EVALUATION OF ALGINATE MICROSPHERES WITH METRONIDAZOLE OBTAINED BY THE SPRAY DRYING TECHNIQUE

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Abstract: In the present study, nine formulations (F1-F9) of alginate microspheres with metronidazole were prepared by the spray drying technique with using different drug : polymer ratio (1 : 2, 1 : 1, 2 : 1) and different sodium alginate concentration (1, 2, 3%). The obtained microspheres were characterized for size, morphology, drug loading, ζ potential and swelling degree. Mucoadhesive properties were examined using texture analyzer and three different models of adhesive layers – gelatin discs, mucin gel and porcine vaginal mucosa. In vitro drug release, mathematical release profile and physical state of microspheres were also evaluated. The obtained results indicate that sodium alginate is a suitable polymer for developing mucoadhesive dosage forms of metronidazole. The optimal formulation F3 (drug : polymer ratio 1 : 2 and 1% alginate solution) was characterized by the highest metronidazole loading and sustained drug release. The results of this study indicate promising potential of ALG microspheres as alternative dosage forms for metronidazole delivery.

Keywords: metronidazole, sodium alginate, microspheres, spray drying technique, mucoadhesive properties

Multicompartment dosage forms, such as microparticles, 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). One of the advanced methods used in microparticles production is spray drying. Spray drying is a one-step process, which depends on spraying a solution, emulsion or suspension in a stream of drying gas - compressed air or nitrogen. Increased contact area between the phases leads to an intensive exchange of heat and almost immediate removal of the solvent to form dry particles. Parameters of the process, e.g., atomization devices, drying chambers, aspirator and feed rate, drying temperature, spray air flow and properties of the material affect the characteristics of the dried product. Properly selected parameters allow to obtain dry particles with desired properties (2).

One of the polymers used for preparation of microparticles is sodium alginate (ALG), which commonly occurs in seaweed. It is a heteropolysaccharide composed of monomers of β-D-mannuronic acid and α-L-guluronic acid. ALG possesses a number of advantages: non-toxicity, biocompatibility and biodegradability. In addition, mucoadhesive properties of this polymer can increase the residence time of the dosage form and in the consequence improve the drug bioavailability (3–5).

Metronidazole (MT) is synthetic, chemotherapeutic drug, which is a derivative of nitroimidazole. Its activity includes strictly anaerobic bacteria and protozoa. Mechanism of MT action involves the penetration of bacterial cells in the process of passive diffusion and generation of active product in the reduction of the nitro group, which causes damage of cellular DNA (6, 7). MT is one of the most effective drugs in the eradication of Helicobacter pylori, which resides mainly in the gastric mucosa and is an etiologic factor in the development of the gastritis, gastric ulcer and gastric carcinoma (8). MT is also widely used to treat trichomoniasis – the most common nonviral sexually transmitted disease, which affects about 170 million people a year and is caused by the protozoan Trichomonas vaginalis (9). Registered preparations with MT include tablets for oral or vaginal administration, gels, creams and intravenous dosage forms. However, multicompartment sustained release forms with MT, which could provide greater uniformity and reproducibility of the delivered dose, are not available (10), therefore the
Objective of this study was to prepare MT loaded ALG mucoadhesive microspheres by the spray drying technique. The effect of the drug : polymer ratio and concentration of ALG solution on the properties of prepared microspheres was evaluated. The obtained microspheres (formulations F1-F9) were characterized for size, morphology, drug loading, entrapment efficiency, swelling properties and ζ potential. Mucoadhesive properties of the microspheres were examined by using texture analyzer and three different models of adhesive layer: gelatin discs, mucin gel and porcine vaginal mucosa. The physical state of microspheres was determined by differential scanning calorimetry. The in vitro drug release and mathematical modeling of MT release were also evaluated.

EXPERIMENTAL

Materials

Metronidazole (MT) was purchased from Amara (Kraków, Poland). Sodium alginate (ALG) low viscosity (a viscosity of 2% solution: 100-300 cP) was purchased from Sigma Aldrich (Steinheim, Germany). Potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid, 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). Mucin type II from porcine stomach and gelatin type B from bovine skin was purchased from Sigma Aldrich (Steinheim, Germany). Porcine vaginal mucosa from large white pigs weighting ≈ 200 kg was obtained from the veterinary service (Turośń Kościcelna, 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.

Preparation of microspheres

Microspheres were produced using Büchi Mini Spray Dryer B-290 (Büchi, Flawil, Switzerland). In order to choose the optimal parameters of spray drying to obtain product of the desired properties, a number of tests were conducted and the experimental parameters of the process were set as follows: inlet temperature 150°C, aspirator flow 37 m^3/h, feed flow 5 mL/min, spray flow 600 L/h. Microspheres (F1–F9) were prepared by using different drug : polymer ratio (1 : 1, 1 : 2, 2 : 1) and different concentrations of sodium alginate (1, 2, 3%) (Table 1).

Evaluation of microspheres

Morphology and particle size distribution

Measurements of the particle size and mean diameter of microspheres were performed using an optical microscope equipped with a camera (Motic BA400, Wetzlar, Germany) and Zetasizer NanoZS90 (Malvern Instruments, Malvern, United Kingdom). Morphology of the microspheres formulation F3 (with the highest MT loading) was additionally examined by scanning electron microscope (SEM) (Hitachi S4200, Tokyo, Japan).

Table 1. Characteristics of MT loaded ALG microspheres (formulation F1–F9).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug: polymer ratio</th>
<th>ζ potential (mV)</th>
<th>Production yield (%)</th>
<th>Encapsulation efficiency (%)</th>
<th>Percent loading (%)</th>
<th>Mean diameter (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1:2</td>
<td>-61.33 ± 9.71</td>
<td>51.15 ± 1.81</td>
<td>92.80 ± 2.32</td>
<td>35.88 ± 1.16</td>
<td>0.74 ± 0.04</td>
</tr>
<tr>
<td>F2</td>
<td>1:1</td>
<td>-66.80 ± 9.53</td>
<td>46.92 ± 1.25</td>
<td>94.52 ± 2.13</td>
<td>51.19 ± 1.38</td>
<td>1.51 ± 0.13</td>
</tr>
<tr>
<td>F3</td>
<td>2:1</td>
<td>-71.93 ± 7.92</td>
<td>42.49 ± 1.42</td>
<td>91.07 ± 1.91</td>
<td>62.17 ± 1.89</td>
<td>1.91 ± 0.15</td>
</tr>
<tr>
<td>F4</td>
<td>1:2</td>
<td>-65.60 ± 9.74</td>
<td>44.69 ± 1.22</td>
<td>76.28 ± 2.96</td>
<td>34.81 ± 1.34</td>
<td>2.27 ± 0.13</td>
</tr>
<tr>
<td>F5</td>
<td>1:1</td>
<td>-66.80 ± 8.32</td>
<td>40.25 ± 1.76</td>
<td>86.36 ± 2.65</td>
<td>39.52 ± 2.48</td>
<td>2.24 ± 0.14</td>
</tr>
<tr>
<td>F6</td>
<td>2:1</td>
<td>-72.77 ± 9.21</td>
<td>31.04 ± 1.88</td>
<td>88.31 ± 3.19</td>
<td>51.43 ± 1.71</td>
<td>1.29 ± 0.19</td>
</tr>
<tr>
<td>F7</td>
<td>1:2</td>
<td>-67.77 ± 8.91</td>
<td>35.59 ± 1.17</td>
<td>85.69 ± 3.29</td>
<td>34.94 ± 1.51</td>
<td>2.95 ± 0.15</td>
</tr>
<tr>
<td>F8</td>
<td>1:1</td>
<td>-66.87 ± 8.46</td>
<td>38.18 ± 1.36</td>
<td>89.40 ± 2.74</td>
<td>44.86 ± 2.26</td>
<td>3.96 ± 0.16</td>
</tr>
<tr>
<td>F9</td>
<td>2:1</td>
<td>-70.57 ± 8.02</td>
<td>30.68 ± 1.62</td>
<td>79.31 ± 2.15</td>
<td>47.70 ± 2.44</td>
<td>1.84 ± 0.13</td>
</tr>
</tbody>
</table>
**HPLC analysis of MT**

The concentration of MT 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). Data collection and analysis were performed using Chemstation 6.0 software. Isocratic separation was achieved on a Zorbax Eclipse XDB-C18, 4.6 × 150 mm, 5 µm column (Agilent, Waldbronn, Germany). Mobile phase was acetonitrile : 0.01 M phosphate buffer pH 4.7 (15 : 85, v/v), the flow rate was 1.0 mL/min and UV detection was performed at a wavelength of 319 nm (11). 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 was 3.0 min and retention factor \( k \) was 2. Retention factor \( k \) was determined by using the formula: \( k = t_k - t_0 / t_0 \) where \( t_k \) – retention time of the analyte on the column, \( t_0 \) – retention time of a non-retained compound (12). Standard calibration curve was linear over the range of 1–100 µg/mL with the correlation coefficient \( R^2 \) 0.999.

**Determination of MT loading, encapsulation efficiency and production yield**

MT loading in the microspheres was determined by dissolving an accurately weighted amount of microspheres (20 mg) in 10 mL of distilled water and agitating for 24 h at 150 rpm in a water bath (13). After filtration through 0.45 µm cellulose acetate (CA) Millipore filters (Billerica, MA, USA), concentration of MT was determined by HPLC method. Each sample was analyzed in triplicate. The mean drug encapsulation efficiency was calculated by formula:

\[
EE = Q_a / Q_t \times 100
\]

where \( EE \) – percentage of encapsulation efficiency, \( Q_a \) – actual drug content, \( Q_t \) – theoretical drug content.

The percentage yield of MT in the ALG microspheres was determined by using the formula:

\[
Y = W_a / W_t \times 100
\]

where \( Y \) – percentage production yield, \( W_a \) – weight of microspheres and \( W_t \) – theoretical weight of drug and polymer (13).

**ζ potential**

ζ potential measurements were performed using a Zetasizer NanoZS90 (Malvern Instruments, Malvern, United Kingdom).

**Swelling properties**

Swelling properties of microspheres were examined in modified simultaneous vaginal fluid (SVF) pH 4.2 or in 0.1 M HCl pH 1.2. SVF was prepared by dissolving sodium hydroxide, hydrochloric acid, sodium chloride, potassium hydroxide, calcium hydroxide, lactic acid, acetic acid, glycerol, glucose and urea in water and adjusted to pH 4.2 by using 0.1 M HCl (14). Microspheres (20 mg) were placed in beakers containing 25 mL of medium and stirred at 100 rpm at 37 ± 1°C. The microspheres were periodically weighted at predetermined time interval until a constant weight was obtained. The swelling ratio (SR) was calculated by using the following formula:

\[
SR = (W_s - W_o) / W_o
\]

where \( W_o \) – initial weight of microspheres and \( W_s \) – weight of microspheres after swelling (15).

**Mucoadhesive properties**

Evaluation of mucoadhesiveness was performed using TA.XT.Plus Texture Analyser (Stable Micro Systems, Godalming, United Kingdom) and three different models of adhesive layers: gelatin discs, mucin gel and porcine vaginal mucosa. Experimental parameters of the process were chosen during preliminary tests and set as follows: pretest speed 0.5 mm/s, test speed 0.1 m/s, contact time 180 s, post test 0.1 mm/s, applied force 1 N. Gelatin discs were prepared by pouring 30% w/w aqueous solution into a Petri dish. Layer of mucin was prepared by absorbing of 10% mucin gel on a discs with cellulose fiber (5 mm in diameter). Tests were conducted at 37 ± 1°C. Each adhesive layer was adhered to an upper probe and moisturized with SVF. Mucoadhesive properties were determined as maximum detachment force (\( F_{max} \)) and work of mucoadhesion (\( W_m \)) – calculated from the area under the force versus distance curve and expressed in µJ.

**In vitro MT release**

MT release profiles were obtained according to the modified USP method using dissolution basket apparatus (Erweka Paddle Dissolution tester type DT 600HH, Heusenstamm, Germany). The receptor compartment was filled with 500 mL of modified simulated vaginal fluid (SVF) (pH 4.2) or 0.1 M HCl (pH 1.2) to provide sink conditions. All formulations of microspheres (containing 250 mg of MT for study in 0.1 M HCl or 500 mg of MT for study in SVF) were suspended in dissolution medium and stirred at 50 rpm at 37 ± 1°C for 8 h. Samples were
withdrawn and filtered through 0.45 µm CA Millipore filters (Billerica, MA, USA) at predetermined time intervals and replaced with fresh dissolution medium (16). The amount of released MT was analyzed by HPLC method (as described earlier). The studies were carried out in triplicate.

**Mathematical modeling of MT release profile**

MT release data were analyzed according to zero order kinetic, first order kinetic, Higuchi model and Korsmeyer–Peppas equation to characterize mechanism of the drug release. Constants of release kinetics and regression coefficients ($R^2$) were calculated from the slope of plots by linear regression analysis.

Zero order kinetic describes formula:

$$Q_t = Q_0 + K_0 t$$

where $Q_t$ is the amount of drug dissolved in time $t$, $Q_0$ – the initial amount of drug in the solution, and $K_0$ – the zero order release constant.

First order kinetic formula:

$$\log Q_t = \log Q_0 + \frac{kt}{2.303}$$

where $Q_t$ is the amount of drug released in time $t$, $Q_0$ – the initial amount of the drug in the solution and $k$ – the first order release constant.

Higuchi model describes equation:

$$Q = kHt^{1/2}$$

where $Q$ is cumulative amounts of the drug released at time $t$ and $kH$ – the Higuchi dissolution constant.

Korsmeyer-Peppas model is expressed by the following equation:

$$\frac{M_t}{M_\infty} = k t^n$$

where $M_t$ and $M_\infty$ are amounts of the drug released at time $t$ and infinite time, $k$ is the constant incorporating structural and geometrical characteristics and $n$ – diffusion release exponent used to interpretation of diffusion release mechanism (17, 18).

**Differential scanning calorimetric studies**

Differential scanning calorimetric (DSC) analysis of MT, ALG and formulation F3 of microspheres (with the highest drug loading) was performed using an automatic thermal analyzer system (DSC TEQ2000, TA Instruments, New Castle, DE, USA). Each sample was precisely weighted (5 mg) and placed in sealed aluminium pans. An empty pan was used as a reference. Temperature calibrations were performed using indium and zinc as standard. Samples were heated from 25 to 230°C at scanning rate of 10°C/min under nitrogen flow of 20 mL/min (19).

**Statistical analysis**

Quantity variables were expressed as the mean and standard deviation. Statistical analysis was performed using nonparametric Kruskal-Wallis test and conducted by using STATISTICA 10.0 software. Differences between groups were considered to be significant at $p < 0.05$.

**RESULTS AND DISCUSSION**

Frequently encountered problems with conventional dosage forms are differences in bioavailability, relatively short residence time in the gastrointestinal tract and possibility of irritation caused by local drug release (20, 21). In contrast, multicomartment dosage forms due to the high surface area offer numerous advantages, which include reduction of individual differences in bioavailability, improved efficacy and reduced toxicity (22). Drug absorption in the stomach is a complex process which depends on physiological factors: pH, presence of food, peristalsis and stomach emptying. In acidic fluid, the sodium alginate is converted to the insoluble, swelling alginic acid. Application of ALG to obtain mucoadhesive microspheres with MT could prolong residence time in the stomach and improve effectiveness in the eradication of *H. pylori* (23, 24). MT is also one of the most effective drugs for common vaginal infections – bacterial vaginosis and trichomoniasis. However, the currently available traditional vaginal delivery systems with MT have limitations. ALG, as anionic polymer with mucoadhesive properties, could prolong residence time of the dosage form in the site of application and in the consequence improve therapeutic efficacy of MT (25, 26).

**Characteristics of ALG microspheres with MT**

In the present study, MT loaded microspheres were successfully prepared by the spray drying method using sodium alginate as polymer matrix. Spray drying technique is relatively simple to carry out, however obtaining the product with desired properties is a complex process, which depends on several factors. The optimal spray drying process parameters included: inlet temperature 150°C, aspirator flow 37 m³/h, feed flow 5 mL/min, spray flow 600 L/h. The characteristics of microspheres obtained using different drug : polymer ratio and different concentration of ALG solution are shown in Table 1. The mean diameter of microspheres ranged from 0.74 ± 0.04 µm (F1) to 3.96 ± 0.16 µm (F8). The minimum drug loading was observed in formulations F1, F4, F7, when drug : polymer ratio was 1 : 2. Maximum drug loading was in formulation F3 (drug : polymer ratio 2 : 1, 1% ALG solution). The encapsulation efficiency ranges from
The increase in the drug : polymer ratio resulted in an improvement of MT percent loading, but entrapment efficiency was slightly decreased, which could be caused by the insufficient amount of ALG to cover MT particles completely. The results obtained from tests performed with an optical microscope indicated that all formulations of microspheres had spherical shape, smooth surface and did not aggregate (Fig. 1). The morphology of microspheres formulation F3 (with the highest MT loading) examined by scanning electron microscopy (SEM) is shown in Figure 2.

ζ potential

The stability of many systems is directly related to the magnitude of their ζ potential. In general, if the value of this parameter is more negative or more positive, the system is more stable. Conversely, if the microspheres ζ potential is relatively closer to zero, the particles have a tendency to aggregate. All performed formulations of microspheres possessed negative ζ potential with value from -61.33 ± 9.71 to -72.77 ± 9.21 mV (Table 1). The negative charge of the microparticle surface is mainly a result of the negative charge of ALG and -CH₂-CH₂-OH group of MT (27). ALG is anionic polymer with carboxyl and sulfate functional groups, which give rise to an overall negative charge at pH values exceeding the pKa of the polymer. It was also observed that value of ζ potential decreased with an increased amount of loaded MT.

Swelling and mucoadhesive properties

Swelling is the first step in the formation of bonds between polymer and mucous membrane and

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Gelatin</th>
<th>Mucin</th>
<th>Porcine vaginal mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1 0.12 ± 0.91</td>
<td>79.77 ± 0.17</td>
<td>0.22 ± 1.15</td>
<td>113.30 ± 0.41</td>
</tr>
<tr>
<td>F2 0.15 ± 1.10</td>
<td>89.23 ± 0.15</td>
<td>0.18 ± 0.98</td>
<td>112.50 ± 0.23</td>
</tr>
<tr>
<td>F3 0.23 ± 0.90</td>
<td>119.87 ± 0.45</td>
<td>0.27 ± 1.51</td>
<td>163.70 ± 0.52</td>
</tr>
<tr>
<td>F4 0.12 ± 0.91</td>
<td>86.00 ± 0.15</td>
<td>0.22 ± 1.85</td>
<td>104.60 ± 0.24</td>
</tr>
<tr>
<td>F5 0.18 ± 0.82</td>
<td>152.00 ± 0.26</td>
<td>0.31 ± 0.89</td>
<td>158.30 ± 0.82</td>
</tr>
<tr>
<td>F6 0.21 ± 0.58</td>
<td>153.80 ± 0.45</td>
<td>0.32 ± 1.67</td>
<td>183.83 ± 0.26</td>
</tr>
<tr>
<td>F7 0.11 ± 1.71</td>
<td>62.93 ± 0.14</td>
<td>0.11 ± 1.90</td>
<td>140.30 ± 0.24</td>
</tr>
<tr>
<td>F8 0.22 ± 1.23</td>
<td>100.60 ± 0.52</td>
<td>0.21 ± 1.56</td>
<td>138.30 ± 0.77</td>
</tr>
<tr>
<td>F9 0.24 ± 0.98</td>
<td>136.50 ± 0.49</td>
<td>0.19 ± 0.89</td>
<td>148.90 ± 1.10</td>
</tr>
</tbody>
</table>

Fmax – Maximum detachment force. Wad – Work of adhesion
in the creating a spatial network with adhesive properties (28). As it is shown in Figure 3A, in microspheres examined in modified SVF, an initial rapid rise of swelling ratio (SR) in the first 30 min in all formulations was observed. The maximum swelling was observed in formulation F4. It was also noted that MT : ALG ratio had significant effect on SR. Formulations with higher MT loading and lower ALG content (F3, F6 and F9) were characterized by lower swelling ability (Fig. 3A). Due to the faster conversion of sodium alginate to the insoluble alginic acid in more acidic pH, the rise of SR in microspheres evaluated in 0.1 M HCl was significantly weaker (Fig. 3B).

Mucoadhesive properties were investigated using TA.XT.Plus Texture Analyser and gelatin discs, mucin gel and porcine vaginal mucosa as different adhesive layers. Porcine vaginal mucosa model is often used to reflect behavior of dosage forms in vivo because of its similarity to human mucosa in terms of histology, ultrastructure and composition (29). It was found that all formulations were characterized by mucoadhesive properties (Table 2). ALG swells and facilitates the adhesive interactions with mucosa and contributes to the formation of a cohesive layer. The numerous carboxyl functional groups of ALG can form hydrogen bonds with mucin molecules, thus producing some adhesive force and electrostatic interactions between polymer and adhesive layer (30, 31). Unexpectedly, higher work of adhesion was observed in formulations with lower amount of ALG (F3, F6 and F9).

**In vitro MT release and mathematical models of release profile**

**In vitro** release of MT was examined from formulations F3, F6, F9 (with the highest MT loading) in SVF (pH 4.2) or in 0.1 M HCl (pH 1.2) (Fig. 4). In SVF, after 0.5 h of the study, significant burst release of MT was observed (75.76 ± 3.76%, 55.32 ± 4.17% and 61.26 ± 3.91% of MT was released
Evaluation of alginate microspheres with metronidazole... 575

from F3, F6 and F9, respectively) and drug was continuously released up to 4 h (Fig. 4A). Contrary, in 0.1 M HCl there was no burst effect, MT release was significantly slower (80% of MT was released after 3 h) and sustained up to 6 h (Fig. 4B). Sustained MT release in 0.1 M HCl is caused by the higher (at acidic pH) conversion of sodium alginate to the insoluble alginic acid.

Mechanism of MT release from obtained microspheres was analyzed according to various mathematical models: zero order kinetic, first order kinetic, Higuchi model and Korsmeyer–Peppas equation to find out the coefficient of correlation ($R^2$) and $n$ value (Table 3). In Korsmeyer-Peppas model, $n$ is the release exponent and provides information about mechanism of the drug release from different geometry. When $n$ takes a value of 0.43, it indicates diffusion mechanism, $n = 0.85$ - indicates swelling-controlled release, $n$ between 0.43 and 0.85 – mechanism of drug release, which includes both phenomena (anomalous transport) (18). In all formulations examined in SVF, the obtained $n$ values were below 0.43 indicating diffusion as MT release mechanism. Interestingly, in 0.1 M HCl solution, value of $n$ was above 0.43 indicating anomalous transport based on both diffusion and swelling con-

Figure 3. Swelling ratio (SR) of microspheres formulations F1-F9 in SVF (pH 4.2) (A) and in 0.1 M HCl (pH 1.2) (B)
trolled release. In all formulations, the highest value of $R^2$ was observed in first order kinetic model, which indicates that MT release was concentration dependent (Table 3).

Differential scanning calorimetric studies

The physical state of MT inside ALG microspheres was assessed by thermal analysis. DSC thermograms of MT, ALG and microspheres of formulation F3 (with the highest drug loading) are shown in Figure 5. Under the experimental conditions, endothermic peak of sodium alginate close to 108.25°C was found indicating glass transition of the polymer, and MT exhibited a sharp endothermic peak at 163.45°C, corresponding to the melting point of pure MT. In thermogram of microspheres F3 sharp peak of MT was observed, suggesting that drug was stable within the polymer matrix (32).
CONCLUSIONS

The obtained data suggest that ALG microspheres with MT can be successfully prepared by the spray drying technique. MT release and mucoadhesive properties of the microspheres can be altered by varying the drug : polymer ratio and concentration of polymer. The optimal formulation of microspheres – F3 is characterized by the highest MT loading and sustained MT release (up to 4 h in SVF and up to 6 h in 0.1 M HCl). All microspheres possess swelling and mucoadhesive properties. The results of this study indicate promising potential of ALG microspheres as alternative dosage forms for MT delivery. Preparation and evaluation of gelatin capsules containing ALG microspheres with MT and tableting these microspheres is underway and will be described in a due course.

Acknowledgments

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