DEVELOPMENT AND CHARACTERIZATION OF MICROBALLONS BASED DRUG DELIVERY SYSTEM OF MESALAMINE HYDROCHLORIDE

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ABSTRACT

Objective: An objective of the present investigation was to prepare Eudragit S-100: Eudragit RS-100 microballons of mesalamine hydrochloride and evaluate for their anti-inflammatory activity. Material method: Microballons were prepared by quasi solvent evaporation method using different ratios of Eudragit S-100: Eudragit RS-100 (1:1 to 1:4 % w/w), mesalamine hydrochloride (40 to 100% w/w), PVA concentration (0.5 to 1.25 %), stirring speeds (300-500 rpm) and temperature (25°C, 37°C and 45°C). The yield of preparation and encapsulation efficiency was high for all hollow microballons formulation. Results and Discussion: Microballons prepared by using Eudragit S-100: Eudragit RS-100 ratio 1:2 %w/w, 80:100% w/w) drug concentration, 0.75 % w/v concentration of surfactant (PVA), stirring speed 400 rpm, and temperature 37°C were selected as an optimized. The optimized microballs formulation were evaluated for their surface morphology, particle size and size distribution, percentage drug entrapment and in vitro mesalamine release in SGF (pH 1.2), and PBS (pH 7.4). The % Cumulative release was found 91.2±3.5% in SGF (pH 1.2) and 89.2±3.5 in PBS (pH 7.4) up to 24 hrs. The data of drug released revealed that the microballs formulation follows a diffusion controlled drug release mechanism. In vivo evaluation of the optimized microballs formulation were carried out in healthy male albino rats by measuring anti inflammatory activity produced after oral administration of optimized microballs formulation at a dose of (equivalent to 50 mg/kg of mesalamine hydrochloride). The progressive reduction in paw volume was observed till the end of study and maximum upto 0.4 ml after 2 hr. Conclusion: It is concluded from the present investigation that Eudragit S-100: Eudragit RS-100 microballons bearing mesalamine are promising controlled release vector for effective treatment of inflammation. Keywords: microballs, hollow microspheres, anti-inflammatory activity, mesalamine hydrochloride, solvent diffusion evaporation method.

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. From immediate release to site specific delivery, oral dosage forms have greatly progressed. It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time. Dosage forms with a prolonged GRT, i.e. gastro retentive dosage forms (GRDFs) will provide us with new and important therapeutic options.

Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, e.g., treatment of peptic ulcer disease. Furthermore, improved bioavailability is expected for drugs that are absorbed readily in the GI tract upon release such drugs can be delivered ideally by slow release from the stomach for sustained action.

Microballons are gastro-retentive drug delivery systems based on non-effervescent approach. Microballons are in strict sense, spherical empty particles without core. They are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid biodegradable microballons incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Gastro-retentive floating microballons are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. When microballons come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microballons. However a minimal gastric content needed to allow proper achievement of buoyancy.

The mesalamine hydrochloride requires frequent dosing due to short biological half-life (5hr) and absorbed 20-30% orally. The traditional oral sustained release formulations release mesalamine hydrochloride but erratically absorbed through the intestine and mucosal wall of large intestine were the narrow absorption window exist is also responsible for colonic metabolism and poor bioavailability of drug (10-35%). Therefore sustained
release dosage form of mesalamine hydrochloride prepared by the conventional technology may not be very successful and clinically acceptable so that controlled release intragastric floating microballons formulation of mesalamine hydrochloride eliminates the problems associated with conventional dosage forms.

MATERIAL

Eudragit S-100 and Eudragit RS-100 was generously supplied as a gift samples by Rohm GmBH, Germany. Mesalamine Hydrochloride generously supplied as a gift sample from Sun Pharma Vadodara, Polyvinyl alcohol, Dichloromethane and ethanol were purchased from CDH India. All other chemicals and reagents were used of analytical grade.

METHOD AND PREPARATION OF MICROBALLONS FORMULATION

Microballons with an internal hollow structure were prepared by solvent diffusion evaporation method described by Kawashima et al., (2001) with little modification. For this 500 mg of eudragit S-100 and 500 mg of eudragit RS-100 was dissolved in 1:1 (ethanol: dichloromethane) then 100 mg of mesalamine was homogeneously dispersed in it. This solution was slowly introduced into 200 ml of 0.75% w/v PVA solution with constant stirring at 400 rpm using a mechanical stirrer equipped with a blade propeller (Remi, India) for 3-4 hr. The microballons were formed, collected by filtration, washed three times with distilled water and dried at room temperature.

Optimization of Formulation and Process Variables

Various formulation and process variables i.e. polymer and drug concentration, phase volume ratio, surfactant concentration, stirring time and stirring speed which could affect the preparation and properties of microspheres were identified and studied. The optimization was done on the basis of particle size and drug entrapment efficiency.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Formulation code ($)</th>
<th>Formulation / Process variables</th>
<th>Particle size (µm)</th>
<th>Particle Shape</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>MC1</td>
<td>Eudragit S-100 and Eudragit RS-100 (% w/w)</td>
<td>65.7±1.4</td>
<td>Hollow Ellipsoidal</td>
</tr>
<tr>
<td>2.</td>
<td>MC2</td>
<td>1:2</td>
<td>78.2±2.5</td>
<td>Hollow Circular</td>
</tr>
<tr>
<td>3.</td>
<td>MC3</td>
<td>1:3</td>
<td>91.4±1.92</td>
<td>Circular</td>
</tr>
<tr>
<td>4.</td>
<td>MC4</td>
<td>1:4</td>
<td>128.3±3.3</td>
<td>Irregular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mesalamine Hydrochloride Conc. (% w/w)</td>
<td></td>
<td>% EE</td>
</tr>
<tr>
<td>1.</td>
<td>MC2D1</td>
<td>40:100</td>
<td>71.4±3.1</td>
<td>82.8±1.5</td>
</tr>
<tr>
<td>2.</td>
<td>MC2D2</td>
<td>60:100</td>
<td>79.4±2.1</td>
<td>87.5±1.4</td>
</tr>
<tr>
<td>3.</td>
<td>MC2D3</td>
<td>80:100</td>
<td>83.3±2.6</td>
<td>91.2±1.8</td>
</tr>
<tr>
<td>4.</td>
<td>MC2D4</td>
<td>100:100</td>
<td>85.4±2.1</td>
<td>75.2±2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surfactant PVA conc. (% w/v)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>MC2D3E1</td>
<td>0.5</td>
<td>89.4±3.4</td>
<td>82.5±3.2</td>
</tr>
<tr>
<td>2.</td>
<td>MC2D3E2</td>
<td>0.75</td>
<td>81.2±2.9</td>
<td>90.2±3.4</td>
</tr>
<tr>
<td>3.</td>
<td>MC2D3E3</td>
<td>1.0</td>
<td>78.6±2.4</td>
<td>73.8±1.6</td>
</tr>
<tr>
<td>4.</td>
<td>MC2D3E4</td>
<td>1.25</td>
<td>66.8±1.9</td>
<td>67.7±1.9</td>
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<tr>
<td></td>
<td></td>
<td>Stirring Speed (rpm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>MC2D3E2R1</td>
<td>300</td>
<td>88.4±3.9</td>
<td>82.8±3.9</td>
</tr>
<tr>
<td>2.</td>
<td>MC2D3E2R2</td>
<td>400</td>
<td>74.2±3.5</td>
<td>91.4±3.2</td>
</tr>
<tr>
<td>3.</td>
<td>MC2D3E2R3</td>
<td>500</td>
<td>68.2±2.7</td>
<td>74.3±2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temperature ( ºC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>MD4C5E2R2T1</td>
<td>25 ºC</td>
<td>81.4±3.1</td>
<td>82.8±1.5</td>
</tr>
<tr>
<td>2.</td>
<td>MD4C5E2R2T2</td>
<td>37 ºC</td>
<td>74.4±2.1</td>
<td>87.5±1.4</td>
</tr>
<tr>
<td>3.</td>
<td>MD4C5E2R2T3</td>
<td>45 ºC</td>
<td>87.3±2.6</td>
<td>77.2±1.8</td>
</tr>
</tbody>
</table>

Optimization of polymer (Eudragit S-100 and Eudragit RS-100) concentration

For optimization of polymer concentration, the microballons formulations were prepared with varying concentration of Eudragit S-100 and Eudragit RS-100 i.e. 1:1 to 1:4 % w/w) while keeping other parameters constant. Optimization was done on the basis of average particle size and shape. The observations are recorded in Table 1.
Optimization of Mesalamine Hydrochloride concentration

For optimization of drug concentration, the microballons formulations (MC2) were prepared with varying percentage of mesalamine viz, 40:100, 60:100, 80:100 % w/w of drug while keeping other parameters constant. Optimization was done on the basis of drug loading and particle size. The observations are recorded in Table 1.

Optimization of surfactant (PVA) concentration

For optimization of surfactant (PVA) concentrations, the microballons formulation (MC2D3) was prepared with varying concentrations of surfactant viz 0.5 to 1.25 % w/v in external phase while keeping the other variables constant. Furthermore optimization was done on the basis of drug loading and particle size. The observations are recorded in Table 1.

Optimization of stirring speed

For the optimization of stirring speed, formulation (MC2D3E2R2) was selected and microballons were prepared by taking varying stirring speed i.e. 300, 400 and 500 rpm by mechanical stirring (Remi, India) while keeping the other variables constant. The optimization was done on the basis of average particle size and maximum % drug loading. The observations are recorded in Table 1.

Optimization of temperature

For the optimization of temperature formulation (MC2D3E2R2) was selected and microballons formulation were prepared by taking varying stirring time i.e. 25°C, 37°C and 45°C while keeping the other variables constant. The optimization was done on the basis of average particle size and maximum % drug loading efficiency. The observations are recorded in Table 1.

On the basis of formulation and process variable studies the optimized microballons were prepared by the following formula:

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Variables</th>
<th>Optimized value</th>
<th>Final code for optimized preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Eudragit S-100: Eudragit RS-100 Conc. (% w/w).</td>
<td>1:2</td>
<td>MD4C5E2R2T2</td>
</tr>
<tr>
<td>2.</td>
<td>Mesalamine Conc. (%w/w)</td>
<td>80:100</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>PVA Conc.</td>
<td>1.5 (% w/v)</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Stirring speed</td>
<td>500 rpm</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Temperature (° C)</td>
<td>37 C</td>
<td></td>
</tr>
</tbody>
</table>

Characterization of Optimized Microballons Formulation

Scanning electron microscope (SEM) for surface morphology study

SEM was used as a visualizing aid for surface morphology. The samples for SEM were prepared by lightly sprinkling the microspheres powder on a double adhesive tape, which was stuck on an aluminium stub. The stubs were then coated with gold to a thickness of about 300 Å using a sputter coater. All samples were examined under a scanning electron microscope (LEO 435 VP, Eindhoven Netherlands) at an acceleration voltage of 25 kV and photomicrographs were taken at suitable magnification.

Table 2: The optimized variables for the preparation of microballons were selected as follows

![Figure 1: (A) Phase contrast photograph (100X) and (B) SEM Photomicrograph of microballons at (650X)](image)

Average particle size, surface charge and polydispersity index

The average particle size was determined by optical microscopy method using calibrated stage and ocular micrometer (Erma, Japan). The particle size distributions are represented by the average size. The polydispersity
The polydispersity index (PDI) is a dimensionless measure for the breadth of a particle size distribution and was calculated using the following formula:

\[
PDI = \frac{\text{Standard deviation}}{\text{Average particle size}}
\]  

Theoretically polydispersity index is zero for a monodisperse colloidal suspension. However the standard dispersion of particles with a PDI of about 0.05 is considered as monodispersed and with PDI greater than 0.5 is assumed to have a broad size distribution. The zeta potential of a particle is the overall charge that the particle acquires in a particular medium and measured by a Zetasizer (Malvern Instruments, UK). The magnitude of the measured zeta potential is an indication of the repulsive force that is present and can be used to predict the long term stability of the product.

### Table 3: Characterization of optimized microballs formulation

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation Code</th>
<th>Particle size (µm)</th>
<th>Zeta Potential (mV)</th>
<th>PDI</th>
<th>% EE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>MD4C5E2R2T2</td>
<td>78.2 ±3.4</td>
<td>-5.4</td>
<td>0.37</td>
<td>91.3 ± 1.2%</td>
</tr>
</tbody>
</table>

* Eudragit S-100: Eudragit RS-100 Conc.: 1:2 (% w/w), drug conc.: (80 % w/w), pva conc.: (0.75 % w/v), stirring speed: 500 rpm, and temperature 37°C. Values are expressed as mean ±SD, n=3.

### In vitro buoyancy test

The floating test of optimized mesalamine hydrochloride microballs formulation (MD4C5E2R2T2) was carried out using dissolution test apparatus USP XXII method II. 500 mg of microballs were immersed in 900 ml simulated gastric fluid SGF (pH 1.2) maintained at 37 ± 2°C, which was agitated by a paddle rotated at 100 rpm. The paddle blades were positioned at the surface of dissolution medium. The microballs floating on the surface of SGF (pH 1.2) were recovered with a sieve No 120 (34µm) at every 1 hr time interval for 8 hours. The microballs so collected were dried and weighed. The floating percentage of the microballs was defined as the weight ratio of the floating microballs against the total weight of microballs in the floating test. The buoyancy of the microballs was calculated by the following equation:

\[
\text{Bouyancy (％)} = \frac{Q_f}{Q_f + Q_s} \times 100
\]

where Q<sub>f</sub> and Q<sub>s</sub> are the weights of the floating and settled microballs respectively. The buoyancy (％) of optimized mesalamine hydrochloride microballs formulation in SGF (pH 1.2) is shown in Figure 2 and 3.

![Figure 2: Photographs of in vitro buoyancy of optimized microballs in SGF (PH 1.2)](image-url)
100 mg of microballons were taken, crushed by trituration and suspended in 10 ml of dichloromethane for digestion of the microballons. The digested homogenate was centrifuged at 3000 rpm for 5 min filter through of 0.2 μm (Millipore, USA). After appropriate dilution with 0.1N HCl mesalamine concentration was assayed spectrophotometrically (Shimadzu 1800, Japan) at 300 nm.

The encapsulation efficiency (EE) and the loading capacity (LC) of the microballons for mesalamine were calculated by the following equations:

\[
\% \text{EE} = \frac{(X-Y)}{X} \times 100\% \\
\% \text{LC} = \frac{(X-Y)}{Z} \times 100\%
\]

Where X is the total amount of the drug added, Y was the free amount of the drug in the supernatant, and Z is the weight of microballons.

The in vitro mesalamine release study from microspheres was carried out by the paddle type-II dissolution apparatus specified in USP XXIII. For this 500 mg of microspheres was spread over the surface of 900 ml of dissolution medium. The content was rotated at 100 rpm by placing the paddle on surface but dipped medium and thermostatically controlled at 37±2°C. Perfect sink condition was prevailed during the drug dissolution. The release was tested in dissolution medium of SGF (pH 1.2) and PBS (pH 7.4). An aliquot of the release medium was withdrawn at predetermined time intervals and an equivalent amount of fresh medium was added to the release medium. The collected samples were filtered through 0.45µm-syringe filter (Millipore, India) and analyzed spectrophotometrically. The observations are graphically shown in Figure 5.

**STABILITY STUDIES:**

**Effect of storage temperature on structural integrity and particles size**

The change in structural integrity and particles size of the optimized microballons formulation when stored in amber colored glass bottles at 4±1°C, 25±1°C and 40±1°C temperatures was determined using optical microscopy method (Erma, Japan) after a definite period of time of i.e. 15, 30 and 45 days.
Figure 5: Effect of storage temperature on particle size of microballons formulation.

Effect of storage on % residual drug content
The % residual drug content of stored optimized microballons formulation after storage for a specified period of time i.e. 15, 30 and 45 days was determined by digesting the microballons with 5 ml of dichloromethane then the digested homogenate was centrifuged at 3000 rpm for 5 min filter through of 0.2 μm (Millipore, USA). After appropriate dilution with PBS (PH-7.4) mesalamine was assayed spectrophotometrically at 300 nm. The % residual drug content of each sample was determined in triplicate and values are shown in Figure 7.

Figure 6: Effect of storage temperature on % residual drug content in microballons formulation.

IN VIVO RADIOGRAPHICAL STUDY
In order to assess the gastro-retentive efficacy and buoyancy microballons formulation, the % buoyancy was determined by using barium sulphate X-ray contrast medium containing 15% barium sulphate. The study was carried out with three healthy male rabbits free of detectable gastrointestinal diseases or disorders. The study was carried out under the guidelines compiled by CPCSEA (Committee for the purpose of control) Supervision of Experiments on Animal, Ministry of Culture, Government of India and the local institutional Animal Ethics Committee of Adina institute of pharmaceutical sciences approved the study protocol. The rabbits were fasted overnight. The rabbits were administered optimized microballons formulation (MD4C5E2R2T2) with 25 ml of water and intragastric behaviour of the microballons was observed by taking a series of X-ray photographs at different time intervals as shown in Figure 8 (a, b, c, d).
**IN VIVO ANTI-INFLAMMATORY ACTIVITY**

The albino rats (150-200) gm of either sex were randomly distributed into four groups containing 6 rats in each group and they kept under standard laboratory housing conditions. The animal weight range. They were fasted for 24 hr before drug treatment. The animals were deprived of food and water during the experiment. The initial paw volume of right and left paw of each group of rats were determined by mercury displacement method\(^7\). Right paw of each groups of animal and kept as control. Rats of group I were administered 0.1 ml of (1% w/v) carrageenan in the plantar region of the left paw and kept as a negative control group. The groups II were administered 10 ml solution of plain drug (equivalent to 50 mg/kg of mesalamine hydrochloride p.o) 30 min prior administration 0.1 ml of (1% w/v) carrageenan in the plantar region of the left paw. The groups III were administered 10 ml optimized microballons (MD4C5E2R2T2) suspension (equivalent to 50 mg/kg of mesalamine hydrochloride p.o) 30 min prior administration 0.1 ml of (1% w/v) carrageenan in the plantar region of the left paw.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation code</th>
<th>Dose</th>
<th>Paw volume measured by mercury displacement (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time (min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Control (0.1 ml of 1% w/v carrageenan)</td>
<td>50 mg/kg</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>Plain drug solution</td>
<td>Equivalent to (50 mg/kg of mesalamine hydrochloride)</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>MD4C5E2R2T2</td>
<td>Equivalent to (50 mg/kg of mesalamine hydrochloride)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

**RESULT AND DISCUSSION**

Eudragit S-100 and Eudragit RS-100 microballons were prepared by solvent diffusion method as reported by Kawashima et al., (2001). 1:2 Eudragit S-100 and Eudragit RS-100 matrix solution was sequentially dispersed in 0.75% w/v PVA solution. PVA solution was chosen as the external phase because ethanol/ dichloromethane mixture
as an internal phase is not miscible with PVA solution and the Eudragit S-100 and Eudragit RS-100 is not soluble in it. As the dispersed droplets of Eudragit S-100 and Eudragit RS-100 solution collided in PVA solution, they formed an inter polymer complex. The droplets of polymer gradually solidified and forming a hollow cavity by ethanol and DCM diffusion from the internal phase. The effect of formulation variables e.g. polymer ratio, drug concentration, surfactant concentration and process variables e.g. stirring speed and temperature were studied in order to optimized the formulation. These variables influence the shape, size and total drug loading efficiency and in vitro drug release hence these parameters were optimized to prepare microballs of small size, good drug loading efficiency and good drug release at the gastrointestinal pH.

Eudragit S-100 and Eudragit RS-100 employed in the preparation of microballs formulation was optimization by varying ratio of concentration viz. 1:1, 1:2, 1:3 and 1:4% w/v etc. The formulation was optimized on the basis of average particle size and shape. Increasing the concentration of Eudragit RS-100, particle size increased but above 1:2 polymer ratio the shape was drastically changed to ellipsoidal and deformed integrity. So that formulation MC2 showed size of 78.2±2.5 µm with hollow in nature and circular in shape (Table 1) were selected as optimum for study.

The loading of drug was also optimized on the basis of average particle size and maximum drug entrapment efficiency. For this microballs formulation were prepared with varying concentration mesalamine hydrochloride viz. 40, 60, 80 and 100 mg /100 mg of polymer. It was observed that on increasing the concentration of drug, the entrapment efficiency increased up to 80 mg, while on further increasing drug concentration the entrapment efficiency gradually decreased. This could be due to the saturation of polymer with the drug and particle size does not significantly change was observed (Table 1) so that formulation MC2D3 was selected for further optimization process.

The particle size found to be decreased upon increasing the concentration of PVA up to 0.75% w/v. This might be due to the decrease the surface tension between organic phase and aqueous phase which ultimately seem to allow formulation of micro size range particles. Optimum size of particles 81.2±2.9 µm with 90.2±3.4% drug entrapment were obtained at surfactant concentration 0.75% w/v (Table 1). However on further increasing surfactant concentration although the particle size decrease because of the formation of micelles but entrapment efficiency also decrease because of the leaking out of the drug so that formulation MC2D3E2 was selected for further optimization process.

The process variable, stirring speed was optimized in terms of average particle size and maximum drug entrapment efficiency. Increase in stirring speed decrease an average particle size of microballs was observed. At 400 rpm formulation MC2D3E2R2 produced size distribution 74.2±3.5 µm with hollow and spherical shape with 91.1±3.2% drug entrapment efficiency (Table 1).

Average particle size of microballs reduces with increased in temperature. Narrow size distribution 74.4±2.1 µm with hollow shape and 87.5±1.4% entrapment efficiency was found to formulation MD4C5E2R2T2 at 37°C temperature. Temperature for more than 37°C causes the external phase to separate due to agglomeration of the polymer (Table 1).

The scanning electron microscopic photomicrograph of the optimized microballs formulations (MD4C5E2R2T2) showed spherical in shape having hollow cavity. This could be due to the evaporation of solvent during the preparation of microballs (Figure 1).

In vitro buoyancy test of optimized microballs formulation was studied in SGF (pH 1.2) showed that the percentage buoyancy of microballs formulation was significantly decreased after 5 hr (Figure 3) suggesting that the density of microballs increased because water permeated into the hollow cavity of polymer which may be erode and swollen of the polymer matrix.

In vitro mesalamine hydrochloride releases from optimized microballs (MD4C5E2R2T2) were carried out in SGF (pH 1.2) and PBS (pH 7.4). No initial burst release was observed in any medium suggested that the mesalamine hydrochloride molecules are entrapped over the hollow cavity of the microballs. Nearly linear relationship between the % cumulative release of mesalamine hydrochloride and the square root of time was obtained for the first 10 hr suggested that the microballs formulation follows a diffusion controlled drug release mechanism (Lee, 1985). The % Cumulative amount of drug release was found 91.2±3.5% in SGF (pH 1.2), 89.2±3.5% in PBS (pH 7.4) upto 24 hrs. The results clearly suggested that microballs formulation could be used for sustained drug delivery purpose.

Stability studies were carried out with optimized formulation MD4C5E2R2T2 which was stored for a period of 45 days at 4±1°C, 25±1°C and 40±1°C. The particle size of formulation was determined by optical microscopy using a calibrated ocular micrometer. The particle size of the microballs was found to increase at 25±1°C may be attributed to the aggregation of microballs at higher temperature. At 40±1°C the microballs aggregated and a change in spherical shape to ellipsoidal shape with irregular hollow cavity of microballs was observed i.e. these microballs were unstable at higher temperature like 40±1°C (Figure 5). The percent residual drug content of the optimized formulation are shown in (Figure 6). It was observed that the formulation stored at 4±1°C and 25±1°C was quite stable as fewer drugs was degraded on storage for 45 days while it was quite unstable at 40±1°C for 45 days.

X-ray contrast medium containing microballs was conducted to determine the in vivo floating performance and assessment of gastroretentive of the formulation. X-ray photograph taken after each 1hr interval shows intragastric behavior of the microballs. It is clear from the X-ray
photographs that microballs remained buoyant even after 4 hrs (Figure 7) which indicated that gastroretentive property obtained by microballs formulation.

Anti inflammatory activity of optimized microballs formulation in carrageenan induced rats showed when animals of group I acute inflammation were produced by injecting 0.1 ml of (1% w/v) carrageenan in the plantar region of the left paw. The paw volume measured by mercury displacement was found to be 1.7 ml after 2 hr. In case of animals of group II, which were administered 10 ml plain drug solution (equivalent to 50mg/kg of mesalamine hydrochloride) 30 min prior to administration of 0.1 ml of (1% w/v) carrageenan in the plantar region of the left paw. The paw volume was recorded 0.8 ml after 2 hr. The group III of animal were administered 10 ml suspension of optimized microballs formulation MD4C5E2R2T2 (equivalent to 50mg/kg of mesalamine hydrochloride) 30 min prior to administration of 0.1 ml of (1% w/v) carrageenan in the plantar region of the left paw. The paw volume was recorded 0.4 ml after 2 hr. The results showed that the microballs formulation released mesalamine hydrochloride released slowly which is desirable for the absorption of drug through upper part of the gastrointestinal tract where the absorption window exists and will maintain the peak serum level for a long time. Therefore it is clear from this study that the microballs formulations protect paw oedema/inflammation completely.

CONCLUSION

REFERENCES


The result obtained from all the experiments suggested that it is possible to prepare an intragastric floating and sustained release hollow microballs preparation using combination of Eudragit S-100 and Eudragit RS-100 by solvent evaporation method. Hollow microballs drug delivery system provides the possibility of enhancing the bioavailability and control the release of mesalamine hydrochloride exhibiting absorption window by prolonging the gastric emptying time ensuring availability of drug at the absorption site for the desired period of time. The hollow microballs showed a good buoyancy and drug release properties so that it has a great potential for its use both in powder form for dry suspension and granular form for tabletting.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.