Trilayer Mucoadhesive Gastro Retentive Tablets: Formulation and \textit{In vitro} Evaluation

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\textbf{ABSTRACT}

The present study deals with drug release enhancement of Metformin HCl using mucoadhesive technology by optimization of mucoadhesive agent to improve the mucoadhesion time. Metformin HCl is an oral antihyperglycemic agent of biguanide class used in treatment of type 2 Diabetes. It is hydrophilic drug which absorbed slowly and not completely from the gastrointestinal tract. The absolute bioavailability is reported to be 50-60\%. The sustained release trilayered mucoadhesive tablets of Metformin HCl were formulated by direct triple compression method using various mucoadhesive polymers. First and third layer (mucoadhesive layers) were comprises a blend of polymers such as Carbopol 940 and HPMC K100M. The second layer which is sandwiched between first and third layer contained 250 mg Metformin HCl along with release retardant Ethyl Cellulose. Batches F1, F2 and F3 were formulated. The formulated tablets were evaluated for weight variation, hardness, thickness and friability. Tablets were also evaluated for swelling index, mucoadhesive force, mucoadhesion time and in vitro drug release study. All the tablets were hydrated rapidly, mucoadhesive time were found highest in batch F2 which comprises of 1:2 ratio of Carbopol 940 and HPMC K100M in both first and third layer. The 83.80\% drug released was observed in batch F2 within 8 hrs.

\textbf{Keywords:} Trilayer tablets, gastroretention, mucoadhesion, metformine HCl

\textbf{INTRODUCTION:}

Despite tremendous advancement in the drug delivery system, oral route remains the preferred route for the administration of therapeutic agents and because of low cost therapy and ease of administration leads to higher levels of patient compliance. Conventional oral dosage forms such as tablets and capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. The design of oral controlled drug delivery system should be primarily aimed to achieve more predictable and increased bioavailability.\textsuperscript{[1]}

Conventional tablet have limitation of low residence time at absorption site and so repetitive administration of drug to obtain required bioavailability leading to poor patient compliance and hence loss of therapeutic efficacy.\textsuperscript{[2]}

An incomplete release of the drug and shorter residence time of the dosage forms in the upper GIT, which is a prominent site for the absorption of many drugs, leads to decreased bioavailability.\textsuperscript{[3]}

Drug absorption from gastrointestinal tract is a complex procedure and is subject to many variables. It has been reported that the extent of GIT drug absorption is related to contact time with the small intestinal mucosa. Gastro retentive systems can remain in the gastric region for several hours and therefore significantly prolong the gastric residence time of drugs.\textsuperscript{[4]}

Many approaches have been reported in the literature for the formulation of gastroretentive drug delivery systems viz. mucoadhesion, floatation, sedimentation, expansion, modified shape systems or by the simultaneous administration of pharmacological agents which delay gastric emptying. Both single unit systems (tablets or capsules) and multiple unit systems (multi particulate systems) have been reported in the literature.\textsuperscript{[5]}

The major absorption zone, stomach or upper part of intestine, can result in incomplete drug release from the drug delivery system leading to diminished efficacy of the administered dose. Therefore, localizing the drug delivery in a specific region of the gastrointestinal tract due to its mucoadhesiveness increases the intimacy and duration of contact between the drug containing polymer and the mucous surface.\textsuperscript{[6]}

Metformin HCl is an orally administered biguanide derivative widely used in the treatment of non-insulin dependent diabetes mellitus. It improves glycaemic control by enhancing insulin sensitivity in the liver and muscles. The drug has also exhibited beneficial effects on several cardiovascular risk factors such as dyslipidemia, elevated plasma plasminogen activator inhibitors, other fibrinolytic abnormalities, and hyperinsulinemia and insulin resistance.\textsuperscript{[7]}

Metformin HCl is an anti-hyperglycemic agent, which improves glucose tolerance in type II diabetes. It has been reported that the absolute bioavailability of Metformin HCl when given orally is 50–60\%. Biological half-life of Metformin HCl is 1.5–1.6 h and the main site of its absorption is proximal small intestines.\textsuperscript{[8]}

The formulation suitable for Metformin HCl, therefore, should be a gastro retentive dosage form, which releases the drug slowly in the stomach for gradual absorption in the intestines. The slow but complete drug release in the stomach is expected to increase bioavailability of the drug as well its complete utilization which may results to lower dose and GI side effects.

\textbf{MATERIAL AND METHOD:}

Metformin HCl was supplied as a gift sample from Centaur Pharmaceutical Ltd., Pune. HPMC K100M was brought from Ranbaxy. Carbopol 940 was procured from Pure Chem Laboratory and Ethyl Cellulose was supplied from Thomas Baker hem Ltd.

\textbf{Preparation of trilayer mucoadhesive compressed tablet:}

Composition of the trilayer tablet is given in Table 1. In preliminary study several batches were formulated and evaluate and the three best batches were selected for further study. Trilayer Mucoadhesive Tablets were prepared by direct triple compression method. Mucoadhesive layer (First & Third Layer) HPMC K100M and Carbopol 940 while sustain release layer (Second Layer) contains drug and Ethyl Cellulose. Tablets were prepared in three stages using 12 mm die on CIPS Lab Press. Initially, first layer of mucoadhesive polymer blend was compressed (first compression) for 5-10 seconds then second layer blend was added and a second compression was performed for 20-25 seconds further third layer ingredients are added and compressed to get

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Layer & Composition & Blend 1 & Blend 2 & Blend 3 \\
\hline
First Layer & Metformine HCl, Ethyl cellulose & Carbopol 940, HPMC K100M & & \\
\hline
Second Layer & & & & \\
\hline
Third Layer & & & & \\
\hline
\end{tabular}
\caption{Composition of the trilayer tablet.}
\end{table}

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trilayer tablet.

Evaluation of Tablet:

1. Tablet weight variation:
Twenty tablets were randomly selected and accurately weighed and were evaluated for weight variation.

2. Tablet thickness:
A vernier caliper was used to determine thickness of 10 randomly selected tablets.

3. Drug content uniformity:
For drug content uniformity, 20 tablets were weight and crushed. An accurately weighed 0.05 g drug equivalent powder was transferred to 100 ml of 0.1 N HCl. This suspension was stirred on a magnetic stirrer for 5 h. The suspension was then filtered and the drug content was determined at 233 nm by making suitable dilutions.

4. Tablet friability:
According to the BP specifications, 10 tablets were randomly selected and placed in the drum of a tablet friability test apparatus (Electrolab). The drum was adjusted to rotate 100 times in 4 min. The tablets were removed, dedusted and accurately weighed. The percent weight loss was calculated.

5. Swelling index:
Swelling index were determined for each formulation batch, one tablet was weighed and placed in a beaker containing 200 ml of 0.1 N HCl. After each interval the tablet was removed from beaker and weighed again up to 6 hours. The swelling index was calculated using following formula,

Swelling Index (S.I.) = (Wt – Wo)/Wo
Where,
S.I. = Swelling index
Wt = Weight of tablet at time t
Wo = Weight of tablet before placing in the beaker

6. Exvivo Bioadhesion Studies:
The exvivo adhesion studies were conducted using a modification of a test assembly described by Madgulkar et al. The sheep stomach mucosa was kept frozen in 0.1 N HCl and thawed to room temperature before use. The membrane was excised by removing the underlying connective and adipose tissue and was equilibrated at 37±0.5°C for 30 min in 0.1 N HCl before the study. The tablet was placed on mucosa under constant weight of 5 g for a total contact period of 1 min. Bioadhesive strength was assessed in terms of weight (grams) required for detaching the tablet from the membrane.(Fig. 1)

7. Exvivo mucoadhesion time:
The fundus tissues of the sheep were fixed on internal side of beaker with cyanoacrylate glue. Each tablets previously wetted 0.1 N HCl was attached to the fundus tissue by applying a light force with fingertips for 20 seconds. The beaker was filled with 900 ml of 0.1 N HCl and kept at 37°C after 2 min. stirring rate of 50 was applied until complete detachment occurred.

8. In Vitro drug release studies:
Drug release studies of the prepared trilayer mucoadhesive tablets were performed, in triplicate, in a USP Dissolution Tester Apparatus, type - II (Paddle method) (Electrolab TDT -06P) at 37 ± 0.5°C. The paddles rotated at a speed of 50 rpm. The tablets were placed into 900 mL of 0.1 N HCl (pH 1.2). Aliquots of 10 mL were withdrawn from the dissolution apparatus at different time intervals and filtered through a 0.45µm membrane. The drug content was determined spectrophotometrically at a wavelength of 233 nm, as mentioned before. At each time of withdrawal, 10 mL of fresh medium was replaced into the dissolution basket.

RESULT AND DISCUSSION:

Physical evaluation:
The prepared mucoadhesive tablets were evaluated for various physical parameters such as weight variation, hardness, friability and drug content. All the batches were produced under conditions to avoiding processing variables. Physical evaluation of compressed matrix tablets showed all physical parameters to be within specifications. Tablet weights varied between 699 and 702 mg; thickness, between 4 mm and 5 mm; and hardness, between 8-9 kg/cm². The assay content of Metformin HCl varied between 90.2% and 97.8%, and the friability ranged between 0.3% and 0.6%.

Swelling ability:
Swelling index for all the formulations was carried out in the 0.1N HCl. Graphical representation swelling index of all the batches are shown in Fig. 2.

Exvivo bioadhesion strength determination:
Results concur with observed facts that increase in concentration of Carbopol 940 increased bioadhesion. The HPMC K100M, because of its ability to take up water, causes polymers to swell and interpenetrate quickly and to a greater extent. The water uptake reduces glass transition temperature below ambient conditions; hydrogels become progressively rubbery due to coiling of polymer chains; and subsequently, mobility of polymer chains is increased. Table-3 indicates bioadhesive strength in grams for all formulations. The value of bioadhesive strength ranged between 13.44, 15.14 and 17.73 g for batches F1, F2 and F3 respectively. The bioadhesion is highest when Carbopol 940 concentration is maximum.

In vitro release studies:
In vitro dissolution studies were performed for all the formulations using

Fig 2: Swelling index curve of Metformin HCl tablet.

Fig 3 : In vitro drug release curve for Metformin HCl tablet

Table 1: Composition for trilayer mucoadhesive tablet.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of Ingredient</th>
<th>Batch Code (Qty in mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Layer 1</td>
<td>HPMC K100M</td>
<td>50 66.6 33.3</td>
</tr>
<tr>
<td></td>
<td>Carbopol 940</td>
<td>50 33.3 66.6</td>
</tr>
<tr>
<td>Layer 2</td>
<td>Metformin HCl</td>
<td>250 250 250</td>
</tr>
<tr>
<td></td>
<td>Ethyl cellulose</td>
<td>250 187.5 125</td>
</tr>
<tr>
<td>Layer 3</td>
<td>HPMC K100M</td>
<td>50 66.6 33.3</td>
</tr>
<tr>
<td></td>
<td>Carbopol 940</td>
<td>50 33.3 66.6</td>
</tr>
</tbody>
</table>

Table 2: Physicochemical parameter of tablet

<table>
<thead>
<tr>
<th>Batches</th>
<th>Hardness (Kg/cm²)</th>
<th>Weight (mg)</th>
<th>Friability (%)</th>
<th>%Drug Content</th>
<th>Swelling index (%) in 6 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>8.09</td>
<td>700</td>
<td>0.5</td>
<td>90.2</td>
<td>162.8</td>
</tr>
<tr>
<td>F2</td>
<td>8.95</td>
<td>699</td>
<td>0.3</td>
<td>97.8</td>
<td>179.1</td>
</tr>
<tr>
<td>F3</td>
<td>9.05</td>
<td>702</td>
<td>0.6</td>
<td>95.1</td>
<td>141.1</td>
</tr>
</tbody>
</table>

USPXXII Tablet dissolution tester employing paddle type at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. The samples withdrawn were analyzed by using UV spectrophotometer. As per the results of dissolution study formulations F1, F2 and F3 showed 71.68%, 83.80% and 81.12% respectively. This showed that the drug release from the tablet was sustained for 8 hr. Graphical representation drug release profile of all the batches were shown in Fig. 3.

CONCLUSION:
The Metformin HCl trilayer mucoadhesive tablets formulated with HPMC and /carbopol were shown a variable mucoadhesion strength depending on the ratio of concentration of the polymers used. The release of Metformin HCl from the prepared trilayer tablet was slow and spread over 8 hr and depended on concentration of ethyl cellulose in the tablet. Formulation F3 showed better sustained release than the other formulations. This approach can also be useful to overcome formulation problems associated with BCS class II drugs along with BCS class I drugs.

REFERENCES:
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