

Solubility & Dissolution Enhancement of Antihypertensive Agent(S) using Solid Dispersion Techniques

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Abstract: *Drugs having poor aqueous solubility present one of the major confronts better absorption for good bioavailability of such drugs. Solid dispersion of Hydrochlorothiazide and valsartan (12.5 mg : 80 mg) in a fixed dose combination was prepared. The major problem with these drugs is their low aqueous solubility, which results into poor bioavailability after oral administration. The purpose of this study was to prepare and characterize solid dispersions of the poorly water soluble antihypertensive agents Hydrochlorothiazide and valsartan with water soluble carriers such as PEG-6000, Urea, and PVP K-30 to improving its aqueous solubility and rate of dissolution. The solid dispersions of drug were prepared by solvent evaporation technique, fusion method, & co-grinding methods. The observed results showed the solid dispersion of drug were found increased in aqueous solubility than pure drug. Evaluation of the dispersions were performed using aqueous solubility and dissolution studies, the results obtained showed that the aqueous solubility and rate of dissolution of fixed dose combination hydrochlorothiazide and valsartan was significantly improved when formulated in solid dispersions as compare to pure drugs.*

Keywords: *Hydrochlorothiazide and valsartan, solid dispersions, Aqueous solubility and rate of dissolution*

1. INTRODUCTION

Solid dispersion is one of the approaches employed to improve dissolution of poorly soluble drugs whose absorption is dissolution rate limited.

Chiou and Riegelman defined the term solid dispersion as “a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures.” The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method.

1.1. Classification of Solid Dispersion

Based on their molecular arrangement, six different types of solid dispersions can be distinguished. Moreover, in various studies the designation of solid dispersions is based on the method of preparation.

The solid dispersion enhances the drug solubility by the various mechanisms:

- By reducing the particle size
- By increasing porosity
- By converting the crystalline forms of drug into amorphous form.

The various water soluble carriers such as PVP, PEG, Urea, Mannitol, etc. can be used for increasing the solubility of drugs.

Hydrochlorothiazide–Valsartan is used in a fixed dose combination in the management of hypertension.

Hydrochlorothiazide is a thiazide diuretic acting by reducing reabsorption of electrolyte from the renal tubules, thereby increases the excretion of Na⁺ and Cl⁻.

It is administered 12.5mg daily, either alone or in combination with 80mg Valsartan.

Valsartan, is used in the treatment of hypertension. It is a n angiotensin II receptor blocker (ARB).

Valsartan is poorly water-soluble ARBs and is administered orally.

The present study was directed towards developing solid dispersion of hydrochlorothiazide and Valsartan in combination

Both drugs commercially available in a fixed dose combination for the management of hypertension

Table1. Classification of solid dispersion

Sr. No.	Solid dispersion type	Matrix *	Drug **	Remarks	No. of phases
I	Eutectics	C	C	The first type of solid dispersion prepared	2
II	Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2
III	Solid solutions				
	Continuous solid solutions	C	M	Miscible at all composition, never prepared	1
	Discontinuous solid solutions	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed.	2
	Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed.	1or 2
	Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug in helical interstitial spaces of PEG.	2
IV	Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in	2
				amorphous matrix	
V	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate. Many solid dispersions are of this type.	2
VI	Glass solution	A	M	Requires miscibility OR solid solubility, complex formation or upon fast cooling OR evaporation during preparation, many examples especially with PVP.	1

*A: matrix in the amorphous state, C: matrix in the crystalline state.

**A: drug dispersed as amorphous clusters in the matrix.

C: drug dispersed as crystalline particles in the matrix.

M: drug molecularly dispersed throughout the matrix.

2. MATERIALS

Hydrochlorothiazide (USP) and Valsartan were obtained as gift samples from IPCA Pharmaceuticals, Ltd. (Mumbai, India). Other chemicals were of analytical reagent grade.

2.1. List of Equipment

Table2. List of Equipments used

S. No.	Name of equipment	Model	Manufacturer
1.	UV Spectrophotometer	UV 1800	Shimadzu, Japan
2.	Dissolution Test Apparatus	DS8000	Labindia
3.	Digital Ultrasonicator	RQ-126/D	Raj analytical service, Mohali
4.	Hot air Oven	NSW143	Narang Scientific
5.	P ^H meter	Pico ⁺	Shimadzu, Japan
6.	Digital Balance	AUX220	Shimadzu, Japan
7.	Water bath shaker	NSW133	Narang Scientific

3. METHODS

3.1. Identification of Drug

3.1.1. By UV Spectroscopy

UV Spectroscopy was used to determine the specific wavelength at which the drug shows maximum absorbance. Calibration Curve of Hydrochlorothiazide (USP) and Valsartan using Shimadzu UV-Visible double beam spectrophotometer (UV 1800), the sample solution was scanned and the peak with distinguishable peak area was selected.

3.2. Solubility Studies of Pure Drug and Solid Dispersions

Solubility of drugs in presence of carriers like Urea, and PVP K-30. This was done by dissolving excess amount of drug in centrifuge tube containing different concentrations of carriers in different ratios (1:1 1:3, 1:5) in distilled water. The centrifuge tube were shaken mixing by vortexing intermittently and kept aside for 24 hours. The solutions were filtered and absorbance was measured at 251nm and 272 after dilution. Solid dispersions produced using Urea, and PVP K-30 as carriers in three different ratios were checked for their solubility.

3.2.1. Preparation of Solid Dispersions

Various methods used to prepare solid dispersions of Hydrochlorothiazide and Valsartan includes in combination: physical mixture; fusion method and solvent evaporation method in the weight ratios of 1:1, 1:3, and 1:5 with Urea and PVP-30.

3.2.2. Drug Content

Solid dispersions equivalent to 12.5 mg of hydrochlorothiazide and 80 mg of Valsartan were accurately weighed and dissolved in 10 ml methanol, from that 0.1 mL of solution was diluted and assayed for drug content.

3.2.3. In Vitro Dissolution Studies

Dissolution studies of hydrochlorothiazide and valsartan in pure form, SDs, and PMs were performed using a digital USP dissolution Apparatus 2. (Veego India, Mumbai) at a paddle rotation speed of 100 rpm using 900 mL of 0.1N HCL as dissolution medium at 37 ± 0.5 °C

4. RESULTS AND DISCUSSION

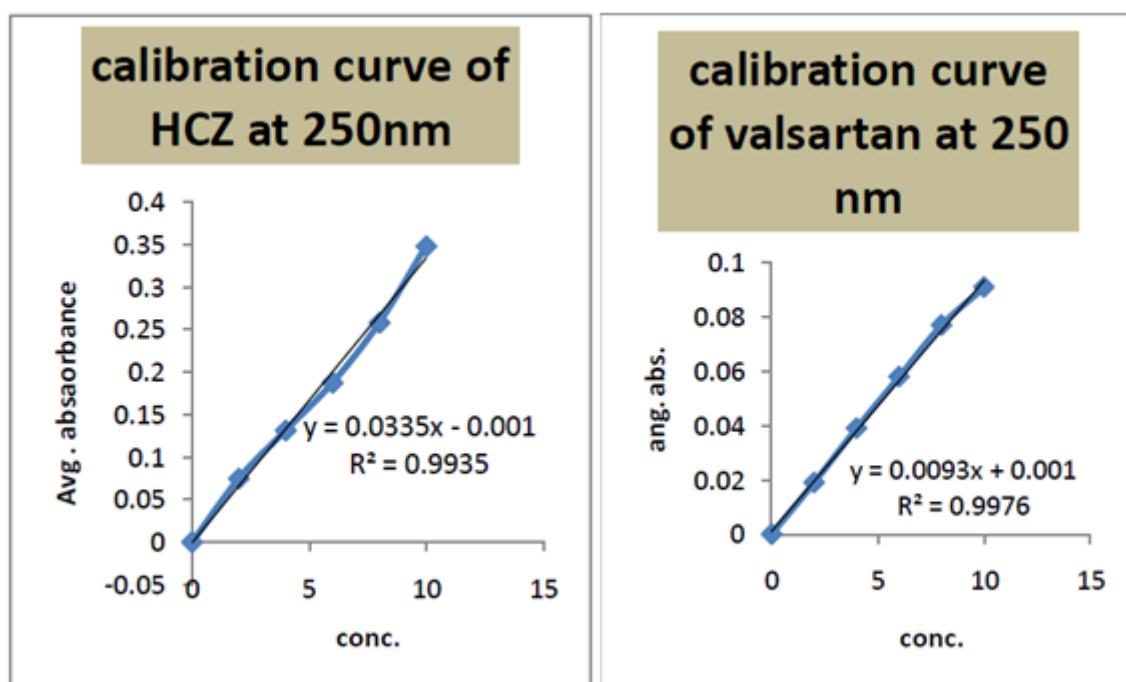


Figure1&2. Calibration Curve of Hydrochlorothiazide (USP) and Valsartan at 250 nm in 0.1 N HCl

Drug Content: Drug content of all the formulations found between the range of 98.34 ± 0.823 to 99.42 ± 0.823 percent

4.1. Solubility Studies of Pure Drug and Solid Dispersions

Table3. Solubility of Drugs using Different Carriers

S. No.	Drugs	Polymers	Drug polymer ratios/solubility (mg/ml)		
			1:1	1:3	1:5
1	Valsartan	Urea	0.0122	0.0144	0.0179
		PVP K-30	0.0141	0.0180	0.0208
2	Hydrochlorothiazide	Urea	0.187	0.229	0.276
		PVP K-30	0.293	0.374	0.588

Table4. Solubility of solid dispersions containing drugs

S. NO.	Drugs	Methods	Polymers	Drug polymer ratios/solubility (mg/ml)		
				1:1	1:3	1:5
1	Valsartan	Physical mixture	Urea	0.0132	0.0153	0.0188
			PVP K-30	0.0139	0.0192	0.0216
		Fusion method	Urea	1.061	1.533	1.881
			PVP K-30	2.109	2.251	2.362
		Solvent evaporation	Urea	1.352	1.623	1.914
			PVP K-30	2.181	2.274	2.432
2	Hydro chlorothiazide	Physical mixture	Urea	0.237	0.293	0.387
			PVP K-30	0.313	0.408	0.659
		Fusion method	Urea	3.870	4.291	4.933
			PVP K-30	4.113	4.881	5.257
		Solvent evaporation	Urea	4.587	5.109	6.182
			PVP K-30	4.913	5.981	7.157

- The solubility study with water and various hydrophilic carriers shows an increase in the solubility of the drug in the presence of the carriers (**Table 3 and Table 4**).
- All SD formulations with various polymers exhibited higher rate of dissolution values than pure drugs and corresponding physical mixtures (**Figure 3 to Figure 6**).
- From the results concluded that SDs prepared with PVP K-30 (1:5) using SE method showed better solubility and in vitro dissolution profiles than Urea.

4.2. In Vitro Dissolution Studies

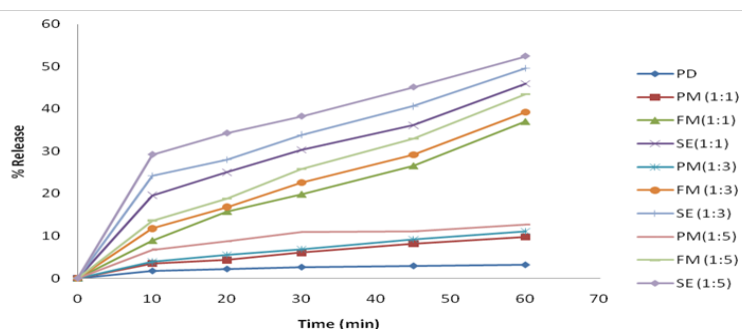


Figure3. In vitro dissolution profiles of pure Valsartan, Physical mixtures (PMs), solid dispersion of Fusion methods (FMs) and Solvent evaporations (SEs) of different ratios with urea

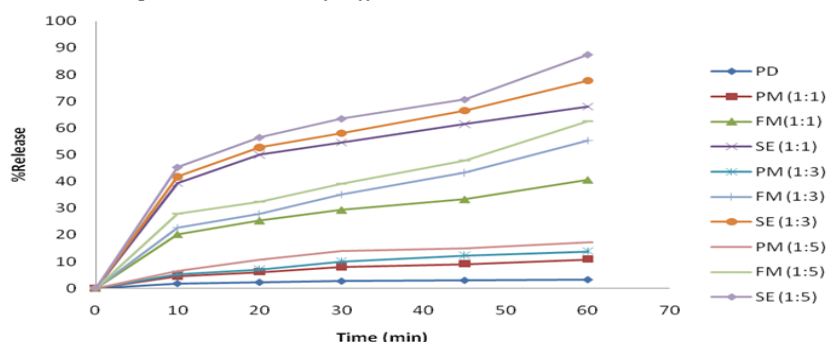


Figure4. In vitro dissolution profiles of pure Valsartan, Physical mixtures (PMs), solid dispersion of Fusion methods (FMs) and Solvent evaporations (SEs) of different ratios with PVP K-30

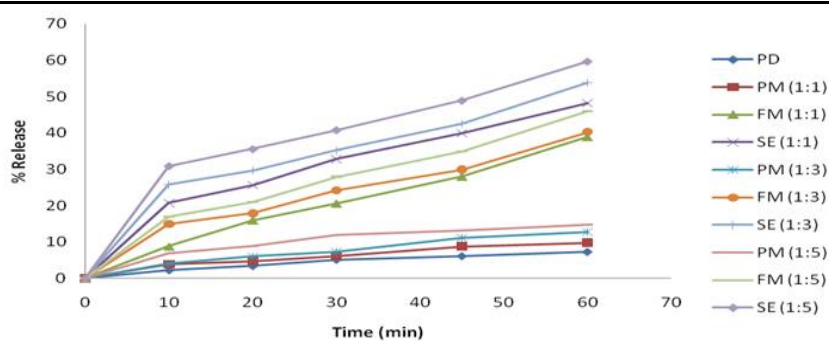


Figure5. *In vitro* dissolution profiles of pure Hydrochlorothiazide Physical mixtures (PMs), solid dispersion of Fusion methods (FMs) and Solvent evaporations (SEs) of different ratios with urea

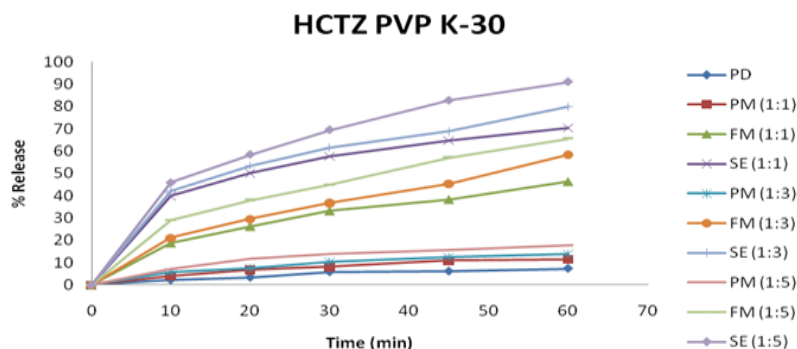


Figure6. *In vitro* dissolution profiles of pure Hydrochlorothiazide Physical mixtures (PMs), solid dispersion of Fusion methods (FMs) and Solvent evaporations (SEs) of different ratios with PVP K-30

5. CONCLUSION

The concept of formulating the solid dispersions of Hydrochlorothiazide and valsartan with water soluble carriers such as PEG-6000, Urea, and PVP K-30 offer a suitable and practical approach in serving desired objective of higher solubility, faster dissolution rate and improved bioavailability of drug. Solid dispersions of the poorly water soluble antihypertensive agents Hydrochlorothiazide and valsartan with water soluble carriers such as PEG-6000, Urea, and PVP K-30 to improving its aqueous solubility and rate of dissolution. The solid dispersions of drug were prepared by solvent evaporation technique, fusion method & co-grinding methods. The observed results showed the solid dispersion of drug were found increased in aqueous solubility than pure drug. Evaluation of the dispersions were performed using aqueous solubility and dissolution studies, the results obtained showed that the aqueous solubility and rate of dissolution of fixed dose combination hydrochlorothiazide and valsartan was significantly improved when formulated in solid dispersions as compare to pure drugs.

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