Research Article

APPLICATION OF MODIFIED PULSINCAP TECHNIQUE FOR ORAL CONTROLLED DRUG DELIVERY OF GLICLAZIDE

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ABSTRACT

Gliclazide is an oral antidiabetic drug characterized with poor aqueous solubility. So in the present investigation the solubility of Gliclazide was enhanced by using Methyl β Cyclodextrin (MβCD). The complexation between Gliclazide and MβCD was conformed by phase solubility studies and X Ray diffraction studies. The formed Glicalzide- MβCD complex was used as a core in further studies. In the present study the release of the prepared core was controlled by Modified Pulsincap technique and by using Sodium CMC as polymer. The invitro dissolution studies of the Modified Pulsincaps of the core indicate that the release of the drug from the pulsincaps was decreased by increasing the polymer concentration. So this technique is more suited for preparing better controlled release formulations.

Keywords: Gliclazide, Methyl β Cyclodextrin, Solubility enhancement, X Ray diffraction studies, Modified Pulsincap technique, Sodium CMC, Controlled release.

INTRODUCTION

In the recent past, controlled release concept and technology has received increasing attention because of growing awareness to drugs toxicity. Controlled release systems are classified into diffusion controlled, osmotically controlled, chemically controlled, hydro gels, pH dependent and independent formulations, altered density formulations, pulsatile drug delivery systems and many others [1].

Pulsincap system is one of the methods of pulsatile drug delivery systems which is used to get the drug release after a pre determined lag time [2, 3]. In the present investigation these pulsincap method was modified to prepare "Modified Pulsincaps" in order to prepare controlled drug delivery systems.

Methyl β-Cyclodextrins are cyclic oligosaccharides containing seven glucopyranose units attached by α-(1, 4) glucosidic bonds which form a cone-like cavity into which drug may enter and form a water-soluble complex and thus change the drug's physicochemical properties and there by increases the solubility, bioavailability and stability of drugs [4-6].

Gliclazide is an oral hypoglycemic sulphonylurea used for the treatment of non-insulin dependent diabetes mellitus (NIDDM) which is characterized by a low solubility, leading to poor oral bioavailability [7].

Drugs with poor aqueous solubility can exhibit slow or incomplete release from the formulations, resulting in poor in vivo bioavailability unless the drug release rate through the formulation was suitably enhanced. Thus, materials that increase drug solubility within the formulation and there by enhance the rate of drug release are of greatest interest and this concept is important when a sustained release dosage form for a poorly soluble drug was developing [8].

Therefore, this study has been designed to investigate the solubility enhancing potential of Methyl β Cyclodextrin (MβCD) and to improve the delivery of a poorly soluble Gliclazide.

MATERIALS AND METHODS

Materials

Gliclazide was supplied by courtesy of Dr.Reddy's Laboratories Ltd, India, and MβCD was provided by Roquette Pharma. All other materials were of analytical reagent grade**.**

Phase solubility studies

The stability constant for inclusion complex between Gliclazide and MβCD was determined by using the phase solubility method [9]. 50 milligrams of Gliclazide was added into glass-stopper flasks containing 50ml of MβCD solutions of increasing concentrations (0, 0.02, 0.04, 0.06, 0.08 and 0.1M). The flasks were sealed and shaken at room temperature. After equilibration for 72 h, the solutions were filtered through membrane filter (0.22 μm pore size). Then the filtrates were suitably diluted and the concentration of Gliclazide was estimated by UV spectroscopy at 226 nm. The apparent stability constant (Kc) of the complex with MβCD was calculated from the phase solubility diagram using the equation proposed by Higuchi and Connors (1965).

$$K_c = \frac{slope}{Intersept(1-slope)}$$

Where, the intercept is the apparent solubility of Gliclazide.

Complex formation between Gliclazide and MβCD by Solvent evaporation method (Core)

The alcoholic solution of Gliclazide is simply added to the aqueous solution of MβCD (1:0.25molar ratio) .The resulting mixture is stirred and evaporated under vacuum at 45º C. The dried mass was pulverized and passed through a 60-sieve and stored in desiccators until used [10].

Detection of inclusion complexation in solid state by Powder X-ray Diffraction (PXRD)

The powder X-ray diffraction patterns for Pure drug (Gliclazide), MβCD and their complexes (1:0.25MR) were recorded using Phillips Diffractometer (PW 140). The samples were exposed to Cu-Kα radiation at 56 kv and 182 mA over the 2θ range form 0^0 to 80^0 C.

Dissolution studies of prepared inclusion complexes

Invitro dissolution studies of pure drug and the binary system prepared were carried out in 900ml of alkaline phosphate buffer of pH 7.4 using USPXXIV type 1 (basket method) Dissolution rate test apparatus (model DISSO 2000,M/S Lab India). Samples equivalent to 60 mg of Gliclazide were taken in baskets. A speed of 100 rpm and a temperature of 37±0.5⁰ C were used in each test. A 5 ml aliquot was withdrawn at different time intervals, filtered using 0.45μ nylon disc filter and replaced with 5ml of fresh dissolution medium. The filtered samples were suitably diluted if necessary and assayed for Gliclazide content by measuring the absorbance at 226nm. The dissolution experiments were conducted in triplicate [11].

Preparation of core-polymer mixture

The drug - polymer mixtures were prepared in the ratios of 1:0.25, 1:0.5 1:0.75, 1:1, 1:1.25, 1:1.5 using Sodium CMC. All the ingredients

used in the preparation of core-polymer mixtures were passed through mesh no. 100 and accurately weighed quantity of drug, polymer along with other ingredients were mixed to obtain a homogeneous mixture by using geometric dilution technique as shown in **Table 1**.

Table 1: composition of core polymer mixtures

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Gliclazide-MβCD Solvent evaporated mixture (1:0.25MR)(*Core*)	116	116	116	116	116	116
Sodium CMC	29	58	87	116	145	174
Spray dried Lactose	185	156	127	98	69	40
Total weight	330	330	330	330	330	330

Evaluation of the prepared of drugs - polymer mixtures

Micromeritic properties [12, 13]

Carrs compressibility index (CI)

Carrs index is the measure of bulk density to the tapped density of the material. It is calculated by using the following formula

$$CI = ((Dt-Db)/(Dt)) \times 100$$

Where

CI = Carrs compressibility index

Dt = tapped density of the powder (g/ml)

Db = bulk density of the powder (g/ml)

Carrs index values for the pure drug and polymer blends were determined by measuring the initial volume (Vb) and final volume (Vt) of a known weight (W) of material by subjecting to tapping till the constant volume is obtained. From these volumes, the bulk density (Db=W/Vb) and the tapped density (Dt=W/Vt) values were calculated and then the CI values are determined by using the above equation

Hausners ratio

The Hausners ratio is a number related to the flow properties of powder or granular material. It is useful in finding out the inter locking of the particles which hinder the free flowing of powders.

$$\text{Hausners ratio} = Dt/Db$$

Where

Dt is the tapped density of the powder

Db is the bulk density of the powder

Angle of repose

Flow properties of pure drug and polymer mixtures were determined by measuring the angle of repose. The static angle of repose (θ) was measured according to the fixed funnel and free standing core method A funnel with the end of the stem cut perpendicular to its axis of symmetry was secured with its tip 2 cm above a graph paper placed on a flat horizontal surface. 5 gms of powder is carefully poured through the funnel until the apex of the core thus formed just touched the tip of the funnel. The mean diameter of the base of the powder cone was determined and the tangent of the angle of repose (θ) was calculated by the following equation.

$$\theta = \tan^{-1}(h/r)$$

Where

θ = Angle of repose

h = height of the heap

r = radius of the heap

Estimation of the Gliclazide content from the prepared drug-polymer mixtures

Drug content from the prepared drug-polymer mixtures were determined by transferring accurately weighed 330 mg of the mixture into a 100 ml volumetric flask containing 100 ml of methanol and the drug content was estimated by using UV Visible Spectrometer at 226 nm.

Preparation of modified Pulsincaps [14, 15]

The selected '0' size hard gelatin capsules (blue cap with white body) were taken, their bodies and caps were separated. The bodies were placed on a wire mesh and spread as a single layer. They were placed in a desiccator, containing formaldehyde liquid at the bottom, which is equilibrated with its vapor. The bodies of capsules were exposed for varying periods of time viz., 3, 6, 10 and 24 hrs. The capsule bodies were removed from the desiccators after the required exposure time and dried at 50^0 C for 30 min to ensure the reaction between gelatin and formaldehyde vapour Later they were dried in desiccators for 12 hrs to ensure the removal of residual formaldehyde and stored in an air tight container.

Qualitative chemical test for free formaldehyde [16]

In this study 0.002% w/v of formaldehyde is used as standard formaldehyde solution and sample solution is formaldehyde treated bodies. One formaldehyde treated capsules was cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1 h with a magnetic stirrer, to solubilize the free formaldehyde. The solution was then filtered into a 50ml volumetric flask, washed with distilled water and volume was made up to 50 ml with the washings. To 1ml of this sample solution, 9ml of water was added. One milliliter of resulting solution was taken into a test tube and mixed with 4ml of water and 5ml of acetone reagent. The test tube was warmed in a water bath at 40^0 C and allowed to stand for 40 min. Then the color comparison was made by examining tubes down their vertical axis

Dissolution studies of formaldehyde exposed capsules

Dissolution test was performed for both untreated and treated capsules. The formaldehyde treated body joined with untreated cap and was tested for dissolution. Dissolution test was carried out by using USP XXIV Type-II dissolution rate test apparatus (model DISSO 2000, M/S Lab India) by paddle method at a stirring rate of 100 rpm for both treated and untreated capsules. The dissolution media used is 900ml of 0.1N Hcl and 900 ml of phosphate buffer medium of pH 7.4 at 37^0 C.

Formulation of Modified Pulsincaps of Gliclazide

Bodies of the gelatin capsules hardened with formaldehyde were taken for preparing the Modified Pulsincaps. All the formulations (F1-F6) were weighed and filled into the hardened capsule body by hand filling method. Finally the soluble cap was locked into the body to form the Modified Pulsincaps of Gliclazide.

Evaluation of Modified Pulsincaps

Uniformity of weight

From each batch 20 Pulsincaps were selected at random, weighed together and individually. The mean and standard deviation were determined.

Estimation of drug content

From each batch of the prepared Pulsincaps of Gliclazide ten Pulsincaps were randomly selected and the contents were emptied

into a 100 ml volumetric flask. The respective drug contents were estimated by using UV Visible Spectrometer at 226 nm.

In vitro dissolution studies of prepared Modified Pulsincaps

In vitro drug dissolution studies were conducted by using USP XXIV Type-II dissolution rate test apparatus (paddle system) apparatus (model DISSO 2000, M/S Lab India). For in vitro dissolution studies of Gliclazide Pulsincaps, 900 ml of 0.1N Hcl is used as dissolution media for first 2 hr followed by 900 ml of phosphate buffer of pH 7.4 for remaining period of dissolution at a temperature of 37^0 C ± 0.5^0C. The stirring rate was 100 rpm. 5 ml samples of dissolution fluid were withdrawn at predetermined time intervals with a pipette fitted with a filter. The volume withdrawn at each time interval was replaced with 5ml of fresh dissolution medium maintained at the same temperature. The collected samples were suitably diluted wherever necessary and analyzed for the drug content by using UV Visible Spectrometer at

226 nm. Each dissolution study was performed for three times and mean values taken were reported.

Drug release mechanisms

The dissolution data obtained was fitted to model dependent methods like Zero order, First order, Higuchi, Erosion, and pepass equation to understand the order and mechanism of drug release from the prepared Modified Pulsincaps [17-21].

RESULTS AND DISCUSSION

Phase solubility studies

Fig. 1 represents the solubility of Gliclazide, MβCD complexes. It shows A_L type profile which indicates a linear increase in solubility of Gliclazide with increasing concentrations of MβCD. Since the slope of the diagram was less than one (0.0144), the complex stoichiometry was assumed to be 1:1. The value of the stability constant was found to be 365.25M^{-1}.

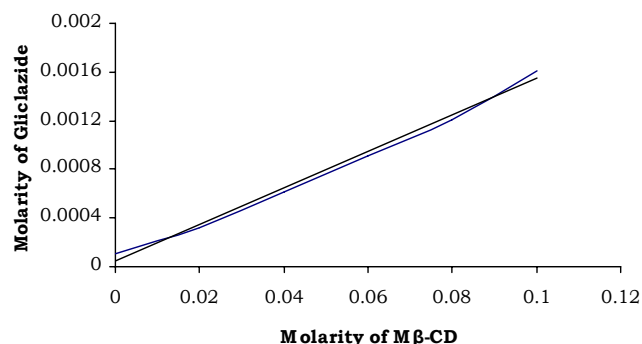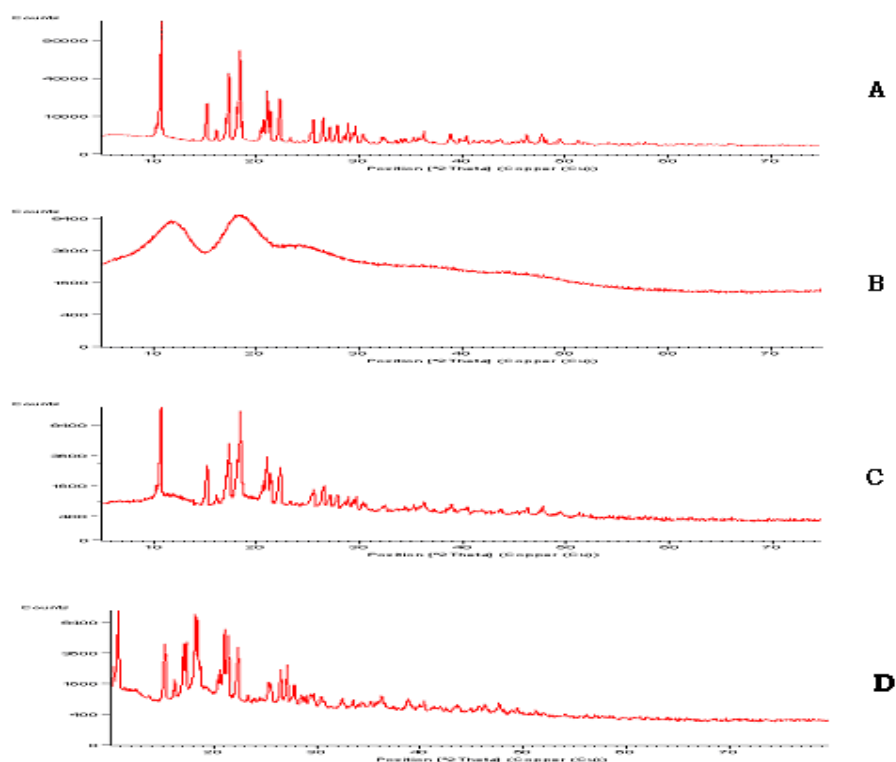Fig. 1: Phase solubility diagram of Gliclazide-MβCD inclusion complex at room temperature.

Fig. 2: XRD spectra of: A) Gliclazide, B) MβCD, C)Physical mixture of Gliclazide and MβCD, D) Gliclazide- MβCD inclusion complexes by solvent evaporation method

Complex formation between Gliclazide and MβCD by Solvent evaporation method (Core)

A complex formed between Glicalzide and MβCD (at 1:0.25 molar ratio) was determined by using X Ray Diffraction (XRD) studies as discussed in earlier section.

X Ray Diffraction (XRD) studies

Powder X-Ray Diffractometry is useful method for detection of complexation in powder or microcrystalline states. The diffraction pattern of complexes was supposed to be clearly distinct from that of superposition of each component if a true inclusion complex is formed

Fig.2A. indicates the diffraction pattern of Gliclazide, which displays peaks at 10, 15.3, 17, 17.3, 18.2, 18.418.6, 20.721, 21.4, 22.3, 25.6 and 26.5 ^{0} 2θ which indicates its crystalline structure, where as **Fig.2B.** indicates diffraction patterns of MβCD.

Fig.2C. indicates diffraction patterns of physical mixture where all the principle peaks of Gliclazide and MβCD were present with low intensities. The decrease in peak height was the evidence to the decline in crystallinity of physical mixture with respect to pure Gliclazide.

Fig.2D. indicates diffraction patterns of solvent evaporated system which is quite different to that of corresponding physical mixture and pure Gliclazide with existence of newer peak at 27 ^{0} 2θ and absence of peaks at 20.6, 21and 25.5 ^{0} 2θ indicating formation of solid inclusion complexes.

Dissolution studies

Fig.3 shows the dissolution behavior of Gliclazide alone, from physical mixture and from inclusion complexes of Gliclazide and MβCD (1:0.25 molar ratio). The release rate profiles were drawn as the percentage Gliclazide dissolved from the pure drug, physical mixture and inclusion complexes versus time. From the dissolution studies it is evident that complex of the drug and MβCD exhibited faster dissolution rates than the pure drug and physical mixture where as the physical mixture exhibited faster dissolution rate than the pure drug.
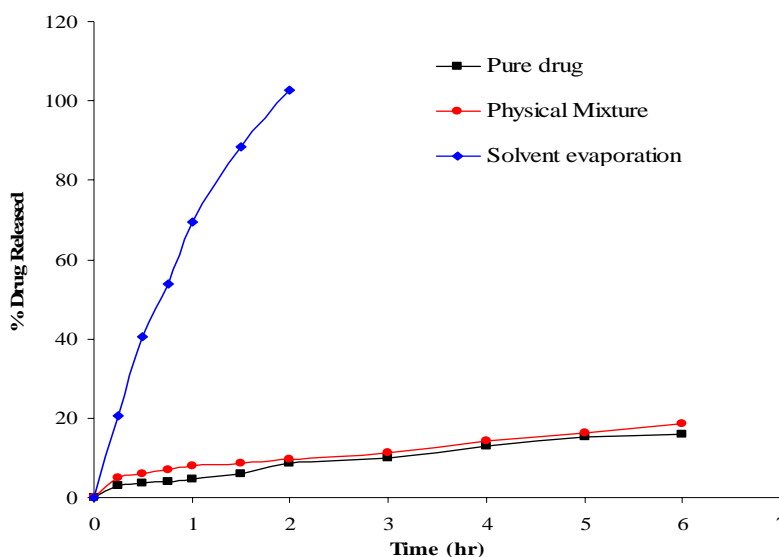
Fig. 3: Dissolution profiles of Pure Gliclazide, Gliclazide -MβCD Physical mixture and Gliclazide- MβCD solvent evaporated systems at 1:0.25 molar ratio

Preparation of core-polymer mixture

Core (*Gliclazide- MβCD solvent evaporated systems at 1:0.25 molar ratio*) and polymer (*Sodium CMC*) mixtures were prepared as discussed in earlier section.

Evaluation of the prepared of drugs - polymer mixtures

Micromeritic properties

The micromeritic properties such as Compressibility Index, Haussons ratio and Angle of repose of powders depend mainly on particle size distribution, particle shape and tendency of the particles to adhere together. These micromeritic properties are often referred to as the derived properties of powders. They play an important role in the filling of capsules since the flow characteristics of the powder mass are very important. Compressibility index (CI) values up to 15% exhibits good to excellent flow properties and indicate desirable packing characteristics. Compressibility Index less than 25% indicates good flow properties and more than 25% indicates poor flow properties. Similarly Hausner ratio values of less than 1.25 indicate a good flow property and more than 1.25 indicate poor flow property. Values for angle of repose ≤30^0 usually indicate a free flowing material and the values ≥40^0 suggest a poorly flowing material

In the present investigation, spray dried lactose (Pharmatose) was added as diluent to the capsule to make up the volume of the capsule, which is also used to increase the flow properties of the powders. The result of the study indicated that, by the addition of the Pharmatose, the flow properties of the core -polymer mixtures were improved. Compressibility Index, Hausner ratio and Angle of Repose for the prepared core-polymer mixtures were observed to limits which indicates good flow properties. The results of the Micrometric properties of core-polymer mixtures were shown in **Table 2.**

Estimation of the Gliclazide content from the prepared drug-polymer mixtures

The percent drug content of the prepared core-polymer mixtures (F1-F6) were indicated in **Table 2.** All the prepared core-polymer mixtures satisfied the drug content as they contained 100+2% of the drug when assayed. In all the cases low standard deviation values in the drug content indicated the uniformity of the drug distribution in each batch of the prepared core-polymer mixtures.

Table 2: micrometric properties of core, core-polymer mixtures and their drug contents

Formulation	CI	HR	AR	% of drug content ±s.d.(n=3)
core	23.11	1.17	25.70	99.97 + 0.33
F1	18.48	1.22	24.86	99.99 + 0.22
F2	18.69	1.23	27.76	99.88 + 0.88
F3	18.85	1.23	26.25	99.24 + 1.02
F4	20.32	1.25	25.16	98.97 + 1.15
F5	20.32	1.25	24.52	98.95 + 1.24
F6	20.32	1.25	24.52	99.99 + 0.57

Preparation of modified Pulsincaps

Qualitative chemical test for free formaldehyde

The qualitative chemical test for the detection of formaldehyde was conducted as discussed in earlier section and the results showed that the intensity of color obtained by the test is less than the standard color, which indicates that the formaldehyde content of the prepared Pulsincaps were with in the limits.

Dissolution studies of formaldehyde exposed capsules

The hardened capsules were tested for their dissolution using 0.1N HCl and pH 7.4 phosphate buffers. The effect of dissolution studies on the hardened bodies of the capsules which were exposed to formaldehyde vapours for 2 hours, 4 hours, 6 hours, 8 hours, 10 hours and 12 hours were shown in **Table 3.** The results indicated that the dissolution time was little shorter in acidic medium i.e. 0.1N HCl than the corresponding alkaline medium i.e. pH 7.4 phosphate buffer. As the time of exposure was increasing the time taken for dissolution was also increased for the hardened bodies of the capsules. The results indicated that the capsule bodies exposed to formaldehyde vapour for 10 hours were intact up to 24 hours and did not dissolve even up to 48 hours in both 0.1N HCl and in pH 7.4 phosphate buffer. So capsules that were exposed for 10 hours to formaldehyde vapours were selected for further studies. The cap of treated capsule was dissolved within 15 minutes, but in case of untreated capsules both the body and cap were dissolved within 15 minutes.

Table 3: dissolution studies of formaldehyde treated capsule bodies

Time of exposure (hr)	Observation in the dissolution medium	
	0.1 N Hcl	phosphate buffer pH 7.4
2	Shaped out in 4 hr	Shaped out in 6 hr
4	Shaped out in 10 hr	Shaped out in 12 hr
6	Softened in 10 hr	Softened in 12 hr
8	Softened in 20 hr	Softened in 22 hr
10	Intact up to 24 hr	Intact up to 24 hr
12	Intact up to 36 hr	Intact up to 36 hr

Preparation of Modified Pulsincaps of Gliclazide

Bodies of the gelatin capsules of size 0 hardened with formaldehyde for 10 hours were taken for preparing the Modified Pulsincaps. All the formulations (F1-F6) were accurately weighed and filled into the hardened capsule body by hand filling method. Finally the soluble cap was locked into the body to form the Modified Pulsincaps of Gliclazide.

Uniformity of weight

The prepared Pulsincaps in each batch showed uniformity of weight and the weight variation of the Pulsincaps was within the limits [23]..The results are shown **Table 4.** These results indicated the uniformity in the method of filling into the capsules.

Estimation of drug content

The Modified Pulsincaps of Gliclazide were prepared from the core-polymer mixtures (F1-F6). The drug contents of all the prepared Pulsincaps were estimated and shown in **Table 4.** The percent drug content of all the formulations of Gliclazide Modified Pulsincaps was found to be uniform. All the formulations satisfied the drug content as they contained 100±2% of the drug when assayed spectrophotometrically at 226 nm. Low standard-deviation (s.d.) values in the drug content estimation indicated the uniformity of the drug content.

In vitro dissolution studies of prepared Modified Pulsincaps

The dissolution profiles of Gliclazide from various formulations were shown in **Fig 4**. In all the cases the cap was dissolved with in 15min. From the dissolution studies it is clear that the drug release form the hardened capsules were directly proportional to polymer concentration. At lower concentrations of polymer the drug release from the hardened capsule was quick which might be due to insufficient polymer to form a thick cake. But as the polymer concentration was increased, the drug release from the hardened capsule was also increased which might be due to formation of a thick gel. It clearly indicates that higher concentrations of polymer was preventing the entry of dissolution fluid and there by preventing the release of drug from the prepared Modified Pulsincaps.

Table 4: uniformity of weight and estimated drug content of prepared gliclazide modified pulsincaps

Formulation	Weight [a] (mg)	Drug content [b] (%)
F1	441 ± 1.22	98.88 ± 1.23
F2	438 ± 1.45	100.01 ± 0.94
F3	440 ± 0.89	99.88 ± 1.55
F4	439 ± 0.97	97.31 ± 2.01
F5	436 ± 1.62	98.43 ± 0.81
F6	439 ± 1.44	99.92 ± 1.37

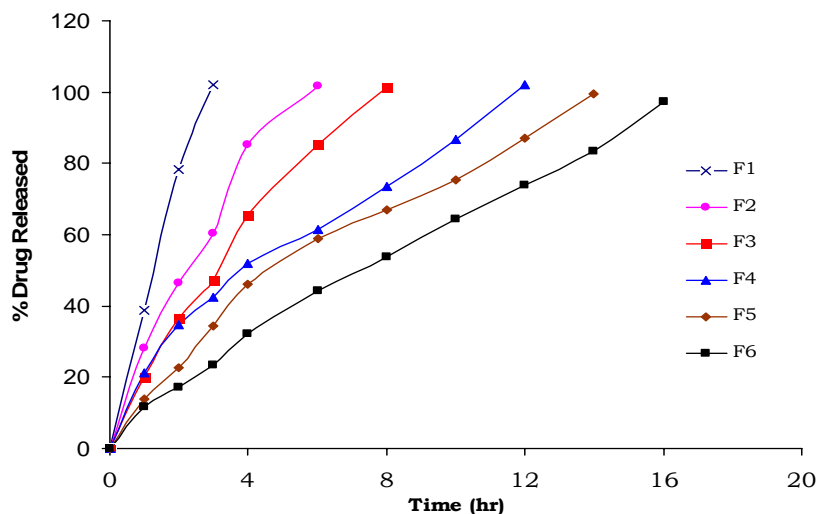a: Mean + s.d.., n = 20 Pulsincaps,b: Mean + s.d.., n = 10 Pulsincaps

Fig. 4: Dissolution profiles of Gliclazide from different Pulsincaps prepared by Sodium CMC

Drug release kinetics of Gliclazide Pulsincaps

The values of correlation coefficients (r) were obtained by fitting the dissolution data of prepared Modified Pulsincaps to five popular release models namely Zero order, First order, Higuchi, Erosion and Pepass equation and the values were given in **Table 5.**

When percent released was plotted against time, straight lines were obtained for all prepared Pulsincaps which indicates that the release pattern followed Zero order kinetics. The drug release from all the prepared Pulsincaps followed Zero order kinetics proved by r values (0.982-0.996) which were slightly higher when compared with r values of First order release model (0.905-0.982). The decrease in K_0 values as function of core-polymer ratio in all the prepared Modified

Pulsincaps showed that the released rate was decreased as the polymer concentration was increased. The relative contributions of drug release were further confirmed by subjecting the dissolution data to Higuchi model and Erosion model. It was found that the diffusion (r=0.977-0.99) governs the drug releases form all the prepared Modified Pulsincaps. The plots of log fraction drug released versus log time of all the prepared Modified Pulsincaps were found to be linear. It was found that diffusion exponent (n) values of all the prepared complexes were ranging from 0.45 -0.89 indicating that the release mechanism followed anomalous diffusion.

The results of the study indicated that the release of drug from all the prepared Pulsincaps followed Zero order kinetics via anomalous (non-Fickian) diffusion.

Table 5: kinetic parameters of various gliclazide pulsincaps prepared by sodium CMC

Formulation	Zero Order		First Order		Higuchi	Errosion	Pepass
	Ko	r	K_1	r	r	r	n
F1	34.602	0.994	0.76367	0.979	0.977	0.849	0.8
F2	16.9290	0.982	0.44079	0.956	0.981	0.806	0.739
F3	12.5450	0.988	0.31574	0.982	0.981	0.877	0.786
F4	7.5662	0.987	0.18263	0.979	0.993	0.796	0.605
F5	6.5906	0.989	0.01573	0.982	0.99	0.813	0.767
F6	5.7441	0.996	0.1718	0.905	0.979	0.867	0.78

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