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PREPARATION AND *IN VITRO AND IN VIVO* PHARMACODYNAMIC EVALUATION OF GLICLAZIDE MICROPARTICLES USING STARCH ACETATE AND CHITOSAN

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ABSTRACT

Recently much emphasis is being laid on the development of microparticles because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying. The objective of the present study is to prepare gliclazide microparticles using starch acetate (a new modified starch) and Chitosan (a mucoadhesive polymer) and to evaluate the resulting microparticles by in vitro and in vivo Pharmacodynamic methods. A comparative evaluation of the two types of microparticles was made. An emulsification-solvent evaporation method was used to prepare starch acetate microparticles. A new method namely emulsification-desolvation-crosslinking method was used for the preparation of chitosan. Spherical, discrete and free flowing microparticles of gliclazide could be prepared by emulsification-solvent evaporation method with starch acetate and by emulsification -desolvation -crosslinking method with Chitosan. The methods are reproducible with regard to size and size distribution, drug content and encapsulation efficiency of the microparticles. Gliclazide release from the microparticles was slow and spread over longer periods of time and the drug release was depended on the polymer used and proportion of core: coat ratio. Good linear relationships were observed between percent coat and release rate (K_o) with both the polymers indicating their rate controlling effect. Chitosan microparticles gave relatively slow release of gliclazide than starch acetate microparticles. Gliclazide release from the microparticles prepared was by diffusion

controlled mechanism. Non Fickian (anomalous) diffusion was the release mechanism in the case of all starch acetate microparticles and Chitosan microparticles CHF3 and CHF4. In the case of CHF1 and CHF2 the release was by Fickian diffusion. In the *in vivo* Pharmacodynamic evaluation gliclazide gave a rapid reduction in serum glucose levels, 55.3% at 1.0 h, and the glucose levels recovered rapidly to the normal level within 6-8 h. In the case of microparticles, the reduction in glucose levels was slower and the reduced blood glucose levels were sustained over longer periods of time. A significant hypoglycemic effect was maintained during the period from 0.5 h to 4 h in the case of gliclazide pure drug. Whereas the hypoglycemic effect was maintained during 0.5 h to 5.0 h in the case of SAF2 and from 2 h to 12 h in the case of CHF3 microparticles. Chitosan microparticles exhibited hypoglycemic effect over longer periods of time than starch acetate microparticles. The hypoglycemic effect of gliclazide could be sustained over 12 h with CHF3 microparticles.

KEYWORDS: Gliclazide, Starch Acetate, Chitosan, Microparticles, Pharmacodynamic study.

INTRODUCTION

The design of microparticulate drug delivery systems (Microparticles) is an efficient technique to provide the sustained and controlled delivery of drugs over long periods of time. Microparticulate drug delivery systems[1] consist of small particles of solids or small droplets of liquids surrounded by walls of natural and synthetic polymer films of varying thickness and degree of permeability acting as a release rate controlling substance and have a diameter up to the range of 0.1µm-200µm**.** Microparticulate dosage forms[2] are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into capsules, encapsulated or compressed into a tablet. Microparticulate drug delivery systems contain discrete particles that make up a multiple-unit system. They provide many advantages over single-unit systems because of their small size. Multiparticulates are less dependent on gastric empty time, resulting in less inter and intra-subject variability in gastrointestinal transit time. They are also better distributed and less likely to cause local irritation.[3] They offer several benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying.[4]

Design of microparticulate drug delivery systems requires a suitable polymer to serve the intended purpose. Though several polymers such as cellulose nitrate, cellulose acetate, ethyl

cellulose, polymethyl methacrylate, Eudragits and chitosan have been used in the design of microparticulate drug delivery systems[5,6] there is a continued need to investigate newer polymers for microparticles for controlled release. In the present study starch acetate (a new modified starch) and Chitosan (a mucoadhesive polymer) were investigated for the preparation of microparticles of gliclazide for oral controlled release. Starch acetate is reported[7,8] to have excellent bond forming ability and suitable for coating and controlled release applications. Chitosan (poly (b-(1-4)-2-amino-2-deoxy-d-glucose)) is a mucoadhesive, biocompatible and non-toxic polymer widely studied[9,10] for various pharmaceutical purposes.

The objective of the present study is to prepare and to evaluate microparticles of gliclazide using starch acetate and Chitosan for oral controlled release. The microparticles prepared were evaluated for *in vitro* drug release and *invivo* hypoglycemic effect in comparison to gliclazide pure drug. Gliclazide is a potential second generation, short-acting sulfonylurea oral hypoglycemic agent widely used for the treatment of non-insulin-dependent diabetes mellitus.[11] The dose of Gliclazide is 40-80mg as conventional tablets and 60mg as sustained release tablets. The conventional tablets are to be taken 2-3 times a day to maintain normal plasma glucose levels. Sustained release formulations offer better patient complains by reducing the frequency of dosage administrations and also provide continuous effect.

MATERIALS AND METHODS

Materials: Gliclazide was a gift sample from M/s Micro Labs, Pondicherry. Chitosan, 75-85 percent deacetylated was obtained from Central Institute of Fisheries Technology, Cochin, India. . Starch acetate with a percent acetylation of 28.38 % and a degree of substitution (DS) of 2.75 was prepared in the laboratory as per the method described earlier.[12] Sodium tri polyphosphate (Sigma), Acetic acid (Qualigens), Chloroform (Qualigens) and Soyabean oil were used. All other materials used were of pharmacopoeial grade.

METHODS

Estimation of Gliclazide: An UV Spectrophotometric method based on the measurement of absorbance at 227 nm in phosphate buffer of pH 7.4 was used for the estimation of gliclazide. The method was validated for linearity, accuracy, precision and interference by the excipients. The method obeyed Beer's law in the concentration range of 1 – 10 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of

variance (RSD) were found to be 0.80% and 1.2% respectively. No interference by the excipients used in the study was observed.

Preparation of Starch Acetate-Gliclazide Microparticles: An emulsification solvent evaporation method was used for preparation of starch acetate- gliclazide microparticles (12). Starch acetate (0.2 g) was dissolved in chloroform (10mL) to form a homogeneous solution. Core material, gliclazide (0.8 g) was added to the polymer (starch acetate) solution (5 ml) and mixed thoroughly. The resulting mixture was then added in a thin stream to 200 ml of an aqueous mucilage of sodium CMC (0.5 % w/v) contained in a 450 ml beaker while stirring at 1000 rpm to emulsify the added dispersion as fine droplets. A Remi medium duty stirrer with speed meter (model RQT 124) was used for stirring. The solvent, chloroform was then removed by continuous stirring at room temperature (28 ºC) for 3 h to produce spherical microparticles. The microparticles were collected by vacuum filtration and washed repeatedly with water. The product was then air dried to obtain discrete microparticles. Different proportions of core:coat namely 9:1 (SAF1), 8:2 (SAF2), 7:3 (SAF3) and 6:4 (SAF4) were used to prepare microparticles with varying amount of coat polymer.

Preparation of Chitosan--Gliclazide Microparticles: An emulsification -desolvation - crosslinking method[13] was tried for the preparation of chitosan-gliclazide microparticles. Chitosan solution (2%w/v) was prepared by dissolving 2g of chitosan in 100 ml of 1% v/v acetic acid solution by sonication for 30 minutes to form a homogeneous solution. Core material, gliclazide (0.8 g) was added to 10 ml of polymer (chitosan) solution, which contain 0.2 g of chitosan and dispersed thoroughly. This provides a core: coat ratio of 8:2. The chitosan - drug dispersion was added in a thin stream to 300 ml of Soyabean oil containing 10 percent chloroform taken in a 600 ml beaker while stirring at 1000 rpm to emulsify the added dispersion as fine droplets. A Remi medium duty stirrer with speed meter (Model RQT 124) was used for stirring. Stirring was continued for 20 minutes to remove acetic acid from polymer solution into chloroform (desolvation) and to form chitosan-gliclazide microparticles. Tripolyphosphate solution (5 % w/w, pH 5.0) containing 1 %glutaraldehyde (100 ml) was added while stirring as crosslinking agent. Stirring was continued for 30 minutes for crosslinking and hardening of the chitosan microparticles formed. The rigid microparticles formed were collected by decantation and washed repeatedly with petroleum ether to remove the adhering oil. The product was then air dried to obtain discrete microparticles of chitosan - gliclazide. Different proportions of core: coat namely 19:1

(CHF1), 9:1 (CHF2), 8:2 (CHF3) and 7:3 (CHF4) were used to prepare microparticles with varying amount of coat polymer.

Estimation of Drug Content and Encapsulation Efficiency: Four samples of 100mg each were taken from each batch of microparticles prepared and assayed for gliclazide content at 227nm .Encapsulation efficiency was estimated using the equation, Encapsulation efficiency (%)==[Estimated drug content,%/Theoretical drug content%]X100.

Size Analysis: For the size distribution analysis, different fractions in a batch were separated by sieving using a range of standard sieves. The amounts retained on different sieves were weighed.

Drug Release Study: Release of gliclazide from the microparticles of size 35/50 mesh was studied in phosphate buffer of pH 7.4 (900 ml) using an 8 station dissolution rate test apparatus (model Disso-2000, M/s Lab. India) with a paddle stirrer (Apparatus 2) at 50 rpm. A temperature of 37º ± 1 ºC was maintained throughout the experiment. A sample of microparticles equivalent to 60 mg of gliclazide was used in each test. Samples (5 ml) were withdrawn through a filter (0.45 µ) at different time intervals over 12 h and were assayed at 227nm for gliclazide content. The sample (5 ml) taken at each sampling time was replaced with drug free dissolution fluid and a suitable correction was applied for the amount of drug lost in sampling for the estimation of amount of drug released at various times. Each drug release experiment was conducted in triplicate (n=3).

Analysis of Release Data: Drug release data were analyzed as per zero order, first order, Higuchi[14] equation and Korsmeyer-Peppas[15] equation models to assess the release kinetics and mechanism.

***In Vivo* Pharmacodynamic Evaluation:** Pharmacodynamic evaluation studies were conducted on (i) gliclazide, (ii) Starch acetate microparticles (F2) and (iii) Chitosan microparticles F3 in normal, healthy rabbits by measuring serum glucose levels following their oral administration at a dose equivalent to 3 mg/kg of gliclazide. The dose for experimental rabbits was calculated as suggested by Bikash Medhi and Ajay Prakash.[16] The experiments were conducted as per a crossover randomized block design (n = 6). *In vivo* study protocols were approved by Institutional Animal Ethics Committee (No. CPCSEA/CH/ORG/2015-051). The products were administered orally in the morning

following overnight fasting. No food or liquid other than water was given during the experimental period. After the zero-hour blood sample was collected, the product in the study was administered orally. Blood samples (0.5 mL) were collected from marginal ear vein at 0.5,1,2,3,4,6,8,10,12,16,20,24 hours after administration. Serum glucose concentrations were determined by a known oxidase-peroxidase method[17] as described below employing a glucose kit supplied by Dr Reddy's Laboratory, Diagnostic Division (Hyderabad, India). The method was revalidated, and the relative standard deviation in the estimated values was found to be 1.2%.

Blood samples collected were allowed to clot without any anticoagulant and were centrifuged immediately at 5000 rpm for 20 minutes to separate the serum. To the serum (0.02 mL) and standard (0.02 mL) in separate clean, dry test tubes, enzyme reagent (2 mL) was added, mixed well, and incubated at 37°C for 10 minutes. The solutions were diluted to 5 mL with distilled water, and the absorbance of the pink-colored solutions was measured in a spectrophotometer at 510 nm using a reagent blank. Serum glucose levels (mg/dL) and percentage reduction in serum glucose levels were calculated.

RESULTS AND DISCUSSION

The objective of the study is prepare and evaluate microparticulate DDS in the form of microparticles of gliclazide for oral controlled release. Two different types of polymers namely starch acetate (a new modified starch) and Chitosan (a mucoadhesive polymer) were used for the preparation of gliclazide microparticles. Methods based on emulsification and solvent removal were used for the preparation of microparticles with both the polymers. In each cases different ratios of polymer: drug namely 19:1, 9:1, 8:2, 6:4 were used to prepare microparticles with different amounts of coat material. A comparative evaluation of the two types of microparticles was made by *in-vitro* and *in-vivo* methods.

Emulsification -solvent evaporation method used gave spherical, discrete, and free flowing microparticles with both the polymers. The physical characteristics of the gliclazide microparticles prepared are given in table 1.Size analysis indicated that about 65-70% of the microparticles are in the size range 35/50 mesh (398.5µm**)** in all the cases.

Gliclazide content of the microparticles was within 2% of the labeled (theoretical) content and the encapsulation efficiency was in the range of 96.0-99.3 in the case of starch acetate and 97.1 -99.5 % in the case of Chitosan microparticles. The result of the three batches of microparticles prepared under identical condition in each case indicated that the

emulsification and solvent removal method used were reproducible with regard to size and size distribution and drug content.

The methods used were also industrially feasible as it involves emulsification as a critical step, which can be precisely controlled.

Gliclazide release from the various microparticles of size 35/50 was studied in phosphate buffer pH 7.4. The drug release profiles are shown in Fig.1.The release data were analyzed as per Zero order, First order, Higuchi[14] equation and Korsmeyer-Peppas[15] equation models to assess the release kinetics and mechanism. Kinetic parameters (r^2 values, rate constants and n values) in the analysis of release data as per various kinetic models are given in Table 2.

Gliclazide release from all the microparticles prepared was slow and spread over longer periods of time and depended on the polymer used and core:coat ratio in each case.

Table 1: Physical Characteristics of the Microparticles Prepared.

DDS	Mesh Size	Mean size (µm)	Core:Coat ratio	Gliclazide content (%) ($\bar{x}$±sd)	Encapsu Lation efficiency (%)	Percent Coat Polymer
SAF1	20/35	670	9:1	87.2±1.6	96.9	12.8
	35/50	398.5	9:1	86.4±1.4	96.0	13.6
SAF2	20/35	670	8:2	79.2±1.2	993	20.8
	35/50	398.5	8:2	78.6±1.4	98.3	21.4
SAF3	20/35	670	7:3	69.5±1.3	99.3	30.5
	35/50	398.5	7:3	68.4±1.4	97.7	31.6
SAF4	20/35	670	6:4	58.2±1.2	97.0	41.8
	35/50	398.5	6:4	58.4±1.1	97.3	41.6
CHF1	20/35	670	19:1	94.2±1.2	99.0	5.8
	35/50	398.5	19:1	94.6±1.8	99.5	5.4
CHF2	20/35	670	9:1	87.4±1.3	97.1	12.6
	35/50	398.5	9:1	87.6±1.1	97.3	12.4
CHF3	20/35	670	8:2	79.2±1.9	99.0	20.8
	35/50	398.5	8:2	79.4±1.6	99.2	20.6
CHF4	20/35	670	7:3	68.2±1.6	97.4	31.8
	35/50	398.5	7:3	68.6±1.5	98.0	31.4

Table 2: Kinetic Parameters (R^2 Values, Rate Constants and n values) in the Analysis of Release Data as per Various Kinetic Models.

DDS	Zero order		First order		Higuchi	Korsemeyer Peppas	
	K_0	R^2	R^2	K_1	R^2	n	R^2
SAF1	10.8	0.8502	0.9800	0.4604	0.9898	0.454	0.9950
SAF2	7.4	0.9397	0.9300	0.3220	0.9663	0.471	0.9979
SAF3	6.2	0.9522	0.9410	0.1612	0.9195	0.454	0.9886
SAF4	5.6	0.9765	0.9853	0.1150	0.9317	0.542	0.9965
CHF1	11.49	0.6464	0.9855	0.929	0.9003	0.24	0.9929
CHF2	6.94	0.8380	0.9308	0.506	0.9788	0.40	0.9792
CHF3	4.53	0.9703	0.9436	0.230	0.9890	0.64	0.9977
CHF4	3.25	0.9782	0.9793	0.120	0.9825	0.79	0.9881
CHCP	5.09	0.9602	0.9492	0.262	0.9691	1.00	0.9725

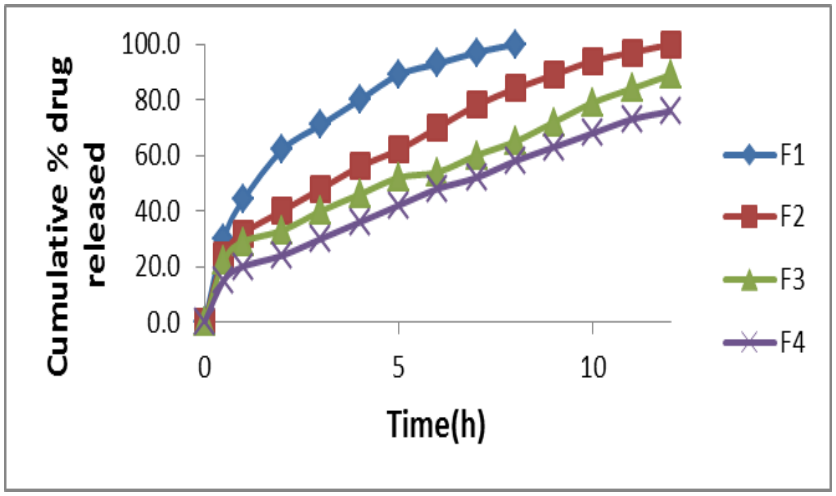

Fig. 1: Gliclazide Release Profiles of Various Starch Acetate Microparticles (F1=SAF1, F2=SAF2, F3=SAF3, F4=SAF4).

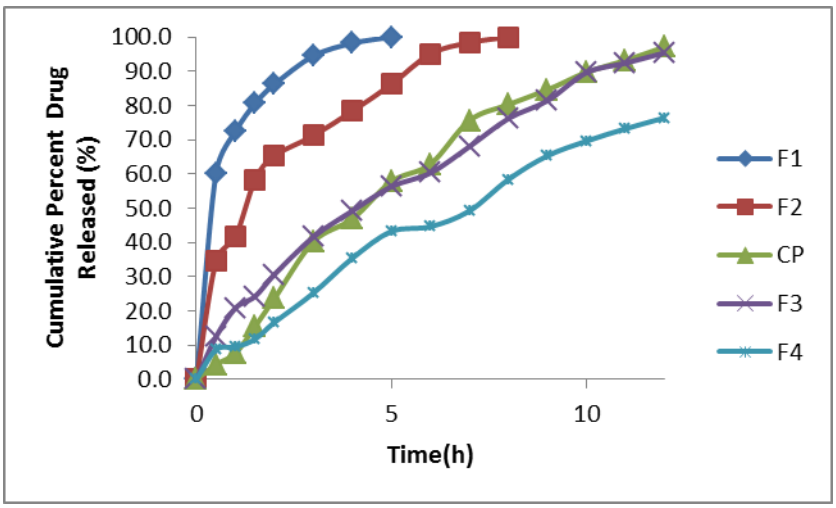

Fig. 2: Gliclazide Release Profiles of Various Chitosan Microparticles (F1=CHF1, F2=CHF2, F3=CHF3, F4=CHF4, CP=Commercial Product).

As the coat proportion was increased the release rate was decreased with both the polymers. Good linear relationships between percent coat and release rate (K_o) was observed in each case. The relationships could be expressed by the linear equation, y = 12.18-0.173x in the case of starch acetate and y =11.849-0.3035x in the case of Chitosan where x is percent coat and y is release rate (K_o).

Chitosan microparticles gave relatively slow release of gliclazide than starch acetate microparticles and as such were found more suitable for controlled release application. A comparison of R^2 values in various models revealed that the R^2 value was higher in the case of Korsemeyer Peppas equation model in all the cases. As such the release data of all the microparticles tested obeyed Korsemeyer Peppas equation model which indicates that the drug release from the microparticles was by diffusion mechanism. The release exponent (n) in Korsemeyer Peppas equation model was in the range 0.454-0.79 in the case of all SA microparticles and Chitosan microparticles, CHF3, CHF4 indicating that the drug release from these microparticles was by non- Fickian (anomalous) diffusion. The release exponent (n) was 0.24 and 0.40 in the case of Chitosan microparticles CHF1 and CHF2 respectively indicating that the drug release from these microparticles was by Fickian diffusion mechanism. In the case of commercial product the release exponent (n) was found to be 1.00 indicating that the drug release from the commercial SR tablets was by zero order diffusion mechanism.

Pharmacodynamic Evaluation: *In vivo* Pharmacodynamic evaluation of selected microparticles(SAF2 and CHF3) was carried out in healthy, normal rabbits by measuring the hypoglycemic effect produced after their oral administration at a dose equivalent to 3 mg/kg of gliclazide, in comparison to gliclazide (pure drug) at the same dose. The serum glucose levels estimated and the percentage reduction in glucose levels following the oral administration of gliclazide pure drug and its microparticles are given in Table 4. When gliclazide was administered, a rapid reduction in serum glucose levels was observed; a maximum reduction of 55.3% was observed at 1.0 h after administration, and the glucose levels recovered rapidly to the normal level within 6-8 h. In the case of microparticles, the reduction in glucose levels was slower and it reached a maximum of 37.7% and 35.0% in the case of SAF2 and CHF3 respectively at 3 h after their administration. The reduction in blood glucose levels was sustained over longer periods of time in the case of microparticles.

A 25% reduction in glucose levels is considered as a significant hypoglycemic effect[18]. The hypoglycemic effect was maintained during the period from 0.5 h to 4 h following the administration of gliclazide pure drug. Whereas the hypoglycemic effect was maintained during 0.5 h to 5.0 h in the case of SAF2 and from 2 h to 12 h in the case of CHF3 microparticles. The sustained hypoglycemic effect observed over longer periods of time in the case of microparticles is due to the slow release and absorption of gliclazide over longer periods of time. Chitosan microparticles exhibited hypoglycemic effect over longer periods of time then starch acetate microparticles. The hypoglycemic effect of gliclazide could be sustained over 12 h with CHF3 microparticles.

Table 3: Serum Glucose Levels (mg/dl) Observed Following The Oral Administration Of Gliclazide Pure Drug And Its Starch Acetate and Chitosan Microparticles.

Time (h)	Serum Glucose Levels (mg/dl) (Percentage Glucose Reduction)		
	Gliclazide ($\bar{x}$±sd)	SAF2 ($\bar{x}$±sd)	CHF3 ($\bar{x}$±sd)
0	99.5±4.2 (0)	99.6±3.2(0)	99.8±3.6 (0)
0.5	58.4±2.5 (41.3)*	71.6±2.9(28.11)*	84.8±3.2 (15.0)
1	44.4±3.2 (55.3)	64.2±3.1(35.5)	79.2±2.9 (20.6)
2	51.3±2.8 (48.4)	62.9±3.3(36.8)	73.6±3.5(26.2)
3	59.4±3.1 (40.3)	62.0±3.7(37.7)	64.8±3.9 (35.0)
4	73.8±3.8 (25.8)	70.2±4.3(29.5)	66.2±4.1 (33.6)
6	89.6±4.2 (9.9)	79.4±3.1(20.3)	68.4±3.2 (31.4)
8	92.6±4.6 (6.9)	84.6±3.9(15.06)	69.6±3.8(30.2)
10	94.2±3.7 (5.3)	88.2±2.6(11.4)	71.1±2.9 (28.7)
12	95.4±4.1 (4.1)	95.2±4.1(4.41)	72.8±4.2 (27.0)
16	97.2±3.9 (2.3)	98.3±4.3(1.3)	84.9±4.6 (14.9)
20	98.1±3.6 (1.4)		87.8±3.9 (12.0)
24	98.4±4.2 (1.1)		91.5±4.6 (8.3)

* *Figures in parentheses are Percentage Glucose Reduction values.*

CONCLUSIONS

1. Spherical, discrete and free flowing microparticles of gliclazide could be prepared by emulsification-solvent evaporation method with starch acetate and by emulsification - desolvation -crosslinking method with Chitosan. The methods are reproducible with regard to size and size distribution, drug content and encapsulation efficiency of the microparticles.
2. Gliclazide release from the microparticles was slow and spread over longer periods of time and the drug release was depended on the polymer used and proportion of core: coat ratio.
3. Good linear relationships were observed between percent coat and release rate (K_o) with both the polymers indicating their rate controlling effect.

4. Chitosan microparticles gave relatively slow release of gliclazide than starch acetate microparticles.

5. Gliclazide release from the microparticles prepared was by diffusion controlled mechanism. Non Fickian (anomalous) diffusion was the release mechanism in the case of all starch acetate microparticles and Chitosan microparticles CHF3 and CHF4. In the case of CHF1 and CHF2 the release was by Fickian diffusion.

6. In the *in vivo* Pharmacodynamic evaluation gliclazide gave a rapid reduction in serum glucose levels, 55.3% at 1.0 h, and the glucose levels recovered rapidly to the normal level within 6-8 h.

7. In the case of microparticles, the reduction in glucose levels was slower and the reduced blood glucose levels were sustained over longer periods of time.

8. A significant hypoglycemic effect was maintained during the period from 0.5 h to 4 h in the case of gliclazide pure drug. Whereas the hypoglycemic effect was maintained during 0.5 h to 5.0 h in the case of SAF2 and from 2 h to 12 h in the case of CHF3 microparticles.

9. Chitosan microparticles exhibited hypoglycemic effect over longer periods of time than starch acetate microparticles. The hypoglycemic effect of gliclazide could be sustained over 12 h with CHF3 microparticles.

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