

Modified Release of Metformin Hydrochloride using Ion Exchange Resin Complex in Floating Mucoadhesive Tablets

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Abstract

Background: Metformin hydrochloride (HCl) is an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin HCl is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents and very successfully used as drug of first choice. It has 50-60% oral bioavailability. It is believed to be predominantly absorbed in the upper part of the intestine, and estimated time for its complete absorption is approximately 6 h. Clinical trials with metformin have demonstrated decreased bioavailability at higher doses, suggesting saturable intestinal absorption. There is need and scope to increase oral bioavailability of metformin HCl. These details led to an idea of development of SR tablet with more gastric/duodenum retention and was designed as SR tablet using ion exchange principle in floating, mucoadhesive matrix. **Aim:** The objective of this research was to formulate floating mucoadhesive tablet of metformin HCl in complex with ion exchange resin, for the therapeutic dose of 250 mg. **Materials and Methods:** Metformin HCl being cationic drug can be complexed with cation exchange resin like indion 244. This study began with formulation and optimization of drug-resin complex (DRC). Various parameters like the use of batch and column process, complexation time, temperature, and pH were studied and optimized. DRC was characterized by infrared spectroscopy and X-ray diffraction pattern. The efficient drug loading was evident in a batch process using activated indion 244 with a drug-resin ratio of 1:1. Drug complexation enhanced with pH 3.5, temperature 60°C. Infrared spectroscopy revealed complexation of: -NH group of the drug with -C=O stretching of aryl acids of indion 244. Optimized DRC obtained was amorphous in nature. This DRC was put into tablet which could sustain the release of metformin in the favorable region of gastric pH because of inherent slow release from DRC along with a matrix of hydroxypropylmethylcellulose (HPMC) K100M and Carbopol 974P. HPMC K100M along with sodium bicarbonate made this tablet float and Carbopol 974P gave the additional property of mucoadhesion. The quantity of carbopol optimized first and quantity of HPMC and carbopol using 32 factorial design. **Results:** The tablets were evaluated for hardness, thickness, friability, drug content, weight variation, floating lag time, floating time, mucoadhesive strength, and in vitro drug release. Tablets thus formulated (Batch M-3) provided sustained release using floating and mucoadhesion approaches over a period of 12 h. The project is open for in vivo studies. **Conclusions:** Metformin HCl (250 mg) table as drug resin complex in mucoadhesive floating matrix can provide advantage for early cases of diabetics. Floating mucoadhesive tablet having metformin HCl complexed with indion 244 is not available in the market and not yet reported in research paper as per literature survey. This could be one of the attempts to increase the oral bioavailability of metformin HCl.

Key words: Drug-resin complex, indion 244, metformin HCl

INTRODUCTION

Diabetes is one of the most prevailing and advancing diseases in the world having affected 6.6% of the world population. Metformin hydrochloride is the most widely used oral antidiabetic drug in the world.^[1] Metformin HCl shows high aqueous solubility and low cell membrane permeability. The usual

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dosage for metformin HCl is 250-500 mg 3-4 times daily, up to a maximal of 2.5 g/day. The absolute bioavailability of metformin hydrochloride is 50-60% and is having a short biological half-life of 6.2 h. The use of metformin HCl therapy has the high incidence of gastrointestinal side effects.^[2,3]

Ion exchange resins have versatile properties as drug delivery vehicles and have been extensively studied in the development of novel drug delivery systems. Cation exchange resins containing strong sulfonic acid group form a strong bond with cationic drugs, and elution of drug from resinate is slower.^[4] Ion exchange resins are cross-linked; water insoluble, polymer-carrying, ionisable functional groups. Drugs can be loaded onto the resins by an exchanging reaction, and, hence, a drug-resin complex (DRC) is formed.^[5] The drug is released from the resins by exchanging with ions in the gastrointestinal fluid, followed by drug diffusion.^[6] Being high molecular weight water-insoluble polymers, the resins are not absorbed by the body and are therefore inert.^[7]

The present research was directed toward the development of sustained release dosage form of metformin HCl using ion exchange resin with incorporation of polymer matrix indion 244 IER and polymers such as hydroxylpropylmethylcellulose (HPMC) K 100 M and carbopol 974P. Indion 244 is a strong cation exchange resin with $\text{SO}_3^- \text{H}^+$ functionality which exchanges cations stoichiometrically in an equilibrium driven reaction. Due to the presence of $\text{SO}_3^- \text{H}^+$ group Indion 244 shows ionization at all body pH values. However, simple DRCs may not satisfy the requirement of sustained release, in such cases, resins are incorporated into the matrix systems, microencapsulated or coated.^[8] In this research the resin is incorporated into floating mucoadhesive matrix where the floatation property is created with the use of HPMC K100M along with sodium bicarbonate and mucoadhesive property is created with the use of carbopol 974P. Metformin HCl in the resin form in a floating mucoadhesive gastroretentive tablet is not yet reported as per literature survey done during this study.

The drug delivery inside gastric region is a suitable approach for drugs, preferentially absorbed through upper part of the gastric region. Several approaches have been utilized for sustaining drug delivery inside gastric region such as floating, bioadhesion, and swellable system are some dosage forms developed for drug release within the gastric region.^[9]

Response surface methodology is a widely practiced approach in the development and optimization of drug delivery devices.^[10-14] Based on the principle of design of experiments, the methodology encompasses the use of various types of experimental designs, generation of polynomial equations, and mapping of the response over the experimental domain to determine the optimum formulations.^[11-14] The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective than the conventional

methods of formulating dosage forms. The tablets incorporating resin into HPMC matrix were developed employing 3^2 factorial design.

MATERIALS AND METHODS

Metformin hydrochloride-IP was a gift sample from Micro Laboratories (Bengaluru, India). Indion 244 was obtained from Ion Exchange India Ltd., Mumbai, India. Microcrystalline cellulose (MCC) (pH 102) and HPMC (K100M) were obtained from Research Lab, Mumbai, India. All other chemicals and reagents used were of the high analytical grade.

Purification of ion exchange resin

Indion 244 was washed with distilled water. The wet resin was activated by 0.1 N HCl 300 ml followed by washing with distilled water and was dried overnight in hot air oven at 50°C and was stored in an air-dried glass vials.

Preparation of DRC (resinate)

Resins were prepared by batch process. An accurately weighed amount of drug (0.1 g) was dissolved in 100 ml of distilled water. Then, ion exchange resin (0.1 g) was added and stirred on a magnetic stirrer. Resinate thus formed was filtered and washed with copious amount of deionized water to remove any uncomplexed drug. It was then dried at 50°C and the drug content was determined spectrophotometrically at 232 nm.^[15,16]

Evaluation of micromeritic properties of resinate

The different micromeritic properties of resinate like flow properties, bulk density, tap density.^[17,18]

Characterization of DRC

The different characterization studies of DRC like determination of drug content and confirmation of complexation were studied below in detail.

Determination of drug content in the resinate

An accurately weighed amount of drug equivalent resinate (0.1 g) was dissolved in 100 ml of 0.1 N HCl and stirred for 5 h. Then, the suspension was filtered, further dilutions were made, and the drug content was determined at 232 nm using 0.1 N HCl as a blank.

Confirmation of complexation

a. Fourier transform infrared (FTIR) studies: Metformin HCl, indion 244, and physical mixture of both and DRC were subjected to FTIR spectroscopy studies. Samples

were prepared using KBr disc method, and spectra were recorded over the range 400-4000/cm. Spectra were analyzed for drug-resin interactions and functional groups involved in the complexation process

- b. Powder X-ray diffraction studies: X-ray diffractograms of metformin HCl, Indion 244, and DRC were recorded using Philips PW 3710 diffractometer and analyzed for interactions between drug and resin and confirmation of complexation.^[19,20]

Formulation and development

This research aimed at design and development of metformin HCl resinate in a floating mucoadhesive tablet. After the successful development of DRC, the quantity of carbopol 974P was optimized and quantity of HPMC K100M and sodium bicarbonate was optimized using 3² factorial design. In this design, two factors were evaluated at three different levels and experimental trials were performed at all nine possible compositions. The amount of release rate modifying HPMC K 100M and sodium bicarbonate were selected as independent variables while floating lag time (FLT) and % drug release were selected as dependent variables.^[21,22]

Formulation of metformin HCl floating-mucoadhesive tablets [Table 1]

Different nine batches (M1-M9) of metformin HCl floating-mucoadhesive tablets were prepared by applying 3² factorial design. In this the design two independent factors are HPMC (X1) and sodium bicarbonate (X2) was set at different levels.

Preparation of tablets

Wet granulation method

Required quantity of resinate, HPMC (K100M) and MCC were blended in a geometric fashion. Deionized water was added to powder blend and dispersed thoroughly to get the wet mass. The damp mass was shifted through sieve No. 22 to obtain granules. Keep it for drying in oven at 40°C for 1½ h.

Add carbopol 974P into the dried granules (previously shifted through sieve No. 60). Tablets were prepared using 12 station tablet punching machine using 13 mm die.^[17]

Pre-compression evaluation of tablet powder blends

The different micromeritic properties of powder blend like angle of repose, bulk density, tap density, compressibility index were studied.

Evaluation of tablets

Tablets were evaluated for various official and nonofficial specifications. Thickness was measured with the help of Vernier caliper. The hardness of tablets was measured with Monsanto hardness tester. For drug content uniformity, 20 tablets were weight and crushed. An accurately weighed 0.01 g drug equivalent resinsates and transferred to 100 ml of 0.1 N HCl. This suspension was stirred on magnetic stirrer for 5 h. The suspension was then filtered, and the drug content was determined at 232 nm by making suitable dilutions. Friability is the measure of tablet strength. Roche type friabilator was used for testing the friability. Matrix integrity was observed throughout in vitro dissolution studies by visually inspecting the swollen mass of the tablets for integrity (should remain as intact mass).

Determination of floating (buoyancy) behavior of tablets

Buoyancy lag time

This test was performed in dissolution vessel containing 900 ml dissolution medium maintained at 37°C. The time required for the tablet to rise to the surface and float was determined as buoyancy lag time.

Buoyancy time

Buoyancy time is the total time for which the tablets float in dissolution medium (including buoyancy lag time) before getting disintegrated or settling down.

Table 1: Formulae for the preparation of metformin HCl floating-mucoadhesive tablets as per factorial design

Ingredients	M1	M2	M3	M4	M5	M6	M7	M8	M9
DRC	332.44	332.44	332.44	332.44	332.44	332.44	332.44	332.44	332.44
HPMC	90	70	80	80	90	90	70	80	70
Sodium bicarbonate	90	70	90	80	70	80	90	70	80
Carbopol 974P	52	52	52	52	52	52	52	52	52
MCC	49.66	89.56	53.56	69.56	69.56	53.56	69.56	79.56	79.56
Magnesium stearate	8	8	8	8	8	8	8	8	8
Talc	8	8	8	8	8	8	8	8	8
Subtotal	630	630	630	630	630	630	630	630	630

MCC is added to each tablet to make the weight to 630 mg. MCC: Microcrystalline cellulose, HPMC: Hydroxypropylmethylcellulose, DRC: Drug resin complex

Swelling behavior of tablets

Swelling behavior of tablets was carried out using USP dissolution apparatus II. Tablets from each batch were placed in the dissolution medium and after selected time intervals, i.e., 0, 1, 2, 4, 6, 8, 10, 12 h tablets were withdrawn and blotted to remove excess water and weighed. The swelling index was calculated by using the following formula:

$$\% \text{Swelling index} = \frac{W_1 - W_0}{W_1} \times 100$$

Where; W_0 = Initial weight of tablet, W_1 = Final weight of tablet at time t .

Matrix erosion of tablet

The swollen tablets in swelling study at 24 h were dried at 60°C in vacuum oven subsequently dried in desiccators for 2 days and reweighed (W_3). Matrix erosion at 24 h calculated by using following formula:

$$DS = (W_1 - W_3) * 100 / W_1$$

Where, W_1 - Initial weight of tablet, W_3 - Weight of tablet dried at 60°C for 24 h in vacuum oven.

Ex-vivo mucoadhesive strength

To perform the *ex-vivo* mucoadhesive strength fresh goat stomach tissue was obtained from a local slaughterhouse and used within 2 h of slaughter. The membrane was washed with distilled water and transferred to 0.1 N HCl buffer pH 1.2. The membrane was then fastened and then attached to a rubber cork suspended above the Perspex block with the mucoadhesive layer facing the membrane and the other layer fastened to the cork with double sided tape. The string was coiled around a pulley, and the cylindrical vessel was suspended freely. The cork was lowered until the tablet came in contact with the mucosal membrane. Water was added dropwise in the suspended vessel until the tablet got dislodged from the mucosal membrane. The volume of water (ml) required to dislodge the tablet from the mucosal membrane was correlated with the mucoadhesion strength (g) and the calculation was done by using the following formulas:

- Mucoadhesive strength in kg needed in the following formula was calculated by the amount of water required to put in the vessel to detach the tablet from goat stomach tissue.

$$\text{Mucoadhesive strength (Nm}^{-2}\text{)} = \frac{\text{Mucoadhesive strength in kg} \times 9.8}{\text{Surface area}}$$

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength}}{1000} \times 9.81$$

$$\text{Mucoadhesive strength (Nm}^{-2}\text{)} = \frac{\text{Force of adhesion}}{\text{Surface area}}$$

Ex-vivo residence time

Ex-vivo residence time study was carried out in dissolution apparatus. Isolated fresh goat stomach mucosa was tied on the glass slide; each tablet was wetted with 1 drop of 0.1 N HCl buffer pH 1.2 and pasted to the goat stomach mucosa by applying light force with a fingertip for 30 s. The glass slide was then placed in the vessel; the mucoadhesive property was evaluated using 300 ml of 0.1 N HCl buffer pH 1.2, at $37 \pm 1^\circ\text{C}$ with slow stirring speed of 50 rpm to simulate the stomach environment, tablet adhesion was monitored for 8 h. Time for the tablet to detach from the porcine stomach mucosa was recorded as the mucoadhesion time.

In-vitro dissolution studies metformin hydrochloride

The release rate of metformin HCl from floating-mucoadhesive tablet was determined using USP dissolution test apparatus II (Paddle type). The dissolution test was performed using 900 ml, 0.1 N HCl buffer pH 1.2, at $37 \pm 0.5^\circ\text{C}$ at 100 rpm. A 5 ml of sample solution was withdrawn from the dissolution apparatus after 1, 2, 3 up to 24 h. The samples were filtered through Whatman filter paper (45 μm) and solutions were analyzed at 232 nm by ultraviolet (UV) Spectrophotometer (SHIMADZU V-630, Japan). Cumulative percentage drug release was calculated.^[23-25]

Stability study

The optimized formulation was wrapped in aluminum foil and subjected to $40 \pm 0.5^\circ\text{C}$ temperature as per ICH guideline Q1A (R2) in oven for the period of 1-month. The formulation was analyzed for organoleptic properties, hardness, drug content, dissolution, FLT, floating time, mucoadhesion study.

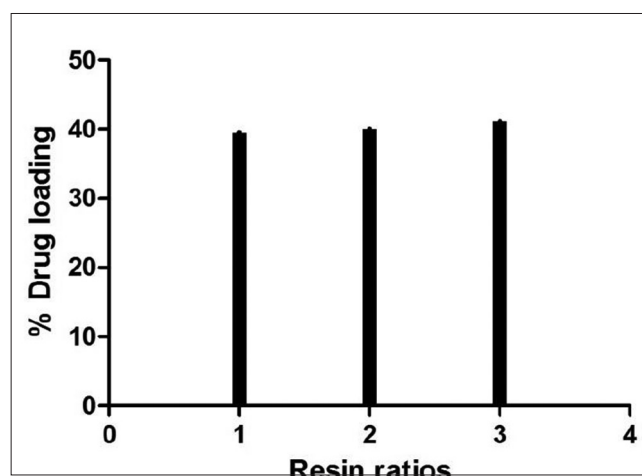


Figure 1: Effect of drug resin ratio (1-1:1 drug: resin, 2-1:2 drug: resin, 3-1:3 drug:resin)

RESULT AND DISCUSSION

Drug loading in metformin hydrochloride-resin complex

Effect of metformin hydrochloride: Resin ratio

The DRC was tried in different drug:resin ratios ranging from 1:1 to 1:3 in aqueous medium and it was observed that there was a sharp increase in drug entrapment (39.5-41.2%) with increase in the ratio from 1:1 to 1:3. Increase in the amount of resin increases the amount of drug adsorbed from the solution but decreases the drug content a 100 mg of resonates [Figure 1].

Effect of stirring time

Drug entrapment of metformin hydrochloride: Indion 244 resin was measured in the time range of 2-6 h. The maximum drug entrapment was observed at 5 h. After which, not much increase in (%) drug entrapment was found with time [Figure 2].

Effect of temperature on drug loading

Increased temperature during complexation increases ionization of drug and resin. Higher temperatures tend to increase the diffusion rate of ions by decreasing the thickness of exhaustive exchange zone. Maximum drug loading on the resin occurs at a temperature of 60°; a maximum of 69.28.30 ± 1.31, for indion 244 [Figure 3].

Effect of pH on drug loading

Maximum drug loading on the resin occurs at pH 3.5; a maximum of 46.57 ± 0.47, for indion 244. As pH increases

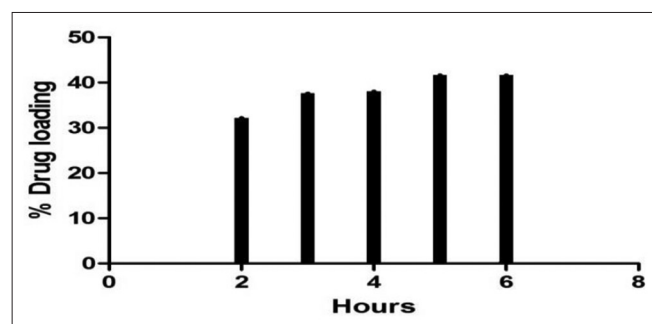


Figure 2: Effect of stirring time

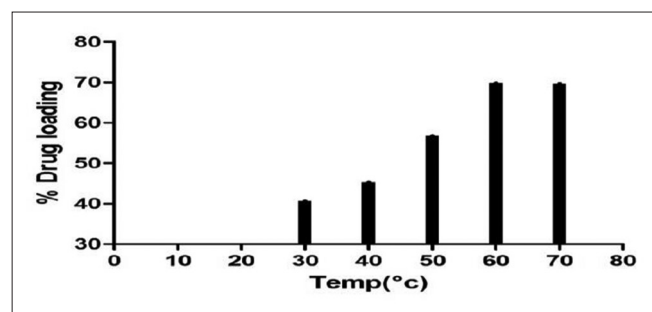


Figure 3: Effect of temperature

above 3.5, percentage of drug loading decreases. This may be due to fact that the fraction of metformin hydrochloride (pK_a 11.5) protonation decreases as the pH increases and reduces the interaction with the resin [Figure 4].

Effect of mixing mode on drug loading

Complexation was found to be optimum in case of stirring, a maximum of 48.53 ± 1.23 , for indion 244 and in the case of shaking 45.14 ± 0.92 . This finding may indicate the significant involvement of van der Waals forces taking place along with drug exchange during complexation.^[26,27]

Effect of quantity of distil water on drug loading

Maximum drug loading on resin occurred in 100:50 resin:distilled water, this finding indicates that significant binding has taken place along with drug exchange during complexation.

The different micromeritic properties resinate such as shape, flow properties, bulk density, tap density, and packing ability were studied (Table 2).The results showed that the resinate has good flow properties, bulk density.

Table 2: Micromeritic properties of resinate

Resin	Angle of response (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (ic)
Indion 244	24.86	0.386	0.482	0.137969

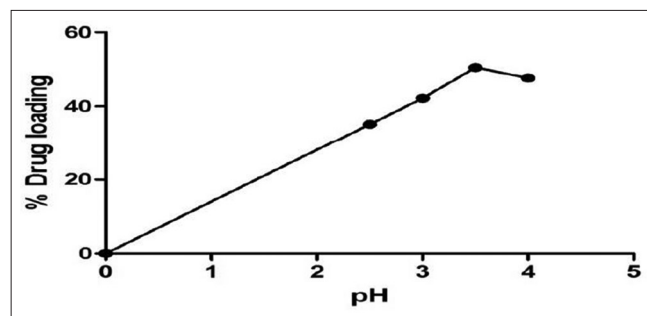


Figure 4: Effect of pH



Figure 5: (a) Metformin HCl, (b) Indion 244, (c) metformin HCl: indion 244 complex

The infrared spectra of drug, indion 244 resins and resin are depicted in Figure 5. FTIR spectra of the drug shows peak at 1028/cm corresponding to the NH stretching in a secondary amine. Indion 244 shows characteristic peaks at 1674/cm corresponding to $\text{C}=\text{O}$ stretching of aryl acids and due to aromatic $\text{C}=\text{C}$ stretching. The absence of peak at 1028/cm in DRC confirms the complexation of the secondary amine group in the drug with resin. The X-ray diffraction study of the drug shows highly crystalline nature. Resins indion 244 showed amorphous nature and the resonates showed non-crystalline characteristics. This might be because of entrapment of drug molecule in the polymer matrix of the resins. From all the evidence, it can be concluded that the drug resin was a chemical complex [Figure 6]. Studies have shown that the molecules of the entrapped drug changes from crystalline to amorphous state.

Determination of floating behavior

An effervescent floating drug delivery was used to achieve *in vitro* buoyancy. All the batches were prepared using HPMC K100M and sodium bicarbonate was added as gas generating

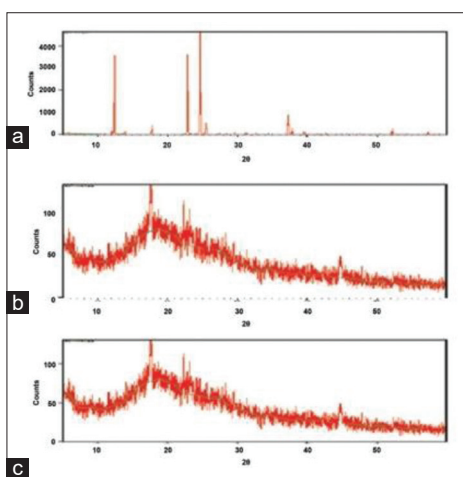


Figure 6: (a) Metformin HCl, (b) Indion 244, (c) metformin HCl: indion 244 complex

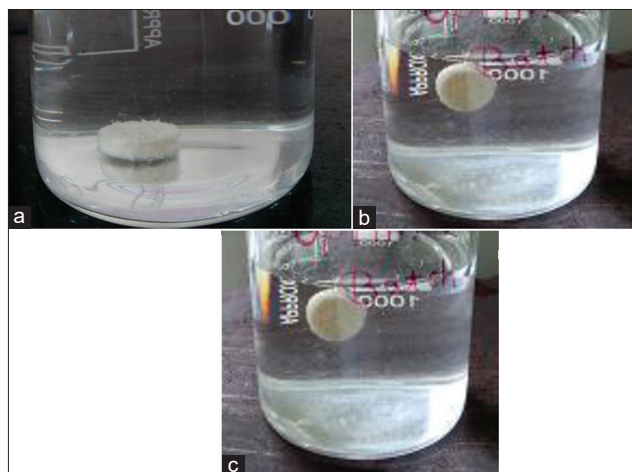


Figure 7: Floating lag time, (a) At time 0s, (b) after 10s, (c) after 15s, (d) after 25s, (e) after 30s

agent. Sodium bicarbonate-induced CO_2 generation in the presence dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel, formed by hydration of polymer, thus decreasing the density of the tablet. As the density of tablet falls below 1, the tablet becomes buoyant. All the tablet produced good gel strength, entrapping CO_2 gas and imparting stable and persistent buoyancy. All tablet batches (M1-M9) exhibited satisfactory floatation ability and remain buoyant for more than 8 h. In dissolution medium (0.1 N HCl). FLT of all batch showed good FLT in the range of 25-30 s. Floating time of all batch showed good FT more than 8 h [Figure 7].^[28]

Determination of swelling index and matrix erosion

The effect of HPMC on swelling index and % erosion was found to be highly significant. The percentage water uptake of the formulations (M1-M9) at 24 h ranged from 320.87 to 515.02 shown in Figure 8. Because of hydrophilic nature of both the polymers, the percentage water uptake was found to be increased on increasing the concentration of HPMC K100M in formulations and, hence, the water uptake capacity increases. Drug diffusion of tablet depends on the water content of the tablet. This may be because the mobility of the polymer chains is dependent on the water content of the system. In the case of high water content, polymer chain relaxation takes place with volume relaxation takes place with volume expansion resulting in marked swelling of the system. Furthermore, higher water content could lead to greater penetration of gastric fluid into the

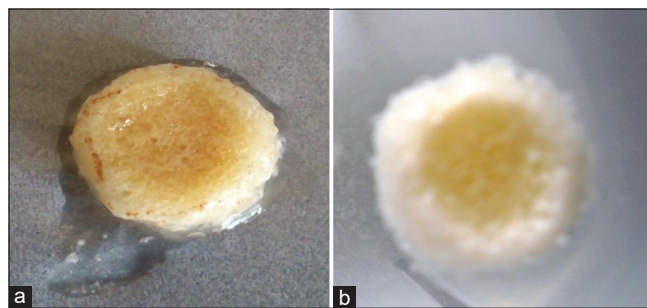


Figure 8: (a) Tablet after 4 h, (b) tablet after 12 h (swelling study)

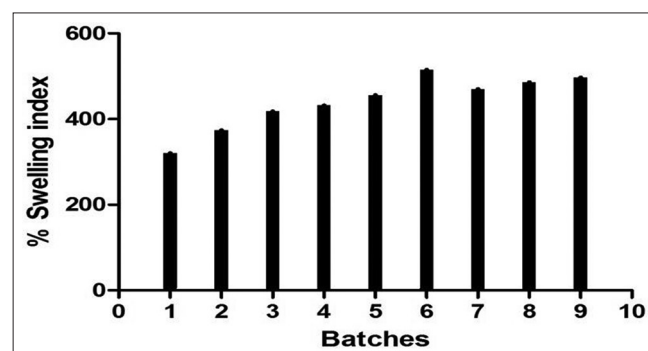


Figure 9: Plot of % water uptake (% swelling) of tablet batches M1-M9

tablet leading to faster carbon dioxide gas generation, thereby reducing the FLT. Consequently, faster and greater swelling of the tablet would lead to an increase in the diffusion pathway and, thus, a reduction in the diffusion rate. But the matrix erosion was found to be decreased on decreasing the concentration of HPMC because HPMC forms matrix gel, hence the drug release rate decreases with increases in the concentration of HPMC.

Figure 9 demonstrate the swelling index of formulation batches M1-M9. Formulation batches M1-M9 containing different concentration of HPMC K100M and Carbopol 974P showed good swelling index and maintain matrix integrity till 12 h. It has been observed that the % cumulative drug release (CDR) decrease with increasing concentration of polymer and swelling index. The reason attributed to this fact is slow erosion of the gelled layer from the tablet containing a higher amount of polymer.

Ex-vivo mucoadhesion measurement

The results of the detachment force of metformin HCl floating tablet formulations showed as the concentration of HPMC increased, the detachment force increased, mucoadhesive strength and force of adhesion increases [Figure 10].

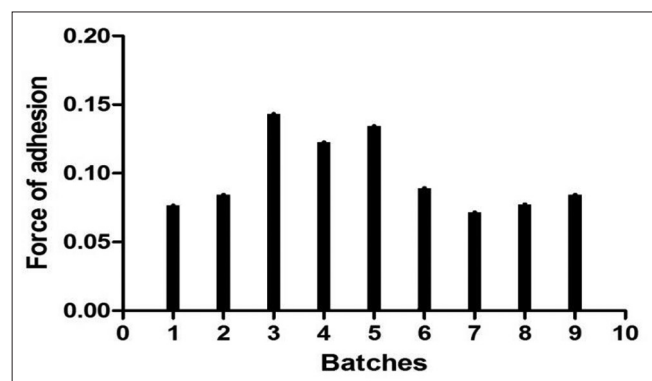


Figure 10: Force of adhesion of formulation batch M1-M9



Figure 11: Residence time study

Determination of duration of mucoadhesion (residence time)

In all formulations, the duration of mucoadhesion was found to be more than 8 h [Figures 11 and 12].

In-vitro dissolution studies for metformin HCl

Results of the *in vitro* release studies of various formulations designed and manufactured are shown in Figures 13 and 14. The result showed that, in the case of indion 244 resinate tablet, was more than 86.69-92.48% of drug released from tablets formulation with HPMC (K100M) in 90 mg concentration within 8 h (Batch M1-M3). This may be because of strong binding properties of HPMC, which binds the fine particles of resinate. The drug release from these tablets was simply due to slow erosion and ion exchange. The



Figure 12: Mucoadhesion residence time (h) of formulation batch M1-M9

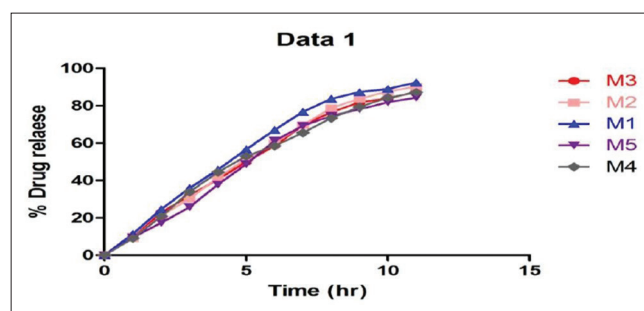


Figure 13: *In vitro* drug release profile of batch M1-M5

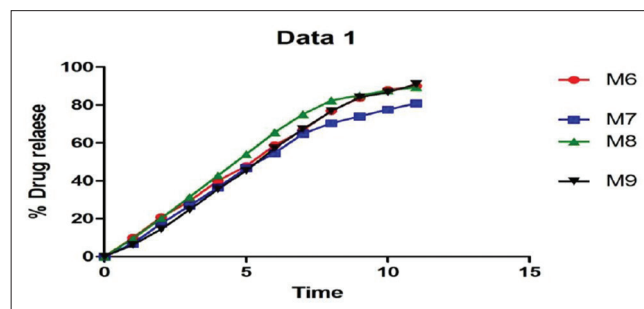


Figure 14: *In vitro* drug release profile of batch M6-M9

addition of 80 mg, 70 mg HPMC (K100M) does not affect the drug release significantly (Batch M3). This may be due to rapid disintegration of tablets in dissolution medium because of larger particle size of indion 244 resinate.

Thus, from the above M1-M9 batches formulation M3 containing HPMC in the concentration of 90 mg was selected as the best formulation and was kept constant throughout further studies, this is due to lower and optimum concentration of NaHCO_3 with a higher concentration of HPMC.

Optimization data analysis

A 3^2 (three factor-two level) full factorial design was adopted for optimization of metformin hydrochloride floating mucoadhesive tablet. The purpose of using a full factorial experimental design was to conduct a comprehensive study of the effect of the process parameters and their interactions by applying one-way ANOVA at 0.05 levels. A mathematical modeling was carried out by using Equation 2 to obtain a polynomial equation depending on significant influences among the independent factors (X_1 , and X_2) of the factorial design model. Two independent factor variables measured: HPMC (X_1) and sodium bicarbonate (X_2) was set at three different levels. The dependent response variable measured was drug entrapment using the results of 9 runs in the factorial design.

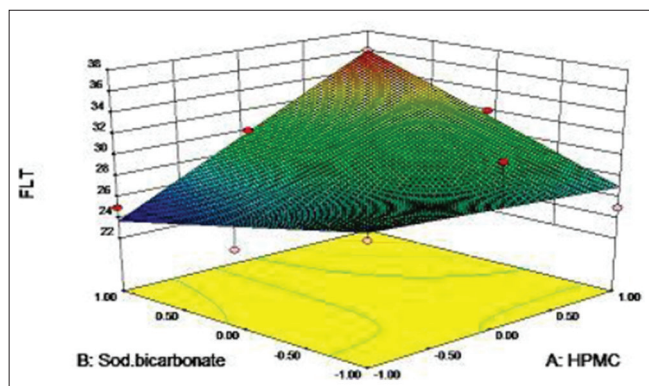


Figure 15: Response surface plot of Y_1 (floating lag time)

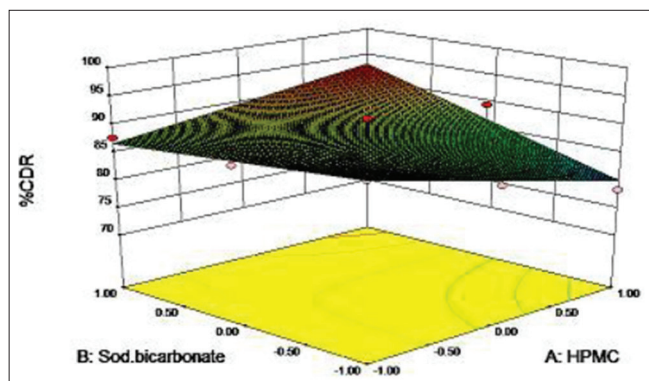


Figure 16: Response surface plot of Y_2 (% cumulative drug release)

$$Y_1 = + 26.44 + 2.00X_1 - 1.83X_2 \dots\dots (1)$$

Where $Y_1 = \text{FLT}$, X_1 , and $X_2 = \text{Main effects}$

$$Y_2 = + 90.81 - 3.47X_1 + 3.23X_2 \dots\dots (2)$$

Where, $Y_2 = \% \text{CDR}$, X_1 and $X_2 = \text{Main effects}$

The Equations 1 and 2 had statistical significance ($P < 0.05$) for response Y_1 (FLT), Y_2 (%CDR). From the regression equation for metformin hydrochloride, it is evident that both X_1 and X_2 exerts a significant effect. As the concentration of HPMC K100M (X_1) increases FLT was also increases and increase in concentration of NaHCO_3 there was decrease FLT [Figure 15]. As the concentration of HPMC K100M (X_1) increases % CDR was decreases and as the concentration of NaHCO_3 (X_2) increases % CDR also increases [Figure 16].

Stability testing

Optimized floating mucoadhesive tablet of metformin hydrochloride tablet (S3) was subjected to stability studies. These formulations were stored at $30 \pm 2^\circ\text{C}/65\% \pm 5\% \text{RH}$, and $40 \pm 2^\circ\text{C}/75\% \pm 5\% \text{RH}$. The color of all the tablets was similar before and after stability studies. There was no significant change in the FLT and floating time, mucoadhesive properties of OP3 tablet formulation [Figure 17]. The dissolution profile of the formulation considered at time zero and after 1-month of storage at $40^\circ\text{C}/75\% \text{RH}$ are nearly superimposable. These observations indicate that the drug retained within the formulation, and was stable enough during storage conditions [Figure 18].

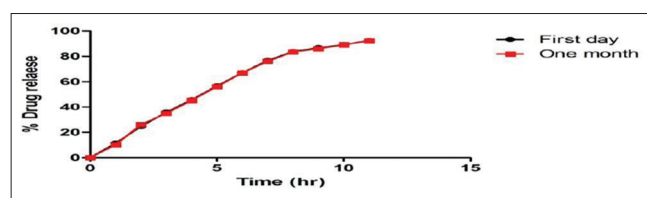


Figure 17: Dissolution profile



Figure 18: Floating lag time (OP3 batch after stability study)

CONCLUSION

On the basis of the present study, it was concluded that floating mucoadhesive tablets of metformin hydrochloride in complex with indion 244 showed increase in the gastric residence time and provided sustained release of drug over a period of 8-h. The release of metformin HCl from resinate controls the diffusion of the drug molecule through the polymeric material into the aqueous medium. Such technology could be useful to improve bioavailability of metformin HCl and could be useful drug delivery for the early cases of diabetics.

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