IJPSR (2017), Vol. 8, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 01 October, 2016; received in revised form, 27 February, 2017; accepted, 05 March, 2017; published 01 April, 2017

FORMULATION AND *IN VITRO* EVALUATION OF GASTRORETENTIVE FLOATING DRUG DELIVERY OF VALSARTAN USING HOT MELT EXTRUSION TECHNIQUE

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Keywords:

Hot Melt Extrudates, Hot melt extrusion technique, solubility, Dissolution rate

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ABSTRACT: The aim of present study is to improve the aqueous solubility of valsartan by utilizing hot melt extrusion technique (HME). Hot melt extrudates were prepared by novel polymeric matrices such as HPMCAS and Plasdone S630 copovidone at different ratios. The solubility studies of extrudates, showed a significant improvement in aqueous solubility. Gastroretentive floating tablets of valsartan using its extrusion complex with plasdone S630 copovidone were formulated by, direct compression method. The tablets comprised of HPMC K4M, HPMC K15M, as release retarding polymers to control the drug release. Preliminary trials applied to optimize the drug release profile. A 10.5 fold increase in the solubility of valsartan was observed with valsartan: plasdone S630 copovidone complex in the ratio of 1:2. Trial batches of tablets showed best results for formulation F3 (20% HPMC K15M and pregelatinized starch 12%) released 99.41% of valsartan in 20 h, with desired floating lag time (18 sec) and constantly floated on dissolution medium for more than 24 h. Accelerated stability studies were conducted at 40±2 ºC temperature and 75±5% RH to determine the effect of aging on the physical and chemical stability of the drug, the results showed no significant loss of activity of drug in the prepared formulations. From the study it was concluded that a gastroretentive floating drug delivery of poorly soluble valsartan can be formulated using hot melt extrusion technique.

INTRODUCTION: Gastric emptying of dosage forms is an extremely complex process and ability to prolong and control the gastric emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Valsartan was first developed by Novartis and was sold under the brand name DIOVAN.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(4).1813-19

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (4).1813-19

In the USA, valsartan is registered by the Food and Drug Administration (FDA) for use in the treatment of hypertension in children of 6 years and older and adolescents in the December 2008. Valsartan is an orally active Angiotensin II receptor type 1 antagonist which facilitates reduction in blood pressure and is used in treatment of hypertension.

It has an absolute bioavailability is 10-35% and this is not influenced by food ingestion. It has an elimination half-life of 6-9 hours and its plasma protein binding is more than 90%. The elimination of valsartan occurs mainly as unchanged drug in the bile (86%) and to a lesser extent (13%) in the urine by the renal excretion [1].

According to the Biopharmaceutical Classification System (BCS), valsartan is considered a BCS class II compound with low solubility and high permeability. Valsartan is a potent, orally active nonpeptide tetrazole derivative and selectively inhibits Angiotensin II Receptor type 1 which causes reduction in blood pressure and is used in treatment of hypertension. Valsartan is poorly soluble and the aqueous solubility is reported to be less than 1 mg/mL [2]. The drug is rapidly absorbed following oral administration, with a bioavailability of about 23%. Peak plasma concentrations of valsartan occur 2 to 4 h after an oral dose and 94% to 97% of the drug is bound to plasma protein [3, 4].

Hot-melt extrusion has been proved to provide sustained, modified, and targeted drug delivery [5, 6]. In our previous study, we prepared, optimized, the valsartan-loaded Plasdone s-630 copovidone based hot melt extrudates. The formulations with different drug/polymer ratio of 1:1, 1:2 and 1:4 were prepared and the solid dispersions were obtained by hot melt extrusion technique. We found a significant increase in the solubility of valsartan with valsartan: plasdone S630 copovidone complex in the ratio of 1:2 in comparison with the plain drug [7, 8, 9]. The simplicity and scalability of the hot melt extrusion process lead us to prepare gastroretentive floating tablets of valsartan, using its extrusion complex with plasdone S630 copovidone.

MATERIALS AND METHODS:

Materials: Valsartan was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad. Hypromellose acetate succinate (HPMCAS), plasdone S630 copovidone were obtained as a gift sample from Ashland Inc., USA. HPMC K4M, HPMC K15M, hydroxy propyl cellulose, pregelatinized starch were supplied by Colorcon Ltd., England. Micro crystalline cellulose, sodium bi carbonate, magnesium stearate were obtained from S.D Fine-Chem. Private Ltd., Bengaluru, India.

Methods:

Preparation of valsartan floating tablets: After finding the best suitable combination for hot melt extrudates of drug and polymers, Valsartan floating tablets were prepared by using direct compression technique (**Table 1**) and evaluated for pre-compression parameters like angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio. Post-compression evaluation of floating tablets like hardness, thickness, drug content, and weight variation, friability, floating lag time, total floating time, dissolution studies and stability studies were studied.

TABLE 1: FORMULATION CHART FOR PRELIMINARY TRIALS OF VALSARTAN FLOATING TABLETS

Ingredients (mg)	FT-1	FT-2	FT-3
Valsartan HME	150	150	150
HPMC K4M	100	100	-
L-Hydroxy propyl cellulose	30	-	-
HPMC K15M	-	-	100
Pregelatinised starch	30	60	60
Micro crystalline cellulose	135	135	135
Sodium bi carbonate	50	50	50
Magnesium stearate	5	5	5
Tablet total weight	500	500	500

RESULTS AND DISCUSSIONS: Solubility of valsartan in various media: To assess the solubility of valsartan in various solvents, 50 mg of drug was added to 100 mL of each solvent and the samples were rotated at 50 rpm in a water bath (37.0±0.5°C) for 48 hours [10]. The samples were then filtered and analyzed, with the help of a UV spectrophotometer at 249 nm (**Table 2, Fig. 1**).

TABLE 2: SOLUBILITY OF VALSARTAN DRUG IN VARIOUS MEDIA

Media of solubility	Solubility, mg/mL (AM±SD) (n=3)
Water	0.046±0.0001
0.1N HCl	0.055±0.0001
0.01N HCl	0.024±0.0001
pH 4.5 Acetate buffer	0.285±0.001
pH 6.8 Phosphate buffer	0.324±0.001
pH 7.5 Phosphate buffer	0.336±0.001
pH 8.0 Borate buffer	0.286±0.001

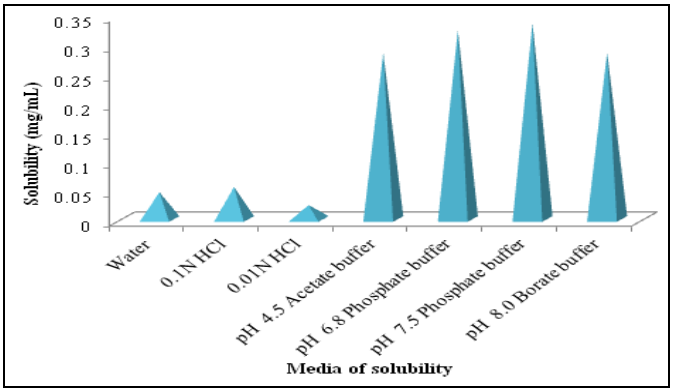

FIG. 1: SOLUBILITY OF VALSARTAN IN DIFFERENT MEDIA

Aqueous solubility studies of valsartan preliminary hot melt extrudates: For selection of a suitable polymer for preparation of valsartan solid dispersions, the solubility of valsartan pure drug and preliminary trials of solid dispersions prepared with Plasdone S630 copovidone, were conducted in distilled water (**Table 3**). An excess of valsartan powder (VAL, about 1 g) and preliminary trials of solid dispersions (HME 1 – HME 3, about 1 g) were added to 10 ml of water, followed by shaking in a water bath at 25 ºC for 24 h, and then centrifuged and filtered through a membrane filter (0.45 µm) [11, 12]. UV spectroscopy performed at 249 nm for analysis of the concentration of valsartan in the resulting solution.

TABLE 3: AQUEOUS SOLUBILITY STUDIES OF VALSARTAN PRELIMINARY HOT MELT EXTRUDATES

Formulation code	Physical mixture	Aqueous solubility (mg/mL) (AM±SD)(n=3)
VAL	Valsartan powder	0.046±0.001
HME 1	VAL+ Plasdone S630 copovidone	0.485±0.0007
HME 2	VAL + HPMCAS	0.317±0.001
HME 3	VAL + Plasdone S630 copovidone + HPMCAS	0.526±0.001

Among the two polymers tested, plasdone S630 copovidone showed the highest solubility of valsartan, which was approximately 0.485 mg/mL. Thus, plasdone S630 copovidone was selected as suitable polymer for development of the valsartan solid dispersions by hot melt extrusion technique.

Preparation of valsartan floating tablets: Valsartan floating tablets were prepared by using direct compression technique and evaluated for pre-compression parameters (**Table 4**) and post-compression parameters [13].

TABLE 4: PRE-COMPRESSION PARAMETERS

Formulation Code	(AM±SD) (n=3)				
	Angle of repose (º)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
FT-1	29.36±0.084	0.42±0.012	0.46±0.008	11.14±0.009	109±0.008
FT-2	28.21±0.08	0.48±0.007	0.52±0.007	12.5±0.084	1.08±0.004
FT-3	28.16±0.008	0.43±0.007	0.52±0.007	11.11±0.003	1.23±0.040

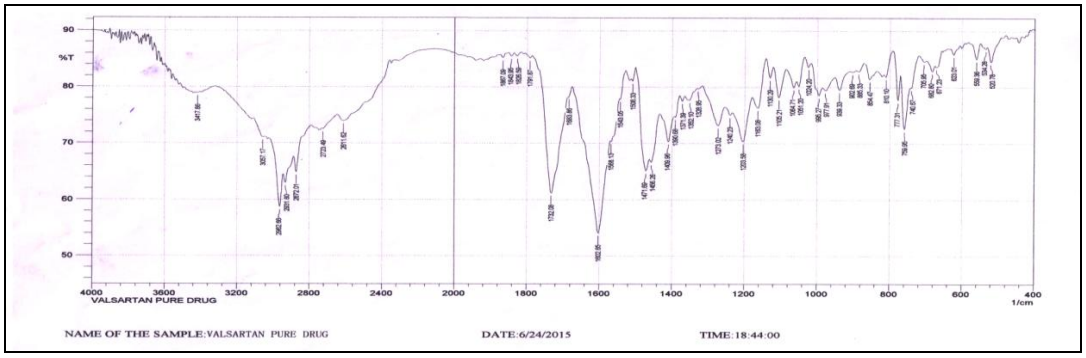

FIG. 2: INFRARED SPECTRUM OF VALSARTAN POWDER

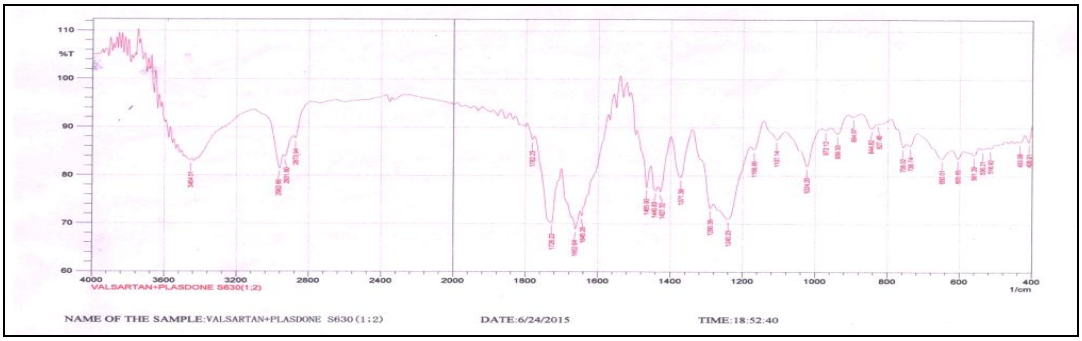

FIG 3: INFRARED SPECTRA OF VALSARTAN AND PLASDONE S630 COPOVIDONE

The characteristic peaks and positions of the peaks, of pure drug was compared with the IR spectra of the hot melt extrudates. The results of the IR analysis revealed that there was no interaction between drug and carrier (**Fig. 2** and **Fig. 3**).

Post-compression parameters: Post-compression parameters for floating tablets such as hardness, thickness, weight variation, friability, drug content, floating lag time, total floating time, swelling study, dissolution studies and stability studies were performed and tabulated (**Table 5**) [14].

TABLE 5: PHYSICOCHEMICAL PROPERTIES OF VALSARTAN FLOATING TABLETS

Formula Code	(AM±SD) (n=3)				
	Hardness (kg/cm^2)	Thickness (mm)	Weight variation(mg)	Friability (%)	Drug content (%)
FT-1	5.34±0.012	3.53±0.008	499.6±0.084	0.27±0.008	101.3±0.483
FT-2	5.47±0.009	3.63±0.009	501.5±0.420	0.25±0.004	99.8±0.084
FT-3	5.26±0.008	3.43±0.008	500.3±0.405	0.22±0.004	100.3±0.405

Carbon dioxide is formed within the tablet containing effervescent agent when it is brought in contact with acidic medium (0.1 N HCl) to provide buoyancy to the tablets (**Table 6** and **Fig.4**).

TABLE 6: FLOATING TEST FOR VALSARTAN FLOATING TABLETS

Formulation code	Floating lag time (Sec)	Total Floating time (h)
FT-1	19	22
FT-2	21	23
FT-3	18	24

0 sec **8 sec** **18 sec** **10 h** **24 h**

FIG. 4: BUOYANCY OF VALSARTAN FLOATING TABLETS

Swelling study: Swelling ratio describes the amount of water retained within the hydrogel at equilibrium and is a function of the network structure, hydrophilicity. Swelling study was performed on all the batches for 20 hours. The study showed that swelling of tablet increased up to 7-8 hours. The results of swelling index were given in **Table 7**. The release retarding polymers like HPMC K15 M definitely have contributed in swelling properties apart from their release retarding property (**Table 7** and **Fig. 5**).

TABLE 7: SWELLING STUDY OF VALSARTAN FLOATING TABLETS (FT-1 TO FT-3)

Formulation code	Increase in weight at different time intervals (mg)				Swelling Index (%) (AM±SD) (n=3)
	Time, h				
	2	4	6	8	
FT-1	856	953	1287	1467	193.4±0.816
FT-2	874	988	1467	1653	230.6±0.498
FT-3	898	1204	1768	1920	284±0.816

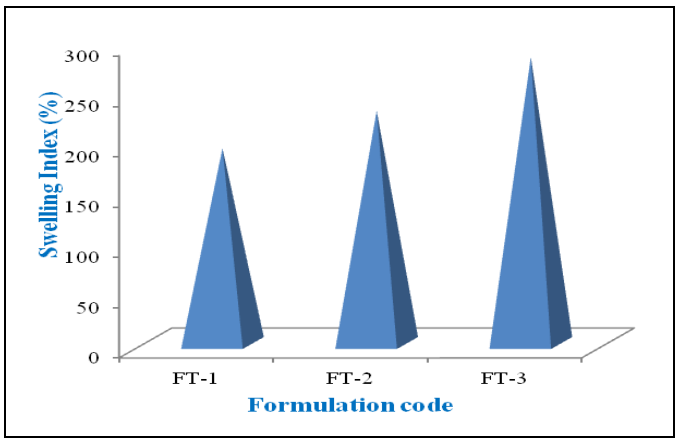

FIG 5: SWELLING STUDY OF VALSARTAN FLOATING TABLETS

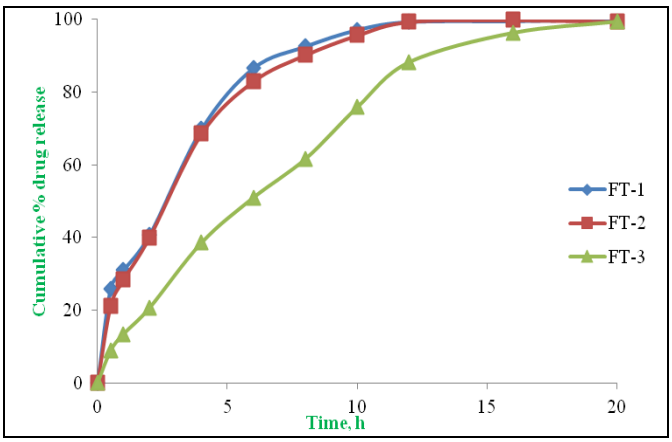

FIG 6: *IN VITRO* DISSOLUTION PROFILES OF VALSARTAN FT-1, FT-2, FT-3 IN 0.1 N HYDROCHLORIC ACID BUFFER

***In vitro* dissolution study:** The dissolution studies of the formulations were performed using USP dissolution rate testing equipment, Type 2 (Lab India Instrument Pvt. Ltd., Gurgaon, India) at a temperature of 37 ºC and a stirring rate of 50 rpm (**Table 8** and **Fig. 6**).

TABLE 8: *IN VITRO* DISSOLUTION PROFILE OF VALSARTAN HME FLOATING FORMULATIONS (FT-1 TO FT-3)

Time, h	Cumulative percentage of valsartan release (AM±SD) (n=3)		
	FT-1	FT-2	FT-3
0.5	25.92±0.08	21.12±0.08	8.87±0.05
1	31.03±0.07	28.39±0.05	13.47±0.05
2	40.67±0.08	40.04±0.05	20.65±0.05
4	69.87±0.52	68.58±0.52	38.58±0.30
6	86.91±0.79	83.04±0.52	50.99±0.80
8	92.66±0.60	90.27±0.52	61.63±0.53
10	97.23±0.29	95.70±0.80	75.89±0.51
12	99.42±0.003	99.40±0.00	88.26±1.04
16	99.66±0.30	99.87±0.30	96.32±0.80
20	100.09±0.003	99.45±0.52	99.41±0.52

The dissolution medium was 900 ml of 0.1 N HCl with pH 1.2. Samples of 10 mL were withdrawn at time intervals of 0.5, 1, 2, 4, 6, 8, 10, 12, 16 and 20 h. The samples were filtered using 0.45 µm pore size nylon filters (Whatman International, England) and drug concentrations were measured using an UV spectrophotometer at 249 nm (Lab India, Double Beam Spectrophotometer Maharashtra, India).

Accelerated Stability Studies of FT-3: The stability studies were conducted to determine the effect of aging on the physical and chemical stability of the drug in various formulations. The tablets prepared with best suitable HME extrudates, FT-3 were stored in amber colored bottles tightly plugged with cotton and capped. Stability studies were carried out at 40±2 ºC temperature and 75±5% RH for 6 months. The samples were collected at 1, 3 and 6 months intervals and were characterized by, physicochemical properties**,** drug content and dissolution studies (**Table 9, Table 10** and **Fig.7**).

TABLE 9: CHARACTERIZATION OF VALSARTAN FT-3 AFTER ACCELERATED STABILITY STUDY AT 40 ºC/75% RH

Sampling time (months)	(AM±SD) (n=3) Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	FLT (Sec)	TFT (h)
0	5.26±0.008	500.3±0.405	0.22±0.004	100.3±0.405	18	24
3	5.25±0.007	500.6±0.483	0.26±0.004	99.7±0.029	17	24
6	5.23±0.008	500±0.700	0.28±0.004	99.5±0.040	16	24

TABLE 10: *IN VITRO* DISSOLUTION PROFILES OF VALSARTAN FT-3

Time, h	Cumulative percentage of valsartan release (AM±SD) (n=3)		
	Day 1	After 90 days	After 180 days
0.5	8.87±0.05	8.75±0.10	8.65±0.10
1	13.47±0.05	13.44±0.12	13.30±0.12

2	20.65±0.05	20.55±0.08	20.45±0.08
4	38.58±0.30	38.47±0.17	38.37±0.17
6	50.99±0.80	50.40±0.34	50.70±0.34
8	61.63±0.53	61.54±0.22	61.24±0.22
10	75.89±0.51	75.77±0.36	75.57±0.36
12	88.26±1.04	88.21±0.39	88.16±0.39
16	96.32±0.80	96.29±0.58	96.26±0.58
20	99.41±0.52	99.34±0.42	99.29±0.42

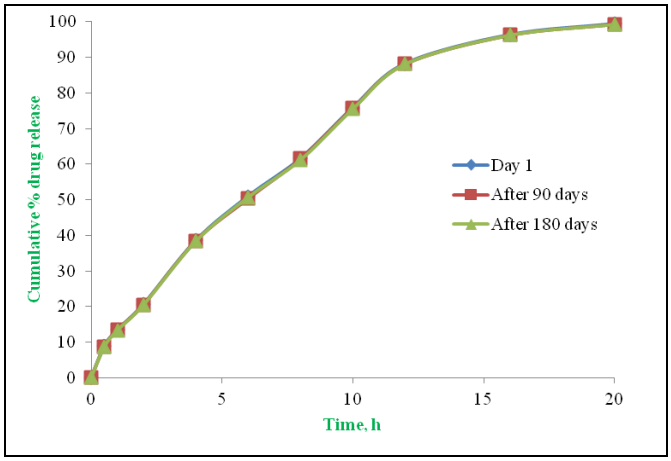

FIG 7: *IN VITRO* DISSOLUTION PROFILES OF VALSARTAN FT-3 IN 0.1 N HYDROCHLORIC ACID BUFFER

CONCLUSION: Valsartan loaded hot melt extrudates based on plasdone S-630 copovidone were pre¬pared by using HME technique. The gastroretentive floating tablets were obtained by direct compression technique and evaluated for the pre-compression parameters, post-compression parameters like hardness, thickness, drug content, and weight variation, friability, floating lag time, total floating time, dissolution studies and stability studies and the results are found to be within limits. Based on the performance with respect to floating lag time, total floating time and the dissolution profile, formulation FT-3 was selected as the best (Preliminary formulation) as it showed a floating lag time of 18 sec and a total floating time of more than 24 h. Drug release from FT-3 was improved as compared to the pure drug. Thus plasdone S-630 copovidone based hot melt extrudates, prepared by the HME technique, can be used to improve the solubility, oral bioavailability of poorly soluble valsartan. In future the work can be extended for its in vivo studies.

CONFLICT OF INTEREST: The researchers declare no conflict of interest.

ACKNOWLEDGEMENT: Authors are grateful to Dr. Reddy's Laboratories, Hyderabad for providing valsartan and Ashland Inc., USA for providing hypromellose acetate succinate (HPMCAS), plasdone S630 copovidone for this research. Authors are thankful to University College of Technology, Osmania University, Hyderabad for providing facilities to carry out the research work.

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How to cite this article:
Pamu S, Subrahmanyam CVS, Patnaik KSKR: Formulation and *in vitro* evaluation of gastroretentive floating drug delivery of valsartan using hot melt extrusion technique. Int J Pharm Sci Res 2017; 8(4): 1813-19.doi: 10.13040/IJPSR.0975-8232.8(4).1813-19.