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### RESEARCH ARTICLE

#### FORMULATION DEVELOPMENT OF MUCOADHESIVE BILAYER TABLET WITH METFORMIN HYDROCHLORIDE.

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#### Abstract

In the present study, an attempt was made to design and evaluate bilayer gastroretentive drug delivery system exhibiting a combination of an immediate release layer and a sustained release mucoadhesive layer as second layer to prolong residence time in stomach using Metformin HCl as a model drug to reduce frequency of administration and to overcome bioavailability problems. A total of 5 formulations of bilayer tablets containing the drug were prepared by direct compression method using 5 different mucoadhesive polymers in 5 different formulations (F<sub>1</sub>-F<sub>5</sub>) respectively to impart mucoadhesion. Formulated bilayer tablets were evaluated by different parameters such as; *ex vivo* mucoadhesion strength, *ex vivo* mucoadhesion time, *In vitro* drug release study. *In vitro* drug release data were fitted to various kinetic models (Zero order, 1<sup>st</sup> order, Higuchi model, Korsmeyer- Peppas model). Upon R<sup>2</sup> value analysis it was observed that release from F<sub>1</sub>, F<sub>3</sub>, F<sub>5</sub> followed Higuchi model and F<sub>2</sub>, F<sub>4</sub> followed Korsmeyer- Peppas kinetic model. Mechanism of drug release was found to be Fickian diffusion (value of n < 0.45). F<sub>4</sub> with Na CMC was found to be more promising in *ex vivo* mucoadhesion study showing residence time of 4.08 hrs. This study concludes that formulated bilayer tablets were satisfactory in providing prompt release from 1<sup>st</sup> layer then maintained sustained release effect with promising mucoadhesion behavior in stomach.

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#### Introduction:-

The new drug delivery system with better efficacy and safety with reduced dosing frequency and improved patient compliance is the current area of research by formulation development scientists. Tablet being most preferred dosage form for its ease of manufacturing and patient convenience is always a first choice of dosage form. The single layer tablets leads to frequent dosing and unpredicted plasma level for drugs with shorter half-lives. Number of diseases require immediate release of drug for instant effect and then plasma concentration has to be maintained for prolong effect of the drug. So, in order to deliver drugs in a predictable time frame, multilayered oral controlled release delivery systems are designed. These systems enhance the efficacy, minimize the adverse effects and increase the bioavailability of drugs.

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Mucoadhesive drug delivery is a topic of interest in the design of drug delivery systems to prolong the residence time of the dosage form at the site of application or absorption and thereby to facilitate the intimate contact of dosage form, thus to improve and enhance the bioavailability.

Dosage forms designed for mucoadhesive drug delivery should be small and flexible enough to be acceptable for patients and should not cause irritation. Other desired characteristics of a mucoadhesive dosage form include high drug loading capacity, controlled drug release (preferably unidirectional release), good mucoadhesive properties, smooth surface, tastelessness, and convenient application. Erodible formulations can be beneficial because they do not require system retrieval at the end of desired dosing interval. A number of relevant mucoadhesive dosage forms have been developed for a variety of drugs (Boddupalli et al., 2010).

The mechanism of adhesion of certain macromolecules to the epithelium of a mucous tissue is understood. They are characterized with an epithelial level whose surface is protected by mucus. The mucus contains glycoproteins, lipids, inorganic salts and 95% water by mass, making it a highly hydrated system. Mucin is the significant glycoprotein of mucus and is responsible for its structure. The principal functions of mucus are covering and lubricating the epithelium and some other functions based on the epithelium protection. Mucus width can change from 50-450  $\mu\text{m}$  in the stomach to less than 1  $\mu\text{m}$  in the oral cavity (Smart, 2005).

The mucous area, majorly used for the drug administration and absorption, is gastrointestinal mucus. The mucoadhesion ought to extend over the substrate to initiate the close connection, enhance the surface contact, and in turn increase the diffusion of its chains inside the mucus. The mechanism of mucoadhesion is usually separated in two stages, the contact stage and the consolidation stage. The first stage is characterized by the contact between the mucoadhesion and the mucous membrane, with covering and swelling of the formulation and initiating its deep contact with the mucous level (Hägerstrom and Edsman, 2003).

The development of sustain release dosage form can achieve the aim of releasing the drug slowly for a long period but this is not sufficient to get sustained therapeutic effect. They may be cleared from the site of absorption before emptying the drug content. Instead, the mucoadhesive dosage form will serve both the purposes of sustain release and presence of dosage form at the site of absorption.

In the recent times, multi-layer matrix tablets are gaining importance in the design of oral controlled drug delivery systems. Bi-layer tablets are novel drug delivery systems where combinations of two or more drugs are given in a single unit. They are preferred for the following reasons: To co-administer two different drugs in the same dosage form, to minimize physical and chemical incompatibilities, for staged drug release, IR and SR in the same tablet, for chronic condition requiring repeated dosing.

In the present research, an attempt was made to develop oral mucoadhesive bilayered tablet of Metformin HCl (MH) using Xanthan gum, NaCMC, HPMC 100CPS, HPMC (K-100LV) and Methocel K4M polymers. Metformin HCl, chemically N,N-Dimethyl imido dicarbonimidic diamide, is a biguanide anti hyperglycemic agent used for treating non-insulin-dependent diabetes mellitus (NIDDM). It improves glycemic control by decreasing hepatic glucose production, decreasing glucose absorption and increasing insulin-mediated glucose uptake. Metformin is the only oral anti hyperglycemic agent that is not associated with weight gain. Metformin may induce weight loss and is the drug of choice for obese NIDDM patients. When used alone, metformin does not cause hypoglycemia; however, it may potentiate the hypoglycemic effects of sulfonylurea's and insulin. The half-life of metformin is 6.2 hrs (Kadhe and Arasan, 2002; Desvergne and Wahli, 1999; Berger and Moller, 2002). It is freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride (Chawla et al., 200; Chinetti et al., 2000; Willson et al., 2001).

It is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract, and the absolute bioavailability of a single 500 mg dose is reported to be 50% to 60%. This indicates the need to develop dosage forms that can retain the drug in the stomach for better absorption. An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea that especially occur during the initial weeks of treatment. The compound also has relatively short plasma elimination half- life (1.5 - 4.5hrs). Sustained release formulations may be administered once or twice daily. By considering above parameters, mucoadhesive bilayer tablet of metformin may be utilized.

This study describes the preparation of bilayer device comprising Metformin HCl as API and mucoadhesive layer of polymer to prolong its duration of action and improve patient compliance.

## Materials and methods:-

### Materials:-

Metformin HCl was received as a gift sample from Square Pharmaceutical Ltd, Bangladesh.; Methocel was purchased from Colorcon; Hydrochloric acid was obtained from Merck, Germany; and Xanthan gum, NaCMC, HPMC 100CPS, HPMC (K-100LV), Lactose, Magnesium stearate, Talc and Aerosil were obtained from local market. All other ingredients were of analytical grade.

### Methods:-

#### Preparation of bilayer tablet:-

A total of 5 different types of formulations were prepared in 2 stages using a 13 mm- diameter die on an infrared hydraulic press with 5N compression force for a total of 1 minute 30 seconds. Initially the mucoadhesive layer was prepared according to Formulation plan (Table-1) for 30 seconds by simple thumb pressure then the 2<sup>nd</sup> layer (immediate release layer) was prepared by final compression force of 5N for 1 minute.

**Table 1:-** Formulation plan:

Ingredients (mg/tablet)	Immediate release layer	Mucoadhesive sustained release layer				
	(F <sub>1</sub> - F <sub>5</sub> ) Composition is same for all formulations	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>	F <sub>4</sub>	F <sub>5</sub>
Metformin HCl	150	250	250	250	250	250
HPMC100cps	-	200	-	-	-	-
HPMC(K-100LV)	-	-	200	-	-	-
NaCMC	-	-	-	200	-	-
Methocel K4M	-	-	-	-	200	-
Xanthan gum	-	-	-	-	-	200
Lactose	100	50	50	50	50	50
Magnesium stearate	1	1	1	1	1	1
Talc	1	1	1	1	1	1
Aerosil	1	1	1	1	1	1
<b>Total weight</b>	253	503	503	503	503	503

### Evaluation of physical and biological parameters of formulated bilayer tablets:-

#### *In vitro* drug release study for mucoadhesive bilayer tablet:-

*In vitro* release profile for each formulated bilayer tablet was performed using USP type II dissolution apparatus (Electrolab, Mumbai, India). Dissolution studies were carried at rotation speed of 50 RPM, in 900 ml of 0.01 N HCl of pH 2.0 at 37 ± 0.5<sup>o</sup> C. Aliquot of 5 ml was withdrawn upto 8 hrs. The withdrawn volume was replaced with same volume of dissolution medium in order to keep the total volume constant. The absorbance of sample was measured by an UV spectrophotometer at 233 nm after suitable dilution if necessary. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug (Singh et al., 2012).

#### Kinetic modeling of *in vitro* drug dissolution profile:-

*In vitro* drug release data of all the bilayer tablet formulations of Metformin HCl was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetics and according to Higuchi's and Korsmeyer-Peppas models to ascertain mechanism of drug release.

#### Measurement of *ex-vivo* mucoadhesive strength:-

Bioadhesive strength of the tablets was measured on modified physical balance. A piece of goat stomach mucosa was pasted to a petri-dish with cyanoacrylate adhesive and the mucus membrane was wetted with 2-3 drops of 0.01 N HCl media. The tablets were tied with thread and attached with the mucous membrane. Another end of thread tied with one side of the physical balance. The weight required to detach the tablet from the mucosal surface was taken as the measure of mucoadhesive strength. Force of adhesion was calculated from the mucoadhesive strength as per following equation:

**Force of adhesion (N) = (mucoadhesive strength × 9.81) ÷ 1000:**

**Measurement of *ex-vivo* residence time:-**

The *ex-vivo* residence time was determined using a locally modified USP disintegration apparatus. A segment of goat stomach mucosa was glued to the surface of the beaker, vertically attached to the apparatus. The mucoadhesive tablet was then pasted to the mucosal membrane by applying a light force with a finger trip for 30 seconds. Then the tablet and mucosa was hydrated by the medium of 800 ml 0.01 N hydrochloric acid of pH 2.0, allowing the apparatus to move up and down maintaining  $37^{\circ} \text{C} \pm 0.5^{\circ} \text{C}$ ; monitoring the tablet adhesion for 8 hours to see retention time and correlate with sustaining property of formulation. The time for the tablet to detach from the goat stomach mucosa was recorded as the mucoadhesion time (Umarji et al., 2012).

**Results and Discussion:-**

The main goal of this work was to develop new mucoadhesive bilayer tablets of metformin HCl; consisting of an immediate release and a of sustained release layer. The double layered structure design was expected to provide immediate release of metformin HCl from the outer layer to produce a prompt pharmacological action then sustained release from second layer to provide a sustained release of enough drug over an extended period of time and retain in stomach for an extended period of time.

A total of 5 formulations of mucoadhesive bilayer tablets were prepared and evaluated for biological and physical parameters. The composition of final bilayer formulation had been chosen from the previous single sustained release layer formulation which gives the best average percent release and best fitted with kinetics model of dissolution release pattern. Different amounts (150 mg, 180 mg, 200 mg, 220 mg) of 5 different mucoadhesive polymers (HPMC 100 cps, HPMC K-100LV, Xanthun gum, NaCMC, Methocel K4M) were used to prepare single sustained release layer. The study indicated that increase of concentration of polymer decreases *In vitro* drug release and gives larger  $T_{50\%}$  value; which indicates more sustained release effect. Thus the middle amount of polymers (200 mg) was selected for the final bilayer formulation.

According to work plan, the formulated bilayer tablets were evaluated for their *in vitro* drug release profile study, *ex vivo* mucoadhesive strength, *ex vivo* residence time,  $T_{50\%}$ ,  $T_{25\%}$ ,  $T_{70\%}$  determination.

**Physical appearance:-**

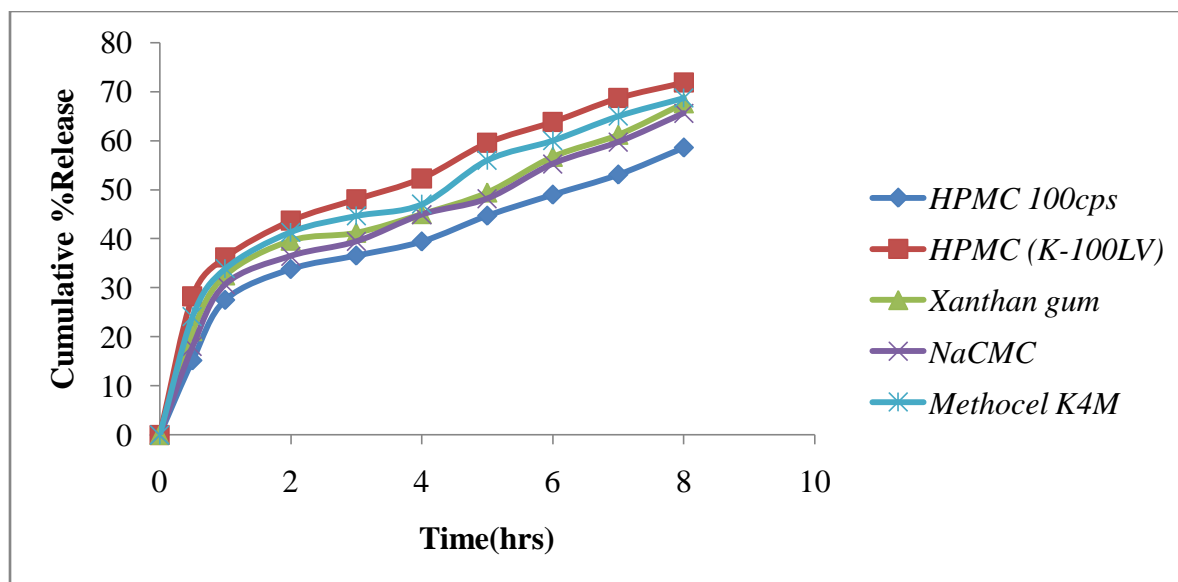
The appearance of bilayer tabs was smooth and uniform on physical examination.

**Kinetic modeling of *in vitro* drug dissolution profile:-**

*In vitro* drug release studies were conducted and fitted to different kinetic models. Cumulative percent of drug release from the formulations upto 8 hrs is shown in the Figure-1; release rate kinetic constants and  $R^2$  values obtained from different kinetic models are tabulated in the following Table 2.

**Table 2:-** Interpretation of release rate constants and  $R^2$  values for different release kinetics of formulated bilayer tablets:

Formulations	Zero order		First order		Higuchi		Korsmeyer	
	$K_0$	$R^2$	$K_1$	$R^2$	$K_H$	$R^2$	N	$R^2$
F <sub>1</sub>	5.935	0.873	-0.040	0.940	19.25	0.978	0.426	0.956
F <sub>2</sub>	7.084	0.839	-0.059	0.950	23.36	0.971	0.328	0.988
F <sub>3</sub>	6.614	0.864	-0.050	0.940	21.48	0.970	0.370	0.962
F <sub>4</sub>	6.648	0.883	-0.048	0.953	21.46	0.980	0.414	0.964
F <sub>5</sub>	6.851	0.854	-0.054	0.948	22.42	0.974	0.354	0.978

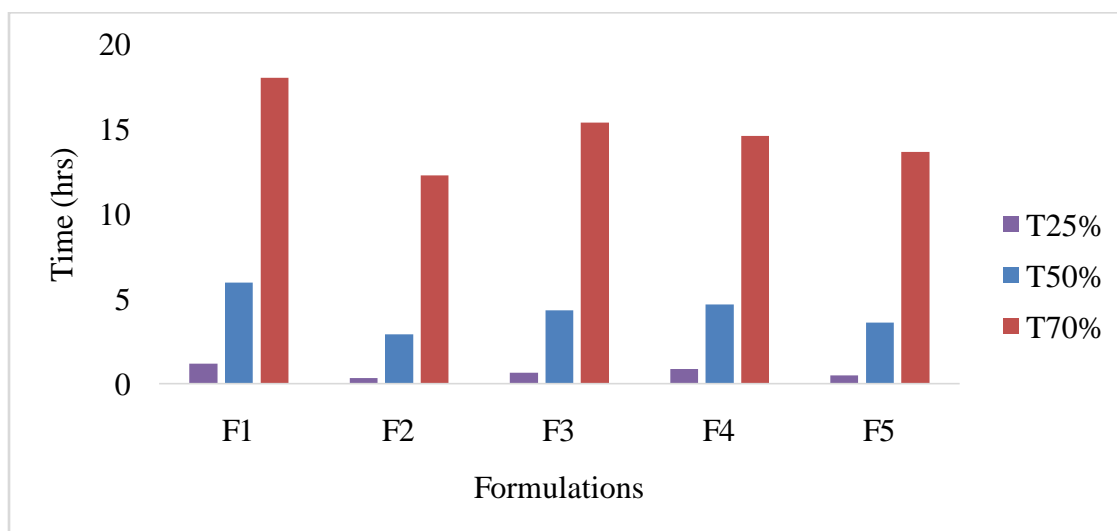


**Fig 1:-** *In vitro* release profile of formulated bilayer tablets containing different types of polymers. Here, used mucoadhesive polymer indicated the formulations. F<sub>1</sub> is formulated with HPMC 100 cps, F<sub>2</sub> is formulated with HPMC (K-100LV), F<sub>3</sub> is formulated with Xanthun gum, F<sub>4</sub> is formulated with NaCMC, F<sub>5</sub> is formulated with Methocel K4M.

The *in vitro* release data are treated with different model of release kinetics in the above Table 2 and the best fitted model was explained by the help of R<sup>2</sup> value in Table 3 given below. Evaluated, T<sub>25%</sub>, T<sub>50%</sub>, T<sub>70%</sub> were also tabulated in the Table 3 and n values were also mentioned for drug transport mechanism explanation. Fig 2 illustrates the evaluated values of successive fractional dissolution time of formulated bilayer tablets.

**Table 3:-** Drug release kinetics and dissolution parameters of formulated bilayer tablets:

Formulations	Best Fit Model	R <sup>2</sup>	n	K <sub>H</sub>	T <sub>25%</sub>	T <sub>50%</sub>	T <sub>70%</sub>
F <sub>1</sub>	Higuchi	0.978	0.426	19.25	1.18	5.98	18.03
F <sub>2</sub>	Korsmeyer	0.988	0.328	-	0.35	2.93	12.27
F <sub>3</sub>	Higuchi	0.970	0.370	21.48	0.66	4.32	15.37
F <sub>4</sub>	Korsmeyer	0.978	0.414	-	0.88	4.69	14.6
F <sub>5</sub>	Higuchi	0.980	0.354	22.42	0.51	3.62	13.67



**Fig 2:-** Successive fractional dissolution time of formulated bilayer tablets.

$T_{50\%}$  values of formulations manifest the drug release rate of dosage form and the retarding efficacy of polymers. Higher  $T_{50\%}$  value indicates a higher drug retarding ability of polymer and vice versa. Fig - 2 indicates better sustained release effect was found in  $F_1$  and  $F_3$  compared to other formulations.

Diffusional release mechanism of the formulations was interpreted from *in vitro* drug release data by analyzing the  $n$  values by fitting in Korsmeyer Peppas kinetic model and results are tabulated in Table 4.

**Table 4:-** Interpretation of diffusional release mechanism from *in vitro* drug release data from formulated bilayer tablets:

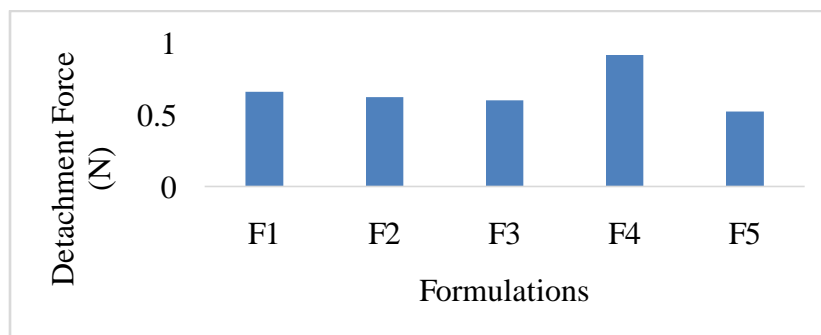
Formulation	$n$ (Release exponent)	Drug Transport Mechanism
$F_1$	0.426	Fickian diffusion
$F_2$	0.328	Fickian diffusion
$F_3$	0.370	Fickian diffusion
$F_4$	0.414	Fickian diffusion
$F_5$	0.354	Fickian diffusion

**Ex-vivo study for evaluation of mucoadhesive behavior of bilayer tablets:-**

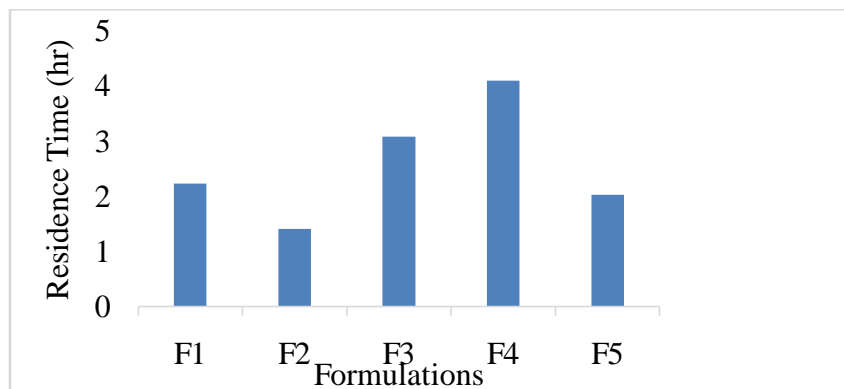
The *Ex- vivo* mucoadhesive strength of the tablets was determined for different formulations using goat stomach mucosa. *Ex vivo* residence time was evaluated by conducting a study for 8 hrs by recording the time for complete detachment of tablet from mucosal surface. The evaluation results are tabulated in Table 5 and illustrated in Fig 3, Fig 4.

**Table 5:-** *Ex- vivo* evaluation of mucoadhesive behavior of formulated bilayer tablets:

Formulations	Detachment force (N)	Residence time (hrs)
$F_1$	0.661	2.22
$F_2$	0.621	1.4
$F_3$	0.6	3.07
$F_4$	0.916	4.08
$F_5$	0.523	2.02



**Fig 3:-** Detachment force of different formulation containing different mucoadhesive polymer.



**Fig 4:-** Ex vivo residence time of different formulation containing different ratio of mucoadhesive polymer.

From the Table 4, Fig 3 and Fig 4; it was observed that the highest mucoadhesive strength was observed with the formulation showing highest detachment force. F<sub>4</sub> containing NaCMC showed highest mucoadhesive strength. Tablet containing an increased concentration of polymer showed higher mucoadhesion with long residence time (4.08 hrs). This finding is owing to the hydrophilic nature of NaCMC; it is hydrated easily with less contact time and forms a strong interpenetrating network with mucin molecules because of the polymer's long linear chain structure. A linear increase in mucoadhesion was observed with an increase in contact time.

### Conclusion:-

In the present study, 5 different formulations of mucoadhesive bilayer tablet of metformin HCl (F<sub>1</sub> – F<sub>5</sub>) were prepared by using 5 different Polymers by direct compression method. The results of *in-vitro* drug release profile of bilayered tablets were satisfactory. But, F<sub>1</sub> and F<sub>4</sub> provided better controlled and sustained *In vitro* drug release compared to other three formulations. The T<sub>50%</sub> values of these five formulations which is an important parameter for knowing the retarding ability of drugs were also found satisfactory. Results from *ex vivo* evaluation of mucoadhesive behavior of these five formulations were also good which provides increased residence time of drug in GIT and gave clear understanding about the bioadhesion properties of the bilayer tablet. However, an appropriate balance between various levels of the five polymers is needed to acquire proper release and mucoadhesion. Finally, it can be concluded that by formulating mucoadhesive bilayer tablets of metformin HCl, its complete release can be ensured prior to absorption and hence the problem of incomplete drug release and erratic absorption of pure metformin HCl can be solved by increasing the retention time of drug in GIT for a longer period with the help of mucoadhesive polymers.

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