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ENHANCE SOLUBILITY AND BIOAVAILABILTY OF BCS CLASS IV DRUG DELAFLOXACIN

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ABSTRACT:

Solid dispersion technique has been used as effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs. Delafloxacin is an Anti-bacterial agent and is used in the treatment of bacterial infections in body, skin. The present study has demonstrated the possibility of improving dissolution performance of Delafloxacin, a poorly soluble drug by solid dispersion technique using PEG-4000 and HPMC polymer. For preparation of solid dispersions, various solid dispersion methods (Solvent evaporation, Fusion method) were used. The effect of several variables to both solid dispersionprepa rations was investigated. IR and UV spectralanalysis, Differential Scanning Calorimetry were used to characterize solid dispersions. Solid dispersions prepared by various methods were evaluated by methods like Saturationsolubility, percent drug content, and byin-vitro dissolution method for percent cumulative drug release. Hence, the study strongly recommends that developed Solid dispersion of Delafloxacin can be further utilized for the formulation of suitable dosage form such as tablets. Further, the drastic increase in the aqueous solubility of Delafloxacin afforded by the 'solid dispersion technique' approach will enable new formulation technologies to be tested inthe development of new more effective anti-bacterial products.

Index Terms **-** Solid dispersion, Delafloxacin, Solubility, Dissolutionrate, Anti-Bacterial.

INTRODUCTION

The oral route of drug administration is the most general and suitable method of delivery because of patient convenience and ease of administration. From a patient's point of view, swallowing a dosage form is a secure and a familiar means of taking dosage form.[1]Despite the oral route of administration is favoured, for several drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption leads to poor bioavailability is paramount amongst the potential issues that can be experienced when delivering an active molecule through oral route.[2, 3, 4]

Drug absorption through gastrointestinal (GI) tract can be restricted by a diversity of parameters with the most remarkable contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active molecule orally, it must primarily dissolve in gastric fluids before it can then cross the membranes of the GI tract to reach blood circulation. Hence, a drug with poor aqueous solubility will generally shows dissolution rate limited absorption, and a drug with poor membrane permeability will normally reveal permeation rate limited absorption. Therefore, two waysof pharmaceutical research that target on increasing the oral bioavailability of active molecule consists of: (i) Increasing solubility and dissolution rate of poorly water-soluble drugs and (ii) Increasing permeability of poorly permeable drugs. So, solid dispersion technology is utilized to enhance the dissolution properties of poorly water-soluble drugs and also their oral bioavailability.[5]

Solubility :

Solubility is the characteristics of a solid, liquid, or gaseous chemical substance called solutes to dissolve in a solid, liquid, or gaseous solvent to produce a homogeneous solutionof the solute in the solvent.[6] The solubility of a substance basically based upon the solvent used and also temperature and pressure. The range of solubility of a substance in a neededsolvent is measured as the saturation concentration where adding more solute doesn't increase its concentration in the solution. The extent of solubility ranges largely, from infinitely soluble like ethanol in water, to poorly soluble, such as silver chloride in water. The term insoluble is frequently used to poorly or very poorly soluble compounds.[7] Solubility is called in quantitative words as the concentration of the solute in a saturated solution at a definite temperature. In qualitative words, solubility may be known as the spontaneous connection of two or more substances to make a homogeneous molecular dispersion.[8] A saturated solution is one in which the solute is in equality with the solvent. The solubility of a drug may be described as parts, percentage, molarity, molality, and volume fraction and mole fraction. Solubility happens under dynamic equilibrium, which states that solubility results from the concurrent and opposing processes of dissolution andphase joining. Solubility equilibrium takes place when the two processes begin at a uniformrate. Under definite conditions equilibrium solubility may be run over to give a so-called supersaturated solution, which is metastable.[9] Solubility is not to be jumbled with the ability to disperse a substance, since these processesmay takes place not only because of dissolution but also due to a chemical reaction. For example, zinc is insoluble in hydrochloric acid, but does disperse in it by chemically reacting into zinc chloride and hydrogen, where zinc chloride is miscible with hydrochloricacid. Solubilization may be called as the formation of a thermodynamically stable solution of a substance that is generally insoluble or very slightly soluble in a given solvent, by theaddition of one or more amphiphilic parts.[10]

The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying a drug substance based on solubility, permeability, and dissolution criteria.[12]

According to the BCS, drug substances are classified as follows:

- Class I: high permeability and solubility.
- Class II: high permeability and low solubility.

- Class III: low permeability and high solubility.
- Class IV: low permeability and low solubility.

Bioavailability :

According to US FAD, Bioavailability is termed as "the rate and extent to which the activedrug ingredient is absorbed from a drug product and becomes available at the site of drug action". Because in practice it is limited that drug concentrations can be evaluated at the site of action. Bioavailability can also suggest to other types of dosage form, like intramuscular injections, ointments and other topical preparations, transdermal patches, and implants, which also required an absorption process before to reaching the systemic circulation. Only intravenous routes give 100% bioavailability because the amount of drugdirectly reaches in to the systemic circulation.[78] The pharmacological definition cannot used for substances because utilization and absorption is a function of the nutritional status and physiological state of the subject, leading to even greater differences from individual to individual (inter-individual variation). Therefore, bioavailability for dietary supplements can be defined as the ratio ofa substance able of being absorbed and available for use or storage.[14, 15]

By definition, when a drug is administered intravenous route, its bioavailability is 100%. However, when a drug is administered via other routes (such as oral), its bioavailability decreases (owing to incomplete absorption or first-pass metabolism). The measurement ofthe amount of the drug in the plasma at periodic time intervals indirectly indicates the rateand extent at which the drug is absorbed from the drug product and becomes available at the site of action. Bioavailability is one of the important factor in pharmacokinetics, as it must be considered when calculating dosages for non-intravenous routes of administration.It is described as either absolute or relative bioavailability.[18]

Factors Influencing Bioavailability :

Extra vascular administered drugs must cross some obstruction to reach the systemic circulation and/or their site of action. Many studies clarify those differences in manufacturing procedures as well as the composition of the dosage form that can affect the bioavailability of a drug product. The bioavailability of a drug product can also be affected by the physiology of the patient and other factors, such as the content of the gastrointestinal tract.[19]

A major parameter determining the bioavailability ofanorallyadministered drug product is the dissolution rate of the drug. A drug must be in solution to be absorbed from the gastrointestinal tract taking in thought the possibilities of drug precipitates as a result of low solubility in the fluids of the gastrointestinal tract.

Novel Drug Delivery system :

Drugs having poor solubility carrying the tough plan in formulation by applying typical process as they present problems like slow onset of action, poor oral bioavailability, lack of dose proportional, failure to obtain steady state plasma concentration, and side effects. The regular dosage forms thus may result in over- or under medication and poor patient compliance. These challenges are also reduced by making them as

novel drug delivery systems which can offers edges such as reduction in dose frequency, lowering of dose size,specific targeting, increased porosity, and enhancement in oral bioavailability. Nanotechnology is a very good and promising approach in which the development of drug delivery systems for those potent drugs whose clinical development was unsuccessful because to their poor solubility, low permeability, inadequate bioavailability, and other poor biopharmaceutical properties.[21]

DRUG PROFILE

DELAFLOXACIN:

Delafloxacin is a fluoroquinolone of fourth generation with increased effectiveness against gram-positive bacteria and unusual infections. Delafloxacin has been connected to minor ALT increases during treatment, but it hasn't been connected to any cases of idiosyncratic acute liver injury with symptoms and jaundice, as have been reported with other fluoroquinolones.

A fluoroquinolone of the fourth generation, delafloxacin (del" a flox' a sin) has extended activity against gram-positive bacteria, including strains of Streptococcus pneumoniae that are multidrug resistant. Delafloxacin is effective against a variety of aerobic gram- positive and gram-negative organisms, just like other fluoroquinolones. The bacterial DNA gyrase and topoisomerase IV, which are necessary for the production of bacterial mRNAs (transcription) and DNA replication, are thought to be the targets of the quinolones' action. Contrarily, DNA gyrases are absent from human [and other eukarotic] cells, and the topoisomerases that do exist there are not affected by fluoroquinolone suppression. Delafloxacin, which goes by the brand name Baxdela, was authorised for use in the UnitedStates in 2018. Infections of the skin and the structures of the skin caused by sensitive organisms are the only signs at the moment. Delafloxacin comes in 450 mg tablet and 300 mg lyophilized powder forms that are both suitable for parenteral administration and oral administration. A 450 mg oral dose or a 12-hour intravenous infusion every day for five to fourteen days is advised as a treatment plan. Gastrointestinal distress, motion sickness, diarrhoea, headaches, skin rashes, and allergic responses are typical adverse effects. Seizures, hallucinations, peripheral neuropathy, tendon rupture, severe hypersensitivity reactions, Stevens Johnson syndrome, angioedema, photosensitivity, and Clostridium difficile-associated diarrhoea are among the less frequent but more severe side effects of delafloxacin that are also present in other fluoroquinolones. Delafloxacin is a fourth generation fluoroquinolone with expanded activity against gram-positive bacteria as well as atypical pathogens. Delafloxacin has been linked to mild AL Televations during therapy, but has yet to be linked to instances of idiosyncratic acute liver injury with symptoms and jaundice as have been described with other fluoroquinolones.

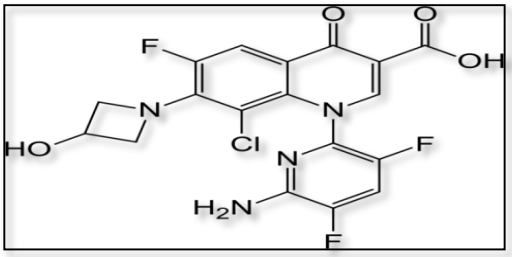

Figure No 1: Structure of Delafloxacin

Chemical Formula: $C_{18}H_{12}ClF_3N_4O_4$.

IUPAC Name: 1-(6-amino-3,5-difluoropyridin-2-yl)-8-chloro-6-fluoro-7-(3- hydroxyazetidin-1-yl)-4-oxoquinoline-3-carboxylic acid.

Indication : Delafloxacin is indicated for the treatment of acute bacterial skin and skin structure infections caused by the Gram- positive organisms Staphylococcus aureus (including methicillin-resistant and methicillin-susceptible isolates), Staphylococcus haemolyticus, Staphylococcus lugdunensis, Streptococcus agalactiae, Streptococcus anginosus Group (including Streptococcus anginosus, Streptococcus intermedius, and Streptococcus constellatus), Streptococcus pyogenes, and Enterococcus faecalis as well as the Gram-negative organisms Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, and Pseudomonas aeruginosa.

Mechanism of action : Delafloxacin inhibits the activity of bacterial DNA topoisomerase IV and DNA gyrase (topoisomerase II). This interferes with bacterial DNA replication by preventing the relaxation of positive supercoils introduced as part of the elongation process. The resultant strain inhibits further elongation. Delafloxacin exerts concentration-dependent bacteriocidal activity.

Half life : The mean half life of elimination of Delafloxacin is 3.7 hours after a single intravenous administration. The mean half life of elimination for multple oral administrations is 4.2-8.5 hours.

Toxicity : The most common adverse reactions noted with Delafloxacin were nausea (8%), diarrhea (8%), headache (3%), transaminase elevations (3%), and vomiting (2%). Fluoroquinolones are associated with increased frequency of tendon rupture and tendonitis, increased risk of peipheral neuropathy, excacerbation of myasthenia gravis, and development of Clostridium difficile-associated diarrhea. Fluoroquinolones are also associated with an increased risk of central nervous system reactions (CNS), including: convulsions and increased intracranial pressure (including pseudotumor cerebri) and toxic psychosis. Fluoroquinolones may also cause CNS reactions of nervousness, agitation, insomnia, anxiety, nightmares, paranoia, dizziness, confusion, tremors, hallucinations, depression, and suicidal thoughts or acts.

Route of elimination : After a single intravenous dose, 65% of Delafloxacin was excreted in the urine either unchanged or as glucuronidemetabolites with 28% excreted unchanged in the feces. Aftera single oral dose, 50% of Delafloxacin was excreted in the urine either unchanged or as glucuronide metabolites with 48% excreted unchanged in the feces.

RESEARCH METHODOLOGY

Preformulation Study: Preformulation is the primary activity that begins early in drug development. Preformulation studies are designed to determine the compatibility of initial excipients with the active substance for a biopharmaceutical, physicochemical, and analytical investigation in support of promising experimental formulations. Data from preformulation studies provide the necessary groundwork for formulation attempts. The selected drugs and excipients were standardized as per respective Pharmacopoeial specifications, wherever applicable.

Identification of Drugs: The identification of procured drug is one of the preliminary tests are performed to verify and ensure the purity of drug sample. Identification test is also included as a compendial test to provide a support in verifying the individuality of articles as they are purported. In the present research work, identification of drug was performed by its appearance, solubility, melting point and Fourier-transform infrared (FT-IR) spectroscopy.

Melting Point: Melting point is one of the identification tests for organic compounds. The melting point of the drug was determined using capillary melting point method. The drug was filled in a thin walled capillary tube, with sealed one end. The capillary was then placed in melting point apparatus and the temperature of the apparatus was gradually increased. The temperature range in excess of which the drug melts was observed visually.

Solubility Determination: Solubility studies for pure Delafloxacin were carried in purified water, ethanol and Phosphate buffer 6.8 pH. In every case excess quantity of sample was added to 10 ml of solvent and agitated at 37°C in a rotary test tube shaker for 24 hrs. After equilibration, the samples were filtered using m Millipore filters, suitable diluted and analyzed 0.45 µm forthe content Delafloxacin by measuring the absorbance at 295 nm using UV 3200, Lab India UV-Visible spectrophotometer.

Identification of Drug by FTIR: Fourier transform Infra-red (FT-IR) is the tool for solid state characterization of Pharmaceutical solids. The identification of the drug was done by (FT-IR) spectroscopic method using Model No 630, Agilent FTIR spectrophotometer. The drug was mixed with suitable amount of KBr and converted into pellets using KBr press at 20 psi for 10 min. The disc thus prepared was placed in a sample compartment and scanned at transmission mode in the region of 4000 to 400 cm^{-1}. Hence, the wave numbers of peaks in IR spectrumof the drug thus obtained was compared with the theoretical values of the wave number corresponding to the structure of drugs.

Standard calibration curve for Delafloxacin in phosphate buffer pH 6.8 Determination of absorption maxima (λ max): A solution of Delafloxacin containing the concentration 10 µg/ml was prepared in phosphate buffer 6.8pH; UV spectrum was taken using Double beam UV-VIS

spectrophotometer (Lab India). The solution was scanned in the range of 200 – 400 nm.

Preparation calibration curve: Delafloxacin drug 10 mg was weighed accurately and then it dissolve in the 10 ml phosphate buffer of pH 6.8 in the 10 ml of volumetric flask, then to make (1000 µg/ml) standard stock solution. Then from it take 1 ml of stock solution was taken from the 10 ml volumetric flask, to make (100 µg/ml) standard stock solution. 1 ml stock solution was taken in another 10 ml volumetric flask and then final concentration were prepared 10, 20, 30, 40, 50 µg/ml with phosphate buffer 6.8 pH. The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 295 nm.

Standard calibration curve for Delafloxacin in 0.1 N HCl Preparation of standard stock and calibration curve:

The 10 mg of Delafloxacin was dissolved in the 10 ml of Methanol until the drug dissolved entirely then make up the volume to 100ml with the 0.1 N of HCl it gives concentration of the 0.1 mg/ml (100 µg/ml). From the above standard solution (100µg/ml) 1ml was taken and diluted to 10 ml with 0.1N HCl to give a concentration of 0.01 mg/ml (10 µg/ml). from this stock solution aliquots of the 1, 2, 3, 4, 5 ml were pipetteout in the 10ml volumetric flask and the volume was then making up to the mark with 0.1N HCl to produce concentration of 10,20,30,40,50 µg/ml respectively. When this solution was scanned in the UV range i.e. from 200nm to 400nm λ max was found to be 298 nm for Delafloxacin in 0.1N HCl as a blank in UV-Visible Spectrophotometer. The absorbance (abs) of each concentration was measured at 298 nm.

Preparation and evaluation of Delafloxacin solid dispersion: Solid dispersion technology can be used to improve the solubility and bioavailability of poor water soluble drug. Delafloxacin is BCS class- II drug which is solubility is low. The dissolution rate from solid dispersion was affected by the carrier concentration. HPMC and PEG-4000 were used as carriers in the preparation of Delafloxacin solid dispersion. And the solid dispersion of Delafloxacin prepared by two methods is the fusion method and solvent evaporation method.

Procedure for preparation of the Delafloxacin solid dispersion by fusion method: In fusion Method, the drug with PEG-4000 and HPMC were prepared by separately at three different ratios 1:1, 1:2, 1:3. The polymer has been taken in china disc and kept in a mantle for a melting. After reaching melting point than add the drug with continuous stirring with a glass rod. After taking it out from the mantle, kept immediate for cooling in an ice bath, after cooling take it out and kept in desiccators.

Procedure for preparation of Delafloxacin solid dispersion by solvent evaporation method: In Solvent evaporation method, drug with PEG-4000 and HPMC were prepared by separately at three different ratios 1:1, 1:2 and 1:3. Accurately weighed 100mg drug was taken and mixed with 100, 200

and 300mg of PEG- 4000 and HPMC were dissolved with constant stirring. Solution was evaporated under low pressure to get the solid dispersion.

Dissolution studies: IN-VITRO dissolution studies of all formulations were carried out using 900 ml of 0.1 Nhydrochloric acid containing 0.5 % of Sodium lauryl Sulphate at 37 ± 0.5°C as the dissolution medium in a Type II apparatus (LABINDIA, DISSO) at a stirring speed of 100 rpm. The sodium Lauryl sulphate adds to dissolution medium to maintain sink condition. Accurately weighed pure Delafloxacin solid dispersions containing 100 mg of were used sprinkled directly to surface of the dissolution medium. Five milliliter sample solution of dissolution medium were withdrawn at the time interval 10, 20, 30, 40, 50 and60min and immediately replaced with an equal volume of the dissolution medium (maintained at 37 ± 0.5°C) in order to maintain constant volume of dissolution medium. The withdrawn samples were filtered and analyzed for drug content at 295 nm and cumulative percentage of drug dissolved was calculated. The amount of drug removed in each sample was compensated in the calculations. All experiments were performed in triplicate.

Stability Study: After preparation of the solid dispersions, the samples with acceptable dissolution profiles were stored separately for 8 weeks at 25 °C and 45 °C under an RH of 70%. Every week during this time, changes in the dissolution rates of the samples were studied. To evaluate the effect of humidity on the dissolution rates of solid dispersions, the obtained powders were kept under varying RHs for 4 weeks. Dissolution tests were performed at the start and then at one-week intervals during this period.

RESULTS AND DISCUSSION

Preformulation Study:

Identification of Drug:

Identification of the procured drug sample and ensuring its purity is a prerequisite before proceeding with the formulation development. The identification tests and the inferences for the drug sample based on its appearance and melting point determination are summarized in Table No. 1.

Parameters	Observations	Reported	Inferences
Appearance	Light Yellow to Tan Cake	Light Yellow to Tan Cake	Complies
Melting point	224 - 226 °C	227°C	Complies

Table No.1 : Identification of Delafloxacin

Solubility Determination :

The solubility of Delafloxacin was determined in distilled water, 0.1N HCl, methanol, phosphate buffer 6.8 pH. Solubility of drug in solvents so obtained compiled in.

Sr. No.	Solvent	Solubility
1	Distilled water	0.0699 mg/mL
2	0.1 N HCl	4.67 µg/ml
3	pH 6.8 Phosphate buffer	5.30 µg/ml
4	Methanol	Slightly soluble

Table No.2 : Solubility Determination

Drug and Polymer Compatibility Studies By FTIR:

In FTIR spectra the peaks of physical mixture was compared with the original spectra. Same peaks were observed, there is no possible molecular interaction between the drug and the polymer.

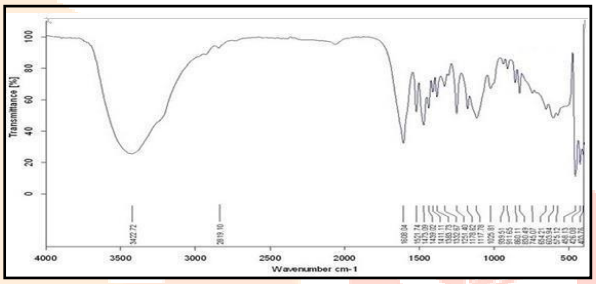

Figure No. 2 : FTIR Spectra of Delafloxacin

Construction of Standard curve of Delafloxacin:

Calibration Curve of Delafloxacin in phosphate buffer pH 6.8:

Determination of λ max:

UV- Spectra of pure Delafloxacin was obtained from UV- Spectrophotometer and the absorption maximum was found to be 295 nm.

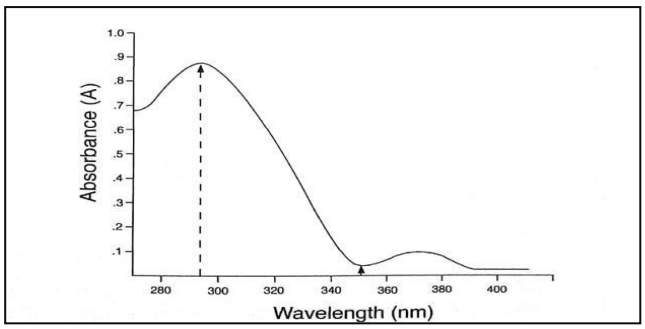

Figure No 3 : UV Absorption spectra of Delafloxacin in Phosphate buffer 6.8 pH

Development of Calibration Curve:

Sr. No	Concentration (µg/ml)	Absorbance (λ_{max} = 295 nm)
1	0	0
2.	10	0.156
3.	20	0.304
4.	30	0.456
5.	40	0.589
6.	50	0.728

Table No: 3 Standard Calibration Curve of Delafloxacin in Phosphate buffer 6.8pH

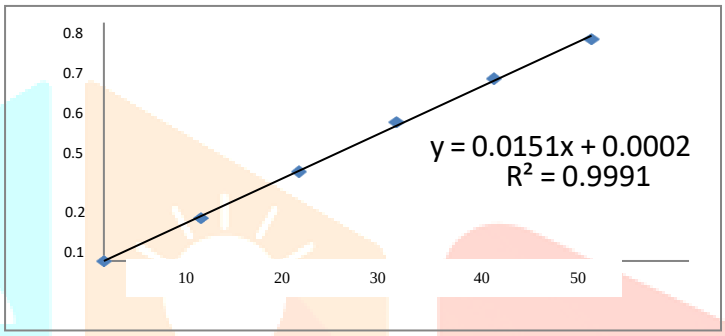

Figure No. 4 : Calibration Curve of Delafloxacin in Phosphate buffer 6.8 pH

Calibration Curve of Delafloxacin in 0.1N HCl:

Determination of λ max: UV- Spectra of pure Delafloxacin was obtained from UV- Spectrophotometer and theabsorption maximum was found to be 298 nm.

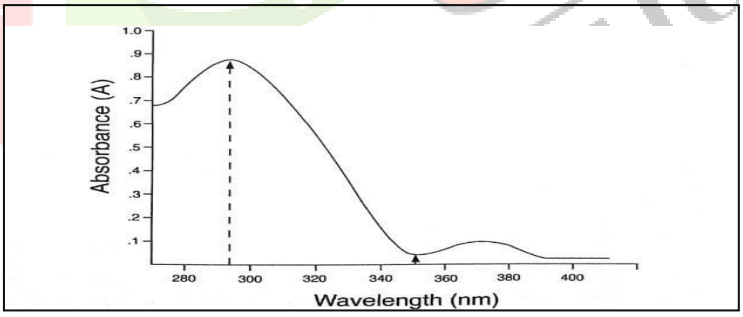

Figure No.5 : UV Absorption spectra of Delafloxacin in 0.1 N HCl

Sr. No	Concentration (µg/ml)	Absorbance (λmax = 298 nm)
1	0	0
2.	10	0.145
3.	20	0.301
4.	30	0.466
5.	40	0.612
6.	50	0.745

Table No 4: UV Absorption spectra of Delafloxacin in 0.1 N HCl

Parameters	Bulk Density (g/cm3) ±S.E.M.	Tapped Density(g/cm3) ±S.E.M.	% Compressibility index	Hauser sratio	Angle of repose
Formulation code					
DHF1	0.323± 0.005	0.348 ± 0.004	13.6	1.12	30°37'
DHF2	0.286 ± 0.008	0.344 ± 0.006	12.67	1.14	30°56'
DHF3	0.324 ± 0.007	0.345 ± 0.005	12.93	1.16	27°28'
DPF1	0.336± 0.004	0.349 ± 0.004	13.15	1.14	31°17'
DPF2	0.278 ± 0.006	0.336 ± 0.005	12.34	1.12	30°47'
DPF3	0.335± 0.004	0.372 ± 0.004	11.56	1.13	27°21'
DHS1	0.333± 0.006	0.352 ± 0.005	12.34	1.11	31°57'
DHS2	0.282 ± 0.007	0.348 ± 0.007	11.78	1.13	32°46'
DHS3	0.335± 0.008	0.379 ± 0.006	12.45	1.14	28°67'
DPS1	0.337± 0.005	0.367 ± 0.004	13.5	1.12	31°52'
DPS2	0.282 ± 0.007	0.348 ± 0.008	12.78	1.14	31°56'
DPS3	0.329 ± 0.006	0.359 ± 0.007	12.37	1.13	29°28'

Table No. 5: Micromeritic studies of pure drugs and solid dispersion formulation

Micromeritic studies of mixture blend drug Content:

The entire prepared solid dispersions formulations equivalent to 100 mg of Delafloxacin was weighed accurately and dissolved in 100 ml of phosphate buffer pH 6.8 in a separate volumetric flask. The solution was filtered, diluted suitably with same solvent and drug content is analyzed at 295 nm by UV-spectrophotometer.

Percentage yield of Delafloxacin SD:

The results of percentage yield of solid dispersion of Delafloxacin formulations wereas below

Sr. No.	Formulation code	% yield
1	DHF1	82.14
2	DHF2	86.65
3	DHF3	91.75
4	DPF1	96.16
5	DPF2	93.46
6	DPF3	94.27
7	DHS1	89.65
8	DHS2	97.20
9	DHS3	91.24
10	DPS1	90.88
11	DPS2	97.95
12	DPS3	93.23

Table No.6: Percentage yield of solid dispersion of Delafloxacin

Post Compression Parameters for evaluation:

IR Spectral analysis:

IR of Delafloxacin Solid Dispersion:

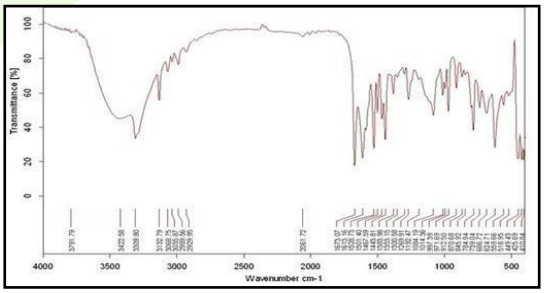

Figure No. 6 : IR of Delafloxacin Solid Dispersion

SEM Studies:

By using the SEM, observed pure drug Delafloxacin their solid dispersion surface characteristics. The graph depicts the SEM analysis of the SD formulation using PEG 4000. Also observed definite morphological changes in crystal of drug.

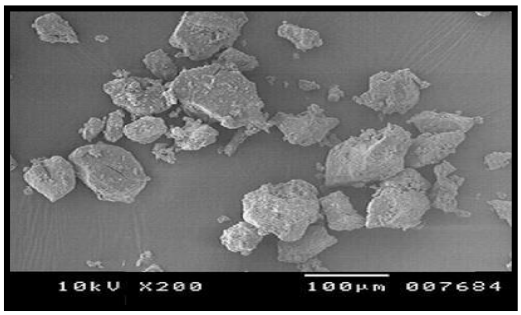

Figure No. 7 : SEM Study of Solid dispersion

Estimation of Drug Content :

Sr. No.	Formulation Code	% Drug Content
1	DHF1	83.23
2	DHF2	81.77
3	DHF3	86.19
4	DPF1	85.88
5	DPF2	87.89
6	DPF3	83.53
7	DHS1	93.89
8	DHS2	95.39
9	DHS3	91.99
10	DPS1	94.39
11	**DPS2**	**98.39**
12	DPS3	92.92

Table No. 7: Estimation of Drug Content

Dissolution studies of Delafloxacin and Release Kinetics:
invitro release of pure delafloxacin:

Sr. No.	Time in (min)	% drug release
1	0	0
2	10	10.20±1.8
3	20	18.20±1.6
4	30	21.9±1.0
5	40	27.20±1.3
6	50	29.10±1.5
7	60	35.6±1.0

Table No. 8: Invitro release of pure Delafloxacin

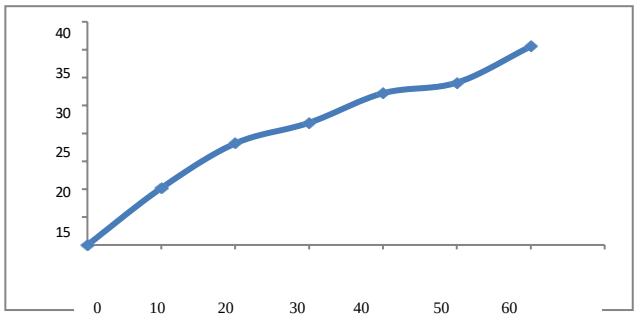

Figure No. 8: Invitro drug release of pure Delafloxacin

Invitro Drug release of Delafloxacin Solid Dispersion by fusion method byusing HPMC:

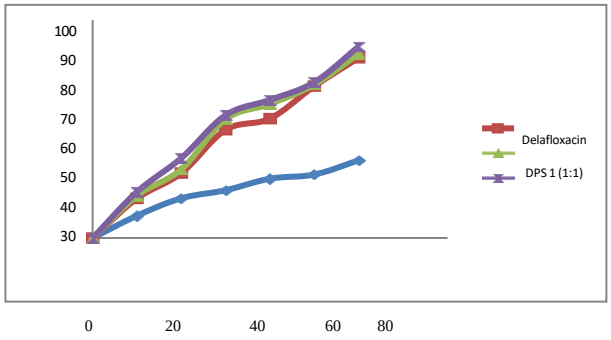

Figure No 9 : Invitro Drug Release of Delafloxacin Solid Dispersion by fusion method by using HPMC

Kinetics Release:

Time (min)		% Drug Release		
	Delafloxacin	DHF1(1:1)	DHF2(1:2)	DHF3(1:3)
0	0	0	0	0
10	10.21±1.8	8.8± 1.2	10.3 ± 1.02	11.6± 1.07
20	18.21±1.6	18.7± 1.23	20.9± 1.04	22.8± 1.12
30	21.8±1.0	31.7± 1.03	34.8± 1.65	36.09± 1.09
40	27.21±1.3	47.5± 1.01	46.6± 1.22	48.03± 1.43
50	29.11±1.5	54.6± 1.03	57.5± 1.23	58.06± 1.09
60	35.8±1.0	65.9± 1.06	68.8± 1.35	70.2± 1.29

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer R^2
DHF1 (1:1)	0.993	0.989	0.969	0.996
DHF2 (1:2)	0.998	0.982	0.977	0.998
DHF3 (1:3)	0.999	0.98	0.978	0.997

Table No. 9 : Release kinetics of Delafloxacin solid dispersion by fusion method by using HPMC

In-*Vitro* Drug Release of Delafloxacin Solid Dispersion by Solvent Evaporation method by using HPMC:

Time in (min)	% Drug Release			
	Delafloxacin	DHS1 (1:1)	DHS2 (1:2)	DHS3 (1:3)
0	0	0	0	0
10	10.21±1.8	18.4± 1.12	19.3± 1.02	21.4± 1.11
20	18.21±1.6	29.8± 1.11	31.4± 1.1	36.9± 1.02
30	21.8±1.0	49.6± 1.01	54.4± 1.14	56.6± 1.06
40	27.21±1.3	54.6± 1.5	61.4± 1.10	63.6± 1.03
50	29.11±1.5	69.4± 1.06	70.5± 1.03	71.7± 1.05
60	35.8±1.0	82.3± 1.16	84.6± 1.15	87.6± 1.09

Table No. 10 : *In-Vitro* Drug Release of Delafloxacin Solid Dispersion by SolventEvaporation method by using HPMC

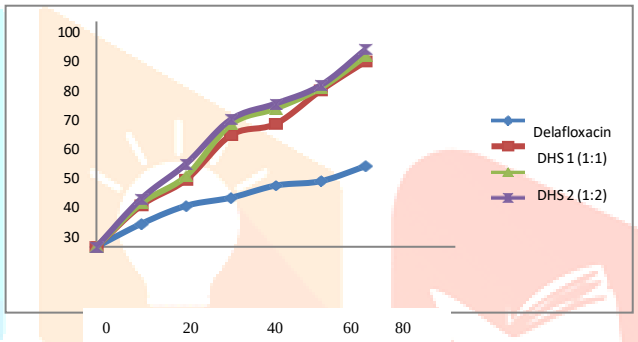

Figure 10 : In-Vitro Drug Release of Delafloxacin Solid Dispersion by SolventEvaporation method by using HPMC

Release kinetics of Delafloxacin solid dispersion by solvent evaporationmethod by using HPMC:

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer R^2
DHS1 (1:1)	0.988	0.964	0.975	0.989
DHS2 (1:2)	0.994	0.954	0.982	0.995
DHS3 (1:3)	0.995	0.915	0.990	0.995

Table No. 11 : Release kinetics of Delafloxacin solid dispersion by solventevaporation method by using HPMC

Zero order kinetics:

When the data is plotted as cumulative % drug release versus time, if the plot is linearthen the data obeys zero- order release Kinetics, with a slope equal to K0.

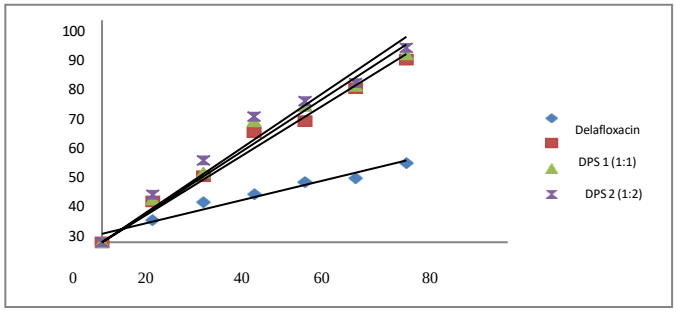

Figure No. 11 : Zero order kinetics of solid dispersion of Delafloxacin with HPMC by Solvent evaporation method

Korsmeyer equation/ Peppa's model :

When the data is plotted as log of drug released versus time, yields a straight line with a slope equal to n and the K can be obtained from y- intercept. To study the mechanism of drug release, the release data were also fitted to the well-known exponential equation (Korsmeyer equation/ Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

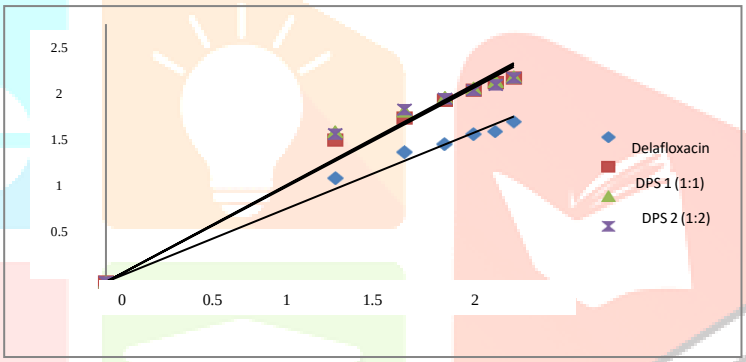

Figure No. 12: Korsmeyer / Peppas model of solid dispersion of Delafloxacin withPEG- 4000 by Solvent evaporation method.

The invitro dispersion studies of pure drug and all solid dispersion formulation with different ratios 1:1, 1:2, 1:3 by using two different carriers such as PEG 4000 and HPMC. The prepared solid dispersions of Delafloxacin equivalent to 100 mg of pure drug and dissolution studies were carried out in dissolution USP Type II apparatus containing 900 ml of 0.1 N hydrochloric acid containing 0.5 % of Sodium lauryl Sulphate at 37 ± 0.5°C. The samples were taken at different interval of time. 0 min, 10 min, 20 min, 30 min, 40 min, 50 min, 60min. also absorbance were recorded at 265 nm. From this invitro studies the solid dispersion containing drug and PEG4000 (1:2) released maximum 97.7% W/V (Solvent evaporation method). From this invitro studies it conclude that the solid dispersion containing Delafloxacin and PEG4000 (1:2) (Solvent evaporation method) showed high release. The studies proved that one of the fast releasing dosage form for poorly water soluble Delafloxacin by using solid dispersion technology.

Results of Stability Studies:

The effects of temperature and moisture on the dissolution profile of the Delafloxacin solid dispersion as shown in Figure 7.31 . The samples were stored separately for 8 weeks at 25 °C and 45 °C under an RH of 70%.

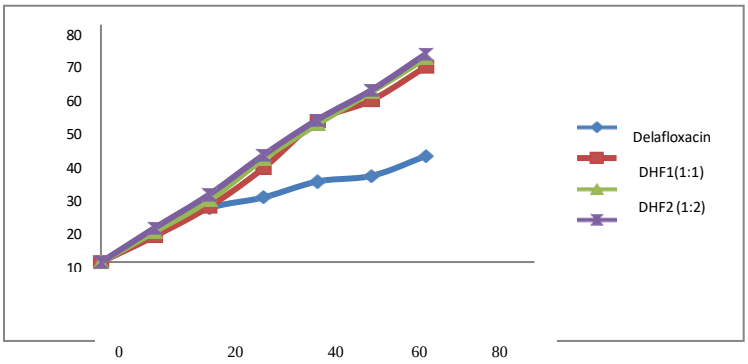

Figure No. 13: The dissolution rates of Delafloxacin solid dispersion samples afterstoring at 45 °C

The dissolution studies indicated that after 8 weeks, there were no significant differences between the dissolution profiles of Delafloxacin-PEG 4000 solid dispersions at 25 °C However, a significant reduction in the dissolution rate was shown after 4 weeks for the samples at 45 °C. All samples were kept at an RH of 70%.

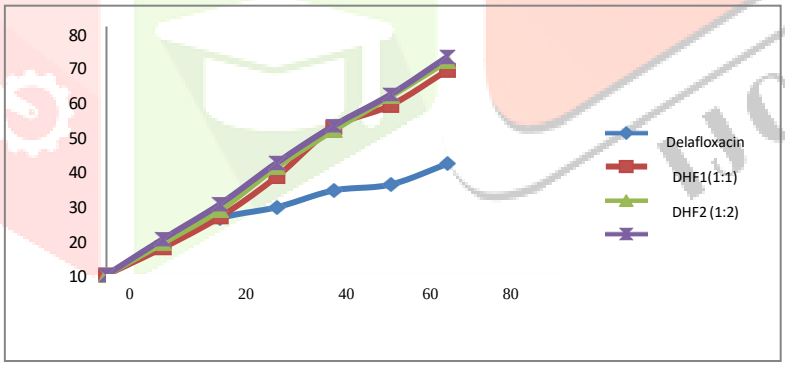

Figure No. 14: The dissolution rates of Delafloxacin solid dispersion samples afterstoring at 60% RH.

The effects of different humidity conditions on the dissolution rates of Delafloxacin solid dispersions are shown in Fig 7.32. The data illustrated no significant difference in the dissolution rate at RH of 60%

CONCLUSION

From the present study following conclusion were observed Delafloxacin drug are falls in class IV as per BCS classification and possesses limited water solubility, resulting in poor bioavailability. The dissolution rate from solid dispersion was affected by the carrier concentration. HPMC and PEG-4000 were used as carriers in the preparation ofDelafloxacin solid dispersion. And the solid dispersion of Delafloxacin prepared

by two methods is the fusion method and solvent evaporation method. All the prepared Solid Dispersion formulations of both polymers were showed multifold improvement in solubility. All the prepared Solid dispersion formulation of drug showed rapid drug releasein 60 min time, when tested for in vitro dissolution. Among the two polymer used for Solid Dispersion preparation, PEG 4000 gives better solubility and drug release. According to findings of this research investigation, the conclusion was made that solid dispersion technique is effective in boosting the solubility, dissolution and ultimately bioavailability of less aqueous soluble drug like Delafloxacin.

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