RESEARCH PAPER

Solubility and Dissolution enhancement of poorly water-Soluble Drugs Using Different Techniques of Liquisolid Compact System

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ABSTRACT
Poor water solubility and dissolution is one of major problem with any pharmaceutical formulation.Liquisolid compact is an approach of solubility enhancement and dissolution of drug. In this technique, Carrier and coating material is used to transform drug, drug solution or drug suspension into a volatile solvent into free flowing and compressible powder. Different formulation parameters, including the type of non-volatile solvent, carrier-to-coating material ratio, and drug concentration, play a crucial role in optimizing the system. This technology efficiently works on BCS class II & IV to solubility of the drugs for oral administration. Duloxetine Hydrochloride drug used is a drug which primarily targets major depressive disorder (MDD), generalized anxiety disorder. Aerosil200 & AvicelPH 102(MCC) is used as Coating Material & carrier material for this technique. The liquisolid compact
system offers a simple, cost-effective, and efficient method for improving the dissolution profile of hydrophobic drugs, making it a promising technique for oral drug delivery. Overall, this study highlights the potential of liquisolid systems as a versatile strategy to overcome solubility limitations and improve drug performance.

KEY WORDS: Liquisolid compact,carrier material,coating material,solubility, duloxetine hydrochloride
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1. INTRODUCTION OF DRUG DELIVERY SYSTEM [1]

Solubility of drug is one of the important parameters for bioavailability of drug. In recent years, approximately70%ofnewdrugscandidateand40%ofmar ketednew drugs in oral immediate release dosage form exhibits low aqueous solubility. Mainly oral route is preferred for administration of the drugs because of patient compliance, convenience and low-cost factor. When oral route for administration of the drug is chosen then that drug should be sufficiently dissolved in gastric fluids for its proper absorption.

If the drugs have less solubility in the gastric fluids, then it will be less available for its absorption and due to this its bioavailability will be less. Thus, one of the greatest challenges the pharmaceutical industries face today is the application of technological strategies towards improving the dissolution performance of drugs, producing formulations with adequate bioavailability and therapeutic effectiveness. Several methods are studied for increasing dissolution performance and bioavailability including micronization, Nanonisation, complexation with cyclodextrins, solid dispersion, self-emulsifying system, liquisolid systems, etc.

- **Various methods used for enhancing solubility and thus bioavailability of drug are: [2, 3]**

1. **Micro nization:** This process involves reducing the size of the drug particles to 1 to 10 microns commonly by spray drying or by using air attrition methods (fluid energy or jet mill). The process is also called micro milling. *e.g.* micro nization of griseofulvin.
2. **Nanonization:** It is the process in which drug powder is converted into nanocrystals of sizes 200-600nm. *e.g.* amphotericin B
3. **Use of surfactants: Surfactants** are very useful as absorption enhancers and enhance both dissolution rate as well as permeability of drug. They enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into solid drug particles.
4. **Use of salt forms: Salts** have improved solubility and dissolution as compared to the original drug. Alkali metal salts of acidic drugs like penicillin and strong acid salts of basic drugs like atropine are more water soluble than parent drugs.
5. **Supercritical fluid recrystallization:** Supercritical fluids (e.g.carbondioxide) are the fluids whose temperature and pressure are greater than their critical temperature (Tc) and critical pressure (Tp), allow in GIT to assume properties of both liquid and gas. At near critical temperatures, SCFs are highly compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that determines its solvent power. Once drug particles are solubilized in SCFs, they may be greatly recrystallized at greatly reduced particle sizes.
6. **Solid dispersion: These** are generally prepared by

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the solvent or co precipitation method whereby both the guest solute and carrier solvent are dissolved in common volatile solvent systems such as alcohol. The liquid solvent is removed by evaporation under reduced pressure or by freeze drying, which results in amorphous precipitation of guests in a crystalline carrier.

7. **Complex with cyclodextrins:**The beta and gamma cyclodextrins and their several derivatives have unique abilityto form molecular inclusion complexes with hydrophobicdrugs havingpooraqueous solubility. e.g.thiazide diuretics, barbiturates, benzodiazepines and number of NSAIDs.

8. **Use of Amorphous, Anhydrates, Solvates and Metastable Polymorphs:** Depending upon internal structure of solid drugs, selection of proper form of drug is with greater solubility is important. In general, amorphous are more soluble than metastable polymorphs, anhydrates are more soluble than hydrates and solvates are more soluble than non-solvates.

- **Liquisolid technique:**

A liquisolid system refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents, into dry, non-adherent, free flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials.

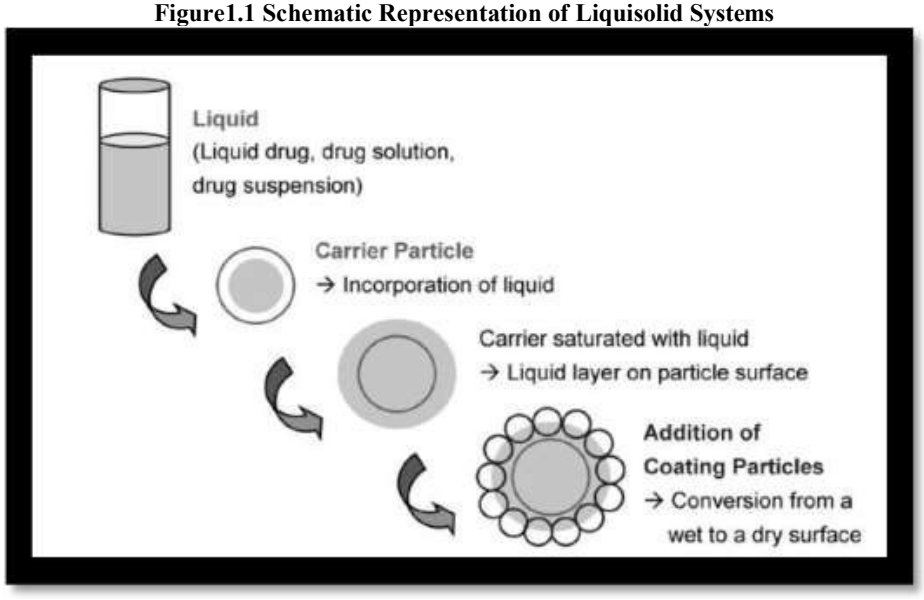
- **Need of liquisolid technique:**

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance, and low medicine production costs. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in gastric fluids. Thus, one of the major challenges to drug development today are poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. The dissolution rate of these drugs can be improved by decreasing particle size, decreasing crystallinity, and/or increasing the surface area. Several studies have been carried out to increase the dissolution rate of drugs by decreasing the particle size, by creating nanoparticles and microparticles. However, fine drug particles have a high tendency to agglomerate due to Vander Waals attraction or hydrophobicity, which both result in a decrease in surface area over time. Another way of increasing the dissolution rate is to adsorption the drug onto a high-surface area carrier. In this technique, the drug is dissolved in an organic solvent followed by soaking of the solution by a high surface area carrier such as silica. Here, agglomeration of the drug particles is prevented due to the binding of drug to the carrier. However, due to the presence of residual solvents in drug formulation, it is disadvantageous to use toxic solvents. To overcome the problem, the technique of 'liquisolid compacts' is a new and promising approach towards dissolution enhancement.

- **Concept of liquisolid technique:**

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; *i.e.* the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid on to the internal and external surfaces of the porous carrier particles occur. The coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics.

Figure1.1 Schematic Representation of Liquisolid Systems



• **Mechanism of enhancement of solubility:** [5]
The wettability of the compacts in the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Non-volatile solvent present in the liquisolid system facilitates wetting of drugparticlesbydecreasinginterfacialtensionbetweendis solutionmediumandtablet surface. Thus, due to substantial increase in wettability and effective surface area for dissolution, liquisolid compacts may be expected to reveal enhanced release profiles of water-insoluble drugs. Since dissolution of a non-polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates. However, the drug release profile entirely depends on the characteristics of drug, carrier, and vehicle used. Thus, by altering these variables, liquisolid techniques can be used for enhancing or regarding drug release.

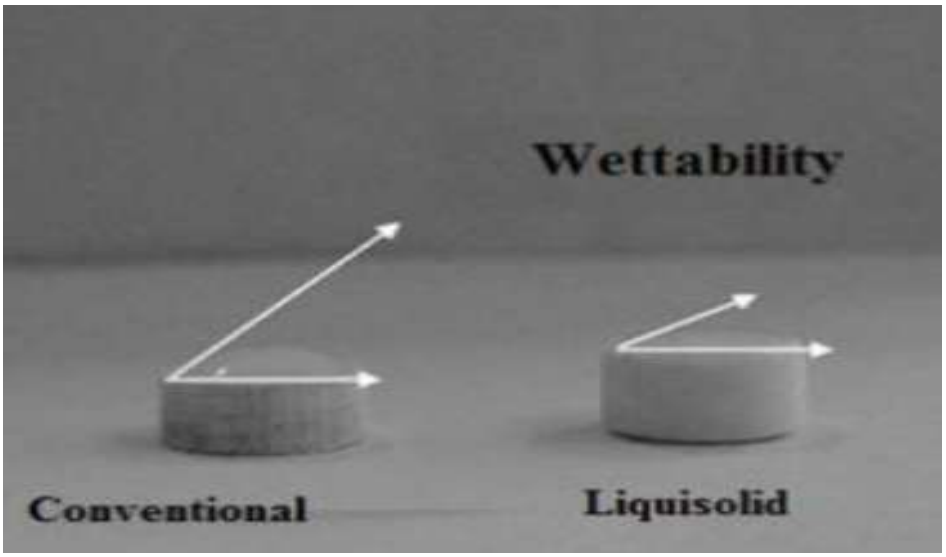


Figure1.2 Comparison of Wett ability of Conventional and Liquisolid Tablets

• **Merits of liquisolid techniques:** [6]
- Number of water-insoluble solid drug can be formulated into liquisolid systems.
- Can be applied to formulate liquid medication such as oily liquid drugs.
- Better availability of an orally administered water insoluble drug.
- Lower production cost than that of soft gelatin capsules.
- Production of liquisolid system is similar to that of conventional tablets.
- Viability of industrial production.
- Can be used for formulation of liquid oily drugs.
- Exhibits enhanced in-vitro drug release as compared to commercial counterparts, including soft gelatin capsule preparations.
- Can be used in controlled drug delivery.
- Optimized sustained release, liquisolid tablets or capsules of water in soluble drugs demonstrate constant dissolution rates (zero order release).
- Drug can be molecularly dispersed in the formulation.

• **Demeritsofliquisolidtechniques:**[6]
- Formulation of high dose lipophilic drugs the liquisolid tablet is one of the limitations of this technique.

• To achieve acceptable flowability and compatibility for liquisolid powder formulation, high levels of carrier material and coating materials should be added. This will increase the weight of tablets to above one gram which makes it difficult to swallow.

2. LITERATURE REVIEW OF DULOXETINE HYDROCHLORIDE

• **Sudipta D et al** [7]developed enteric coated tablets of Duloxetine HCl. HP-55 (Hypromellose phthalate) used for enteric coating. Thus, three formulations were prepared and all of them had the same amount of ingredients but only difference in percentage of coating applied. In vitro evaluation was carried out by using U.P.S. dissolution testing apparatus. Successful formulation was found in a good release profile in 45

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min. One commercial tablet was compared with this formulated tablet.

- **Raja S et al [8]** formulated as table Duloxetine HCl delayed release pellets with the aid of non-ionic protective layer between drug layer and enteric layer. Duloxetine HCl is highly unstable at acidic environment. The Preformulating study reveals, Duloxetine HCl is incompatible with enteric polymers, due to the presence of free acid in the enteric polymer. Duloxetine HCl is also unstable at alkaline PH. Hence, a nonionic polymer is selected in barrier coating. Duloxetine hydrochloride enteric coated pellets were formulated using fluidized bed processes with different levels of barrier coating. Three separate layers, the drug layer, the barrier layer and the enteric layer, were coated on to the inert core pellets and sugar spheres. The enteric coated pellets were top coated using film coating material and encapsulated in a hard gelatin capsule shell.

- **Zakir H et al [9]**developed a delayed release pellets dosage form of duloxetine hydrochloride with a suitable polymer by using a suspension layered method. Drug loaded nuclei was prepared using a suspension layered technique in a Fluidized Bed Processor. The nuclei were coated with an acid-resistant acrylic polymer (Eudragit L30-D55) and compared acid resistant properties with HPMC phthalate. Theen tire coating process per medina Fluidized Bed Process or different thickness. The *invitro* dissolution studies were conducted in 0.1N HCl for 2 hours followed by phosphate buffer (pH 6.8) for 1 hour with USP dissolution tester (type II). The results generated in this study showed that proper selection of polymer material based ontheir physicochemical properties as well as polymer load is important in designing delayed release pellets dosage form with best fit of dissolution profile.

- **Anupama S et al [10]** formulate and systematically evaluate in vitro performance of enteric coated mucoadhesive microspheres of duloxetine hydrochloride (DLX), an acid labile drug. DLX microspheres were prepared by simple emulsification phase separation technique using chitosan as carrier and glutaraldehyde as a cross-linking agent. Microspheres prepared were coated with Eudragit L-100 using an oil-in-oil solvent evaporation method. Eudragit L-100was used as enteric coating polymer with the aim to release the drug in small intestine The microspheres prepared were characterized by particle size, entrapment efficiency, swelling index (SI), muco adhesion time, in vitro drug release and surface morphology.

- **Amr M et al [11]**approaches to formulate and evaluate buccal mucoadhesive films for improving the bioavailability of duloxetine. The protocol of the study includes performing a pharmacokinetic study on healthy human volunteers to compare the selected film formulation that achieves the best physicochemical characteristics with DH reference product (Cymbalta oral capsules) to confirm the delivery of DH via the buccal mucosa. The study also includes performing accelerated stability studies to investigate the stability of DH in selected films.

- **Karishma D et al [13]** prepared microemulsion with oleic acid as oil, water, and Smix ratio of tween 20 to propylene glycol (1:3). Pseudo-ternary phase diagrams were constructed to determine the region of existence of microemulsions prepared using the oil titration method. Optimization of formulations was done based on the in vitro diffusion studies. The microemulsion was gelled using Carbopol 934p and HPMCK 100 as the gelling agent.

3. MATERIALS AND EQUIPMENTS

Table 3.1 List of materials

SR. NO.	MATERIAL	FUNCTION
1.	Duloxetine Hydrochloride	API
2.	Sodium Starch Glycolate (SSG), Cross povidone Croscarmellose Sodium	Disintegrant
3	PEG400,	Non-Volatile Solvent
4	Aerosil200	Coating Material
5	Avicel PH 102 (MCC)	Carrier Material

Table 3.2 List ofEquipments

SR. NO.	EQUIPMENT'S
1.	Digital weighing balance
2.	Dissolution apparatus
3.	U.V. Spectrophotometer
4.	FTIR

5.	Magnetic Stirrer
6.	Tablet compression machine
7.	Vernier Calipers

4. EXPERIMENTALWORK

• Determination of λ max of Duloxetine Hydrochloride

To ascertain the wavelength of maximum absorption (λ max) of the drug solution (25µg/ml) in 1.2 pH, 0.1 N HCl were scanned using UV-Visible spectrophotometer within the wavelength region of 200–400 nm against reagent blank.

➢ Preparation of standard curve of Duloxetine Hydrochloride in pH 1.2, 0.1 N HCl

Duloxetine Hydrochloride (10 mg) was dissolved in 100 ml 1.2 pH, 0.1 N HCl in 100 ml volumetric flask. From the above solution, 10 ml (100µg/ml) was further diluted with 0.1 N HCl. The volume of volumetric flask was made up to 100 ml. From this stock solution (10µg/ml) 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 ml were withdrawn into 10 ml volumetric flasks and diluted up to the volume with 0.1 N HCl. Absorbance of each solution was measured at 288nm by UV/VIS double beam Spectrophotometer using 1.2 pH, 0.1 N HCl as a reference standard. The calibration curve was generated for entire range from 5 to 30 µg/ml.

DRUG EXCIPIENTS COMPATIBILITY STUDY

• FTIR study

Drug: excipients compatibility was checked by using FTIR. FTIR spectra of pure drug and the physical mixture of drug with excipients were compared. For this purpose, well known method called Potassium bromide (KBr) pellet method was used.

➢ Solubility Study

The Solubility study was performed using volatile and nonvolatile solvents. Drug was dissolved in that solvent and saturated solutions were prepared. The prepared solution was analyzed by the UV spectrophotometer at 288 nm.

PREPARATION OF DULOXETINE HYDROCHLORIDE LIQUISOLID COMPACTS

➢ Selection of Vehicle

Initially, Duloxetine Hydrochloride solubility was checked in different solvents. Solubility of a drug Duloxetine Hydrochloride in a nonvolatile vehicle is one of the most important key parameters for the preparation of liquisolid compacts. Improvement in solubility directly affects the dissolution rate. Finally, according to solubility data of drug Duloxetine Hydrochloride, PEG 400 was selected as the vehicle for further study.

➢ Liquid load factor (Lf)

• Liquid Loading factor was calculated for carriers and for the non-volatile solvent system.

Lf(Liquid Loading factor)=W/Q

Where,

W: Amount of liquid medication

Q: Amount of carrier material

➢ Carrier to Coating Ratio (R)

Carrier to coating ratio was calculated as per below;

R= Q/q

Where,

Q: Amount of carrier material (AvicelpH102)

q: Amount of coating material (Aerosil)

➢ Drug Concentration in liquid(Cd)%w/w

Cd was calculated as per below:

Cd=Drug amount/Drug + liquid load

➢ Manufacturing Method

Table 4.1 Formulation table of Duloxetine Hydrochloride Liquisolid Compacts trial batches

Trial	Drug	Liquid Load	Cd (%w/w) (W)	Carrier agent (Q)	Coating Agent (q)	Carrier to Coating ratio (Q/q)	Liquid Load factor	Total Weight oftablet	4%of tablets weight	Final weight of tablet (mg)	Type of Disintegrant
Batch	Duloxetine HCl (mg)	PEG 400 (mg)	Con.Of drug in liquid (mg)	Avicel (mg)	Aerosil (mg)	R	Lf	Weight (mg)	DT Agent (mg)		
T1	20	80	20	100	10.0	10.0	0.800	210.0	8.4	218.4	SSG
T2	20	80	20	100	5.0	20.0	0.800	205.0	8.2	213.2	SSG
T3	20	80	20	100	3.3	30.0	0.800	203.3	8.1	211.5	SSG
T4	20	80	20	100	10.0	10.0	0.800	210.0	8.4	218.4	CCS
T5	20	80	20	100	5.0	20.0	0.800	205.0	8.2	213.2	CCS
T6	20	80	20	100	3.3	30.0	0.800	203.3	8.1	211.5	CCS
T7	20	80	20	100	10.0	10.0	0.800	210.0	8.4	218.4	CP
T8	20	80	20	100	5.0	20.0	0.800	205.0	8.2	213.2	CP

T9	20	80	20	100	3.3	30.0	0.800	203.3	8.1	211.5	CP

SSG= Sodium Starch Glycolate CCS= Croscarmellose Sodium CP= Crospovidone DT= Disintegrating Agent

- **Preparation of trial batches of Duloxetine Hydrochloride Liquisolid Compacts: -**

Trial batches were prepared to check the type of disintegrant and its amount. Three different types of disintegrants are used which is sodium starch glycolate, Crospovidone and croscarmellose sodium. Drug concentration in liquid carrier in all batches remain constant 20%. Liquidload factor is also taken constant 0.800 in all nine batches. Disintegrant amount in all batches are taken 4% of the tablet weight. The formulation table was given below in table 4.1

- **Preparation of factorial batches of Duloxetine Hydrochloride Liquisolid Compacts:**

Based on trial batches, it was found that the Croscarmellose sodium as a disintegrating agent found satisfactory and shows good results as compared to other DT agents. Hence, the factorial design was applied to optimize the formulation taking Carrier to coating agent ration (R) and Load factor Lf as independent factors. The factorial design table is given below in table 4.2.

3^2 Full factorial Experimental Design Layout

Variables for Experimental Designs

- Independent variable:
- X1=Liquid Load Factor(Lf)
- X2=Excipient ratio (carrier:coatingmaterial,R)
- Dependent variable:
- Y1=Disintegration Time(sec)
- Y2=DrugReleaseat30 min. (%)

Table 4.2 Coded levels and actual values of the variables

Batch Code	Variable level sin coded form		Translation of coded levels to Actual values	
	X1	X2	X1	X2
F1	-1	-1	0.600	10.0
F2	-1	0	0.600	20.0
F3	-1	+1	0.600	30.0
F4	0	-1	0.800	10.0
F5	0	0	0.800	20.0
F6	0	+1	0.800	30.0
F7	+1	-1	1.000	10.0
F8	+1	0	1.000	20.0
F9	+1	+1	1.000	30.0

X1= Liquid Load Factor (Lf)

X2= Excipient ratio (carrier: coating material, R)

Table 4.3 Formulation table of Duloxetine Hydrochloride Liquisolid Compacts factorial batches

Trial Batch	Drug Duloxetine HCl (mg)	Liquid Load PEG 400 (mg)	Cd (%w/w) (W) Con. Of drug in liquid (mg)	Carrier agent (Q) Avicel (mg)	Coating Agent (q) Aerosil (mg)	Carrier to Coating ratio (Q/q) R	Liquid Load factor Lf	Total Weight of tablet Weight (mg)	4%of tablets weight DT Agent (mg)	Final weight of tablet (mg)	Type of Disintegrant
F1	20	80	20	133.4	13.3	10.0	0.600	246.7	9.9	256.6	CCS
F2	20	80	20	133.4	6.7	20.0	0.600	240.1	9.6	249.7	CCS
F3	20	80	20	133.4	4.4	30.0	0.600	237.8	9.5	247.4	CCS
F4	20	80	20	100	10.0	10.0	0.800	210.0	8.4	218.4	CCS
F5	20	80	20	100	5.0	20.0	0.800	205.0	8.2	213.2	CCS
F6	20	80	20	100	3.3	30.0	0.800	203.3	8.1	211.5	CCS
F7	20	80	20	80	8.0	10.0	1.000	188.0	7.5	195.5	CCS
F8	20	80	20	80	4.0	20.0	1.000	184.0	7.4	191.4	CCS
F9	20	80	20	80	2.7	30.0	1.000	182.7	7.3	190.0	CCS

CCS=Croscarmellose Sodium DT=Disintegrating Agent

Evaluation of Duloxetine Hydrochloride Liquisolid Compacts

A. Precompression parameters

- **Bulk density**

The bulk density in gm/ml was calculated by using the following formula.

Bulk density=Weight of the powder/Bulk volume of Powder

- **Tapped density**

The tapped density in gm/ml was calculated by using the following formula.

Tapped density=Weight of powder taken/Tapped Volume

- **Compressibility index**

The Compressibility index was calculated using following formula;

Compressibility index (%) =ρt –ρo* 100/ ρt

Where ρt =Tapped density gram/ml, ρo =Bulk density gram/ml.

- **Hausner's ratio**

Hausner's ratio=Tapped density/Bulk density

- **Angle of repose**

The funnel method was used to measure angle of repose. Angle of repose is calculated using the following equation;

tan= θ h/r

Where, h and rare the height and radius of the powder cone.

B. Post-compression parameters

- **Thickness and Hardness test**

The digital Vernier caliper was used to check the thickness of the tablets. The hardness of the tablets was tested by using the Monsanto tester. Both the parameters were checked in triplicate.

- **Friability test**

The friability of the tablets was determined using Roche friabilator. The % friability calculated based on following formula:

Friability=([W–W]/WO) *100

Where, Wo=initial weight of tablet; W=after test weight of tablet.

- **Weight variation test**

Accurately weigh 20 tablets individually using an electronic balance and calculate the average weight of tablets and compare the individual tablet weights to the average.

- **In-vitro dispersion time**

The tablet was carefully placed in the center of the Petridish containing 10 ml of water and the time required for the tablet to completely disintegrate into fine particles was noted. Three tablets from each formulation were randomly selected and In vitro dispersion time was measured.

- **In-vitro disintegration test**

The test was carried out on 6 tablets using a tablet disintegration tester. Water at 37 ± 2˚C was used as a disintegration media and the time taken for complete disintegration of the tablet was noted with no passable mass remaining in the apparatus was measured.

- **Wetting time**

A piece of tissue paper was folded twice and placed in a small petri dish containing sufficient water. A tablet was kept on the paper, and the time for complete wetting of the tablet was measured.

- **Drug content determination**

Three tablets were selected randomly, and the average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of tablet powder was taken from the crushedblendandtransferreditintoa100mlvolumetricflask.10mlof0.1NHClwas added and sonicated for 10 minutes. Then volume was made up to 100 ml with 0.1 N HCl. The 1mL of resultant solution was diluted to 100mL with buffer (pH 1.2). The absorbance of the above solution was measured in UV spectrophotometer at 288 nm.

- **Dissolution studies**

The release rate of Duloxetine HCl from liquisolid tablets was studied using USP II Dissolution Testing Apparatus. The dissolution test was performed using 900 ml of 0.1 N HCl pH 1.2, at 37 ± 0.5°C and 50 rpm. Sample around 2 ml withdrawn from the dissolution apparatus at different time intervals like 0, 5, 10, 15, 30, 45, 60 minutes intervals. The samples were filtered and checked in UV.

- **Stability studies**

Stability study was performed as per ICH guideline for short term period of 1 month. The final optimized formulation will be kept at 40˚C and 75% RH condition for 1 month and evaluated for hardness, % drug content, and disintegration time and % drug release.

5. RESULTS &DISCUSSION

API Characterization

Initially, drug Characterization was done for physical verification, and the results are given in the table below.

Table 5.1 Characterization of Duloxetine HCl

Sr. No.	Parameters	Observations
1	Appearance	White to slightly brownish white solid Powder
2	Color	White to slightly brownish
3	Odour	Odorless
4	Melting Point	170°C

Solubility Study

Table 5.2SolubilityStudy of DuloxetineHCl

Sr No.	Name of Solvent	Solubility (mg/ml)
1	Water	0.09
2	Methanol	2.5
3	Ethanol	3.9
4	0.1 NHCL	0.8
5	4.5pHAcetate Buffer	0.9
6	6.8pHPhosphateBuffer	0.8
7	7.4pHPhosphateBuffer	0.7
8	PEG400	5.2

Calibration Curve of Duloxetine HCl

The calibration curve of Duloxetine HCl was found to over a concentration range 5-30 µg/ml. (R^2=0.999) the data for calibration curve is given in table 5.1 and the calibration curve is shown in fig.5.1.

Table 5.3 Calibration curveofDuloxetineHClin0.1 NHCl at315 nm

Sr. No	Concentration (µg/ml)	I	II	III	Absorbance ± SD (n=3)
1	5	0.152	0.156	0.160	0.156 ± 0.005
2	10	0.305	0.303	0.307	0.305 ± 0.007
3	15	0.445	0.448	0.451	0.448 ± 0.003
4	20	0.620	0.621	0.622	0.621 ± 0.005
5	25	0.743	0.745	0.747	0.745 ± 0.003
6	30	0.865	0.861	0.869	0.865 ± 0.002

Figure 5.2 Calibration curve of Duloxetine in 0.1N HCl at 288 nm

5.2 Drug excipients compatibility study

From the results of FTIR, it seems that the reference peak observed in drug sample was also presence in the FTIR spectra physical mixture sample (drug and excipients mixture). Figure 5.3 - 5.7 was given below and it indicates that the drug was found compatible with selected excipients which were used in the formulation. Table 5.4 describes the comparison of peaks value

Table 5.4 Drug-Excipients compatibility studies by FTIR

Sr. No.	Assignment	Peakreportin Pure Drug (cm^{-1})	Peakreportin Physical Mixture (cm^{-1})
1	C-O stretch	1033.85	1043.49
2	C-N stretch	1359.82	1359.82

5.3 Evaluation of Liquisolid Compact Tablets of trial batches.

Trialbatcheshavebeencheckedfortheselectionofdisintegranttypeandlevel.Based on trial batches results, it was observed that the CCS is most satisfactory among all disintegrants as it gives lowest DT time for tablets to disintegrate. The results of trials batches evaluation were given in the table below.

Table 5.5 Pre compression parameters of T1-T9

Batch	Bulk Density (gm/ml) (n=3)	Tapped Bulk Density (gm/ml) (n=3)	Compressibility % (n=3)	Hauser Ratio (n=3)	AngleofRepose (□) (n=3)
T1	0.296±0.02	0.329±0.03	10.03±0.02	1.11±0.01	28.5±0.3
T2	0.284±0.03	0.324±0.04	12.35±0.06	1.14±0.02	30.1±0.4
T3	0.281±0.01	0.309±0.01	9.06±0.01	1.10±0.01	29.5±0.2
T4	0.276±0.04	0.301±0.05	8.31±0.03	1.09±0.03	31.8±0.3
T5	0.271±0.03	0.299±0.03	9.36±0.02	1.10±0.02	30.8±0.1
T6	0.269±0.04	0.295±0.04	8.81±0.04	1.10±0.01	29.5±0.4
T7	0.259±0.02	0.291±0.03	11.00±0.02	1.12±0.03	33.5±0.3
T8	0.255±0.01	0.289±0.03	11.76±0.03	1.13±0.01	28.2±0.1
T9	0.251±0.03	0.288±0.02	12.85±0.04	1.15±0.02	31.5±0.3

Post-Compression Parameters

The tablets were subjected to preliminary characterization such as % weight variation, thickness, hardness, friability, and drug content. The evaluated parameters were within acceptable range for all the T1-T9 formulations. The values are indicated in table no. 6.6. FormulationT1-T9 found within weight variation limit. No tablet weight deviation is found in all formulations. So T1-T9 formulations pass weight variation tests. Thickness of T1-T9 batches found between 2.8 to 3.1 mm. Hardness of all batches T1-T9 found between 4.7 to 5.0 kg/cm^2. It means all bacthes have good mechanical strength. Friability of T1-T9 batches found below 1%.

Table 5.6 Post compression parameters of T1-T9

6. 7. Batch	8. Weight Variation (mg) 9. (n=10)	10. Thickness (mm) 11. (n=3)	12. Hardness (kg/cm^2) (n=3)	13. 14. Friability%

15. T1	16. 218±2.1	17. 3.1±0.1	18. 4.8±0.4	19. 0.68
20. T2	21. 214±1.9	22. 2.9±0.2	23. 4.7±0.2	24. 0.71
25. T3	26. 212±2.7	27. 3.0±0.1	28. 4.7±0.3	29. 0.69
30. T4	31. 219±2.4	32. 3.1±0.1	33. 4.9±0.1	34. 0.66
35. T5	36. 213±1.7	37. 3.2±0.1	38. 4.9±0.2	39. 0.61
40. T6	41. 210±1.4	42. 3.0±0.1	43. 5.0±0.4	44. 0.56
45. T7	46. 219±1.3	47. 2.9±0.2	48. 4.8±0.4	49. 0.69
50. T8	51. 213±2.2	52. 2.8±0.1	53. 4.7±0.3	54. 0.76
55. T9	56. 211±2.6	57. 2.8±0.1	58. 4.7±0.2	59. 0.78

- **Disintegration time**

It was found that as concentration of super dis-intigrating agent was increased and disintegration time was reduced in all formulations. This is because of internal structure of tablets that is pore size distribution; water penetration into tablets and swelling of disintegration ingredients are suggested to be the mechanism of disintegration.

- **Drug Content**

%Drug content of formulation T1-T9 found within acceptable limit

Table 5.7 Post compression parameters of formulation T1-T9

Batch	Disintegration time (Seconds) (n=3)	% Drug Content (n=3)
T1	175±8	99.2±1.4
T2	206±5	98.1±1.8
T3	219±7	97.9±1.3
T4	98±4	98.9±1.7
T5	109±9	99.2±1.1
T6	135±6	98.7±0.9
T7	139±4	99.1±2.6
T8	169±7	99.2±1.8
T9	189±3	99.5±1.4

- **Invitrodissolution studies**

The data obtained in the in vitro release for formulations T1-T9 are tabulated in the tableno.5.8.Alltheformulations showed rapid % drug release. But the rapid drug dissolution was noticed in T4 formulationscomparedtootherformulationswhichrelease morethan90 %drugin 45 min. From the above data it concluded that disintegrating agent in formulation help to drug release faster than the other agent used in formulation.

Table 5.8 % Drug Release of FormulationT1-T9

Batch	%Drug Release in mins						
	0	**5**	**10**	**15**	**30**	**45**	**60**
T1	0	11.3	23.2	35.9	59.5	71.3	77.9
T2	0	8.1	16.9	28.4	51.3	64.2	68.5
T3	0	7.4	14.2	24.3	49.5	61.2	66.3
T4	**0**	**35.9**	**56.3**	**67.8**	**86.9**	**93.1**	**97.3**
T5	0	29.4	48.6	61.3	80.8	87.6	92.3
T6	0	21.3	40.8	55.6	72.9	80.3	84.9
T7	0	19.2	37.6	49.4	67.9	76.4	80.2
T8	0	14.8	29.4	40.2	60.9	71.2	77.9
T9	0	8.6	19.5	31.2	56.3	68.3	71.3

Table 5.9 Post compression parameters of F1-F9

Batch	Weight Variation (mg) (n=10)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability%
F1	247±2.5	3.4±0.2	4.6±0.1	0.71
F2	240±3.1	3.5±0.1	4.7±0.3	0.74
F3	238±1.8	3.4±0.4	4.6±0.1	0.72
F4	211±1.6	3.2±0.2	4.8±0.1	0.68

F5	205±2.1	3.0±0.3	4.7±0.2	0.69
F6	203±2.3	3.1±0.1	4.9±0.1	0.64
F7	187±1.8	2.8±0.4	5.2±0.3	0.56
F8	186±1.4	2.9±0.2	5.4±0.2	0.42
F9	183±1.9	2.9±0.2	5.5±0.2	0.48

Table 5.10 Post compression parameters of formulation F1-F9

Batch	Disintegration time (Seconds) (n=3)	% Drug Content (n=3)
F1	45±2	98.1±1.9
F2	56±4	99.2±2.3
F3	59±3	98.5±1.7
F4	102±7	98.9±2.0
F5	111±5	98.5±1.6
F6	126±9	99.3±2.4
F7	149±4	98.1±2.3
F8	163±3	99.6±1.7
F9	174±7	99.8±1.5

- **Invitro dissolution studies**

A drug release study of factorial batches F1-F9 was done, and the data are tabulated in the table below. The comparative dissolution profiles are also prepared and given in below figure.

Table 5.11 % Drug Release of Formulation F1-F9

Batch	%Drug Release in mins						
	0	**5**	**10**	**15**	**30**	**45**	**60**
F1	0	42.9	63.1	74.5	85.8	93.9	99.1
F2	0	41.5	60.3	72.1	82.3	92.4	98.2
F3	0	38.4	58.9	70.9	79.2	90.5	96.8
F4	0	36.9	55.8	67.1	76.8	88.3	94.9
F5	0	33.8	54.2	63.9	74.9	85.9	93.1
F6	0	30.1	51.8	61.9	71.3	83.5	90.2
F7	0	27.8	50.3	59.8	69.5	81.8	89.4
F8	0	25.3	48.2	57.2	66.8	79.6	87.5
F9	0	24.7	45.9	55.1	64.2	77.2	85.9

Figure 5.3 %Drug Release from Formulation F1-F9

5.4 Analysis of factorial design

The factorial design was applied for formula optimization using Design Expert software. For analysis purpose following data fitted into software for 3^2 design and the outcome of the regression analysis recorded below

Table 5.12 Factorial design table

Batch	Coded Factors		Actual factors		Response	
	X1	**X2**	**X1**	**X2**	**Y1**	**Y2**
F1	-1	-1	0.600	10.0	45	85.8
F2	-1	0	0.600	20.0	56	82.3
F3	-1	+1	0.600	30.0	59	79.2

F4	0	-1	0.800	10.0	102	76.8
F5	0	0	0.800	20.0	111	74.9
F6	0	+1	0.800	30.0	126	71.3
F7	+1	-1	1.000	10.0	149	69.5
F8	+1	0	1.000	20.0	163	66.8
F9	+1	+1	1.000	30.0	174	64.2

levelsof3^2FullFactorialdesigns

Independent Factors	**Levels**		
	Low(-1)	**Medium(0)**	**High (1)**
X_1=LiquidLoad Factor (Lf)	0.600	0.800	1.000
X_2=Excipient ratio (carrier: coating material, R)	10.00	20.00	30.00
Dependent Factors			
Y1=Disintegration Time(sec)			
Y2=%Drug releaseat 30min			

ANOVA for Quadratic model
Response1:Disintegration time

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	18462.69	5	3692.54	470.83	0.0002	significant
A-LiquidLoad Factor (Lf)	17712.67	1	17712.67	2258.52	<0.0001	
B-Excipient ratio (R)	661.50	1	661.50	84.35	0.0027	
AB	30.25	1	30.25	3.86	0.1443	
A^2	56.89	1	56.89	7.25	0.0742	
B^2	1.39	1	1.39	0.1771		
Residual	23.53	3	7.84			
Cor Total	18486.22	8				

Factor coding is **Coded**.
Sum of squares is **Type III– Partial**
The **Model F-value** of 470.83 implies that the model is significant. There is only a 0.02% chance that an F-value this large could occur due to noise.
P-values less than 0.0500 indicate that model terms are significant. In this case, A, B are significant model terms. Values greater than 0.1000 indicate that the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model

Final Equation in Terms of Actual Factors
Disintegration Time=
-191.44444
+457.50000Liquid Load Factor (Lf)
+0.283333Excipientratio(R)
+1.37500Liquid Load Factor (Lf) *Excipient ratio(R)
-133.33333Liquid Load Factor $(Lf)^2$
-0.008333Excipientratio$(R)^2$
The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor, and the intercept is not at the center of the design space.

Figure 5.4 Contour plot for disintegration time

Figure 5.5 Surface plot for disintegration time

- **ANOVA for Quadratic model** Response2:%DrugReleaseat30min

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	416.18	5	83.24	501.93	0.0001	significant
A-LiquidLoadFactor (Lf)	365.04	1	365.04	2201.25	<0.0001	
B-Excipientratio(R)	50.46	1	50.46	304.28	0.0004	

AB	0.4225	1	0.4225	2.55	0.2087	
A^2	0.1800	1	0.1800	1.09	0.3741	
B^2	0.0800	1	0.0800	0.4824	0.5373	
Residual	0.4975	3	0.1658			
CorTotal	416.68	8				

The **Mode lF-value** of 501.93 implies that the model is significant. There is only a0 .01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate that model terms are significant. In this case A, Bare significant model terms. Values greater than 0.1000 indicate that the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Final Equation in Terms of Actual Factors
%Drug Release at 30min =
+118.06667
-54.25000Liquid Load Factor (Lf)
-0.340000Excipientratio(R)
+0.162500Liquid Load Factor (Lf) *Excipient ratio(R)
+7.50000Liquid Load Factor$(Lf)^2$
-0.002000Excipientratio$(R)^2$
The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor, and the intercept is not at the center of the design space.

Figure 5.6 Contour plot for drug release at 30mins

Figure 5.7 Contour plot for drug release at 30mins

Validation of optimized formulation:
A checkpoint batch was designed in accordance with the desirability function, as shown in the table below and figure. To assess the validity of prediction, a checkpoint batch F10 was prepared and evaluated under the same conditions as outlined for the other batches. The response data was compared with that of the required data.

Discussion: The obtained response variables of check point batch compared with target response parameters. The bias for predicted versus observed responses was acceptable.

Figure 5.8 Overlay plot for check point batch Table

5:13 Check point batch Analysis

BatchF10	Disintegration time(Sec)	%Drugreleaseat30 mins
Predicted	84	77.0
Actual	82	76.8
%Change	1.02	1.00

- **Optimized Formulation**
- **Optimized batch:**

Finally, optimized batch F11 was taken from the overlay plot and complete analysis was done and finally loaded for stability study.

Figure 5.9 Overlay plot for optimized batch F11

Table 5.14 Formulation table of optimized batch F11

Batch	F11
Drug	20
PEG 400	80
Avicel	126.5
Aerosil	7.1
Croscarmellose Sodium	9.3
Final weight of tablet	242.9
R	17.8
Lf	0.632

Table 5.15 Evaluation of optimizedbatchF11

Evaluation Parameters	Results
Weightvariation(mg)	243 ± 3.9
Thickness(mm)	4.2 ± 0.3
Hardness (Kg/cm^2)	5.8 ± 0.1

Friability	0.63 ± 0.02	
Drug Content(%)	99.1 ± 1.3	
Disintegrating time(sec)	63 ± 5	
% Drug Release	**Time(min)**	**% Drug Release**
	0	0
	5	40.1 ± 2.9
	10	62.9 ± 2.5
	15	73.6 ± 2.2
	30	82.1 ± 1.7
	45	94.5 ± 1.4
	60	99.4 ± 1.2

Table 5.16 Comparison with marketed product

Time(min)	%Drug Release of F11	%Drug Release of Marketed Product
0	0	0
5	40.1 ± 2.9	21.3 ± 2.4
10	62.9 ± 2.5	32.8 ± 2.1
15	73.6 ± 2.2	40.9 ± 2.0
30	82.1 ± 1.7	52.3 ± 1.8
45	94.5 ± 1.4	61.6 ± 1.2
60	99.4 ± 1.2	72.9 ± 1.0

TheformulationF11wasfoundsatisfactoryduringphysicalevaluation.Thedissolution data of F11 was found faster as compared to marketed product.

- **Stability Study**

Stability study of final formulation F11 was performed for 1 month and the results were recorded. Formulation found stable during stability study. The samples were analyzed for various evaluating parameters before and after stability study. The results showed good similarity with that of before evaluated parameters.

Table 5.17 Stability study Results

Parameters	Initial	After1month
Drug Content (%)	99.1 ± 1.3	98.9 ± 1.8
Disintegration time (Seconds)	63 ± 5	64 ± 7
%Drug release (60 min)	99.4 ± 1.2	99.2 ± 1.4

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