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RESEARCH ARTICLE

DEVELOPMENT AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF DILTIAZEM HYDROCHLORIDE

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Abstract:
The main aim of the present work was to develop and evaluate Diltiazem hydrochloride press coated pulsatile tablets which releases the total amount of drug at early morning to tackle the difficulties that occur at cardiac diseases in morning such as angina attack in morning, hypertension, heart attacks etc. prevent hypertension in patients. These systems are designed according to the circadian rhythm of the body, and the drug formulation release drug rapidly and completely as a pulse after a lag time. PDDS (Pulsatile drug delivery system) system employed for treating diseases which show their intense influence at early morning, This press-coated Pulsatile tablets containing Diltiazem hydrochloride in the inner core was formulated with different superdisintegrants fan outer barrier layer by HPMC K4M / HPMC K15M / HPMC K100 / Sodium alginate. The inner core tablet was prepared by the direct compression method and outer barrier layer was applied by press coating technique. The effect of polymer on the lag time of drug release was investigated. Prepared Press Coated Tablets was evaluated for all physical tests. Among all the polymers HPMC K100 showed best lag time for a period of 6 hours and the drug release was prolonged for a period of 8 hours. Compatibility studies carried out by FTIR and DSC studies revealed that all the excipients and polymers were compatible with drug.

Keywords: Chronotherapeutics, Time controlled, lag time, press coated tablets, Diltiazem hydrochloride.

Introduction

Oral controlled release drug delivery system offer anumber of advantages over the conventional immediate release delivery preparations. These systems aredesigned to deliver the drugs at a controlled and predetermined rate thus maintaining their therapeutically effective concentration in systemic circulation fo rprolonged periods. On the other hands, for certain therapies a pulsatile drug release pattern, where the drug is released after well defined lag time, exhibits significant advantages. It is well documented that most of the body functions display circardian rhythms, e.g.heart rate, stroke volume, blood pressure, gastric pH.[1] Time controlled drug delivery system are dosage forms that are designed to mimic the circadian rhythm of the disease by releasing the drug at the appropriate time, by means of an internal pre-programmed clock that is initiated when the dosage forms come in contact with gastrointestinal fluids. Time controlled drug delivery system have been formulated as pellets [2], capsules [3-4] and tablets[5-9]designed to release the drug only after defined lag time. Particularly in the case of cardiovascular disease, bronchial asthma and rheumatoid arthritis, which mostly exhibit circadian manifestations in the early morning, the efficacy and tolerability of a therapy could notably be improved by delivery systems intended to timely release the drug few hours after bedtime administration, thus providing pharmacological protection when it is especially required without involving an unnecessarily

extended patient exposure to the active molecule nor impairing the overall treatment compliance.[10]

The objective of study to develop and evaluate of pulsatile drug delivery system containing diltiazem hydrochloride for the treatment of hypertension which is use deliver the drug at specific time as per pathophysiological needs of the disease and improvement of therapeutic efficacy and patient compliance.

MATERIALS

Diltiazem hydrochloride, all super disintegrants and all grades of HPMC was provided by Indira college of pharmacy, Vishnupuri, Nanded, Maharashtra.

METHODS

Cup method

Preparation of core tablet by direct compression

Core tablets of Diltiazem hydrochloride were prepared by direct compression method. All ingredients were weighed accurately and blended homogeneously for 15mins. Blended drug/polymer mixture of the formulations were subjected for pre-compressional evaluation such as bulk and tapped density, compressibility index, Hausner's ratio and angle of repose Tablets were compressed in Minipress Tablet Compression Machine using 8 mm round concave punches. The composition of core tablet is given in Table No.1

Preparation of press coated tablet

A **RSM** was used in this study. In this design 2 factors were evaluated, each at 2 levels, and experimental trials were performed at all 12 possible combinations. HPMC K4M, HPMC K15M, HPMC K100M, Sodium alginate.. Coating layer were selected as independent variables. The times required for maintaining lag time (Y) were selected as dependent variables. HPMC K4M, HPMC K15M, HPMC K100M, Sodium alginate are in different concentrations. The experimental design with corresponding formulation outline in Tableno.2

RESULT AND DISCUSSION

FTIR Spectrophotometer of drug

The IR spectrum of the pure drug Diltiazem shows in figure No. 1

Pre-compression Parameters of Core Tablet Powder Blend

Bulk Density & Tapped Density

Bulk density & tapped density were evaluated which were found as near about 0.51 g/cm3.

Angle of repose

The powder blends indicated good flowability with the angle of repose values ranging from 25 to 33° according to fixed funnel method

Carrs index & Hausners ratio

The result of compressibility index was between 9 to 15, which indicates good to fair flow properties & for Hausners ratio was near/less about 1.22, which indicates free flowing powder.

Post-compression Parameters of Coated Tablets

Hardness: The hardness of all core tablets was between 6-7kg/cm2 and coated tablets between 8-9kg/cm2.

Friability

In the present study, the loss in total weight in friability test was in the range of 0.75 to 0.94% that indicates, the percentage friability for all the formulations was found below 1% indicating that friability (%) is within the acceptable limits.

Weight variation test

In a weight variation test, the pharmacopoeia limit for the percentage deviation for tablets weighing more than 250 mg is ±5%. The average percentage deviation of all tablet formulations was found to be within limit, and hence all formulations passed the test for uniformity of weight as per the official requirement.

In vitro drug release study of tablets

In-vitro dissolution testing is important in the development of solid dosage forms. It provides decisive information on formulation selection, the critical processing variables. In order to provide this information, dissolution testing should be conducted in physiochemical and hydrodynamically defined conditions to simulate the environment that the dosage form encounters in the GI tract. Conventional dissolution testing proposed in USP appears unable to discriminate drug mechanisms. For in-vitro evaluation of Pulsatile drug delivery systems, the ideal dissolution testing should closely mimic the in-vivo conditions with regard to pH, bacteria, types of enzymes, enzymatic activity, fluid volume and mixing intensity. Apparently, such dissolution specifications will be very difficult, if possible at all, to be standardized and validated. Dissolution testing of Pulsatile delivery systems with the conventional paddle method at 50 rpm and 37+0.5has usually been conducted in different buffers for different periods of time to simulate the GI tract pH and transit time that the Pulsatile delivery system might encounter in-vivo The ability of the coats/carriers to remain intact in the physiological environment of the stomach and small intestine is generally assessed by conducting drug release studies in pH 1.2 buffer for 2 hours (mean gastric emptying time) and in pH 6.8 phosphate buffer for remaining hours (mean small intestinal transit time) using USP dissolution rate test apparatus. The samples were withdrawn at regular intervals and analysed by UV spectrophotometer for the presence of the drug at the lambda max 237 nm.

Table No. 1 Composition of Core Tablet

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug(mg)	90	90	90	90	90	90	90	90	90	90	90	90
CP(mg)	2.5	5	7.5	10	-	-	-	-	-	-	-	-
SSG(mg)	-	-	-	-	2.5	5	7.5	10	-	-	-	-
CCS(mg)	-	-	-	-	-	-	-	-	2.5	5	7.5	10
MC(mg)	55.5	53	50.5	48	55.5	53	50.5	48	55.5	53	50.5	48
MS(mg)	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%

Total weight of core tablet 150 mg; SSG-Sodium starch glycolate, CP- Crospovidone, CCS- Crosscarmellose sodium, MCC- Microcrystalline cellulose and MS-Microcrystalline cellulose

Table No.2 composition of compression coated Tablet

Sr. No	Polymer	F1	F2	F3	F4	F5	F6	F	F8	F9	F10	F11	F12
1	HPMC K4M	120	240	360	_	_	_	_	_	_	_	_	_
2	HPMC K15M	_	_	_	120	240	360	_	_	_	_	_	_
3	HPMC K100M	_	_	_	_	_	_	120	240	360	_	_	_
4	SA	_	_	_	_	_	_	_	_	_	120	240	360
5	MCC	280	160	40	280	160	40	280	160	40	280	160	40

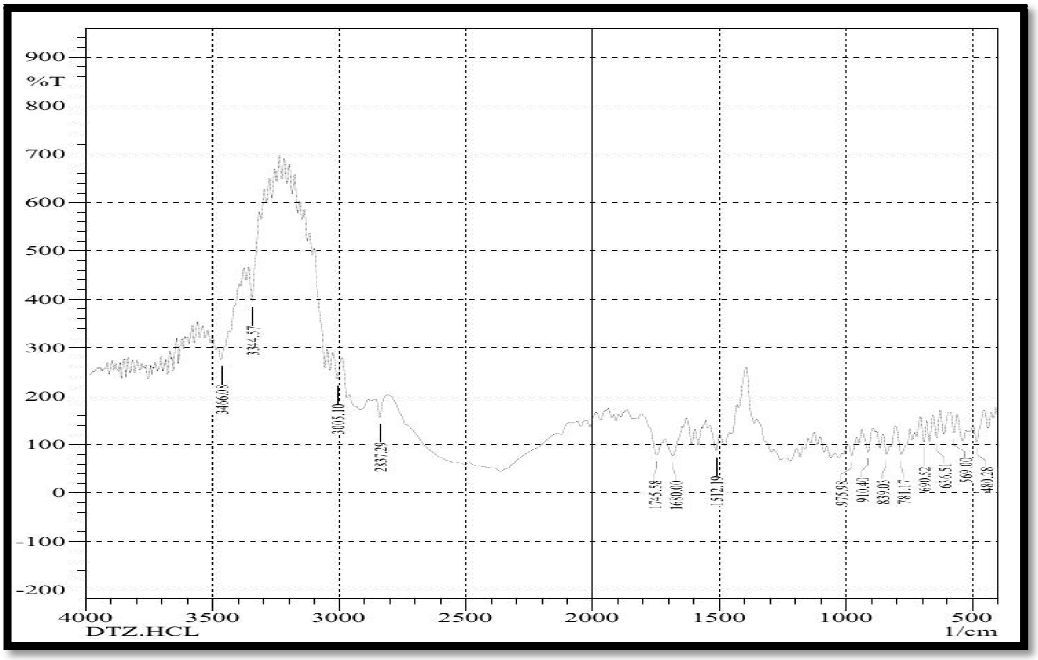


Figure No 1: IR spectrum of the Diltiazem Drug

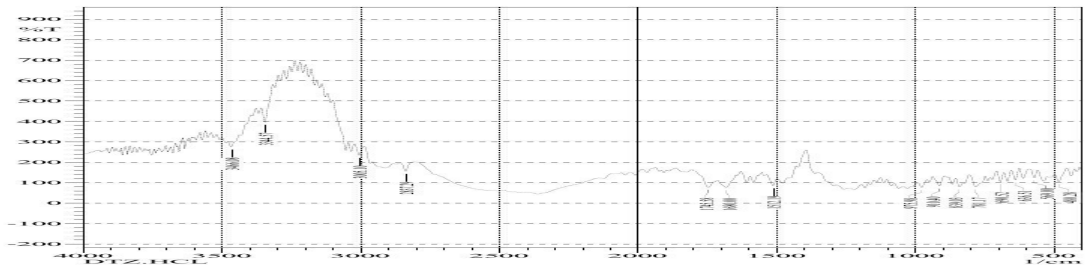
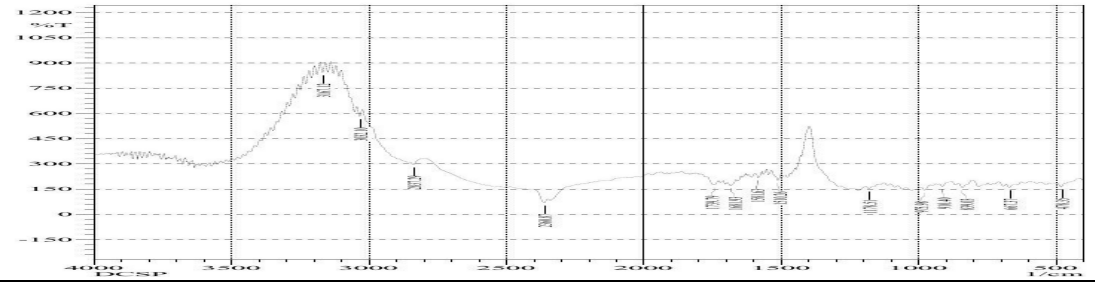
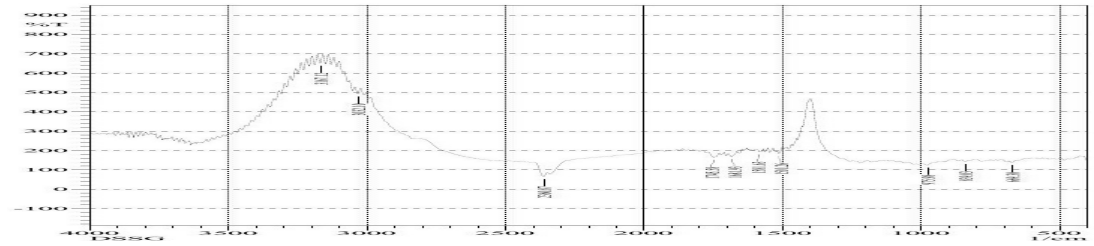
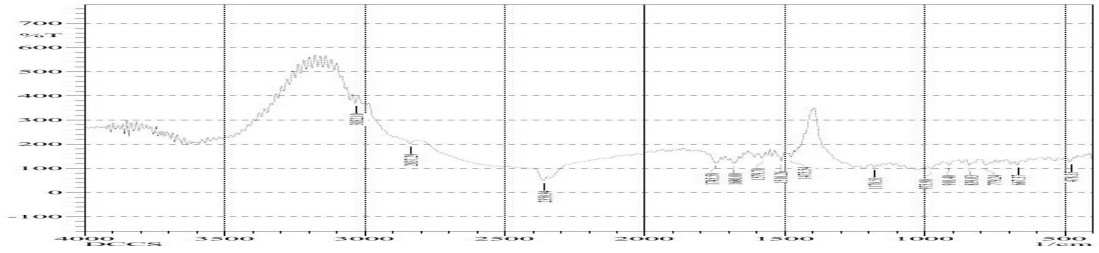
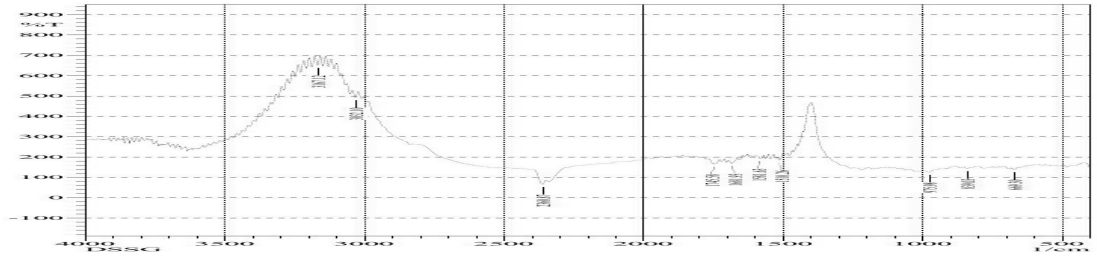
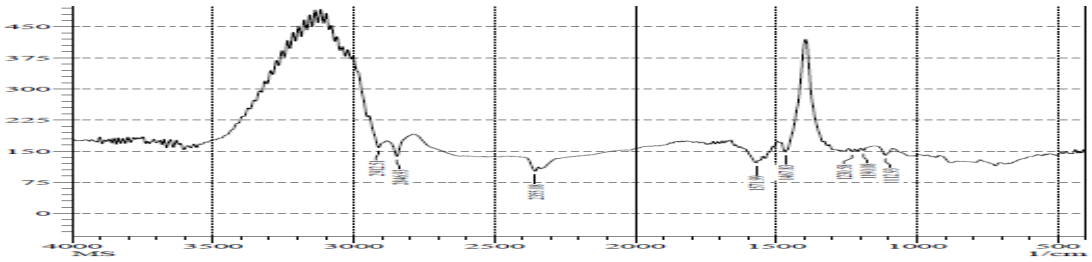
A	
B	
C	
D	
E	
f	

Figure No.2: Overlay IR spectras A)Drug B)Drug+crospovidone C)Drug+SSG D)Drug+CCS E)Drug+MCC F)Drug+MS

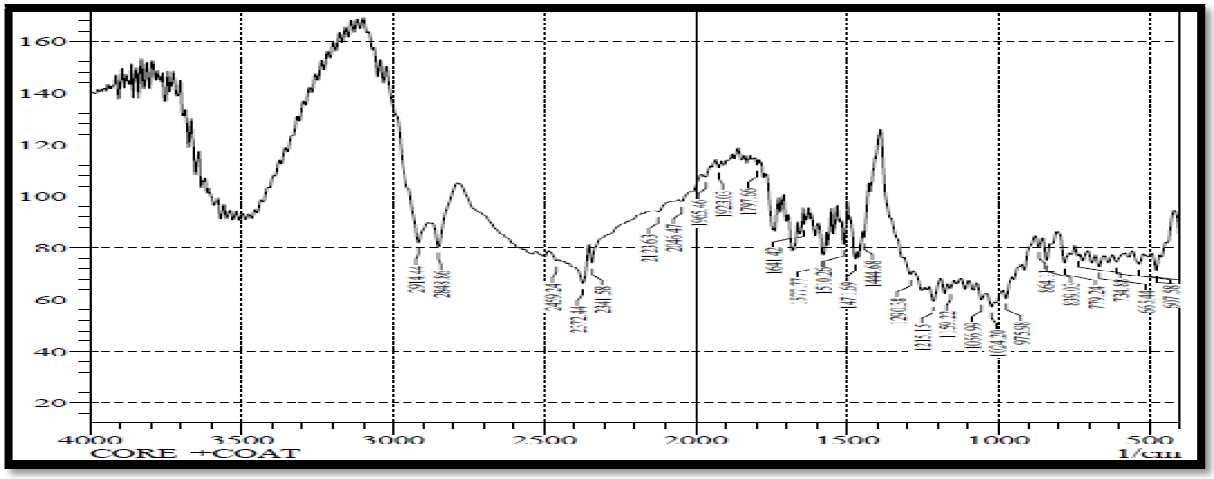


Figure No.3: IR spectrum of Core + Coat

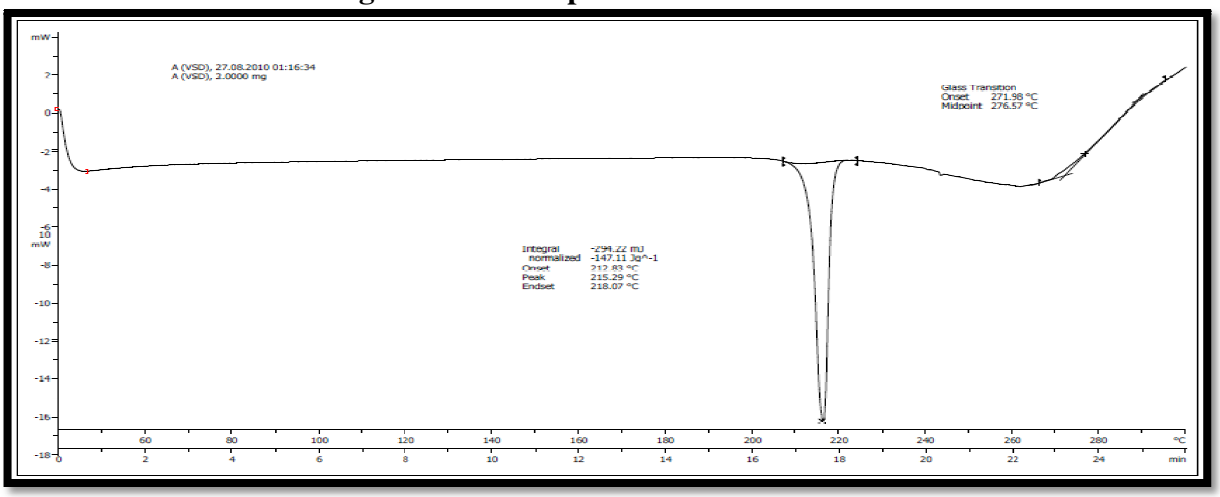


Figure No.4: DSC Thermogram of diltiazem hydrochloride

Table No.3: Pre-Compression Parameter For Powder Blend of Core Tablet of F1 – F6

Batches	F1	F2	F3	F4	F5	F6
Bulk Density(g/cm^3)	0.5 ± 0.046	0.454 ± 0.045	0.454± 0.045	0.5 ± 0.045	0.5 ± 0.049	0.454 ± 0.046
Tapped Density(g/cm^3)	0.555 ± 0.045	0.555 ± 0.046	0.555 ± 0.046	0.625 ± 0.045	0.625 ± 0.048	0.555 ± 0.045
Hausners ratio	1.11 ± 0.035	1.15±	1.22 ± 0.036	1.2 ± 0.042	1.2 ± 0.042	1.2 ± 0.041
Carrs index(%)	9.9 ± 0.48	13.12 ± 0.47	11.04 ± 0.48	14.33 ± 0.45	12.67 ± 0.45	10.25 ± 0.46
Angle of Repose (θ)	29.33 ± 1.143	29.33 ± 1.125	25.17 ± 1.145	30.48 ± 1.146	31.52 ± 1.146	33.13 ± 1.145

Table No.4: Pre-Compression Parameter For Powder Blend of Core Tablet of F7 – F12

Batches	F7	F8	F9	F10	F11	F12
Bulk Density(g/cm^3)	0.5 ± 0.048	0.454 ± 0.046	0.454 ± 0.048	0.5 ± 0.047	0.5 ± 0.048	0.454 ± 0.046
Tapped Density(g/cm^3)	0.555 ± 0.045	0.625 ± 0.051	0.555 ± 0.052	0.555 ± 0.048	0.555 ± 0.047	0.5 ± 0.049
Hausners ratio	1.11 ± 0.048	1.37 ± 0.042	1.22 ± 0.048	1.11 ± 0.040	1.1 ± 0.045	1.2 ± 0.043
Carrs index(%)	9.9 ± 0.48	15.03 ± 0.46	10.36 ± 0.45	9.9 ± 0.48	9.9 ± 0.49	9.2 ± 0.47
Angle of Repose(θ)	33.65 ± 1.147	27.87 ± 1.149	25.34 ± 1.148	27.95 ± 1.152	25.55 ± 1.153	26.98 ± 1.158

Table No.5: Post-compression parameters for core tablets

Batch	Hardness (Kg/cm^2)	Thickness (mm)	Diameter (mm)	Weight variation(%)	Disintegretion time (min)	% Drug release	Friability (%)
F1	6.5±0.50	4±0.005	7.01±0.007	150±0.78	1.1	65.06	0.149
F2	7±0.50	4±0.005	7.00±0.012	149±0.78	1	62.99	0.145
F3	6.5±0.50	4±0.005	7.00±0.008	148±0.78	0.45	98.95	0.148
F4	7±0.50	4±0.005	7.02±0.012	150±0.78	1.12	52.99	0.147
F5	6.5±0.50	4±0.005	7.01±0.011	150±0.78	1.4	68.53	0.142
F6	6.5±0.50	4±0.005	7.01±0.008	149±0.78	1.55	57.47	0.145
F7	7±0.50	4±0.005	7.01±0.015	150±0.78	1.42	58.97	0.146
F8	6.5±0.50	4±0.005	7.01±0.009	150±0.78	1.45	56.59	0.148
F9	6.5±0.50	4±0.005	7.00±0.007	150±0.78	3.15	65.97	0.142
F10	6.5±0.50	4±0.005	7.01±0.015	150±0.78	3	61.88	0.143
F11	6.5±0.50	4±0.005	7.01±0.009	150±0.78	3.39	66.78	0.146
F12	6.5±0.50	4±0.005	7.00±0.007	150±0.78	3.25	62.38	0.142

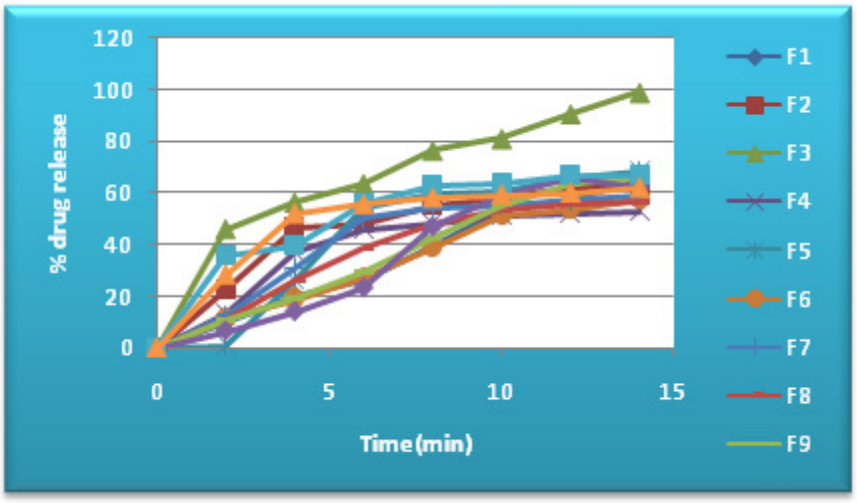


Figure No.5: % Drug Release of core tablets

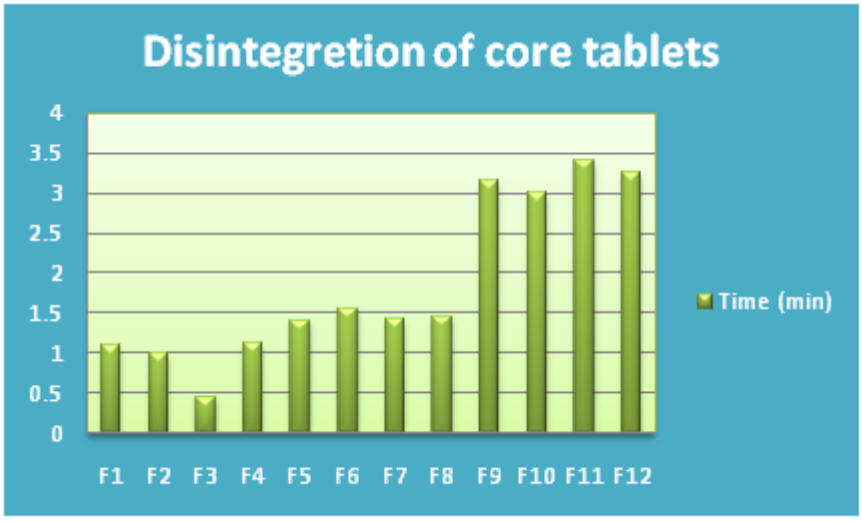


Figure No.6: Disintegretion studies of core tablets

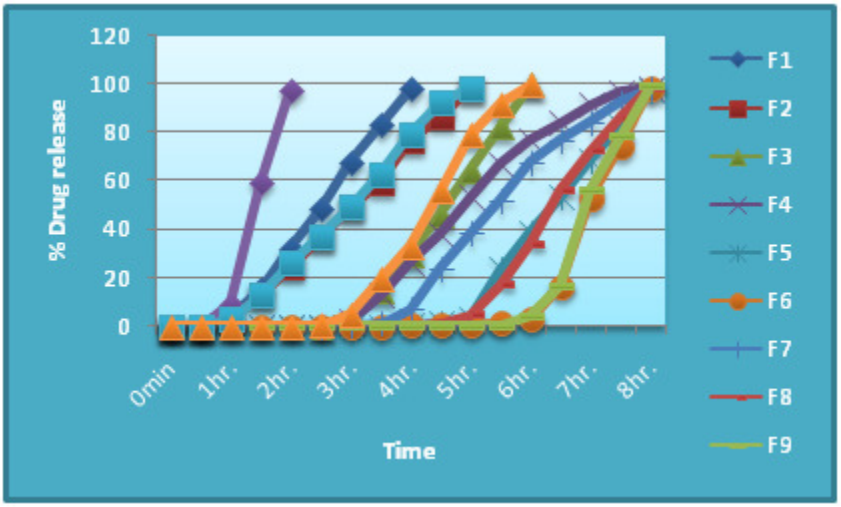


Figure No.7: In-vitro % drug release of coated formulations

Table No.6: Post-compression parameters for coated tablets

Batch	Hardness (Kg/cm^2)	Thickness (mm)	Diameter (mm)	Weight variation(%)	Disintegretion time(min)	% Drug release	Friability(%)
F1	6.5±0.50	4±0.005	7.01±0.007	150±0.78	1.1	65.06	0.149
F2	7±0.50	4±0.005	7.00±0.012	149±0.78	1	62.99	0.145
F3	6.5±0.50	4±0.005	7.00±0.008	148±0.78	0.45	98.95	0.148
F4	7±0.50	4±0.005	7.02±0.012	150±0.78	1.12	52.99	0.147
F5	6.5±0.50	4±0.005	7.01±0.011	150±0.78	1.4	68.53	0.142
F6	6.5±0.50	4±0.005	7.01±0.008	149±0.78	1.55	57.47	0.145
F7	7±0.50	4±0.005	7.01±0.015	150±0.78	1.42	58.97	0.146
F8	6.5±0.50	4±0.005	7.01±0.009	150±0.78	1.45	56.59	0.148
F9	6.5±0.50	4±0.005	7.00±0.007	150±0.78	3.15	65.97	0.142
F10	6.5±0.50	4±0.005	7.01±0.015	150±0.78	3	61.88	0.143
F11	6.5±0.50	4±0.005	7.01±0.009	150±0.78	3.39	66.78	0.146
F12	6.5±0.50	4±0.005	7.00±0.007	150±0.78	3.25	62.38	0.142

CONCLUSION

The main objective of the studies described was to develop a time-controlled release formulation of Diltiazem hydrochloride based on compression coating technique. The intention is that the formulation should be administered in the night at 22:00 for treating Hypertension in which symptoms are worse in the early morning hours (from 04:00 to 06:00). The compression coated tablets of Diltiazem hydrochloride, a BCS Class 1st drug had been successfully developed with various coating polymers to achieve maximum release drug after a predetermined lag time of 6 h. The *in-vitro* drug release studies showed that amongst all the formulations F6 and F9 could release the drug completely after a distinct lag time of 6 h. The high viscosity of polymers such as HPMC K15M and HPMC K100M were found to be responsible for delaying drug release, thus making these formulations useful as chronotherapeutic drug delivery systems for the treatment of Hypertension which follow circadian rhythms.

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