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Formulation Development and Characterization of Diltiazem Pulsin Cap for Pulsatile Drug Delivery

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ABSTRACT

The aim of this work is to develop modified drug release by using Pulsin Cap technique with Diltiazem as model drug. From the above experimental results, it can be concluded that, Formulated granules gave satisfactory results for various micromeritic properties, dissolution and drug content. Formulated Pulsin Cap gave satisfactory results for various physicochemical parameters like weight variation. HPMC, Ethyl cellulose has predominant effect on the lag time, while also shows significant effect on drug release. Diltiazem Pulsin Cap shows a delayed release pattern. Among all the Diltiazem granules formulations F5 was selected based on drug release within a given period of time. In-vitro release rate studies showed that the PF5 was optimized based on less amount of drug release during lag time. Formulations PF5 found to be stable at 40^{o} C and 75% RH for a period of 3 months. FT-IR studies revealed that there was no interaction between Diltiazem and the polymers.

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INTRODUCTION

Controlled drug delivery systems have acquired a center stage in the area of pharmaceutical R &D sector. Such systems offer temporal &/or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of controlled drug delivery systems for obvious advantages of oral route of drug administration. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-value fluctuation, reduction in dose of drug, reduced dose frequency, avoidance of side effects and improved patient compliance. In such systems the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms. However, there are certain conditions, which demand release of drug after a lag time. Such a release pattern is known as pulsatile release [1].

Pulsatile drug delivery systems

New global trends in drug discovery and development

In this century, the pharmaceutical industry is caught between pressure to keep prices down and the increasing cost of successful drug discovery and development. The average cost and time for the development of a new chemical entity are much higher (app $500 million and 10-12 years) than those required to develop a novel drug delivery system (NDDS or ChrDSS) ($20-$50 million and 3 to 4 years). In the form of an NDDS or ChrDDs, an existing drug molecule can get a new life thereby increasing its market value and competitiveness and extending patent life [2,3].

Among modified-release oral dosage forms, increasing interest has currently turned to systems designed to achieve time specific (delayed, pulsatile) and site-specific delivery of drugs. Systems for delayed release are meant to deliver the active principle after a programmed time period following administration. These systems constitute a relatively new class of device the importance of which is especially connected with the recent advances in chronopharmacology. It is by now well-known that the symptomatology of a large number of pathologies as well as the pharmacokinetics and pharmacodynamics of several drugs follow temporal rhythms, often resulting in circadian variations. Therefore, the possibility of exploiting delayed release to perform chronotherapyis 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. The delay in the onset of release has so far mainly been achieved through osmotic mechanisms, hydrophilic or hydrophobic layers, coating a drug-loaded core and swellable or erodible plugs sealing a drug containing insoluble capsule body [4].

Delivery systems with a pulsatile release pattern are receiving increasing interest for the

development of dosage forms, because conventional systems with acontinuous release are not ideal. Most conventional oral controlled release drug delivery systems release the drug with constant or variable release rates. A pulsatile release profile is characterized by a time period of no release rates (lag time) followed by a rapid and complete release.

These dosage forms offer many advantages such as

- Nearly constant drug levels at the site of action.
- Avoidance of undesirable side effects.
- Reduced dose and
- Improved patient compliance.
- Used for drugs with chronopharmacological behaviour, a high first pass effect, the requirement.

The conditions that demand pulsatile release include:

- Many body functions that follow circadian rhythm i.e. their waxes and wanes with time. Ex: hormonal secretions.
- Diseases like bronchial asthma, myocardial infraction, angina pectoris, rheumatoid diseases, ulcer and hypertension display time dependence.
- Drugs that produce biological tolerance demand for a system that will prevent continuous present at the biophase as this tend to reduce their therapeutic effect.
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium (ex: peptide drugs) irritate the gastric mucosa or induce nausea and vomiting.
- Targeting to distal organs of GIT like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.

All these conditions demand for a time-programmed therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by pulsatile drug delivery system, which is characterized by a lag time that is an interval of no drug release followed by rapid drug release [1].

Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastrointestinal motility, etc. these time-controlled systems can be classified as single unit (tablet or capsule) or multiple unit (e.g., pellets) systems [1,5].

Single Unit Systems

Drug delivery systems with eroding or soluble barrier coatings

Most pulsatile delivery systems are reservoir devices coated with a barrier layer. The barrier

dissolves or erodes after a specify lag period, after which the drug is released rapidly from the reservoir core. In general, the lag time prior to drug release from a reservoir type device can be controlled by the thickness of the coating layer. E.g. The Time Clock® system and chronotropic® system consists of a drug containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release.

Drug delivery systems with rupturable coatings

In this the drug is released from a core (tablet or capsule) after rupturing the surrounding polymeric layer, caused by inbuilt pressure within the system. The pressure necessary to rupture the coating can be achieved with gas-producing effervescent excipients, osmotic pressure or swelling agents.

Capsular shaped systems

Several single unit pulsatile dosage forms with a capsular design have been developed. Most of them consist of an insoluble capsule body, containing the drug and a plug, which gets removed after a predetermined lag time because of swelling, erosion or dissolution. E.g., Pulsincap® system and Port® system.

The **Pulsincap®** system consists of a water-insoluble capsule body (exposing the body to formaldehyde vapor which may be produced by the addition of trioxymethylene tablets or potassium permanganate to formalin or any other method), filled with the drug formulation and plugged with a swellable hydrogel at the open end. Upon contact with dissolution media or gastrointestinal fluid, the plug swells and comes out of the capsule after a lag time, followed by a rapid release of the contents. The lag time prior to the drug release can be controlled by the dimension and the position of the drug. In order to assure a rapid release of the drug content, effervescent agents or disintegrants were added to formulation, especially with water-insoluble .

Studies in animals and healthy volunteers proved the tolerability of the formulation (e.g., absence ofgastrointestinal irritation). In order to overcome the potential problem of variable gastric residence time of a single unit dosage forms, the Pulsincap® system was coated with an enteric layer, which dissolved upon reaching the higher pH regions of the small intestine [6].

The plug consists of;

- Swellable materials coated with insoluble, but permeable polymers (e.g., polymethacrylates)
- Erodible compressed materials (e.g., HPMC, polyvinyl alcohol, polyethylene oxide)
- Congealed melted polymers (e.g., saturated polyglycoated glycerides or glycerylm

onooleate).

FORMULATION DEVELOPMENT [7]

Preparation of Cross-Linked Gelatine Capsules:

Formaldehyde treatment has been employed to modify the solubility of gelatine capsules. Exposure to formalin vapours results in an unpredictable decreases in solubility of gelatine owing to the cross linkage of the amino group in the gelatine molecular chain aldehyde group of formaldehyde by Schiff's base condensation.

Method

Hard gelatine capsule of size 0 was taken. Bodies were separated from cap, 25 ml of 15% (v/v) formaldehyde was taken into desiccators and a pinch of potassium permanganate was added to it, to generate formalin vapours. The wire mesh containing the empty bodies of capsule was then exposed to formaldehyde vapours. The caps were not exposed leaving them water-soluble. The desiccators were tightly closed. The reaction was carried out for 12 h after which the bodies were removed and dried at 50^0C for 30 min to ensure completion of reaction between gelatine and formaldehyde vapours. The bodies were then dried at room temperature to facilitate removal of residual formaldehyde. These capsule bodies were capped with untreated caps and stored in a polythene bag.

Solubility study of treated capsules

The capsule bodies were exposed to 15% formaldehyde solution in varying time intervals. Then exposed capsule bodies were dried in hot air oven. The solubility of bodies was tested in 0.1N HCL. The time at which the capsule dissolves or forms a soft fluffy mass was noted. Qualitative test for free formaldehyde Standard used is formaldehyde solution and sample solution is formaldehyde treated bodies (about 25 capsules), cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1 hrs with a magnetic stirrer, to solubilize the free formaldehyde. The solution was then filtered into a 50 ml volumetric flask, washed with distilled water and volume was made up to 50 ml with the washings. Method 1ml of sample solution, 9ml of water was added. One millilitre of resulting solution was taken into a test tube and mixed with 4ml.

Method

1ml of sample solution, 9ml of water was added. One millilitre of resulting solution was taken into a test tube and mixed with 4ml of water and 5ml of acetone reagent. The test tube was warmed in a water bath at 40^{o}C and allowed to stand for 40 min. The solution was less intensely colored than a reference solution prepared at the same time and in the same manner using 1ml of standard

solution in place of the sample solution. The comparison was made by examining tubes down their vertical axis.

Optimization of hydrogel plug:

The formulation of pulsincap 90mg and 100mg hydrogel plug was prepared by compressing equal amount of different polymers using 7mm punches and dies on rotary tablet press keeping variation in thickness and hardness values of tablet plug. This plug was then fitted into the body of hard gelatin capsule (containing granules equivalent to 30mg of Diltiazem) which was cross linked by exposing the capsule bodies to formaldehyde vapour in desiccator for 12 hours.

Characterization of prepared hydrogel plug:

The prepared hydrogel plug evaluation was carried out for hardness, thickness and lag time test. The prepared hydrogel plugs were plugged to capsule bodies containing formulated granules and the cap was closed. The lag time test was conducted using USP II dissolution testing apparatus using 7.4 pH for phosphate buffer for 6 hrs. The drug release was observed.

Preparation of Diltiazem granules:

Diltiazem granules were prepared by wet granulation method. The composition of different formulations used. The powders were blended and granulated with starch. Isopropyl alcohol was used as granulating agents. The wet mass was passed through a mesh and granules were dried at 50^0C for 1 hr.

Characterization of Diltiazem granules :

The prepared granules were evaluated for different flow properties which include angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio, dissolution profile and drug content. The drug content was evaluated by an UV spectrophotometric method based on the measurement of absorbance at 240 nm.

Table 1: Composition of Granules

Ingredients (mg)	DTZ 1	DTZ 2	DTZ 3	DTZ 4	DTZ 5	DTZ 6
Diltiazem (mg)	30	30	30	30	30	30
CCS (%)	15	20	---	---	---	---
CP (%)	---	---	15	20	---	---
SSG (%)	---	---	---	---	15	20
Starch (mg)	5	5	5	5	5	5
Magnesium stearate (mg)	4	4	4	4	4	4
Talc (mg)	4	4	4	4	4	4
MCC (mg)	q.s	q.s	q.s	q.s	q.s	q.s
Total wt (mg)	150mg	150mg	150mg	150mg	150mg	150mg

MCC: Micro crystalline cellulose, CCS: Cross caramellose sodium, CP- Cross Povidone, SSG: Sodium starch glycolate.

Table 2: Composition of Plug

Press coat	PDTZ1	PDTZ2	PDTZ3	PDTZ4	PDTZ5	PDTZ6
Weight of core tablet	**150**	**150**	**150**	**150**	**150**	**150**
HPMCE15	45	90	--	50	100	--
Ethyl cellulose	45	--	90	50	--	100
Total wt(mg)	240	240	240	250	250	250

Formulation of pulsatile (modified pulsincap) drug delivery system:

Preparation of modified pulsincap Equivalent to 30 mg drug granules were filled in the capsule bodies and plugged with hydrogel plug. The treated body and the cap of the capsules were sealed with a small amount of 5% ethyl cellulose ethanolic solution.

EVALUATION OF PULSINCAP Capsules [8]

Evaluation of rapid release core (RRCT) and PULSINCAP of Diltiazem

Weight variation:

Twenty Capsules were randomly selected from each batch weighed individually. The average weight and standard deviation was calculated.

In-vitro Dissolution methods for Pulsin Cap of Diltiazem [9]

In –vitro Dissolution studies of Pulsatile delivery systems was done with the conventional paddle method of Diltiazem Pulsin cap were performed at 37 ± 0.5 °C using 0.1N HCL for 2hrs and then replaced with 6.8 phosphate buffer in USP II paddle method at 50 rpm. 5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh buffer maintained at the same temperature. The samples were analysed at 240nm using a UV spectrophotometer. The lag time and percentage release was determined for each formulation.

Stability Studies:

The stability study of the formulations was carried out according to ICH guidelines at 40 ± 2^{o} C/75 ± 5 % RH for three months by storing the samples in stability chamber (Lab-care, Mumbai).

The purpose of stability testing is to provide evidence of the quality of the drug substance or drug product, and how it varies with time under the influence of a variety of environmental conditions (heat, humidity, light, air etc). The final formulation was packed in suitable packing like blister and strip packs and then they will be kept at different temperature, humidity conditions and the samples will be analyzed for their physical and chemical properties.

STABILITY STUDIES STORAGE CONDITIONS [10]

Table 3: Stability studies Storage conditions

Study	Storage conditions	Minimum time period covered by data at submission.
Long term	25 ± 2°c / 60 ± 5% RH Or 30 ± 2°c / 75 ± 5% RH	12 months
Intermediate	30 ± 2°c / 65 ± 5% RH	6 months
Accelerated	40 ± 2°c / 75 ± 5% RH	6 months

PRE-FORMULATION STUDIES [40]

Preformulation testing was an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It was the first step in the rational development of dosage forms.

Objective /Purpose of Preformulation study

Pre-formulation studies on active pharmaceutical ingredients (API), inactive ingredients (Excipients), and their combinations were carried out to serve following purposes:

- To Finalize specifications of active pharmaceutical ingredients (API)
- To Study the compatibility between active and inactive ingredient
- Characterization of reference product

Scope:

The use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

Class: -Preformulation study can divided into two subclasses:

- API characterization
- Compatibility study

Active pharmaceutical ingredient (API) characterization: -

Organoleptic evaluation:

These are preliminary characteristics of any substance which is useful in identification of specific material. Following physical properties of API were studied.

Table 4: Organoleptic Evaluation

Parameter	Properties of Diltiazem
Organoleptic Evaluation	A white crystalline powder.
Solubility Analysis	Freely soluble in methanol, in water, sparingly soluble in ethanol, practically insoluble in ether.

EVALUATION PARAMETERS FOR PRE COMPRESSION BLEND[41]

Bulk density

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring pre sieved blend into a graduated cylinder via a large funnel and measure the volume and weight. Bulk density was expressed in g/cc.

Bulk density = Weight of blend/ Bulk volume of blend

Tapped density:

Tapped density is determined by placing a graduated cylinder containing a known mass of blend and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

Tapped density = Weight of blend/ Tapped volume of blend

Carr's Index (CI):

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

CI = (TD-BD) x100/ TD

Where TD = Tapped density

BD = Bulk density

Table 5: Flow properties and corresponding Carr's Index values

Excellent	<10
Good	11 – 15
Fair	16 – 20
Possible	21 – 25
Poor	26 – 31
Very poor	32 – 37
Very very poor	>38

Hausner's Ratio:

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or blend.

Hausner's Ratio = Tapped density/Bulk density

Table 6: Flow Properties and Corresponding Hausner's ratio

Excellent	1.00 – 1.11
Good	1.1 – 1.18
Fair	1.19 – 1.25
Possible	1.26 -1.34
Very poor	1.35 -1.45

Very very poor	>1.60

Angle of repose:

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The method used to find the angle of repose is to pour the powder ion a conical heat on a level, flat surface and measure the included angle with the horizontal.

$$\mathbf{Tan\theta = h/r}$$

Where,

h= height of the heap

r= Radius of the heap

Table 7: Flow Properties and Corresponding Angle of Repose

Angle of repose	Powder flow
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very poor

RESULTS AND DISCUSSIOIN

PRE-FORMULATION STUDIES

Description

These test results were illustrated below:

Table 8: Description of Diltiazem (API)

Test	Description
Colour	White to off white crystalline powder
Odour	Free of odour

Solubility

These tests results were illustrated below:

Table 9: Description of Diltiazem (API)

Solvents	Solubility
Water	Freely Soluble
Methanol	Freely Soluble
Ethanol	Sparingly soluble
Ether	practically insoluble

Melting Point

Table 10: Melting point of Diltiazem API

Material	Literature value Melting Point
Diltiazem	187-188^{o}C

Standard calibration curve of Diltiazem

Table 11: Concentration and absorbance of Diltiazem in 0.1N Hcl

S.No	Concentration	Absorbance at 240nm
1	0	0
2	5	0.154
3	10	0.315
4	15	0.492
5	20	0.648
6	25	0.861

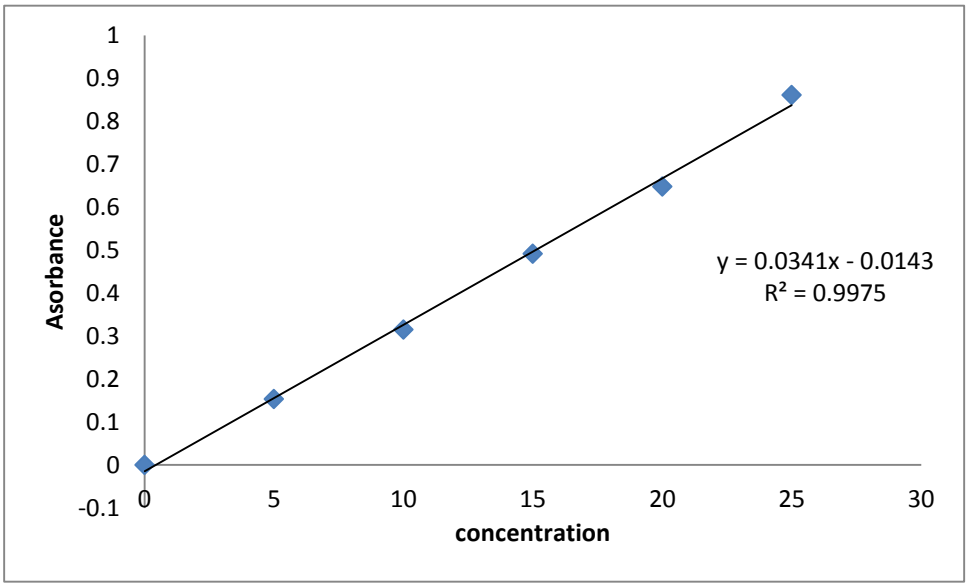

Figure 1: Calibration curve of Diltiazem

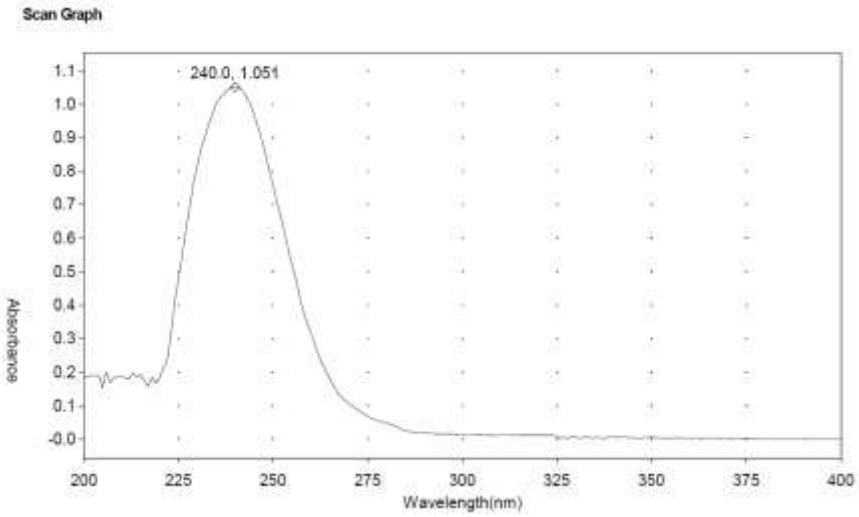

Figure 2: UV –Visible spectrum of Diltiazem at 240nm

DRUG EXCIPIENT COMPATIBILITY STUDIES

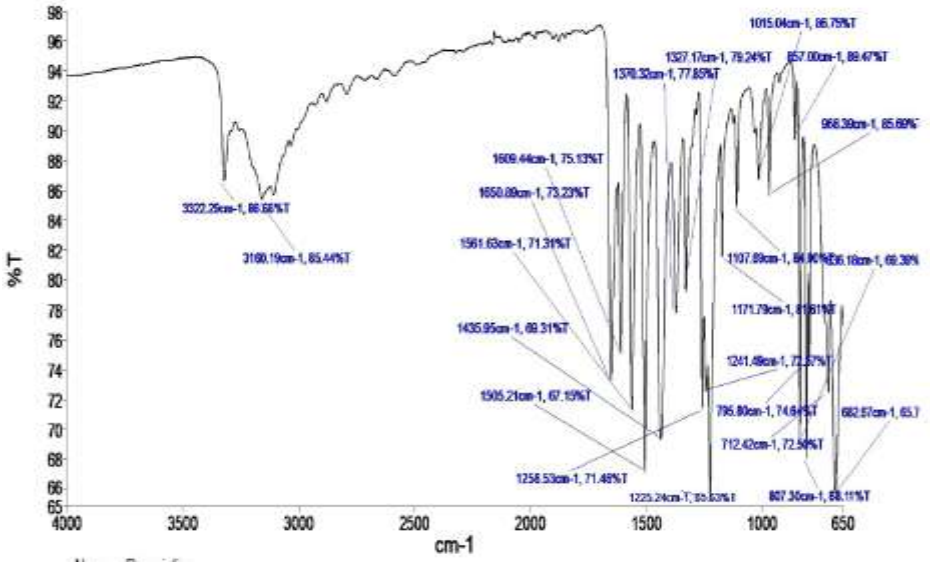

Figure 3: FTIR spectra of pure drug

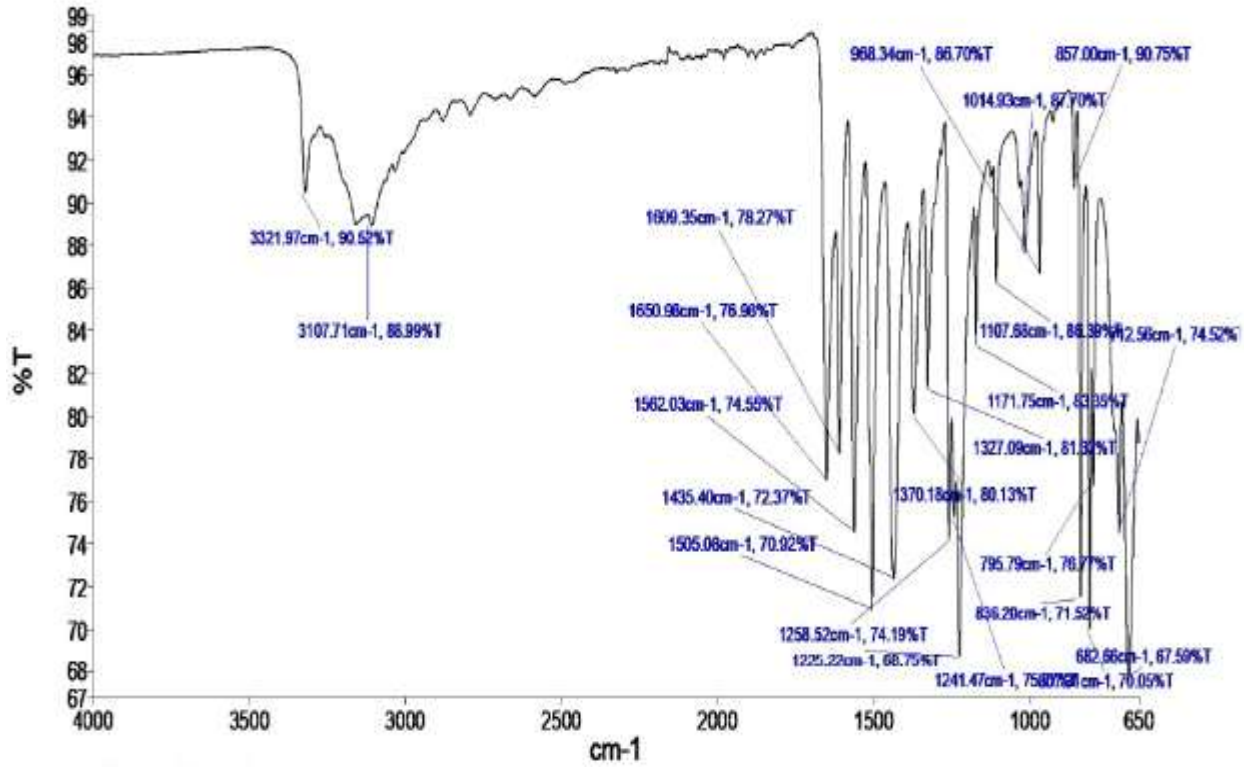

Figure 4: FTIR spectra of optimized formulation

Table 12: Interpretation data of Pure and Optimized formulation

Functional group	Range	Diltiazem pure	Diltiazem optimized
N-H stretch	3350-3310	3322.29	3321.97
C═O	1710-1685	1650.89	1650.98
C-N stretch	1342-1250	1258.53	1258.52

PRE FORMULATION PARAMETERS

Table 13: Pre-compression parameters for Diltiazem granules

Formulation code	Bulk density (gm/mL)	Tapped density (gm/mL)	Compressibility index (%)	Hausner's ratio	Angle of repose	Flow property
F1	0.42±0.042	0.47 ± 0.06	10.63±0.5	1.11±0.04	23.58±0.15	Very good
F2	0.43±0.041	0.49 ± 0.08	12.24±0.7	1.13±0.08	25.44±0.11	Very good
F3	0.44±0.044	0.51 ± 0.04	13.72±0.2	1.15±0.06	26.36±0.13	Very good
F4	0.46±0.046	0.53± 0.02	13.20±0.4	1.15±0.08	29.52±0.19	Very good
F5	0.41±0.044	0.46 ± 0.01	10.86±0.8	1.12±0.09	27.32±0.19	Very good
F6	0.43±0.042	0.48 ± 0.04	10.41±0.6	1.11±0.09	25.69±0.19	Very good

Evaluation of formulation treated empty capsules

The evaluation of treated empty capsule (cap and body) was carried out by length and diameter of capsules,

It showed Average capsule length

- Before formaldehyde treatment (untreated cap and body): 20.85 mm
- After formaldehyde treatment (treated body and untreated cap): 19.72 mm
- Average diameter of capsule body Before formaldehyde treatment: 7.12mm
- After formaldehyde treatment: 6.84 mm
- Average length of capsule body Before formaldehyde treatment: 17.84mm
- After formaldehyde treatment: 16.92mm

Evaluation of hydrogel plug

The prepared hydrogel plugs were evaluated by thickness, hardness and lag time. It was found that 90 mg plug showed 4 hrs lag time and 100 mg plug showed 12 hrs lag time. Therefore 100 mg plug was optimized. Hydrogel plug was optimized based on the lag time.

Table 14: Physical Evaluation Parameters For Hydrogel Plug

S. No	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6
1	Weight (mg)	91.2	90.5	91.4	100	102	101.5
2	Hardness(Kg/cm^2)	3.5	3.8	3.9	4.1	4.0	3.7
3	Thickness(mm)	2.25	2.22	3.0	3.05	2.9	3.0
4	Lag time(hrs)	3	4	4	7	8	11

Table 15: Dissolution for Diltiazem Granules

Time(mins)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	15.16	26.76	37.52	12.07	40.08	21.68
10	24.06	39.19	63.09	22.18	72.19	35.25
15	36.72	47.58	74.26	30.58	99.76	41.06
30	52.38	58.44	96.45	42.32	-	59.27

45	65.24	66.71	-	69.79	-	85.36
60	95.42	99.86	-	101.34	-	94.56

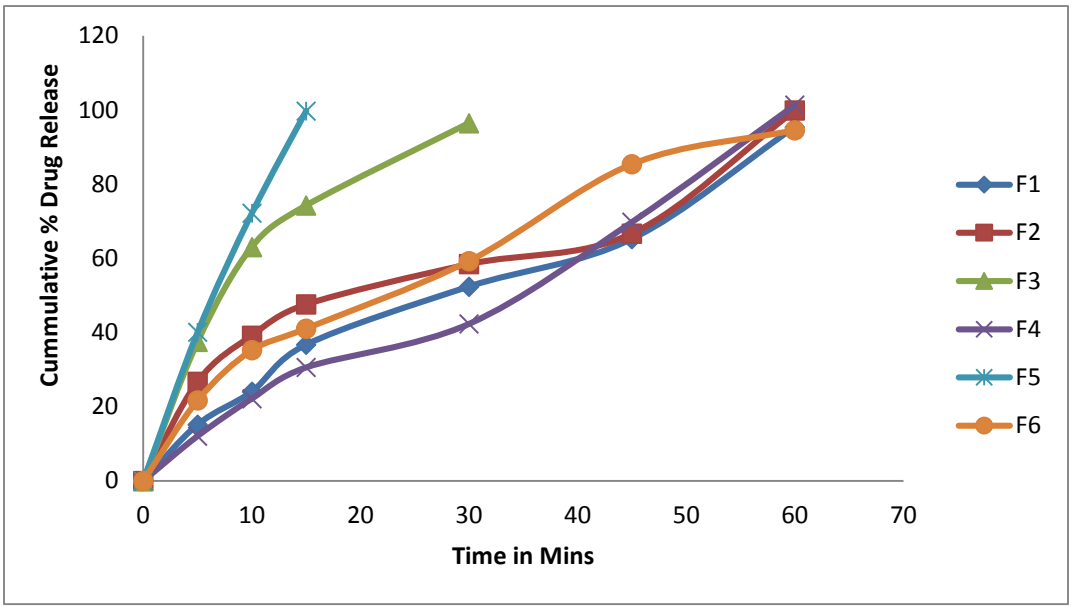

Figure 5: **Dissolution graph for Diltiazem Granules F1-F6**

Based on the drug release within the required time period F5 was optimized and further filled in formaldehyde treated Capsules Body.

Table 16: Dissolution data for Diltiazem Pulsin Cap

Time in Hrs	PF1	PF2	PF3	PF4	PF5	PF6
0	**0**	**0**	**0**	**0**	**0**	**0**
0.5	3.4	2.8	4.7	0.4	1	0
1	5.9	5.4	6.4	0.9	2.4	0.55
2	11.2	9.6	9.7	1.3	3.2	1.6
3	15.8	13.2	12	1.5	5.4	4
4	99.1	17.8	15.2	1.7	7.7	6
5	99.3	69.3	77.2	2	8.6	7.2
6	-	96.6	89.6	3.1	10.9	8.4
7	-	-	99.7	3.9	11.4	9.2
8	-	-	-	98	12.8	10.4
9	-	-	-	-	101.2	12
10	-	-	-	-	101.2	12.4
11	-	-	-	-	101.4	16.9

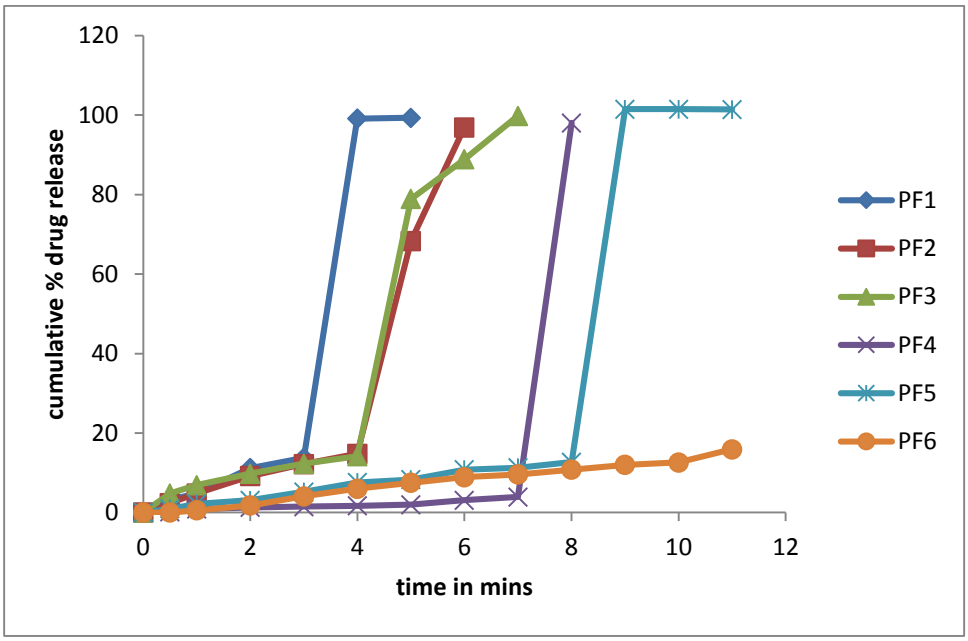

Figure 6: Dissolution graph for press coated pulsin cap formulation

From the above formulations PF5 pulsin cap was selected as best formulation based on the lag time 0f 9 hrs which was obtained by using HPMC, Ethyl cellulose in 50 mg and 50 mg respectively.

STABILITY STUDIES

Table 17: Cumulative % drug release during 9h

Sampling interval	25^0C/60%RH	30^0C/65%RH	40^0C/75%RH
0 Days	101.2	101.0	100.2
30Days	101.0	100.9	100.0
60 Days	100.2	100.2	99.8
90 Days	99.8	99.2	99.2

Stability studies of the formulation PF5 of Diltiazem Pulsin Cap were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 25^{O}C/60%RH, 30 ºC/65% RH and 40 ºC/75% RH for 90 days. There was no significant change in the physical property and percent of drug release was within the limits ±4 during 8hour during the stability period.

CONCLUSION

From the above experimental results it can be concluded that, Formulated granules gave satisfactory results for various micromeritic properties, dissolution and drug content.

Formulated Pulsin Cap gave satisfactory results for various physicochemical parameters like weight variation. HPMC, Ethyl cellulose has predominant effect on the lag time, while also shows

significant effect on drug release.

- Diltiazem Pulsin Cap shows a delayed release pattern.
- Among all the Diltiazem granules formulations F5 was selected based on drug release within a given period of time.
- In-vitro release rate studies showed that the PF5 was optimized based on less amount of drug release during lag time.
- Formulations PF5 found to be stable at 40^{o} C and 75% RH for a period of 3 months.
- FT-IR studies revealed that there was no interaction between Diltiazem and the polymers.

REFRENCES

1. Gothaskar, AV, Joshi AM, Joshi, NH, 2004. Pulsatile drug delivery system a review. Drug Del. Technol. 4, http://www.drugdeliverytech.com/id article=250.
2. Shivkumar HG, Promod KTM, Kashappa GD. Pulsatile drug delivery systems .Indian JPharma Edu 2003 July-Sep : 37(3) : 125:8.
3. Abraham S, Srinath MS. Development of modified pulsincap drug delivery system of metronidazole for drug targeting Indian J Pharm Sci 69(1):18-23.
4. Srisagul Sungthongjeen, Satit Puttipipatkhachorn, Ornlaksana Paeratakul, Andrei Dashevsky, Roland Bodmeier. Development of pulsatile release tablets with swelling and rupturable layers. J Control Rel 2004:147 159.
5. Sharma S, Pawar SA, Low density multiparticulate system for pulsatile release of meloxicam. Int J Pharm 2006; 313: 150-158.
6. Bhavana V, Khopade AJ, Jain VVD, Jain NK. Oral pulsatile drug delivery.Eastern pharmacist 1996 Aug; 39 (464):21-6.
7. Myers RH, Montgomery DC. Response Surface Methodology: Process and product optimization using designed experiments. 2nd ed. New York, NY: Wiley; 2002.
8. Ding X, Alani AWG, Robinson JR. Extended release and targeted drug delivery systems. In: Gennaro AR, editor, Remington: The Science and Practice of Industrial Pharmacy. 21st ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2006:993–940.
9. Collett J, Moreton C. Modified release peroral dosage forms. In: Aulton ME, editor. Pharmaceutics: The Science of Dosage Form Design. 2nd ed. London, UK: Churchill Livingstone; 2002:289–306.
10. Kshirsagar SJ, Patil SV, Bhalekar MR. Statistical optimization of floating pulsatile drug

delivery system for chronotherapy of hypertension. Int Pharm Invest. 2011;1: