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Formulation and Evaluation of Multi Unit Pellet System (MUPS) for the Immediate Release of Valsartan to Treat Hypertension

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ABSTRACT

The purpose of present study was to prepare immediate release multi unit pellet system of valsartan which produce better dissolution of the drug for better bioavailability and solubility using sodium starch glycolate and crosspovidone as a superdisintegrant and polysorbate as a surfactant. From present study it can be concluded that immediate release pellets of valsartan were formed and showed satisfactory drug release. Sodium starch glycolate shows immediate drug release as compared to crosspovidone. The maximum drug content of immediate release pellet was found the formulation F2 is 94% and F6 is 92% respectively. The size range of pellet is observed through the microscope and average particle size was found to be 0.756mm. The evaluation studies of capsule loaded with pellets were carried out. Weight variation of capsules was found to be 4.81% as per the limit of Indian pharmacopoeia. The disintegration time was found 10 min 23 sec and it also revealed that the capsules disintegrate immediately and release the pellets into the gastro intestinal tract.

1. INTRODUCTION

Valsartan is indicated for active and maintenance therapy of different variety of cardiac conditions including hypertension and heart failure. Valsartan lowers blood pressure by antagonizing the renin-angiotensin-aldosterone system (RAAS); it competes with angiotensin II for binding to the type-1 angiotensin II receptor subtype and prevents the blood pressure increasing effects of angiotensin II. It is combined with other antihypertensive agents such as hydrochlorothiazide, amlodipine, nevibolol and sacubitril. Absolute bioavailability of valsartan is approximately 25% (ranges between 10%-35%). The bioavailability of the suspension is 1.6 times higher than that of the oral tablet. Food decreases the exposure to valsartan by approximately 40% and peak plasma concentration approximately 50%. AUC and Cmax values of valsartan genereally increase linearly with increasing dose over the therapeutic dose range. This drug undergoes minimal liver metabolism. Oral bioavailability in man has been reported to be low and variable due to its poor aqueous solubility. Since for poorly water soluble drugs (like valsartan) the dissolution rate is often the rate-limiting step of the solubility and the surface area of the drug. Thus, dissolution rate will increase if the solubility of the drug is increased, and it will also increases with an increase in the surface area of the drug.

Multiple-unit dosage form have several advantage compared with single-unit dosages form including more stable plasma profile and little risk of local side effects. Various types of multiple-unit dosage forms, pellets have attracted more attention due to their unique and technical advantages. Pellets as a drug delivery system offer therapeutic advantages like less irritation of the gastro-intestinal tract and a lowered risk of side effects due to dose dumping. Pellets disperse freely in the gastrointestinal (GI) tract and maximize drug absorption, reduce peak plasma fluctuation and minimize potential side effects without appreciably lowering drug bioavailability.

The aim of present is to improve bioavailability of valsartan using superdisintegrants sodium starch glycolate and crosspovidone and also increases solubility using polysorbate as a surfactant. In addition, immediate release pellets containing valsartan will be formulated so as to study the impact of multi unit pellet system on the in vitro dissolution rate of the drug from the pellets.

2. EXPERIMENTAL WORK

2.1. MATERIALS

Valsartan was purchase by DK Pharma, Maharashtra, India. HPMC E 15 and Mannitol (Loba Chemie, Mumbai, India. The surfactant, Tween 60, was provided by SDFCL Industrial estate, Mumbai, SSG and PVP K30 HiMedia laborateries Pvt. Ltd. Mumbai, Ethanol and other chemicals were analytical reagent grade.

2.2 PREFORMULATION STUDIES: Preformulation testing is the first thing in the research and development of new dosage forms. It involves all studies based on new drug molecule for the formulation of a stable, biopharmaceutically suitable and efficient drug dosage form. Preformulation studies were carried out in terms of tests for identification (physical appearance, melting point, FTIR, DSC and partition coefficient), solubility profile and quantitative estimation of drug.

2.2.1. PHYSICAL APPEARANCE: Through visual inspection, the physical appearance of pure drug was carried out.

2.2.2. MELTING POINT: It is one of the important parameters to judge the purity of crude drugs. The melting point was determined by the capillary method using Melting point apparatus.

2.2.3 FLOW PROPERTIES

A) DETERMINATION OF BULK DENSITY AND TAP DENSITY

From this the bulk density of the sample can be calculated by using the formula given below. After the procedure for each set of taps the cylinder is taken and the volume (Vf) occupied by the dry powder is measured and continued the operation till the two consecutive reading were equal. The tapped density is calculated using the formula.

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

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

Where, W = Weight of powder

V_o = Initial volume

V_f = Final volume

B) COMPRESSIBILITY INDEX AND HAUSNER'S RATIO

The compressibility index and the Hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder. The formula which was used for calculating the compressibility index and the Hausner's ratio given.

$$\textbf{\% Compressibility} = (Pt - PO / Pt) \times 100$$

Where,

Pt = Tapped density and

Po = Bulk density

Hausner's ratio = Tapped density/Bulk density

The standard values for the compressibility index and the Hausner's ratio is given during the discussion of pre-formulation studies of the pure drug.

C) ANGLE OF REPOSE

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic relates to inter-particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

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

$$\theta = \text{Tan}^{-1}\, h/r$$

Where,

θ = angle of repose

h = height

r =radius.

D) SOLUBILITY STUDY: Solubility is defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. The solubility of drug was tested in various common solvents. A definite quantity (10 mg) of drug was dissolved in 10

ml of each investigated solvents at room temperature. The solubility was observed only by UV method. Solubility is defined as the two or more substances to form a homogenous molecular dispersion. The solubility of drug was tested in various common solvents.

E) FTIR (Fourier transform infrared spectroscopy)

FTIR relies on the fact that the most molecules absorb light in the infra-red region of the electromagnetic spectrum. Absorption range corresponds specifically to the bonds present in the molecule. Frequency range are measured as wave numbers typically over the range 4000 – 600 cm-1. FTIR is used particularly for the identification of organic molecular group and compounds due to the range of functional groups, side chains and cross-links involved, all of which will have characteristic vibrational frequencies in the infra-red range.

F) DSC (Differential scanning calorimetry**)**

It is a technique in which the difference in the amount of heat required to measured as a function of temperature the sample and reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature for the DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned.

Table 1: Formula for preparation of valsartan pellets:

Ingredients	FR1 (mg)	FR2 (mg)	FR3 (mg)	FR4 (mg)	FR5 (mg)	FR6 (mg)
Valsartan	40	40	40	40	40	**40**
Sugar sphere	50	50	50	50	50	**50**
Mannitol	07	03	01	07	03	**01**
PVP	06	06	06	06	06	**06**
HPMC E15	02	02	02	02	02	**02**
Sodium starch glycolate	04	08	10	-	-	**-**
Crosspovidone	-	-	-	04	08	**10**
Polysorbate 60	10	10	10	10	10	**10**
Safranin	01	01	01	01	01	**01**
Methanol	Q.S	Q.S	Q.S	Q.S	Q.S	**Q.S**
TOTAL (Quantity in mg)	**120**	**120**	**120**	**120**	**120**	**120**

2.3 PREPARATION OF VALSARTAN IMMEDIATE RELEASEPELLETS

In suspension layered method pellets was prepared by 2 sequential coatings:

2.3.1 DRUG COATING:

Preparation of core mixture suspension

The required quantities of drug and the excipients was taken and mixed in methanol with continuous stirring until a uniform suspension is formed.

Preparation of core drug pellets

The non-pariel seeds (sugar spheres 24/30) was accurately weighed and transferred into the coating pan. The drug suspension is sprayed on the non-pariel seeds at the given set of conditions which are given below. The coating was done by the solution layering technique.

Drying of the core drug pellets

Then these pellets were dried at 40-45°C for 6-8 hrs. The moisture content should be less than 2% in the pellets. Then the pellets was sifted and passes through the sieve and the pellets of size 14/20 are collected and was taken for coating.

2.3.2 SUB COATING:

Preparation of sub coating material

The sub coating material is prepared by dissolving the required quantities of the Hydroxy propyl methyl cellulose in methanol and it is stirred for 15min to form a uniform solution. Then this is taken to coat the core drug pellets.

Coating of the core drug pellets

The sub coating solution was sprayed on the core pellets in the Pan coater. This makes the immediate release layer around the core pellet.

Drying of the core drug pellets

The pellets after sub coating was taken and dried. Then the pellet was taken and the passes through the sieve of required range and the required pellets was collected. The pellets of size

16/20 are collected.

Filling of core pellets into the capsules

The obtained pellets were taken and are transferred into the capsule of suitable size each capsule should be with drug equivalent to 40mg.

2.4 EVALUATION OF VALSARTAN IMMEDIATE RELEASE PELLETS

2.4.1 PARTICLE SIZE ANALYSIS: Particle size was determined by optical microscopy of pellets. Pellet formulation containing valsartan all the formulation evaluation is important for determining the surface, size and shape. The pellets were smooth and sphericity was also express good.

2.4.2 FRIABILITY OF PELLETS: Friability is characterized as the weight loss of a sample (%), the mean pellet diameter reduction (%) or the difference in areas under the curve of pellet size distribution before and after the friability testing. According to B.P. Friability was NMT 0.8 %.

2.4.3 DRUG CONTENT OF PELLETS: Accurately weigh 120 mg of valsartan drug layered pellet and dissolve them in a mixture of methanol and 0.1 N HCL. After mixing of the pellets in a desired solvents, now 2ml solution is collected from that above stock solution and transferred into 10ml volumetric flask and makeup the volume with 0.1N HCL solution. The supernatant was filtered and measured spectrophotometrically. The valsartan content was calculated using calibration curve.

2.4.4 IN VITRO RELEASE STUDY: The drug release profiles of pellets were measured in vitro. The release measurement were performed using USP type II dissolution testing apparatus at 50 rpm paddle speed temperature of bath was maintained at 37°C. An accurately weighed amount of the prepared formulation was added to flask. The test was run into dissolution vessel containing 900ml of simulated gastric fluid. The resulting samples was withdrawn from the system at definite time interval and filtrated with 100 nm filter. The filtrate was determined by UV spectrophotometer (UV-1800 Shimadzu Spectrophotometer) at 250nm. The percentage of drug release was determined as a function of time.

3. EVALUATION OF CAPSULES

3.1. UNIFORMITY OF WEIGHT: Weigh 20 capsules individually and determine the average weight of the capsules. Not more than two of the individual weight deviated from the average weight.

The average weight was calculated by using the following formula.

$$\text{Weight variation} = \frac{\text{(Weight of capsule-Average weight)}}{\text{Average weight of capsules}} \times 100$$

Weight variation should not be more than 7.5%.

3.2. UNIFORMITY OF CONTENT: The Valsartan content in pellets was determined by powdering 10 capsules in each batch. Powder equivalent to 100 mg of Valsartan was dissolved in Methanol. 1 ml of filtrate was further diluted to 100 ml with 0.1 N HCL and it was determined by spectroscopy at 250 nm.

3.3. DISINTEGRATION TIME: The disintegration test was performed using disintegrating apparatus. Placed one capsule in each of the six tubes of the basket and operate the apparatus using 0.1NHCl maintained at 37±0.5ºC as the immersion fluid. Then note down the time to complete disintegration of capsules.

3.4. IN-VITRO DISSOLUTION STUDY: The sample was taken from the formulated trial batches. These sample was filled in the capsules. Then these capsules was subjected to the in-vitro dissolution tests. The samples was taken at specific intervals and the percentage of drug release is calculated. Cumulative percentage drug release of different trial was compared with that of the drug release profile. The drug release profile of the trial which matches with that of the innovator drug release profile is taken and the evaluation tests for this optimized and formulation is carried out.

4. RESULTS AND DISCUSSION

The present study was carried out to formulate Valsartan immediate release pellets (120 mg). The study involves pre-formulation studies of drug and excipients, formulation and

processing development along with evaluation of pellets made with the optimized formulation. Finally immediate release pellets were evaluated by in-vitro methods.

4.1. PRE-FORMULATION STUDIES

Table 2: Preformulation studies of valsartan pure drug:

S.N.	CHARACTERISTICS	RESULT
1.	Solubility	**Freely soluble in water, soluble in methanol and sparingly soluble in ethanol.**
2.	Bulk density	**0.375 gm/ml**
3.	Tapped density	**0.5727 gm/ml**
4.	Compressibility index	**24.55**
5.	Hausner's ratio	**1.28**
6.	Loss on drying	**0.19%**
7.	**Angle of repose (°)**	**37.23°**

4.2 IDENTIFICATION OF DRUG BY-

4.2.1 FTIR (Fourier transform infrared spectroscopy):

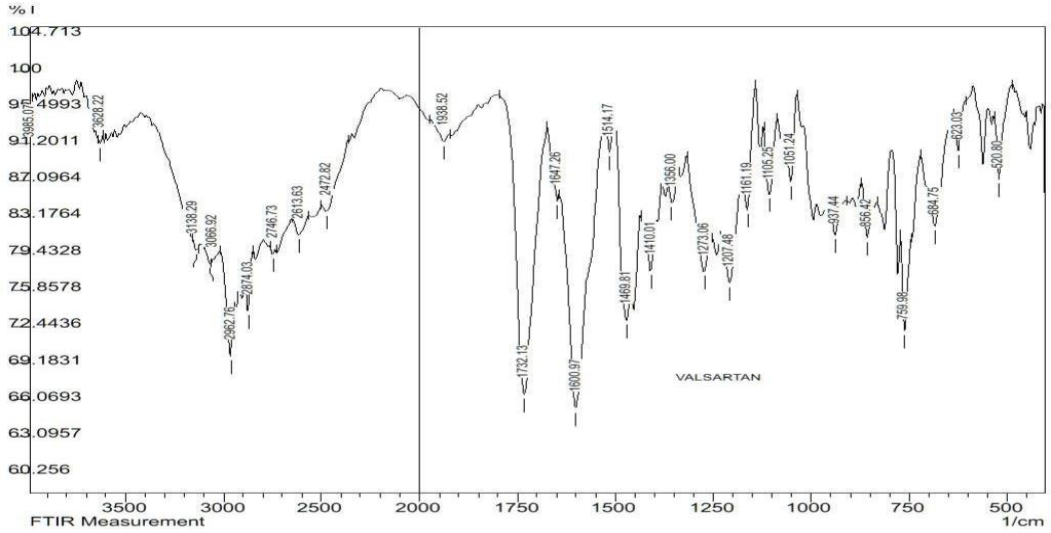

Figure 1: FTIR spectrum of valsartan

Table 3: FTIR studies of valsartan:

s.no.	Frequency	Functional group
1.	3985-3628	O-H
2.	3138-3066	=C-H
3.	2962-2874	-C-H
4.	2874-2746	O=C-H
5.	1732-1600	-C=O-C
6.	1514-1469	-C=C-
7.	1207-1051	C-N

4.3.1 DSC (Differential scanning calorimetry):

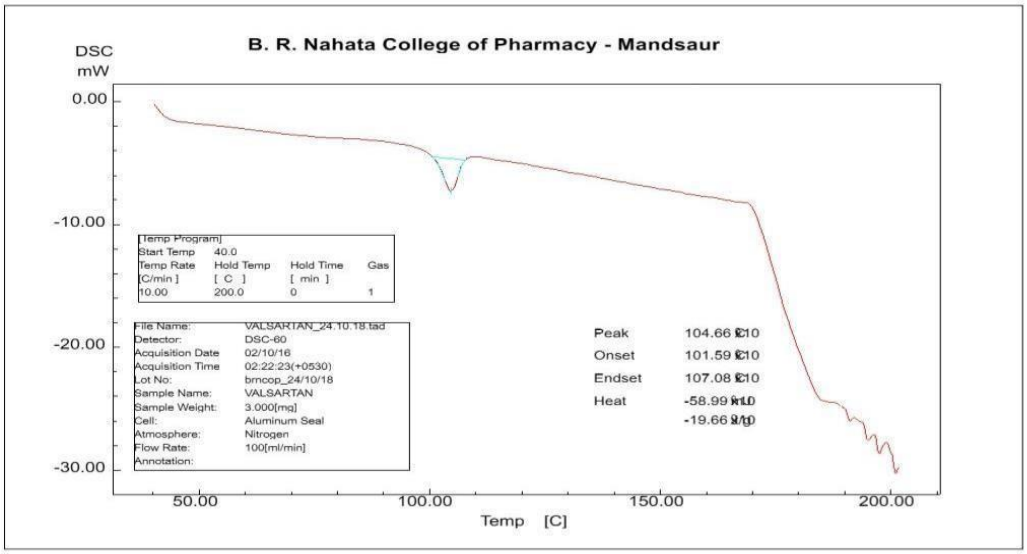

Figure 2: DSC curve between temperature and heat flux

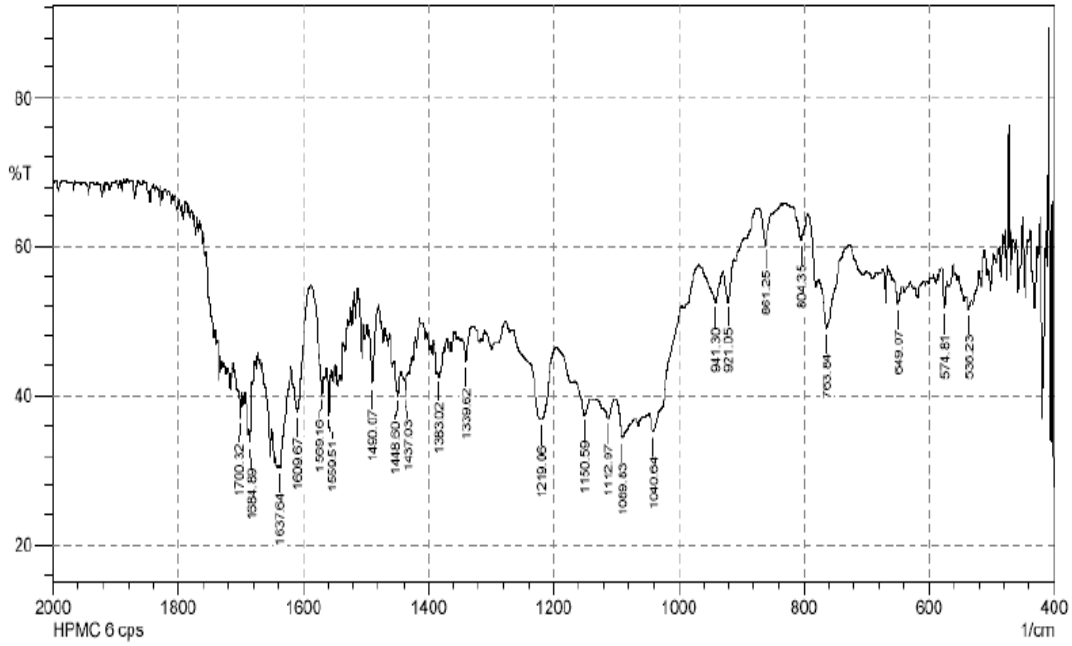

Figure 3: FTIR spectrum of HPMC

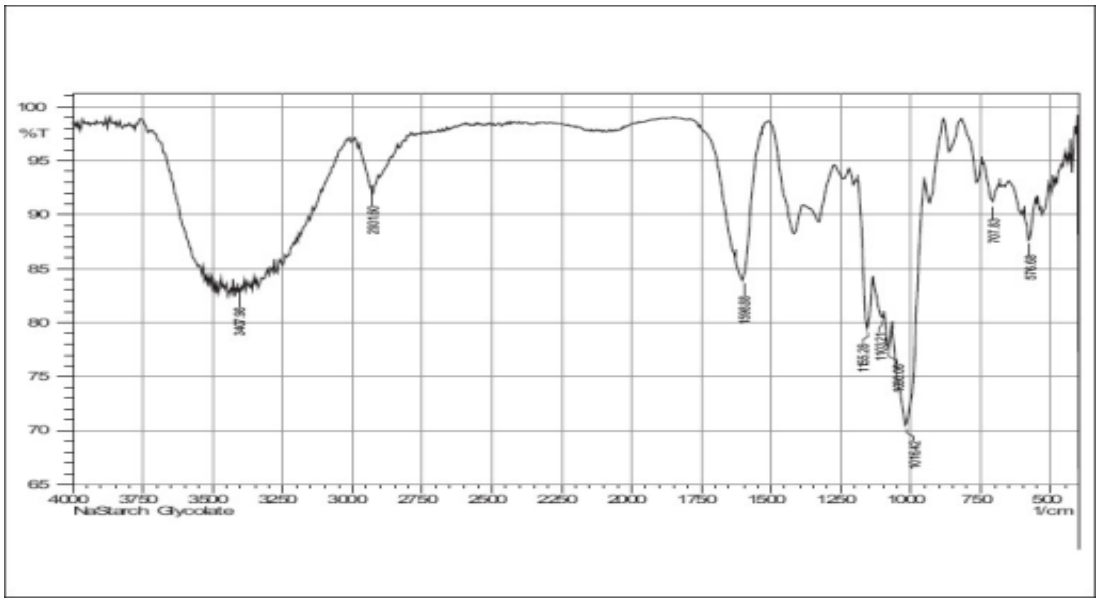

Figure 4: FTIR spectra of sodium starch glycolate

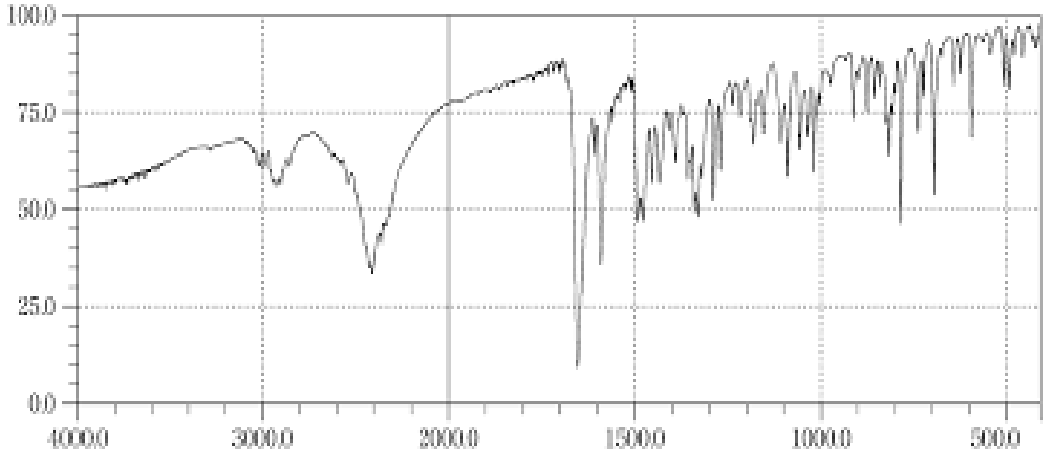

Figure 5: FTIR spectra of crosspovidone

4.3.2 UV SPECTROPHOTOMETRY:

DETERMINATION OF ABSORPTION MAXIMA OF VALSARTAN

The UV absorption maxima was determined by scanning solution of Valsartan in the range of 200-400 nm by Shimadzu – 1800 UV/Visible spectrophotometry.

STANDARD CURVE OF VALSARTAN WITH 0.1N HCL

Standard curve of valsartan was prepared in 0.1N HCL. Valsartan showed maximum absorbance in 0.1N HCL at 250nm.

Table 4: Standard curve of valsartan

Concentration(ug/ml)	Absorbance
0	0
0.5	0.093
1	0.155
1.5	0.326
2	0.532
2.5	0.745

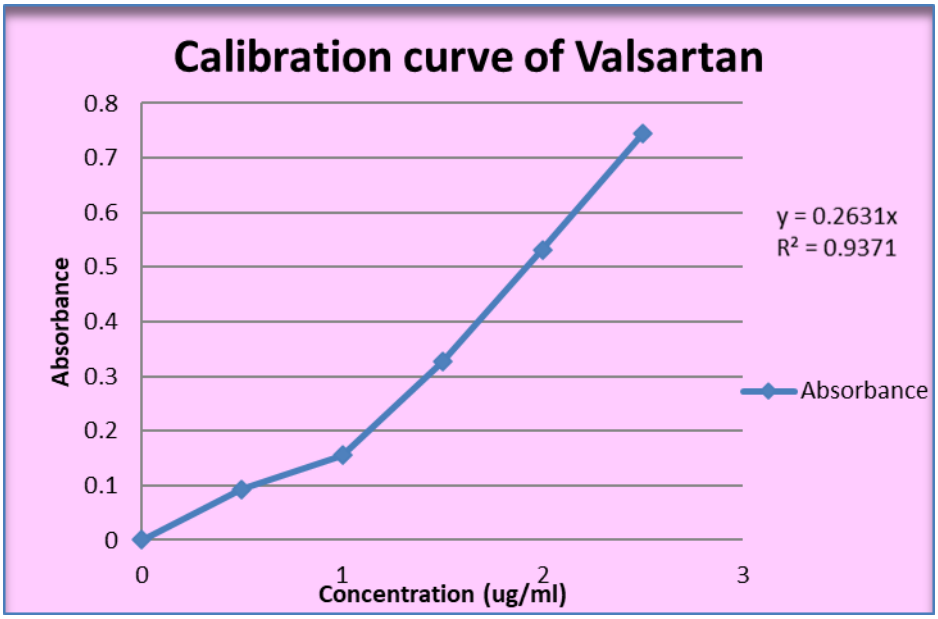

Figure 6: Calibration curve of valsartan

➢ **λmax** refers to the wavelength in the absorption spectrum where the absorbance is maximum. Generally, molecules absorb in a wavelength range centered around the lambda max. It acts as a single quantitative parameter to compare the absorption range of different molecules.

5.1 EVALUATION OF PELLETS:

5.1.1. PARTICLE SIZE ANALYSIS: Particle size was determined by optical microscopy of the pellets and the particle size was found to be 0.756 mm.

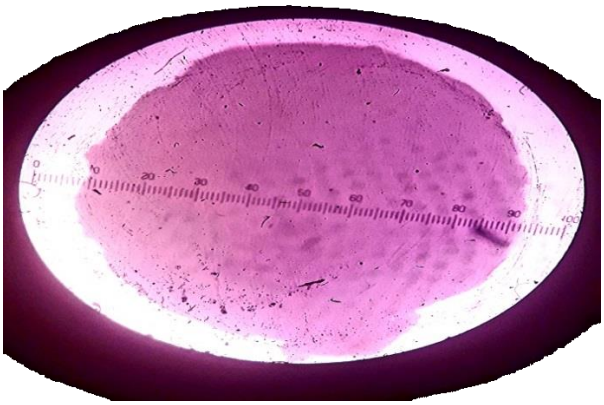

Figure 7: Microscopic image of pellet

5.1.2. FRIABILITY OF PELLETS: Friability of immediate release pellets were found to be 0.717%.

5.1.3 DRUG CONTENT: The maximum drug content of immediate release pellet was found the formulation F2 is 94% and F6 is 92% respectively.

Table 5: % Drug content of different valsartan pellet

Formulation	Drug content
F1	91 %
F2	94 %
F3	90 %
F4	90 %
F5	91 %
F6	92 %

5.1.4 IN VITRO RELEASE STUDY OF THE PELLETS: In-vitro release of pellets formulation F6 batch 97.45% has shown maximum drug release with in 30 min.

Table 6: % In-vitro drug release study of pellets

TIME	F1	F2	F3	F4	F5	F6
0 min	0	0	0	0	0	0
5 min	48.54	59.53	57.3	58.37	51.53	53.45
10 min	62.19	74.56	71.2	74.27	64.56	70.59
15 min	73.81	81.19	74.32	79.12	75.19	76.86
20 min	78.35	89.32	80.17	83.13	79.32	80.52
25 min	81.54	93.29	83.45	89.37	83.29	87.5
30 min	93.12	95.12	89.84	93.65	95.98	97.45

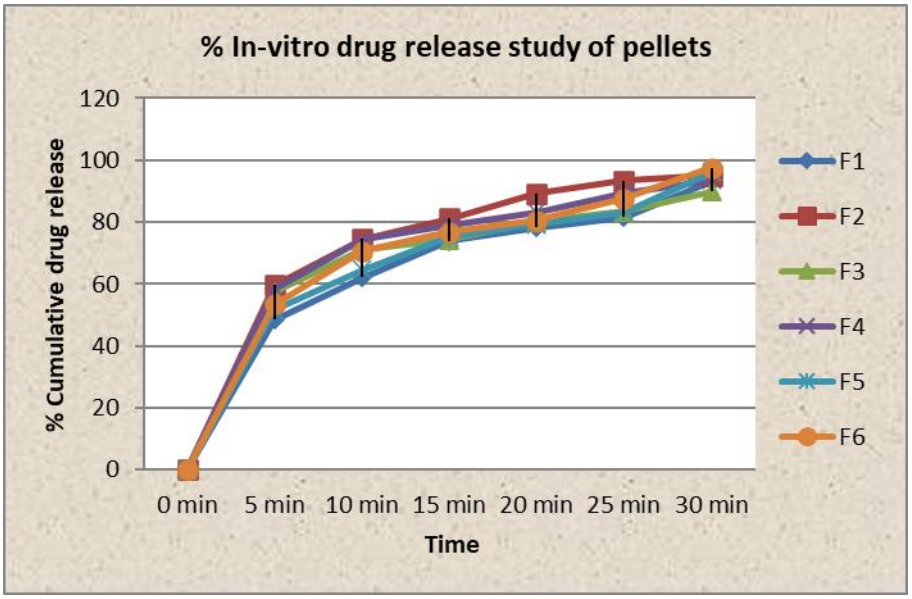

Figure 8: % In-vitro drug release of pellet

6.1 EVALUATION OF CAPSULES: The evaluation studies of capsule loaded with pellets were carried out. Weight variation of capsules was found to be 4.81% as per the limit of Indian pharmacopoeia. The disintegration time was found 10 min 23 sec and it also revealed that the capsules disintegrate immediately and release the pellets into the gastro intestinal tract.

Table 7: Evaluation parameter of capsule

S. No.	Physical parameter	F1	F2	F3	F4	F5	F6
1	Weight variation	4.74%	4.35%	4.10%	3.69%	3.50%	4.81 %
2	Content uniformity	90.6%	102.2%	93.9%	101.6%	91.7%	105.5%
3	Disintegration time	8min 45sc	9min 23sec	9min 45sec	9min 56sec	10min 12sec	10min 23sec

6.2. IN-VITRO DISSOLUTION STUDIES OF THE CAPSULES: The In-vitro release of capsules formulation F6 has shown maximum drug release 98.41% with in 65 min.

Table 8: % In-vitro release of capsules

TIME	F1	F2	F3	F4	F5	F6
0 min	0	0	0	0	0	0
15 min	48.54	59.53	57.3	58.37	51.53	53.45
25 min	62.19	74.56	71.2	81.27	84.56	68.59
35 min	73.81	81.19	74.32	79.12	75.19	76.86
45 min	78.35	89.32	80.17	83.13	79.32	83.52
55 min	81.54	95.29	83.45	93.37	83.29	91.52
65 min	92.14	97.13	93.55	94.92	91.43	98.41

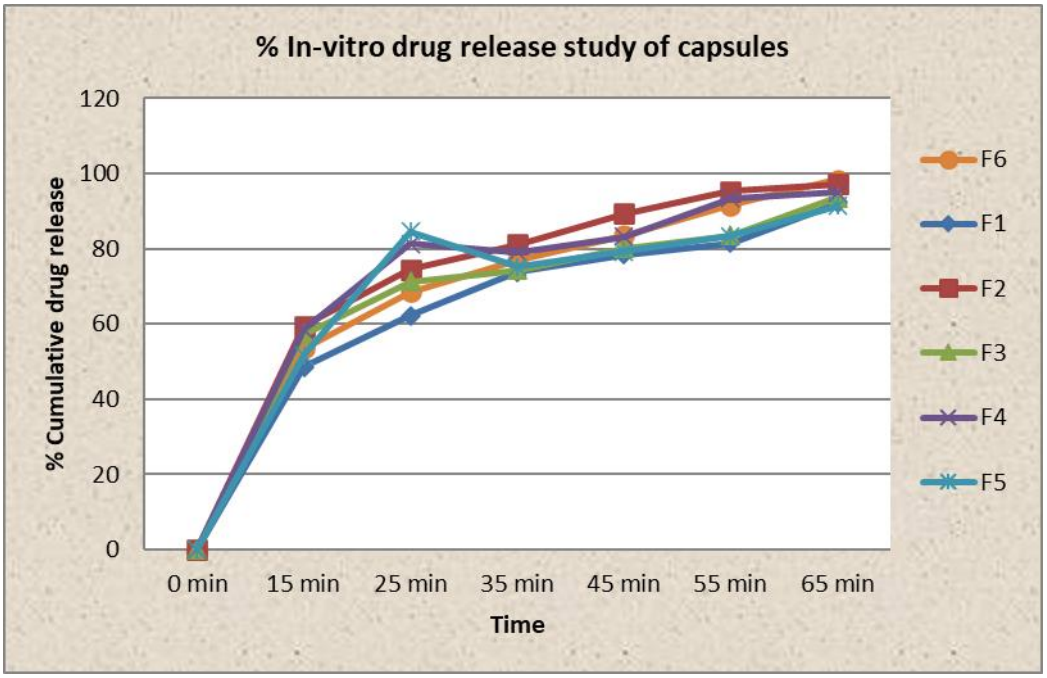

Figure 9: % In-vitro drug release of capsules

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