IJPSR (2015), Vol. 6, Issue 4 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 July, 2014; received in revised form, 29 November, 2014; accepted, 20 March, 2015; published 01 April, 2015

FORMULATION AND EVALUATION OF CHRONOMODULATED COLONIC DRUG DELIVERY OF NIFIDIPINE

Renu Dinkar [1], Govind Mohan[2] and Kumud Upadhyaya[3*]

Gyani Inder Singh Institute of Professional Studies [1], Dehradun, Uttarakhand, India
Department of Pharmacy [2], NIMS University, Jaipur, Rajasthan, India
Department of Pharmaceutical Sciences [3], Kumaun University, Nainital, Uttaarkhand India

Keywords:

API, Chronopharmacological, Lag time, pH-dependent, Pulsatile.

Correspondence to Author:
Dr. Kumud Upadhyaya

Department of Pharmaceutical Sciences, Kumaun University, Nainital, Uttarakhand, India.

E-mail: upkuupku@gmail.com

ABSTRACT: The pulsatile drug delivery works upon the system that releases active pharmaceutical ingredient completely and rapidly after a desired lag time. This type of approach was advantageous for: Drugswith extensive first pass metabolism and biological tolerance. Locally absorbed or acting drugs to a specific site in the intestinal tract (e.g. colon). Adaptation of therapy according to chronopharmacological needs. The pH-dependent polymers in pulsatile drug delivery were insoluble at low pH levels but with increase in pH solubility of polymer increases. The objective of present study was to develop a pulsatile compression coated tablet. The system was developed into two steps: Firstly core tablet was prepared containing Nifidipine as API. Secondly core tablet was coated with polymer blend of Eudragit S100and Eudragit L100. The lag time was the time in which less than 10% of drug was released. From *in vitro* release study we had concluded that drug release at pH 6.8 was inversely proportional to the amount of polymer Eudragit L100, which might be due to pH-dependent solubility of Eudragit S 100 at pH above 7. We also concluded that compression coated tablet containing higher proportion of Eudragit L 100 follows Higuchi kinetic model, whereas First order kinetic model was followed by compression coated tablet containing higher proportion of Eudragit S100.

INTRODUCTION: Pulsatile drug release is such a system where drug is released suddenly after well-defined lag time or time gap according to circadian rhythm of disease states. No drug is released from the device within this lag time [1]. For achieving this various approaches were developed which were either drug specific (Prodrug) or formulations specific (coated or matrix preparations).

Use of pH-dependent polymers depends on different pH levels throughout the GI tract [2]. The polymers described as pH-dependent in pulsatile drug delivery were insoluble at low pH levels but become increasingly soluble as the pH rises [3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(4).1445-51

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(4).1445-51

The principal group of polymers used for the training of colon targeted dosage forms has been the Eudragit, more specifically Eudragit L and S. At low pH these polymers were anionic and water impermeable. Eudragit L 100 and S100 were copolymers of methacrylic acid and methyl methacrylate [4]. The ratio of the carboxyl ester groups in these polymers was approximately 1:1 and 1:2 respectively. As well as these also form salts and dissolve at a pH above 6 and 7 respectively, this was based on the assumption that the GI pH increases progressively from the stomach to the colon.

In fact, the pH in the distal small intestine was around to 7.5, while the pH of proximal colon was closer to 6 [5]. The aim of the present study was to develop a pulsatile compression coated tablet. The system was developed in two steps: firstly core tablet was prepared containing nifidipine; secondly core tablet was coated with a polymer blend of Eudragit S 100 and Eudragit L 100 (Enteric polymer).

MATERIALS AND METHODS:

Materials:

Nifidipine supplied by High media, Polyvinylpyrrrolidone was supplied by ISP, Sodium carboxymethylstarch was obtained from the Linghu Food Ltd. Co., Eudragit L 100 (Supplied by Rohm), Eudragit S 100 (Supplied by Rohm). All other chemicals are of analytical grade.

Method:

Preparation of Pulsatile Release Tablet:

Preparation of core tablet:

Nifedipine tablet core were prepared by wet granulation. The mixture for compression of core tablets was obtained by manually granulating the Nifedipine(30mg), cross-linked polyvinyl pyrrrolidone (40mg) or sodium carboxy methylstarch (40mg) with 10% cornstarch paste. Following drying and sieving, magnesium stearate (1%w/w) and talc (2%w/w) were added and blended for 10minute. Core tablets (diameter, 6 mm; average tablet weight, 120mg) were compressed within 6mm of punches on Cadmach 16 station compression machine under a common compression force of 3-4 Kg/cm^2.

Preparation of compression coated tablet:

Six mm diameter drug cores were compression-coated with pH dependent polymer (Eudragit S 100 and Eudragit L 100). The different coat mixtures were shown in **Table 1**. Compression coated tablet were prepared by first filling half of the polymer blend in the die cavity, then centrally positioning the tablet core on the powder bed followed by filling the remaining half of the polymer blend on top. Then compressed the powder in Cadmach 16 station compression machine with a compression force to obtain tablets with hardness in the range of at 6-7 Kg/cm^2.

TABLE 1: FORMULATION OF PRESS COATED TABLET

Formulation code	Polymer (%)	
	Eudragit L 100	Eudragit S100
CCT 7	100	0
CCT 8	0	100
CCT 9	50	50
CCT 10	20	80
CCT 11	80	20
CCT 12	33.3	66.7
CCT 13	66.7	33.3

Drug Excipients Compatibility Study:

FT-IR spectra of drug and physical mixture of excipients and drug (1: 1) were recorded with a FT-IR spectrophotometer (Shimadzu Corporation, Japan, 8400s) using KBr disc method. Each sample was gently triturated with KBr powder in a weight ratio of 1: 100 and pressed using a hydrostatic press (Kimaya Engineers, Mumbai, India) at a pressure of 10 tons for 5min. The disc was placed in the sample holder and scanned from 4000 to 500 cm^{-1} at a resolution of 1cm^{-1}.

Pre-Compression Characterization [6]:

The quality of tablet, once formulated by rule, was generally dictated by the quality of physicochemical properties of blends. There were many formulations and process variables involved in mixing steps and all these can affect the characteristics of blend produced.

a) Bulk Density: Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of powder (M) was determined. The bulk density was calculated as follows

$$\rho b = \frac{M}{Vb}$$

Where M=Mass; Vb= Bulk Volume

b) Tapped Density: The measuring cylinder containing a known mass of blend was tapped 100 times using density apparatus. The constant minimum volume (Vt) occupied in the cylinder after tapping's and the weight (M) of the blend was measured. The tapped density (ρt) was calculated using the formula

$$\rho t = \frac{M}{Vt}$$

Where M=Mass; Vt= True Volume

c) Compressibility Index: The simplest way for measurement of flow of the powder was its compressibility, an indication of the ease with which a material can be induced to flow. It is expressed as compressibility index (I) which can be calculated as follows

$$I = \frac{(\rho t - \rho b)\, X100}{\rho t}$$

Where, ρt = Tapped density; ρb = Bulk density.

d) Hausner's Ratio: Hausner's ratio (HR) is an indirect index of ease of powder flow. It was calculated by the following formula

$$HR = \frac{\rho t}{\rho b}$$

Where, ρt is tapped density and ρb is bulk density.

e) Angle of Repose: Angle of Repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a specified cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula.

$$\tan = \frac{h}{r}; \text{ Therefore; } = \tan^{-1}\frac{h}{r}$$

Where, θ is angle of repose; h is height of cone; r is radius of cone.

Post-Compression Characterization[7]:

After compression of powder blends, the prepared tablets were evaluated for weight variation, tensile strength, thickness, friability and drug content.

a) Weight Variation: The weight variation test would be satisfactory method of determining the drug content uniformity. As per USP42, twenty tablets were taken and weighted individually, calculating the average weight, and comparing the individual tablet weights to the average. The average weight of one tablet was calculated.

b) Tablet Thickness: Ten tablets were taken and their thickness was recorded using micrometres (Mityato, Japan).

c) Friability: Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inch in each revolution. Preweighed sample of tablets was placed in the Friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F %) was determined by the formula

$$F\% = \left(1 - \frac{Wo}{W}\right).100$$

Where, W_0 is initial weight of the tablets before the test and W is the weight of the tablets after test.

d) Tensile Strength: The tensile strength of tablets was determined using aUbique tensile tester by keeping tablet between upper and lower platen (60001; Ubique Enterprises, Pune, India). The test was performed by applying a diametrical load, measuring the maximum load *F* at the tablet fracture and calculating the radial tensile strength T using the following equation

$$T = \frac{2F}{\pi DH}$$

Where *D* is the tablet diameter and *H is* the tablet thickness.

e) Drug Content: Select a number of tablets, equivalent to about 420 mg of Nifedipine. Finely powder the tablets and transfer the powder to a 250-mL volumetric flask containing 130 mL of water, homogenize until a uniform suspension is achieved (about 2 minutes), and transfer the suspension with the aid of a mixture of acetonitrile and methanol (1:1) to a 250mL volumetric flask. Add a mixture of acetonitrile and methanol (1:1) to volume, and stir for 30 minute. Centrifuge the resulting solution to obtain a clear supernatant stock solution. Transfer 3.0mL of the stock solution to a 50-mL volumetric flask, dilute with acetonitrile and methanol (1:1) to volume, mix and the drug content was analysed spectrophotometrically (Shimadzu, UV-1601) at 350nm [8].

***In Vitro* drug release study:** To study how composition of the coat and core to coat ratio interfere drug release profile of tablet. The dissolution test was carried out using the USP XXXIII type II apparatus (Paddle apparatus TDL 08 L; Electro lab India Pvt. Ltd., Mumbai, India) with a rotation speed of 100rpm and 900mL medium at 37±0.5 ^{0}C.

With the medium change method, the release was performed in pH 1.2 for 2h, followed by pH 6.8 for another 3h and finally, phosphate buffer (pH 7.4) till the endof the 12 h to simulate the pH pertaining to the stomach, proximal and middle small intestine (duodenum and jejunum),and distal small intestine (ileum), respectively. 5mL sample was withdrawn at pre-determined time interval (1, 2, 3, 4, 5, 6, 8, 10 and 12h) and replaced by the fresh dissolution medium. All the samples were filtered and analysed by UV spectrophotometer (to volume, mix and the

drug content was analysed spectrophotometrically (Shimadzu, UV-1601) at wavelengths of 350 nm. The lag time was taken as the time of <10% drug released [9].

Kinetics of drug release from coated tablet:

The release from the different formulations was determined by curve fitting method Data obtained from in vitro release studies were fitted to various kinetic equations. The kinetic models used were:

$Q_t = k_o t$ (zero-order equation),

$ln Q_t = ln Q_0 - k_1 . t$ (first-order equation),

Q_t = K .S. $\sqrt{t} = k_H . \sqrt{t}$ (Higuchi eqn based on Fickian diffusion)

Where, Q is the amount of drug release in time t, $Q_0$is the initial amount of drug in the microsphere, S is the surface area of the microcapsule and k_o, k_1 ,and k_H are rate constant of zero order, first order and Higuchi rate equations respectively [10]. In addition to these basic release models, there are several other models as well. One of them is Peppas and Korsmeyer equation (power law).

$$Mt / M\infty = k \cdot t^n$$

Where Mt is the amount of drug release at time t and M∞ is the amount release at time t = ∞, thus Mt / M∞ is the fraction of drug released at time t, k is the kinetic constant, and n is the diffusion exponent.

RESULTS AND DISCUSSION:

Drug Excipients Compatibility Study:

Fourier Transformed Infrared Spectroscopy: FT-IR spectra of, drug and physical mixture of excipients and drug (1: 1) shown in **Fig.1 (a), (b).**The characteristic absorption peaks of Nifedipine were also found in FT-IR spectra of physical mixture.

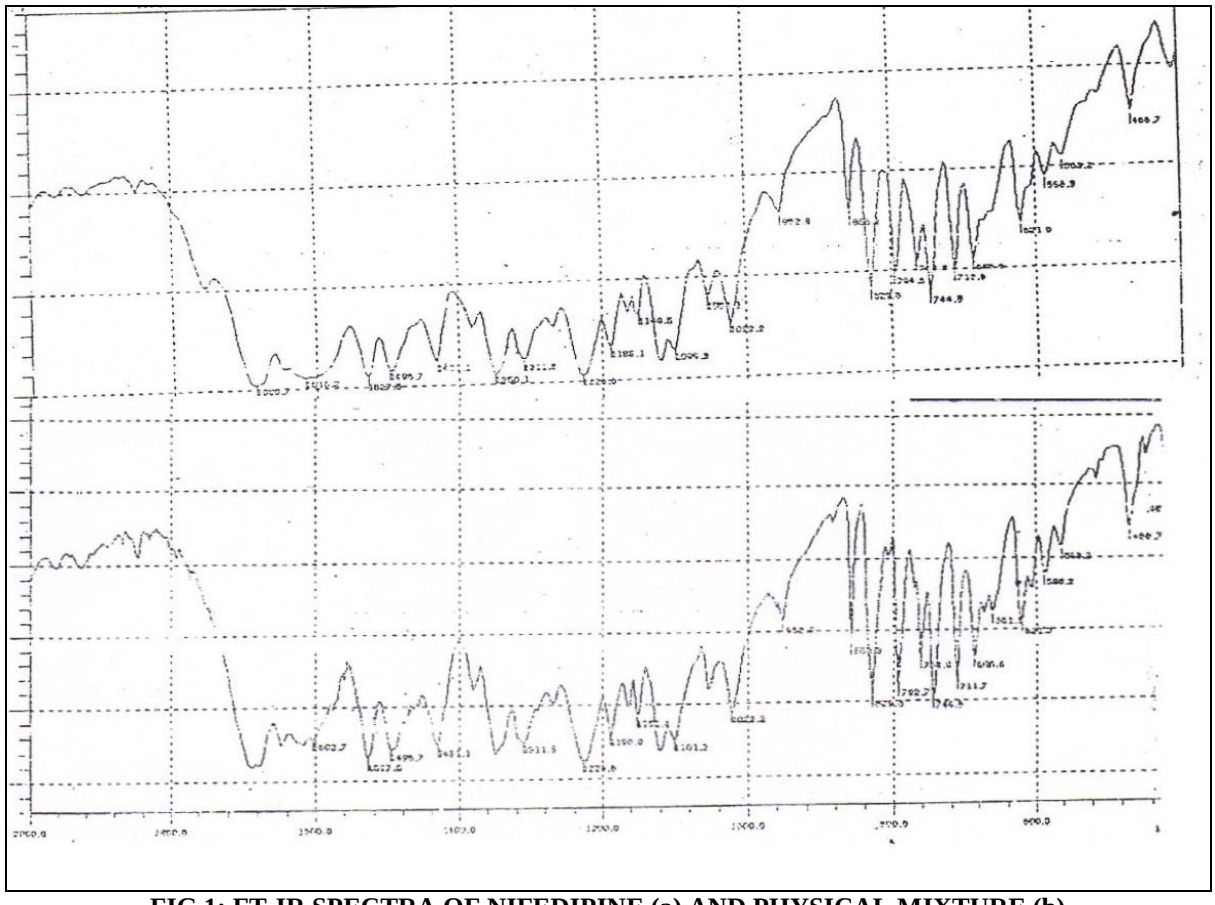

FIG.1: FT-IR SPECTRA OF NIFEDIPINE (a) AND PHYSICAL MIXTURE (b)

Pre compression characterization of coating powder blend and core tablet powder blend:

The bulk density of powder blend varied between 0.52±0.018-0.63±0.021gm/cc. The tapped density was found in the range of 0.59±0.011-0.78±0.013gm/cc. The results indicated good packaging capacity of powder blend. By using these two density data, Hausner's ratio and

compressibility index was calculated. If the bed particle was more compressible then the powder will be less flowable and vice versa. The value of compressibility index was found between 06.00±0.090- 20.50±0.311%. The powder blend had Hausner's ratio less than 1.25 indicating good flow characteristics. The compressibility–flow ability correlation data indicating a good flow ability of the powder blend. The flow ability of the powder blend was also evidenced by the angle of repose. The angle of repose below 30^0 ranges indicates well to excellent flow properties of powder. The angle of repose was found to be in range 17.26±1.439-27.58±1.016^0. The results showed good flow property of the powder blend. (**Table 2**)

TABLE 2: PRE-COMPRESSION CHARACTERISTICS

Formulation Code	Parameters				
	Bulk Density ± S.D	Tapped Density ± S.D	Hausner's Ratio ± S.D	Compressibility Index (%) ± S.D	Angle of Repose (θ) ± S.D
Core Tablet	0.39±0.012	0.42±0.013	1.07±0.012	6.60±1.330	23.34±1.363
CCT 7	0.60±0.019	0.64±0.017	1.06±0.035	6.25±0.064	18.52±1.170
CCT 8	0.63±0.014	0.75±0.021	1.19±0.058	16.00±0.332	26.93±1.159
CCT 9	0.62±0.016	0.66±0.016	1.11±0.062	06.00±0.090	17.26±1.439
CCT 10	0.52±0.018	0.59±0.011	1.13±0.048	11.53±0.299	22.57±1.416
CCT 11	0.62±0.015	0.78±0.013	1.25±0.082	20.50±0.311	28.53±2.001
CCT 12	0.62±0.017	0.70±0.014	1.12±0.078	11.43±0.281	20.97±1.565
CCT 13	0.63±0.021	0.76±0.022	1.20±0.057	17.10±0.312	27.58±1.016

Data represents Mean ± Standard deviation, n= 3

Post-compression characterization:

Weight variation was found to be within USP limit. The tensile strength of core and compression coated tablets were found to be within the range 3.40±0.06to 4.62±0.34MPa. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. Drug content was observed within the range 92.11±0.10-98.70 ± 0.32%. (**Table 3**)

TABLE 3: EVALUATION OF CORE AND COMPRESSION COATED TABLET

Formulation code	Thickness (mm)±S.D	Friability (%)	Tensile strength (MPa)± S.D	Drug Content (%)± S.D
Core	2.1±0.005	0.21	3.14±0.13	92.11±0.10
CCT 7	4.19±0.005	0.19	43.94±0.46	93.40 ± 0.43
CCT 8	4.17±0.005	0.13	3.40±0.06	96.30 ± 0.61
CCT 9	4.22±0.01	0.15	4.62±0.34	97.99 ± 0.55
CCT 10	4.64±0.057	0.34	4.28±0.47	98.70 ± 0.32
CCT 11	4.47±0.005	0.24	3.85±0.32	93.18 ± 0.66
CCT 12	5.04±0.01	0.19	4.25±0.22	96.68 ± 0.92
CCT 13	4.87±0.05	0.34	4.53±0.31	95.85 ± 0.51

Data represents Mean ± Standard deviation, n=3

***In Vitro* Drug release study:**

The in-vitro release study of the compression coated tablet was carried out using USP rotating paddle method at 100 rpm at 37 ºC. Dissolution study was performed pH 1.2 for 2h, followed by pH 6.8 for 3 h and phosphate buffer (pH 7.4) till the end of the 12 h**. Table 4** and **Fig.2** shows the drug release profile of different compression coated tablet. Dissolution shows that all tablets compression-coated with pH-dependent polymers showed low release percentage in 0.1 N HCl (pH 1.2) after 2h ranging from 4.8 % to 9.8%. Drug release in phosphate buffer pH 6.8 for another 3 h, CCT 7 exhibited the fastest release. It released 68.34 % of the drug in next 3 h.

On the other hand, CCT 8 showed the slowest release in this medium where it released only 13.55%. Release of the drug from drug in pH 6.8 was inversely proportional to eudragit L 100.This might be due to pH-dependent solubility of Eudragit S100 in pH above 7.

TABLE 4: *IN VITRO* DRUG RELEASE OF DIFFERENT COMPRESSION COATED TABLET

Time (hrs)	Cumulative drug release (%)						
	CCT 7	CCT 8	CCT 9	CCT 10	CCT 11	CCT 12	CCT 13
0	0	0	0	0	0	0	0
1	5.9	2.1	3.8	2.3	4.3	2.1	4
2	9.8	4.8	6.8	5.8	9.2	6.2	7.9
3	23.6	6.9	15.34	8.9	23.12	18.23	18.3
4	44.75	8.4	31.57	16.4	34.13	33.12	33.12
5	68.34	13.5	42.09	30.03	49.01	42.5	46.14
6	75.21	19.2	49.63	35.32	57.48	47.6	52.12
7	83.26	24.6	56.34	39.88	69.34	55.3	64.36
8	88.21	29.4	64.36	43.98	74.26	60.17	70.76
9	93.21	34.13	71.8	47.31	80.13	64.36	77.81
10	95.62	39.26	76.9	52.34	86.23	67.29	81.2
11	97.83	45.25	83.1	55.06	92.4	70.23	87.6
12	99.78	49.23	89.5	59.64	96.3	73.4	93.4

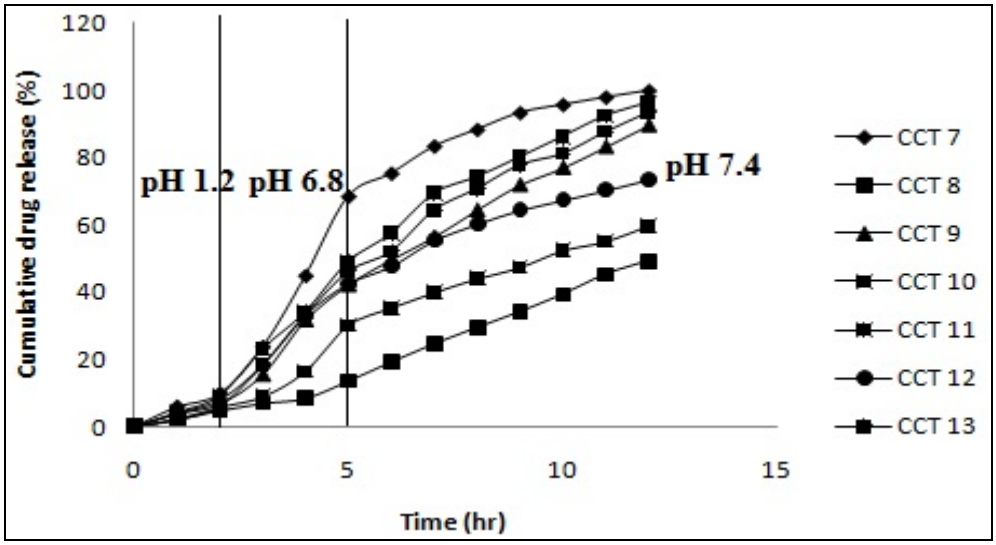

FIGURE 2: DISSOLUTION PROFILE OF COMPRESSION COATED TABLET

Drug Release kinetic:

In order to know the mechanism of drug release from compression coated tablet, data was fitted in kinetic model like Zero order, Higuchi, First order & Korsmeyer-Peppas. Model fitting data of release profile for formulation CCT 7-CCT 13 was shown in **Table 5**. Result indicated that compression coated tablet containing higher proportion of eudragit L 100 followed Higuchi's kinetic, whereas first order kinetic model was followed by compression coated tablet containing higher proportion of eudragit S 100. By using Korsmeyer and Peppas Equation, the n values were obtained between 1.1- 1.909 (**Table 5**) for all compression coated tablet. These values are characteristic of super case –II transport (n>0.89), possibly outstanding to polymer chain relaxation and swelling of polymer.

TABLE 5: *IN VITRO* DRUG RELEASE KINETIC DATA

Formulation Code	Zero Order	Higuchi's	First order	Korsmeyer Peppas	
				Regression	Slope
CCT 7	0.834	0.896	0.89	-	-
CCT 8	0.985	0.98	0.995	0.989	1.518
CCT 9	0.977	0.994	0.967	0.940	1.909
CCT 10	0.948	0.978	0.984	0.916	1.276
CCT 11	0.964	0.989	0.943	0.993	1.324
CCT 12	0.931	0.970	0.988	0.939	1.1
CCT 13	0.966	0.990	0.961	0.968	1.465

CONCLUSION: From the study it was concluded that release of the drug from drug in pH 6.8 was inversely proportional to eudragit L 100.Thismight be due to pH-dependent solubility of Eudragit S100 in pH above 7. Also we concluded that compression coated tablet containing higher proportion of Eudragit L 100 followed Higuchi's kinetic, whereas first order kinetic model was followed by compression coated tablet containing higher proportion of Eudragit S 100.

REFERENCES:

1. Geest S, Koker J, Demeester J, De Smedt S, Hennink WE. Pulsed in vitro release and in vivo behavior of exploding microcapsules. J. Control Release 2009; 135:268–73.
2. Krishnaiah YS, Satyanarayana S and Prasad YV: Studies of guar gum compression-coated 5- Amino salicylic acid tablets for colon-specific drug delivery. Drug Dev Ind Pharm 1999; 25(5):651-657.
3. Rudolph MW, Klein S, Beckert TE, Petereit H and Dressman JB: A new 5-Aminosalicylic acid multi-unit dosage form for the therapy of ulcerative colitis. Eur J Pharm Biopharm 2001; 51(3):183-190
4. Wilding IR, Davis SS, Bakhshaee M, Stevens HN, Sparrow RA and Brennan J: Gastrointestinal transit and systemic absorption of Captopril from a pulsed-release formulation. Pharm Res 1992; 9:654–657.
5. Gazzaniga A, Sangalli ME and Giordano F: Oral Chronotopic drug delivery systems: achievement of time and/or site specificity. Eur J Pharm Biopharm 1994; 40:246–250.
6. Bussemer T, Otto I and Bodmeier R: Pulsatile drug-delivery systems. Crit Rev Ther Drug Carrier Syst 2001; 18(5):433–458.
7. Lemmer B: Circadian rhythms and drug delivery. J Control Release 1991; 16:63–74.
8. Abhijit M, Manish K, Rohit S. formulation and evaluation of press-coated Indomethacin tablets for pulsatile drug delivery system. J Pharm Res 2011; 4(3):564-566.
9. Sangalli M, Maroni A, Zema L, Busetti C, Giordano F and Gazzaniga A: In vitro and in vivo evaluation of an oral system for time and/ or site-specific drug delivery. J Contr Rel 2001; 73:103–110.
10. Surendra Kumar K, Rama Kotaiah M, Prasada Rao M: Formulation and Evaluation of Pulsatile Drug Delivery System of Metoprolol Tartrate. International journal of Pharmaceutical Research and Bio-Science 2013; 2(5):246-257.

How to cite this article:
Dinkar R, Mohan G and Upadhyaya K: Formulation and Evaluation of Chronomodulated Colonic Drug Delivery of Nifidipine. Int J Pharm Sci Res 2015; 6(4): 1445-51.doi: 10.13040/IJPSR.0975-8232.6(4).1445-51.