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Development of Metronidazole-Loaded Colon-Targeted Microparticulate Drug Delivery System

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of the article

Abstract

Background. Crohn's disease and ulcerative colitis are the main autoimmune inflammatory bowel diseases. Metronidazole is the most commonly used drug for the treatment of Crohn's disease. However, the pharmacokinetic profile of this drug indicates that the largest amount of the drug is absorbed from the upper part of the intestines and very little concentration of the drugs reaches the colon.

Objectives. The aim of this investigation was to formulate metronidazole loaded microspheres for the efficient therapy of inflammatory bowel diseases.

Material and Methods. Microspheres were prepared using the emulsification-solvent evaporation method. The effect of Eudragit S100 concentration and the ratio of liquid paraffin (light: heavy) on percentage yield, particle size, morphology, drug encapsulation and in vitro drug release was examined. Drug-polymer interaction was investigated using Fourier Transformed Infrared Spectroscopy (FTIR).

Results. The results showed that the particle had good flow properties, encapsulation efficiency (56.11 ± 1.51–81.02 ± 2.14%) and cumulative drug release (64.14 ± 0.83–79.69 ± 2.45%) in a phosphate buffer (pH 6.8) after 10 h of the dissolution study. An increased particle size was observed with an increasing polymer concentration. It was observed that the Eudragit had a positive effect on the drug encapsulation and negative effect on drug release. Aggregation of drug-polymer droplets was observed at a lower level of magnesium stearate during microsphere preparation. The results of FTIR spectroscopy revealed the absence of any drug-polymer interactions. However, slight peak shifting and suppression in peak height was observed. This might be due to the minor ionic interactions. The microspheres were discrete, spherical and free-flowing. The spherical shape of the microspheres was confirmed from SEM photomicrographs. The developed microspheres showed a controlled drug release and were found to follow Higuchi's model. The release mechanism of metronidazole from the microspheres was Fickian diffusion without swelling.

Conclusions. The results suggest that the developed microspheres could enhance drug entrapment, and inflect the drug release **(Polim. Med. 2015, 45, 2, 57–65).**

Key words: microspheres, inflammatory bowel diseases, colon targeting, emulsification-solvent evaporation.

Inflammatory bowel disease (IBD), a complex and chronic inflammation disease of the digestive tract, develops as a consequence of the interaction of genetic and environmental factors. The term IBD is mainly used to describe Crohn's disease and ulcerative colitis [1]. The disease ulcerative colitis affects the colon (large intestine) segment only, while Crohn's disease affects the entire digestive system. It is believed that alterations to enteral bacteria can contribute to inflammatory bowel diseases [2]. IBD is an autoimmune disease, in which the digestive system is attacked by the body's own immune system. It has been reported that IBD affected individuals have 30–50% reduced biodiversity of commensalism bacteria, such as Firmicutes and Bacteroidetes [3].

Two approaches can be used for treating IBD: "step-up," which starts with milder drugs first, versus "top-down," which gives people stronger drugs earlier in the treatment process. Metronidazole is the most commonly used drug for the treatment of Crohn's disease. But,

the pharmacokinetic profile of this drug indicates that the largest amount of the drug is absorbed from the upper part of the intestine and the localized release of the drug in the colon using conventional delivery systems is a serious drawback. Metronidazole has also been shown to reduce the recurrence of Crohn's disease for the first three months after ileum resection surgery. It has been reported that more than 50 percent of patients treated using metronidazole had better effects in managing perineal Crohn's disease (involving the pelvic area) effectively [4, 5].

To maintain the drug level within the therapeutic range after drug administration and the maintenance of a steady state for prolonged time periods using conventional oral drug delivery systems, it is necessary to administer the dosage form several times a day, which may result in significant fluctuation in plasma drug concentration. Conventional dosage forms are not desirable where multiple doses are mandatory for the treatment of chronic disease conditions. The goal of designing a controlled or sustained delivery system is to reduce the frequency of dose administration and to increase the effectiveness of the drug for better therapeutic effect. Therefore, it was thought worthwhile to develop a suitable microparticulate colon-targeted drug delivery system.

The object of the present research work is the preparation of metronidazole microspheres for targeted delivery to the colon by using the pH sensitive polymer Eudragit S 100. The major benefit of the preparation method is the lack of exposure of the drug to a high processing temperature, due to which the drug stability is increased, which ultimately leads to higher encapsulation efficiencies of the drug in the prepared system. The proposed formulation is to treat IBD by directly targeting the drug to the colon, so that the maximum concentration of the drug reaches the colon and increases the residence time of the drug there. If the concentration of the drug in the colon increases, the local effect of the drug will significantly increase. A colon-targeted drug delivery system of metronidazole can be a better alternative for patients suffering from chronic IBD.

Materials and Methods

Materials

Metronidazole was purchased from Central Drug House Pvt. Ltd., New Delhi. Eudragit S 100 was received as gift sample from Dr. Reddy's Laboratory, Hyderabad. Acetone was purchased from Merck Specialities Private Limited, Mumbai. N-hexane was purchased from RFCL Ltd., New Delhi. Magnesium stearate was purchased from Qualikems Fine Chemicals Pvt. Ltd., Vadodara. Liquid Paraffin was purchased from SD Fine Chemicals Ltd., Mumbai.

Methods

Pre-Formulation Studies

Pre-formulation studies focus on those physicochemical properties of the compounds that affect the drug performance and development of an efficacious dosage form. A thorough understanding of these properties, ultimately, provides a rationale for formulation design. Drug and excipient identification tests (physically characterized on the basis of appearance, color, odor, melting point and scanning of λ_{max}), compatibility studies using the KBr disk method by FTIR spectral peak matching approach, and observation of color changes in a physical mixture after 60 days at room temperature (25°C) were done in this phase to provide useful support in the development of dosage forms.

Preparation of Microspheres

Microspheres were prepared by solvent evaporation method using an acetone/liquid paraffin system [6]. Eudragit S 100 was dissolved in 20 ml of acetone. Metronidazole (300 mg) was dissolved in the polymer solution. Magnesium stearate (50 mg) was dispersed uniformly by ultrasonication (Soniweld, Imeco Ultrasonic Mumbai, India). The resulting dispersion was added drop-wise to a mixture of different ratios of light and heavy liquid paraffin and n-hexane with continuous stirring in a mechanical stirrer (Remi, Mumbai, India). The formulation parameters are presented in Table 1. The stirring was continued for 1.5 h at room temperature (≤ 25°C), until the acetone evaporated completely. After evaporation of the acetone, the microspheres were collected by vacuum filtration. The microspheres were washed 4–5 times (40 ml n-hexane for each wash) and dried at room temperature in a desiccator for 24 h.

Microsphere Characterization

Determination of bulk density and tapped density

Microspheres (1 g) were taken into a 10 ml measuring cylinder and the initial volume was recorded. The measuring cylinder was tapped 50 times using USP bulk density apparatus (ETD 1020, Electrolab, Mumbai, India). The bulk density and tapped density were determined using the following formula [7]:

$$\text{Bulk density} = \frac{\text{Weight of the microspheres}}{\text{Initial volume}},$$

$$\text{Tapped density} = \frac{\text{Weight of the microspheres}}{\text{Final volume after tapping}}.$$

Determination of Hausner ratio

The Hausner ratio was determined by the following formula [8]:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}.$$

Table 1. Central composite design with the levels of independent variables

Formulation code	Drug: Eudragit S 100	Liquid paraffin (light) : Liquid paraffin (heavy) : n-hexane (ml)	Speed (rpm)
F1	–1 (1:1.25)	–1 (40:30:15)	–1 (800)
F2	+1 (1:1.75)	–1 (40:30:15)	–1 (800)
F3	–1 (1:1.25)	+1 (50:40:25)	–1 (800)
F4	+1 (1:1.75)	+1 (50:40:25)	–1 (800)
F5	–1 (1:1.25)	–1 (40:30:15)	+1 (1200)
F6	+1 (1:1.75)	–1 (40:30:15)	+1 (1200)
F7	–1 (1:1.25)	+1 (50:40:25)	+1 (1200)
F8	+1 (1:1.75)	+1 (50:40:25)	+1 (1200)
F9	–a (1:1)	0 (45:35:20)	0 (1000)
F10	+a (1:2)	0 (45:35:20)	0 (1000)
F11	0 (1:1.5)	–a (35:25:10)	0 (1000)
F12	0 (1:1.5)	+a (55:45:30)	0 (1000)
F13	0 (1:1.5)	0 (45:35:20)	–a (600)
F14	0 (1:1.5)	0 (45:35:20)	+a (1400)
F15	0 (1:1.5)	0 (45:35:20)	0 (1000)

Determination of angle of repose

For the determination of the angle of repose, the microspheres were poured through a funnel, which was fixed at a position such that its lower tip was at a height of 2 cm above the surface. The microspheres were poured till the time when the tip of the microsphere pile surface touched the funnel. The $\tan^{-1}$ ratio of the height of the pile and the radius of the pile base gave the angle of repose. The angle of repose was determined by the following formula [8]:

$$\theta = \tan^{-1}\frac{h}{r}.$$

Determination of Carr's index

The Carr's index was determined using the following formula [8]:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100.$$

Determination of particle size and morphological characterization

The mean particle size of the microspheres was determined using an optical microscope containing a micrometer with a calibrated eyepiece (7001-IMS Vaiseshika, Ambala, India). The mean particle size was calculated by measuring 300 particles. The morphological characterization was done by using a scanning electron microscope (EVO-50, ZEISS, Birmingham, UK). The samples were coated with silver under vacuum using a Polaron SEM coater (Polaron, Birmingham, UK) [9].

Determination of drug loading and entrapment efficiency

Precisely weighed (10 mg) microspheres were crushed and dispersed into 25 ml phosphate buffer (pH 6.8) without any material loss for the determination of encapsulation efficiency. The prepared mixture was shaken for 24 h. After 24 h, the solution was filtered, and the filtrate was analyzed for the drug content by a UV spectrophotometer (UV-3000$^+$, LabIndia Instruments, Mumbai, India) at 277 nm after suitable dilution. The drug loading and entrapment efficiency were calculated using the following formula [10].

$$\text{Drug loading (\%)} = \frac{\text{Drug weight within the microspheres}}{\text{Weight of microspheres}} \times 100,$$

$$\text{Drug entrapment (\%)} = \frac{\text{Actual amount of drug present in microspheres}}{\text{Theoretical amount of drug added in the microspheres}} \times 100.$$

Assessment of metronidazole release from the microspheres and mathematical modeling of release data

The drug release rate from different formulations was determined using USP type II dissolution apparatus (DS8000, LabIndia, Mumbai, India). A dissolution medium (phosphate buffer, pH 6.8, 900 ml) filled in the dissolution vessel and the temperature was maintained at 37 ± 0.5°C. Microspheres equivalent to 50 mg of metronidazole were placed in the dissolution vessel and the paddle was rotated at 50 rpm. Aliquots were withdrawn at every 15 min in the first hour and then at every hour till the 4th h followed by 6th and 8th h. Samples were then analyzed by a UV-spectrophotometer at 277 nm. The study was conducted in triplicate.

Release kinetics

To determine the release kinetics of metronidazole from the microspheres, the drug release data was fitted according to zero and first-order equations. Further, the dissolution data was plotted according to Higuchi and Peppas equations to find out the exact release mechanism. The following sets of kinetic equations were used to fit the *in vitro* drug release data to determine the drug release kinetics and mechanism [11].

Zero-order kinetic model

$$M_0 - M_t = k_0 t,$$

First-order model

$$\ln (M_0/M_t) = K_1 t,$$

Higuchi's model

$$Mt = K\sqrt{t},$$

Peppas' model

$$M_t/M_\infty = kt^n.$$

where, M_o, M_t and M_∞ are drug amount taken initially, at a particular time, and at infinite time, respectively. M_o and M_t are the weight of the drug taken initially and at time t, respectively. The terms k, k_o, k_1 and K refer to the release kinetic constants.

Results and Discussion

Pre-Formulation Studies

Physical characterization of metronidazole was done for its physical properties, and it was observed that the metronidazole used for the development of the microspheres was an odorless, white, free-flowing, crystalline powder. The physical properties were found to be similar to those reported in the literature (Moffat et al., 2005). This proved the identity of metronidazole. On calibration of the melting point apparatus with L-ascorbic acid AR (observed melting point 141°C, reported melting point 142–145°C) and sodium bicarbonate AR (observed melting point 271°C, reported melting point 270°C), a correction factor of –1°C was documented. The observed melting point of metronidazole was 160°C, which corresponds to the literature value of 158–163°C, and proves the identity and purity of the metronidazole. The solution of metronidazole, having a concentration of 8 µg/ml in phosphate buffer (pH 6.8), was scanned for λ_{max} in 200–400 nm in the spectrum basic mode. The experimental λ_{max} was 276 nm, corresponding to the reported λ_{max} value of 277 nm. The scan spectrum of metronidazole in phosphate buffer (pH 6.8) is shown in Figure 1.

A compatibility study between the selected drug (metronidazole) and excipients was carried out using the FTIR peak matching method. The results of the FTIR studies of metronidazole, Eudragit S 100 and a physical mixture of metronidazole and Eudragit S 100 to determine any possible interaction between the drug and the polymer are shown in Figure 2. The major spectral bands of the metronidazole and Eudragit S 100 are presented in Table 2. The characteristic peaks of metronidazole were also present in the FTIR spectrum of the physical mixture of the drug and excipients with some broadening and reduction in peak intensity. There were no extra peaks in the spectrum of the physical mixture, which is evidence that there was no chemical interaction between the drug and the polymer. No significant changes in terms of peak sifting, appearance or disappearance of the peaks were noted with the drug, polymers and mixtures. This confirmed the absence of chemical interaction between the metronidazole and the excipients. No change in color of the physical mixture was observed after 60 days at room temperature (25°C).

Characterization of Developed Microspheres

Formulation F11, F12 and F13 were not formed, which might be due to the insufficient stirring effect (F13), or either insufficient (F11) or excess amount (F12) of the solvent. This leads to the precipitation or agglomeration of the polymer. The bulk density and tapped density of the microspheres were determined

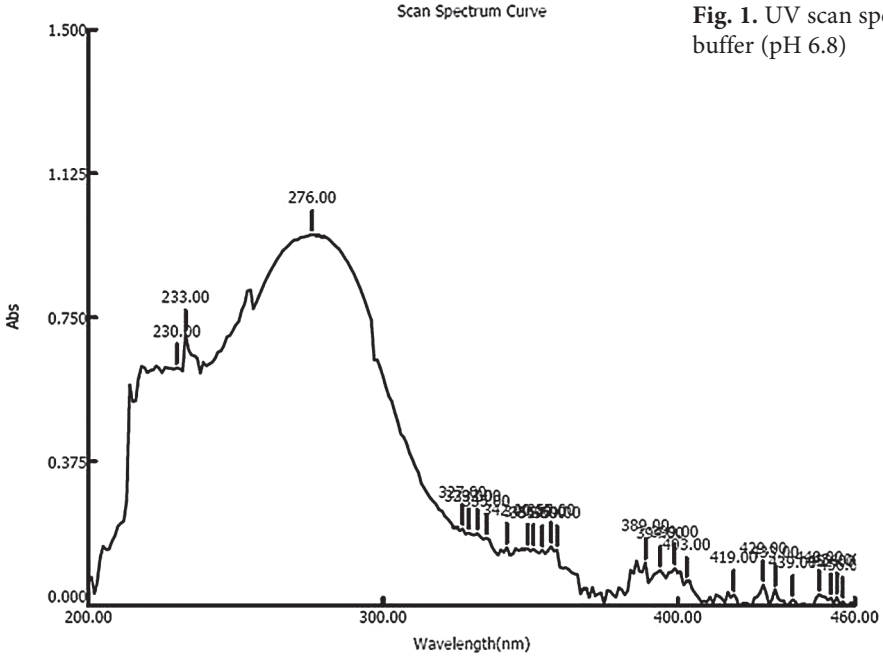

Fig. 1. UV scan spectrum of metronidazole in phosphate buffer (pH 6.8)

Table 2. Assignment of bands in FTIR spectra for metronidazole and Eudragit S 100

Sample	Standard IR peaks (cm^{-1})	Observed IR peaks (cm^{-1})	Assignment
Metronidazole	1550–1350	1537	N=O
	3100–3000	3097	=C-H stretch
	1475–1365	1408, 1390	-CH3 bending
	1465	1475	-CH2 bending
	1300–1000	1074	-C-O alcohol
	1600 and 1475	1475	C=C alkene
Eudragit S 100	1725–1700	1720	C=O carboxylic acids
	3400–2400	3170	O-H carboxylic acids
	1375 and 1450	1375	-CH3 bend
	1750–1730	1732	C=O ester
	3000–2850	2953	-C-H stretch
	3100–3000	3005	C-H stretch alkene

using USP bulk density apparatus and the results are represented in Table 3. The bulk density and tapped density of all the formulations were found to be almost similar, indicating similar flow properties. A slight difference in bulk density and tapped density indicates that the change in volume is very small even after 50 tappings, which confirms the similar particle size range and reproducibility in drug content.

Hausner ratio

Hausner ratio is related to inter-particle friction. It is an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of the particles. A higher Hausner ratio and more fine particles indicate greater cohesion between particles while a low range of Hausner ratio indicates good flowability. The desirable value of the Hausner ratio is < 1.25 for good flow of particles. The Hausner ratio of different formulations was determined and found to be in the range of 1.046 ± 0.309 to 1.270 ± 0.413 (Table 3). The results of the Hausner ratio test suggest that formulation F3, F4 and F7 exhibited good flow property. Formulation F1 exhibited very poor flow property, while the other formulations exhibited poor flow property.

Angle of repose

It is well experienced that the particle size and shape influences flowability. The fine particles (< 100 mm) tend to be more cohesive and therefore less free-flowing, whereas larger, denser particles tend to be free-flowing. The angle of repose value increases in the case of a particle having irregular surface. In the present study, the angle of repose increased from 24.29 ± ± 0.33 to 34.21 ± 0.61, indicating a decrease in flowability of the microspheres (Table 3). This is also supported by the results of the Hausner ratio calculations. Characterizing the flow property, the angle of repose values of all microspheres did not exceed 33.25° and the microspheres were accepted as free-flowing.

Carr's index

A high Carr's index is indicative of the tendency to form bridges between the particles. The smaller the Carr's index value, the better the flow properties. A value of 5–15 indicates excellent, 12–18 good, 19–21 fair, 22–35 poor, 36–40 very poor and > 40 extremely poor flow. The results show that formulations F3–F6 (13.24 ± 0.4 to 14.76 ± 0.54) had a good flow property, which is also supported by the Hausner ratios (Table 3). On the other hand, the other formulations exhibited fair to poor flow property.

Particle size and morphology

From the SEM micrographs it is apparent that the metronidazole-loaded microspheres were predominately spherical in appearance and had small particle size (680.90 μm to 890.03 μm). The surface was observed to be smooth and dense (Figure 3 and 4). The results suggest a positive effect of polymer concentration on mean particle size. This effect might be due to the increase in viscosity of the solution. The solvent system and increasing stirring rate had a negative effect on particle size.

Drug loading and entrapment efficiency

The drug entrapment efficiency of metronidazole was found to be high in almost all of the formulations. It was observed that as the concentration of polymers increased, the drug entrapment efficiency also increased. This might be due to the enhanced viscosity. Initially, the drug entrapment efficiency was increased with an increase in the amount of solvent system (formulation F10, 81.02 ± 2.14) and then decreased with

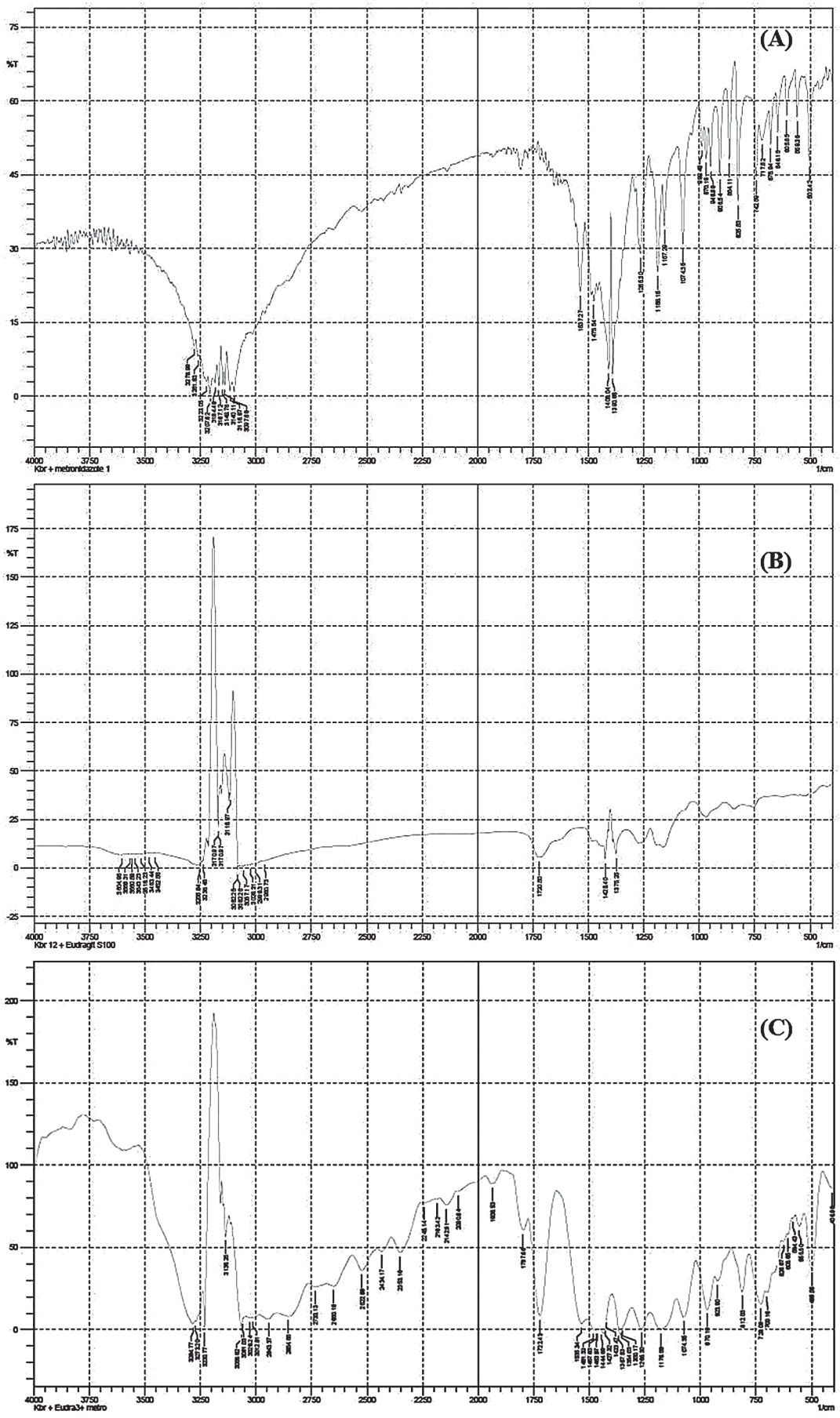

Fig. 2. FTIR spectrum of pure metronidazole (A), Eudragit S 100 (B) and physical mixture (C)

Table 3. Evaluation parameters of developed microspheres (mean ± SD, n = 3)

Formulation code	Evaluation parameters							
	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner ratio	Angle of repose (μ)	Carr's index	Drug loading (%)	Drug entrapment (%)	Particle size (μm)
F1	0.124 ± 0.032	0.205 ± 0.068	1.650 ± 0.521	33.25 ± 0.42	19.51 ± 1.36	4.53	60.15 ± 2.14	730 ± 0.52
F2	0.134 ± 0.021	0.169 ± 0.098	1.270 ± 0.413	29.21 ± 0.35	20.71 ± 0.56	4.67	56.11 ± 1.51	890 ± 0.46
F3	0.144 ± 0.079	0.150 ± 0.051	1.046 ± 0.309	28.21 ± 0.22	14.40 ± 0.24	7.05	69.41 ± 4.26	755 ± 1.22
F4	0.127 ± 0.053	0.149 ± 0.013	1.173 ± 0.032	31.51 ± 0.23	14.76 ± 0.54	7.11	71.32 ± 5.45	860 ± 0.82
F5	0.131 ± 0.032	0.151 ± 0.092	1.152 ± 0.142	27.32 ± 0.29	13.24 ± 0.4	5.94	65.25 ± 3.05	770 ± 1.11
F6	0.137 ± 0.017	0.158 ± 0.142	1.153 ± 0.215	24.29 ± 0.33	13.29 ± 0.32	7.54	73.22 ± 3.12	840 ± 0.64
F7	0.129 ± 0.112	0.168 ± 0.026	1.302 ± 0.124	29.64 ± 0.56	23.21 ± 0.32	6.72	68.43 ± 2.31	680 ± 0.37
F8	0.132 ± 0.078	0.163 ± 0.061	1.234 ± 0.041	34.21 ± 0.61	19.01 ± 0.41	6.97	75.95 ± 4.25	870 ± 2.41
F9	0.121 ± 0.018	0.153 ± 0.074	1.264 ± 0.056	33.16 ± 0.10	20.91 ± 0.44	4.94	59.25 ± 3.05	690 ± 0.81
F10	0.139 ± 0.015	0.193 ± 0.011	1.388 ± 0.192	26.22 ± 0.25	27.97 ± 0.64	8.59	81.02 ± 2.14	880 ± 0.57
F14	0.123 ± 0.041	0.161 ± 0.017	1.308 ± 0.121	28.29 ± 0.32	23.60 ± 0.54	7.14	68.43 ± 3.54	830 ± 1.21
F15	0.128 ± 0.022	0.164 ± 0.032	1.281 ± 0.081	27.12 ± 0.11	21.95 ± 0.43	6.90	72.22 ± 2.34	800 ± 3.21

further increases in solvent amount. This might be due to the decrease in the system viscosity and matrix density at higher solvent levels.

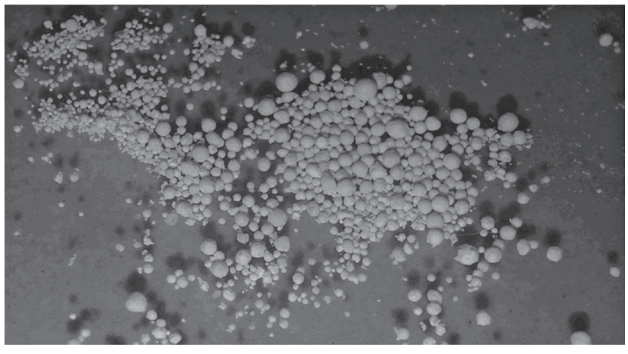

Fig. 3. Photomicrograph of the optimized batch (formulation F15)

***In vitro* metronidazole release from the microspheres**

Since the acrylic polymer used for the development of the microspheres is not soluble at acidic pH, a phosphate buffer of pH 6.8 was selected for the dissolution study. An initial burst release might be due to the release of surface drug. Stirring speed had a positive effect on drug release at lower polymer concentrations. A sustained drug release was observed from all the formulations during the 10 h dissolution study. Formulation F9 showed maximum drug release (79.69 ± 2.45%) after 10 h. This might be due to the lower level of polymer and smaller particle size. The rate of drug release was decreased with an increase in polymer concentration. This might be due to the increased viscosity of the solution, which leads to increase in particle size (Figure 5).

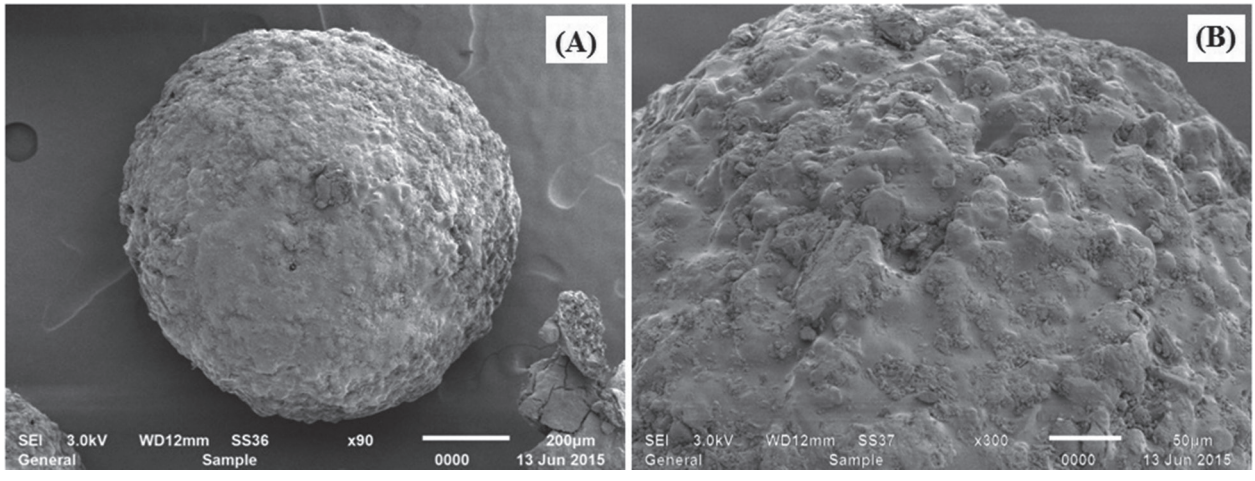

Fig. 4. SEM images of the optimized batch (formulation F15), showing the general appearance (A) and surface morphology (B). Scales are given on individual micrograph

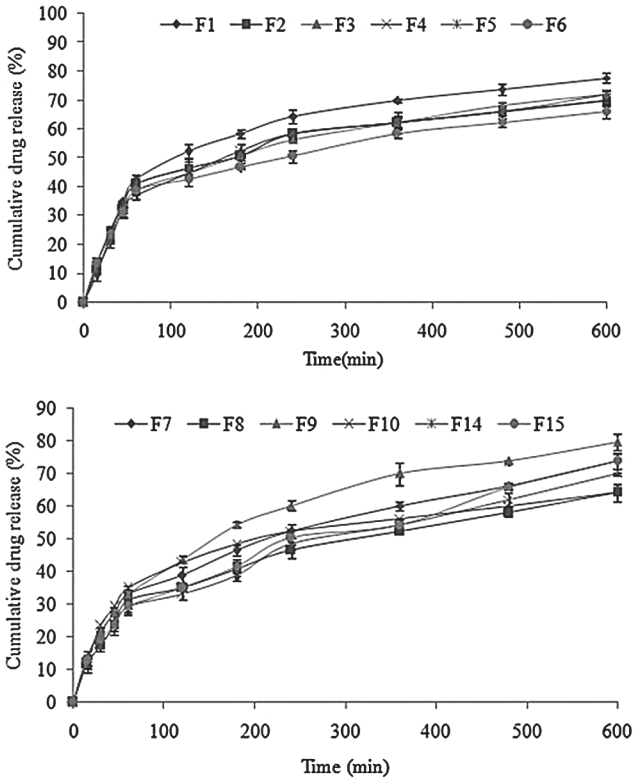

Fig. 5. *In vitro* drug release profiles of different batches of microspheres (formulation F1–F15) containing metronidazole in phosphate buffer, pH 6.8 (mean ± SD, n = 3)

The drug release data was analyzed using the zero order and first order equations to determine the drug release kinetics from the beads. For further confirmation of order of release, the dissolution data was plotted according to the Higuchi equation, which gives steady state drug release.

$$Q = (D\ \varepsilon/\tau)\ (2C_{tot} - C_s)\ C_s\ t_{1/2}\ ,$$

where Q is the amount of drug released per unit area exposed to the solvent, D is the diffusion coefficient of the drug in the permeating fluid, ε Is the porosity of the matrix, τ is the tortuosity of the matrix, C_{tot} is the concentration of the solid drug in the dissolution medium, C_s is the saturation drug and t is the time. Assuming that the diffusion coefficient and other parameters remain constant during the release, the above equation reduces to

$$Q = Kt_{1/2}\ .$$

Thus, for a diffusion-controlled release mechanism, a plot of the cumulative percentage of drug released Vs square root of time should be linear. The linearity of the plots was confirmed by the calculation of a correlation coefficient.

To find out the mechanism of drug release, and also to verify whether diffusion is Fickian or non-Fickian, the *in vitro* dissolution data of all the batches was plotted according to the Peppas equation, in which the log cumulative percentage of drug release was plotted against log time. From the kinetic data, it was evident that the zero and first order kinetic models were not followed by the drug release data. The Higuchi plots were linear and had correlation coefficients ranging between 0.913 and 0.991 in a phosphate buffer (pH 6.8) which indicates diffusion-controlled drug release. The developed microspheres were found to follow Higuchi's kinetic model. Further, the drug release data followed Peppas' model for all the formulations and the release was diffusion controlled. The calculated slope values of the Peppas equations gave a value less than 0.5, which confirmed that the release mechanism of metronidazole from the microspheres was a Fickian diffusion without swelling (Table 4).

Table 4. Correlation coefficient values (r) and release exponent (n) for drug release from different batches of developed microspheres (Formulation F1–F15)

Formulation Code	Zero order	First order	Higuchi's model	Peppas' model	
	r^2	r^2	r^2	r^2	n
F1	0.733	0.527	0.915	0.826	0.484
F2	0.730	0.566	0.913	0.888	0.431
F3	0.778	0.647	0.945	0.937	0.410
F4	0.748	0.620	0.930	0.925	0.398
F5	0.743	0.576	0.920	0.891	0.434
F6	0.750	0.629	0.926	0.918	0.379
F7	0.784	0.739	0.981	0.977	0.431
F8	0.840	0.717	0.973	0.967	0.436
F9	0.842	0.720	0.977	0.981	0.470
F10	0.738	0.611	0.924	0.922	0.395
F14	0.891	0.774	0.989	0.981	0.459
F15	0.898	0.793	0.991	0.989	0.453

A controlled release system (microspheres) of metronidazole was designed and optimized effectively to increase its concentration at the target site, the colon, for the effective treatment of IBD. Microspheres were prepared via the solvent evaporation method. The major advantages of the preparation technique are short processing time, lack of exposure of the drug to high temp, and high drug encapsulation. Microspheres of acrylic polymer such as Eudragit S100 were successfully prepared. The drug:polymer ratio (1:1.5) and liquid paraffin (heavy:light, 1:1) and 20 ml n-hexane supported the formation of the microspheres with a high level of drug encapsulation. The drug was dispersed in the shell of the microsphere but showed an initial burst effect during its release in phosphate buffer (pH 6.8). The release of the drug was found to follow Fickian diffusion without swelling. Eudragit S 100 showed excellent control on the release of the drug from the microspheres in the phosphate buffer (pH 6.8), due to their enteric nature. The system showed extended release. Based on the results obtained from the laboratory tests, formulation F15 was selected as the optimized formulation. Overall, a controlled-release colon-targeted microparticulate system for metronidazole has been successfully developed. The developed microspheres had ideal physical properties such as that they were smaller in size, had high drug entrapment and controlled drug release over a period of 10 h in the colonic conditions, which, in turn, improved the local availability of the drug. This optimized system (formulation F15) is expected to provide clinicians with a new choice of safe product with better bioavailability for the treatment of IBD. Therefore, it can be concluded that the microspheres are a suitable drug delivery system for metronidazole, and may be used for effective treatment of IBD. The preliminary laboratory test results of the present research work gave an idea about the formulation aspects of microparticulate (microspheres) controlled-release dosage forms.

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