COMPARATIVE STUDY OF MUCOADHESIVE POLYMERS CARBOPOL 974P AND SODIUM CARBOXYMETHYL CELLULOSE FOR SINGLE UNIT DOSAGE OF IMATINIB MESYLATE

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The aim of this study was to design and develop controlled release Imatinib mesylate (IM) oral dosage form by fabricating gastroretentive mucoadhesive tablet which can retain the drug in the stomach for prolonged duration and to achieve therapeutic levels over an extended period of time for the treatment of myelogenous leukemia (CML) and gastrointestinal stromal tumor (GIST). Single unit formulations containing carboxyl 974P or sodium carboxymethyl cellulose (MC) which helps the drug in adhering to the gastric mucosa for an extended period of time were formulated and evaluated. Gastroretentive tablets of IM were prepared by direct compression. The results obtained showed no physicochemical incompatibility between the drug and other excipients used in the formulations. The prepared tablets were evaluated by different parameters such as thickness, weight variation, hardness, content uniformity, swelling index and mucoadhesive strength. Indigenously fabricated assembly was used to measure the bioadhesive strength of the mucoadhesive tablets, and goat gastric mucosa was used as a model tissue. Bioadhesive strength increased with increasing the amounts of carbopol 974P and sodium CMC in the formulations. The physicochemical compatibility of the drug with other excipients used in the formulations was studied by FTIR analysis. The tablets were also evaluated for in vitro drug release in 0.1N HCl for 12 h in USP Type II dissolution apparatus. In order to determine the mode of release, the data was fitted into various kinetic models and the optimised formulation followed Korsmeyer peppas model and the ‘n’ value was greater than one indicated super case II mechanism of drug release. The radiographic pictures of the rabbits confirm the in vivo mucoadhesion in the stomach for 6 h.

Keywords: Gastroretentive, Mucoadhesive, Imatinib mesylate, Radiography

INTRODUCTION

Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion and has been extensively reviewed (Vinod et al. 2010a, b; Streubel 2006; Moes 1993). The potential of mucoadhesive polymers was shown in ocular, nasal, vagina and buccal drug delivery systems leading to a significantly prolonged residence time of sustained release delivery systems on these mucosal membranes. In addition, the development of oral mucoadhesive delivery systems was always of great interest as delivery systems capable of adhering to certain

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gastrointestinal (GI) segments would offer various advantages. With few exceptions, however, mucoadhesive drug delivery systems have so far not reached their full potential in oral drug delivery, because the adhesion of drug delivery systems in the GI tract is in most cases insufficient to provide a prolonged residence time of delivery systems in the stomach or small intestine (Lenaerts and Gurny 1990).

The aim of this research work was to develop a single unit controlled release Imatinib mesylate (IM) oral dosage form which can retain the drug in the stomach for prolonged duration by mucoadhesive nature of the dosage form and to achieve therapeutic levels over an extended period of 12 hours for the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumour (GIST). CML is a myeloproliferative disorder, in fact the first neoplastic disease to be linked to a consistent acquired genetic abnormality, the Philadelphia (Ph) chromosomes. Blast crisis is the final phase of CML and behaves like an acute leukemia with rapid progression and short survival rate (Jabbour et al. 2007; David, Richard and John 1997). GIST is one of the most common mesenchymal tumours of the gastrointestinal tract (1%–3% of all gastrointestinal malignancies). They are typically defined as tumours whose behaviour is driven by mutations in the Kit gene or PDGFRα gene. Imatinib is currently marketed by Novartis as Gleevec (USA) or Glivec (Europe/Australia) as its mesylate salt, imatinib mesylate (INN). It is used in treating CML, GIST and a number of other malignancies (O'Brien et al. 2003). It is the first member of a new class of agents that act by inhibiting particular tyrosine kinase enzymes, instead of non-specifically inhibiting rapidly dividing cells (Mishra 2007).

For the successful performance of oral control release drug delivery system (CRDDS) the drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion (Liu et al. 2005; Chowdary et al. 2003). IM is primarily absorbed from the proximal part of the small intestine and is unstable in the fluids whose pH is >5.5, hence gastroretention will be suitable (Elg, Chan and Hernandez 2007). Ironically, IM though a right candidate for the gastroretentive delivery system, much attention has not been given. We have conducted a market survey within the selective states of Andhra Pradesh, Kerala and Delhi and no gastroretentive IM forms were available. The real issue in the development of oral controlled release dosage form is to extend the duration of action of drug from the small intestine. The mucin glycoproteins are the most important structure-forming component of the mucus gel, resulting in its characteristic gel-like, cohesive and adhesive properties. The thickness of this mucus layer varies on different mucosal surfaces, from 50 to 450 µm in the stomach, to less than 1 µm in the oral cavity. With the intention of fabricating IM mucoadhesive single unit dosage form, the work was initiated. In this manuscript we highlighted how the dosage form was designed, evaluated and also discussed some of the critical technical problem solving issues. It was hypothesised that gastro retention of the drug would be enhanced by mucoadhesive nature of the dosage form.

MATERIALS AND METHODS

IM and carbopol 974P (CP) were generously supplied from Caron Life Sciences (Hyderabad). Dysymmetrix Laboratory (Hyderabad) provided gift sample of sodium carboxymethyl cellulose (CMC). Talc microcrystalline cellulose (MCC). Avicel 102 was purchased from S.D. Fine chemical Pvt. Ltd. (Mumbai). All other reagents used in this project were of analytical grade.

Fabrication of IM Mucoadhesive Tablets

IM tablets were prepared by direct compression (Lachman, Lieberman and Kanig 1991). In all formulations the drug concentration was kept constant. Two different mucoadhesive polymers were considered, carbopol 974P and sodium CMC with their formulations coded as Mca and Msc respectively. All the formulation contained 1% talc and 2% magnesium stearate. MCC was used as filler. The compositions of different formulations trials with different polymers are presented in Table 1. Accurately weighed quantities of polymer and Avicel were mixed in geometrical ratio. To this mixture, required quantity of IM was added and mixed slightly with pestle. This mixture was passed through 40# mesh (0.425 mm diameter), collected in a plastic bag and blended for 5 min. The required quantity of magnesium stearate and talc were added, and the final blend was again passed through 40#. The blend was mixed thoroughly for 10 min and compressed into tablets of average weight of 205.5 mg with same force using 8 mm round single punch tableting machine (Cadmach Machinery Ltd., Ahmedabad, India).

Table 1: Formulations containing carbopol 974P, sodium CMC and MCC.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Drug (%)</th>
<th>Carbopol 974P (%)</th>
<th>Sodium CMC (%)</th>
<th>MCC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mca1</td>
<td>100</td>
<td>50</td>
<td>–</td>
<td>50</td>
</tr>
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<td>Mca2</td>
<td>100</td>
<td>60</td>
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<td>40</td>
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<td>Mca3</td>
<td>100</td>
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<td>30</td>
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<td>Mca4</td>
<td>100</td>
<td>80</td>
<td>–</td>
<td>20</td>
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<td>Msc1</td>
<td>100</td>
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<td>Msc2</td>
<td>100</td>
<td>–</td>
<td>60</td>
<td>40</td>
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<td>Msc3</td>
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</tr>
<tr>
<td>Msc4</td>
<td>100</td>
<td>–</td>
<td>80</td>
<td>20</td>
</tr>
</tbody>
</table>

Characterisation and Evaluation

The flow properties of powder blend for compression were characterised for angle of repose, Carr index and Hausner ratio (Nagare et al. 2010; Sinko 2006).

Angle of repose = \( \tan^{-1} \left( \frac{h}{r} \right) \),

where \( h \) is height of the pile and \( r \) is the radius of its base of pile.

Hausner ratio (HR) and Carr index (CI) were calculated according to the two equations given below:

\[
HR = \frac{\rho_t}{\rho_b}
\]

\[
CI = \frac{(\rho_t - \rho_b)}{\rho_t}
\]

where \( \rho_t \) is tapped density and \( \rho_b \) is bulk density.
Physical and organoleptic characterisation of tablet

The tablet size, shape and colour were observed in natural light above a white background. Drug content uniformity was determined by assay, thickness by vernier caliper, weight variation, hardness test using Monsanto hardness tester and friability by Roche-type friabilator were performed as part of evaluations.

Water Uptake Studies

The water uptake study of the dosage form was conducted by using USP dissolution apparatus-II (ElectroLab, Mumbai) in a 900 mL of distilled water which was maintained at 37.0±0.5°C, rotated at 50 rpm. At selected regular intervals the tablet was withdrawn by nylon meshed filtered spatula, kept over a filter paper to absorb excess buffer solution and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU) (Chandira et al. 2010; Strusi et al. 2008; Chavanpatil, Chaudari and Vavia 2005).

\[ WU = \frac{(W_t - W_0) \times 100}{W_0} \]

where \(W_t\) is the weight of the swollen tablet and \(W_0\) is the initial weight of the tablet.

Fourier Transform Infrared Spectroscopy

The infrared spectra of IM pure drug, physical mixture of drug and excipients were recorded between 400 to 4000 cm\(^{-1}\) on FTIR. The infra-red [I spectra for the test samples of 1 mg (1:100 of sample: KBr ratio)] were obtained using KBr disk method using an FTIR spectrometer (Shimadzu Corp, Japan) (Ashutosh 2009; Skoog, James and Stanley 2007).

Measurement of Bioadhesive Strength

Mucoadhesive strength of the tablet was measured on the modified physical balance (Deshmukh, Jadhar and Sakarkar 2009; Jacky, Shamling and Krishnat 2009; Mahesh et al. 2006; Gupta, Garg and Khar 1992). The design of device used for measuring the mucoadhesive strength was shown in Figure 1. The apparatus consisted of a modified double beam physical balance in which the right pan was replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. Another glass arrangement of suitable height and diameter was prepared, which was kept in beaker filled with 0.1N HCl (pH 1.2), and then placed below the right side of the balance.

Goat stomach mucosa was used as a model membrane and buffer media 0.1N HCl (pH 1.2) was used as moistening fluid. The goat stomach mucosa was obtained from local slaughter house and kept in a Krebs buffer (D-glucose 2 g/L, magnesium sulphate 0.141 g/L, potassium phosphate monobasic 0.16 g/L, potassium chloride 0.35 g/L, sodium chloride 6.9 g/L) during transportation. The underlying mucous membrane was separated carefully using surgical blade and washed thoroughly with 0.1N HCl (pH 1.2). It was then tied over the glass arrangement using a thread. The block was then kept in glass beaker. The beaker was filled with 0.1N HCl (pH 1.2) up to the upper surface of the goat stomach mucosa to maintain stomach mucosa viability during the experiments.
Fabrication of Imatinib Mesylate Mucoadhesive Tablet

One side of the tablet was attached to the glass slide of the right arm of the balance. The beaker was raised slowly until contact between goat mucosa and mucoadhesive tablet was established. A preload of 10 mg was placed on the slide for 5 min (preload time) to establish adhesion bonding between mucoadhesive tablet and goat stomach mucosa. The preload weight and preload time were kept constant for all formulations. After the speculated time, preload was removed from the glass slide and water was then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water was stopped when mucoadhesive tablet was detached from the goat stomach mucosa. The weight of water required to detach mucoadhesive tablet from stomach mucosa was noted as mucoadhesive strength in grams.

Drug Release Studies

Drug release studies were performed by dissolution test apparatus (United States Pharmacopoeia XXIII, ELECTROLAB TDT-08L, Mumbai) at 50 rpm, using 0.1N HCl (gastric pH 1.2, 900 mL) by USP type 2 apparatus (paddle method) at 37.0±0.5°C. Aliquot samples of 1 mL were withdrawn at pre scheduled intervals and replaced with fresh dissolution medium to maintain sink condition. Each sample was diluted suitably and analysed at 236 nm using double beam UV-visible spectrophotometer (Shimadzu, Japan) against reagent blank. For statistical data analysis and curve fitting, GraphPad software (GraphPad Software Inc., San Diego) were used. The experiment was carried out in triplicate and mean values of drug release % versus time were plotted (Suresh et al. 2010; Prakash et al. 2009).

Fig. 1: Clockwise from top: (A) indigenously fabricated bioadhesive strength testing unit; (B) bioadhesion process; (C) tablet before wetting; (D) after wetting with 0.1N HCl (camera: Canon SP800UZ, supermacro mode, WB auto, ISO 3200, exposure ~1.5).
Model Fitting for Drug Release

The suitability of several equations that are reported in the literature to identify the mechanisms for the release of drug was tested with respect to the following equations:

Zero order model (Danbrow and Samuelov 1980)

\[ M_t = M_0 + K_0 t \]

Higuchi model (Higuchi 1973, 1961)

\[ M_t = M_0 + K_H t^{0.5} \]

Korsmeyer - Peppas model (Peppas 1985; Korsmeyer et al. 1983)

\[ M_t = M_0 + K t^n \]

where \( M_t \) is the amount of drug dissolved at time \( t \), \( M_0 \) is the initial amount of the drug, \( K_0 \) is the zero order release constant, \( K_H \) is the Higuchi rate constant, \( K \) is a release constant and \( n \) is the release exponent that characterises the mechanism of drug release.

In vivo Confirmation of Gastroretention by Using Radiographic Studies

Institutional animal ethical committee certificate (Nalanda College of Pharmacy/Indian Animal Ethical Committee, approved/11/2010) was obtained prior to the commencement of pharmacological studies. Since we want to reduce the number of experimental animals (male Nippon rabbits 2.0–3.0 kg), in vivo studies were done only for the optimised formulation. The animals were housed in separate cages and conditioned to the normal diurnal (day time) and nocturnal (night time) rhythms. The animals were fed with leafy vegetables, standard laboratory diet and water ad libitum. After overnight fasting of 12 h (accessibility to water was not restricted), six rabbits were given the tablets p.o. and water ad libitum. A reinforced flexible tube was inserted into the oral cavity and after feeding 10 mL water the tablet was administered, followed by another 10 mL of water. Radiographs of rabbits’ stomach from the ventral side were obtained at different time intervals like before the administration of tablet, 30 min, 3 h, 6 h and 24 h after drug administration. During these periods rabbits were allowed to take water (Sasa et al. 2000; Ingani, Timmermans and Moes 1987).

RESULTS

Imatinib oral tablets were found be 8 mm round, flat surfaced and pale yellow in colour. There was no chipping and mottling. Derived properties of powders like compressibility index (CI), angle of repose and HR were observed to be in the range of 11.20±0.04 to 14.80±0.10, 26.70±0.07° to 30.20±0.02° and 1.08±0.06 to 1.18±0.61 respectively and are described in Table 2. The tablets were round and flat with an average diameter of 8.0±0.1 mm and a thickness ranged from 3.31±0.02 to 3.42±0.07 mm. The weight of the tablet varied between 203.18±2.16 to 208.19±1.83 mg for different formulations with low standard deviation (SD) values. The hardness and friability of different formulations were found to be between 5.90±0.15 to 6.23±0.35 kg/cm² and 0.12% to 0.28% respectively. The force required to break the table across its diameter is recorded as the hardness for the tablet. The results are summarised in Table 2. Drug content uniformity in all formulations was calculated and

the percent of active ingredient ranged from 97.62±0.28% to 99.75±0.70%. Water uptake was measured for all formulations with two polymers. The data was made into a histogram as shown in Figure 2. The integrity of the tablet after sorption also was observed. Mucoadhesive strength of formulations with two polymers; carbopol 974P [Mca] and sodium CMC [Msc] were obtained as weight (g) and represented by histograms (Fig. 3). To find out the possibility of pharmaceutical interactions, FTIR spectral analysis was done on the pure drug as well as their formulations. Figures 4 represents FTIR spectral data of the pure drug and the formulations containing various polymers. The peaks were measured and interpreted. Figure 5 stated that maximum drug release in 0.1N HCl using carbopol 974 and sodium CMC was 94.25% and 95.90% respectively. Radiological studies of the optimised formulation were done periodically on healthy male rabbits and X-ray was obtained (Fig. 6).

Table 2: Derived property of powder blend and physical characterisations of tablet.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>CI</th>
<th>Θ</th>
<th>Ø</th>
<th>Weight variation (mg)</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mca1</td>
<td>11.20±0.04</td>
<td>27.90±1.83</td>
<td>1.13±0.35</td>
<td>208.19±1.83</td>
<td>3.37±0.04</td>
<td>5.90±0.15</td>
<td>97.62±0.28</td>
</tr>
<tr>
<td>Mca2</td>
<td>13.40±0.06</td>
<td>26.70±0.70</td>
<td>1.18±0.61</td>
<td>206.38±2.65</td>
<td>3.38±0.07</td>
<td>6.23±0.35</td>
<td>99.75±0.70</td>
</tr>
<tr>
<td>Mca3</td>
<td>14.20±0.35</td>
<td>27.60±0.35</td>
<td>1.08±0.06</td>
<td>204.08±4.36</td>
<td>3.42±0.07</td>
<td>6.20±0.1</td>
<td>98.15±0.35</td>
</tr>
<tr>
<td>Mca4</td>
<td>12.30±0.61</td>
<td>26.70±0.07</td>
<td>1.13±0.04</td>
<td>203.18±2.16</td>
<td>3.33±0.06</td>
<td>6.10±0.1</td>
<td>98.97±0.28</td>
</tr>
<tr>
<td>Msc1</td>
<td>13.30±1.83</td>
<td>29.30±0.70</td>
<td>1.12±1.83</td>
<td>205.12±1.2</td>
<td>3.36±0.02</td>
<td>5.97±0.2</td>
<td>98.9±0.24</td>
</tr>
<tr>
<td>Msc2</td>
<td>14.20±0.04</td>
<td>29.60±1.2</td>
<td>1.09±0.07</td>
<td>205.41±1.6</td>
<td>3.34±0.01</td>
<td>6.05±0.6</td>
<td>99.24±0.61</td>
</tr>
<tr>
<td>Msc3</td>
<td>14.60±0.28</td>
<td>30.20±0.02</td>
<td>1.14±1.32</td>
<td>204.24±0.9</td>
<td>3.32±0.04</td>
<td>6.12±0.3</td>
<td>99.52±0.38</td>
</tr>
<tr>
<td>Msc4</td>
<td>14.80±1.32</td>
<td>30.10±1.2</td>
<td>1.16±0.28</td>
<td>206.12±0.8</td>
<td>3.31±0.02</td>
<td>6.14±0.5</td>
<td>98.72±1.32</td>
</tr>
</tbody>
</table>

DISCUSSION

As it was mentioned earlier, the present work was envisaged with the intention of developing a mucoadhesive single unit device so that gastric retention could be achieved.
there by increasing the efficacy of IM in terms of bioavailability. Since the absorption window of IM is primarily in the proximal part of the small intestine and is unstable in the fluids with pH >5.5, drug for gastroretentive mucoadhesion was optimised. At the initial level of research, we were trying to prepare microspheres by solvent evaporation method. But the drug being highly lipophilic in nature, leached out of the microspheres into liquid paraffin. Researchers trying various partition coefficient studies had to solve the issue by selecting tablet dosage form. Here the advantage we gained was not only that one did not have to be concerned about the drug loading, but this also involved limited usage of excipients (economical).

![Graph showing mucoadhesive strength of formulations with two polymers]

**Fig. 3:** Mucoadhesive strength of formulations with two polymers; carbopol 974P [Mca] and sodium CMC [Msc].

It was mandatory to verify the derived properties of powders (pre compaction) as these could affect the packing arrangements, tablet integrity, uniformity and weight variation (post compaction). Since the tablet was formulated by direct compression, bulk density primarily was affected by the compaction. The values of HR, angle of repose and CI are in the order of 1.25–1.5, less than 30° and 11–15 respectively. The results of angle of repose indicate the suitability of the powder for direct compression with optimum inter particle friction which is supported by the values obtained from HR and CI. The HR is not an absolute property of a material, its value can vary depending on the methodology used to determine it. The CI, named after the pharmacologist Charles Jellef Carr gives indication of the compressibility of a powder (Podczek and Brian 2007).

The weight variation of the tablets was within the permissible limits of 7.5%, as specified for tablet weighing more than 130 mg (Aulton 2002). The hardness of the tablets was fixed at 6 kg/cm² and was maintained for all the batches in order to minimise the effect of hardness on the drug release. This was done because the effect of polymer and its concentration on the drug release was the area of interest. The results showed that the hardness of the tablets were almost the same. Tablet thickness was also used to assess the quality of tablets. Under uniform conditions of manufacture, the total weight of tablet and thickness were linearly related. Friability test of all the formulations were found satisfactory as the obtained values were below the permitted value of 5% showing enough resistance to the mechanical shock and abrasion. The weight loss was found to be less than 0.29%.
Fig. 4: FTIR spectral analysis of (A) pure drug, (B) formulation containing carbopol 974P and (C) formulation containing sodium CMC.
Fig. 5: Cumulative drug release (%) profile of gastroretentive mucoadhesive tablets incorporated with carbopol 974P (Mca) (A) and sodium CMC (Msc) (B) in 0.1N HCl, detected UV spectrophotometrically at λ max 236 nm. Data represents mean±SD (n=3).

Mucoadhesive polymer exhibits its adhesive property only when it is in contact with water or GI solution. When in contact with the water, the tablet swells mainly by imbibitions, by which the water will be taken up by the mass and swells because of the inter- and intra-distance between the polymer chains get distanced. The swelling behaviour of dosage unit can be measured either by studying its dimensional changes, weight gain or water uptake. The formulations with carbopol 974P and sodium CMC showed good swelling and tablet integrity. Complete swelling was achieved towards the end of 6 h, then diffusion and erosion took place. The formulation Mca4 containing carbopol 974P showed higher swelling compared to that of the formulations containing sodium CMC. The swelling index of the tablets increased with an increase in the polymer viscosity grades.

Different interactions of mucoadhesion is postulated like bonds of ionic, covalent, hydrogen, Van-der-Waals and hydrophobic. Mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage.

Step 1 — Contact stage: An intimate contact (wetting) occurs between the mucoadhesive and mucous membrane.
Fig. 6: Radiographic pictures of gastroretentive mucoadhesive tablets were taken (A) before the administration of the tablet, (B) after 30 min of administration, (C) after 3 h, (D) after 6 h and (E) after 10 h. Dosage form identified at in vivo conditions are marked with the circle.
Step 2 – Consolidation stage: Various physicochemical interactions occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion. These interactions and mechanisms depend on the swelling index and bioadhesion. Both are characteristics of the polymers of discussion. Bioadhesion strength of the tablet indicates the strength with which the tablet interacts with the mucosa of the stomach. The results obtained clearly indicate that increase in polymer quantity increased bioadhesion. This pattern is the same for both the mucoadhesive polymers used in the study, carbopol 974P and sodium CMC. Maximum bioadhesion strength was seen in the formulation containing carbopol 974P (Mca4). As the polymer concentration increased the bioadhesion with the mucous membrane (mucoadhesion) also increased with both the polymers. This statement was supported by the results of the swelling index. Both swelling index and bioadhesion were found to be directly proportional. A comparison of the histograms of both polymers were found to have almost equal bioadhesive strength as shown in Figure 2. While fabricating mucoadhesive tester, at the initial trials, mucoadhesive tester was designed with the weight to check the adhesive strength. As the results were not reproducible and adhesive strength between two consecutive weights could not be detected, weights equivalent to break point were determined by the quantity of water added. The total weight of water gave the accurate results which were reproducible.

FTIR spectral analysis was carried out to rule out the possibility of drug-excipient interaction. Vibrational spectroscopy (IR) describes same kind of molecular information and can be used to supplement or complement each other. Middle IR (400–4000cm⁻¹; vibration-rotation region) was used for analytical purpose. The atoms held by a chemical bond are the main participants in vibration. Vibrations depend on mass of two vibrating atoms, force constant of bond between two atoms and other atoms attached. Thus vibrations are characteristic for a group. In FTIR spectrogram results shown in Figure 4, the functional region is important for stretching and the fingerprint region for bending. Transmission peaks at 3000–3100 cm⁻¹ indicated aromatic functional group and 3300–3700 cm⁻¹ indicated hydrogen bonding (O-H). The peaks were intact in both the formulations as it appeared in the pure drug which indicated that the excipients neither altered the configuration of the drug nor disturbed its bonds.

In vitro drug release of tablets with carbopol 947P was found to have maximum drug release for Mca1 (94.25%) and minimum for Mca4 (77.70%) in 12 h. The release studies clearly indicated polymer concentration was inversely proportional to drug release. It was assumed that due to the higher viscosity of carbopol 974P the drug release was retarded. Formulations Mca2, Mca3 and Mca4 failed to meet the desired drug release profile. Formulation Mca1 exhibited the desired drug release profile and showed good swelling and mucoadhesive strength values, for these reasons Mca1 was considered as the best formulation among all these four formulations.

In vitro drug release of tablets with sodium CMC was found to have maximum drug release for Msc1 (95.9%) and minimum for Msc4 (80.05%) in 12 h. The release studies clearly indicated that polymer concentration was inversely proportional to drug release. The results indicate that due to the lower viscosity of sodium CMC the drug release was higher when compared to the formulations containing carbopol 974P. The results also showed that with the increase in polymer concentration the drug release was retarded. Formulations Msc2, Msc3 and Msc4 failed to meet the desired drug release profile. Formulation Msc1 obtained the desired drug release profile and showed good swelling and mucoadhesive strength values, for these reasons it was considered as the best formulation among all the four formulations. When comparing both the polymers, sodium
CMC (95.9%) have a slight advantage over carbopol 974P (94.25%) in terms of drug release. This could be related to the higher molecular weight of carbopol 947P (500,000 D) than sodium CMC (5000 D).

The mechanism of release for the optimised formulations was determined by finding the $R^2$ value for each kinetic model viz. Zero-order, first-order, Higuchi and Korsmeyer-Peppas corresponding to the release data of formulations. For most of the formulations the $R^2$ value of Korsmeyer-Peppas and zero-order model is very near to 1 than the $R^2$ values of other kinetic models. Thus it can be said that the drug release follows Korsmeyer-Peppas mechanism and zero-order model (Table 3).

### Table 3: Release kinetics of optimised formulations which can be constructed into model fitting curves.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Peppas</th>
<th>n value</th>
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<td>0.9754</td>
<td>0.9913</td>
<td>1.0853</td>
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<td>Mca2</td>
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<td>0.9773</td>
<td>0.9677</td>
<td>0.9911</td>
<td>0.9930</td>
</tr>
<tr>
<td>Mca3</td>
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<td>0.9776</td>
<td>0.9701</td>
<td>0.9940</td>
<td>0.9854</td>
</tr>
<tr>
<td>Mca4</td>
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<td>0.9637</td>
<td>0.9859</td>
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<td>1.1456</td>
</tr>
<tr>
<td>Msc1</td>
<td>0.9815</td>
<td>0.7351</td>
<td>0.9763</td>
<td>0.9259</td>
<td>1.256</td>
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<td>Msc2</td>
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<td>0.8782</td>
<td>0.9698</td>
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<tr>
<td>Msc3</td>
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<td>0.9351</td>
<td>0.9698</td>
<td>0.9692</td>
<td>1.009</td>
</tr>
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</table>

The $n$ values of Korsmeyer-Peppas model of the best formulations were in between 0.55–0.85. Therefore the most probable mechanism of the release patterns of the formulations followed was non-fickian diffusion or anomalous diffusion.

Results of mucoadhesion and drug release for the two polymers, carbopol 974P and sodium CMC were conflicting with each other. When mucoadhesion properties of carbopol 974P (Mca4) was found to be higher than sodium CMC (Msc1), drug release of Msc1 (95.25%) was found be greater than Mca4 (77.70%). Msc1 showed adequate mucoadhesive property and the drug release was higher than Mca4; formulation having carbopol 947P was optimised. Also it was understood that even though the adhesive property was compromised, the tablet could retain in the stomach for the speculated time, the benefit of maximum drug release was achieved.

For the convenience of radiological studies and considering the comparatively narrow alimentary track of rabbits, tablets were incorporated with barium sulphate (BS) as a radio-opaque agent and the size of the tablets were reduced to 4 mm. To know how much quantity of the active pharmaceutical ingredient (API) should be replaced with BS, we have conducted an array of various ratios of drug:BS and found out 20% of the drug when replaced with the BS got the comparable in vitro lag and flotation time. Adequate precautions were taken for the specially designed tablets to get comparable in-vitro mucoadhesive property with that of the original tablets in discussion. By reducing the size of the tablet, gastroretentive behavior was achieved not because of inability to leave the stomach by the swollen tablet, but rather with its ability to adhere to the GI mucosal
surface. X ray was also taken prior to the per oral administration of the tablet to make sure that the observed opaque substance in the stomach of rabbit was due to the administered substance but not due to some foreign matter already existed. From the radiographic pictures obtained at different time intervals, it could be observed that the tablet was adhered up to 6 h. The radiographic pictures are shown in Figure 6. It was also observed that tablet was cleared after 10 h [Fig. 6 (e)]. The tablet has overcome the peristaltic movements of the GIT and was able to retain in the stomach as hypothesised. It is assumed that tablet could not retain up to 10 h because of the mucus turnover. It is logical to assume that some amount of the drug may be released in the upper part of the small intestine. Again there are other factors which affects the gastric transit time which includes food and its nature, whether solid or liquid (Zaware et al. 2011; Janardhan et al. 2010).

CONCLUSION

Gastroretention of IM single unit dosage form was achieved by mucoadhesion using both polymers, carbopol 974P and sodium CMC. Drug release profile using the later polymer was preferred to the former. Hence sodium CMC can be optimised although carbopol 974P showed better adhesive nature. The mucoadhesive nature was proven to be effective by in vivo studies. The authors believe that a good research work could be facilitated by fabricating analytical instruments which can furnish reproducible results.

CONFLICT OF INTEREST

All authors unanimously declare that there is no competing interest pertaining to this article submission.

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REFERENCES


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