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Design And Development Of Pulsatile Drug Delivery Of Glibenclamide Using Pulsincap Technology

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Abstract: The main objective is to formulate and evaluate the pulsincap for anti diabetic drug Glibenclamide to control the increased blood glucose level after food consumption in diabetic patient by allowing the drug to release immediately after a lag time (after meals). Microsponges of different concentrations were prepared and selected the best formulation for the development of pulsincap and the optimized microsponges were subjected to scanning electron microscopy, FT-IR, and *In vitro* studies. *Invitro* release studies were carried out for formulated pulsincaps. The release studies indicates that all the dosage forms released their first pulse within two hours and then release their second pulse after the swelling of hydrogel plug. The results showed that pulsincap dosage form of Glibenclamide could be effectively control the blood glucose levels after breakfast and lunch in respect to release of two pulses (i.e. first pulse after breakfast and second pulse after lunch). Hence it is found to be suitable for the diabetic patient to manage the blood glucose levels which are high after food consumption.
Key words: Pulsincap;Microsponges;Lag time;Pulsatile release.

INTRODUCTION

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body[1]. Circadian rhythm regulates many body functions in humans, viz., metabolism, physiology, behavior, sleep patterns, hormone production, etc. It has been reported that more shocks and heart attacks occur during morning hours. The patients suffering from diabetes are reported to have high blood sugar levels after meals compared to other timings.

The pulsatile effect[1,2,3,4], i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time. Such systems are also called time controlled as the drug released is independent of the environment. These systems beneficial for drugs having high first-pass effect, drugs administered for diseases that follow chronopharmacological behavior, drugs having specific absorption site in GIT, targeting to colon, and cases where night time dosing is required.

In recent years considerable attention has been focused on the development of pulsatile drug delivery system. Delivery system with pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal. Oral controlled drug delivery systems are generally used due to convenient dosage form & it also releases drug in constant or variable rates[3,4,5]. In these system drug release generally occurs within therapeutic window for prolong

period of time. Hence these systems show sustained release of drug from dosage form.

A Microsponge Delivery System (MDS) is "Patented, highly cross-linked, porous, polymeric microspheres polymeric system consisting of porous microspheres that can entrap wide range of actives. Generally with a size of 10-40µm[6,7]. The aim of the present study is to prepare microsponges by quasi-emulsion solvent evaporation method and incorporate in to the hard gelatin capsule as second pulse and insert hydrogel plug in to it and again incorporate immediate release layer as first pulse to achieve the objective of controlling the increased blood glucose level after food consumption in diabetic patient by allowing the drug to release immediately after a lag time (after meals).

MATERIALS & METHODS

Materials

Glibenclamide was obtained as a gift sample from Tablets India Pvt.Ltd.Ethyl cellulose was purchased from Otto chemika.Biochemika. Poly ethylene glycol and Gelatin was obtained from Sisco Research laboratories; Polyvinyl alchohol and Ethanol was purchased from CDH fine chemicals.

Methods

Preparation Of Glibenclamide Microsponges:

Glibenclamide microsponges were prepared by Quasi-emulsion solvent diffusion method. In this method, the internal phase containing of glibenclamide, ethylalchohol, ethyl cellulose and polyethylene glycol which was added at an amount of 20% of the polymer in order to facilitate plasticity. Thus the prepared internal phase was added to external phase consisting of polyvinylalchohol (PVA) as emulsifying agent in distilled water. The mixture was continuously stirred for 2 hours in order to evaporate solvent. Then the mixture was filtered to separate microsponges and dried in vacuum oven at 40^0c.

Evaluation of the effect of drug: polymer ratio on the physical characteristics of microsponges, different ratios of drug to ethyl cellulose (1:1,1.5:1,1:2,1:1.5 and 2:1) were tried. In all these formulations the amount of emulsifier, volume of organic solvent and volume of aqueous phase were kept constant. Formula for different batches of Glibenclamide microsponges were given in Table.2.

Table.1.Diseases which follows Chronological behavior

Chronological behavior	Drugs used	Diseases
Acid secretion is high in the afternoon and at night	H2 blockers	Peptic ulcer
Precipitation of attacks during night or at early morning	β2 agonist, Antihistamines	Asthma
BP is at its lowest during the sleep cycle and rises steeply during the early morning	Nitroglycerin, calcium channel blocker, ACE inhibitors	Cardiovascular diseases
Pain in the morning and more pain at night	NSAIDs, Glucocorticoids	Arthritis
Increase in blood sugar level after meal	Sulfonylureas Insulin, pioglitazone	Diabetes mellitus
Cholesterol synthesis is generally higher during night than day time	HMG CoA reductase inhibitors Hypercholesterolemia	Hypercholesterolemia

Table.2.Formula for different batches of Glibenclamide Microsponges

F.no	Glibenclamide in (mg)	Ethyl cellulose in (mg)	Volume of Aqueous phase (ml)	Volume of Ethanol (ml)
F1	10mg	10mg	100ml	40ml
F2	15mg	10mg	100ml	40ml
F3	10mg	20mg	100ml	40ml
F4	10mg	15mg	100ml	40ml
F5	20mg	10mg	100ml	40ml

Formulation of pulsincap dosage forms:

The microsponges equivalent to 10mg (Second pulse) of drug were incorporated into the formaldehyde treated body of empty capsule shell. Then, it was plugged with formulated hydrogel plug and again incorporate immediate release layer (first pulse) equivalent to 10mg , there after fixed the normal gelatin capsule cap(Soluble) .Formula for different batches of pulsincap dosage forms were shown in **Table.3.**

Development Of Pulsincap Dosage Forms:

This delivery device uses the basic concept of pH and lag time dependent drug delivery system. The pulsincap is similar in appearance to the hard gelatin capsule, but the main body is water insoluble which was made by treatment of bodies of capsule shell with formaldehyde. The contents are contained within the body by a hydrogel plug, which is covered by water soluble cap.In *in-vivo* once the cap had dissolved, the hydrogel plug begins to swell. When the swelling reaches a critical point, the plug pops out of the capsule body and the contents are released. Depending on the properties of plug used, the time at which this occurs can be controlled.

CHARACTERIZATION

Characterization of Glibenclamide microsponges:

Fourier transform infrared spectroscopy (FTIR):

The FTIR spectroscopic studies were carried out for the standard Glibenclamide, Ethylcellulose and a physical mixture of Glibenclamide-Ethylcellulose and Glibenclamide microsponges formulation by KBr pellet technique using FT-IR spectrophotometer. The spectrum of standard Glibenclamide to assess the compatibility of the excipients with glibenclamide.

Scanning electron microscopy:

The morphology of microsponges was examined with a scanning electron microscope (FEI QUANTA FEG 200) operating at 15 kv.The samples were mounted on a metal stub with double adhesive tape and coated with platinum/palladium alloy under vacuum.

***In-vitro* dissolution studies of Microsponges:**

Microsponges equivalent to 10mg of drug were taken in 900ml of pH 6.8 phosphate buffer maintained at 37^{o}C.The dissolution media was rotated at 50rpm.At preset time intervals aliquots were withdrawn and replaced by an equal volume of dissolution medium to maintain constant volume. Withdrawn samples were filtered and suitably diluted with phosphate buffer pH 6.8 .The absorbance of the filtrates was determined at wavelength of 225nm against phosphate buffer of pH 6.8 as the blank. The amount of drug present in the filter was then determined from the calibration curve and cumulative percentage of drug release was calculated.

***In vitro* release studies of pulsincap:**

Dissolution studies were carried out in a USP XXIII dissolution apparatus I, in 900 ml medium at 37^{o}c at a rotation speed of 100 rpm.

Depending on the lag time the formulated pulsincaps were tested at 0.1M HCl initially for 2 hours and the rest of the dissolution was carried out in pH 6.8. At pre-set time intervals aliquots were withdrawn and replaced by an equal volume of dissolution medium to maintain constant volume. The samples withdrawn were then filtered. The absorbance of the filtrate was determined at 225nm against respective dilution media as blank.

Table.3.Formula for Pulsincap Dosage Forms

Trials	% of Formaldehyde used for treating the body of the capsule	Hydrogel plug used	Thickness of Hydrogel plug
P1	15%	Gelatin	5mm
P2	15%	Gelatin	8mm
P3	15%	Gelatin	10mm

RESULTS & DISCUSSION

Fourier Transform infra red spectroscopy (FTIR):

The Drug-Polymer compatibility was assessed by I.R spectra of the Drug, polymer, Drug and Polymer and prepared microsponges using BOMEN MB SERIES FTIR instrument. From the interpretation it is understood that there is no significant changes in the wave numbers of the drug and drug polymer combinations. Hence the drug and polymer are compatible with each other.

Mean particle size of Glibenclamide Microsponges

The mean particle size of the prepared microsponges were determined and represented in **Fig.4** As the polymer concentration and drug concentration increases, the particle size increases in the particle size due to increase in the polymer concentration was when compared to the particle size increase due to increase in the drug concentration. These results shown that the viscosity of internal phase was an important factor for the preparation of Microsponges. The average values were given.

Scanning electron microscopy

The scanning electron micrographs of optimized batch was taken and shown in the **Fig.5.**. Scanning electron microscopy indicated that the formulated microsponges are spherical and smooth surface.

In vitro release studies of microsponges:

Comparative study of the dissolution profiles of the drug from different batches of glibenclamide microsponges prepared with various drug: polymer ratios were studied and tabulated.The cumulative percentage of drug release was plotted against time versus drug release was shown in **Fig.6.**

The formulations F1, F2 and F5 released 42.73%, 63.69% and 60.92% respectively at the end of 8 hr, Whereas F3 and F4 have shown the release of 93.67% and 72.78% respectively at the end of 8 hr. Therefore, among the five formulations F3 was selected as the best formulation for the development of pulsincap dosage form based on its effective release nature and good encapsulation efficiency where the drug and polymer in the ratio of 10:20 mg

The *Invitro* release results showed that drug: polymer ratio influenced the release of drug from microsponges.

Fig.1.FTIR Spectrum of Glibenclamide.

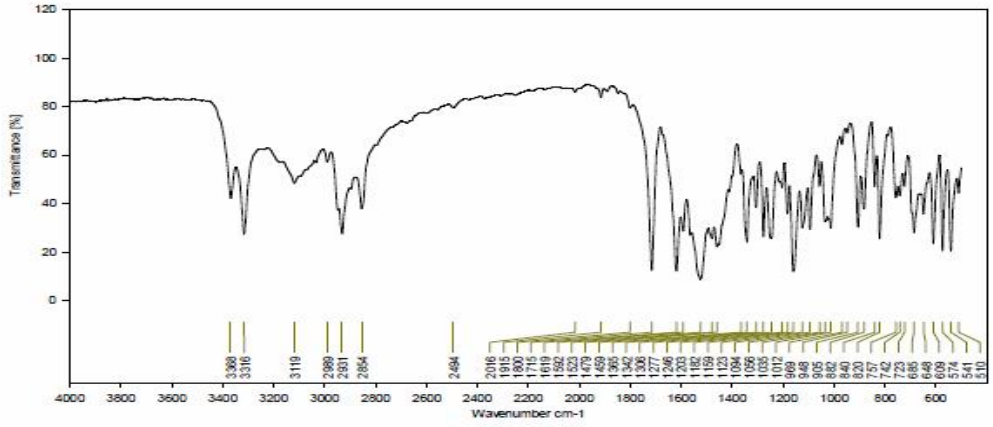


Fig.2.FTIR spectrum of Glibenclamide and Ethylcellulose

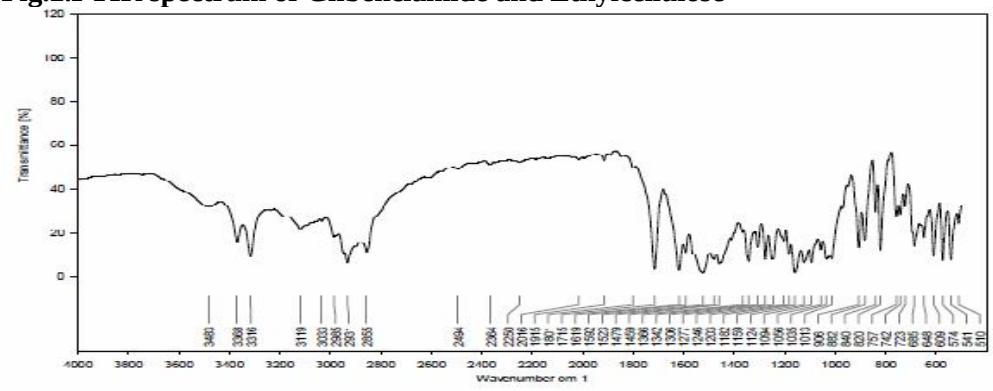


Fig.3. FTIR spectrum of Glibenclamide Microsponges

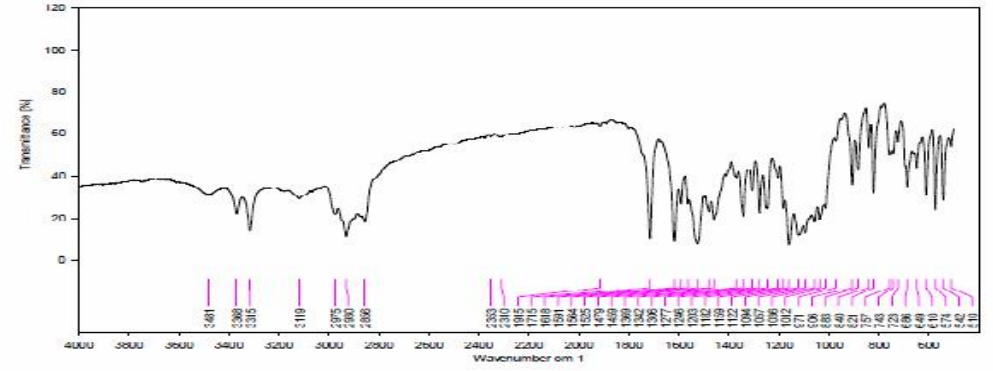


Fig.4.Mean particle size of Glibenclamide Microsponges

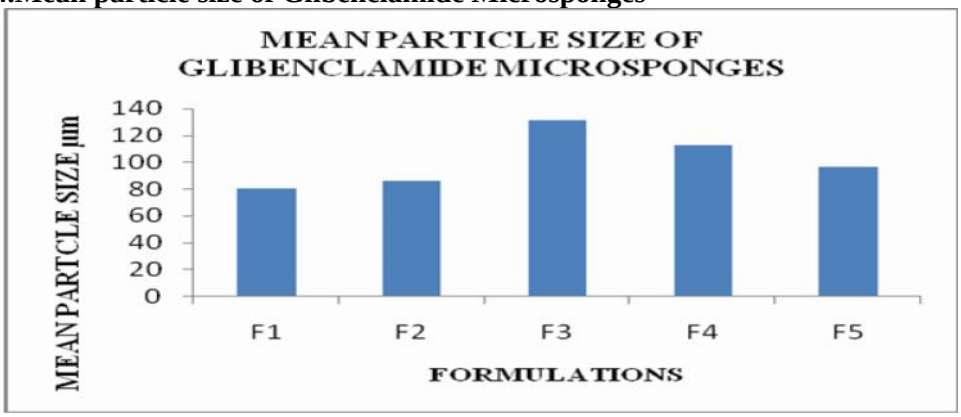


Table.4. *In-vitro* dissolution studies of Microsponges

S.No	Time (hrs)	Cumulative % Drug Release Of Glibenclamide Microsponges*				
		F-1	F-2	F-3	F-4	F-5
1	1	4.05±0.837	7.47±0.981	20.7±0.166	11.7±0.166	4.95±0.114
2	2	7.51±0.346	15.38±0.417	38.03±0.60	23.53±0.381	10.85±0.733
3	3	11.33±1.365	23.57±0.540	49.02±0.766	37.16±0.846	20.82±0.514
4	4	19.56±0.987	38.06±0.419	67.14±0.757	48.11±0.495	23.63±0.627
5	5	23.7±0.520	42.72±0.905	79.94±1.147	50.03±0.378	35.36±0.419
6	6	38.06±0.329	49.07±0.634	81.88±0.321	63.55±1.067	46.29±0.207
7	7	39.12±0.330	62.64±0.562	88.2±0.316	70.9±0.493	56.31±0.326
8	8	42.73±0.274	63.69±1.180	93.67±0.447	72.78±0.173	60.92±0.505

***Mean±Standard deviation (n=3)**

Fig.5. SEM Photograph of Glibenclamide Microsponges

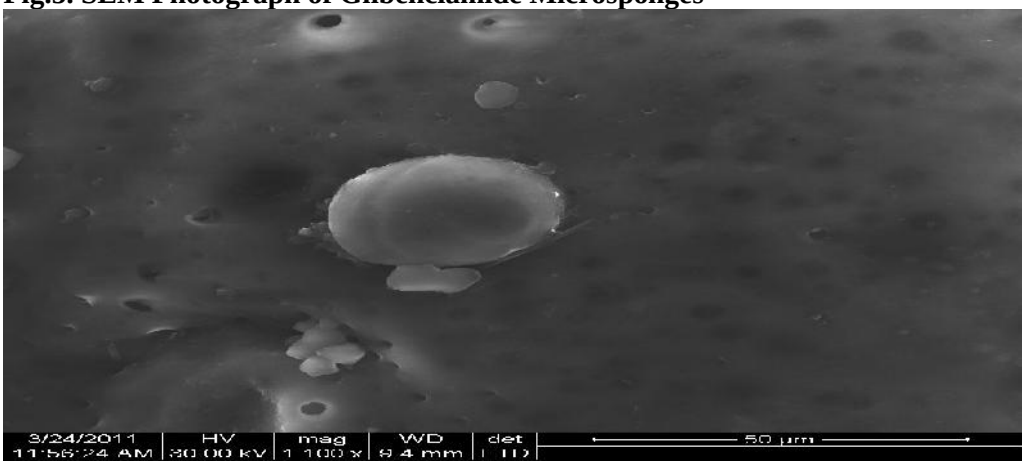
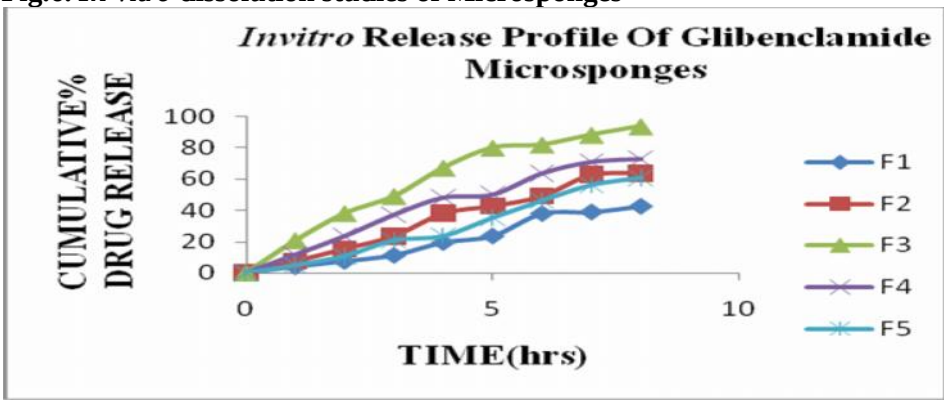


Fig.6. *In-vitro* dissolution studies of Microsponges



***In Vitro* Release Studies of Pulsincap:**

The In vitro dissolution test was done in pH media of 1.2 and 6.8 to simulate gastric and small intestine pH respectively. The formulations P1, P2, P3 released 90.8%, 92.88% and 88.91% of drug for an extended period of 8 hrs and the release profiles are shown in **Table.5 &6.**

Based on the *in vitro* release values **Trial 1** was selected for final formulation of pulsincap

It indicates that all the dosage forms released the drug uniformly without any significant difference. The cumulative percentage drug release was plotted against time (Fig.7). The graphical representation revealed that first pulse of drug was released immediately and the release of second pulse was started after lag time in order to swelling of hydrogel plug and the P-2 formulation showed better first pulse as well as second pulse release compared to P-1 and P-3 formulations.

Table.5. *In vitro* Release Studies of Immediate release layer in in pH media of 1.2

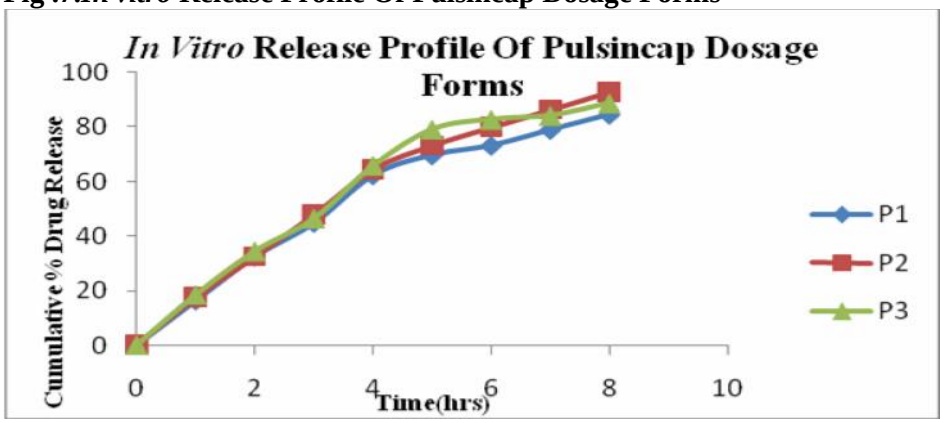
S.No	Trial 1	Trial 2	Trial 3
Assay	100.08%	100.15%	100.2%
Dissloution	99.58%CDR	96.64%CDR	94.82%CDR

Table.6. *In vitro* Release Profile Of Glibenclamide Pulsincap in in pH 6.8 buffer

Time (hrs)	Cumulative % Drug release* of Glibenclamide from Pusincap Dosage Forms		
	P1	P2	P3
1	18.9±0.563	17.5±0.421	18.5±0.452
2	34.4±0.836	32.49±0.325	34.45±0.325
3	47.18±0.561	47.86±0.521	46.55±0.408
4	66.22±0.459	64.52±0.303	65.93±0.690
5	79.93±0.372	73.21±1.340	79.21±0.650
6	81.88±0.667	79.89±0.511	82.86±0.808
7	86.4±0.843	86.34±0.85	84.29±0.263
8	90.8±0.750	92.88±0.297	88.91±0.779

***Mean ± Standard deviation (n=3)**

Fig .7.*In vitro* Release Profile Of Pulsincap Dosage Forms



SUMMARY & CONCLUSION

In the present study, an attempt has been made to prepare pulsincap to deliver two pulses of glibenclamide. Immediate release layer (First pulse) containing 6 mg of cross carmellose sodium was selected.

Microsponges (As Second pulse) using different ratios of drug and polymer prepared by Quasi-emulsion solvent diffusion technique. The prepared microsponges were characterized for particle size, Scanning electron microscopy, Entrapment efficiency and *Invitro* release studies. Batch **F3** formulation was selected for the development of pulsincap based on its effective release.

Hydrogel plugs of different thicknesses (5mm, 8mm and 10mm) were prepared and selected for the development of pulsincap in respect to achieve its maximum swelling ratio for the pulsatile release of drug. P2 pulsincap with the thickness of 8mm showed better release among other pulsincap formulations [P1(5mm) and P3(10mm)]. *Invitro* release studies were carried out for formulated pulsincaps. The release studies indicate that all the dosage forms released their first pulse within two hours and then release their second pulse after the swelling of hydrogel plug.

It has been concluded from the above investigation that pulsincap dosage form of Glibenclamide could be effectively control the blood glucose levels after breakfast and lunch in respect to release of two pulses (i.e. first pulse after breakfast and second pulse after lunch). Hence it is found to be suitable for the diabetic patient to manage the blood glucose levels which are high after food consumption.

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