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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF MUCOADHESIVE BILAYER TABLET CONTAINING GLICLAZIDE AND METFORMIN HCL.

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Abstract

Bi-layer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. The objective of the study was to formulate and evaluate Gliclazide-Metformin HCl bilayer tablet containing Gliclazide in immediate release (IR) layer and Metformin HCl in sustained release (SR) layer. Gliclazide-Metformin HCl bilayer tablets were prepared and evaluated by *ex vivo* and *in vitro* studies. A total of 4 formulations (F₁-F₄) were prepared by direct compression using 4 different mucoadhesive polymers (carbopol 971, HPMC K4M, HPMC K15M and HPMC K100M) in each formulation. Formulated tablets were evaluated for *ex vivo* mucoadhesive strength, *ex vivo* mucoadhesion time, and *in vitro* drug release. F₁ containing carbopol 971 demonstrated prolonged *ex vivo* mucoadhesion with highest mucoadhesive strength (detachment force =1.118N) and longest residence time (6.2hrs). On the other hand, better release retardation from SR layer was observed for F₄ with HPMC K100M as drug carrier (61.63% Metformin HCl release in 8 hrs). Drug release from IR layer complied with compendial requirements and followed zero order kinetics. Sustained release from F₁ and F₂ followed Higuchi ($R^2 = 0.993$ and 0.991 , respectively) and Korsmeyer- Peppas was found best fitted for F₃ and F₄ ($R^2 = 0.994$ and 0.996 , respectively). Non-Fickian diffusion/class-II transport ($n > 0.45$) was the predominant mechanism of drug release for all the formulations. The results suggest that a mixture of carbopol 971 and HPMC K100M- ratio of the individual ingredient to be determined by mix design- will better serve the purpose.

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Introduction:-

Conventional single layered (SL) tablets lead to frequent dosing and wide range of fluctuation in drug concentration in the blood stream and tissues with subsequent undesirable toxicity and poor efficiency for drugs with shorter half-lives [1, 2]. The repetitive dosing and erratic absorption from the SL tablet led to the concept of controlled drug delivery systems [3]. Mucoadhesive drug delivery, a controlled release (CR) drug delivery system, has become 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 [4]. Combination of SL with CR technology imparts some pharmacokinetic advantages which rely on the fact that drug release from fast releasing granules leads to an initial rapid rise in the blood concentration and the blood level is maintained at steady state with release from SR layer [5]. Hence, the multilayered tablet concept has long been utilized to develop sustained release formulations [6]. On the other hand, combination therapy has various advantages over mono-therapy such as problem of dose dependent side effects are minimized [7, 8]. A low dose combination of different agents reduces the dose related risk because the addition of one agent may counteract some deleterious effects of the other [9, 10]. Using low doses of different agents in a tablet minimizes the clinical and metabolic side effects that might occur with higher dose of an individual component [11]. Thus, mucoadhesive bilayer tablet is suitable for sequential use of two incompatible drugs in combination and also for sustained action required for diseases like type 2 diabetes mellitus [12].

Gliclazide, a second generation sulphonyl urea, acts via stimulating β cells of pancreas to release insulin and also increases peripheral sensitivity of insulin [13, 14]. In a large randomized study on type II diabetic patients, 30–120 mg once daily dose of Gliclazide was found as effective as 80–320 mg twice daily dose of Gliclazide in reducing glycosylated haemoglobin (HbA1C), with fewer side effects and less risk of hypoglycemia [15–17]. Metformin HCl, in particular, increases sensitivity to insulin in peripheral tissues of the hosts. It is also involved in inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, inhibition of fatty acid oxidation [18], and may potentiate the hypoglycemic effects of sulfonylureas and insulin [19]. Another study reports that a combination of Gliclazide with metformin HCl achieves good glycemic control and improves lipid levels with better tolerability profile [20]. The elimination half-lives ($t_{1/2}$) of Gliclazide and metformin HCl are 8.1–20.5 hours [14] and 6.2 hours [21], respectively which also suggest their potential to be formulated as bilayer tablet.

The present study aims to develop and evaluate a combined therapy for type 2 diabetes mellitus in the form of bilayer tablet with Gliclazide in IR layer and Metformin HCl in SR layer employing mucoadhesive polymers such as HPMC K4M, HPMC K15M, HPMC K100M or Carbopol 971. A total of four formulations were prepared and evaluated for *ex vivo* mucoadhesive strength, *ex vivo* mucoadhesion time, and *in vitro* drug release.

Materials and methods:-

Materials:-

Metformin HCl and Gliclazide were kind gifts from Incepta Pharmaceutical Ltd, Bangladesh. Hydrochloric acid was purchased from Merck, Germany. HPMC K4M, HPMC K15M, HPMC K100M, carbopol 971, lactose, magnesium stearate, talc and aerosil were obtained from local market of Dhaka, Bangladesh. Goat stomach mucosa for determining bioadhesive strength was collected from a local slaughter house of Dhaka, Bangladesh. All other ingredients used were of analytical grade.

Formulation optimization:-

To optimize the best formulation, several single SR layer containing different amounts (150 mg, 200 mg, and 250 mg) of the selected polymers and several single IR layer containing different amounts of lactose (140 mg, 160 mg or 180 mg) and SSG (40 mg and 20 mg) along with the APIs were prepared and tested for *in vitro* release. 250 mg was the selected amount of the polymers for the SR layer which exhibited the best average % release. Single IR layer formulated with 140 mg lactose and 40 mg SSG showed highest average % drug release (83.35% at 60 minutes) and thus was selected as the IR layer for the final formulation of the bilayer tablets.

Methods:-

Preparation of bilayer tablets:-

The bilayer tablets comprising of Gliclazide in IR layer and metformin HCl in SR layer were prepared by direct compression using 4 different mucoadhesive polymers (carbopol 971, HPMC K4M, HPMC K15M and HPMC K100M) in SR layer in each formulation is shown in the Figure-1. Amount of various ingredients used in different formulations (F₁-F₄) are presented in Table 1. Appropriate amounts of the mixture were accurately weighed with an electronic balance for the preparation of each layer. Initially mucoadhesive SR layer of the tablets was compressed with simple thumb pressure for 30 seconds, then powders of IR layer was placed over it and finally the tablets were prepared using 13mm diameter die on an infrared hydraulic press with 5N compression force. Before compression, the surface of the die and punch were lubricated with magnesium stearate. All the preparations were then stored in airtight containers at room temperature for further studies.

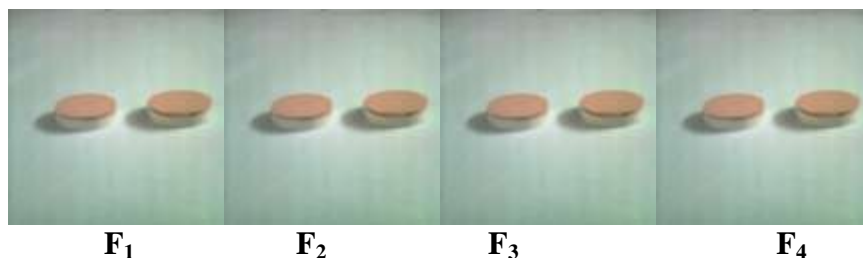
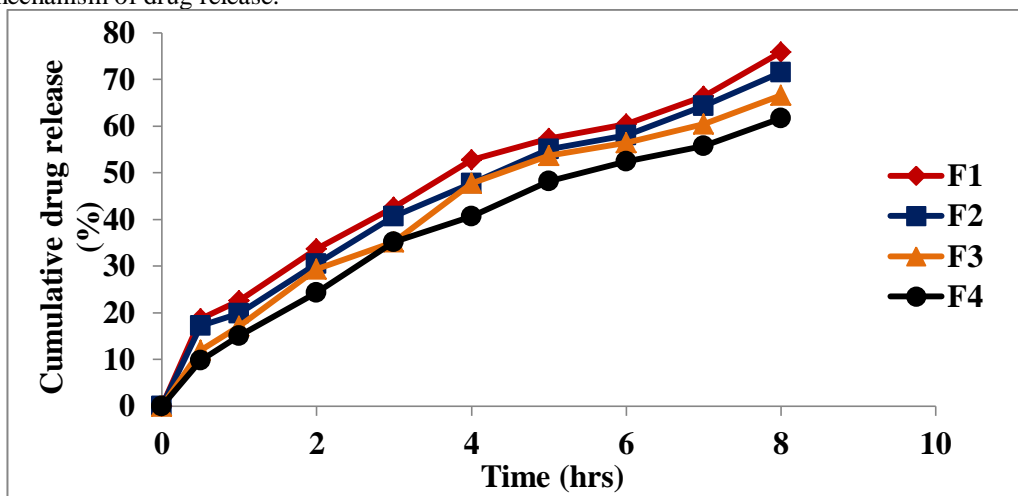
Fig. 1:- Formulated tablets (F₁-F₄).

Table 1:- Formulation plan:

Ingredients	IR layer	SR layer			
	F ₁ -F ₄ (mg)	F ₁ (mg)	F ₂ (mg)	F ₃ (mg)	F ₄ (mg)
Metformin HCl	-	250	250	250	250
Gliclazide	60	-	-	-	-
Carbopol 971	-	250	-	-	-
HPMC K4M	-	-	250	-	-
HPMC K15M	-	-	-	250	-
HPMC K100M	-	-	-	-	250
Lactose	140	-	-	-	-
Sodium starch glycolate (SSG)	40	-	-	-	-
Magnesium stearate	1	1	1	1	1
Talc	1	1	1	1	1
Aerosil	1	1	1	1	1
Total weight	243	503	503	503	503

***In vitro* drug release studies and kinetic modeling:-**

In vitro release profile for each formulated bilayer tablet (F₁- F₄) was performed using USP type II dissolution apparatus (Electrolab, Mumbai, India) and shown in the Figure 2 and Figure 3. Dissolution conditions in all cases were maintained as follows: 900 ml 0.01N HCl (pH 2.0) as dissolution media, 50 rpm, vessel temperature 37 ± 0.5°C. The study was carried out for 8 hrs. The absorbance of the withdrawn samples of metformin HCl and Gliclazide was measured at 233 nm and 227nm respectively after suitable dilution if necessary, using appropriate blank by Shimadzu UV spectrophotometer. The cumulative percentage of drug released for each layer was calculated and plotted against time separately. The data were also subjected to goodness of fit test by linear regression analysis according to zero order kinetics, first order kinetics, Higuchi and Korsmeyer- Peppas models to propose mechanism of drug release.

Fig. 2:- *In vitro* drug release of F₁- F₄ from SR layer.

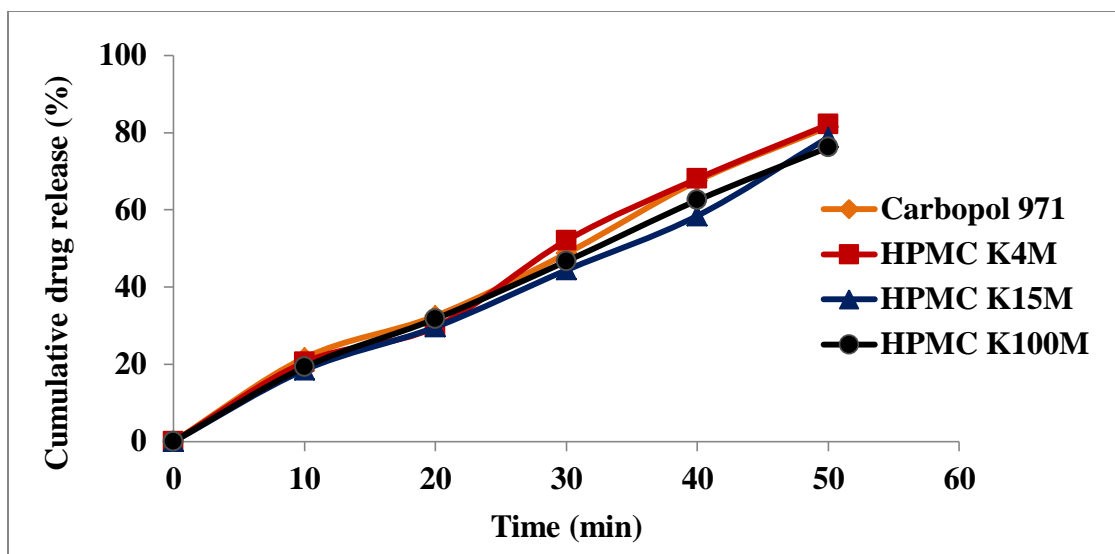


Fig. 3:- *In vitro* drug release of F₁- F₄ from IR layer.

***Ex vivo* mucoadhesive strength measurement:-**

Bioadhesive strength of the tablets was measured according to the method described by Umarji *et al.* [22]. A piece of goat stomach mucosa was pasted to a petri-dish with cyanoacrylate adhesive and the mucus membrane of the same was wetted with 2-3 drops of 0.01 N HCl media. Each tablet was tied with a thread and attached with the mucous membrane. Another end of thread was tied with one side of a 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.

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

***Ex vivo* residence time measurement:-**

The *ex vivo* residence time of the prepared tablets was determined using a locally modified USP disintegration apparatus by following established protocol [22]. The disintegration medium composed of 800 ml pH 2.0, 0.01 N HCl buffer maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. 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 fingertip for 30 seconds. Then the tablet and mucosa was hydrated by the medium allowing the apparatus to move up and down. The time for complete erosion or detachment of the tablet from the mucosal surface was recorded as the mucoadhesion time.

Results and discussion:-

In the study, a total of 4 formulations (F₁-F₄) of mucoadhesive bilayer tablets comprising IR layer of Gliclazide and SR layer of metformin HCl were prepared taking carbopol 971, HPMC K4M, HPMC K15M and HPMC K100M as polymers, respectively. The formulated tablets were evaluated for *in vitro* drug release from both IR & SR layers and *ex vivo* mucoadhesive properties. The data obtained from the *in vitro* dissolution studies were fitted to different release kinetic models and T_{25%}, T_{50%}, T_{80%} were determined to characterize the polymer's drug retarding effect and the graph was shown in the Figure 4.

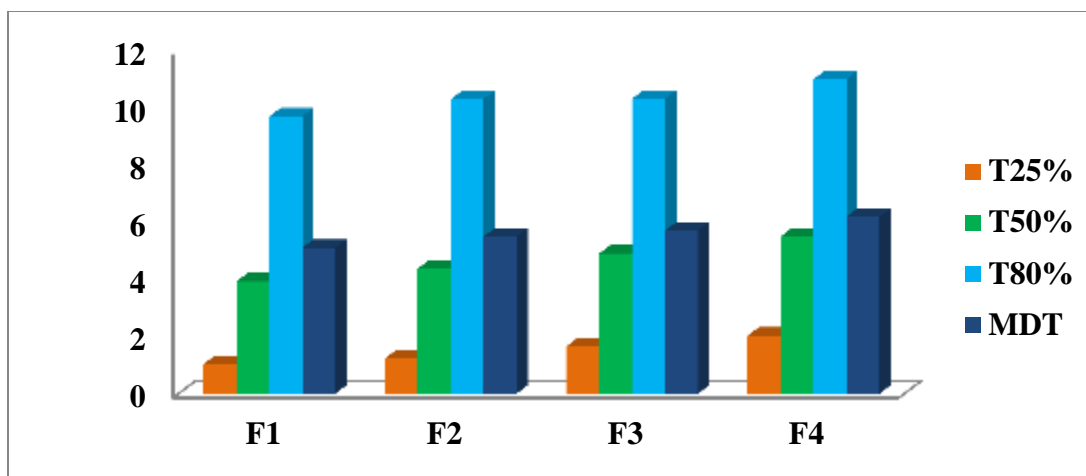


Fig. 4:- Successive fractional dissolution time of F₁-F₄.

***In vitro* drug release studies and kinetic modeling:-**

The results of *in vitro* drug release from SR layer are illustrated in Fig. 2 which depicts F₄ containing HPMC K100M retarded maximum drug release (cumulative % drug release = 61.63% after 8 hrs) compared to the other formulations F₁ (75.86%), F₂ (71.45%), F₃ (66.55%). The curve fitting analysis also corroborated the finding for F₄ which exhibited highest MDT (6.19). In kinetic analysis, F₁ and F₂ followed Higuchi model ($R^2 = 0.993$ and 0.991 , respectively), F₃ and F₄ followed Korsmeyer- Peppas model ($R^2 = 0.994$ and 0.996 , respectively). Non-Fickian diffusion/class-I transport ($n > 0.45$) was the predominant mechanism of drug release for all the formulations (Table 2 & 3).

Table 2:- Release kinetics of F₁- F₄ for SR layer:

Formulation Code	Zero order		First order		Higuchi		Korsmeyer- Peppas		
	K _o	R ²	K ₁	R ²	K _H	R ²	N	K	R ²
F ₁	8.284	0.941	-0.050	0.993	26.09	0.993	0.518	0.246	0.988
F ₂	8.044	0.947	-0.056	0.987	25.24	0.991	0.546	0.223	0.982
F ₃	7.847	0.944	-0.062	0.988	24.63	0.989	0.633	0.182	0.994
F ₄	7.395	0.961	-0.067	0.980	22.97	0.986	0.689	0.153	0.996

Table 3:- Best fitted model, release mechanism, successive fractional dissolution time and MDT of F₁-F₄:

Formulation Code	Best Fitted Model	Release Mechanism	T _{25%}	T _{50%}	T _{80%}	MDT
F ₁	1 st order, Higuchi	Non- Fickian diffusion	1.03	3.93	9.7	5.1
F ₂	Higuchi	Non- Fickian diffusion	1.23	4.38	10.3	5.5
F ₃	Korsmeyer- Peppas	Non- Fickian diffusion	1.65	4.9	10.32	5.71
F ₄	Korsmeyer- Peppas	Non- Fickian diffusion	2.03	5.5	11	6.19

It is evident from the results that drug release from the HPMC K100M, a higher viscosity grade of HPMC, was slightly lower than those of the other two viscosity grades (HPMC K4M and HPMC K15M) owing to higher molecular weight which accounts for its forming a viscous gel [23, 24]. Due to its higher viscosity than the other two, HPMC K100M enhanced the thickness of the gel layer and the tortuosity of the drug diffusion path was increased and thus a slow release was observed. In addition, slow swelling and production of swollen particles of smaller volumes [25] also contributed to the release retardation [26]. On the other hand, carbopol 971 opens up

easily at lower concentration and forms porous channels to exhibit the drug release [27] which underscore the observed lesser sustained effect of F₁.

To investigate the kinetics of drug release from controlled release formulations, several methods have been adopted [28]. Model dependent methods include zero order, firstorder, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, Baker-Lonsdale and Weibull model [29, 30]. In our study, analysis of release kinetics revealed Higuchi as the best fit for F₁ and F₂ and Korsmeyer-Peppas for F₃ and F₄. Hence, it can be concluded that the findings are suggestive of their being formulated as SR dosage forms. In Korsmeyer-Peppas model, the value of 'n' from the curve fitting to a power law equation is indicative of drug release mechanism such as Fickian diffusion ($n \leq 0.45$), non-Fickian/case II transport ($0.45 < n < 0.89$), or anomalous transport ($n > 0.89$) [31] whereas 'k' is the release rate constant with bigger values demonstrating faster drug release. Mathematically, a bigger 'n' value and a smaller 'k' value are expected to achieve a delayed release pattern [32]. In our study, highest 'n' and 'k' values are in consonance with lowest cumulative % drug release (61.63 %) and highest MDT (6.19) for F₄ to further demonstrate the highest release retardation by HPMC K100M. In addition, values of n are also indicative of non-Fickian diffusion for all the formulations.

Cumulative percent Gliclazide releases from IR layer were found as follows: F₁: 81.54%, F₂: 82.11%, F₃: 78.78% F₄: 76.19% in 50 minutes and drug release followed zero order kinetics (Table 4). The results met the compendial requirements.

Table 4:- Release kinetics of F₁- F₄ for IR layer:

Formulation Code	Zero order		First order		Higuchi	
	K _o	R ²	K ₁	R ²	K _H	R ²
F ₁	1.604	0.994	-0.015	0.944	85.37	0.928
F ₂	1.644	0.992	-0.014	0.948	89.18	0.914
F ₃	1.509	0.993	-0.014	0.949	81.46	0.905
F ₄	1.501	0.997	-0.012	0.965	82.04	0.932

Ex vivo mucoadhesive strength and residence time:-

The results of *ex vivo* mucoadhesive properties (strength & time) of the formulated tablets on goat stomach mucosa are tabulated in Table 5 and illustrated in Fig 5. Highest mucoadhesion was observed for F₁ containing carbopol 971. Slight cross-linkage with a "fishnet" gel structure [27] and better rheological properties [33] of carbopol 971 might account for this finding because the density of cross-link is inversely proportional to the degree of swelling [34]. The lower the cross-link density, the higher the flexibility and hydration rate; the larger the surface area of the polymer, the better the mucoadhesion. Besides, Carbopol 971 possesses numerous hydrophilic functional groups, such as hydroxyl and carboxyl. These groups allow hydrogen bonding with the mucous membrane, swelling in aqueous media, and thereby allowing maximal exposure of potential anchor sites [35].

Table 5:- *Ex vivo* mucoadhesive properties of F₁-F₄:

Formulation Code	F ₁	F ₂	F ₃	F ₄
Detachment force (N)	1.118	0.937	1.030	0.788
Residence time (hrs)	6.2	4.33	4.45	4.08

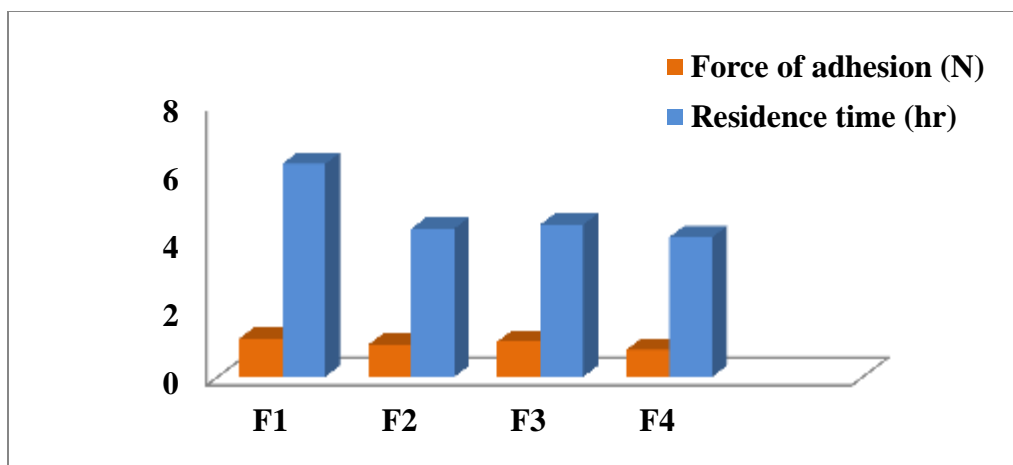


Fig. 5:-*Ex vivo* mucoadhesive properties of F₁-F₄.

Conclusion:-

In the present study, four formulations of Gliclazide-Metformin HCl bilayer tablet were prepared taking carbopol 971, HPMC K4M, HPMC K15M and HPMC K100M in each formulation, respectively as mucoadhesive polymer. In the formulated tablets, Gliclazide formed the IR layer and Metformin HCl was in the SR layer. The mucoadhesive strength and adhesion time of the tablets were evaluated *ex vivo* on a goat stomach mucosa. The drug release profile of the test tablets were determined by *in vitro* dissolution study. Mechanism of drug release was explored by linear regression analysis according to zero order kinetics, first order kinetics, Higuchi and Korsmeyer- Peppas models. It was observed that the formulated tablet containing carbopol 971 demonstrates prolonged *ex vivo* mucoadhesion with highest mucoadhesive strength and longest residence time. On the other hand, better release retardation from SR layer was observed for the formulation with HPMC K100M as drug carrier. Thus we conclude that a combination of carbol 971 and HPMC K100M in the same formulation of Gliclazide-Metformin HCl bilayer tablet will best serve the purpose of a mucoadhesive bilayer tablet in which the former will impart mucoadhesion and the latter release retardation and prolonged action.

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