RESEARCH ARTICLE

Studies on influence of process variables on performance of gliclazide mucoadhesive microcapsules

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Microencapsulation is a unique technique of controlled drug delivery system and is of major importance for effective alteration of drug release required to produce a novel formulation with desired characteristics to overcome the disadvantages of the conventional therapeutic dosage forms. Microcapsules offer efficient absorption and enhanced bioavailability owing to their higher surface area, however, mucoadhesive microcapsules render more intimate contact with the mucus membrane thereby leading to increase in the gastro intestinal residence time. Gliclazide is an oral hypoglycemic second generation sulfonyl urea, which is useful for a long-term treatment of non-insulin dependent diabetes mellitus. In the present investigation, the gliclazide microcapsules are formulated to control the release rate and improve the absorption across gastrointestinal membrane by employing ionic gelation method. The effect of various process variables such as curing time, stirring speed, stirring time, volume and concentration of curing reagent on entrapment efficiency, and drug release rate was studied. The microcapsules were evaluated for drug content, encapsulation efficiency, *in vitro* drug release studies. The optimized formulation was selected based on the entrapment efficiency and drug release rate. The optimized formulation of gliclazide microcapsules were evaluated for rheological properties, moisture content, swelling index, erosion studies, wall thickness and *in vitro* wash off test. The microcapsules formulated with 2:1 coat:core ratio by using 150 ml of 0.1M $Cacl_2$ solution as curing reagent, at a stirring speed of 400 rpm for 60 minutes and a curing period of 48 hrs were found to be the optimum formulation. The drug release followed zero order kinetics and was controlled by peppas mechanism. The pharmacodynamic activity of optimized gliclazide microcapsules was conducted by measuring blood glucose levels in healthy albino rabbits. The percentage glucose reduction was calculated and the data was treated statistically. The hypoglycemic activity was extended up to 10 hours in case of microcapsules.

Key words: *Gliclazide, hypoglycemic activity, mucoadhesive microcapsules, process variables*

INTRODUCTION

Microencapsulation is a useful method to prolong the drug release from dosage forms and reducing adverse effects. Micro particles constitute an important part of these novel drug delivery systems, by virtue of their small size and efficient carrier characteristics. However, the success of micro particles is limited due to their short residence time at the site of absorption. Therefore, providing an intimate contact of the drug delivery system with the absorbing membranes is advantageous to the effective drug delivery. It can be achieved by coupling bioadhesion characteristics to microparticles and developing novel delivery systems referred to as "bioadhesive microparticles". Bioadhesive microparticles have advantages such as efficient absorption and enhanced bioavailability of drugs owing to their high surface to volume ratio, a much more intimate contact with the mucus layer, and specific targeting of drugs to the absorption site.[1]

Gliclazide is an oral hypoglycemic second generation sulfonyl urea drug useful for a long-term treatment of non-insulin dependent diabetes mellitus (NIDDM). For an oral hypoglycemic drug, rapid absorption

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from the gastrointestinal tract is required for effective pharmacological activity. The absorption rate of gliclazide from the gastrointestinal tract is slow and varied among the subjects. The slow absorption has been suggested to be due to either poor dissolution of gliclazide owing to its hydrophobic nature or poor permeability of the drug across the GI membrane. Incorporation of gliclazide in controlled release dosage forms may regulate its absorption from the gastrointestinal tract and overcome the variability problems. The modified-release preparation demonstrates very high bioavailability and allows reduction in the effective dose to 30−120 mg/d from 80−360 mg/d. [2]

The extent and rate of drug release from microcapsules is affected by various formulation variables and different processing conditions such as stirring speed, stirring time, volume of curing reagent, concentration of curing reagent and curing time. So the effect of these parameters was studied and results are reported here.

MATERIALS AND METHODS

Gliclazide was procured from Aurobindo pharmaceuticals, Hyderabad as a gift sample. Sodium alginate and calcium chloride were obtained from SD Fine chemicals, Mumbai. Hydrochloric acid, sodium acetate, glacial acetic acid, potassium dihydrogen phosphate, sodium hydroxide, and acetonitrile AR purchased from Qualigens fine chemicals, Mumbai were used in this investigation.

UV- Visible spectrophotometer (Shimadzu, UV- 1700), magnetic stirrer (Remi Motors, Model No RO123R, Mumbai), mechanical stirrer (Remi Motors Pvt. Limited, Mumbai), 8 stage dissolution test apparatus (Shimadzu, TDT 08L, Mumbai), and hot air oven (Thermo Labs), Mumbai were used in this investigation.

Preparation of gliclazide microcapsules

The gliclazide loaded calcium alginate beads were prepared by employing ionic gelation with and without subjecting to mechanical stirring.[3] The gliclazide (300 mg) was accurately weighed, dispersed in 10 ml of sodium alginate solution (0.6% w/v) and was agitated thoroughly on magnetic stirrer to form a viscous homogenous dispersion. Then the dispersion was dropped through the 20 mm stainless steel needle into the 150 ml of 0.1 M calcium chloride solution, stirred up to 30 min, allowed to retain in calcium chloride solution for curing up to 12−72 hrs. The microcapsules were then separated by filtration, washed three times with deionized water and dried at room temperature for 24 hrs. To study the influence of stirring speeds, the microcapsules were further formulated by keeping different revolutions during agitation (200, 400, 600, and 800 rpm). To study the effect of stirring time, the microcapsules were further formulated by employing various stirring times (15, 30, 45, and 60 minutes) after the addition of dispersion in to calcium chloride solution. To study the influence of volume of curing reagent, the microcapsules were further formulated by keeping different volumes (100,150, and 200 ml) of curing reagent (0.1 M $CaCl_2$ solution). To study the effect of concentration of curing reagent, the microcapsules were further formulated by employing various concentrations of curing reagent (0.05, 0.08, 0.1, 0.12, and 0.15 M). The composition and the conditions observed during the processing of the microcapsules are shown in Table 1.

Characterization of gliclazide microcapsules

Rheological properties

Optimized formulation of gliclazide microcapsules were evaluated for the following rheological properties:[4]

Bulk density and tapped density

Bulk density and tapped density were measured by using 10 ml graduated cylinder. The pre weighed sample of microcapsules was placed in a cylinder, tapped mechanically for 100 times, and then tapped volume was recorded. Bulk density and tapped density were calculated from the following formulae:

$$\text{Bulk density} \quad \frac{\text{Mass of microcapsules}}{\text{Bulk volume}} \tag{1}$$

$$\text{Tapped density} \quad \frac{\text{Mass of microcapsules}}{\text{Tapped volume}} \tag{2}$$

Carr's index

Carr's index or compressibility index (CI) value of microcapsules was computed according to the following equation:

$$CI(\%) = \left[\frac{pt - pb}{pt}\right] \times 100 \tag{3}$$

Where
pt - Tapped density
pb - Bulk density
Hausner's ratio

Hausner's ratio of microcapsules was determined by comparing the tapped density to the bulk density using the equation:

$$HR = \frac{pt}{pb} \tag{4}$$

Where
pt - Tapped density
pb - Bulk density

Table 1: Composition of gliclazide mucoadhesive microcapsules

Formulation	Curing time (hr)	Stirring speed (rpm)	Stirring time (min)	Volume of curing reagent (ml)	Concentration of cross linking agent (M)
F_1	12	-	-	150	0.1
F_2	24	-	-	150	0.1
F_3	36	-	-	150	0.1
F_4	48	-	-	150	0.1
F_5	60	-	-	150	0.1
F_6	72	-	-	150	0.1
F_7	12	400	30	150	0.1
F_8	24	400	30	150	0.1
F_9	36	400	30	150	0.1
F_{10}	48	400	30	150	0.1
F_{11}	60	400	30	150	0.1
F_{12}	72	400	30	150	0.1
F_{13}	48	200	30	150	0.1
F_{14}	48	600	30	150	0.1
F_{15}	48	800	30	150	0.1
F_{16}	48	400	15	150	0.1
F_{17}	48	400	45	150	0.1
F_{18}	48	400	60	150	0.1
F_{19}	48	400	60	100	0.1
F_{20}	48	400	60	200	0.1
F_{21}	48	400	60	150	0.05
F_{22}	48	400	60	150	0.08
F_{23}	48	400	60	150	0.12
F_{24}	48	400	60	150	0.15

Moisture content

Accurately weighed amount of microcapsules were placed in a hot air oven maintained at 60°C and at regular time intervals the dried microcapsules were reweighed.[5] This experiment was continued until the constant weight was attained (equilibrium moisture content). The % moisture content and % loss on drying was calculated from the following formulae:

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100 \quad (5)$$

$$\% \text{ Loss of drying} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad (6)$$

Drug content

Microcapsules containing 30 mg of gliclazide were weighed and crushed to fine powder in a mortar and was extracted with 5 ml of acetonitrile. The slurry was filtered and the filtrate was made up to 100 ml with phosphate buffer pH 7.4. One milliliter of the sample was collected, suitably diluted with phosphate buffer pH 7.4, and the absorbance was measured at 227 nm.[6]

Drug entrapment efficiency

Microencapsulation efficiency[7] was calculated using the following formula:

$$\text{Microenapsulation efficiency} = \frac{\text{Estimated drug content}}{\text{Theoretical drug content}} \times 100 \quad (7)$$

In vitro drug release study

Microcapsules containing equivalent to 30 mg of gliclazide were subjected to *in vitro* drug release studies.[8] Release of gliclazide from the beads was studied in phosphate buffer pH 7.4 using a USP TDL-08L dissolution test apparatus (Shimadzu, Mumbai) with a rotating basket stirrer operated at 100±2 rpm and temperature was maintained at 37±1°C. Then at regular intervals of time (30 min), 5 ml of samples were collected and same volume was replenished with fresh dissolution medium. The withdrawn samples were filtered through what man filter paper (no.41), suitably diluted and analyzed spectrophotometrically at a λ_{max} of 227 using Shimadzu UV-1700 double beam spectrophotometer.

Swelling index

Pre-weighed microcapsules were transferred into a petri plate containing 25 ml of phosphate buffer pH 7.4 and subjected to swelling studies.[9] At regular intervals of time, the microcapsules were collected and blotted to remove the excess water and reweighed. The swelling index (SI) was measured with following formulae:

$$\text{Swelling index (\%)} = \frac{\text{Final weight initial weight}}{\text{Initial weight}} \times 100 \quad (8)$$

Erosion study

Pre-weighed microcapsules (W_0) were placed in a petri plate containing 25 ml of phosphate buffer (pH 7.4) and subjected to erosion studies.[9] At regular intervals of time (30 min) the microcapsules were collected and blotted to remove the excess water and dried in a hot air oven kept at 50°C and then the microcapsules were cooled to room temperature. The weight of dried microcapsules was noted as We. The percentage of erosion (E %) was calculated with the following formulae:

$$\text{Erosion (\%)} = \frac{W_0 - W_e}{W_0} \times 100 \quad (9)$$

Where
W_0= Initial weight of microcapsules
We= weight of eroded microcapsules

Wall thickness

Wall thickness of microcapsules was determined by the method of Luu *et al.*[10] using the equation:

$$h = \frac{\bar{r}\,(1 - p)\,d_1}{3\,[pd_2 + (1-p)\,d_1]} \quad (10)$$

Where
h - wall thickness,
$\bar{r}$ - arithmetic mean radius of the coat material,
d_1 - density of the core material
d_2 - density of the coat material
p - Proportion of the medicament in the microcapsules

In vitro wash-off test for microcapsules

The mucoadhesive property of the microcapsules was evaluated by an *in vitro* adhesion testing method known as the *in vitro* wash-off test.[11] The mucoadhesiveness of these microcapsules was compared with that of a control, calcium alginate microcapsules. Freshly excised pieces of intestinal mucosa (2 × 2 cm) from sheep were mounted on to glass slides (3 × 1 inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support. About 50 microcapsules were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hanging on to the arm of the USP table disintegrating test machine. When the disintegrating test machine was operated, the tissue specimen was given a slow, regular up-and-down movement in the test fluid at 37°C contained in 1L vessel of the machine. At the end of 1st hr, and at hourly intervals up to 6 hours, the machine was stopped and the number of microcapsules still adhering to the tissue was counted. The test was performed in both gastric pH (0.1N HCl, pH 1.2) and intestinal pH (phosphate buffer, pH 7.4).

Pharmacodynamic studies on rabbits

Adult albino rabbits weighing between 1.3 and 1.5 kg obtained from the animal house of Bapatla College of pharmacy (1032/ac/07/CPCSEA); Bapatla, were maintained at a constant temperature at 26±2°C, 30−40% RH with 12 h light/ dark cycle, throughout the study. The rabbits were housed in clean rabbit cages in an air conditioned animal house and were fed with commercial rabbit feed and sterile water. The experimental protocol (IAEC/III/02/BCOP/2011) was approved by the institutional animal ethical committee (IAEC) of Bapatla College of Pharmacy; Bapatla and was in accordance with the guidelines of the committee for the purpose of control and supervision of experimentation of animals.

To study the hypoglycemic activity of gliclazide and its microcapsules, adult healthy albino rabbits were used (n=5). All the animals were fasted for a period of 18 hrs prior to the experiment and water was fed *ad libitum*. The animal dose of gliclazide and its microcapsules relevant to the human dose was calculated, i.e., 1.4 mg/kg and 1 ml of the prepared dose of gliclazide was injected orally. The blood samples were collected from the marginal ear vein at time intervals of 0, 1, 2, 3, 4, 6, 8, 10, 12, and 16 hours and blood glucose levels were measured using Accucheck™ glucometer. The animals treated with pure gliclazide were treated as control. After completion of this phase, animals were allowed for one week wash out period. The microcapsules containing equivalent to 1.4 mg/kg were accurately weighed and filled in to capsule and given orally. The blood samples were collected and analyzed for glucose levels and the percent reduction in blood glucose level of the microcapsule was calculated as that of the pure drug.

The percent reduction in blood glucose levels was calculated using the following formulae:

$$\text{\% reductionin bloodglucose} = \frac{G0 - GT}{G0} \times 100 \quad (11)$$

Where
G0-Initial blood glucose concentration
Gt-Glucose concentration at time (t)

The percent reduction in blood glucose levels observed from gliclazide and its microcapsules were compared.

RESULTS AND DISCUSSION

Microcapsules of gliclazide were formulated with a view to minimize the variability in absorption attributed by the poor solubility of gliclazide and to sustain the drug release. To study the influence of curing time on entrapment efficiency and drug release rate, the microcapsules formulated by employing a curing time of 12, 24, 36, 48, 60, and 72 hr were evaluated for entrapment efficiency and subjected to drug release studies.

The entrapment efficiency observed from such microcapsules is showed in Table 2. The microencapsulation efficiency was not influenced by the curing time up to 48 hrs and then the efficiency was decreased. It may be due to possible leaching of drug from the microcapsules (low entrapment efficiency). The drug release profiles observed from these microcapsules is showed in Figure 1. The drug release was influenced by curing time and reduction in release rate was noticed with increased curing time. It may be due to the possible incomplete conversion of sodium alginate to calcium alginate and inadequate deposition of calcium alginate over the gliclazide. So a curing time of 24 hrs was found to be optimum to achieve good entrapment efficiency as well as desired sustained release. The same procedure was carried out to study the influence of curing time on entrapment efficiency and drug release rate in presence of stirring rate (400 rpm). The entrapment efficiency observed from these microcapsules collected from the curing reagent at different curing times is showed in Table 2. The microencapsulation efficiency is not influenced by the curing time up to 48 hrs; later the efficiency was decreased. The drug release profiles observed from these microcapsules is showed in Figure 2. A curing time of 48 hrs exhibited better entrapment and desired sustained release. So, a curing time of 48 hrs was selected.

To investigate the influence of stirring observed during the dispersion of polymer dispersion in curing reagent solution on the encapsulation efficiency and drug release rate different rates of agitation was maintained (200, 400, 600, and 800 rpm) and other process variables kept constant. The encapsulation efficiency of the prepared microcapsules is showed in Table 2. The microencapsulation efficiency was not affected by stirring speed up to 400 rpm however beyond that rpm entrapment efficiency was reduced. The drug release profiles observed from these microcapsules is showed in Figure 3. Sustained drug release rate was noticed from the microcapsules formulated by maintaining a stirring speed of 400 rpm and then the drug release rate was increased. It may be due to vortex formation at high agitation rates which was resulted in improper shape of the microcapsules and hence influenced the encapsulation efficiency and drug release rate. The microcapsules formulated by employing stirring speed of 400 rpm yielded an entrapment efficiency of 72.711 and the drug release was extended up to 11 hrs. Hence, 400 rpm was selected as an optimum stirring speed.

To study the effect of stirring time on entrapment efficiency and drug release rate, so microcapsules were formulated by maintaining 400 rpm of agitation while transferring the polymer

Table 2: Entrapment efficiency observed from the gliclazide mucoadhesive microcapsules formulated by employing various process variables

Formulation	Drug content (mg)		Encapsulation efficiency (%)
	Theoretical	Practical	
F_1	30	29.416	98.052
F_2	30	28.839	96.131
F_3	30	26.536	88.452
F_4	30	25.384	84.613
F_5	30	26.305	87.685
F_6	30	16.400	54.666
F_7	30	24.002	80.006
F_8	30	17.552	58.506
F_9	30	19.894	63.113
F_{10}	30	21.813	72.711
F_{11}	30	16.745	55.818
F_{12}	30	15.433	51.442
F_{13}	30	22.277	74.256
F_{14}	30	17.905	59.682
F_{15}	30	16.540	55.132
F_{16}	30	26.996	89.988
F_{17}	30	21.880	72.933
F_{18}	30	21.467	71.556
F_{19}	30	20.817	69.389
F_{20}	30	19.625	65.417
F_{21}	30	17.39	57.967
F_{22}	30	21.950	73.165
F_{23}	30	21.398	71.325
F_{24}	30	15.47	51.567

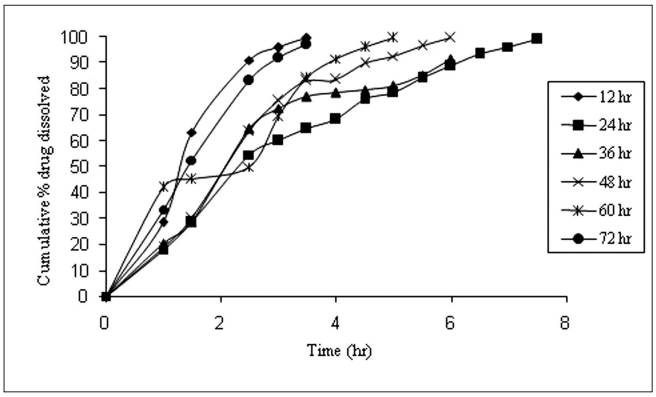

Figure 1: Comparative *in vitro* drug release profiles of gliclazide microcapsules formulated by employing calcium chloride as curing reagent and allowing for curing at different time intervals

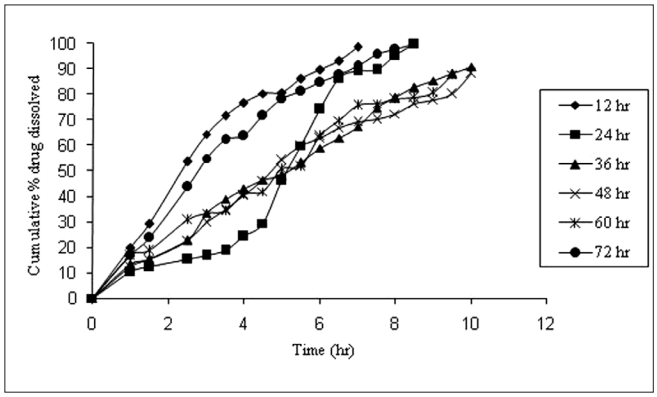

Figure 2: Comparative *in vitro* drug release profiles of gliclazide microcapsules formulated by maintaining at 400 rpm for 30 min and allowing for curing at different time intervals

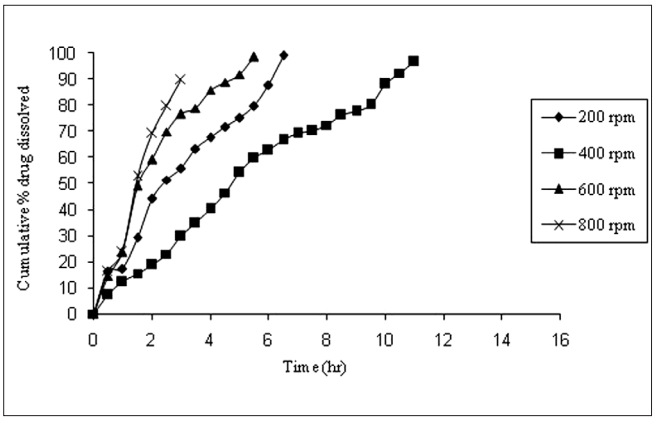

Figure 3: Comparative *in vitro* drug release profiles of gliclazide microcapsules formulated with different revolutions during agitation

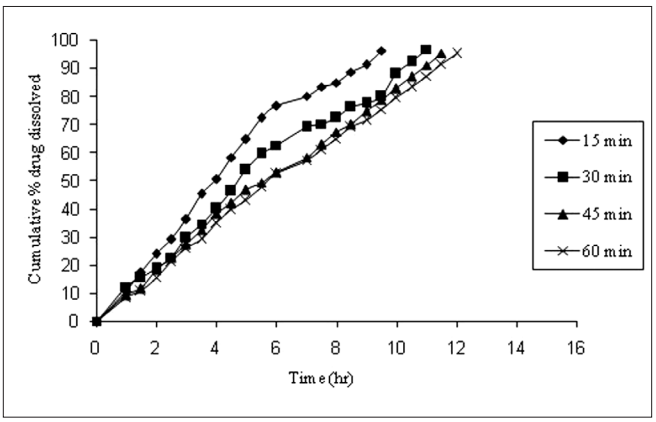

Figure 4: Comparative *in vitro* drug release profiles of gliclazide microcapsules formulated with various stirring times after the addition of dispersion in to calcium chloride solution

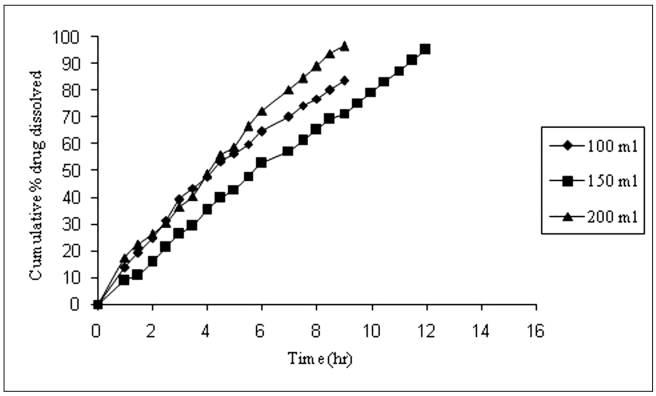

Figure 5: Comparative *in vitro* drug release profiles of gliclazide microcapsules formulated with different volumes of curing reagent

dispersion in to the curing reagent solution and maintained different time periods (15, 30, 45, and 60 min) and then the contents were kept aside for 48 hrs. The microencapsulation efficiency observed from these microcapsules is showed in Table 2. The microencapsulation efficiency was not affected by the stirring time. The drug release profiles observed from these microcapsules is showed in Figure 4. The desired drug release rate and good entrapment efficiency (71.556) were observed from the microcapsules prepared by employing stirring time of 60 min. So, 60 min stirring time was selected as an optimum stirring time.

To study the influence of the volume of curing reagent on entrapment efficiency and drug release rate the microcapsules were formulated by employing different volumes (100, 150, and 200 ml) of the curing reagent (0.1 M calcium chloride) solution. The entrapment efficiency observed from the formulated microcapsules is showed in Table 2. The entrapment efficiency was found to be increased with increase in the volume of calcium chloride up to 150 ml and then entrapment efficiency was decreased. The drug release profiles observed from these microcapsules is showed in Figure 5. The reduction in entrapment efficiency may due to leaching of the drug in larger volumes of the curing solution. The gliclazide microcapsules formulated by employing 150 ml as the volume of curing reagent were showed good entrapment efficiency and desired drug release rate. Hence, 150 ml of curing reagent was recommended.

To study the effect of concentration of curing reagent, the microcapsules were formulated by employing the various concentrations (0.05, 0.08, 0.1, and 0.12 M) of curing reagent by maintaining the remaining process variables at their optimum values. The entrapment efficiency observed from the formulated microcapsules is showed in Table 2. The microencapsulation efficiency was dependent on the concentration of the curing reagent and entrapment efficiency was found to be high in the microcapsules formulated with 0.08−0.12 M of calcium chloride solution. The drug release profiles observed from these microcapsules is showed in Figure 6. The gliclazide microcapsules formulated by employing 0.1 M concentration yielded good entrapment efficiency 71.556 and desired drug release rate. So, 0.1 M concentration of calcium chloride was selected as optimum concentration.

The drug release from the all formulations followed zero order kinetics and the mechanism of drug release was found to be non-fickian diffusion [Table 3].

The optimized microcapsules were evaluated for various micromeretic properties like bulk density, tapped density, carr's index, and hausner's ratio; results are shown in Table 4. From the observed data the microcapsules has shown good flow properties as they are having carr's index 7.647 and hausner's ratio 1.076. The percentage moisture content and percent loss on drying were also studied and results are mentioned in Table 4. The results indicated that the microcapsules had lower % of loss on drying (8.662), which indicated that the microcapsules are free from hygroscopic nature. The wall thickness of the microcapsules was measured and noted as 157.14 μm. The microcapsules also subjected for swelling and erosion studies in phosphate buffer pH 7.4 and results are showed in Figure 7. The results indicated that

the % swelling and erosion of the drug from the microcapsules were dependent on time. The extent of swelling was more up to 2.5 hr and then it was decreased. The microcapsules were also subjected to adhesive strength by employing *in vitro* wash off test. This test was conducted in 0.1 N HCl and phosphate buffer pH 7.4. The data is represented in Figure 8. Higher mucoadhesive strength was detected in 0.1 N HCl compared to phosphate buffer pH 7.4.

To study the effect of gliclazide and its microcapsules (1.4 mg/kg) on the blood glucose levels in fasted albino rabbits, the blood glucose levels were measured. From the blood glucose levels, the percent reduction in blood glucose levels were calculated and shown in Figure 9. The maximum percent reduction of blood glucose was observed at 3rd hour for pure drug, however in case of formulation the same effect was observed at 4th hour and extended up to 10th hour. The % reduction in blood glucose levels observed at 3rd and 12th hour were subjected to *t*-test and very significant differences ($p < 0.001$) were noticed. The microcapsules of gliclazide are more effective compared to gliclazide for reduction of blood glucose levels and they can be recommended for once a day administration.

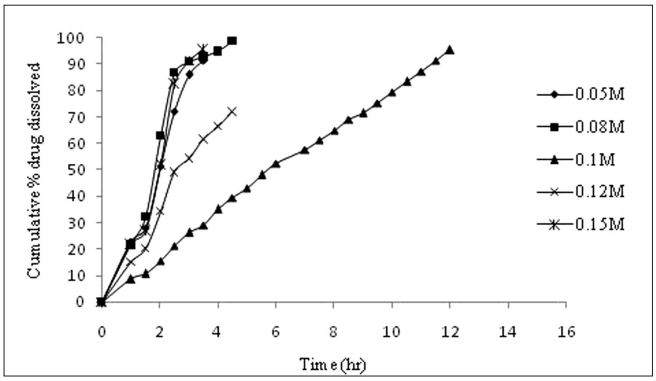

Figure 6: Comparative *in vitro* drug release profiles of gliclazide microcapsules formulated with various concentrations of curing reagent

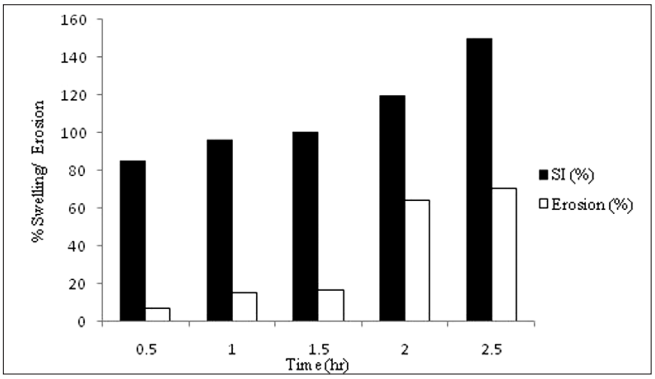

Figure 7: Percentage swelling and erosion of gliclazide microcapsules in phosphate buffer pH 7.4

Table 3: *In vitro* drug release kinetics of gliclazide microcapsules formulated by employing various process variables.

Formulation	Correlation coefficient				Release kinetics			Exponential coefficient (n)
	Zero order	First order	Higuchi	Peppas	K mg/hr	T_{50}	T_{90}	
F_1	0.9584	0.8972	0.9555	0.9576	9.9686	1.5	2.7	0.8306
F_2	0.9526	0.8998	0.9767	0.9820	4.5732	3.3	5.9	0.7363
F_3	0.9310	0.9800	0.9549	0.9760	5.3642	2.8	5.0	0.8900
F_4	0.9581	0.9116	0.9562	0.9838	5.8199	2.6	4.6	0.9427
F_5	0.9556	0.8396	0.9714	0.9465	6.6303	2.3	4.1	0.6052
F_6	0.9864	0.9510	0.9716	0.9911	9.1259	1.6	3.0	0.8677
F_7	0.9488	0.9282	0.9705	0.9854	4.8560	3.1	5.6	0.7721
F_8	0.9414	0.7697	0.8007	0.9418	3.3061	4.5	8.2	1.2627
F_9	0.9805	0.9514	0.9640	0.9916	3.024	5.0	8.9	0.7244
F_{10}	0.9847	0.9750	0.9507	0.9949	2.8002	5.4	9.6	0.8761
F_{11}	0.9822	0.9631	0.9489	0.9740	2.9497	5.1	9.2	0.6901
F_{12}	0.9598	0.8608	0.9729	0.9906	4.0872	3.7	6.6	0.8201
F_{13}	0.9696	0.7973	0.9683	0.9802	4.7675	3.1	5.7	0.7541
F_{14}	0.9283	0.9244	0.9742	0.9728	6.2853	2.4	4.3	0.8072
F_{15}	0.9892	0.9594	0.9313	0.9789	9.4504	1.6	2.9	1.0363
F_{16}	0.9797	0.9735	0.9412	0.9916	3.4134	4.4	7.9	0.9765
F_{17}	0.9949	0.9852	0.9360	0.9959	2.5785	5.8	10.5	0.9715
F_{18}	0.9645	0.8641	0.8670	0.9544	2.4836	6.4	11.5	0.7605
F_{19}	0.9681	0.9662	0.9731	0.99250	2.8780	5.2	9.4	0.7454
F_{20}	0.9862	0.8480	0.9540	0.9833	3.340	4.5	8.1	0.7349
F_{21}	0.9877	0.9574	0.9458	0.9710	9.897	1.5	2.7	0.8618
F_{22}	0.9528	0.9483	0.9258	0.9719	7.7450	1.9	3.5	1.0207
F_{23}	0.9900	0.9831	0.9283	0.9825	5.0909	2.9	5.3	0.9661
F_{24}	0.9801	0.9430	0.9297	0.9643	10.484	1.4	2.6	0.9413

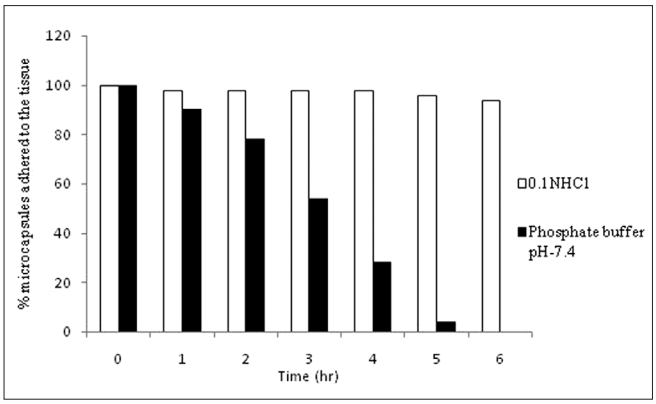

Figure 8: *In vitro* wash off test data of gliclazide mucoadhesive microcapsules in 0.1 N HCl and Phosphate buffer pH 7.4

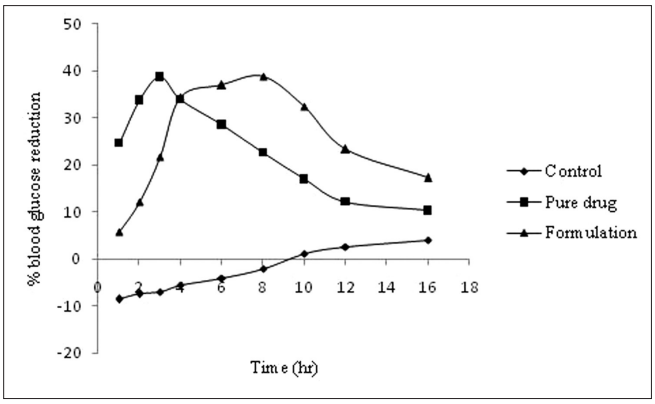

Figure 9: Comparative % blood glucose reduction profiles observed from control, pure drug, and microcapsules of gliclazide

Table 4: Characterization of the gliclazide microcapsules

Parameter	Result
Bulk density (g/ml)	0.693
Tapped density (g/ml)	0.746
Carr's index (%)	7.647
Hausner's ratio	1.076
Wall thickness (µm)	157.14
Moisture content (%)	9.484
Loss on drying (%)	8.662

CONCLUSION

Gliclazide mucoadhesive microcapsules were formulated with a view to release gliclazide at a uniform rate for extended period of time and to confirm the absence of dose dumping. To meet this objective, the microcapsules were formulated by varying the processing conditions. The *in vitro* studies demonstrated that the microcapsules formulated with 0.6% w/v sodium alginate as coating polymer, 150 ml of 0.1 M aqueous calcium chloride solution as curing reagent offered required release rates. The stirring speed of 400 rpm for 60 minutes was required for the effective dispersion of mucilage containing the drug and polymer in the calcium chloride solution. It was also observed that, a curing time of 48 hours was necessary to complete the curing reaction between sodium alginate and calcium chloride. The optimized mucoadhesive microcapsules exhibited good flow properties, mucoadhesive potential, better entrapment efficiency, and the desired release characteristics. Based on the results obtained from *in vitro* studies, the formulation was further subjected for the evaluation of its *in vivo* effectiveness in rabbit model. The formulation was found to exhibit better extension of the hypoglycemic activity, for a period of 10 hours when compared to pure gliclazide. The mucoadhesive microcapsules of gliclazide were found to be more suitable in sustaining the hypoglycemic activity. Thus, this study concludes that the performance of the microcapsules can be altered by changing the processing variables involved in the production of microcapsules.

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