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# Prediction of the drug release stability of different polymeric matrix tablets containing metronidazole

Virág Szente[a,b], Ferenc Baska[c], Romána Zelkó[b,*], Károly Süvegh[d]

[a] Gedeon Richter Plc., Formulation R&D, Gyömrői Str. 19-21, H-1103 Budapest, Hungary
[b] University Pharmacy Department of Pharmacy Administration, Semmelweis University, Hőgyes Endre Str. 7-9, H-1092 Budapest, Hungary
[c] Cooperation Research Centre, Semmelweis University, Rippl-Rónai Str. 37, H-1062 Budapest, Hungary
[d] Laboratory of Nuclear Chemistry, Eötvös Loránd University/HAS Chemical Research Center, P.O. Box 32, 1518 Budapest 112, Hungary

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ABSTRACT

The aim of the present study was to predict the structural changes of polymeric excipients in the course of storage causing undesired changes in drug release stability of tablets containing different polymers. Matrix tablets were formulated with metronidazole as a model drug, using polyvinylpyrrolidone and carbopol as matrix materials. 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. FT-IR measurements were carried out to track the structural changes of the physical mixtures of metronidazole and polymers during storage. The changes of the characteristic peaks of the FT-IR spectra of metronidazole-polymer mixtures were in good correlation with the significant changes of release parameters of tablets. The latter was confirmed by *ab initio* calculations. The work showed that the combination of *ab initio* calculations with structural examinations could predict the possible instability of drug release and, thus, enables the screening of polymeric excipients of undesired physical stability.



## 1. Introduction

The main factors determining the drug release properties of a dosage form based on a hydrophilic polymer – are the swellability and erosibility of the polymeric matrix, as well as the diffusibility of drug molecules in the matrix. Swellability and the erosibility of the matrix depend on the hydration tendency of the polymer and the interaction between polymer molecules [1–3]. In the case of amorphous or partly amorphous polymers, this latter property can strongly be influenced by a phenomenon known as physical ageing. As such polymers are not in equilibrium below their glass transition temperature, they usually undergo spontaneous, although slow, transformations towards low-energy equilibrium states. The natural humidity of air initiates these processes and the plasticization effects of water and $CO_2$ are enough to change the crystallinity or the glass transition temperature of the polymer significantly [4–7]. Here we report the possible changes in the drug release behavior of this polymers caused by storage, and the effects of different polymer-binding ability and hydration tendency. Matrix tablets were formulated using different hydrophilic polymers, and dissolution tests were carried out before and after storing the dosage forms under stress conditions for different time intervals. The purpose of the present study was to illustrate the effect of the absorbed water on the FT-IR spectra of the physical mixtures of amorphous polymers and an anti-infective drug, the metronidazole, during storage. Another aim was to compare the changes of the characteristic FT-IR peaks of the physical mixtures with the drug release parameters of matrix tablets containing the same polymeric excipients. Polymer–drug, polymer–water and drug–water interactions possibly taking place during storage were modeled by means of computer simulation. The aim of this part of the work was to find structures having been formed by the polymers and metronidazole molecules by means of hydrogen bonds. As the formation of such complexes might prevent the release of the drug, their formation energies (together with the hydration energy of the drug) provide significant information on the drug release properties of a drug from a given formula.

## 2. Experimental

### 2.1. Materials and methods

Metronidazole (Unichem Laboratories Ltd., Maharashtra, India) was used as a model drug, Avicel 101 (FMC) as an inert crys-

* Corresponding author. Tel.: +36 1 2170927; fax: +36 1 2170927.
*E-mail address:* zelrom@gytk.sote.hu (R. Zelkó).

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talline ingredient, Carbopol 71G (Noveon) a granulated form of carbomer in use of direct compression formulations, two kinds of vinylpyrroldone-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, and magnesium stearate (Hungaropharma Ltd., Budapest, Hungary) as a lubricant for the formulation of matrix tablets.

### 2.2. Tablet preparation

Three kinds of tablets were prepared, each containing 30 mg Metronidazole, 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 thoroughly in a mortar, tablets were directly compressed with a Diaf type (Denmark) single punch press at constant compression force.

### 2.3. Storage conditions

Samples of the three kinds of tablets and powder mixtures for FT IR analysis were stored in closed containers at 40 °C ± 2 °C and 75% ± 5% relative humidity for 4 weeks.

### 2.4. Dissolution tests

Dissolution tests of the tablets were carried out in a Hanson SR8-Plus (Hanson Research, Chatsworth, USA) type dissolution tester. The temperature of the dissolution fluid was 37 ± 1 °C and the speed rotation was 75 rpm, using rotating paddles. The tests were made with two different dissolution mediums: 900 ml of a buffer of pH 1.2 and 900 ml of a buffer of pH 6.8. Samples were taken at predetermined time points with AutoPlus Maximizer system and an Auto Plus MultiFill type collector (Hanson Research, Chatsorth, USA). The sample volume was 10 ml, which was replaced each time with the equivalent 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 (pH 1.2) and 320 nm (pH 6.8) on the basis of a calibration curve recorded earlier.

### 2.5. Comparison of the dissolution curves

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 according to Eqs. (1) and (2) proposed by Moore and Flanner [8] and implemented by FDA CDER.

The two factors are:

$$f_1 = \frac{\sum_{t=1}^{n'} ||R_t - T_t||}{\sum_{t=1}^{n'}} \times 100 \quad (1)$$

$$f_2 = 50 \times \log \sqrt{\left(1 + \frac{\sum_{t=1}^{n'} (R_t - T_t)^2}{n'}\right)} \times 100 \quad (2)$$

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.

### 2.6. Computer simulations

The computation capacity available to us 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. For the calculations, the GAUSSIAN computer code was used [9]. The DFT (density functional theory) 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.

Different initial geometries and constitutions were probed but only those are given which provided positive binding energies. To determine hydration energies, we have always considered a single water molecule and considered the result as the representation of the effects of water on the given molecule.

### 2.7. FT-IR spectroscopy

1:1 physical mixtures of metronidazole and the excipients were prepared by their mass and then mixed thoroughly for 5 min in a mortar. The obtained mixtures were stored at 40 ± 2 °C, 75% relative humidity (achieved by oversaturated NaCl solution) for 4 weeks.

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 spectrometer. 16 scans were performed at a resolution of 4 $cm^{-1}$.

## 3. Results and discussion

Figs. 1–3 represent the drug release profiles of metronidazole from different polymeric matrix tablets after 1, 2 and 4 weeks of storage at pH 1.2 and 6.8. As it was expected, the pH value of the dissolution medium influenced the kinetic profile of metronidazole release. The fast first order release at pH 1.2 indicates that the drug release is determined by the intrinsic dissolution of metronidazole 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. The kinetics of the dissolution was found similar by the two kinds of vinylpirrolidon-type polymers.

Significant difference was found after 2 weeks of storage by carbopol-based metronidazole tablets at pH 6.8. Difference and similarity factors summarized in Table 1 indicating that the dissolution curve of tablets containing Carbopol cannot be considered equivalent with the original sample after 2 weeks storage.

Fig. 4 illustrates the FT-IR spectra of different polymers and metronidazole. Characteristic peaks could be observed in each polymer at near to 3000 $cm^{-1}$ which could be attributed to the presence of water in the hydrophilic polymers. Characteristic peaks of carbopol at 1710 $cm^{-1}$, 1171 $cm^{-1}$ and 1114 $cm^{-1}$ wavenumbers were found to refer to the carbonyl group. These peaks were shifting in the metronidazol–carbopol mixtures. Characteristic peaks were found similar by the two kinds of vinylpyrrolidon-type polymers: CH-stretch at 2954 or 2966 $cm^{-1}$ and carbonyl amid at 1662 $cm^{-1}$ or 1664 $cm^{-1}$. Only new peaks appeared by Kollidon SR at 1741 $cm^{-1}$, 1238 $cm^{-1}$ and 1021 $cm^{-1}$ indicating the presence of ester carbonyl groups in the copolymer.

A broad hydroxyl absorption band was found at 3220 $cm^{-1}$ by metronidazol, and many peaks between 1535 $cm^{-1}$ and 1367 $cm^{-1}$ indicating the presence of $NO_2$ group. The OH stretch peak loses it characteristic shape in the case of metronidazole–carbopol

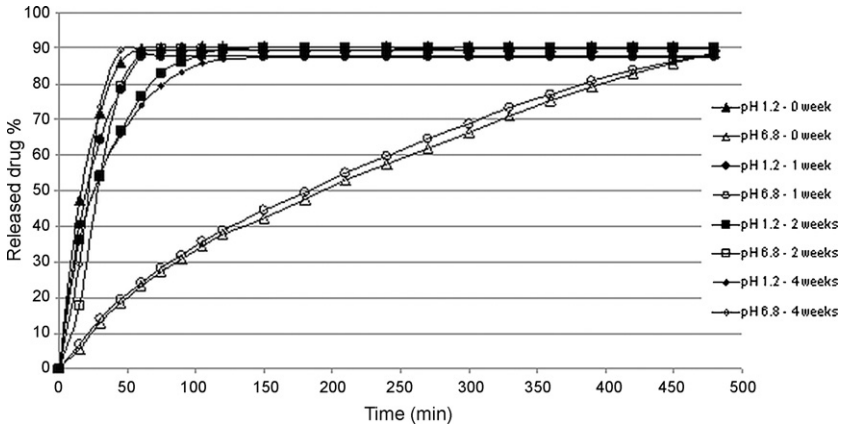


**Fig. 1.** Drug release profiles of Carbopol matrices containing metronidazole.

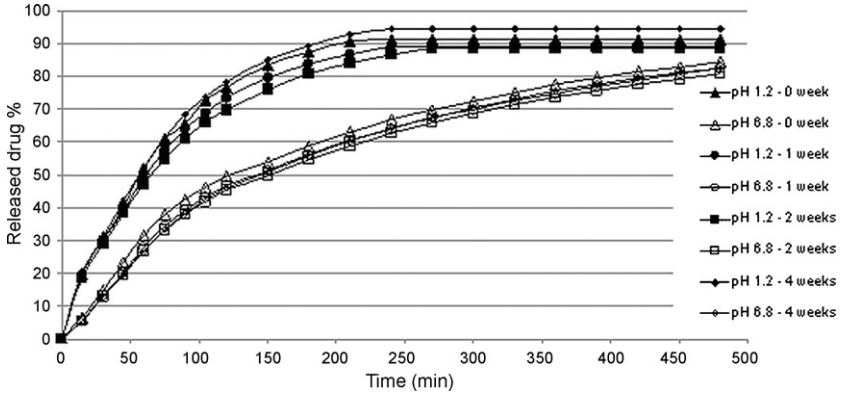


**Fig. 2.** Drug release profiles of Kollidon SR matrices containing metronidazole.

mixtures along with storage (Fig. 5). The FT-IR spectra of the metronidazole–vinylpyrrolidone mixtures were not changed significantly as a function of storage. The results of *ab initio* calculations confirmed the above phenomenon.

The performed *ab initio* calculations showed that all of the polymer segments and the metronidazole molecule are able to form hydrogen bonds with water. However, none of these bonds proved to be extremely strong. The energies calculated for the hydrogen bonds varied between 30 and 45 kJ/mol. Moreover, the metronidazole molecule was able to form hydrogen bonds with all of the studied polymer segments. All of the obtained structures (Fig. 6) provided similar binding energies except the one formed between metronidazole and Carbopol in a special arrangement (Fig. 7). While the normal binding energy varied between 36 and 46 kJ/mol (Fig. 6), the one exceptional complex proved to be extremely stable (Fig. 7), showing a binding energy of 65 kJ/mol.

Therefore, on the basis of the calculations, we can state, that all of the studied polymers form an H-bound complex with metronidazole, the model drug. In the case of Carbopol, this bond is extremely stable. However, water molecules from the humidity of air can break the bonds and release drug molecules. This is while the drug release properties of these formulas changes so much during the storage period.

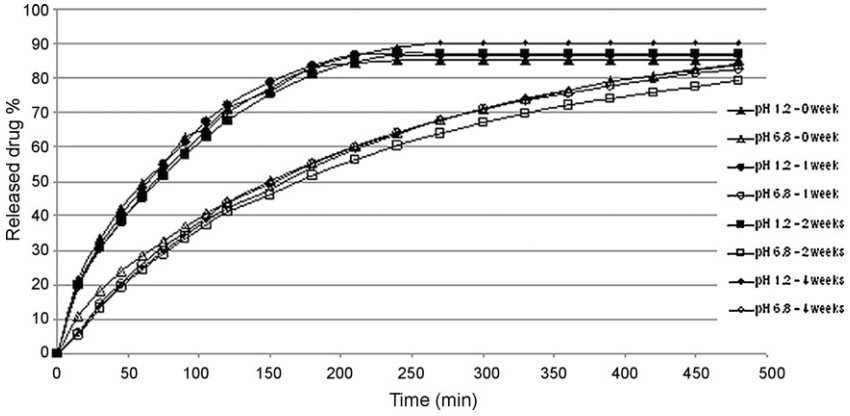


**Fig. 3.** Drug release profiles of Povidone matrices containing metronidazole.

**Table 1**
Difference and similarity factors of various matrix tablets containing metronidazole.

| | $f_1$ | $f_2$ |
|---|---|---|
| Carbopol 71G matrices | | |
| 0–1 week | | |
| pH 1.2 | 3.63 | 71.44 |
| pH 6.8 | 3.18 | 86.42 |
| 0–2 weeks | | |
| pH 1.2 | 4.42 | 57.43 |
| pH 6.8 | 67.29 | 20.67 |
| 0–4 weeks | | |
| pH 1.2 | 3.71 | 55.60 |
| pH 6.8 | 71.87 | 19.33 |
| Kollidon SR matrices | | |
| 0–1 week | | |
| pH 1.2 | 3.34 | 77.73 |
| pH 6.8 | 4.66 | 77.63 |
| 0–2 weeks | | |
| pH 1.2 | 5.28 | 67.73 |
| pH 6.8 | 6.88 | 70.04 |
| 0–4 weeks | | |
| pH 1.2 | 3.01 | 78.43 |
| pH 6.8 | 4.95 | 75.74 |
| Povidone matrices | | |
| 0–1 week | | |
| pH 1.2 | 2.18 | 86.45 |
| pH 6.8 | 2.55 | 83.77 |
| 0–2 weeks | | |
| pH 1.2 | 3.20 | 78.84 |
| pH 6.8 | 7.77 | 68.44 |
| 0–4 weeks | | |
| pH 1.2 | 4.79 | 70.97 |
| pH 6.8 | 3.06 | 80.49 |

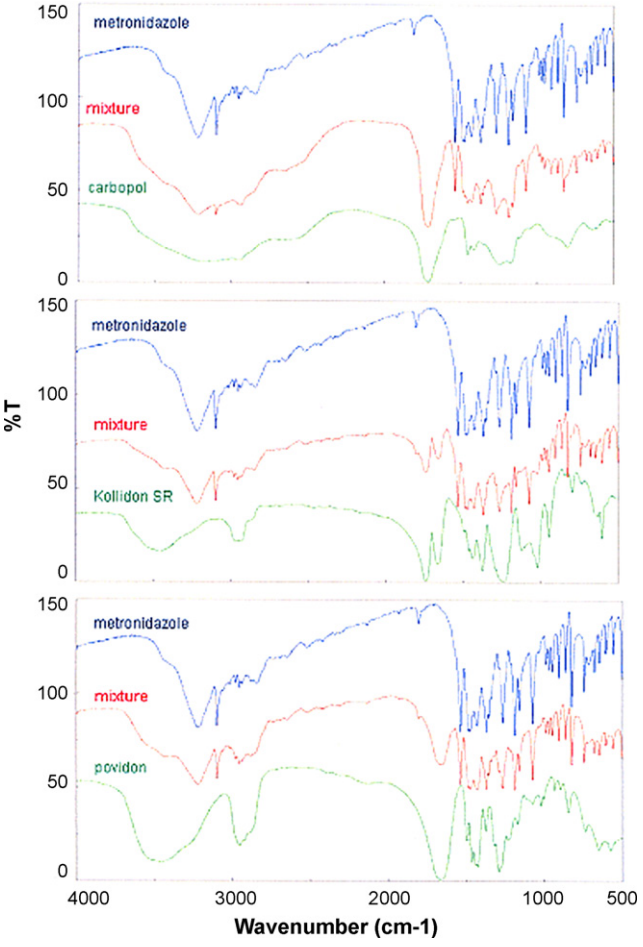


**Fig. 4.** FT-IR spectra of metronidazole-polymer mixtures.

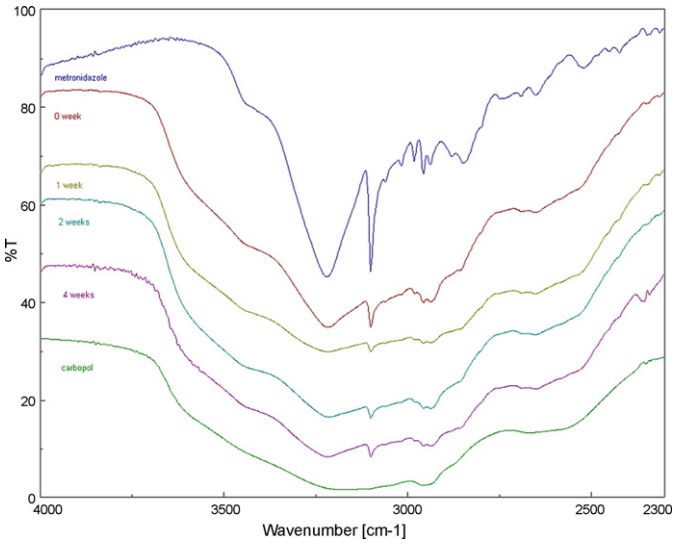


**Fig. 5.** FT-IR spectra of the physical mixtures of metronidazol and Carbopol 71G as a function of storage time.

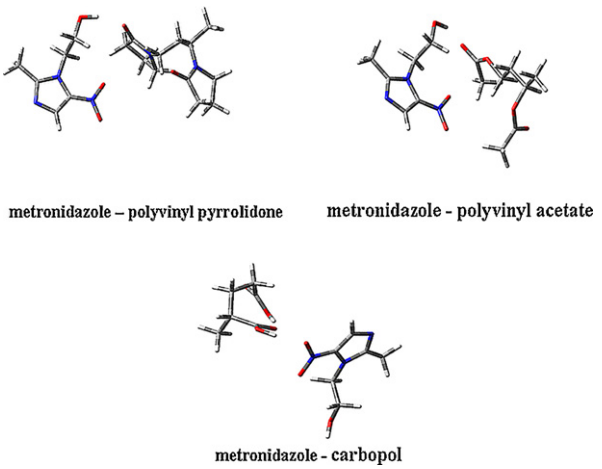


**Fig. 6.** Optimum geometries for some metronidazole-polymer complexes.

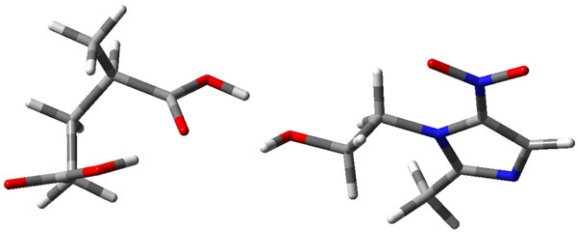

**Fig. 7.** The most stable hydrogen-bound complex formed by metronidazole and the studied polymers. The polymer is Carbopol in this case.

## 4. Conclusion

The structural changes between the polymers and drugs could significantly change the drug release stability even in the course of relatively short storage. The combination of in vitro drug release studies with *ab initio* calculations could predict the possible structural changes, thus *ab initio* calculations provide a valuable tool for the design of new formulas containing polymeric excipients.

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