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DESIGN AND DEVELOPMENT OF GLIBENCLAMIDE LOADED MICROPARTICLES

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Abstract:

Controlled release drug delivery systems are more preferred than the conventional drug delivery systems due to its enhanced bioavailablity and patient compliance. Glibenclamide is a sulfonylurea used in the management of diabetes mellitus.The aim of this study was the formulation and physicochemical characterization of Glibenclamide by using polymers like chitosan and Arachis oil at different concentrations. microparticles were prepared by Emulsification Crosslinking method by using chitosan as polymer and various concentrations of Trypolyphosphate (10-25mg/ml) in aqueous solution as cross linking agent. The polymeric systems obtained were characterized in terms of particle size and morphology,IR spectroscopy, entrapment efficiencyand drug loading, Swelling degree, the release of active substances from the chitosan matrix and the other micromeritic studies like Carr's index, Hausner's ratio, and angle of repose.It was observed from the invitro release studies, formulations F7and F8 showed sustained drug release for desired time of 12h and the drug release from microparticles follow non-Fickian diffusion mechanism.

Key words: *Glibenclamide, Chitosan, Emulsification Crosslinking method, Tripolyphosphate*

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INTRODUCTION:

Antidiabetic drugs have always been in the forefront of research because the diabetes disorders are on an increase globally due to the complicated life styles of humanbeings . Now a day's millions of people are suffering from with diabetes specially the Type-2, which are not dependent on insulin production .Treatment for Type-2 diabetes is a long term therapy where noncompliance is high[1]. Hence prolonged release dosage forms are required for quality health care. The diabetic condition requires the continuous availability of antidiabetic drugs in the systemic circulation. Extensive work is being taken up not only to develop newer more specific molecules for type-2 diabetes but also develop proper delivery system to maintain the activity of the drug over a prolong period of time so the proper compliance of taking the drugs regularly [2]. The principal aim of the investigation undertaken is to develop a microparticulate drug delivery systems for non-insulin dependent type-2 diabetes mellitus drug such as Glibenclamide .

Glibenclamide, a second generation sulphonylurea is an oral hypoglycaemic agent used in the management of type II diabetes. Its biological haif life is 4-6hrs. Due to its low biological half lives (5 hrs), it requires frequent administration [3-4].To reduce the dosing frequency and to improve patient compliance prolonged release dosage forms are required. Hence, there is a scope for continued interest and need for developing controlled release formulations. In the present investigation glibenclamide loaded chitosan microparticles were prepared by emulsification crosslinking Crosslinking and Ionotropic Glation with an objective of developing microparticles for oral controlled release .

MATERIALS AND METHODS:

Materials:

Glibenclamide was obtained as gift sample from Orchid Pharma Ltd, Chennai. Sodium alginates (Loba chem Pvt. Ltd. Mumbai, India), chitosan (yarrow chem. Pvt.ltd), Calcium chloride (Loba chem Pvt. Ltd. Mumbai, India).

Preparation of microparticles:

150mgof Glibenclamide was added into 50mlof 2%acetic acid solution containing 750mgofchitosan with magnetic stirrer toform water phase. 250*ml* of liquid paraffin and 2.5 *ml* of Span-80 were mixed by stirring at room temperature to form oil phase.Then total of 50*ml* water phase was dripped into above oil phase at a speed of 40-60 drops per minute. The mixture was emulsified at 1500rpm stirring speed until stable emulsion formed. To crosslink and separate the microparticles 20 ml of various concentrations of Trypolyphosphate(10-25mg/ml) in aqueous solution was added to the system. This was done by slowly adding with a micropipette. The stirring was continued for about 1hr. The preparation was then centrifuged at 2000 rpm and then the supernatant was decanted.The microparticles at the bottom was collected and washed with the petroleum ether. Then the washed microparticles were air dried and stored in desiccators. [5-6]

Characterization of microparticles:

Size Distribution and Size Analysis [7]:

For size distribution analysis, 250 mg of the microcparticles of different sizes in a batch were separated by sieving, using a range of standard sieves. The amounts retained on different sieves were weighed. The mean particle size of the microcapsules was calculated by the formula.

$$\text{MeanParticleSize} = \frac{\sum(\text{MeanParticleSizeof theFractionX WeightFraction})}{\sum(\text{Weight Fraction})}$$

Evaluation of Flow Properties: The flow properties of different microcparticleswere studied by measuring the angle of repose employing open tube method (2.3 cm diameter) method. The angle of repose was calculated by using the following formula [7].

$$\text{Tan}\,\alpha = \frac{h}{r} \text{ or } \alpha = \text{Tan}^{-1}\frac{h}{r}$$

Where h = height of the pile, cm r = radius of the base of the pile, cm

Bulk Density: [7] The bulk density was determined by measuring the volume occupied by the pre weighed microcparticles. It was calculated with the formulae.

$$\text{Bulk density} = \frac{\text{Mass of microparti cles}}{\text{bulk Volume}}$$

Tapped Density:[7]Accurately weighed 10 g of the beads and transferred in to 25 ml measuring cylinder. It was subjected to tapping for 3 times and the

volume occupied by the beads was noted. Tapped Density is estimated by using the following formula[9].

$$\text{Tapped Desity} = \frac{\text{Weight of the microparti cles}}{\text{Bulk volum e o microparti cles}}$$

Carr's Index:[7]The percentage of compressibility of microspheres was determined by Carr's compressibility index**.**

$$\text{Carr's index (\%)} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Hausner Ratio:[7] Hausner ratio of microcparticles determined by comparing the tapped density to the bulk density using the formulae.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Wall Thickness: Wall thickness of microcparticles was determined by the method of Luu et al using the equation[8].

Where h is the wall thickness

$$h = \frac{\bar{r}(1-p)d1}{3[pd2+(1-p)d1]}$$

$\bar{r}$ is the arithmetic mean radius of the microparticles

d_1 is the density of the core material

d_2 is the density of the coat material

p is the proportion of the medicament in the microparticles

Estimation of drug content of Glibenclamide microparticles: Accurately 100 mg microparticles were weighed and transferred in to a mortar. Powdered and dissolved in 100 ml of pH 7.4 phosphate buffer, suitably diluted the absorbance of the resulting solution was measured at 228 nm[9].

Entrapment Efficiency of Glibenclamide microcparticles: Entrapment efficiency[10] was calculated using the formula.

$$\text{Entrapment efficiency} = \frac{\text{Estimated percent drug content}}{\text{Theoretica l percent drug content}} X 100$$

Estimated percent drug content was determined from the analysis of 100 mg microcparticles. And the theoretical percent drug content was calculated from the employed core:coat ratio in the formulation of microcparticles.

Drug Release Studies of Glibenclamide microparticles: Release of Glibenclamide from the microcparticles, was studied in phosphate buffer of pH 7.4 (900 ml) using Eight Station Dissolution Rate Test Apparatus (M/s. Electrolab) with a paddle stirrer at 100 rpm[11] and at 37 ^{O}C ± 0.5 ^{O}C. A sample of microcparticle (equivalent to 5 mg of Glibenclamide was used in each test. Samples were withdrawn through a filter (0.45) at different time intervals and were assayed at 229 nm for Glibenclamide using Shimadzu double beam UV spectrophotometer. The drug release experiments were conducted in triplicate.

SEM Analysis: The samples for the SEM analysis were prepared by sprinkling the microparticles on one side of the double adhesive stub[12]. The stub was then coated with fine gold dust. The microparticles were then observed with the scanning electron microscope (Leica Electron Optics, Cambridge, USA) at 10kv.

IR spectral studies: The IR Spectra for the formulation, pure drugs and excipients were recorded on JASCO FT-Infra Red Spectrophotometer using KBr pellet technique[13] (1:100) at the resolution rate of 4 cm^{-1}. Spectrum was integrated in transmittance mode at the wave number range 380 to 4368 cm^{-1}.

RESULTS AND DISCUSSIONS:

The microparticles were prepared by Emulsification Crosslinking method by using chitosan as polymer and various concentrations of Trypolyphosphate (10-25mg/ml) in aqueous solution as cross linking agent.The method employed gave discrete, spherical, non-sticky and free flowing microparticles. As aggregates these microparticles were also non-sticky and free flowing. The formation of a stable emulsion in the early stages is important if discrete microparticles are to be isolated. An optimal concentration of emulsifier is required to produce the finest stable dispersion. Below optimal concentration the dispersed globules/droplets tend to fuse and produce larger globules because of insufficient lowering in interfacial tension, while above the optimal concentration no significant decrease in particle size is observed, because a high amount of emulsifying agent increases the viscosity of the dispersion medium. The optimal concentration of span 80 was found to be 1 %. Microscopic examination of the formulations revealed that the microparticles were spherical and appeared as aggregates or discrete particles. The particle size of

the microparticles ranged between 153.26 and 189.56 µm. All formulations had a narrow particle size distribution.The mean particle size of microparticles was influenced by the concentrations of Trypolyphosphate used and its proportion in the formulation. The mean size increased with increasing concentrations of Trypolyphosphate. It would appear that increasing concentrations of Trypolyphosphate produced a significant increase in viscosity of the internal phase, thus leading to an increase of emulsion droplet size and finally a higher microparticle size.

These microparticles were characterized for size analysis, flow properties, % Drug Content, % Encapsulation Efficiency. The results are given in Table 2. .All the formulations offered good flow property. The technique also showed good entrapment efficiency. The microparticles were subjected to *In-vitro* release studies by employing 7.4 pH phosphate buffer and the data was shown in Table 5.3 and Figure 5.1. When the amount of drug release values were plotted against time straight lines were obtained in all the cases indicating that the rate of drug release from these microparticles followed zero order kinetics Figure 5.2. To ascertain the mechanism of drug release from various microcapsules plot of log %Released vs log time (peppas plots) were drawn. The plots were found to be linear (Figure5.3) with all microparticles. Release Kinetics of Glibenclamide microparticles were shown in Table 5.4. The exponential coefficient(n) values were found to be in between 1.0591 to 1.1032 indicating supercase –II transport diffusion mechanisam. These results indicated that the release rate was found to decrease with increase in concentration of coating material applied. The wall thickness of microparticles was found to be increased with the increase in concentration of coating material applied. There exists a good correlation ship in between wall thickness and release rate constant Figure 5.

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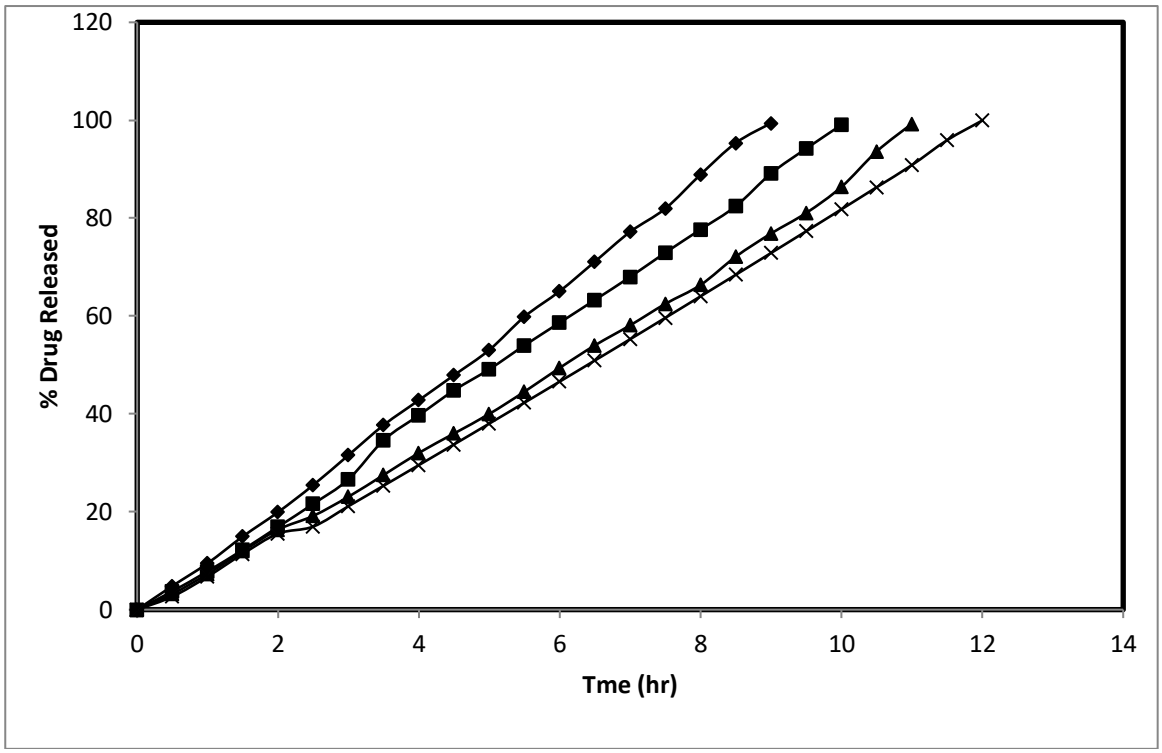
Table 1: List of Glibenclamide Microparticles Prepared

Emulsification Crosslinking method		
Formulation Code	**Chitosan concentration (% w/v) (polymer)**	**TPP concentration (% w/v) (crosslinking agent)**
F-1	1.5	1
F-2	1.5	1.5
F-3	1.5	2
F-4	1.5	2.5

Table.2: Physical Properties of Glibenclamide microparticles Prepared by Emulsification Crosslinking method

Formulation	**Angle of repose**	**Bulk Density (g/cm^3)**	**Tapped density**	**Carr's Index**	**Hausner's Ratio**	**Average Particle Size (µm)**	**% Drug Content**	**% Encapsulation Efficiency**
F-1	26.37	0.350±0.013	0.408±0.011	14.21±0.022	1.161±0.014	153.26	12.86	94.34
F-2	25.65	0.320±0.022	0.370±0.009	11.89±0.009	1.134±0.017	164.32	11.83	94.67
F-3	22.76	0.319±0.005	0.362±0.021	11.87±0.017	1.130±0.024	178.37	11.11	96.42
F-4	21.13	0.276±0.014	0.314±0.013	12.10±0.024	1.137±0.012	189.56	10.40	97.16

Figure 1: Release Profiles of Glibenclamide microparticles Prepared by Emulsification Crosslinking method



(-■-)Glibenclamide Microparticles prepared with 1%W/V crosslinking agent
(-◆-)Glibenclamide Microparticles prepared with 1.5%W/V crosslinking agent
(-▲-)Glibenclamide Microparticles prepared with 2%W/V crosslinking agent
(-×-)Glibenclamide Microparticles prepared with 2.5%W/V crosslinking agent

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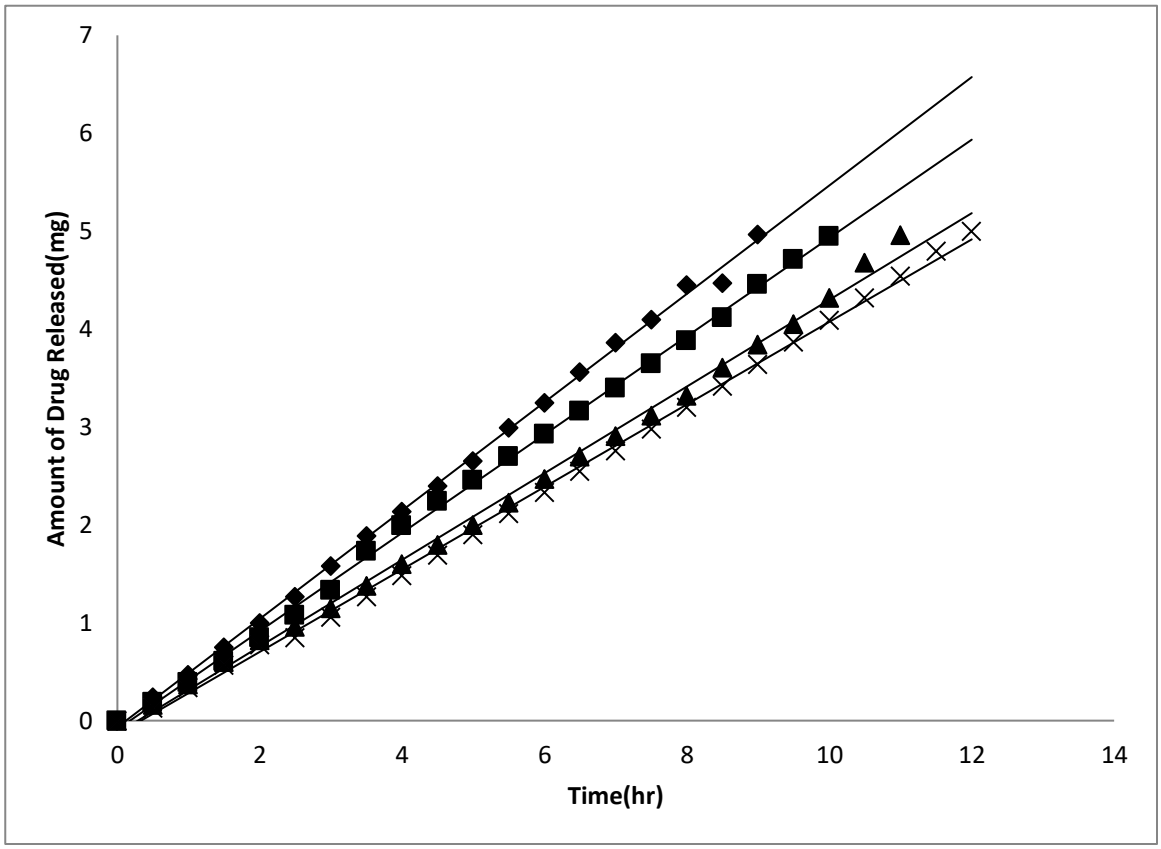
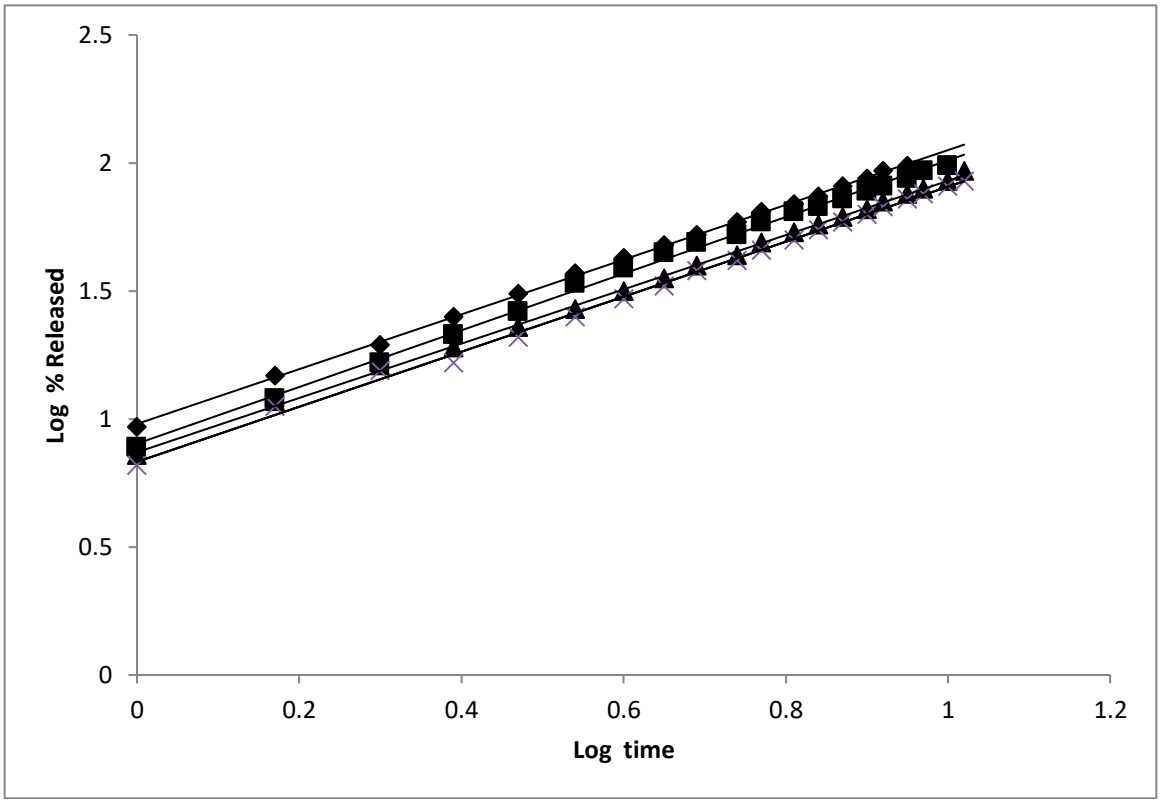
Figure 2: Zero Order Plots of Glibenclamide microparticles Prepared by Emulsification Crosslinking method



(-■-)Glibenclamide Microparticles prepared with 1%W/V crosslinking agent
(-◆-)Glibenclamide Microparticles prepared with 1.5%W/V crosslinking agent
(-▲-)Glibenclamide Microparticles prepared with 2%W/V crosslinking agent
(-×-)Glibenclamide Microparticles prepared with 2.5%W/V crosslinking agent

Figure 3: Peppas Plots of Glibenclamide microparticles Prepared by Emulsification Crosslinking method



(-■-)Glibenclamide Microparticles prepared with 1%W/V crosslinking agent
(-◆-)Glibenclamide Microparticles prepared with 1.5%W/V crosslinking agent
(-▲-)Glibenclamide Microparticles prepared with 2%W/V crosslinking agent
(-×-)Glibenclamide Microparticles prepared with 2.5%W/V crosslinking agent

Figure 4: Correlation ship between Wall Thickness and Release Rate Constant of Glibenclamide microparticles Prepared by Emulsification Crosslinking method

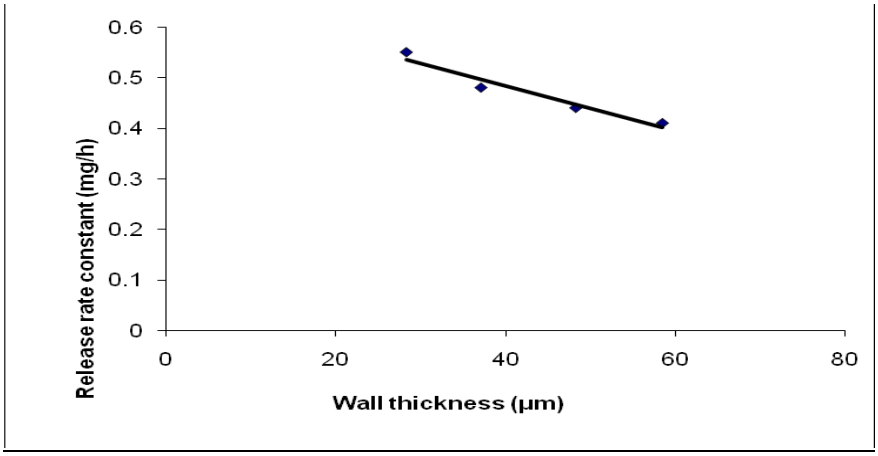


Table 3: Release Kinetics of Glibenclamide microparticles Prepared by Emulsification Crosslinking method

Formulation code	Correlation Coefficient Values (R^2)				Release Rate Constant (mg/hr) Ko	$t_{50\%}$	$t_{90\%}$	Wall Thickness (µm)	n value
	Zero Order	First Order	Higuchi Model	Peppas Model					
F-1	0.9992	0.7949	0.9128	0.9998	0.55	4.6	8.2	28.37	1.0591
F-2	0.9990	0.8165	0.9135	0.9993	0.48	5.1	9.2	37.13	1.1013
F-3	0.9974	0.7757	0.9031	0.9994	0.44	5.9	10.6	48.26	1.0791
F-4	0.9980	0.6792	0.9034	0.9988	0.41	6.2	11.1	58.43	1.1032