EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 5
391-401
Year: 2016

DEVELOPMENT AND CHARACTERIZATION OF EXTENDED RELEASE SWELLABLE TABLETS OF VALSARTAN

Dr. Shaik Md. Zakir Hussain*[1], Dr. S. Vijay Kumar, K. R. Manasa[3] and G. Swapna[4]

[1]Associate Professor, Department of Pharmaceutics, Sri Krishna Chaitanya College of Pharmacy (SKCP)
[2]Professor, Department of Pharmacognosy, (SKCP)
[3]M.Pharm, Department of Pharmaceutics, (SKCP)
[4] Assistant Professor, Department of Pharmaceutics, (SKCP) Madanapalle (Chittur Dist) Andhra Pradesh. India.

***Author for Correspondence: Dr. Shaik Md. Zakir Hussain**
Associate Professor, Department of Pharmaceutics, Sri Krishna Chaitanya College of Pharmacy (SKCP) Madanapalle (Chittur Dist) Andhra Pradesh. India.

Article Received on 03/03/2016 **Article Revised on 26/03/2016** **Article Accepted on 16/04/2016**

ABSTRACT
A gastro retentive, controlled release drug delivery system of Valsartan was formulated in an effort to increase the gastric retention time of the dosage form and to control drug release. Various grades of HPMC viz., HPMCK100M, HPMCK15M, HPMCK4M were incorporated for gel forming properties. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. In vitro drug release studies were performed, and drug release kinetics was evaluated using the zero order, first order, Higuchi's model and Korsmeyer-peppas kinetic models. The kinetic study results suggested that the drug was released by fickian diffusion in case of all the developed floating matrix tablet formulations of Valsartan The biological half-life (3-6 hours) and maximum absorption in initial part of gastro intestinal tract of Valsartan favours development of gastro retentive floating dosage form. In the present study Valsartan floating tablets were prepared by effervescence method using sodium bicarbonate and citric acid as a gas generating agent. The drug-excipient compatible studies were performed by FTIR, and the study revealed that there is no drug excipient interaction. The prepared floating tablets were evaluated for various physicochemical parameters. The in-vitro drug release pattern of Valsartan floating tablets was fitted to different kinetic models which showed highest regression for zero order kinetics with Higuchi mechanism.

KEYWORDS: Valsartan, Floating tablets, HPMC, Eudragit, direct compression, Effervescent system, sustained release.

INTRODUCTION
- Oral administration is the most convenient and preferred means of any drug delivery to the systemic circulation. Oral controlled drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages Ease of dosing administration.

1) Patient compliance.
2) Flexibility in formulation.

- Drugs that are easily absorbed from gastrointestinal tract (GIT) have short half lives and eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time.
- After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT) [1, 10]. These drug delivery systems suffer from mainly two adversities:
- The short gastric retention time (GRT).
- Unpredictable short gastric emptying time (GET).

Gastrointestinal Tract Physiology

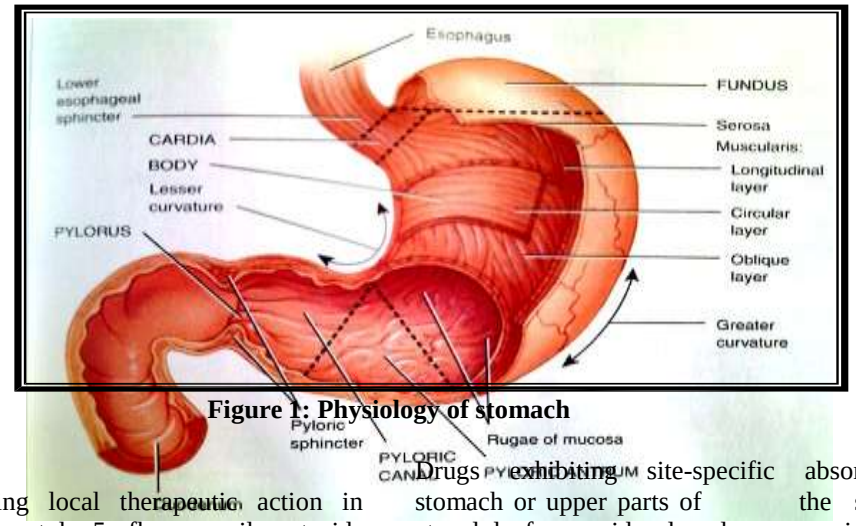

Figure 1: Physiology of stomach

Need of GRDDS[2]

Drugs required exerting local therapeutic action in the stomach: misoprostol, 5- fluorouracil, antacids and antireflux preparations, anti Helicobacter pylori agents and certain enzymes.

Drugs exhibiting site-specific absorption in the stomach or upper parts of the small intestine: atenolol, furosemide, levodopa, p-aminobenzoic acid, riboflavin-50-phosphate, salbutamol (albuterol), sotalol, sulpiride and thiamine.[11, 12]

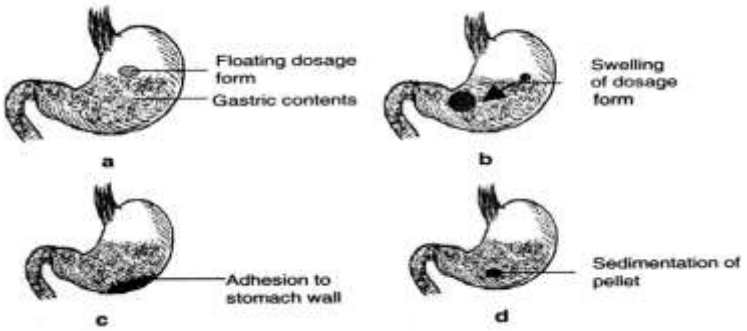

Figure .2. Various forms of gastro retentive systems; (a) Floating gastro-retentive drug delivery systems; (b) Swelling gastro-retentive drug delivery systems; (c) Bioadhesive gastroretentive drug delivery systems; (d) High-density gastro retentive drug delivery systems.

Floating drug delivery system [13-14, 15]

- These have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy. Floating drug delivery systems are classified depending on the use of two formulation variables, effervescent and non-effervescent systems.

MATERIAL AND METHODS

Material

- Drug, povidone, Microcrystalline cellulose (101.102), Lactose monohydrate, Crospovidone (Polyplasdone XL 10), Colloidal silicon dioxide, Magnesium Stearate, Xanthan gum, Acrylamide, Acrylic acid, Span 80, *N*,*N*′-methylenebisacrylamide (Bis), Ammonium per sulfate (APS), *N*,*N*,*N*′,*N*′-tetramethyl-ethylenediamine (TEMED), Sodium bicarbonate, Croscarmellose Sodium

Methods

Drug-Excipients compatibility study

Fourier transforms infrared spectroscopy (FT-IR)

- The chemical structures of the synthesized SPH were investigated by using FT-IR spectroscopy (Shimadzu FTIR 8000, Japan). Disk samples were prepared as KBr (potassium bromide) disks compressed under a pressure of 150 lbs. The spectra were scanned over a frequency range of 4,000–500 cm^{-1}.
- Method: 1 mg of drug is mixed with the 100 mg of Spectroscopic grade of KBr and triturated for uniform mixing. The thin and transparent pellet is prepared by applying 150 lbs pressure. The prepared pellet is exposed to IR beam and spectra are recorded by using FT-IR**.**

Formulation of Valsartan Swellable Tablets

- Valsartan used in the formulation has very poor flow; to avoid processing problems. Wet granulation process was selected for this formulation to improve the flow properties.[3] First the materials are dry mixed, where after liquid is added during mixing. Then the moist mass is wet massed in order to achieve a narrow particle size distribution. Thereafter the granules are wet sieved, dried and sieved again. The liquid amount is critical, because the process is susceptible for over-wetting, which leads to uncontrollable agglomerate growth. Variations in raw materials may affect the liquid requirement.[4] Impeller torque and power consumption of mixers has been used to monitor the properties of wet masses during agglomeration. The above method of measurement gives a measure of the amount of resistance the impeller experiences to keep a certain rotational speed.[5]

Evaluation of tablets

Weight variation

- 20 tablets were taken and weighed individually on a digital weighing balance. Average weight was calculated and the individual tablet weight was compared to the average. The tablet pass the U.S.P. test if no more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

$$\text{Average weight} = \frac{\text{Weight of 20 tablet}}{20}$$

Thickness

- Thickness of tablet is important for uniformity of tablet size. Thickness of tablets can vary with no change in weight because of the difference in the density of the granulation and the pressure applied to the tablets, as well as the speed of the compression machine. Ten tablets were randomly selected and thickness was measured using vernier calipers and recorded.

Crushing strength or Hardness

- Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength. Any change in hardness results in differences in disintegration and dissolution characteristics. The crushing strength of the tablet was determined using Schleuniger hardness tester.

Friability test

- This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. For tablets weighing up to 650 mg each, take a sample consisting of the minimum number of tablets that makes a total mass of more than 6.5 gm

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Swelling Behavior

- The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all formulation was studied. One tablet from each formulation was kept in a petridish containing pH 6.8 phosphate buffers
  S.I = {(Mt-Mo) / Mo} X 100,

Invitro Dissolution studies

- Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of liquid/solid interface, temperature and solvent composition. It is a dynamic property that changes with time and explains the process by which a homogenous mixture of a solid or a liquid can be obtained in a solvent. The test determines the time required for formulation.

Method II

Preparation of Superporous Hydrogel Composite

- SPHC were synthesized using various vinyl monomers. The monomers used in this study were acryl amide (AM), acrylic acid (AA), (2.5%) bis acrylamide as cross linker, span- 80 as foam stabilizer. Initially all the ingredients were added sequentially into a test tube. 50%(w/v) AM and 50%AA(v/v) as monomers, (2.5%w/v) Bis acrylamide as cross linker, span- 80 (10%v/v) as foam stabilizer, 20%(w/v) APS, and 20% (v/v) TEMED(tetra methyl ethylene di amine) as polymerization initiator pair, double distilled water (DDW), and 150 mg of sodium bicarbonate. The test tube was shaken to mix the solution after each ingredient was added. The pH of the AA was adjusted to pH5 by using 2 M NaOH. Ac-Di-Sol was used as composite material. Sodium bicarbonate was added to the monomer solutions and whole mixture was stirred using a spatula for several seconds to properly distribute the gas bubbles. Sodium bicarbonate was used as a foaming or gas blowing agent which increases the pH of the solution and accelerated the polymerization reaction. The synthesized SPH was removed from the test tube by adding 2 ml of absolute ethanol. The absence of monomers was ensured spectrometrically by ensuring that the water of the washings did not contain any trace of monomers. The formed composite was dried in an oven at 60°C for 6 hours.[6]

Evaluation procedure

Mechanical strength

- The penetration pressure of the SPH composite was measured using a bench comparator as described by Chen *et al*. with modifications. The fully swollen hydrogel was put longitudinally under the lower

touch and weights were successively applied to the upper touch until the polymer completely fractured. The penetration pressure could be calculated from the following equation.[8]

PP = W/S

Measurement of density:

The density (d) of the dried hydrogels was calculated by following Equation.

$D = W_d/V_d$

Measurement of porosity

- For porosity measurement, the solvent replacement method was used. Dried hydrogels were immersed overnight in absolute ethanol and weighed after excess ethanol on the surface was blotted. The porosity was calculated from the following equation:

Porosity = (M2– M1) / ρV

Drug content uniformity:

- A weight of superporous hydrogel containing required amount of drug is taken in 100 ml volumetric flask. About 10 ml of required buffer is added, mixed well and make up to volume. The mixture is filtered and drug content is determined using UV-Visble spectrophotometer at appropriate wavelength

Invitro dissolution studies

- The release of drug was determined in USP XXX dissolution apparatus II. The dissolution test was carried out for 12 hours, using 900 ml of 0.1 N HCl at 37 ± 0.5˚C and 50 rpm. Volumes of 10 ml were withdrawn at different time intervals from the dissolution medium and replaced with fresh medium. The sample was filtered by 0.5mm pap filters. The filtered samples were analyzed spectrophotomerically at 248 nm

Zero order kinetics:

$$F_t = K_0 t$$

Where, $F_t = 1 - (W_t / W_O)$, W_O is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage form at time t.

F_t represents the fraction of drug dissolved in time t and K_o the apparent dissolution rate constant or zero order release constant.

First order kinetics

$$\ln (1- F) = - K_1 t$$

Where F represents the fraction of drug released in time t and K_1 is the first order release constant.

Higuchi model

$$F = K_2 t^{1/2}$$

Where F represents the fraction of drug released in time t and K_2 is the Higuchi dissolution constant

Korsmeyers-Peppes model

$$F = K_4 \cdot t^n$$

Where K_4 is a constant incorporating the structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug dissolved fraction at time t. This equation was further simplified and proposed by Ritger and Peppas as

- $Mt/M=K.t^n$

Where Mt is the drug released at time t, M is the amount of drug released at infinite time, K is a kinetic constant, and n is the diffusion exponent. The value of n indicates the drug release mechanism.

Stability studies

- Stability studies were performed at a temperature of 40^0 C at 75 % RH, over a period of three months (90 days) for the optimized superporous hydrogel. These were packed in HDP bottles and kept in stability chamber maintained at $40^0 \pm 1^0$C & 75 % RH. Samples were taken at monthly intervals for drug content estimation. At the end of three months period, dissolution test and drug content studies were performed to determine the drug release profiles and drug content.[9]

RESULTS

Table.1 Composition of screening trials (F1-F6)

	F1	F2	F3	F4	F5	F6
Ingredients	**mg/tablet**	**mg/tablet**	**mg/tablet**	**mg/tablet**	**mg/tablet**	**mg/tablet**
Intra Granular Portion						
Valsartan	320.000	320.000	320.000	320.000	320.000	320.000
Microcrystalline cellulose(101)	200.000	190.000	160.000	200.000	190.000	160.000
Lactose monohydrate	40.000	40.000	40.000	40.000	40.000	40.000
Povidone K30	20.000	20.000	20.000	20.000	20.000	20.000
Crospovidone (Polyplasdone XL 10)	40.000	40.000	40.000	40.000	40.000	40.000
Colloidal Silicon Dioxide	5.000	5.000	5.000	5.000	5.000	5.000

Water	15 %	15%	15%	15%	15 %	15%
Extra Granular Portion						
Microcrystalline cellulose(102)	50.000	40.000	20.000	50.000	40.000	20.000
Crospovidone (Polyplasdone XL 10)	30.000	30.000	30.000	30.000	30.000	30.000
Xanthan Gum	30.000	50.000	100.000	-	-	-
Carrageenan	-	-	-	30.000	50.000	100.000
Colloidal Silicon Dioxide	5.000	5.000	5.000	5.000	5.000	5.000
Magnesium Stearate	10.000	10.000	10.000	10.000	10.000	10.000
Core Tablet Weight	750.000	750.000	750.0000	750.000	750.000	750.000

Table. 2. Composition for formulation of super porous hydrogel

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Valsartan(mg)	300	300	300	300	300	300
Acrylic acid(µl)	200	200	200	200	200	200
Acrylamide(µl)	300	300	300	300	300	300
N,Nmethylene Bisacrylamide(µl)	50	50	100	150	200	250
Ammoniumpersulphate(µl)	50	50	50	50	50	50
Span-80(µl)	50	50	50	50	50	50
Double distilled water(µl)	400	400	400	400	400	400
Ac-Di-Sol(mg)	--	30	45	60	75	90
Sodium bicarbonate(mg)	150	150	150	150	150	150

Flow properties

Table.3. Flow properties of Valsartan

Test	**Observations**
Bulk density	0.25 gm/ml
Tapped density	0.417 gm/ml
Compressibility Index	40.05 %
Hausner's ratio	1.67

Table No.4. solubility data show that the Valsartan is poorly soluble in water and has better solubility in 0.1N HCl

S. No.	**Medium**	**Solubility (mg/mL)**
1	Water	0.422
2	pH 1.2	1.32
3	pH 4.5	0.92

Table. 5. Particle size analysis by sieve shaker

Sieve Mesh Number	**Sieve Size Opening µm**	**Mass of Sample Retained (gms)**	**Percentage of Sample Retained (%)**	**Cumulative Percentage Of Sample (%)**
#20	841	2.3	9.25	9.25
#30	595	3.85	15.49	24.74
#40	400	3.09	12.43	37.1
#60	250	9.29	37.38	74.5
#80	177	1.67	6.72	81.2

#100	149	2.37	9.53	90.8
Bottom pan	-	2.28	9.17	99.97

Table. 6. Blend characterization of formulations of trial batches

Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility Index (CI) (%)	Hausner's ratio (HR)
F1	0.498	0.579	13.98	1.16
F2	0.489	0.569	14.05	1.16
F3	0.497	0.584	14.89	1.17
F4	0.496	0.574	13.58	1.15
F5	0.499	0.583	14.40	1.16
F6	0.493	0.574	14.11	1.16
F7	0.488	0.570	14.38	1.16
F8	0.494	0.578	14.53	1.17

Method I: Charecterization of Swellable Tablets

Table. 7. Results of blend characterization of formulations of trial batches

Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility Index (CI) (%)	Hausner's ratio (HR)
F1	0.498	0.579	13.98	1.16
F2	0.489	0.569	14.05	1.16
F3	0.497	0.584	14.89	1.17
F4	0.496	0.574	13.58	1.15
F5	0.499	0.583	14.40	1.16
F6	0.493	0.574	14.11	1.16
F7	0.488	0.570	14.38	1.16
F8	0.494	0.578	14.53	1.17

Physical parameters of screening trials (F1 – F6)

Table.8. Results of Physical parameters of screening trials (F1 – F6)

Observations	Weight variation (mg)	Thickness(mm)	Hardness (kp)	Friability (%)	Swelling index
F1	748	7.44-7.49	5.6	0.07	42.6
F2	752	7.48-7.50	5.4	0.06	54.4
F3	749	7.46-7.49	5.9	0.07	95.8
F4	748	7.48-7.53	5.9	0.08	33.4
F5	750	7.42-7.49	5.6	0.07	38.2
F6	752	7.46-7.50	5.2	0.08	46.7

Dissolution profile of Screening Trials

Table.9. Dissolution Results of Screening Trials (F1 – F6)

Time in Hrs	%Drug Release Medium:0.1N HCL; RPM:50					
	F 1	F 2	F 3	F 4	F 5	F 6
2	8.3	7.2	5.4	7.5	7.8	5.9
4	18.6	16.3	13.1	17.8	15.9	12.5
6	28.7	23.2	21.5	29.3	23.9	22.2
8	39.2	37.4	30.2	38.4	37.8	31.2
12	41.1	40.6	33.9	46.8	40.1	33.6
16	53.3	48.1	40.2	55.2	48.3	41.1
18	65.4	59.2	57.3	66.3	60.2	57.8
20	82.5	68.3	65.5	78.2	68.9	65.7
24	98.8	91.5	86.2	95.8	91.1	88.2

Drug release kinetics

Table.10. Drug Release Kinetics for Optimized Formula F14

	ZERO ORDER	FIRST ORDER	HIGUCHI	PEPPAS
	1	4	2	3
	Q Vs T	Log % of drug Remain Vs T	Q Vs √T	LogC (Vs) LogT
Slope	0.285	0.017	2.703	0.002
R^2	0.364	1.46	0.968	0.364

Table. 11. Results of Dissolution profile of Screening Trails F9-F14

Time in Mins	%Drug Release Medium 0.1N HCL; RPM 50 T 37±5^0 C					
	F9	F10	F11	F12	F13	F14
5	11	9	8	8	7.5	6.5
10	18	16	14	13	10	14
15	24	20	18	17	14	12
20	30	24	22	21	18	14
30	38	29	27	26	21	15
60	52	36	32	29	27	22
120	71	51	43	38	34	27
180	82	69	54	49	41	31
240	-	77	65	53	48	37
300	-	84	79	58	55	43
360	-	-	86	65	64	48
420	-	-	92	77	73	56
480	-	-	-	84	82	64
540	-	-	-	93	88	70
600	-	-	-	-	96	78
660	-	-	-	-	-	87
720	-	-	-	-	-	98

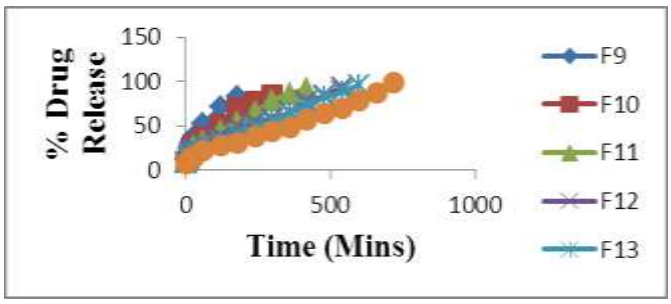

Figure .3. Dissolution profile of screening trails F9-F14

FTIR of Valsartan

Figure 4. FTIR of Valsartan

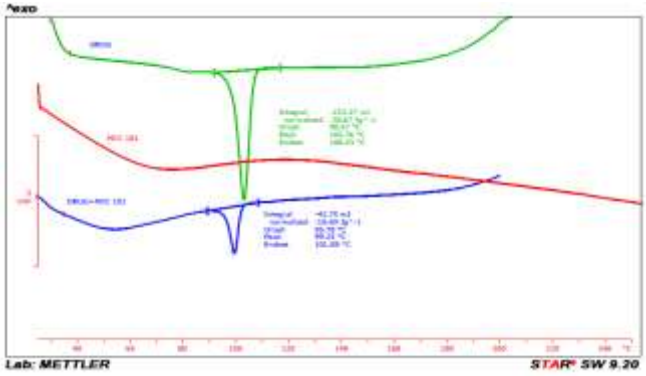

Figure.5 DSC thermogram of Valsartan, Avicel PH 101, drug and avicel PH 101 mixtures

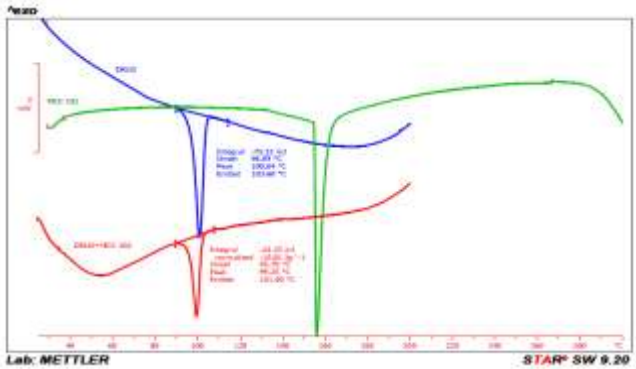

Figure .6. DSC thermogram of Valsartan, avicel PH 102, Valsartan and avicel PH 102 mixtures

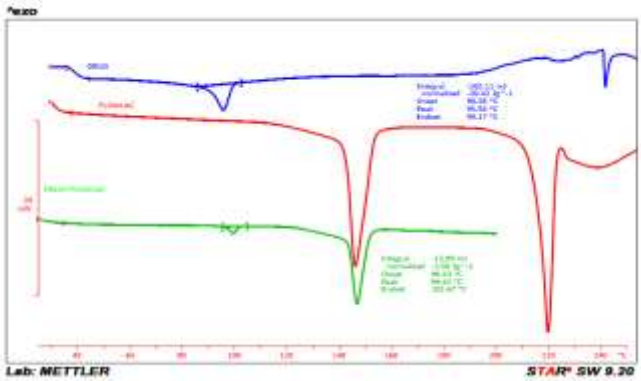

Figure.7. DSC thermogram of Valsartan, lactose monohydrate, Valsartan and lactose monohydrate mixture

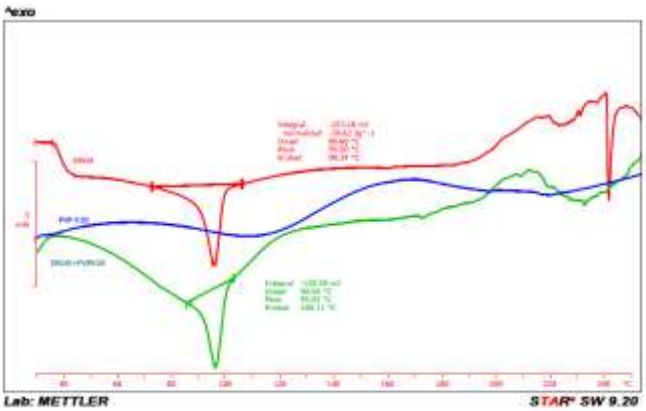

Figure.8. DSC thermogram of Valsartan, Povidone K_{30}, Valsartan and Povidone K_{30} mixture

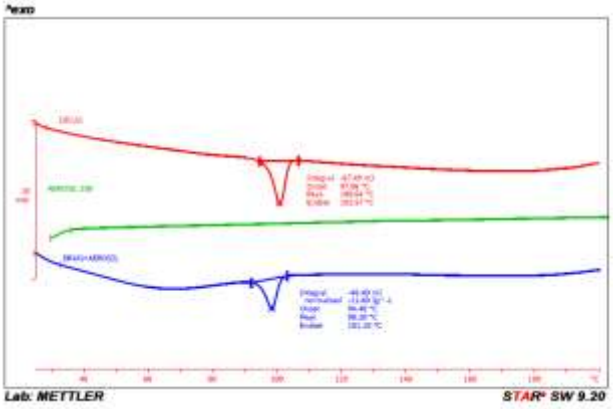

Figure.9. DSC thermogram of Valsartan, Colloidal silicon dioxide, Valsartan and Colloidal silicon dioxide mixture

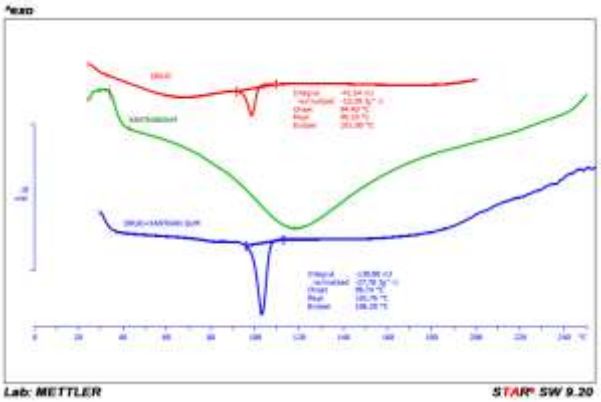

Figure.10. DSC thermogram of Valsartan, Xanthan gum, Valsartan and Xanthan gum

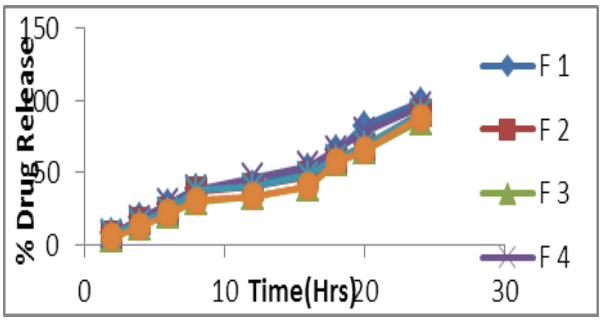

Figure .11. Dissolution profile of Screening Trial F1 to F6

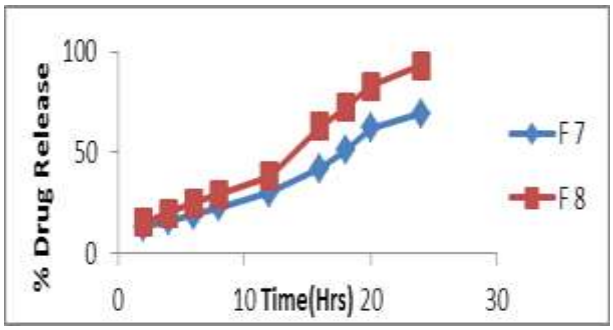

Figure.12. Dissolution profile of Screening Trial F7 - F8

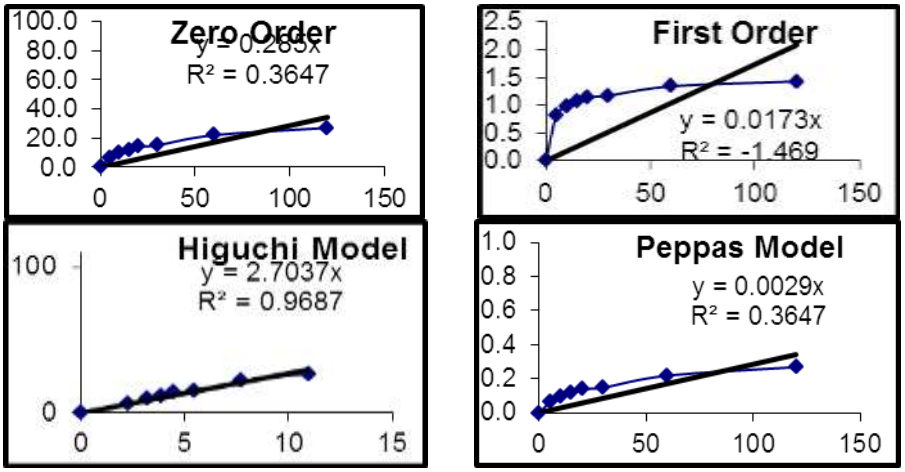

Figure.13. Different plots showing release of drug in various methods

CONCLUSION

In extended release swellable tablet (method1)

Different polymers like Xanthan gum and Carrageenan were used to retard the drug release, swelling index was increased with increasing the polymer concentration and the release profile of the Valsartan was retarded as the concentration of the swelling polymer increased. The Valsartan extended release swellable tablets were prepared by wet granulation method semi synthetic polymers, povidone k30,xanthan gum, carrageenan were used as release retarding agent the tablets were compressed using 13mm round punch. weight variation for all the tablets showed compliance with the official specification (IP,2007) as non of the product deviated by up to 5% from its average weight .in addition thickness of these tablets was found uniform the hardness of these tablets were within the range 5.63±0.43 to 6.92±0.33Kg/cm^2 the friability of all the formulated tablets was found within the range.

Further trials were carried out in Xanthan gum 30mg (F3) by varying disintegration concentration 40% was found satisfactory.F3 formulation with swelling index of 95% in 720mins.

- *Invitro* dissolution profile containing drug with xanthan gum 30mg has shown satisfactory dissolution results. The percentage drug release was up to 98%

Drug excipient compatibility studies was carried out using FTIR and DSC, the results shown that there was no compatibility between Valsartan and Excipients used.

In superporous hydrogels (method II)

The F9 trial has shown poor mechanical strength, further trials were carried out to improve the mechanical strength of hydrogels and to obtain sustained drug release.F14 has shown satisfactory mechanical strength with high concentration (90mg) of acdisol.

The swelling index of superporous hydrogel was performed. It has shown 95% of swelling index in 9mins (F14) *In vitro* dissolution profile containing drug, Acdisol (90mg) F14 has shown. 98% of drug release Superporous hydrogels (F14) showed 95% of swelling index in 9 mins where has swelling index of swellable tablets showed 95% in 720 mins. The FTIR, DSC analyses indicated that there was absence of any chemical interaction between the drug and the excipients. Accelerated stability studies were performed (40˚C/75%RH) the hydrogels were packed in HDP bottles and was kept in stability chamber for 3 months.

ACKNOWLEDGMENT

- All authors would like to thanks Sri Krishna Chaitanya College of Pharmacy, Madanapalle chittur dist Andhra Pradesh. India for supporting in the fulfillment of this work. I would like to thanks hon' ble principle **Dr. S. Vijay Kumar** for giving his support in all aspects.

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