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FORMULATION DEVELOPMENT AND IN-VITRO EVALUATION OF CHRONOTHERAPEUTIC DRUG DELIVERY OF ROSUVASTATIN BY COMPRESSED COATED TECHNIQUE

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ABSTRACT

Rosuvastatin is an HMG –COA reductase inhibitor, primarily used for the treatment of hyper cholestremia associated with cardiovascular diseases. It belongs to BCS class II having a half-life of 19 hrs and 20% bioavailability. The purpose of the present work was to develop a press-coated, chronotherapeutic drug delivery system. The core tablet was formulated using the super-disintegrants and croscarmellose sodium. A press-coated tablet contained the polymers ethyl cellulose, eudragit L 100 &S 100. The tablets were evaluated for physical characteristics are pre and post compression parameters, lag time, FTIR, DSC, and *in vitro* the 10% superdisintgrant showed good results. The FTIR and DSC study predicted no chemical interactions between the drug and excipients. The lag time for the tablet coated with 100 mg ethyl cellulose was 9±0.1 hrs with90±1.5% drug release; with 100 mg eudragit L100, the lag time was 6±0.1 hrs with 89.71±1.2% drug release; and with 100 mg eudragit S100, the lag time was6±0.2 hrs with 88±1.7% drug release. The release mechanism of the tablet followed the Korsmeyer-Peppas equation and a first-order release pattern& lag time behavior have shown good *in vitro* release.

Key words: Rosuvastatin, Ethyl cellulose, eudragit L 100 &S 100, Press-coated, Chronotherapeutic Drug Delivery System.

INTRODUCTION

In recent years, oral drug delivery systems with zero order sustained-release kinetics have been developed to control drug release using various mechanisms, including matrices with controllable swelling, diffusion, erosion, and osmotically driven systems [1] Efforts are being made to avoid typical plasma concentration peak- trough fluctuations and to reduce frequency of drug administration for better patient compliance. Recently, novel systems have been developed that release the drug after a programmable lag time. Changes in the biological rhythms of the human body (ie, chronobiology) may precipitate serious medical conditions, eg, myocardial infarction or stroke, in addition to the manifestation and severity of symptoms of chronic diseases, including allergic rhinitis, asthma, nocturnal acid reflux, and arthritis. For such chronopathological conditions, chronotherapeutic systems play an important role, because these formulations take into account probable time-dependent variation in the risk or symptoms of disease. Such systems are designed to enable a pulsatile release of drug after a predetermined off-release period (lag time) which mimics the chronopathological symptoms [2, 3].

A pulsatile therapeutic system can be a single unit (eg, a tablet or capsule) or be multiparticulate (eg, pellets) [4, 5]. Capsule-based pulsatile release systems have also been developed which are coated with a water-impermeable or semipermeable membrane containing a hydrogel polymer plug which swells with time after coming into contact with gastrointestinal fluid, and exerts an internal pressure leading to release of drug after rupture of the membrane [6–8]. Pulsatile tablet formulations are manufactured with a rapid-release core (reservoir) encased in a barrier layer formed by rupturable press coating or liquid coating of erodible and swelling polymer [9–11]. Polymers like various grades of Eudragit ® or ethyl cellulose have been tested as film coating to achieve the desired lag time [11–14]. However, a potential problem associated with the film-coated pulsatile systems is delayed drug release after loss of the barrier coat. To get

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immediate release of the drug after a desired lag time, press-coated systems with a rupturable coat have been suggested [15, 16]. In addition, press coating overcomes the draw- backs of a liquid coating because it does not require use of a solvent and requires a relatively shorter manufacturing process. With newer technologies, tablet compression and press coating can be achieved in a single step. In addition, it is possible to control lag time by changing the coating thickness and composition [17].

Hypercholesterolemia or high cholesterol, occurs when there is too much cholesterol in the body. Cholesterol is a soft, waxy, fat-like substance that is natural component of all the cells of the body. Our body makes all the cholesterol it needs. Any added cholesterol, which comes from the food you eat, can cause harm. High cholesterol raises your risk for heart diseases, heart attack and stroke. When there is too much cholesterol circulating in the blood, it can create sticky deposits (called plaque) along the artery walls. Plaque can eventually narrow or block the flow of blood to the brain, heart and other organs [18] Blood cells that get caught on the plaque form clots, which can break loose and completely block blood flow through an artery, causing heart attack or stroke [19].

In the present research Rosuvastatin is formulated into pulsatile drug delivery system by using various polymers which help in release of drug at predetermined rates.

MATERIALS AND METHODS

Rosuvastatin calcium ,Ethyl cellulose, Eudragit L 100 & S 100 , SSG ,Cross caramellose sodium, Talc, Mg. stearate& MCC(P_H 102) Powder type. Apparatus: Double beam UV/VIS spectrophotometer, mini press tablet machine, disintegration apparatus, dissolution apparatus (tablex), roche friabilator, monosanto hardness tester.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes.The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preparation of Rosuvastatin core tablets formulations

Tablets of Rosuvastatin were made by direct compression method as shown in Table1. All ingredients were weighted accurately and mix well in mortar-pastle for15 min. microcrystalline cellulose was used as direct compressing agent. Croscarmellose sodium, sodium starch glycolate were used in different compositions as disintegrating/s welling agents for various formulations. Talc and magnesium stearate were used as lubricant. Tablets were made in minipress tablet machine.

Compression coating of Rosuvastatin core tablets

Components of the coat were mixed for 10 minutes. Die filling, core centralization and machine operation were under taken using by a standardized manual process. Half of the powder mass for one tablet coat was weighed into a die. A lower coating layer was consolidated and the core centered on an even bed. The remaining powder was then added to the die and compressed into tablets using single punch tablet machine in concave punch (Diameter10mm.

Evaluation of powder blends for precompression parameters (Angle of repose, Carr's index, Hausner's ratio)

The angle of repose of granules was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone, θ is the angle of repose.

Angle of repose values more than 40 indicates excellent, good poor flow properties. An accurately weighed quantity of the granules/powder(W) was carefully poured into the graduated cylinder and volume (V0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP model). The density apparatus was set for 100 tabs and after that the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formula.

$$\text{Bulk density} = W/V0$$

$$\text{Tapped density} = W/Vf$$

Where, W = weight of the powder; V0 = initial volume; Vf = final volume

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is.

$$CI = (TD - BD) \times 100 / TD$$

Where, TD is the tapped density and BD is the bulk density.

Hausner's ratio is the ratio of tapped density and bulk density. Hausner found that this ratio was related to inter particle friction and as such could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

Evaluation of tablets for post compression parameter (Hardness, Thickness, Friability and weight variation)

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. The thickness of three randomly selected tablets

from each formulation was determined in mm using a Screw gauge. The weight variation test was performed as per procedure of IP. The weight (mg) of each of 20 individual tablets, selected randomly from each formulation was determined by dusting each tablet off and placing it in an electronic balance.

Tablet strength was tested by Roche friabilator. Preweighed tablets were allowed for 100 revolutions (4mint), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets. The %friability was then calculated by,

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{intial})} \times 100$$

Where, W_{iniial}= initial weight of tablet, W_{final}=final weight of tablet

Drug content

The Rosuvastatin tablets were tested for their drug content. Ten tablets were finely powdered. The require quantities of the powder equivalent to 100 mg of Rosuvastatin were accurately weighed and transferred to a 100-mL of volumetric flask. The flask was filled with distilled water and mixed thoroughly. The solution was made up to Volume and filtered. Dilute1mLofthe resulting solution to 100mL with distilled water and measure the absorbance of the resulting solution at the maximum at 243nm using UV spectrophotometer (Shimadzu1800,Japan). The linearity equation obtained from calibration curve as described previously was use for estimation of Rosuvastatin in the tablets formulations.

Disintegration time of Rosuvastatin core tablets

Disintegration test was carried out using the tablet disintegration test apparatus (Serve well Instruments Pvt. Ltd., Electrolab ED-2L, India) specified in Indian Pharmacopoeia. Distilled water at 37±0.5ºC was used as the disintegration media and the time in second taken for complete disintegration of the tablet with nopalpable mass remaining on the screen was measured in seconds.

***In* vitro drug release study of pulsatile Rosuvastatin tablets**

***In vitro* drug release of Rosuvastatin core tablets**

In vitro dissolution studies were carried out using USPXXIII TypeII (paddle method) apparatus. Distilled water was used as dissolution medium. Release pattern was studied visually by taking sample of 5mL at the specific time intervals. Also the sample was analyzed at 243 nm using a UV spectrophotometer.

Determination of lag time (t^{10}) of pulsatile tablets

In vitro dissolution studies were carried out using USPXXIII TypeII (paddle method) apparatus. The dissolution profiles how slag time with the coated formulations (F1-F9). The intention of the study was to develop a tablet which will be protected from gastric environment and will release the drug rapidly in the intestine after administration. Therefore above formulations showed various in lag time with respect to their coating level. The lag time was determined while performing the dissolution test. When performing the experiment, 0.1NHCl medium was used for 2hr (since the average gastric emptying time is 2hr). Then removed and fresh phosphate buffer (pH6.8) was added for subsequent hours in 900ml of dissolution medium was used at each time and stirred at 50 rpm at 37±0.5^{o}C. 5mL of dissolution media was with draw at pre determined time interval and fresh dissolution media was replaced. The withdrawn samples were analyzed at243nm using a UV spectrophotometer.

RESULTS AND DISCUSION

Drug – excipient compatibility studies

Evaluation

Drug content and physical evaluation of rosuvastatin pulsatile compressed coated tablets of the proposed formulations were subjected to various evaluation tests such as hardness, uniformity of weight, drug content and friability.

Postcompression parameters of rosuvastatin core

Dissolution (in-vitro) studies of rosuvastain core : The dissolution studies were carried out for the formulations F1 to F4 from the results, the formulations F1, F2 are formulated by using sodium starch glycolate as super disintegrating agent with polymer concentration 10%, 20% shows percentage drug release 46.4%, 70% respectively, the formulations F3, F4 are formulated by using croscaramellose (CCS) sodium as super disintegrating agent with polymer concentration 10%, 20% shows percentage drug release 100%,121%respectively at 5 min. The F3 formulation CCS as super disintegrant shows 100% drug release within 5-10 mins.F3 formulae is suitable for our experiment.

Post compression parameters of rosuvastatin compressed coated tablets

Physical evaluation of rosuvastatin pulsatile compressed coated tablets of the proposed formulations were subjected to various evaluation tests such as hardness, uniformity of weight, drug content and friability.

In –vitro release of Rosuvastatin compressed coated tablets: The dissolution studies were carried out for the formulations RF1 to RF9 from the results, the formulations RF1, RF2&RF3 are formulated by using ethyl cellulose as a hydrophobic coating agent for modified release tablets with polymer concentration 8.30%, 16%& 33% respectively. It shows no percentage drug release in before lag time at 30 % 0f polymer used, the formulations RF4-RF9 are formulated by using eudragit L100 &S 100 as copolymer with polymer concentration8.3%, 16%&33% respectively. It shows some percentage drug release before lag time. Finally ethyl cellulose perfect suitable for our experiment it is hydrophobic agent. RF1-RF3 formulations shows the increases lag time of rosunvastatin compressed coated tablets is 5 hrs.

Table 1. Formulation for preparation Rosuvastatin core tablets (100mg)

Sl.No.	Ingredients	F1	F2	F3	F4
1	Rosuvastatin	10 mg	10 mg	10 mg	10 mg
2	SSG	10 mg	20mg	-	-
3	CCS	-	-	10 mg	20mg
4	Talc	2 mg	2 mg	2 mg	2 mg
5	Magnesium stearate	2 mg	2 mg	2 mg	2 mg
6	MCC	76 mg	66 mg	76 mg	66 mg

Table 2. Composition of coat over Rosuvastatin core tablet (200mg)

SL.No	Ingredients	RF1	RF2	RF3	RF4	RF5	RF6	RF7	RF8	RF9
1	Ethyl cellulose	25mg	50mg	100mg	-	-	-	-	-	-
2	Eudragit L-100	-	-	-	25mg	50mg	100mg	-	-	-
3	Eudragit S-100	-	-	-	-	-	-	25mg	50mg	100mg
4	Talc	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg
5	Mg.Steareate	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg
6	PVP	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
7	Micro crystalline cellulose(MCC)	166	141	91	166	141	91	166	141	91

Table 3. Post compression parameters of rosuvastatin core

Formulation code	Weight variation(%)	Hardness (kg/cm^2)	Thickness(mm)	Friability(%)	Disintegration (sec)
F1	0.99	3	2.1	0.7	14
F2	0.89	2.9	2.6	0.6	16
F3	1.00	3	2.7	0.59	15
F4	0.97	2.8	2.5	0.8	13

Table 4. *In-vitro* release of rosuvastatin core

	% 0f drug release with formulation codes			
Time (min)	**F1**	**F2**	**F3**	**F4**
5	46.4	70	103.2	121
10	59	69	97	98
15	50	70.5	96.5	97
20	47.7	67	95	94
30	49	68.5	94	94
45	47.8	74	95.5	96
60	49	67	94	108

Table 5. Post compression parameters of rosuvastatin compressed coated tablets

Formulation code	weight variation(%)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration (sec)
RF1	0.99	5	3.1	0.7	30
RF2	0.89	5.2	3.8	0.6	34
RF3	1.00	5.1	3.9	0.59	33
RF4	0.97	5.4	3	0.8	35
RF5	0.97	4.9	3	0.8	30
RF6	0.98	5.2	3.1	0.4	33
RF7	0.99	5	3.5	0.5	32
RF8	1.00	5.1	3.7	0.6	34

Table 6. In –vitro release of Rosuvastatin compressed coated tablets

	% 0f drug realese with formulation codes								
Time (hr)	**RF1**	**RF2**	**RF3**	**RF4**	**RF5**	**RF6**	**RF7**	**RF8**	**RF9**
30 mins	2.2	1.1	-	3	2	-	4.3	3.2	-
1	3	2.9	-	5	2.5	-	6	5	-
2	5	6	-	7.8	3	-	9	17	-
3	11	9	-	19	9	13	11	18	14
4	15	11	-	22	18	25	17	19	17

5	16	13	-	35	30	37	28	22	28
6	40	33	4	66	35	45	33	34	36
7	61	66	7	76	45	55	49	49	44
8	70	77	11	81	77	66	62	60	49
9	90	89	67	91	88	70	91	87	69

Fig 1. FTIR spectrum of Rosuvastatin

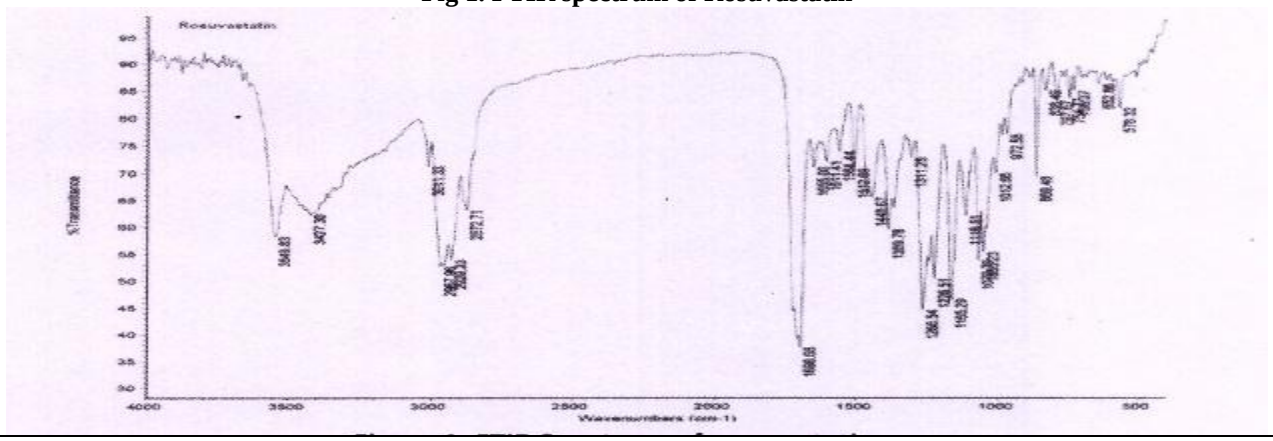


Fig 2. FTIR of Rosuvastatin +MCC+Mg.stearate

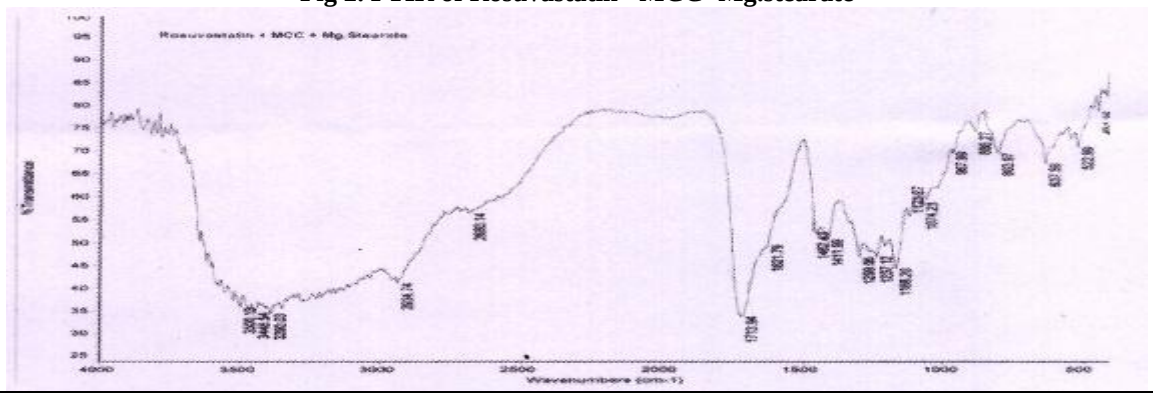
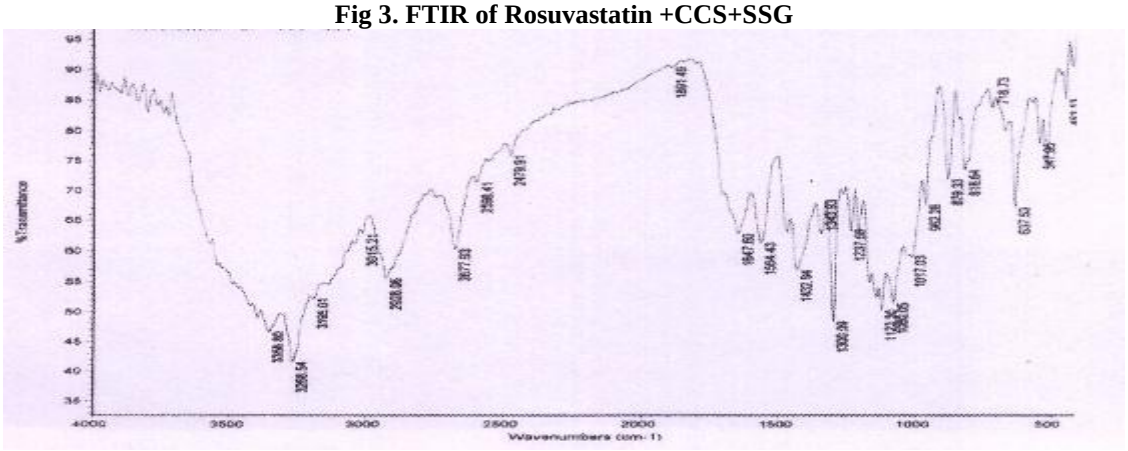


Fig 3. FTIR of Rosuvastatin +CCS+SSG



CONCLUSION

The lag time of drug release from the rosuvastatin pulsatile release formulation can be readily modulated by varying the concentration of ethyl cellulose, eudragit L100&S100 are the compression coating agents. I was observed between the *in vitro* performance of the rosuvastain pulsatile release tablet, suggesting that the robust and reliable ability to produce a lag time before drug release may make this formulation useful as a chronotherapeutic drug delivery system. It can be considered as one of the promising formulation techniques for preparing rosuvastatin pulsatile drug release system.

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REFERENCES

1. Anal AK. Time-controlled pulsatile delivery systems for bioactive compounds. *Recent Pat Drug DelivFormul*, 1, 2007, 73–79.
2. Lemmer B. Chronobiology, drug-delivery and chronotherapeutics. *Adv Drug Deliv Rev*, 59, 2007, 825–827.
3. Smolensky MH, Peppas NA. Chronobiology, drug delivery and chronotherapeutics. *Adv Drug Deliv Rev*, 59, 2007, 828–851.
4. Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. *Crit Rev Ther Drug Carrier Syst*, 18, 2001, 433–458.
5. Roy P, Shahiwala A. Multiparticulate formulation approach to pulsatile drug delivery: Current perspectives. *J Control Release*, 134, 2009, 74–80.
6. Krogel I, Bodmeier R. Pulsatile release from an insoluble capsule body controlled by an erodible plug. *Pharm Res*, 15, 1998, 474–480.
7. Ross A. Chronopharmaceutical drug delivery from a pulsatile capsule device based on programmable erosion. *J Pharm Pharmacol*, 52, 2000, 903–909.
8. Ueda S, Hata T, Asakura S. Development of a novel drug release system, time-controlled explosion system (TES). I. Concept and design. *J Drug Target*, 2, 1994, 35–44.
9. Efentakis M, Koligliati S, Vlachou M. Design and evaluation of a dry coated drug delivery system with an impermeable cup, swellable top layer and pulsatile release. *Int J Pharm*, 311, 2006, 147–156.
10. Pozzi F, Furlani P, Gazzaniga A, Davis SS, Wilding IR. The Time Clock ® system: A new oral dosage form for fast and complete release of drug after a predetermined lag time. *J Control Release*, 31, 1994, 99–108.
11. Sungthongjeen S, Puttipipatkhachorn S, Paeratakul O, Dashevsky A, Bodmeier R. Development of pulsatile release tablets with swelling and rupturable layers. *J Control Release*, 95, 2004, 147–159.
12. Sinha VR, Bhinge JR, Kumria R, Kumar M. Development of pulsatile systems for targeted drug delivery of celecoxib for prophylaxis of colorectal cancer. *Drug Deliv*, 13, 2006, 221–225.
13. Malah YE, Nazzal S. Novel use of Eudragit ® NE 30D/Eudragit ® L 30D-55 blends as functional coating materials in time-delayed drug release applications. *Int J Pharm*, 357, 2008, 219–227.
14. Roy P, Shahiwala A. Statistical optimization of ranitidine HClfloating pulsatile delivery system for chronotherapy of nocturnal acid breakthrough. *Eur J Pharm Sci*, 37, 2009, 363–369.
15. Bussemer T, Peppas NA, Bodmeier R. Time-dependant mechanical properties of polymeric coatings used in rupturable pulsatile release dosage forms. *Drug DevInd Pharm*, 29, 2003, 623–630.
16. Dashevsky A, Bussemer T, Mohamad A, Bodmeier R. Process and formulation variables affecting the performance of a rupturable capsule based drug delivery system with pulsatile drug release. *Drug DevInd Pharm*, 30, 2004, 171–179.
17. Fukui E, Miyamura N, Uemura K, Kobayashi M. Preparation of enteric coated timed-release press-coated tablets and evaluation of their function by in-vitro/in-vivo test for colon targeting. *Int J Pharm*, 204, 2000, 7–15.
18. LemmerB. The clinical relavence of Chronopharmacology in therapeutics. *Pharmacacol. Res*., 33, 1996, 107-115.
19. Francesco P, Ramon CH. "Circadian rhythms in cardiac arrhythmias and opportunities for their chronotherapy". *Adv Drug Delivery rev*, 59, 2007, 940-951.