International Journal for Pharmaceutical Research Scholars (IJPRS)

V-3, I-3, 2014 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Chronotherapeutic Drug Delivery System of Diltiazem Microspheres by Using Pulsincap Technology for the Treatment of Hypertension

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Manuscript No: IJPRS/V3/I3/00387, Received On: 16/09/2014, Accepted On: 19/09/2014

ABSTRACT

The aim of the present work was to develop colon specific drug delivery system for Diltiazem using natural polymers as carriers. We have investigated colon specific, pulsatile device to achieve time and site specific release of Diltiazem based on chronopharmaceutical considerations. The basic design consists of an insoluble hard gelatin capsule body, filled with Diltiazem surface solid dispersions and sealed with guar gum hydrogel plug. The entire capsule was coated with ethyl cellulose, so that the variability in gastric emptying time can be overcome and a colon specific release can be achieved. Surface solid dispersions (SSDs) of Diltiazem were prepared using natural polymers such as Guar gum (GG), sodium alginate and Xanthan gum (XG) in the weight ratios of 1:2,1:4 and 1:6 by using emulsification solvent evaporation method. Physicochemical properties of the prepared SSD were characterized by FTIR and SEM. Optimized SSD were obtained by practical yield, drug content, solubility and dissolution studies and were selected for further fabrication of pulsincaps. Guar gum was used as hydrogel plug material to maintain a suitable lag period. The prepared pulsincaps were evaluated for in-vitro release. Pulsincap formulated with Diltiazem : Sodium alginate at 1:2 ratio of surface solid dispersions showed highest drug release over the period of 19 hr and release was found to be Higuchi model kinetics. The present research study results have confirmed that the modified pulsincap of Diltiazem is a suitable device for the time dependent and site specific delivery to the colon segment of GIT.

KEYWORDS

Pulsatile, Colon Specific, Diltiazem, Chitosan, Guargum, Xanthan Gum, Sodium Alginate

INTRODUCTION

Angina (an-JI-nuh or AN-juh-nuh) is chest pain or discomfort that occurs when an area of heart muscle doesn't get enough oxygen-rich blood. Angina may feel like pressure or squeezing in chest. The pain also may occur in shoulders, arms, neck, jaw, or back. It can feel like indigestion. Angina is usually a symptom of CAD, the most common type of heart disease.

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CAD occurs when a fatty material called "plaque "(plak) builds up on the inner walls of the coronary arteries. These arteries carry oxygen-rich blood to heart. When plaque builds up in the arteries, the condition is called "atherosclerosis".

Diltiazem hydrochloride is a calcium channel blocker. It also acts as cardiovascular agent and as vasodilator agent. It inhibits the influx of extracellular calcium across both the myocardial and vascular smooth muscle cell membrane. The resultant inhibition of the contractile processes of the myocardial smooth muscle cell

leads to dilation of the coronary and systemic arteries and improved oxygen delivery to the myocardial tissue. The half life of Diltiazem hydrochloride is 3 to 4.5 hrs, protein binding 70% to 80%, normal dose is 30mg orally.

A pulsatile drug delivery system that can be administered at night (before sleep) but that release drug in early morning would be a promising chronopharmaceutic system. Drug pharmacokinetics too shows circadian variation for various anti-hypertensive drugs which have greater absorption in morning as compared to evening, and site-specific absorption from colon. Therefore, to develop dosage form for chronopharmacotherapy the desired drug release should be time-specific as well as site-specific also. The site-specific delivery of the drugs to the target sites has the potential to reduce the side effects and improved the pharmacological response. The widely used approaches for colon specific targeting are bacterially triggered, pressure controlled, pH dependent and time dependent control drug delivery system

In this context, Diltiazem hydrochloride has been found to be suitable drug candidate for the development of time and pH dependent pulsatile drug delivery system. Therefore, the objective of the present study is to develop a pulsatile drug delivery system for Diltiazem hydrochloride which is beneficial for the chronotherapeutic treatment of angina pectoris.

MATERIALS AND METHOD

Diltiazem hydrochloride was gifted from Dr. Reddy's laboratories, Hyderabad, chitosan, guar gum and xanthan gun were gifted from Yarrow chem. Products, Mumbai. Sodium alginate is purchased from Finar chemicals Ltd, Ahmedabad. Redson Pharmaceuticals Pvt Ltd. has also supplied hard gelatin capsules as gift.

Preparation of Diltiazem Microspheres

Method used: Emulsification – Solvent Evaporation Method

Accurately weighed chitosan were dissolved in 10ml of 1% glacial acetic acid to form a homogenous polymer solution. Core material, Diltiazem was added to the polymer solution and mixed thoroughly. This organic phase was slowly poured at 30ºC into liquid paraffin (100 ml) containing 1% w/w of span-80 with stirring at 900 rpm for 30min and then add 1ml of glutaraldehyde solution to form a smooth emulsion. Thereafter, it was allowed to attain room temperature and smooth walled, rigid and discrete microspheres were formed. The microspheres were collected by decantation and the product was washed with petroleum ether (40-60ºC), three times and dried at room temperature for 3 hrs. The microspheres were then stored in a desiccator over fused calcium chloride.

Table 1: Formulation formula for Diltiazem microspheres using chitosan

S. No	Batch code	Drug: polymer ratio
1	A-1	1:0.5
2	A-2	1:1
3	A-3	1:1.5
4	A-4	1:2

Preparation of Crossed-Linked Gelatin Capsule

Formaldehyde Treatment

About 100 hard gelatin capsules size '0' were taken. Their body was separated from the cap and placed on a wire mesh. 25 ml of 15% v/v of formaldehyde solution was taken in a beaker and kept in dessicator. To this 5 g of potassium permanganate was added.

On the top of beaker a wire mesh containing the body of the capsule was kept and immediately the dessicator was tightly closed and sealed. The body of the capsule was made to react with formaldehyde vapors for 12 h.

Then they were removed and kept on a filter paper and dried for 48 h 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 with untreated cap and stored in a polythene bag.

Formulation of Modified Pulsincap Drug Delivery System

Formaldehyde treated hard gelatin capsules of size '0' were chosen for the formulation. The bodies and caps separated manually. Diltiazem microspheres equivalent to 50 mg of Diltiazem were accurately weighed and filled into the treated bodies by hand filling. The capsules containing the Diltiazem microspheres were then plugged with different polymers like sodium alginate (B1 , B2, B3), Xanthan gum (C1 ,C2, C3) and Guar gum (D1, D2 , D3) at different concentrations and loaded with 10mg of pure drug as a loading dose. The treated capsules were completely coated with 5% ethyl cellulose to prevent variable gastric emptying. Coating was repeated until 8-12% increase in weight of capsules. percentage weight gain of the capsules before and after coating was determined. (5% w/v solution of ethyl cellulose was prepared by using acetone: ethanol (8:2) as solvent and dibutyl phthalate as plasticizer (0.5%)). Dip coating method was followed to develop the pulsincap. The capsules were alternatively dipped in 5% ethyl cellulose solution and dried. Coating was repeated until an expected weight gain 8-12% was obtained and capsules resists disintegration in 0.1N Hcl for minimum of 2 h).

Evaluation of Diltiazem Microspheres

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- 400 cm^{-1} . FTIR study was carried on Diltiazem, physical mixture of Diltiazem and polymer, Diltiazem microspheres and blank microspheres.

Surface Morphology (SEM)

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of brass stub and coated with in an ion sputter. Picture of Diltiazem microspheres were taken by random scanning of the stub.

Frequency Distribution Analysis

Determination of average particle size of Diltiazem microspheres was carried out by optical microscopy in which stage micrometer was employed. A minute quantity of Diltiazem microspheres was spread on a clean glass slide and average size of 300µm Diltiazem microspheres was determined in each batch. In order to be able to define a frequency distribution and compare the characteristics of particles with many different diameters, the frequency distribution can be broken down into different size ranges, which can be presented in the form of a histogram. Histogram presents an interpretation of the frequency distribution and enables the percentage of particles having a given equivalent

Percentage Yield

Percentage practical yield of Diltiazem is calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of Diltiazem microspheres recovered from each batch in relation to the sum of starting material. The percentage yield of prepared Diltiazem microspheres was determined by using the formula

% yield = Practical yield/ theoretical yield×100

Determination of Percentage Drug Entrapment (PDE)

Efficiency of drug entrapment for each batch was calculated in terms of percentage drug entrapment as per the following formula

Practical drug entrapment = practical drug loading/ theoretical drug loading × 100

Theoretical drug loading was determined by calculation assuming that the entire Diltiazem present in the polymer solution used gets entrapped in Diltiazem microspheres, and no loss occurs at any stage of preparation of Diltiazem microspheres.

Practical drug loading was analyzed by using the following procedure

To the 100mg of weighed microspheres add 100ml of distilled water and stir it until the drug present on the surface of the microspheres is dissolved. Filter the solution and check the absorbance of the sample. To the above water treated microspheres add 100ml of water and keep for stirring on magnetic stirrer until the entrapped drug is dissolved from the microspheres for 24h.then check the absorbance of the sample.

In- vitro Dissolution Studies

In - vitro dissolution profile of each formulation was determined by employing USP XXIII apparatus by rotating paddle method in different media like stimulated gastric fluid p^H 1.2 buffer for 2 h (since the average gastric emptying time is 2 h), stimulated intestinal fluid p^H 7.4 buffer for 3h (average small intestinal transit time is 3 h) and colonic fluid p^H 6.8 buffer for subsequent h. The dissolution media were maintained at a temperature of 37± 5ºC, the speed rotation of paddle maintained at 50 rpm. Diltiazem microspheres equivalent to 50 mg Diltiazem was loaded into the paddle of the dissolution apparatus. 5 ml of the samples withdrawn from dissolution media at suitable intervals and same amount was replaced with fresh buffer. The absorbance was measured at 268 nm.

Data obtained was also subjected to kinetic treatment to understand release mechanism.

Kinetics of Drug Release

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) is the respectively, 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.

In short, the results obtained from in vitro release studies were plotted in four kinetics models of data treatment as follows:

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation)

Evaluation of Formaldehyde Treated Capsules

Physical Tests

A. Identification Attributes

The size '0'capsules chosen were opaque, with white colored body and yellow cap. They were lockable type, odorless, soft and sticky when touched with wet hand. After treating with formaldehyde, there were no significant changes in the capsules. The body of the capsule was hard and non-sticking even when touched with wet hand.

B. Visual Defects

Among 100 capsules body which were treated with formaldehyde, about 15 to 20 of them were found to be shrunk or distorted into different shapes due to the complete loss of moisture.

C. Solubility Test for Formaldehyde Treated Capsules

The empty hard gelatin capsule was stirred vigorously in 100ml of dissolution medium taken in 250 ml beaker, with magnetic stirrer. The dissolution medium was used as water, 1.2 pH, 7.4 pH and 6.8 pH phosphate

buffer. The time at which the capsule dissolves or forms a soft mass was noted.

D. Dimensions

Variation in dimensions between formaldehyde treated and untreated capsules were studied. The length and diameter of capsules were measured before and after formaldehyde treatment, using vernier caliper due to loss of water vapour from capsules.

Chemical Test

A. Qualitative Test for Free Formaldehyde

a. Standard Formaldehyde Solution

Dilute a suitable volume of formaldehyde solution with water to give a solution containing 20 µ g/ml concentration of formaldehyde.

b. Sample Solution

25 formaldehyde treated capsule bodies were cut into small pieces and taken into a beaker containing distilled water (40 ml). This was stirred for 1h with a 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 water.

Procedure

To 1 mL of sample solution in a test tube, add 4 mL of water and 5 mL of acetyl acetone solution, place the test tube in a water bath at 40 ^{0}C for 40 min, at the same time reference solution is placed in the same manner using 1 mL of standard formaldehyde solution. The sample solution is not more intensely colored than the standard solution inferring that less than 20 µ g/mL of free formaldehyde is present in 25 capsules body.

Evaluation of Modified Pulsincap

Thickness of Ethyl Cellulose Coating

The thickness of the ethyl cellulose coating was measured by using vernier caliper. Its values were 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 Profile

In -vitro dissolution profile of each formulation was determined by employing USP XXIII apparatus by rotating paddle method in different media like stimulated gastric fluid p^H 1.2 buffer for 2 h (since the average gastric emptying time is 2h), stimulated intestinal fluid p^H 7.4 buffer for 3h (average small intestinal transit time is 3h) and colonic fluid p^H 6.8 buffer for subsequent h.

The dissolution media were maintained at a temperature of 37± 5ºC, the speed rotation of basket maintained were 50 rpm. Diltiazem microspheres equivalent to 50 mg Diltiazem modified pulsing capsules were placed in paddle type dissolution vessel to prevent floating. 5 mL of the samples withdrawn from dissolution media at suitable intervals and same amount was replaced with fresh buffer. The absorbance was measured at 268 nm.

Data obtained was also subjected to kinetic treatment to understand release mechanism.

Kinetics of Drug Release

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) is the respectively, 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.

In short, the results obtained from in vitro release studies were plotted in four kinetics models of data treatment as follows:

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- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs log Time (Peppas exponential equation).

RESULTS AND DISCUSSION

Drug Polymer Interaction (FTIR) Study

Table 2: Table showing the peaks of pure drug

S.No.	Peaks(nm)	Groups	Stretching/ Deformation
1	2950.49	C-H	Stretching
2	1712.38	C=0	Stretching
3	1445.26	C=C	Stretching
4	1388.32	C-H	Deformation
5	1154.26	C-N	Stretching
6	963.64	C-O	Stretching
7	752.13	C-H	Rocking
8	631.23	C-S	Stretching

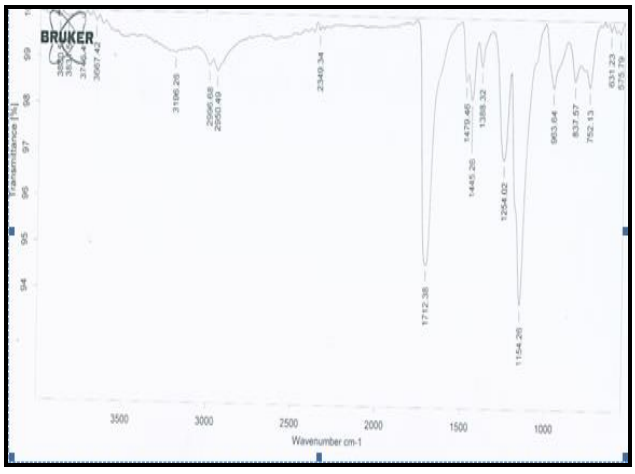

Figure 1: IR spectrum of Diltiazem pure drug

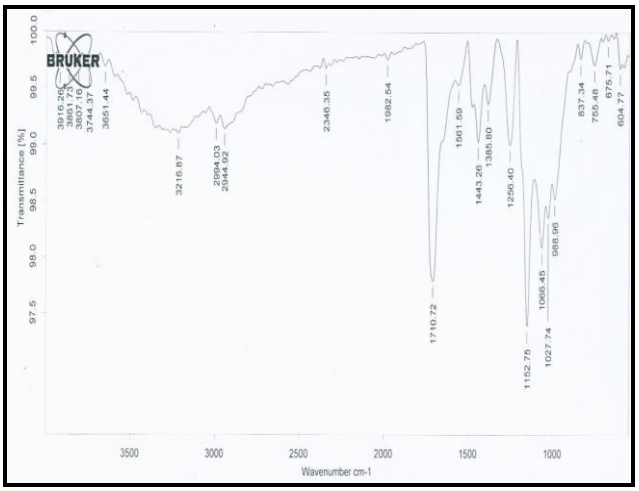

Figure 2: IR spectrum of Diltiazem + chitosan polymer

Surface Morphology (SEM)

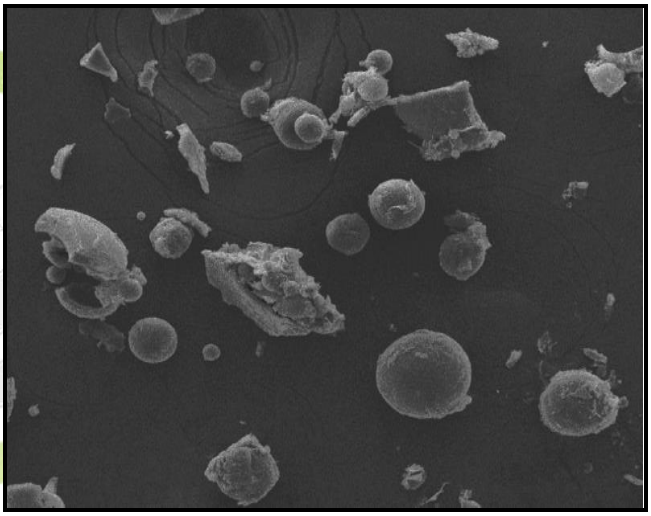

Figure 3: SEM images of Diltiazem microspheres (A4)

From the images of scanning electron microscopy it was observed that the surface of the microspheres (A4) was smooth, regular in texture and the surfaces of remaining formulations(A1,A2,A3) was rough and irregular in texture.

Frequency Distribution Analysis

From table3 it was observed that the particle sizes of formulations A1, A2, A3 and A4 were 260, 296, 336 and 360 µm respectively. As the particle size of A4 increases, surface area decreases and drug release was delayed. So, the formulation was more sustained.

Table 3: Average diameter of Diltiazem microspheres

S.No	Formulation	Average particle size(µm)
1	1:0.5	260
2	1:1	296
3	1:1.5	336
4	1:2	360

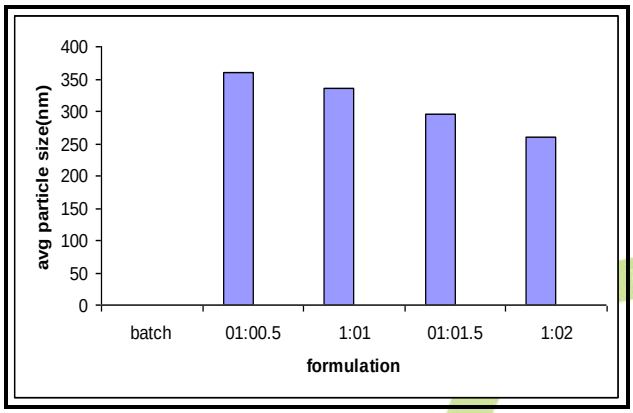

Figure 4: Average diameter of Diltiazem microspheres

Percentage Drug Entrapment Efficiency

The percentage drug content and percentage entrapment efficiency of diltiazem microspheres (A1,A2,A3 and A4) were found to be 61.7%,63.3%,72.4%,79.84% and 75.09%,79.56%,81.4%,85.83% respectively. Microspheres prepared with 1:4 ratio was selected as best formulation.

Table 4: Drug content and entrapment efficiency of Diltiazem microspheres

S.No	Formulation	Drug content (%)	Entrapment Efficiency (%)
1	1:0.5	61.7	75.09
2	1:1	63.3	79.56
3	1:1.5	72.4	81.4
4	1:2	79.84	85.83

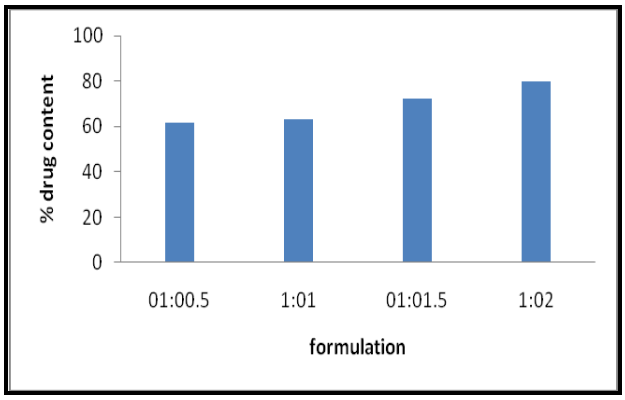

Figure 5: Drug content of Diltiazem microspheres

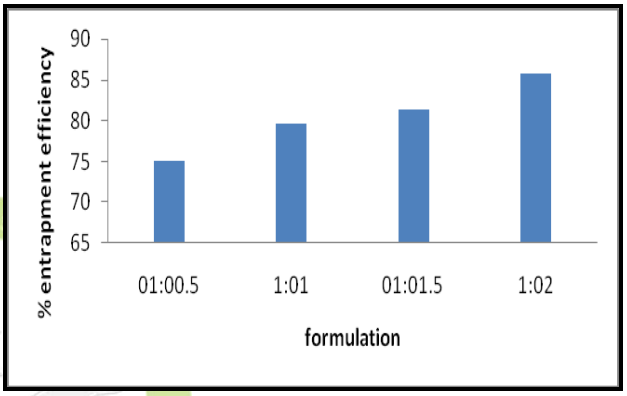

Figure 6: Drug entrapment efficiency of Diltiazem microspheres

***In-vitro* Dissolution Studies**

The dissolution studies were carried out in gastric fluid p^H 1.2 buffer for 2 h (since the average gastric emptying time is 2h), stimulated intestinal fluid p^H 7.4 buffer for 3h (average small intestinal transit time is 3h) and colonic fluid p^H 6.8 buffer for subsequent h.

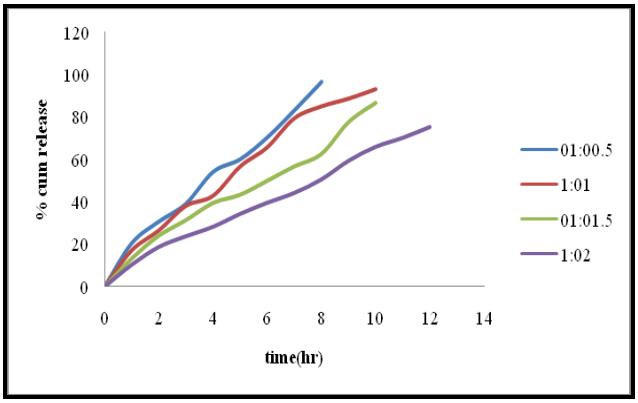

Figure 7: *In-Vitro* Dissolution Profile Of Diltiazem Microspheres

Table 5: *In-Vitro* release data of Diltiazem microspheres

Time (h)	% Drug Release			
	A1	A2	A3	A4
0	0	0	0	0
1	20.465	17.120	13.291	10.430
2	30.71	26.494	24.073	18.836
3	39.12	38.068	31.379	23.913
4	54.08	42.822	39.477	28.836
5	60.07	56.597	43.350	34.460
6	70.35	65.663	49.951	39.741
7	83.13	79.306	56.729	44.406
8	96.51	84.895	62.582	50.787
9	-	88.548	77.589	59.589
10	-	92.993	86.611	66.191

The Diltiazem microspheres (A1, A2, A3 and A4) shown 96.5% for 8h, 92.993%, 86.611% for 10h and 75.565% for 12h respectively. Microspheres prepared with 1:4 ratios were proved more efficient of all other ratios.

Release Kinetics

Zero Order Release Kinetics of Diltiazem Microspheres

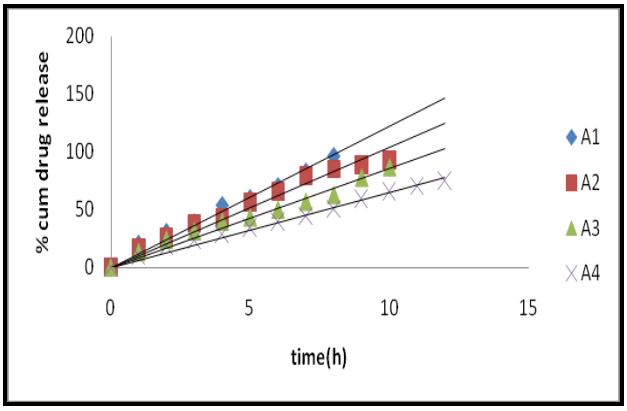

Figure 8: Zero order release kinetics of Diltiazem microspheres

First Order Release Kinetics of Diltiazem Microspheres

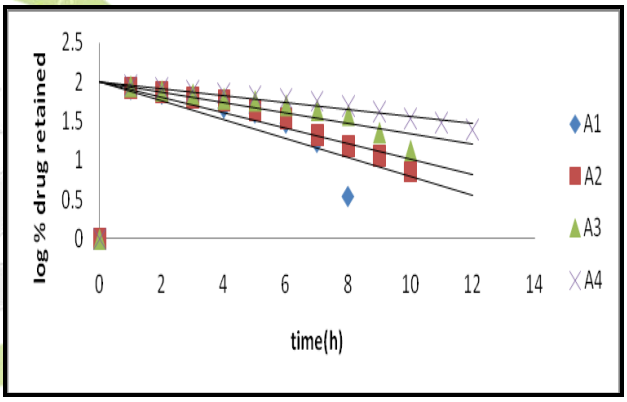

Figure 9: First order release kinetics of Diltiazem microspheres

Higuchi Release Kinetics of Diltiazem Microspheres

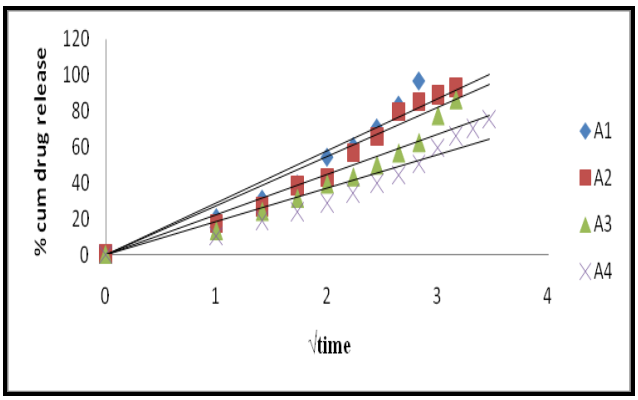

Figure 10: Higuchi release kinetics of Diltiazem microspheres

Peppas Release Kinetics of Diltiazem Microspheres

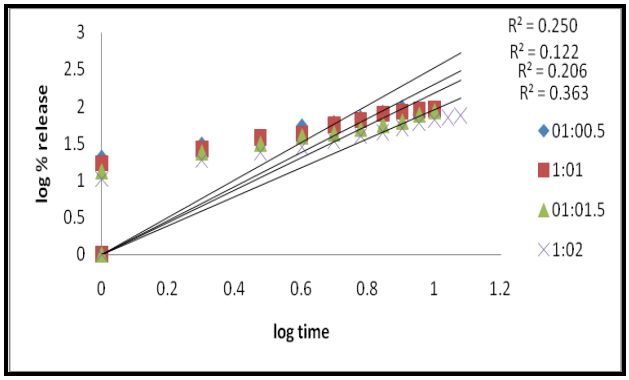

Figure 11: Peppas release kinetics of Diltiazem microspheres

Regression Coefficient (R^2) Values of different Kinetic Models of Diltiazem Microspheres

Table 6: Regression coefficient (R^2) values of different kinetic models of Diltiazem microspheres

Form^n code	Zero order	First order	Higuchi's	Peppas
	r^2	r^2	r^2	r^2
A1	0.979	2.059	0.922	0.122
A2	0.964	0.1874	0.929	0.206
A3	0.974	0.059	0.905	0.250
A4	0.986	2.562	0.903	0.363

Evaluation of Formaldehyde Treated Capsules

Dimensions

a. Average Capsule Length

• Before formaldehyde treatment (untreated cap and body) : 20.6 mm

• After formaldehyde treatment (treated body and untreated cap) : 19.3 mm

b. Average Diameter of Capsule Body

• Before formaldehyde treatment : 7.3 mm

• After formaldehyde treatment : 6.7 mm

c. Average Length of Capsule Body

• Before formaldehyde treatment : 17.7 mm

• After formaldehyde treatment : 16.8 mm

d. Solubility Studies for the Treated Capsules

When the capsules were subjected to solubility studies in different buffers for 24 h, the following observations were made

• In all the case normal capsules, both cap and body dissolved within fifteen minutes

• In the case of formaldehyde treated capsules, only the cap dissolved within 15 min, while the capsule remained intact for about 24 hrs.

Qualitative for Free Formaldehyde

The formaldehyde capsules were tested for the presence of free formaldehyde. The sample solution was not more intensity colored than the standard solution interring that less than 20µg of free formaldehyde is present in 25 capsule bodies.

Evaluation of Modified Pulsincap

Thickness of Ethyl Cellulose Coating

Table 7: 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	0.067
C2	0.059
C3	0.061
D1	0.072
D2	0.069
D3	0.071

Weight Variation

The filled capsules pass the weight variation test as their weights are within the specified limits .

***In-vitro* Release Profile of Diltiazem Modified Pulsincap Formulations**

Table 8: *In-vitro* release data of Diltiazem modified pulsincap formulations of sodium alginate hydrogel plug

Time(h)	% Drug Release		
	B1	B2	B3
1-4	0	0	0
5	8.626	0	0
6	10.43	8.274	0
7	18.836	10.34	8.934
8	23.913	18.836	10.430
9	28.836	23.913	18.836
10	34.460	28.836	23.913
11	39.741	34.460	28.836
12	44.406	39.741	34.460
13	50.787	44.406	39.741
14	59.589	50.787	44.406
15	66.191	59.589	50.787
16	70.460	66.191	59.589
17	75.565	70.460	66.191
18	78.924	75.565	70.460
19	81.867	77.345	75.565

Table 9: *In-vitro* release data of Diltiazem modified pulsincap formulations of xanthan gum hydrogel plug

Time(h)	% Drug Release		
	C1	C2	C3
1-4.10	0	0	0
5.10	8.846	0	0
6.10	10.43	0	0
7.10	18.836	8.450	0
8.10	23.913	10.34	0
9.10	28.836	18.836	0
10.10	34.460	23.913	0
11.10	39.741	28.836	0
12.10	44.406	34.460	8.978
13.10	50.787	39.741	10.240
14.10	59.589	44.406	18.836
15.10	66.191	50.787	23.913
16.10	70.460	59.589	28.836
17.10	75.565	66.191	34.460
18.10	77.923	70.460	39.741
19.10	79.347	75.565	44.406
20.10	81.562	77.923	50.787
21.10	82.998	79.347	59.589
22.10	84.014	81.562	66.191
23.10	86.256	82.998	70.460
24.10	87.889	84.014	75.565

Table 10: *In-vitro* release data of Diltiazem modified pulsincap formulations of guar gum hydrogel plug

Time(h)	% drug release		
	D1	D2	D3
1-3.30	0	0	0
4.30	8.450	0	0
5.30	10.43	0	0
6.30	18.836	8.670	0
7.30	23.913	10.340	9.918
8.30	28.836	18.863	10.340
9.30	34.460	23.913	18.836
10.30	39.741	28.836	23.913
11.30	44.406	34.460	28.836
12.30	50.787	39.741	34.460
13.30	59.589	44.406	39.741
14.30	66.191	50.787	44.406
15.30	70.460	59.589	50.787
16.30	75.565	66.191	59.589
18.30	78.376	70.460	66.191
19.30	81.079	75.565	70.460
20.30	83.043	78.376	75.565

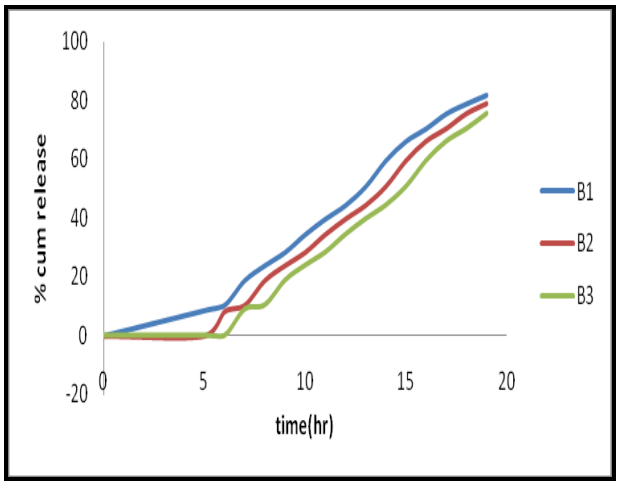

Figure 12: *In-vitro* release data of Diltiazem modified pulsincap formulations of sodium alginate hydrogel plug

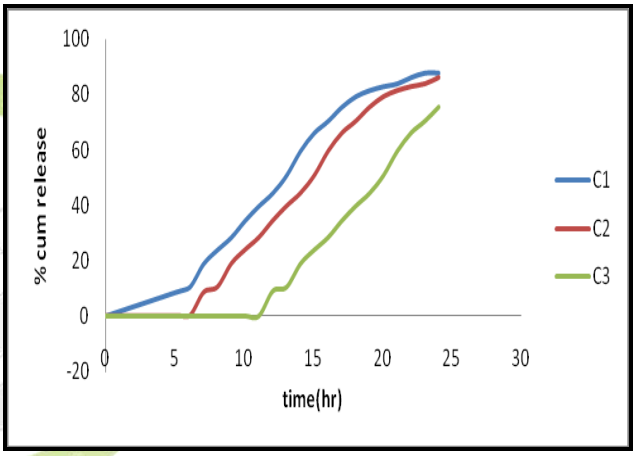

Figure 13: *In-vitro* release data of Diltiazem modified pulsincap formulations of xanthan gum hydrogel plug

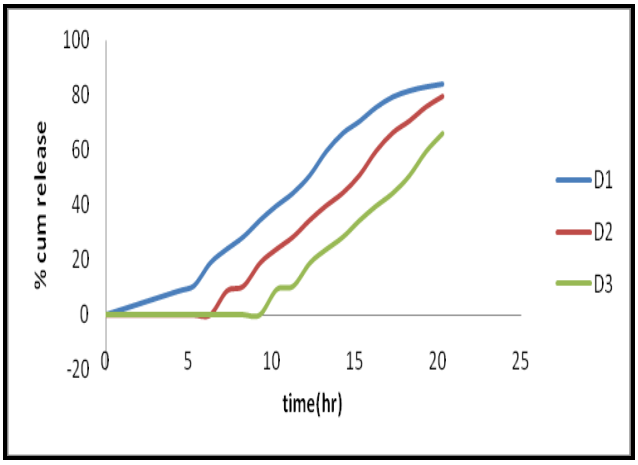

Figure 14: *In-vitro* release data of Diltiazem modified pulsincap formulations of guar gum hydrogel plug

Kinetics of Diltiazem Modified Pulsincap Formulations

Zero Order

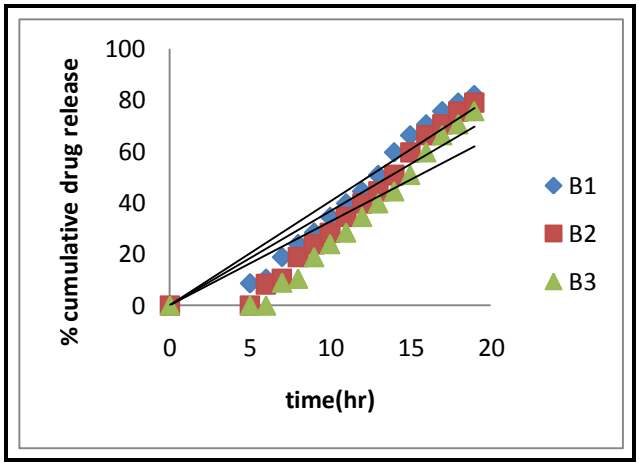

Figure 15: Zero order release kinetics of Diltiazem modified pulsincap formulations of sodium alginate hydrogel plug

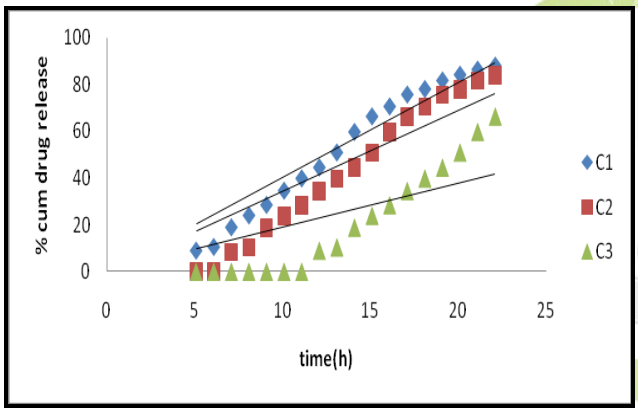

Figure 16: Zero order release kinetics of Diltiazem modified pulsincap formulations of xanthan gum hydrogel plug

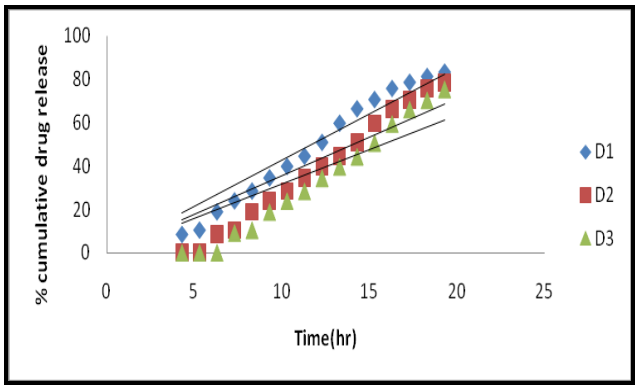

Figure 17: Zero order release kinetics of Diltiazem modified pulsincap formulations of guar gum hydrogel plug

First Order

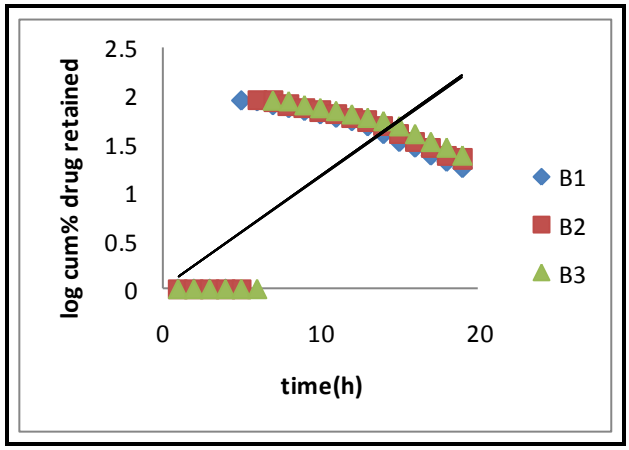

Figure 18: First order release kinetics of Diltiazem modified pulsincap formulations of sodium alginate hydrogel plug

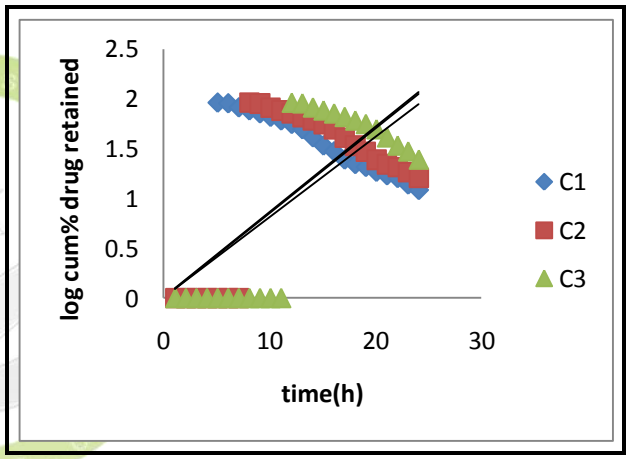

Figure 19: First order release kinetics of Diltiazem modified pulsincap formulations of xanthan gum hydrogel plug

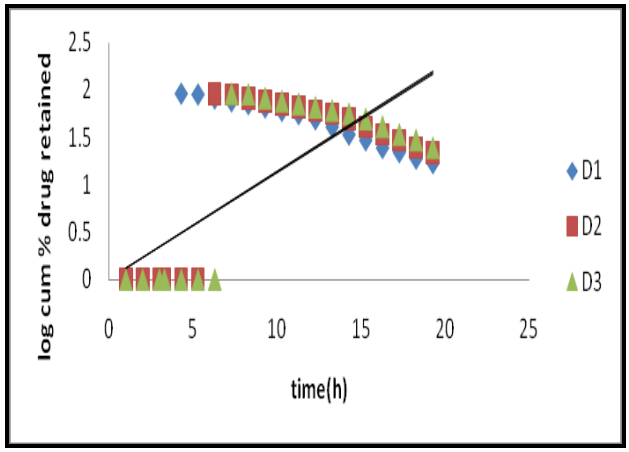

Figure 20: First order release kinetics of Diltiazem modified pulsincap formulations of guar gum hydrogel plug

Higuchi's Matrix

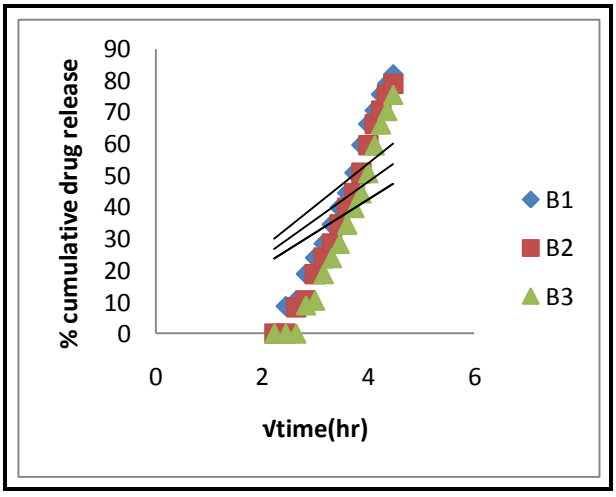

Figure 21: Higuchi's release kinetics of Diltiazem modified pulsincap formulations of sodium alginate hydrogel plug

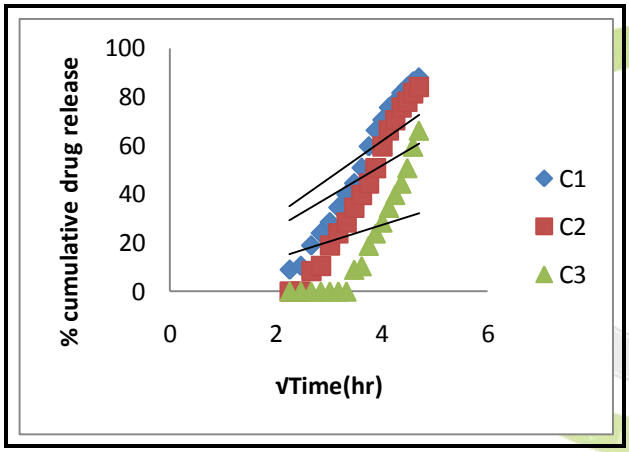

Figure 22: Higuchi's release kinetics of Diltiazem modified pulsincap formulations of xanthan gum hydrogel plug

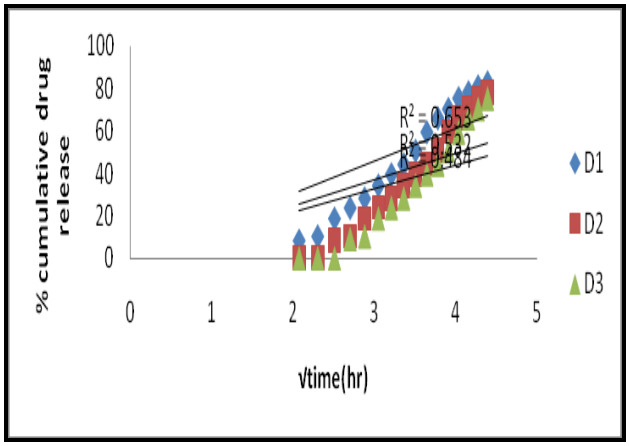

Figure 23: Higuchi's release kinetics of Diltiazem modified pulsincap formulations of guar gum hydrogel plug

Peppas Release

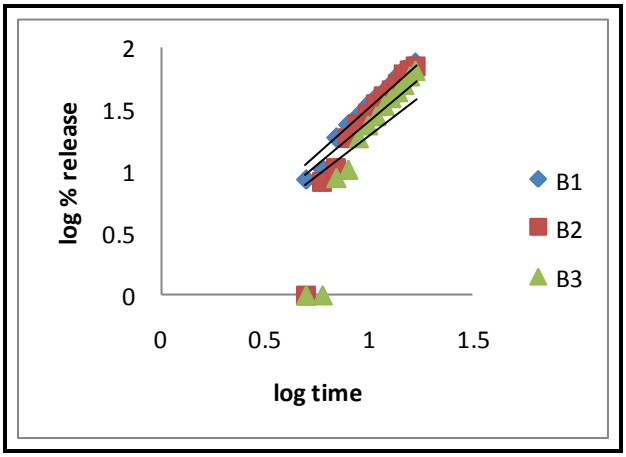

Figure 24: Peppas kinetics of Diltiazem modified pulsincap formulations of sodium alginate hydrogel plug

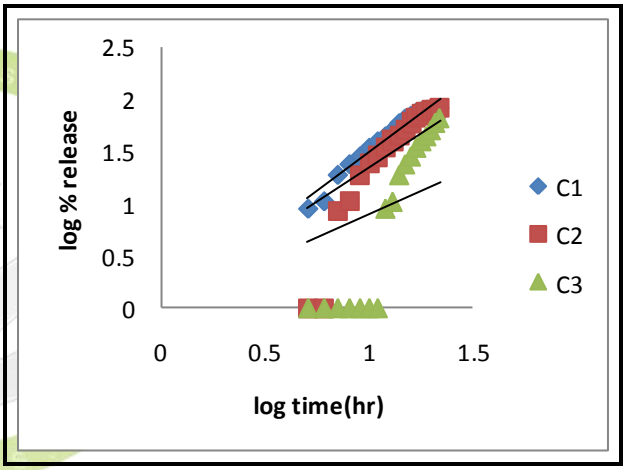

Figure 25: Peppa's release kinetics of Diltiazem modified pulsincap formulations of xanthan gum hydrogel plug

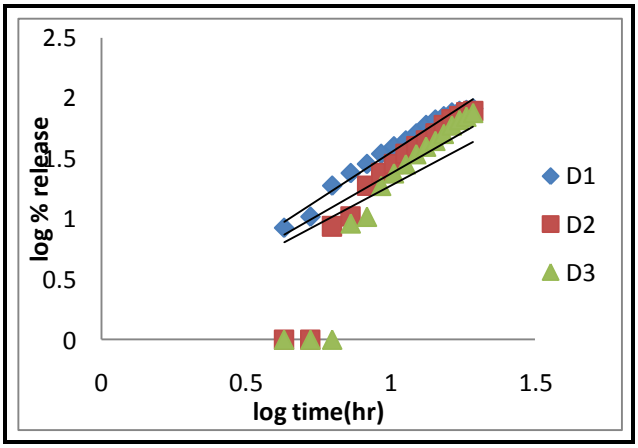

Figure 26: Peppa's release kinetics of Diltiazem modified pulsincap formulations of guar gum hydrogel plug

Regression Coefficient (r^2) Values of Different Kinetic Models of Diltiazem Modified Pulsincap Formulations

Table 11: Regression coefficient (r^2) values of different kinetic models of diltiazem Modified pulsincap formulations

Formulation code	Zero order	First order	Higuchi's	Peppas	
	r^2	r^2	r^2	r^2	N
B1	0.925	0.155	0.557	0.959	1.801
B2	0.9703	0.3052	0.503	0.643	2.793
B3	0.9175	0.472	0.458	0.534	3.428
C1	0.927	0.469	0.652	0.960	1.580
C2	0.9441	0.3159	0.538	0.618	3.007
C3	0.9095	0.5998	0.343	0.350	3.687
D1	0.939	-0.157	0.653	0.977	1.555
D2	0.939	0.3859	0.532	0.643	2.86
D3	0.989	0.5187	0.484	0.566	3.22

CONCLUSION

The aim of this study was to explore the feasibility of time and p^H dependent colon specific, pulsatile drug delivery system of Diltiazem to treat the hypertension.

From the results obtained from executed experiments it can be concluded that:

- The Preformulation studies like p^H, melting point, solubility and UV-analysis of Diltiazem were complied with BP standards
- The FTIR Spectra revealed that, there was no interaction between polymer and drug. Polymers used were compatible with Diltiazem.
- Surface smoothness of the Diltiazem microspheres was increased by increases in the polymer concentration, which was confirmed by SEM.
- Increase in amount of polymer increased the particle size and drug entrapment efficiency of the Diltiazem microspheres. Maximum Diltiazem content was found in formulation A4.
- *In- vitro* drug release of microspheres showed biphasic release pattern for all microspheres with initial burst release effect, which may be attributed to the Diltiazem loaded on to surface of the particles.
- Chitosan is suitable for preparation of Diltiazem microspheres for colon targeting.
- On the basis of drug entrapment efficiency, particle size and morphology, in vitro release studies, A4 was selected as an optimized formulation for designing pulsatile device.
- The solubility studies of empty gelatin capsule bodies, which were cross linked with formaldehyde treatment, revealed that they are intact for 24 hrs, and hence suitable for colon targeting.
- The polymer like sodium alginate, Xanthum gum and Guar gum can be used as hydrogels to delay the Diltiazem release until the formulation reaches the colon and thereafter the Diltiazem released in the colon. In the hydrogel plugs B3 of

sodium alginate, C2 of xanthum gum and D3 of guar gum was found to be best formulations because of burst of plug and release of drug will be in time and decreases blood pressure levels in early morning hours.

- In conclusion, pulsatile drug release over a period of 4-24 hrs, this system can be considered as one of the promising formulation technique for preparing colon specific drug delivery systems and hence in chronotherapeutic management of hypertension, From the preliminary trials it was concluded that it possible to formulate the colon targeted by design of time and p^H dependent modified chronopharmaceutical formulation by using Diltiazem microspheres.

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