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LIQUISOLID TECHNIQUE AS A PROMISING TOOL TO ENHANCE SOLUBILITY AND DISSOLUTION OF POORLY WATER SOLUBLE DRUG VALSARTAN

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ABSTRACT

"Liquisolid Technique" considered as new technique to enhance solubility and dissolution rate of poorly water soluble drugs. These formulations are prepared by mixing drug in liquid state (solution, suspension or emulsion using non-volatile solvent) with carrier and coating material to form dry, free-flowing, readily compressible powder. In the current research work liquisolid technique is employed to enhance solubility and dissolution of antihypertensive drug Valsartan, which is poorly water soluble (0.021mg/ml) possessing very low bioavailability of 23%. Liquisolid formulation VLS9, containing Tween 80 (non-volatile solvent), Avicel PH102 (carrier) and Aerosil 200 (coating material) showed better flow properties and high *in-vitro* dissolution profile.

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INTRODUCTION:

Solubility is one of the key parameters to achieve desired concentration of drug in systemic circulation for showing affective pharmacological response. Low aqueous solubility is the major problem with formulation development of new chemical entities. Solubility enhances dissolution which in turn may increase bioavailability of poorly water soluble drugs. "Liquisolid Technique" also known as "Powder Solution Technology" is considered new, safe and economic technique to enhance solubility and dissolution profile of poorly water soluble drugs. Liquisolid formulations are prepared by converting liquid drug or drug in liquid state (solution, suspension or emulsion using non-volatile solvent) into dry, non-adherent, free-flowing, readily compressible powder by blending liquid medication with carrier and coating materials. Due to their significantly improved wetting properties a greater drug surface area is exposed to the dissolution media, resulting in increased dissolution rate and bio availability [1]. Valsartan is an angiotensin II receptor antagonist used in the management of hypertension [2]. Valsartan is an antihypertensive drug having low aqueous solubility of 0.021mg/ml and low bioavailability of 23%. The aim of current research work was to enhance solubility and dissolution of poorly water soluble drug.

MATERIALS AND METHODS:

Valsartan was gift sample received from Hetero Drugs, Hyderabad. Other excipients include Avicel PH 102, Aerosil 200, Propylene glycol (PG), polyethylene glycol 600 (PEG600), Tween 80. All reagents used were of analytical grade.

Methods

Saturation solubility studies

Saturation solubility studies of Valsartan were carried out in distilled water, propylene glycol, PEG 600 and Tween 80. Saturated solutions prepared in above vehicles were kept in an orbital shaker (Remi motors Pvt. Ltd Mumbai, India.) for 48 h at 25 °C. The solutions were then filtered and drug content was determined using UV- VIS spectrophotometry (Shimadzu 1800, Japan) at 250 nm. . From these results, the solubility of valsartan in the respective liquid vehicle was calculated. Each experiment was carried out in triplicate [3].

Preparation of liquisolid formulations

This drug solution or suspension is incorporated into specific quantity of carrier material which should possess sufficient absorption properties. The resulting wet mixture is then converted into a dry–looking, non adherent, free-flowing and readily compressible powder by the simple addition and mixing of a calculated

amount of coating material having high adsorptive properties.

Evaluation of liquisolid formulations

Characterization of flow properties of liquisolid formulations

Rania *et al*. (2008) suggested the pre compression evaluation parameters of Liquisolid powder systems. Flow properties of liquisolid systems were determined by estimating angle of repose, Carr's index and Hausner's ratio. Angle of repose was measured by fixed funnel method. Bulk density and taped density were also determined for the calculation of Hausner's ratio and Carr's index.

Calculation of liquid load factor (L_f): Load factor is calculated by dividing weight of liquid medication (W) to weight of carrier material (Q) and is given by:

$$Lf=W/Q$$

Percentage yield of liquisolid formulation:

The percentage yield of the liquisolid system was determined using the following equation:

$$\% \text{ Yield}=L/ Lo \times 100$$

Where, L = weight of prepared liquisolid formulation and Lo = total expected weight of formulation.

Drug Content:

Calculated amount of liquisolid powder formulation equivalent to single dose is dissolved in methanol and analysed for drug content using UV-visible spectrophotometer at 257nm.

***In vitro* Dissolution Study**:

In-vitro drug release from liquisolid formulations is determined using USP Type II Dissolution Apparatus (paddle type). The dissolution study was carried out in 900ml phosphate buffer pH 7.4 at 37°C ± 2 °C and 50 rpm. At regular time intervals, aliquots of 5 ml samples were withdrawn up to 60min and the dissolution medium was replaced with 5ml fresh dissolution medium to maintain sink conditions. The samples were filtered through Whatman filter paper no. 1 and analysed for drug content after suitable dilution using UV-Visible spectroscopy. Finally, cumulative percentage drug release is calculated for all formulations.

Optimization of prepared liquisolid formulations

The liquisolid formulation with better dissolution profile and good flow properties of powder was optimized and selected for further solid state characterization.

Solid state characterization of optimized liquisolid formulation

Scanning Electron Microscopy

SEM studies are performed to study surface morphology of drug as well excipients also confirm whether drug is present in crystal form or molecularly solubilized form.

Fourier Transform Infrared spectroscopy (FTIR)

FTIR studies are performed to study the compatibility of drug and other excipients in formulation by comparing drug and formulation spectra.

RESULTS AND DISCUSSION:

Saturated solubility studies for drug

Saturated solubility studies were performed to select suitable non-volatile solvent in which drug dissolves to prepare liquid medication.

Preparation of liquisolid formulations of Valsartan

After screening several non-volatile solvents propylene glycol, polyethylene glycol (PEG) 600 and Tween 80 were selected as liquid vehicles. Total 9 liquisolid formulations were prepared using Avicel as carrier material and Aerosil as coating material and shown in table below.

Table 1: Saturation solubility studies of Valsartan in various non-volatile solvents

Non-volatile solvent	Solubility of valsartan (mg/ml)
Distilled water	0.021
Phosphate buffer pH7.4	0.955
Polyethylene glycol 200	60.87
Polyethylene glycol 400	65.22
Polyethylene glycol 600	72.68
Propylene glycol	83.71
Tween 80	94.26

Table 2: Various Liquisolid formulations of Valsartan

Formulation Code	Valsartan (mg)	PEG 600 (mg)	Propylene Glycol (mg)	Tween 80(mg)	Avicel (MCC) (mg)	Aerosil 200(mg)	Formulation weight(mg)
VLS 1	40	100	-	-	100	60	300
VLS 2	40	110	-	-	120	60	330
VLS 3	40	120	-	-	150	60	370
VLS 4	40	-	100	-	100	60	300
VLS 5	40	-	110	-	120	60	330
VLS 6	40	-	120	-	150	60	370
VLS 7	40	-	-	100	100	60	300
VLS 8	40	-	-	110	120	60	330
VLS 9	40	-	-	120	150	60	370

Evaluation of liquisolid formulations of Valsartan

Table 3: Flow properties characterization of liquisolid formulations of Valsartan

Formulation Code	Bulk density (mg/ml)	Tapped density (mg/ml)	Carr's Index	Haussner's ratio	Angle of repose(θ)	Load factor	Percentage yield (%)
VLS 1	0.331	0.431	23.21	1.302	35.5	1.4	98.2
VLS 2	0.343	0.448	23.41	1.306	31.6	1.25	98.6
VLS 3	0.355	0.451	21.28	1.346	27.8	1.06	99.1
VLS 4	0.324	0.433	25.17	1.336	35.8	1.4	98.1
VLS 5	0.353	0.448	21.20	1.269	32.5	1.25	98.7
VLS 6	0.361	0.459	21.35	1.271	27.2	1.06	99.4
VLS 7	0.336	0.432	22.22	1.285	35.7	1.4	98.6
VLS 8	0.363	0.447	18.79	1.231	31.8	1.25	98.9
VLS 9	0.382	0.458	16.59	1.198	26.8	1.06	99.5

Drug content

Drug content of Valsartan liquisolid formulations were determined and given in below table.

Table 4: Drug content of Valsartan liquisolid formulations

Formulation Code	Drug Content (%)
VLS 1	90.05
VLS 2	91.43
VLS 3	95.33
VLS 4	91.45
VLS 5	93.89
VLS 6	94.19
VLS 7	92.88
VLS 8	94.66
VLS 9	96.78

***In Vitro* Dissolution Study**:

In vitro drug release i.e cumulative percent drug release was calculated for all valsartan capsules prepared by liquisolid technique and was compared with pure drug formulations.

Table 5: *In vitro* drug release of Valsartan liquisolid formulations

Time (min)	Pure drug	VLS 1	VLS 2	VLS 3	VLS 4	VLS 5	VLS 6	VLS 7	VLS 8	VLS 9
5	5.77	28.43	29.65	30.78	31.66	32.55	33.67	34.88	34.98	35.11
10	7.98	30.76	32.66	34.66	35.88	37.23	38.54	39.55	40.66	42.44
15	10.65	45.66	46.32	48.54	49.55	50.43	51.87	53.66	54.75	55.32
30	15.22	67.44	69.65	70.22	71.64	72.15	73.88	76.89	79.54	80.34
45	21.45	71.56	74.71	75.54	76.34	77.97	78.43	79.55	80.43	82.51
60	27.82	83.74	85.52	86.31	87.48	88.76	89.22	93.64	94.43	98.77

From the results of in vitro drug release it was observed that liquisolid formulation VLS9 showed better release profiles compared to that of pure drug. The mechanism for enhanced drug release postulated in liquisolid systems include increased surface area, improved wettability of drug particles due to reduction in interfacial tension which lead to increased aqueous solubility of the drug in microenvironment surrounding system. The reason may be due to greater wettability property of hydrophilic solvent Tween 80 having surfactant property of reducing interfacial tension. Valsartan within the liquisolid system is completely dissolved in Tween 80 and is located in the powder substrate still as solubilised, molecularly dispersed state. Thus the surface area of drug available for release is much greater than that of drug particles available in directly compressed tablets.

Solid state characterization of optimized liquisolid formulation

Scanning Electron Microscopy

SEM studies were conducted for drug, excipients as well as for optimized liquisolid formulation. The results of SEM studies revealed that crystalline form of drug has been converted to amorphous state.

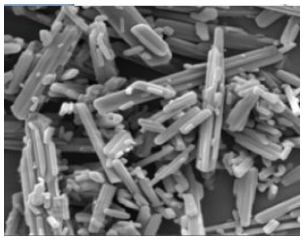

Figure1: SEM of Valsartan

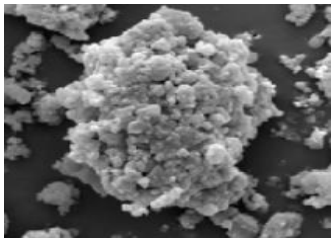

Figure 2: SEM of VLS9 Formulation

Fourier Transform Infrared spectroscopy (FTIR)

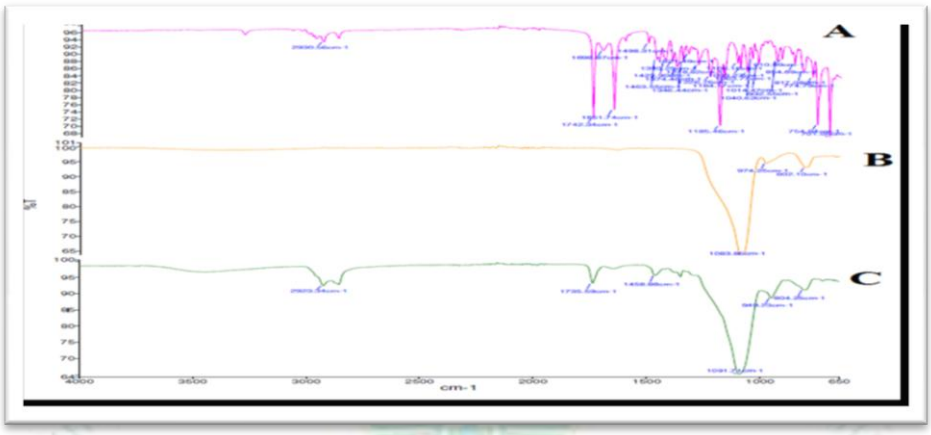

Figure 3: a. Valsartan b. Aerosil 200 c. VLS9 formulation

Results of FTIR showed that characteristic peaks in VLS 9 liquisolid formulation contained both peaks that of pure drug and Aerosil indicating no interaction between drug and excipients occurred.

CONCLUSION:

Successfully liquisolid formulations of valsartan was prepared using with remarkable improvement in dissolution profile and thus proved the potential of liquisolid technique as safer, efficacious method in enhancing solubility as well dissolution profile of poorly water soluble drugs.

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