

FORMULATION AND *IN VITRO* EVALUATION OF CHRONOTHERAPEUTIC PRESS-COATED TABLETS OF VALSARTAN WITH CONTROLLED TIME -RELEASED POLYMERS**Dr. A. Bharathi* and D. Chandra Sekhar Naik**

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ABSTRACT

Chronotherapeutic press-coated tablets are basically time-controlled drug delivery systems in which the system controls the lag time and drug is released in an immediate or extended fashion. The current investigation was conducted to formulation and evaluation of chronotherapeutic press-coated tablets of valsartan for hypertension disease. The compression coated tablets consisted of a core tablet containing drug with natural ocimum gratissimum mucilage a novel superdisintegrant used, which was further press coated by controlled time released polymers such as HPMC E50, HPMC E15 in varying ratios. After carrying out preformulation studies, the developed tablets were evaluated for post-compression parameters like weight variation, thickness, hardness, friability, drug content and in-vitro drug release study. The best formulation was selected based on post-compression parameters and was subjected to accelerated stability studies for 3 month. Amongst 5 formulations prepared for coating tablets we are F2CC1 produced convincing results with a maximum cumulative drug release of 99.74% in 8 hr and Also the formulation didn't show any significant changes during 3 month period of stress testing. By virtue of its release pattern and delivering the drug at the right time, right place and in right amounts, the developed delivery system holds good promises of benefiting the patients suffering from hypertension.

KEYWORDS: Chronotherapeutic, press-coated, valsartan, mucilage, Gardenia Gummifera.**INTRODUCTION**

Oral controlled drug delivery system releases the drug with constant rate to maintain drug concentration in the human body, regardless of the patient physiological conditions. These dosage forms offer many advantages such as reduction in dose of the drug, prevention of peak-valley fluctuation, nearly constant drug levels at the site of action, reduced dosing frequency, promoting drug efficacy, and improved patient compliance.^[1] However, long-term constant drug concentrations in the human body can cause problems such as resistance, tolerability and drug side effects.^[2] and activation of the physiological system. People are different in their physiological and biochemical conditions due to the circadian rhythm during any 24 hr period, and as a result, the constant drug delivery into the body seems unnecessary and undesirable. However, there are certain diseases such as allergic rhinitis, cardiovascular diseases, asthma, cancer, peptic ulcers, rheumatoid arthritis, and osteoarthritis shows circadian rhythms in their pathophysiology. Hence, chronomodulated systems are gaining a lot of interest and attention these days as these systems deliver the drugs on specified time as per the pathophysiological need of the disease resulting in improved patient therapeutic efficacy and compliance.^[3]

Chronomodulated system is also known as pulsatile system or sigmoidal system. The pulsatile drug delivery system is a system that releases the drug at the fast or controlled rate with a programable lag time after administration. These systems are useful for the drugs having chronopharmacological behavior (where night time dosing is required), first pass effect and having specific site of absorption in gastrointestinal tract (GIT).

Compression coating or press coating technique is one of the simple and unique approaches of a chronotherapeutics drug delivery system which offers many advantages. Thick coating can be applied rapidly and no special coating solvent or coating equipment is required for manufacturing of the tablet.^[4] It has been used to protect hygroscopic, light sensitive, oxygen labile or acid labile drug,^[5] to combine and separate different therapeutic drugs,^[6] and to modify a drug release pattern (delayed pulsatile and programmable release of different drugs in one tablet).^[7] The outer polymer layer can erode or rupture or dissolve after a certain lag time, after which the drug is released from core tablet. The rupturing of the barrier is obtained by an expanding core on water penetration through the barrier coating such as swelling agents.^[8]

The objective of the current investigation is to design and evaluate valsartan press coated tablets so as to optimize the drug release after a certain lag time expecting an improvement in its bioavailability and to meet therapeutic needs relating to particular pathological conditions.

MATERIALS AND METHODS

Materials: Valsartan pure drug obtained from yarrow chemicals Mumbai. *Ocimum gratissimum* mucilage isolated, Mannitol was obtained from Yarrow chem. products, Mumbai. Microcrystalline cellulose was bought from Qualigens fine chemicals, Mumbai. Talc and magnesium stearate was obtained from Molychem, Mumbai.

Methods

Pre compression studies of rapid release core tablet blend Flowability of the pre compression blend of rapid release core tablet was evaluated by angle of repose, compressibility index (%Carr's index) and Hausner's ratio.^[18] and were calculated using the following formulae.

$$\text{LBD} = \frac{\text{Mass of powder}}{\text{Volume of packing}}$$

$$\text{TBD} = \frac{\text{Mass of powder}}{\text{Tapped volume of packing}}$$

$$\% \text{ Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra of mucilage were recorded on samples prepared in potassium bromide (KBr) disks using a, (Tokyo, Japan). The scanning range was 500 to 4000 Cm^{-1} Samples were mixed with (KBr) to form disks by means of a hydrostatic press at 6-8 tons pressure.^[8]

Differential scanning calorimetry (DSC) DSC thermograms of valsartan and their mixtures with *Ocimum gratissimum* were recorded on Perkin Elmer thermal analyser samples (2-5 mg) were sealed into aluminum pans and scanned at a heating rate of 10 $^{\circ}\text{C min}^{-1}$ over a temperature range 30–350 $^{\circ}\text{C}$.^[8]

Friability The friability of tablets was measured using a Roche friabilator. Tablets were rotated at 25 rpm for 4 min or up to 100 revolutions. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.^[10]

Preparation of rapid release core tablets

The tablets were prepared by direct compression method employing superdisintegrants i.e., *Ocimum gratissimum*. The composition of the different formulation of valsartan fast dissolving tablets is shown in table no 1 in which the levels of superdisintegrants were selected at 2 levels i.e., lower and higher level concentrations. For *Ocimum gratissimum* (A), the lower level i.e., 10% concentration and upper level i.e. 10% concentration. For sodium starch glycolate (B) and croscarmellose sodium(C), the lower level is zero concentration and higher level i.e., 10% concentration. For uniformity in particle size, each ingredient was passed through # 100 mesh sized screen before mixing. *Ocimum gratissimum*, sodium starch glycolate, croscarmellose sodium, mannitol and microcrystalline cellulose were accurately weighed and mixed using mortar and pestle, and the added to valsartan. Finally, talc and magnesium stearate were added to the powder mixture. Finally, the mixed blend was compressed by using eight station rotator press Karnawathi Machinerics Pvt, Ltd., Ahmedabad, India). The press coating selected for the optimized formula of F2.

Table 1: Formulae of Valsartan fast dissolving tablets employing *Ocimum gratissimum* mucilage.

Ingredient(Mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Valsartan	40	40	40	40	40	40	40	40
<i>Ocimum gratissimum</i>	---	20	---	20	---	20	---	20
SSG	---	---	20	20	---	---	20	20
CCS	---	---	---	---	20	20	20	20
Mannitol	30	20	20	10	20	10	10	---
MCC	112	112	112	102	112	102	102	92
Talc	4	4	4	4	4	4	4	4
Magnesium Stearate	4	4	4	4	4	4	4	4
Total weight	200	200	200	200	200	200	200	200

Table 2: Preparation of chronotherapeutic press-coating optimized formulae.

Formula code	HPMC E50 (mg)	HPMC E15 (mg)
F2CC1	200	----
F2CC2	150	50
F2CC3	100	100
F2CC4	50	150
F2CC5	-----	200

Drug content uniformity For content uniformity, ten tablets were weighed and powdered a quantity of powder equivalent to 10 mg of valsartan was extracted into pH 1.2 HCl buffer and filtered. The Valsartan content was determined by measuring the absorbance spectrophotometrically at 212 nm after appropriate dilution with pH 1.2 HCl buffer. The drug content was calculated as an average of three determinations.^[10]

Wetting time The wetting time of tablets was measured by placing five circular tissue papers in a petri dish of 10 cm in diameter. 10 ml of water containing a water-soluble dye (amaranth) was added to the petri dish. A tablet was carefully placed on the tissue paper. The time required for water to reach the upper surface of the tablet was noted as wetting time.^[11,12]

Water absorption ratio A piece of tissue paper folded was kept in a small petri dish to which 6 ml of water was added. A tablet was kept on the tissue paper and allowed to completely wet. The wetted tablet was then weighed. Water absorption ratio R was determined using the following equation.^[11,12]

***In-vitro* disintegration time**

Disintegration time for tablets was determined using USP disintegration apparatus 0.1 N HCl buffer. The volume of medium was 900 ml and the temperature was 37 ± 0.2 °C. The time taken for complete disintegration of the tablet was measured.^[13]

***In-vitro* dissolution studies**

In vitro dissolution study was performed by using type II apparatus (paddle method) at a speed of 50 rpm at 37 ± 0.5 °C using 0.1 N HCl for 2 hrs initially and replaced with 6.8 pH phosphate buffer. Sample was withdrawn at regular intervals and analyzed spectrophotometrically at 205 nm using UV visible spectrophotometer. (Shimadzu 1800, Japan).

Stability Studies: The objective of stability testing is to check the quality of drug product varies with time under the influence of environmental factors such as temperature, humidity and light. The accelerated stability study was carried out as per the ICH guidelines for 3 month for optimized formulation. The sample were packed in an aluminium foil placed in a tightly closed high density polyethylene bottle and kept at 40 ± 2 °C and relative humidity at $75 \pm 5\%$. Samples were taken at regular time interval of 1 month for a period of 3 months and analyzed. Any changes in evaluation parameters, if observed were noted. Test were carried out in triplicate and mean value was noted with standard deviation.

RESULT AND DISCUSSION

Calibration curve

Standard calibration curve of valsartan was carried out in phosphate buffer of pH 6.8. The curve shown linearity which was indicated in Fig. 1.

FT-IR Studies: FT-IR spectrum of pure drug shows characteristic absorption peaks and found that there were no interactions of drug with excipients and polymers. Hence it indicate no change in chemical integrity of the drug. FT-IR spectrums were shown in Fig. 2.

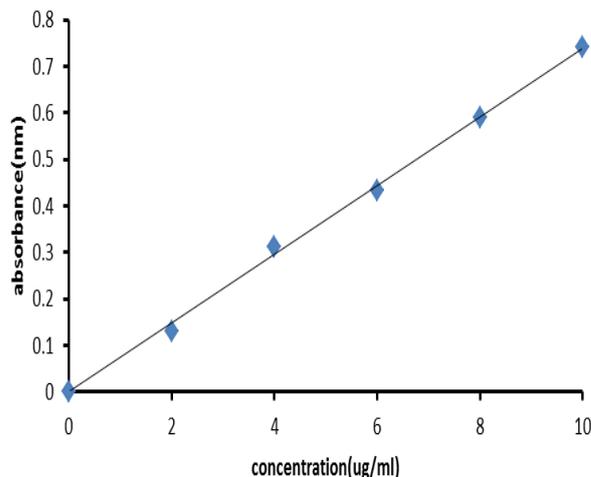


Fig. 1: Calibration curve of valsartan.

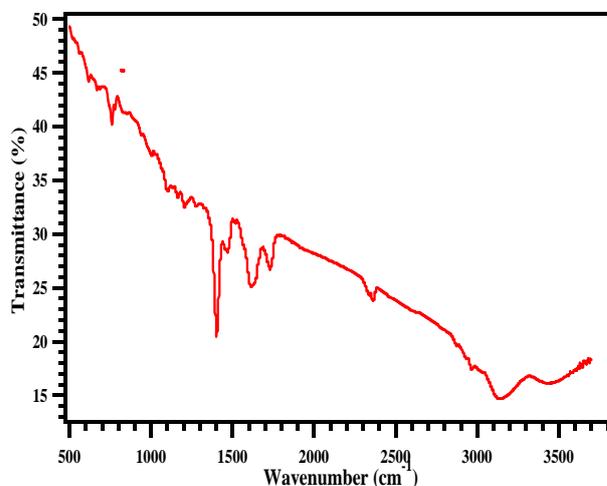


Fig. 2: FTIR graph for valsartan.

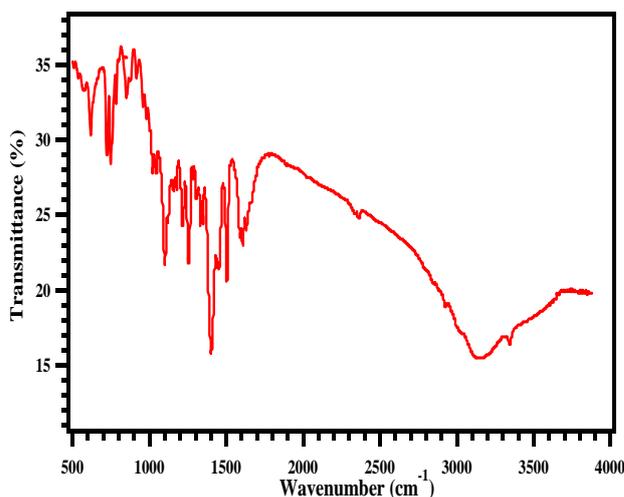


Fig. 3: FTIR for pure mucilage.

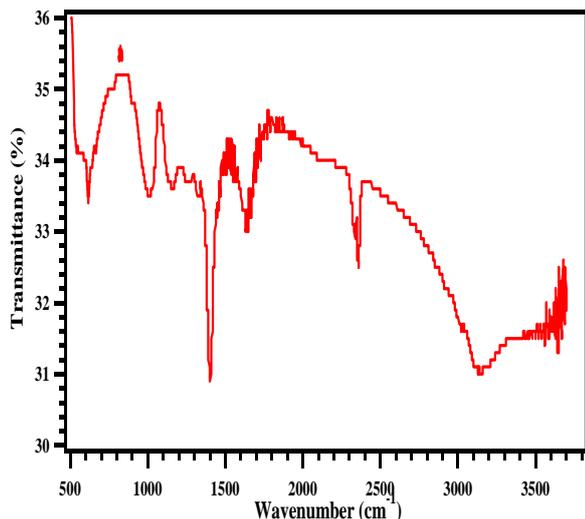


Fig. 4: FTIR graph for valsartan and mucilage.

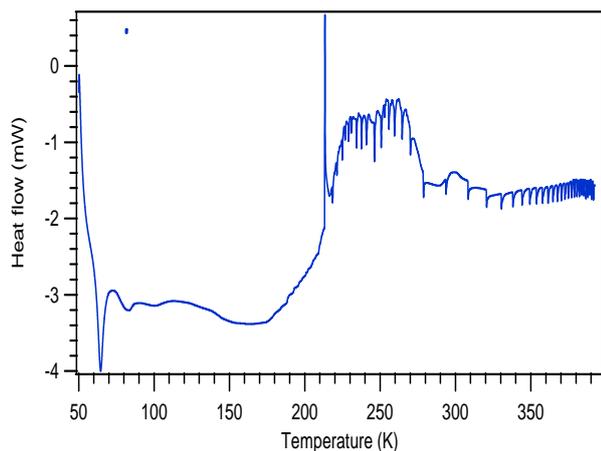


Fig. 5: DSC thermo gram of valsartan pure drug.

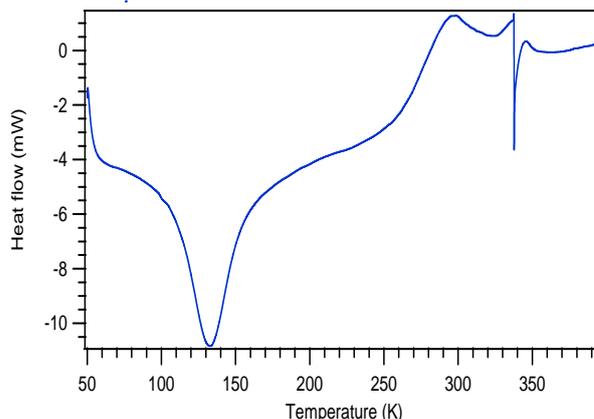


Fig. 6: DSC thermo gram of mucilage pure drug.

In order to check the quality control standards, various tests such as weight variation, hardness and friability, disintegration, thickness, dissolution and content uniformity were performed. The weight variation of all core and coated tablets passed the test indicating average percentage weight variation was found within the pharmacopoeia limits. Hardness of core tablets was found in the range of 3.4 to 3.7 kg/cm² and for coated tablets 9.9 to 9.3kg/cm². Friability values for core and coated tablets were found to be 0.99 to 0.56 and for coated tablets 0.92 to 0.29 respectively. The drug content for core tablets was found in the range of 41 ± 0.37 to 38 ± 0.55 and for coated tablets as 99.34 ± 0.52 to 99.73 ± 0.68 respectively.

Table 3: Post Compression Parameters of core Tablets.

Formulation code	Hardness (kg/cm ²)	% Friability	Disintegration time (sec) mean	Wetting time (Sec) mean	Water Absorption ratio (%)	Uniformity of content mean
F1	3.4±0.003	0.8±0.067	239±0.10	171±0.84	104.06±0.73	40±0.37
F2	3.7±0.05	0.6±0.72	57±0.83	81±0.69	322.1±0.81	41±0.82
F3	3.5±0.07	0.99±0.35	53±0.35	43±0.68	116.16±0.93	40±0.91
F4	3.4±0.09	0.56±0.79	51±0.84	72±0.23	305±0.75	38±0.55
F5	3.6±0.03	0.79±0.78	62±0.84	119±0.15	175.3±0.78	40±0.46
F6	3.4±0.31	0.46±0.38	62±0.72	110±0.37	323.4±0.37	41±0.37
F7	3.5±0.032	0.67±0.71	60±0.46	40±0.39	109.13±0.52	39±0.28
F8	3.3±0.015	0.61±0.39	47±0.83	53±0.47	383.8±0.14	41±0.14

Table 4: Post Compression Parameters of coated Tablets.

Batch code	Weight variation	Hardness (Kg/cm ²)	Friability (%)	Thickness (mm)	Wetting time (Sec) mean	Water Absorption ratio (%)
F2CC1	399±0.34	9.2±0.84	0.29±0.73	4.37±0.93	83±0.11	723±0.76
F2CC2	401±0.73	9.8±0.92	0.72±0.51	4.12±0.46	177±0.28	545±0.96
F2CC3	398±0.83	9.5±0.46	0.92±0.33	4.83±0.62	201±0.48	550±0.26
F2CC4	400±0.14	9.3±0.74	0.42±0.90	4.19±0.63	179±0.76	596±0.93
F2CC5	401±0.83	9.9±0.21	0.84±0.41	4.36±0.37	179±0.15	642±0.46

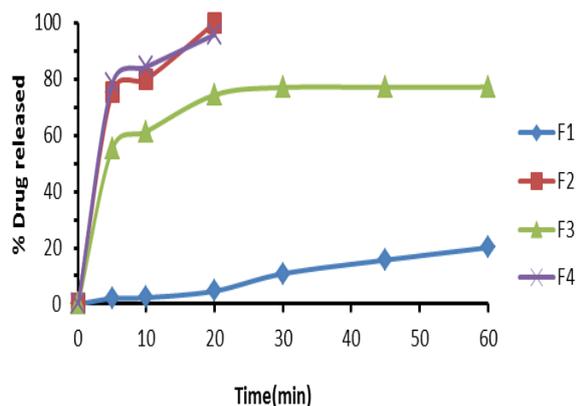


Fig 7: Dissolution profiles of valsartan fast dissolving tablets prepared employing occimum gratissimum mucilage involving mannitol as a diluents (F1-F4) (n=3, mean±SD).

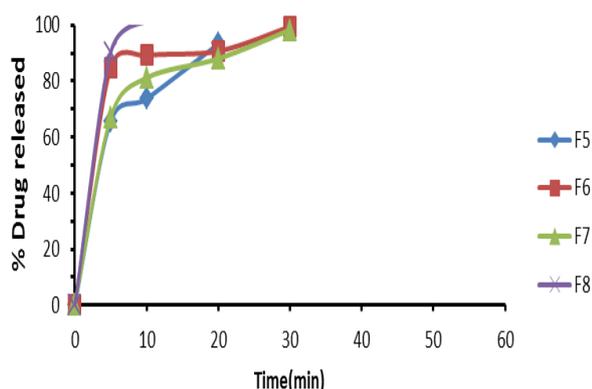


Fig 8: Dissolution profiles of valsartan fast dissolving tablets prepared employing occimum gratissimum mucilage involving mannitol as a diluents (F5-F9) (n=3, mean±SD).

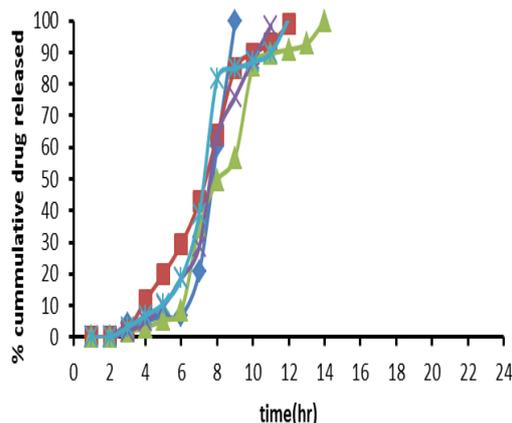


Fig. 9: Dissolution data graph for press coated tablets.

In vitro drug dissolution studies were carried out both for core and coated tablets using USP type II apparatus (paddle method). Based on the drug release study, F2 was selected as optimized batch for press coating as it has very less disintegration time and maximum released data within a less time. Batches of coating tablets F2CC1 to F2CC5 shown minimum average i.e 6 hours to 12 hr lag time and complete drug was released in 12 hours, where the F2CC3 was equal ratios of t time released time released polymer very lag time compared to other formulations. Where as F2CC1 shown complete drug release were found to be within 9 hours. The drug release patterns were observed with different combinations as shown in (Fig.7-9).

Table 5: Accelerated Stability Study Of Optimized Batch F2CC1.

Parameters	Initial	After 1 month	After 2 month	After 3 month
Appearance	White	No change	No change	No change
Hardness	9.5	9.4	9.5	9.4
Drug content	99.67	98.53	99.35	99.05

Table 6: Dissolution Kinetics Models.

Batch code	Zero order (R2)	First order (R2)	Higuchi (R2)	Hixson (R2)	Korsmeyer-Peppas (R2)
F2CC1	0.917	0.037	0.698	0.032	0.935
F2CC2	0.948	0.032	0.756	0.025	0.956
F2CC3	0.976	0.025	0.815	0.018	0.975
F2CC4	0.889	0.039	0.657	0.036	0.890
F2CC5	0.933	0.035	0.721	0.030	0.944

The data obtained from *in-vitro* release studies of all batches were fitted into various kinetics models such as zero order, first order, Higuchi model, Hixson model and Korsmeyer-Peppas model to find out the release mechanisms of drug release from chronotherapeutics tablets. Regression coefficient values R2 were shown in

Table 6. Results shown that formulation batch follows zero order kinetics which was found to be more than all models value indicated that drug concentration was independent on time.

CONCLUSION

The basic objective of developing chronotherapeutics tablets of valsartan was to prevent the cardiovascular complications such as early rise in blood pressure followed by heart failure. For achieving this goal, chronotherapeutics drug delivery was formulated containing inner immediate release tablet and outer coating with combinations of time released polymers (gums). HPMC E50 was selected because of its good swelling and rupturable behaviour. Optimized batch was selected as F2CC1 as having highest lag time of 8 - 12 hrs and released 99.67% of drug after 9 hr. It was observed that time released polymers as well as synthetic polymer action. Optimized batch F2CC1 checked for its stability and found to be successful.

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