Research Article

Liquisolid Compact: A New Technology for Optimization of Paliperidone Tablets by Central Composite Design.

Vinod Valjibhai Siju[1*], Dr. Moinuddin Soniwala[2]

[1] PhD scholar, School of Pharmacy, RK University, and Production Executive, RPG Lifescience PVT Ltd, Ankleshwar, India.

[2] Associate professor, B K Mody government pharmacy college, Rajkot, India.

***Corresponding author's E-mail:** Vinod.siju@gmail.com

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ABSTRACT

The objective of the work was to improve the dissolution rate of the practically insoluble antipsychotic class of medications drug, Paliperidone (PLP) by adopting the liquisolid compact (LS) technique. The study is to determine the effect of different excipients on dissolution of tablets. The liquisolid tablets prepared by the PEG 400 and drug in PEG 400 concentration of, 10%w/w to 30%w/w are used. Avicel PH 102, Aerosil 200, Cross carmellose sodium is used as a carrier, coating and disintegrant respectively. In this method Avicelph 102 used as a adsorptive agent and Aerosil 200 as a absorptive agent. From the dissolution rate liquisolid compact is having higher dissolution than marketed tablets.

Keywords: Liquisolid compact, Paliperidone, PEG 400, Aerosil 200, Liquid load factor.

INTRODUCTION

The liquisolid technique given by Spireas, in which liquid convert into a free flowing, powder by simple blending with carrier and coating material. Liquid portion is liquid drug or a liquid concentrate is added in to carrier material which is a diluent solvent mainly a PG, PEG and glycerine[1].

As an addition of liquid absorb on surface of carrier material, and liquid layer formation occur on particle surface. Liquisolid compact are a powder form which is prepared by a liquid and diluent.

Liquid medication means liquid drug or a insoluble drug mixed in a solvent. By liquisolid compact drug with solvent converted into a dry, non- sticking, compressible powder by using a diluent and a lubricant [2].

In the liquisolid compact, the drug is liquid form or a solid form which is convert in to a solubilize form[3].

As a liquid add into a drug is solubilize in it and addition of carrier material absorption occur on a drug layer and as addition of carrier material adsorption occur.

Quantity of carrier and coating material calculate from the equation (1) – (3), and depend on that flowable liquid retention potential calculate from that [4].

The maximum amount of the solvent retain by the carrier and coating material ''Liquid load factor" (Lf). Excipient ration (R) is used to calculate 'optimum flowable load factor" (Lf)

$L_f=\phi_{CQ}(1/R)+\Phi_{CA}$ .....(1)

Where Φ_{CA} is the Phi value of the carrier and is the ϕ_{CQ}phi value of the coating material [5].

$Q= W/L_f$ ..... (2)

$q=Q/R$ ..... (3)

Liquisolid compact mainly used for the low dose water-insoluble drugs. Liquisolid compact technology mainly enhance solubility and dissolution rate [6-9].

MATERIALS AND METHODS

Materials

Paliperidone was obtained from J.B. Chemicals, Ankleshawar. Aerosil 200, Cab-o-Sil M-5 (Evonik, Mumbai), Microcrystalline cellulose (AvicelPH102, PH 101, PH 112, PH 200), polyethylene glycol 400 (Merck), Starcap 1500 (colorcone ltd, Goa), cross carmellose sodium, Fujicalin(FMC Biopolymer). All materials were of analytical grade.

UV Analysis

The UV-Spectrophotometric method of Paliperidone was performed in methanol at 237 nm using a UV-visible spectrophotometer. Standard curve prepared by diluting an aqueous solution 5-25 µg/mL using methanol as a diluent[10-11]. For dissolution determination in pH 0.1 N HCL at 237 nm in concentrations in the range of 10-40 µg/mL[12].

Selection of solvent

Selection of solvent was done on the basis of solubility study. Solubility study of drug was performed in PG, Polysorbate 20, Polysorbate 80, PG 600, PG 200, PG 400, Glycerin, Liquid paraffin, Cremophore® EL, Span 80, and Span 20 solvents to select suitable non-volatile solvent. More amount of API was container which contains 2 ml of solvents[10-13]. Then solvent vortex and mix on rotary shaker and analyzed by UV method[14].

Angle of slide measurement

In this study lab model was used. Model contains wooden blocks joined. Upper wooden block is polished[15-16].

10 gms of carrier and coating material take and add optimize solvent add till powder started to slide. Angle at 33^0 called as ideal.

Phi value determination

Take 10 gm of each material and addition of optimized solvent and mixed it. Phi value calculates from equation[18].

$$\text{Phi} - \text{value} = \frac{\text{Weight of liquid(g)}}{\text{Weight of solid(g)}}$$

Phi-value plotted in graph to the angle of slide Φ). The phi-value 33^0 called as flowable liquid retention potential of coating and carrier material[19].

Calculation for carrier and coating material

As per the Phi-value of carrier and coating material liquid load factor calculated.[20-21]

$L_f = \phi_{CQ}(1/R) + \Phi_{CA}$

$Q = W/ L_f$

$q = Q/ R$

Where,

L_f=Liquid load factor
Φ_{CA}= Phi value for carrier material
ϕ_{CQ}= Phi value for coating material
R=Excipient ratio (Q/q)
W=Amount of liquid
Q=Amount of carrier material
q= Amount of coating material

Method for Preparing Liquisolid Compacts

Take drug and solvent in one beaker and heated to 40^0-50^0C with mixing. Add drug and solvent to the carrier material and mix properly. Then add coating material to it and mix well. Add lubricant and disintegrant to the powder and finally compress the tablets[23-24].

Experimental Design

In experiment design, change in one or more variable to saw the effect of variable on result. The design of experiment is good procedure for doing experiments so that data obtained is analyze and find a conclusion from that

Design of experiment starting with a choosing an objective of the practical and selecting the processing factor for the study. Good design maximize the good results. Design of experiment used in preparation and development of liquisolid compact preparation.

Different design in experimental design[25-26]

The excipients ratio (R) and weight of solvent (w) play a crucial role in the preparation of PLP liquisolid compact. Center composite design (CCD) was used for systemic study of joint influence of the effect of Independent variables [Excipients ratio (R) (X_1) and weight of solvent (w) (X_2)] on responses such as hardness, cumulative percentage release at 5 min (CPR_{5min}) and cumulative percentage release at 10 min (CPR_{10min}).
The dependent variables were done on the basis of the aim of the present investigation (enhanced solubility and dissolution rate of PLP)[27]. In this design, two factors with five levels were probed to investigate the main effects and interaction of the two factors on five levels. A design consists of thirteen runs.

$Y_1 = Bo + b_1X_1 + b_2X_2 + b_3 X_1X_2 + b_4X_1^2 + b_5 X_2^2$

Where, Y_1 is the dependent variables, b_0 is arithmetic mean response of the 13 runs and b_1 is the estimated coefficient for factor X_1.

Data analyzed by Microsoft Excel® 2010 version. Analysis of variance (ANOVA) was implemented to check that was no difference between the models. The Response surface and contour plots were plotted using DOE® 7.1.5 (Stat-Ease, Inc. Minneapolis, USA)[28].

Evaluation of powder material

Powder material is used to determine flow of the powder and compressibility of the powder byCarr's compressibility index and Hausner' s ratio, angle of repose, bulk density, tapped density,

Evaluation of Liquisolid tablets

Hardness

Monsanto Hardness tester used measure hardness expressed in Kg/cm^2.

Friability

6.50 gm of tablets taken from the batch and tablets were initially weighed ($W_{initial}$) and add in to Roche's friabilator. And friabilator operate at 25 rpm for 4 minutes. Then tablets were weighed again (W_{final}).

Weight variation

20 Tablets are selectedweight variations of individual tablets were determined with respect to average weight and % weight variation.

Disintegration

Disintegration test was performed in 900ml distilled water at 37±0.5 °C temperature and at the rate of 30±2 cycles/min.

Drug Content Uniformity

The PLP content was determined in 20 tablets. Each tablet was then crushed and a quantity of powder equivalent to 6 mg of PLP was dissolved in 100 mL

methanol and 1 mL of this solution was diluted to 10 mL with methanol and measured spectrophotometrically at λmax of 237nm[29-30].

In Vitro Drug Release

Dissolution studies were performed using USP Dissolution apparatus type II (paddle type) with 900 mL 0.1 N HCL as dissolution medium. All studies were carried out at 37± 0.5° C, 50 RPM speed for 30 min at a fixed time intervals 5 mL aliquots were withdrawn, filtered with whatman filter paper fresh dissolution medium were added to maintain constant volume throughout the test period sample was determined by UV-Visible spectrophotometer at 237 nm.

RESULTS AND DISCUSSION

Selection of solvent

The solubility in various non-volatile solvent in Table 1 The table shows that solubility of drug in PEG 400 is higher. For this reason, PEG 400was selected to be the suitable solvent for preparing liquisolid compact[31].

Table 1: Selection of solvent

Sr. no.	Solvents	Solubility (mg/mL)*
1.	Propylene glycol	2.25 ± 0.041
2.	PEG-200	6.15 ± 0.12
3.	**PEG-400**	**40.52 ± 0.38**
4.	PEG-600	10.76 ± 0.26
5.	Glycerin	4.756 ± 0.316
6.	Labrafil M 1944 CS	3.14±0.46
7.	Cremophore® EL	3.55 ± 0.29
8.	Tween 20	19.1 ± 0.348
9.	Tween 80	9.65 ± 0.19
10.	Span 80	2.74 ± 0.37
11.	Span 20	15.41 ± 0.083
12.	Liq. Paraffin	0.88 ± 0.041
13.	Oleic acid	4.29±2.00
14.	Tributyrin	31.26±1.26
15.	Captex 200 P	13.03±0.55
16.	Labrafac CC	7.18±0.34
17.	Captex 355 EP/NF	6.58±1.36
18.	Migloyl 829	5.67±0.21
19.	Maisine 35-1	5.19±0.03
20.	Peceol	3.59±0.07

*All the values are in mean ± SD (n=3)

Angle of slide measurement and flowable liquid retention potential determination

Angle of slide for carrier and coating materials was used to calculate flowable liquid retention potentials, which are needed for calculation of the liquid load factor(Lf).

For the carrier material 5 gm of the powder was used for determine angle of slide. But in case of the coating material i.e.cab-o-sil M5 and aerosol 200 having low density. So it was not convenient to take 10gm of material for measurement. It is show that Phi-value corresponding to an angle of slide of 33^0 was higher for Avicel PH 102 and Aerosil 200 as carrier and coating material respectively.

Table 2: Selection of carrier material

Carrier	Flowable liquid retention potential(Phi value at 33^0)
Lactose	0.21
Starch	0.275
Avicel	0.425
Ethocel	0.39
Neusilin	0.25
Avicel PH 101	0.425
Avicel PH 102	**0.525**
Avicel PH 112	0.3
Avicel PH 200	0.224
Starcap 1500	0.336
Fujacalin	0.05
Coating	**Flowable liquid retention potential (Phi value at 33^0)**
Aerosil	1.38
Aerosil 200	**1.68**
Silica	0.75
Cab-o-sil	1.38
Cab-o-sil M 5	1
Silica gel	1.38

From the graph flowable liquid retention potential of Avicel PH 102 is found to 0.525 and flowable liquid retention potential of Aerosil 200 is found to be 1.68.

$$L_f=\Phi_{CA}+\phi_{CO}(1/R)$$

$$L_f=0.525+1.68\ (1/R)$$

Experimental Design

From the trial batch depending on different weight of solvent and different R ratio trial batches taken. The drug concentration ranged from 10 % to 20 % taken. Above 20 % of drug concentration not used because the tablet weight goes below 80 mg so cant compression of that weight done. If drug concentration below 10 % is taken than weight of solvent is increased so difficulty occurs in compression. So from that design is applied. Design batches mentioned in Table 3,4,5

For Dependent variable Y_1 (Hardness) For the Y_1 response, the interaction between factors X_1 and X_2 can be elucidated by using response surface plot as illustrated in Figure By keeping X_2 constant X_1 increased from -1 to +1 the hardness decreases from 3.9 to 3.6 kg/cm^2. A lowest

hardness of 3.5 kg/cm^2 was observed with excipient ratio (R) 15 and weight of solvent (W) 54.14 (Batch 8). A highest hardness of 4.5 kg/cm^2 was observed with excipient ratio (R) 15 and weight of solvent (W) 40 described in fig 1.

For Dependent variable Y_2 (CPR 5 min) For the Y_2 response, the interaction between factors X_1 and X_2 can be elucidated by using response surface plot as illustrated in Figure If, X_2 level increased from – α to + α CPR at 5 min increases 35 to40 %.A lowest CPR at 5 min of 20.15 % was observed with excipients ratio (R) 20 and weight of solvent (W) 50 (Batch 6). A highest CPR at 5 min 43.52 % observed with excipients ratio (R) 15 and weight of solvent (W) 40 described in fig 1

For Dependent variable Y_3 (CPR_{10MIN}) For the Y_3 response, the interaction between factors X_1 and X_2 can be elucidated by using response surface plot as illustrated in Figure**.** If, X_1 level increased from -α to +0 cumulative percentage release at 10 min increases 60 to 100 %. A lowest CPR_{10min} of 60 % was observed with excipient ratio (R) 7.93 and weight of solvent (W) 40. (Batch 9). A highest CPR_{10min} of 100 % observed with excipients ratio (R) 15 and weight of solvent (W) 40.(Batch 10) described in fig 1

Table 3: Factors and their different levels for Central composite design for preparation liquisolid tablets

Independent Variables	Levels				
	Lowest (-α)	Low (-1)	Medium (0)	High (+1)	Highest (+α)
X_1 (Excipients ratio R)	7.93	10	15	20	22.07
X_2 (weight of solvent) (W) (%)	25.86	30	40	50	54.14
Transformed values	-1.414	-1	0	+1	+1.414
Dependent Variables	Y_1(Hardness) (kg/cm^2)				
	Y_2(Cumulative percentage release at 5 min)($CPR_{5\ Min}$)				
	Y_3(Cumulative percentage release at 10 min)(CPR_{10Min})				

Table 4: Formulation of liquisolid compact (Design Batches)

Batch code	Weight of solvent (mg) [X_2] (W)	Drug conc (%)	R=Q/q [X_1]	L_f = 0.525+ 1.68 (1/R)	Avicel PH 102 Q=W/Lf(mg)	Aerosil 200 q=Q/R(mg)	CCS 5% (mg)	Total weight (mg)
LS_1	25.86	23.20	15.00	0.637	40.59	2.70	3.45	74.77
LS_2	40.00	15	15.00	0.637	62.79	4.186	5.64	122.15
LS_3	40.00	15	15.00	0.637	62.79	4.186	5.64	122.15
LS_4	50.00	12	10.00	0.693	72.15	7.21	6.46	139.89
LS_5	40.00	15	15.00	0.637	62.79	4.186	5.64	122.15
LS_6	50.00	12	20.00	0.609	82.10	4.10	6.81	147.30
LS_7	30.00	20	20.00	0.609	49.26	2.46	4.38	94.86
LS_8	54.14	11.08	15.00	0.637	84.99	5.66	7.23	156.58
LS_9	40.00	15	7.93	0736	54.34	6.85	5.05	110.00
LS_{10}	40.00	15	15.00	0.637	62.79	4.186	5.64	122.15
LS_{11}	40.00	15	15.00	0.637	62.79	4.186	5.64	122.15
LS_{12}	30.00	20	10.00	0.693	43.29	4.32	4.18	87.79
LS_{13}	40.00	15	22.07	0.601	66.55	3.01	5.47	120.00

Evaluation of powder parameters

Powder flow property is crucial in handling and processing of powder material. Angle of repose, Carr's index, Hausner's ratio are parameter included in check powder flow material. The Hausner ratio lower than 1.2 has good flow and more than 1.2 have poor flow. Angle of repose 25^0 having good flow and more than 40^0 have poor flow.

Table 6shows that all the tested batches of liquisolid compact had a good flow property. The range was from 32.4 to 35.56 for liquisolid compact. All batches LS 1 to LS 13 shows good angle of repose, Hausner's ratio.

Evaluation of Prepared Tablets

Thickness of tablets was between 2.14±0.09 to 4.12±0.01 mm. That indicate powder have good flow and uniform compression throughout process. The tablet weight is found uniform due to uniform size powder blend. The hardness values shows in table 6and it was in range from 3.2±0.02, 3.8±0.02 and 4.3±0.3. Friability of tablets was found below 1% indicating a good. The disintegration

time for below 15 minutes so it passes as per pharmacopoeial limit. Disintegration time was found to be in the range of 2.20 to 4.23 min. Faster disintegration time indicate rapid release rates. Therefore, promote good content uniformity observed between liquisolid and conventional tablets in study. Uniform drug content was observed for all the formulation from 96.24±0.2 to 102.01±0.04.as described in table 6.

Table 5: Experimental matrix and results

RUN	Independent Variables		Responses		
	X_1	X_2	Y_1 (Hardness) (kg/cm^2)	Y_2(Cumulative percentage release at 5 min)($CPR_{5\ Min}$)	Y_3 ($CPR_{10\ MIN}$)(%)
LS_1	15.00	25.86	4.2	35.00	86.00
LS_2	15.00	40.00	4.5	41.5	99.00
LS_3	15.00	40.00	4.5	42.9	98.50
LS_4	10.00	50.00	3.9	28.00	75.00
LS_5	15.00	40.00	4.5	42.00	99.15
LS_6	20.00	50.00	3.6	20.15	69.00
LS_7	20.00	30.00	4.1	40.00	98.00
LS_8	15.00	54.14	3.5	40.00	91.00
LS_9	7.93	40.00	3.9	20.55	60.00
LS_{10}	15.00	40.00	4.5	43.00	100.00
LS_{11}	15.00	40.00	4.5	43.52	99.15
LS_{12}	10.00	30.00	3.9	20.85	75.00
LS_{13}	22.07	40.00	4.0	29.00	82.00

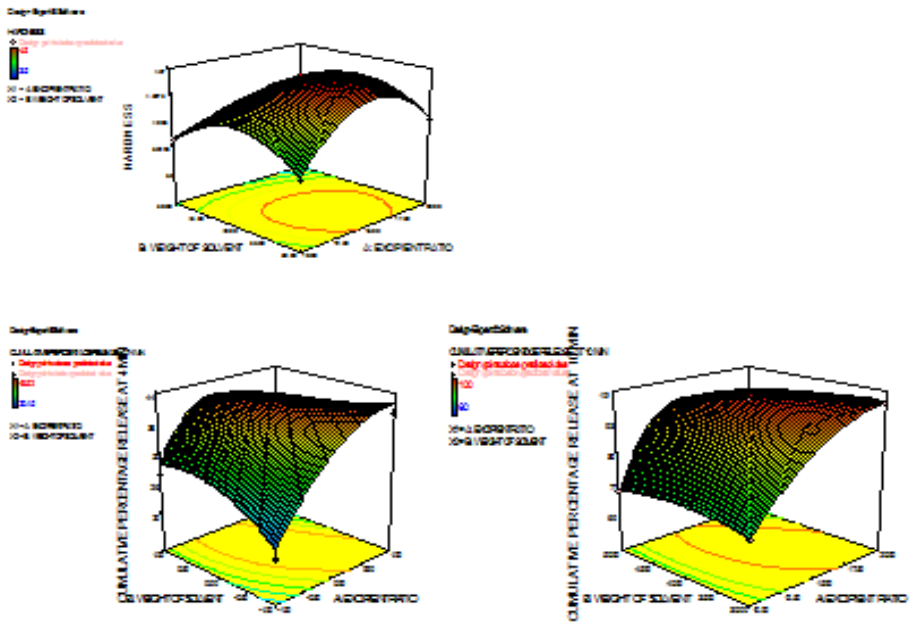

Figure 1: Influence of formulation composition factor on hardness, cumulative percentage release at 5 min and cumulative percentage release at 10 min.

In vitro drug release

Formula LS 1 has the highest dissolution profile in both the rate and the extent of drug dissolved. The percentage of PLP dissolved from LS 1reached 100.11% after only10 min, while the MKT had a maximum PLP content (65%) dissolved after 60 min.

Fig 2-shows the dissolution profile from the LS compact LS-1, LS-13 and marketed tablet (MKT) of PLP. Liquisolid compacts displayed different in-vitro release

characteristics than directly compressed counterparts. The percent drug release at the end of 60th min was, 95.89 % for LS-1, 98.2 % for LS-20 79% and 51.2 % for MKT. The 10th min percent drug release of LS compacts and conventional tablets is shown in Fig 2. It was confirms that LS-1 had highest drug release 34.56 %compared to 8.2 % for conventional tablets.

Table 6: Pre compression parameters of liquisolid compact

Batch code	Angle of repose*	Carr's index*	Hausner's ratio*	Hardness* (kg/cm^2)	Friability* (%)	Thickness * (mm)	Wt variation**	Disintegration Time(Min.)*	Drug Content* (%)
LS_1	35.56 ± 0.2	14.226±0.94	1.184±0.01	4.2±0.180	0.18±0.23	2.50±0.12	74.77±0.02	3.49±0.12	98.98±0.12
LS_2	32.56 ± 1.3	10.11±0.8	1.11±0.05	4.5± 0.188	0.28±0.13	3.20±0.01	122.15±0.13	2.12±0.12	99.16±0.13
LS_3	32.45 ± 0.6	10.12±0.6	1.18±0.01	4.5± 0.216	0.29±0.1	3.20±0.02	122.15±0.14	2.12±0.07	99.45±0.56
LS_4	32.4 ± 0.4	14.973±2.1	1.29±0.1	3.9 ± 0.163	0.13±0.02		139.89±0.45	4.20±0.09	99.12±0.01
LS_5	33.56 ± 0.42	11.46±2.3	1.13±0.04	4.5 ± 0.163	0.23±0.03	3.23±0.04	122.15±0.21	2.20±0.06	102.01±0.04
LS_6	35.56 ± 0.90	17.1±0.7	1.116±0.6	3.6 ± 0.094	0.26±0.05	3.50±0.2	147.30±0.03	2.45±0.2	101.01±0.1
LS_7	33.3 ± 1.35	9.666±1.2	1.048±0.2	4.1 ± 0.094	0.14±0.4	2.68±0.01	94.86±0.1	2.10 ±0.05	100.02±0.4
LS_8	32.58 ± 0.54	14.383±1.1	1.103±0.07	3.5 ± 0.094	0.10±0.03	3.60±0.05	156.58±0.02	2.40±0.04	99.12±0.09
LS_9	32.58 ± 1.40	12.06±0.8	1.053±0.02	3.9 ± 0.094	0.24±0.09	3.00±0.04	110.00±0.05	3.14±0.09	100.14±0.2
LS_{10}	32.58 ± 0.28	12.60±0.4	1.126±0.04	4.5 ± 0.163	0.29±0.07	3.20±0.3	122.15±0.07	2.20±0.12	98.23±0.5
LS_{11}	33 ± 0.40	12.486±1.2	1.086±0.8	4.5 ± 0.094	0.19±0.03	3.54±0.01	122.15±0.01	2.12±0.12	100.24±0.2
LS_{12}	33.45 ± 0.28	12.666±2.4	1.183±0.2	3.9 ± 0.094	0.13±0.8	2.60±0.09	87.79±0.09	4.05±0.02	98.56±0.1
LS_{13}	33 ± 0.55	12.413±0.6	1.073±0.05	4.0 ± 0.094	0.31±0.05	3.19±0.12	120.00±0.13	3.40±0.12	99.67±0.13

Hausner's ratio and Carr's index were calculated from the density value. In case of Carr's index below 20 giving good result. So in the all batches result shows good flow property

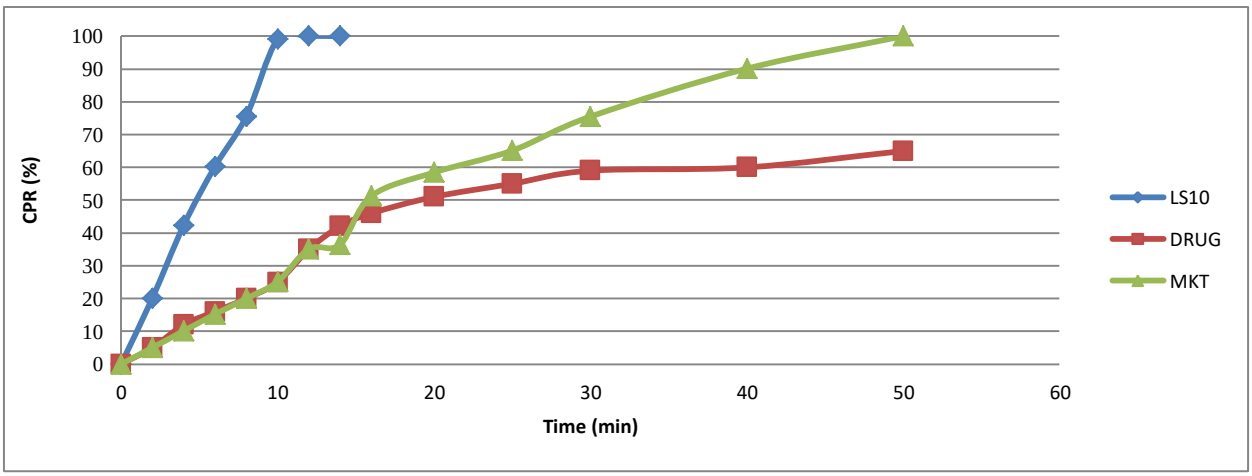

Figure 2: *In vitro* release study of formulation

CONCLUSION

The Liquisolid technique is a promising alternative for improvement of dissolution property of water-insoluble drugs, such as PLP. The higher dissolution rate showed by Liquisolid compacts may enhanced oral bioavailability due to the increased wetting properties and surface of drug available for dissolution. The Liquisolid compact of PLP made in PEG 400 showed better dissolution rate than marketed tablet based upon solubility.

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REFERENCES

1. Horter, D., Dressman JB, Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract, *Adv. Drug.Deliv. Rev*.46, 1997, 75–87.
2. Vemula, VR., Lagishetty, V, and Lingala s., Solubility enhancement technique. *Int. J.Pharm. Sci.Rev.Res*. 5(1), 2010.
3. Kulkarni, A., Alookar, N., and Mane M., and Gaja J., Liquisolid systems: a review. *Int. J. of Pharm.Sci. Nanotech*. 3(1), 2010, 795-802.
4. Javadzadeh, Y., Siahi, M., Asnaashari, Nokhodchi, A., Liquisolid technique as a tool for enhancement of poorly water-soluble drugs and evaluation of their physicochemical properties, *ActaPharm*. 57, 2007, 99–109.

5. Jarowski, C.,Rohera, B., Spireas, S., Powdered solution technology: principles and mechanism. Pharm Res. 9, 1992, 1351-1358.
6. Spireas, S., Bolton, M., Liquisolid systems and methods of preparing same, US Patent 5968, 1999; 550.
7. Amidon, G., Houghton, M., The effect of moisture on the mechanical and powder flow properties of microcrystalline cellulose, *Pharm. Res*. 121, 1995, 923–929.
8. El-Houssieny, B., Wahman, L., Arafa, N., "Bioavailability and biological activity of liquisolid compact formula of repaglinide and its effect on glucose tolerance in rabbits." *Bio.Sci. Trends*. 4, 2010, 17-24.
9. Spireas, S., Sadu, S., Enhancement of prednisolone dissolution properties using liquisolid compacts, *Int. J. Pharm.* 166, 1998, 177–188.
10. Javadzadeh, Y., Musaalrezaei, L., Nokhodchi, A., Liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices,*Int. J. Pharm*. 362, 2008, 102–108.
11. Spireas, S., Sadu, S., Grover, R., In vitro release evaluation of hydrocortisone liquisolid tablets, *J.Pharm. Sci*.87, 1998, 867–872.
12. http://drugbank.ca/drugs/ DB01267
13. Spireas, S., Wang, T., and Grover, R., Effect of powder substrate on the dissolution properties of methylclothiazideliquisolid compacts, *Drug Dev. Ind. Pharm*. 25,1999, 163–168.
14. Khaled, A., Formulation and evaluation of hydrochlorothiazide liquisolid tablets, *Saudi Pharm. J.* 6, 1988, 39–46.
15. Karmarkar Amrit, B., GonjariIndrajeet, D., and Hosmani Avinash, H., Liquisolid Tablets: A Novel Approach for Drug Delivery.2(1), 2009, 45-50.
16. Grover, R., Tsamboukos, K., Matharu, A., Combined effect of cyclodextrins and liquisolid compact technology on the dissolution profile of methylclothiazide, *A PhA. Annual Meeting,* 1995, 142-161.
17. Khaled, K., Asiri, Y., Sayed Y., In-Vivo evaluation of hydrochlorothiazide liquisolid tablets in beagle dogs, *Int. J. Pharm*. 222, 2001, 1–6.
18. Kalariya, D., Ronak, D., Vadalia, v., Solubility Enhancement of Olmesartan Medoxomil by Solid Dispersion and Formulation of Mouth Dissolving Tablet. *Inventi Rapid: Pharm Tech*, (3), 2012, 1-10.
19. Fahmy, R., Kassem, M., Enhancement of famotidine dissolution rate through liquisolid tablets for evaluation: *In vitro and in vivo evaluation. Eur. J. Pharm.Biopharm*. 69, 2008, 993–1003.
20. Tayel, S., Soliman,II., Louis, D., Improvement of dissolution properties of Carbamazepine through application of the Liquisolid tablet technique. *Eur. J. Pharm.Biopharm*. 69, 2008, 342-347.
21. Yousef, J., Bahar, B., Nokhodchi, A., Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (Carbamazepine)*Int. J. of Pharm*. 341, 2007, 26-34.
22. Tiong, N., Elkordy, A., Effects of liquisolid formulation on dissolution of naproxen.*Eur. J. Pharm.Biopharm.* 73, 2009, 373-384.
23. Burra, S., and Galipelly, S.,Enhancement of solubility and dissolution rate of frusemide through liquisolid technique. *Der. Pharmacia.Lettre*, 2(6), 2010, 321-328.
24. Nokhodchi, A., Javadzadeh, Y., Siahi-Shadbad, 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.* 8, 2005, 18–25.
25. Jackson EK. Goodman and Gilman'sthe Pharmacological Basis of therapeutics.McGraw-Hill, NewYork, 1996.
26. StaniforthJ., "Powder flow" In: "Pharmaceutics, the Science of Dosage Form Design" M. Aulton (ed.) Churchill Livingstone, Edinburgh, 2nd ed., 2002, 197.
27. Vikas, A., Saharan and VipinK., Dissolution Enhancement of Drugs. PartI: Technologies and Effect of Carriers, *Int. j. of Health. Res*. 2(2), 2009, 107-124.
28. Shah, C., Patel, H., Shah V., Design, Development and Optimization of Valsartan Liquisolid Tablets Using Box-Behnken Design. *Int. J. Pharm. Sci. Res.* 3(8), 2012, 2741-2753.
29. Martin A. Physical Pharmacy, Philadelphia: Lippincott Williams and Wilkins; Edition 4, 444, 1993.
30. Mahajan,H., Dhamne, M., Gattani, S., Enhanced Dissolution Rate of Glipizide by a Liquisolid Technique. *Int. J. of Pharm. Sci. and Nan*. 3(4), 2011 1205-1213.

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