

## Formulation and evaluation of mucoadhesive glipizide films

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Glipizide is mainly absorbed in the proximal areas of the gastrointestinal tract. The purpose of this study was formulation and evaluation of mucoadhesive films to prolong the stay of drug in its absorption area. Glipizide was formulated in a mucoadhesive film that could be retained in the stomach for prolonged intervals. Polymeric films were designed with various compositions of hydroxypropyl cellulose and polyethylene glycol 400 (PEG 400). Properties of the mucoadhesive film such as tensile strength, percentage elongation, swelling index, moisture content, pH and viscosity of polymeric dispersion, film thickness, content uniformity and mucoadhesion in a simulated gastric environment were characterized. In addition, percentage drug retained in stomach mucosa was estimated using a simulated dynamic stomach system as a function of time. Increase in hydroxypropyl cellulose concentration resulted in a higher tensile strength and elongation at break, while increase in concentration of PEG 400 was reflected in a decrease in tensile strength and increase of elongation at break. Glipizide/hydroxypropyl cellulose/PEG 400 (2.5:1:0.5) (GF5) was found to be the optimal composition for a novel mucoadhesive stomach formulation that showed good peelability, relatively high swelling index, moderate tensile strength, and stayed on rat stomach mucosa up to 8 h. *In vivo* testing of the mucoadhesive films with glipizide demonstrated a potential hypoglycemic effect.

**Keywords:** glipizide, mucoadhesive film, factorial design, desirability function, hypoglycemic effect

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Oral sustained-release technology provides oral delivery for 24 h; however, in substances that cannot be well absorbed throughout the whole gastrointestinal tract, may be disadvantageous (1). Extended-release dosage forms with prolonged residence times in the stomach are highly desirable for drugs with narrow absorption windows, stability problems in the intestinal or colonic environments, locally acting in the stomach, and

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poor solubility in the intestine (2). Recent approaches to increasing the gastric residence time of drug delivery systems include bioadhesive devices, swelling devices that increase their size, low density devices, floating systems, high density systems, magnetic systems, unfoldable and expandable systems, superporous, biodegradable hydrogel systems and microparticulate systems (3).

The otherwise excellent concept of floating system suffers from the disadvantage that it is effective only when the fluid level in the stomach is sufficiently high. However, as the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage form may be impeded (4). This serious limitation can be overcome by coupling mucoadhesion characteristics to the dosage form and developing mucoadhesive films. Floating and bioadhesive drug delivery systems have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio, a much more intimate contact with the mucus layer, and specific targeting of drugs to the absorption site. The various buoyant preparations include microballoons, microspheres, granules, powders, gel, capsules, tablets, and laminated films (5, 6). Matrix tablets based on hydroxypropyl methylcellulose (HPMC K4M) have been developed by Li *et al.* (7), and microparticulate systems using natural polymers have been evaluated for stomach specific drug delivery of glipizide (8).

Glipizide is a second-generation sulfonylurea that can acutely lower the blood glucose level in humans by stimulating the release of insulin from the pancreas: it is typically prescribed to treat type II diabetes (non-insulin-dependent diabetes mellitus). Its short biological half-life ( $3.4 \pm 0.7$  h) necessitates to be administered in 2 or 3 doses of 2.5 to 10 mg per day. Thus, the development of controlled-release dosage forms would clearly be advantageous. Researchers have formulated oral controlled-release products of glipizide by various techniques (9, 10). Moreover, the site of glipizide absorption is in the stomach. Dosage forms that are retained in the stomach would increase absorption, improve drug efficiency, and decrease dose requirements.

The hypothesis for this research work is that if glipizide can be delivered in a controlled manner to the duodenum at a rate that does not exceed the maximum rate of its absorption, then the oral bioavailability of glipizide could be improved. Based on this hypothesis, the mucoadhesive films were designed in such a way that they should be retained in the stomach for a prolonged period of time, thus maximizing the exposure of the drug to its absorption site.

## EXPERIMENTAL

### *Materials*

Glipizide was obtained as a gift sample from USV Ltd. (India), hydroxypropyl methylcellulose (HPMC E15) was donated by Colorcon Asia Pvt. Ltd. (India), hydroxypropyl cellulose (HPC) was purchased from Innovative Chemicals (India), sodium alginate, hydroxyethyl cellulose (HEC) were purchased from Himedia (India), D-sorbitol, glycerol and polyethylene glycol 400 (PEG 400) were purchased from S. D. Fine Chemicals (India). All other chemicals used were of analytical grade.

## Animals

Six-month-old, mixed sex, specific pathogen-free healthy Wistar rats (weighing 250–300 g), were obtained from Zydus Cadila (India) and maintained under standard laboratory conditions (room temperature  $23 \pm 2$  °C, relative humidity  $55 \pm 5$  %; 12/12 h light/dark cycle) with free access to a commercial rodent diet and tap water.

## Drug-excipient compatibility

Compatibility of glipizide and different polymers to be used for the development of film formulations was studied using a differential scanning calorimeter (DSC 60, Shimadzu, Japan) at a nitrogen flow of  $30 \text{ mL min}^{-1}$  and heating rate of  $15$  °C  $\text{min}^{-1}$  from 35 to 300 °C. Results of glipizide-excipient compatibility study performed by DSC are shown in Fig. 1.

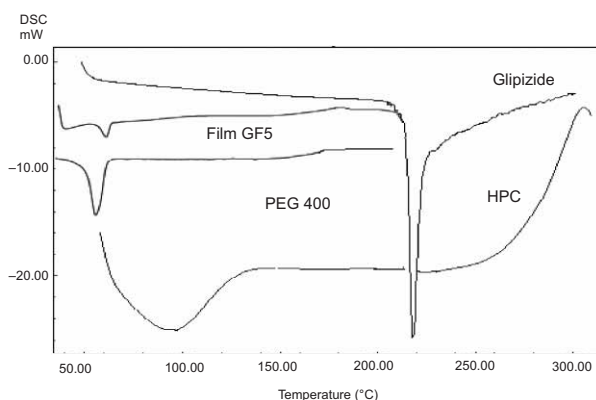


Fig. 1. Representative DSC thermogram for glipizide-excipient compatibility study.

## Preparation of films

Mucoadhesive films were prepared by the solvent evaporation technique (11), using glipizide, plasticizer and other film forming polymers. Glipizide was added into distilled water and sonication was done for 15 min to obtain an aqueous dispersion. Subsequently, the film forming polymer and plasticizer were added to this dispersion. This polymeric dispersion was stirred on a magnetic stirrer (Remi Equipments Ltd., India) for 30 min, followed by sonication for 15 min and kept for 3 h to remove all the entrapped air bubbles. Polymeric dispersion was uniformly spread onto a plastic plate of defined area ( $10 \text{ cm}^2$ ) and dried in vacuum oven at 50 °C for 20 h. Dried films were carefully peeled off from the plate surface, cut into pieces of defined size ( $1.0 \times 1.0 \text{ cm}$ ). Then, films were sealed in sachets prepared from polyethylene laminated aluminum foil and stored at a temperature of  $30 \pm 2$  °C and relative humidity  $60 \pm 5$  % until further analysis. Composition of glipizide films prepared with various polymers and plasticizers and their physical characteristics are reported in Table I.

Table I. Composition of the glipizide film with various polymers and plasticizers and their physical characteristics

Film	Polymer	Plasticizer	Composition (glipizide/polymer/ plasticizer, %, <i>m/m</i> )	Physical characteristic
GLF1	–	D-sorbitol	1.0:0:0.5	Not removable from casting surface
GLF2	–	glycerol	1.0:0:0.5	Not removable from casting surface
GLF3	–	PEG 400	1.0:0:0.5	Not easily removable from casting surface
GLF4	HEC	PEG 400	1.0:1.0:0.5	Non homogeneous surface, more soft, easy to peel
GLF5	Sodium alginate	PEG 400	1.0:1.0:0.5	Brittle, hard to peel
GLF6	HPC	PEG 400	1.0:1.0:0.5	Homogeneous surface, soft, easy to peel

HEC – hydroxyethyl cellulose, HPC – hydroxypropyl cellulose, PEG 400 – polyethylene glycol 400

### Factorial design and the desirability function

To study all possible combinations of all factors at all levels (two factors, three levels), full factorial design was constructed and conducted in a fully randomized order. The dependent variables to be measured were tensile strength, elongation (%) and drug released from films after 8 h ( $Y_8$ , %). The composition and responses of the  $3^2$  factorial design are shown in Tables I and II. Two independent factors, concentration of HPC ( $X_1$ ) and PEG 400 ( $X_2$ ), were set at three different levels. High and low levels of each factor were coded as 1 and –1, respectively, and the mean value as zero. The range of a factor was chosen in order to adequately measure its effects on the response variables. This design was selected because it provides sufficient degrees of freedom to resolve the main effects as well as factor interactions.

The desirability function was used for optimization of the formulation composition. In addition, the responses had to be combined in order to produce a product of desired characteristics. The application of the desirability function combines all the responses in one measurement and offers the possibility to predict optimum levels for the independent variables.

The combination of responses in one desirability function requires the calculation of individual functions. An ideal film should have moderate tensile strength, high elongation and high percentage of drug retained on the stomach mucosa. The individual desirability and prediction profiles for each response were calculated using the JMP 5.1 (JMP®, USA) statistical discovery software (12).

In this study, there were no specific requirements for tensile strength of the optimum formulation. Therefore, the range of values of produced formulations was selected. As moderate tensile strength was desired, the formulation that had the value within

the range of 7.0–10.0 had a desirability of 1, while the formulations that had values out of this range had a desirability of 0. This can be described by the following equations:

$$\begin{aligned}d_1 &= 0 \text{ for } Y_i < Y_{\min} \\d_1 &= 1 \text{ for } Y_{\min} < Y_i < Y_{\max} \\d_1 &= 0 \text{ for } Y_i > Y_{\max}\end{aligned}$$

where,  $d_1$  is the individual desirability of tensile strength.  $Y_i$  is the experimental result,  $Y_{\min}$  is the minimum result and  $Y_{\max}$  is the maximum result. In addition, the optimum mucoadhesive film should have high elongation and high percentage of drug retained on the stomach mucosa. Desirability functions of these responses were calculated using the following equation:

$$\begin{aligned}d_2 \text{ or } d_3 &= \frac{Y_i - Y_{\min}}{Y_{\text{target}} - Y_{\min}} \text{ for } Y_i < Y_{\text{target}} \\d_2 \text{ or } d_3 &= 1 \text{ for } Y_i > Y_{\text{target}}\end{aligned}$$

where  $d_2$  is the individual desirability of elongation (%) and  $d_3$  is the individual desirability of drug retained (%) on stomach mucosa after 8 h. The values of  $Y_{\text{target}}$  and  $Y_{\min}$  for percentage elongation are 69.85 and 50.31 and the values of  $Y_{\text{target}}$  and  $Y_{\min}$  for percentage drug released 82.36 and 93.47 while  $Y_i$  is the experimental result. The overall desirability values were calculated from individual values by using the following equation:

$$D = (d_1 d_2 d_3)^{1/3}$$

*Physico-chemical characterization.* – Mucoadhesive film was characterized for various aesthetic (appearance, odor, color, flexibility and peelability) and physico-chemical properties such as moisture content, pH and viscosity of polymeric dispersion, swelling index, tensile strength, elongation, film thickness, drug concentration uniformity, drug release and mucoadhesion.

Thickness of each sample was measured using a thickness tester (Model 110, 0.01 mm capacity, Mitutoyo Manufacturing Corporation Ltd., Japan) at five locations (center and four corners) and mean thickness was calculated.

Viscosity of polymeric dispersion was determined with a Brookfield cone and plate rheometer (LVDVIII, Brookfield, USA). To study viscosity and pH of the film dispersion, one unit of formulation was dispersed in 10 mL of distilled water and simulated gastric fluid (SGF) each. Viscosity of films was measured at  $37 \pm 1$  °C by keeping the spindle speed 10 rpm and shear rate  $10 \text{ s}^{-1}$ .

The pH of film dispersion ( $1.0 \times 1.0$  cm film dissolved in 10 mL each, water and SGF) was measured with a pH meter (LABINDIA Pvt. Ltd, India) at 30 °C.

For determination of moisture content, the film sample ( $1.0 \times 1.0$  cm) was weighed and kept in a desiccator containing calcium chloride at  $40^\circ\text{C}$  for 24 h. Films were removed from desiccators and reweighed until a constant weight was obtained.

Film swelling study was carried out in simulated gastric fluid. Each film sample with a surface area  $1.0 \times 1.0$  cm was weighed and placed in a preweighed stainless steel basket with 0.074-mm aperture. Then, the mesh containing film sample was submerged into 15 mL of medium in a glass beaker. Film was removed from the basket at preset time intervals, and reweighed until no further change in weight. Results of the swelling index of batches GF1 to GF9 are shown in Table II and Fig. 2.

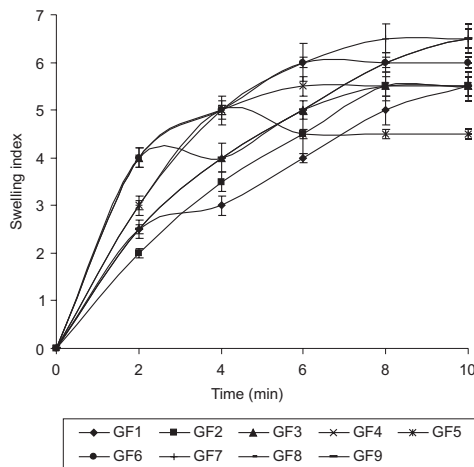


Fig. 2. Swelling index of films of various composition (mean  $\pm$  SD,  $n = 3$ ).

Mechanical properties of films were evaluated using an Instron Universal Testing Instrument (Model 1121, Instron Limited, UK) equipped with a 100 kg load cell. The film was cut into narrow strips of  $1.0 \times 1.0$  cm. A film strip free from air bubbles or physical imperfections was placed between two clamps positioned at a distance of 10 mm in the same plane. During measurement, the lower clamp was fixed and the strip was pulled by the top clamp at a rate of  $100 \text{ mm min}^{-1}$ . The force and elongation at the moment of break were recorded. The results of tensile strength and elongation of batches GF1 to GF9 are shown in Table II.

*Drug concentration.* – To ensure uniformity of glipizide distribution in film, the average drug content in the film was measured. In addition, samples ( $1.0 \times 1.0$  cm) were collected from five different locations (centre and four corners) within the film, weighed and dissolved in 10 mL phosphate buffer (pH 7.4). After 24 h, the solution was filtered and the filtrate was analyzed spectrophotometrically (Shimadzu UV-1601 UV/Vis double beam spectrophotometer, Japan) using the Lambert-Beer's equation ( $R^2 = 0.9979$ ) for the drug content at 276 nm. The content of glipizide was calculated using a preconstructed calibration curve for glipizide ( $5\text{--}50 \mu\text{g mL}^{-1}$ ) in phosphate buffer (pH 7.4).

Table II. Composition and responses for 3<sup>2</sup> factorial designs

Batch	Variable		Glipizide (%, m/m)	Response value			Overall desirability
	X <sub>1</sub>	X <sub>2</sub>		Tensile strength (N mm <sup>-2</sup> )	Elongation (%)	Y <sub>8</sub> (%)	
GF1	-1	-1	70.0	7.45	50.31	85.14	0.00
GF2	-1	0	67.5	7.12	54.41	87.52	0.00
GF3	-1	1	65.0	7.02	55.95	93.47	0.00
GF4	0	-1	65.0	10.54	61.68	82.36	0.83
GF5	0	0	62.5	9.75	66.95	83.12	0.90
GF6	0	1	60.0	9.19	69.85	86.61	0.79
GF7	1	-1	60.0	10.33	60.02	84.56	0.67
GF8	1	0	57.5	9.81	61.10	85.14	0.69
GF9	1	1	55.0	9.25	64.15	87.94	0.63

Independent variables	Level		
	Low	Medium	High
X <sub>1</sub> – concentration of hydroxypropyl cellulose (%, m/m)	20	25	30
X <sub>2</sub> – concentration of polyethylene glycol 400 (%, m/m)	10	12.5	15

Concentration of glipizide 62.5 % (m/m).

*Mucoadhesion.* – The mucoadhesive property of the film was assessed in a simulated gastric environment (13) using a texture analyzer equipped with a 2.0 kg load cell (Model 1121, Instron Limited). Isolated rat stomach mucosa free from supporting tissues was stored in a deep freezer at –20 °C. For experiments, the stomach intubation tube (thawed in normal saline) was incised longitudinally and held on the lower platform of the texture analyzer. The film was applied to the upper probe with the help of a double-sided adhesive tap. The stomach mucosa was moistened with SGF. Mucosal membrane was kept in contact with the film for 3 min to allow formation of an adhesive bond. Upper probe of the texture analyzer was moved at a speed of 0.1 mm s<sup>-1</sup>. The force re-

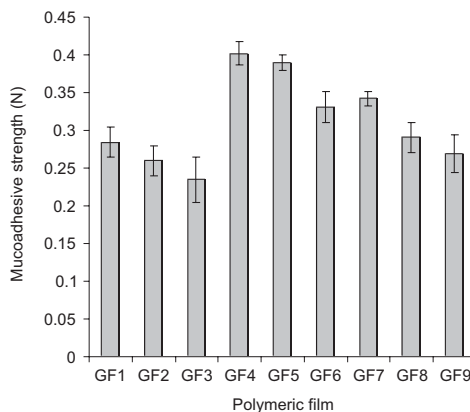


Fig. 3. Mucoadhesive strength of films with various polymers-to-plasticizer ratio (mean  $\pm$  SD,  $n = 3$ ).

quired to detach the film from the tissue surface was determined as mucoadhesive strength. Results of the mucoadhesive strength of batches GF1 to GF9 are shown in Table II and Fig. 3.

### Drug release

The drug release study was performed using a USP basket apparatus (Electrolab, TDT-06T, India) at  $37 \pm 0.5$  °C and at 50 rpm using 900 mL of phosphate buffer (pH 7.4) as dissolution medium ( $n = 5$ ) as per the dissolution test prescribed for glipizide extended release tablets (14). The polymeric film ( $1.0 \times 1.0$  cm) equivalent to 10 mg of glipizide was used for the test. Five milliliters of sample solution were withdrawn at predetermined time intervals, filtered through a  $0.45\text{-}\mu\text{m}$  membrane filter, suitably diluted, and analyzed spectrophotometrically. An equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. The average values of  $Y_8$  for batches GF1 to GF9 are given in Table II and the percentage of drug released is shown in Fig. 4.

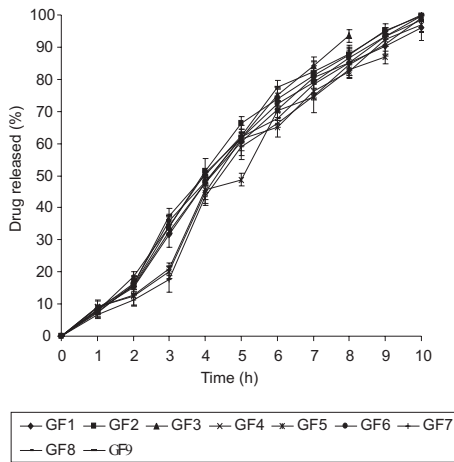


Fig. 4. *In vitro* dissolution of glipizide from mucoadhesive films of batches GF1-GF9 (mean  $\pm$  SD,  $n = 3$ ).

### Data fitting

An attempt was made to fit the dissolution data into the Hixon-Crowell model (15) represented by:

$$m = 100 \left( \frac{1}{3} - kt \right)^3$$

where  $k$  is the Hixon-Crowell constant [ $\text{mass}/(\text{time})^{1/3}$ ]. In this model, the percentage drug unreleased *vs.* cube root of time is linear.



The data was treated with the Korsmeyer-Peppas model (16) to characterize the mechanism of drug release:

$$M_t/M_\infty = K_p t^n$$

where  $M_t/M_\infty$  represents the fraction of drug released at time  $t$  and  $K_p$  is the kinetic constant characterizing the polymeric system and  $n$  stands for the diffusion exponent.

The dissolution data was also analyzed using the Weibull equation (15) to determine the kinetics of drug release from different batches of mucoadhesive films:

$$m = 1 - \exp[-(t-t_i)^b/a]$$

where  $a$  is the scale parameter which defines the time scale of the process,  $t_i$  is the location parameter which represents the lag period before the actual onset of dissolution process (in most cases  $t_i = 0$ ) and  $b$  is the shape parameter. In this model, the plot of  $\log$  of time *vs.*  $\log(1-m)$  is linear. The results of  $F$ -statistics were used for selection of the most appropriate model.

### In vivo study

*In vivo* evaluation studies for glipizide mucoadhesive films were performed in normal healthy Wistar rats weighing 250–300 g each. The Approval of the Institutional Animal Ethics Committee was obtained before starting the study (Nootan Pharmacy College, Gujarat, India). The study was conducted in accordance with standard institutional guidelines. Two groups of Wistar rats (5 in each group), which were fasted (with water) at least 12 h before the experiment, were used for the study. Before drug administration, a blood sample as control was taken from each Wistar rat from behind the eyeball through the angle of ocular cavity using a small capillary tube. The blood glucose level for

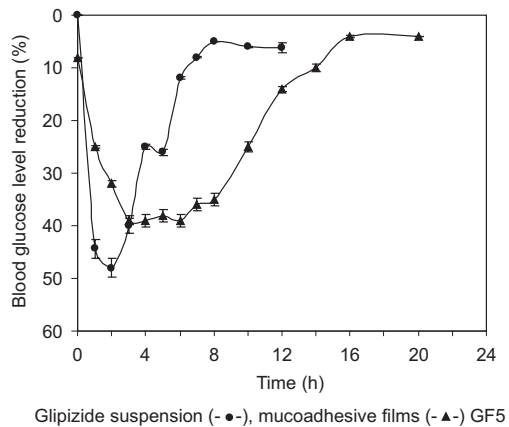


Fig. 5. Reduction in blood glucose levels following oral administration of glipizide and its mucoadhesive films in Wistar rats (mean  $\pm$  SD,  $n = 5$ ).

control and test samples was determined using the glucose-measuring instrument (Mediscence Abbott Laboratories, USA). The instrument was self-calibrated, and the samples were allowed to dry before the results were read to avoid lens contamination. A dose of  $800 \mu\text{g kg}^{-1}$  of glipizide suspension (freshly prepared in distilled water) and mucoadhesive films of glipizide were administered orally to each group using stomach intubation. Blood samples were collected at predetermined intervals up to 24 h and the blood glucose level was measured and depicted in Fig. 5.

## RESULTS AND DISCUSSION

### *Drug-excipient compatibility*

Drug-excipient compatibility studies were conducted with the objective of selecting a reasonable composition for mucoadhesive films. Any kind of incompatibility between glipizide and film-forming polymer affects its performance to a significant extent. Results of glipizide-excipient compatibility study performed by DSC are shown in Fig. 1. The DSC curve of pure glipizide exhibits a single endotherm (at  $217^\circ\text{C}$ ) corresponding to the melting point of glipizide. The onset of the melting point was observed at  $170.8^\circ\text{C}$  and the corresponding heat of fusion was  $170.8 \text{ J g}^{-1}$ , whereas pure PEG 400 shows a melting endotherm at  $47.8^\circ\text{C}$  and pure HPC shows a melting endotherm at  $74.4^\circ\text{C}$ . Thermogram of film GF5 shows complete absence of the glipizide melting peak and one endothermic peak at  $70.2^\circ\text{C}$  suggesting that glipizide was completely soluble in the liquid phase of the polymer and that the crystalline nature of glipizide was lost.

### *Mechanical properties*

Physical characteristics and other mechanical properties of glipizide films containing HPC and PEG 400 were found acceptable and were therefore selected for further optimizations of the formulation. The results of mechanical properties shown in Table II indicate that an increase in HPC concentration resulted in higher tensile strength (*TS*) and elongation at break (*EB*), while increased amount of PEG 400 reflected a decrease in *TS* and increase in percentage of *EB*. An interesting finding was the decrease in *TS* and increase in percentage of *EB* of the film as a function of plasticizer by weakening the intermolecular interactions between polymer chains. Hence, the optimum level of HPC and PEG 400 was desired because a high PEG 400 content produced more flexible and softer films. Glipizide films with HPC were tougher and softer than those without HPC.

Among the tested variables, HPC concentration seems to be the most prominent factor in determining response values of the film. An interesting observation was improved tensile strength, elongation,  $Y_8$  and swelling index as the content of HPC in the film increased. High concentration of PEG 400 can decrease  $Y_8$  and *TS* values of mucoadhesive films and increases the *EB* value. Desirability function was utilized to find out the optimum level of HPC and PEG 400 among the nine batches. Desirability function was calculated for *TS*, *EB* and  $Y_8$ . Batch GF5 showed the highest overall desirability of 0.90. This batch was therefore considered to be optimized and the values of independent variables of this batch were considered to be optimum values for mucoadhesive films.

The optimized composition of the film was glipizide (62.5 %, *m/m*), HPC (25 %, *m/m*) and PEG 400 (12.5 %, *m/m*).

### *Physico-chemical properties*

The newly developed glipizide films are colorless, odorless, flexible, uniform and possess smooth surface. Films of three different batches of GF5 were found to have similar aesthetic, mechanical and chemical properties. This suggests that films with desired properties can be prepared consistently and reproducibly. All the performance parameters of the GF5 film are given in Table III. High viscosity of the polymeric dispersion of the film was found in SGF compared to water. Viscosity and dispersibility of the formulation in stomach environment after administration governs the spreading and retention of formulations, which is essential to achieve the desired efficacy. The developed film was dispersed rapidly in SGF and formed a mucoadhesive layer over stomach mucosa in order to bring the drug in contact with the target tissue for a sufficient period of time. The pH of the polymeric film was found to be slightly acidic in SGF. The moisture content in the optimized film was  $7.0 \pm 0.2$  % (*m/m*). The small amount of moisture in formulations helped them to remain stable and prevented them from being completely dry and brittle. The results of scanning electron photomicrographs (not shown) of the film confirmed that film surface was free from any scratches or transverse striations.

Swelling indices of films with various composition are shown in Fig. 2. Films were found to be rapidly swollen within 5 min and thereafter slowly reached the plateau. Maximum swelling was seen with films containing a high content of HPC. As the concentration of PEG 400 in the film increased, the swelling index decreased.

Table III. Optimum characteristics of the mucoadhesive glipizide film

Parameter	Optimum value
Size (cm <sup>2</sup> )	1.0 × 1.0
Mass (mg) <sup>a</sup>	221.5 ± 4.5
Thickness (mm) <sup>a</sup>	0.24 ± 0.026
Moisture content (% <i>m/m</i> ) <sup>a</sup>	6.96 ± 0.22
Tensile strength (N mm <sup>-2</sup> ) <sup>b</sup>	9.75 ± 0.20
Elongation at break (%) <sup>b</sup>	66.95 ± 2.13
pH of dispersion <sup>a</sup>	
in water	7.54 ± 0.05
in SGF	4.90 ± 0.04
Viscosity of dispersion (m Pas) <sup>a</sup>	
in water	7.52 ± 0.30
in SGF	7.63 ± 0.12
Bioadhesive strength (N) <sup>b</sup>	0.39 ± 0.01
Drug release after 8 h (%)	83.1

<sup>a</sup> Mean ± SD, *n* = 3.

<sup>b</sup> Mean ± SD, *n* = 5.

Fig. 3 shows the effect of various polymer/plasticizer ratios on mucoadhesive strength of the film. The film mucoadhesive strength was improved with increasing HPC concentration up to a certain extent, and then it decreased. As the concentration of PEG 400 in the film increased, its mucoadhesive strength was found to decrease. This finding suggests that adhesion will improve with the extent of hydration until an optimum point where overhydration leads to a decrease in adhesive force due to disentanglement at the polymer/tissue interface. Amongst nine films, GF5 showed good mucoadhesion in simulated stomach environment.

Retention behavior of films was studied using a simulated dynamic stomach system that mimicked the physycodynamic conditions of the stomach. The film softened on the stomach mucosa after absorbing SGF and became a swollen structure, helping it to adhere to the stomach mucosa.

The time required for entire removal of the polymeric film from stomach mucosa varied with the film composition. Film containing a high content of HPC and PEG 400 was removed rapidly from stomach mucosa. As the ratio of HPC to PEG 400 in the film increased, the residence time of the film increased until an optimum point and then decreased. This indicates that retention properties of polymeric films can be controlled by the varying HPC/PEG 400 ratio. Results of this study clearly indicate that the amount of HPC and PEG 400 is an integral factor of the residence time of mucoadhesive films.

The percentage of glipizide release as a function of time is shown in Fig. 4. Optimized batch (GF5) exhibited an  $Y_8$  of 83.1 % and seems to be a promising candidate for achieving drug release up to 12 h. The drug release profile of batch GF5 is shown in Fig. 4. The dissolution data of batch GF5 was further analyzed to ascertain the mechanism of drug release. The mechanism of drug release from the films was found to be diffusion controlled because plots of cumulative drug release percentage *vs.* square root of time were found to be linear ranging from 0.9890–0.9971 for the best batch. The release profile was fitted to the Weibull equation (15);  $F$ -value was found to be 8.14 and was found to be 0.9762. For the release profile fitted to the Korsmeyer-Peppas equation (16),  $F$ -value was found to be 24.66 and  $R^2$  0.9845, and after fitting to Hixon-Crowell equation (15),  $F$ -value was found to be 12.52 and  $R^2$  0.9789. The results of  $F$ -statistics were used for the selection of the most appropriate model; it was thus concluded that the release profile fitted best to Weibull equation.

### *In vivo study*

*In vivo* efficiency of the optimized batch GF5 was tested on healthy normal Wistar rats by measuring the hypoglycemic effect produced after oral administration. The drug was administered at a dose equivalent to 800  $\mu\text{g kg}^{-1}$  pure glipizide, and glipizide mucoadhesive films were used. Pure glipizide was administered in a suspension at the same dose. When pure glipizide suspension was administered, a rapid reduction in blood glucose level was observed; maximum reduction of 48 % was observed within 2 h after oral administration. Blood glucose levels recovered rapidly to the original level within 8 h (Fig. 5). In the case of glipizide mucoadhesive films, the reduction in blood glucose levels was slow and reached maximum reduction within 4 h after oral administration. This reduction in blood glucose levels ( $\leq 25$  %) was sustained over a longer period of time (12 h). Kahn *et al.* (17) have suggested that a 25 % reduction in blood glucose levels is consi-

dered to be a potential hypoglycemic effect. Potential hypoglycemic effect (25 %) was maintained only from 0.5 to 5 h after oral administration of glipizide, whereas in the case of mucoadhesive glipizide films, potential hypoglycemic effect (25 %) was maintained for a period of 2 to 12 h. Sustained hypoglycemic effect observed over a longer period of time in the case of mucoadhesive films was due to the slow release and absorption of glipizide over longer periods of time. Glipizide sustained release formulation is significantly more effective than the immediate release formulation of glipizide in reducing fasting plasma glucose levels and side effects (18).

## CONCLUSION

The overall results obtained during this investigation suggest that glipizide mucoadhesive films possessed desirable aesthetic, pharmaceutical and biological properties. The *in vivo* study demonstrated potential hypoglycemic activity of the mucoadhesive film with glipizide.

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## S A Ž E T A K

### Priprava i evaluacija mukoadhezivnih filmova glipizida

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Glipizid se pretežno apsorbira u proksimalnom dijelu gastrointestinalnog trakta. Cilj rada je priprava i evaluacija mukoadhezivnih filmova s kojima bi se produljilo zadržavanje lijeka u predjelu apsorpcije. Pripravljene su mukoadhezivni filmovi glipizida koji se produljeno zadržavaju u želucu. Polimerni filmovi sadržavali su različite količine hidroksipropil celuloze i polietilen glikola 400 (PEG 400). Evaluirana su sljedeća svojstva mukoadhezivnih filmova: čvrstoća, postotak elongacije, indeks bubrenja, sadržaj vlage, pH i viskoznost polimerne disperzije, debljina filma, koncentracija lijeka, jednolikost i mukoadhezivnost u simuliranom želučanom soku. Na dinamičkom modelu želuca određivan je i postotak lijeka koji se zadržava u sluznici želuca u ovisnosti o vremenu. Povećanjem koncentracije hidroksipropil celuloze povećavaju se čvrstoća i elongacija, dok se povećanje koncentracije PEG 400 reflektira na smanjenje čvrstoće i povećanje elongacije kod loma. Omjer glipizid/hidroksipropil celuloza/PEG 400 (2,5:1:0,5) (GF5) bio je optimalan za pripravu mukoadhezivnih formulacija, s dobrom kalavošću, relativno visokim indeksom bubrenja, umjerenom čvrstoćom te zadržavanjem u sluznici želuca štakora do 8 h. U *in vivo* testiranjima mukoadhezivni filmovi s glipizidom pokazali su potencijalni hipoglikemijski učinak.

*Ključne riječi:* glipizid, mukoadhezivni film, faktorijalno dizajniranje, funkcija poželjnosti, hipoglikemijski učinak

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