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Original Research Article

SOLUBILITY ENHANCEMENT OF A POORLY AQUEOUS SOLUBLE DRUG USING SOLID DISPERSION TECHNIQUE

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Abstract: The purpose of present work was to enhance the solubility and dissolution rate of Valsartan by solid dispersion technology employing various carriers such as sodium starch glycolate (SSG), Mannitol. Solid dispersions were prepared by physical mixing and solvent evaporation method. Various ratios of drug and carriers were used in the preparation in the ratio of 1:1, 1:1.5, 1:2, 1:2.5 and 1:3, 1:3.5. All the SD prepared was found to be fine free flowing powders and the drug content was uniform in all batches. The results of the disintegration test revealed that FT5 has faster disintegration within (5.3 min.)

Keywords: BCS Class II, Solubility, Carriers, Solid dispersion, Physical mixing, Solvent evaporation.

Introduction: Valsartan is potent, specific, and competitive antagonist of angiotensin II AT_1-receptor. It is more selective for AT1 receptor, does not block any kind of receptors therefore possess minimum side effects as compared to other drugs[1]. It blocks overall action of angiotensin II (AII), i.e. vasoconstriction, central and peripheral sympathetic stimulation, release of aldosterone and adrenaline etc. thus act as antihypertensive whose effect last for long time (> 18 hr); but it has one major limitation of its poor solubility and low bioavailability i.e. approx. 25% is because of its low dissolution and pH dependent solubility profile in gastric media (HCL) [2].

Valsartan is marketed in the form of conventional tablet and capsule only; but both oral solid dosage forms have limited solubility and dissolution profile. To overcome this problem manufacturer incorporated high amount of disintegrant (10-80%) which is hazardous to patient and also inflate overall cost of product. Another limitation of the existed dosage form is that they are very porous and thus not very hard and consequence they cannot broken in two more pieces, this porous tablet tends to be very sensitive to humidity therefore

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they cannot be stored for some days once the blister is opened[3]. The poor stability and low oral bioavailability (BA) with poor aqueous solubility warrants the administration of large dosage of valsartan to maintain desired therapeutic concentration in blood. Poor aqueous solubility can be improved by applying SD (SD) technique which will not only improve the solubility but also can improve stability and bioavailability[4].

Hence the main objective of the present work was to improve solubility by means of SD technique. SD can deliver the drug in both solubilize form and in a predictable manner which is independent of pH in gastro intestinal tract. By preparing its SD we can reduce amount of disintegrant in formulation in contrast to present dosage form. Thus it reduces overall cost of the product and prevents the patient form exposure of such a high concentration of disintegrant. SD can also improve flow property by which drug can be compressed in tablet form or it can be suitably dispensed in capsule form[5].

Materials and Methods: Valsartan was obtained as gift sample from Aurobindo Pharma Ltd, India. Mannitol, Methanol, Sodium starch glycolate (SSG),Microcrystalline cellulose (MCC), Talc, Magnesium stearate (Mg) were purchased from Lobachem, India. All reagent and solvent were of analytical garde and supplied without need to purification.

Preparation of SD: Different SD formulations of valsartan were prepared with two methods, solvent evaporation (SE) and physical mixing (PM) [6].Valsartan SD were prepared by using carriers (i.e. mannitol, SSG) in proportions viz. drug: carrier (1:1, 1:1.5, 1:2, 1:2.5 and 1:3, 1:3.5) were weighed and taken in a glass mortar, were mixed thoroughly. The resultant mixture was passed through sieve number 80 # and stored in a desiccator for the complete removal of moisture.

Similarly solvent evaporation method valsartan and each of surface active carriers were weighed accurately and transferred to china dish containing sufficient quantity of methanol to dissolve. Methanol was evaporated on heating mantle at 60^0C. The resulting SD was stored for 24 hr in desiccator to congeal. The mass obtained was crushed, pulverized. Finally, dispersions were passed through sieve number 80# and were stored in air tight containers till further use**.**

Table 1 Composition of different SD formulation

Method Carrier	**Physical mixing**		**Solvent evaporation**	
Mannitol	**Batch**	**Ratio**	**Batch**	**Ratio**
	PM1	1:1	**SE1**	1:1
	PM2	1:1.5	**SE2**	1:1.5
	PM3	1:2	**SE3**	1:2
	PM4	1:2.5	**SE4**	1:2.5
	PM5	1:3	**SE5**	1:3
	PM6	1:3.5	**SE6**	1:3.5
SSG	**PM7**	1:1	**SE7**	1:1
	PM8	1:1.5	**SE8**	1:1.5
	PM9	1:2	**SE9**	1:2
	PM10	1:2.5	**SE10**	1:2.5
	PM11	1:3	**SE11**	1:3
	PM12	1:3.5	**SE12**	1:3.5

Optimization of SD: Prepared SD formulations were optimized on the basis of different parameters like % practical yield, drug content, solubility studies, and bulk characterization.

Percentage practical yield: Percentage practical yield was calculated to know about percent yield and efficiency of method used. This method helps in selection of appropriate method of production. For determination of yield SD were collected and weighed and further calculated from the following equation [6, 7].

$$PY\ (\%) = \frac{\text{Practical mass (SD)}}{\text{Theoretical mass (Drug+carrer)}} \times 100$$

Drug content: SD equivalent to 100 mg of valsartan were weighed accurately and dissolved in the 100 ml of methanol. Prepared solution was filtered, diluted suitably and drug content was analyzed at 250 nm by UV spectrophotometer. The Actual Drug Content was calculated using the following equation as follows:

$$\%\text{Drug content} = \frac{\text{Actual amount of drug in SD}}{\text{Theoretical amount of drug in SD}} \times 100$$

Solubility studies: Solubility study was performed according to method reported by Higuchi and Connors. Excess (usually more than1mg/ml concentration) of SD were added to 25 ml distilled water taken in stopper conical flasks and mixture were shaken for24 hr in rotary flask shaker. After shaking to achieve equilibrium,2 ml sample was withdrawn at 1hr intervals and filtered through whatmann filter paper. The filtrate was diluted if necessary andanalyzed by UV- spectrophotometer at 250 nm [4, 8].

Table 2 Solubility of different SD

Formulation code	Solubility (mg/ml)	Formulation code	Solubility (mg/ml)
Pure drug	0.0089	-	-
PM1	0.0101	**SE1**	0.0119
PM1	0.0113	**SE2**	0.0130
PM3	0.0130	**SE3**	0.0153
PM4	0.0164	**SE4**	0.0186
PM5	0.0218	**SE5**	0.0242
PM6	0.0234	**SE6**	0.0269
PM7	0.0126	**SE7**	0.0130
PM8	0.0135	**SE8**	0.0142
PM9	0.0167	**SE9**	0.0178
PM10	0.0198	**SE10**	0.0213
PM11	0.0234	**SE11**	0.0263
PM12	0.0276	**SE12**	0.0302

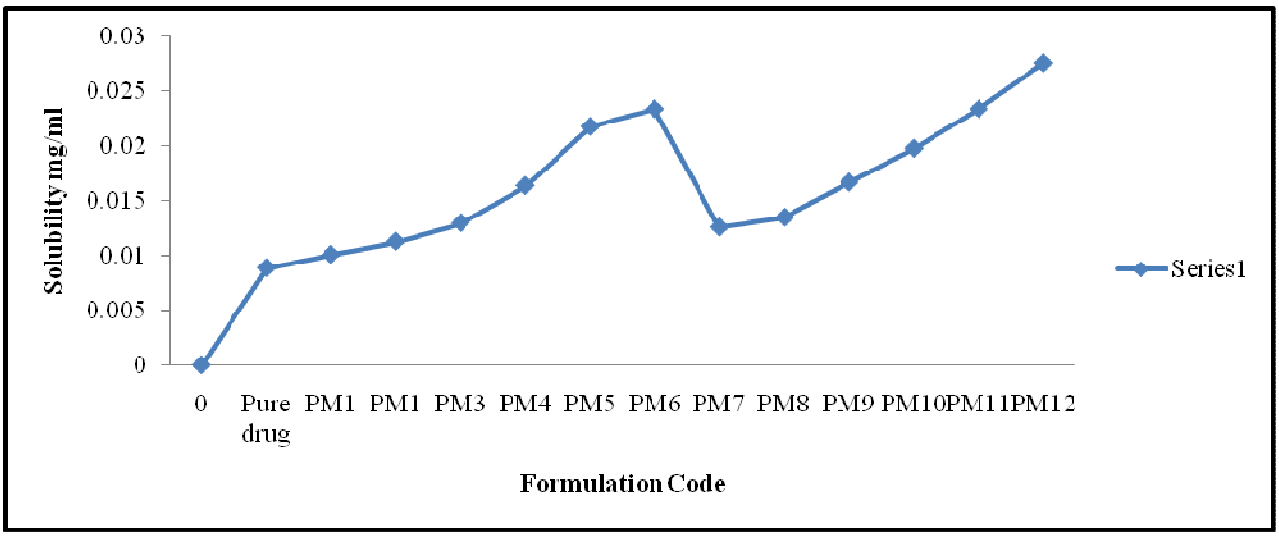

Fig 1 (a) Solubility of SD with physical mixing method

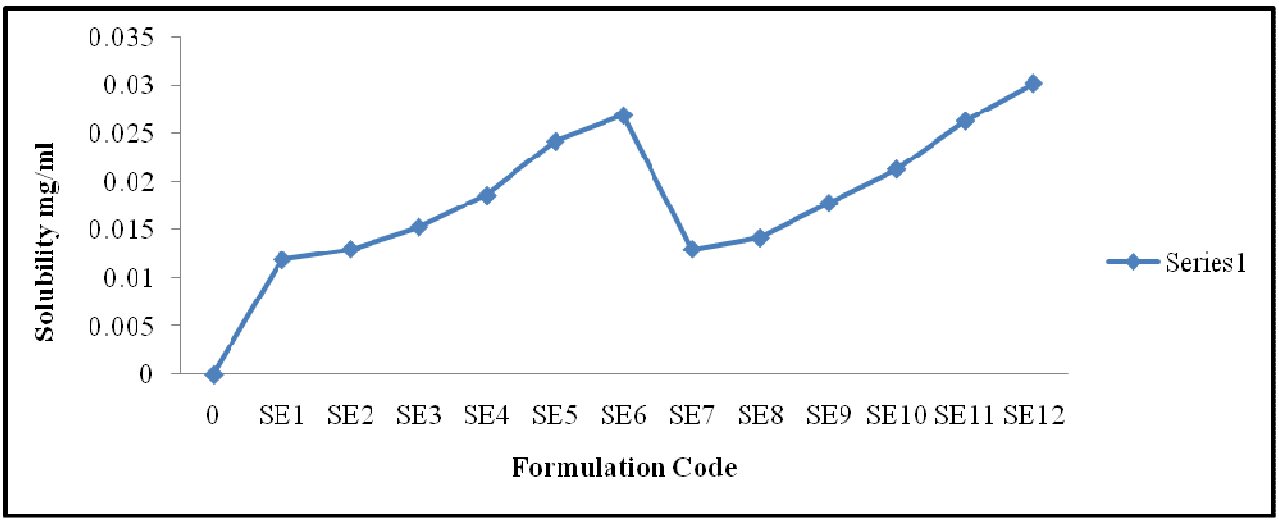

Fig 2 (b) Solubility of SD with solvent evaporation method

On the basis of above experimental design it was concluded that the SD prepared by physical mixture method showed low solubility of drug. While the SD prepared by solvent evaporation method showed high solubility. Therefore on the basis of above study we have selected the solvent evaporation method for further study. Other evaluation parameters were selected on the basis of solubility of SD formulation. A selected formulation was SE5, SE6, SE11 and SE12 batch were found to be suitable and selected for further formulation and characterization.

Bulk characteristic of optimized SD: The bulk characteristic of optimized SD with solvent evaporation methods were characterized by flow properties such as angle of repose, bulk density, tapped density Carr's index and Hausner's ratio were performed[6].

Table 3 Bulk characteristic of optimized SD with solvent evaporation method

S. No.	SDs	Angle of repose (^{0}C)	Bulk density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio
1	**Valsartan**	39.19^0±0.89	0.271±0.001	0.423±0.001	35.93±0.15	1.56±0.006
2	**SE5**	26.21^0±0.67	0.369±0.03	0.398±0.06	17.69±0.10	1.07±0.005
3	**SE6**	25.82^0±0.12	0.373±0.004	0.413±0.06	13.05±0.09	1.15±0.001
4	**SE11**	26.63^0±0.29	0.364±0.01	0.401±0.01	9.22±0.09	1.10±0.001
5	**SE12**	27.94^0±0.10	0.380±0.01	0.415±0.006	8.43±0.01	1.09±0.002

Formulation of Valsartan Tablets: Based on maximum % practical yield, drug content, solubility, bulk characteristic optimization parameters was formulated as tablets and direct compression method was used for the preparation of tablets. In this, microcrystalline cellulose (MCC) was used as direct compressible vehicle; mannitol and SSG was used as superdisintegrants, talc is diluent, magnesium stearate as lubricant and glidants respectively. All the ingredients were blended in a closed dry plastic container. The blend of powder was compressed into tablet machine. In each case twenty tablets were prepared. The tablets were stored in a tightly closed container and evaluated for following characteristics in triplicate [4].

Table 4 Composition of valsartan SD containing tablets

Ingredients (mg/tablet)	FT1	FT2	FT3	FT4	FT5
Pure valsartan	40	-	-	-	-
SE5 (1:3)	-	120	-	-	-
SE6 (1:3.5)	-	-	160	-	-
SE11 (1:3)	-	-	-	120	-
SE12 (1:3.5)	-	-	-	-	160
Mannitol	-	-	-	20	20
SSG	20	20	20	-	-
MCC	160	80	40	80	40
Mg stearate	10	10	10	10	10
Talc	20	20	20	20	20
Total weight of Tablet (mg)	250	250	250	250	250

Evaluation of Physical Parameters for Different Tablets: Various physical parameters such as hardness, friability, weight variation,*in-vitro*disintegration test, drug content and *in-vitro* dissolution study were evaluated [5].

Table 5 Evaluation of Physical Parameters for Different Tablets

Formula	FT1	FT2	FT3	FT4	FT5
Hardness (Kg/cm^2)	3.5±0.5	3.8±0.35	3.0±0.25	3.2±0.26	3.81±0.12
Friability %	0.68±0.6	0.45±0.11	0.28±0.03	0.35±0.14	0.23±0.08
Wt. variation (mg)	248±4	245±5	251±2	247±4	251±2
Disintegration time (min)	10.3±1.36	6.8±1.02	6.1±1.14	5.6±1.05	5.3±0.45
Drug content %	97.48 ± 0.12	98.12 ± 0.14	98.61 ± 0.21	98.05 ± 0.09	99.39 ± 0.04

***In-vitro* dissolution study of tablets:** *In-vitro* dissolution study of the tablets (Pharmacopoeia of India, 1996; USP, 2000) was conducted using USP dissolution type II apparatus, at 50 rpm using pH-6.8 phosphate buffer as a dissolution media, and temperature was maintained at $37^oC±0.5^oC$. Samples were withdrawn at various time intervals (10, 20, 30,40, 50, 60 and 90,120 min), an equal volume of fresh dissolution medium was replaced to maintain the sink condition and filtered through a 0.45µwhatman filter paper, diluted, aliquots were measured at 250 nm UV/Visible spectrophotometer.

Table 6 % cumulative drug release of different formulation

% Cumulative drug release of SD tablets						
S. No.	**Time (Min)**	**FT1**	**FT2**	**FT3**	**FT4**	**FT5**
1	**0**	0	0	0	0	0
2	**10**	5.12 ± 0.88	9.60 ±0.63	11.32 ± 0.84	7.09 ± 0.32	13.50 ± 0.61
3	**20**	11.39 ± 0.71	17.24 ± 0.77	21.64 ± 0.47	14.19 ± 0.96	20.59 ± 0.73
4	**30**	16.10 ± 0.53	31.29 ± 0.41	37.82 ± 0.61	28.35 ± 0.77	37.32 ± 0.54
5	**60**	37.69 ± 0.66	53.93 ± 0.98	59.12 ± 1.37	51.64 ± 0.63	57.19 ± 0.48
6	**90**	48.93 ± 1.22	71.02 ± 0.76	78.09 ± 0.98	73.89 ± 1.02	78.10 ± 1.12
7	**120**	55.29 ± 0.91	89.12 ± 1.14	91.03 ±0.87	88.03 ± 1.27	94.54 ± 1.27

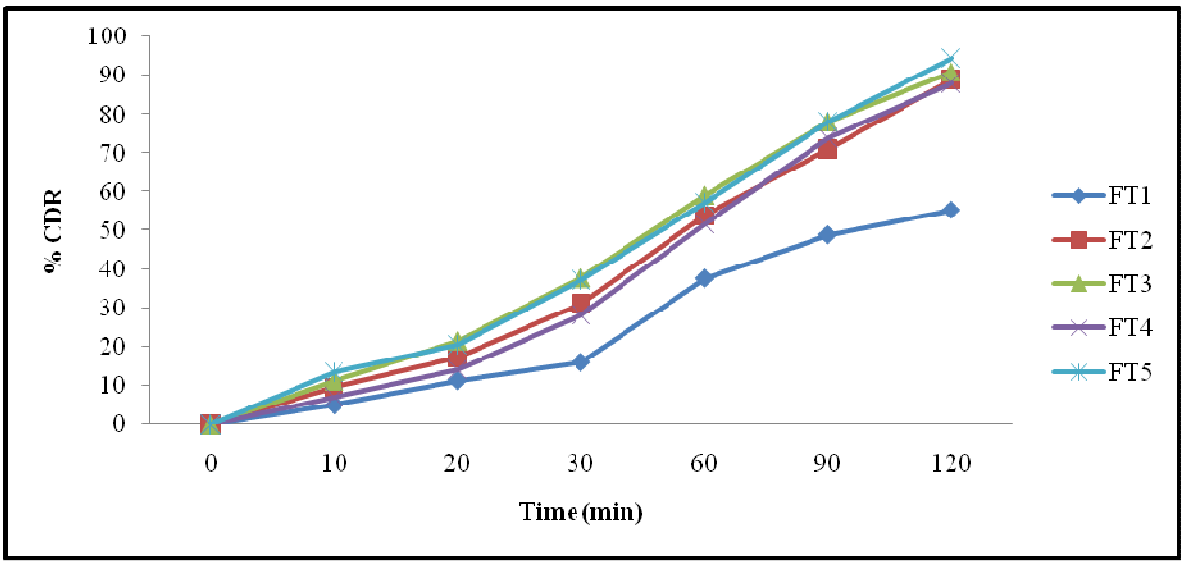

Fig 3 % cumulative drug release of different formulation

Results and Discussion: Preparation of SD were carried out solvent evaporation method and different batches were selected and optimized on the basis of % practical yield, drug content, solubility, bulk property.

SD of valsartan was prepared by solvent evaporation method. The carriers like sodium starch glycolate and mannitol were used in the preparation of SD. Various ratios of drug and carrier such as 1:1, 1:1.5, 1:2, 1:2.5, 1:3 and 1:3.5 were used in the preparation.

The % practical yield all formulation of SD was found to be range 95-98.22 % the result of % practical yield studies**.** Maximum yield was found to be 98.62 % in SE11.

Percent drug content of all formulations SD**.** The % drug content was found to be range 98.32-99.12 %. Maximum % drug content was found to be 98.62 % in SE5.

Solubility data after physical mixing method and solvent evaporation method was determined. It was observed that as the concentration of carrier is increased the solubility was increased and it was also noticed that at the same concentration of carrier, the SD prepared with solvent evaporation method displayed greater solubility than physical mixing method.

Optimized batches of SD prepared were found to be fine free flowing powders. Angle of repose, bulk density, tapped density, carr's index, Hasusner's ratio and drug content was calculated and were found to be in the range of 27.94-39.19, 0.380-0.271, 0.415-423, 8.43-35.93, 1.09-1.56. All the above values showed that the powder possess good compressibility and optimum flow rate.

Based on optimization parameters tablet formulation were prepared for optimized batches obtained with different carriers and different method. Five formulations FT1, FT2, FT3, FT4 and FT5 were prepared. Out of these FT5 was found to be best based on different evaluation parameters. Results obtained for FT5 formulation after weight variation, thickness, hardness, friability, diameter,*in-vitro* disintegration time and % drug content were found to be 251 ± 2 mg, 3.80 ± 0.03 kg/cm^3, 3.81 ± 0.12 %w/w, 0.23 ±0.08 mm, 5.3 ± 0.45 min. and 99.39% , respectively. Result concluded that all the parameter were in accordance to the standard limit.

Conclusion: The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. Among the various methods of enhancement of the

dissolution rate and oral bioavailability, SD technologies were found to be more successful with a number of drugs. In the present investigation, studies were carried out on enhancement of dissolution rate of valsartan by SD technology employing various water dispersible carriers. A new class of tablet excipients called 'super disintegrants' was evaluated as carriers for SDs and for enhancing the dissolution rate of poorly soluble drugs. Among the super disintegrants tested SSG gave highest enhancement of dissolution rate and efficiency of valsartan. In each case the dissolution rate were increased as the concentration of carriers in the SDs was increased. The order of increase in dissolution rate with various superdisintegrant was SSG>mannitol.

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