinks" was ruined by excess water molecules [11]. Note that, according to our results, the drug, famotidine has not changed during the ageing study. Thus, any change should be attributed to the carrier, in this case, to Kollidon. The anomalous structural transition of Kollidon SR, tracked by the free volume structure, resulted in changes in the viscoelastic properties of the polymer. This influenced the extent and rate of drug release, which was confirmed by the difference and similarity factors of the formulated tablets (Table 1). Difference and similarity factors summarized in Table 1 indicate that the dissolution curve of tablets containing Kollidon SR (composition 2) cannot be considered equivalent with the original sample even after 1-week storage.

## 4. Conclusions

Classic drug release measurements were combined with positron annihilation measurements. According to the results, the positron annihilation lifetime method can not only be recommended as a sensitive tool for stability tests but for compatibility studies under ambient temperature, as well. The latter is of a great interest from the point of view of preformulation of pharmaceutical dosage forms containing polymeric excipients.

## References

[1] J.M.G. Cowie, R. Ferguson, Polymer 34 (1993) 2135–2141.
[2] B.C. Hancock, G. Zografi, J. Pharm. Sci. 86 (1997) 1–12.
[3] J.H. Guo, J. Pharm. Sci. 83 (1994) 447–449.
[4] K. Süvegh, R. Zelkó, Macromolecules 35 (2002) 795–800.
[5] M. Yoshioka, B.C. Hancock, G. Zografi, J. Pharm. Sci. 84 (1995) 983–986.
[6] R. Nair, S. Gonen, S.W. Hoag, Int. J. Pharm. 240 (2002) 11–22.
[7] M. Lovrecich, F. Nobile, F. Rubessa, G. Zingone, Int. J. Pharm. 131 (1996) 247–255.
[8] A.S. Vincente, R.M. Hernandez, A.R. Gascón, M.B. Calvo, J.L. Pedraz, Int. J. Pharm. 208 (2000) 13–21.
[9] N.A. Nafee, F.A. Ismail, N.A. Boraie, L.M. Mortada, Int. J. Pharm. 264 (2003) 1–14.
[10] R. Zelkó, K. Süvegh, Eur. J. Pharm. Sci. 24 (2005) 351–354.
[11] R. Zelkó, Á. Orbán, K. Süvegh, J. Pharm. Biomed. Anal. 40 (2006) 249–254.
[12] J.W. Moore, H.H. Flanner, Pharm. Technol. 20 (1996) 64–74.
[13] P. Kirkegaard, M. Eldrup, O.E. Morgensen, N. Pedersen, J. Comput. Phys. Commun. 23 (1981) 307–338.
[14] A. Shukla, M. Peter, L. Hoffmann, Nucl. Instrum. Methods A 335 (1993) 310–325.
[15] R. Zelkó, Polym. Degrad. Stabil. 87 (2005) 355–359.