WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 11, 1697-1718 Research Article ISSN 2278 – 4357

FORMULATION AND EVALUATION OF FLOATING MATRIX TABLETS CONTAINING VALSARTAN SOLID DISPERSIONS

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Article Received on
22 Sept. 2018,

Revised on 12 Oct. 2018,
Accepted on 01 Nov. 2018

DOI: 10.20959/wjpps201811-12714

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ABSTRACT

In the present study, an attempt has been made for the formulation of gastro retentive floating tablets of Valsartan (VAL) using solid dispersion method, one of the most successful techniques to improve dissolution rate of poorly aqueous soluble drugs. Valsartan (VAL) is a potent, highly selective and orally active antihypertensive drug belonging to the family of angiotensin II type 1 receptor antagonists. VAL has much greater affinity for the angiotensin II type 1 (AT1) receptor than for the angiotensin II type 2 (AT2) receptor, thereby relaxing blood vessels and causing them to widen, which lowers blood pressure and improves blood flow. Moreover, it belongs to BCS class-II owing to its poor solubility and high permeability and hence has poor oral bioavailability about 25%. The main purpose of this investigation was to increase the solubility and dissolution rate of VAL by preparing its solid dispersions (SDs) with PVP K30 and mannitol as carriers using solvent evaporation method. Solid dispersions (SDs) and Physical mixtures (PMs) of VAL were prepared in various proportions (1:1, 1:2, 1:3, 1:4, 1:5 and 1:6). Prepared SDs and PMs were optimized for solubility studies, percent drug content and percent dissolution rate studies. The floating tablets containing SDs of VAL were evaluated for uniformity of weight, hardness, friability, drug content, *in vitro* buoyancy and dissolution studies. The study revealed that, floating tablets using SDs of VAL with PVP K30 can enhance its solubility and dissolution rate.

KEYWORDS: Solid Dispersions (SDs), Physical mixtures (PMs), Valsartan (VAL), Polyvinyl pyrrolidone (PVP), mannitol.

INTRODUCTION

Valsartan (VAL) is a potent, highly selective and orally active antihypertensive drug belonging to the family of angiotensin II type 1 receptor antagonists. VAL has much greater affinity for the angiotensin II type 1 (AT1) receptor than for the angiotensin II type 2 (AT2) receptor, thereby relaxing blood vessels and causing them to widen, which lowers blood pressure and improves blood flow.[1] Moreover, it belongs to BCS class-II owing to its poor solubility and high permeability and hence has poor oral bioavailability about 25%. It is absorbed from the upper part of the GIT.[2] Solid dispersion (SD) is one of the most successful strategies to improve dissolution rate of poorly aqueous soluble drugs. SDs can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties.[3] SDs can be prepared by various methods such as solvent evaporation or melting method. Solid dispersion technique has been extensively used to increase the solubility of a poorly water-soluble drug. The mechanism by which the solubility and the dissolution rate of the drug are increased includes: reduction of the particle size of drug to submicron size or to molecular size in the case where solid solution is obtained. The particle size reduction generally increases the rate of dissolution; secondly, the drug is changed from amorphous to crystalline form, the high energetic state which is highly soluble; finally, the wettability of the drug particle is improved by the hydrophilic carrier.[4]

Oral route is the most convenient and extensively used route for drug administration. Over the years the oral dosage forms have become sophisticated with development of controlled release drug delivery system (CRDDS). CRDDS release drug at predetermined rate, as determined by drug's pharmacokinetics and desired therapeutic concentration.[5] This helps in achieving predictable drug plasma concentration required for therapeutic effect. A number of oral controlled release systems have been developed to improve delivery of drugs to the systemic circulation.

One of the most feasible approaches for achieving prolonged and predictable drug delivery profile in the GI tract is to control gastric residence time (GRT). The gastroretentive drug delivery systems (GRDDS) can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GI tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Various gastro retentive techniques were used,

including floating, swelling, high density, and bioadhesivity have been explored to increase the gastro retention of dosage forms. Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach without affecting the gastric emptying rate for a prolonged period of time.[6] While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration and improve oral bioavailability of VAL.

The objective of the present work was to improve the dissolution rate and bioavailability of VAL by formulating gastro retentive floating tablets using solid dispersion method in order to control the drug release.

MATERIALS AND METHODS

Valsartan was received as a gift sample from M/S Abbott Health Care Pvt. Ltd, Baddi, H.P. Hydroxypropyl methylcellulose (HPMC K4M, K15M, K100M) were obtained as a gift samples from M/S Leo chem, Bangalore, Karnataka. Lactose, sodium bicarbonate, PVP K30, magnesium stearate, talc, Hydrochloride acid and all other chemicals used were of analytical grade.

Methods

Preparation of Physical Mixtures (PM)

The different physical mixtures of Valsartan and carriers viz. Mannitol and PVP K30s were prepared by homogeneously mixing of both the drug and carrier in different ratios with the help of mortar and pestle and the mixtures thus obtained were passed through sieve # 60.

Preparation of Solid Dispersions (SDs) by Solvent Evaporation Method

All the solid dispersions of Valsartan were prepared using water-soluble carriers *viz.* Mannitol, PVP K30 in various ratios employing solvent evaporation method. In this method, the drug and carriers in different ratios were dissolved in ethanol. The solution was stirred at room temperature, and then evaporated at room temperature. Solid residue was dried in a desiccator for 24 h, the product thus obtained was passed through sieve #60 after grounding in a mortar and stored in amber coloured container.

Evaluation of Prepared SDs and PMs

Drug content estimation studies

The drug content in physical mixtures as well as solid dispersions prepared using VAL: mannitol and VAL : PVP K30 in various ratio like 1:1, 1:2, 1:3, 1.4, 1:5 etc. was estimated by dissolving quantities of physical mixtures and solid dispersions equivalent to 20 mg of VAL in ethanol and final volume was made up to 100 mL with 0.1N HCL. UV absorbance was recorded at 249 nm and the drug content was determined from standard curve.

***In vitro* dissolution studies of physical mixtures and solid dispersions**

Dissolution studies were carried for all the formulation combinations in triplicate, employing USP XXIII paddle (Apparatus 2) using 900 mL 0.1N HCL as the dissolution medium at 50 rpm and 37±0.5^{0}C. An aliquot sample (5 mL) was periodically withdrawn at suitable time intervals and volume replaced with equivalent amount of plain dissolution medium. The samples were analyzed using spectrophotometrically at 249 nm using UV-visible spectrophotometer.

Formulations of Floating matrix Tablets

Matrix tablets of Valsartan solid dispersions with other excipients were prepared by direct compression. The weight of Valsartan solid dispersions was kept constant in all the prepared tablets at 300 mg/tablet and the proportions of all other ingredients were varied for obtaining tablets with desired characteristics. Different viscosity grades of HPMC namely HPMC K4M, HPMC K15M, HPMC K100M were chosen as polymeric matrix materials. Lactose was selected as tablet diluent to maintain the tablets at constant weight. Magnesium stearate was used as a lubricant. Sodium bicarbonate was tried as an effervescence producing agent in varying proportions. Before compression magnesium stearate and talc were used as lubricant and glidant respectively in reported concentrations. At first, HPMC K4M alone was used as floating matrix polymer in varying proportions of 25-75 mg and the proportions of other excipients were also varied in a systemic manner with a thirst to formulate still better tablet with desired characteristics. Once the concentrations of all the excipients were fixed, other floating polymers *viz.* HPMC K15 M and HPMC K100 M were also tried in different concentrations, as given in table 1. Initially the net weight of the tablet was not fixed as the quantity of the excipients used was also varying, but once the quantity of the polymers to be used was ascertained, the net weight of tablet was also finalized to be 300 mg. This weight was finalized on the basis of observations made from the formulations F1- F10. To make

powder mixtures, the drug, polymer, binders, sodium bicarbonate, and lactose were thoroughly mixed for 3 minutes by means of pestle mortar. Micromeritic properties were studied of the blends after addition magnesium stearate and talc. The mixtures were compressed into tablets using 9 mm flat face round tooling. The force of compression was adjusted so that hardness of all the prepared tablets ranges from 6-7.5 kg/cm^2.

Table 1: Composition of various formulations of floating matrix tablets containing Valsartan solid dispersions.

Ingredients (mg)	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Valsartan solid dispersion	120	120	120	120	120	120	120	120	120	120
HPMC K4M	-	25	50	75	-	-	-	-	-	-
HPMC K15M	-	-	-	-	25	50	75	-	-	-
HPMC K100M	-	-	-	-	-	-	-	25	50	75
Sodium bicarbonate	12	12	12	12	12	12	12	12	12	12
Lactose	158	133	108	83	133	108	83	133	108	83
Magnesium stearate	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5
Total weight	300	300	300	300	300	300	300	300	300	300

Micromeritics studies

Angle of repose

Static angle of repose was measured according to the fixed funnel and free standing core method of Banker and Anderson. Blends were carefully poured through the funnel, fixed at height (h) of 4 cm from the surface, until the apex of the conical pile so formed just reached the tip of the funnel.[7,8] Thus, with r being the radius of the base of the granules conical pile and the angle of repose (θ) was calculated by using the eqn 1

$\tan \theta = h/r$, therefore , $\theta = \tan^{-1} h/r$

…(1)

Bulk density/Tapped density

Both bulk density (BD) and tapped density (TD) were determined. A suitable amount of powder blend was introduced into a 100 mL measuring cylinder. After observing its initial volume, the cylinder in the density tapper instrument and density is measured according to USP method II (up to1250 taps). The tapping was continued until no further change in volume was noted. Volume of packing after tapping was noted. BD and TD were calculated using eqn. 2 and 3 respectively

BD = weight of the powder / volume of the packing

…(2)

TD = weight of the powder / tapped volume of the packing

…(3)

Compressibility index

Compressibility index of the powder was determined by Carr's compressibility index as given by eqn. 4[57]

Carr's index (%) = [(TD – BD) x 100] / TD

…(4)

Hausner's ratio

It is the ratio of tapped to bulk density and was calculated by using the eqn. 5

Hausner's ratio = TD/BD

…(5)

Evaluation of floating matrix tablets of Valsartan

Tablet hardness

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The crushing strength of prepared tablets was determined for six tablets of each batch using Monsanto hardness tester.

Friability

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 minutes dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were reweighed and the percentage loss in tablet weight was determined acc to eqn 6.

% loss = Initial wt. of tablets - Final wt. of tablets/ Initial wt. of tablets x 100

...(6)

Weight variation

Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated.

Tablet Thickness/ Diameter

Thickness and diameter of tablets was important for uniformity of tablet size. Six tablets were examined for their thickness and diameter using micrometer and the mean thickness and diameter value was calculated.

Floating or buoyancy test

The time taken for tablet to emerge on the surface of the medium is called the floating lag time (FLT) or buoyancy lag time (BLT) and duration of time the dosage form constantly remains on the surface of the medium is called the total floating time (TFT). The buoyancy of the tablets was studied using USP type II dissolution apparatus at 37±0.5^{o}C in 900 ml of simulated gastric fluid at pH 1.2. The time of duration of floatation was observed visually.[9]

Drug content uniformity

For the drug content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 20 mg of Valsartan was dissolved in 100 mL of 0.1 N HCL and liquid was filtered using whatman filter paper and diluted up to 50µg/mL. The Valsartan content was determined by measuring the absorbance at 249 nm using UV spectrophotometer, after appropriate dilution with 0.1 N HCl.

***In-vitro* dissolution studies**

Dissolution studies were conducted to determine the release pattern of the Valsartan from the product. Dissolution test for drug was carried out as per USP method for dissolution test for tablets and capsules using apparatus II (paddle type). Dissolution medium used was 900 of 0.1 N HCl, rotating the paddle at 50 rpm at 37±0.5^{0}C. An aliquot of 5 mL of sample was withdrawn at different time periods. These samples were filtered and diluted. Absorbance of the resulting solution was measured at 249.0 nm.

RESULTS AND DISCUSSION

Valsartan (VAL) is a potent, highly selective and orally active antihypertensive drug belonging to the family of angiotensin II type 1 receptor antagonists. VAL has much greater affinity for the angiotensin II type 1 (AT1) receptor than for the angiotensin II type 2 (AT2) receptor, thereby relaxing blood vessels and causing them to widen, which lowers blood pressure and improves blood flow.[1] Moreover, it belongs to BCS class-II owing to its poor solubility and high permeability and hence has poor oral bioavailability about 25%. It is absorbed from the upper part of the GIT.[10] Keeping in view these characteristics of

Valsartan it can be hypothesized that a suitable solubility enhancement technique can improve its dissolution profile and hence its bioavailability. From the available literature, it was found that a solid dispersion is a very much credited solubility enhancement technique and literature supports the conversion of solid dispersions into floating matrix tablets. Moreover, floating matrix tablets can improve the patient compliance due to reduce number of drug administrations. Hence, it was thought worthwhile to formulate solid dispersions of Valsartan and convert them as floating tablets if dissolution profiles would be promising.

Various SDs of VAL were prepared using Mannitol and PVP K30, as carriers by solvent evaporation technique to increase the solubility as well as dissolution of poorly aqueous soluble drug VAL. The prepared SDs and PMs of VAL were evaluated for drug content, and *in-vitro* dissolution studies.

Drug content estimation studies

The drug content in physical mixtures as well as solid dispersions prepared using Valsartan: Mannitol, Valsartan: PVP K30 in various ratios (1:1, 1:2, 1:3, 1:4, 1:5 and 1:6) was determined by following the procedures mentioned in table 2. As shown in table 2 the values have been observed that drug content in all the formulations (physical mixtures & solid dispersions) vary in between 93.52-103.59% i.e., well within the permissible limits (90-110%)[11] indicating uniform drug content in all the developed formulation of physical mixtures and solid dispersions.

Table 2: Percent drug content values for physical mixtures and solid dispersions of Valsartan.

S.No	Drug	Carrier	Drug: Carrier	% Drug Content	
				Physical mixtures	Solid dispersions
1	Valsartan	Mannitol	1:1	94.03	95.71
			1:2	103.59	97.82
			1:3	101.32	98.83
			1:4	98.65	99.57
			1:5	98.07	102.35
			1:6	98.02	98.38
2	Valsartan	PVP K30	1:1	97.48	93.52
			1:2	101.54	99.26
			1:3	94.55	97.92
			1:4	93.72	94.87
			1:5	99.56	99.57
			1:6	98.42	98.31

***In vitro* dissolution studies**

The dissolution performance of various physical mixtures and their corresponding solid dispersions prepared using Mannitol and PVP K30 in different ratios.

Fig. 1 reveals that the physical mixture of Valsartan (VAL) developed using Mannitol in different drug: carrier ratio (1:1, 1:2, 1:3, 1:4, 1:5 and 1:6), there is minor influence on the drug release rate studied till 120 min. However, improvement in the release rate of the drug was seen when VAL and PVP K30 were used in various ratios. Fig. 2 exhibits the values of cumulative percent drug release at varied times for physical mixtures of VAL with PVP K30 respectively. From these table values it is clearly evident that the physical mixtures exhibited higher percent drug release vis-à-vis pure drug. With PVP K30 drug dissolution rate was consistently increased by increasing the concentration of carrier up to 1:5 (VAL: PVP K30). As the amount of carrier was further increased from 1:5 to 1:6 (VAL: PVP K30), a remarkable reduction in % drug release. As indicative from the dissolution data of the physical mixtures, improvement in the drug dissolution rate could be attributed to the higher wettability and dispersibility. Mixing of drug with hydrophilic carriers *viz.* mannitol and PVP K30 results in greater wetting and increases surface availability for dissolution by reducing interfacial tension between the hydrophobic drug and the dissolution medium. During the dissolution studies, it has been observed that drug- carrier system sinks immediately whereas pure drug keeps floating on the surface for a longer time interval. Furthermore, kneading results in uniform distribution of drug in the polymer crust in a highly dispersed state. Thus, when such a system comes in contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in precipitations of the embedded drug into the fine particles, which increase the dissolution surface available. This explains the improvement of dissolution rate of the drug when mixed with a carrier.

On the other hand, if the percentage of carrier mannitol and PVP K30 is too high the dissolution rate decreased. This could be attributed to changes in the type of VAL polymorph during the dissolution in the presence of high concentration of mannitol and PVP K30 or might be due to formation of viscous layer around the drug particles leading to decrease in the dissolution rate.[12]

The Mannitol dispersions had significant influence on the release profile of VAL. It has been observed that on increasing the concentration of VAL: Mannitol, 1:1 to 1:5, release rate of drug was increased. In case of 1:6 ratio, the release rate of drug was decreased because of

presence of the high concentration of the carrier. Fig.2 implies the cumulative percent drug release at varied times for pure VAL vis-à-vis VAL:PVP K30 solid dispersions (SD 7 – SD 12). From Fig. 2 it is evident that the VAL: PVP K30 dispersions up to a ratio of 1:5 showed distinct improvement in the release rate of drug. Maximum drug release (95.94±2.71%) was observed in case of SD 11 solid dispersions in 120 min. Also, 4-5 fold increase in drug release rate was observed in case of VAL: PVP K30 solid dispersions vis-à-vis pure VAL.

Fig.1 and 2 reveal the drug release profiles of all the physical mixture formulations (PM 1- PM 12) and solid dispersion formulations (SD 1- SD 12) vis-à-vis pure drug respectively. On comparing Fig.1 with 2 it can be concluded that the release performance of solid dispersions was distinctly superior to that of their corresponding physical mixtures developed using different carriers.

Possible explanation of the increased dissolution rate of solid dispersion has been proposed by Craig[229] and include: reduction of drug crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and hydrophilic carrier, inhibition of fine particle aggregation, conversion of the drug to amorphous state, and finally a combination of the above mentioned mechanisms.

On mutually comparing the dissolution profiles of all the solid dispersion formulations (SD 1- SD 12), it has been observed that the maximum drug release rate was found in case of SD 11, i.e. VAL.

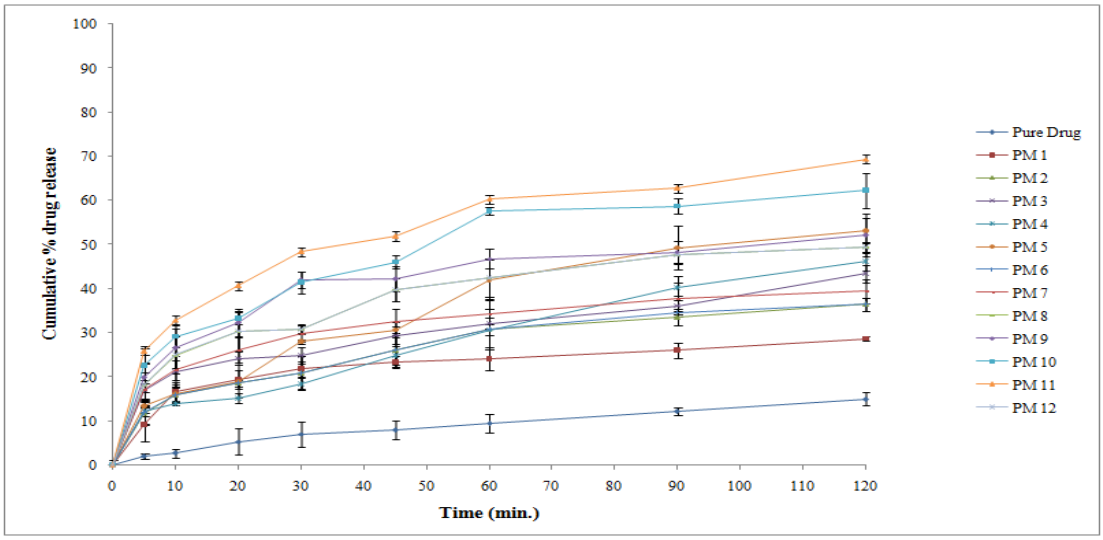

Fig. 1: Plot between mean percent drug release and time for Physical mixture of VAL (PM 1- PM 12).

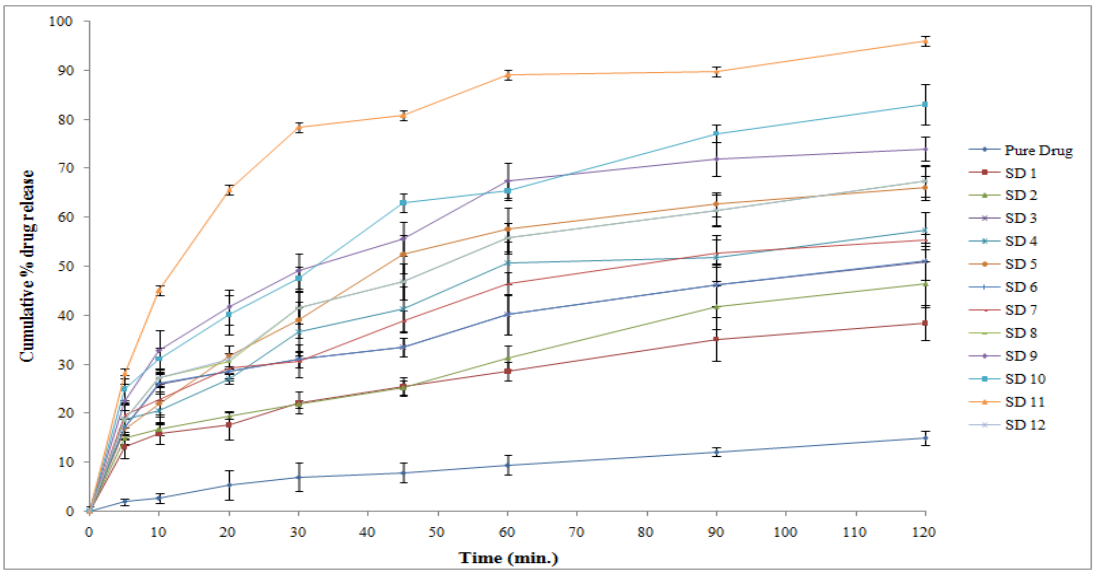

Fig. 2: Plot between mean percent drug release and time for solid dispersion of VAL (SD 1- SD 12).

PVP K30 (1:5) solid dispersions. Hence, on the basis of cumulative percent drug release studied till 120 min, solid dispersion formulation SD 11 was selected.

Formulation and development of Valsartan floating matrix tablets using VAL-PVP K30 solid

Dispersion

Precompression studies

Various formulation blends were evaluated for their flow properties as described in table 3.

Angle of repose

The angles of repose (θ) for the blend of various formulations F1 to F10 were calculated and the value of θ for each formulation is shown in Table 3. As vivid from Table 3, the angle of repose of precompressed blend of Valsartan of formulations F1 to F10 was in the range 22.98^0 to 27.36^0, indicating that the studied blend have good to excellent flow properties because for a blend to have good and excellent flow properties, θ should be 25^0-30^0 and $<25^0$ respectively.[13]

Bulk and tapped density

The BD and TD for the granules of various formulations F1 to F10 were determined and their respective values are shown in Table 3. As observed from Table 3, BD and TD for all the formulations were found in the range between 0.463 to 0.529 and 0.534 to 0.600 respectively.

Compressibility index

The compressibility indices for the blend of various formulations F1 to F10 were calculated and the value of compressibility index for each formulation is shown in Table 3. As vivid from Table 3, the compressibility index of precompressed blends of Valsartan formulations F1 to F10 was in the range of 5.48±1.23% to 14.33±1.32%.[13] These values indicate the excellent flow properties for blends of various formulations.

Hausner's ratio

The Hausner's ratios for the blend of formulations F1 to F10 were calculated and the value of hausner's ratio for each formulation is shown in Table 3. As evident from Table 3, the hausner's ratio of precompressed blends of Valsartan formulations was in the range 1.05±0.02 to 1.16±0.02 indicating that the studied blends have good flow rate.

Low Hausner's ratio (≤1.178), compressibility index (≤15.11) and angle of repose (≤27.35) values indicated a good flowability of powder mixture.[14] These results were indicative of solid dispersions compressed as tablet.

Table 3: Parameters evaluated for powder blend of Valsartan.

Formulation code	Angle of repose (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index	Hausner's ratio
F1	27.36±0.12	0.508±0.003	0.593±0.006	14.33±1.32	1.16±0.02
F2	26.01±0.37	0.±5170.006	0.547±0.011	5.48±1.23	1.05±0.02
F3	25.72±1.04	0.501±0.004	0.566±0.004	11.48±1.02	1.12±0.04
F4	22.98±0.92	0.468±0.008	0.508±0.014	7.87±2.34	1.08±0.01
F5	24.32±0.11	0.518±0.008	0.568±0.011	8.80±0.62	1.09±0.02
F6	25.39±0.79	0.514±0.005	0.563±0.005	8.70±0.38	1.09±0.03
F7	23.62±1.82	0.500±0.004	0.581±0.013	13.94±0.76	1.16±0.02
F8	25.17±1.38	0.529±0.006	0.600±0.012	11.83±1.15	1.13±0.01
F9	25.96±0.8	0.486±0.008	0.563±0.015	13.67±062	1.15±0.04
F10	26.53±0.3	0.463±0.007	0.534±0.004	13.14±0.43	1.15±0.02

Evaluation of floating matrix tablets of Valsartan (Post compression test)

As the tablet powder mixture was free flowing, the tablets were produced by direct compression method and following evaluating parameters were studied.

Tablet hardness

Hardness of the developed formulations (F1-F10) was found to be in the range of 6.0±0.59 to 7.6±0.67 kg/cm^2 (Table 4), it show that the floating lag time decreased if the hardness

increased and indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling.

Friability

The loss in total weight of the tablets due to friability was found to be in the range of 0.23% to 0.59% (Table 4) in all the studied formulations and the friability value in each case was found to be less than 1% which ensures that the formulated tablets were mechanically stable.

Weight variation

The percentage weight variations for all formulations (F1-F10) were tabulated in table 4. All the formulated tablets passed the weight variation test as the % weight variation was within the standard Pharmacopoeia[11] limits of±7.5% of the average weight.

Tablet Thickness/ Diameter

Thickness of the studied tablet formulations (F1-F10) was found to vary from 3.68±0.02 mm to 3.73±0.03 mm (Table 4) and the average thickness value was found to be in the range of±5% and hence within the standard Pharmacopoeia limits.[11]

Floating or buoyancy test

All formulations (F1- F10) shows the floating lag time less than three minute and good floating time of more than 20 h (Table 4).

Drug content uniformity

The drug content in tablet formulations (F1-F10) was highly uniform and was found in the range of 97.69±0.89 to 99.22±1.56 (Table 4). It is within the limits specified by IP.[11]

Table 4: Various physical parameters evaluated for all batches of Valsartan floating matrix tablets.

Formulation Code	Avg. tablet wt. (mg) n=20	Hardness (Kg/cm^2) n=10	Thickness (mm)	Friability %	Floating lag time (min)	Floating duration time(h)	Drug content % n=3
F1	298.86±6.01	6.9±0.77	3.68±0.04	0.37	1:04	> 12	99.22±1.56
F2	299.53±5.27	7.3±0.48	3.71±0.05	0.23	1:34	> 24	97.99±0.86
F3	300.99±4.14	6.4±0.55	3.71±0.03	0.55	1:02	> 24	99.01±1.15
F4	298.65±4.66	7.4±0.61	3.68±0.04	0.46	2:15	> 24	98.89±1.45
F5	300.00±4.17	7.6±0.67	3.70±0.05	0.27	2:17	> 24	98.69±1.12
F6	299.77±4.49	7.2±0.59	3.72±0.02	0.35	2:00	> 24	98.85±1.10
F7	300.85±3.88	6.9±0.44	3.73±0.02	0.35	1:15	> 24	99.10±0.72
F8	299.69±4.67	7.1±0.42	3.73±0.03	0.59	2:25	> 24	98.01±1.60
F9	300.27±4.97	6.5±0.48	3.68±0.02	0.31	2:10	> 24	97.69±0.89
F10	299.95±3.89	6.0±0.59	3.72±0.03	0.45	2:05	> 24	98.24±1.08

***In-vitro* dissolution studies**

The task of designing floating matrix tablets having increased residence in stomach began with the selection of Valsartan, selection of potential polymers *viz.* HPMC K4M, HPMC K15M and HPMC K100M etc that allow matrices with sustained delivery characteristics and have bulk density <1.

For Hydrodynamically balanced floating tablets of Valsartan, selection of gas forming agent like sodium bicarbonate was mandatory. Owing to their excellent potential for release controlling ability, non-toxicity, non-irritating and stability at GI, HPMC was selected in three viscosity grades i.e. HPMC K4M, K15M, and K100M. The formulation of solid dispersion that is SD 11 was selected for compressing it into floating tablets. Many attempts were made to get floating matrix tablets containing SD of Valsartan having desired characteristics. Various formulations were prepared using polymers *viz* HPMC K4M, K15M, K100M in variable amounts. Variable quantity of excipients were also tried to get the blend which could be compressed into the tablets with sufficient hardness, floating lag time and floating duration.

All formulations from F1 to F10 were able to float in 0.1N HCL with a lag time ranging from 1:04 min. to 2:25 min. and they were able to swell. A sizable number of reports tend to

appear in literature, where various grades of HPMC have been used to formulate floating matrix tablets containing solid dispersion of drugs.

Initially selected solid dispersion of VAL i.e SD11 was compressed using 25 mg HPMC K4M followed by increasing the polymer by 25 mg (F3) and by 50 mg (F4). From Fig.3, it is reflected that after one hour 28.64% VAL was released which about one percent was less when compared to F3 and about two percent less than that of F4. In other words increase in the quantity of HPMC K4M in these formulations increases the drug release in an ordered manner. In case of HPMC K15M in fig 3 shows that by increasing the polymer 25 mg to 75 mg in formulation F5-F7, the decrease in drug release is seen due to high viscosity of HPMC K15M. In case formulation containing HPMC K100M polymer, the decrease in drug release as compare to HPMC K15M.

As we compare the dissolution profiles of pure drug with those of various formulations of floating matrix tablets which, it is seen that these formulations are able to sustain the drug release in a significant manner. From *in vitro* drug dissolution profile of Valsartan matrix tablet, it was found that more than 25% drug was released till 1 h from F1 to F10 formulations. After 8 h more than 70% of the drug was released from all the formulations. After 16 h the release rate decreased slightly and a sustained release pattern was observed in case of F2-F10. The F1 formulation contained Valsartan solid dispersion (VAL and PVP K30) and excipients except polymer. It was observed that the drug release rate 87.42±1.49 till 24 h. The hydrophilic matrix of HPMC controlled the Valsartan release effectively for 16 h. It was observed that formulation with HPMC K4M (F2-F4) showed high % drug release in the decreasing range of 92.37±1.21% to 80.32±1.75% when compared to tablets containing HPMC K15M (F5-F7) and HPMC K100M (F8-F10) which showed a drug release rates from 83.36±3.52% to 80.47±5.13% and 79.01±1.48% to 76.44±2.79% respectively. Moreover, it was also observed that HPMC K4M sustained the drug release for longer time periods as compared to HPMC K15M and HPMC K100M.

The order of drug release from the selected polymers were found to decrease in the following order HPMC K4M > HPMC K15M > HPMC K100M. Among the three grades of HPMC polymer used the tablets prepared with lower viscosity grade i.e. HPMC K4M, have shown drug release rate (92.37±1.21% to 80.32±1.75%) and the higher viscosity grade polymers i.e. HPMC K15M (91.47±1.13% to 83.36±1.52%). From the dissolution data of Valsartan matrix tablet formulations F1-F10 it has been observed that when the viscosity and content of

HPMC are increased, the release of drug tends to become slower. HPMC particles of increasing viscosity grades will swell more slowly and produce swollen particles of smaller volume; then matrices made of particles of HPMC with higher viscosity grade will contain pores of smaller diameters and will show slower release rate than those made of HPMC particles with lower viscosity grades. Increase in polymer level further reduces the release of Valsartan from matrix tablets. This finding might be due to increase in resistance of gel layer to drug dissolution and gel erosion. At a higher polymer level, formation of tightly swollen gel layer caused by more intimate contact between the particles of HPMC results in decreased mobility of insoluble drug particles in swollen matrices, which leads to decreased release rate. This give in according with the reference in literature.[15]

The dissolution parameters of all the ten formulations developed using various polymers. Fig.3 shows *in vitro* drug release profile of various floating matrix tablet formulations (F1-F10) of Valsartan. Formulation F4 containing 25% of HPMC K4M (75mg) exhibited short buoyancy lag time, floated for more than 16 h, showed drug content (98.89±1.45%) upto 16 h in a controlled manner without changing the physical integrity of tablets in the released medium. Hence formulation F4 was found to be satisfactory to pass all characteristics of a floating matrix tablet. Finally when we compare the drug profiles of SD 11 and formulation F4, the drug release is decreased by 3%. Seeing the popularity of a tablet dosage form, over a solid dispersion SD11, also the convenience of administration of a tablet, the formulation F4 of a floating tablet is recommended for scale up. This narrow decrease in drug release of SD11 and F4 can be compensated with the benefits associated with tablet dosage form.

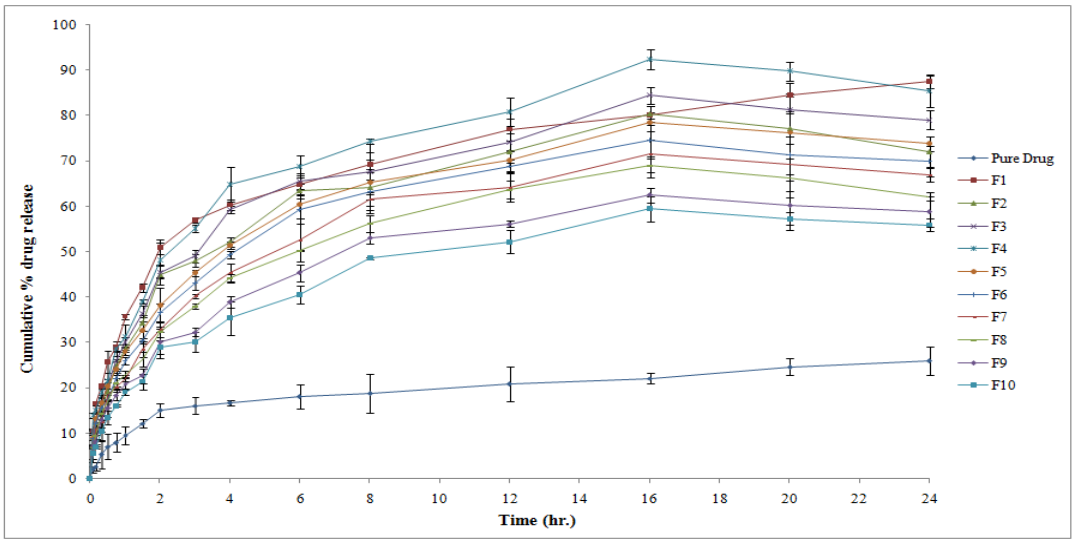

Fig 3: Comparison of cumulative % release of all formulations (F1-F10) and pure drug.

Kinetic analysis of dissolution data

The dissolution data of floating matrix tablet of Valsartan of optimized formulation F4 was fitted to zero order, first order, Higuchi's and Korsmeyer-Peppas model to ascertain the kinetic modeling of drug release.

The following methods were adopted for deciding the most appropriate model,

1. Percent drug released versus time (zero-order kinetic model)
2. Log percent drug remaining versus time. (first-order kinetic model)
3. Percent drug released versus square root of time (Higuchi's model)
4. Log percent drug released versus log time (Korsmeyer-Peppas model)

The data were processed for regression analysis using MS-EXCELL statistical function. The kinetic analysis data of the formulation F4 is shown in Table 5 and their corresponding zero order, order, Higuchi's and Korsmeyer-Peppas model profiles are depicted in Fig.4-7 respectively. At the outset drug release data of the formulation was fitted to zero order, first order and Higuchi's model and from the respective profiles values of slope, intercept and r^2 were calculated in each case. These values are shown in Table 6. As the model with highest correlation coefficient (r^2) was considered to be best model therefore form the kinetic parameters shown in table 6 it can be concluded that the release of drug from formulation F4 of Valsartan followed Higuchi model. Hence in current investigation, *in vitro* release profile could be best expressed by Higuchi model for the formulation F4 which shows good linearity (r^2) and indicated that diffusion is dominant mechanism of drug release from Valsartan formulation.

All the formulations were further treated to Korsmeyer-peppas plots by taking log % drug release versus log time. The data obtained in case of formulations F4 for peppas model are shown in table 6. From the table it has been observed that the regression value (n-value) of formulations F4 is 0.282. This suggests that the drug was released by Fickian diffusion mechanism.

Table 5: Kinetic analysis of drug release data of formulation F4.

Time (h)	% Drug release	Log % drug release	% drug remained	Log % drug remained	Kinetic Root time	Log time (h)
0	0	0	100	2	0	0
0.08	13.81	1.140	86.19	1.935	0.2828	-1.096
0.16	14.92	1.174	85.08	1.929	0.4	-0.7958
0.33	18.90	1.276	81.1	1.909	0.5	-0.481
0.50	21.49	1.332	78.51	1.895	0.70	-0.301
0.75	28.55	1.456	71.45	1.854	0.86	-0.124
1.00	31.12	1.493	68.88	1.838	1	0
1.50	38.97	1.591	61.03	1.786	1.22	0.176
2	48.04	1.682	51.96	1.716	1.41	0.301
3	55.13	1.741	44.87	1.65	1.73	0.477
4	64.89	1.812	35.11	1.54	2	0.602
6	68.75	1.837	31.25	1.49	2.44	0.778
8	74.25	1.870	25.75	1.41	2.82	0.903
12	80.71	1.906	19.29	1.28	3.46	1.07
16	92.37	1.965	7.63	0.88	4.00	1.204
20	89.71	1.953	10.29	1.01	4.47	1.30
24	85.37	1.931	14.63	1.16	4.89	1.38

Table 6: Summary of parameters obtained from kinetic analysis of F4.

Zero Order	**Slope(K)**	3.355
	Intercept	29.04
	r^2	0.722
First Order	**Slope(K/2.303)**	-0.0182
	K	-0.042
	Intercept	1.852
	r^2	0.848
Higuchi's model	**Slope(K)**	18.76
	Intercept	13.15
	r^2	0.912
Korsemeyer-Peppas model	**Slope(n)**	0.552
	Intercept(log K)	0.063
	K	1.158
	r^2	0.282

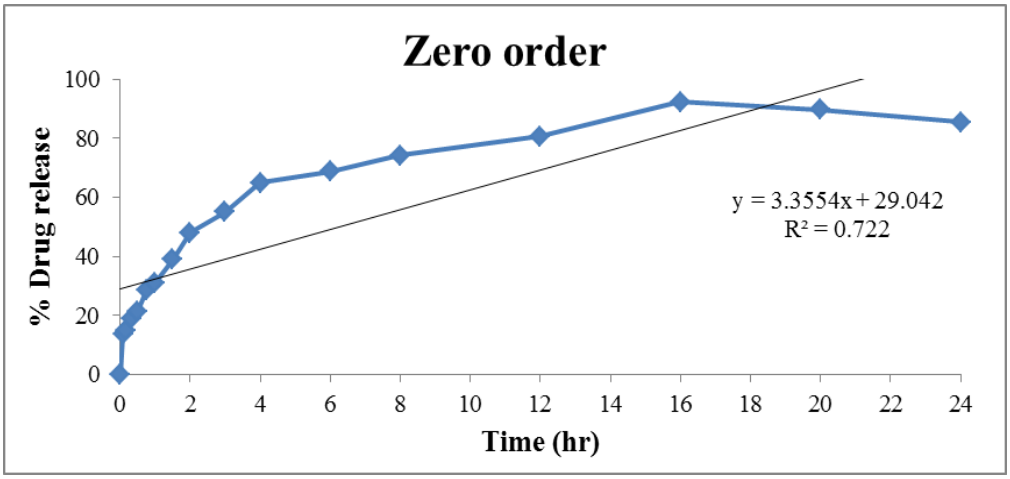

Fig.4: Percent drug release vs time plot of selected formulation F4 showing zero order kinetics.

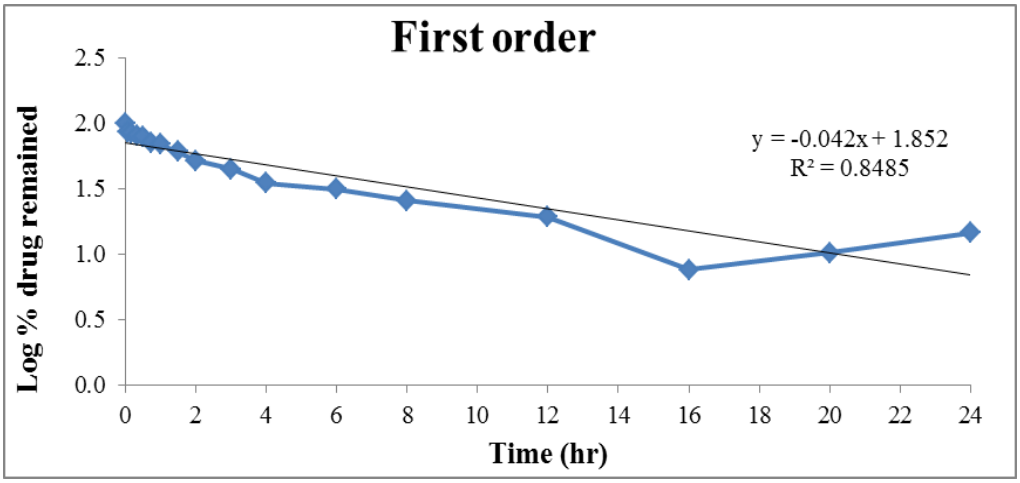

Fig 5: Log % drug remained vs time plot of selected formulation F4 showing first order kinetics.

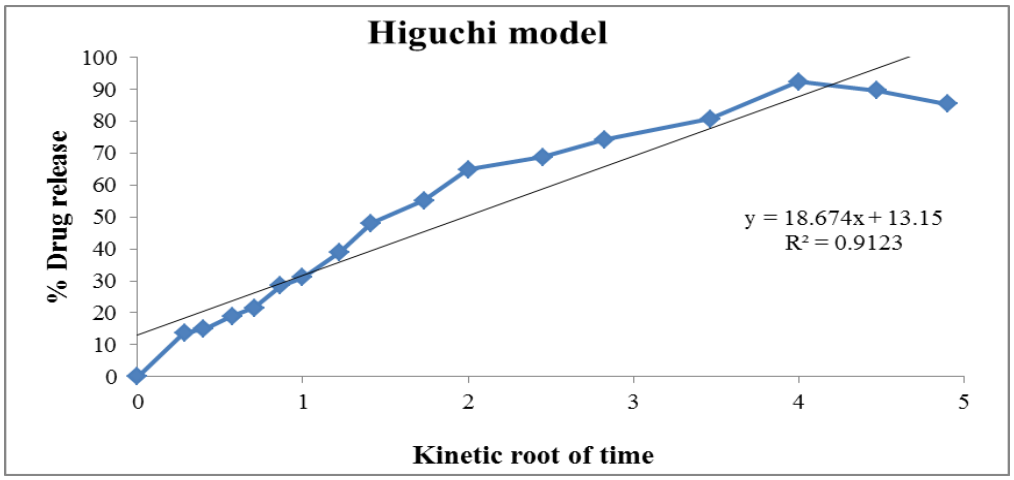

Fig.6: Percent drug release vs Kinetic root time plot of selected formulation F4 showing Higuchi's model.

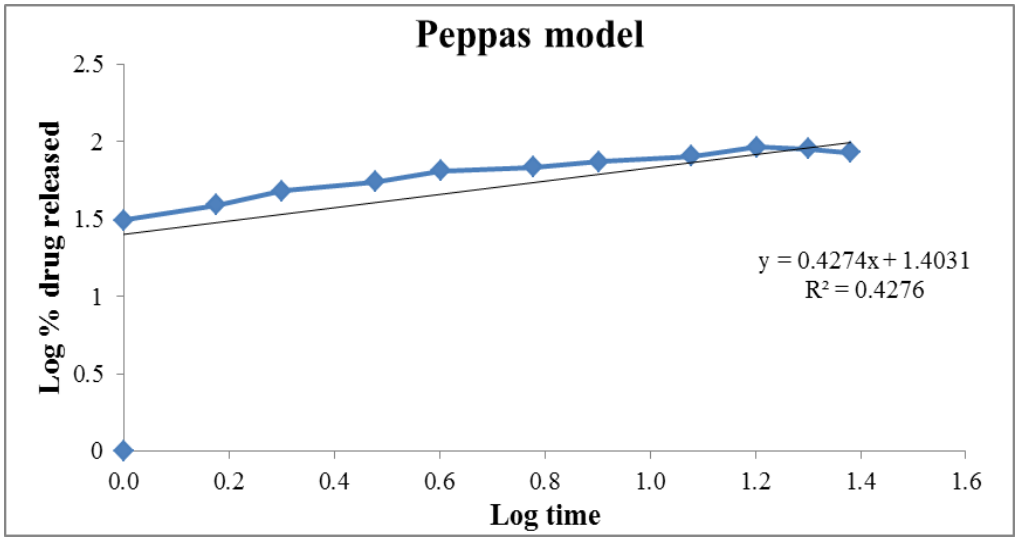

Fig.7: Log % drug release vs log time plot of selected formulation F4 showing Korsmeyer-peppas model.

CONCLUSION

From the present investigation it can be concluded that.

- Solubility of Valsartan can be successfully increased by formulating its solid dispersions with Mannitol and PVP K30.
- Prepared solid dispersions can be successfully incorporated into controlled release gastroretentive floating matrix tablets of Valsartan using various viscosity grades of HPMC *viz.* HPMCK4M, HPMCK15M, HPMCK100M.
- This effervescent based floating drug delivery is a promising approach to achieve *in vitro* buoyancy.
- The addition of gas generating agent sodium bicarbonate is essential to achieve *in vitro* buoyancy.
- Formulation F4 fulfilled the criteria of evaluation like hardness, friability, weight variation and drug content.
- Formulations developed using HPMCK4M sustained the drug release till 16 h.
- The kinetic study results suggest that the drug was released by fickian diffusion in case of all the developed floating matrix tablet formulations of Valsartan.
- Formulation F4 was found to be optimum because it had shown most consistent drug release of about 92% upto 16 h with floating lag time of 2:15 min.
- On comparing the overall release performance of the optimum formulation F4 with that of conventional marketed tablet formulation of Valsartan, it was concluded that F4 exhibited highly controlled release till 16 h.

- On the basis of this investigation finally, it can be concluded that controlled release floating matrix tablets of Valsartan may be used in clinical practice for various infectious diseases, thereby improving the bioavailability and more patient compliance. However, stability studies and *in vivo* studies in human subjects need to be carried out on floating matrix tablets of Valsartan.

ACKNOWLEDGEMENTS

I take this privilege and pleasure to acknowledge the contributions of many individuals including my guide Assit. Prof Mr. Jagtar Singh Chohan and co-guide Prof (Dr.) Yash Paul, Lord Shiva college of Pharmacy, Mysore who have been inspirational and supportive throughout my work undertaken and endowed with the most precious knowledge to see success in my endeavor.

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