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FORMULATION AND EVALUATION OF VALSARTAN SUSTAINED RELEASE COMPRESSION COATED TABLETS

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ABSTRACT

The present investigation was aimed to prepare Valsartan sustained release tablets compression coated using different concentrations of HPMC K4M, K15M, Ethyl cellulose and combination of Ethyl cellulose and HPMC K15M. The prepared Valsartan sustained release compression coated granules were subjected to pre-compression properties to comply with pharmacopoeial limits and the prepared tablets were characterized for weight variation, hardness, thickness, friability drug content, swelling studies and invitro dissolution studies. The *in vitro* drug release study F14 was the most successful formulation which includes both HPMC K15M and Ethyl cellulose, extended the drug release up to 12 h and exhibited satisfactory drug release in the initial hours. Mechanism of drug release was estimated by using different kinetic models like zero order, first order, Peppas and Higuchi's. The drug release from optimized formulation (F14) followed first-order kinetics via non-fickian (anomalous) diffusion.

KEYWORDS

BP = British Pharmacopoeia
Conc. = Concentration
cps = Centipoises
CC = Compression coated
CRDDS = Controlled Release Drug Delivery System
°C = Degree Centigrade
EC = Ethylcellulose
FTIR = Fourier Transform Infrared Spectroscopy

GIT = Gastrointestinal tract
HPMC = Hydroxypropylmethylcellulose
IP = Indian Pharmacopoeia
ISA = Intrinsic sympathomimetic activity
LD = Lethal Dose
LR = Laboratory Reagent
MCC = Microcrystalline cellulose
mcg = Microgram
MDT = Mean dissolution time
MEC = Minimum Effective Concentration
mPa s = Milli Pascal Second
MS = Magnesium Stearate
MSC = Maximum Safe Concentration
n = Diffusion coefficient
N = Normality
nm = Nanometer
RH = Relative Humidity
rpm = Revolutions per minute
SD = Standard Deviation
SR = Sustained-Release
USP = United States Pharmacopoeia
UV = Ultraviolet
w/w = Weight by weight
μm = Micrometer

INTRODUCTION

The majority of conventional oral dosage forms like tablets and capsules are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Finally, plasma drug concentrations fall below the minimum effective plasma concentration, resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An

alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms. In recent years, various modified-release drug products have been developed to control the release rate of the drug and/or the time for drug release. The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized". Several types of modified-release drug products are recognized (Leon Shargel et al., 2004).

Extended-release drug products: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.

Delayed-release drug products: A dosage form that releases a discrete portion or portions of drug at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

Targeted-release drug products: A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

The term controlled-release drug product was previously used to describe various types of oral extended-release-rate dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery.

Conventional Drug Delivery System

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid/immediate absorption (Robinson, 1987). As can be seen in the graph (Figure 1), administration of the conventional dosage form by extra vascular route does not maintain the drug level in blood for an extended

period of time. The short duration of action is due to the inability of conventional dosage form to control temporal delivery.

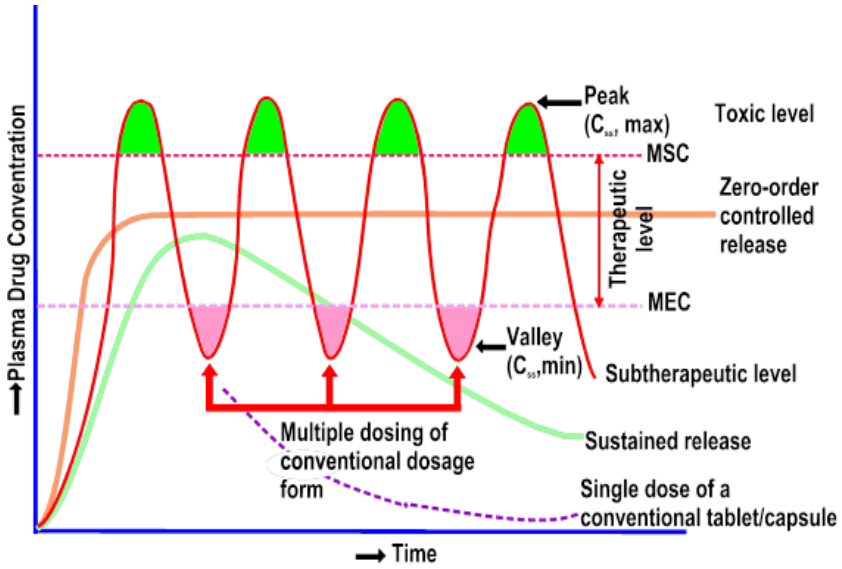

Figure 1: A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

The conventional dosage forms like solution; suspension, capsule, tablets and suppository etc. have some limitations such as

1) Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance.
2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the steady state concentration values fall or rise beyond the therapeutic range.
3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits (Chien, 1992).

Controlled/Sustained Release Drug Delivery Systems

More precisely, Sustained delivery can be defined as

1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.

Advantages of Sustained release Dosage Forms

1. Overcome patient compliance problems.
2. Employ less total drug

a) Minimize or eliminate local side effects.
b) Minimize or eliminate systemic side effects.
c) Obtain less potentiation or reduction in drug activity with chronic use.
d) Minimize drug accumulation with chronic dosing.

3. Improve efficiency in treatment

a) Cures or controls condition more promptly.
b) Improves control of condition i.e., reduced fluctuation in drug level.
c) Improves bioavailability of some drugs.
d) Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.

Disadvantages of Sustained release Dosage Forms

1) Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
2) Poor in vitro – in vivo correlation.
3) Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions

Oral Controlled Drug Delivery Systems

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the

course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action (Vora et al., 1996).

Classification of Oral Controlled/ Sustained Release Systems

A) Diffusion Controlled Systems

I. Reservoir Devices: A core of drug (the reservoir) surrounded by a polymeric membrane characterizes them. The nature of the membrane determines the rate of drug release. The characteristics of reservoir diffusion systems are

1. Zero order drug release is possible.
2. The drug release rate is dependent on the type of polymer.
3. High molecular weight compounds are difficult to deliver through the device. Coating and microencapsulation technique can be used to prepare sub devices.

II. Matrix Devices: It consists of drug dispersed homogeneously in a matrix. The characteristics of the matrix diffusion system is

1. Zero order release cannot be obtained.
2. Easy to produce than reservoir devices.
3. High molecule weight compounds are delivered through the devices.

B) Dissolution controlled systems

I. Matrix Dissolution Controlled System: Aqueous dispersions, congealing, spherical agglomeration etc. can be used.

II. Encapsulation Dissolution Control: Particles, seeds or granules can be coated by technique such as microencapsulation.

C) Diffusion and Dissolution Controlled System: In a bioerodible matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism or by hydrolysis or by enzymatic attack.

Table 3: Classification of Matrix Systems.

Type of the Matrix System	Mechanism
Hydrophilic Matrices	- Unlimited swelling delivery by diffusion - Limited swelling controlled delivery eg: Hydroxyethyl cellulose, Hydroxypropyl methylcellulose
Inert Matrices	- Inert in nature - Controlled delivery by diffusion eg: Ethylcellulose
Lipidic martices	- Delivery by diffusion & erosion eg: Carnauba wax.
Biodegradable Matrices	- Non lipidic nature - Controlled delivery by surface erosion
Resin Matrices	- Drug release from drug-resin complex eg: Ion exchange resins

Mechanism of Drug Release from Matrix Tablets

As shown in Figure 2, in erodible matrices, polymer erosion from the surface of the matrix determines the drug release; whilst in hydrophilic matrices, formation of the gel layer and its dynamics as a function of time determines the drug release. Gel layer thickness, which determines the diffusion path length of the drug, corresponds to the distance between the diffusion and erosion fronts. As the swelling process proceeds, the gel layer gradually becomes thicker, resulting in progressively slower drug-release rates; however, due to continuous hydration, polymer disentanglement occurs from the surface of the matrix, resulting in a gradually decreasing depletion zone and an increased dissolution rate.

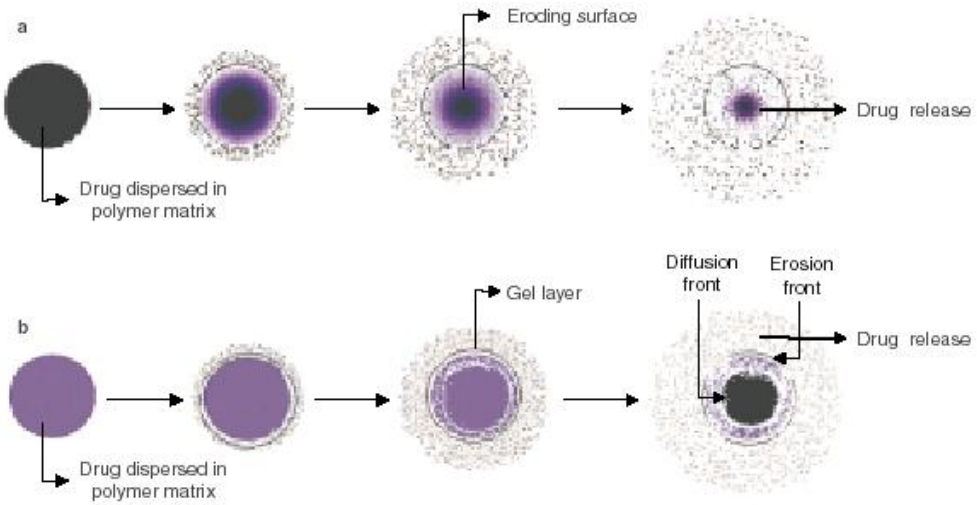

Figure 2: Schematic drug release from matrix diffusion controlled-release drug delivery systems with the drug homogenously dispersed in: (a) an erodible polymer matrix; and (b) a hydrophilic, swellable polymer matrix.

Compression coating method

Compression coating method involves the compression of coating materials around a preformed core tablet using conventional or specially designed tablet compression machine and it doesn't require use of any special solvent for coating purpose. Hence it is also known as press coating or solvent-less coating technique or dry coating technique. By composition, compression coated tablet has two parts: internal core and surrounding coat. The core tablet is small porous tablet and prepared on one turret and to prepare compression coating of core tablet, another turret with a bigger die cavity is used. Compression coated tablets are prepared by putting half of the quantity of the coating material in the die cavity, then the core tablet is carefully placed in the centre of the die cavity and finally it is filled with the other half of the coating material to surround the core tablet and compress the powder, which has the core tablet inside. Getting a reproducible central positioning of the core tablet within compression coated tablet is the major limitation for this method (Vemula, 2016).

Advantages of compression coating

- Compression coating is considered as the absolute dry coating without use of solvent and heat.
- Compression coating has no limitation for the cores and overcomes the adhesion problem found in spraying methods.
- This method eliminates the time-consuming and complicated solvent coating and also improves the stability of the drug by protecting it from moisture.
- This method has many advantages because no special coating solvent or coating equipment are needed for coating of tablet and manufacturing speed is faster.

Limitations of compression coating

- Compression coating involves the multistep processes and multiple compressions.
- Reproducible central positioning of the core tablet within compression coating is a major challenge for large scale industrial manufacturing.
- In some cases, difficulties in achieving good friability values after compression coating of immediate release powder onto controlled release tablet.
- Material should possess the ability to flow into a die during production.

Drug Release Kinetics -Model Fitting of the Dissolution Data

Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner. The pharmaceutical industry and the registration authorities do focus, nowadays, on drug dissolution studies. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q=f(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Hixson–Crowell, Higuchi, Korsmeyer–Peppas models. (Mulye and Turco, 1995; Colombo et al., 1999; Kim et al., 1997; Manthena et al., 2004; Desai et al., 1996; Higuchi et al., 1963).Different models expressing drug release kinetics were given in Table 4

Zero order kinetics

$$Q_1 = Q_0 + K_0 t$$

Where Q_1 is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0=0$) and K_0 is the zero order release constant.

$$f_t = K_0 t$$

Where $f_t = 1-(W_t/W_0)$ and f_t represents the fraction of drug dissolved in time t and K_0 the apparent dissolution rate constant or zero order release constant. In this way, a graphic of the drug-dissolved fraction versus time will be linear if the previously established conditions were fulfilled.

Use: This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs, coated forms, osmotic systems, etc. The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

First order kinetics

Kinetic equation for the first order release is as follows

$$\text{Log } Q_t = \log Q_0 + K_1 t/2.303$$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and K_1 is the first order release constant. In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs

in porous matrices, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model

$$f_t = K_H t^{1/2}$$

Where K_H is the Higuchi dissolution constant treated sometimes in a different manner by different authors and theories. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water-soluble drugs.

Hixson-Crowell model

Hixson and Crowell (1931) recognizing that the particle regular area is proportional to the cubic root of its volume derived an equation that can be described in the following manner

$$W_0^{1/3} - W_t^{1/3} = K_s t$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and K_s is a constant incorporating the surface–volume relation. This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time. A graphic of the cubic root of the unreleased fraction of drug versus time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the pharmaceutical dosage form diminishes proportionally over time. This model has been used to describe the release profile keeping in mind the diminishing surface of the drug particles during the dissolution.

Mechanism of Drug Release

To find out the drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix, first 60% drug release data can be fitted in Korsmeyer–Peppas model which is often used to describe the drug release behavior from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved (Korsmeyer et al., 1983).

$$\text{Log}\ (M_t / M_\infty) = \text{Log}\ K_{KP} + n\ \text{Log}\ t$$

Where, M_t is the amount of drug release at time t, M_∞ is the amount of drug release after infinite time; K_{KP} is a release rate constant incorporating structural and geometrical characteristics of the tablet, and n is the release exponent indicative of the mechanism of drug release.

Table 4: Drug Release Kinetics.

Kinetic Model	Relation	Systems Following the Model
First order	$\ln Q_t = \ln Q_o + K_t$ (release is proportional to amount of drug remaining)	Water-soluble drugs in porous matrix
Zero order	$f_t = K_o t$ (independent of drug concentration)	Transdermal systems Osmotic systems
Higuchi	$f_t = K_H t^{1/2}$ (proportional to square root of time)	Matrix formulations
Hixson-Crowell	$W_o^{1/3} - W_t^{1/3} = K_s t$	Erodible isometric matrices
f_t = fraction of dose release at time 't'; **K_H, K_o, and K_s =** release rate constants characteristic to respective models; **Q_o** = the drug amounts remaining to be released at zero hour; **Q_t** = the drug amounts remaining to be released at time 't'; **W_o** = initial amount of drug present in the matrix; **W_t** = amount of drug released at time't'.		

List of Materials

S. No	Materials	Manufacturer
1	Valsartan	MSN Laboratories, Hyderabad, India.
2	Hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M)	MSN Laboratories, Hyderabad, India.
3	Ethyl cellulose	MSN Laboratories, Hyderabad, India.
4	Avicel PH 102	Qualikems Fine chem (P) Ltd, Delhi, India.
5	Magnesium Stearate	Qualikems Fine chem (P) Ltd, Delhi, India.
6	Talc	Qualikems Fine chem (P) Ltd, Delhi, India.

List of Instruments

S. No	Instruments	Manufacturer
1	Analytical weighing balance	Shimadzu corporation, Japan.
2	8-Station tablet punching machine	Riddhi, Mumbai, India
3	USP Disintegration apparatus	Electrolab, ED-2L, Mumbai, India.
4	Dissolution test apparatus-II USP	Electrolab,TDT-06T, Mumbai, India.
5	Hardness tester	Cyber lab, India.
6	Friability tester	Sisco, India.
7	UV-Visible spectrophotometer	Shimadzu corporation, Japan.

METHODOLOGY

Preparation of pH 6.8 phosphate buffer: Accurately measured 50 ml of 0.2 M potassium dihydrogen orthophosphate was transferred to a 200mL volumetric flask and 22.4 ml of 0.2 M sodium hydroxide was added to it. Volume was made up to 200 ml with distilled water, mixed and pH was adjusted to 6.8 with 0.2 M sodium hydroxide.

Preparation of 0.2 M potassium dihydrogen phosphate solution: Accurately weighed 27.218 g of monobasic potassium dihydrogen phosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 ml of distilled water and mixed.

Construction of Standard Graph

Accurately weighed amount of 100 mg valsartan was transferred into a 100ml volumetric flask. 20 ml of phosphate buffer pH 6.8 was added to dissolve the drug and volume was made up to 100 ml with the same. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'. From this stock solution 10ml was taken and diluted to 100 ml with phosphate buffer pH 6.8 which has given the solution having the concentration of 100 mcg/ml. Necessary dilutions were made by using this second solution to give the different concentrations of valsartan (4, 8, 12, 16 and 20 mcg/ml) solutions. The absorbances of above solutions were recorded at λ_{max} 262 nm) of the drug using double beam UV-Visible spectrophotometer.

Preparation of Valsartan core tablets

Each core tablet consisted of valsartan, microcrystalline cellulose, talc and magnesium stearate. The materials were weighed, mixed and passed through mesh 60 to ensure complete mixing. Then the uniform powder blend was compressed into tablets using 6 mm round, flat and plain punches on a multi-station tablet machine.

Table 5: Composition of Valsartan core tablet.

Ingredients	Quantity (mg)
Valsartan	20
Avicel PH102	77
Talc	2
Magnesium stearate	1
Total Weight	100

Compression coating of Valsartan core tablets

The core tablets were compression coated with different quantities of coating material containing of different weights of polymers [hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M), ethyl cellulose (EC)]. Microcrystalline cellulose (Avicel PH102) was included in the coat formulations to impart enough hardness, and to make up the weight to 200 mg. Half the quantity of the coating material was placed in the die cavity; the core tablet was carefully placed in the centre of the die cavity and was filled with the other half of the coating material. The coating material was compressed using 10 mm round, flat and plain punches.

Table 6: Composition of Compression coated Tablets Containing HPMC K4M & K15M.

Formulation	Core tablet (mg)	HPMC K4M (mg)	HPMC K15M (mg)	Avicel PH 102 (mg)	Magnesium Stearate (mg)	Talc (mg)	Total (mg)
F1	100	20	-	125	2.5	2.5	250
F2	100	40	-	105	2.5	2.5	250
F3	100	60	-	85	2.5	2.5	250
F4	100	80	-	65	2.5	2.5	250
F5	100	-	20	125	2.5	2.5	250
F6	100	-	40	105	2.5	2.5	250
F7	100	-	60	85	2.5	2.5	250
F8	100	-	80	65	2.5	2.5	250

Table 7: Composition of Compression coated Tablets Containing Ethyl cellulose.

Formulation	Core tablet (mg)	Ethyl Cellulose (mg)	Avicel PH 102 (mg)	Magnesium Stearate (mg)	Talc (mg)	Total (mg)
F9	100	20	125	2.5	2.5	250
F10	100	40	105	2.5	2.5	250
F11	100	60	85	2.5	2.5	250
F12	100	80	65	2.5	2.5	250

Table 8: Composition of Compression coated Tablets Containing Combination of HPMC K15M and Ethyl Cellulose.

Formulation	Core tablet (mg)	HPMC K15M (mg)	Ethyl Cellulose (mg)	Avicel PH 102 (mg)	Magnesium Stearate (mg)	Talc (mg)	Total (mg)
F13	100	30	10	105	2.5	2.5	250
F14	100	20	20	105	2.5	2.5	250
F15	100	10	30	105	2.5	2.5	250

Evaluation of Precompression Blend

a) Angle of Repose

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 (Raghuram et al., 2003).

$$\text{Tan } \theta = h/r$$

Where h and r are the height and radius of the powder cone, θ is the angle of repose. Angle of repose values less than 25, 25-30, 30-40, and more than 40 indicates excellent, good, passable, and poor flow properties respectively.

b) Determination of Bulk Density and Tapped Density

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal (Lachman et al., 1987). The bulk density and the tapped density were calculated using the following formulae.

$$\textbf{Bulk density} = W/V_0$$

$$\textbf{Tapped density} = W/V_f$$

Where, W= Weight of the powder; V_0 = Initial volume; V_f = final volume

c) Compressibility Index (Carr's Index)

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is (Lachman et al., 1987).

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

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

Table 9: Carr's Index Values.

S. No	Carr's Index	Properties
1	5-12	Free flowing
2	13-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

d) Hausner's Ratio

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties (Lachman et al., 1987). Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

Evaluation of Compression coated Tablets

i) Weight Variation Test: To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

$$\% \text{ weight variation} = (W_A - W_I) \times 100 / W_A$$

As the total tablet weight was 120 mg, according to IP 1996, out of twenty tablets ±7.5% variation can be allowed for not more than two tablets. ccording to USP 2004, ±10% weight variation can be allowed for not more than two tablets out of twenty tablets.

ii) Thickness: Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper. Average thickness and standard deviation values were calculated.

iii) Hardness: Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

iv) Friability Test: From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss. Note: No tablet should stick to the walls of the apparatus. If so, brush the walls with talcum powder. There should be no capping also. % friability was calculated as follows

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

Where W_1 = Initial weight. W_2 = Final weight after testing.

v) Drug Content: The drug content of the compression coated tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 90% to 110% of the standard amount. Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 100 mg of valsartan was transferred to a 100 ml volumetric flask containing phosphate buffer pH 6.8. It was shaken by mechanical means for 1h.Then it was filtered through a Whatman filter paper and diluted to 100 ml with phosphate buffer pH 6.8. From this resulted solution absorbance was measured against blank at 262 nm.

vi) *In vitro* Drug Release Study: Drug release was assessed by dissolution test under the following conditions: n=3, USP type II dissolution apparatus (paddle method) at 50 rpm in 900 ml phosphate buffer pH 6.8 from 3 to 12 hours, maintained at 37°C ± 0.5°C. An aliquot (5ml) was withdrawn at specific time intervals and replaced with the same volume of pre-warmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper and drug content in each sample was analyzed by UV-visible spectrophotometer at 262 nm.

vii) Kinetic Analysis of Dissolution Data: To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Hadjiioannou et al., 1993). The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble compression coated as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K_0 t$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log } C = \text{Log } C_0 - K_1 t / 2.303$$

Where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2}$$

Where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t$$

Where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation. The following plots were made using the in-vitro drug release data.

- Cumulative % drug release vs. time (Zero order kinetic model);
- Log cumulative of % drug remaining vs. time (First order kinetic model);
- Cumulative % drug release vs. square root of time (Higuchi model);
- Cube root of initial concentration minus the cube root of percentage of drug remaining in the compression coated vs. time (Hixson-Crowell cube root law).

viii) Mechanism of drug release: Koresmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n$$

where M_t / M∞ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms. A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table10. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release (Peppas, 1985).

Table 10: Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape.

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

ix) Swelling and Erosion Studies: Swelling and eroding behavior was determined by a method similar to that reported by Avachat and Vikram (Avachat and Vikram, 2007).The dissolution jars were marked with the time points of 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours. One tablet was placed in each dissolution jar containing 500 ml of phosphate buffer pH 6.8 at 37 °C ± 0.5 °C, and the apparatus was run at 100 rpm using paddle. The tablets were taken out after completion of the respected stipulated time span as mentioned above and weighed after the excess of water at the surface had been removed with filter paper. The wetted samples were then dried in an oven at 40 °C up to constant weight. The increase of the weight

on the tablet reflects the weight of the liquid uptake. It was estimated according to following equation

$$Q = 100(W_w - W_i) / W_i$$

Where Q is the percentage swelling, and Ww and Wi are the masses of the hydrated samples before drying and the initial starting dry weight, respectively (Lopes et al., 2006).

The degree of erosion (expressed as percentage erosion of the polymer content, E) was determined using following equation.

$$E = 100(W_i - W_f) / W_i$$

Where W_f is the final mass of the same dried and partially eroded sample.

x) FTIR Studies: FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wave numbers 4000 and 400 cm^{-1}.

RESULTS AND DISCUSSION

Standard Graph of Valsartan

The standard graph of Valsartan (Table 11) has shown good linearity with R^2 values 0.999 9 in pH 6.8 buffer (Figure 4), which suggests that it obeys the "Beer-Lambert's law".

Table 11: Standard Graph of Valsartan in phosphate buffer pH 6.8 (n=6).

Concentration (µg/ml)	Absorbance
0	0
4	0.241
8	0.432
12	0.642
16	0.861
20	0.955

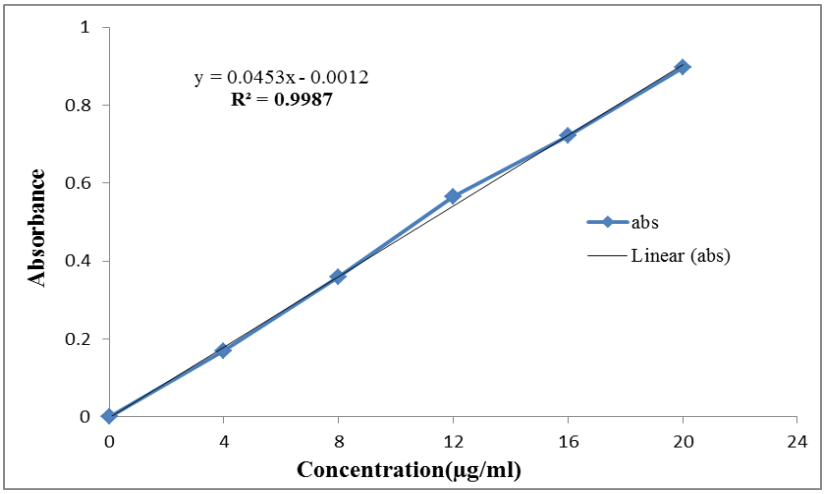

Figure 4: Standard graph of Valsartan in phosphate buffer pH 6.8.

Table 12: Physical Properties of Precompression Blend.

Formulations	Angle of repose (°)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's ratio
F1	25.49	0.214	0.251	14.74	1.17
F2	26.24	0.308	0.364	15.38	1.18
F3	29.05	0.276	0.322	14.28	1.16
F4	26.97	0.341	0.388	12.11	1.13
F5	29.25	0.324	0.376	13.82	1.16
F6	32.27	0.320	0.397	19.39	1.24
F7	33.65	0.521	0.629	17.17	1.20
F8	33.21	0.518	0.627	17.38	1.21
F9	26.56	0.422	0.506	16.60	1.19
F10	28.75	0.481	0.572	15.90	1.18
F11	27.33	0.475	0.566	16.07	1.19
F12	25.38	0.524	0.599	12.52	1.14
F13	26.43	0.412	0.483	14.69	1.17
F14	24.77	0.488	0.537	9.12	1.10
F15	26.42	0.439	0.521	15.73	1.18

Table 13: Physical Evaluation of Compression coated Tablets.

Formulation	Weight (mg)‡	Hardness (kg/cm^2) †	Thickness (mm)‡	Friability (%)	Drug content* (%)
F1	249.8±1.48	5.50±0.44	3.24±0.17	0.36	98.25±1.37
F2	250.4±0.54	5.50±0.31	3.27±0.25	0.39	97.28±0.80
F3	248.6±0.41	5.58±0.40	3.24±0.80	0.43	99.12±2.47
F4	249.8±1.64	5.66±0.55	3.20±0.20	0.12	100.22±0.88
F5	250.6±1.14	4.25±0.57	3.28±0.66	0.54	100.24±1.25
F6	248.2±0.83	4.08±0.30	3.31±0.25	0.58	99.53±1.87
F7	249.9±0.67	4.25±0.57	3.24±0.71	0.64	99.28±1.99
F8	248.1±0.43	4.41±0.60	3.31±0.89	0.37	95.35±1.14
F9	250.5±0.80	5.00±0.44	3.30±0.73	0.77	96.34±2.18
F10	251.2±0.83	5.00±0.31	3.30±0.68	0.42	99.29±0.98
F11	252.1±0.93	5.08±0.37	3.26±0.88	0.48	97.35±0.43
F12	251.2±0.97	5.41±0.70	3.29±0.36	0.15	98.88±0.88
F13	249.2±0.83	4.33±0.50	3.26±0.46	0.27	98.57±1.22
F14	251.2±0.92	4.58±0.57	3.28±0.38	0.29	99.35±2.09
F15	250.0±1.22	4.75±0.77	3.28±0.37	0.53	99.54±2.15

Table 14: *In vitro* Release Data of Valsartan from HPMC K4M CC tablets (n=3)

Time (h)	F1	F2	F3	F4
0.5	22.64±1.12	19.22±0.86	16.98±0.41	14.57±0.78
1	41.94±0.87	39.96±0.93	37.12±1.22	36.78±1.53
2	53.88±0.44	50.99±0.68	50.20±0.37	48.13±1.12
3	74.58±1.10	67.43±0.49	63.09±0.96	62.99±0.84
4	82.35±1.35	80.50±1.77	77.61±0.42	75.35±0.59
6	94.28±1.79	89.47±1.35	86.23±1.49	83.30±0.97
8	-	97.55±0.21	93.83±0.74	91.15±0.68
10	-	-	-	98.47±0.81
12	-	-	-	-

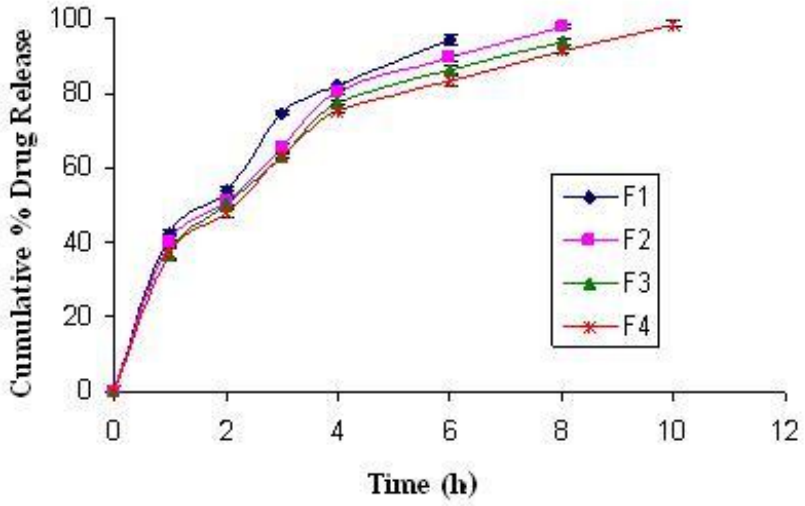

Figure 5: Release Profiles of Valsartan from HPMC K4M CC tablets.

Table 15: *In vitro* Release Data from HPMC K15M CC tablets (n=3).

Time (h)	F5	F6	F7	F8
0.5	19.54±1.34	17.15±1.23	16.14±0.32	13.91±0.63
1	37.23±0.97	35.38±1.47	35.16±1.32	34.93±0.58
2	51.72±1.68	50.46±0.83	50.08±1.27	49.86±0.94
3	71.58±0.87	69.17±0.65	67.58±0.94	66.97±0.75
4	80.71±0.54	78.32±0.87	77.73±1.57	76.82±0.38
6	89.43±1.63	86.87±0.42	83.83±0.59	81.87±0.96
8	97.29±0.53	94.55±0.74	90.87±1.79	89.89±0.72
10	-	98.25±1.62	96.14±1.05	93.97±0.27
12	-	-	-	98.77±0.12

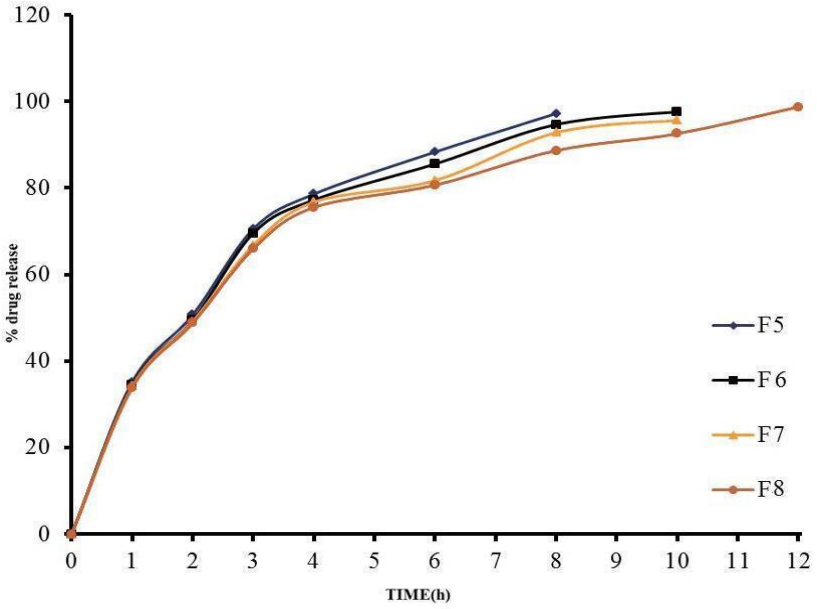

Figure 6: Release Profiles of Valsartan from HPMC K15M CC tablets

Table 16: *In vitro* Release Data from Ethyl Cellulose CC tablets (n=3).

Time (h)	F9	F10	F11	F12
0.5	20.56±0.24	18.25±1.21	16.12±0.28	12.36±0.12
1	42.27±0.57	38.7±0.82	28.64±1.42	22.31±0.54
2	52.47±0.67	47.28±0.69	35.62±0.71	32.42±0.62
3	64.86±0.73	59.73±0.87	42.34±0.54	42.83±0.81
4	77.27±0.84	74.95±0.31	56.84±0.37	54.86±0.42
6	86.63±0.79	82.62±0.64	64.92±0.84	68.03±1.57
8	98.31±0.52	91.59±0.63	75.72±0.53	72.26±0.46
10	-	99.34±0.87	83.56±0.83	80.92±0.75
12	-	-	97.28±0.27	89.56±0.71

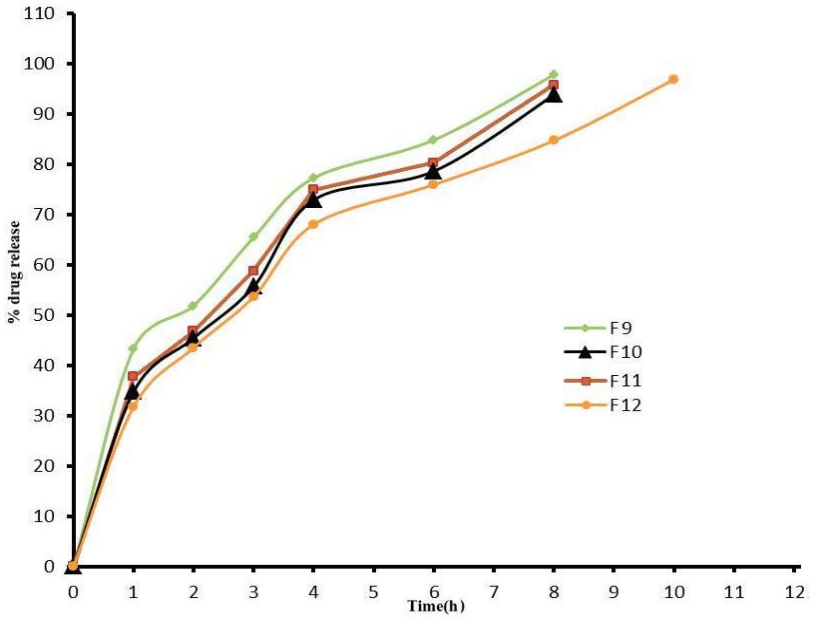

Figure 7: Release Profiles of Valsartan from Ethyl Cellulose CC tablets.

Table 17: *In vitro* Release Data from HPMC K15M and EC CC tablets (n=3).

Time (h)	F13	F14	F15
0.5	19.42±0.24	14.25±0.64	11.62±0.57
1	27.06±0.85	25.38±1.54	19.56±0.42
2	40.68±0.93	37.09±1.65	31.86±1.36
3	54.27±1.29	51.93±1.69	44.35±1.54
4	66.82±1.48	62.15±1.99	51.84±0.79
5	80.72±1.79	73.88±2.01	59.43±1.46
6	88.25±1.88	81.09±2.92	68.24±0.27
7	95.17±2.38	88.04±2.48	76.82±1.04
8	-	99.21±2.59	87.43±1.96

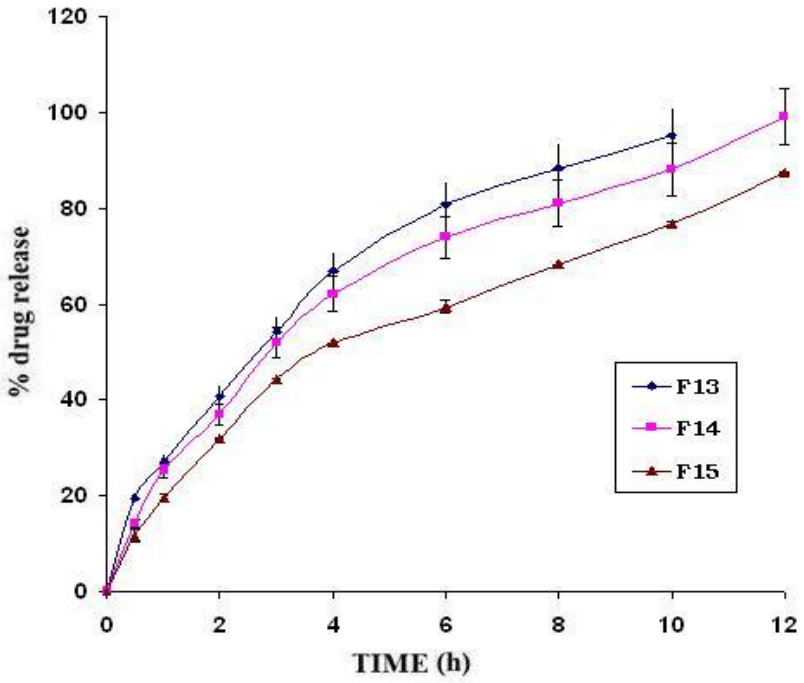

Figure 8: Release Profiles of Valsartan from HPMC K15M and EC CC tablets.

Table 18: Drug Release Kinetics of Optimized (F14) Compression coated Tablets.

Zero order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
r^2	$K_0(h^{-1})$	r^2	$K_1(h^-)$	r^2	$K_H(h^{-1/2})$	r^2	$K_{HC}(h^{-1/3})$	r^2	n	$K_{KP}(h^{-n})$
0.898	5.881	0.995	0.201	0.966	27.839	0.980	0.1997	0.974	0.66	0.3238

- r^2 = Correlation coefficient; K = Kinetic constant; n= Diffusional exponent.

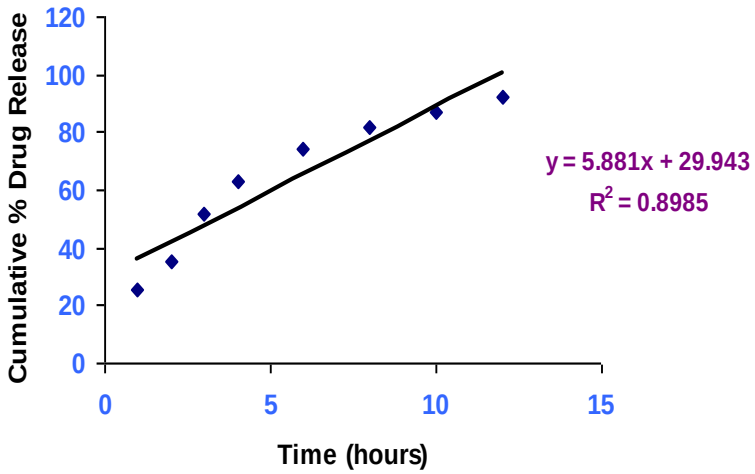

Figure 9: Zero Order Graph of Optimized Formulation (F14).

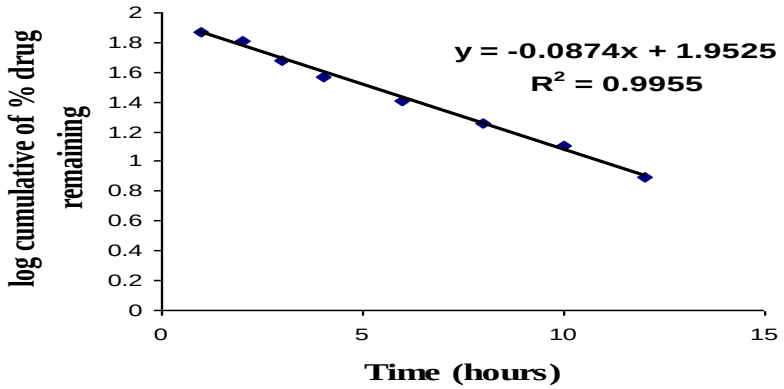

Figure 10: First Order Graph of Optimized Formulation (F14).

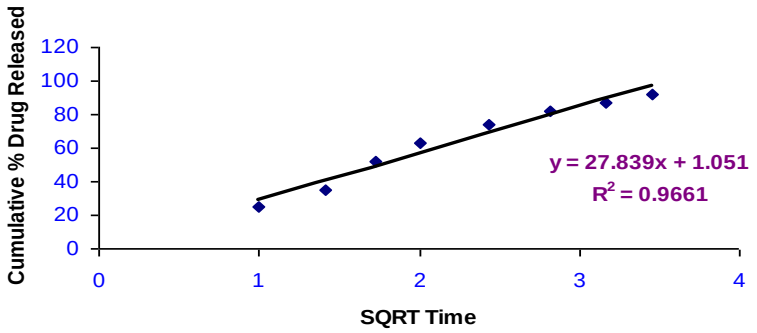

Figure 11: Higuchi Plot of Optimized Formulation (F14).

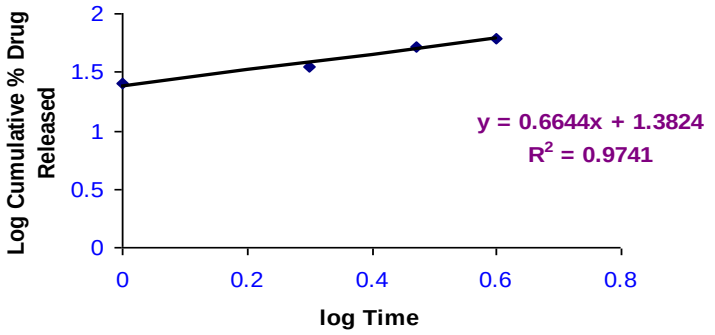

Figure 12: Korsmeyer-Peppas Graph of Optimized Formulation (F14).

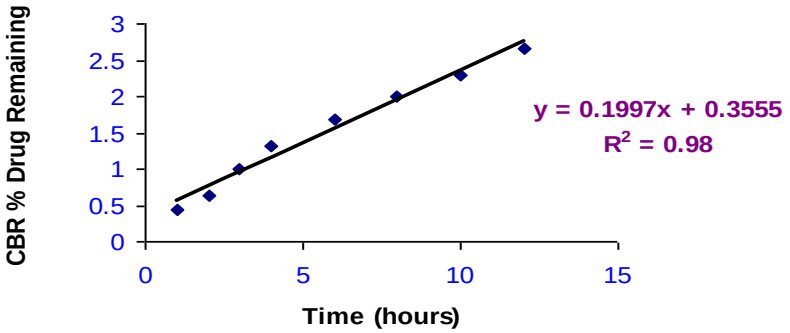

Figure 13: Hixson-Crowell Plot of Optimized Formulation (F14).

Table 19: Swelling and Erosion Study of Optimized Formulation (F14).

Time (hours)	% Swelling	% Erosion
1	76.43	18.72
2	128.35	24.37
3	84.57	28.73
4	71.94	42.62
6	60.64	56.83
8	49.53	64.52
10	36.72	72.41
12	24.83	93.29

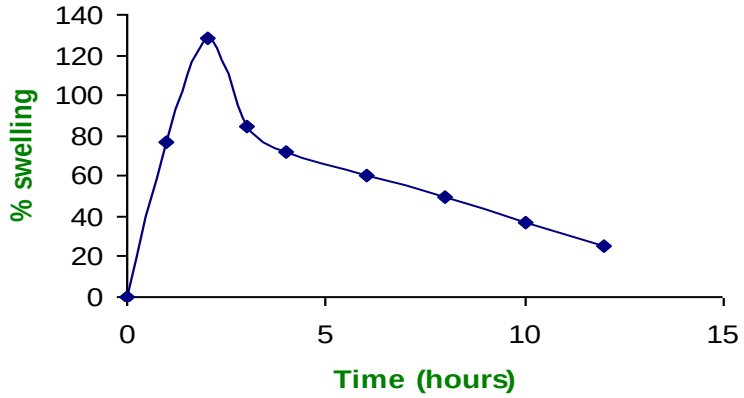

Figure 14: Swelling Study of Optimized Formulation (F14).

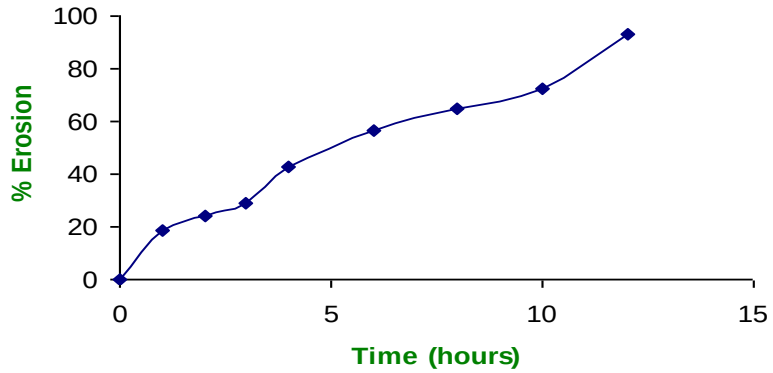

Figure 15: Erosion Study of Optimized Formulation (F14).

7.8. Fourier transform infrared spectroscopy (FTIR)

FTIR study was done to verify if there was any interaction between the pure drug and excipients were employed. The various FTIR graphs both of pure drug and excipients were mixed and the blend was formulated into IR pellet and scanned. The graphs are shown below.

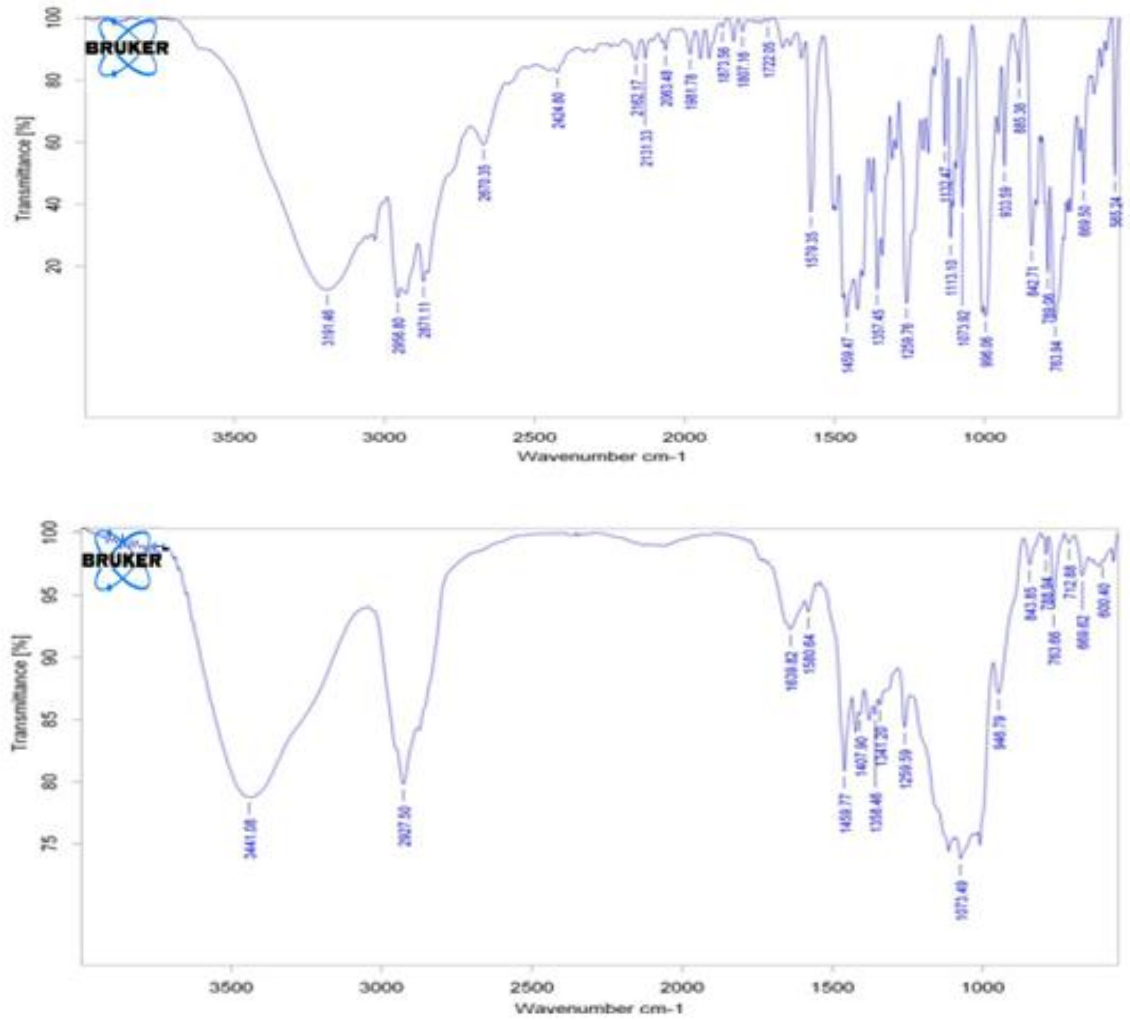

Figure 16: FTIR Spectra of Pure Valsartan and Optimized Formulation (F).

CONCLUSION

- Compression coated tablets were compressed without any problem and do not require any change in ratio of excipients in formulation. Results of the present study demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained-release compression coated tablets of valsartan.
- All the formulations containing extended the drug release for 6 to 12 h.
- Among the compression coated formers, the rate of drug release was in the following order HPMC K4M > HPMC K15M>EC.

Sustained release dosage form of valsartan can provide better patient compliance and prolonge drug release. Due to its short half life of valsartan, this drug will be a suitable candidate to formulate into sustained release dosage forms. The present study was investigated to formulate valsartan sustained release with addition of release retarding

polymer HPMC, Ethyl cellulose and combination. From the *in vitro* drug release studies, F14 was the best formulation and sustained the drug release for 12 h. The release process involves anomalous diffusion mechanism or diffusion coupled with erosion, as indicated by the n value of 0.66 in Korsmeyer's plot. There was an alteration in the surface area and diameter of the tablets with the progressive dissolution of the compression coated as a function of time, as indicated in Hixson-Crowell plot. FTIR studies combined with stability studies proved the integrity of the developed compression coated tablets. Further the efficacy of the developed formulations has to be assessed by pharmacokinetic studies in humans.

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