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Title: **Formulation and Evaluation of Controlled Release Drug Delivery System of Microspheres of Anti-Diabetic Drug Using Biodegradable Polymers**

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Abstract:

The purpose of the present investigation was to encapsulate pure gliclazide (GLZ) and GLZ–hydroxypropyl-β-cyclodextrin (HPβCD) complex in cellulose-based matrix microspheres. The system simultaneously exploits complexation technique to enhance the solubility of low-solubility drug (pure GLZ) and subsequent modulation of drug release from microspheres (MC) at a predetermined time. The microspheres of various compositions were prepared by an oil-in-oil emulsion–solvent evaporation method. The effect of complexation and presence of cellulose polymers on entrapment efficiency, particle size, and drug release had been investigated. The in vitro drug release profiles from these microspheres showed the desired biphasic release behavior. After enhancing the solubility of gliclazide by inclusion into HPβCD, the drug release was easily modified in the microsphere formulation. The release kinetics of from gliclazide microspheres followed quasi-Fickian and first-order release mechanisms. Microsphere code (MC6) containing GLZ –HPβCD complex, showed sustained release of drug (94.6%) over a period of 24h.

***Keywords*:** Gliclazide, hydroxypropyl-β-cyclodextrin, complexation, release kinetics, microspheres

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1. Introduction:

Multiple-unit solid dosage forms such as microspheres have gained in popularity as oral drug delivery systems because of more uniform distribution of the drug in the gastrointestinal tract, more uniform drug absorption, reduced local irritation, and elimination of unwanted intestinal retention of polymeric material when compared to non-disintegrating single-unit dosage forms (1–3). Entrapment of medicinal agents within polymeric microspheres is a unique technology which has been utilized by many formulation scientists in the recent past. This technology brightens the possibility of reduction of toxicity, enhancement of control over release activity, and maximization of the bioavailability of both soluble and insoluble drugs. Conventional dosage (oral) form does not usually provide any controlled release or target specificity because of its immediate release. Many shortcomings of the conventional dosage form may be overcome by microspheres technology (4-8). Versatile uses of cyclodextrin have been reported earlier especially as a complexing agent and a drug release modulator (9). Cyclodextrin enhances the solubility of a poorly soluble guest molecule by fitting in lipophilic cavity (10). Recently, substituted cyclodextrins (hydroxypropyl-β-cyclodextrin) have received considerable attention because of their better physiochemical properties than that of the natural counterpart (11). The problem of poor bioavailability and development of toxicity in the use of poorly soluble drug can be overcome by its complexation with substituted cyclodextrin (12).

Gliclazide, 1-(3-azabicyclo (3.3.0) oct-3-yl)-3-p-tolylsulphonylurea is an oral hypoglycemic agent used in the treatment of non-insulin-dependent diabetes mellitus (13). Its plasma half-life is 6–14 h (14). After a single oral dose of 80 mg to 23 subjects, peak plasma concentrations of 0.7– 4.9 mg L^{-1} were attained in about 4 h (15). The release of gliclazide over a 24-h period has been shown to parallel the circadian glycemic profile of type 2 diabetics (16). In spite of the good clinical results of this sustained release formulation, the binding of gliclazide to sulfonylurea receptors on pancreatic β-cells is very rapidly reversible (17).

Thus, in this study an attempt was made to development of matrix type microspheres loaded with Gliclazide–hydroxypropyl-β-cyclodextrin (HPβCD) inclusion complex by solvent evaporation method. The effect of formulation factors and processing conditions were studied by determining microencapsulation efficiency, particle size analysis, and in vitro release studies. Verification of some properties of microsphere formulations such as surface

texture, state change, and interaction between ingredients by instrumental analysis were conducted. Furthermore, the hypoglycermic effect of prepared gliclazide microspheres on the diabetic albino rats was determined.

Materials and Method

Materials

Gliclazide and Hydroxypropyl –β-cyclodextrin (HPβCD) were obtained as a gift sample from Dr. Reddy's Laboratories Ltd., Hyderabad, India. HPMC (having a viscosity of 50 cps in a 2% w/v aqueous solution at 20°C), ethyl cellulose (Signet Chemical Corporation Pvt. Ltd, India); heavy liquid paraffin was obtained from Central Drug House (CDH, Mumbai, India) and Span-80 was obtained from Loba Chemie, Mumbai. Other reagents and solvents used were of analytical grade.

Methods

Preparation of Gliclazide–Cyclodextrin Complex

Using HPβCD (carrier), solid dispersion of Gliclazide was prepared by the solvent evaporation method. Accurately weighed amount of Gliclazide (700 mg) and carrier (3,500 mg) were dissolved in 70 mL mixture of ethanol and water at a ratio of 7:3 (v/v). Then, the mixed solvent was evaporated under room temperature (25°C) for 48 h. After complete evaporation of solvent, solid dispersion was pulverized by a glass mortar and pestle. The 120-μm sieve fraction was then used for further studies. Actual drug content was found as 60 mg in 300 mg of solid dispersion (20%) after its assay in a UV spectrophotometer.

Preparation of Microspheres

Various compositions of drug-loaded microspheres (Table 1) were prepared by oil-in-oil (O/O) emulsion solvent evaporation method (18, 19). To prepare Gliclazide microspheres, 100 mg of Gliclazide was dissolved in a 10 mL mixture of chloroform and ethanol (1:1, v/v). The use of appropriate combination of solvents minimizes excess use of solvent. Weighed amount of HPMC was added to it and stirred for 15 min in a magnetic stirrer and subsequently ultrasonicated (Takashi, Japan) for 5 min to make homogeneous dispersion. This dispersion was added drop wise to 125 mL of heavy liquid paraffin containing Span 80 at 2% (v/v). The resultant mixture was stirred at a speed of 1,000 rpm at room temperature for 3 h. After the formation of primary emulsion, the solvent present in the emulsion droplet diffuses into the continuous paraffin phase and gets evaporated (20). Heavy liquid paraffin was used to retard the fast diffusion of solvent because slow diffusion facilitates bridging between the drug and polymer. To harden the microspheres, 25 mL of petroleum ether (non-solvent) was added to it, and the stirring was continued for the next

2 h. The hardened microspheres were collected by filtration and washed with 100 mL of petroleum ether and air-dried for 12 h. After washing with excess quantity of petroleum ether, microspheres turned from a pale yellow color to white. Later, the used petroleum ether was collected and recovered by a distillation process for reuse. The prepared matrix microspheres were found to be spherical, discrete, and well-defined in shape. These were designated as MC1 to MC4. By using the same technique, Gliclazide-HPβCD microspheres were prepared and were designated as MC5 to MC8.

Type of MC	Formulation Code	Theoretical Drug Content (mg)	HPMC (mg)	EC (mg)	HPMC/EC Ratio	Total amount of polymer matrix used
MC of gliclazide	MC1	100	--	300	NA	300
	MC2		100	300	1:3	400
	MC3		200	300	2:3	500
	MC4		300	300	3:3	600
MC of gliclazide-HPβCD Complex[a]	MC5		--	300	NA	300
	MC6		100	300	1:3	400
	MC7		200	300	2:3	500
	MC8		300	300	3:3	600

[a] Percent of drug in solid dispersion (complex) is 20%. Amount of complex was calculated as per the theoretical drug content (mg) of microsphere formulation

Table 1: Composition of MC

Estimation of Gliclazide

Gliclazide was estimated by ultraviolet visible (UV/Vis) spectrophotometric method (Shimadzu UV–1700) based on the measurement of absorbance at 226.5 nm in phosphate buffer of pH 7.4. The method was validated for linearity, accuracy and precision. The method obeys Beer's law in the concentration range of 2 to 20 μg/ml.

Encapsulation Efficiency (%)

An appropriate amount of microcapsules were first crushed and then weighed and suspended in methanol to extract the drug from microcapsules while assuring that there was no loss of material in the process (21). After 24 h, the filtrate was assayed spectrophotometrically at 229 nm for drug content against ethanol as blank.

Encapsulation efficiency (%) =

$$\frac{\text{actual weight of gliclazide in sample}}{\text{theoretical weight of gliclazide}} \times 100$$

Particle Size Determination

Particle size analysis study of the prepared microspheres were determined by sieving them on a mechanical shaker using a nest of standard sieves (BP test sieves) with a shaking time of 15 min. In the current study, microspheres with a mean diameter of 240 μm were used for further investigations.

In Vitro Drug Release Study

The drug release was performed using USP 24 (paddle type) apparatus at 37±0.5°C and at 100 rpm in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.4) as dissolution medium. Microcapsules 100 mg of gliclazide were used for the test. Five milliliters of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45μm membrane filter, diluted suitably and analyzed spectrophotometrically at 226.5 nm. An equal amount of fresh dissolution medium was replaced immediately after withdrawal of test sample. The drug release experiments were conducted in triplicate (n=3).

Drug Release Kinetics

To ascertain the mechanism of drug release, in-vitro release data were fitted into various kinetic models such as Zero order, First order, Higuchi and Korsmayer Peppas and there correlation co-efficient (r^2) values and slope value (n) were studied.

Results and Discussions:

The cellulose matrix microspheres of Gliclazide –HPβCD complex were prepared using O/O emulsion solvent evaporation technique. The purpose of preparing the Gliclazide – HPβCD inclusion complex was to improve the solubility and dissolution rate and to find the feasibility of its use in the formation of controlled-release microspheres. The emulsion solvent evaporation method has been successfully used to incorporate plain drug (Gliclazide) or the Gliclazide –HPβCD inclusion complex into the polymeric matrix. Heavy liquid paraffin, an immiscible liquid, was used as a continuous phase since the dispersed phase contained the hydrophilic complex. Selection of suitable dispersion media enhances the entrapment efficiency. Earlier, it was found that the drug was molecularly dispersed within microspheres due to the evaporation of the solvent (22).

Microspheres were characterized to examine the yield (%) of microspheres, drug content, entrapment efficiency (%), drug loading (%), and average particle size (Table 2).

Formulation Code	Percentage yield	Drug content (mg)	Entrapment efficiency (%)	Drug loading (%)	Average particle size (µm)
MC1	76.84±2.798	80.94±2.718	80.94±2.718	26.33±0.133	168.93±7.781
MC2	77.72±1.625	83.15±1.973	83.15±1.973	21.4±0.832	139.25±3.981
MC3	79.17±2.145	79.27±2.526	79.27±2.526	21.22±0.451	278.58±12.724
MC4	82.36±2.812	80.11±1.945	80.11±1.945	20.86±0.233	298.83±18.845
MC5	73.56±2.812	68.38±1.758	68.38±1.758	14.32±0.562	361.51±36.412
MC6	78.31±2.39	76.46±2.016	76.46±2.016	13.4±0.289	422.27±22.779
MC7	84.16±2.227	78.63±1.824	78.63±1.824	12.7±0.371	402.66±15.996
MC8	87.62±2.713	79.76±2.535	79.76±2.535	12.38±0.406	386.17±20.093

Data are the means of at least three experiments ± SD ($p<0.05$). Yield is calculated with respect to the total weight of solid dispersion (300 mg of gliclazide –HPβCD complex) and polymers

Percent yield depends on the mass fraction of polymers, other ingredients (drug, carrier), and the physicochemical properties of the materials involved in dispersion. If any ingredient diffuses out from one liquid phase to another, then there will be lower yield due to this loss. This happens when the solvent migrates/evaporates from microspheres along with the soluble content to the dispersion medium, and this fact also causes greater porosity of the polymeric network. We found a lower percentage yield (76.84) in MIC1 in comparison to MIC4. There was a gradual increase in percentage yield when either total polymer content or mass faction of HPMC in the matrix was enhanced. The effect of a higher percentage of HPMC was found to increase the drug content. This is due to the hydrophobic and less swellable in nature of EC.

Drug content is higher in MC2 compared to MC4 due to presence of higher concentration of EC. Same thing is applicable in drug entrapment percentage.

Percentage drug loading is the percent of drug with respect to the yield of microspheres that depends upon the amount of polymer. In MC1 the drug loading percentage was higher as there was no presence of HPMC polymer. But the same value decreases significantly ($p\leq0.05$) with rise in HPMC concentration (MC2- MC4).

The average particle size of MC1 and MC2 was comparatively lesser than in MC3 and MC4. It might be due to rise in HPMC and EC polymeric ratio. But the particle size is larger in MC5-MC8 since the latter contained some quantity of HPβCD due to complexation.

Physicochemical properties of EC (hydrophobicity, rigidity) may influence average particle size. Factors such as speed of agitation, volume of external phase, and concentration of surfactant influence the size of the particle. In the present study, all the factors were kept constant for all formulations. The hydrophilicity and swellability of HPMC make the microspheres less porous, and as a result, it retards the possible migration of drug into continuous medium.

In vitro release study shows that there was increment in the dissolution from the Gliclazide–HPβCD complex was higher than that of pure Gliclazide as shown in Figure No 1.

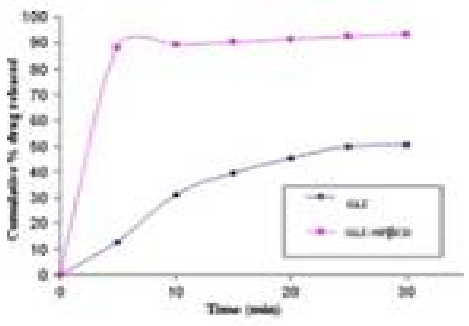

Figure No.1 Dissolution profiles of pure Gliclazide and Gliclazide in Gliclazide-HPβCD complex

In the Gliclazide–HPβCD complex, 92.42% of drug was released at the end of 30 min with an initial burst release of 86.34%, whereas a 12.62% release at 5 min and then 50.15% at 30 min were observed in the pure drug. Higher solubilization capability of substituted cyclodextrin favors the amorphous behavior of drug. Each release profile exhibits a biphasic pattern: initial burst release phase and subsequent slower release phase. The percentage release varies with various compositions of polymers (EC: HPMC). The initial burst release increases with the higher dissolution ability of drug in complex form when compared with pure gliclazide. Therefore, the drug's solubility and polymer's characteristics play a combined role in the release of drug from microspheres. It is well known that the polymer having more permeability to water and swellability facilitates higher dissolution and drug release from a dosage form. Retardation effect of EC and fast release effect of HPMC were coupled to achieve the targeted extended release. The drug release rate from the microspheres could also be related to the particle size. Microspheres of the complex (MC5, MC8) showed a comparatively smaller particle size that provided a large surface area and caused an increased release (%) of drug. The particle size depends on the viscosity and concentration of polymeric dispersion.

In the present study, the cumulative percentage of drug releases (M) at various time (t) intervals were fitted to zero-order, first-order, Higuchi's, and Korsmeyer–Peppas' model. Correlation

coefficient (r^2) as summarized indicates that the release data of drug from almost all the MIC formulations fitted well into the Korsmeyer–Peppas model (logM = logk + nlogt; r^2 = 0.9292–0.9953), but n values were not within the range 0.5–1. Similar values were obtained when the equation was applied to the first 60% of fractional release of drug from microspheres. It suggests that drug release obeys a quasi-Fickian release mechanism (n<0.5) where drug diffuses slowly through a swollen matrix and water filled pores of microspheres. Release of drug was not supported by Fickian (n=0.5, Higuchi equation), non-Fickian (0.5<n<1), and case II transport (n=1) release mechanisms as values of n ranges from 0.1 to 0.34. The correlation coefficients (r^2) as per Higuchi's equation were in the range 0.826–0.995, which showed nonlinearity in some cases. In zero order, the drug dissolution occurs at a constant rate from beginning to end. Finally, it is concluded that drug releases exponentially from all microspheres, and the drug release patterns could be explained by quasi-Fickian and first order release mechanisms.

Conclusion

Microspheres were successfully prepared with Glipizide–HPβCD complex The formulation MC8 containing various polymers (HPMC, EC) in the ratio of 1:1 was found to be the best formulation. Drug releases exponentially from all microspheres, and the drug release patterns could be explained by quasi-Fickian and first order release mechanisms. We conclude that cellulose matrix microspheres loaded with the complex is a new sustained-release delivery system of Glipizide that has a potential in administering the drug orally.

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