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Research Article

FORMULATION AND CHARACTERIZATION OF LIQUISOLID TABLETS OF VALSARTAN FOR IMPROVEMENT OF DISSOLUTION RATE

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ABSTRACT

Objective: The solubility and dissolution properties of any drug are vital determinants of its oral bioavailability. The objective of this study is to screening of non-volatile solvent in which drug shows maximum solubility and then formulation of different liquisolid (LS) compacts using mathematical equations to increase the dissolution rate of drug.

Materials and Methods: Different LS compacts were prepared using a mathematical model for calculating required quantities of powder and liquid ingredients to produce an acceptably flowable and compressible admixture. Avicel PH 102, aerosil 200 and crospovidone were employed as a carrier, coating material and disintegrant, respectively. The prepared LS systems were evaluated for their flow behavior and possible drug-excipient interactions by infrared (IR) spectra analysis and X-ray diffraction (XRD). Morphological changes in the final formulation were investigated by scanning electron microscopy (SEM), liquisolid compacts were prepared and evaluated for their tableting properties.

Results: Valsartan shows maximum solubility in propylene glycol a non-volatile solvent. The IR studies ruled out any significant interaction between the drug and excipients. The XRD analysis confirmed formation of a solid solution inside the compact matrix. SEM indicates that the drug was totally solubilized in the LS system. The tableting properties of the LS compacts were within the acceptable limits. The release rates of LS compacts were markedly higher compared with directly compressed tablets due to increasing wetting properties and surface area of the drug.

Conclusion: This study shows that the LS technique is a promising alternative tool for improvement of the dissolution rate of biopharmaceutical classification system Class II drug.

Keywords: Dissolution rate, Liquisolid compact, Valsartan, Non-volatile solvents, Liquid load factor.

INTRODUCTION

One of the major challenges of present pharmaceutical research is to enhance the dissolution profile, absorption efficiency and bioavailability of water insoluble drugs. The solubility, the dissolution behavior of a drug, is frequently the rate-limiting step to absorption of drugs from the gastrointestinal tract for orally administered drugs. During the past few years, many techniques have been developed such as drug micronization, solid dispersions [1], co-precipitation, lyophilization, microencapsulation, use of the prodrug, drug derivetization processes and inclusion of drug solutions into soft gelatin capsules to improve the solubility and bioavailability. Formulation of liquisolid (LS) compact is a novel "powder solution technology," which makes use of liquid medications admixed with suitable carriers and coating materials and formulated into a moderately flowing, dry looking, non-adherent and compressible powder forms have increased the drug dissolution rate profiles [2-5]. Due to their significantly increased wetting properties and surface of drug available for dissolution, LS compacts of water-insoluble substances may be expected to display enhanced drug release properties, and consequently, improved bioavailability [5-9].

Valsartan is an angiotensin II receptor antagonist used in the management of hypertension [10]. It improves symptoms and quality-of-life in patients with chronic heart failure [11]. Valsartan treatment had no demonstrable negative effects on growth and development and were used safely as an antihypertensive agent in children <6 years old [12]. The drug is rapidly absorbed following oral administration with a bioavailability of about 23% [13]. It is a weakly acidic drug that has tetrazole derivative containing acid and carboxylic acid groups with pKa values of 4.73 and 3.9 respectively. Peak plasma concentrations occur in 2-4 hrs and its plasma half-life is about 7.5 hrs [14]. Therefore, improvement in its solubility and dissolution rate may lead to enhancement in bioavailability. Dissolution of drugs from solid dosage forms is a key parameter in assessing the product quality and uniformity at the formulation stage and as well as throughout the shelf-life of the product [15].

MATERIALS AND METHODS

Valsartan was obtained as a gift sample from alembic research center, Baroda. Crospovidone, avicel, aerosil, tween 20, tween 80, polyethylene glycol (PEG200, PEG400), propylene glycol (PG), sodium hydroxide, potassium dihydrogen orthophosphate were purchased from S.D. Fine Chemicals Ltd. (Mumbai, India). All other chemicals, reagents and solutions used, were of analytical grade.

Saturation solubility studies

To select the best non-volatile solvent to dissolve valsartan, solubility studies of valsartan were carried out in six different non-volatile solvents, i.e., PEG200, PEG400, tween 20, tween 40, tween 80 and PG. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the incubator shaker for 48 hrs at 25°C. Accurately weighed quantities of the filtered supernatants were further diluted with methanol and analyzed spectrophotometrically at 250 nm for their drug content. From these results, the solubility of valsartan in the respective liquid vehicle was calculated. Each experiment was carried out in triplicate [16].

Calculation of load factor (L_f)

In an LS system, the amount of liquid retained by the carrier and coating materials depends on the excipient ratio (R), while maintaining acceptable flow and compression properties. The excipient ratio R of a powder is defined as the ratio between the weights of carrier (Q) and coating materials (q) present in the formulation. Preparation of an LS

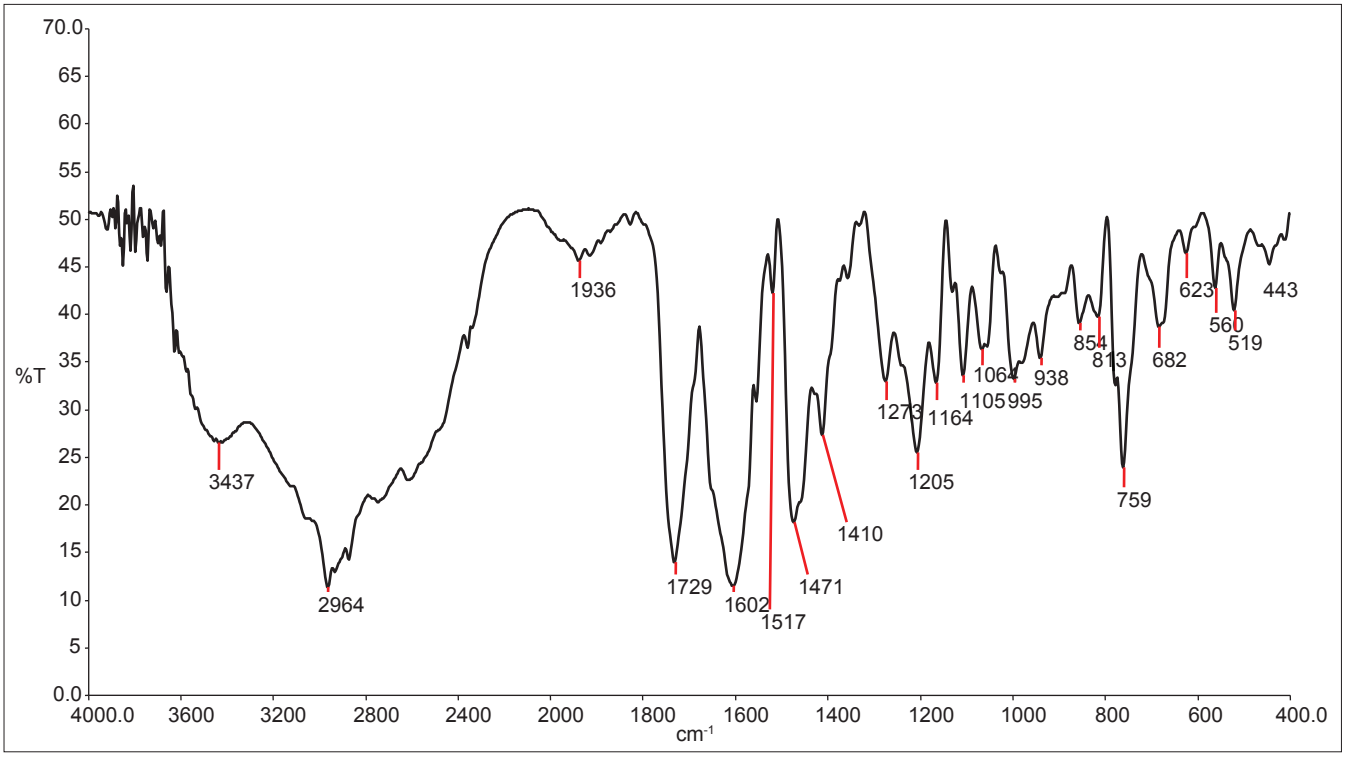

Fig.1: Infrared spectra of valsartan

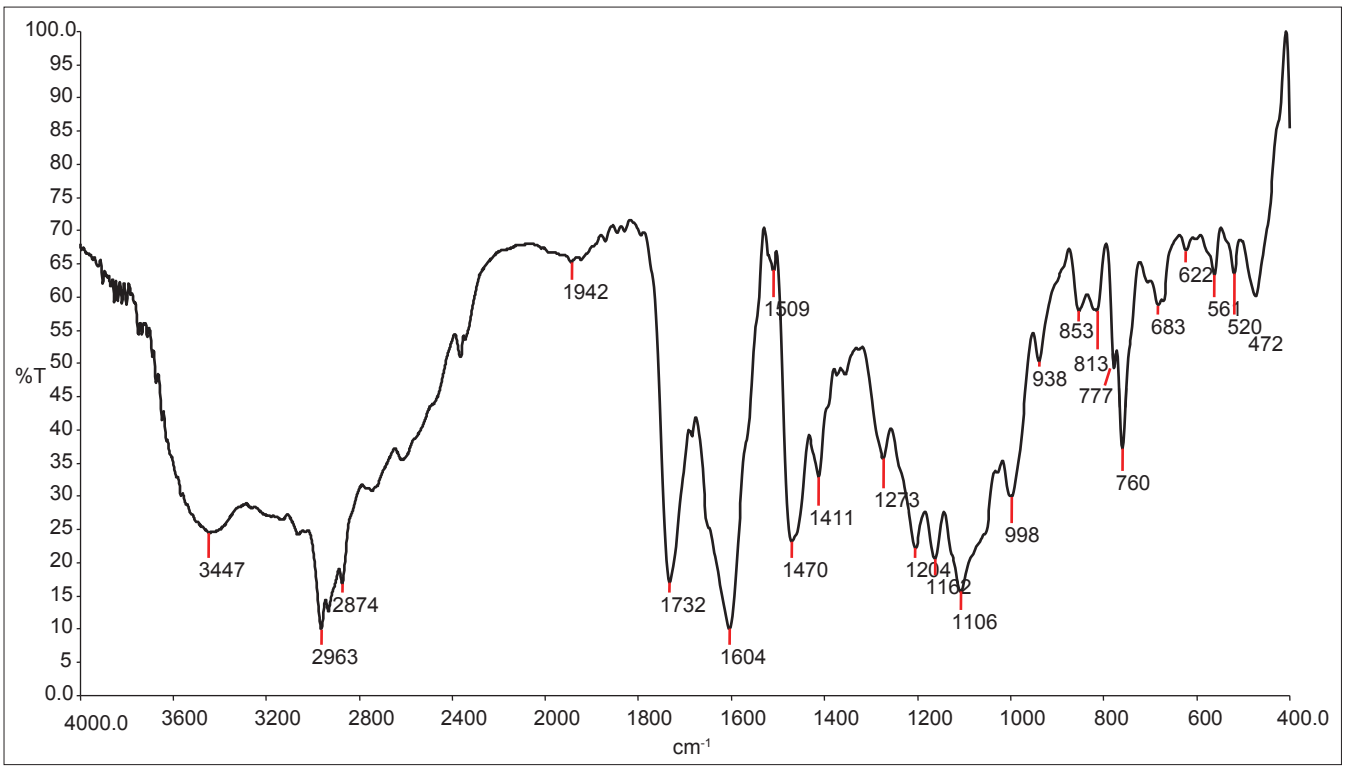

Fig.2: Infrared spectra of valsartan liquisolid compact

system with an acceptable flow rate and compressibility is possible when a maximum amount of retained liquid of the carrier material is not exceeded. This characteristic amount of liquid is termed as liquid L_f. The liquid L_f is defined as the weight ratio of the liquid medication (W) and carrier powder (Q) in the system. To calculate the loading factor, non-volatile solvent was added to 10 g carrier material and blended for 1 minute. The above procedure was repeated until a powder with acceptable flow rate was obtained [17].

Drug excipient interaction study

The drug excipient interaction study was carried out by Fourier transform infrared (FTIR) (Shimadzu, Japan). Previously, dried powder

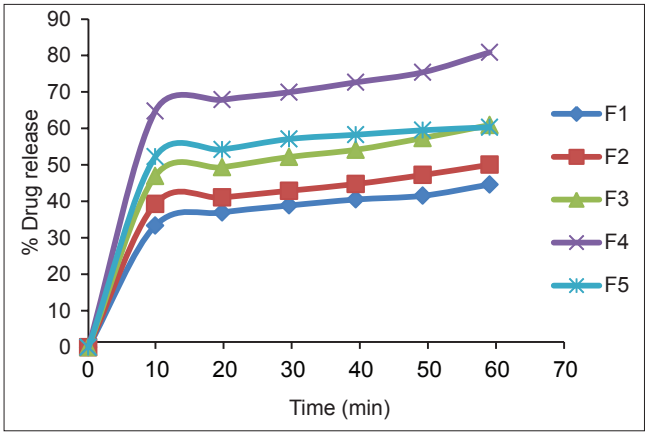

Fig. 3: Dissolution profile of F1 to F5

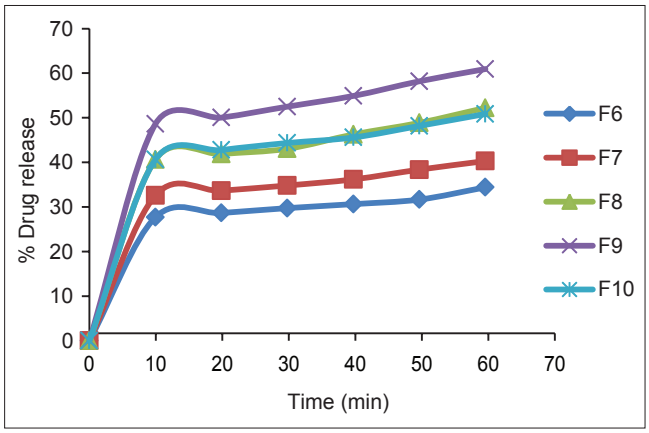

Fig. 4: Dissolution profile of F6 to F10

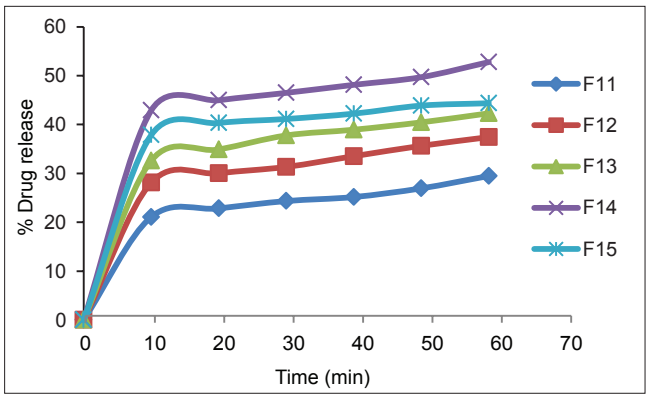

Fig. 5: Dissolution profile of F11 to F15

of drug was taken and mixed with previously dried KBr powder with the proportion of 1:100 in mortar and pestle. Then, the powder was added in the cell of FTIR instrument. Then, record the FTIR spectra.

Formulation of conventional tablet and LS compacts

Valsartan conventional tablets were produced by mixing the drug with microcrystalline for a period of 10 min. The mixture was mixed with the crospovidone for 10 min. Finally, the mixture was compressed with tablet compression machine. This formulation was denoted as directly compressed tablets and each tablet contains 40 mg valsartan, 150 mg microcrystalline cellulose, 7.5 mg of aerosil and 5% crospovidone. Several LS compacts were prepared by using PG. Initially, drug was dispersed in PG. The resulting medication was incorporated into

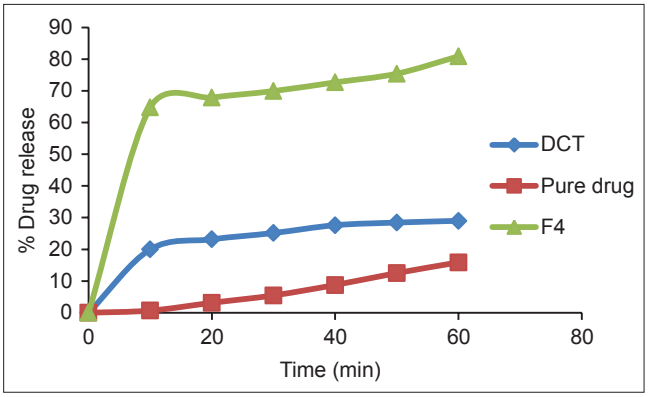

Fig. 6: Comparative dissolution profile of pure drug, directly compressed tablets and F4 formulation

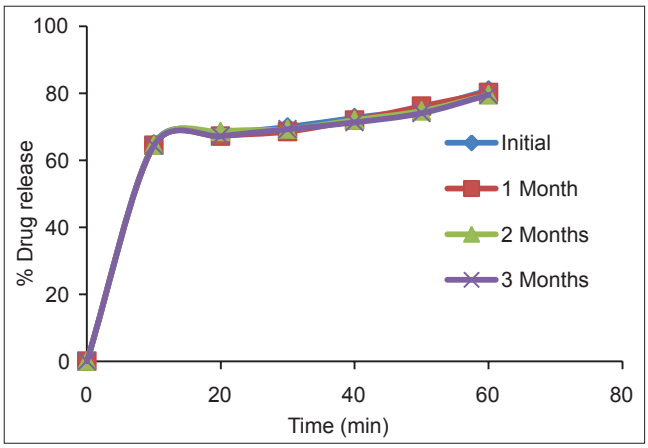

Fig. 7: Dissolution profile of F4 after 3 months

Table 1: Formulation of valsartan liquisolid compacts

Formulation code	Drug conc. in PG	R	L_f	Avicel ($Q=W/L_f$)	Aerosil ($q=Q/R$)	Unit dose (weight)
F_1	20%	5	0.822	0.243	0.048	0.348
F_2		10	0.491	0.407	0.041	0.512
F_3		15	0.380	0.526	0.035	0.631
F_4		20	0.325	0.615	0.030	0.719
F_5		30	0.270	0.740	0.024	0.844
F_6	30%	5	0.822	0.161	0.032	0.245
F_7		10	0.491	0.270	0.027	0.354
F_8		15	0.380	0.350	0.023	0.434
F_9		20	0.325	0.409	0.020	0.492
F_{10}		30	0.270	0.492	0.016	0.575
F_{11}	40%	5	0.822	0.121	0.024	0.194
F_{12}		10	0.491	0.203	0.020	0.276
F_{13}		15	0.380	0.263	0.017	0.336
F_{14}		20	0.325	0.308	0.015	0.381
F_{15}		30	0.270	0.370	0.012	0.443
DCT		-	-	150	7.5	0.230

*All formulations contain 40 mg of valsartan and 5% of crospovidone as super disintegrant. PG: Propylene glycol, DCT: Directly compressed tablets

calculated quantities of carrier and coating materials at a fixed ratio. The appropriate amounts of the carrier and coating materials used in the LS formulation were derived from their Ø-value and liquid L_f. This mixture was mixed for 10 minutes in mortar. Finally, crospovidone was

Table 2: Determination of flow properties (mean±SD, n=3)

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)	Angle of repose
F_1	0.354±0.004	0.410±0.008	1.16±0.022	13.88	32.50±0.40
F_2	0.373±0.011	0.423±0.004	1.15±0.030	13.56	30.65±0.43
F_3	0.395±0.004	0.449±0.006	1.13±0.023	12.09	34.63±0.15
F_4	0.435±0.017	0.477±0.004	1.09±0.056	8.73	24.75±0.57
F_5	0.451±0.010	0.500±0.006	1.10±0.025	9.80	28.14±0.18
F_6	0.346±0.014	0.362±0.004	1.04±0.036	04.32	22.74±0.66
F_7	0.382±0.004	0.424±0.008	1.11±0.011	09.97	31.03±0.15
F_8	0.403±0.005	0.486±0.005	1.20±0.023	17.12	38.21±0.18
F_9	0.434±0.05	0.498±0.003	1.14±0.043	12.78	32.46±0.26
F_{10}	0.387±0.012	0.515±0.006	1.33±0.055	24.90	36.76±0.53
F_{11}	0.326±0.026	0.390±0.005	1.20±0.114	16.38	34.69±0.17
F_{12}	0.354±0.014	0.413±0.006	1.17±0.054	14.74	35.09±0.17
F_{13}	0.403±0.013	0.477±0.005	1.18±0.029	15.49	38.39±0.41
F_{14}	0.389±0.007	0.488±0.004	1.25±0.033	20.21	40.06±0.29
F_{15}	0.458±0.012	0.529±0.004	1.15±0.033	13.35	35.50±0.53

SD: Standard deviation

Table 3: Physical evaluation of valsartan liquisolid compacts (mean±SD, n=3)

Formulation code	Hardness (kg/cm^2)	Friability (g)	Disintegration (minute)	HFR	Content uniformity (%)
F_1	3.77±0.15	0.252	4.05±0.105	14.94	100.25±0.22
F_2	4.33±0.31	0.201	3.28±0.204	21.55	100.06±0.087
F_3	5.43±0.20	0.150	3.25±0.243	36.22	99.51±0.42
F_4	4.06±0.11	0.110	1.71±0.121	55.15	100.25±0.34
F_5	6.83±0.06	0.049	2.78±0.194	139.45	99.26±0.26
F_6	4.03±0.15	0.190	4.33±0.242	21.22	100.35±0.13
F_7	4.63±0.21	0.162	3.83±0.163	28.60	99.90±0.26
F_8	5.66±0.32	0.126	3.35±0.394	44.97	99.51±0.42
F_9	6.30±0.26	0.091	2.70±0.155	69.23	99.30±1.18
F_{10}	6.06±0.11	0.023	3.20±0.228	263.76	98.77±0.69
F_{11}	3.27±0.12	0.293	4.87±0.266	11.14	97.44±0.75
F_{12}	4.26±0.38	0.202	4.20±0.341	21.12	100.23±1.05
F_{13}	5.23±0.20	0.174	3.83±0.242	30.08	99.39±0.50
F_{14}	5.77±0.12	0.113	2.98±0.471	51.03	100.40±0.26
F_{15}	5.23±0.25	0.064	2.92±0.264	81.77	99.24±0.30

SD: Standard deviation, HFR: Hardness-friability ratio

mixed for a period 10 minutes and then powder was compressed into tablets using tablet compression machine [18] (Table 1).

Evaluation of flow properties [19]

The formulations were evaluated for the following properties such as angle of repose, bulk density, tapped density, Hausner's ratio, Carr's index (Table 2).

Evaluation of LS compacts [20,21]

The prepared LS compacts were evaluated for carrying out various tests such as assay, content uniformity, friability, weight variation, hardness and disintegration. All tests were carried out according to the United States Pharmacopeia (USP) compendia specifications (Table 3).

Evaluation for *in vitro* dissolution

Dissolution studies of LS tablets were carried out in USP Apparatus II (Paddle type) (Electro Lab). Tablets were placed in the dissolution vessel containing 900 ml simulated gastric fluid maintained at 37±0.5°C and stirred at 50 rpm. Aliquots of 5 ml were withdrawn at specified time intervals for 60 min and replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 250 nm.

Stability study

After determining the drug content and release studies, the optimized formulation was charged for the accelerated stability studies according to International Conference on Harmonization guidelines (40±2°C and 75±5% RH) for a period of 3 months in a stability chamber. The optimized formulations were placed in USP Type I flint vials and hermetically closed with bromobutyl rubber plugs and sealed with aluminum caps. The samples were withdrawn at 30, 60 and 90 days and evaluated for the *in vitro* drug release [22].

X-ray diffractometry study

Polymorphic changes in the drug are important since they might affect the dissolution rate and bioavailability; therefore, it was necessary to study the polymorphic changes of valsartan in LS compacts. X-ray diffraction (XRD) spectra of optimized sample was recorded using a high-power powder X-ray diffractometer (Ru-200B, Pune, India) with Cu as target at a scan speed of 4°/min. The samples were analyzed at a 2θ angle range of 2-45°. The operating voltage and current were 40 kV and 55 mA, respectively.

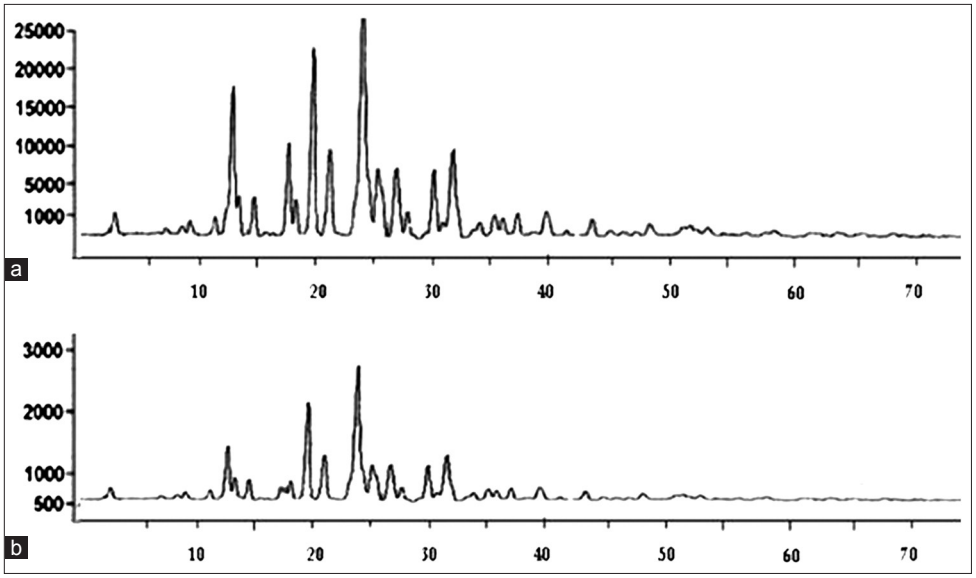

Fig. 8: X-ray diffraction pattern of (a) valsartan (b) liquisolid compact

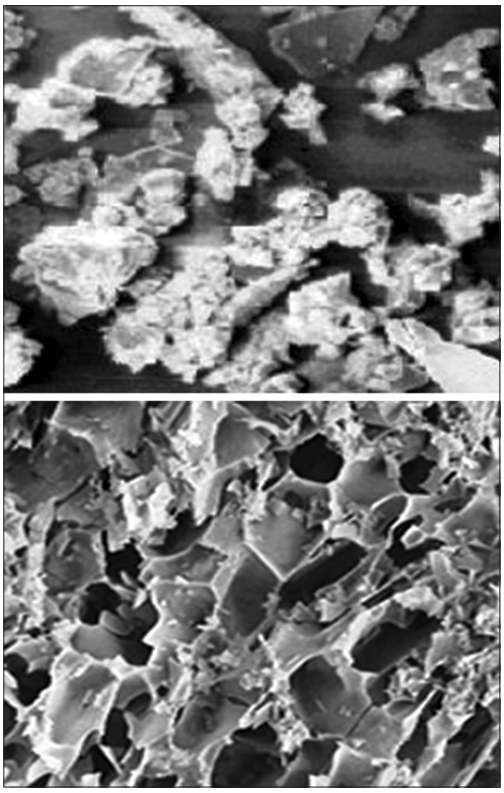

Fig. 9: Scanning electron images of valsartan and liquisolid powder system

Scanning electron microscopy (SEM) analysis

In order to investigate morphological changes in final formulation, SEM was performed for valsartan and LS formulation.

RESULT AND DISCUSSION

Vehicle selection

The solubility of valsartan was determined in a number of solvents. Drug solubility in a non-volatile vehicle is the most important aspect in LS systems. The solubility of the drug contributes to molecular dispersion in a non-volatile solvent which will improve the dissolution rate. The solubility of valsartan in PG was found to be 113.33±1.52 g/L which was maximum than the solubility in other selected non-volatile solvents. Hence, PG was selected as the vehicle for valsartan.

FTIR Spectroscopy

Valsartan LS compacts were subjected for FTIR spectroscopic analysis to ascertain whether there are any major changes in spectrum (Fig. 1). Here no characteristic bands of pure drug were affected without any major change in their positions. Following are the FTIR spectra's of LS compact (Fig. 2).

***In vitro* dissolution study**

Figs. 3-7 show the study of *in vitro* dissolution.

X-ray diffractometry study

The diffraction spectrum of pure valsartan showed that the drug was of crystalline in nature as demonstrated by numerous, distinct peaks at 2θ of 5.6°, 10.5°, 12.9°, 18.8°, 20.6°. The spectrum LS system showed that some peaks of pure valsartan were absent, and intensity of peaks was reduced. The result indicates that the drug in complex form and LS system is amorphous as compared to the pure drug. Hence, increased dissolution of the drug was observed (Fig. 8).

SEM

SEM analysis showed pure valsartan of irregular shapes and sizes. SEM analysis of the final LS system signifies the complete disappearance of valsartan crystals, a fact that indicates that the drug was totally solubilized in the LS system. This fact proved the LS formulation hypothesis that even though the drug is in a solid dosage form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties (Fig. 9).

CONCLUSION

For LS technique, different amount of liquid and ratio of carrier to the coating material were employed. PG was used as a liquid vehicle Different evaluation tests like FTIR, pre- and post-compression parameters, XRD, SEM was carried out. The LS tablet technique can prove to be an effective and efficient way for dissolution rate improvement of water insoluble drugs such as valsartan as it shows faster release than that of pure drug and direct compressed tablet. Enhanced dissolution rates obtained in the present study can be attributed to increased wetting and surface area available for dissolution.

REFERENCES

1. Daravath B, Tadikonda R. Formulation and evaluation of meclizine hydrochloride fast dissolving tablets using solid dispersion method. Asian J Pharm Clin Res 2014;2:98-102.
2. Yalkowsky SH, Rubino JT. Solubilization by cosolvents I: Organic solutes in propylene glycol-water mixtures. J Pharm Sci 1985;74(4):416-21.
3. Sugawara M, Kadomura S, He X, Takekuma Y, Kohri N, Miyazaki K. The use of an *in vitro* dissolution and absorption system to evaluate oral absorption of two weak bases in pH-independent controlled-release formulations. Eur J Pharm Sci 2005;26(1):1-8.
4. Youn YS, Jung JY, Oh SH, Yoo SD, Lee KC. Improved intestinal delivery of salmon calcitonin by Lys18-amine specific PEGylation: Stability, permeability, pharmacokinetic behavior and *in vivo* hypocalcemic efficacy. J Control Release 2006;114(3):334-42.
5. Spireas S, Sadu S, Grover R. *In vitro* release evaluation of hydrocortisone liquisolid tablets. J Pharm Sci 1998;87(7):867-72.
6. Spireas S, Wang T, Grover R. Effect of powder substrate on the dissolution properties of methyclothiazide liquisolid compacts. Drug Dev Ind Pharm 1999;25(2):163-8.
7. Nokhodchi A, Javadzadeh Y, Siahi-Shadbad MR, Barzegar-Jalali M. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. J Pharm Pharm Sci 2005;8(1):18-25.
8. Javadzadeh Y, Siahi-Shadbad MR, Barzegar-Jalali M, Nokhodchi A. Enhancement of dissolution rate of piroxicam using liquisolid compacts. Farmaco 2005;60(4):361-5.
9. Spireas S, Sadu S. Enhancement of prednisolone dissolution properties using liquisolid compacts. Int J Pharm 1998;166:177-88.
10. Leidig M, Bambauer R, Kirchertz EJ, Szabã T, Handrock R, Leinung D, *et al.* Efficacy, safety and tolerability of valsartan 80 mg compared to irbesartan 150 mg in hypertensive patients on long-term hemodialysis (VALID study). Clin Nephrol 2008;69(6):425-32.
11. Baumhäkel M, Müller U. Valsartan improves symptoms and quality of life in patients with chronic heart failure. MMW Fortschr Med 2008;150(49-50):55.
12. Flynn JT, Meyers KE, Neto JP, de Paula Meneses R, Zurowska A, Bagga A, *et al.* Efficacy and safety of the Angiotensin receptor blocker valsartan in children with hypertension aged 1 to 5 years. Hypertension 2008;52(2):222-8.
13. Kshirsagar SJ, Bhalekar MR, Madgulkar AR, Sable PN, Gupta SR. Dissolution improvement of poorly water soluble drug valsartan and improving flow properties of solid dispersion. Lat Am J Pharm 2010;29:393-400.
14. Goodman LS, Gilman A. The Pharmacological Basis of Therapeutics. 10th ed. New-York: McGraw Hill Medical Publishing Division;2001.
15. Srivastava V, Mishra G. Dissolution enhancement of a poorly soluble model drugs using different formulation approaches for immediate release solid dosage form. Asian J Pharm Clin Res 2014;7(1):63-6.
16. Gubbi S, Ravindra J. Formulation and characterisation of atorvastatin calcium liquisolid compacts. Asian J Pharm 2010;5(2):50-60.
17. Fahmy RH, Kassem MA. Enhancement of famotidine dissolution rate through liquisolid tablets formulation: *In vitro* and *in vivo* evaluation. Eur J Pharm Biopharm 2008;69(3):993-1003.
18. Tayel SA, Soliman II, Louis D. Improvement of dissolution properties of Carbamazepine through application of the liquisolid tablet technique. Eur J Pharm Biopharm 2008;69(1):342-7.
19. Banker GS, Anderson NR. Tablets. In: Lachman L, Lieberman HA, editors. The Theory and Practice of Industrial Pharmacy. New Delhi: CBS Publishers;2009. p. 293-345.
20. Bi YX, Sunada H, Yonezawa Y, Danjo K. Evaluation of rapidly disintegrating tablets prepared by a direct compression method. Drug Dev Ind Pharm 1999;25(5):571-81.
21. Zhao N, Augsburger LL. Functionality comparison of 3 classes of superdisintegrants in promoting aspirin tablet disintegration and dissolution. AAPS Pharm Sci Tech 2005;6(4):E634-40.
22. Venkatesh GS, Averineni R, Usha Y, Armugam K. Enhanced dissolution and bioavailability of gliclazide using solid dispersion techniques. Int J Drug Deliv 2010;2:49-57.