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Research Article

Once-a-Day Pulsincap Drug Delivery system of Diltiazem for Better Maintenance of Angina Pectoris

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ABSTRACT

Present investigation aims colon specific, pulsatile device to achieve time release of Diltiazem, based on chrono-pharmaceutical consideration. Formulations of modified pulsincapdrug delivery of Diltiazem microspheres to achieve timed release in colon. The design consists of an insoluble hard gelatin capsule body, filled with Diltiazem Microspheres prepared by Emulsion-solvent evaporation method employing chitosan in varying ratio and sealed with a hydrogel plug; capsules were coated with 5% ethyl cellulose to prevent variable gastric emptying. Microspheres were evaluated for particle size, entrapment efficiency, SEM, IR and *in vitro* release study. Optimized microspheres were formulated as pulsatile device with different hydrogel polymers (Sodium alginate, Xanthan gum, Guar gum) and evaluated for dimensions, thickness of CAP and *in vitro* release kinetics study. Results: Spherical microspheres were confined by SEM with average particle size in range 260 - 360µm.Hydrogel plug showed a lag time of 4-8 hours with release of 83% at the end of 20 hours and followed zero order kinetics. Conclusion: Diltiazem microspheres can be formulated with chitosan. Desired lag period can be achieved and the order of sustaining capacity of pulsatile device is Sodium alginate, Guar gum and Xanthan gum for better maintenance of Angina Pectoris.

INTRODUCTION

Traditionally, drug delivery has meant for getting a simple chemical absorbed predictably from the gut or from the site of injection. Pharmaceutical drug discovery is very tedious and exorbitant process. For economic issues now-a-days the emphasis of pharmaceutical research is focused in discovery of more efficient drug delivery system of existing molecules than to discover new lead molecules, this led to the discovery of second-generation drug delivery systems with a goal of perfection of continuous, constant rate delivery of bioactive agents. However, living organisms are not "zero-order" in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle, which will maximize desired and minimize undesired drug effects [1, 2].

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Nowadays, concept of chrono-pharmaceutics has emerged, wherein; research is devoted to the design and evaluation of drug delivery systems that releases a therapeutic agent at a rhythm that ideally matches the biological requirement of given disease therapy. A number of chrono-therapeutic medications, aiming at synchronizing medications and the intrinsic biorhythms of disease have been developed by novel drug delivery technologies, which deliver drugs in accordance to the biological cycles, Circadian rhythms. Diseases where constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of "Pulsatile Drug Delivery Systems", is characterized by a lag time that is an interval of no drug release followed by rapid drug release [3]. Pulsatile systems are generally classified into time release systems & site specific systems, release from first class is controlled by the system where as the release from second class is controlled by the biological environment of the GIT; such as pH, enzymes etc.,

Angina is a strangling feeling in the chest due to ischemia of the heart muscle, due to general obstruction or spasm of the coronary arteries. Common types include stable, unstable & variant angina. Diltiazem, a potent vasodilator of coronary and peripheral vessels, member of the class known as calcium channel blockers, acts by increasing blood flow and variably decreasing the heart rate via strong depression of A-V node conduction, which reduces peripheral resistance and after load. It is extensively protein bound 70-80%, with oral bioavailability of 40% and $t_{1/2}$ of about 3-4.5 hours, requires a dosage of about 30mg thrice a day [4].

Diltiazem can be targeted to colon in a pH and time dependent manner, to modulate the drug level in synchrony with the circadian rhythm of angina pectoris. A pulsatile dosage form, taken at bedtime with a programmed start of Diltiazem release in early morning hours, can prevent a sharp increase of angina pectoris. Present research Diltiazem is formulated as a Pulsincap® system- consisting of water insoluble body containing the drug formulation system is closed with a swellable hydrogel.

MATERIALS AND METHODS

Diltiazem was obtained as gift sample from Dr. Reddy's laboratories, Hyderabad. Chitosan, Sodium alginate, Guar gum and Xanthan Gum were purchased form Yarrow chemical Products, Mumbai. Disodium hydrogen orthophosphate and Potassium hydrogen phosphate were purchased from Finar chemicals Ltd, Ahmadabad. And all other chemicals used were of analytical Grade.

***Drug polymer interaction (FTIR) study*:** FTIR spectroscopy was performed on Fourier transformed infrared spectrophotometer (IR-Affinity-1, Shimadzu, Japan). The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra were scanned in the wave number range of 4000- 600 cm^{-1}. FTIR study was carried on Diltiazem, physical mixture of diltiazem and polymer.

Formulation of Diltiazem Microspheres:

Emulsification – solvent evaporation method was used in the preparation of microspheres, accurately weighed chitosan were dissolved in 10 mL of 1% glacial acetic acid to form a homogenous polymer solution [5]. Core material, Diltiazem was added to the polymer solution and mixed thoroughly. At 30ºC, the organic phase was slowly poured into liquid paraffin (100 mL) containing 1% w/w of Span-80 under stirring at 900 rpm for 30min. Then 1mL of glutaraldehyde solution was added to form a smooth emulsion. Thereafter, it was allowed to attain room temperature and smooth walled, rigid and discrete microspheres were formed. Microspheres were collected by decantation and the product was washed with petroleum ether (40-60ºC) for three times and dried at room temperature for about 3 hours. The microspheres were then stored in a desiccator over fused calcium chloride [6]. Four batches of such microspheres were prepared with varying polymer concentrations shown in Table.1.

Table 1: Parameters of Diltiazem microspheres

Code	Ratio	Average particle size (µm)	Drug content (%)	Entrapment Efficiency (%)
A1	1:0.5	360	61.7	75.09
A2	1:1	336	63.3	79.56
A3	1:1.5	296	72.4	81.4
A4	1:2	260	79.84	85.83

Evaluation of diltiazem Microspheres:

Surface Morphology

Scanning electron microscopy (SEM) JEOL JSM-6360 has been used to determine surface topography, texture of diltiazem microspheres. The solid sample for SEM analysis was coated with a thin layer of platinum using physical vapor deposition (PVD) process at 30mA current from the distance of 50mm during 180 seconds [7].

Particle size determination

All the prepared batches A1 to A4 were analyzed for particle size determination using optical microscope. First the eye piece micrometer was calibrated using a stage micrometer and then on a clean glass slide, a small quantity of microspheres was placed using a thin brush. Then they were covered carefully with a cover-slip and observed under 10 x magnifications [8, 9]. A hundred particles each were counted and average particle diameter was calculated by the following Eq. (1):

$$Average\ particle\ diameter = \frac{\Sigma n \times d}{N} \quad \text{Eq. (1)}$$

Where, n = Total no. of particles in that size interval; d = Diameter of the particles of that size range; N = Total no. of particles.

Percentage yield

Practical yield was calculated as the weight of Diltiazem microspheres recovered from each batch in relation to the sum of initial materials used. The percentage yield of prepared Diltiazem microspheres was determined by using the following equation Eq. (2):

$$Percentage\ Yeild = \frac{Practical\ Yeild}{Theoretical\ Yeild}\ X\ 100 \qquad \text{Eq. (2)}$$

Percentage drug entrapment (PDE)

Practical drug loading was analyzed by weighing amount of diltiazem microspheres equivalent to 100 mg of Diltiazem and dissolved in 100 mL of distilled water and kept overnight for complete dissolution of Diltiazem in water. Further dilutions were made to make 10 µg/mL concentration. The absorbance of solutions was measured at 268 nm using double beam UV-Visible spectrophotometer. Theoretical drug loading was calculated assuming that the entire diltiazem present in polymer solution entrapped in diltiazem microspheres [10].

Efficiency of drug entrapment for each batch was calculated in terms of percentage drug entrapment as per the following equation Eq. (3):

$$PDE = \frac{Practical\ Drug\ loading}{Theoretical\ Drug\ loading}\ X\ 10 \qquad \text{Eq. (3)}$$

***Invitro* dissolution studies**

Invitro dissolution profile of each formulation was carried out using USP XXIII apparatus with rotating basket method in different media like stimulated gastric fluid pH 1.2 buffer for 2 hours (since the average gastric emptying time is 2 hours), stimulated intestinal fluid pH 6.8 buffer for 3 hours (average small intestinal transit time is 3 hours) and colonic fluid pH 7.4 buffer for subsequent hours. The dissolution media was maintained at 37± 0.5ºC, at rotation speed of 50rpm. Diltiazem microspheres equivalent to 50mg Diltiazem was loaded into the basket of dissolution apparatus. 5mL of aliquots was withdrawn at predetermined time intervals maintaining sink conditions. The aliquots were diluted and analyzed spectro-photometrically at 268 nm to determine the concentration of drug present [10].

Drug release kinetics from Microspheres

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q_0 -Q) v/s t], Higuchi's square root of time(Q v/s $t^{1/2}$) and Korsemeyer Peppas double log plot (log Q v/s log t), where Q is the cumulative percentage of drug released at time t and (Q_0 – Q) is the cumulative percentage of drug remaining after time t.

Preparation of crossed-linked Gelatin capsules:

Formaldehyde treatment

About 100 hard gelatin capsules size '0' were taken with their body separated from cap. A beaker containing 25 mL of 15% v/v of formaldehyde solution was placed in an empty glass desiccator. To this 5g of potassium permanganate was added. Body of the capsules were kept on a wire mesh which was placed on top of beaker to ensure that formaldehyde vapors pass through them and the desiccator was tightly closed and sealed for 12 hours. Then they were removed and kept on filter paper and dried for 48 hours to ensure completion of reaction between gelatin and formaldehyde vapors, afterwards the capsules were kept in an open atmosphere, to facilitate removal of residual formaldehyde. These capsule bodies were capped and stored in a polythene bag [11].

Evaluation of Formaldehyde treated capsules: Physical Tests

The capsules treated with formaldehyde were evaluated for various physical properties like identification attribute of size, visual defects, dimensions and solubility tests.

Chemical test: Qualitative test for free Formaldehyde

About 25 formaldehyde treated bodies were cut into small pieces and taken into a beaker containing distilled water (40 mL). This was stirred for 1 hour with magnetic stirrer, to solubilize the free formaldehyde. The solution was filtered into a 50 mL volumetric flask, washed with distilled water and volume was made up to 50 mL with washings. To 1 mL of sample solution taken in a graduated test tube, 4 mL of water and 5 mL of acetyl acetone solution was added and placed in a water bath at 40^0c for 40 min; also a reference solution containing 1 mL of standard formaldehyde solution was kept. The sample solution should not be colored more intensely than the standard solution inferring that less than 20µg/mL of free formaldehyde is present in 25 capsules body [6].

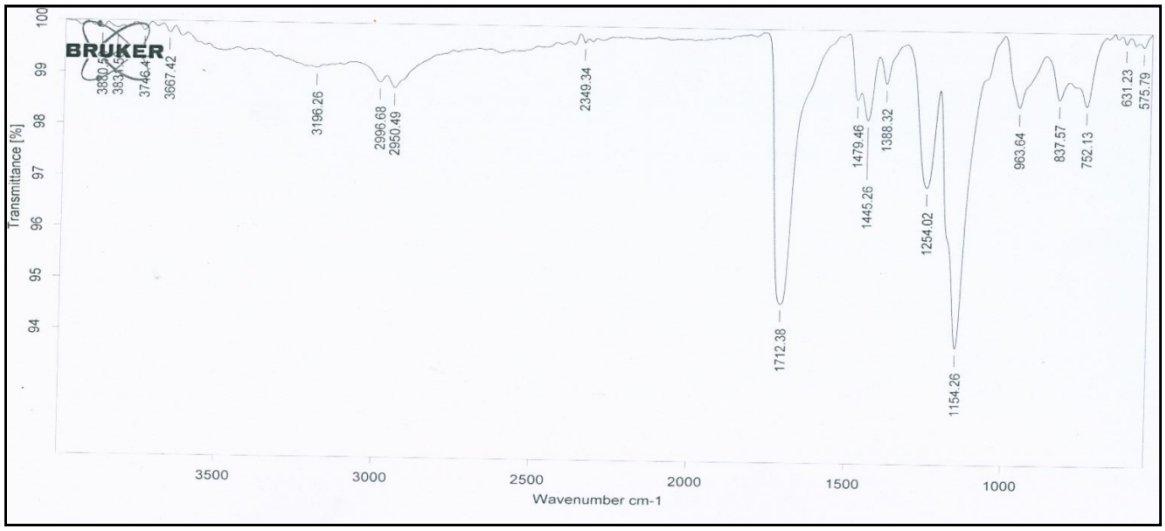

Figure 1a: IR spectrum of Diltiazem pure drug

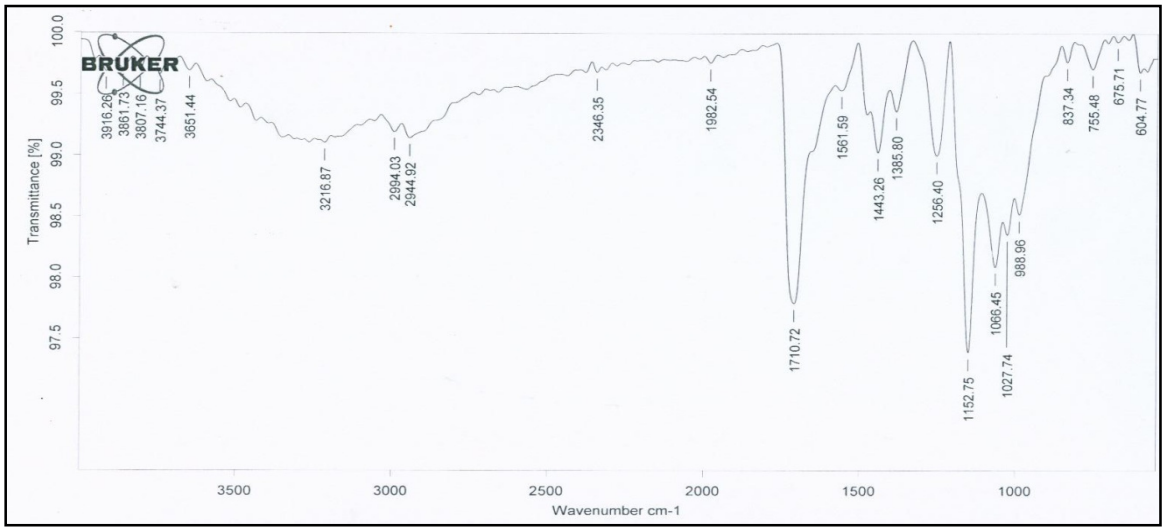

Figure 1b: IR spectrum of Diltiazem + chitosan polymer

Formulation of modified pulsincap Drug Delivery System

Formaldehyde treated hard gelatin capsules of 'size 0' were chosen for the formulation. The bodies and caps were separated manually. Diltiazem microspheres equivalent to 50 mg of Diltiazem were accurately weighed and filled into bodies by hand. Capsules containing Diltiazem microspheres were then plugged with polymers like sodium alginate (B1,B2, B3), Xanthan gum (C1,C2, C3) and Guar gum (D1, D2, D3) at different concentrations (20 mg, 40 mg, 60 mg respectively) and loaded with 10mg of pure drug as loading dose. Then capsules were Dip coated with 5% ethyl cellulose (prepared using acetone: ethanol (8:2) as solvent and 0.5% dibutyl phthalate as plasticizer) to prevent variable gastric emptying. Coating was repeated until an 8-12% increase in weight. Percentage weight gain of the capsules before and after coating were determined [12-14].

Evaluation of modified Pulsincap

Thickness of ethyl cellulose coating

Thickness of ethyl cellulose coating was measured using caliper; expressed in mm.

Weight variation

10 capsules were selected randomly from each batch and weighed individually for weight variation. The test requirements are met if none of the individual weights are less than or more than 110% of the average.

***In vitro* release studies of Pulsin capsules**

Invitro dissolution studies of pulsin capsules with various hydrogel plugs were carried as mentioned for diltiazem microspheres.

Kinetics of drug release

Dissolution data obtained was fitted to zero order, first order, Higuchi and Koresmayer-Peppas to understand the order and mechanism of drug release from the Pulsincap [15].

RESULTS AND DISCUSSION

Drug polymer interaction (FTIR) study

The spectrum of Diltiazem has shown functional groups at frequencies 3880.50, 3831.52, 3746.4, 3667.42, 3196.26, 2996.68, 2950.49, 2349.34, 1712.38, 1479.46, 1445.26, 1388.32, 1254.02, 1154.26, 963.64, 837.57, 752.13, 631.23, and 575.79 (Figure 1a). From the spectra of Diltiazem pure drug, combination of Diltiazem with polymer was observed that all characteristic peaks of Diltiazem were present in the combination spectrum, thus indicating compatibility of drug and polymer (Figure 1b).

Morphology of Diltiazem microspheres

Scanning electron microscopy revealed formation of spherical microspheres with smooth surface texture shown in Figure 2.

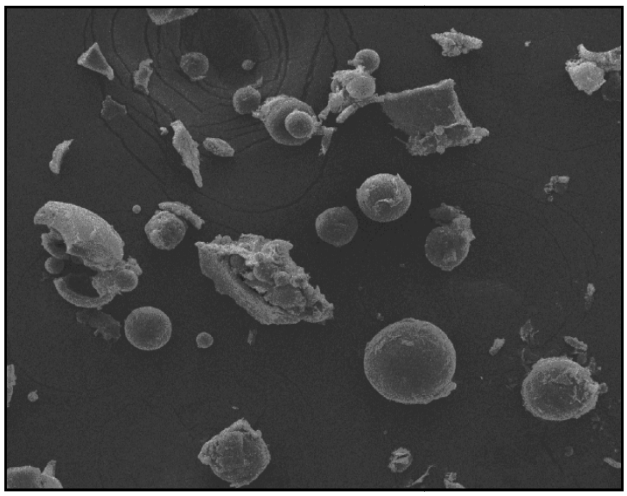

Figure 2: SEM of Diltiazem microspheres

Particle size determination

The frequency size distribution analysis of Diltiazem microspheres are in size range of 260 - 360 µm and tabulated in Table 1. From the data it can be understood that effect of increasing chitosan concentration was more prominent which decreased the average particle size of microspheres.

Entrapment efficiency

The entrapment efficiency of the diltiazem microspheres were in the range of 75.09% - 85.83% shown in Table 1. Maximum percentage entrapment efficiency was observed for formulation A4 where in the effect of chitosan was significant in drug entrapment.

In vitro Release studies of Diltiazem microspheres

In vitro release profiles of diltiazem microspheres were shown in Figure 3. Formulation A4 with drug polymer ratio 1:2 showed a maximum release of 75.56 % at the end of 12hours. Chitosan has played a pivotal role in retarding the drug release. Increase in concentration of chitosan has significantly sustained the drug release which is evident from Figure 3.

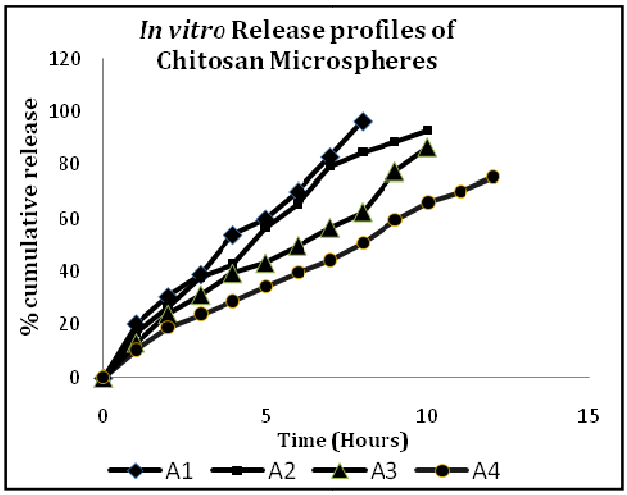

Figure 3: *In vitro* dissolution profile of Diltiazem microspheres

Release Kinetics

The co-efficient of determination indicated that the release data best fits with zero order kinetics. Higuchi equation explains the diffusion controlled release mechanism. The r^2 values of different kinetic models of diltiazem microspheres were also shown in Table 2.

Table 2: Regression coefficient (r^2) values of different kinetic models of diltiazem microspheres

Code	Zero Order Plot	First Order Plot	Higuchi's Plot	Korsemeyer Peppas
A1	0.976	0.799	0.944	0.987
A2	0.986	0.954	0.956	0.985
A3	0.973	0.886	0.934	0.970
A4	0.980	0.965	0.942	0.997

Additional evidence for diffusion controlled mechanism was obtained by fitting the release data with Korsemeyer-Peppas equation. The diffusion exponent 'n' values were in the range of 0.5 to 1 for Diltiazem microspheres indicating Non-Fickian.

Evaluation of Formaldehyde treated capsules: Dimensions

Changes in the dimensions of capsule are indicated in Table 3.

Table 3: Dimensions of Capsules before and after formaldehyde treatment

Evaluation	Formaldehyde treatment	
	Before	After
Average capsule length	20.6 mm	19.3 mm
Average diameter of capsule body	7.3 mm	6.7 mm
Average length of capsule body	17.7 mm	16.8 mm

Solubility

In all cases normal capsules, both cap and body dissolved within fifteen minutes. But formaldehyde treated capsules, only the cap dissolved within 15 min, whilethe body remained intact for about 24 hours.

Qualitative test for free Formaldehyde

The orally tolerated limit of formaldehyde is 0.1% [16]. The sample solution was not more intensity colored than the standard solution inferring that less than 20µg of free formaldehyde was present in 25 capsule bodies.

Coating layer thickness of ethyl cellulose coated capsules

The coating layer thickness of ethyl cellulose coated capsules is tabulated in Table 4.

Table 4: Coating layer thickness of ethyl cellulose coated capsules

Formulation code	Thickness of coating layer(mm)
B1	0.052
B2	0.055
B3	0.054
C1	0.061
C2	0.059
C3	0.067
D1	0.071
D2	0.069
D3	0.072

In vitro release profiles of Pulsincap formulation

During dissolution studies, it was observed that the enteric coat of ethyl cellulose was intact for 2 hours in pH1.2, but dissolved in intestinal pH leaving the soluble cap, which dissolved in pH 7.4, and then the exposed polymer plug swelled absorbing surrounding fluid, and released the drug through swollen matrix. A soft mass formed after complete wetting of plug was easily ejected out of the capsule body, releasing the chitosan microspheres into simulated colonic fluid (pH 6.8 phosphate buffer). Initial burst release is due to the loading dose.

Formulations with sodium alginate as hydrogel plug has shown a desirable lag time of 6-8 hours and have sustained the drug release for prolong hours when compared with Guar gum which shown a short lag time of 3-7 hours and Xanthan gum with a lag time of 2-5 hours.

The formulations B1, B2 & B3 showed 44.06 %, 39.74 % & 34.46 % respectively at the end of 12th hour and showed 81.86%, 77.34% & 75.56% at the end of 20th hour respectively (shown in Figure 4).The formulations C1, C2 & C3 showed 50.787%, 44.406% & 39.741% respectively at the end of 12th hour and showed 81.49 %, 79.541 % & 77.621 % at the end of 20th hour respectively (shown in Figure 5).The formulations D1, D2 & D3 showed 50.78 %, 39.74 % &34.46 % respectively at the end of 12th hour and showed 83.043 %, 78.376 % & 79.5656 % at the end of 20th hour respectively (shown in Figure 6).

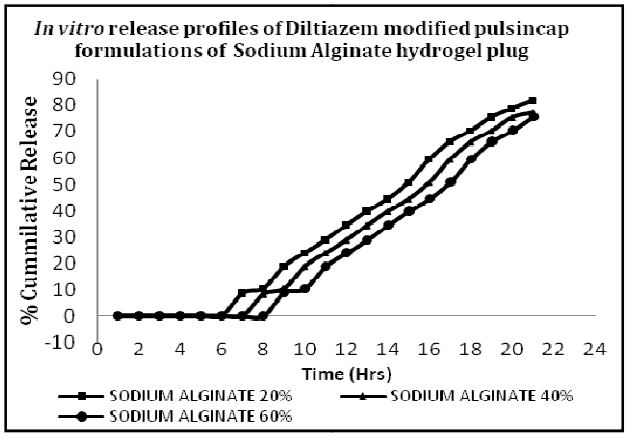

Figure 4: *In vitro* release profiles of Diltiazem modified pulsincap formulations of sodium alginate hydrogel plug

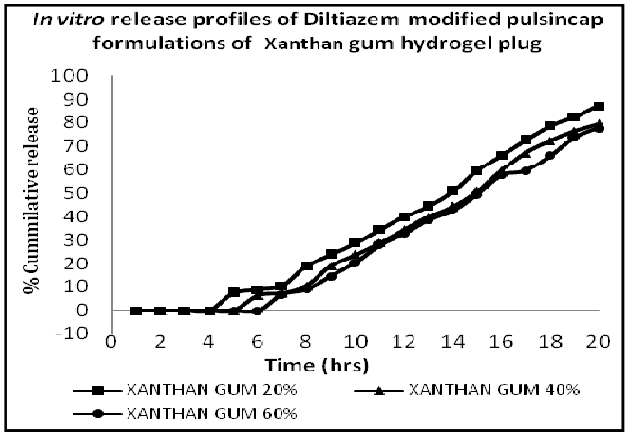

Figure 5: *In vitro* release profiles of Diltiazem modified pulsincap formulations of xanthan gum hydrogel plug

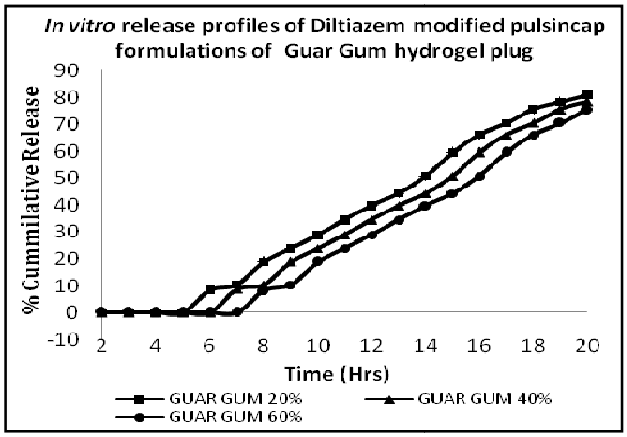

Figure 6: *In vitro* release profiles of Diltiazem modified pulsincap formulations of guar gum hydrogel plug

Release kinetics study

The release of Diltiazem from the pulsincap followed zero order kinetics which is indicated from their correlation coefficient values shown in Table 5.

Table 5: Regression coefficient (r^2) values of different kinetic models of diltiazem modified pulsincap formulations

	ZERO ORDER	FIRST ORDER	HIGUCHI	KORESMAYER PEPAS	
				r^2	n
B1	0.995	0.926	0.991	0.984	1.810
B2	0.995	0.909	0.985	0.980	1.458
B3	0.995	0.880	0.991	0.979	1.373
C1	0.987	0.955	0.978	0.986	1.562
C2	0.992	0.932	0.966	0.988	1.789
C3	0.989	0.906	0.952	0.990	1.969
D1	0.990	0.950	0.979	0.986	1.578
D2	0.991	0.934	0.979	0.984	1.798
D3	0.996	0.902	0.986	0.980	1.863

In the case of the controlled or sustained release formulations, diffusion, swelling, and erosion are the three most important rate controlling mechanisms. Formulation containing swelling polymers show swelling as well as diffusion mechanism because the kinetic of swelling include relaxation of polymer chains and imbibitions of water, causing the polymer to swell and changing it from a glassy to rubbery state. The diffusion exponent n is the indicative of mechanism of drug release from the formulation. For a swellable drug delivery system, the n value of 0.45 is indicative of Fickian diffusion controlled drug release, n value between0.5 and 0.85 signifies anomalous (non-Fickian) transport; n value of 0.85 indicates case II transport, and n value greater than 0.85 indicates super case II transport [17, 18].

Among three polymers, sodium alginate was found to be better in controlling the release with a good lag time and pulsatile release of Diltiazem. The mechanism of drug release was found to be diffusion from correlation of Higuchi plots, where r^2 values obtained were near to 1. From the slopes of Korsemeyer-Peppas plot the mechanism of diffusion was found to be Super-case II transport. i.e., diffusion coupled with erosion as the values of the slopes are greater than 1.

CONCLUSION

Present investigation aims to explore the feasibility of time and pH dependent colon specific, pulsatile drug delivery system of Diltiazem to treat angina pectoris. Based on the results and discussions it was concluded that diltiazem had no interactions with chitosan as proved by FTIR analysis. Also based on evaluation data chitosan was effective in providing controlled zero-order release of Diltiazem from microspheres. Hence, both can be used in formulation of microspheres. A4 was selected as the optimal formulation and was considered for formulation of Pulsin capsule. From results, it was evident that polymers sodium alginate, Xanthangum and Guar gum can be used as hydrogel plugs to lag drug release until the formulation reaches colon with order of sustaining capacity of polymer is Sodium alginate>Guar gum >Xanthan Gum. It was concluded that modified pulsincap drug delivery is suitable for the delivery of drug according to circadian rhythms of angina. Future studies in animals and human beings would be necessary to establish its safety, efficacy and acceptability.

COMPETING INTEREST

The authors declare that they have no competing interest

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