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Formulation and evaluation of once a day bilayer floating tablet of antihypertensive drug involving dissolution enhancement approach

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ABSTRACT

Valsartan, a widely prescribed anti-hypertensive drug which is an angiotensin II type 1 receptor antagonists belongs to BCS class II. It shows absorption window in stomach area, which makes it a good candidate for gastro retentive dosage forms. The objective of the study is to develop a bilayer floating tablets of Valsartan to increase the Bioavailability of Valsartan by increasing dissolution and give sustained release action upto 24hrs by Single unit dosage. Valsartan:β-cyclodextrin complex was prepared by kneading method. Bilayer Floating Tablets of Valsartan its inclusion complex with β-cyclodextrin (βCD) were formulated by Direct compression method. The immediate release layer comprised of Sodium starch glycholate as a super disintigrant and sustained release layer comprised of Ethyl cellulose and HPMC K100M as release retarding polymers to control the drug release and restrict the region of drug release to stomach. A 3^2 factorial design was applied to optimize the drug release profile. A 5.3 fold increase in the dissolution efficiency of Valsartan was observed with Valsartan:βCD in the ratio of 1:1. Trial batches of IR layer tablet shows best result with SSG 6%. After application of factorial design it was found that formulation F_6 (30% HPMC K100M & 6% Ethyl Cellulose) release 98.44% of Valsartan in 24 hrs. with desired floating lag time (236 sec.) and constantly floated on dissolution medium for upto 24 hrs. From the study it concluded that a sustained release bilayer dosage form of Valsartan for 24hrs can be formulated using dissolution enhancement approach.

Key words: Bilayer floating tablet, Valsartan, β-cyclodextrin, Floating lag time, Total Floating time.

INTRODUCTION

The Oral route is considered as the most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process [1]. Drugs that are easily absorbed from the GIT and having a short half-life are eliminated quickly from the blood circulation[2]. To avoid these problems oral controlled drug delivery systems have been developed as they release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time, achieving more predictable and increased bioavailability of drugs, reducing frequency of dosing, reduced gastro intestinal (GI) side effects, Better patient convenience and compliance[3].

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. prolonging the gastro-retentive of a delivery system is desirable for achieving greater therapeutic benefit of the drug substance. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract and drugs that are less soluble may benefit from prolonged gastric retention[4]. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [5]. Floating drug delivery systems (FDDS) or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. FDDS are of particular interest for drugs that act locally in stomach, are primarily absorbed in stomach, are poorly soluble at an alkaline pH and characterized by narrow absorption

window[6]. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration [7].

Bilayer Floating tablets contain two layers an immediate release layer and a sustained release layer. Two drugs can also be incorporated in two layers[8]. Immediate release layer provide rapid absorption of drug and sustained release layer provides prolonged release of drug over a period of time in a productive and predictable way. After the release of immediate layer, the second layer i.e sustained release layer forms colloidal gel barrier on the surface by absorbing gastric fluid and it forms a density less than gastric fluid due to this it remain by floating in the stomach for an extended time period[9].

Valsartan is a highly selective and orally active antihypertensive drug belonging to the family of angiotensin II type 1 receptor antagonists. Valsartan is used in the treatment of cardiac conditions including hypertension, diabetic nephropathy and heart failure. Valsartan has short Biological half-life i.e.,6 hrs. Valsartan is having the pKa 4.7. It is largely present in unionized form in acidic pH. Thus well absorbed from the acidic pH of the stomach than the basic pH condition of intestine. Valsartan is an ARB that selectively inhibits the binding of angiotensin II to AT1, which is found in many tissues such as vascular smooth muscle and the adrenal glands. This effectively inhibits the AT1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in a decrease in vascular resistance and blood pressure[10].

MATERIALS AND METHODS

Valsartan was obtained as a gift sample from Torrent pharmaceuticals, Ahmadabad. HPMC K100M, Ethyl Cellulose, Sodium bicarbonate were obtained as a gift sample from IPCA Laboratories Pvt. Ltd. Ankleshwar, Gujarat. All other reagents used were of analytical grade.

DRUG-EXCIPIENT COMPATIBILITY STUDY

Fourier Transform Infrared (FTIR): Drug- excipients interactions play a vital role in the release of drug from formulation. Fourier transform infrared spectroscopy (FTIR) has been used to study the physical and chemical interactions between drug and the excipients used. FTIR technique has been used to study the physical and chemical interaction between drug and excipients used.

DSC study : The DSC measurements were performed using a Perkin Elmer Pyris (Shelton, CT) equipped with an intracooler 2P cooling accessory. Samples of 4 mg were placed in standard aluminum pans and sealed with a lid. Heating scans by 10^{o}C/min were applied with a nitrogen purge of 20 ml/min, over a temperature range of 35^{o}C to 380^{o}C. An empty aluminum pan was used as reference. DSC of different Three samples was taken.

PREPARATION OF STANDARD CURVE FOR VALSARTAN IN 0.1N HCl:

- Standard stock solution of Valsartan having concentration 100µg/ml was prepared by dissolving 1 mg of Valsartan in 10 ml of 0.1 N HCl pH 1.2.
- From the standard stock solution, Valsartan HCl (10 µg/ml) solution was scanned between wavelength of 200-400 nm. A wavelength 250 nm was selected for further analytical work.
- From the stock solution (100 µg/ml), aliquot were taken into different volumetric flasks and volume were made up to 10 ml with 0.1 N HCl pH 1.2 solution, so as to get concentration of 5, 10, 15, 20, 25 µg/ml. The absorbance of these solutions was measured at 250 nm. A calibration curve of Concentration v/s Absorbance was plotted.

Formulation of Bilayer Floating Tablets of Valsartan:

Calculation of Loading and Maintenance dose[11]:

- Conventional Dose = 80mg
- Half life ($t_{1/2}$) = 6 hrs
- Elimination constant (K_e) = $0.693/t_{1/2}$ = 0.1155
- T_{max} = 2 to 3hrs
- Dosing interval (T) = 24 hrs

Now, if

Initial Dose(D_i) = C_{SS} V_d / F _____1

where, C_{ss} = Steady state concentration, V_d = Volume of Distribution, F =Fraction of bioavailable dose

But, $C_{SS} = F X_0 / K_e V_d T$ _____2

So, put the value of C_{SS} into the equation no. 1

So, $D_i = F X_0 * V_d / K_e V_d T * F$

Ultimately, $D_i = X_0 / K_e T$

= 80/ 0.1155*24

D_i = 28.86 mg

Desired Rate of drug release (K_s) :

Ks = $D_i * K_e$

= 28.86 * 0.1155

Ks = 3.333 mg/hr

Maintenance Dose (D_M) :

D_M = Ks * 24

= 3.333 * 24

D_M = 80 mg

Corrected Initial Dose (D^*_i) :

$D^*_I = D_i – (Ks * t_p)$

= 28.86- (3.333 * 2.5)

D^*_I = 20 mg

Total Dose D_T **= D^*_I + D_M**

= 20 + 80

D_T = 100 mg

COMPLEXATION OF VALSARTAN With β-CYCLODEXTRIN BY KNEADING METHOD[12]:

The inclusion complex of Valsartan with β-cyclodextrin were prepared in different rations(1:0.25, 1:0.5, 1:0.75, 1:1, 1:1.25, 1:1.5) by kneading method. Thick slurry was prepared by adding one third water by weight to excipients. Under stirring the appropriate qty. of drug was added to it and then dried in oven at 45^0C until dry. The dried mass was pulverized and sieved through sieve no 60.

PHASE SOLUBILITY STUDIES[13]:

The phase-solubility technique permits the evaluation of the affinity between β-cyclodextrin (βCD) and Valsartan in solvent. Phase-solubility studies were performed according to the method reported by Higuchi and Connors. Valsartan in amounts that exceeded its solubility, was taken in to 25ml Stoppard conical flask to which were added 15ml of solvent containing different %w/v of βCD. The flasks were sealed and shaken for 72 hrs at room temperature (28^0C) on a rotary flask shaker. After equilibrating for 72 hrs aliquots of 2ml were withdrawn and filtered immediately using 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for Valsartan by measuring absorbance 250 nm against blanks.

SOLUBILITY STUDY OF INCLUSION COMPLEX[14]:

Solubility study was carried out to determine the increased solubility of drug in inclusion complex. The known excess amount of pure drug and inclusion complex from each og batch equivalent to 10mg of drug were added to

10ml of 0.1N HCl in 10 ml volumetric flask. Sample were sonicated for 30min and stirred at 37.0±0.5^{0}C for 48hrs. The samples were centrifused and take supernant layer from sample, suitably diluted, and analyzed by uv spectrophotometer at 250nm.

Experimental Design:

A 3^2 full factorial design was used for the optimization. In this design 2 factors were evaluated at each level and experimental trials were performed using all 9 combinations. In the present investigation Polymer HPMC K100M (X_1), and Ethyl cellulose (X_2) were selected as independent variables. Floating lag time (FLT) (Y_1), Total Floating Time (TFT) (Y_2) and % Drug release at 17 hrs (Y_3) were selected as dependent variables

Table No.1: Levels and their actual values

Level	Code	X_1(HPMC K100M)(%)	X_2(Ethyl cellulose)(%)
Low	-1	20	4
Medium	0	25	6
High	+1	30	8

Table No.2: Factors combinations as per the chosen experimental design

Formulation Code	Coded Values	
	X_1	X_2
F_1	-1	-1
F_2	0	-1
F_3	+1	-1
F_4	-1	0
F_5	0	0
F_6	+1	0
F_7	-1	+1
F_8	0	+1
F_9	+1	+1

Preparation of Immediate release layer

All the ingredients (Valsartan: βCD, SSG, and MCC) were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min to obtain uniform distribution of the drug in formulation. 130 mg of the powder mix was accurately weighed and manually fed into the die and compressed using 8-station rotary tablet press machine.

Table No.3: Formula For Immediate Release Layer(IR layer)

INGREDIENTS	IR(mg)
Valsartan:βCD	72
Sodium starch glycholate	7.8
Micro crystalline cellulose	46.2
Talc	2
Magnesium stearare	2
Sunset yellow	q.s
Total Weight	**130**

Table No.4: Formula for Floating Sustaining Release Layer

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Valsartan:ßCD(mg)	288	288	288	288	288	288	288	288	288
HPMC K 100 M (mg)	130	162	195	130	162	195	130	162	195
Ethyl Cellulose(mg)	26	26	26	39	39	39	52	52	52
Micro crystalline cellulose(mg)	107	75	42	94	62	29	81	49	16
Sodium Bicarbonate(mg)	85	85	85	85	85	85	85	85	85
Talc(mg)	7	7	7	7	7	7	7	7	7
Magnesium stearate(mg)	7	7	7	7	7	7	7	7	7
Total weight(mg)	**650**	**650**	**650**	**650**	**650**	**650**	**650**	**650**	**650**

Preparation of Floating sustained release layer

Bilayer floating tablets were prepared by direct compression using HPMC K100M and Ethyl celullose as the release controlling polymers, and sodium bicarbonate as a gas generating agent. The optimum concentrations of the above ingredients were determined under experimental conditions and on the basis of trial batches of the tablets.All the ingredients of floating matrix sustained release tablet of Valsartan:βCD were passed through No.100 sieve in order to get particles having uniform size. Then the required amount of ingredients was weighed using balance. Valsartan:βCD was mixed with polymers sodium bicarbonate, Mg. Stearate and MCC in a mortar for uniform

mixing. Then tablets with 650 mg average weight were prepared by direct compression using 8-station rotary tablet press machine.

Evaluation of Physical Properties of Tablets:
The formulated tablets were evaluated for the following parameters :

Hardness[15]:
Hardness of tablet is defined as force applied across the diameter of the tablet in the order to break the tablet. Hardness of the tablets was measured using Monsanto hardness tester.

Friability[15]:
Friability of the tablet determined using friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dedusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = \frac{\text{Initial wt.- final wt}}{\text{Initial wt}} \times 100$$

Determination of drug content in complexes[16]:
The inclusion yield of complexes was determined by dissolving the 10mg of complex in 10ml of HCl. Then the drug content was measured by filtering the samples and analyzed the drug at 250 nm.

Disintegration test of immediate release tablet[17]:
The disintegration test was performed using disintegration test apparatus (Electro lab ED2AL). Six tablets were placed in each six tubes. The tubes were allowed to move up and down in a bath of 0.1 M HCl maintained at 37±2°C in a suitable vessel, preferably a 1000 ml and time required to disintegrate tablets was noted.

***In-vitro* buoyancy/floating studies:**
The in vitro buoyancy was be characterized by Floating lag time (FLT) and Total floating time TFT). The FLT and TFT were measured during dissolution studies. The time required for the tablet to rise to the surface of the dissolution medium and the duration of time the tablet constantly floated on the dissolution medium were noted as Floating lag time and Total floating time respectively.

***In-vitro* drug release study of bilayer tablet of Valsartan[18]:**
The in-vitro drug release study was carried out by USP dissolution test apparatus Type-II paddle apparatus using 900 ml of 0.1N HCl at paddle rotation of 50 rpm at $37^{o}C \pm 0.5^{o}C$ for 24 hours. Two milliliter samples were withdrawn at an interval of 1 hour, filtered and analyzed spectrophotometrically by double beam UV-Visible spectrophotometer (Shimadzu UV- 1700) at 250 nm after suitable dilution of the samples Equal volume of the fresh dissolution medium (2 ml, pre warmed at 37^{o} C ± 0.5^{o} C) was replaced after each withdrawal.Absorbance values were transformed to concentration with reference to a standard calibration curve obtained experimentally.

Kinetics Modeling of Drug Dissolution Profiles[19]:
The dissolution profile of all the batches was fitted to Zero order, First order, Higuchi model and korsmeyer to ascertain the kinetic modeling of the drug release. Korsmeyer-Peppas model explains simple relationship which described drug release from a polymeric system equation to find out the mechanism of drug release.

$$\mathbf{Mt/M\infty = kt^{n}}$$

Where Mt is amount of drug release at time t, M∞ is total amount of drug present in formulation, k is release rate constant depend on geometry of dosage form and *n* is diffusion exponent indicating the mechanism of drug release.

Table No.5: Diffusion exponent and solute release mechanism

Diffusion Exponent (n)	Overall Solute Diffusion Mechanism
0.5	Fickian diffusion
0.5<n<1.0	Non-fickian transport
1	Case-II (relaxational) transport
>1.5	Super case-II transport

***In-vivo* floating study in rabbit[20]:**

An *in vivo* X-rays study was approved by the Institutional Animal Ethical Committee (reference no. LJIP/IAEC/12-13/58). The floating property of the selected F_6 tablets was studied by X-ray technique. Male rabbits with weight of 2.5 kg and with age of 12 months were selected. The Animal was housed under environmental condition (25°C, 12 h light and dark cycle). The rabbit was fasted 36 h and allowed free accesses to water only. The rabbit was administrated with best formulation (F_6). The tablet was administered orally by placing them in hollow polyethylene tube. The tube was inserted into the mouth of rabbit and blown using rubber bulb. X-rays were taken at interval of 0 h, 3 h and 8 h.

Accelerated stability study[20]:

Gastro retentive tablets of Valsartan formulated in the present study were subjected to accelerated stability studies in Aluminum/Aluminum pouch pack as aluminum strip is considered the best protecting packaging material but in the present study simulation was made using aluminum foil pouch. As the dosage form is formulated for drug delivery to stomach, no change should occur in its floating lag time and drug dissolution profile. Dose dumping and failure of buoyancy are probable effects anticipated during the stability study of such dosage forms. The tablets of best batch were packed in aluminium pouch and charged for accelerated stability studies at 40 °C and 75% RH for 1* month in a humidity jar According to ICH guidline. (*optimized formulations are kept for further stability study.)

RESULTS AND DISCUSSION

Preparation of Calibration Curve

Calibration curves of Valsartan were prepared in 0.1N HCl. Calibration curve data were subjected to linear regression analysis. R^2 values were found to be 0.998 in 0.1N HCl which indicate linearity as seen in following Fig 1.

Table No.6: Data for Calibration curve of Valsartan in 0.1N HCl

Concentration (µg/ml)	Absorbance ± S.D (n=3)
5	0.192 ± 0.002
10	0.367 ± 0.002
15	0.554 ± 0.002
20	0.701 ± 0.002
25	0.883 ± 0.001

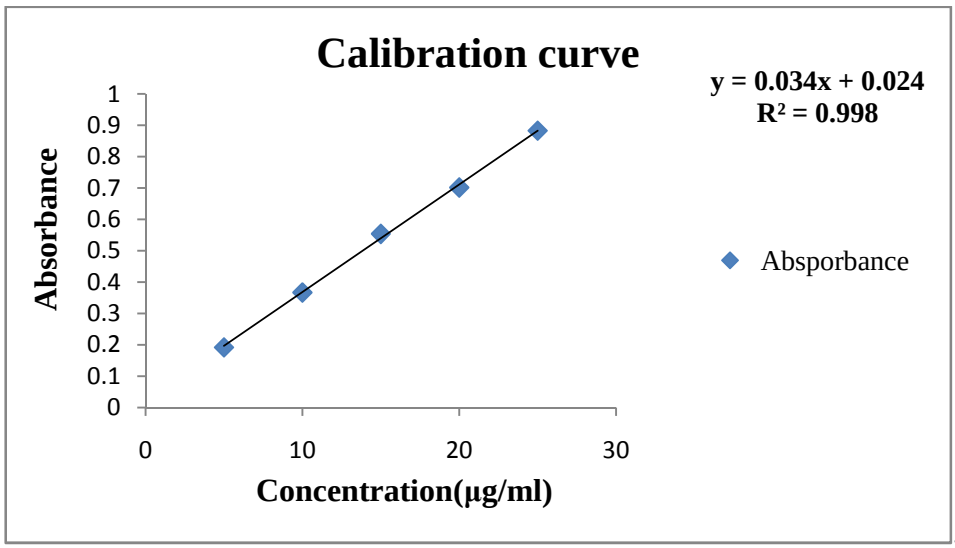


Figure No.1: Calibration curve of Valsartan in 0.1N HCl at 250 nm

DRUG EXCIPIENT COMPATIBILITY STUDY
FT-IR Study

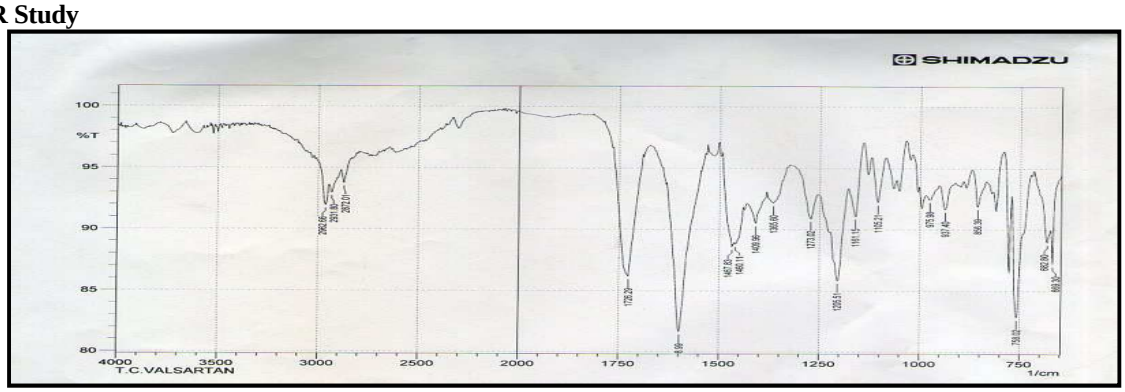


Figure No.2: FTIR spectrum of pure drug Valsartan

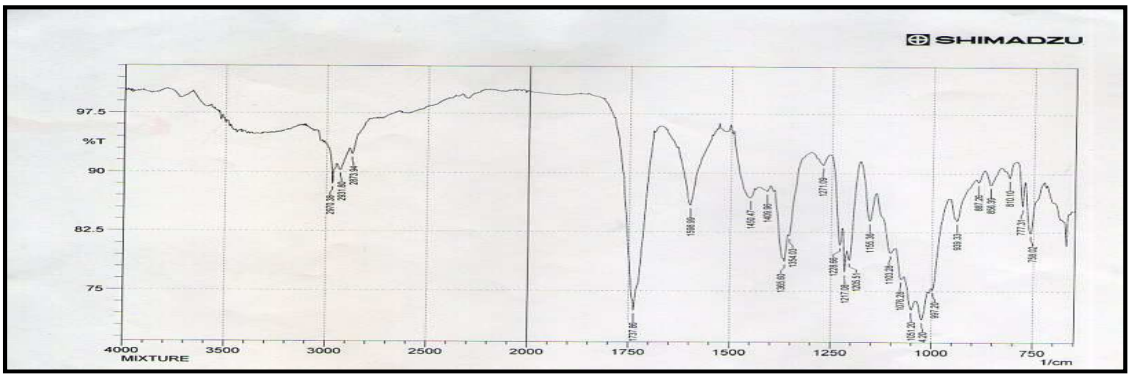


Figure No.3: FTIR spectrum of Valsartan + β-CD + HPMC K100M + EC

Table No.7: Interpretation of FT-IR data

Functional group	N=N bending (Aromatic secondary amine)	C=C stretching	C-H stretching (Alkane)	C=O stretching (Acyclic saturated)
Valsartan	1598.99 cm^{-1}	1409.96 cm^{-1}	2872.01 cm^{-1}	1726.29 cm^{-1}
Valsartan + βCD+ HPMC K100M + Ethyl cellulose	1598.99 cm^{-1}	1409.96 cm^{-1}	2873.94 cm^{-1}	1737.86 cm^{-1}

- The interaction of Valsartan and Polymers like HPMC K100M and Ethyl cellulose was studied using FT-IR spectroscopy method and it was found that Valsartan had not any interaction with Polymers as revealed from figures and Tables.
- The presence of peaks at the expected range confirms that the materials taken for the study. So, Valsartan is compatible with β-cyclodextrin and Polymers.

DSC STUDY

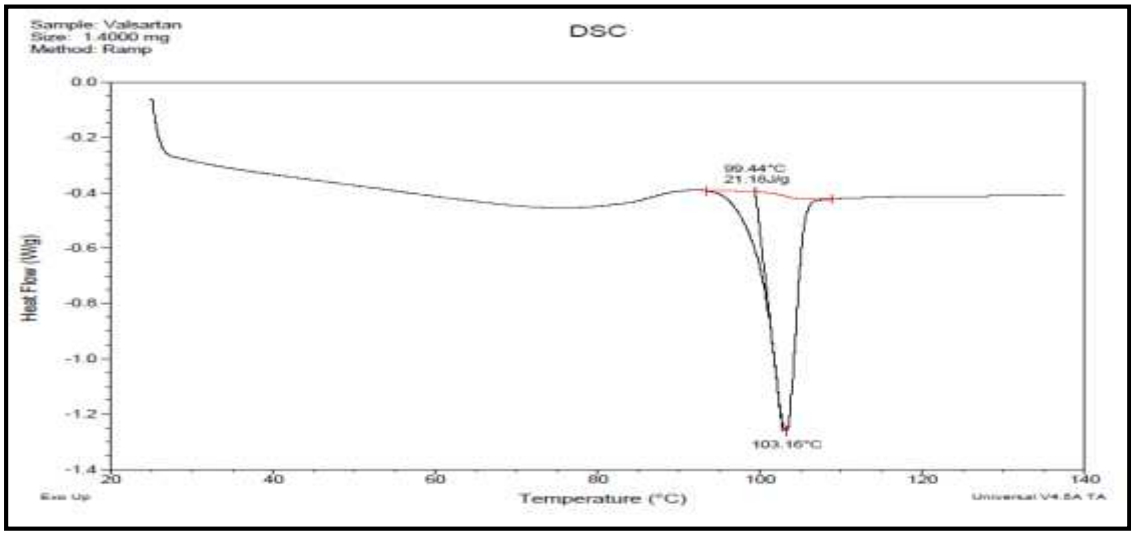


Figure No.4: DSC Spectrum of Valsartan pure drug

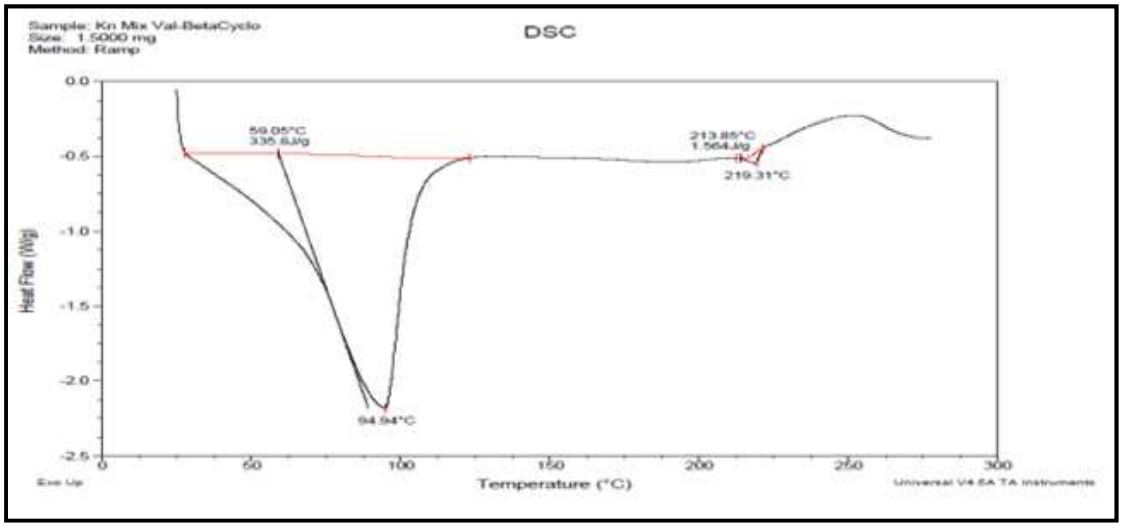


Figure No.5: DSC Spectrum of kneaded mixture of Valsaran with βCD

• The DSC thermograms for the Valsartan and Valsartan: βCD complexes were assayed. Valsartan exhibited a characteristic endothermic fusion peak at 103^0C corresponding to its melting point, hence no polymorphs of Valsartan could be found. Further more βCD shows a broad endothermic peak at 108.10^0C.

• The DSC thermograms for the Valsartan: βCD kneaded complexes show the persistence of endothermic peak of Valsartan, indicating that the kneading process didn't substantially affect their solid state properties. For kneaded complexes there is reduction in the peak intensity; this can be explained on the basis of a major interaction between the drug and cyclodextrin. The characteristic endothermic effect of βCD is slightly shifted to low temperatures indicating that Valsartan got complexed with βCD.

PHASE SOLUBILITY STUDY:

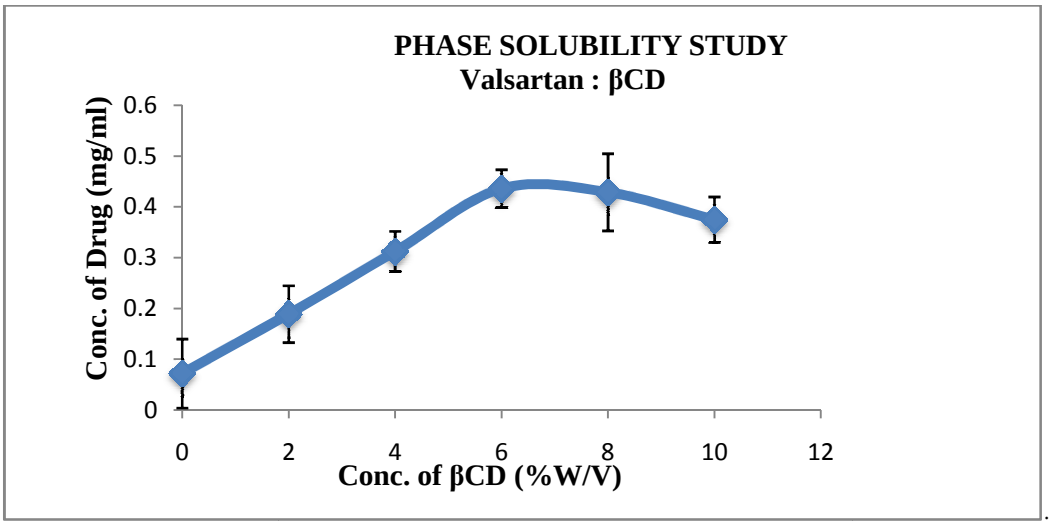


Figure No.6: Phase solubility diagram of Valsartan: βCD complexes

•The phase-solubility diagram for the complexes of Valsartan with βCD is shown in Figure 6. The phase solubility diagram was of **Bs** type according to Higuchi and Connors.

•The solubility of Valsartan was suddenly increased linearly due to the formation of soluble complexes. As the ascending portion of the phase solubility diagram may be considered as A_L type phase solubility diagram. At the βCD concentration value of 6%w/v, the solubility limit of this complexes is reached and so further addition of βCD results in precipitation of the complexes.

SOLUBILITY STUDY:

Table No.8: Solubility study of Valsartan-βCD complexes

Batch no.	Drug:ßCD Molar Ratio	Method of preparation	Concentration (mg/ml)	Fold increase in solubility
0	Drug	Kneading method	0.061±0.001	---
1	1:0.25	Kneading method	0.166±0.004	1.69
2	1:0.5	Kneading method	0.271±0.005	3.39
3	1:0.75	Kneading method	0.347±0.004	4.62
4	**1:1**	**Kneading method**	**0.388±0.002**	**5.3**
5	1:1.25	Kneading method	0.359±0.005	4.82
6	1:1.5	Kneading method	0.343±0.006	4.55

• In Solubility study of Valsartan: βCD complexes, A 5.3 fold increase in the dissolution efficiency of Valsartan was observed in the molar ratio of 1:1. So this ratio is taken in the formulation of final batches.

Table No.9: Micromeritics of Valsartan Bilayer floating tablets

No. of Batches	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index	Hausner's Ratio	Angle of Repose
F_1	0.523	0.618	15.37	1.181	29.05
F_2	0.56	0.680	15.29	1.180	29.74
F_3	0.591	0.666	11.26	1.126	30.26
F_4	0.552	0.647	14.68	1.172	32.48
F_5	0.544	0.629	13.61	1.156	28.39
F_6	0.566	0.647	12.5	1.143	29.74
F_7	0.557	0.680	18.2	1.220	28.62
F_8	0.544	0.647	15.91	1.189	33.72
F_9	0.596	0.708	15.86	1.187	31.41

Evaluation of Physicochemical Parameters of developed bilayer floating tablets

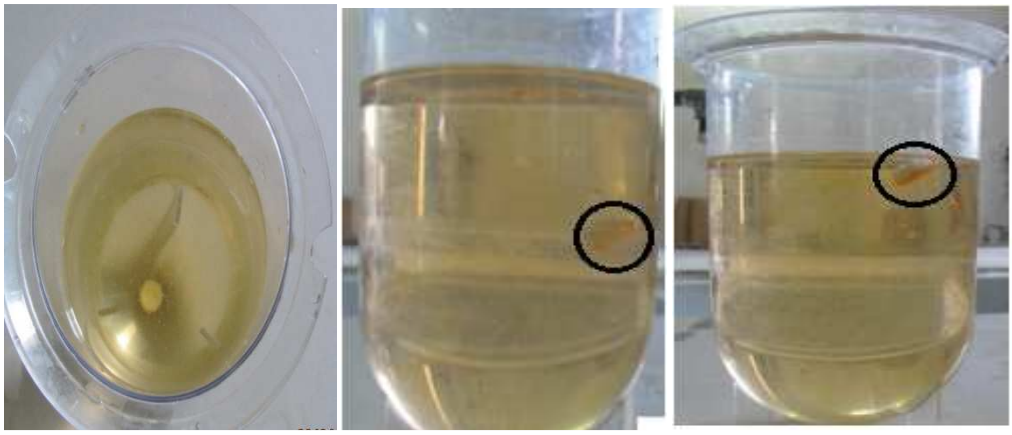
Table No.10: Physicochemical Parameters of Bilayer floating tablets of Valsartan

Batch No	Avg. Weight (mg)	Hardness (kg/cm^2)	Friability	% Drug content
F_1	768	6.0 ±0.12	0.667	99.48
F_2	782	6.2 ±0.10	0.387	98.86
F_3	794	6.5 ±0.08	0.426	97.72
F_4	772	6.0 ±0.16	0.758	101.12
F_5	776	6.2 ±0.09	0.450	98.74
F_6	785	6.4 ±0.05	0.358	99.25
F_7	788	6.2 ±0.18	0.684	102.68
F_8	775	6.4 ±0.15	0.335	96.82
F_9	790	6.7 ±0.17	0.264	97.46

In vitro buoyancy studies

Table No.11: *In vitro* buoyancy studies of Batch F1 to F9

Batch No	FLT (sec)	TFT (hrs)
F_1	218	17
F_2	222	18
F_3	226	20
F_4	224	19
F_5	231	21
F_6	236	24
F_7	229	20
F_8	234	23
F_9	240	26



At 0 sec. **At 234 sec.** **At 236 sec.**

Figure No.7: *In vitro* buoyancy studies

In-vitro buoyancy study showed that all the batches from F_1 to F_9 have FLT of less than 5 minute because of evolution and entrapment of carbon dioxide inside the hydrated polymeric matrices, resulting from the interaction between the gas generating agent and dissolution medium which led to lowering of the density of matrices enabling the tablets to float. On the other hand, as solvent front penetrated the polymer layer, the swelling of **HPMC K100M and Ethyl cellulose** caused increase in volume of the tablet resulted in net reduction in density of the tablet, which prolonged the duration of floatation up to 24 hrs.

***In-vitro* drug release of Bilayer tablets**

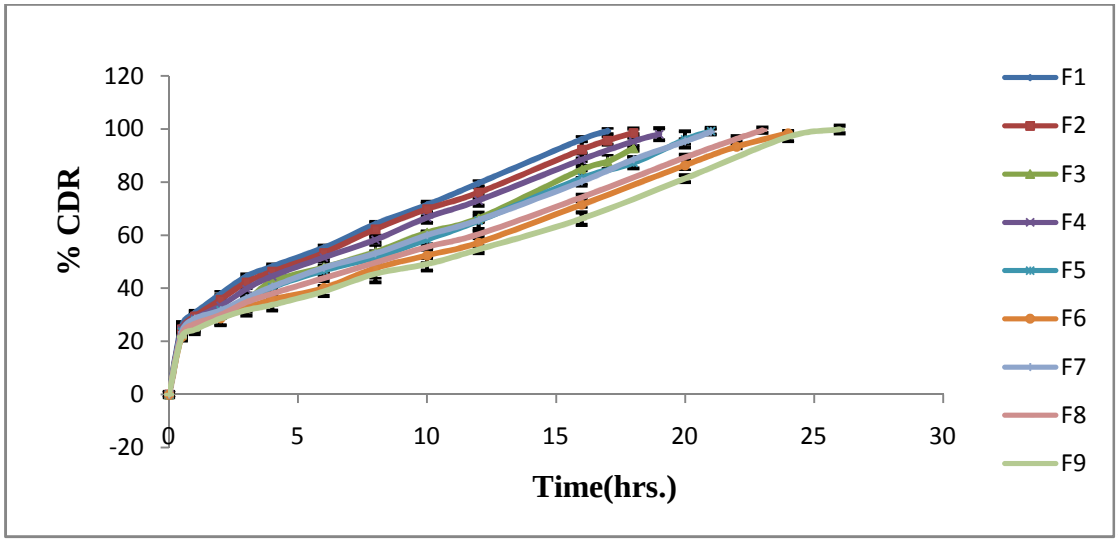


Figure No.8: *In vitro* drug release profile of batch F_1 to F_9

•The cumulative amount of Valsartan release versus time profile for the formulations shown in Table no. indicates that release of drug in first hour was affected by overall concentration of polymer. The initial burst release of drug with lower concentration of polymers in first hour may be due to presence of sodium bicarbonate present in the formulation.

•From the above result, it was concluded that by using polymer like HPMC K100M and Ethyl cellulose showed drug release profile was desirable.

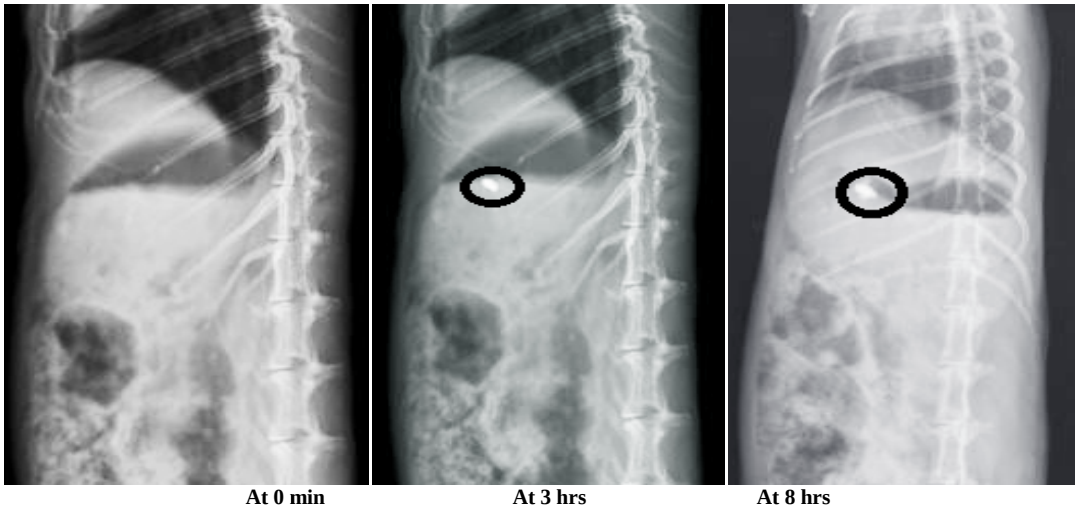
***In vitro* drug release kinetics study**

Table No.12: Release kinetic models data

Formulation code	Parameters	Models				
		Zero Order	First Order	Higuchi Plot	Hixon Crowell	Korsmeyer-Peppas
F_6	R^2	0.9821	0.6938	**0.9878**	0.8702	0.5995
	Slope	3.5070	0.0437	0.0510	0.2789	0.4816
	Intercept	16.416	1.1367	0.1887	3.9396	-0.5053

The kinetics of the dissolution data were well fitted to zero order, Higuchi model and Korsemeyer-Peppas model as evident from regression coefficients. The diffusion exponent n is the indicative of mechanism of drug release from the formulation. The value of diffusion exponent n for formulation F_6 was found to be 0.4816 indicating Fickian diffusion Transport. From the result shown in the Table 12. The release profile of the bilayer floating tablet, was fitted to Zero-order Which having highest R^2 value (0.9821). Drug release kinetics was explained by Higuchi's equation, as the plots showed the highest linearity, but a close relationship was also noted with zero-order kinetics.

***In vivo* Buoyancy study in rabbit**



At 0 min **At 3 hrs** **At 8 hrs**

Figure No.9: *In vivo* Buoyancy study in rabbit

Accelerated Stability Study of Optimized Batch

Stability studies were carried out at 40 ± 2 ^{0}C temperature and 75 ± 5 % RH for 1* month. The optimized formulation (F_6) was packed in amber-coloured bottles tightly plugged with cotton and capped and % drug remained undecomposed was checked at regular time intervals. At the end of studies, samples were analyzed for the weight variation, % Drug content, Friability, Hardness, Floating lag time, Total floating time and *in vitro* Drug release drug content, were carried out which was shown in Table No.13 which concludes that there was no change in physical and chemical properties of formulation. Hence, the results of stability studies reveal that the developed formulation has good stability. so the F_6 formulation was stable at the end of 1* month.

Table No.13: Evaluation of formulation (F_6) kept for stability study at 40^{0}C/75%RH

Parameters	Initial	After 1* month
Weight variation	Pass	Pass
% Drug content	99.25	97.72
Hardness	6.4	6.6
Friability	0.359	0.486
Floating Lag Time(FLT)	236	238
Total Floating Time(TFT)	24	24

Table No.14: In-vitro drug release study of formulation (F_6) kept for stability Study at 40^{0}C/75%RH

Time(Hrs.)	% Cumulative Drug Release	
	Initials	After 1* month
0	0	0
0.5	21.69±1.26	21.86±1.05
1	25.94±2.45	24.12±1.68
2	28.75±2.68	27.98±0.96
3	32.62±1.59	30.43±1.48
4	35.17±1.98	34.75±2.24
6	40.12±1.06	38.16±1.92
8	47.56±3.75	46.25±2.48
10	52.38±2.69	51.68±1.53
12	57.22±1.45	56.35±1.14
16	71.52±1.06	70.59±1.76
20	86.37±1.69	85.76±2.59
22	93.38±0.86	91.34±1.48
24	98.44±1.08	97.22±1.69

CONCLUSION

Valsartan is used in the treatment of cardiac conditions including hypertension, diabetic nephropathy and heart failure. Moreover, the site of absorption of Valsartan is in the stomach. The half life of Valsartan was found to be 6-7 hrs. Therefore, the present investigation was concerned with the development of the Once a day Bilayer floating tablets with dissolution enhancement approach, which after oral administration were designed to provide an

immediate release of drug for quick onset of action and Sustained release of drug for prolong the gastric residence time and thus to improves the bioavailability of the drug. The tablets were obtained by direct compression for all the formulations F_1 to F_9 and evaluated for the buoyancy lag time and floating time, hardness, weight variation and drug content. Based on the performance with respect to buoyancy lag time, floating time and the release characteristics, the formula (F_6) was selected as the best formula (Prototype formulation) as it showed a buoyancy time 236 sec. and a Total floating time upto 24 hrs. It may be concluded that bilayer floating tablets of Valsartan by direct compression technology had shown good floating property and sustained drug release characters. In future the work can be extended for its *in vivo* studies for *in vivo-in vitro* correlation.

REFERENCES

[1] Golla U, Nalla B, Talla R, Gajam P and Voore S, *Der Pharmacia Sinica*, **2011**, 2(4), 33-39.
[2] Manmohan, Shukla T P, Mathur A, Upadhyay N and Sharma S, *Int J of Pharmaceutical Sciences Review and Research*, **2011**, 8(2), 176-182.
[3] Chien YW, *Med Prog Techn*. **1989,** 15, 21-46.
[4] Rao N. G., Panchal H A, Pentewar Ram, *Der Pharmacia Sinica*, **2011**, 2(2), 236-248.
[5] Mayavanshi AV and Gajjar SS, *Research Journal of Pharmacy and Technology*, **2008,** 1(4), 345-348.
[6] Pahwa R, Neeta, Seema, Garg R and Nanda S, *Der Pharmacia Sinica*, **2011**, 2 (5)110-120.
[7] Desai S, Bolton S, *PharmRes*., **1993**, 10, 1321-1325.
[8] Maniya S, Shah S, Upadhyay P, *Am. J. PharmTech Res.* **2012**, 2(2) 2249-3387
[9] Kaur P, Dhiman S and Arora S, *Int J of Pharm*, **2013**, 19(1), 112-122
[10] Rang HP, Dale MM, Ritter JM, Moore PK, pharmacology,Elsevier, **2003**.
[11] Soumya M and Saritha M, *Int j of pharmaceutical & Biological archives*, **2011**, 2(3), 914-920.
[12] Murthy TG and Sowjanya G, *Asian J of Biochemical and Pharmaceutical Research*, **2011**, 1(2), 676-683.
[13] Higuchi T, Connors K, *Adv Anal Chem Instrum*, **1965**.
[14] Kane RN and Kuchekar BS, *Asian j pharmaceutics*, **2010**, 2, 1-8.
[15] Patel BK, Bhople S, Prajapati PA and Patel PU, *Der Pharmacia Sinica*, **2010**, 1 (2): 5-16
[16] Yadav AA, Yadav DS, Karekar PS, Pore YV and Gajare P, *Der Pharmacia Sinica*, **2012**, 3(2)160-169.
[17] Md. S, Keerthi P, Reddy C, Udupi H and Doddayya H, *International Journal of Drug Development & Research*, **2012**, 4(3), 335-347.
[18] Pahade AA, Jadhav VM, Kadam MR, *Int J of Pharma and Bio Sciences*, **2010**, 305-314.
[19] Swarbrick, J, Banakar U. V, "Pharmaceutical Dissolution Testing." Drug and the Pharmaceutical Sciences, Marcel Dekker, New York, **1992**.
[20] Kumar PD, Rathnam G, Prakash CR, Saravanan G, Karthick V and Panneer TS, "*rasayan journal*, **2010**, 368-374.