Studies on losartan novel extrudates design and evaluation to treat hypertension

Putta Rajesh Kumar*, Jagannath M, Earshad Md, Gowtham K.K, Hafsa M, Shanta Kumar S.M.
*Department of Pharmaceutics and Pharmaceutical chemistry, V.L. College of Pharmacy, Raichur, Karnataka, India.

INTRODUCTION

Mucoadhesive dosage forms provide intimate contact between dosage form and the absorbing tissue, which may result in high localized drug concentration and hence high drug flux across the absorbing tissue. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucus by the gastric mucosa to replace the mucus that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force (Robinson et al., 2005; Nathalie et al., 1997). These systems are used to localize a delivery device within the lumen and cavity of body to enhance the drug absorption process in site specific manner. Various bioadhesive polymers are used for achieving the effective bioadhesion. These polymers tend to form hydrogen and electrostatic bonds at the mucus membrane polymer boundary. Rapid hydration in contact with the mucoeperithelial surface appears to favor adhesion. For drugs with relatively short biological half life, sustained and slow input from mucoadhesive systems may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy (Khar RK et al., 2002). Arterial blood pressure is directly proportional to the product of the cardiac output and the peripheral vascular resistance. Cardiac output and peripheral resistance are controlled mainly by two overlapping control mechanisms: the baroreflexes, which are mediated by the sympathetic nervous system, and the renin-angiotensin-aldosterone system. Most antihypertensive drugs lower blood pressure by reducing cardiac output or decreasing peripheral resistance (Mundaya et al., 1989). The angiotensin II receptor antagonists/blockers (ARBs) are alternatives to the ACE inhibitors. These drugs block the AT1 receptors. Losartan potassium (LSP) is the prototypic ARB; currently, there are six additional ARBs. Their pharmacologic effects are similar to those of ACE inhibitors in that they produce arteriolar and venous dilation and block aldosterone secretion, thus lowering blood pressure and decreasing salt and water retention. ARBs do not increase bradykinin levels. ARBs decrease the nephrotoxicity of diabetes, making them an attractive therapy in hypertensive diabetics.

The drug release from the mini-matrices is mainly by diffusion controlled and swelling plays an important role to obtain complete drug release. Though variety of approaches have been
used for the preparation of sustained release formulations such as matrix tablets, microcapsules, transdermal films, etc., the concept of mini tablets and mini-matrices are gaining greater importance in the design of sustained release formulations (Dias et al., 2005; Jain et al., 2000). Mini matrices offer maximum surface area for dissolution because of their fewer diameters 3 to 5 mm and provide approximately zero order drug release.

Mini matrices are prepared by either by extrusion method or compression method. Extrusion is the process of forming a raw material into a product of uniform shape and density by forcing it through an orifice or die under controlled conditions. The spheroids, pellets/ granules usually are coated with a polymer to control the rate of drug release and filled into hard gelatin capsules to yield a multiple unit dosage form (Ewart et al., 1990; Gudsoorkar et al., 1993; Robinson et al., 1987).

LSP is an orally active non-peptide angiotensin-II receptor antagonist used in treatment of hypertension due to mainly blockade of AT1 receptors and it has short biological half life 1.5-2 h. LSP is an antihypertensive agent, non peptide angiotensin II receptor (type AT1) antagonist. LSP competitively inhibits the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. LSP is 1,000 times more selective for AT1 than AT2. Conventional tablets administered 3-4 times to maintain plasma drug concentration. To increase therapeutic efficacy, reduce frequency of administration and for better patient compliance twice daily sustained release LSP matrix tablets are prepared by using HPMC, Xanthan gum and Carbopol (Garg et al., 1997).

Remon et al developed ibuprofen mini-matrices by hot-melt extrusion using ethylcellulose as sustained-release agent. Changing the xanthan gum concentration as well as its particle size modified the in vitro drug release. Increasing xanthan gum concentrations yielded a faster drug release due to a higher liquid uptake, swelling and erosion rate. Vervaet et al developed metoprolol tartrate Mini-matrices by hot-melt extrusion and ethylcellulose as sustained-release agent. Changing the hydrophilic polymer concentration and molecular weight modified the in vitro drug release: increasing concentrations yielded faster drug release. The sustained-release effect of the experimental formulations was limited, and relative bioavailabilities of 66.2% and 148.2% were obtained for 5% and 20% PEO 1,000,000 mini-matrices. Verhoeven E, et al developed sustained release mini-matrices via hot melt extrusion using Ibuprofen as the model drug and ethyl cellulose as sustained release agent. Ibuprofen release from the Ibuprofen-ethyl cellulose matrices (60:40w/w) was too slow (20% in 24 h). Other excipients (HPMC, xanthan gum) were added to the formulation to increase the drug release. They observed that the drug release from mini-matrices was mainly diffusion controlled and swelling played an important role. The present work is planned to prepare mucoadhesive mini matrices containing LSP by extrusion method. To evaluate the prepared mini matrices for drug content, SEM, particle size, analysis of drug release mechanism, stability studies. To determine the effects of different mucoadhesive polymers in the release of drug profile (Remon et al., 2006; Vervaet et al., 2009; Verhoeven et al., 2009).

**MATERIALS AND METHODS**

LSP obtained as complimentary sample from Reddy labs, Hyderabad. HPMC is procured from Sigma Aldrich, Germany; Eudragit RL100 gifted by Rohm polymers. Mercury was purchased from Central drug house Pvt. Ltd., Mumbai. HPMC 15 cps is procured from DOW Chemicals, USA. Di-butyl Phthalate, Methanol, Potassium dihydrogen orthophosphate, Sodium hydroxide and alcohol was obtained from S.D Fine chemicals. Methanol was supplied by Qualigens fine chemicals, Mumbai. All other ingredient used was of analytical grade.

**LSP Analytical method used for the study**

Absorption maxima are the wavelength at which maximum absorption takes place. For accurate analytical work it is important to determine the absorption maxima of the substance under study. 100 mg of LSP was dissolved in 100 ml 0.1N HCl to set stock solution of 1mg/ml. From this 10 ml solution was transferred into a 100 ml volumetric flask, volume was made up to 100 ml with 0.1N HCl which was considered as second stock solution. From this 0.6 ml of solution was transferred into a 10 ml volumetric flask and volume was made up to 10 ml with 0.1N HCl and subjected for scanning at the UV range using Hitachi-U2000 spectrophotometer. From the spectral data, the absorption maxima obtained was 245nm.

**Preparation of calibration curve**

For the preparation of calibration curve 0.2, 0.4, 0.6, 0.8 and 1.0 ml of the second stock solution was transferred into a series of 10 ml volumetric flask and volume was made up to 10 ml with 0.1N HCl to get the optical density values of resulting solutions which were measured at 245 nm by using Hitachi-U2000 spectrophotometer.

**Drug-Excipient Interaction Studies**

The drug-excipient interaction studies were carried out by employing IR spectroscopic technique, which is one of most powerful analytical techniques that offer possibility of chemical identification. The IR spectra of LSP, HPMC, lactose and formulation were obtained by KBr pellet method (Remon et al., 2006).

**Preparation of mini-matrices by extrusion**

In the present work extrusion method using Galaxy Extruder figure 1 has been used to prepare mini-matrices of LSP. Drug, polymer and channeling agent as per table 1 were powered separately and passed through 80 mesh. The weighed quantities of the above ingredients are mixed thoroughly with the help of a glass mortar and pestle. After incorporation of the plasticizer into the mixture by trituration, the mixture was transferred to a China dish.
Then a wet extrudable dough mass was made by adding toluene-ethanol (1:1) mixture in case of ethyl cellulose mini-matrices or ethanol (70%) in case of hydroxy propyl methyl cellulose and hydroxy propyl cellulose mini-matrices. The dough mass was fed into the cylinder of the extruder and was extruded in the form of long rods through the nozzle. The rods were kept for overnight air-drying on a glass plate, and then dried at 55°C in a hot air oven for 48 h. The length of the mini-matrices was measured and the length equivalent to 50 mg of LSP was calculated. Then the rod shaped mini-matrices was cut into pieces each containing approximately 50 mg of the drug these pieces were further cut into small mini-matrices of 3 mm thickness with the help of a parallel bladed cutter specially fabricated for the purpose. These mini-matrices were filled in zero size hard gelatin capsule shells for further studies (Remon et al., 2006; Vervaet et al., 2009; Verhoeven et al., 2009).

### Diameter Uniformity

The diameter of the mini-matrices was measured using vernier calipers at different spots of the extrudates (Vervaet et al., 2009).

### Weight Uniformity

The mini-matrices were cut into pieces of 3 mm thickness and were weighed individually on a digital balance. The average weights and standard deviations are calculated (Vervaet et al., 2009).

### Swelling studies

The swelling ability of them mini matrices in physiological media was determined by swelling them to their equilibrium (Jain et al. 2004). Accurately weighted amounts of mini matrices (50 mg) were immersed in a little excess of 0.1 N HCl (pH 1.2) and kept for 6 h. The following formula was employed in the calculation of percentage of swelling:

\[
S_{sw} = \frac{(W_s-W_o/W_s)}{W_s} \times 100.
\]

Where, \(S_{sw}\) = Percentage swelling of mini matrices, \(W_o\)=initial weight of microspheres, and \(W_s\)=weight of mini matrices after swelling (Perez Marcos et al., 1993).

### In vitro wash-off test

The mucoadhesive property of mini matrices was evaluated by an in vitro adhesion testing method known as wash-off method. Freshly excised piece of gastro intestinal mucosa was taken from albino rat. It was mounted on to glass slides with adhesive. About 50 mini matrices were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hung on the arm of a USP tablet disintegrating test machine. By operating the disintegrating test machine the tissue specimen was given a slow regular up and down movement in the test fluid at 37°C taken in the vessel of the machine. At the end of every one hour up to 6 h, the machine was stopped and number of mini matrices still adhering onto the tissue was counted (Secard DL. et al., 1962).

### Formulation details of LSP mucoadhesive mini matrices.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>H1</th>
<th>H2</th>
<th>H3</th>
<th>HX1</th>
<th>HX2</th>
<th>HX3</th>
<th>HC1</th>
<th>HC2</th>
<th>HC3</th>
<th>XC1</th>
<th>XC2</th>
<th>XC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSP</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
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<td>500</td>
<td>750</td>
<td>250</td>
<td>500</td>
<td>750</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>90</td>
<td>120</td>
<td>150</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>125</td>
<td>250</td>
<td>375</td>
</tr>
<tr>
<td>Carbopol</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>90</td>
<td>120</td>
<td>150</td>
<td>125</td>
<td>250</td>
<td>375</td>
</tr>
<tr>
<td>P. glycol 5% w/w</td>
<td>37.5</td>
<td>50</td>
<td>62.5</td>
<td>37.5</td>
<td>50</td>
<td>62.5</td>
<td>37.5</td>
<td>50</td>
<td>62.5</td>
<td>37.5</td>
<td>50</td>
<td>62.5</td>
</tr>
</tbody>
</table>

**Evaluation of mini matrices of LSP**

**Physical Appearance**

This includes visual inspection of the prepared mini-matrices (Remon JP. et al., 2006).

**Surface Texture**

The mini-matrices were observed under Scanning Electron Microscope (SEM, JSM-840A, Jeol, Japan) for SEM study. A piece of the mini-matrices was coated with gold in ion sputtering device and mounted directly on the SEM sample stub using double sided sticking tape and the instrument was run at 20 KV and then the mini-matrices were scanned (Chittam et al., 2012).

**Table. 1:** Formulation details of LSP mucoadhesive mini matrices.
In Vitro Drug Release Studies

In vitro release of LSP from the prepared Mini-matrices was studied using USP XXIII dissolution test apparatus (Electro Lab) employing the basket stirrer (Apparatus-1). 900 ml of 0.1N HCl was used as dissolution medium for 12 h. The temperature of the dissolution medium was maintained at 37±0.5ºC and the basket was rotated at 50 rpm. 5 ml of samples were withdrawn by means of a syringe fitted with prefilter at appropriate time intervals and immediately replaced with 5ml of fresh medium. The absorbance of the samples was measured at 245 nm in 0.1N HCl suitable dilution with the medium. The results of in vitro release profile obtained for all formulations were plotted in modes of data treatments as follows: Zero-order kinetic model (cumulative percent drug released versus time), First order kinetic model (log cumulative percent drug remaining versus time), Higuchi’s model (cumulative percent drug released versus square root of time) and Peppa’s model (log cumulative percent drug released versus log time) (Verhoeven E. et al., 2009).

RESULTS AND DISCUSSION

The IR spectrum of LSP exhibits a characteristic peaks at 713.76 cm⁻¹, 1013 cm⁻¹, 1433 cm⁻¹, 1559.88 cm⁻¹ and 2957 cm⁻¹ due to chloride moiety, secondary hydroxyl group, aromatic ring, nitrogen moiety and an aliphatic chain respectively. The peaks obtained are similar in formulation also, showing the compatibility of drug with polymer.

In the present work an attempt has been made to prepare mucoadhesive gastro retentive minimatrices of LSP for sustained/controlled release of drug by extrusion method using hydroxypropyl methylcellulose (HPMC), xanthan gum, carbopol, with plasticizer (propylene glycol). The prepared mini-matrices were evaluated for physical appearance, surface texture (SEM), uniformity of diameter, thickness and weight. They were also subjected to drug content uniformity, moisture content, In vitro drug release. The results of all these evaluations are given in table 2. All the prepared mini-matrices are white and rod shaped with apparently smooth outer surface. The SEM studies of the mini-matrices reveal that the addition of plasticizer improves the pore distribution pattern, flexibility and surface smoothness of the rod shaped extrudate figure 3.

The thickness, diameter and weight variation results are shown in table 2 and were found to be uniform as indicated by the low values of standard deviation and coefficient of variation. The thickness, diameter and weight of the matrices were found to be in the range of 2.86±0.15 to 3.10±0.10mm; 2.83±0.18 to 3.03±0.0.6 mm and 22.00±0.73 to 28.66±1.08 mg respectively. The drug content of the mini-matrices was quite uniform as can be observed from table 2. The percent drug content of the matrices was found to be within the range of 95.76±0.20 to 98.06±0.11 with low value of standard deviation and coefficient of variation. The moisture content of the matrices as determined by Karl fisher method was found to be in the range of 0.83 to 1.52% w/w.

Swelling studies by weight method was carried out, the swelling depends upon the polymer concentration, ionic strength as well presence of water was indicated in figure 4. The relative swelling of 1gm matrices formulations were found in the range of 1.40, 1.50, 1.62 for HPMC alone matrices, for HX1, HX2, HX3, HC1, HC2, HC3 it was 1.72, 1.96, 2.22, 1.58, 1.74, 1.90, 1.70, 1.94 and 2.06 respectively. Relative swelling for XC1, XC2 and XC3 was 1.70, 1.94 and 2.06 respectively. The ability of polymeric matrix to absorb enough water is an important factor in the formation of the gel layer, which controls the drug release. From the analysis of swelling data, it was possible to conclude that
The polymers under investigation accept water at different rates and swelling increases with increasing concentration of polymer.

The mucoadhesion is a phenomenon in which two materials, at least one of which is biological are held together by means of interfacial force. The figure 5 shows in vitro mucoadhesion data of mucoadhesive mini matrices carried out with everted rat intestinal mucosa in presence of phosphate buffer pH 1.2.

![Fig. 5: In vitro wash off test with Percentage adherence of LSP mini matrices.](image)

The percentage of microspheres retained on everted intestinal mucosa after 6 h in HPMC formulations were found be 67, 69, 72, for H1,H2,H3 and for HPMC with Carbopol and xanthan gum (HX1,HX2,HX3,HC1,HC2,HC3) 65,67,70,62,64,68 respectively and for XC1, XC2 and XC3 were found in the range of 60, 64, 67 respectively. The overall results suggest that concentration and type of mucoadhesive polymer does not showed much more difference in the mucoadhesive property. In vitro drug release studies were carried out using USP XXIII tablet dissolution test apparatus by rotating basket method at 50 rpm (Apparatus-I), 900 ml of 0.1N HCl at 37±0.5°C was used as dissolution medium for 12 h. The mini-matrices prepared from HPMC as matrix material released approximately 90.66 to 93.66% of the drug in 12 h, whereas the HPMC matrices with 20% xanthan gum and carbopol have 79.3 to 84 % and 68.5 to 75.2%, the matrices formulated using xanthan gum and carbopol has released 64.83 to 71.1 % of the drug in the same period. The comparative dissolution profiles of mini matrices are shown in figure 6.

![Fig. 6: Cumulative percentage drug release of LSP from mucoadhesive mini matrices.](image)

The formulation H1 prepared from HPMC (drug: polymer(1:0.5)) has released 93.66% of drug in 12 h was found to be promising because of its zero order release kinetics as from correlation.

### Table 2: Diameter, Thickness, Weight, Percent Moisture and DC of LSP Mini matrices.

<table>
<thead>
<tr>
<th>Code</th>
<th>Diameter ±SD (mm)</th>
<th>Thickness ±SD (mm)</th>
<th>Weight±SD (mg)</th>
<th>% Moisture content±SD</th>
<th>% drug content ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>2.96±0.09</td>
<td>2.90±0.12</td>
<td>26.66±1.53</td>
<td>0.90±0.01</td>
<td>96.86±0.41</td>
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<tr>
<td>H2</td>
<td>2.93±0.08</td>
<td>2.83±0.06</td>
<td>26.66±1.15</td>
<td>0.83±0.15</td>
<td>95.76±0.20</td>
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<tr>
<td>H3</td>
<td>2.86±0.15</td>
<td>3.02±0.05</td>
<td>22.00±0.73</td>
<td>0.93±0.25</td>
<td>97.76±0.05</td>
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<tr>
<td>HX1</td>
<td>2.83±0.18</td>
<td>2.86±0.15</td>
<td>26.33±0.57</td>
<td>0.93±0.21</td>
<td>98.06±0.11</td>
</tr>
<tr>
<td>HX2</td>
<td>3.03±0.06</td>
<td>3.00±0.10</td>
<td>28.66±1.08</td>
<td>0.99±0.05</td>
<td>97.06±0.11</td>
</tr>
<tr>
<td>HX3</td>
<td>2.90±0.10</td>
<td>3.06±0.11</td>
<td>25.66±0.57</td>
<td>1.00±0.09</td>
<td>98.96±0.05</td>
</tr>
<tr>
<td>HC1</td>
<td>2.83±0.16</td>
<td>3.10±0.10</td>
<td>26.00±1.73</td>
<td>1.26±0.08</td>
<td>96.8 ±0.26</td>
</tr>
<tr>
<td>HC2</td>
<td>3.00±0.10</td>
<td>3.00±0.14</td>
<td>29.33±2.08</td>
<td>1.44±0.07</td>
<td>95.8±0.17</td>
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<tr>
<td>HC3</td>
<td>3.06±0.05</td>
<td>3.03±0.12</td>
<td>28.33±0.56</td>
<td>1.52±0.10</td>
<td>98.36±0.05</td>
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<tr>
<td>XC1</td>
<td>2.98±0.05</td>
<td>2.89±0.15</td>
<td>28.45±0.58</td>
<td>1.00±0.09</td>
<td>97.8±0.17</td>
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<td>2.85±0.16</td>
<td>26.33±0.57</td>
<td>0.94±0.19</td>
<td>97.8±0.41</td>
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<td>XC3</td>
<td>2.89±0.16</td>
<td>2.92±0.14</td>
<td>29.38±2.10</td>
<td>1.46±0.09</td>
<td>99.16 ±0.15</td>
</tr>
</tbody>
</table>

### Table 3: Model fitting values and Korsemeyer-Peppas parameters of LSP mini matrices.

<table>
<thead>
<tr>
<th>Code</th>
<th>Zero order</th>
<th>1st order</th>
<th>Matrix</th>
<th>Peppas</th>
<th>Hix Crow</th>
<th>n</th>
<th>Best fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>0.9985</td>
<td>0.9944</td>
<td>0.9154</td>
<td>0.9578</td>
<td>1.0302</td>
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<td>H3</td>
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<tr>
<td>HX1</td>
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<td>0.9974</td>
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<td>0.9981</td>
<td>0.9892</td>
<td>0.9716</td>
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<tr>
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<td>0.9567</td>
<td>0.9991</td>
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<tr>
<td>HX3</td>
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<tr>
<td>HC1</td>
<td>0.9855</td>
<td>0.9969</td>
<td>0.9441</td>
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<td>0.9516</td>
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<tr>
<td>HC2</td>
<td>0.9925</td>
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<td>0.9078</td>
<td>0.9825</td>
<td>1.2712</td>
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<tr>
<td>HC3</td>
<td>0.9945</td>
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<td>1.2712</td>
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<tr>
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</tr>
<tr>
<td>XC3</td>
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<td>0.9883</td>
<td>0.9078</td>
<td>0.9871</td>
<td>1.4031</td>
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CONCLUSION

The mini-matrices prepared by extrusion method were found to be of uniform thickness, diameter and weight and of smooth surface texture with uniform drug content. The moisture content was found to be within the range of 0.83 to 1.5% w/w. FTIR spectras of selected mini matrices showed all the characteristic absorption bands of LSP with little shifting toward lower /higher wavelength indicating minor or no interaction. Hence, it can be concluded that the drug is in free state and can release easily from the formulation.

The swelling ratio depends upon concentration of polymer and type of mucoadhesive polymer used in the formulation. Swelling ratio shows direct relationship with HPMC concentration and increased with increasing concentration of HPMC. The formulations having xanthan gum as mucoadhesive polymer exhibited good swelling property compared to other mucoadhesive polymers.

The in vitro wash-off test results suggest that concentration and type of mucoadhesive polymer does not show much more difference in the mucoadhesive property. An increase in the proportion of matrix-polymer (HPMC, gum and cabopol) in the mini-matrices decreases the rate of drug release. All the HPMC mini-matrices displayed nearly zero-order release kinetics, except HX1 and HC1 showing first order release. Formulation H1 prepared with drug-polymer ratio 1:0.5 and 5% propylene glycol (by weight of polymer) as plasticizer showed promising results as a controlled release dosage form and released approximately 93% of the drug in 12 h. Extrusion method can be used for designing controlled release drug delivery systems providing nearly zero-order drug delivery over a period of 12 h.

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coefficient ‘r’ =0.9985. The data obtained was subjected to statistical analysis and found to be significant (p<0.05).

The mini-matrices prepared by extrusion method were found to be of uniform thickness, diameter and weight and of smooth surface texture with uniform drug content. The moisture content was found to be within the range of 0.83 to 1.5% w/w. FTIR spectras of selected mini matrices showed all the characteristic absorption bands of LSP with little shifting toward lower /higher wavelength indicating minor or no interaction. Hence, it can be concluded that the drug is in free state and can release easily from the formulation.

The swelling ratio depends upon concentration of polymer and type of mucoadhesive polymer used in the formulation. Swelling ratio shows direct relationship with HPMC concentration and increased with increasing concentration of HPMC. The formulations having xanthan gum as mucoadhesive polymer exhibited good swelling property compared to other mucoadhesive polymers.

The in vitro wash-off test results suggest that concentration and type of mucoadhesive polymer does not show much more difference in the mucoadhesive property. An increase in the proportion of matrix-polymer (HPMC, gum and cabopol) in the mini-matrices decreases the rate of drug release. All the HPMC mini-matrices displayed nearly zero-order release kinetics, except HX1 and HC1 showing first order release. Formulation H1 prepared with drug-polymer ratio 1:0.5 and 5% propylene glycol (by weight of polymer) as plasticizer showed promising results as a controlled release dosage form and released approximately 93% of the drug in 12 h. Extrusion method can be used for designing controlled release drug delivery systems providing nearly zero-order drug delivery over a period of 12 h.

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