Research Article

A Novel Approach to Enhance Solubility of Olmesartan Medoxomil by Liquisolid Compact Technique

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ABSTRACT
Olmesartan medoxomil is an antihypertensive agent administered orally it is poorly water soluble drug with absolute bioavailability of 26%. The objective of present investigation was to develop liquisolid compacts to improve the dissolution rate.The liquisolid compacts were prepared using polyethylene glycol 400, propylene glycol and Tween-80 as non-volatile solvents. Neusilin as carrier material and Aerosil-200 as coating material. The interactions between drug and excipients were characterized by FTIR studies and no interactions were reported. The powder characteristics were evaluated by different flow parameters to comply with pharmacopoeial limits. The dissolution studies for liquisolid compacts and conventional formulations were performed and it was found that liquisolid compacts with Neusilin and Tween-80 showed significant higher drug release than conventional. Neusilin is an effective carrier and total of eight formulations were prepared and F8 was optimized formulation with drug release of 97.11%.

Keywords: Liquisolid, Neusilin, Olmesartan medoxomil, Tween-80.

INTRODUCTION

This is a novel concept in which a liquid may be transformed into a free flowing readily compressible dry powder by simple physical blending with selected carriers and coating material. The liquid portion which can be a liquid drug, drug suspension or drug solution in suitable non-volatile liquid vehicle is included into porous carrier material. The drug might be in solid dosage form it is held within the powder substrate in solution or in solubilized molecularly dispersed state due to this increased wetting properties and surface area of drug available for dissolution enhances the drug release and improved oral bioavailability.
The concept of absorption and adsorption takes place the liquid initially absorbed in the interior of particles is captured by its internal structure and after saturation of this process adsorption of liquid onto the internal andexternal surfaces of porous carrier particles occur, then the coating material having high adsorption properties and large specific area gives the liquisolid system the desirable flow characteristics. Various methods have been described to improve the solubility among them this is one of the most promisingand new technique.

MATERIAL AND METHODS

Olmesrtan medoxomil was received as a gift sample fromTorrent pharma.The following materials were gifted by Sd fine-chem Pvt., Mumbai and were used as received; Propylene glycol, Polyethylene glycol-400, Tween-80, Microcrystalline cellulose (Avicel-102), Sodium starch glycolate, Aerosil-200, Magnesium stearate, Talc. Neusilin(Magnesium Aluminometasilicate) was obtained as gift sample from Fuji chemical Industry- co limited.

EXPERIMENTAL METHODS

Solubility studies

These were assessed by using shake flask methods. The solubility of Olmesartan as pure drug was determined in distilled water, propylene glycol, polyethylene glycol-400, Tween-80 and phosphate buffer pH 6.8. Excess quantities of pure drug was added in 25ml of solvent in 250ml conical flask and shaken for 72 hours at room temperature on

rotary flask shaker. The entire samples were protected from light by wrapping the flask by aluminum foil. Absorbance of resulting solution was measured by UV spectrophotometer at 257nm.

Measuring Angles of slide

Before designing the liquisolid compacts this experiment is done to measure the flowable liquid retention potential (Φ- value) for Avicel pH-102 (MCC), Neusilin-carrier material (Φ_{ca}), Aerosil-200-coating material (Φ_{co}), the optimum load factor (L_f).

Determination of liquid flowable retention potential (Φ)

$$\Phi\text{value} = \frac{\text{Weight of non} - \text{volatile liquid}}{\text{Weight of carrier or coat material}}$$

Calculation of Liquid load factor (L_f)

$$Lf = \frac{W}{P} = \frac{\text{Weight of liquid medication}\left(\frac{W}{W}\right)}{\text{Weight of carrier Powder}}$$

Powder admixtures containing carrier or coating material with increasing quantity of non-volatile liquid vehicle were mixed and then placed on shiny metal plate, the plate is tilted until the admixture slides, the angle formed at which admixtures slides were measured at angle of slide(θ). Each admixture has specific Φvalues which are determined. The Φ- value that corresponds to an angle of slide of 33^o is optimum for flow of powder.

PREPARATION OF STANDARD CALIBRATION CURVE FOR OLMESARTAN

100mg of Olmesartan pure drug was accurately weighed and transferred into a100ml volumetric flask, dissolved in little quantities of methanol, then made up to100ml withmethanol (1000µg/ml). From this solution, 10ml of solution waswithdrawn into a 100ml volumetric flask and made up to 100ml with PH 6.8 Phosphatebuffer to get a concentration of 100µg/ml. From this, again pipette out 10ml ofsolution and diluted to 100ml with PH 6.8 Phosphate buffer to get a concentration of10µg/ml. Absorbance of this was measured at 257 nm usingUV/VISspectrophotometer against blank (pH 6.8 phosphate buffer).

Table 1: Calibration curve of Olmesartan medoxomil

Concentration (µg/ml)	Absorbance at 257 (nm)
0	0
2	0.168
4	0.321
6	0.463
8	0.614
10	0.755

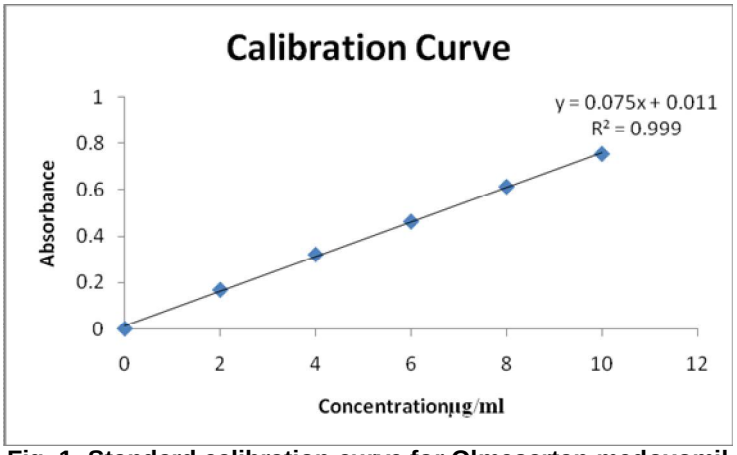

Fig. 1: Standard calibration curve for Olmesartan medoxomil

Preparation of powder for liquisolid compacts

1. A drug was initially dispersed in the non-volatile solvent systems (Tween-80, Propylene glycol, PEG 400) termed as liquid vehicles with different drug : vehicle ratio.
2. Then a mixture of carrier (Neusilin) and coating materials (Aerosil-200) were added to the above liquid by continuous mixing for a period of 10 to 20 minutes in a mortar. The amount of carrier and coating materials are enough to maintain acceptable flow and compression properties.
3. To the above mixture disintegrant like sodium starch glycolateand other remaining additives are added according to their application and mixed in a mortar.
4. The final mixture was compressed to achieve tablet hardness.
5. Characterize the final liquisolid granules for solubility, flowability, compressibility and dissolution.
6. The liquisolid systems compressed into tablets by using a tablet compression machine Karnavathi mini press I with ten station rotary machine.

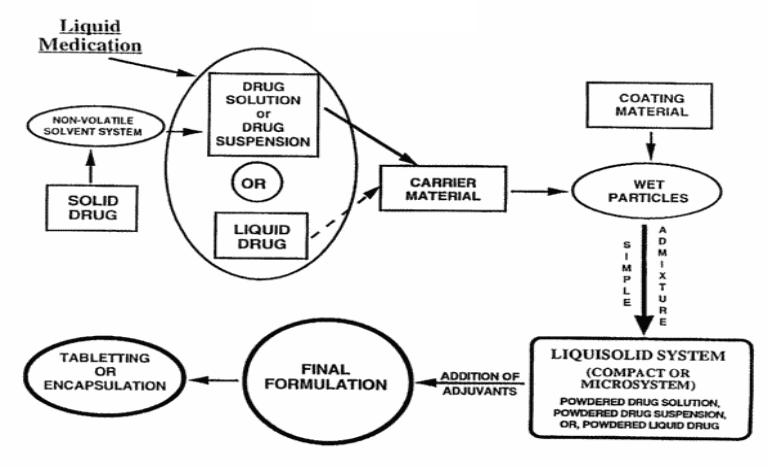

Fig. 2: Preparation of liquisolid compacts

Table 2: Loading factor values of Formulations

Formulation	R	Lf	Q=w/Lf gram
F1	**20**	**0.226**	**0.018**
F2	**20**	**0.27**	**0.015**
F3	**20**	**0.243**	**0.012**
F4	**20**	**0.236**	**0.010**
F5	**20**	**0.226**	**0.009**
F6	**20**	**0.27**	**0.019**
F7	**20**	**0.243**	**0.008**
F8	**20**	**0.236**	**0.007**

Table 3: Composition of Olmesartan Tablets

Ingredient	C*	F1	F2	F3	F4	F5	F6	F7	F8
Olmesartan	20	20	20	20	20	20	20	20	**20**
Poly ethylene glycol-400	---	10	----	----	20	----	----	----	**----**
Propylene glycol	---	----	10	----	----	20	----	----	**----**
Tween-80	---	----	----	10	----	----	20	20	**20**
AVICEL- PH 102 (Microcrystalline Cellulose)	120	100	100	100	120	120	120	100	**90**
Neusilin	---	----	----	----	----	----	----	20	**30**
Aerosil-200	6	5	5	5	6	6	6	6	**6**
Sodium Starch Glycolate	10	10	10	10	10	10	10	5	**5**
Magnesium stearate	2	3	3	3	2	2	2	2	**2**
Talc	2	2	2	2	2	2	2	2	**2**
Total weight(in mg)	160	150	150	150	180	180	180	180	**180**

C*: Conventional tablets

Pre-Compression Studies of the Prepared Liquisolid Systems

1. Determination of angle of Repose

The angle of repose (θ) was calculated using fixed height funnel method

$\theta = \tan^{-1}h/r$, where h,r – height and radius of powder cone.

2. Compressibility Index

The compressibility index of the powder blend was calculated by Carr's compressibility index. The formula is

$$\text{Carr's Index\%} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \text{ X } 100$$

3. Hausner's Ratio

It is calculated from:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

FOURIER-TRANSFORM INFRARED SPECTROSCOPY (FTIR ANALYSIS)

It was performed by using the infrared spectrophotometer (Alpha-brooker FTIR-Tokyo, Japan). Samples of 2-3 mg were mixed with about 400mg of dry potassium bromide powder and compressed into transparent discs under a pressure of 10,000 to 15,000 pounds per square inch. The spectra were scanned over the wave number range of 4000 to 400cm^{-1}.

EVALUATION OF COMPRESSED TABLETS (POST-COMPRESSION PARAMETERS)

Physical and chemical characterization of liquisolid tablets

The prepared tablets were evaluated accordingly: weight variation (Digital weighting machine – Schimadzu ATY 244), Thickness(Electric micrometer model C), Drug content, In-vitro disintegration- (Disintegration apparatus Lab India dt 1000), Hardness – Pfizer hardness tester(IntexInd corporation, Mumbai), Friabilator (Roche – Electro lab Pvt. limited, India),USP dissolution apparatus (LAB INDIA DS 8000),UV-visible double beam spectrophotometer- Elicosl 164 double beam), and solubility(Rotary flask shaker secor, India).

1. Friability test

It is performed by using Roche friabilator.

$$\text{\% Friability} = \frac{(W1-W2)}{W1} \text{ X } 100$$

W_1 – Weight of tablets before test

W_2 – Weight of tablets after test

2. Hardness

The hardness of the tablets was determined by using Pfizer hardness tester. Its Units are Kg/cm^2. Six tablets from each formulation were tested for hardness.

3. In-vitro Disintegration time

The disintegration time of tablets were measured in distilled water (37± 2^oC) using disintegration test apparatus. Six tablets from each formulation were tested and it is useful quality assurance tool for dosage form.

4. Content Uniformity

Five tablets were powdered; 20mg equivalent weight of olmesartan was accurately weighted and transferred into 100ml volumetric flask. Initially 10ml of methanol was added and shaken for 10 minutes. The volume is made up to 100ml with pH 6.8 phosphate buffer. The solution in the flask was filtered, diluted and analyzed at 257nm.

5. In-vitro Drug Release study

The dissolution of tablets were performed by USP dissolution apparatus type II paddle type apparatus at 37C ± 0.5^oC using Phosphate buffer pH 6.8(900ml) as dissolution medium at 50rpm. At pre-determined interval 5ml samples were withdrawn & diluted and then assayed at 257nm using UV-Visible double beam spectrophotometer cumulative percentage drug release was calculated using equation obtained from calibration curve.

RESULTS AND DISCUSSIONS

Solubility study of olmesartan

Solubility of Olmesartan medoxomil in various liquid vehicles is shown in Table 4. It is found to bemore soluble in Tween-80.

Table 4: Solubility of Olmesartan medoxomil in the below solvents

S.No	Name of Excipient	Avg. Amount of drug dissolved mg/ml
1	PEG 400	4.52 ± 0.98
2	Propylene glycol	2.23 ± 0.88
3	Tween-80	1.21 ± 0.14
4	Water	0.185 ± 0.11
5	PH 6.8 Phosphate buffer	0.194 ± 0.32

Formulations containing Neusilin showed improved flowability. The ingredient quantities required to achieve acceptable flowability was calculated using the Φvalues of powder excipients as shown in Table 2.

Angle of Repose

The angle of repose of each liquisolid system is shown in the Table 5.All the formulations with an angle of repose < 30 were found to be with acceptable flowability, as smaller the angles of repose the more the flowable the powder.

Table 5: Flow properties of the powder blend of formulations

Formulation	Bulk density	Tapped density	Carr's Index	Hausner's Ratio	Angle of Repose
Prepared Conventional	0.371	0.457	18.81	1.231	28.86
F1	0.318	0.389	18.25	1.223	24.93
F2	0.331	0.399	17.04	1.205	24.25
F3	0.329	0.396	16.91	1.203	25.05
F4	0.345	0.409	15.64	1.185	26.40
F5	0.356	0.411	13.38	1.154	25.79
F6	0.389	0.444	12.38	1.141	27.56
F7	0.362	0.410	11.70	1.132	27.66
F8	**0.338**	**0.378**	**10.58**	**1.118**	**28.67**

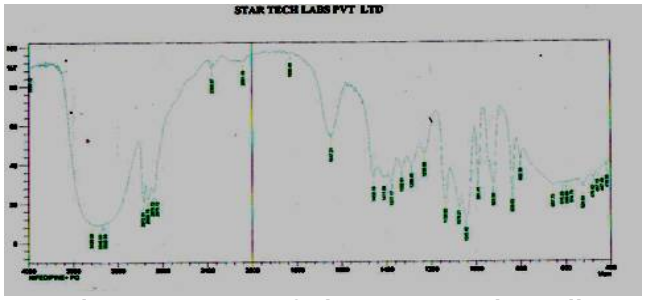

Fig. 3: IR spectra of Olmesartan medoxomil

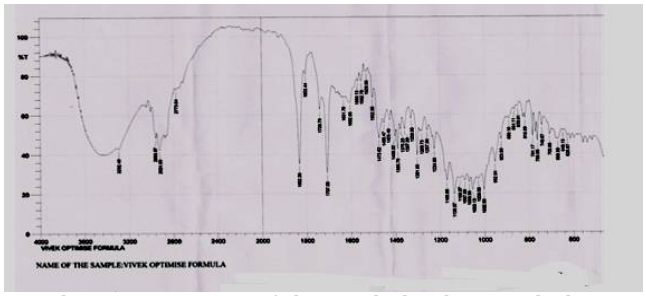

Fig. 4: IR spectra of the Optimized Formulation

FTIR

figure 3shows the pure olmesartan medoxomil spectra with characteristics peaks at 2923.56cm^{-1}, 2995.87cm^{-1} (C-H str) 1708 cm^{-1}, 1832 cm^{-1} (C-O str) and 3300-3100 cm^{-1} (N-H str). Preparation of liquisolid compacts with different excipients did not result in disappearance or addition of peaks which indicates absence of physical and chemical interaction between drug and carriers employed. Fig. 4 shows the IR spectra of optimized formulation of F8.

Physical and Chemical Evaluation of Liquisolid Tablets

All prepared liquisolid formulations shown in Table 11 have acceptable physical properties as per the I.P pharmacopoeial limits. The hardness of all formulations was found to be in the range of 4.1 to 5.3 kg/cm^2;all formulations show Friability below 1% indicating good mechanical resistance, Thickness of 1.85 to 1.98mm was reported. The percentage weight variation was within pharmacopoeial limits i.e. ± 7.5% with the drug content uniformity of

99.02 to 99.8% indicating uniform distribution of drug in tablets.

IN- VITRO DISSOLUTION RATE STUDIES

The dissolution rates of prepared liquisolid tablets were compared to that of conventional directly compressed tablets(DCT). All the prepared liquisolid tablets showed fast dissolution profits that DCT as indicated **by** the amount of drug dissolved after 10 minutes. It was observed that upon using drug concentration 20% of Tween-80, Neusilin 30% the dissolution rate is enhanced to 97.11% after 60 minutes for F8 formulation, it had highest dissolution pattern rate and extent of drug dissolute compared to DCT the percentage of drug release was 82.43% after 60 minutes. However higher dissolution rates observed in liquisolid tablets could be related to large surface area of the dispersed drug particles exposed to the dissolution medium.

Table 6: Dissolution profile of prepared conventional formulation

TIME (min)	% Cumulative drug release
0	0
10	29.3
20	45.63
30	57.55
40	68.71
50	76.24
60	82.43

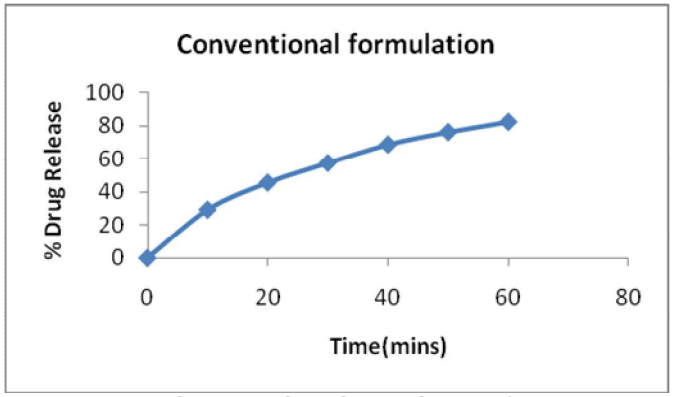

Fig. 5: In vitro drug release of Prepared Conventional Formulation

Table 7: Dissolution profile of prepared liquisolid compact formulations

Time (mins)	F1	F2	F3	F4	F5	F6	F7	F8
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	25.84	40.15	22.15	20.53	63	49.15	34.15	**52.15**
20	61.9	56.75	53.78	51.05	77.31	73.69	72.84	**76.73**
30	73.66	62.68	64.53	67.76	82.08	79.12	82.18	**86.81**
40	77.01	68.21	72.16	71.05	83.21	82.99	87.69	**89.6**
50	78.3	69.87	73.87	71.82	87.42	86.27	89.8	**93.8**
60	80.07	71.78	76.51	75.13	85.5	89.12	95.38	**97.11**

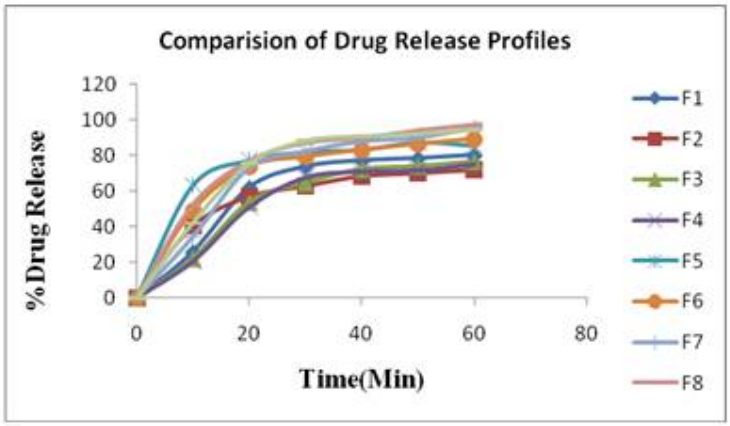

Fig. 6: Comparison of drug Release profiles

Table 8: Dissolution profile of marketed & Optimized formulation (F8)

Time (In Minutes)	% Cumulative Drug Release Of Marketed Formulation	% Cumulative Drug Release Of Optimized Formulation (F8)
0	0	0
10	36.53	52.15
20	48.39	76.73
30	56.94	86.81
40	64.13	89.60
50	72.44	93.80
60	89.39	97.11

Table 9: Comparison of in vitro Dissolution profile of Prepared Conventional &Optimized formulation

Time (in minutes)	% Cumulative Drug Release of Prepared Conventional Formulation	% Cumulative Drug Release Of Optimized Formulation (F8)
0	0	0
10	29.3	52.15
20	45.63	76.73
30	57.55	86.81
40	68.71	89.60
50	76.24	93.80
60	82.43	97.11

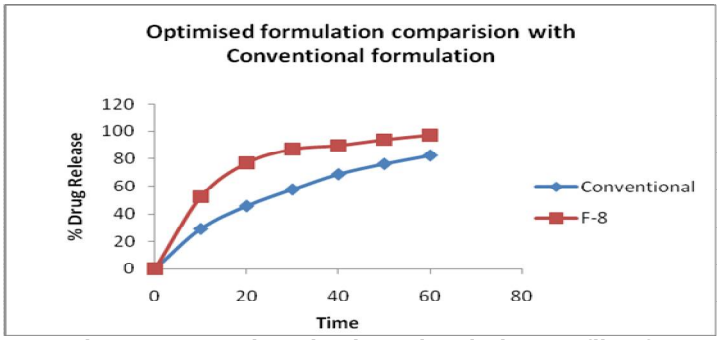

Fig. 7: Comparison in vitro Dissolution profile of Prepared Conventional and Optimized formulation

Table 10: In vitro Dissolution profile of marketed, prepared conventional and optimized formulation

Time (In Minutes)	% Cumulative Drug Release Of Marketed Formulation	% Cumulative Drug Release Of Prepared Conventional Formulation	% Cumulative Drug Release Of Optimized Formulation (F8)
0	0	0	0
10	36.53	29.3	52.15
20	48.39	45.63	76.73
30	56.94	57.55	86.81
40	64.13	68.71	89.60
50	72.44	76.24	93.80
60	89.39	82.43	97.11

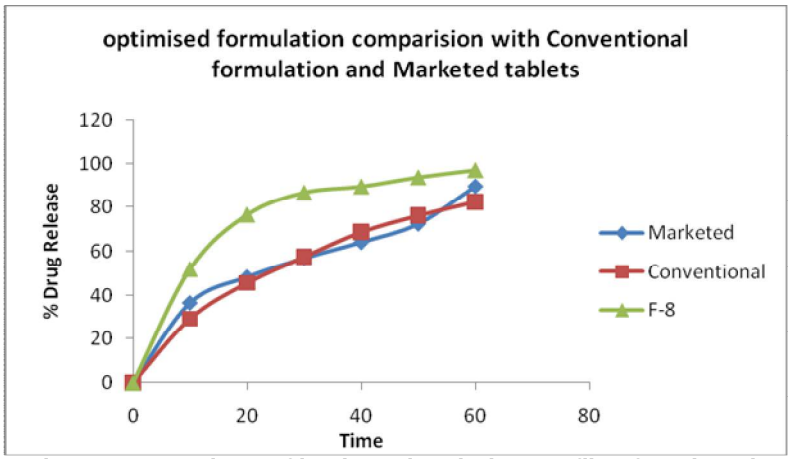

Fig. 8: Comparison of in vitro Dissolution profile of Marketed, Prepared Conventional & Optimized formulation

Table 11: Post compression parameters

Formulation	Weight Variation(mg)	Thickness (mm)	Hardness Kg/cm^2	Friability (%)	Drug Content (%)	Disintegration Time(sec)
C	152±0.16	1.72±0.003	4.1±0.16	0.15	86%	202
F1	160±0.13	1.85±0.005	4.1±0.11	0.14	95.69	142
F2	149 ±0.53	1.91±0.0071	4.5±0.12	0.12	94.67	89
F3	149±0.69	1.9±0.0042	5.3±0.23	0.14	96.19	96
F4	150±0.11	1.95±0.0026	4.9±0.10	0.12	93.67	75
F5	180±0.16	1.86±0.0035	4.5±0.29	0.13	93.15	65
F6	180±0.17	1.92±0.0083	5.0±0.34	0.12	95.18	148
F7	180±0.18	1.91±0.0012	4.4±0.30	0.14	95.16	143
F8	181±0.10	1.93±0.0013	4.8±0.11	0.11	98.16	76

CONCLUSION

The Liquisolid technique succeeded to improve the dissolution rate of practically insoluble drug such as olmesartan medoxomil. Among the eight formulations F8 formulation showed 97.11% dissolution rate containing Tween-80 as solvent and Neusilin as carrier compared to other formulations. Neusilin having the liquid adsorption capacity increases by many folds.

REFERENCES

1. Prajapati ST, Bulchandani HH, Patel DM, Dumaniya SK and Patel N. Formulation and evaluation of liquisolid compacts for olmesartan medoxomil. Journal of Drug Delivery. 2013;8:75-79.
2. Spireas S, Sadu S and Grover R. In vitro evaluation of hydrocortisone liquisolid tablets," Journal of Pharmaceutical Sciences. 1998;87(7):867–872.
3. Warner GT and Jarvis B. Olmesartan medoxomil Drugs. 2002;62(9):1345–1353.
4. Neutel JM, Elliott WJ, Izzo L, Chen CL and Masonson HN. Antihypertensive efficacy of olmesartan medoxomil, a new angiotensin II receptor antagonist, as assessed by ambulatory blood pressure

measurements. Journal of Clinical Hypertension. 2002;4(5):325–331.
5. Nakagomi-Hagihara R, Nakai D and Kawai K. OATP1B1, OATP1B3, and Mrp2 are involved in hepatobiliary transport of olmesartan, a novel angiotensin II blocker. Drug Metabolism and Disposition. 2006;34(2):862–869.
6. Elkordy AA, Essa EA, Dhuppad S and Jammigumpula P. Liquisolid technique to enhance and to sustain griseofulvin dissolution: effect of choice of non-volatile liquid vehicles," International Journal of Pharmaceutics. 2012;434(1-2):112–132.
7. Valaei I, Hassan-Beygi SR, Kianmeh MH and Massah J. Investigation of avalanche time and carr's index of poultry litter powder as flowability indices. CercetăriAgronomiceÎn Moldova. 2012;45(2):15–27.
8. Sinha S, Ali M, Baboota S, Ahuja A, Kumar A and Ali J. Solid dispersion as an approach for bioavailability enhancement of poorly water-soluble drug ritonavir. AAPS PharmSciTech. 2010;11(2):518-27.
9. Hiremath SN, Raghavendra RK, Sunil F, Danki L S, Rampure MV, Swamy PV and Bhosale UV. Dissolution enhancement of gliclazide by preparation of inclusion complexes with β- cyclodextrin. Asian Journal of Pharmaceutical Sciences. 2008;2:73-6.
10. Rajarajan S, Baby B, Ramesh K and singh D. Preparation and evaluation of ternary mixing Itraconazole solid dispersions by spray drying method. Journal of pharmaceutical Science and Research. 2009;1(1):22-5.
11. Spireas S. Liquisolid systems and methods of preparing same, US patent 6,423,339 B1, 2002
12. Khaled K A, Asiri Y A and El-Sayed YM. In-vivo evaluation of hydrochlorothiazide liquisolid tablets in beagle dogs. International Journal of Pharmaceutics. 2001;222(1):1-6.
13. Dhavalkumar M P and Ajaykumar T. A research on improvisation in dissolution of olmesartan medoxomil by enhancement its solubility using solid dispersion techniques. World Journal of Pharmaceutical Research. 2013;2(5):1793-1816.
14. Rowe RC, Sheskey PJ and Weller PJ. Handbook of Pharmaceutical Excipients. American Pharmaceutical Association, Chicago. 2003;4th ed, 108–111, 161–164, 355–361, 407–466.
15. Shah V, Patel D, Sandeep M and Upadhyay U. Solubility and dissolution rate enhancement of licofelone by using modified guar gum. International Journal of PharmaTech Research. 2010;2(3):1847-54.