EVALUATION OF HARD GELATIN CAPSULES WITH ALGINATE MICROSPHERES CONTAINING MODEL DRUGS WITH DIFFERENT WATER SOLUBILITY

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Abstract: The aim of this study was to prepare and evaluate multicompartment hard gelatin capsules with alginate microspheres containing model drugs with different water solubility: slightly soluble metronidazole and freely soluble – ranitidine hydrochloride and metformin hydrochloride. All prepared capsules were characterized by weight and drug content uniformity and adhesion to the mucosal surface. Capsules with metronidazole microspheres provided sustained drug release according to zero order kinetics (MT 2 formulation). Capsules containing microspheres with freely soluble ranitidine hydrochloride and metformin hydrochloride did not sufficiently prolong the release time of drugs. Moreover, capsules with ranitidine hydrochloride did not successfully pass the accelerated stability test. To prolong release of metformin hydrochloride, microspheres crosslinking with chitosan was additionally performed. It was shown that crosslinking process provided sustained dissolution of drug and the release profile was similar to the extended-release commercially available tablets.

Keywords: multicompartment dosage forms, sodium alginate, microspheres, hard gelatin capsules, metronidazole, ranitidine hydrochloride, metformin hydrochloride

Multicompartiment dosage forms, compared to the traditional one-unit formulations, provide high surface area of drug release and short diffusion way, which in the consequence enables improvement of therapeutic efficacy and reduction of drug toxicity (1, 2). Microspheres are an example of multicompartiment carriers with diameter 1-500 µm, where the active substance is incorporated in natural or synthetic polymer matrix. The properties of microspheres depend on the type of polymer and the method of their preparation (3-5). One of the advanced methods used in microparticles production is the spray drying – process, in which a solution, emulsion or suspension is sprayed in a stream of drying gas – compressed air or nitrogen (6, 7).

Capsules are solid dosage form, where drug and excipients are enclosed in hard or soft gelatin shell. Hard gelatin capsules are divided into two pieces – cap and body, which are most often obtained from gelatin, sugar and water. Gelatin possesses ability to form non-toxic gel, which is readily soluble in biological fluids and is characterized by strong flexibility (8, 9). Capsules filling might consist of pure active substance, active substance with excipients or multiple units dosage forms such as pellets, microspheres, microcapsules or microgranules. In comparison to tablets production, capsules filling avoids process of compression, which could destroy structure of multi units forms. Moreover, the number of excipients involved in capsules production is significantly lower (9-11).

Sodium alginate (ALG) is a natural, biocompatible and non-toxic heteropolysaccharide polymer with mucoadhesive and swelling properties. Mucoadhesive dosage forms with prolonged gastric residence time are particularly suitable for drugs, which are absorbed in the stomach, are unstable in the intestines or are poorly soluble in the high pH (12, 13). Our earlier studies have shown that ALG microspheres containing commonly used active substances – metronidazole (MT), ranitidine hydrochloride (RNT) and metformin hydrochloride (MF) were successfully prepared by the spray drying method and possessed mucoadhesive properties (14-16).

MT is slightly water soluble nitroimidazole chemotherapeutic drug, which activity includes strictly anaerobic bacteria and protozoa. ALG microspheres with MT after oral administration may

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extend the residence time of the drug in the stomach and improve the effectiveness of *Helicobacter pylori* eradication. MT is also used in the treatment of common vaginal infections – bacterial vaginosis and trichomoniasis (17, 18). In the case of vaginal infections, ALG might prolong residence time of the microspheres in the application site and, in the consequence, increase therapeutic efficacy of MT. RNT is histamine receptor antagonist, mainly used in the treatment of gastro-esophageal reflux disease, gastric and duodenal ulceration and Zollinger-Ellison syndrome. However, in the lower segment of the gastrointestinal tract, RNT is poorly absorbed and may be degraded (19, 20). MF is an orally administered antidiabetic agent from biguanide group, which is the first line therapy in type 2 diabetes. MF is freely soluble in water and its bioavailability after oral administration in conventional dosage forms is below 50% (21-23). It is assumed that ALG microspheres with RNT and MF can increase drug bioavailability by prolonged contact of the dosage form with the stomach mucous membrane. It is necessary to notice that sustained release forms with MT and RNT are not available. In case of MF, film coated, polymer matrix or osmotic technology tablets providing extended release are commercially available. However, no multicompartment dosage forms with MF are registered.

The aim of this research was to prepare multicompartment hard gelatin capsules with ALG microspheres containing MT, RNT and MF in order to improve drug residence time. In case of ALG microspheres with MF, to prolong drug release, crosslinking with chitosan was additionally performed. To investigate mucoadhesiveness of microspheres and capsules, the *in vitro* residence time to the porcine vaginal mucosa was determined. Microspheres with MT, RNT and MF were prepared using Mini Spray Dryer B-290 (Büchi, Flawil, Schweiz). Parameters of the spray drying process and characterization of obtained microspheres were described earlier (14-16). Microspheres formulations with the highest drug loading were selected for capsule preparation. In order to prolong MF release, microspheres crosslinking with chitosan was additionally performed. 0.1% chitosan solution in acetic acid pH 4.5 was added to 2% water solution of ALG and then obtained mixture was spray dried. Parameters of the process were set as follows: inlet temperature 150°C, aspirator flow 37 m³/h, feed flow 5 mL/min, spray flow 600 L/h.

**EXPERIMENTAL**

**Materials**

Metronidazole (MT) was purchased from Amara (Kraków, Poland), ranitidine hydrochloride (RNT) was obtained from Zakłady Farmaceutyczne Polpharma S.A. (Starogard Gdański, Poland), metformin hydrochloride (MF) was obtained from Debao Fine Chemical CO (Henan, China). Sodium alginate (ALG) low viscosity (2%, 100-300 cP) and chitosan (medium molecular weight, viscosity of 1% solution in 1% acetic acid: 200 cP) were purchased from Sigma Aldrich (Steinheim, Germany). Potassium dihydrogen phosphate, sodium hydroxide, methanol, acetonitrile, sodium chloride, potassium hydroxide, calcium hydroxide, lactic acid, acetic acid, glycerol, urea and glucose were obtained from Chempur (Piekary Śląskie, Poland). Water was distilled and passed through a reverse osmosis system Milli-Q Reagent Water System (Billerica, MA, USA). Porcine stomach and vaginal mucosa from Large White Pigs weighting 200 kg were obtained from the veterinary service (Turoń Kościelna, Poland). Samples were stored at -20°C and before the experiment were defrosted and cut into 5 mm in diameter and 2 mm thick pieces. Empty hard gelatin capsules were obtained from Eprus (Bielsko-Biała, Poland).

Microspheres with MT, RNT and MF were prepared using Mini Spray Dryer B-290 (Büchi, Flawil, Schweiz). Parameters of the spray drying process and characterization of obtained microspheres were described earlier (14-16). Microspheres formulations with the highest drug loading were selected for capsule preparation. In order to prolong MF release, microspheres crosslinking with chitosan was additionally performed. 0.1% chitosan solution in acetic acid pH 4.5 was added to 2% water solution of ALG and then obtained mixture was spray dried. Parameters of the process were set as follows: inlet temperature 150°C, aspirator flow 37 m³/h, feed flow 5 mL/min, spray flow 600 L/h.

**Microspheres flow properties**

**Angle of repose**

The angle of repose was examined using manual powder flow tester (Electrolab EFT-01, Mumbai, India) according to European Pharmacopoeia (24) using 5 g of microspheres. The angle of repose (α) was calculated as follows:

$$\tan \alpha = \frac{h}{r}$$

where, h – height of the cone formed, r – radius of receipt disc (24).

**Bulk and tapped density**

Bulk and tapped densities of 50 g microspheres were determined using Electrolab ETD-1020 Tap Density Tester (Electrolab, Mumbai, India) accord-
Compressibility (Carr’s index and Hausner ratio)

Carr’s compressibility index (CI) and the Hausner ratio (HR) were determined according to the European Pharmacopoeia (24):

\[
CI = \left( \frac{\rho_{\text{tap}} - \rho_{\text{bulk}}}{\rho_{\text{tap}}} \right) \times 100
\]

\[
HR = \frac{\rho_{\text{tap}}}{\rho_{\text{bulk}}}
\]

where \(\rho_{\text{tap}}\) is the tap density and \(\rho_{\text{bulk}}\) – the bulk density.

Moisture content

In order to determine the moisture content, 20 mg of microspheres were placed in the aluminium pan of moisture analyzer Radwag WPS 50SX (Warsaw, Poland), heated from 30°C to 120°C.

Capsules preparation

In each series, fifty hard gelatin capsules were filled by using manual capsule machine Capsunorm® (Eprus, Bielsko-Biała, Poland). Composition of prepared capsules is presented in Table 1.

Capsules evaluation

Weight variation test and drug content uniformity

Weight uniformity was evaluated by weighing accurately twenty randomly selected capsules and the mean mass of capsules were calculated (24).

To asses drug content uniformity, ten randomly chosen capsules were weighted accurately and microspheres were placed in 100 mL of water in flat-bottomed flasks. The flasks were shaken for 24 h in a shaking water bath at 25 ± 1°C with a rotation speed of 250 rpm to extract the total entrapped drug in microspheres. The solution was then filtered through 0.45 µm syringe nylon filters (Witko, Łódź, Poland). Samples (1 mL) were suitably diluted and analyzed by HPLC method.

HPLC analysis

The amount of MT, RNT and MF was determined by the HPLC system Agilent Technologies 1200 equipped with a G1312A binary pump, a G1316A thermostat, a G1379B degasser and a G1315B diode array detector (Agilent, Waldbronn, Germany). Isocratic separation of MT and RNT was achieved on a Zorbax Eclipse XDB–C18, 4.6 x 150 mm, 5 µm column (Agilent, Waldbronn, Germany). Mobile phase for MT was acetonitrile : 0.01 M phosphate buffer pH 4.7 (15 : 85, v/v), methanol : phosphate buffer pH 7.0 (1 : 3, v/v) for RNT and for MF – acetonitrile : methanol : phosphate buffer pH 3.0 (20 : 20 : 60, v/v). UV detection was performed at a wavelength of 319 nm (MT), 224 nm (RNT) and 240 nm (MF) (14-16). The flow rate was 1.0 mL/min and the column temperature was maintained at 25°C. For injection into the HPLC system, 20 µL of sample was used. All reagents used for analysis were HPLC grade. The retention time of MT and RNT was 3.0 min, and MF – 2.8 min. The standard calibration curves in all substances were linear over the range of 1 – 100 µg/mL with the coefficient of determination (\(R^2\)) of 0.999.

In vitro drug release profile

The in vitro MT, RNT and MF release tests were conducted using apparatus type I (Erweka Dissolution tester type DT 600HI, Heusenstamm, Germany). Capsules were placed in the basket, immersed in 900 mL of 0.1 M HCl (pH 1.2) and stirred at 75 rpm (24). In case of capsules with MT, modified simulated vaginal fluid (SVF, pH 4.2) as dissolution medium was additionally used. Non modified commercial available tablets with studied substances were used as controls. In case of MF, extended release polymer matrix tablet as control was additionally used. Samples were withdrawn and filtered through 0.45 µm cellulose acetate Millipore filters (Billerica, MA, USA) at predetermined time intervals and replaced with fresh dissolution medium. During the dissolution process the temperature was maintained at 37 ± 1°C. The amount of released drugs was analyzed by HPLC method as described above.

Mathematical modeling of drug release profile

MT, RNT and MF release data were analyzed according to zero order kinetic, first order kinetic,
Higuchi model, Korsmeyer – Peppas equation and Hixson-Crowell cube root law. The constants of release kinetics and the regression coefficients ($R^2$) were calculated from the slope of plots by linear regression analysis. The constants of release kinetics and the regression coefficients ($R^2$) were calculated from the slope of plots by linear regression analysis.

Zero order kinetics:
\[ F = k \times t, \]
First order kinetics:
\[ \ln F = k \times t, \]
Higuchi model:
\[ F = k \times \sqrt{t}, \]
Korsmeyer-Peppas model:
\[ F = k \times t^n, \]
Hixson-Crowell model:
\[ 1 - (1 - F)^{1/3} = k \times t, \]
where \( F \) is the fraction of drug release, \( k \) – the release constant and \( t \) – the time. For the Korsmeyer-Peppas model, the fraction of drug remaining at time \( t \) was determined for every time interval \( \log (M_t/M_8) \) and plotted against the log of time \( t \). The slope of the line was taken as the value of \( n \) – diffusional release exponent used to interpret the mechanism of release (25, 26).

**Disintegration time test**

The disintegration test was carried out for six capsules from each formulation by using disintegration tester (Electrolab ED-2L, Mumbai, India). The study was conducted in 500 mL of water, 0.1 M HCl (pH 1.2) or SVF (pH 4.2) at 37 ± 0.5°C (24).

**Residence time test**

Residence time was evaluated by the *in vitro* adhesion test, known as “wash off” method. It was performed using self-constructed apparatus (by modifying USP disintegration tester), according to Nakamura et al. (27), where plexiglass cylinder (6

![Figure 1. Modified pharmacopoeial disintegration apparatus (according to 27)](image)
cm diameter, weight 280 g) moving up and down was vertically fixed (Fig. 1). In case of microspheres and capsules intended for oral administration, segments of porcine stomach mucosa (2 cm long) were glued to the internal side of a beaker above the level of 500 mL 0.1 M HCl (pH 1.2) at 37 ± 0.5°C. To study residence time of microspheres and capsules with MT, segments of porcine vaginal mucosa (2 cm long) and 500 mL of SVF (pH 4.2) at 37 ± 0.5°C were additionally applied. After moisturizing the microspheres and capsules with 100 µL of HCl or SVF, a hydrated surface was put in contact with the mucosal membrane and immersed completely in the medium. Microspheres were used in the amount corresponding to their content in the capsules. Time required for entire detachment of the microspheres and capsules from the mucosa was noted (28).

**Stability test**

Organoleptic properties, weight, drug content uniformity and drug release from capsules were assessed directly after preparation and after 14, 30 and 180 days of storage at 25 ± 2°C, RH 60 ± 5% and 40 ± 2°C, RH 75 ± 5%.

**Statistical analysis**

Quantitative variables were expressed as the mean and standard deviation. A statistical analysis was performed using nonparametric techniques: the Kruskal–Wallis and Mann-Whitney U-test with the Statistica 10.0 software. Differences between groups were considered to be significant at p < 0.05.

**RESULTS AND DISCUSSION**

Determination of flow powder properties is crucial for tablet designing and capsule filling process. The powder flowability is directly related to the physical features of material and depends on particle size, shape, surface area and density. Cohesive forces (e.g., van der Waals and various electrostatic forces) possess the higher values when the degree of organization of molecules is greater (29, 30).

The angle of repose is a traditional method for powder flow properties evaluation and is related to internal friction and resistance movement among particles. When angle of repose is higher — the powder is more cohesive (24, 31, 32). The angle of repose of microspheres (α) is shown in Table 2. The flow of analyzed microspheres was rated as “passable which may hang up” for MT (42.25 ± 2.6°) and RNT microspheres (44.75 ± 1.7°). In case of MF microspheres, angle of repose was 38.56 ± 1.3°, which indicates “fair” flow and in chitosan crosslinked ALG microspheres with metformin hydrochloride (MF CL) it was “good flow” (33.62. ± 2.4°).

The bulk density is the ratio of untapped powder mass to its volume and depends on density of particles and their spatial arrangement. Tapped density is obtained after mechanically tapping of powder sample (24). Microspheres flow properties are presented in Table 2. Carr’s index (CI) and Hausner ratio (HR) values are directly related with bulk and tapped density. Hence, in case of good powder flow properties, particles interactions are lower, the bulk density and tapped density possess lower values, and CI and HR are also characterized by lower results (24, 31, 32). Obtained data suggest that MT and RNT microspheres were characterized by “very poor” flow properties, MF — by “poor” flow, and MF CL – by “passable” flow.

As hard gelatin capsules can absorb humidity and lose their shape, therefore moisture content is a key factor in capsules production process. Moisture content in analyzed microspheres was below 10% (Table 2), which should not affect capsules stability (33).

Hard gelatine capsules with ALG microspheres containing MT, RNT and MF were prepared by using manual capsule machine CapsunormÆ. All capsules were characterized by low values of mean

<table>
<thead>
<tr>
<th>Drug loading (%)</th>
<th>MT</th>
<th>RNT</th>
<th>MF</th>
<th>MF CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moisture content (%)</td>
<td>62.17 ± 1.89</td>
<td>70.9 ± 1.52</td>
<td>75.6 ± 1.54</td>
<td>76.51 ± 3.41</td>
</tr>
<tr>
<td>Angle of repose (°)</td>
<td>42.25 ± 2.61</td>
<td>44.75 ± 1.71</td>
<td>38.56 ± 1.32</td>
<td>33.62 ± 2.44</td>
</tr>
<tr>
<td>Bulk density (g/mL)</td>
<td>0.21 ± 0.02</td>
<td>0.22 ± 0.01</td>
<td>0.25 ± 0.02</td>
<td>0.24 ± 0.03</td>
</tr>
<tr>
<td>Tapped density (g/mL)</td>
<td>0.36 ± 0.05</td>
<td>0.38 ± 0.06</td>
<td>0.34 ± 0.07</td>
<td>0.32 ± 0.04</td>
</tr>
<tr>
<td>Carr's index (%)</td>
<td>41.62 ± 2.15</td>
<td>42.13 ± 1.65</td>
<td>26.54 ± 1.61</td>
<td>25.47 ± 2.41</td>
</tr>
<tr>
<td>Hausner's ratio</td>
<td>1.72 ± 0.42</td>
<td>1.73 ± 0.57</td>
<td>1.36 ± 0.32</td>
<td>1.33 ± 0.91</td>
</tr>
</tbody>
</table>
mass deviation and high uniformity of drug content (Table 3). However, in order to improve the flowability of microspheres, for preparation capsules by automatic capsule filling machine, use of lubricants seems to be necessary (34).

**In vitro drug release profile**

The *in vitro* release profiles of MT, RNT, and MF from formulated capsules and commercially available tablets (used as controls) are shown in Figure 2. ALG ability to gel formation in acidic pH leads to closing of pores in the microspheres matrix and hinders the entrance of water. As a result, swelling and gelling of microspheres creates reservoir which prolongs drug dissolution. Differences in drug release profiles were associated with different drug solubility, and drug and ALG content in the microspheres. Therefore, the higher amount of microspheres was used, the drug release was more sustained. Entrapment of microspheres in capsule shell decreased surface access to medium, decreased the dissolution area and prolonged drug release in comparison to pure microspheres. In case of...
MT, which is characterized by slightly solubility (24, 35), drug release was the most extended. After 8 h, about 70% and 90% of MT was released from MT 2 and MT 1 capsules, respectively (Fig. 2A, 2B). RNT and MF are characterized by freely solubility (24, 35) and after just 4 h about 80% of RNT and 90% of MF was released (Fig. 2C, 2D). Crosslinking of microspheres containing MF and electrostatic attraction between anionic carboxyl groups of alginate and cationic amino groups of chitosan provided sustained dissolution of drug. Release profile from capsules formulation MF CL was similar to the modified commercially available tablet – after 6 h of the study, about 80% of MF was released.

In order to investigate mechanism responsible for drug release from prepared capsules, obtained dissolution data were fitted to zero order, first order equations, Higuchi, Korsmeyer-Peppas and Hixson-Crowell models (Table 4). It was found that in all capsules formulations (except MT 2) the plots showed the highest regression correlation coefficient in the Higuchi model. The best fit curve in this model with $R^2(0.994)$ was observed for capsules formulation MF CL. Drug release from capsules MT 2 was according to the zero order kinetics, where the release rate is independent of drug concentration. The obtained data from Korsmeyer-Peppas equation (n value was ranged from 0.14 to 0.33) indicate that drug release from capsules (except MT 2) was controlled by Fickian diffusion mechanism. The high values of $R^2$ obtained in the Hixson-Crowell model indicate that this equation can also describe the release of drugs and suggest that drug release rate is limited by the capsules erosion and diffusion process (36-38).

Disintegration time test revealed that disintegration of capsules was related with their weight, solubility of drugs and type of medium used. Disintegration time evaluated in water was ranged from 38.6 ± 3.5 min (RNT 1) to 57.3 ± 4.2 min (MT 2) (Table 3). Because of gel formation, all prepared capsules did not disintegrate in acidic pH (0.1 M HCl or SVF pH 4.2) for 48 h of the study.

<table>
<thead>
<tr>
<th>Capsules formulation</th>
<th>Drug content (mg)</th>
<th>Disintegration time (h)</th>
<th>Residence time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight (mg)</td>
<td>H2O</td>
<td>0.1 M HCl</td>
</tr>
<tr>
<td>MT 1</td>
<td>405.1 ± 6.3</td>
<td>44.5 ± 2.6</td>
<td>-*</td>
</tr>
<tr>
<td>MT 2</td>
<td>809.2 ± 5.8</td>
<td>57.3 ± 4.2</td>
<td>-*</td>
</tr>
<tr>
<td>RNT 1</td>
<td>115.7 ± 8.4</td>
<td>38.6 ± 3.5</td>
<td>-*</td>
</tr>
<tr>
<td>RNT 2</td>
<td>221.5 ± 7.3</td>
<td>39.3 ± 2.4</td>
<td>-*</td>
</tr>
<tr>
<td>MF 1</td>
<td>668.2 ± 5.6</td>
<td>41.4 ± 3.8</td>
<td>-*</td>
</tr>
<tr>
<td>MF CL</td>
<td>641.7 ± 4.3</td>
<td>52.2 ± 4.1</td>
<td>-*</td>
</tr>
</tbody>
</table>

*capsules did not disintegrate over 48 h of experiment;  ** test performed in SVF (pH 4.2).

Table 4. Mathematical modeling of drug release from capsules with ALG microspheres containing metronidazole (MT 1, MT 2), ranitidine hydrochloride (RNT 1, RNT 2), metformin hydrochloride (MF 1) and chitosan crosslinked ALG microspheres with metformin hydrochloride (MF CL).

<table>
<thead>
<tr>
<th>Capsules formulation</th>
<th>Zero order kinetics</th>
<th>First order kinetics</th>
<th>Higuchi model</th>
<th>Korsmeyer-Peppas model</th>
<th>Hixson-Crowell model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R¹</td>
<td>Kₐ</td>
<td>R¹</td>
<td>Kₐ</td>
<td>R¹</td>
</tr>
<tr>
<td>MT 1</td>
<td>0.864</td>
<td>9.12</td>
<td>0.706</td>
<td>0.17</td>
<td>0.986</td>
</tr>
<tr>
<td>MT 2</td>
<td>0.996</td>
<td>9.32</td>
<td>0.818</td>
<td>0.25</td>
<td>0.962</td>
</tr>
<tr>
<td>RNT 1</td>
<td>0.831</td>
<td>5.91</td>
<td>0.743</td>
<td>0.76</td>
<td>0.935</td>
</tr>
<tr>
<td>RNT 2</td>
<td>0.927</td>
<td>8.77</td>
<td>0.865</td>
<td>0.15</td>
<td>0.958</td>
</tr>
<tr>
<td>MF 1</td>
<td>0.767</td>
<td>6.72</td>
<td>0.652</td>
<td>0.11</td>
<td>0.891</td>
</tr>
<tr>
<td>MF CL</td>
<td>0.950</td>
<td>9.55</td>
<td>0.855</td>
<td>0.07</td>
<td>0.994</td>
</tr>
</tbody>
</table>
In order to assess capsules residence time, “wash off” test was performed using a self-constructed apparatus, according to Nakamura et al. (27). ALG is characterized by high bioadhesive properties, which mechanism is defined by interaction between carboxyl groups of polymer and mucin through electrostatic adsorption, van der Waals and hydrogen bonds. Carboxyl groups of ALG penetrate into the mucus network and finally the formation of bonds between the mucus and the polymer occurs. Porcine stomach and porcine vaginal mucosa were used as adhesive models due to their similar anatomy and physiology to the human tissue (39). All examined microspheres and capsules adhered to the mucosal surface. However, the residence time of free microspheres was significantly higher (>24 h) than when they were encapsulated (Table 3). This might be due to the higher contact area of microspheres with the mucosa membrane.

Stability evaluation plays significant role during development of pharmaceutical delivery systems. Designed capsules were examined directly after preparation and after 14, 30 and 180 days of storage at 25 ± 2°C, RH 60 ± 5% and 40 ± 2°C, RH 75 ± 5%. No significant changes in physical appearance, drug and mass content uniformity, and drug release profiles from capsules with microspheres containing MT and MF were observed. However, after one month storage of RNT 1 and RNT 2 capsules in 40 ± 2°C, RH 75 ± 5%, brown decomposition product of RNT (40, 41), which absorbed moisture and dissolved gelatin capsule shell was observed.

CONCLUSIONS

The results of this study suggest that designed capsules with ALG microspheres could be considered as multicompartment carriers for slightly soluble MT. Capsules with MT were characterized by sustained drug release (according to zero order kinetics in MT 2 formulation). Capsules containing microspheres with freely soluble RNT and MF did not sufficiently prolong the release time of drugs. Moreover, capsules with RNT did not successfully pass the accelerated stability test. Chitosan crosslinking of ALG microspheres containing MF provided sustained dissolution of drug and release profile from capsules formulation MF CL was similar to the modified commercially available tablet – after 6 h of the study, about 80% of MF was released.

Acknowledgments

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