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Research Article

DISSOLUTION ENHANCEMENT OF TELMISARTAN BY LIQUISOLID COMPACTS

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ABSTRACT

Objective: The main objective of this study was to enhance the dissolution of a practically insoluble antihypertensive drug (telmisartan) by liquisolid compact technique. Liquisolid compact is one of the most promising and new techniques, which promotes dissolution rate of water-insoluble drugs.

Methods: In this study, all liquisolid tablets were prepared using propylene glycol, Avicel PH 102, Aerosil 200 and indion 414 as non-volatile solvent, carrier, coating and super-disintegrant respectively.

Telmisartan was formulated in form of liquisolid compacts in different concentration of drug in non-volatile vehicle: 20% w/w, 30% w/w and 40% w/w with different excipients ratio (R): 10:1, 15:1, and 20:1 and the effect of these two variables on the in-vitro dissolution characteristics at two different dissolution media (HCl pH 1.2 and phosphate buffer pH 6.8) was studied and the release behavior was compared with that of the marketed tablet.

Before compression, the prepared liquisolid powders were evaluated for their flow properties by measuring angle of repose, Carr's compressibility index and Hausner's ratio and also were evaluated for post compression parameters such as hardness, friability, drug content uniformity, disintegration time and dissolution test. Fourier transform infrared (FTIR) analysis, differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and scanning electron microscopy (SEM) were performed.

Results: The results showed that liquisolid formulas exhibited acceptable flowability and compressibility and markedly higher percentage of drug release than of the marketed tablet and it was found that excipients were compatible with the drug in the prepared liquisolid system that was determined by fourier transform infrared spectroscopy and differential scanning calorimetry. The X- ray diffraction and the scanning electron microscopy showed conversion of drug from crystalline to amorphous (solubilized) form that lead to increase the dissolution rate. **Conclusion:** From this study it was concluded that the liquisolid technique is an effective approach to enhance the dissolution rate of telmisartan.

Keywords: Liquisolid compacts; telmisartan; dissolution.

INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability, which is dependent on the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown [1].

Formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in pharmaceutical industry [2]. The challenge for these poorly water-soluble drugs is to enhance the rate of dissolution. This in turn subsequently improves absorption and bioavailability [3].

Bioavailability of class II drugs is limited by their solubility and dissolution. Several methods were used to enhance the solubility of these drugs: solubilization, micronization, complexation with polymer, salt formation, use of pro-drug, addition of surfactant, solid dispersion, however, among them, the technique of ''liquisolid compacts" is one of the most promising techniques [4].

The liquisolid systems are generally considered as acceptably flowing and compressible powdered forms of liquid medications (that implies liquid lipophilic (oily) drugs, or water-insoluble solid drugs dissolved in suitable water-miscible non-volatile solvent systems). Such liquid medication may be converted into a dry-looking, non-adherent, free flowing and readily compressible powders by a simple admixture with selected powder excipients referred to as the carrier and coating materials [5].

However, even though in the liquisolid and powdered solution systems the drug might be in a solid dosage form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state.

Therefore, due to their significantly increased wetting properties and surface of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release properties, and consequently, improved bioavailability [6].

Telmisartan is angiotensin II receptor blocker (ARB), which is used in the prevention and treatment of hypertension [7]. It belongs to class II drugs, these types of drugs according to biopharmaceutical classification system characterize by low aqueous solubility and high permeability [8] and often solubility is the rate-limiting step for absorption [9]. Thus, one of the major problems with telmisartan is its low solubility in biological fluids, which results into poor bioavailability after oral administration (~42%) and late onset of action [10].

In this study, telmisartan was selected as a model drug, since it is a very slightly water-soluble drug, and thus, it establishes an ideal candidate for testing the potential of rapid-release liquisolid compacts. The flowability and compressibility of liquisolid compacts were addressed simultaneously in the ''new formulation mathematical model of liquisolid systems", which was used to calculate the appropriate quantities of the excipients (carrier and coating materials) required to produce acceptably flowing and compressible powders based on new fundamental powder properties called the flowable liquid retention potential (Φ -value) [11].

MATERIALS AND METHOD

Materials

The following materials were used in this study: Telmisartan (Hetero drugs limited, India). Avicel PH 102 (FMC, USA). Aerosil 200 (Wacker HDK, Germany). Indion 414 (Ion exchange LTD, India). Propylene glycol (DOW, Germany). Magnesium stearate (Robert

E.M.TILG, Germany). Dihydrogen phosphate (Merck, Germany). All reagents used were of analytical grade.

Method

Application of mathematical model for design of liquisolid compacts

The formulation design of liquisolid systems was done in accordance with new mathematical model described by Spireas et al. [11].

In this study: propylene glycol, Avicel PH 102 (Microcrystalline Cellulose-MCC), and Aerosil 200 were used as a liquid vehicle, carrier and coating materials respectively. The concentration of the drug (telmisartan) in propylene glycol was taken as 20% w/w, 30% w/w and 40% w/w and the carrier: coating ratio (*R*) was 10:1, 15:1 and 20:1.

The excipients ratio (*R)* of powder is defined as:

$R=Q/q$ … (1)

Where *R* is the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation.

Liquid load factor (Lf) is defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the liquisolid system, which should be possessed by an acceptably flowing and compressible system. i.e.

$Lf = W / Q$ … (2)

Flowable liquid retention potential (Φ value) of powder excipients was used to calculate the required ingredient quantities. Therefore, powder excipients ratios (R) and liquid load factors (Lf) of the formulations are related as follows:

$Lf = \Phi + \Phi (1 / R)$ … (3)

Where, Φ and *Φ* are the Φ values of carrier and coating materials, respectively.

Hence to calculate the required weights of the excipients used, first from equation (3), and according to ratio of carrier: coating materials (*R*), Lf was calculated. Then by applying equation (2), amount of carrier can be determined. Finally, amount of coating can be calculated from equation (1).

Preparation of directly compressible tablet (DCT)

A conventional formulation of telmisartan or a direct compressible tablet (DCT) which represents the physical mixture of liquisolid system was prepared by using 40 mg drug, 200 mg Avicel PH 102, 10 mg Aerosil 200, 5% superdisintegrant and 1% lubricant (without addition of any non-volatile liquid vehicle). All the ingredients were mixed in the mortar for 10 min and final mixture was directly compressed using Korsch EKO (Germany) tablet compression machine [12].

Determination of telmisartan solubility

Saturated solutions were prepared by adding excess amount of the drug (telmisartan) to the appropriate solvent (propylene glycol) and shaking on water shaker bath for 48 h at 25°C under constant vibrations. The solutions were filtered through a 0.45 micron filter, diluted suitably and analyzed by UV-visible spectrophotometer (Carry win UV, Varian, Australia) at 298 nm. The saturation solubility of the drug was also done in simulated gastric fluid pH 1.2 (SGF) and simulated intestinal fluid pH 6.8 (SIF).

Evaluation of liquisolid formulations

Precompression evaluation

1. Flow behavior: Flow properties of liquisolid formulations were studied by measuring angle of repose, Carr's compressibility index and Hausner's ratio [13].

2. Differential scanning calorimetry (DSC): The thermal behavior and the thermotropic properties of the drug, physical mixture (DCT) and the prepared liquisolid system were determined by DSC. It also shows any possible interaction between excipients used in the formulas [9]. This was done by using Shimadzu differential scanning calorimeter Mettler. The thermal behaviors of the samples were investigated at a scanning rate of 10°C/ min, covering a temperature range of 0 -300°C [14].

3. Fourier transforms spectroscopy (FTIR): FTIR spectra were performed by the KBr pellet method using the fourier transform infrared spectrophotometer (Shimadzu, Japan). A baseline correction was made using dried potassium bromide, and then the spectra of telmisartan, DCT and liquisolid system were obtained [15].

4. X-ray diffractometery (XRD): The crystallinities of pure telmisartan, carrier and liquisolid formula were evaluated by XRD measurement. It has been seen that polymorphic changes of the drug are important factors, which may affect the drug dissolution rate and bioavailability [16].

5. Scanning electron microscopy (SEM): SEM is utilized to assess the morphological characteristics of the raw materials and the drug–carrier systems [9]. In this study the photomicrographs were performed for the drug (telmisartan) and liquisolid system by coating them with gold and scan at specific magnification using VEGA easyprobe (Germany) scanning electron microscopy [17].

Post compression evaluation

1. Hardness and friability: The hardness of formulated liquisolid tablets was determined by using Erweka (Germany) TBH 100 hardness tester, and the mean hardness of the three liquisolid tablets was determined. The friability of the prepared liquisolid tablets was measured using Erweka (Germany), TAR 120 type apparatus, and the drum was rotated for 4 min at 25 rpm [18]. The losses of the mass of 20 tablets before and after rotation were determined, and by applying equation (4), the percentage of friability was calculated as follow:

%Friability = (loss of mass/initial mass) x100 % … (4)

2. Content uniformity: Drug content was assessed for six randomly selected tablets. The tablets were crushed and total content of the six tablets was mixed thoroughly. The powder weighed for 40 mg tablets was 25 mg dissolved in sufficient quantity (25 mL) of methanol. The solution was sonicated for 10 mins to extract the drug in methanol and volume was made up to 25 ml to obtain stock solution I. Stock solution I was filtered and suitably diluted to obtain solution A. The absorbance of solution A was read at 298 nm on UV-visible spectrophotometer. The same procedure was followed for all tablets. The concentration of telmisartan was calculated from the standard curve [19].

3. Disintegration time: The disintegration time was carried out in HCl pH 1.2 at 37±0.5°C using Erweka ZT 322 (Germany) disintegration testing apparatus with a basket rack assembly containing six open-ended tubes and 10-mesh screen on the bottom. A tablet was placed in each tube of the basket and the time for complete disintegration of the six tablets was recorded [20].

4. In-vitro drug release studies: The in-vitro dissolution studies were done using USP-paddle type (Copley dissolution 8000, Copley scientific, UK, dissolution tester apparatus) to study the variations in release behavior among the prepared liquisolid tablets (which differ in drug concentrations & *R* value), conventional tablet and marketed tablet. In this method, 900ml of both HCl pH 1.2 (SGF) and phosphate buffer pH 6.8 (SIF) were used as dissolution media. The rate of stirring was 75 rpm. The amount of telmisartan was 40 mg in all formulas, the temperature was maintained at 37±0.5°C. 5ml of the samples were withdrawn at appropriate intervals (5, 10, 20, 30, 40, 50, 60 and 70 min), filtered and then analyzed at 298 nm by UV-visible spectrophotometer (Carry win UV, Varian, Australia), the dissolution media was replaced with 5ml fresh dissolution fluids to maintain sinks conditions.

RESULTS AND DISCUSSION

Application of new mathematical model for design of liquisolid systems

Mathematical model equation for Avicel PH 102 and Aerosil 200 in

propylene glycol can be given according to values of (Φ) and (*Φ*) as given by Spireas et al [21] as follow:

Lf = 0.16 + 3.31 (1 / *R)* ... (3)

Based on this equation, Lf is calculated by using different *R* values and based on value of W (liquid medication), amount of carrier can be calculated according to equation (2), and then amount of coating can be calculated by applying equation (1) depending on *R* value. The liquisolid tablets were formulated as were represented in table (1).

Table 1: Composition of telmisartan liquisolid formulas prepared according to mathematical model (All liquisolid formulas contain 40mg telmisartan)

Liqui-solid system	Drug conc. in liquid medication (%w/w)	Carrier: Coating Ratio (R)	Liquid Load factor (Lf)	Liquid Vehicle (mg) PG	Carrier Q (mg) Avicel PH102	Coating Q (mg) Aerosil 200	Disintegrant Indion 414 (mg)	Lubrica-nt Mg stearate (mg)	Unit dose (mg)
LS-1	20	10	0.491	160	407.3	40.73	34.1	6.8	688.93
LS-2	20	15	0.381	160	525.4	35	40	8	808.4
LS-3	20	20	0.326	160	613.5	30.7	44.4	8.9	897.5
LS-4	30	10	0.491	93.33	271.56	27.16	22.74	4.55	459.34
LS-5	30	15	0.381	93.33	350	23.33	26.66	5.33	538.65
LS-6	30	20	0.326	93.33	409	20.45	30	6	598.78
LS-7	40	10	0.491	60	203.67	20.37	17.1	3.4	344.54
LS-8	40	15	0.381	60	262.5	17.5	20	4	404
LS-9	40	20	0.326	60	306.75	15.34	22.22	4.44	448.75

Solubility of telmisartan

Determination of solubility is the most important aspect in formulation of liquisolid systems. This may contribute to formation of molecular dispersion of the drug in non-volatile solvent such as propylene glycol. The solubility of telmisartan in propylene glycol was found to be 5.212±0.532 that is much higher than the solubility of telmisartan in SGF pH 1.2 and SIF pH 6.8 as were represented in table (2). So, propylene glycol was the appropriate solvent in preparation of telmisartan liquisolid tablets.

Table 2: Solubility of telmisartan in various solvents

Solvent	Solubility (%w/w) ± S.D.*
SGF (pH 1.2)	0.0089 ± 0.000411
SIF (pH 6.8)	0.0031 ± 0.000235
PG	5.212 ± 0.532

*S.D. Standard deviation from mean, n=3

Precompression evaluation

1. Flow behavior: flowability of a powder is of critical importance in the formulation and industrial production of tablet dosage form. As a general guide, powders with angles of repose greater than 50 have poor flow properties, whereas minimum angles close to 25 correspond to very good flow properties [22].

When the Hausner's ratio is lower than 1.2, the powder has good flowability, while if the ratio is more than 1.2 this indicates that the flowability is bad [23]. Powders showing Carr's (compressibility) index up to 21 are considered of acceptable flow properties [13].

From table (3), it can be concluded that all the formulas were found to be within the specification limits. Moreover it can be concluded that LS-3 was the best formula prepared with suitable flow properties.

Table 3: Flowability parameters of prepared liquisolid tablets

LS system	Angle of repose (Θ) ±S.D.*	Compressibility index (%) ±S.D.*	Hausner's ratio ±S.D.*
LS-1	36.8±0.774	16.28 ±0.442	1.194 ±0.012
LS-2	30.96 ±0.437	12 ±0.386	1.136 ±0.011
LS-3	28.61 ±0.263	11 ±0.145	1.123 ±0.01
LS-4	41.2 ±0.648	17.11 ±0.434	1.202 ±0.011
LS-5	36 ± 0.582	13.6 ±0.452	1.156 ±0.01
LS-6	32.47 ±0.338	12.14 ±-.0.363	1.139 ±0.01
LS-7	42.76 ±0.874	17 ±0.534	1.204 ±0.012
LS-8	36.4 ±0.741	12.61 ±0.411	1.146 ±0.01
LS-9	34.9 ±0.466	12.24 ±0.357	1.14 ±0.011

*S.D. Standard deviation from mean, n=3

2. Differential scanning calorimetry: DSC of pure telmisartan showed a characteristic, sharp endothermic peak at 270°C which is associated with the melting point of the drug and indicated the crystalline nature of telmisartan (figure 1). The thermogram of DCT (figure 2) exhibited endothermic peak at 270°C, which is the peak of the drug, indicated that there is no interaction between the drug and excipients used in the formulation. (Figure 3) showed complete disappearance of characteristic peak of telmisartan and this is due to the formation of drug solution in the liquisolid-powdered system, i.e., the drug is molecularly dispersed within the liquisolid matrix. This disappearance of drug peak upon formulation into a liquisolid system was in agreement with McCauley and Brittain [24] who declared that the complete suppression of all drug thermal features undoubtedly indicates the formation of an amorphous solid solution. In addition, Mura et al. [25] found out that the total disappearance of the drug melting peak indicates that drug amorphization had taken place.

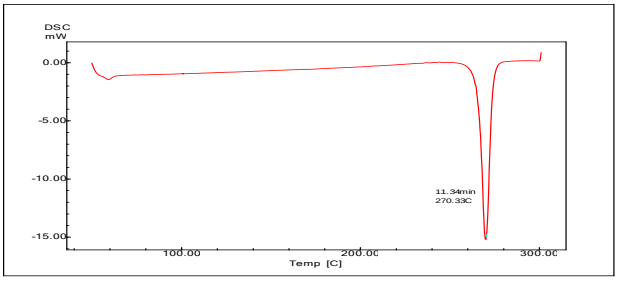


Fig. 1: DSC thermogram of telmisartan.

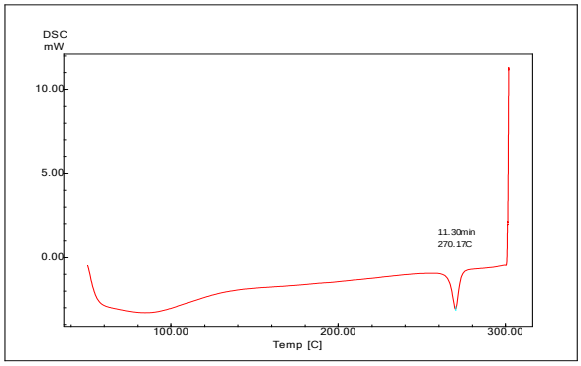


Fig. 2: DSC thermogram of DCT.

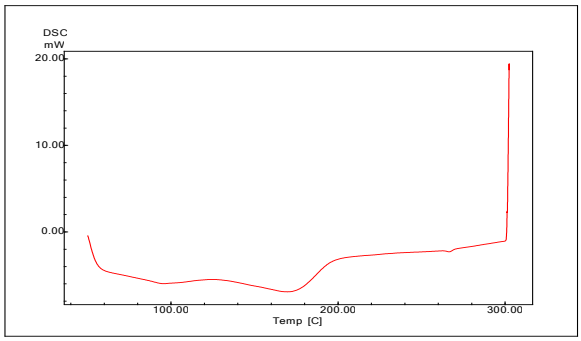


Fig. 3: DSC thermogram of liquisolid powder system.

3. Fourier transform spectroscopy: The FTIR spectrum of pure telmisartan (figure 4) showed the characteristic peak of the drug at 3400 cm-1 of O-H stretching of – COOH acid and other peaks at 2960 cm-1 due to C-H stretching vibration of aromatic group, -OH bending and – C=O stretching of – COOH acid at 1385 cm-1, C=C stretching of aromatic group at 1600 cm-1 and functional group of (-COOH) at 1697 cm-1.

Figure (5) showed the FTIR spectrum of DCT with the presence of the characteristic peaks of telmisartan but with lower intensity, indicating that there was no interaction between drug- excipients used in the study and no hydrogen bond formation in DCT.

Absence of the characteristic peak (3400 cm-1) of telmisartan was observed in liquisolid formula (figure 6), which might be due to formation of hydrogen bonding between the carboxylic group of telmisartan and the hydroxyl group of the liquid vehicle in liquisolid formula; this resulted in drug dissolution enhancement [26].

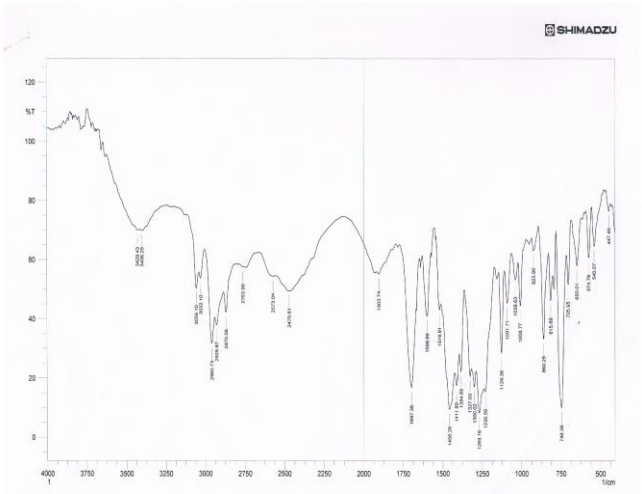


Fig. 4: FTIR spectrum of pure telmisartan.

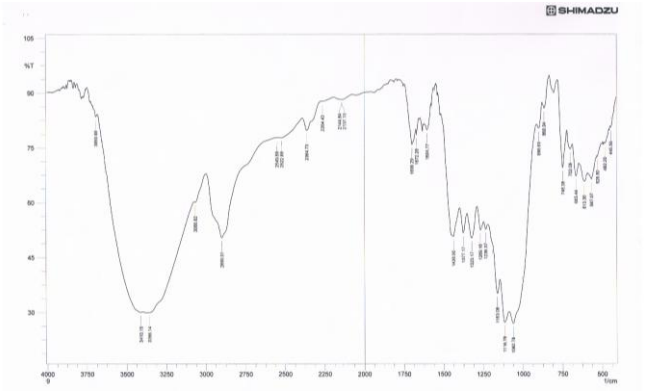


Fig. 5: FTIR spectrum of DCT.

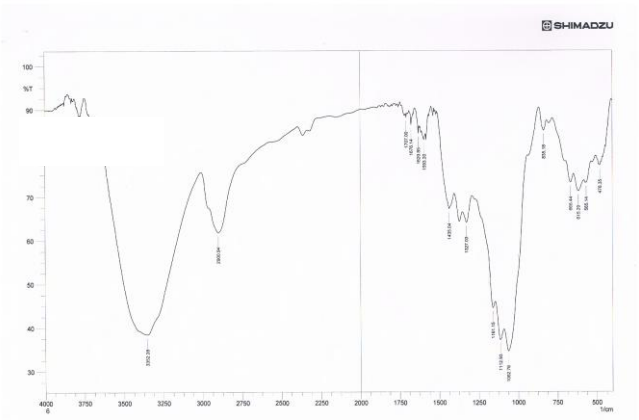


Fig. 6: FTIR spectrum of liquisolid powder system.

4. X-ray diffractometery pattern: The X- ray diffractogram of telmisartan (figure 7) exhibited several sharp peaks at different angle (2θ) 7.0θ, 14.0θ, 18.0θ, 23.0θ, 25.0θ suggested that the drug existed as crystalline material. (Figure 9) displayed X-ray diffraction pattern of liquisolid powder showed only one sharp diffraction peak 22.0θ at (2θ) belonging to Avicel PH 102 (figure 8), indicating that only Avicel PH 102 remained in crystalline state.

The lack of crystallinity in the liquisolid system was because the drug was solubilized in the liquid vehicle (propylene glycol) i.e., the drug has formed a solid solution within the carrier matrix. The amorphization or solubilization of drug in the liquisolid system may cause the marked improvement in the solubility and therefore the dissolution rate of the drug [27].

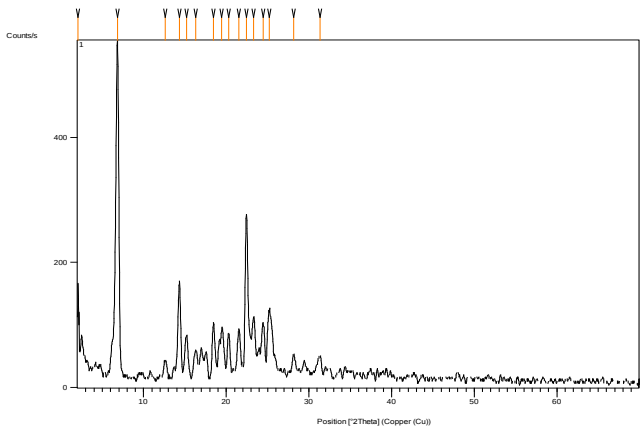


Fig. 7: X-ray diffraction of pure telmisartan.

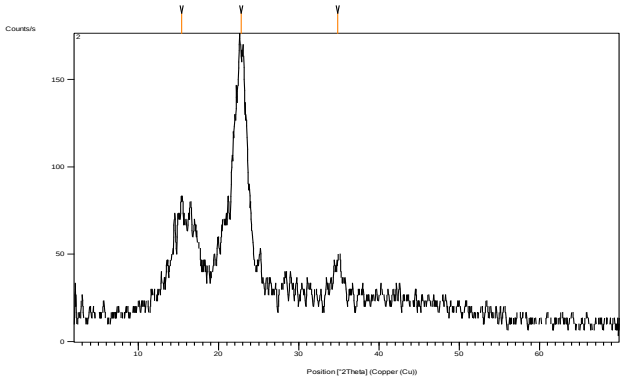


Fig. 8: X-ray diffraction of Avicel PH 102.

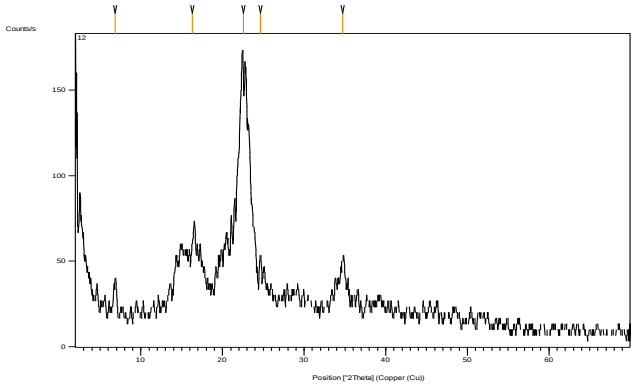


Fig. 9: X-ray diffraction of liquisolid powder system.

5. Scanning electron microscopy: (Figure 10) illustrated the photomicrograph of the pure drug (telmisartan), it showed that the drug had crystalline nature as was proved previously by the DSC and XRD. (Figure 11) displayed the photomicrograph of the final liquisolid system and it showed the complete disappearance of telmisartan crystals. This fact indicates that even though the drug is in solid dosage form, it is held within the powder substrate in solution or in solubilized, almost molecularly dispersed state which contributes to enhance drug dissolution property [28].

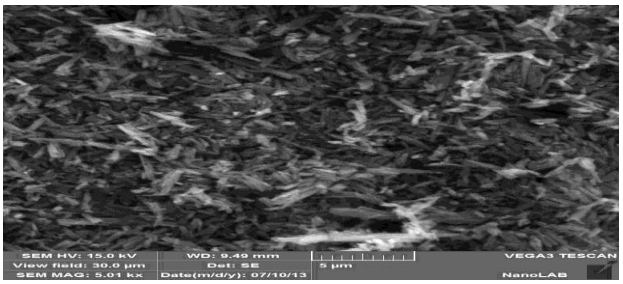


Fig. 10: SEM of pure telmisartan.

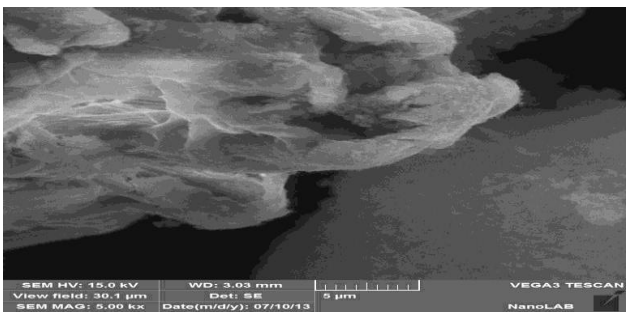


Fig. 11: SEM of telmisartan liquisolid powder system.

Post compression studies of liquisolid compacts

1. Hardness and friability*:* All the prepared batches had hardness in acceptable range, from 5.46±0.48 to 6.82±0.48 kg/cm^2. Generally, the ideal tablet hardness should be produced without applying excessive compression force where rapid tablet disintegration and drug dissolution are maintained at the same time [22]. It was seen that as the amount of Avicel goes on increasing, hardness also increases. With a decrease in R-values, hardness was found to decrease. This low hardness could be attributed to the less amount of added Avicel and poor compressibility of Aerosil [29].

All the liquisolid tablets showed acceptable friability, the percentage did not exceed 1% of the tablet weight, and no tablet was broken or deformed [30]. Hardness and friability were represented in table 4.

2. Content uniformity*:* The percentage of content uniformity of all telmisartan liquisolid compacts (table 4) was between 92.46% and 101.1%; this complied with pharmacopoeial requirements, in which each individual content was between 90% and 110% of the average content.

3. Disintegration time: All the prepared liquisolid tablets had a disintegration time less than 3 min. The batches prepared with increasing drug concentration exhibited an increasing disintegration time as shown in table (4).

Table 4: Hardness, friability, content uniformity and disintegration time of liquisolid formulas

LS	Hardness (kg/cm2) ± S.D.*	% Friability	Disintegration time (sec) ±S.D.*	%Content uniformity
LS-1	6.47 ±0.55	0.44	72 ±4.11	96.12
LS-2	6.73 ±0.52	0.33	43 ±3.58	97.58
LS-3	6.82±0.48	0.24	38 ±2.82	101.1
LS-4	5.93±0.54	0.48	93 ±4.37	94.33
LS-5	6.43±0.51	0.41	77 ±4.47	98.76
LS-6	6.76±0.42	0.32	72 ±3.26	97.62
LS-7	5.46 ±0.48	0.42	118 ±5.33	92.46
LS-8	6.28 ±0.43	0.38	78 ±4.64	94.4
LS-9	6.61±0.38	0.27	81 ±4.15	97.74

*S.D. Standard deviation from mean,n=3

4. In-vitro drug release: Dissolution rates of liquisolid formulas were compared with conventional tablet (DCT) and marketed tablet as represented in (figure 12, 13).

The concentration of drug in liquid medication is an important aspect as it affects drug release. From the obtained results it can be seen that there was an inverse relationship between concentration of drug and in-vitro drug release i.e: when the concentration increases, the release will decrease as shown in figures 12 and 13.

The release rate from liquisolid preparations of the lower concentration (20%) was more than that of concentration 30%, and the latter had more release rate than that of concentration 40%.

The powder excipient ratio (*R*) also plays an important role in drug release rate, it can be concluded from obtained data that there was a direct relationship between the powder excipient ratio (*R)* and the release of drug from liquisolid tablets, When *R* value increases, the release rate will also increase. i.e.: liquisolid tablets of *R* =20 had higher drug release than liquisolid tablets of *R* =15, which had more release rate than that tablets of *R* =10. So, it can be concluded from given data that LS-3 was the best liquisolid formula having optimized release profile among all other preparations.

From figures 12 and 13, it can be seen that the release rate of liquisolid compacts was markedly higher than that of DCT and marketed tablet, the percentage drug release in HCl pH 1.2 at 10th min was 100.14, 55.8 and 42.15% for LS-3 (best formula), DCT and marketed tablet respectively. And the percentage drug release in phosphate buffer (pH 6.8) at 10th min was 90.26, 52.13 and 47.12 %

for LS-3, DCT and marketed tablet respectively.

This increase in dissolution rate of liquisolid tablets is because these formulations contain a solution of the drug in non-volatile vehicle used for preparation of the liquisolid compacts; the drug surface area available for dissolution is significantly increased. Therefore, in the case of liquisolid compacts, the surface area of drug available for dissolution is much greater than that of the DCT and the marketed tablet [31].

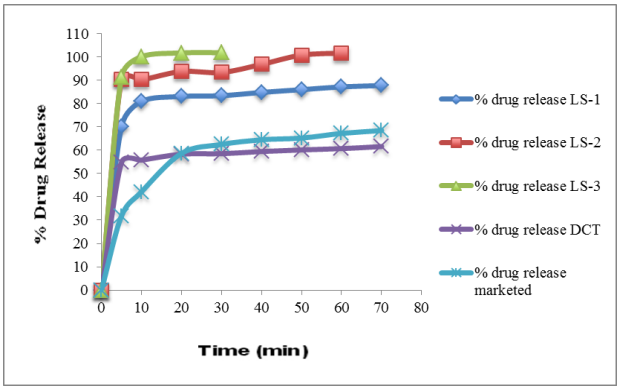
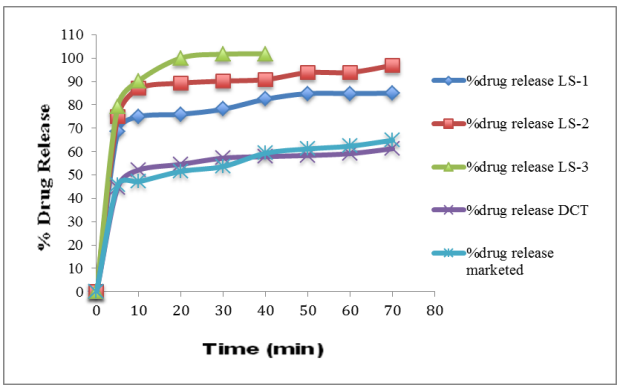


Fig. 12: Dissolution profiles of liquisolid compacts, directly compressible tablet (DCT) and marketed tablet at SGF (pH 1.2)



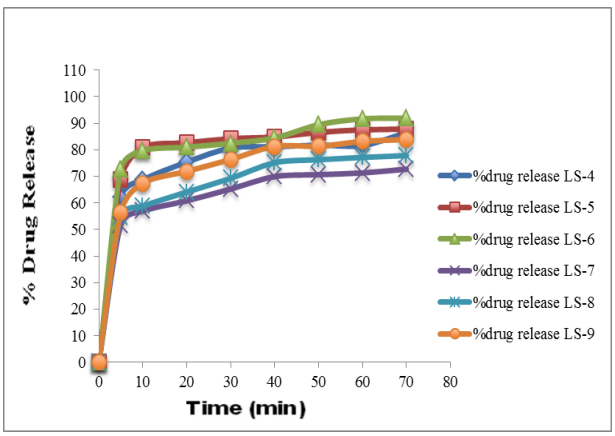


Fig. 13: Dissolution profiles of liquisolid compacts, directly compressible tablet (DCT) and marketed tablet at SIF (pH 6.8)

CONCLUSION

The present work showed that liquisolid compacts technique can be effectively used for preparation of immediate release tablets of practically insoluble drugs such as telmisartan. The liquisolid tablets formulated with the propylene glycol at drug concentration of 20% with excipients ratio (*R*)=20 is the best formulation among all the batches of the prepared liquisolid tablets, in terms of good flow properties, rapid disintegration, superior dissolution behaviors and acceptable tablet properties. It can also be concluded from this study, the release rate of the prepared liquisolid compacts is inversely proportional with drug concentration in non-volatile vehicle and it is directly proportional with excipients ratio (*R*).

The enhanced rate of drug dissolution from liquisolid tablets is probably due to an increase in wetting properties and surface area of drug particles available for dissolution, thus, liquisolid compacts technique leads to enhance dissolution rate and subsequently improve bioavailability of poorly water-soluble drugs.

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