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PREPARATION AND EVALUATION OF STARCH ACETATE-GLICLAZIDE MICROPARTICULATE DRUG DELIVERY SYSTEMS FOR ORAL CONTROLLED RELEASE: *INVITRO* STUDIES

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Abstract:

Recently much emphasis is being laid on the development of microparticulate DDS in preference to single unit systems 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 and characterize starch acetate and to evaluate its application in the preparation of microparticulate drug delivery systems for oral controlled release of gliclazide. Starch acetate was prepared by acetylation of potato starch with acetic anhydride. The prepared starch acetate was characterized and evaluated.

Starch acetate with a degree of substitution 2.75 could be prepared by acetylation of potato starch with acetic anhydride. The starch acetate prepared was feely soluble in chloroform and insoluble in several aqueous fluids and organic solvents. Chloroform could be used as solvent for starch acetate in the preparation of microparticles, microcapsules and in film coating Spherical starch acetate- Gliclazide microparticles could be prepared by the emulsification-solvent evaporation method. The method is industrially feasible as it involves emulsification and removal of the solvent, which can be controlled precisely. The emulsification solvent evaporation method was reproducible with regard to size and size distribution of the microparticles. About 65-70% of microparticles in each batch were in the size range 35/50 mesh (398.5µm) Encapsulation efficiency was in the range 96.0-99.3 % in the preparation of microparticles.

Gliclazide release from the starch acetate microparticles was slow and spread over longer periods of time. The drug release depended on the proportion of core:coat in the microparticles. A good linear relationship (R^2 = 0.826) between percent coat and release rate (k_o) was observed. The relationship could be expressed by the linear equation, y = 12.18-0.173x where x is percent coat and y is release rate (k_o). Gliclazide release from the starch acetate microparticles was by non fickian (anomalous) diffusion. Formulation F2 prepared using a Core :coat ratio of 8:2 gave slow, controlled and complete release(100%) of Gliclazide over 12 hours. As such formulation F2 is considered as a promising microparticulate DDS for oral control release of Gliclazide over 12 hours for b.i.d administration

Key words: *Multiparticulate drug delivery systems, Starch acetate, Gliclazide, Oral controlled release*

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INTRODUCTION:

The design of microparticulate drug delivery systems is an efficient technique to provide the sustained & 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 & synthetic polymer films of varying thickness & degree of permeability acting as a release rate controlling substance & have a diameter upto 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]. Recently much emphasis is being laid on the development of microparticulate dosage forms in preference to single unit systems because of their potential 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. Several polymers such as benzyl cellulose, cellulose nitrate, cellulose acetate, epoxy resin, ethyl cellulose, polyethylene, polymethyl methacrylate, polystyrene, polyvinyl acetate, Eudragit S-100, chitosan have been used in the design of microparticulate drug delivery systems [5,6]. In the present investigation Starch acetate, a new modified starch was tried for the preparation of microparticulate drug delivery systems of gliclazide for oral controlled release. Modified starches have been used [7,8] for various pharmaceutical purposes such as fillers, superdisintegrants and matrix formers in capsules and tablet formulations. One of the important modification of starch is acetylated starch. Starch acetate is reported [9,10] to have excellent bond forming ability and suitable for coating and controlled release applications. Much of the literature on starch acetate and its industrial applications are patented.

The objective of the present study is to prepare and characterize starch acetate and to evaluate its application in the preparation of microparticulate drug delivery systems for oral controlled release of gliclazide. Gliclazide is a potential second generation, short-acting sulfonylurea oral hypoglycaemic agent widely used for the treatment of non-insulin-dependent diabetes mellitus [11]. In general, rapid gastrointestinal absorption is required for oral hypoglycaemic drugs in order to prevent a sudden increase in blood glucose level after food intake in patients with diabetes mellitus. However, the absorption rate of gliclazide from the gastrointestinal tract is slow and varied among subjects. Slow absorption of a drug usually originates from either poor dissolution of the drug from the formulation or poor permeability of the drug across the gastrointestinal membrane [12] .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. The reported [5,6] methods for the preparation of microparticulate drug delivery systems include emulsion–solvent evaporation (o/w, w/o, w/o/w), phase separation (non solvent addition and solvent partitioning), interfacial polymerization, spray drying, emulsion extraction process, jet milling technique, fluidization & solvent precipitation method, and pan coating. In the present study emulsification-solvent evaporation method [13-20] was tried for the preparation of starch acetate-gliclazide microparticles.

MATERIALS AND METHODS:

Materials:

Gliclazide was a gift sample from M/s Micro Labs Limited, Pondicherry. Potato starch (SD Fine chemicals), acetic anhydride (Qualigens), sodium hydroxide (Qualigens) and chloroform (Qualigens) were procured from commercial sources. 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:
Potato starch (20 parts), acetic anhydride (80 parts) and sodium hydroxide 50 % solution (40 parts) were mixed and refluxed for 5 h at 160 ºC. The reaction mixture was added to cold water to precipitate the starch acetate formed. The product was collected by vacuum filtration, washed repeatedly with water and dried at 80 ºC for 4 h.

Characterization of Starch Acetate:
The prepared starch acetate was characterized by determining the extent of acetylation and degree of substitution and by IR spectra. Solubility characteristics (qualitative) were also tested in various solvents.

Determination of Degree of Substitution:
A powdered starch acetate sample (1.0 g) was placed in a 250 mL flask and 50 mL of 75 % ethanol in distilled water solution were added. The mixture was agitated, warmed to 50 ºC, held at that temperature for 0.5 h and cooled, then 40 mL of 0.5 N potassium hydroxide were added. The mixture was then allowed to stand for 72 h with occasional mixing. The excess alkali was back titrated with standard 0.5 N hydrochloric acid using phenolphthalein as indicator. A blank was titrated in the same way using an original sample of starch. The acetylation level was calculated using the equation, acetylation (%) = [mL (blank) – mL (sample) × normality of acid × 0.043 × 100]/[weight of sample in g (dry basis)]. The degree of substitution was calculated using the equation, degree of substitution = [162 × acetylation %]/[4300 × (42 × acetylation %)].

IR Spectra:
IR spectra were recorded on Perkin-Elmer spectrometer, 1000 Model, using chloroform as solvent.

Preparation of Starch Acetate-Gliclazide Microparticulate DDS:
An emulsification solvent evaporation method was tried for preparation of starch acetate- gliclazide microparticulate DDS. 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 (F1), 8:2 (F2), 7:3 (F3) and 6:4(F4) 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,%/Theoritical 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 20/30 and 30/50 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 through out 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 [21] equation and Korsmeyer-Peppas[22] equation models to asses the release kinetics and mechanism.

RESULTS AND DISCUSSION:

Starch acetate was prepared by acetylation of potato starch with acetic anhydride .Starch acetate prepared was found to be a white crystalline powder. The percent acetylation was 28.38 % and the degree of substitution was 2.75. The IR spectrum of starch acetate showed the acetyl carbonyl stretching at 1749 cm^{-1}, which was absent in the IR spectrum of potato starch, indicating the acetylation of the native starch. The starch acetate prepared was insoluble in water, aqueous buffers of pH 1.2 and 7.4, methanol, petroleum ether, dichloromethane and cyclohexane. It is freely soluble in chloroform. Hence chloroform was used as the solvent for starch acetate in the preparation of microparticulate DDS.

An emulsification - solvent evaporation method was used for the preparation of micropaticles of starch acetate-gliclazide. The method involves emulsification of the polymer (starch acetate) solution in chloroform containing the dispersed drug particles in an immiscible liquid medium (0.5 % w/v solution of sodium CMC) as microdroplets, followed by removal of the solvent, chloroform by continuous stirring to form rigid microparticles. The microparticles were collected by vacuum filtration and washed repeatedly with water. The product was then air dried to obtain discrete microparticles. The microparticles were found to be discrete, spherical and free flowing. The sizes could be separated readily by sieving and a more uniform size range of microparticles could easily be obtained. The sieve analysis of different batches of microparticles prepared indicated that a large proportion,65-70%, in each batch were in the size range of 35/50 mesh(398.5µm).The reproducibility of the method with regard to size distribution of the microparticles was evaluated by preparing three batches of microparticles under identical conditions in each case. Size analysis indicated that about 65-70% of the microparticles are in the size range 35/50 mesh in all the batches. Microparticles of the size (398.5µm) were selected for further evaluation.

The physical characterstics of the microparticulate DDS prepared are given in Table 1.

Table 1: Physical Characterstics of the Microparticulate DDS Prepared

DDS	Mesh Size	Mean size (µm)	Core:Coat ratio	Gliclazide content(%) ($\bar{x}$±sd)	Encapsulation efficiency (%)	Percent Coat Polymer
F1	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
F2	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
F3	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
F4	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

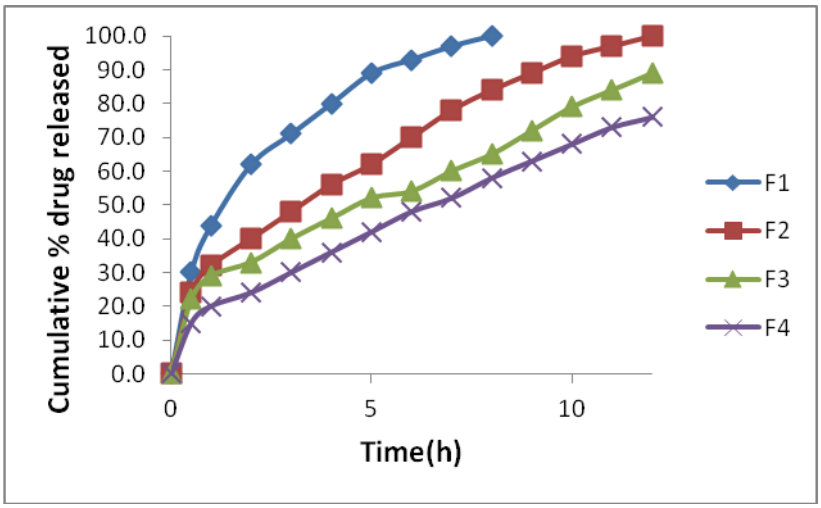

Fig.1: Gliclazide Release Profiles of Various Microparticulate DDS Prepared

Low coefficient of variation (cv) in percent drug content (< 2.0 %) indicated uniformity of drug content in each batch of microparticles. The encapsulation efficiency was in the range 96.0-99.3 %. Drug content of the microparticles was found to be the same in the two sizes, 20/35, 35/50 mesh. A t-test of significance indicated that the difference in the drug content of the two sizes in each case is not significant (P>0.05).

Gliclazide release from the various microparticles of size 3 5/50 was studied in phosphate buffer pH 7.4. The drug release profiles are shown in Fig.1.the release data data were analyzed as per Zero order, First order, Higuchi[21] equation and Korsmeyer-Peppas[22] equation models to asses the release kinetics and mechanism. The 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.

Gliclazize release from all the starch acetae microparticles tested was slow and spred over longer periods of time.The release depended on proportion of core and coat in the microparticles.As the coat proportion was increased the release rate was decresed. A good linear relationship (R^2 = 0.826) between percent coat and release rate (k_o) was observed as shown in Fig2.

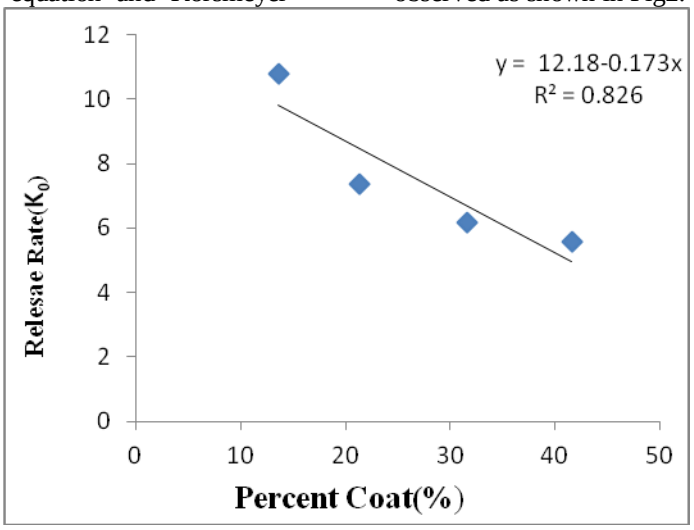

Fig.2: Relationship between Percent Coat and Release Rate (K_0) of Microparticulate DDS (Size 398.5µm)

The relationship could be expressed by the linear equation, y = 12.18-0.173x where x is percent coat and y is release rate (k_o).

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
F1	10.8	0.8502	0.9800	0.4604	0.9898	0.454	0.9950
F2	7.4	0.9397	0.9300	0.3220	0.9663	0.471	0.9979
F3	6.2	0.9522	0.9410	0.1612	0.9195	0.454	0.9886
F4	5.6	0.9765	0.9853	0.1150	0.9317	0.542	0.9965

A comparision of R^2 values in various models revealed that the R^2 value was higher in the case of korsmeyer peppas model in all the cases. As such the release data of all the microparticles tested obeyed korsmeyer peppas equation model which indicates that the drug release from the microparticles was by diffusion mechanism. The release exponent (n) in korsmeyer peppas equation model was in the range 0.454-0.542 in all the cases indicating that the drug release from the microparticles was by non- fickian (anomalous) diffusion.

The results of the present study, thus, indicated that starch acetate- Gliclazide microparticles could be prepared by emulsification solvent evaporation method using chloroform as solvent for starch acetate. These microparticles could be used for oral control release of Gliclazide. Formulation F2 prepared using a Core :coat ratio of 8:2 gave slow, controlled and complete release(100%) of Gliclazide over 12 hours. As such formulation F2 is considered as a promising microparticulate DDS for oral control release of Gliclazide over 12 hours for b.i.d administration.

CONCLUSIONS:

1. Starch acetate with a degree of substitution 2.75 could be prepared by acetylation of potato starch with acetic anhydride.
2. The starch acetate prepared was feely soluble in chloroform and insoluble in several aqueous fluids and organic solvents.
3. Chloroform could be used as solvent for starch acetate in the preparation of microparticles, microcapsules and in film coating
4. Spherical starch acetate- Gliclazide microparticles could be prepared by the emulsification-solvent evaporation method. The method is industrially feasible as it involves emulsification and removal of the solvent, which can be controlled precisely.
5. The emulsification solvent evaporation method was reproducible with regard to size and size distribution of the microparticles. About 65-70% of microparticles in each batch were in the size range 35/50 mesh(398.5µm)
6. Encapsulation efficiency was in the range 96.0-99.3 % in the preparation of microparticles.
7. Gliclazide release from the starch acetate microparticles was slow and spread over longer periods of time. The drug release depended on the proportion of core:coat in the microparticles.
8. A good linear relationship ($R^2 = 0.826$) between percent coat and release rate (k_o) was observed. The relationship could be expressed by the linear equation, $y = 12.18-0.173x$ where x is percent coat and y is release rate (k_o).
9. Gliclazide release from the starch acetate microparticles was by non fickian (anomalous) diffusion.
10. Formulation F2 prepared using a Core :coat ratio of 8:2 gave slow, controlled and complete release(100%) of Gliclazide over 12 hours. As such formulation F2 is considered as a promising microparticulate DDS for oral control release of Gliclazide over 12 hours for b.i.d administration

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