ORIGINAL ARTICLE

Preparation and Assessment of Clomiphene Citrate Liquisolid Tablets for Solubility Enhancement

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Abstract

Introduction: Clomiphene citrate is a nonsteroidal ovulation inducer used in the treatment of infertility. This drug belongs to biopharmaceutical classification system Class-II often possesses challenges concerning solubility or poor dissolution, drug release, and thereby enhance the bioavailability. **Aim:** The aim of the study was to improve the solubility of the drug as well as to make the formulation more feasible liquisolid technique was adopted. **Materials and Methods:** Here, Avicel PH 102(Q) and Aerosil 200(q) in varying ratios ranging from 5, 10, 20, and 25 were employed as coating and carrier materials (R=Q/q), and their quantities incorporated into formulation were calculated based on the mathematical formulae developed by Spireas and final powder substrate developed was compressed into a tablet by direct compression method. Twelve formulations LS1 to LS12 were prepared and subjected to drug excipient interactions studies, pre-compression, and post-compression studies and compared with the marketed formulation. **Results and Discussion:** The Fourier transform infrared spectroscopy results showed no interaction between drug-excipients. Scanning electron microscopy and X-ray diffractometry analysis indicated that the clomiphene citrate is held within the powder substrate in a solubilized, almost molecularly dispersed state and in liquisolid as an amorphous powder with no signs of instability on storage. An optimized formulation was selected based on the i*n vitro*, drug release studies. LS2 formulation containing Avicel PH 102(Q):Aerosil 200(q) a ratio of 10:1 and drug concentration 10% exhibited the controlled and complete/highest drug release rate of 96.46% in 30 min in comparison with the marketed product. **Conclusion:** Thus, we propose that liquisolid technique can be chosen as the most economical and alternative approach to enhance the solubility of clomiphene citrate.

Key words: Aerosil 200, clomiphene citrate, liquisolid compacts, microcrystalline cellulose, super disintegrants

INTRODUCTION

Drastic innovations and research developments happening in the field of biotechnology and drug discovery revealing the potential of drug molecules[1] are the therapeutical solutions for many disease and disorders, but the bioavailability is the one question needs to be addressed equally because most of the drugs are highly lipophilic, bearing high molecular weight, and least aqueous solubility.[2] These drugs when administered can also result in dose variability among the individuals and also within the individuals resulting in poor absorption.[3] Thus, enhancement of bioavailability is the most approachable target. Usually, drugs belonging to biopharmaceutical classification system (BCS)-II as limited solubility and dissolution.[4] Therefore, several methods are being tried and found successful to improve the solubility such as solubilization, micronization, complexation with polymer, salt formation, use of pro-drug, the addition of surfactant, and solid dispersion; nevertheless, among, the technique of liquisolid compact would be

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most optimistic techniques[5] wherein the medicament is within the liquisolid compacts are available in the solution form but as a free-flowing nature in outward appearance. Thus, the availability of the drug in solution form can be advantageous for the better dissolution and absorption of a drug belonging to BCS Class II drugs.[6] Formulation of liquisolid compact enhances the flow ability and compressibility of the drug. Significant increase in wetting property due to the preparation of liquisolid compact and also increase in the area available for dissolution of drug improves their drug release and bioavailability.[7] Spireas and Sadu 1998 developed a formula that gives information on the number of powder excipients to be incorporated into the formulation.[8] This approach addressed simultaneously flowable (Φ-value) and compressible (Ψ-value) liquid retention potential introducing constants for each powder/liquid combination/ratio.[9] The mechanism involved in liquisolid technique can be explained as follows: Initially, the drug is dissolved in a nonpolar solvent and then incorporated into a carrier material such as cellulose. This carrier material has a porous surface and closely matted fibers on which both absorption and adsorption of the drug takes place. Here, absorption of liquid takes place in the internal structure until the excess liquid gets inside and gets completed wetted. Thereafter absorption onto the internal and external surfaces of the porous carrier particles occurs. Since the coating material is incorporated as a larger specific surface area the desired flow characteristic are obtained from a liquisolid system.

In liquisolid systems, the drug is already in a liquid vehicle, while at the same time, it is carried by the powder particles such as microcrystalline cellulose and silica. Thus, due to significantly increased wetting properties and surface area of drug available for dissolution, liquid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and consequently, improved oral bioavailability.[10] Numerous studies have been demonstrated that favor solubility of the insoluble drug by liquisolid technique incorporating the varying amounts of coating and carrier material.

Clomiphene citrate is a nonsteroidal drug, a selective receptor modulator indicated to treat female infertility due to anovulation. Clomiphene citrate belongs to BCS Class II drugs, a triphenyl stilbene derivative, orally-administered, with a half-life of 5–6 days, which possess poor bioavailability.

In the current study, clomiphene citrate has been chosen as a model drug for testing the efficacy of liquisolid compact compressed tablets formulation and to study its solubility thereafter.

MATERIALS AND METHODS

The following materials are used in this study: Clomiphene Citrate (Palam pharma, Gujarat), Avicel PH 102 (Balaji Chemicals, Gujarat), Aerosil 200 (Balaji Chemicals, Gujarat), Propylene glycol (Balaji Chemicals, Gujarat), Magnesium stearate (LobaChemie Private Ltd. Mumbai), and Carboxymethylcellulose (Marksans Pharma, Goa). All the chemicals of analytical grade were used for the study.

Studies for solubility of clomiphene citrate

The solvents such as propylene glycol and polyethylene glycol (PEG) 400 were used for the solubility of the drug. The shake flask method was used for the determination of solubility using an incubator shaker (Labon) for 48 h by maintaining the temperature of 25 ± 1°C. After this for a period of 12 h solutions were allowed to stand and then subjected to centrifugation at 3000 rpm and the supernatant was collected. The drug dissolved in the supernatant was analyzed spectrophotometrically (Shimadzu)[11] at 293 nm and the values were reported as mean along with standard deviation (SD). The results are reported in Table 1.

Mathematical approach for liquisolid compact formulation/calculation of liquid load factor[8,12]

Spireas and Sadu have developed constants for flowability and compressibility by a mathematical approach from which required amounts of carrier and coating materials required for the study were calculated.[5] The variables of clomiphene citrate liquisolid compact were investigated at different levels. (i) Non-volatile solvent used; propylene glycol, (ii) drug:nON-volatile solvent ratios 1:9, and (iii) carrier:coating ratio (R = 5, 10, 20 as well 25). From the literature, the values for flow ability index of Avicel PH 102 and Aerosil 200 with propylene glycol were 0.16 and 3.31, respectively, and values for compressibility index of Avicel PH 102 and Aerosil 200 with Propylene glycol was 0.224 and 0.560, respectively.

Table 1: Solubility of clomiphene citrate in various solvents

Media	Solubility (mg/ml)	Nonvolatile solvent	Solubility (mg/ml)
Distilled water (pH-7.0)	0.104±0.23*	Propylene glycol+Distilled Water	7.45±0.16
	0.104±0.23	PEG 400+Distilled Water	6.02±0.2
Phosphate buffer (pH-7.4)	0.174±0.03	Propylene glycol+Phosphate buffer	7.11±0.77
	0.174±0.03	PEG 400+Phosphate buffer	5.89±0.89

Mean±S.D (*n*=3), PEG: Polyethylene glycol

Preparation and evaluation of liquisolid compact[8,13]

The liquisolid compact of clomiphene citrate was formulated by a simple mixing method as per the formulae given in Table 2. Drug clomiphene citrate and propylene glycol a non–volatile solvent were heated to 80°C, as the drug completely gets in the solution, the calculated amount of MCC (Q) and Aerosil 200 (q) as carrier and coating material were incorporated into it, followed by mixing. Each formulation from LS1 to LS12 was formulated using varying amounts of the carrier to coating material ratios (R = Q/q, i.e., 5, 10, 20, and 25) given in Table 2.

The resultant mixture was blended with sod. carboxymethylcellulose for 30 s. The compact was dried in an oven at 40°C for 20 min to expel any retained moisture content. Finally, magnesium stearate was added. Also compact was prepared without the addition of solvent containing 25 mg of drug with excipients and coded as directly compressed tablet (DCT). DCT tablets were evaluated by pre-compression and post-compression parameters.

Evaluation of pre-compression parameters

All the prepared compacts from LS1-LS12 were initially checked for pre-compression parameters, which include Angle of a slide, bulk, and tap densities to calculate the Hausner's ratio and compressibility index.[14] The following observations are reported in Table 6. Later compacts of different formulation LS1-LS12 were compressed into the flat-faced DCT by a single punch tablet compression apparatus (Cadmach, Ahmedabad).

Evaluation of post-compression parameters

All compressed tablets were subjected to post-compression studies and the parameters checked were thickness (Vernier calipers), hardness (Monsanto tester, Pharmalab, Ahmedabad, India), friability (Roche friabilator, Pharmalab, Ahmedabad, India), weight variation test, disintegration time, and*in vitro* dissolution studies.

This test was done by randomly selecting ten tablets from each batch of liquisolid tablets prepared using different concentrations and thereby thickness of each tablet was measured with a help of a screw gauge that reads the value in micrometer (Digimatic micrometer, Mitutoyo, Japan) followed by calculating its mean ± SD.

For performing, weight variation test tablets were chosen from each batch, weighed using a digital balance (Shimadzu). The mean ± SD and relative SD were recorded and values are shown in Table 6.

Here Monsanto hardness tester (Pharmalab, Ahmedabad, India) was made use to check the hardness or crushing strength of each formulation. USP-type Roche friabilator was used to check the friability of a tablet. Initially, 20 tablets are weighed and subjected to the test and friabilator was set to revolve at a speed of 25 revolutions per min for 4 min. On completion of the stated period time, the tablets are dedusted and reweighed to check the percentage weight loss, and values are shown in Table 6. The percentage drug content in each batch having a different concentration of carrier:coating ratio was performed as follows: from each about batch randomly five tablets were weighed and powdered, a weight equivalent to 25 mg clomiphene citrate was made to dissolve with the solvent methanol with further dilution to upto 100 ml. Using a ultraviolet (UV)-visible spectrophotometer absorbance was determined at 293 nm and values are displayed in Table 6. The disintegration time of liquisolid tablet was checked using the USP tablet disintegration apparatus maintained at 37 ± 0.5°C, with media distilled water. The time taken for the disintegration of tablets is checked using a stopwatch. One tablet can be analyzed at a time to obtain an accurate value. The disintegration test is said to be complete when no

Table 2: Formulation design of clomiphene citrate liquisolid tablets

Formulation	Vehicle	Drug Conc. in vehicle (%w/v)	Carrier	Coating Material	R=Q/q	Loading Factor
LS 1	PG	10	MCC	Aerosil	5	0.67
LS 2	PG	10	MCC	Aerosil	10	0.41
LS 3	PG	10	MCC	Aerosil	20	0.28
LS 4	PG	10	MCC	Aerosil	25	0.26
LS 5	PG	20	MCC	Aerosil	5	0.67
LS 6	PG	20	MCC	Aerosil	10	0.41
LS 7	PG	20	MCC	Aerosil	20	0.28
LS 8	PG	20	MCC	Aerosil	25	0.26
LS 9	PG	30	MCC	Aerosil	5	0.64
LS 10	PG	30	MCC	Aerosil	10	0.41
LS 11	PG	30	MCC	Aerosil	20	0.28
LS 12	PG	30	MCC	Aerosil	25	0.26

palatable mass remains on the surface of the screen.[15] The results are displayed in Table 6.

USP type-II dissolution apparatus (Disso 2000, Lab Thane, India) was used to complete i*n vitro* dissolution studies. Media used for dissolution was distilled water to mimic the GI tract *in vivo* and the temperature was kept sustained at 37 ± 0.5°C. The sample was withdrawn at 5 min intervals for about 30 min. Aliquots were filtered using Whatman filter paper and diluted using distilled water and it was further analyzed for the presence of drug content using UV visible spectrophotometer at 293 nm. Soon after dissolution medium is replaced with fresh solvent to maintain sink condition. The percentage of drug release and cumulative percentage drug release were recorded and tabulated in Table 7. *In vitro* dissolution test of marketed tablets was carried out and results are tabulated in Table 8. Comparison of results of optimized tablet LS2 over-marketed product and DCT were carried out and the data were analyzed by a plotting graph of % drug release verse time.[8,16,17]

The optimized LS2 formulation was subjected to stability studies, samples were kept at 40 ± 20°C/75% ± 5% RH for 1 month.[18,19] After 30 days, tablets were examined for the post-compression studies, and results are displayed in Table 9.

RESULTS AND DISCUSSION

The solubility of clomiphene citrate was determined in various solvents such as propylene glycol, PEG 400.[20] Findings revealed that for clomiphene citrate (drug), propylene glycol acts as a good cosolvent for solubilizing and the same was used for further studies [Table 1].

The potential of liquisolid systems of clomiphene citrate to enhance the solubility of poorly soluble BCS Class-II drugs was explored. Clomiphene citrate liquisolid tablets each containing drug equivalent to 25 mg and Avicel PH 102, Aerosil 200 as carrier and coating materials were prepared by direct compression method. A total of 12 formulations were designed [Table 3], evaluated, and then compared with the marketed formulation. Initially, the pre-compression parameters are evaluated on the liquisolid compacts, followed by compression of these compacts into liquisolid tablets. These tablets are further subjected to post-compression studies.

Pre-compression studies

Pre-compression parameters check the flow properties of the compacts. These flow properties, in turn, influence the uniformity of the tablet weight and rate of drug release. The Bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio, and observations are given in Table 4. Bulk density and tapped density can be used to determine Carr's index and Hausner's ratio. From this study, it is evident that all the formulations (LS1–LS12) have satisfactory flow and compressibility properties and can be chosen for further studies. In comparison, among the pre-compression values determined of all the formulations, LS2 was found to possess the best granule characteristics, ensured good flow and compressibility properties; thereby LS2 formulation is depicted in Table 5 that was used for further works.

Drug excipient compatibility study

Drug excipient incompatibility studies were carried out by Fourier transform infrared spectroscopy (FTIR) studies. Spectra of both drugs and LS2 formulation were recorded in between wavenumber 3500 and 700 cm^{-1}. FTIR spectra of LS2 formulation show the main peaks such as C-H at 3150–3050 cm^{-1} (Str) and 900–690 cm^{-1} (Bending), C = C at 2250–2100 cm^{-1}, C-O (Ether) at 1300–1000 cm^{-1}, C = O (Carboxylic acid) at 1725–1700 cm^{-1}, O-H (Carboxylic acid) at 1300–1000 cm^{-1}, and C-Cl at 785–540 cm^{-1}. The different functional groups and peaks observed in IR spectra are shown in Figure 2a. After spectral comparison of clomiphene citrate pure drug in Figure 2a and LS2 formulation in Figure 2b.There were no new peaks formed or the disappearance of characteristic peaks. The FT-IR spectrum of standard drug clomiphene citrate and its physical mixture with polymers correspond to similar

Table 3: Formulation design of clomiphene citrate liquisolid compact

Ingredients (mg)	Drug: Solvent				Drug: Solvent				Drug: Solvent			
	LS1	LS2	LS3	LS4	LS5	LS6	LS7	LS8	LS9	LS10	LS11	LS12
Clomiphene citrate	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
PG (L_f)	225.00	225.00	225.00	225.00	100.00	100.00	100.00	100.0	58.00	58.00	58.00	58.00
(R=Q/q) (%)	5	10	20	25	5	10	20	25	5	10	20	25
MCC	373.00	609.00	892.00	961.00	186.00	304.00	446.00	480.0	123.0	202.0	296.0	312.0
Aerosil	74.00	60.90	44.00	38.00	37.00	30.00	22.00	19.00	24.00	20.00	14.00	12.00
CMC Na	20.00	27.00	35.00	37.47	10.00	13.00	17.00	18.00	6.00	9.00	11.00	12.00
Mg stearate	7.00	9.00	12.00	12.86	3.00	4.00	6.00	6.00	2.00	3.00	4.00	4.00

*In all formulations, the concentration of drug in liquid medication was 25 mg and additive was 5%, 10%, 20%, and 25%, and Lfis the liquid loading factor

Table 4: Pre-compression parameters of liquisolid compacts

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index	Hausner's ratio	Angle of repose (Θ)
LS1	0.315±0.0014	0.382±0.005	17.54±1.85	1.212±0.0221	24°±1.49
LS2	0.326±0.0056	0.365±0.004	10.68±1.42	1.120±0.049	23°±0.69
LS3	0.3350.003	0.415±0.003	19.28±0.01	1.239±0.001	26.49°±0.75
LS4	0.3450.0012	0.405±0.0012	14.81±0.15	1.174±0.002	26.98°±1.25
LS5	0.366±0.0047	0.435±0.0049	15.86±1.38	1.189±0.029	27.4°±0.04
LS6	0.365±0.003	0.412±0.009	11.41±0.01	1.129±0.001	24.24°±0.04
LS7	0.388±0.004	0.460±0.001	15.65±0.1	1.180±0.001	27.17°±0.96
LS8	0.414±0.001	0.480±0.003	13.75±0.17	1.159±0.001	26.34°±0.4
LS9	0.450±0.003	0.523±0.002	13.96±0.001	1.162±0.001	27.30°±1.23
LS10	0.355±0.04	0.398±0.001	10.80±0.17	1.121±0.0038	25.35°±1.23
LS11	0.380±0.001	0.434±0.15	12.44±0.01	1.142±0.004	29.34°±0.6
LS12	0.387±0.01	0.456±0.009	15.13±1.2	1.178±0.0034	28.33°±0.75
Compact of DR (Drug+R)	0.386±0.03	0.545±0.013	29.17±0.14	1.412±0.0021	38.38°±0.63

DR is (D [clomiphene citrate]+R [ratio of carrier and coating material]),*Mean±S.D

Table 5: Formulation design of clomiphene citrate (LS2) liquisolid compact

Ingredients	DCT (mg)
Clomiphene citrate	25.00
Microcrystalline cellulose	609.00
Aerosil	60.00
Sodium carboxyl methyl cellulose	27.00
Magnesium stearate	9.00
Unit weight	955.00

DCT: Directly compressed tablet

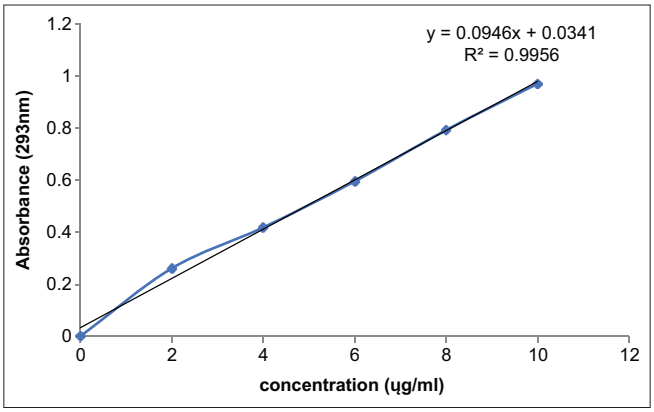


Figure 1: Calibration curve of clomiphene citrate

wavenumbers. This indicates an intact active ingredient with no intermolecular forces developed with the polymer.

Scanning electron microscopy (SEM)

The shape and surface morphology of pure drug and LS2 liquisolid compact were analyzed by SEM techniques. SEM photograph of pure clomiphene citrate and LS2 formulation is shown in Figure 3a and Figure 3b. Photograph of LS2 formulation was found to be a homogenous form. This indicates that the drug was solubilized in the liquisolid system and proved that even though the drug is in solid dosage form, it is held within the powder substrate as the solution, or in a solubilized form, almost in the molecularly dispersed state, which contributes to the enhanced solubility of the drug.

X-ray powder diffraction analysis

X-ray diffraction patterns of pure drug and liquisolid formulations (LS2) are shown in Figure 4a and b**.** The disappearance of high-intensity diffraction peak of clomiphene citrate in liquisolid compacts but the presence of sharp diffraction peak at (2Θ) angle of 22.5 belonging to Avicel PH 102 indicating that only Avicel PH 102 maintained its crystalline state showing that clomiphene citrate is entirely converted into an amorphous form or solubilized as powdered drug solution in liquisolid compact.

Post-compression studies

All the prepared liquisolid formulation was subjected to post compression studies that include thickness, hardness, friability, disintegration time, weight variation, and percentage deviation from the initial weight. The results of the studies are compiled in Table 6. Values reported in Table 6 are the mean values of three trials performed.

The thickness of LS2 liquisolid tablets was 4.81 ± 0.045 mm and friability were about 0.48% ± 0.004% maximum loss of weight after undergoing friability test was <1% which signifies that the tablet can cope up with possible pressures exerted during transportation and shipments. Studies

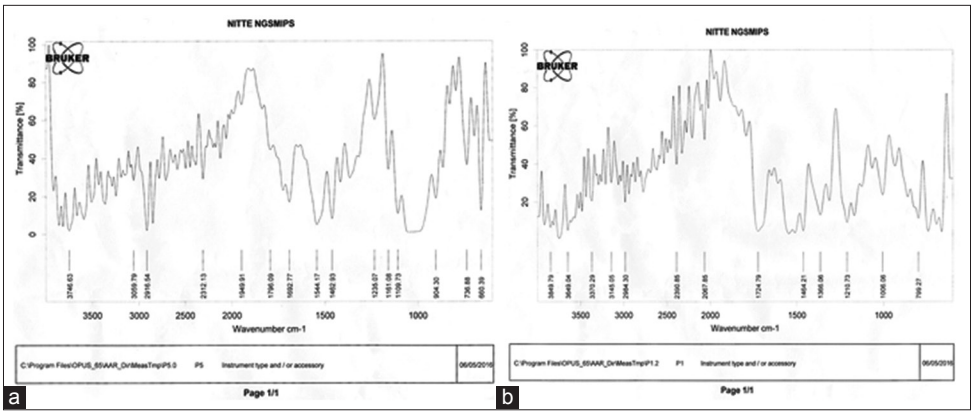


Figure 2: FTIR of clomiphene drug (a) and LS2 formulation (b)

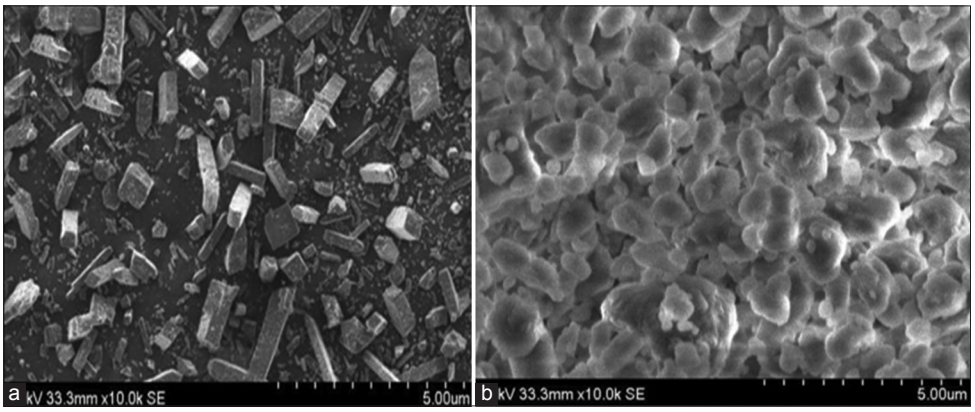


Figure 3: (a) Scanning electron microscopy (SEM) of clomiphene citrate, (b) SEM of liquisolid formulation

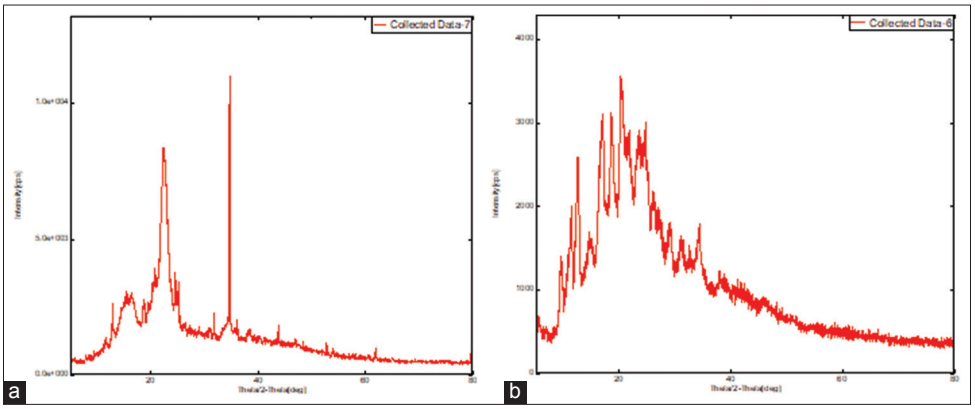


Figure 4: (a) X-ray diffractometry (XRD) of clomiphene citrate, (b) XRD of liquisolid formulation

reported colloidal silicon dioxide (Aerosil®), acts both as a glidant and lubricant and also helps inappreciably decreasing tablet friability by restoring the binding properties of the excipients.[21] The hardness of the LS2 liquisolid tablets was reported to be 5.78 ± 0.018 kg/cm^2 which met the criteria as displayed in the I.P between 5 kg/cm^2 and 6 kg/cm^2, the data reveal that the LS2 tablet is having good mechanical strength. Sufficient hardness of tablet may be due to the presence of hydrogen bond between the drug and the Avicel PH102 that contribute to strength and cohesiveness among the particles.[22] And the presence of Avicel in the formulation increases the hardness of the tablets. Higher R values represent a greater presence of carrier material which indicates the tablet's good hardness and attributes to the more uniform distribution of drugs either by adsorption or absorption into the carrier.[23] The weight variation of LS2 liquisolid tablets was 1.1 ± 0.0890 mg this shows that there was no much variation in weights. Disintegration time was found to be 55 ± 2.4 s which was <5 min. Disintegration occurs as a result of the rapid uptake of water, followed by rapid and enormous swelling, which is its primary mechanism of action was reported by Yen *et al*. in 1997.[24] The disintegration time is also reflected *in vitro* dissolution testing, which showed an increased drug release at initial time points where disintegration was faster. Avicel

Table 6: Results of thickness, hardness, friability, disintegration time, drug content, and weight variation of clomiphene citrate liquisolid tablets

Formulation code	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Disintegration time (s)	Weight variation (%)	Drug content (%)
LS1	4.02±0.044	5.9±0.081	0.65±0.012	50±1.9	1.6±0.538	97.26±0.1
LS2	4.81±0.045	5.78±0.018	0.48±0.004	55±2.4	1.1±0.089	99.57±0.1
LS3	5.21±0.032	5.34±0.081	0.61±0.004	63±0.4	2.0±0.499	97.26±0.3
LS4	5.5±0.040	5.1±0.0816	0.57±0.012	58±2.6	1.3±0.59	97.5±0.7
LS5	3.85±0.0926	4.9±0.052	0.58±0.012	48±3.0	1.7±0.58	96.8±0.5
LS6	4.25±0.016	4.72±0.04	0.51±0.008	53±1.7	1.2±0.22	96.3±0.4
LS7	4.75±0.016	4.56±0.049	0.46±0.009	60±2.0	1.9±0.62	98.5±0.9
LS8	5.03±0.01	3.97±0.05	0.48±0.012	62±2.8	2.1±0.72	97.7±0.3
LS9	3.5±0.03	6.3±0.049	0.39±0.012	43±1.4	2.2±0.4	98.5±0.1
LS10	3.74±0.06	6.45±0.053	0.42±0.09	45±1.2	1.8±0.24	96.1±0.2
LS11	4.11±0.32	6.39±0.004	0.41±0.001	51±0.4	1.4±0.23	99.3±0.3
LS12	4. 33±0.43	6.1±0.81	0.47±0.012	54±0.6	1.5±0.38	96.5±0.5
Compact of DR (Drug+R)	3.8±0.37	3.8±0.083	0.71±0.017	98±1.7	2.2±0.12	95.8±0.4

*Mean±S.D

102 used in the formulation could facilitate disintegration property by absorbing the moisture and cause the breaking of the tablets. The drug content of all the formulations (LS1-LS12) ranges from 96.3% to 99.3%. This suggested drug contents of all the formulations were uniform and contain a therapeutic dose of the active ingredients. Reports are shown in Table 6 and Figure 5.

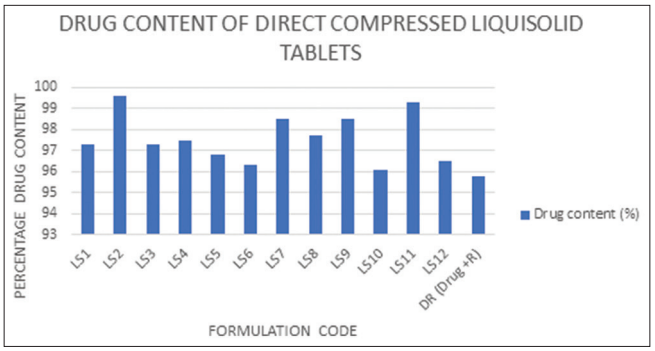
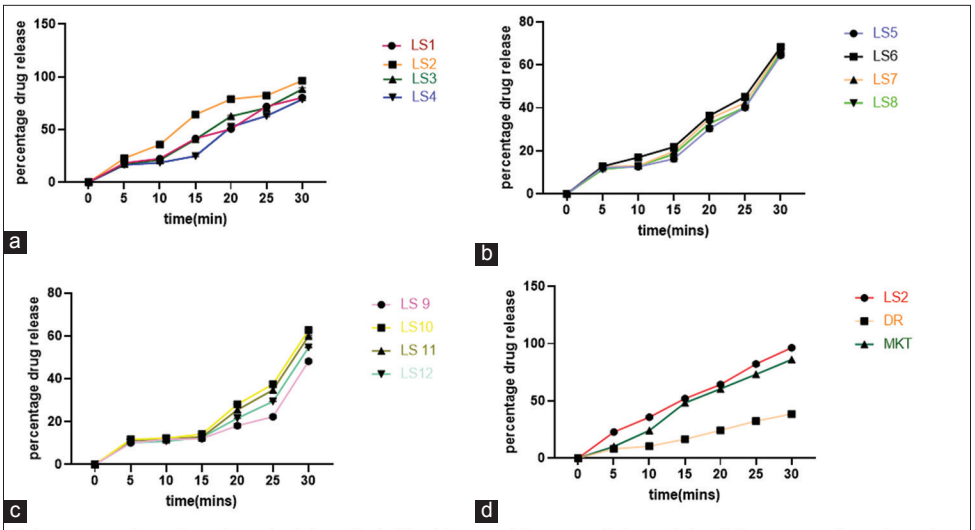


Figure 5: Drug content of formulated clomiphene citrate liquisolid tablets

In vitro drug release studies

Information regarding *in vitro* percentage drug release from the liquisolid tablet in 30 min intervals is given in Table 7.

As demonstrated in Figure 6a-c graph was plotted taking time on the Y-axis and % age drug release on the X-axis. Liquisolid formulations (LS9, LS10, LS11, and LS12) containing 30% drug solution exhibited drug release of 48.24%, 62.77%, 59.96%, and 54.73% in 30 min. Liquisolid formulations LS5, LS6, LS7, and LS8 containing 20% drug solution exhibited drug release of 64.48%, 68.35%, 67.42%, and 65.82% in 30 min. Liquisolid formulations LS1, LS2, LS3, and LS4 containing 10% drug solution exhibited drug release of 80.27%, 96.46, 88.27%, and 78.67% in 30 min. Finally, based on the work presented in this paper, an observation was done that formulation containing low drug concentration had better flow properties as well as drug release. A reduction in the ratio of carrier to coating from 20:1 to 10:1 showed an increase in the dissolution in the clomiphene citrate but when this ratio was further reduced to 5, a lower dissolution rate was observed.[25] This is because liquisolid compacts with lower R-values contain relatively smaller amounts of carrier powder (cellulose), and larger quantities of fine drug-loaded silica particles and the ratios of the amounts of their liquid medication per powder substrate are relatively higher. On the other hand, liquisolid compacts with higher R-values contain low ratios of the amounts of their liquid medication per powder substrate, high presence of carrier material, and low presence of coating material. This could be directly associated with enhanced wicking, disintegration, and deaggregation properties. The slight decrease in drug release with an increase in microcrystalline concentration may also be due to increased swelling of microcrystalline cellulose, which could have retarded drug release. The study published in an article by Dias *et al.* reported that improvement in the dissolution of lower drug batches in the studies may be due to the presence of an increased amount of carrier material. This could have attributed to the formation of pores that helps in the faster dissolution of the drug. From the above result, it is evident that LS2 formulation with the carrier:coating ratio 10:1 with a 10% drug solution exhibited a better dissolution profile. The rate



[A]-percentage drug release from clomiphene liquisolid tablets containing 10% of drug solution, [B]-percentage drug release from clomiphene liquisolid tablets containing 20% of drug solution, [C]-percentage drug release from clomiphene liquisolid tablets containing 30% of drug solution, [D]-comparison of drug release from LS2, DR and MKT

Figure 6: (a-d) *In vitro* drug release profile of clomiphene citrate liquisolid tablets containing 10% drug solution

Table 7: *In vitro* drug release profile of clomiphene citrate liquisolid tablets

Tablets containing 10% drug solution				
Time (min)	**LS1 (%)**	**LS2 (%)**	**LS3 (%)**	**LS4 (%)**
0	0	0	0	0
5	18.24±0.14*	22.83±0.8	17.33±0.7	16.48±1.02
10	22.42±0.23	35.78±1.2	21.18±0.8	18.52±1.09
15	41.54±0.01	64.34±1.2	40.81±0.8	24.89±0.8
20	50.52±0.42	78.90±1.3	62.70±0.8	52.59±1.11
25	71.98±0.61	82.29±1.5	70.61±0.8	62.95±0.8
Tablets containing 20% drug solution				
Time (min)	**LS5 (%)**	**LS6 (%)**	**LS7 (%)**	**LS8 (%)**
0	0	0	0	0
5	12.18±1.06	12.85±1.18	12.73±1.04	11.41±0.9
10	12.64±0.9	16.99±0.9	13.12±1.01	13.05±1.05
15	16.32±1.3	21.80±0.9	19.75±1.2	18.53±1.2
20	30.38±1.3	36.44±1.3	34.96±0.8	32.76±1.2
25	40.16±1.1	45.21±0.9	42.36±1.1	40.25±0.3
30	64.48±1.01	68.35±0.9	67.42±0.4	65.82±0.4
Tablets containing 30% drug solution				
Time (min)	**LS9 (%)**	**LS10 (%)**	**LS11 (%)**	**LS12 (%)**
0	0	0	0	0
5	10.12±1.0	11.76±0.05	11.07±1.04	10.23±0.28
10	11.73±1.12	12.29±1.34	11.97±1.01	10.87±1.04
15	12.09±1.12	14.19±0.1	12.82±1.2	12.72±1.12
20	18.16±1.01	28.13±0.08	25.52±1.2	21.60±0.04
25	22.31±0.74	37.52±0.9	34.83±1.1	29.46±0.09
30	48.24±0.9	62.77±0.43	59.96±0.4	54.73±0.16

*Mean±S.D

Table 8: *In vitro* dissolution profile of LS2, DR, and conventional clomiphene citrate tablet

Time (min)	**% Cumulative drug release**		
	LS_2	**DR (Drug+R)**	**Conventional tablet**
5	22.83±0.8*	08.23±0.1	10.15
10	35.78±1.2	10.42±0.9	24.23
15	52.02±1.2	16.50±1.2	48.32
20	64.34±1.3	24.27±1.4	60.55
25	82.29±1.5	32.45±0.5	73.22
30	96.46±0.9	38.56±0.6	86.18

*Mean±S.D

of dissolution when the process is diffusion-controlled can be well explained using the "Noyes and Whitney" equation.

$$DR = (D/h)\ A\ (Cs - C)$$

Here, D is the diffusion coefficient, A is the surface area, Cs is the concentration of drug in the diffusion layer/stagnant layer, C is the concentration of drug in the bulk of the solution, and h is the thickness of the diffusion layer.

According to Noyes and Whitney, the rate of drug dissolution is directly proportional not only to the concentration gradient (Cs-C) of the drug in the stagnant layer but also to its surface area (A) available for dissolution. Moreover, since all dissolution tests for both clomiphene citrate preparations were carried out at a constant rotational paddle speed (50 rpm) and in identical dissolving media, it is assumed that the thickness (h) of the stagnant diffusion layer and the diffusion coefficient (D) of the drug molecules transported through it remain almost identical under each set of dissolution conditions. Furthermore, the above findings tend to support

Table 9: Results of hardness test, friability, disintegration time, and % drug content of selected formulation (LS2) after accelerated stability study

Formulation code	Hardness (kg/cm²)		Friability (%)		Disintegration time (s)		% Drug content	
	Before charging	After 30 days of charging	Before charging	After 30 days of charging	Before charging	After 30 days of charging	Before charging	After 30 days of charging
LS2	5.78	4.9	0.52	0.35	35	39	96.57	95.3

Table 10: *In vitro* dissolution study of LS2 after accelerated stability study

Formulation code	Time (min)	Percentage drug release	Percentage drug release
		Before charging	After 30 days of charging
LS2	5	34.5	32.33
	10	72.08	70.8
	15	82.2	80.4
	20	86.81	82.32
	25	88.4	82.65
	30	98.1	96.33

the assumption that the drug remains, probably, in solution within the powder substrate of the liquisolid compact, thereby improving its dissolution properties. This carrier material can absorb the moisture and helps in converting it into an amorphous or solubilized form which, in turn, enhances the surface area. Therefore, the significantly increased surface area of the molecularly dispersed clomiphene citrate liquisolid compacts may be principally responsible for their higher observed dissolution rates. The consistent and higher dissolution rate displayed by liquisolid compacts will enable the improvement of the absorption of the drug from the GI tract and may also imply enhanced oral bioavailability.

Comparison of dissolution profile of LS2 over conventional tablet and DCT

Comparative study of *in vitro* dissolution rate of optimized tablet LS2 over DCT and conventional clomiphene citrate tablet was performed with distilled water as a medium [Table 8 and Figure 6d]. Optimized LS2 formulation as well-conventional tablet showed more than 50% drug release in 30 min. When compared LS2 formulation showed an excellent release of 96.46% in 30 min, whereas conventional tablet showed 86.18% at 30 min containing 25 mg of clomiphene citrate.

Stability studies

Final optimized formulation LS2, when subjected to accelerated stability studies for 1 month at 40 ± 2°C/75 ± 5% RH for 1 month, proved that there was no change in physical appearance and color. Post-compression studies focusing on *in vitro* drug release were carried out after subjecting optimized formulation to stability studies [Table 10 and Figure 6d], the results show that 96.33% of drug release at the end of 30 min indicating no significant changes in dissolution profile of the formulation after subjecting to stability studies. This concludes that liquisolid compacts a superior dissolution rate formulation than the conventional tablets. Propylene glycol decreases the interfacial tension between the dissolution medium and surface of the drug particles and thereby increases the wetting of the drug particles. Hence, the enhanced dissolution of optimized formulation might be due to the drug already present in a solubilized state. The higher dissolution rate displayed by the liquisolid tablets may also enhance the bioavailability of clomiphene citrate.

Limitations

During the process of liquisolid compacts punching into the tablet, there are the chances of liquid drug squeezing out of the liquisolid tablet resulting in tablets of unsatisfactory hardness hence resulting in batch-to-batch variations.

CONCLUSION

It can be concluded that the dissolution rate of clomiphene citrate, a poorly soluble drug could be enhanced by liquisolid technique. The liquisolid technique can be a promising alternative for the formulation of water-insoluble BCS Class II drugs. Thus, higher dissolution rate displayed by the liquisolid tablets could enhance the bioavailability of these drugs. This may, in turn, decrease the dose and associated side effects of these drugs. But further to check its efficacy *in vivo* clinical trials must be performed on the developed liquisolid formulation**.**

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