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Research Article

DEVELOPMENT AND CHARACTERIZATION OF DILTIAZEM HYDROCHLORIDE PULSATILE DRUG DELIVERY SYSTEM FOR CHRONOMODULATED THERAPY

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ABSTRACT

Pulsatile drug delivery system is characterized by a time period of no drug release (lag time) followed by a rapid and complete drug release (pulse release). In present study pulsatile drug delivery system of Diltiazem hydrochloride is formulated to achieve colon specific drug release. This technique overcomes first pass metabolism, increases bioavailability, reduces dosing frequency and proves most beneficial when taken at bedtime, considering nocturnal angina. Core tablets of Diltiazem hydrochloride were prepared by direct compression method using microcrystalline cellulose and evaluated for physiochemical parameters. DSC studies revealed compatibility of the drug with formulative excipients. Effect of coating pH sensitive polymers Eudragit L-100, Eudragit S-100, Cellulose acetate succinate (CAS) and Ethyl cellulose (EC) at different coating level (14% & 24%) was investigated. All the above pH sensitive polymers delayed drug release, Lag time with Eudragit S-100 at 24% coating level showed a lag time of 5.5 hrs with cumulative drug release of 98% within 10 hrs. Kinetic studies showed first order release, Scintigraphic images clearly indicate that the dosage form remains intact till it reaches colon.

Key words*:* Pulsatile drug delivery, Chronotherapeutics, Lag time, Nocturnal angina, Gamma scintigraphy.

INTRODUCTION

With the advancement of technology in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few decades. Presently, the emphasis of pharmaceutical galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecules rather than going for new drug discovery because of inherent hurdles posed in drug discovery and development process[1].

The concept of chronotherapeutics has emerged where in, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirements of a given disease therapy. Disease conditions where constant drug levels are not preferred but need a pulse of therapeutic concentration in a periodic manner acts as a push for the development of pulsatile drug delivery system. These systems have a peculiar mechanism of delivering drug rapidly and completely after a "lag time" i.e. a period of no drug release, characterized by a programmed drug release. Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount. These systems are beneficial for drugs having high first pass effect; drugs administered for diseases that follow chronopharmacological behavior, drugs having specific absorption site in GIT, targeting to colon and cases where night time dosing is required[2].

Pulsatile delivery systems are generally classified into time controlled and site specific delivery systems. The release from the first group is primarily controlled by the system, while the release from the second group is primarily controlled by the biological environment in the gastro intestinal tract such as pH or enzymes[3].

Diltiazem HCl is an antianginal drug belonging to the class of calcium channel blocker. It is highly protein bound 70-90% , undergoes extensive first pass metabolism with relatively poor oral bioavailability of 40% .The half life of the drug being 3 to 4.5 hrs necessitates administering 30 mg of drug three times a day by oral route[4].

A therapeutic system that would synchronize the drug delivery with the circadian variation in periods of increased risk is highly desirable for an antianginal regimen. This can be achieved by bed time administration of a drug delivery system having a delayed start of drug release, which can provide adequate protection in early morning. The objective of present study is to develop colon specificpulsatile delivery system of Diltiazem HCl in a pH and time dependent manner.

MATERIALS AND METHODS

MATERIALS

Diltiazem HCL was obtained as a gift sample from Inventia Health care Pvt. Ltd.(Mumbai, India). Eudragit S-100 and Eudragit L-100 were obtained as gift sample from Evonic Pvt. Ltd. Mumbai. Ethyl cellulose was gifted by Colcorcon Asia Pvt. Ltd. (Goa, India). Cellulose acetate succinate was gifted by Arihant trading. Co. Microcrystalline cellulose and Crospovidone, were gifted by Cipla Ltd. Mumbai. All other excipients used were of analytical grade.

METHODS

Preformulation studies

Preparation of core tablet

Core tablets of Diltiazem hydrochloride were prepared by direct compression method. All ingredients were weighed accurately and blended homogeneously for 15 mins. Blended drug/polymer mixture of the formulations were subjected for precompressional evaluation such as bulk and tapped density, compressibility index , Hausner's ratio and angle of repose[5].

Tablets were compressed in Minipress Tablet Compression Machine using 8 mm round concave punches. (Rimek minipress-11 MT, Karnavati Engineering Ltd., Ahmedabad, India). The composition of core tablet is given in Table 1.

Evaluation of core tablets

Prepared core tablets were evaluated for various physical properties - diameter and thickness by using vernier calipers, uniformity of weight determined using a Sartorious electronic balance (Model CP-224 S), hardness using a dial type hardness tester (Model 1101, Shivani Scientific Ind), friability using a Roche friabiliator (Camp-bell Electronics, Mumbai), disintegration time using a disintegration test apparatus (Electrolab ED-2 Bowl USP, Mumbai).

Drug Content

Randomly selected five formulated core tablets were pulverized; weight equivalent to 50 mg of Diltiazem Hydrochloride was extracted with 100 ml phosphate buffer (pH 7.4). Aliquot from subsequent filtered solution was suitably diluted with phosphate buffer (pH 7.4) and analyzed spectrophotometrically in triplicate at 237 nm. The amount of Diltiazem Hydrochloride was estimated using standard calibration curve of the drug[6].

Table 1: Composition of Diltiazem Hydrochloride Core Tablets

INGREDIENTS (mg/tablet)	FORMULATION F1
Diltiazem hydrochloride	30
Microcrystalline cellulose	65
Lactose	129
Crospovidone	2
Talc	2
Aerosil	2
Total	230

Table 2: Composition of Coating Solution

INGREDIENTS	FC 1	FC 2	FC 3	FC 4	FC 5	FC 6	FC 7	FC 8
[1]Eudragit S 100	50	50	*	*	*	*	*	*
[1]Eudragit L 100	*	*	50	50	*	*	*	*
[1]Cellulose acetate succinate	*	*	*	*	50	50	*	*
[1]Ethyl cellulose	*	*	*	*	*	*	50	50
[2]Dibutyl phthalate	1	1	1	1	1	1	1	1
[1]Titanium dioxide	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
[2]Isopropyl alcohol	25 0	25 0	25 0	25 0	25 0	25 0	25 0	25 0
[2]Acetone	25 0	25 0	25 0	25 0	25 0	25 0	25 0	25 0
% Coating	14	24	14	24	14	24	14	24

[1]Quantity in gms [2]Quantity in ml

***In vitro* disintegration test for tablet**

The *in vitro* disintegration time of a tablet was determined using disintegration test apparatus. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 SIF (simulated intestinal fluid) and pH 7.4 SCF (simulated colonic fluid) maintained at 37°±2°C as the immersion liquid, the assembly being raised and lowered between 30 cycles per minute respectively. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. The experiment was carried in triplicate[7].

Preparation of coating solution

Homogeneous coating solutions **(**10% w/v) of different pH sensitive polymers Eudragit L100, Eudragit S100, Ethyl cellulose and Cellulose Acetate Succinate were prepared separately by dissolving in mixture of acetone and isopropyl alcohol on magnetic stirrer. 2% plasticizer Dibutyl phthalate and 5% opacifying agent Titanium dioxide (% based on polymer weight) were added to above solution. Coating of core tablets was carried with process conditions as follows - inlet temperature (40-45°C), exhaust temperature (30-35°C), spray rate (3-5 ml /min), Spray nozzle diameter (1 mm), Distance(Tablet bed-spray gun) 10 – 15 cm, Pan speed(20 rpm).Composition of coating solution is given in Table 2.

The core tablets were coated with above coating solution at coating level of 14% and 24% respectively on basis of % weight gain by core tablet.

The % weight gain calculated using the following equation:

$$\% \text{ weight gain} = \left(\frac{W_T - W_0}{W_0}\right) \times 100$$

Where W_t is the weight of the tablet after coating, W_o is the initial weight of tablet. The tablets were dried in an oven at 50°C for 12 hrs.

EVALUATION OF PULSATILE RELEASE TABLETS

Lag time of coated tablets

Coated tablets were evaluated for lag time in pH 6.8 followed by pH 7.4 phosphate buffer respectively. Formulated coated tablets were placed in 900 ml of above mentioned buffers, agitated at 75 rpm maintained at 37±0.5°C. The time taken for outer coating to rupture was monitored and reported as lag time[8].

Dissolution studies of the coated tablets

Drug release study of coated tablets was studied using USP XXIII dissolution test apparatus I. Initially tablets were placed in 900 ml of 0.1 N HCl for 2 hrs, followed by pH 6.8 phosphate buffer for 3 hrs and pH 7.4 for 5 hrs at 75 rpm, 37±0.5°C. Aliquots of 5 ml were collected manually at predetermined time intervals replacing with fresh buffer to maintain sink condition and analysed for drug content using a UV-visible spectrophotometer at λ max of 237 nm[9].

DATA ANALYSIS

To study the mechanism of drug release and release rate kinetics from the dosage form, the data obtained from *in vitro* drug release studies was fitted and analyzed for zero order and first order kinetic models[10].

Drug Excipient Compatibility Studies

To study the compatibility of drug with different formulation excipients, DSC studies are performed on samples of pure Diltiazem Hydrochloride (DH) and mixture of DH+Microcrystalline cellulose + Crospovidone + lactose. DSC studies were performed using a (DSC-50; Shimadzu, Tokyo, Japan) with thermal analysis data system (TA 501 PC), computer, and a plotter interface. Indium/zinc standards were used to calibrate the temperature and enthalpy scale. Accurately weighed 10 mg samples were hermetically sealed in aluminum pans and heated at constant rate of 10°C min^{-1} (from 0° to 300°C) and inert atmosphere was maintained by purging nitrogen gas at a flow rate of 30 mL/min[11].

Gamma-scintigraphic studies

Due permission for conduction of this experiment was obtained from the Institutional Animal Ethical Committee, KLEU'S College of Pharmacy, Belgaum. Two adult male New Zealand white strain rabbits weighing approximately 2-2.5 kgs were used for scintigraphy study. Best selected formulation based on its lag time and drug release was radio labeled and orally administered; rabbit was immobilized and seated comfortably in the rabbit cage. Small sealed source of 0.06MBq ^{99m}T firmly taped to the skin at the position of its shoulder joint and hip joint on the same side served as an anatomical reference marker. The source was also used for repositioning when the images were taken. The gamma scintigraphic imaging was started immediately after dosing, followed for 8 hrs with images taken at specified time interval under the dynamic planer conditions[12, 13].

RESULTS AND DISCUSSION

The angle of repose, compressibility index and Hausner's ratio were found to be in range of 23°.41'to 23°.49'; 14% to 14.30% and 1.16 respectively indicating good flow and compressibility of blend.

The formulated core tablets were round, biconvex having 8mm diameter and thickness 4.2±0.1 mm, hardness 4.5±0.3 kg/cm^2, weight variation in the range 230 ± 2.16 mg, friability 0.86%, drug content 98.77± 0.59%, disintegration time in the range 30 – 32 seconds. Compatibility studies by DSC, depicted in Fig. 1. reveals no significant shift in the endothermic peak of pure drug, and absence of strong interaction between drug and polymer, indicating stability of the drug in the formulation.

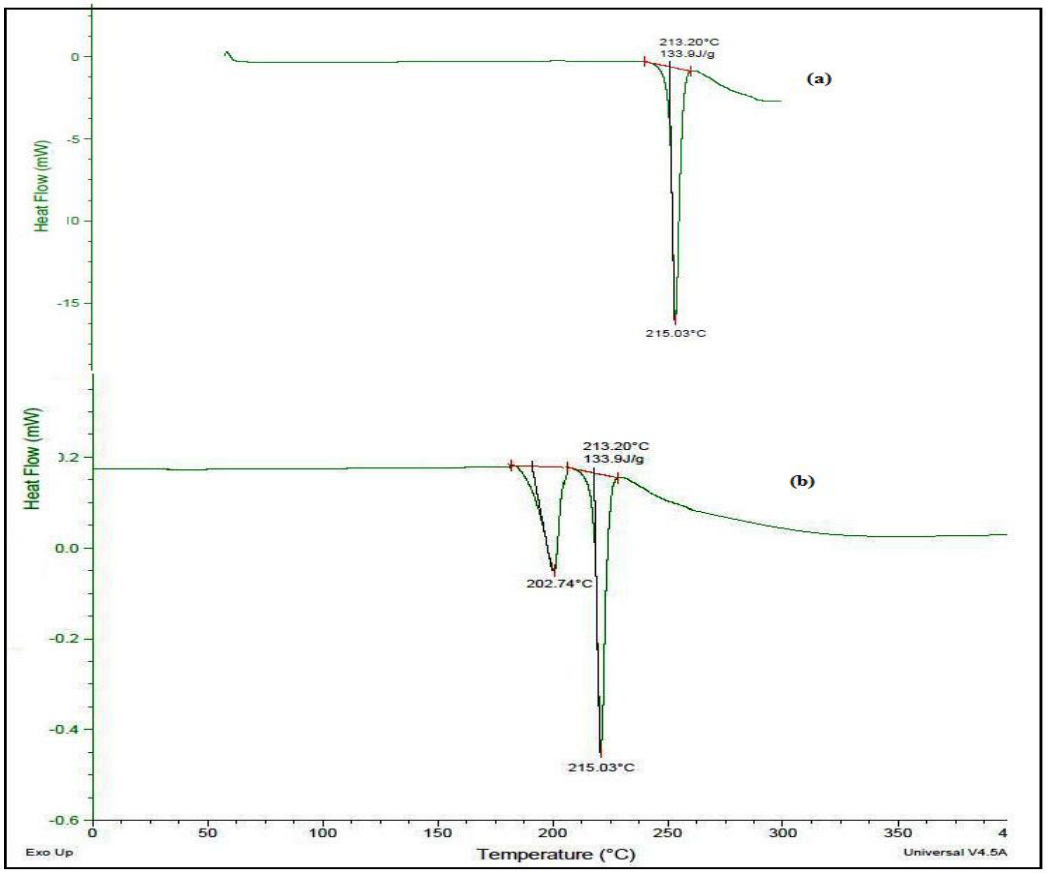


Fig.1: (a) DSC thermogram of Diltiazem hcl
(b) DSC thermogram of drug + mcc + crospovidone + lactose

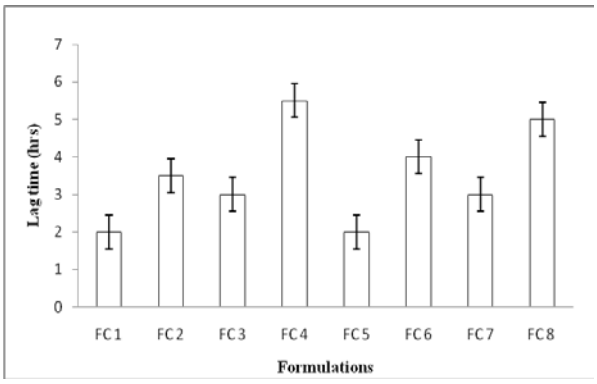


Fig.2: Lag time of formulations.

All the pH sensitive polymers used in the present study (Eudragit L-100, Eudragit S-100, Ethyl cellulose and Cellulose Acetate Succinate) showed no drug release in the first two hrs in the gastric environment. Later a different drug release profile was evident for each polymer.

The preliminary study revealed that all the enteric coating polymers which are being selected in present study produced films with pulsatile release profile. The lag time of the pulsatile release tablets coated with each polymer respectively at different coating levels reveals that it depended on the coating level applied. The rupture time increased with higher coating level because of the increased mechanical strength of the coating and the reduced medium permeation rate at higher coating thickness[14]. The results are depicted in Fig 2.

Formulation (FC-1) achieved 2 hrs lag time with coating level 14% in acidic pH 1.2 followed by 83.58% drug release in the initial 3 hrs of dissolution media pH 6.8. At 24% coating level (FC-2), lag time increased up to 3.5 hrs and drug release reduced to 65.80%, depicted in Fig. 3(A). Concentration and drug release was found to be inversely related. Solubility of Eudragit L-100 being well above the pH 6.8 phosphate buffer there was no considerable decrease in the drug release[15].Formulation (FC-3) achieved 3 hrs lag time with coating level 14% in acidic pH1.2 followed by 76.83% drug release in initial 3 hrs of dissolution media pH6.8 phosphate buffer. At 24% coating level (FC-4), lag time increased up to 5.5 hrs and there was absolutely no drug release in pH 6.8 phosphate buffer and hence changed to pH 7.4 phosphate buffer. At 6th hr, burst effect was observed which can be explained on the basis of the fact that as the coating concentration increased the coat became more impermeable and finally retarded the drug release, depicted in Fig.3 (B).

Formulation (FC-5) achieved 2 hrs lag time with coating level 14% in acidic pH 1.2 followed by 65.42% drug release in the initial 3 hrs of dissolution media pH 6.8 phosphate buffers. At 24% coating level (FC-6), lag time was increased up to 4 hrs and drug release reduced to 35.64%, depicted in Fig.3(C).

Formulation (FC-7) achieved 3 hrs lag time with coating level 14% in acidic pH 1.2 followed by 77.08% drug release in the initial 3 hrs of dissolution media pH 6.8 phosphate buffers. At 24% coating level (FC-8), lag time was increased up to 5 hrs and there was absolutely no drug release in pH 6.8 phosphate buffer. Drug release started in pH 7.4 dissolution media, depicted in Fig. 3(D). This may be attributed to the fact that as the coating level increased, the drug release was retarded suggesting that the thicker film formed by EC was quiet impermeable in pH 6.8 phosphate buffer solution[16].

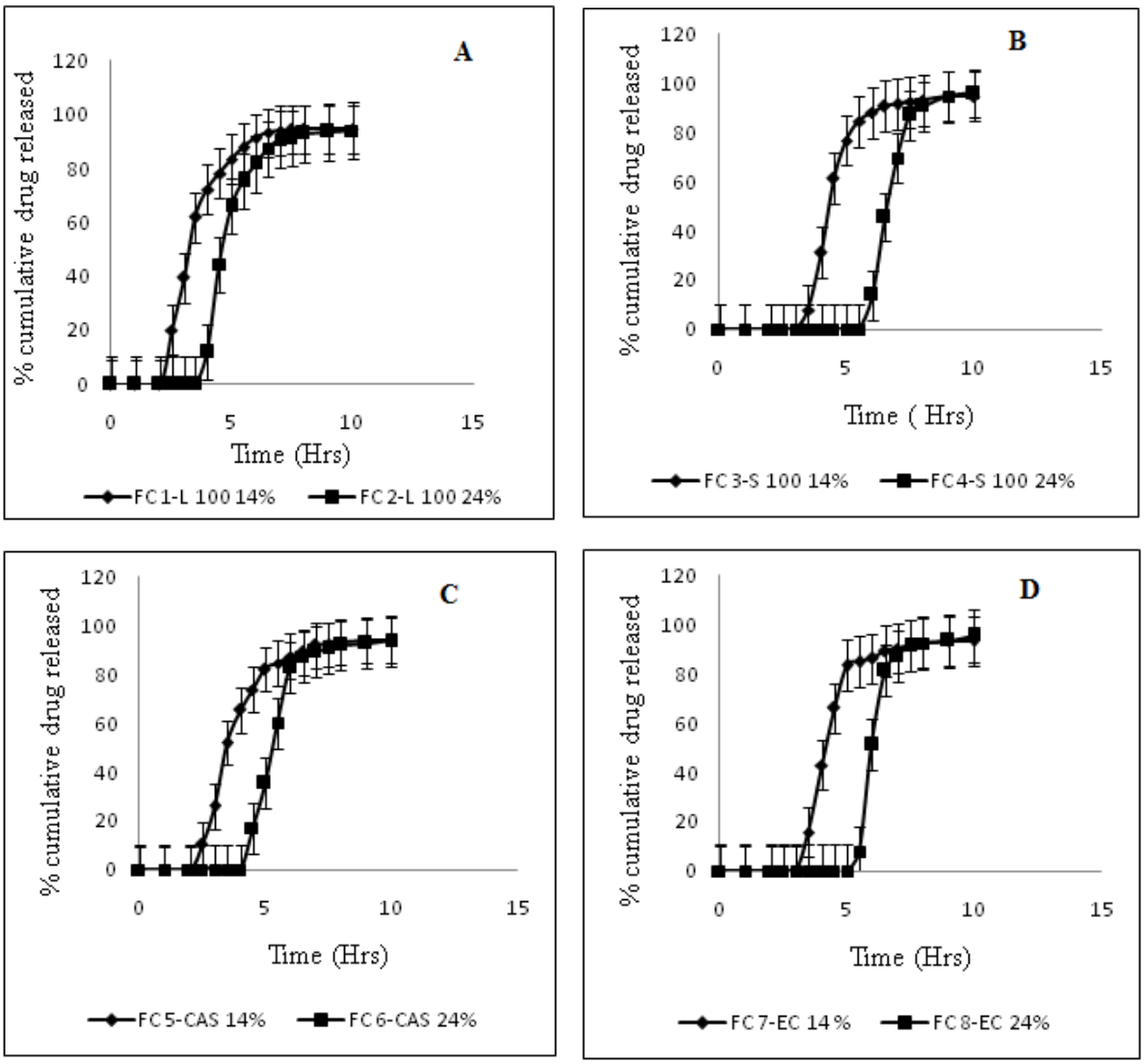
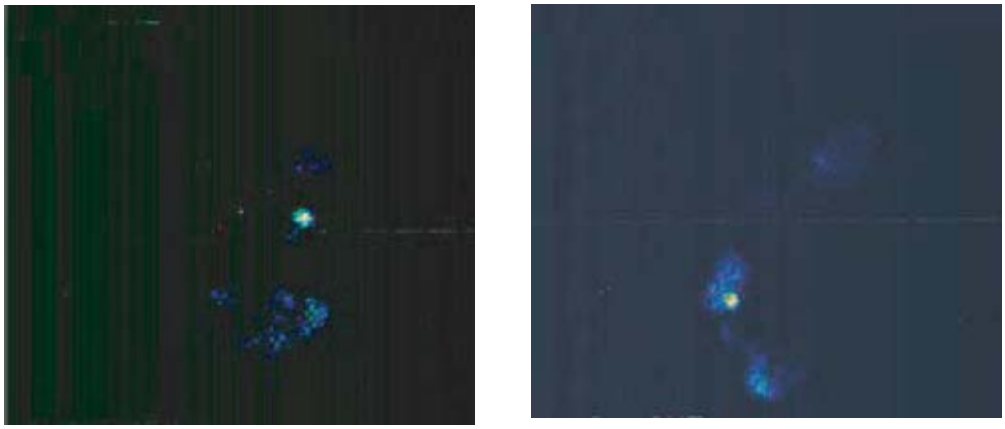
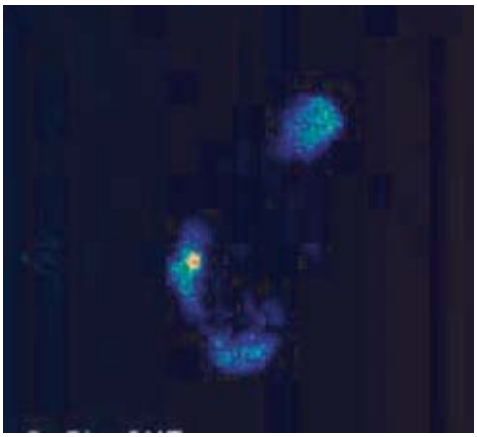


Fig 3: *In vitro* drug release profiles of formulations with different coating solutions.

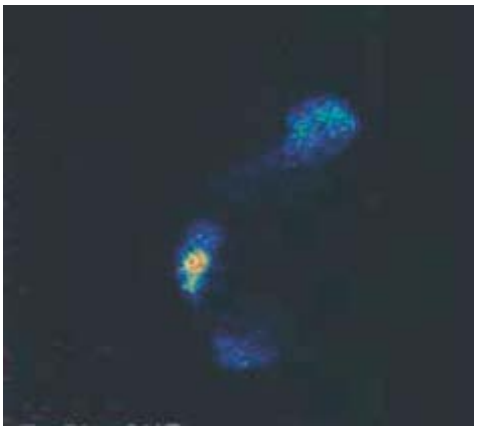


(A) Image taken at 1st hour

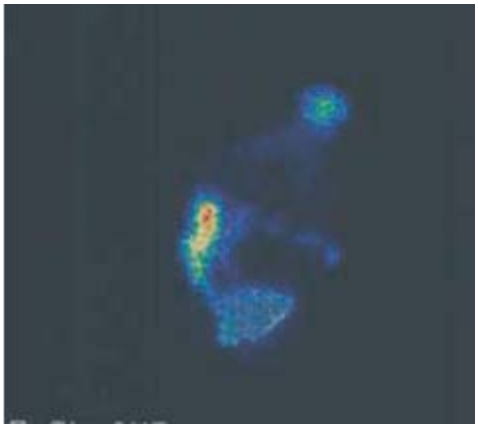
(B) Image taken at 3rd hour



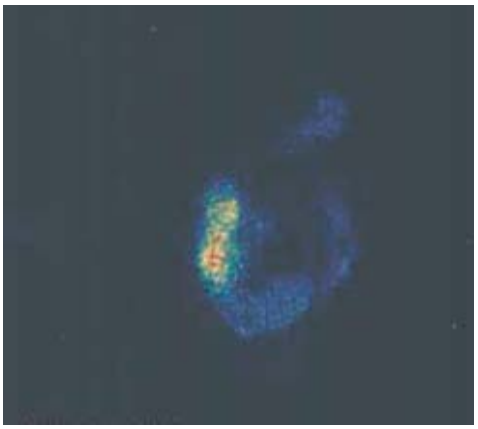
(C) Image taken at 5th hour



(D) Image taken at 6th hour



(E) Image taken at 7th hour



(F) Image taken at 8th hour

Fig 4: Gamma-scintigraphic studies

.The lag time depicted in Fig. 3. and *in vitro* drug release profiles for all four polymer solutions at constant concentration and variable coating levels indicate that lag time is directly proportional and dissolution rate is inversely proportional to the coating level applied. At coating level of 24% Eudragit S 100 and Ethyl cellulose proved to be the most appropriate pH sensitive polymers for pulsatile drug delivery. The drug release profile showed sigmoid release pattern which is considered to be an ideal for the pulsatile drug delivery system[17]. FC 4 was considered as optimum formulation as it showed the desirable lag time and this batch was further evaluated for and *in vivo* Gamma scintigraphic studies.

Scintiscans obtained for selected formulation at different time intervals, shown in Fig.4 reveals that the dosage form remains intact till it reaches colon. Model fitting studies indicate highest Correlation coefficient (r) value for the first order release equation, tabulated in Table 3.

Table 3: Model fitting studies for release profile of formulated tablets.

FORMULATION CODE	MATHEMATICAL MODEL	
	ZERO ORDER	FIRST ORDER
	REGRESSION COEFFICIENT (R VALUES)	REGRESSION COFFICIENT (R VALUES)
FC 1	*0.793*	*0.912*
FC 2	*0.833*	*0.884*
FC 3	*0.818*	*0.891*
FC 4	*0.728*	*0.894*
FC 5	*0.819*	*0.932*
FC 6	*0.823*	*0.838*
FC 7	*0.807*	*0.886*
FC 8	*0.751*	*0.762*

CONCLUSIONS

Consistent lag time, immediate release of the active pharmaceutical ingredient (API) and the requirements for developing the chronotherapeutics was achieved with the developed formulation. At the coating level of 24% Eudragit S100 provided the most appropriate polymer for pulsatile drug delivery providing a suitable lag time. Thus this approach of pulsatile/programmable release where in tablet of Diltiazem hydrochloride is taken at bed time, releasing drug in the morning hours when the symptoms are more prevalent can prove to be a revolution in the treatment of nocturnal angina.

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