SOLUBILITY ENHANCEMENT OF LULICONAZOLE BY SOLID DISPERSION.

Nalanda Rangari, Rushikesh Palkar*, Sonia Singh, Ajit Gund, Sonali Patil

Alard College of Pharmacy, Sr.No. 50, Alard Knowledge Park, Marunje Hinjewadi IT Park, Phase-1, Pune-411057

*Corresponding Author : Mr.. Rushikesh Narayan Palkar, S.Y.M.Pharm Student, Alard College of Pharmacy, rushikeshpalkar3@gmail.com

ABSTRACT:

Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic Effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in water (less than 1µg/ml) and their low dissolution rate in aqueous G.I.T. fluid often leads to insufficient bioavailability. There are few methods to enhance aqueous solubility of poorly soluble drug among them solid dispersion is one of the effective and accepted technique in the pharmaceutical industry. Therefore, in this study attempt is done to improve the physicochemical properties of Luliconazole, a poorly water-soluble drug, by forming dispersion with PEG 6000 as water soluble carrier. The solid dispersions of Luliconazole: PEG 6000 were prepared in ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:6 and 1:7 w/w by melting and physical triturating method. The formulations were characterized for drug content, DSC, FTIR spectrum, XRD & % drug release studies by Franz Diffusion Cell. All the formulations showed marked improvement in the solubility behaviour and improve dissolution rate. Formulation containing drug: PEG 6000 ratio of 1:4 w/w showed the best release 83% in 60 min as compared to the pure drug i.e.,39 % in 60 min. The interaction studies showed no interaction between the drug and the carrier. It was concluded that PEG 6000 as a carrier can be well utilized to improve the solubility of poorly soluble drugs.

KEYWORDS: Luliconazole, PEG 6000, Solubility, Solid Dispersion, Franz Diffusion Cell, FTIR spectrum, XRD, DSC

DOI Number: 10.14704/nq.2022.20.9.NQ44583 Neuro Quantology 2022; 20(9):5050-5058

INTRODUCTION:

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.[2]

The rate or extent of dissolution of drug from any solid dosage form is a rate limiting step in the poor process of water-soluble drug absorption. Potential absorption problem is due to erratic and incomplete absorption from gastrointestinal tract and occurs if the aqueous solubility is less than 1mg/mL. Therefore, for better and quick absorption, dissolution rate enhancement is critical.[4,5] Several techniques have been developed to enhance the solubility and overcome the problems associated with poorly water soluble drugs such as solid dispersion, inclusion complex, ultra-rapid freezing process, melt sono crystallization, solvent change method, melt granulation technique, supercritical solvent, supercritical and cryogenic technique, micronization, cosolvent approach, salt formation, use of surfactant and use of pro-drug.[6,7]

Luliconazole is used to treat tinea pedis (athlete's foot; fungal infection of the skin on the feet and between the toes), tinea cruris (jock itch; fungal infection of the skin in the groin or buttocks), and tinea corporis (ringworm; fungal skin infection that causes a red scaly rash on different parts of the body). Luliconazole is BCS

Class II Drug suffered from low and variable bioavailability which was attributed to its low water solubility. Solid dispersion technique has been widely used to increase the solubility of a poorly water-soluble drug. Based on this method Many methods are available to improve these characteristics including salt formation, micronization and addition of solvent or surface-active agents. In this study polyethylene glycol was selected and solid dispersion was prepared by the method of solvent evaporation.

The increase in dissolution rate of poorly water-soluble drugs from SDs can be attributed to one or combination of different factors Among the popular carriers used in the formulation of SD are polyethylene glycols (PEGs). They are widely used because of their hydrophilicity, low melting point, and low toxicity. The development of a pharmaceutical formulation is usually a trial-and-error technique including a careful control of the variables one at a time in a series of logical steps. This is generally a time-consuming method in which the effect of each experimental variable will be investigated separately, while keeping all others constant.[3] Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of low water-soluble drugs 2-4 there are practical limitation of these techniques. In 1961, Sekiguchi and Obi 5 developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs can be overcome. This method, which was later, termed solid dispersion which involved the formation of eutectic mixture of drugs with water-soluble carriers by the melting of their physical mixtures.[1]

OBJECTIVE OF THIS STUDY IS:

1. To acquire knowledge of solid dispersion.

2. To study the preparation, evaluation, literature of solid dispersion.

3. To study different methods of solid dispersion.

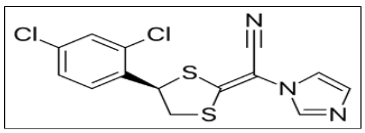
4. To Study the Evolution Parameter of Solid Dispersion.

❖ MATERIALS AND METHODS:

Luliconazole, PEG 6000, Methanol, Sodium Hydroxide, Sodium dihydrogen phosphateate, Disodium hydrogen phosphate.

A. Drug: Luliconazole

- **Monograph of Luliconazole**



- **Synonyms:**

Luliconazole

Lulicon

NND-502

Luzu

- **IUPAC Name:**

(2E)-2-[(4R)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene]-2-imidazol- 1-ylacetonitrile

- **Clinical Data:**
- **Formula:** $C_{14}H_9Cl_2N_3S_2$
- **PKA:** 6.34
- **Molecular mass:** 354.3 g/mol
- **Melting point:** 152°C
- **Half-life:** Up to 24 hrs
- **Drug category:** Antifungal
- **Mechanism of action:**[13]

Luliconazole is an antifungal that belongs to the azole class. Although the exact mechanism of action against dermatophytes is unknown, luliconazole appears to inhibit ergosterol synthesis by inhibiting the enzyme lanosterol demethylase. Inhibition of this enzyme's activity by azoles results in decreased amounts of ergosterol, a constituent of fungal cell membranes, and a corresponding accumulation of lanosterol.

- **Pharmacokinetics:**

a) Absorption:

Although luliconazole is administered topically, clinical studies have shown that after the first dose in patients with tina pedis, a maximum plasma concentration of 0.40 ± 0.76 ng/mL (mean ± SD) occurred in 16.9 ± 9.39 hours (mean ± SD).

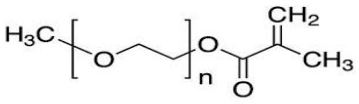
b) Distribution: The distribution was not quantified.

c) Metabolism: The metabolism of luliconazole has yet to be determined.

d) Elimination:

The clearance of luliconazole has yet to be determined.

B. Polyethylene glycol (PEG-6000):[14]



- **Synonym:**

1,2-ethanediol homopolymer

ethylene glycol homopolymer

ethylene glycol polymer

Glycols, polyethylene

- **Molecular weight:**44.05n + 18.02 g/mol
- **Specification:**
  - Appearance (Colour): White
  - Appearance (Form): Flakes/Powder
  - Solubility (Turbidity) :10% aq. Solution: Clear
  - Solubility (Colour) :10% aq. Solution: Colourless
  - pH (5% aq. solution):4.5 - 7.5
  - Melting Point:60 - 63°C
  - Viscosity (25%aq, 20°C): ~ 20 cS
  - Average Molecular weight:5000 – 7000

❖ **METHOD OF PREPARATION OF SOLID DISPERSION**

a. Solvent melting method:

- The required amount of carrier such as PEG 6000 will melted in a China dish
- Then Luliconazole will added to the China dish with continuous stirring till a homogeneous mass will obtained.
- The obtained mass will allow to solidify by placing at room temperature away from moisture. After solidification, the obtained mass will scratch, pulverized and sieved through mesh no. 100 and stored in a desiccator till used.

Table. No1: Preparation of solid dispersion

Formulation Code	Luliconazole (mg)	PEG 6000 (mg)
F1	100	100
F2	100	200
F3	100	300
F4	100	400
F5	100	500

Fig.No:1Solid dispersion of luliconazole

b. Preformulation Studies of Selected drugs:

a. Organoleptic properties: Drugs was tested for organoleptic properties such as appearance, colour, odour, taste, etc.

b. Micromeritics properties: [8,9,11,12]

i.Angle of Repose:

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free-standing surface of a powder heap and the horizontal. [

Angle of repose= tan- (h/r)

Where, h = height r = radius

- **Procedure:**

20gms of the sample was taken the sample was passed through the funnel slowly to form a heap. The height of the powder heap formed was measured. The circumference formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

ii.**Bulk density:**

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup.

Bulk density = M/V.

Where,

M= mass of the powder: Vo-bulk volume of the powder.

iii. Tapped density:

A known quantity of powder was transferred to a graduated cylinder and volume Vo was noted. The cylinder fixed to a density determination apparatus, tapped for 500 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume reading were taken until little further volume changes in observed.

Tap density = M/V

Where,

M = mass of the powder, V= final tapping volume of the powder.

iv. Compressibility index and Hausner ratio: [10]

While there are some variations in the method of determining the compressibility index and Hausner ratio, the basic procedure is to measure the unsettled apparent volume, (VO), and the final tapped volume, (Vf), of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner ratio are calculated as follows.

Compressibility index = 100 x Vo-Vf/Vo

Hausner ratio = Vo/Vf

Where,

Vo = apparent volume, Vf= final tapped volume.

Alternatively, the compressibility index and hausner ratio may be calculated using measured values of bulk density and tapped density as follows:

Compressibility index = 100 x tapped density / bulk density

Hausner ratio = tapped density/bulk density

In a variation of these methods, the rate of consolidation is sometimes measured rather than, or in addition to the change in volume that occurs on tapping. For the compressibility index and the hausner ratio, the generally accepted scale of flow ability is described in the following table. Flow properties and corresponding Angle of repose, Compressibility index and Hausner ratio

Table.No.2: Flow properties determination

Sr. no	Flow Properties	Angle of Repose(ɵ)	Compressibility Index (%)	Hausner ratio
1	Excellent	25-30	<10	1.00-1.11
2	Good	31-35	11—15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Passable	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.59
7	Very very poor	>66	>38	>1.6

c. Drug content:

The Physical mixture and solid dispersion equivalent to 25 mg of model drug were taken and dissolved separately in 25 ml of methanol. The solutions were filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbances of solutions were determined at 296 nm by UV spectrophotometer.

d. Invitro Skin Permeation Study:[15]

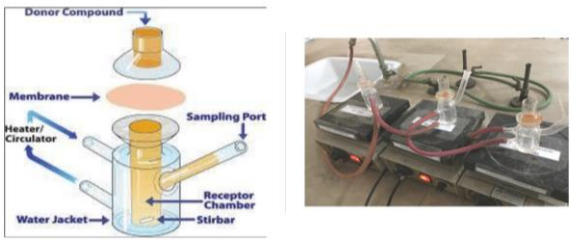


Fig.No:2 Franz Diffusion cell

The Vertical Franz Diffusion Cell is a simple, reproducible test for measuring the in vitro drug release from creams, ointments and gels. The Franz Cell consists of two primary chambers separated by a membrane. The test product is applied to the membrane via the top chamber-donor compartment. The bottom chamber receptor compartment contains fluid. Full thickness chicken mouth portion weighing 200-250gm. The dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels. Equilibrated for an hour in dissolution media or phosphate buffer pH 7.4 before starting experiment and was placed on a magnetic stirrer with a small magnetic needle or beads for uniform distribution of the diffusant. The temperature of

the cell was maintained 37 deg c +/-0.5 deg. C using thermostatically controlled heater. The isolated peace of skin is to be mounted between the compartments of the diffusion cell. Sample volume of definite volume is to be removed from the receptor compartment at regular interval and equal volume of fresh media is to be replaced. Sample to be filtered through filtering medium and can be analysed Spectro photometrically, determined directly at the slope of the curve between amount of drug permeated vs time in hours.

e. Powder X-Ray Diffraction (PXRD) studies:

The powder X-ray diffraction analysis was conducted for pure and treated drug, polymers, physical mixtures and solid dispersions. X-ray diffractograms were obtained using the Siemens (Germany) X- ray diffractometer with Cu-Kα (λ= 1.54 Å) radiation at 40 kV and 30 mA. All samples were scanned over a data is collected at 2θ from ~5° to 70°, angles that are present in the X-ray scan**.**

f. Differential scanning calorimetry (DSC):

Accurately weighed samples (pure PRX, treated PRX, carriers, physical mixtures and solid dispersions) were placed into the standard aluminium pans with lids. Subsequently, the physical status of PRX of the formulations was monitored using the differential scanning calorimetry (DSC60, Shimadzu, Japan). The heating rate was 20 º C/ min and the heat flow was recorded from 25 º C to 250 ºC. The aluminium oxide was used as reference.

g. Fourier Transform Infrared (FT-IR):

spectroscopic analysis FTIR spectra of the treated and pure powder of PRX and all carriers as well as physical mixtures and solid dispersions with drug to carrier ratio of 1:2 were obtained using a spectrophotometer (Bomem, USA) by potassium bromide (KBR, 150 bar) pellet method. The scanning range was 450–4000 cm−1, and the resolution was 4 cm−1.

RESULT AND DISCUSSION:

1. Preformulation results of selected Drugs:

a. Physical characters:

Sr. No	Characters	Inference
1	Nature	Powder
2	Colour	White
3	Odour	Characteristic
4	Melting Point	152

Table. No:3 Physical Character

b. Micromeritics Properties:

Table. No:4. Micromeritics properties

Sr.No.	Parameters	F1	F2	F3	F4	F5
1	Bulk Density g/ml	0.36	0.35	0.33	0.33	0.33
2	Tapped Density g/ml	0.46	0.44	0.40	0.37	0.36
3	Angle of Repose (⁰)	40.02	40	38	34.80	34.70
4	Carrs Index (%)	21.12	19.20	17.60	10.25	8.01
5	Hausners Ratio (%)	1.28	1.24	1.21	1.12	1.09

c. Drug content:

Table. No:5. Drug content

Sr. N0.	Formula No.	drug content
1	F 1	45.8682
2	F 2	53.8914
3	F 3	73.7131
4	F 4	90.2403
5	F 5	89.2403

d. Calibration Curve of Luliconazole:

➢ **UV Spectroscopy (Determination of λmax) for Luliconazole:**

Appropriate dilutions were prepared for drug from the standard stock solution and scanned in the spectrum mode from 400 nm to 200 nm. Luliconazole showed absorbance maxima at 296 nm.

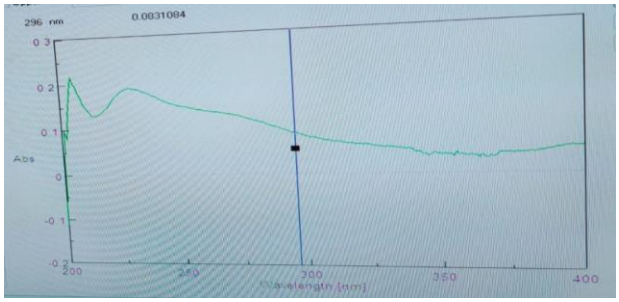


Fig.No:3 UV Spectrum of Luliconazole

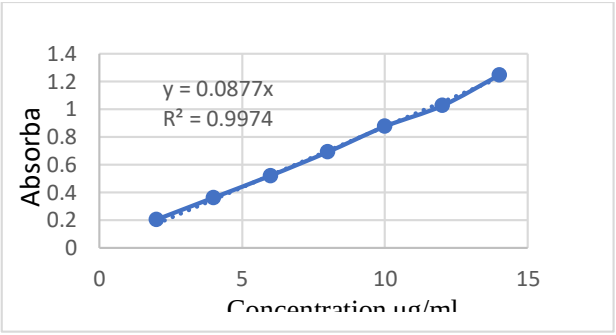


Fig.No:4 Calibration curve of Luliconazole.

➢ **Preparation of standard stock solution:**

Standard stock solution was prepared by transferring 10mg of Luliconazole into 10ml volumetric flask and it was dissolved with methanol. Working standard solution was prepared by taking 2.5ml of stock solution into a 25ml volumetric flask.

The volume was made up to mark to produce 100µg/ml solution with methanol and distilled water. From the above working solution 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1.0ml, 1.2ml and 1.4ml were pipetted and transferred to 6 individual 10 ml volumetric flask and finally the volume was made up to the mark with diluent. Solutions were scanned from 200-400 nm UV range by using UV-Visible double beam spectrophotometer.

➢ **Calibration of Luliconazole:**

Concentration µg/ml	Absorbance at 296 λ_{max}
2	0.20428
4	0.36301
6	0.52263
8	0.69318
10	0.87796
12	1.0271
14	1.24869

Table No.6 Standard calibration of Luliconazole

e. Invitro Skin permeation studies:

The Vertical Franz Diffusion Cell is a simple, reproducible test for measuring the in vitro drug release of Pure Luliconazole, marketed formulation, optimized solid dispersion respectively. chicken buccal portion is used as a permeation membrane or diffusion cell membrane for skin permeation study According to drug release pattern optimized solid dispersion shows high skin permeation as compared with pure Luliconazole. Permeation profile are as follows

Time	% Drug Release	
(min)	Pure drug	Solid dispersion
5	3.10%	10%
10	4.80%	23%
15	9%	31%
30	12%	47%
45	29%	65%
60	39%	83%

Table .no:7 skin permeation study

f. DSC (Differential scanning calorimetry):

The melting point of pure Luliconazole is 152^{0}C. The thermograms of the pure drugs characteristic, sharp exothermic peak at 153.65^{o}C, for pure drug, sharp endothermic peaks at 180.23^{o}C for pure drug (Luliconazole). This conclude that the peaks are associated with the melting point of the drug and indicates the amorphous nature of the drug. The DSC thermogram of pure Drugs, were shown in the following fig.5

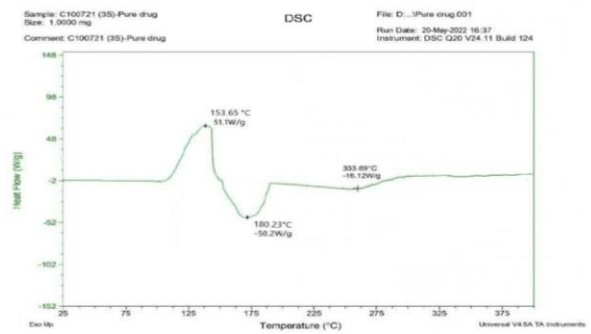


Fig.No: 5 DSC of Luliconazole

The melting point of pure Luliconazole is 152^{0}C and melting point of polymer PEG is 58.23^{0}C. The thermograms of the physical mixture characteristic, sharp exothermic peak at 148.31^{o}C, for physical mixture, sharp endothermic peaks at 165.80^{o}C for physical mixture (Luliconazole: PEG 6000). This conclude that the peaks are associated with the melting point of the drug and indicates the amorphous nature of the drug. The DSC thermogram of physical mixture, were shown in the following fig.

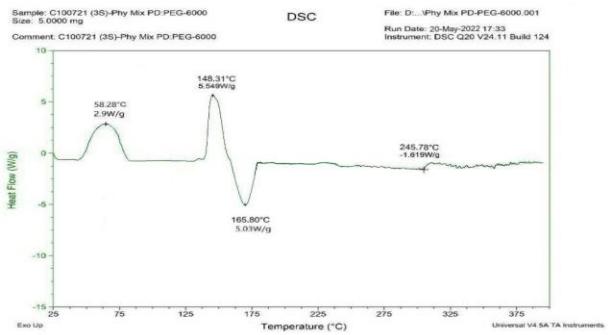


Fig.No:6 DSC of physical mixture Luliconazole: PEG 6000 ,1:1

The melting point of pure Luliconazole is 152^{0}C and melting point of polymer PEG is 58.23^{0}C. The thermograms of the optimized solid dispersion characteristic, sharp exothermic peak at 145.46^{o}C, for optimized solid dispersion, sharp endothermic peaks at 161.3^{o}C for optimized solid dispersion (Luliconazole: PEG 6000,1:4). This conclude that the peaks are associated with the melting point of the drug and indicates the amorphous nature of the drug. The DSC thermogram of optimized solid dispersion, were shown in the following fig.

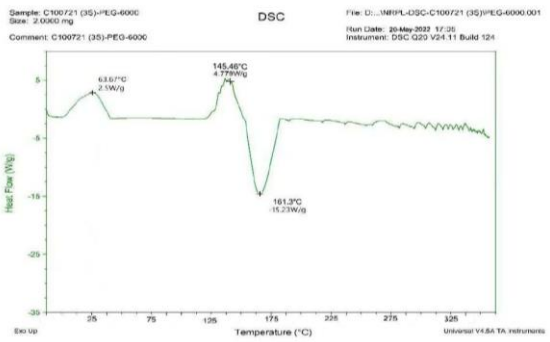


Fig.No:7 DSC of optimized solid dispersion (Luliconazole: PEG 6000, 1: 4)

h. Fourier-transform infrared spectroscopy (FTIR):

- Interpretation of FTIR for all samples are as follows
- Instrument Model: Carry 630
- Instrument S/N: MY16402006
- Software Version: Microlab PC(21CFR11):5.3.1748.0
- Method Name: Analytical chemie
- Range :4000-650

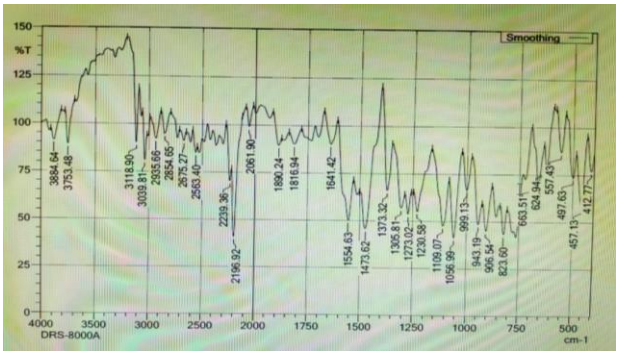


Fig.No:8. FTIR of pure Luliconazole

Table. No:8 Interpretation of FTIR of Pure Drug (Luliconazole)

Sr. No	Frequency	Functional group
1	3753.48	-OH and –NH stretching
2	2935.66, 2854.65	Aromatic –C=C-H
3	1641.4	C=O stretching

4	1554.63	Aromatic –C=C-
5	1273.02	Aromatic-NH
6	1056.99	N-CH3 stretching

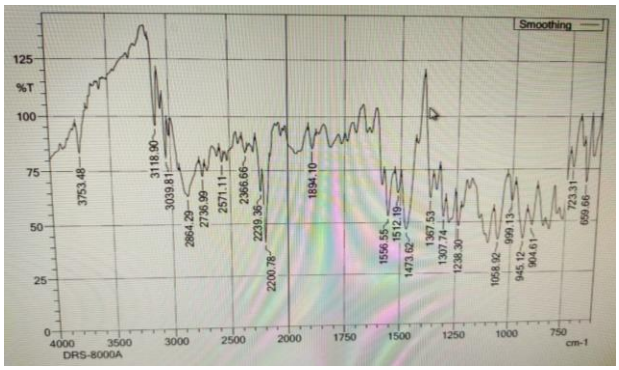


Fig.No:9. FTIR of Physical Mixture (LNZ: PEG-6000)

Table. No:9 Interpretation of FTIR of Physical Mixture (LNZ: PEG 6000)

Sr.No.	Frequency	Functional Group
1	3753.48	-OH and –NH stretching in drug
2	2864.29	C–H stretching of OC_2H_5 in PEG6000
3	1058.92	C–O stretching in PEG 6000
4	1556.55	Aromatic –C=C-
5	1273.02	Aromatic-NH
6	1058.92	N-CH3 stretching in drug molecule

❖ CONCLUSION:

From the present study it can be easily demonstrated that, PEG 6000, has immense potential to improve solubility characters of any less soluble or poorly soluble drug. This work also illustrates the fact that PEG 6000, has characteristics to form molecular dispersions with the drug molecules, thereby, increasing the dissolution rate of drug and decreasing the time of release of drug from the formulated mixture. The results of study clearly indicate that the Optimized solid dispersion concentration of polymer influence particle size of solid dispersion, flow property, drug content profile etc.

From the above study it concluded that high concentration of polyethylene glycol 6000(1:4) are influence drug content, The drug content of the prepared solid dispersions was in the range of 45.86-90.24% indicating the application of the present methods for the preparation of solid dispersions with high content uniformity. The maximum % drug content was found 90.24 % in formulation.

REFERANCES:

1. Akiladevi D, Shanmugapandiyan P, Jebasingh D, Akiladevi D, Shanmugapandiyan P, Jebasingh D, J. Pharm. Sci vol3 (2011).
2. Ford, J. L.; Acta Helv.; 1986; 61:69; 61:69-88.
3. [3] Ulla MR, Gangadharappa HV, Rathod N,Ulla MR, Gangadharappa HV, Rathod N, Pak J Pharm Sci, 2008, 21, 350-355.
4. Adibkia K, Barzegar-Jalali M, Maheri-Esfanjani H, Ghanbarzadeh S, Shokri J, Sabzevari A, et al. Physicochemical characterization of naproxen solid dispersions prepared via spray drying technology. Powder Technology 2013; 246: 448-55. doi: 10.1016/j.powtec.2013.05.044
5. Adibkia K, Barzegar-Jalali M, Mohammadi G, Ebrahimnejhad H, Alaei-Beirami M. Effect of sodium alginate chain length and Ca2+and Al 3+on the release of diltiazem from matrices. Pharmaceutical Sciences 2011; 16: 221-8.
6. De Zordi N, Moneghini M, Kikic I, Grassi M, Del Rio Castillo AE, Solinas D, et al. Applications of supercritical fluids to enhance the dissolution behaviors of Furosemide by generation of microparticles and solid dispersions. Eur J Pharm Biopharm 2012; 81: 131-41. doi: 10.1016/j. ejpb.2012.01.002
7. Vo CL, Park C, Lee BJ. Current trends and future perspectives of solid dispersions containing poorly watersoluble drugs. Eur J Pharm Biopharm 2013; 85:799-813. doi: 10.1016/j.ejpb.2013.09.007
8. Leon Lachmann, Herbert.A. Libermann, Joseph L. Kanig. The theory and practice of

Industrial pharmacy, 4th edition. Bombay Varghese publications. 293-303.
9. Remington. G. Edward Rudnic. The pharmaceutical sciences. 18th edition. Mack publishing company: 2005; 1633.
10. Powder flow. British pharmacopoeia. (2013); pg:1697
11. Indian Pharmacopoeia 1996 volume second, Government of India, Minstery of health & family welfair,New Delhi.
12. Indian Pharmacopoeia 2007 volume First, Government of India, Minstery of health & family welfair,New Delhi.
13. K.D. Tripathi Essentials of Medical Pharmacology, seventh edition, jaypee brother's medical publishers (P) LTD. 176-180.
14. Handbook of Pharmaceutical Excipients Sixth Edition by Raymond C rowe, Paul J Sheskey and Marian E Quinn, P. No. 48, 424, 663, 728.
15. Sing Tirupati K.T & Sakia T.R effect of penetration enhancers on the invitro transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations. Drug Dev.Ind.Pharm. 1993;19:1623-1628.
16. Drug bank---homepage (Information of Drug)
17. Drug.com (Information of Drug)