International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2023-2032 www.ijprajournal.com ISSN: 2249-7781

Enhancement of Solubility of Duloxetine HCL by Solid Dispersion Technique

A.Aroon[1], B.Jayanthi[2]
[1]*Hetero Labs Ltd, Apurupa Colony, Jeedimetla, Telangana, India.*
[2]*Department of Pharmacy, Annamalai University, Chidambaram, Tamilnadu, India.*
**Corresponding Author: A.Aroon, Hetero Labs Ltd, Apurupa Colony, Jeedimetla, Telangana, India.*
Email:aroon.adulapuram@gmail.com

Submitted: 25-05-2023 Accepted: 05-06-2023

ABSTRACT
The core objective of the present study is to enhance the solubility of poorly-water soluble drug Duloxetine HCl, a selective serotonin and norepinephrine reuptake inhibitor antidepressant (SSNRI) by using different hydrophilic carriers and formulating them into solid dispersions with solvent evaporation technique and establishing shelf life of the same by conducting stability studies. The solubility of Duloxetine HCl in various hydrophilic carriers (polymers) such as PVP K30, HPMC, HPMC AS and Killiphor P188 was studied. A total 0f 15 SD formulations were prepared by solvent evaporation technique with different polymers and evaluated for preformulation studies, particle size analysis, drug content, invitro dissolution studies and accelerate stability studies. The dissolution profile of pure SD formulation F14 prepared with HPMC AS in 1:3:(0.5+0.5) ratio of drug:polymer:surfactants [Table.3] showed maximum drug release of 99.94 in 15 mins. Solubility of Duloxetine HCl was also increased by 15 folds in SD formulation F14 when compared to pure drug. Maximum dissolution rate is attributed to use of combination of surfactant which showed synergistic effect in decreasing the interfacial tension and enhancing the wettability. This synergistic effect acted as the key factor in further enhancing the dissolution rate to the maximum.

KEY WORDS: Duloxetine HCl, solid dispersion, solvent evaporation, solubility enhancement

I. INTRODUCTION

One of the most challenging tasks in the pharmaceutical dosage development is enhancing the solubility of drugs[1]. These drugs which are low soluble come under the Class II of BCS classification. Almost 40% of the active pharmaceutical ingredients or moieties are established as poorly water soluble. Thus it becomes practically impossible for these drugs to get in to systemic circulation if they are administered as oral solid dosage forms. To overcome this drawback many techniques have been studied and employed in the pharmaceutical industry to make sure the drug solubility is enhanced by the way of formulating the dosage form with different polymers. Duloxetine hydrochloride isapoorlysoluble,highlypermeableBiopharmaceutics ClassificationSystem(BCS) ClassII compound. DuloxetineHCl is indiacted in the treatment of Major Depressive Disorder(MDD) and Generalized Anxiety Disorder (GAD). The study focuses on three key steps 1) Drug excipient compatibility 2) enhancement of solubility of DuloxetineHCl by solid dispersion technique and 3) establishing shelf life of the prototype product.

Solubility enhancement has been the most critical and key factor in the development of new formulations with New chemical entities in the recent past. Many techniques have been employed for the improvement of solubility and one of the foremost technologies is Solid Dispersion (SD) technology which showed good bioavailability. There are four methods[1] under SD which are 1) Kneading 2) Melting 3) Solvent Evaporation and 4) Melting solvent. Among these methods solvent evaporation(SE) method is preferred method the reason being the SEs obtained can easily show highest process feasibly from pilot to scale up when it comes to commercial manufacturing. These SEs can be used in combination with different excipients to manufacture conventional tablets and capsules which have the highest patient acceptability among all solid oral dosage forms. The poor solubility of Duloxetine HClleads to low bioavailability although it is highly permeable. So the main objective of the work is to elevate the solubility of DuloxetineHCl. It was observed that undergoes excessive first pass metabolism resulting

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2023-2032 www.ijprajournal.com ISSN: 2249-7781

in poor bioavailability (50%) after oral administration thus making it a good candidate for administration via a SE system[2].

II. MATERIALS AND METHODS

MATERIALS

Duloxetine HCl gifted by RA Chem Pharma Ltd, Hyderabad. Hydroxypropyl Cellulose (HPC), Hydroxypropyl Methyl Cellulose (HPMC), HPMC AS, PVA, PVP K30, PEG 6000, Poloxamer 188 andSoluplus were obtained from RA Chem Pharma Ltd, Hyderabad. All other chemicals were of analytical reagent grade except methanol, which was chromatographic grade.

METHODS

Initial solubility studies of Duloxetine HCl

Excess amount of DuloxetineHClwas added to 50 ml of aquous solutions of hydrophilic carriers such as Hydroxypropyl Cellulose (HPC), Hydroxypropyl Methyl Cellulose (HPMC), HPMC AS, PVA, PVP K30, PEG 6000, Polaxamer 188, Soluplus, Tween 80, Sodium Lauryl Sulphate(SLS) in separate capped round bottomed flasks and placed in a orbital shaker for 30 hours at 25˚C±0.5 and 75%RH. The suspensions thus formed were filtered through 0.45µm and this filtered solution was diluted with methanol, and analyzed using UV spectrophotometer at 230nm (Table 1).

Table 1: Initial Solubility studies of Duloxetine HCl pure drug and physical mixtures in ration 1:1

Physical mixture (1:1)	Solubility (mg/ml)*
Duloxetine HCl pure API (active pharmaceutical ingredient)	0.074±0.02
API + HPC	0.173±0.06
API + HPMC	0.210±0.09
API + HPMC AS	0.284±0.03
API + PVA	0.157±0.02
API + PVP K30	0.191±0.04
API + PEG 6000	0.154±0.01
API + Kolliphor P188	0.195±0.05
API + Soluplus	0.146±0.01
API + SLS	0.215±0.04
API + Tween 80	0.207±0.05

Preformuation studies

Based on the initial solubility study results, the pre-formulation study was conducted with the excipients which have shown maximum solubility with Duloxetine HCl. The drug-excipient ratio for pre-formulation was planned as to take excipient quantity not more than the maximum amount of excipient to be used in the final formulation. The list of excipients with drug: excipient ratio is mentioned in table 2

Appropriate quantities of the Duloxetine HCl and excipients that are likely to be used in the formulation will be weighed in different ratios as per the below table.

Table2: Drug Excipient Compatibility study protocol

S.No	Name of the material	Drug: Excepient ratio	Drug: Excipient blend ratio in weights for each Vial. (g)	
			Drug	Excipient
Ex1	Duloxetine HCl + HPMC	1:4	1	4
Ex2	Duloxetine HCl + HPMC AS	1:4	1	4
Ex3	Duloxetine HCl + Kolliphor P 188	1:2	1	2
Ex4	Duloxetine HCl + SLS	1:2	1	2
Ex5	Duloxetine HCl + Tween 80	1:2	1	2

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2023-2032 www.ijprajournal.com ISSN: 2249-7781

Ex6	Duloxetine HCl + PVP K30	1:4	1	4

Preparation of Solid Dispersion (SD's) by Solvent Evaporation technique

As the method[3] involves solvent evaporation the excipients selected were based on the initial solubility studies. The excipients which manifested the maximum solubility in initial solubility studies. The quantitative formula of all the compositions is shown in the table 2. Each excipient is separately dissolved in ethanol under continuous stirring until clear solution was observed. Then, Duloxetine HCl was slowly added to the above solution with stirring for 30 mins and followed by addition of suitable surfactant(s) to get the final solution. Thus obtained solution is allowed to dry in a dessicator and reduced pressure was applied. Thus formed SDs are milled using motor and pestle and passed though #60 mesh. Thus obtained powder is stored in the dessicator until use.

Characterization of Duloxetine SDs

Solubility studies were conducted for all the formulations by placing these formulation is pH 6.8 phosphate buffer separately. If any excess amount of Duloxetine solid dispersion was taken into a conical flask which contains 20ml of media and placed in sonicator for 2hrs at room temperature condition. The sample was then placed in an orbital shaker for 48 hrs. The suspensions thus obtained were subjected to filtration through a Whatman filter paper and filtrate thus obtained is subsequently diluted and analyzed using a double beam UV-Visible spectrophotometer at wavelength of 230nm.

Solubility studies

On the basis of dissolution method development the medium of pH 6.8 phosphate buffer was selected as the most suitable medium for the dissolution drug release studies for all the solid dispersion formulations. All the samples were shaken for 48 h in an orbital shaker by keeping temperature at 37°C. This solution is then filtered by Whatman filter paper and filtrate was further diluted and measured using spectorphotometrically at 230 nm. [4,5]

Determination of particle size[4]

Laser diffraction size analyzer (LS 13 320, Beckman Coulter, CA) was used for the analysis of particle size. To carry out this process, all the sample were separately ultrasonicated for one 2 minutes only after suspending in silicone oil. Thus obtained samples were analyzed by laser diffraction analyzer.

Determination of Drug content

All the samples of various formulations were placed in 25 ml volumetric flask (equivalent to 60 mg of drug). Each sample mixture is added with 10 ml of methanol and allowed to sonicate for 10 mins. The final volume was made up with methanol. This solution is then diluted by methanol up to certain extent so that it can easily be analyzed spectrophotometrically at $\lambda = 230$ nm.

Percentage practical yield (PY)

Percentage PY was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. SDs were collected and weighed to determine PY from the following equation.

$$\% \text{ Practical yield} = \frac{\text{Practical mass(solid dispersion)}}{\text{Theoretical mass(Drug + Polymer + surfactant)}} \times 100$$

Dissolution studies

Dissolution studies were performed using Type II paddle apparatus. The dissolution medium consisted of 900 ml phosphate buffer solution with pH 6.8 containing. The temperature was maintained at 37 ± 0.5 ˚C and stirring speed of 100 rpm.

Samples (equivalent to 60 mg of Duloxetine) were spread on the surface of dissolution medium. 5 ml of aliquots were withdrawn at specific intervals and measured spectorphotometrically for Duloxetine content at wavelength 230 nm. The volume of dissolution medium was kept constant by adding same amount of fresh medium.Drug dissolution was determined by plotting a graph between drug dissolved and time interval. Fresh medium is added to keep the volume of the medium constant.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2023-2032 www.ijprajournal.com ISSN: 2249-7781

Table 3: Quantitative composition of DuloxetineHClSolid Dispersions

Formulation	Ingredients(mg)							
	Duloxetine	PVP K30	HPMC	HPMC AS	Kolliphor P 188	SLS	Tween 80	Methanol
F1	60	60	-	-	-	30	-	Q.S
F2	60	120	-	-	-	60	-	Q.S
F3	60	180	-	-	-	120	-	Q.S
F4	60	-	60	-	-	30	-	Q.S
F5	60	-	120	-	-	60	-	Q.S
F6	60	-	180	-	-	120	-	Q.S
F7	60	-	-	60	-	30	-	Q.S
F8	60	-	-	120	-	60	-	Q.S
F9	60	-	-	180	-	120	-	Q.S
F10	60	-	-	-	60	30	-	Q.S
F11	60	-	-	-	120	60	-	Q.S
F12	60	-	-	-	180	120	-	Q.S
F13	60	-	-	180		90	30	Q.S
F14	60	-	-	180		60	60	Q.S
F15	60	-	-	180		30	90	Q.S

FTIR spectroscopy

FTIR spectrometer Pristige-21(Shimadzu-Japan) was used to study the FTIR spectra of all formulations. The analysis was conducted with KBr disks which were prepared by mixing the samples with potassium bromide. Within the range of 4000-400cm^{-1} and resolution of 2 $cm^{-1}$the samples were analyzed.

X-ray powder diffraction (XRD)

Diffractometer was used to carryout X-ray diffravtion of Duloxetine HCl. The purpose of the using the equipment was to study the polymorphic state of Duloxetine HCl. Recording was made from 3 to 1500 in Si (Li) PSD detector with scanning speed of 30/min. All the process was operated at 40 kV and35 mA.

Scanning electron microscope (SEM) studies

The surface morphology of the layered sample was examinedby using SEM (Hitachi, Japan). The small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stubs. These sample stubs were coated with a thin layer (30 Å) of gold by employing POLARON-E 3000 sputter coater. The samples were examined by SEM and photographed under various magnifications with direct data capture of the images onto a computer.[6]

Stability studies

Prepared SDs were placed inside sealed 40cc HDPE containerwith child resistant cap under controlled temperatureenvironment inside stability chamber (Thermo Lab, India)with relative humidity of 75% ± 5% RH and temperature of40 ± 2°C for stability studies. The samples were removedafter 6months and evaluated for % drug content, in vitro dissolution studies and related compounds (impurities).

III. RESULTS AND DISCUSSION

Preformulation

The weighed quantities were mixed and transferred to glass vials. These glass vials (open and closed) were charged at 40°C/75%RH for a period of 4 weeks. The samples were withdrawn and tested results are mentioned in below Table 4

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2023-2032 www.ijprajournal.com ISSN: 2249-7781

Table 4: Drug –Excipient compatibility study[7] results after 4 weeks at 40°C/75% RH

Batch Number	Single max (%)			Total Impurities (%)		
	Initial	4weeks		Initial	4weeks	
		open	closed		open	closed
EX1	0.07	0.07	0.07	0.07	0.07	0.07
EX2	0.07	0.07	0.07	0.07	0.07	0.07
EX3	0.04	0.09	0.08	0.09	0.08	0.08
EX4	0.06	0.08	0.08	0.09	0.08	0.08
EX5	0.04	0.07	0.07	0.04	0.07	0.07
EX6	0.07	0.07	0.07	0.07	0.08	0.07
EX7	0.06	0.07	0.07	0.06	0.07	0.07

Formulation of SDs

Initially 12 SD formulations were prepared and all the 12 SDs showed good flow property after milling and passing though #40 mesh. Among all the 12 formulations F9 showed best dissolution rate but 100% drug release was not achieved. Further three formulations were prepared with same formula as F9 except that a combination of surfactants was taken in F13, F14 and F15 with SLS:Tween 80 ratio of 3:1,1:1 &1:3 respectively. All the three formulations showed excellent flow property.

Particle size determination

Sieve method was employed to determine particle size. The results showed that particle is in the size range from 50.31 ± 2.14 to 75.65 ± 2.38. SDs obtained from all formulations were analyzed for particle size as it was one of most important critical quality attribute which has a high impact on dissolution of the SDs. The lower is the particle size the higher the surface area and the higher the dissolution rate. The optimized final formulation F14 with optimum particle size was found to show good drug release which is shown in the Table 5.

% Practical Yield

The percentage practical yield for all the SD formulation was reported and it was found to be in the range of 93.32 ± 0.43 to 99.26 ± 0.41. The maximum practical yield was achieved for the SD formulation F14 with a value of99.98±0.47

Drug Content

To control the quality of the product and effectiveness of the process for the preparation of the formulation the drug content determination was carried out. All the SD formulations were analyzed for the determination of drug content which was found to be in the range of92.56-99.95 %. The maximum drug content was reported for the formulation F14 with 99.95%. The distribution of drug within the complexes was found to be homogenous and the result are tabulated in the Table5.

In vitro dissolution studies

As Duloxetine HCl is an acid labile drug and undergoes acid hydrolysis the medium selected for the dissolution studies[8] was pH 6.8 phosphate buffer. All the 15 Duloxetine HCl solid dispersions were analyzed for drug release rate in the selected dissolution medium. Initially 12 SD formulations were taken to optimize the best suitable polymer with maximum drug release rate. The dissolution profile of pure DuloxetineHCl SD prepared with HPMC AS in 1:3:2 ratio of drug: polymer:surfactant showed maximum drug release of 95.84% in 15 mins. Increased dissolution rate are attributed to more polymer concentration used for formulating SDs. Also, the use of surfactant decreased the interfacial tension and enhanced the wettability there by enhanced the solubility. Once the polymer and its quantity was optimized (fixed component), the further formulations were prepared to evaluate the effect of combination of surfactants on the drug release rate. The dissolution profile of pure Duloxetine HCl SD prepared with HPMC AS in 1:3:(0.5+0.5) ratio of drug:polymer:surfactants

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2023-2032 www.ijprajournal.com ISSN: 2249-7781

showed maximum drug release of 99.94 in 15 mins. Maximum dissolution rate is attributed to use of combination of surfactant which has synergistic effect in decreasing the interfacial tension and enhancing the wettability. This synergistic effect acted as the key factor in further enhancing the dissolution rate to the maximum.

Table 5: particle size, % practical yield and drug content of Duloxetine HCl solid dispersions

Formulation code	Particle size in µm	% Practical Yield	% Drug content
F1	64.29±1.39	94.26±0.62	92.56±0.58
F2	61.92±3.42	95.64±0.15	93.84±0.24
F3	59.93±1.95	95.45±0.25	93.57±0.57
F4	75.65 ± 2.38	98.39±0.97	95.42±0.63
F5	61.96±2.87	99.83±0.86	96.21±0.28
F6	54.85±1.16	98.13±0.61	96.34±0.42
F7	59.54±2.29	97.68±0.93	97.28±0.17
F8	58.27±3.16	98.52±0.38	97.48±0.67
F9	50.52±2.63	99.56±0.52	98.63±0.15
F10	65.92±1.48	98.72±0.26	93.38±0.29
F11	71.68±2.98	98.54±0.57	94.43±0.58
F12	72.38±1.68	99.68±0.21	94.95±0.93
F13	63.69±2.98	99.14±0.43	98.25±0.27
F14	53.56±3.87	99.98±0.47	99.95±0.21
F15	54.31±2.14	99.68±0.91	98.54±0.54

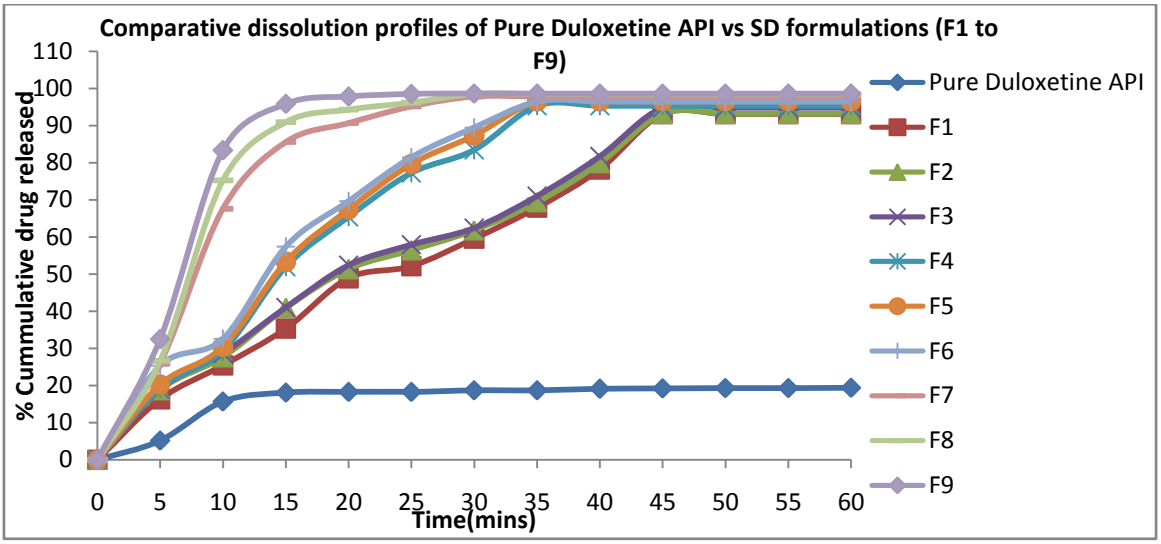

Figure 1: Comparative dissolution profiles of Pure Duloxetine API vs SD formulations (F1 to F9)

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2023-2032 www.ijprajournal.com ISSN: 2249-7781

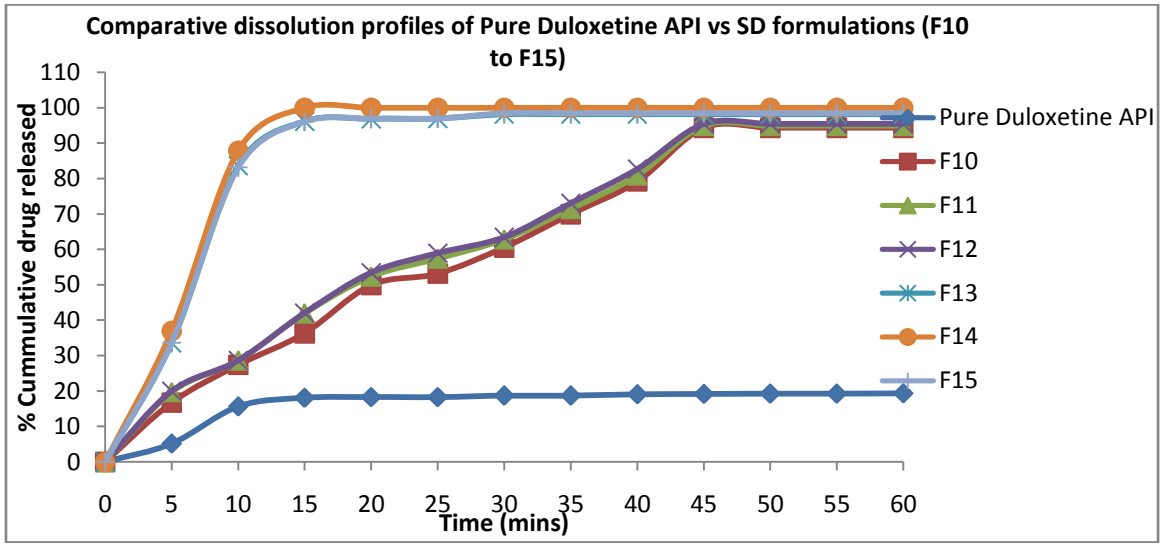

Figure 2: Comparative dissolution profiles of Pure Duloxetine HClAPI vs SD formulations (F10 to F15)

XRD

The DuloxetineHCl SDs were carried out to find out whether the SDs of various drug polymer ratios are crystalline or amorphous. The presence of numerous distinct peaks in the XRD spectrum of pure Duloxetine HCl indicates that it was present as a crystalline material [Figure 4].

From the XRD data of optimized formulation F15 it is concluded that there is no change in the crystalline form of the drug substance in the drug solid dispersion both at initial and also accelerated storage condition (40°C/75% RH up to 6 months) [Figure 5,6] respectively. The characteristic peak of drug substance (18.831 – 18.817 theta) remains unchanged. Hence, no polymorphism of the API is observed in the solid dispersion at initial testing and during accelerated storage conditions. The improved dissolution of Duloxetine HCl is mainly attributed to increased wettability and accordingly solubility due to the higher level of hydrophilicity by the use of polymeric carriers.

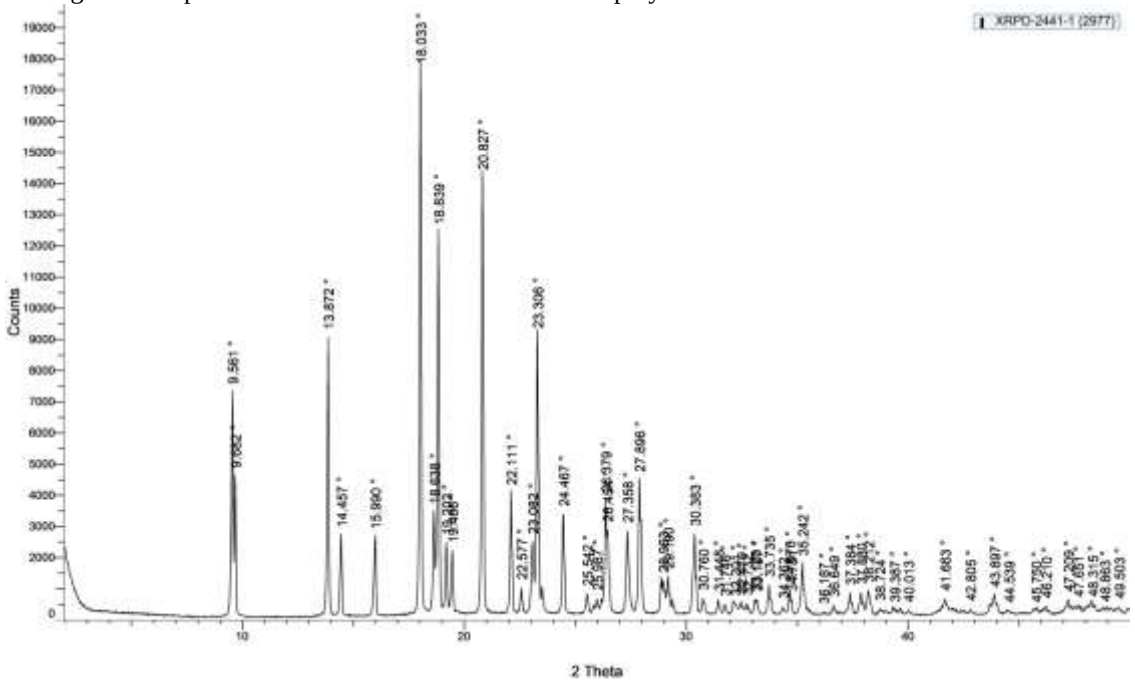

Figure 3. XRD of Duloxetine HClpure drug

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2023-2032 www.ijprajournal.com ISSN: 2249-7781

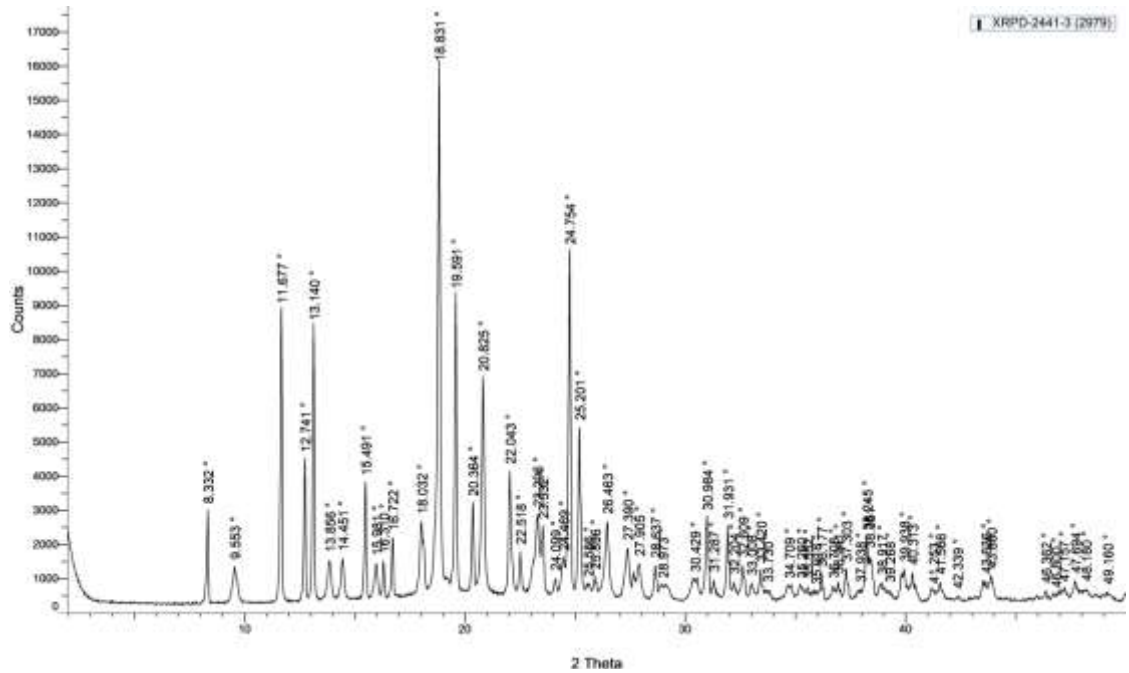

Figure 4. XRD of optimized formulation F14

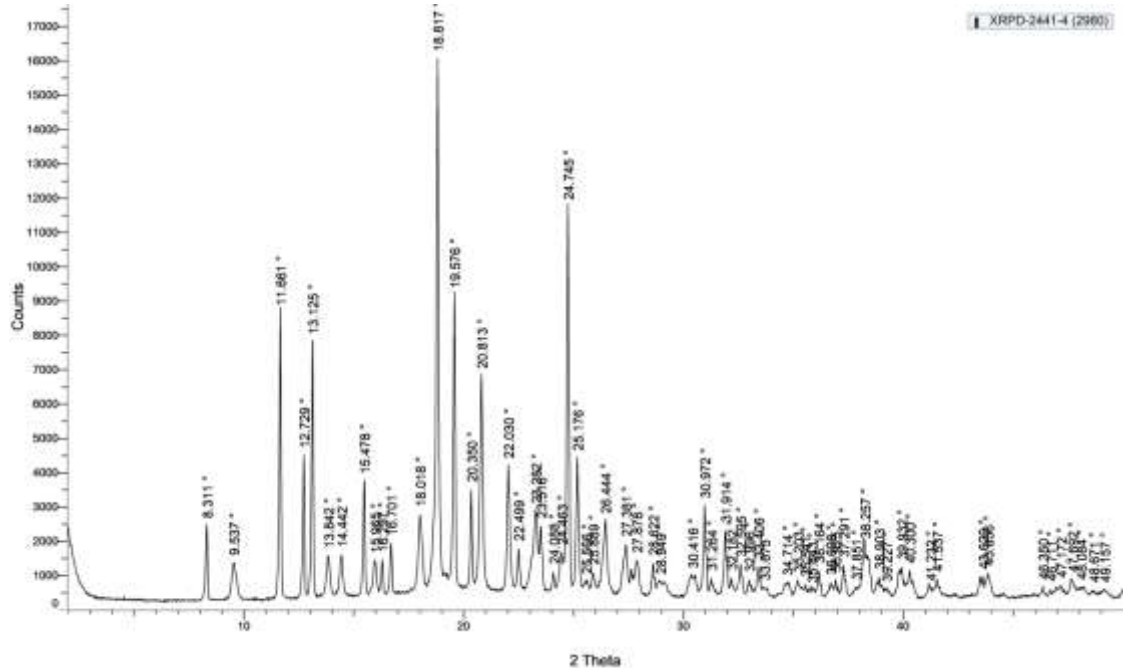

Figure 5. XRD of optimized formulation F14 after 6 months accelerated stability condition of 40°C/75%RH

SEM studies

SEM photographs for pure drug and optimized formulation F14 are shown in Figures 7 and 8. The drug crystals seemed to be smooth-surfaced, irregular in shape and size and in case of SDs, it was difficult to distinguish the presence of drug crystals. The drug surface in SD seems to be more porous in nature. SDs appeared as uniform and homogeneously mixed mass with wrinkled surface. Drug crystals appeared to be incorporated into the particles of the polymers. The SD

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2023-2032 www.ijprajournal.com ISSN: 2249-7781

looked like a matrix particle. The results could be attributed to dispersion of the drug in the molten mass of the polymer.

Stability Studies

Optimized formulation F15 was loaded for stability studies at 40°C±2°C/75% RH±5% to evaluate and formulation was found to be stable. The unloaded samples were tested for the presence of related compounds (impurities) and microbial growth and both the tests showed results well within the limits. There was no significant change in %drug content and in vitro drug release was observed, as shown in Table 7.

Table 6: Stability Study Results in Acceleratedconditions: HDPE Bottle (120 cc)

S.No	Test	Limits	Results
1	Related Compounds	Not more than 0.2 %w/w	0.12 %w/w
2	Mocrobial Limits a) Total aerobic microbial count b) Total combined Yeast & Molds count c) Pathogenic organism i. Escherichia coli i. Salmonella i. Staphylococcus aureus	 a) Not more than 1000 cfu/g b) Not more than 100 cfu/g c) i)Should be absent ii)Should be absent iii)Should be absent	a) <10cfu/g b) <10cfu/g c) i) Absent ii) Absent iii) Absent

Table 7: Evaluation data of optimized formulation at Initial and after 6 months stability at 40°C±2°C/75% RH±5

Retest time for Optimized Formulation (F14)	%Drug Content	Invitro Drug Release (%)
Initial	99.95±0.21	99.94±2.32
6 Months	99.93±0.19	99.91±2.15

IV. CONCLUSION

Duloxetine HCl solid dispersions (SDs) were prepared by solvent evaporation technique, one of the important techniques with highest rate of reproducibility, feasible for its scalability and economically viable technique for commercialization prospect. Totally 15 SD formulations were prepared, all of which showed better drug release profile compared to pure Duloxetine HClActive Pharmaceutical ingredient (API). Initially 12 SD formulations were taken to optimize the best suitable polymer with maximum drug release rate. The solubility of Duloxetine HCl was found to be maximum in HPMC AS which was almost 4 fold and the same reflected in formulation F9 prepared with HPMC AS in 1:3:2 ratio of drug: polymer: surfactant showed maximum drug release of 95.84% in 15 mins. Solubility of Duloxetine HCl was also increased by 11 folds in SD formulation F9 when compared to pure drug. Increased dissolution rate are attributed to more polymer concentration used for formulating SDs. Also, the use of surfactant decreased the interfacial tension and enhanced the wettability there by enhanced the solubility. Once the polymer and its quantity was optimized (fixed component), to further enhance the rate of drug release, formulations were prepared to evaluate the effect of combination of surfactants on the drug release rate. The dissolution profile of pure SD formulation F14 prepared with HPMC AS in 1:3:(0.5+0.5) ratio of drug:polymer:surfactants [Table.3] showed maximum drug release of 99.94 in 15 mins. Solubility of Duloxetine HCl was also increased by 15 folds in SD formulation F14 when compared to pure drug. Maximum dissolution rate is attributed to use of combination of surfactant which showed synergistic effect in decreasing the interfacial tension and enhancing the wettability. This synergistic effect acted as the key factor in further enhancing the dissolution rate to the maximum. XRD and SEM studies reveal that the optimized formulation drug was in crystalline form. Inspiteof retaining the crystalline form the drug release rate was enhanced. Therefore, it can be affirmed that SD technology can be utilized for the improvement of drug release of poorly water soluble drugs like Duloxetine HCl.

Acknowledgments.
This work was financially supported by grants from Princeton College of Pharmacy, Narapally, Telangana, India.

REFERENCES

[1]. Tran P, Pyo YC, Kim DH, Lee SE, Kim JK, Park JS.Overview of the Manufacturing Methods of Solid Dispersion Technology for Improving the Solubility of Poorly Water-Soluble Drugs and Application to Anticancer Drugs.Pharmaceutics. 2019 Mar 19;11(3):132. doi: 10.3390/pharmaceutics11030132. PMID: 30893899; PMCID: PMC6470797.

[2]. Amr Mostafa El Sharawy, Marwa Hassan Shukr& Ahmed HassenElshafeey (2017) Formulation and optimization of duloxetine hydrochloride buccal films: in vitro and in vivo evaluation, Drug Delivery, 24:1, 762-[1]769, DOI: 10.1080/10717544.2017.1402216

[3]. Daravath B, Naveen C, Vemula SK, TadikondaRR.Solubility and dissolution enhancement of flurbiprofen by solid dispersion using hydrophilic carriers. Braz J Pharm Sci 2017;53:e00010.

[4]. Hassnain F, Bashir S, Asad M, Nazir I, Qamar S, Imran M, et al. Formulation and characterization of solid dispersion of nisoldipine by solvent evaporation method. J Pharm Altern Med 2012;2:21-8.

[5]. Lakshmi K, Kumarreddy MP, Kaza R. Dissolution enhancement of telmisartan by surface solid dispersion technology. Int J Innov Pharm Res 2012;3:247-51.

[6]. Patil A, Kumar S. Formulation and evaluation of solid dispersions of an anthelmintic drug for enhancement ofdissolution rate. JIPBS 2017;4:71-4.

[7]. Ganesh M, Ubaidulla U, Hemalatha P, Peng MM, Jang HT. Development of duloxetine hydrochloride loaded mesoporous silica nanoparticles: characterizations and in vitro evaluation. AAPS PharmSciTech. 2015 Aug;16(4):944-51. doi: 10.1208/s12249-014-0273-x. Epub 2015 Jan 22. PMID: 25604699; PMCID: PMC4508298.

[8]. Kumar Chellappan, Dinesh &LakshmanaPrabu, Sakthivel& S, Shanawaz.(2008). Compatibility studies between Duloxetine hydrochloride and tablet excipients using thermal and non-thermal methods.Journal of Pharmaceutical Research. 7. 20-23.

[9]. Rao KR, Nagabhushanam MV, Chowdary KP. In vitro Dissolution Studies on Solid Dispersions of Mefenamic Acid. Indian J Pharm Sci. 2011 Mar;73(2):243-7. doi: 10.4103/0250-474x.91575. PMID: 22303074; PMCID: PMC3267315.