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Risperidone liquisolid compacts–Formulation and evaluation

Shamili Kaparthi* and P. R. Sathesh Babu

Gokaraju Rangaraju College of Pharmacy, Osmania University, Nizampet, Hyderabad, India

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ABSTRACT

The present research is aimed to enhance the dissolution rate of risperidone, low soluble drug. The absorption rate of risperidone is often controlled by the dissolution rate in the GIT due to its poor solubility. The liquisolid compacts (LSC), a promising technique, was employed to overcome low solubility issue. Different formulations were developed using carriers (Neusilin and Fugicalin), coating (aerosil 200) and vehicle (propylene glycol). The empirical method as introduced by Spireas and Bolton was applied to calculate the amounts of carrier and coating materials. Using this method, improved flow characteristics and hardness of the formulation has been achieved by changing the proportion of carrier and coating materials. Further, a 23 factorial design is used and developed LSC using Neusilin (LSC-N1 to LSC-N8) and Fugicalin (LSC-F1 to LSC-F8). The In vitro drug release from these LSC were evaluated in 0.1N HCl and the optimized formulation (LSC-N8) was compared with pure drug (capsule) and marketed product (tablet). The release studies proved that the liquisolid tablets produced higher release profile than pure drug and marketed product due to increase in surface and wetting properties of drug. Thus, LSC confirmed the enhanced dissolution rate of risperidone which in turn helps in improving bioavailability.

Keywords*:* Liquisolid compacts; Risperidone; Neusilin; Fujicalin; BCS class-II drug.

INTRODUCTION

The active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract [1]. The poor dissolution rate of water-insoluble drug is a substantial problem confronting the pharmaceutical industry. The absorption rate of a poorly water-soluble drug from solid oral dosage form is poor due to the low dissolution rate of the drug. Hence, dissolution rate is the rate determining step in drug absorption.

Various methods such as crystallization by solvent change, preparation of inclusion complexes with β-cyclodextrins, formation of water-soluble salts, micellar solubilisation, solid dispersion, lyophilisation, microencapsulation, liquisolid technique and the inclusion of drug solutions or liquid drugs into soft gelatin capsules are some of the techniques that have been reported to enhance the dissolution characteristics of water-insoluble drugs [2]. The technique of liquisolid compacts is one of the most promising techniques [3, 4]. Liquisolid concept is used to enhance the solubility of poorly water soluble drugs at least for the first two hours (active absorption phase) and thereby increasing drug dissolution and absorption rate of drugs.

The liquisolid technique as described by Spireas is a novel concept, where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. Liquisolid powder is a free flowing and a compressible powder form of liquid medication [5]. The term liquid medication implies liquid drug and solution or suspension of water insoluble solid drug carried in suitable non-volatile liquid vehicles. Using formulation technique, a liquid medication can be converted into a dry-looking, non-adherent, free flowing, and readily compressible powder by blending with selected powder excipients referred to as the carrier and coating materials. Various grades of cellulose, starch, lactose silica powder may be used as the coating (or covering) material [6]. In liquisolid compact, the drug is in a tablet or encapsulated dosage

form and it is held in a solubilised liquid state, which consequently contributes to increased drug wetting properties, thereby enhancing drug dissolution. In liquisolid formulation the drug is in either solubilised or molecularly dispersed state in the liquid vehicle, which is absorbed into or onto the carrier and coating material respectively. Hence, increased surface area of drug in powder form and enhanced dissolution of drug [7].

MATERIALS AND METHODS

2.1 MATERIALS

Risperidone is a gift sample (Corey Organic Pvt Ltd), Neusilin and Fujicalin are free samples (Gangwal Chemicals Pvt Ltd). Aerosil 200, PVP K-30, Cross caramellose sodium, Magnesium stearate, Lactose, Propylene glycol (PG), Glycerin, Tween 80, PEG 400, PEG 300 are procured from S.D. Fine Chem. Limited, Mumbai and used in the study.

Risperidone, chemically (4-[2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-1-piperidyl]ethyl]-3-methyl-2,6 diazabicyclo [4.4.0]deca-1,3-dien-5-one), is an antipsychotic drug mainly used to treat schizophrenia , schizoaffective disorder, the mixed and manic states of bipolar disorder, and irritability in people with autism. Risperidone is an official drug and appears as a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N hydrochloric acid. Risperidone has a melting point of 170 – 172 oC; log P value of 3.49 and got a pKa of 7.9. The dose of risperidone ranges between 4 to 6 mg with a maximum dose of 16 mg [8, 9].

2.2 METHODOLOGY

2.2.1 Estimation of risperidone: Risperidone estimation was made in 0.1N hydrochloric acid (pH 1.2) solution at λ_{max} of 272 nm by UV spectrophotometry (UV-1700, Shimadzu, Japan). The calibration curve was obeyed Beer Lambert's law in the concentration range of 0-40 µg/ml (R^2 = 0.997) [10, 11].

2.2.2 Saturation solubility studies: The solubility studies were performed for the selection of best non-volatile solvents. Excess of risperidone was placed in ten ml of five different non-volatile solvents (propylene glycol, Tween 80, PEG 300, PEG 400, and glycerine) and these dispersions were stirred in orbital shaker bath for 72 hours at 25 ^{o}C. The saturated solutions were filtered after 72 hours using Whattman filter paper (0.22 µm) and the filtrate was analyzed spectrophotometrically at 272nm. The studies were conducted triplicate [12, 13, 14].

2.2.3 Binding capacity of adsorbents for the solvents: Binding capacity is defined as the capacity of powder excipients to hold liquid without change in their flow properties. It was determined by the following simple method. A constant weight of 5g of different powder excipients were put into a mortar and propylene glycol was added in increments of 0.01mL. The mixture was triturated after each addition to help distribution of the liquid throughout the powder particles. Addition of liquid was continued until lumps appeared in the powder mixture [15].

2.2.4. Calculation of load factor: In a liquisolid 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 (R=Q/q) of a powder is defined as the ratio between the weights of carrier (Q) and coating materials (q) present in the formulation [16]. Preparation of a liquisolid 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 load factor (L_f). The liquid load factor (L_f) is defined as the weight ratio of the liquid medication (W) and carrier powder (Q) in the system (i.e., L_f=W/Q) [17]. To calculate the loading factor, propylene glycol (liquid medication without drug) was added to 10g carrier material and blended for 1min.Theabove procedure was repeated until a powder with acceptable flow rate was obtained.

2.2.5 Flow properties of liquisolid powders: Fixed funnel and the free-standing cone method were employed to measure the angle of repose. A funnel was secured with its tip at a given height (H) above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The mean radius(r) of the base of the conical pile was determined and the tangent of angle of repose was given by Tan θ=H/r, where θ is the angle of repose [18].

2.3 FORMULATION DEVELOPMENT

The liquisolid compacts of risperidone were developed by using 2^3 factorial design i.e., 3 variables and 2 levels. The variables include concentration of drug in the liquid vehicle (% w/w), concentration of binding agent (PVP K-30) in formulation (%w/w) and concentration of super disintegrant (cross caramellose sodium) in formulation (%w/w). The factorial design was applied at lower and higher levels using two different carries (Neusilin and Fugicalin) and

developed eight formulations for each carrier. The absolute levels of variables used in the study are given in the Table 1 and the plan of experiments with coded levels of variables are given in the Table 2.

Table 1. Absolute valves of levels of variables employed in factorial design

Sl. no.	Variables		Levels	
	Absolute	Coded	-1	+1
1	Concentration of drug in the liquid vehicle (% w/w)	X_1	50	75
2	Concentration of PVP-K30 in the formulation (% w/w)	X_2	2	5
3	Concentration of super disintegrant in the formulation (% w/w)	X_3	2.5	5

Neusilin and Fujicalin were selected as two different carriers and the above mentioned variables and respective levels were assessed individually on both the carriers employed in the study. Using the design of experiments, eight formulations for each of Neusilin (LSC-1N to LSC-8N) and Fugicalin (LSC-1F to LSC-8F) were developed using direct compression technique. Formulations LSC-N1 to LSC-N8 were formulated using neusilin as carrier and formulations LSC-F1 to LSC-F8 were formulated using fujicalin as carrier.

Table 2: Plan of experiments with coded values of variables of risperidone liquisolid compacts formulation using 2^3design

Sl. no.	Run order	Concentration of drug in the liquid vehicle (% w/w)	Concentration of PVP-K30 in the formulation (% w/w)	Concentration of cross caramellose sodium in the formulation (% w/w)
1	LSC-1	-1	-1	-1
2	LSC-2	+1	-1	-1
3	LSC-3	-1	+1	-1
4	LSC-4	+1	+1	-1
5	LSC-5	-1	-1	+1
6	LSC-6	+1	-1	+1
7	LSC-7	-1	+1	+1
8	LSC-8	+1	+1	+1

Table 3: Formulation composition of LSC-N1 to N8 with neusilin as carrier and aerosil 200 as coating material

Ingredient	LSC-1N	LSC-2N	LSC-3N	LSC-4N	LSC-5N	LSC-6N	LSC-7N	LSC-8N
Drug conc in PG (% w/w)	50	75	50	75	50	75	50	75
Risperidone	6	6	6	6	6	6	6	6
PG	8	12	8	12	8	12	8	12
PVP K-30	2	2	4	4	2	2	4	4
Neusilin	47.90	71.85	47.90	71.85	47.90	71.85	47.90	71.85
Aerosil 200	2.39	3.59	2.39	3.59	2.39	3.59	2.39	3.59
CCS	2.5	2.5	2.5	2.5	5	5	5	5
Magnesiun Stearate	1	1	1	1	1	1	1	1
Lactose	80.21	51.06	78.21	49.06	77.71	48.56	75.71	46.51
Total Unit Weight	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0

Table 4: Formulation composition of LSC-F1 to F8 with fujicalin as carrier aerosil 200 as coating materials

Ingredient	LSC-1F	LSC-2F	LSC-3F	LSC-4F	LSC-5F	LSC-6F	LSC-7F	LSC-8F
Drug conc in PG (% w/w)	50	75	50	75	50	75	50	75
Risperidone	6	6	6	6	6	6	6	6
Propylene glycol	8	12	8	12	8	12	8	12
PVP K-30	2	2	4	4	2	2	4	4
Fujicalin	96.38	144.57	96.38	144.57	96.38	144.57	96.38	144.57
Aerosil 200	4.81	7.22	4.81	7.22	4.81	7.22	4.81	7.22
CCS	2.5	2.5	2.5	2.5	5	5	5	5
Magnesiun Stearate	1	1	1	1	1	1	1	1
Lactose	79.31	24.71	77.31	22.71	76.81	22.21	74.56	20.21
Total unit weight	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0

2.3.1 Preparation of liquisolid compacts: The liquisolid compacts were prepared according to the method described by Spireas and Bolton [19]. Risperidone was dissolved in propylene glycol which is used as a liquid vehicle to prepare the drug solution. The mixture of carrier-coating materials (Neusilin and Fujicalin as the carrier powder and Aerosil200 as the coating material) was added to the liquid medication and blended in a porcelain mortar avoiding excessive trituration and particle size reduction. The mixing was done in three stages: first, the system was mixed slowly to allow uniform distribution of liquid medication; second, the mixture was spread as a uniform layer on the surface of the mortar and left standing for a few minutes; finally,10% of disintegrant (croscarmellose sodium) was added to the powder and mixed thoroughly. The final mixture was compressed into

tablets.

2.4 FTIR SPECTROSCOPY:

FTIR spectra of drug, Neusilin, Fujicalin, Aerosil and liquisolid tablet were obtained. About 5mg of sample was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12,000 psi for 3min.The resultant disk was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 4000cm^{-1} to 625cm^{-1} in a scan time of 12min.The resultant spectra were compared for any spectral changes.

2.5 EVALUATION OF LIQUISOLID SYSTEM

The prepared liquisolid tablets were evaluated for hardness, friability and disintegration time. Hardness was determined by the Pfizer hardness tester and friability by a digital tablet friability tester. The disintegration time was measured using a USP disintegration tester (Electrolab). All the studies were done in triplicate.

2.6 DISSOLUTION STUDIES:

Dissolution studies were performed for liquisolid compacts, plain drug and marketed product (RISPERDAL-6 mg).The USP paddle method was used for all in vitro dissolution studies. The dissolution was carried out using different media, i.e., 0.1N HCl (pH1.2). The stirring rate was 50±1 rpm. The amount of Risperidone was 6 mg in all formulations. The dosage forms were placed in 900 ml dissolution medium and maintained at 37±0.5°C. At appropriate intervals (5, 10, 15, 20, 25, 30 and 45min), 5mL of samples were taken and filtered through a 0.45 mm filter. The samples were analyzed at 272 nm by UV–visible spectroscopy.

RESULTS AND DISCUSSION

3.1 SATURATION SOLUBILITY STUDIES

The solubility of Risperidone was determined in a number of solvents and is presented in Table 5. Drug solubility in a non- volatile vehicle is the most important aspect in liquisolid systems. The solubility of the drug contributes to molecular dispersion in a non-volatile solvent which will improve the dissolution rate. Based on the solubility data, PG was selected as the vehicle for Risperidone.

Table 5: Solubility of Risperidone in different solvents

Solvent	Conc (mg/ml) AM* ± SD
PEG 400	1.501± 0.0077
PEG 300	1.603± 0.0076
Tween 80	2.934± 0.0098
Propylene glycol	6.073± 0.0036
Glycerine	2.6271± 0.004

**Each value is an average of 3 determinations.*

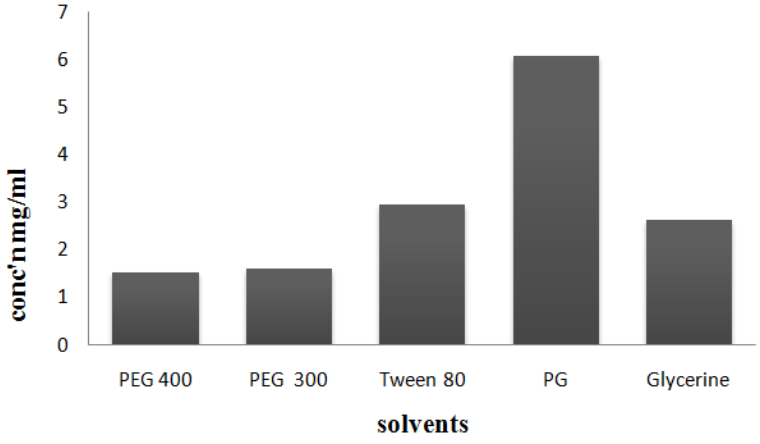

Fig 1: Solubility of risperidone in different solvents

3.2 LIQUISOLID COMPACTS

Spireas et.al [24] suggested that particles with high absorption properties due to a porous surface should be used as the carrier material, such as neusilin (LSC-N1-LSC-N8) and fujicalin (LSC-F1-LSC-F8). Increasing the moisture content of carrier materials may result in decreased powder flowability. The coating material is required to cover the surface, and further maintain the powder flowability [20, 21]. Accordingly, the coating material should be a very

fine and highly adsorptive silica powder. From the preliminary binding capacity experiments conducted with different excipients, as neusilin and fujicalin was selected as carrier and Aerosil 200 as the coat material. Risperidone liquisolid tablets were prepared with different excipient ratios (R) using PG as vehicle. The appropriate amounts of the carrier and coating material were derived from their liquid load factors. The L_f was greater than 0.25 for formulations LSC-1N to LSC-4N and LSC-1F to LSC-4F, showing poor flowability and compressibility [22]. The angle of repose is a result of internal frictional forces of the particles. The angle of repose will be high if the particles are cohesive. Angles of repose ≤ 30° indicate free flow while angles ≥40° indicate poor flow [23]. Powder formulations with angles of repose greater than 40° were not acceptable (formulations LSC-1N to LSC-4N and LSC-1F to LSC-4F). Formulations LSC-5N to LSC-8N and LSC-5F to LSC-8F showed 28°, 35°, 29°and 32°, respectively. Formulations 5, 6, and 7 showed good flowability but required a higher amount of carrier material which increased the tablet weight. Hence formulation LSC-8N and LSC-8F were selected for compression. The tablets should have sufficient hardness to resist the breakage during handling, and at the same time, it should disintegrate after swallowing. Formulation LSC-8N and LSC-8F showed good compressibility with an acceptable hardness (3–4kg). Based on this study, LSC-8N and LSC-8F was selected for further evaluation. Formulations LSC-8N and LSC-8F shows satisfactory flowability (angle of repose 32° and 30°), hardness (3.5 kg and 3.45 kg) and disintegration time (2min and 2.6min) at a total tablet weight of 150 mg and 200 mg respectively.

3.3 FTIR:

Samples of Risperidone, neusilin, fujicalin, aerosil 200 as marketed products and liquidsolid formulations were subjected to FTIR spectroscopic analysis and their spectra are shown in Fig. 2. The IR spectrum of Risperidone (Fig. 2A) exhibits characteristic peaks at 1350 cm^{-1}(C–F functional group), 1747cm^{-1} (C=O group stretching vibration), 1614cm^{-1} (N-H functional group), 1645cm^{-1}(C=N). The peak at 3000 cm^{-1} indicates the presence of methyl group. Appearance of these peaks in the marketed product and liquisolid formulation indicate the absence of chemical interaction between the drug and excipients.

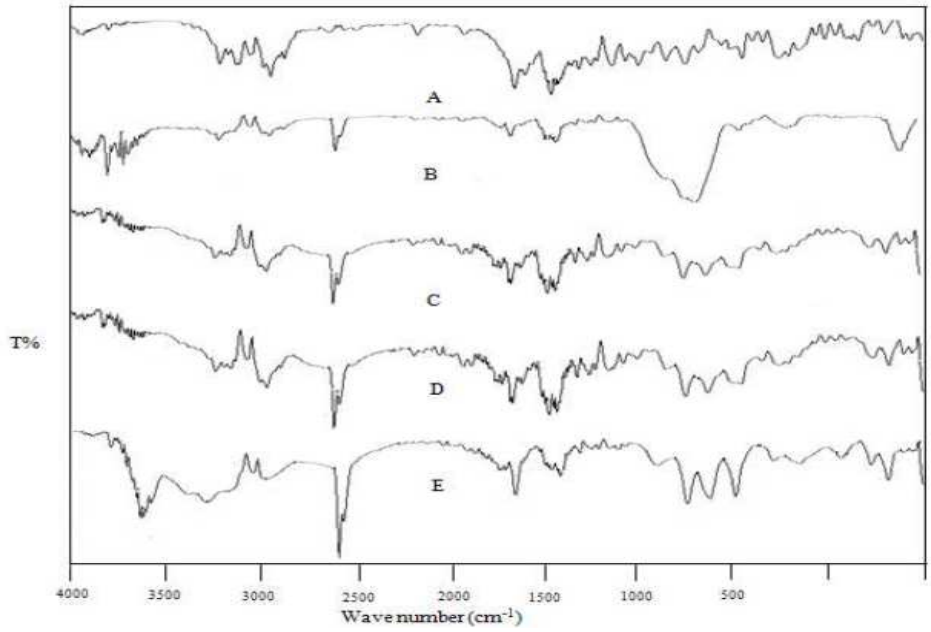

Fig 2: FTIR spectra for (a) pure drug (b) drug with aerosil 200 (c) drug with neusilin (d) drug with fujicalin (e) liquisolid tablet

3.4 DISSOLUTION STUDIES:

Dissolution studies for the liquisolid formulations (LSC-8N and LSC-8F), pure drug and marketed product (RISPERDAL-6 mg) were conducted in 0.1N HCl as noted in Section 2.6, and the percent drug release at different time intervals is shown in Fig. 3

The formulations LSC-N8 and LSC-F8 showed almost complete release in 45 min. The drug release from the marketed product and pure drug were limited to the extent of 67.89 and 60.45% respectively in 45 min. Thus, the *in-vitro* dissolution studies indicated the importance of liquisolid compacts to enhance the solubility and dissolution rates.

The release data obtained for the best formulations (LSC-N8 and LSC-F8) along with pure drug and marketed product were tabulated as a ready reference in the Table 6 and the data was plotted in the Fig 3.

Table 6: *In-vitro* dissolution data obtained for LSC-N8, pure drug, marketed product and LSC-F8

Time (min)	Percentage cumulative drug release* (AM ± SD)			
	LSC-N8	Marketed product	Pure drug	LSC-F8
0	0.00±0.000	0.00±0.000	0.00±0.000	0.00±0.000
5	13.01±0.041	8.22±0.055	6.21±0.002	13.27±0.062
10	25.63±0.065	16.54±0.021	13.34±0.036	28.55±0.039
15	40.11±0.014	28.93±0.063	21.28±0.085	41.79±0.077
20	52.24±0.066	39.64±0.055	35.79±0.069	53.21±0.005
25	70.09±0.037	47.86±0.001	41.12±0.042	67.33±0.063
30	81.57±0.028	51.41±0.069	43.60±0.063	82.60±0.041
35	92.46±0.091	60.73±0.046	50.01±0.085	89.32±0.098
40	96.97±0.004	65.67±0.098	59.83±0.066	93.84±0.077
45	99.93±0.063	67.89±0.075	60.45±0.031	97.08±0.031

**Each value is an average of 3 determinations ± S.D*

These studies illustrated that the drug release from the liquisolid compacts showed a marginal variations with the formulation, i.e., as the concentration of disintegrant (cross caramellose sodium) increased, an increase in drug release has been observed.

The pronounced effect of the carriers was observed on the dissolution profile. However, there is no much difference in enhancement of dissolution rates between the carriers used in the study i.e. both Neusilin and Fujicalin exhibited similar drug release pattern. Hence tensile strength, flow properties and load factor were considered for optimizing the carriers. From these results, Neusilin was proved to be a superior carrier than Fujicalin. Amongst all the formulations, the liquisolid compacts LSC-N8 formulation showed highest drug release i.e. 100% within 45 min. Hence it was selected as optimized formulation.

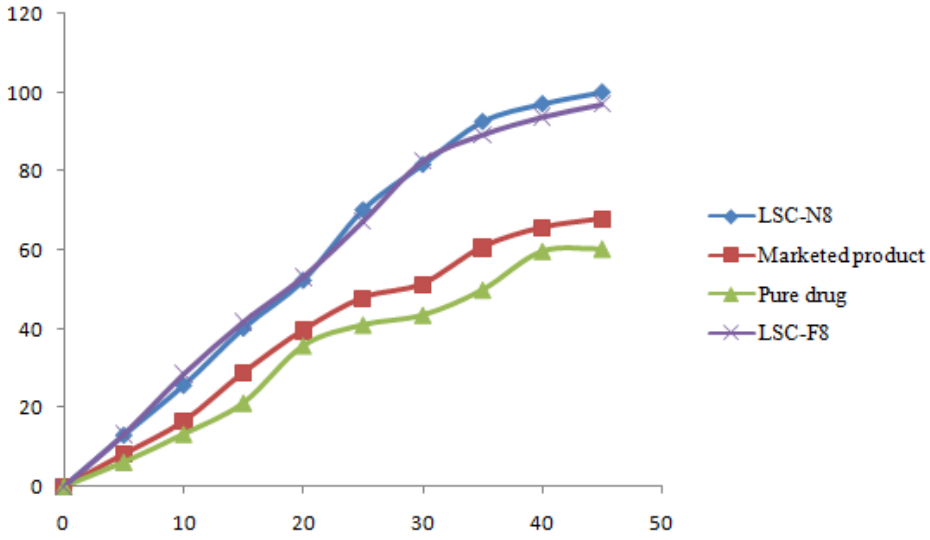

Fig 3: Comparative *in-vitro* dissolution profile of the optimized formulation LSC - N8, pure drug, marketed product and LSC-F8

CONCLUSION

Risperidone being a poorly water soluble drug can be made to provide a better treatment if drug is released effectively and this is achieved by formulating the drug as liquisolid compacts. A 2^3 factorial design was employed and developed 8 different formulations for each of neusilin and fujicalin as carrier materials. The PG was chosen as a best non-solvent based on the saturation solubility studies. Angle of slide studies was considered and selected a ratio of 20. The prepared liquisolid compacts were evaluated for various physicochemical studies and *in-vitro* release studies, which indicated the formulations shower improved drug release in comparison to pure drug and marketed product.

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