Research Article

Dissolution Enhancement of Quetiapine Fumarate by Liquisolid Compacts Technique

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Abstract:

The main objective of present investigation was to develop Liquisolid compacts (LSC) as novel solid oral dosage form of Quetiapine fumarate (QTPF) for its dissolution enhancement. QTPF is a BCS class – II drug, used in schizophrenia. The patents on LSC (US5968550 & US6423339B1) helped in method of preparation and its modification. For QTPF LSC, selection of non volatile liquid vehicle, carrier, coating material (adsorbent), super disintegrant were done. LSCs were developed by using Propylene Glycol (PG) and Capmul MCM30 as a combination of non volatile liquid vehicles, Avicel PH112 as a carrier, Aerosil 300 as an adsorbent (coating material) and Kyron T 314 as super disintegrant. The final batch was characterized by tests like flow property (angle of repose and carr's index), The prepared tablets were evaluated for drug content, weight variation, tablet hardness, friability, disintegration time, X Ray Diffraction (XRD) study, Fourier Transform Infrared Spectroscopy (FTIR) study, in vitro drug release study and dissolution efficiency study. Accelerated stability study was performed for 6 months (at 40^0C ± 2^0C temperature and 75% ± 5 Relative humidity (RH)). The results of all characterization tests were in acceptable range. Results of in vitro drug release study of QTPF final batch showed better improvement in dissolution rate as compared to marketed tablet (Seroquel 25) and pure drug. Stability study of the optimized batch for 6 months showed no significant change in drug content, physical appearance, hardness, % friability and in vitro drug release. This study concluded that LSC is proved as one of the suitable approach for developing stable solid oral dosage form of poorly water soluble drug like QTPF.

Keywords: Dissolution enhancement, LSC, QTPF, Schizophrenia.

INTRODUCTION

Dissolution is the core concept of any physical or chemical science including biopharmaceutical and pharmacokinetic considerations in therapy of any therapeutic agent. The dissolution behaviour of a drug is key determinant to its oral bioavailability being the rate-limiting step in absorption of drugs from the gastrointestinal tract. As a result, more than 40% of new candidates entering drug development pipeline fail because of non optimal biopharmaceutical properties. (Wong S.M. et al (2006)).

Over the years, various techniques have been employed to enhance the dissolution profile, the absorption efficiency and bioavailability of water insoluble drugs and/or liquid lipophilic medication. (Kapsi S G et al (2001)). Nowadays, many dissolution enhancement techniques can be used for solving this problem. (Gubbala L P et al. (2014)). The LSC (LSC) technique is the most promising and considered as commercially effective method for dissolution rate enhancement of poorly water soluble drugs. (Nokhodchi A et al (2005)).

As per the patents' review, it is known that LSC technique was first introduced by Spireas S and Bolton S M (1999) to incorporate water in soluble drugs into rapid release solid dosage forms. The principle of liquisolid system is to contain liquid medications (i.e., liquid drugs, drug solutions or suspensions) in powdered form and delivery of drug in a similar way to soft gelatin capsules containing liquids. The patents on LSC helped in method of preparation and its modification. LSC technique refers to the conversion of liquid medications into apparently dry, non-adherent, free flowing and compressible powder mixtures by blending the liquid medications with suitable excipients, which are generally termed as carriers and coating materials. (Spiridon Spireas (1998))

As per the flow mentioned in Fig.1, a liquid lipophilic drug can be converted into liquisolid system without being further modified. On the other hand, if a solid water-insoluble drug is formulated, it should be initially suspended in suitable non volatile solvent system to produce drug solution or drug suspension of desired concentration. (Spireas S et al. (1998)).

QTPF is a BCS class – II, second-generation 'atypical' antipsychotic agent for the treatment of schizophrenia and bipolar mania. QTPF, 2-[2- (4-dibenzo [b, f] [12, 13] thiazepin-1 1-yl-1-piperazinyl) ethoxy]-ethanol fumarate (2:1) (salt), is belonging to the class dibenzothiazepine derivate. It is extensively metabolized in the liver with sulfoxide metabolite and parent acid metabolite, by sulfoxidation and oxidation; both metabolites are pharmacologically inactive, leading to lower bioavailability (9%) (Potu A. R. et al. (2012)). The active pharmaceutical ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. (Banakar UV (1991)). Oral route is the most commonly used and preferred route for the delivery of drugs, although several factors like pH of gastro intestinal tract, residence time, and solubility can affect drug absorption or availability by this route. For hydrophobic drugs, the dissolution process acts as the rate-controlling step and, which determines the rate and degree of absorption. So, Bioavailability of poorly water-soluble drugs is limited by their solubility and/or dissolution rate. (Porter C. J et al. (2001)). So the objective of the present work was to formulate the LSC of QTPF to improve the dissolution rate which will further lead to increase in bioavailability of drug.

MATERIALS AND METHODS

Materials

QTPF (pure drug) was received as a gift sample from Intas Pharmaceuticals Ltd., Ahmedabad, India. PG, Tween 80 from Merck Specialities Pvt. Ltd., Mumbai, Polyethylene Glycol (PEG) 400, PEG 600 from Loba Chemie Pvt. Ltd., Vadodara, Glycerine from S. D. Fine Chem Ltd., Mumbai, Capmul MCM30 from Abitec, Janesville, WI, Capryol 90, Labrafil from Gattefosse, France, Lauroglycol, Avicel PH101 & PH102, from FMC Biopolymer, Ireland, Avicel PH112 from FMC Biopolymer, Belgium, Lactose Monohydrate (LM) Dicalcium Phosphate (DCP), Aerosil 200, Aerosil 300, Aeroperl 300 from Evonik Industries AG, Germany, Kyron T 314 from Corel Pharma Chem, Ahmedabad were obtained. All other reagents used were also of analytical grade.

Methods

Selection of liquid vehicle

Solubility study of QTPF was carried out in some non-volatile liquid vehicles (i.e. PEG 400, PEG 600, Glycerin, Tween 80, Labrafil, Capryol 90, Capmul MCM30, Lauroglycol and PG) and their blends (mixture of more than one non volatile liquid vehicles), Saturated solutions were prepared by adding excess drug in to the selected liquid vehicles and placed in the rotating stirrer cum incubator (080402, Nova) for 24h at 37^0C. Then after, the solutions were filtered through 0.45µm Millipore filter, diluted with methanol and analysed by UV- spectrophotometer (UV 1800 Shimadzu, Japan) at a wavelength of 291nm against blank sample. Each sample was analyzed thrice to calculate the solubility of QTPF. Same study was performed in to the blend of selected liquid vehicles' ratio. (Sirisolla J. (2015)).

Selection of carrier

Binding capacity is defined as the capacity of powder excipients to hold liquid without change in their flow properties. (Friedrich H. et al. (2006)). To one g of carrier material, liquid blend (50:50, PG: Capmul MCM30) was added in increment of 0.5ml and uniformly mixed. After each addition, Carr's index was measured. Various carrier materials like Avicel PH101, Avicel PH102, Avicel PH112, DCP and LM were used.

Selection of coating material (adsorbent)

To blend of carrier material and liquid, 100mg of coating material was added and uniformly mixed. Carr's index was measured. Various coating materials like Aerosil 200, Aerosil 300, Aeroperl 300 were used. (Friedrich H. et al. (2006))

Method of LSC Preparation

In fig.2, method of LSC preparation is shown. drug was mixed in blend of selected liquid vehicles. Then

after, carrier material was added till saturation of carrier in the mixture. Then, selected coating material was added until flowable mixture achieved. Lastly, Kyron T 314 was added as super disintegrant to improve the powder blend's porosity. (Kumar Nagabandi et al (2011))

Evaluation of LSC

Pre compression studies of LSC

Pre-compression studies may play a key role in dose variations, to get a uniform filling of tablet dies and acceptable flow properties are required for the proposed liquisolid powder systems.

Flow property

Flow properties were studied by Angle of repose and Carr's Index. (Aulton, M. E. (2013)) The fixed height cone method was used to determine the angle of repose in triplicate and the average value was calculated for each powder:

$$\theta=\frac{h}{r} \quad ...Eq.1$$

Where,

θ = perpendicular angle,

h = height of material and

r = radius of the material.

Carr's Index (Compressibility index) of the powder blend was determined by Carr's compressibility index. The formula for Carr's index is as below:

$$\text{Carr's Index } \frac{\text{Tapped Density-Bulk Density}}{\text{Tapped Density}} \times 100 ...Eq.2$$

Method of LSC tablet preparation

Compression was done using a rotary tablet punching machine under constant pressure by a direct compression procedure. The blend of powder mixture was placed in to the die and compressed under a sufficient compression force using a 10 mm diameter, flat punches to keep the hardness of the conventional tablet at 3 to 5kg/cm^2. Die filling, uniform compression and machine operation were undertaken using a standardized manual process for dimensional uniformity. (Kumar Nagabandi V et al. (2011))

Post compression studies for the LSC tablet

a) Drug content

Twenty tablets were weighed and powdered. An amount of powder (QTPF 28.5mg equivalent to Quetiapine 25mg) was dissolved in 100 ml of Methanol, filtered properly. Then it was diluted with suitable solvent and analyzed for drug content at 291 nm using UV-Visible spectrophotometer (UV 1800 Shimadzu, Japan). (Das A. K. et al. (2013))

b) Weight variation

Weight variation was measured by weighing 20 Tablets and average weight was found. Percentage weight variation of the individual tablet should fall within specified limits in terms of percentage deviation from the mean. (Vraníková B et. al. (2015))

c) Tablet Hardness

Hardness of liquisolid tablets (the force in Newton required to crush the prepared tablet) was evaluated using a hardness tester (Toshiba). Ten randomly selected tablets of each batch were tested in both directions (transversely and lengthwise); mean values and standard deviations were calculated. (Vraníková B et al. (2015))

d) Friability

The friability of the tablets was determined using friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber resolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. (Vraníková B et al. (2015)).

The friability is given by the formula:

$$\% \text{ Friability}=\frac{\text{Loss of mass}}{\text{Initial mass}} \times 100 ...Eq.3$$

e) Disintegration time

The disintegration test was performed at 37 ^{0}C ± 2 ^{0}C temperature in distilled water using six tablets from each formulation by disintegration test apparatus (ED2L, Electrolab). The tablets were considered completely disintegrated when no residue remained in the basket. The presented values were the means and SDs of six determinations. (Vraníková B et al. (2015))

Characterization studies for LSC tablet

a) XRD study

XRD patterns were studied using X-ray diffractometer (D2 Phaser, Bruker AXS Inc. Germany). Samples were exposed to 1.540˚A Cu radiation wavelength and analyzed over the 2y range of 2–801. XRD patterns were determined for QTPF pure drug, formulation with drug and placebo. (Fahmy R. H et al. (2008))

b) FTIR study

The IR spectra for QTPF pure drug, formulation with drug and without drug were recorded using an FTIR spectrophotometer [NICOLET – 6700, Thermo Scientific, US]. The samples were scanned over the

frequency range 4000–400 cm-1. The resultant spectra were compared for any spectral changes. (Gubbi S. R et. al. (2010))

c) In vitro drug release study

Dissolution studies were performed for tablets prepared using LSC using dissolution apparatus (TDT-08L, Electrolab), pure drug and marketed product (Seroquel® 25mg – Astra Zeneca). The USP paddle method and dissolution medium were used for all in vitro dissolution studies. The stirring rate was 50 rpm, 900ml 0.1 N HCl was used as dissolution medium and maintained at 37˚C at appropriate intervals (0, 10, 20, 30, 45, 60, 90min). The samples were taken, filtered through a 0.45 µm filter and analyzed at 291nm by UV–visible spectroscopy (UV 1800 Shimadzu, Japan). The mean value of three determinations was used to calculate the drug release from each formulation. For the comparison of dissolution data in dissolution media for each formulation, percentages of drug dissolved were calculated. (Online available at http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp) Similarity factor (f2) and difference factor (f1) were calculated as per the following equations. (Online available at http://www.fda.gov/cder/guidance .htm)

$$f2 = 50 \times \mathrm{Log}\{[(\frac{1}{n})\sum_{t=1}^{n}(Rt - Tt)^2]^{-0.5} \times 100 \quad \text{...Eq. 4}$$

$$f1 = \{[\sum_{t=1}^{n}(Rt - Tt|\}/\sum_{t=1}^{n} Rt]\} \times 100 \quad \text{...Eq. 5}$$

Where,

n is the number of time points,

R is the dissolution value of the reference at time t and T is the dissolution value of the test at time t.

d) Dissolution efficiency study

The dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time-t, is expressed as a percentage of the area of the release assay of the reference formulation and rectangle described by 100% dissolution in the same line. (Costa P. et al (2001))

The % dissolution efficiency was calculated as follows:

$$DE\ \% = \frac{\int_{t1}^{t2} y.dt}{y100 + (t2 - t1)} \times 100 \quad \text{...Eq.6}$$

Where,

y = time duration

y_{100} = time for 100% release

t_2 = Final time duration

t_1 = Initial time duration

f) Accelerated stability study

The Stability studies were performed as per ICH Q1A (R2) guideline. Sample (optimized formulation batch) was packed in aluminium strips and stored in stability chamber (Neutronics, India) at 40˚C 2 temperature & 75% 5 RH. Samples were withdrawn at time intervals of 1, 3 and 6 months and evaluated for physical appearance, drug content, hardness, % friability and *in vitro* dissolution. (Das A. K. et al (2013)).

RESULTS AND DISCUSSIONS

Selection of Non volatile liquid vehicle

Saturation Solubility Study was carried out to select suitable liquid vehicle for liquisolid system. The results of solubility studies of selected non volatile liquid vehicles described that drug's maximum solubility was observed in PG as shown in fig.3. Further in solubility, blends of vehicles were selected as given in Table 1. It showed that the blend of PG and Capmul MCM30 had more solubility of drug. Furthermore, the various ratios of the selected blend were utilized for the solubility studies and resulted maximum solubility of drug in 50:50 ratio of PG: Capmul MCM30 as shown in Table 2.

Selection of Carrier

Different carriers were studied for their binding capacity and flowability. As per the results of binding capacity mentioned in table 3, Avicel PH112 required very less amount of liquid blend for binding so maximum binding capacity was in it with good flowability. So Avicel PH112 was selected as carrier and used for further studies.

Selection of Coating material (Adsorbent)

As per the data shown in table 4, Aerosil 200, Aerosil 300, Aeroperl 300 were used as coating materials. From the results of flow property parameter like angle of repose and Carr's index, it was concluded that Aerosil 300 had better flowability than others so it was selected and used for further study.

Method of preparation of LSC tablets

For preparation of LSC, all the ingredients were used in specific quantities as mentioned in table 5.

Evaluation of LSC batches

Pre compression studies of the LSC

In pre compression studies, flow property tests like Angle of repose and Carr's Index were carried out. Angle of repose (θ) was found 32° ± 0.5 and Carr's index (%) was found 11.06 ± 0.02. These results showed good flow properties of prepared blend for tablet preparation.

Post compression studies for the LSC

Conventional tablets of QTPF were prepared by direct compression technique using PG: Capmul MCM30 (50:50 ratio) as a blend of liquid vehicles,

Avicel PH112 as carrier, Aerosil 300 as a coating material, Kyron T314 as disintegrating agent, Magnesium stearate as a binder. Prepared tablets of above said formulation were subjected to various evaluation tests such as drug content, weight variation, tablet hardness, friability, disintegration time. All the formulated tablets showed acceptable pharmacotechnical properties as compendia requirements of tablet shown in Table.6.

XRD study

Fig.4 shows the X-ray diffractogram of the pure drug and LSC optimized formulation. QTPF pure drug shows sharp peaks (highest intense peaks at 20° and 22° at 2θ) as compared to LSC (in which less sharp peaks at peaks 20° and 22° at 2θ drug) That shows that drug is partially converted into amorphous or solubilized form. The modification of crystallinity of the drug in optimized formulation may be due to the result of solubilisation by liquid vehicle which was absorbed into carrier material and adsorbed into coating material. The amorphization or solublization of QTPF may increase the dissolution rate.

FTIR study

FTIR spectroscopy was used to study the structural changes and possible interactions between pure drug and optimized formulation (as shown in Fig.5). The FTIR spectrum of QTPF pure drug showed its characteristic IR absorption peaks at 3741, 2872, 2315, 1963, 1734, 833 and 652 cm^{-1}. The characteristic peaks for optimized formulation were found at 3742, 2871, 2314, 1962, 1726, 828 and 657 cm^{-1}.These spectra observations indicated that there is no interaction between drug and excipients.

***In vitro* drug release study**

The dissolution profiles of the LSC tablets and marketed tablets of QTPF are shown in Fig.6. The percentage cumulative drug release (CDR) at different time intervals (0, 10, 20, 30, 45, 60, 90min) were calculated and total % CDR calculated. From the dissolution profiles, it can be concluded that LSC optimized formulation improved drug dissolution as compared to reference product and pure drug. It may be due to significantly increased surface area of the drug particles available for dissolution and amorphization through LSC technique. As shown in Fig.7, LSC showed prompt drug release (16.34%) compared to pure drug (9.24%) and reference product (15.24%). Similarity factor (f2) and difference factor (f1) were found 53 and 13 respectively for optimized LSC formulation with comparison of marketed product. Results indicated good similarity between formulated and marketed product.

Dissolution efficiency study

Further in comparison, 100 %DE was calculated from the area under each dissolution curve at time " ", measured using the trapezoidal rule, and as shown in Table 7, 8. They were expressed as percentage of the area of rectangle described by 100% dissolution at the same time which were also calculated. Regarding percentage DE, there was 1.66 time increment in %DE of optimized batch compared to conventional tablets.

$$\%DE_{\text{Optimized batch}} = \frac{1500 \times 100}{90 \times 100} = 16.66\%$$

$$\%DE_{\text{Reference product}} = \frac{1500 \times 100}{150 \times 100} = 10\%$$

$$\%DE = \frac{\text{DE Optimized batch}}{\text{DE Reference product}} = \frac{16.66}{10} = 1.66 \text{ times}$$

Dissolution efficiency of optimized batch and marketed preparation were found to be 16.66% and 10% respectively. So, optimized batch was found to be 1.66 times higher than marketed preparation in term of DE.

Stability study

In 6 months stability study, the final prepared formulation showed good results in parameters like physical appearance, %drug content, hardness, %friability, *in vitro* drug release. All parameters were checked periodically and found to be similar to the initial results as shown in Fig.7 and Table 9. There was not observed any remarkable change in any observed parameters' values for the period of 6 months.

CONCLUSION

From this research work, it can be concluded that LSC technique is a promising alternative for the formulation of water insoluble drug QTPF. Higher dissolution rate of drug from the formulation may give better bioavailability due to solubilisation of drug. Improved disintegration time may also contributed to enhancement in dissolution of drug in the formulation. By this study, it was also summarized that LSC can give stable solid oral dosage form of QTPF having better dissolution, which may enhance the bioavailibilty of the drug used in the treatment of schizophrenia.

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Table.1 Solubility study of liquid vehicles' blend (n=3, mean ± S.D.)

Sr. No.	Liquid Vehicle Blend (50:50)		Solubility (mg/ml)
	I	II	
1	PG	PEG400	55.00 ± 0.47
2	PG	Capmul MCM30	59.00 ± 1.54
3	PG	PEG600	35.00 ± 5.14
4	PG	Capryol-90	12.00 ± 1.56
5	PG	Lauroglycol	38.00 ± 2.92

Table.2 Solubility study of liquid vehicles' blend ratio (n=3, mean ± S.D.)

Sr. No.	Ratio of Liquid Vehicle Blend (PG : Capmul MCM30)	Solubility(mg/ml)
1	50:50	59.00 ± 3.45
2	60:40	39.00 ± 4.64
3	70:30	28.00 ± 5.12
4	80:20	32.00 ± 2.84
5	90:10	37.00 ± 3.42

Table 3: Binding capacity of carriers

Batch No.	Carrier	Binding capacity* (ml/g)	Angle of repose (θ)	Remarks from Angle of repose	Carr's Index	Remarks from Carr's Index
1	Avicel PH101	4.54	39.25	Fair	13.24	Good
2	Avicel PH102	2.72	38.12	Fair	11.16	Good
3	Avicel PH112	5.95	38.24	fair	14.62	Good
4	LM	3.16	40.16	Fair	15.64	Good
5	DCP	2.77	41.82	Passable	17.04	Fair

*ml of liquid^/g of Carrier
[^PG : Capmul MCM30 (50:50)]

Table 4: Selection of Coating material

Batch No.	Coating material	Angle of repose (θ)	Remarks from Angle of repose	Carr's Index (%)	Remarks from Carr's Index
1	Aerosil 200	34.26°	Good	16.69	Fair
2	Aerosil 300	32.04°	Good	13.11	Excellent
3	Aeroperl 300	35.16°	Fair	17.12	Fair

Table 5: Composition of final optimized batch

Functionality of Ingredient	Name of the Ingredient	Weight per tablet
Drug	Quetiapine Fumarate	28.5mg
Liquid Vehicle	PG: Capmul MCM30 (50:50)	0.7ml
Carrier	Avicel PH112	390mg
Coating Material	Aerosil 300	40mg
Disintegrant	Kyron T 314	3%
Binder	Magnesium Stearate	2%
Glidant and Lubricant	Talc	1%

Table 6: Evaluation tests of final batch of LSC Tablet

Sr. No.	Post compression Parameter	Result (n=3, mean ± S.D.)	Remark
1	%Drug content	100% ± 1.05	Passed
2	%Weight variation	<7.5%	Passed
3	Hardness (kg/cm^2)	3.5 ± 0.26	Passed
4	%Friability	0.214 ± 0.03	Passed
5	Disintegration time (min)	2.36	Passed

Table 7: Cumulative dy*dt of Optimized batch for DE

Time (min)	% Release of drug (Y %)	Cumulative dy*dt
0	0	0
15	16.34	245.1
30	32.54	488.1
45	62.58	938.7
60	89.33	1339.95
75	94.56	1418.4
90	100	1500

Table 8: Cumulative dy*dt of Reference Product for DE

Time (min)	% Release of drug (Y %)	Cumulative dy*dt
0	0	0
15	15.24	228.6
30	27.46	411.9
45	58.16	872.4
60	76.32	1144.8
75	82.36	1235.4
90	88.12	1321.8
105	91.28	1369.2
120	96.34	1445.1
135	98.36	1475.4
150	100	1500

Table: 9 Stability study of final batch for 6 months (n=3, mean ± S.D.)

Duration	Physical appearance	% Drug content	Hardness	%Friability
0 Month	Off white and fair	100.00 ± 0.04	3.5 ± 0.26	0.214 ± 0.03
1 Month	Off white and fair	100.00 ± 0.05	3.5 ± 0.30	0.223 ± 0.25
3 Months	Off white and fair	100.00 ± 0.18	3.3 ± 0.36	0.216 ± 0.34
6 Months	Off white and fair	100.00 ±0.23	3.4 ± 0.25	0.232 ± 0.28

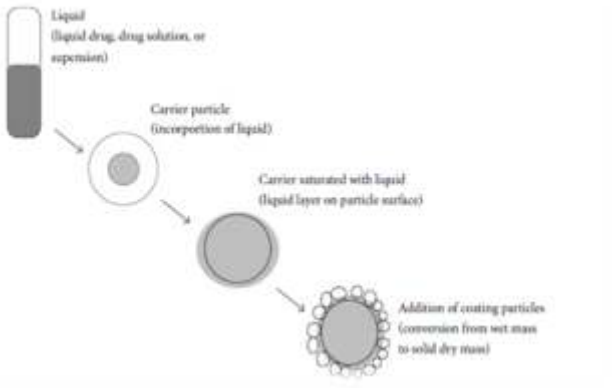
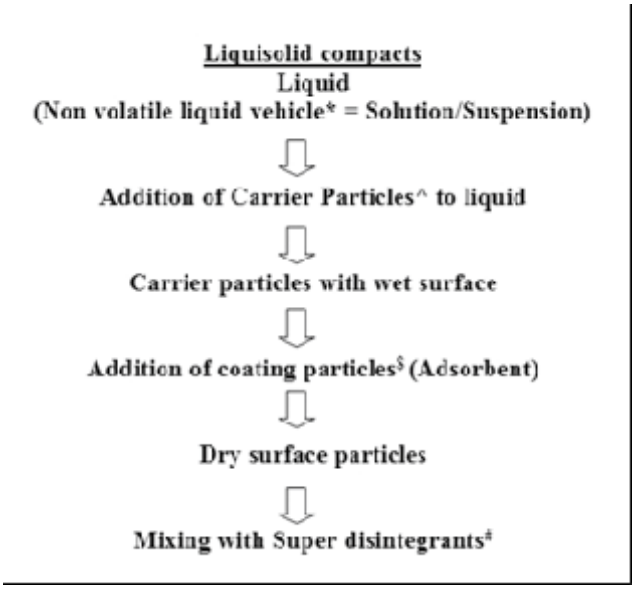


Fig.1: Concept of LSC' composition. (Spireas S et al. (1998))



***Non volatile liquid vehicle:** PEG400, PEG600, PG, Glycerine, Tween 80, Labrafil, Capryol-90, Lauroglycol, Capmul MCM30.

^Carrier particles: Avicel PH101, Avicel PH102, Avicel PH112, LM, DCP

$Coating material: Aerosil 200, Aerosil 300, Aeroperl 300

#Superdisintegrants: Kyron T 314

Fig.2 Method of preparation for LSC

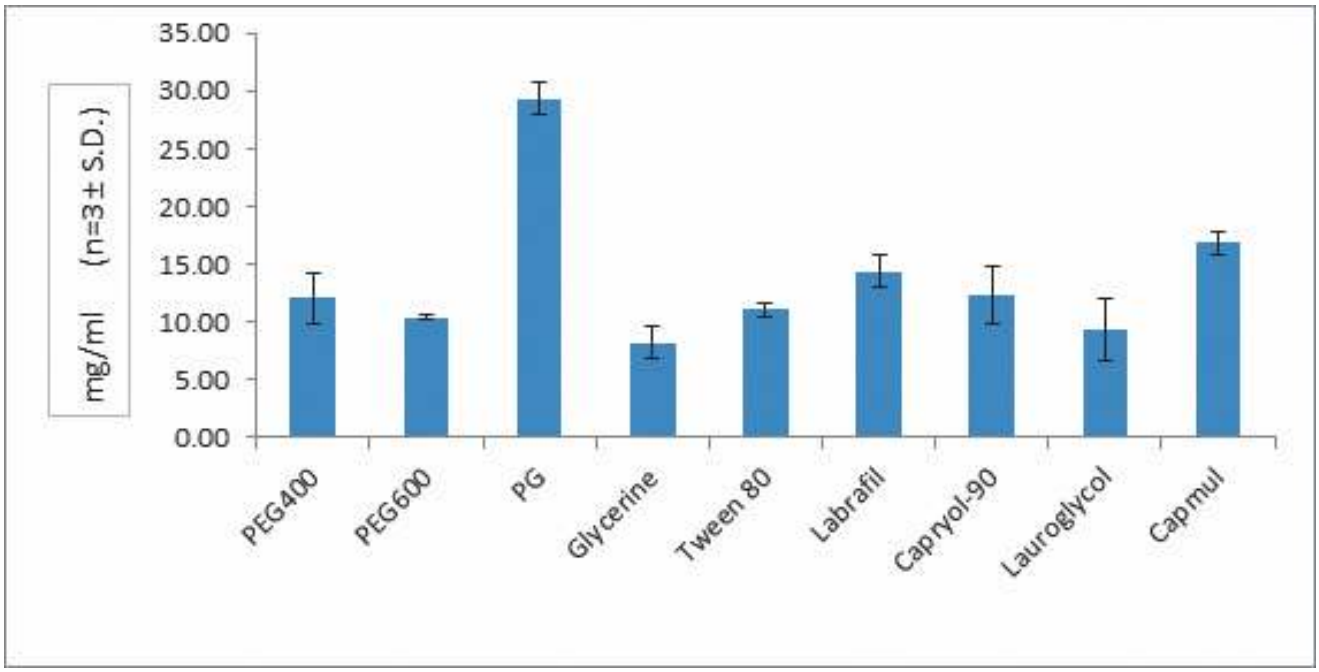


Fig.3: Solubility of liquid vehicles in QTPF (n=3, Mean ± S.D.)

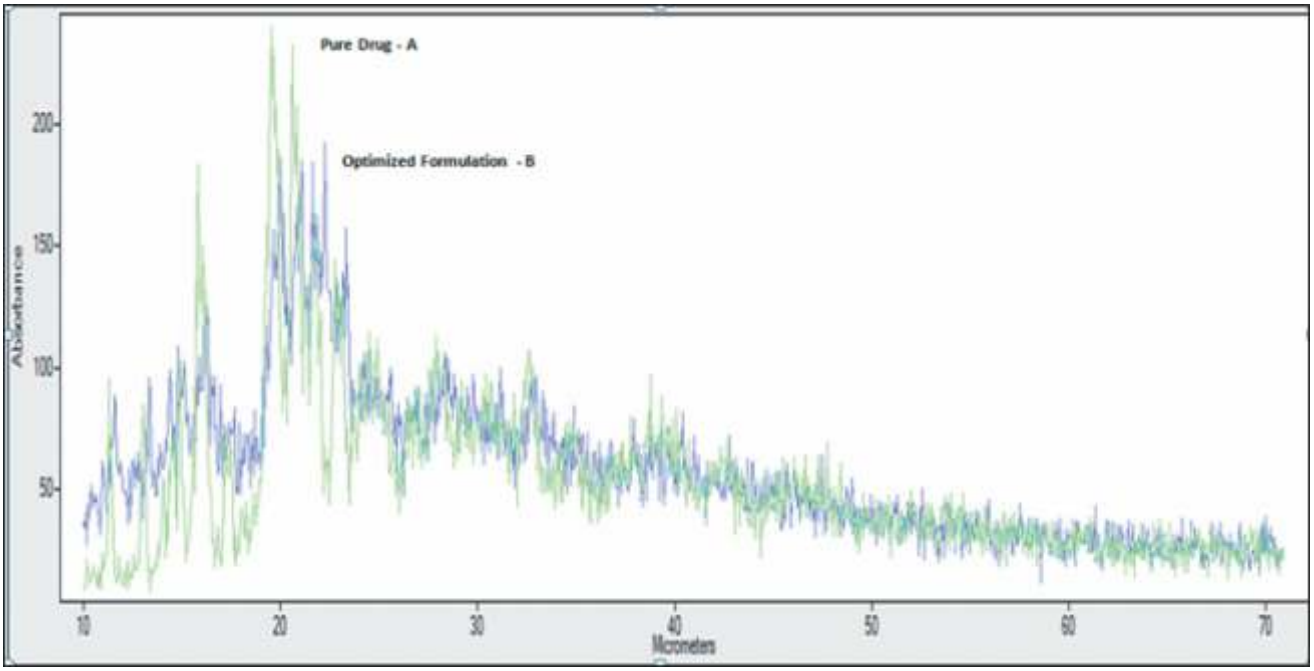


Fig.4 XRD of pure drug (A) and Optimized formulation (B)

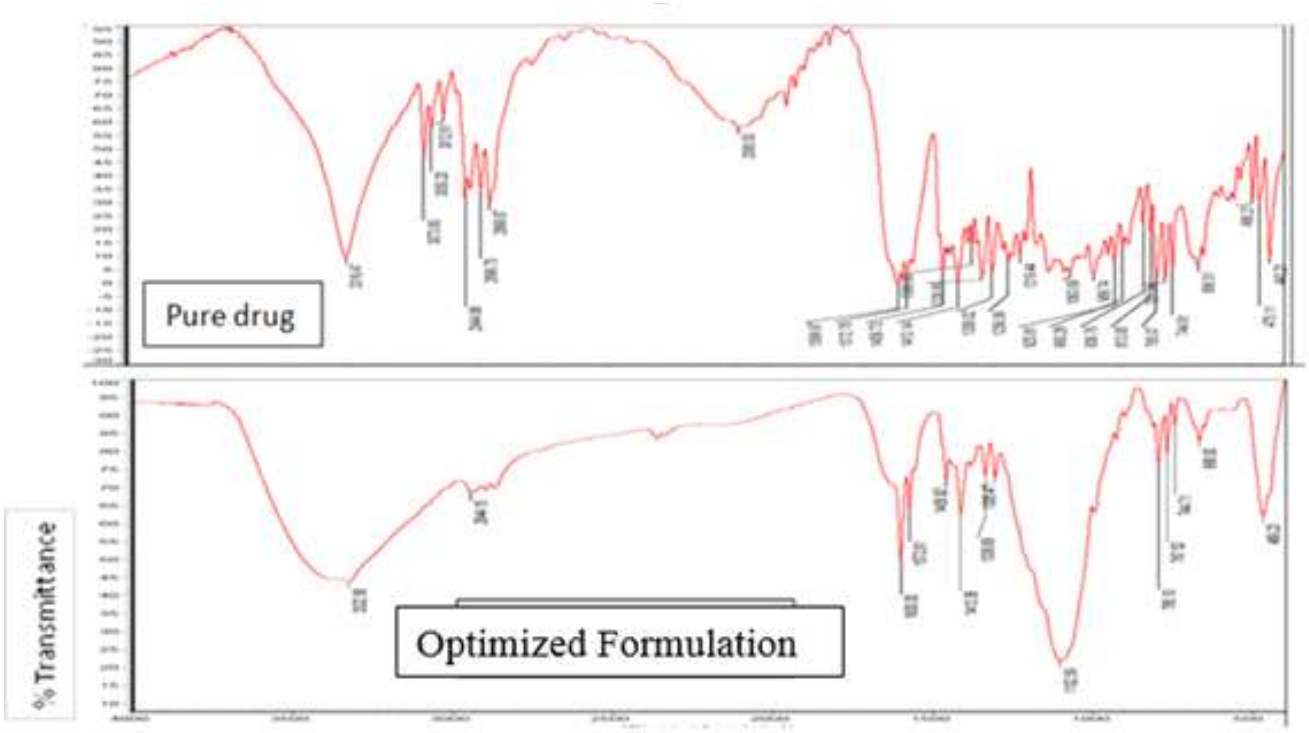


Fig.5: FTIR study comparison of Pure Drug (QTPF) and Optimized formulation

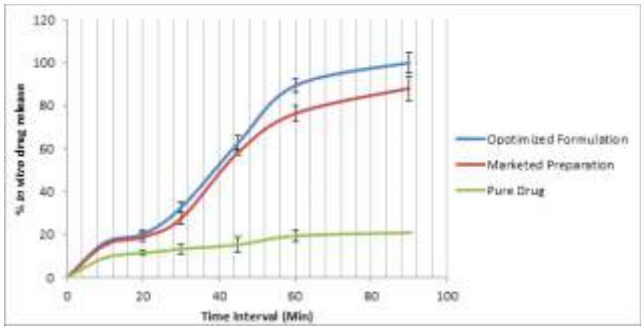


Fig.6 % In vitro drug release of pure drug, optimized formulation and Marketed preparation (n=3 ± S.D.)

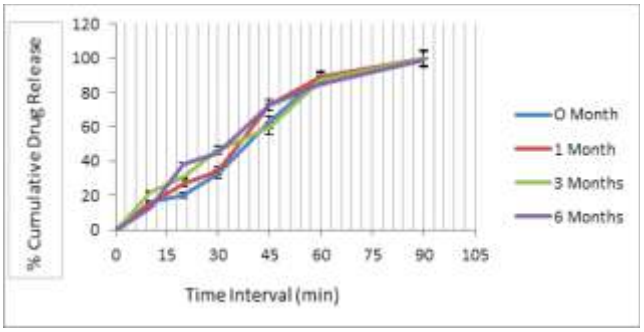


Fig.7 Drug dissolution of stability batches for 3months (n=3 ± S.D.)