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Research Article

# EFFECT OF TYPE OF NON-VOLATILE SOLVENTS ON THE FORMULATION AND RELEASE OF VALSARTAN FROM LIQUID SOLID COMPACTS

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**ABSTRACT**

Objective: The present work was aimed at studying the effect of different non-volatile solvents used in the preparation of liquisolid compacts on the properties of tablets produced and dissolution rate of valsartan from the prepared tablets.

Methods: The solvents selected for this purpose include propylene glycol, poly ethylene glycol 200, 600, Tween 20, and Tween 80. Avicel PH 102 was selected as a carrier, Aerosil 200 as a coating material and croscarmellose sodium as a disintegrant. The liquisolid tablets were prepared according to the mathematical model developed by Spireas and Bolton. The prepared tablets were evaluated for quality control tests like weight variation, uniformity of drug content, tablet hardness, friability test, disintegration and in vitro dissolution studies. In vitro dissolution studies were performed in 0.001 N HCl and compared with that of plain drug, marketed tablet and conventional tablets prepared by direct compression.

Results: The FTIR studies indicated no significant interactions between drug and excipients. The physicochemical properties of the solvent affected tablet weight, hardness and friability. The dissolution studies did not show significant difference in the dissolution rate of valsartan.

Conclusion: The amount of carrier material required to produce dry and free flowing powder depends on the viscosity of the non-volatile solvents where as the drug release was not significantly changed with type of non-volatile solvent.

**Keywords:** Valsartan, Liquisolid compacts, dissolution rate, enhancement in dissolution, poorly soluble, BCS class II.

## INTRODUCTION

The concept of liquisolid tablets was developed from powder solution technology used to formulate liquid medications. A liquisolid system is defined as dry, non-adherent, free-flowing and compressible powder mixtures converted from liquid drugs, drug suspensions or drug solutions in non-volatile solvents with selected powder substrate referred as carrier and coating materials [1]. Two major formulation components present in liquisolid compacts includes: the powder substrate and the liquid medication. The powder substrate consists of (a) relatively large quantity of porous carrier which will enhance the compression, (cellulose) and (b) very fine, coating particles with high adsorption capacity (silica) to enhance the flow [2]. The liquid medication contains oily liquid drugs or solutions, suspensions/emulsions of water-insoluble solid drugs in water miscible non-volatile liquids. Spireas and Bolton developed a mathematical model to calculate the required quantities of carrier and coating material to be added to produce dry, non-adherent, free-flowing, and readily compressible powders based on the flowable liquid-retention potential (Ø-value) of excipients [3]. The Ø-value represents the maximum amount of liquid that can be retained in the powder bulk without compromising its flowability and compressibility. The maximum liquid load on the carrier, known as the load factor ($L_f$) depends on excipient ratio (R) used. The $L_f$ and R were related by the following equation:

$L_f = Ø_{ca} + Ø_{co}\,(1/R)$ Equation (1)

Where, $Ø_{ca}$ is the flowable liquid-retention potential of the carrier, and $Ø_{co}$ is flowable liquid-retention potential of the coating material.

$L_f$ is defined as the ratio of the amount of liquid medication (W) to the amount of carrier material (Q). The studies conducted with different carrier and coating material indicates that, a optimum R value of 20 produces powder systems with optimal flow and compactible properties [4]. Valsartan is a potent, highly selective antagonist of angiotensin II AT1 receptor used orally in the treatment of hypertension. The drug belongs to BCS class II according to biopharmaceutical classification system due to its low aqueous solubility and high permeability. Poor aqueous solubility and slow dissolution rate results in poor oral bioavailability (approximately 23 %). To overcome these problems we have reported formulation of liquisolid compacts for valsartan in our previous study [5].

In present investigation we have studied the effect of different non-volatile solvents used in the formulation on properties of tablets and release of valsartan from the prepared tablets.

## MATERIALS AND METHODS

### Materials

Valsartan was kindly gifted by Aurobindo pharmaceuticals, Hyderabad, India. Tween 20, Tween 80, polyethylene glycol (PEG 200 and PEG 600), propylene glycol, sodium hydroxide, potassium dihydrogen orthophosphate and sodium lauryl sulphate was purchased from Sd Fine-Chem Ltd., Mumbai. Avicel PH 102, Aerosil 200, lactose mono hydrate, dicalcium phosphate (DCP), croscarmellose sodium was purchased from Nehal traders, Hyderabad. All other chemicals, reagents and solutions used were of analytical grade. Marketed product Valzaar 40 mg (Torrent Pharmaceutical Ltd., Ahmadabad) was procured from local pharmacy.

### Solubility studies

The solubility determination was carried out in five non-volatile solvents and at various pH conditions by shake flask method [6]. Excess amount of drug was added to the vials containing selected vehicles. The vials were sealed and the mixture was vortexed using a vertex mixer for 10 min in order to facilitate proper mixing of drug with the vehicles and subjected to equilibrium on the incubator shaker (JEIOTECH, Korea) for 48 h at 25 ± 1 °C. After this period, the solutions were centrifuged and supernatant was filtered through a 0.45 µm Millipore filter, and analysed by UV-spectrophotometer (JASCO V-650, Japan) at a wavelength of 250 nm with appropriate dilutions against blank (blank sample contained the same concentration of specific solvent used without drug). The determinations were carried out in triplicate and its mean along with standard deviation was reported.

**Preparation of liquisolid compacts**

The liquisolid compacts were prepared according to the method described by Spireas and Bolton [2]. Valsartan was dissolved in respective non-volatile solvents to prepare the drug solution. The mixture of carrier and coating materials (Avicel PH 102, Aerosil 200 respectively) was added to the liquid medication and blended in a porcelain mortar avoiding excessive trituration and particle size reduction. The mixing was done in three stages: first, the system was mixed slowly to allow uniform distribution of liquid medication; second, the mixture was spread as a uniform layer on the surface of the mortar and left standing for a few minutes; finally, 10 % of disintegrant (croscarmellose sodium) was added to the powder and mixed thoroughly. The final mixture was compressed into tablets.

**Determination of viscosity of non-volatile liquids**

The viscosity of different nonvolatile liquids used in the formulation was determined using Brookfield viscometer (DV II + Pro EXTRA, Brookfield, USA). The liquid was filled in a tube and selected spindle was inserted in to the liquid. Now the rotation of the spindle generates shear and viscosity at particular shear was displayed. By changing the speed of spindle viscosity at different shear rates can be determined.

**Calculation of load factor**

The powder excipient (5 g) mixed with liquid vehicle was placed at one end of the polished metal plate. The plate was tilted slowly until the powder mix starts to slide. The angle formed by the plate is called as angle of slide [7]. The Ø value at $33^0$ was calculated as follows:

$$\emptyset = \frac{\text{weight of non} - \text{volatile liquid vehicle}}{\text{weight of powder material}} \qquad \text{Equation (2)}$$

**Characterization of LSC**

**Flow properties of liquisolid powders**

The flow properties were determined in terms of angle of repose by fixed funnel and free standing cone method [8]. A funnel was fixed at a given height H, above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The mean radius R, of the base of the conical pile, was determined and the tangent of the angle of repose was given by Tan α = H/R. Where, α is angle of repose.

**FTIR spectroscopy**

The spectra of drug, Avicel PH102, Aerosil, and liquisolid powder were recorded on Perkin Elmer spectrophotometer using KBr pellet from 4000 $cm^{-1}$ to 400 $cm^{-1}$. The pellets were prepared by mixing 5 mg of sample with 100 mg potassium bromide and compacted under vacuum at a pressure of about 12,000 psi for 3 minutes [9].

**Hardness, content uniformity, Friability and disintegration time**

The prepared liquisolid tablet was evaluated for hardness, friability, disintegration time and content uniformity. Hardness was determined by Pfizer hardness tester and friability by digital tablet friability tester. The disintegration time was measured using USP disintegration tester (Electrolab, India). The tests were done in accordance to the procedure in Indian pharmacopoeia (2010). All the studies were done in triplicate.

***In vitro* dissolution study**

Dissolution studies were performed on liquisolid compacts, plain drug, conventional tablet without non-volatile solvent and marketed product. The USP paddle method was used for all in vitro dissolution studies. The dissolution was carried out in 0.001 N HCl (pH 3.0). The stirring rate was 50 ± 1 rpm. The amount of valsartan was 20 mg in all formulations. The dosage forms were placed in 1 L dissolution medium maintained at 37 ± 0.5 °C. Aliquots of 5 ml were taken at appropriate intervals (5, 10, 15, 20, 25, 30 and 45 min), filtered through a 0.45 µm membrane filter and analyzed at 250 nm by UV–visible spectroscopy. The mean value of six determinations was used to calculate the drug release from each formulation.

**Analysis of drug release**

For the comparison of dissolution data, mean dissolution time (MDT) and dissolution efficiency ($DE_{30}$ %) at 30 min were calculated. MDT was calculated as follows [10]:

$$MDT = \frac{\sum_{i=1}^{n} t\Delta M_i}{\sum_{i=1}^{n} M_i} \quad Equation\ (3)$$

Where, 'i' is the sample number, 'n' is the number of dissolution sample times, 't' is the time at the midpoint between t and t–1 and Δ $M_i$ is the additional amount of drug dissolved between t and t–1.

Dissolution efficiency is given by formula,

$$DE = \frac{\int_0^t Y dt}{\int_0^{100} t} \times 100 \quad Equation\ (4)$$

Where, 'Y' is the percent of drug released as a function of time, t is the total time of drug release and '$Y_{100}$' is 100 % drug release [11]. The in vitro release profiles were further compared using similarity factors, $f_2$, as defined by the following equation.

$$f_2 = 50 \log \left\{ \left[ 1 + \frac{1}{n} \sum_{t-1}^{n} (R_t - T_t) \right]^{-0.5} \right\} \quad Equation\ (5)$$

Where, 'n' is number of time points at which % dissolved was determined, '$R_t$' is the % dissolved of one formulation and '$T_t$' is the % dissolved from second formulation at a given time point. The similarity factor has the value between 0 and 100. The value will be 100 when the test and reference profiles are identical and approaches 0 as the dissimilarity increases. An $f_2$ above 50 points out that the two profiles are similar.

**Statistical analysis**

All the data were statistically analyzed by one way ANOVA. Results were quoted as significant where $p < 0.05$.

**RESULTS AND DISCUSSION**

Valsartan is weakly acidic drug with absorption window in the upper part of GIT. However, the poor solubility in acidic environment of the GI tract hinders its absorption resulting in low bioavailability. Rapid onset of action is also desirable to provide fast relief in the treatment of heart failure. Hence, it is necessary to enhance the aqueous solubility and dissolution rate of valsartan to obtain faster onset of action, minimize the variability in absorption, and improve its overall oral bioavailability. Liquisolid tablets were prepared that showed improvement in the dissolution of valsartan compared to plain drug and marketed tablets. The present study was aimed to study the effect of non-volatile solvents on the formulation and characteristics of prepared LS tablets.

**Solubility study**

The solubility of drug in non-volatile solvent is an important factor in the formulation of liquisolid systems, as higher solubility of drug in liquid vehicle can lead to higher dissolution rates due to more amount of molecularly dispersed drug and exposure of larger surface area to dissolution media. The solubility of valsartan in different non-volatile solvents and at different pH conditions are shown in Table 1. Form the solubility data the drug is considered as BCS class II drug as the highest dose of the drug is not soluble in 250 ml of media at pH 1.2 and 3.0.

The use of non-volatile solvents improved solubility significantly. Highest solubility was found in propylene glycol with 1486 fold improvement. The order of valsartan solubility in different solvents was PG > PEG 600 > Tween 80 > Tween 20 ≅ > PEG 200. The results also indicates valsartan is having pH dependant solubility. From the solubility at different pH conditions 0.1N HCl and 0.001 N HCl was selected as the discriminating media for in vitro dissolution studies. The improvement in dissolution in this media will be significant to achieve optimum concentrations in blood.

**Table 1: Solubility of valsartan in different non-volatile solvents and at different pH**

| Solvent | Solubility (mg/ml) | Media | pH | Solubility (mg/ml) |
|---|---|---|---|---|
| Tween 20 | 69.73 ± 2.38 | 0.1N HCl | 1.2 | 0.07 ± 0.09 |
| Tween 80 | 76.57 ± 2.67 | 0.001N HCl | 3.2 | 0.10 ± 0.06 |
| PEG 200 | 65.41 ± 1.23 | Acetate buffer | 4.5 | 1.30 ± 0.46 |
| | | PBS | 6.8 | 5.54 ± 1.54 |
| PEG 600 | 83.91 ± 2.89 | PBS | 7.2 | 8.72 ± 0.88 |
| PG | 109.23 ± 3.21 | Distilled water | 6.8 | 0.21 ± 0.1 |

**Load factor**

The viscosity of solvents were determined using brook field viscometer and presented in Table 2 with load factors calculated for Avicel PH 102 in respective solvent. Liquid load factor ($L_f$) is defined as the ratio of the weight of liquid medication over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquid solid system. Viscosity of liquids is directly proportional to flow properties and inversely to load factor (Fig. 1).

**Table 2: Viscosity and Load factor of solvents**

| Non-volatile liquid | Viscosity (cps) | Liquid load factor ($L_f$) |
|---|---|---|
| Transcutol HP | 2.86 ± 0.40 | 0.247 |
| Propylene Glycol | 41.82 ± 0.5 | 0.224 |
| PEG 200 | 42.13 ± 1.75 | 0.158 |
| PEG 600 | 99.65 ± 1.34 | 0.139 |
| Tween 20 | 339.9 ± 8.17 | 0.107 |
| Tween 80 | 394.4 ± 9.95 | 0.101 |

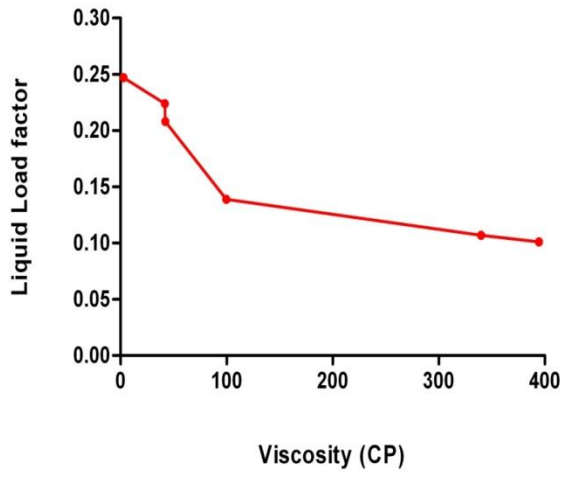


**Fig. 1: Relationship between liquid load factor and viscosity of non-volatile solvent**

**FTIR spectra**

The IR spectrum of valsartan (Fig. 2) exhibits characteristic peaks at 3300 $cm^{-1}$ (N–H functional group), 2963 $cm^{-1}$ (C–H group stretching vibration), 1734 $cm^{-1}$ (carboxyl carbonyl), 1603 $cm^{-1}$ (amide carbonyl group). The peak at 1458 $cm^{-1}$ indicates the presence of C=C aromatic group. Appearance of these peaks in the physical mixture and in all liquisolid formulations (F1 - F5) indicates the absence of chemical interaction between the drug and excipients.

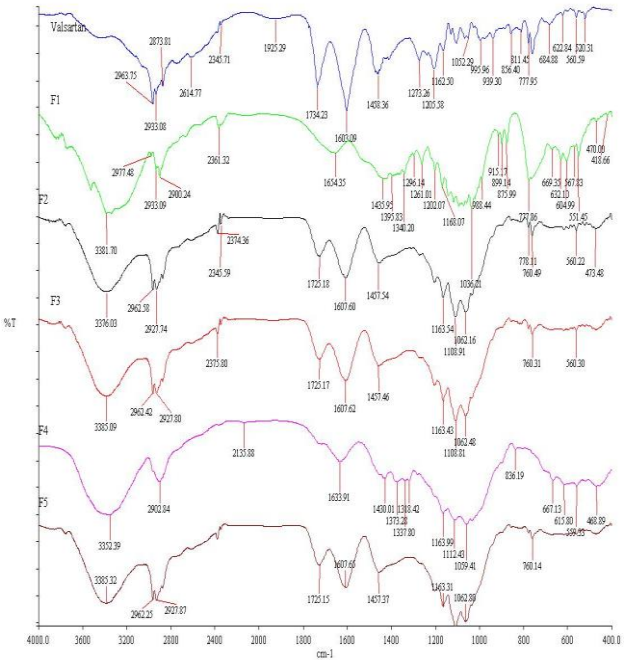


**Fig. 2: FTIR spectra of valsartan plain drug and different liquisolid formulations**

**Preparation of LSC and conventional tablets**

The detailed procedure to prepare valsartan LSC and directly compressible conventional tablet was explained in our previous work [5] and here we will be concentrating on the effect of different non-volatile solvents on the load factor and dissolution of drug from liquisolid tablet. The amount of carrier, coat material added and unit weight of tablet are shown in Table 3. The amount of valsartan in each tablet was kept constant at 20 mg.

**Table 3: Formulation of valsartan liquisolid compacts**

| Formul-ation[a] | Vehicle | $L_f$[b] | Avicel PH 102 (mg) | Aerosil 200 (mg) | Weight of tablet[c] (mg) |
|---|---|---|---|---|---|
| F1 | PG | 0.224 | 250 | 12.5 | 310 |
| F2 | PEG 200 | 0.158 | 350 | 17.5 | 425 |
| F3 | PEG 600 | 0.139 | 320 | 16 | 390 |
| F4 | Tween 20 | 0.107 | 450 | 22.5 | 530 |
| F5 | Tween 80 | 0.101 | 400 | 20 | 484 |

The solubility of drug in the non-volatile solvents plays an important role in the amount of carrier required to produce dry powder. As the solubility decreases more amount of solvent is required to dissolve the given dose of drug. The amount of carrier required to obtain dry and free flowing powder also increases with increasing solvent. At the same time the viscosity of the solvent along with solubility should be considered. As the viscosity of solvent increases the load factor value decreased (Table 2). The increase in load factor will increase the amount of carrier required to produce liquisolid compacts with acceptable flow properties. Hence, the amount of carrier and coat material required and the weight of tablet depends on the solubility of drug in given solvent and also to some extent on the viscosity of non-volatile solvent used.

**Hardness, content uniformity, friability and disintegration time**

The fundamental requirement for all dosage forms is to maintain constant dose of drug between each unit in a batch with sufficient hardness to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing. The evaluation

parameters are shown in Table 4. All the formulations were within acceptable limits except formulation F4 as per Indian pharmacopoeia.

Hardness of the formulation F4 was less and not within acceptable limits (3 – 4 kg/cm²) compared to other formulations. This may be due to high viscosity of the solvent which prevented the uniform distribution of solvent on to the carrier and coating material. This formulation was not considered for further in vitro dissolution studies.

**Table 4: Evaluation parameters of valsartan liquisolid tablets**

| Formulation | Hardness (kg/cm²) | Friability (%) | Disintegration time (min) | Drug content (%) |
|---|---|---|---|---|
| F1 | 4 | 0.45 ± 0.07 | 1.4 ± 0.04 | 98.79 ± 0.64 |
| F2 | 3.5 | 0.54 ± 0.03 | 1.2 ± 0.08 | 99.80 ± 0.65 |
| F3 | 3.5 | 0.68 ± 0.16 | 2.1 ± 0.13 | 99.96 ± 0.59 |
| F4 | 2.5 | 0.89 ± 0.10 | 1.0 ± 0.04 | 96.96 ± 0.90 |
| F5 | 3 | 0.77 ± 0.1 | 1.1 ± 0.04 | 96.53 ± 0.90 |

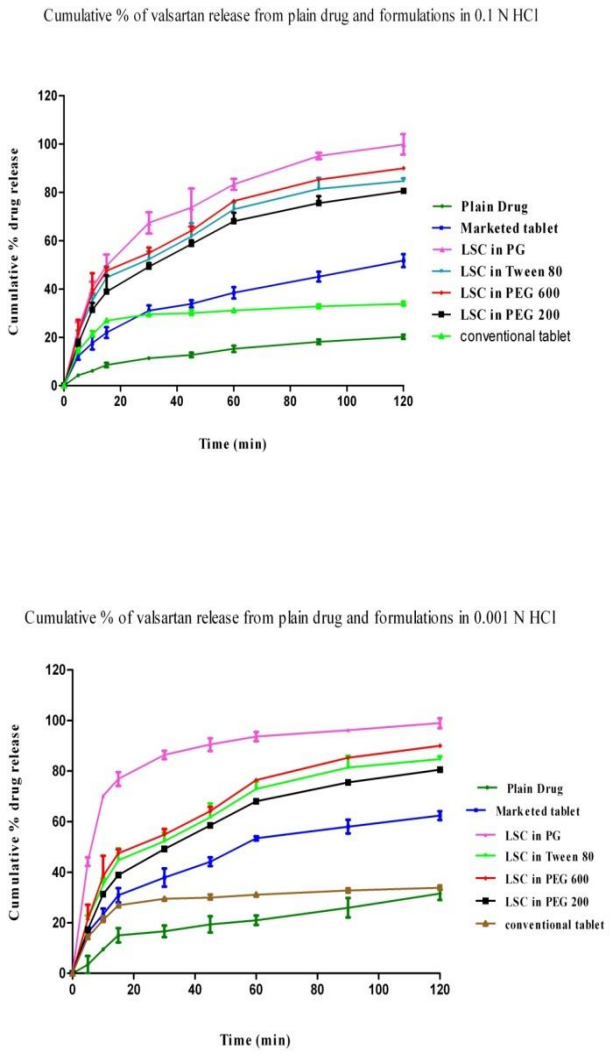


**Fig. 3: Dissolution profiles of valsartan from plain drug, marketed tablet and different LSC formulations in different media.**

***In vitro* dissolution study**

The dissolution profiles of the prepared tablets at two pH conditions (1.2 and 3.0) are shown in Fig. 3. The dissolution rate of valsartan was significantly ($P < 0.05$) increased from all the LSC formulation compared to plain drug, marketed tablet and conventional tablets (Fig. 3). The dissolution studies were performed on four formulations (F1, F2, F3 & F5).

No significant difference in dissolution rate was found between all the formulations when analysed using one way ANOVA in both the media. The dissolution rate was further compared with that of conventional tablets containing same amount of carrier and coat material without non-volatile solvent prepared by direct compression. Significant improvement was observed in the dissolution rate of valsartan from all the formulation compared to conventional tablet (Fig. 3).

This indicates the presence of non-volatile solvent is responsible for the improvement of dissolution rate of poorly soluble drug. This was further supported from the DE % at 30 min and MDT values. This increase in the dissolution with liquisolid formulation was attributed to the increased wettability and surface availability of drug to the dissolving medium. The dissolved drug in a water miscible non-volatile solvents will be precipitated in the form of fine particles with high surface area and hydrophilic carrier material provide improved wetting

**Table 5: Comparative dissolution parameters of valsartan from plain drug and different formulations in 0.1 N HCl**

| Formulation | MDT (min) | $DE_{30}$ % |
|---|---|---|
| F1 | 28.27 ± 4.43 | 14.42 ± 2.44 |
| F2 | 32.03 ± 1.66 | 5.79 ± 0.49 |
| F3 | 38.03 ± 1.78 | 5.96 ± 1.26 |
| F5 | 44.30 ± 0.46 | 4.26 ± 0.68 |
| Plain drug | 223.12 ± 0.59 | 0.17 ± 0.72 |
| Marketed tablet | 120.38 ± 2.20 | 0.86 ± 2.61 |
| Conventional tablet | 198.14 ± 2.66 | 0.19 ± 0.61 |

## CONCLUSION

The liquisolid technique showed promising results in enhancing the dissolution rate of poorly soluble drugs like valsartan. The LSC formulations were prepared using different non-volatile solvents. The solubility of drug in the given solvent and viscosity of the solvent influenced the tableting properties like tablet weight, hardness, disintegration and there by dissolution rate of drug from the tablet in given medium.

PG showed higher drug release compared to other solvents used due to high solubility of valsartan in PG and less viscosity. Hence, careful selection of non-volatile solvent is crucial in the formulation of liquisolid compacts.

**Conflict of Interest**

Authors declare no conflict of interest.

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