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Time Delayed Capsule Device for chronopharmaceutical drug delivery system of Diltiazem hydrochloride-Formulation and Evaluation

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ABSTRACT

For investigation of an oral colon specific, pulsatile device to achieve time and/or site specific release of Diltiazem, based on chronopharmaceutical consideration. The basic design consists of an insoluble hard gelatin capsule body, filled with Eudragit Microspheres of Diltiazem and sealed with a hydrogel plug. The entire device was enteric coated, so that the variability in gastric emptying time can be overcome and a colon-specific release can be achieved. The Diltiazem Microspheres were prepared by solvent evaporation method with Eudragit S-100, L-100 (1:1,1:2) by varying drug to polymer ratio and evaluated for the particle size, angle of repose, percentage yield, drug content, SEM, IR and in-vitro release study. The in-vitro, drug release studies were carried out using pH 6.8 phosphate buffer for 12 hrs. Different hydrogel polymers (Guar gum, HPMC, Sodium alginate) were used as plugs in different ratios, to maintain a suitable lag period. The entire capsule device was coated with 5% CAP. The formulated pulsatile device was evaluated weight variation, thickness of CAP, IR, and in-vitro release kinetics study. The in-vitro release study were carried out using pH 1.2 buffer for a period of 2 hrs then 7.4pH phosphate buffer for a period of 3hrs then 6.8 pH phosphate buffer for a period of 10 hrs. From obtained results, it was found that the order of sustaining capacity of pulsatile device is are HPMC, Sodium alginate and Guar gum.

Keywords: Pulsatile; Colon-specific device; Chronotherapeutics; angina pectoris; Eudragit Microspheres

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INTRODUCTION

The development of oral sustained and controlled release formulation offer benefits like controlled administration of therapeutic dose at the delivery rate, constant blood levels of the drug, reduction of side effects minimizations of dosing frequency and enhancement of patient compliance. Among modified-release oral dosage form increasing interest has currently turned to system designed to achieve time-specific (delayed, pulsatile) and site-specific delivery of drug. The possibility of exploiting delayed release to perform chronotherapy is quite appealing for those diseases, the symptoms of which recur mainly at night time or in the early morning, such as bronchial asthma, angina pectoris and rheumatoid arthritis. Diltiazem Hcl is an important calcium channel blocker and anti anginal properties. Diltiazem Hcl is rapidly eliminated from the blood, its plasma elimination half- life is 3-6 hours and in order to maintain therapeutic plasma levels. [17]The drug must be administered 150-200mg daily by oral in divided doses. To design and characterize an oral, drug delivery system of Diltiazem Hcl intended to approximate the chronobiology of angina pectoris, proposed for colonic targeting. It is a chronopharmaceutical approach for the better treatment of angina pectoris. Pulsincap consists of a non-disintegrating body and a soluble cap. The drug formulations is contained within the capsule body and separated from the water-soluble cap by a hydrogel polymer plug. The entire capsule is enteric coated to prevent variable gastric emptying. The enteric coating prevents disintegration of the soluble cap in the gastric fluid. On reaching the small intestine the capsule will lose its enteric coating and the polymer plug inside the capsule swells to create a lag phase that equals the small intestinal transit time. This plug ejects on swelling and releases the drug from the capsule in the colon. Based on the concept that a formulation on leaving the stomach, arrives at the ileocaecal junction in about 6 hours after administration and difference in pH throughout GIT, a time and pH dependent pulsatile (or modified pulsincap), controlled drug delivery system was designed.

MATERIALS AND METHODS

Materials

Diltiazem Hcl was received as a gift from M/s Microlabs, Bangalore, India. Eudragit S-100,L-100 were obtained Gift sample from Dr.reddys Lab,Hyderabath,India. All other reagents and solvents used were of pharmaceutical or analytical grade.

PREFORMULATION STUDIES OF PURE DRUG

Identification of pure drug: Identification of Diltiazem Hydrochloride was carried out by Infrared Absorption Spectroscopy.

Melting point determination: Melting point of Diltiazem Hydrochloride was determined by Open capillary Method.

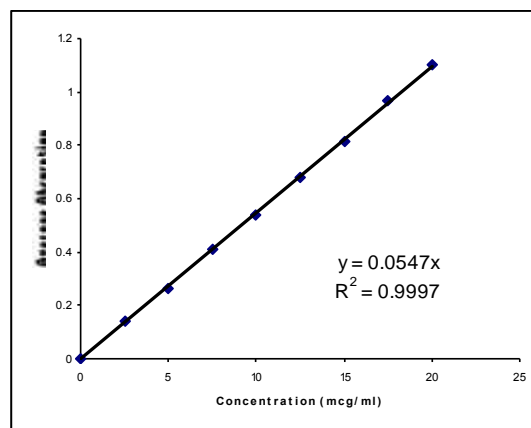
Analysis of Drug

Scanning of Diltiazem Hcl was performed in to solvent methanol, acid buffer pH 1.2, Phosphate buffer 6.8 and 7.4. The characteristics peak, max was found to be 239nm, 237 nm respectively.(Fig 1) (Table 1).Calibration curve of Diltiazem Hcl was plotted in acid buffer (pH 1.2) (Fig2) (Table 2), Phosphate buffer (pH 6.8) (Fig 3) (Table 3) and phosphate buffer (pH 7.4) (Fig 4) (Table 4). The critical values for regression co-efficient (P) in each plot was less 0.001 (i.e., $P < 0.001$). That indicates that there was high correlation between concentrations (0-25 mcg/ml) of drug with absorbance.

Table 1

Conc. Of Drug (mcg/ml)	Average Absorbance (nm) ± S.D.
0	0.0
2.5	0.139 ± 0.008
5.0	0.266 ± 0.009
7.5	0.408 ± 0.008
10.0	0.538 ± 0.008
12.5	0.680 ± 0.010
15.0	0.816 ± 0.009
17.5	0.967 ± 0.006
20.0	1.100 ± 0.005

Fig 1

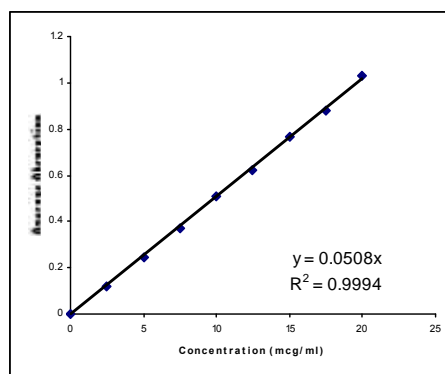


Standard Plot of Diltiazem hydrochloride in Methanol
 Concentration of stock solution = 100 mcg/ml, Drug = Diltiazem hydrochloride
 Maximum wave-length (λ_{max}) = 239 nm, Solvent = Methanol

Table 2

Conc. Of Drug (mcg/ml)	Average Absorbance ± S.D.
0	0.0
2.5	0.121 ± 0.002
5.0	0.245 ± 0.005
7.5	0.372 ± 0.003
10.0	0.507 ± 0.001
12.5	0.623 ± 0.006
15.0	0.767 ± 0.010
17.5	0.882 ± 0.002
20.0	1.034 ± 0.008

Fig 2



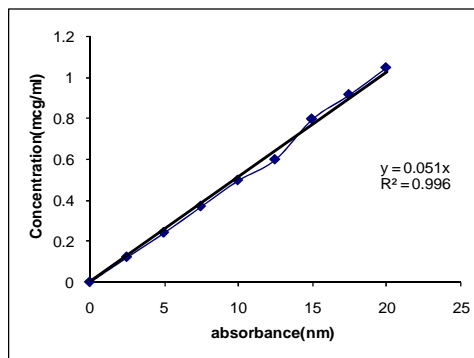
Standard Plot of Diltiazem hydrochloride in Acid Buffer pH 1.2

Concentration of stock solution = 100 mcg/ml, Drug = Diltiazem hydrochloride
 Maximum wave-length (λ_{max}) = 237 nm, Solvent = Acid Buffer pH 1.2

Table 3

Conc. Of Drug (mcg/ml)	Average Absorbance ± S.D.
0	0.0
2.5	0.122 ± 0.002
5.0	0.241 ± 0.004
7.5	0.319 ± 0.006
10.0	0.496 ± 0.003
12.5	0.567 ± 0.003
15.0	0.794 ± 0.003
17.5	0.913 ± 0.005
20.0	1.044 ± 0.003

Fig 3

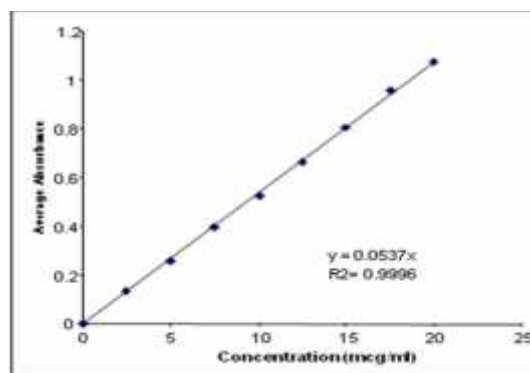


Standard Plot of Diltiazem hydrochloride in Phosphate Buffer pH 6.8
 Concentration of stock solution = 100 mcg/ml, Drug = Diltiazem hydrochloride
 Maximum wave-length (λ_{max}) = 237 nm, Solvent = Phosphate Buffer pH 6.8

Table 4

Conc. Of Drug (mcg/ml)	Average Absorbance ± S.D.
0	0.0
2.5	0.136 ± 0.002
5.0	0.261 ± 0.004
7.5	0.396 ± 0.006
10.0	0.526 ± 0.003
12.5	0.667 ± 0.003
15.0	0.804 ± 0.003
17.5	0.953 ± 0.005
20.0	1.074 ± 0.003

Fig 4



Standard Plot of Diltiazem hydrochloride in Phosphate Buffer pH 7.4
 Concentration of stock solution = 100 mcg/ml, Drug = Diltiazem hydrochloride
 Maximum wave-length (λ_{max}) = 237 nm, Solvent = Phosphate Buffer pH 7.4

Drug - Excipient Compatibility Studies: [14]

A successful formulation of a stable and effective solid dosage form depends on careful selection of excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. If the excipients are new and not been used in formulation containing the active substance, the compatibility studies are of paramount importance.

Compatibility of Diltiazem Hydrochloride with the respective polymers that is Eudragit L100 and S100, and physical mixture of main formulation was established by Infrared Absorption Spectral Analysis (FTIR) (Fig no-5,6,7) . Any changes in the chemical composition after combining with the excipients were investigated with IR spectra.

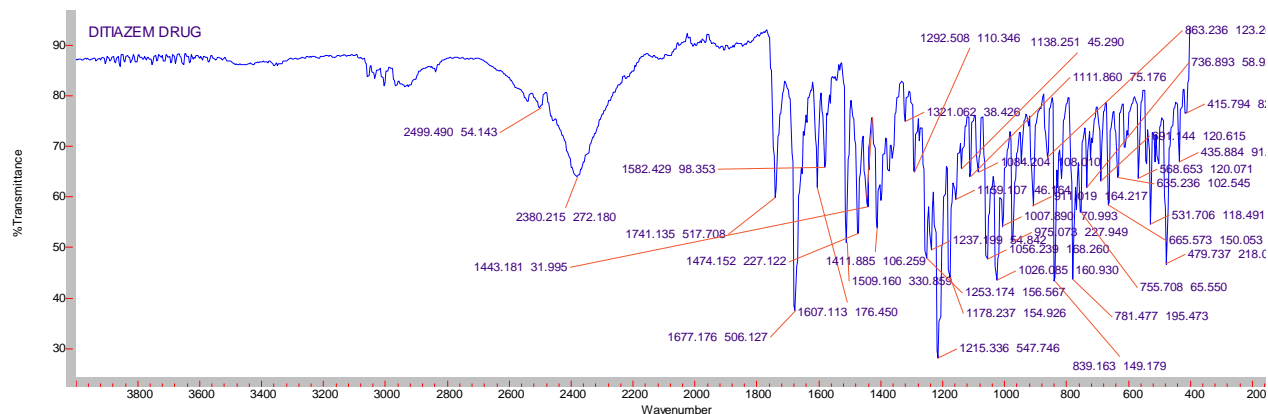


Fig 5:IR Spectrum of Diltiazem Hydrochloride in KBr

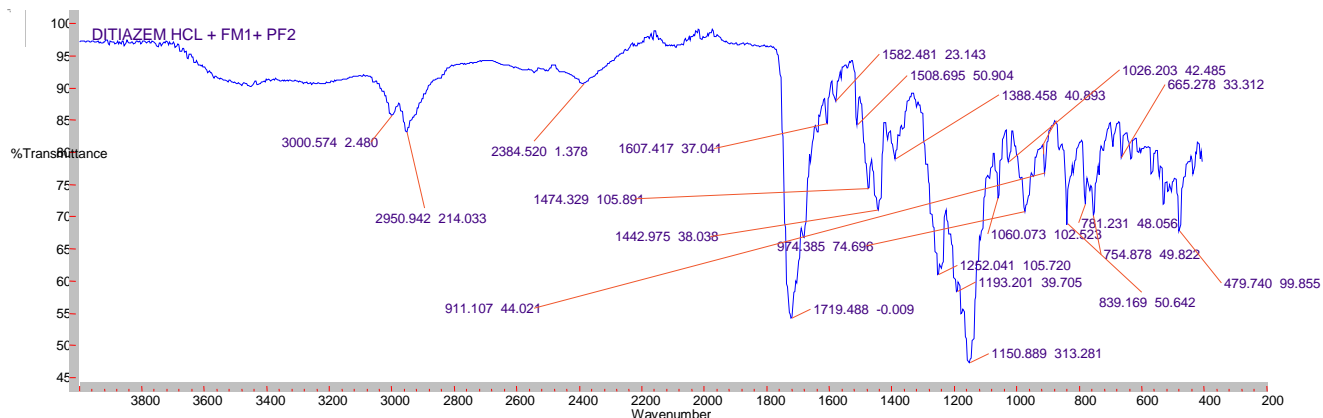


Fig 6:IR spectrum of DTZ.HCl, FM1, PF1(Physical mixture corresponding to FM1)

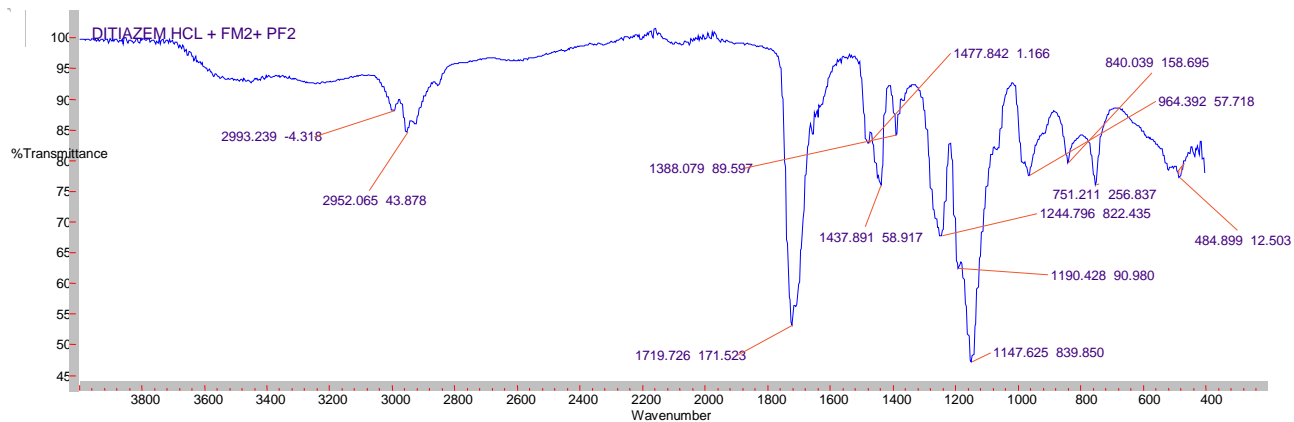


Fig 7: IR spectrum of DTZ.HCl, FM2, PF2 (Physical mixture corresponding to FM2)

Preparation of Diltiazem Hcl microspheres: [3]

Diltiazem hydrochloride loaded microspheres were prepared by solvent evaporation method. The formulation of microspheres (table no-6,7). Diltiazem hydrochloride and each

polymer mixture were dissolved completely in acetone-methanol mixture by stirring at 500rpm with magnetic stirrer. Magnesium stearate was added and the mixture was stirred with magnetic stirrer at 500 rpm in ice-bath at 10° C for 10 minute. Above mixture was poured into the liquid paraffin previously cooled at 10°C, while it was being stirred by mechanical stirrer at 1000 rpm. Resulting emulsion was stirred at 35°C for 4 hours using mechanical stirrer and the organic solvent, acetone-methanol were removed completely by evaporation. Solidified microspheres were filtered through Whatmann filter paper (No.1), washed six times with 50 ml n-hexane. Dried under vacuum at room temperature for 12 h and stored in desiccators containing calcium chloride.

Table 5: Wave- number of different functional groups present in Diltiazem. HCl

Code	Composition	Peak for Diltiazem hydrochloride				
		Aromatic C-H Stretch (cm ⁻¹)	O-CH ₃ C-H stretch (cm ⁻¹)	Amine HCl N-H stretch (cm ⁻¹)	Acetate C=O stretch (cm ⁻¹)	Lactam C=O stretch (cm ⁻¹)
DTZ.HCl	Diltiazem Hydrochloride	3057.27	2837.38	2391.81	1743.71	1681.98
FM1	Formulation FM1	3055.35	2847.03	2391.81	1743.71	1681.98
PF1	DTZ: EL 100	3057.27	2839.31	2389.88	1745.64	1681.98
FM2	Formulation FM2	3055.35	2850.88	2389.88	1743.71	1681.98
PF2	DTZ: ES100	3057.27	285088	2389.88	1745.64	1681.98

Table 6: Formulations of Diltiazem hydrochloride Microspheres prepared with different Polymers and Polymer mixtures (Drug : Polymer =1:1)

Contents of Formulations	FM1	FM2	FM3
Diltiazem hydrochloride (gm)	2.0	2.0	2.0
Eudragit L 100 (gm)	2.0	-	1.0
Eudragit S 100 (gm)	-	2.0	1.0
Magnesium Stearate (gm)	0.300	0.300	0.300
Methanol (ml)	3.0	3.0	3.0
Acetone (ml)	7.0	7.0	7.0
Liquid paraffin (ml)	100	100	100

Table 7: Formulations of Diltiazem hydrochloride Microspheres prepared with different Polymers and Polymer mixtures (Drug : Polymer =1:2)

Contents of Formulations	FM4	FM5	FM6
Diltiazem hydrochloride (gm)	2.0	2.0	2.0
Eudragit L 100 (gm)	4.0	-	2.0
Eudragit S 100 (gm)	-	4.0	2.0
Magnesium Stearate (gm) (Dispersing Agent)	0.600	0.600	0.600
Methanol (ml)	6.0	6.0	6.0
Acetone (ml)	14.0	14.0	14.0
Liquid paraffin (ml)	200	200	200



Formulation of Pulsatile (modified pulsincap) Drug Delivery System: [3]

Microspheres equivalent to 150mg of Diltiazem Hcl were accurately weighted and filled into the previously formaldehyde treated bodies by hand filling. The bodies containing the microsphere were then plugged with different amounts of polymers like guar gum, hydroxypropylmethylcellulose(HPMC) and sodium alginate. Then join the capsule body and cap and sealed with a small amount of the 5% ethyl cellulose ethanolic solution. The sealed capsules were completely coated with 5% Cellulose Acetate Phthalate (CAP) to prevent variable gastric emptying. The whole system thus produced is modified pulsincap.

Coating of pulsincap [3]

5 % w/w solution of CAP was prepared by using acetone: ethanol (8.:2) as a solvent and dibutyl phthalate as plasticizer (0.75%) as a plasticizer. Dip coating method was followed to develop the pulsincap. The capsules were alternatively dipped in 5 % CAP solution and dried. Coating was repeated until an expected weight gain of 8-12% was obtained and the capsule resists disintegration in 0.1 N HCL for a minimum period of 2 hrs.

Evaluation of Modified Pulsincap [3]

Thickness of cellulose acetate phthalate coating

The thickness of the cellulose acetate phthalate coating was measured using screw gauge and was expressed in mm. Ten 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 90% or more than 110% of the average.

Weight variation

10 capsules (00 Size) were selected randomly from each batch and weight individually for weight variation.

Drug Polymer Interaction

FT-IR spectra of physical mixture of Diltiazem Hcl +Guargum, Diltiazem Hcl +HPMC, Diltiazem Hcl +Sodium alginate was carried out by using KBr pellet technique.

Samples were scanned over the 500-4000cm⁻¹ Spectral region at a resolution of 4cm⁻¹ . The ratio of the sample in KBr disc was 1% (shimadzu FT- IR spectrometer).

In vitro release profile[3]

Dissolution studies were carried out by using USP XXIII dissolution test apparatus (Basket) method. Capsules were placed in a basket so that the capsule should be

immersed completely in dissolution media but not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method. When performing experiments, the pH 1.2 medium was first used for 2 hrs (since the average gastric emptying time is 2 hrs) then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 hrs (average small intestinal transit time is 3 hrs) the medium was removed and fresh pH 6.8 dissolution medium was added for subsequent hrs. 900ml of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37 ± 0.5 C. 5 ml of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 237 nm, by UV absorption spectroscopy.

RESULTS AND DISCUSSION

Diltiazem hydrochloride loaded microspheres having a fairly high yield (76.48 – 88.94%) were obtained. The entrapment efficiencies ranged from 86.11 – 98.90%. The incorporation efficiency of formulations, FM4 – FM6 was more than formulations FM1 – FM3. The highest incorporation efficiency of formulation having drug: polymer ratio 1:2 can be explained through the fact that the amount of polymer in per unit drug is greater than that in other formulations.(Table no-9.Fig no-8)

Overview of designed pulsatile device Fig no-8

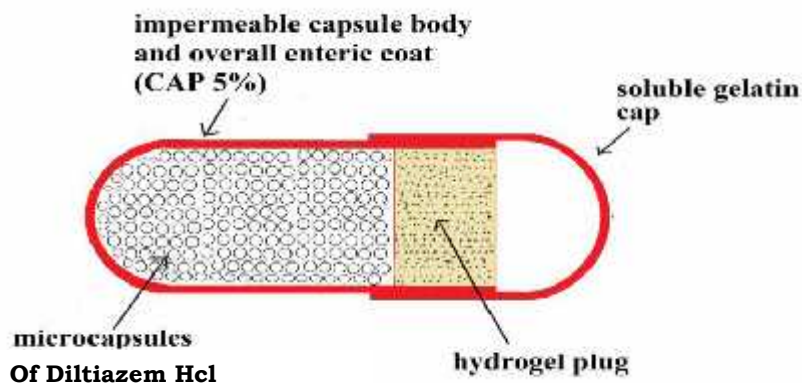


Table 8: Composition for modified pulsatile device on the basis of design summary

Formulation code	Wt.of empty body (mg*)	Wt.of micro capsule (mg)	Polymer used	Wt. of polymer used (mg)	Total weight with cap (mg)	Wt. after CAP coating (mg)
CF-1	68.8	355	Guar gum	20	443.8	454.7
CF-2	67.9	355	Guar gum	30	452.9	462
CF-3	68.5	355	Guar gum	40	463.5	470.18
CF-4	67.5	355	HPMC	20	442.5	451.34
CF-5	67.4	355	HPMC	30	452.4	460.8
CF-6	68.5	355	HPMC	40	463.5	473.25

CF-7	68.0	355	Sod. Alg.	20	443.0	454
CF-8	67.7	355	Sod. Alg.	30	452.7	462.35
CF-9	67.6	355	Sod. Alg.	40	462.6	471.95

HPMC: Hydroxy Propyl Methylcellulose, Sod.Alg: Sodium Alginate, * Microspheres equivalent to 150 mg of drug used

Table 9: Percentage Yield Values and Entrapment Efficiencies of Formulations

Formulation code	Percentage Yield (%)	Theoretical Drug Content (%)	Actual Drug Content (%) * \pm S.D.	Entrapment Efficiencies (%) * \pm S.D.
FM 1	76.48	46.51	40.05 \pm 0.17	86.11 \pm 0.37
FM 2	77.21	46.51	41.32 \pm 0.13	88.84 \pm 0.28
FM3	77.00	46.51	42.70 \pm 0.15	89.10 \pm 0.29
FM4	85.07	30.30	27.00 \pm 0.09	98.73 \pm 0.29
FM5	87.73	30.30	27.96 \pm 0.12	92.28 \pm 0.39
FM6	88.94	30.30	29.33 \pm 0.08	96.80 \pm 0.26

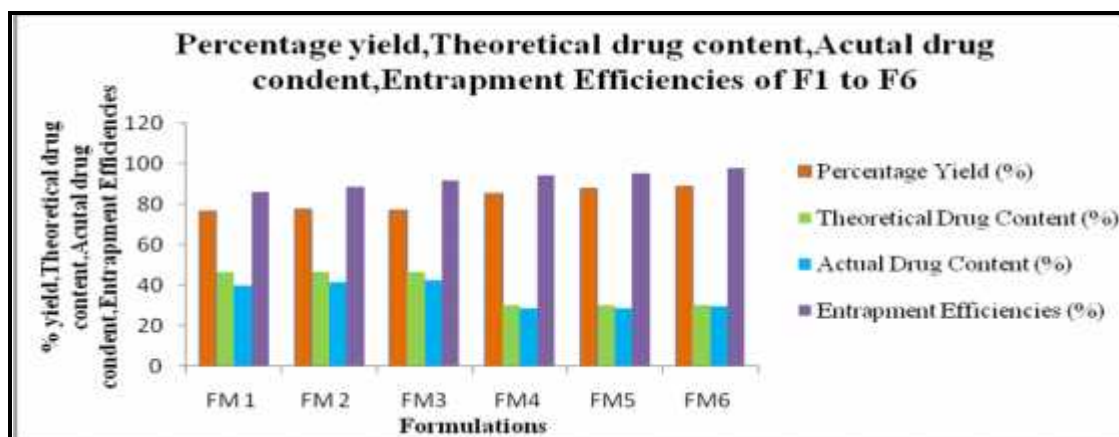


Fig 8: Percentage Yield Values and Entrapment Efficiencies of Formulations

Particle Size Distribution of Formulations FM1 to FM6

It has been observed that the particle size increases with increasing polymer amount.

The increase in the mean size with increasing polymer concentration was attributed to the fact that higher concentration of polymer in the sample leads to increase in viscosity of the dispersed phase, which results in formation of bigger droplets and also, fusion of semi-formed particles and producing an overall increase in the size of the microspheres. Eudragit L,-type

microspheres and Eudragit S-type microspheres prepared with the same polymer concentration did not show any significant variation in their mean size.(Table no-10.Fig no-9)

Table 10: Particle Size Distribution of Formulations FM1 to FM6

Particle Size Range	FM1	FM2	FM3	FM4	FM5	FM6
0-50	0	0	0	0	0	0
50-100	0	0	0	0	0	0
100-150	10	9	8	0	0	3
150-200	41	60	44	8	11	10
200-250	55	71	71	9	28	14
250-300	56	43	41	12	45	26
300-350	23	10	22	28	58	38
350-400	10	3	8	49	28	51
400-450	5	2	4	47	12	25
450-500	0	2	2	22	9	22
500-550	0	0	0	17	6	7
550-600	0	0	0	8	3	4
600-650	0	0	0	0	0	0

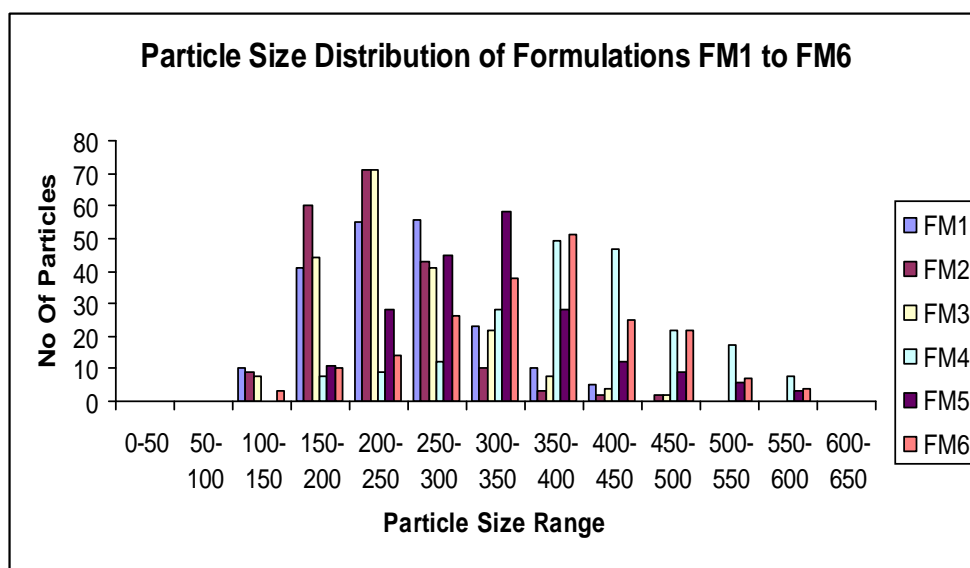


Fig 9: Particle Size Distribution of Formulations FM1 to FM6

SEM Photographs of Microspheres

Instrument used Lieca stereomicroscope EZ4D and Magnified 10x20x and 10x30x.it shows All microspheres were almost spherical in shape and No aggregation of microspheres had taken place. (Fig no-10, 11, 12)

SEM PHOTOGRAPHS OF MICROSPHERES

Instrument: Lieca stereomicroscope EZ4D

Magnification: 10x20x and 10x30x.

Formulation FM1-Fig 10



Formulation FM2 - Fig 11



Formulation FM3-Fig 12

**In- Vitro Release Study of the Microspheres**

The release of Diltiazem hydrochloride from different formulations depended on the type of polymer and the ratio of the polymer in the formulations. The release of Diltiazem hydrochloride from microspheres of Eudragit RL-type was more as compared to Eudragit RS-type. This was due to the presence of more functional quaternary ammonium groups (10%) in RL-type than RS-type (5%). It is also observed that as the amount of polymer in the formulation increased, the drug release decreased. It can be explained on the basis that as the polymer amount increases, the matrix wall of microspheres become thicker. The formation of a thicker matrix wall lead to slower dissolution rate of drug caused by longer diffusion path.

A burst effect of drug release can be observed on the various formulations.(Table no-11, Fig no-13). The burst effect can be attributed to the presence of non-encapsulated drug particles on the surface of the microspheres. The burst effect of drug release also depended upon the drug : polymer ratio. From the figure of release profile, it can be observed that burst effect of drug release is more in formulations having drug: polymer ratio 1:1, while in the formulation having drug : polymer ratio 1:2, burst effect is less.

IN- VITRO RELEASE STUDY OF THE MICROSPHERES

Table 11: Cumulative Percent Released Diltiazem hydrochloride from Microspheres FM1 toFM6

S. NO.	TIME(hr s)	Formulation FM1 (DTZ:EL100, 1:1)	Formulation FM2 (DTZ :ES100, 1:1)	Formulation FM3 (DTZ:EL100: ES100, 1:0.5:0.5)	Formulation FM4 (DTZ:EL100, 1:2)	Formulation FM5 (DTZ:ES100, 1:2)	Formulation FM6 (DTZ: EL100: ERS100, 1:1:1)
		1:1			1:2		
1	0	0	0	0	0	0	0
2	1	41.63	18.95	18.07	23.03	15.82	11.29
3	2	61.18	26.68	34.12	41.58	19.66	17.96
4	3	74.47	33	46.12	53.58	22.95	23.26
5	4	82.37	37.04	55.14	60.42	25.68	25.89
6	5	86.18	39.09	63.63	65.55	29.42	30.94
7	6	88.16	42.16	70.5	71.04	34.77	35
8	7	92.33	45.2	75.9	77.07	38.96	39.12
9	8	98.53	49.32	80.99	81.72	42.74	47.28
10	9	99.24	52.96	85.09	85.03	46.06	52.14
11	10	99.28	57.97	88.56	87.11	49.02	58.53
12	11	99.34	61.99	91.77	89.2	52.23	64.95
13	12	99.37	65.03	93.85	90.8	54.42	72.75

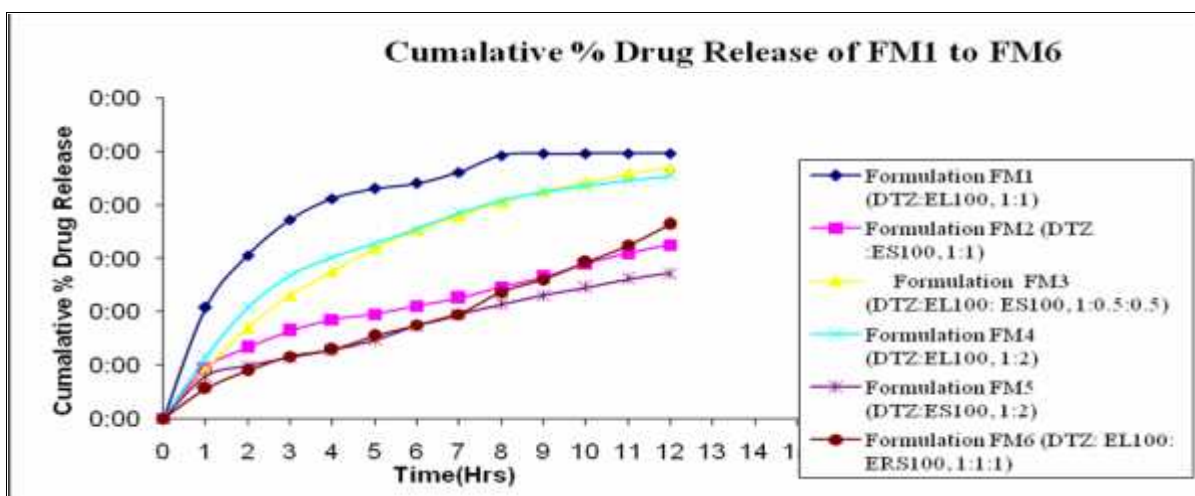


Fig 13: Cumulative Percent Released Diltiazem hydrochloride from Microspheres FM1 toFM6



Evaluation of formaldehyde treated empty capsules

Dimension

Average capsule length:- Before formaldehyde treatment (untreated cap and body) - 23.5 mm, After formaldehyde treatment (treated body and untreated cap) - 22.5 mm. Average diameter of capsule body- Before formaldehyde treatment- 7.9 mm, after formaldehyde treatment -7.5 mm. Average length of capsule body-Before formaldehyde treatment: 20.5 mm, after formaldehyde treatment -19.5 mm.(Table no-8)

Solubility studies for the treated capsules

When the capsules were subjected to solubility studies in different buffers for 24 hrs, the following observation were made a) In all the case of normal capsules, both cap and body dissolved within fifteen minutes. b) In the case of formaldehyde treated capsules, only the cap dissolved within 15minutes, while the capsule remained intact for about 24 hours

Quantity test for free formaldehyde

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

Evaluation of Modified Pulsincap

Weight variation

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

In-vitro release studies:

In-vitro drug release profiles of pulsatile device were found to have very good sustaining efficacy. During dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2 hours in pH 1.2, but dissolved in intestinal pH, leaving the soluble cap of capsule, which also dissolved in pH 7.4 phosphate buffer and then the exposed polymer plug which absorbed the surrounding fluid, swelled and released the drug through the swollen matrix. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body; releasing the eudragit Microspheres into simulated colonic fluid (pH 6.8 phosphate buffer).With all the formulations, there was absolutely no drug release in pH 1.2, thus indicating the efficiency of 5% CAP for enteric coating. Very slight release was observed in pH 7.4 phosphate buffer.

a) Formulations with guar gum as hydrogel plug:

With formulations F1 (20mg), F2 (30mg) and F3 (40mg) at the end of 5th hrs there was 6.050%, 2.777% and 2.212% drug was released respectively and at the end of 15th hrs 74.61%, 69.43% and 62.28% drug release was found in CF1, CF2 and CF3 respectively. (as shown in Table no-13,fig no-14)

Table 13: Evaluation of In-vitro drug release of Prepared Pulsatile Capsule Device

S.No	TIME	% Cum.Drug release		
		CF1	CF2	CF3
1	0	0	0	0
2	1	0	0	0
3	2	0	0	0
4	3	0	0	0
5	4	0.06 ± 0.042	0	0
6	5	6.05 ± 0.034	2.777 ± 0.216	2.213 ± 0.577
7	6	20.20 ± 0.315	20.82 ± 0.625	8.200 ± 0.080
8	7	25.50 ± 0.130	25.59 ± 0.319	15.59 ± 0.546
9	8	34.04 ± 0.310	35.39 ± 0.092	22.59 ± 0.240
10	9	40.93 ± 0.650	39.27 ± 0.086	31.34 ± 0.086
11	10	50.56 ± 1.767	45.44 ± 0.631	37.51 ± 0.239
12	11	54.19 ± 0.317	56.47 ± 0.092	45.80 ± 0.323
13	12	63.94 ± 0.358	59.84 ± 0.160	55.02 ± 0.155
14	13	67.51 ± 0.239	62.27 ± 0.473	57.04 ± 1.123
15	14	71.50 ± 0.536	65.73 ± 0.408	59.01 ± 0.387
16	15	74.61 ± 0.408	69.43 ± 0.234	62.28 ± 0.479

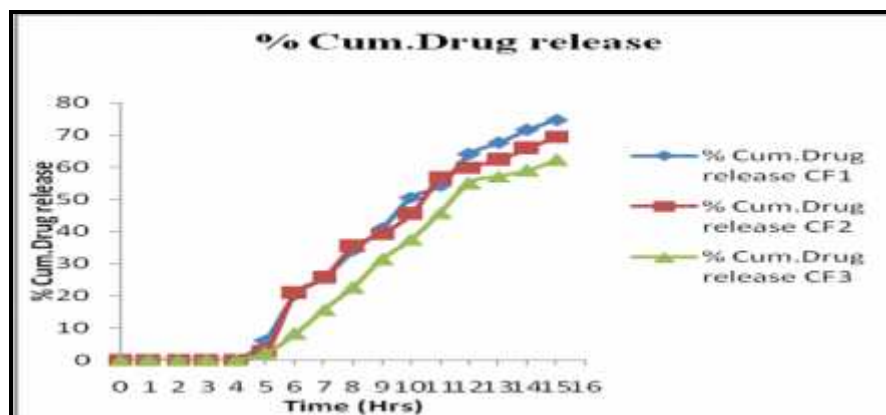


Fig 14: In-vitro release rate profile of CF1, CF2, CF3 containing 20mg, 30mg, 40mg of Guar Gum

b) Formulation with HPMC as hydrogel plug:

With formulation CF4 (20mg), CF5 (30mg) and CF6 (40mg) at the end of 5th hrs 5.990%, 4.613% and 0.483% drug was released respectively and at the end of 15th hrs 76.46%, 71.71% and 59.79% drug released respectively. (as shown in Table no-14, Fig no-15).

Table 14: *In-vitro* release rate profile of CF1, CF2, CF3 containing 20mg, 30mg, 40mg of Guar Gum

S.No	TIME	% Cum.Drug release		
		CF4	CF5	CF6
1	0	0	0	0
2	1	0	0	0
3	2	0	0	0
4	3	0	0	0
5	4	2.497 ± 0.205	0	0
6	5	5.990 ± 0.043	4.613 ± 0.115	0.483 ± 0.063
7	6	28.54 ± 0.768	27.38 ± 0.311	5.300 ± 0.088
8	7	33.57 ± 0.680	31.03 ± 0.086	18.39 ± 0.239
9	8	38.96 ± 0.321	35.54 ± 0.239	29.01 ± 0.086
10	9	43.31 ± 0.735	43.42 ± 0.240	33.78 ± 0.327
11	10	47.51 ± 0.092	49.79 ± 0.086	37.97 ± 0.323
12	11	56.47 ± 0.239	56.09 ± 0.532	42.95 ± 0.387
13	12	64.30 ± 0.629	63.08 ± 0.370	50.25 ± 0.319
14	13	66.10 ± 0.465	64.97 ± 0.310	54.45 ± 0.392
15	14	72.64 ± 0.450	68.96 ± 0.086	57.04 ± 0.536
16	15	76.46 ± 0.802	71.71 ± 0.358	59.79 ± 0.363

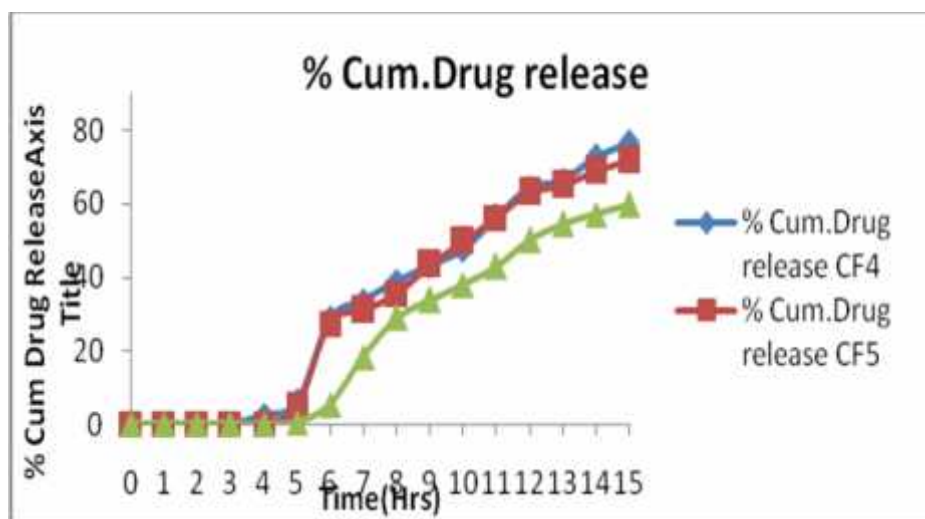


Fig 15: *In-vitro* release rate profile of CF4,CF5, CF6 containing 20mg,30mg,40mg of HPMC

c) Formulations with sodium alginate as hydrogel plug:

With formulations CF7 (20 mg), CF8 (30 mg) and CF9 (40 mg), at the end of 5th hrs around 9.303%, 6.087% and 4.436% drug released respectively and at the end of 15th hrs 82.95%, 70.25% and 77.36% drug was released respectively.(as shown in Table no-15, Fig no-16) From all the above observations, it was found that the order of sustaining capacity of polymer is HPMC > Guar gum > Sodium alginate.

Table 15: *In-vitro* release rate profile of CF4, CF5, CF6 containing 20mg, 30mg 40mg of HPMC

S.No	TIME	% Cum.Drug release		
		CF7	CF8	CF9
1	0	0	0	0
2	1	0	0	0
3	2	0	0	0
4	3	0	0	0
5	4	4.127 ± 0.361	1.247 ± 0.105	3.600 ± 0.398
6	5	9.303 ± 0.057	6.087 ± 0.011	4.436 ± 0.057
7	6	29.58 ± 0.239	23.47 ± 0.542	24.66 ± 0.023
8	7	34.61 ± 0.392	30.36 ± 0.171	27.56 ± 0.473
9	8	39.68 ± 0.092	36.32 ± 0.184	31.50 ± 0.392
10	9	46.73 ± 0.086	42.33 ± 0.179	40.41 ± 0.155
11	10	53.10 ± 0.327	55.80 ± 0.406	49.89 ± 0.265
12	11	60.10 ± 0.086	63.21 ± 0.392	55.59 ± 0.239
13	12	66.11 ± 0.626	64.45 ± 0.315	65.33 ± 0.701
14	13	73.16 ± 0.729	66.21 ± 0.315	70.00 ± 0.645
15	14	79.22 ± 0.450	68.60 ± 0.502	75.33 ± 0.551
16	15	82.95 ± 0.239	70.25 ± 0.155	77.36 ± 1.166

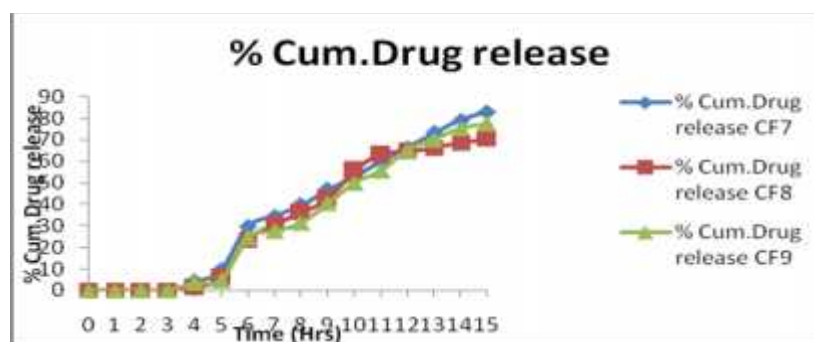


Fig 16: *In-vitro* release rate profile of CF7,CF8,CF9 containing 20mg,30mg,40mg of Sodium Alginate

Release Kinetics Study

The 'r' values for zero order kinetics of CF-1, CF-2, CF-3, CF-4, CF-5, CF-6, CF-7, CF-7, CF-8 and F-9 were 0.955, 0.947, 0.930, 0.958, 0.950, 0.929, 0.967, 0.967, 0.943 and 0.957 respectively. The 'r' values of the first order kinetics of CF-1, CF-2, CF-3, CF-4, CF-5, CF-6, CF-7, CF-7, CF-8 and CF-9 were 0.950, 0.958, 0.929, 0.957, 0.945, 0.943, 0.943, 0.954,

and 0.938 respectively. The 'r' value indicates drug release follows mixed order kinetics. To ascertain the drug release mechanism, the in-vitro data were also subjected to Higuchi diffusion. The 'r' values of Higuchi diffusion was 0.917,0.913, 0.875, 0.930, 0.923 0.930, 0.937, 0.918 and 0.910for formulationCF-1 to CF-9, respectively. It suggests that the Higuchi diffusion plots of all the formulations were fairly linear because 'r' values near about 1 in all the cases. So it confirms the drug release by Higuchi diffusion mechanism. (Table n0-16,17,18 Fig no-17 to25)

Table 16: In-vitro release rate profile of CF7,CF8,CF9 containing 20mg,30mg,40mg of Sodium Alginate

S.No	TIME	Log % Cum.Drug release								
		CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9
1	0	0	0	0	0	0	0	0	0	0
2	1	0	0	0	0	0	0	0	0	0
3	2	0	0	0	0	0	0	0	0	0
4	3	0	0	0	0	0	0	0	0	0
5	4	-1.184	0	0	0.397	0	0	0.615	0.095	0.556
6	5	0.781	0.443	0.344	0.777	0.663	-0.315	0.968	0.784	0.646
7	6	1.305	1.318	0.909	1.455	1.437	0.724	1.47	1.37	1.391
8	7	1.406	1.408	1.192	1.525	1.491	1.264	1.539	1.482	1.44
9	8	1.531	1.548	1.353	1.59	1.55	1.462	1.598	1.56	1.498
10	9	1.612	1.594	1.496	1.636	1.637	1.528	1.669	1.626	1.606
11	10	1.703	1.657	1.574	1.676	1.697	1.579	1.725	1.746	1.698
12	11	1.73	1.751	1.66	1.751	1.748	1.632	1.778	1.8	1.744
13	12	1.805	1.776	1.74	1.808	1.799	1.701	1.82	1.809	1.815
14	13	1.829	1.794	1.756	1.82	1.812	1.735	1.864	1.809	1.845
15	14	1.854	1.817	1.77	1.861	1.832	1.756	1.898	1.836	1.876
16	15	1.872	1.841	1.794	1.883	1.855	1.776	1.918	1.846	1.888

First order release kinetics data of Diltiazem Hcl Pulsincap (CF1- CF9)

Fig no- 17

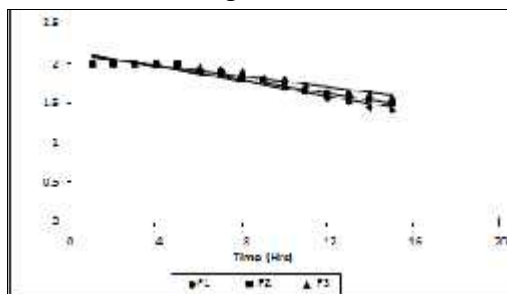


Fig no-18

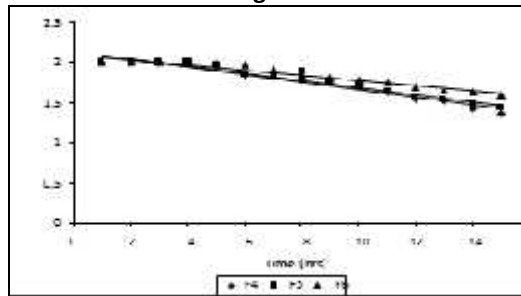


Fig no-19

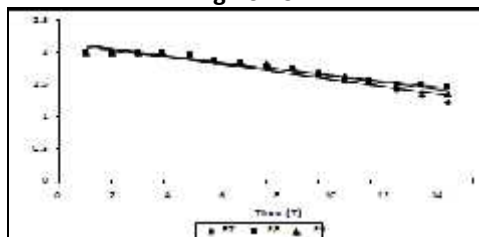


Table 17: Highchi Matrix release kinetics data of Diltiazem Hcl Pulsincap (CF1 to CF9)

S.No	TIME	% Cum.Drug release								
		CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9
1	0	0	0	0	0	0	0	0	0	0
2	1	0	0	0	0	0	0	0	0	0
3	1.414	0	0	0	0	0	0	0	0	0
4	1.732	0	0	0	0	0	0	0	0	0
5	2	0.06	0	0	2.497	0	0	4.127	1.247	3.6
6	2.236	6.05	2.777	2.213	5.99	4.613	0.483	9.303	6.087	4.436
7	2.449	20.2	20.82	8.2	28.54	27.38	5.3	29.58	23.47	24.66
8	2.645	25.5	25.59	15.59	33.57	31.03	18.39	34.61	30.36	27.56
9	2.828	34.04	35.39	22.59	38.96	35.54	29.01	39.68	36.32	31.5
10	3	40.93	39.27	31.34	43.31	43.42	33.78	46.73	42.33	40.41
11	3.162	50.56	45.44	37.51	47.51	49.79	37.97	53.1	55.8	49.89
12	3.316	54.19	56.47	45.8	56.47	56.09	42.95	60.1	63.21	55.59
13	3.464	63.94	59.84	55.02	64.3	63.08	50.25	66.11	64.45	65.33
14	3.6055	67.51	62.27	57.04	66.1	64.97	54.45	73.16	66.21	70
15	3.7416	71.5	65.73	59.01	72.64	68.96	57.04	79.22	68.6	75.33
16	3.8729	74.61	69.43	62.28	76.46	71.71	59.79	82.95	70.25	77.36

Fig no-20

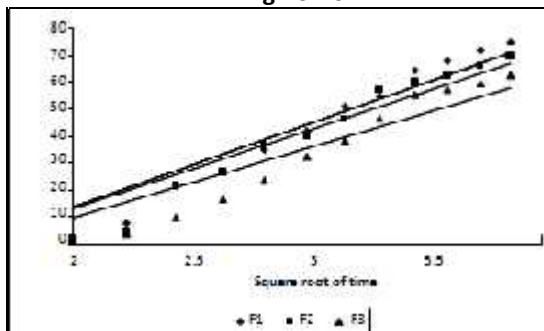


Fig no-21

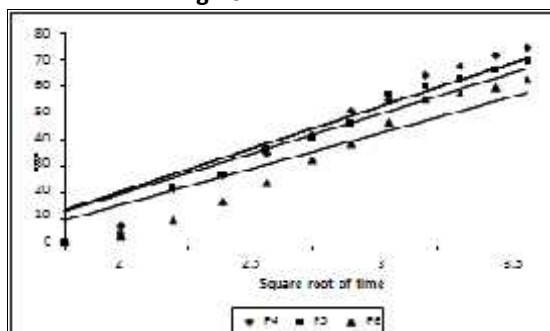


Fig no-22

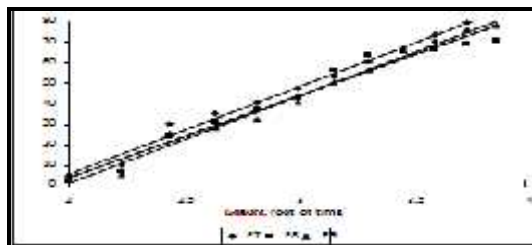


Table 18: Peppas release kinetics data of Diltiazem Hcl Pulsincap (CF1-CF9)

S.No	LOG T	Log % Cum. Drug release								
		CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9
1	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0
3	0.301	0	0	0	0	0	0	0	0	0
4	0.477	0	0	0	0	0	0	0	0	0
5	0.602	-1.184	0	0	0.397	0	0	0.615	0.095	0.556
6	0.698	0.781	0.443	0.344	0.777	0.663	-0.315	0.968	0.784	0.646
7	0.778	1.305	1.318	0.909	1.455	1.437	0.724	1.47	1.37	1.391
8	0.845	1.406	1.408	1.192	1.525	1.491	1.264	1.539	1.482	1.44
9	0.903	1.531	1.548	1.353	1.59	1.55	1.462	1.598	1.56	1.498
10	0.954	1.612	1.594	1.496	1.636	1.637	1.528	1.669	1.626	1.606
11	1	1.703	1.657	1.574	1.676	1.697	1.579	1.725	1.746	1.698
12	1.041	1.73	1.751	1.66	1.751	1.748	1.632	1.778	1.8	1.744
13	1.079	1.805	1.776	1.74	1.808	1.799	1.701	1.82	1.809	1.815
14	1.1139	1.829	1.794	1.756	1.82	1.812	1.735	1.864	1.809	1.845
15	1.1461	1.854	1.817	1.77	1.861	1.832	1.756	1.898	1.836	1.876
16	1.176	1.872	1.841	1.794	1.883	1.855	1.776	1.918	1.846	1.888

Fig no-23

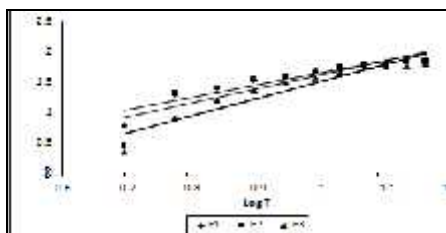


Fig no-24

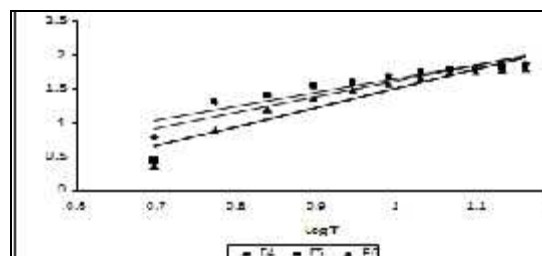
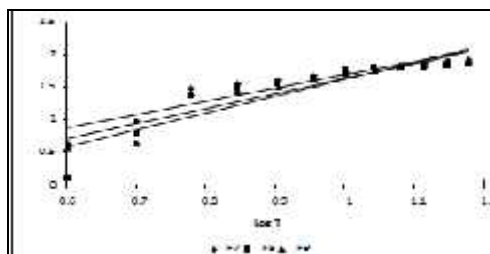


Fig no-25



The formulations were subjected to peppas plots by taking log cum % drug released versus log time. The plots are found fairly linear and the 'r' values are near to 1 and also slope value was calculated (n value) which was in ranges of 2.45 to 2.72, indicating the drug was released by Super Case II transport diffusion mechanism.

CONCLUSION

The aim of this study was to explore the feasibility of time and pH dependent colon specific, pulsatile drug delivery system of Diltiazem Hcl to treat the angina pectoris .A satisfactory attempt was made to develop Microspheres by using pH dependent and independent polymers (Eudragit L/S100) and further the time dependent, pulsatile device was designed for the Microspheres and evaluated. The data obtained from the study of "Development and evaluation of pulsatile drug delivery system of Diltiazem Hcl" reveals following conclusion:

Eudragit L-100 and S-100 are suitable for preparation of Microspheres for colonic targeting. The mean particle size of microspheres was in the range of 163.68 –251.84 mm depending upon the type of polymer used. The particle size increased significantly as the amount of polymer increased. The entrapment efficiency was good in all the cases. This suggested that optimized parameters were used in the method of preparations. *In-vitro* drug release of Microspheres showed biphasic release pattern for all Microspheres with initial burst release effect, which may be attributed to the drug loaded onto the surface of the particles. On the basis of, particle size, drug content, Scanning Electron Microscopy, IR-study, *in-vitro* release studies FM1 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. From all obtained results, it was found that the order of sustaining capacity of polymer is HPMC > Guar gum > Sodium alginate. Hence, finally it was concluded that the prepared pulsatile drug delivery system can be considered as one of the promising formulation technique for preparing colon specific drug delivery systems and hence in Chronotherapeutics management of angina pectoris.



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