Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2010, 2(4): 482-497
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Development and Evaluation of Press Coated Tablets for Chronopharmaceutical Drug Delivery using Gellable and Permeable Polymers

Parag A. Kulkarni*, Mahendra Jaiswal, Santosh B. Jawale, Satish V. Shirolkar and Pramod V. Kasture.

Department of Pharmaceutics, Padmashree Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune-411018, Maharashtra, India

---

ABSTRACT

The role of chronotherapeutics in hypertension management is based on the recognition that blood pressure does not remain constant throughout the day. Instead, it tends to be higher in the early morning hours and lower in the evening hours. The main objective of the present studies reported here was to investigate whether compression coating could be used to produce tablets providing maximum in-vitro drug release 6 to 8 hours after an evening dose taken at approximately 10:00 pm. The basic idea behind the dosage form development is to investigate effect of coating design on lag time and drug release from directly compressed time-controlled release tablet. The aim of the present study was to design time controlled tablet of Diltiazem hydrochloride, as Chronopharmaceutical drug delivery system by compression coating. Formulation design involves coating polymer blend ratio (100:0, 75:25, 50:50, 25:75, 0:100 w/w) of Klucel HF, Klucel HXF and Eudragit RSPO which were exploited for their pulsatile drug release ability. The effect of different weight ratio of combination of permeable polymers and gellable polymer, different particle size of gellable polymer in outer shell polymers blend were studied on the drug release behavior of the time controlled tablet formulation. Coating materials blend were evaluated for micromeritic properties like flow properties, compressibility index, Hausner's ratio and also evaluated the tablet for hardness, thickness, friability, weight variation, water uptake studies. The obtained results showed the capability of the system in delaying drug release for a programmable period of time to attain drug release 6 to 8 hours after an evening dose taken at approximately 10:00 pm according to a time-dependent approach.

Key words: press coated pulsatile tablet; Diltiazem hydrochloride; gellable polymer, permeable polymer and Chronopharmaceutical Drug Delivery.

INTRODUCTION

Chronopharmaceutical drug delivery has been described as a branch of pharmaceutics devoted to the design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy[1].These systems are beneficial for the drugs having chronopharmacological behaviour (where night time dosing is required). From the point of view of therapeutic optimization, maintaining a constant blood level for a drug in the human body is questionable. Long-term constant drug concentration exposed in blood and tissues may induce many problems such as tolerance of drug and activation of physiological system. Recently, chronotherapy has been extensively applied in clinical therapy by modulating the dosing regimen of drug administration according to physiological needs [2]. Diseases wherein Chronopharmaceutical drug delivery is promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, and hypercholesterolemia [3].

The role of chronotherapeutics in hypertension management is based on the recognition that blood pressure does not remain constant throughout the day. Instead, it tends to be higher in the early morning hours and lower in the evening hours. The widespread use of ambulatory blood pressure monitoring has been instrumental in revealing this pattern of blood pressure variation, which is mediated by the body's diurnal circadian rhythms--the "internal clock" exhibited by all mammals that regulates patterns of physiologic changes throughout the day. One of the primary functions of the changes in physiologic responses is the arousal propensity in the morning and the sleep requirement after an awake period. Wake propensity is mediated through such factors as increases in core body temperature, respiration, cortisol and norepinephrine levels, and heart rate and blood pressure. Sleep propensity is mediated by such factors as an increase in melatonin levels and decrease in body temperature and blood pressure [4, 5].

The main objective of the present studies reported here was to investigate whether compression coating could be used to produce tablets providing maximum in-vitro drug release 6 to 8 hours after an evening dose taken at approximately 10:00pm. The basic idea behind the dosage form development is to investigate effect of core and coating design on lag time and drug release from directly compressed time-controlled release tablet.

A dry-coated tablet was recently renewed as a novel system to deliver a drug in a pulsatile way, at predetermined times following oral administration. This novel system is not only rate controlled but is also time controlled. The dry-coated tablets were prepared by a direct compression method. This compression method eliminates the time-consuming and complicated coating or granulation processes and also improves the stability of the drug by protecting it from moisture [6, 7]. There are various problems with pH dependent drug delivery; however the pH in the gastrointestinal tract varies between and within individuals. It is affected by diet and disease. During acute stage of inflammatory bowel disease colonic pH has been found to be significantly lower than normal. In ulcerative colitis pH values have been measured in the proximal parts of the colon [8].

The purpose of this study was to develop press coated tablets for Chronopharmaceutical drug delivery of Diltiazem hydrochloride. The oral press coated tablet was developed to achieve the time-controlled disintegrating or erodible function with a distinct predetermined lag time. Press-coated tablet containing Diltiazem hydrochloride and other excipients in the inner core

was formulated with an outer shell by different weight ratios of gellable polymers (Klucel HF and HXF) and permeable polymer (Eudragit RSPO). Klucel (hydroxypropylcellulose) is nonionic water soluble cellulose ether with a versatile combination of properties.

MATERIALS AND METHODS

Materials

Klucel HF and HXF were kindly supplied by Hercules Incorporated, Wilmington, USA. Diltiazem hydrochloride was supplied by Dr. Reddy's Laboratories Ltd, Hyderabad India. Eudragit RSPO gifted from Degussa India Pvt. Ltd, Mumbai. Microcrystalline cellulose (MCC, Avicel PH-102) and Cross-carmellose sodium (Ac-Di-Sol) were supplied from Maple Biotech Pvt. Ltd, Pune. Magnesium stearate and Aerosil were procured from S.D. Fine-Chemical Ltd., Mumbai, India; all other ingredients were of analytical grade.

Methods

Precompression Parameters of Coating Powder Blend and Core Tablet Powder Blend:

Coating powder blend and core tablet powder blend were evaluated for various precompression parameters such as angle of repose, bulk density, tapped bulk density, Hausner's ratio and compressibility index [9, 10, 11, 12].

Preparation of Diltiazem hydrochloride Core Tablet

The inner core tablet was prepared by direct compression method. The powder mixture of Diltiazem hydrochloride (API), Avicel pH 102 (Diluent), Ac-Di-Sol (superdisingrant) and Ponceau 4R (coloring agent) were dry blended first for 20 minutes followed by the addition of magnesium stearate (lubricant) and Aerosil (glidant). The powder mixture was further blended for 10 minutes. The formulation F1 to F5 had Ac-Di-Sol from 0% to 4% w/w. The resulting powder mixtures were then compressed into tablets (average tablet weight 75 mg) using a rotary tablet machine equipped with 6 mm concave faced punch. The core tablets were evaluated for thickness, hardness, weight variation, friability and drug content. The core compositions for one tablet are reported in Table No.1.

Table No.1: The core compositions with varying concentration of Ac-Di-Sol

Ingredients	***F_{1} (mg)***	***F_{2} (mg)***	***F_{3} (mg)***	***F_{4} (mg)***	**F_{5} *(mg)***
Diltiazem hydrochloride	30	30	30	30	30
Avicel pH 102	43.125	42.375	41.625	40.875	40.125
Ac-Di-Sol	-	0.75	1.5	2.25	3.0
Magnesium stearate (1%)	0.75	0.75	0.75	0.75	0.75
Aerosil (1%)	0.75	0.75	0.75	0.75	0.75
Ponceau 4R (0.5%)	0.375	0.375	0.375	0.375	0.375
Total weight	**75**	**75**	**75**	**75**	**75**

Table No. 2: Effect of permeable polymer (Eudragit RSPO) combined with gellable polymer (Klucel HF) in the outer shell

Formulations		Coating Material (75 mg)	% Ratio	Amount used in upper and lower shell (mg)
Code	Core Tablet			
FA_1	F_5	Eudragit RSPO : Klucel HF	100 : 0	125
FA_2	F_5	Eudragit RSPO : Klucel HF	75 : 25	125
FA_3	F_5	Eudragit RSPO : Klucel HF	50 : 50	125
FA_4	F_5	Eudragit RSPO : Klucel HF	25 : 75	125
FA_5	F_5	Eudragit RSPO : Klucel HF	0 : 100	125
FB_1	F_5	Eudragit RSPO : Klucel HF	100 : 0	150
FB_2	F_5	Eudragit RSPO : Klucel HF	75 : 25	150
FB_3	F_5	Eudragit RSPO : Klucel HF	50 : 50	150
FB_4	F_5	Eudragit RSPO : Klucel HF	25 : 75	150
FB_5	F_5	Eudragit RSPO : Klucel HF	0 : 100	150

Table No. 3: Effect of permeable polymer (Eudragit RSPO) combined with gellable polymer (Klucel HXF) in the outer shell

Formulations		Coating Material (75 mg) Coating Material (75 mg)	% Ratio Ratio %	Amount used in upper and lower shell (mg)
Code	Core Tablet			
FA_1	F_5	Eudragit RSPO : Klucel HXF	100 : 0	125
FC_2	F_5	Eudragit RSPO : Klucel HXF	75 : 25	125
FC_3	F_5	Eudragit RSPO : Klucel HXF	50 : 50	125
FC_4	F_5	Eudragit RSPO : Klucel HXF	25 : 75	125
FC_5	F_5	Eudragit RSPO : Klucel HXF	0 : 100	125
FB_1	F_5	Eudragit RSPO : Klucel HXF	100 : 0	150
FD_2	F_5	Eudragit RSPO : Klucel HXF	75 : 25	150
FD_3	F_5	Eudragit RSPO : Klucel HXF	50 : 50	150
FD_4	F_5	Eudragit RSPO : Klucel HXF	25 : 75	150
FD_5	F_5	Eudragit RSPO : Klucel HXF	0 : 100	150

Preparation of press coated tablets

The compositions of the coated materials are given in the **Table No.2 and 3**. All the powder mixtures were previously passed through the sieve no. 44. 125 and 150 mg of the powder mixture was used for the upper and lower shell. The press coating of tablets was performed using a rotary tablet machine (RIMEK Mini Tablet Press). A half amount of the powder was filled into the die to make a powder bed, in the center of which core tablet was placed manually. Then, the remaining half of the coating material filled in the die, and the contents were compressed under a sufficient compression force, using a concave punch 10 mm in diameter.

Drug Content of Core Tablets

Tablets were finely powdered and quantity of powder equivalent to 10 mg of Diltiazem hydrochloride was accurately weighed and transferred to volumetric flask containing 100 ml phosphate buffer (pH 6.8) and mixed thoroughly. One milliliter of filtrate with suitable dilution was estimated for Diltiazem hydrochloride content at 237 nm using double beam spectrophotometer (Shimadazu Corporation, Japan, UV-1700)

Characterization of Core and Press Coated Tablet

The above core and press coated tablet were evaluated for physical properties like weight variation, diameter, thickness, hardness, thickness, friability.

Dissolution study of Core and Press Coated Tablet [2]

The dissolution test for core tablet was performed in triplicate using a six-station USP type Π (paddle) apparatus (Model-DT 60, Veego, India) at 37°C ± 0.5°C and 100 rpm speed. The dissolution studies were carried out in phosphate buffer pH 6.8 for 20 minutes. At every one minute interval samples of 5 ml were withdrawn from dissolution medium and replaced with fresh medium.

The dissolution test for press coated tablets were performed in triplicate using a six-station USP type Π (paddle) apparatus (Model-DT 60, Veego, India) at 37°C ± 0.5°C and 100 rpm speed in 0.1 N HCl (1st fluid; simulated gastric fluid) for 2 hrs and pH 6.8 phosphate buffer (2nd fluid; simulated intestinal fluid) for rest of time were used as dissolution media. Aliquots of dissolution fluid were removed at specified time intervals of each half hour. Assayed for the amount of Diltiazem hydrochloride released by a spectrophotometer (UV 1700, Shimadzu, Japan) at a wavelength of 236.5 and 237 nm respectively for 0.1 N HCl and pH 6.8 phosphate buffer. The amounts of drug present in the samples were calculated with the help of appropriate calibration curve constructed from reference standard. Cumulative percentage drug release was calculated using PCP Disso v2.08 Software.

Water uptake studies [13]

Water uptake studies were performed for press coated tablets in a simple way that permitted the diffusion of fluids into tablet in both axial as well as radial directions. For this, a simple stainless-steel assembly was fabricated. It contained a stainless-steel cup with circular perforated bottom made up of stainless-steel (Mesh No. 36). Individual tablets were weight and average weight of tablets were considered as dry weight of each type. A tablet of each type was placed at the center of cup, which rested on the rim of the glass beakers. The beakers were filled with distilled water i.e. immersion medium. The assembly was placed in such a way that the stainless-steel perforated bottom remained submerged in distilled water throughout the course of study. The distilled water in beakers was maintained at 37 $\pm 1^0$ C by

placing all the beakers in the thermostatically controlled water bath. The study was conducted for 10 hrs during which the weight gain in tablet due to water uptake was observed. The assembly is shown in **Figure No. 1.**

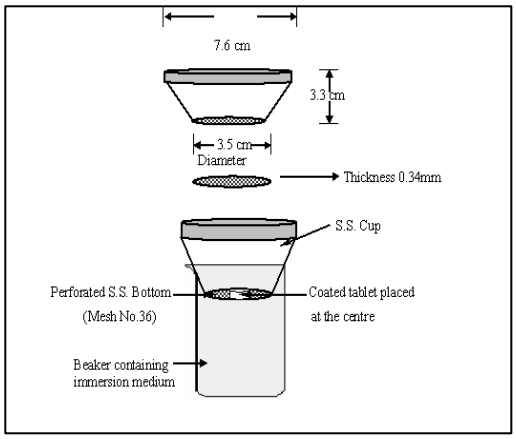


Figure No.1. Schematic representation of assembly for water uptake study

Every one-hour the assembly containing tablet was removed from distilled water, wiped dry with tissue paper and weighed accurately using digital analytical balance and was placed again in the same position. The weights of assembly were recorded over the period of 10 hrs to find out cumulative amount of water uptake by each type of press coated tablets in miligrams. The %water uptake was calculated as follows:

$$\%\text{Water uptake} = \left[\left(\frac{W_t - W_0}{W_0}\right)\right] \times 100$$

Where W_t is weight of wet tablet at time t and W_0 is weight of dry tablet.

Transverse and longitudinal section view of press coated tablets

Tablets were cut transversely and longitudinally by using blade individually. The cutting sections of tablets were evaluated by digital camera.

RESULT AND DISCUSSION

Precompression parameters of Core tablets and coated material powder blend

Core tablets and coated material powder blend were evaluated for angle of repose, bulk density, tapped density, hausner ratio and compressibility index. The values for angle of repose, Hausner ratio and compressibility index were found to be in good correlation indicating that all formulations possess good flow property and compressibility (shown in Table No. 4, 5 and 6)

Table No.4 Precompression parameters of Core tablets

F	Bulk Density * gm/cm^3	Tapped Density *	Hausner Ratio*	Compressi-bility Index*	Angle of Repose *
F_1	0.506 ±0.013	0.625 ±0.00	1.23 ±0.03	18.98 ±2.16	24.07 ±0.87
F_2	0.484 ±0.007	0.585 ±0.018	1.20 ±0.04	17.24 ±2.80	24.41 ±1.15
F_3	0.464 ±0.006	0.592 ±0.020	1.27 ±0.02	21.51 ±3.52	23.98 ±0.28
F_4	0.457 ±0.011	0.579 ±0.009	1.26 ±0.01	21.11 ±0.98	23.76 ±0.28
F_5	0.502 ±0.015	0.597 ±0.010	1.16 ±0.04	15.99 ±2.24	24.63 ±0.49

* Mean ± S.D.; n = 3, F = Formulation Code

Table No. 5 Precompression parameters of coated material powder blend (RSPO: HF)

F	Bulk Density * gm/cm^3	Tapped Density*	Hausner Ratio*	Compressi-bility *	Angle of Repose*
FA_1	0.660 ±0.017	0.820 ±0.010	1.22 ±0.03	19.51 ±1.36	21.84 ±1.23
FA_2	0.499 ±0.012	0.606 ±0.018	1.21 ±0.01	17.58 ±0.46	31.08 ±1.17
FA_3	0.457 ±0.006	0.516 ±0.008	1.12 ±0.005	11.41 ±0.15	31.66 ±0.30
FA_4	0.365 ±0.004	0.397 ±0.004	1.08 ±0.015	8.04 ±1.04	32.65 ±0.29
FA_5	0.331 ±0.003	0.386 ±0.004	1.16 ±0.011	14.39 ±0.96	32.76 ±0.77
FB_1	0.660 ±0.017	0.820 ±0.010	1.22 ±0.03	19.51 ±1.36	21.84 ±1.23
FB_2	0.499 ±0.012	0.606 ±0.018	1.21 ±0.01	17.58 ±0.46	31.08 ±1.17
FB_3	0.457 ±0.006	0.516 ±0.008	1.12 ±0.005	11.41 ±0.15	31.66 ±0.30
FB_4	0.365 ±0.004	0.397 ±0.004	1.08 ±0.015	8.04 ±1.04	32.65 ±0.29
FB_5	0.331 ±0.003	0.386 ±0.004	1.16 ±0.011	14.39 ±0.96	32.76 ±0.77

Mean ± S.D.; n = 3, F = Formulation Code

Table No. 6. Precompression parameters of coated material powder blend (RSPO: HF)

F	Bulk Density * gm/cm^3	Tapped density* gm/cm^3	Hausner Ratio*	Compressi-bility Index*	Angle of Repose*
FA_1	0.660 ±0.017	0.820 ±0.010	1.22 ±0.03	19.51 ±1.36	21.84 ±1.23
FC_2	0.428 ±0.010	0.530 ±0.008	1.23 ±0.025	19.34 ±1.72	28.36 ±0.96
FC_3	0.331 ±0.008	0.389 ±0.011	1.18 ±0.017	15.46 ±1.14	34.75 ±1.03
FC_4	0.306 ±0.005	0.392 ±0.008	1.02 ±0.037	21.91 ±2.05	31.69 ±0.64
FC_5	0.268 ±0.001	0.322 ±0.005	1.19 ±0.015	16.84 ±0.93	33.06 ±1.31
FB_1	0.660 ±0.017	0.820 ±0.010	1.22 ±0.03	19.51 ±1.36	21.84 ±1.23
FD_2	0.428 ±0.010	0.530 ±0.008	1.23 ±0.025	19.34 ±1.72	28.36 ±0.96
FD_3	0.331 ±0.008	0.389 ±0.011	1.18 ±0.017	15.46 ±1.14	34.75 ±1.03
FD_4	0.306 ±0.005	0.392 ±0.008	1.02 ±0.037	21.91 ±2.05	31.69 ±0.64
FD_5	0.268 ±0.001	0.322 ±0.005	1.19 ±0.015	16.84 ±0.93	33.06 ±1.31

* Mean ± S.D.; n = 3, F = Formulation Code

Characterization of Core and Press Coated Tablet

The core tablets were subjected for weight variation, diameter, thickness, hardness friability and percentage drug contents. Weight variation, diameter, thickness and hardness were found to be within acceptable limit. The friability was below 1% for all the formulation, which is an indication of good mechanical resistance of the tablet. Drug content of core tablets were observed within the range 98.26-99.56%. The press coated tablets were subjected for weight variation, diameter, thickness, hardness and friability. Weight variation, diameter, thickness and hardness were found to be within acceptable limit. (Shown in Table No. 7, 8 and 9)

Table No. 7. Characterization of Core-Tablet

F	Weight Variation* (mg)	Diameter# (mm)	Thickness# (mm)	Hardness# (kg/cm^2)	Friability (% loss of Weight)	% Drug content#
F_1	74.58 ±0.35	6.02 ±0.007	2.34 ±0.005	4.5 ±0.50	0.355	99.56 ±0.68
F_2	74.68 ±036	6.02 ±0.011	2.36 ±0.016	4.33 ±0.03	0.361	98.80 ±0.72
F_3	74.47 ±0.31	6.01 ±0.015	2.39 ±0.014	4.00 ±0.00	0.328	98.33 ±0.11
F_4	74.70 ±0.31	6.01 ±0.011	2.40 ±0.008	4.0 0±0.50	0.348	98.26 ±0.30
F_5	74.61 ±0.39	6.02 ±0.008	2.42 ±0.008	3.83 ± 0.23	0.308	98.93 ±0.30

F = Formulation Code, * Mean ± S.D.; n = 20, # Mean ± S.D.; n = 3

Table No. 8. Characterization of press-coated Tablets (RSPO: HF)

F	Weight Variation*	Diameter# (mm)	Thickness# (mm)	Hardness# (kg/cm^2)	Friability % loss of
FA_1	194.70 ±3.40	8.03 ±0.005	4.03 ±0.054	5.16 ±0.288	0.97
FA_2	195.86 ±3.42	8.04 ±0.100	4.01 ±0.078	7.33 ±0.290	0.68
FA_3	198.86 ±2.56	8.02 ±0.005	4.06 ±0.044	9.66 ±0.289	0.36
FA_4	198.05 ±2.41	8.00 ±0.010	4.03 ±0.035	10.50 ±0.00	0.15
FA_5	199.81 ±2.05	8.00 ±0.005	4.07 ±0.020	12.00 ±0.50	0.05
FB_1	218.80 ±2.91	8.03 ±0.005	4.24 ±0.042	7.16 ±0.288	0.96
FB_2	221.34 ±1.37	8.02 ±0.010	4.35 ±0.043	9.33 ±0.287	0.44
FB_3	221.04 ±1.58	8.00 ±0.010	4.48 ±0.025	9.66 ±0.280	0.34
FB_4	223.88 ±0.76	8.01 ±0.005	4.53 ±0.027	11.00 ±0.50	0.17
FB_5	224.40 ±1.02	8.02 ±0.026	4.53 ±0.027	12.16 ±0.28	0.11

F = Formulation Code, * Mean ± S.D.; n = 20, # Mean ± S.D.; n = 3

Table No. 9. Characterization of press-coated Tablets (RSPO: HXF)

F	Weight Variation*	Diameter# (mm)	Thickness# (mm)	Hardness# (kg/cm^2)	Friability % loss of
FA_1	194.70 ±3.40	8.03 ±0.005	4.03 ±0.054	5.16 ±0.288	0.97
FC_2	194.94 ±1.56	8.03 ±0.015	4.04 ±0.066	8.16 ±0.28	0.50
FC_3	196.68 ±2.38	8.00 ±0.013	4.00 ±0.027	10.16 ±0.29	0.20
FC_4	197.10 ±2.79	8.00 ±0.015	3.99 ±0.033	11.00 ±0.00	0.10
FC_5	198.76 ±1.44	8.00 ±0.131	3.99 ±0.048	12.34 ±0.28	0.01
FB_1	218.80 ±2.91	8.03 ±0.005	4.24 ±0.042	7.16 ±0.288	0.96
FD_2	221.96 ±2.05	8.03 ±0.011	4.46 ±0.034	9.67 ±0.28	0.36
FD_3	223.21 ±1.64	8.00 ±0.005	4.50 ±0.031	10.16 ±0.29	0.20
FD_4	223.84 ±1.26	8.01 ±0.005	4.57 ±0.016	11.00 ±0.00	0.10
FD_5	224.57 ±0.48	8.02 ±0.025	4.59 ±0.017	11.67 ±0.28	0.09

F = Formulation Code, * Mean ± S.D.; n = 20, # Mean ± S.D.; n = 3

Dissolution of core tablets:

The effect of Ac-Di-Sol® level on drug release profile from uncoated tablet (Formulations F_1 to F_5) was determined. As amount of Ac-Di-Sol® increases from formulations F_1 to F_5; the formulation containing highest amount of Ac-Di-Sol® (F_5) showed fast disintegration. (Figure No. 2)

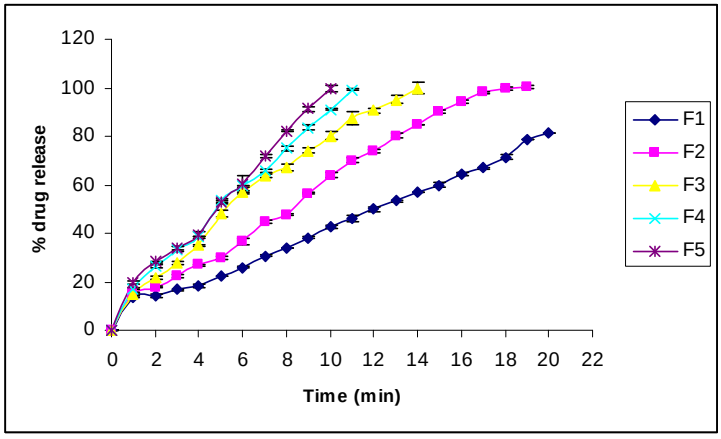


Figure No. 2. Effect of Ac-Di-Sol® level on drug release profile from core Tablets (F_1-F_5)

Dissolution of press coated tablets:

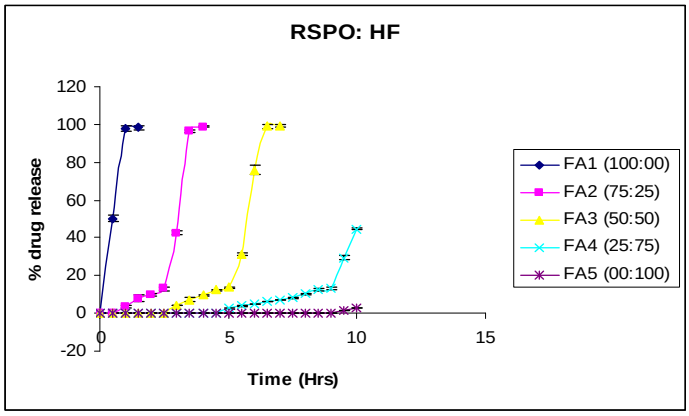
Time required to release 10% of drug was considered as lag time. Formulations FA_1 to FA_5 and FB_1 to FB_5 (Figure No. 3 and 4) showed increase in lag time and decrease in Diltiazem hydrochloride release rate with increase in weight ratio of Klucel-HF. When Klucel -HF combines with Eudragit RSPO, the viscosity of this mixture increases as the ratio increases.

Upon contact with dissolution medium, it forms a gel like structure. But due to presences of Eudragit RSPO, the gel formed is not capable enough to hold drug for long time, instead starts to erode and also allow dissolution medium to penetrate in core tablet.

Formulations FA_1 and FB_1 which contain only Eudragit RSPO showed the drug release with bursting effect, After permeation of medium in to core, pressure generates in core tablet that is enough to break the coating layer in two halves. FA_1 show no lag time while FB_1 shows lag time of 1 hr. The difference observed in FA_1 and FB_1 is because increase in weight ratio of coat: core. Formulations FA_2 and FB_2 contains Eudragit RSPO: Klucel -HF in weight ratio of 75:25. Here similar release pattern was observed as in FA_1, the difference is increase in lag time with increase in weight ratio of Klucel –HF. FA_2 and FB_2 show the lag time of 2.5 hrs and 7 hrs respectively and release last for 4 hrs and 9 hrs respectively. The difference observed in FA_2 and FB_2 is because increase in weight ratio of coat: core. Formulations FA_3 and FB_3 contains Eudragit RSPO: Klucel –HF in weight ratio of 50:50, it forms a more tight gel structure of outer coating layer. FA_3 and FB_3 show lag time of 4.5 hrs and 8.5 hrs respectively. Complete release of drug was observed in FA_3 in 7 hrs. Only 15.16 % drug release was observed with FB_3 within 10 hrs. The difference observed in FA_3 and FB_3 is because increase in weight ratio of coat: core. Formulations FA_4 and FB_4 contain Eudragit RSPO: Klucel -HF in weight ratio of 25:75. Increase in lag time and decrease in release rate of Diltiazem hydrochloride from the gellable barrier formed because high weight ratio of Klucel -HF. FA_4 show lag time of 8 hrs. Only 44.79 % and 6.05 % drug release observed with FA_4 and FB_4 respectively within 10 hrs periods of time. The difference observed in FA_4 and FB_4 is because increase in weight ratio of coat: core. Formulations FA_5 and FB_5 contain Eudragit RSPO: Klucel -HF weight ratio of 00:100. In 10 hrs, FA_5 and FB_5 have shown 2.69% and 0% drug release respectively. Highly delay in lag time may be because absence Eudragit RSPO (responsible for penetration of dissolution medium) in coat. Observation showed that these tablets were swollen coating layer with almost dry core tablet. Formulations FA_1 to FC_5 and FB_1 to FD_5 (Figure No. 5 and 6) showed increase in lag time and decrease in Diltiazem hydrochloride release rate with increase in weight ratio of Klucel-HXF: Eudragit RSPO. When Klucel -HXF combines with Eudragit RSPO, the viscosity of this mixture increases as the ratio increases. The particle size of Klucel-HXF is smaller than particle size of Klucel-HF, so upon contact with dissolution medium it forms tight gel like structure than that of Klucel-HF. Due to presence of Eudragit RSPO, the gel formed is not capable enough to hold drug for long time, instead starts to erode and allow the permeation of dissolution medium to penetrate to core tablets. Formulations FC_2 and FD_2 contains Eudragit RSPO: Klucel-HXF in weight ratio of 75:25. Here similar release pattern was observed as in FA_1, the difference is increase in lag time with increase in weight ratio of Klucel –HXF. FC_2 and FD_2 shows lag time of 7 hrs and 8.5 hrs respectively. Complete release of drug observed in FC_2 in 10 hrs. Only 40.37 % drug release observed with FD_2 within 10 hrs. The difference observed in FC_2 and FD_2 is because increase in weight ratio of coat: core. Formulations FC_3 and FD_3 contains Eudragit RSPO: Klucel -HXF weight ratio of 50:50, it forms a more tight gel structure of outer coating layer. FC_3 show lag time of 8 hrs. Only 78.38 % and 9.80 % drug release was observed with FC_3 and FD_3 within 10 hrs respectively. The difference observed in FC_3 and FD_3 is because increase in weight ratio of coat: core. Formulations FC_4 and FD_4 contain Eudragit RSPO: Klucel –HXF in weight ratio of 25:75. Increase in lag time and decrease in release rate of Diltiazem hydrochloride from the gellable barrier formed because high weight ratio of Klucel -HXF. Only 9.19 % and 1.05 % drug release observed with FC_4 and FD_4 respectively within 10 hrs. The difference observed in FC_4 and FD_4 is because increase in weight ratio of coat: core. Formulations FC_5 and FD_5 contain Eudragit

RSPO: Klucel -HXF weight ratio of 00:100. FC_5 and FD_5 have not shown drug release within 10 hrs periods of time. Highly delay in lag time may be because absences of Eudragit RSPO (responsible for penetration of dissolution medium) in coat. Observation showed that these tablets were swollen coating layer with almost dry core tablet.

Figure No. 3. Effect of permeable polymer (Eudragit RSPO) combined with gellable polymer (Klucel HF) in outer shell



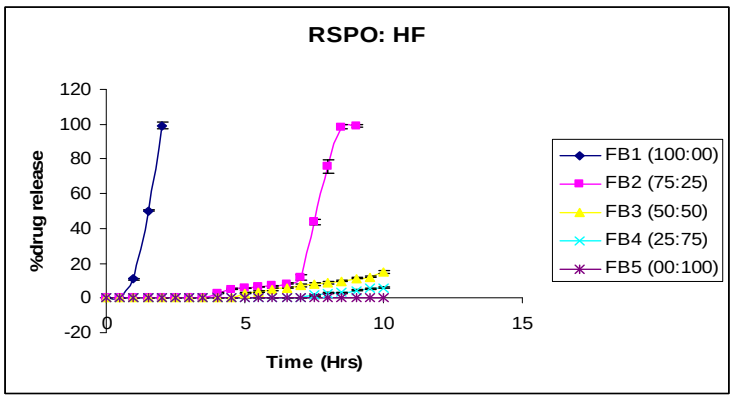


Figure No. 4. Effect of permeable polymer (Eudragit RSPO) combined with gellable polymer (Klucel HF) in outer shell (FB_1- FB_5)

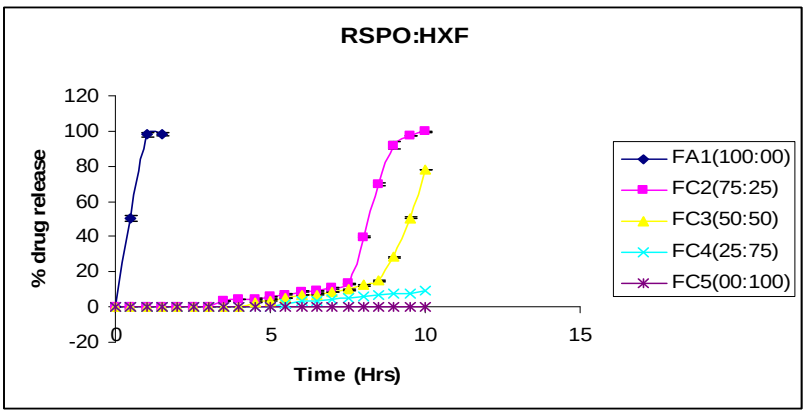


Figure No. 5. Effect of permeable polymer (Eudragit RSPO) combined with gellable polymer (Klucel HXF) in outer shell (FA_1- FC_5)

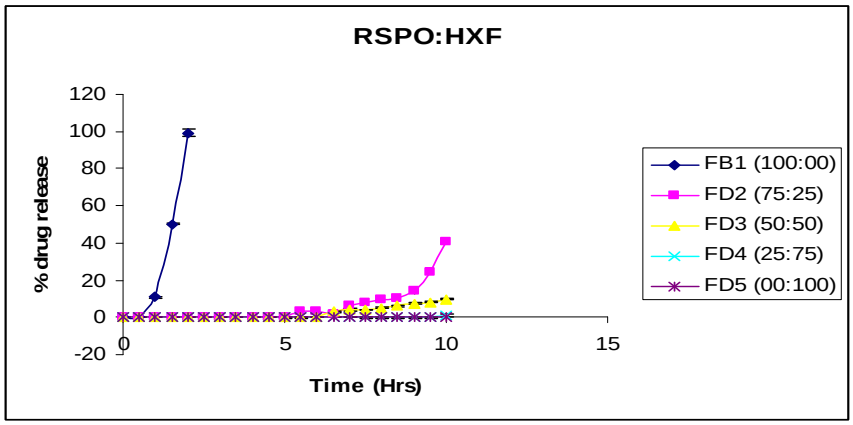


Figure No. 6. Effect of permeable polymer (Eudragit RSPO) combined with gellable polymer (Klucel HXF) in outer shell (FB_1- FD_5)

Effect of outer layer thickness on drug release from the press coated tablet

Increasing the amount of outer shell seemed to prolong lag time since the time required to complete the dissolution or erosion of the outer shell would be longer. The relationship between outer layer weight and lag time is shown in Figure No. 7. This suggested that the lag time could also be adjusted by the weight of coating layer.

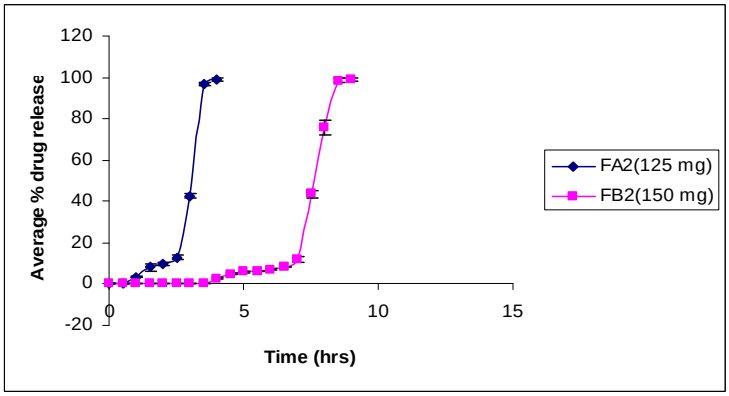


Figure No.7: Effect of outer layer thickness on drug release from the press coated tablet

Effect of particle size of gellable polymer on drug release from the press coated tablets

Decrease the particle size of Klucel seemed to prolong lag time since the time required to complete the dissolution or erosion of the outer shell would be longer. The relationship between different particle size Klucel and lag time is shown in Figure No. 8. Klucel HXF is finely ground as compare to Klucel HF. Formulations FA_2 and FC_2 contains combination of Klucel HF: Eudragit RSPO and Klucel HXF: Eudragit RSPO respectively in weight ratio of 25:75. FA_2 shows a lag time of 2.5 hrs and drug release last up to 4 hrs while FC_2 shows a lag time of 7 hrs and drug release last up to 10 hrs. Thus the decrease the particle size of Klucel, seemed to prolong the lag time because upon contact with dissolution medium it forms tight gel like structure than that of Klucel-HF.

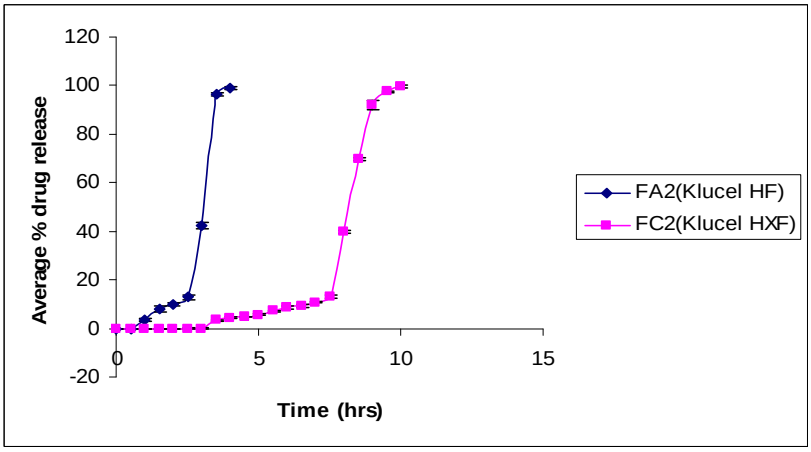


Figure No.8: Effect of particle size of gellable polymer on drug release from the press coated tablets

Water uptake study (% Swelling Index) of Press coated tablets

Klucel HF and Klucel HXF represent swellable and gellable type of polymers. When these polymers come in contact with water or gastrointestinal fluid, they absorb water and undergo hydration and swelling. The rapid formation of a viscous gel layer upon hydration of polymers has been regarded as an essential step in achieving controlled release of the drug from press coated tablet containing outer shell with combination of Klucel HF/Klucel HXF and Eudragit RSPO blend. It is the rate and extent of water absorption that decides the pattern of drug release from press coated tablets. Hence, study of water uptake kinetics of polymers plays a vital role in predicting and interpreting the drug release patterns from swellable press coated tablets.

Water uptake studied for gellable polymers as Klucel HF/Klucel HXF and combination of these polymers with permeable polymer as Eudragit RSPO in different ratios (00/100, 25/75, 50/50, 75/25, 100/00) showed that the plain gellable polymers such as Klucel HF/Klucel HXF have higher water uptake capacity as compared with the combination of these polymers with Eudragit RSPO. The plain permeable polymers such as Eudragit RSPO do not swell on contact with water or gastrointestinal fluid but permit water to penetrate through coating layer. When a plain Eudragit RSPO was used in the formulation (FA_1 & FB_1) burst release was observed, but as the concentration of gellable polymer increases the swelling takes place and because of which the lag time increases. At the highest concentration of gellable polymer swelling was found to be highest (show in formulation FA_5 & FB_5). As coat to core ratio increases, lag time increases may be because of increase in thickness of coating layer on core tablet.

The gellable polymer Klucel HF in combination with Eudragit RSPO indicated following trend for water uptake:

$FA_5 > FA_4 > FA_3 > FA_2 > FA_1$ (Figure No. 9)

$FB_5 > FB_4 > FB_3 >$ FB2 > FB1 (Figure No.10)

At the highest concentration of gellable polymer (in formulation FC_5 & FD_5), swelling was found to be highest. As coat to core ratio increases, lag time increases may be because of increase in thickness of coating layer. At the same time Klucel HXF was studied, the swelling was high and erosion was lesser because of which the lag time obtained for formulation

containing Klucel HXF is higher(in formulation FC_5 & FD_5), which may be because of smaller particle size of Klucel HXF.

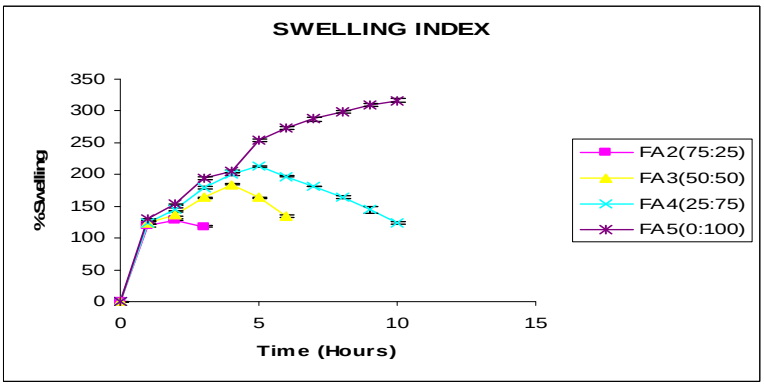


Figure No. 9.Water uptake study (%Swelling) of press coated tablets containing permeable polymer (Eudragit RSPO) combined with gellable polymer (Klucel HF) in outer shell (FA_1- FA_5)

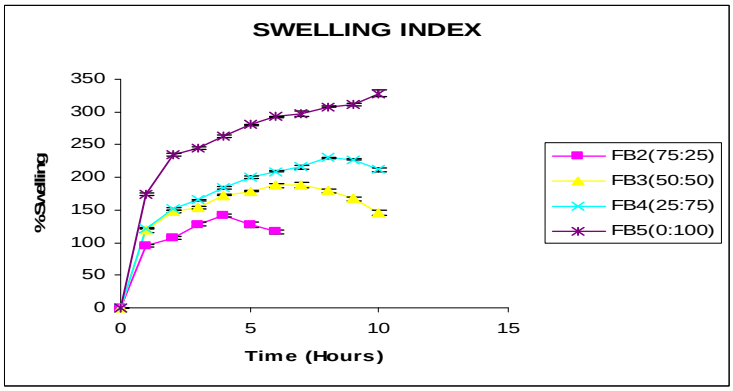


Figure No.10: Water uptake study (%Swelling) of press coated tablets containing permeable polymer (Eudragit RSPO) combined with gellable polymer (Klucel HF)in outer shell (FB_1- FB_5)

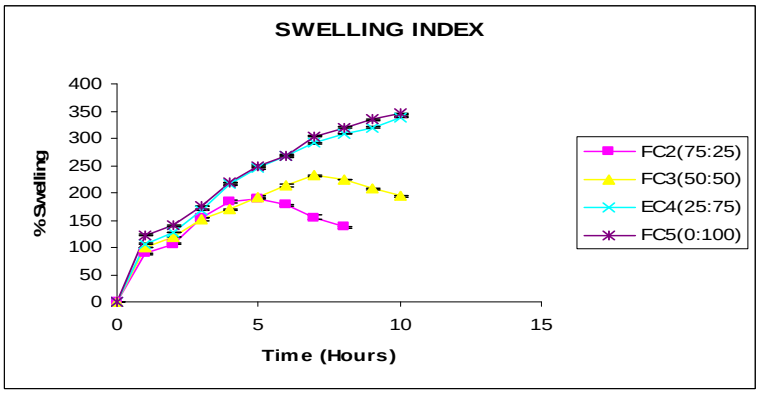


Figure No.11: Water uptake study (%Swelling) of press coated tablets containing permeable polymer (Eudragit RSPO) combined with gellable polymer (Klucel HXF) in outer shell (FA_1- FE_5)

The gellable polymer Klucel HXF in combination with Eudragit RSPO indicated following trend for water uptake:

$FC_5 > FC_4 > FC_3 > FC_2 > FA_1$ (Figure No. 11)

$FD_5 > FD_4 > FD_3 > FD_2 > FB_1$ (Figure No. 12)

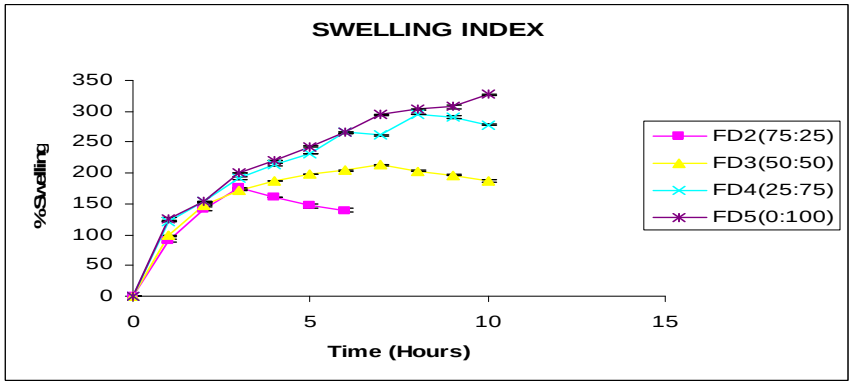
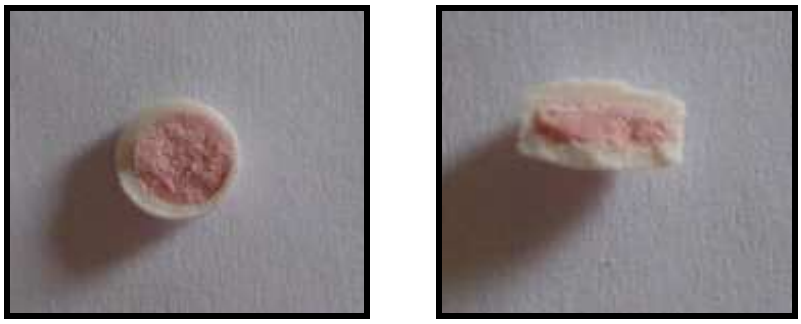


Figure No.12: Water uptake study (%Swelling) of press coated tablets containing permeable polymer (Eudragit RSPO) combined with gellable polymer (Klucel HXF) in outer shell (FB_1- FF_5)

Transverse and longitudinal section view of press coated tablets

Transverse and longitudinal sections of press coated tablets were made using surgical blade in order to verify the position of position of core tablet. Figure No. 13 shows the photographs of these sections. From this, it is clear that core tablet is placed in center of coated tablet.



Transverse section view **Longitudinal section view**

Figure No.13: Transverse and longitudinal section view of press coated tablets

CONCLUSIONS

The use of permeable polymer such as Eudragit RSPO along with gellable polymers such as Klucel HF and HXF in coat allows the production of 'timed-release' pharmaceutical dosage form. Press-coated tablets utilizing hydroxypropylcellulose (Klucel HF and HXF) in the outer shell displayed a timed-release function, i.e. a lag phase was observed in the dissolution profile and the drug was released rapidly after the complete erosion of shell when permeable polymer was used. The effect of amount of outer coating material (thickness of coating) was also investigated, increasing the amount of outer shell seemed to prolong lag time and the time required to complete the dissolution or erosion of the outer shell would be longer. Decrease the particle size of Klucel seemed to prolong lag time since the time required to complete the dissolution or erosion of the outer shell would be longer. Water uptake studies showed that the plain gellable polymers such as Klucel HF/Klucel HXF have higher water uptake capacity as compared with the combination of these polymers with Eudragit RSPO.150 mg compression coat of polymer blend Eudragit RSPO: Klucel HF (75:25) gave a

lag time of 7 hrs followed by complete release in 8.5 hrs. These formulation (FB3) can be considered for chronopharmaceutical delivery of Diltiazem hydrochloride.

Acknowledgements
The authors gratefully acknowledge Dr. P. D. Patil, Chairman, Dr. D. Y. Patil Vidya Pratishthan Society and Dr. A. D. Deshpande, Director of Pharmacy for providing excellent infrastructure facility to carryout this research work. Thanks also go to Dr. Reddy's Laboratories Ltd, Hyderabad for providing drug sample and Hercules Incorporated, Wilmington, USA, for kindly supplying Klucel samples.

REFERENCES

[1] P. Wal, A. Wal , A. K. Rai , A. Saxena, *Journal of Pharmaceutical Science and Technology*, **2009**,1, 2, 59-62.
[2] A.B. Rane, S.G. Gattani, V.D. Kadam , A.R. Tekade, *Chem. Pharm. Bull*, **2009**, 57, 11, 1213-1217
[3] S.S. Shidhaye, V.M. Lotlikar , P.K. Phuthane, V.J. Kadam, *Systematic Reviews in Pharmacy*, **2010**,1, 1, 55-61.
[4] L. Prisant, *Clinical Cornerstone*, **2004**, 6, 4, 7-15.
[5] L.M. Prisant, *The American Journal of Hypertension*, **2001**, 14, 277S–279S.
[6] V.S. Belgamwar, M.V. Gaikwad, G.B. Patil, S. Surana, *Asian Journal of Pharmaceutics*, **2008**, 141-145.
[7] A.K. Anal, Recent Patents on *Drug Delivery & Formulation*, **2007**, 1, 73-79.
[8] U. Conte, L. Maggi, M.L. Torre, P. Giunchedi, A.L. Manna, *Biomaterials*, **1993**, 14, 13,1017-1023.
[9] J. Cooper, C. Gunn, Powder flow and compaction In Carter SJ. Tutorial pharmacy, New Delhi India, CBS Publishers and Distributors, **1986**, 211-233.
[10] M.E. Aulton, T.I. Wells, Pharmaceutics: The science of dosage form Design, London, England, Churchill Livingstone, **1988**, 133-135.
[11] Indian Pharmacopoeia, New Delhi, Ministry of Health and Family Welfare, Government of India, Controller of Publications, Vol II, **2007**, 662-665.
[12] L. Lachman, H.A. Liberman, J,L. Kanig, The Theory and Practice of Industrial Pharmacy, 3rd edition, Mumbai, India, Varghese Publishing House, **1999**,297-299.
[13] D.N. Date, M. Pharm thesis, University of Pune (Pune, India, **2006**).