Study of formulation variables on properties of glipizide mucoadhesive microspheres by factorial design

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ABSTRACT

Background and the Purpose of the study: The purpose of the study was formulate and systemsystematic evaluation in-vitro and in-vivo behaviour of Glipizide mucoadhesive microspheres using 3^2 full factorial design.

Methods: Concentration of Polycarbophil and Sodium Alginate were selected as independent variables and the effects were checked on dependent variables like swelling index, mucoadhesion, drug entrapment efficiency and T_{75}. In vivo studies were also performed to determine hypoglycemic activity of the mucoadhesive microspheres.

Results: The best batch exhibited drug entrapment efficiency of 75%, swelling index of 1.8 and mucoadhesion was 100%. The drug release from the microspheres was also sustained for more than 9 hrs.

Conclusion: The concentration of polycarbophil and sodium alginate had highly significant effects on dependent variables. In-vivo testing demonstrated a significant hypoglycemic effect of glipizide.

Keywords: Polycarbophil, Factorial design, Mucoadhesive microspheres, Glipizide

INTRODUCTION

Microsphere carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for the last several years in sustained drug delivery. Recently dosage forms that can precisely control the release rates and target drugs to a specific body site have created enormous impact in formulation and development of the novel drug delivery systems. Microspheres are an important part of such novel drug delivery systems (1-4). They have various applications and are prepared by using different polymers. However, the success of these microspheres is limited due to their short residence time at the site of absorption. It would, therefore be advantageous to have means to provide an intimate contact of the drug delivery system with the absorbing membranes (5-10). This can be achieved by coupling mucoadhesion characteristics to microspheres which have advantages like efficient absorption and enhanced bioavailability of the drugs due 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 (11-14).

Glipizide is a second-generation sulfonylurea that lowers the blood glucose level in human by stimulating the release of insulin from the pancreas and typically is prescribed to treat type II diabetes (non insulin dependent diabetes mellitus). Its short

biological half-life (3.4 ± 0.7 hrs) necessitates to be administered in two or three doses of 2.5-10 mg per day (15). The development of controlled release dosage forms thus, would clearly be advantageous. Researchers have developed oral controlled release microspheres by various techniques (16, 18). The site of absorption of glipizide lies in the stomach. Dosage forms that are retained in the stomach would increase the absorption, improve drug efficiency and decrease dose requirements.

Thus an attempt was made in the present investigation to use Polycarbophil as a mucoadhesive polymer and prepare microspheres of Glipizide. The mucoadhesive microspheres were evaluated in-vitro and in-vivo, and factorial design was employed to optimize variables.

MATERIALS AND METHODS

Materials

Glipizide was supplied by ICPA Pharmaceuticals. Ltd., Ankaleshwar, Polycarbophil was supplied by Noveon, Mumbai, Sodium Alginate and Calcium chloride dihydrate was purchased from Merck Lab Pvt. Ltd. Mumbai, Other chemicals used were of AR grade.

Methods

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (SDT2960 TA

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Instruments Inc., USA) was performed to assess thermotropic properties and thermal behaviors of Glipizide, sodium alginate and polycarbophil. Samples (3-5 mg) were placed in aluminum pans and lids at constant heating range of 15°C/min, covering temperature range to 300°C. Nitrogen was used as purge gas through DSC cell.

Preparation of Mucoadhesive Microspheres
Microspheres containing glipizide were prepared by using sodium alginate in combination with a mucoadhesive polymer, Polycarbophil. An orifice-ionic gelation process (19, 20) was employed to prepare the microspheres.

Orifice-Ionic Gelation Method
Sodium alginate and the mucoadhesive polymer were dispersed in purified water (50 ml) to form a homogeneous polymer mixture. Glipizide (1 g) was added to the polymer premix and mixed thoroughly to form a smooth viscous dispersion. Resulting dispersion was then sprayed into calcium chloride (10% w/v) solution by continuous stirring. Produced droplets were retained in the calcium chloride solution for 15 minutes to complete the curing reaction and to produce rigid spherical microspheres. The resulting microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then dried at 45°C for 12 hrs.

Effect of Variables
Preliminary studies were carried out to select amounts of variables. These were focused on the formation of microspheres and mucoadhesive properties. Based on these studies values of variables were selected. To study the effect of variables, batches were prepared by using 3^2 full factorial design. Particle size, swelling index, drug entrapment, mucoadhesion and drug release were selected as independent variables. Various batches prepared by using all possible combinations of different levels of experimental variables are listed in tables 1 and 2.

Evaluation of Mucoadhesive Microspheres
Estimation of Glipizide
Glipizide content in the mucoadhesive microspheres was estimated by a UV spectrophotometer at 275 nm in phosphate buffer (pH 7.4) (21). The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range

Table 1. Different batches with their experimental coded level of variables for 3^2 Factorial Design.

Batch Code	Variable levels in Coded form	
	X_1	X_2
MMP-1	-1	-1
MMP-2	-1	0
MMP-3	-1	+1
MMP-4	0	-1
MMP-5	0	0
MMP-6	0	+1
MMP-7	+1	-1
MMP-8	+1	0
MMP-9	+1	+1

of 5-50 µg/ml. When the standard drug solution was analyzed repeatedly (n = 5), the mean error (accuracy) and relative standard deviation (precision) were found to be 0.82% and 1.4% respectively.

Particle size and Swelling Index of Microspheres
The particle size of the microspheres was determined by using optical microscopy method (22-23). Approximately 100 microspheres were counted for particle size using a calibrated optical microscope. For estimation of swelling index, 0.5 ml of microsphere bed was soaked in 5 ml of 0.1 mol/ml of HCl. Volume of microsphere bed was determined after 12 hrs. Swelling index was calculated by using following formula:
Swelling index = Volume after 12 hrs. / Original volume(1).
Three readings were taken and there average values are reported.

Scanning Electron Microscopy
The microspheres were observed under a scanning electron microscope (SEM-Jeol Instruments, JSM-6360, Japan). Scanning Electron photographs were taken at an accelerating voltage of 20 KV, chamber pressure of 0.6 mm Hg.

Drug Entrapment Efficiency
Microspheres (50 mg) were crushed in a glass mortar-pestle and the powdered microspheres were suspended in 10 ml of phosphate buffer (pH 7.4). After 24 hrs, solution was filtered and the filtrate was analyzed for the drug content. The drug entrapment efficiency was calculated by following formula (17).
Microencapsulation efficiency = Practical drug

Table 2. Translation of coded levels in actual units.

Variable levels	Low (-1)	Medium (0)	High (+1)
X_1= Concentration of Sodium Alginate (%w/v)	500 mg	750 mg	1000 mg
X_2= Concentration of Mucoadhesive Polymer (%w/v)	500 mg	750 mg	1000 mg

content / Theoretical drug content × 100 (2).
Three readings were taken and their average values are reported.

Mucoadhesion studies
Falling Film Technique is one of the suitable methods for testing mucoadhesion strength of the mucoadhesive particulate system like mucoadhesive microspheres and suspension. In weight percent method, a fixed weight of microsphere sample was added (50 mg) over a fresh intestinal segment of sheep, mounted on a tilted slide with an angle of 45°and allowed to rest for 15 min. The effluent which was run over the segment collected in a Whattman filter paper and the weight of detached particle was determined. Percentage of mucoadhesion was determined by using following formula (24).
Percent mucoadhesion = {(Wt. of sample - Wt. of detached particles) / Wt. of sample} × 100 (3).
Three readings were taken and their average values are reported.

Drug Release Study
Release of glipizide from the microcapsules was studied in phosphate buffer of pH 7.4 (900 ml) using a Dissolution Rate Test Apparatus with a rotating paddle stirrer at 50 rpm at 37° ± 1°C as described for glipizide tablets in USP XXIV (21). A sample of microcapsules equivalent to 10 mg of glipizide was used in each test. Samples of dissolution fluid were withdrawn at different time intervals and were assayed at 275 nm for glipizide content using a Shimadzu UV-1700 double-beam spectrophotometer (Shimadzu Corporation, Japan).

In Vivo Evaluation
In vivo evaluation studies for glipizide mucoadhesive microspheres (25) were performed on normal healthy Wistar rats weighing 250-300 gm each. The approval of Institutional Animal Ethical Committee was obtained before the start of the study which was conducted in accordance with standard institutional guidelines. Two groups of Wistar rats (5 in each group) fasted (with water) at least 12 hrs before the experiments were used for the study. Before drug administration, a blood sample (1 ml) as a control was taken from each rat from behind the eyeball through the angle of ocular cavity using small capillary tubes. The blood glucose level for the control and test samples was determined. Pure glipizide suspension and mucoadhesive microspheres of glipizide were administered orally to each group using stomach intubations. A dose of 800 μg/kg of glipizide was administrated in a suspension form (freshly prepared) for each rat. Blood samples of 1 ml were collected at pre-determined time intervals at 1, 2, 3, 4, 5, 6, 9, 12, 16, 20, 24 hrs and the blood glucose level was estimated by using a glucose estimation kit and the percentage of reduction in blood glucose level was measured.

RESULTS AND DISCUSSION

Differential Scanning Calorimetry (DSC)
DSC studies were carried out to determine interaction between drug and polymers in the prepared mucoadhesive microspheres. This will also indicate success of stability studies. Glipizide peak was abseved clearly in its DSC thermogram (Figure 1) indicating a sharp characteristic endothermic peak at temperature range 215-225 °C corresponding to its melting temperature (T_m). Which shows that Glipizide which was used was in pure form. The endothermic peak in the case of polycarbophil at 80-100 °C was due to physically bound water or moisture. DSC thermmogram of microspheres as indicated endothermic peak of glipizide. Thus there might not be interaction between the selected variables.

Surface Topography and Particle Size Determination
Surface topography of prepared microspheres is shown in figure 2. Mucoadhesive microspheres of the prepared glipizide were well-rounded spheres with ridges of shrinkage due to presence of polycarbophil. The drug-loaded microspheres were spherical and yellowish white in appearance change to whiteness gradually by increase in polycarbophil concentration. Microspheres with a coat of mucoadhesive polymer were found to be discrete, spherical, free flowing and of monolithic matrix type. The microspheres were uniform in size for each batch. Micromeritic property such as particle size which was in the range of 202 μm to 372 μm was mainly governed by the polymer concentration. Particle size increased with
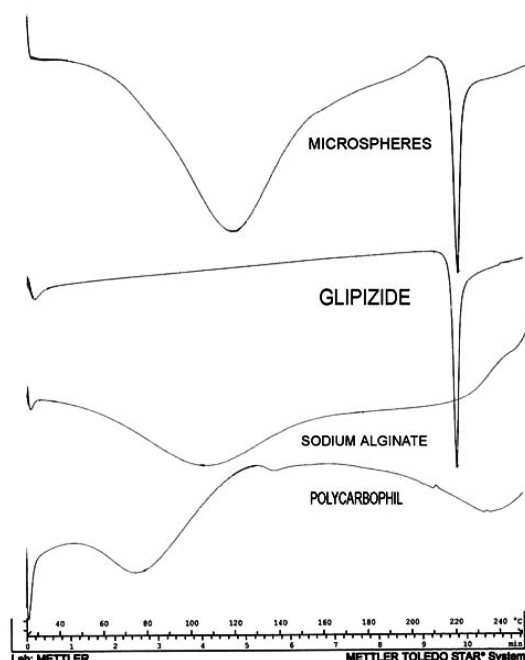

Figure 1. DSC Thermograms of polycarbophil. Sodium alginate, glipizide and prepared microspheres.
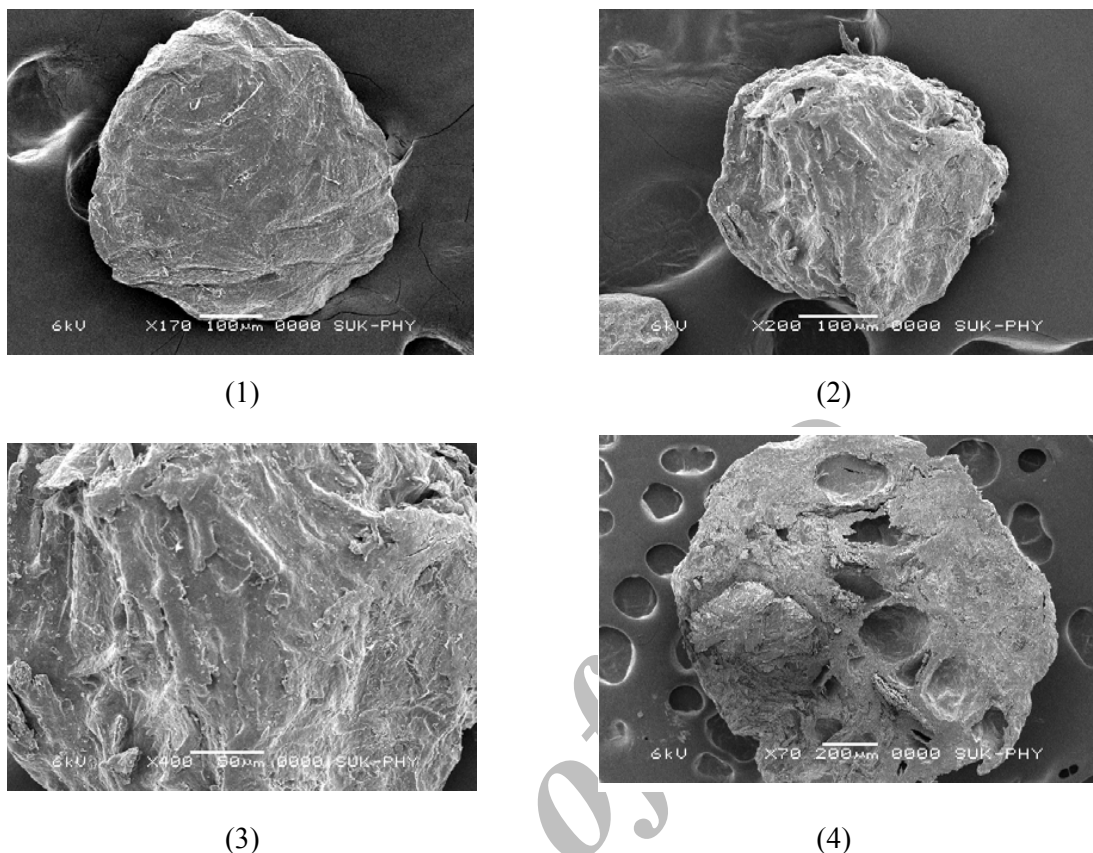
(1)

(2)

(3)

(4)

Figure 2. Scanning Electron Micrograph of Glipizide Mucoadhesive Microspheres.
(1) Plain Microsphere without mucoadhesive polymer, (2) Mucoadhesive microsphere with Polycarbophil. (3) Batch MMP-6 at 400X, (4) Cut way view.

increasing polymer concentration which may be due to increased viscosity of the dispersion, which affects the performance of spraying of the mixture and results in the formation of larger droplets. Under scanning electron microscope, it was found that there are lots of crystals scattered on the surface of the microspheres. Through the cut way view of the microspheres it was also observed that glipizide crystals are present in the inner part of the microspheres. Inner part of the microspheres was dense and porous.

3^2 Full Factorial Design Studies

Results of preliminary studies indicated that, at concentrations below 500 mg of both polymers there was no formation of rigid microspheres and also mucoadhesion observed was poor. Based on these studies, variables were selected. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2$$

Where, Y is the dependent variable, β_0 is the arithmetic mean response of the nine runs, and β_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average results of changing one factor at a time from low to high value. The interaction terms ($X_1 X_2$) show how the response

changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. Multiple regression analysis and F statistics were used to identify statistically significant term. The results of multiple regression analysis are summarized in table 3. Influence of formulation variables on evaluation parameters is discussed under the following sub headings.

Percentage of mucoadhesion and Swelling Index

The falling film test for percent of mucoadhesion varied from 92 to 100% and showed good correlation coefficient (0.9673). Examination of the equation indicated that both factors (X_1 & X_2) showed positive effect, but the effect of X_2 (Polycarbophil concentration) was much pronounced and higher than that of X_1 (Sodium alginate concentration). This may be due to the capacity of Polycarbophil to adhere to gastric mucosa as well as gelation of sodium alginate. The gelation may be considered to reduce the mucoadhesion property of sodium alginate. At higher concentrations of both variables mucoadhesion increases, which may be attributed to increase in particle size by increase in the amount of mucoadhesive polymer that causes
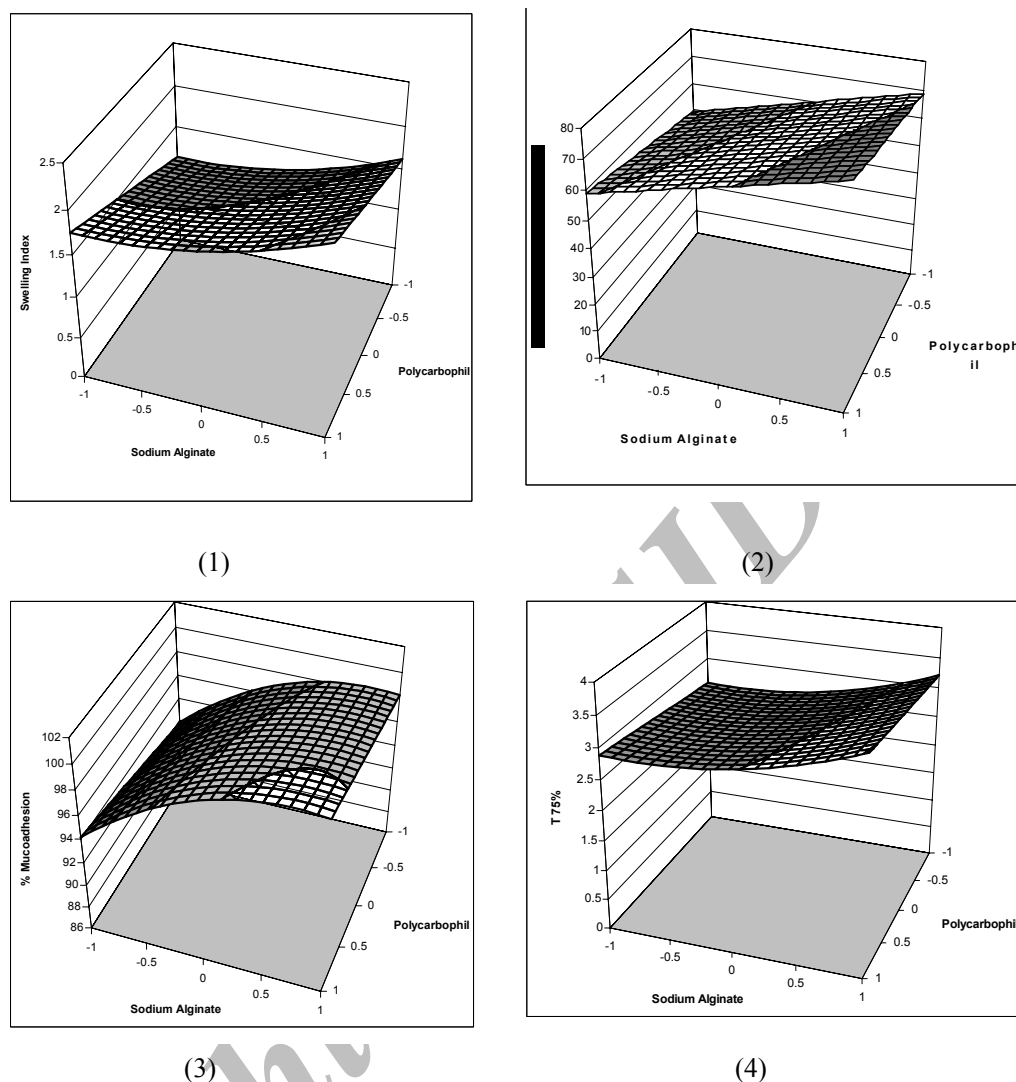
(1)

(2)

(3)

(4)

Figure 3. Surface graphs showing effect of variables on (1) Swelling of mucoadhesive microspheres; (2) Drug entrapment efficiency; (3) Mucoadhesion; (4) T_{75}

increase in mucoadhesion. However this increase in mucoadhesion does not show linearity, as indicated by the negative term in polynomial equation. The amount of polymer directly affected the solvent transfer rate and thus, as the polycarbophil concentration increases the swelling index also increases. The swelling index varied from 1.1 to 2.2 (Figure 3) and showed good correlation coefficient (0.9881). Thus it may be concluded that the amount of polycarbophil and sodium alginate directly affects the percentage of mucoadhesion and swelling index.

Drug Entrapment Efficiency and T_{75}
The drug entrapment efficiency and T_{75} are important variables for assessment of the drug loading capacity of microspheres and their drug release profiles, thus suggesting the amount of drug available at the site. These parameters are dependent on the process of preparation, physicochemical properties of the

drug and formulation variables. Low coefficient of variation (< 2.0%) in percentage of drug content indicated uniformity of drug content in each batch of microspheres. The drug entrapment efficiency were 48 to 75% (Figure 3) and yields were 90 to 97 %. Interpretation of equation indicates that encapsulation efficiency is a combined effect of both factors X_1 and X_2. However it is more significantly dependent on X_2 than that of X_1. Encapsulation efficiency increased by increase in the concentration of sodium alginate, but later on it decreased with increase in the amount of sodium alginate. At higher concentrations, factors showed negative linearity which may be due to the achievement of saturation concentration, thus there would be a competition for space between drug molecule and swelled polycarbophil chains in the sodium alginate network of microspheres.
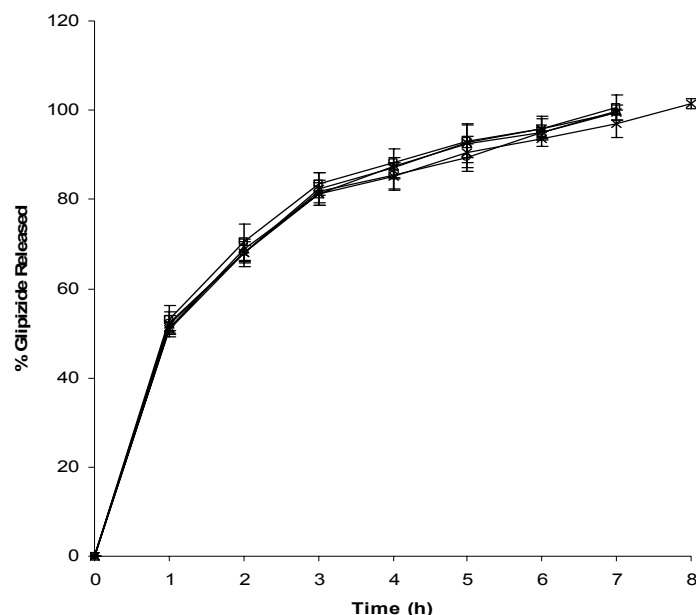Figures 4 and 5 showed that the release studies of Polycarbophil microspheres depend to polymer

Figure 4. Dissolution Profile of Glipizide Mucoadhesive Microspheres with Polycarbophil. MMP-1 (□), MMP-2 (Δ),MMP-3 (x), MMP-4(*), MMP-5(◊)
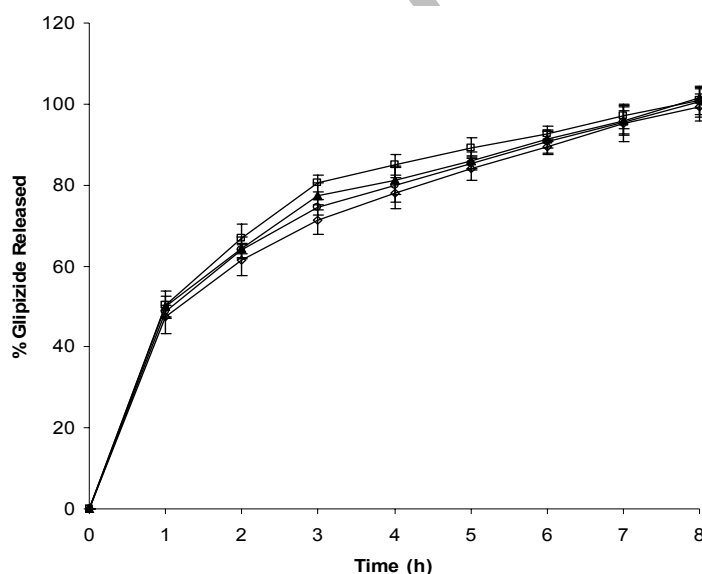

Figure 5. Dissolution Profile of Glipizide Mucoadhesive Microspheres with Polycarbophil. MMP-6 (□), MMP-7 (▲), MMP-8 (○), MMP-9 (◊).

concentration. Both factors contributed to the controlled release of drug. Concentration of Polycarbophil was found to be slightly less dominant factor than concentration of sodium alginate. Increase in the polycarbophil concentration causes drug retardation upto 8 hrs. T_{75} was found to be lengthened as the concentration of Polycarbophil and sodium alginate increased. The 'n' values (Table 4) are less than 0.5, which is an indication of the non-Fickian release. Initially there is rapid release, which is followed by overtime tailing off. The dissolution profile was found to be of Peppas type. The initial faster release may be due to drug dissolution from the surface of microspheres. The factorial study of T_{75} indicates a good correlation coefficient of 0.9909, which may be due to the both factors. The effect may depend on both the factors. The retardation may be due to the hydrogel structure of calcium alginate, which encapsulates the drug in its network and the swelling of Polycarbophil. However, concentration of Polycarbophil was found to be slightly less significant than that of sodium alginate because of the fact that

Table 3. Regression Analysis of Different Evaluation Parameters for Mucoadhesive microspheres of Glipizide. (n=3).

Coefficient	Swelling Index	% Drug Entrapment	% Mucoadhesion	T_{75}(Hr)
β_0	1.533*	63.87*	96.88*	2.8133*
β_1	0.25*	9.68*	1.166*	0.323*
β_2	0.3166*	4.76*	3.166*	0.16*
β_{11}	0.15*	-1.1686	-2.112*	0.233*
β_{12}	0.015	-0.2982	-0.325	0.0185
β_{22}	-0.055	-0.1227	-0.275	0.0395
R^2	0.9881	0.9195	0.9673	0.9951
F	49.9945	6.8592	17.7722	122.1183
P	0.0000	0.0000	0.0000	0.0000

*Significant terms at P < 0.005
n is the number of samples tested for each experiment.

Table 4. Analysis of release mechanism of Polycarbophil Microspheres.

Batch code	MMP-1	MMP-2	MMP-3	MMP-4	MMP-5	MMP-6	MMP-7	MMP-8	MMP-9
n	0.32237	0.33863	0.32004	0.33391	0.32439	0.32464	0.32961	0.33795	0.35251
K	55.3087	53.3263	53.5136	53.7928	53.8707	52.6567	51.1359	49.8814	47.8243
R	0.9879	0.9893	0.9827	0.9898	0.9905	0.9884	0.9956	0.9978	0.9996
T_{75}	2.572	2.737	2.871	2.705	2.773	2.972	3.196	3.342	3.583
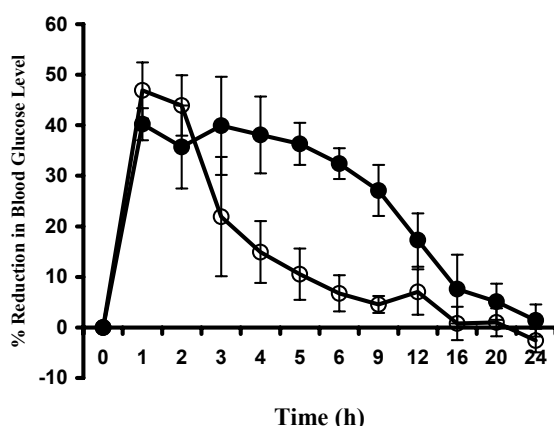
Figure 6. Percentage reduction in serum glucose following oral administration of Glipizide (o) and its mucoadhesive microspheres MMP-6(•) in normal rats (n=5).

Polycarbophil particles have a high concentration of ionic groups inside, which causes the large influx of water by osmosis and swelling of the particles until the cross-links are strained. This will leads to rapid diffusion of drug out of the polymer. Results indicate that higher levels of polymer favors cross-linking reaction and thus higher T_{75} is obtained.

In-vivo Studies
The best batch MMP-6 was selected as the best batch on the basis of the drug entrapment efficiency, mucoadhesion and drug release pattern. In vivo efficiency of these formulations was carried out in healthy normal Wistar rats by measurement of the

hypoglycemic effect after oral administration. When pure glipizide suspension was administered a rapid reduction in blood glucose levels was observed and maximum reduction of 46.91 % was observed within 1 hrs after oral administration and the blood glucose levels were also recovered rapidly to the normal level within 6 hrs. (Figure 6). In the case of glipizide mucoadhesive microspheres, the reduction in blood glucose levels was reached maximum within 4 hrs after oral administration and this reduction in blood glucose levels was sustained over 9 hrs.

A 25 % reduction in blood glucose levels is considered as a significant hypoglycemic effect (%25) (15) which was maintained only for 0.5 to 2 hrs period after oral administration of the pure glipizide. In the case of glipizide microspheres with Polycarbophil, significant hypoglycemic effect was maintained for a period of 1 to 9 hrs. Glipizide mucoadhesive microspheres are significantly more effective than immediate release formulation of glipizide in reducing fasting plasma glucose levels and side effects (26). Formulation of glipizide as mucoadhesive sustained release dosage forms could also exhibit a decrease in side effects.

CONCLUSION
The results of a 3^2 full factorial design revealed that the concentration of polycarbophil and sodium alginate affected the dependent variables of % mucoadhesion, swelling index, drug entrapment efficiency, and T_{75} significantly. The mucoadhesive microspheres exhibited good mucoadhesive properties in an in-vitro test. Glipizide release from these microspheres

was slow and extended over longer periods of time and was dependent to the composition of coat. Drug release was diffusion controlled and followed Peppas type of diffusion kinetics. In the in-vivo evaluation, glipizide mucoadhesive microspheres could sustain the hypoglycemic effect over a 9 hrs period. These mucoadhesive microspheres are thus suitable for oral controlled release of glipizide.

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