# PREPARATION AND EVALUATION OF SOLID DISPERSION OF GATIFLOXACIN BY USING MANNITOL

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## 1. INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability.[1]

### 1.1 SOLUBILITY DEFINITION

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. The solubility can also be defined as the ability of one substance to form a solution with another substance.[3] The substance to be dissolved is called as solute and the dissolving fluid in which the solute dissolve is called as solvent, which together form a solution. The process of dissolving solute into solvent is called as solution, or hydration if the solvent is water[4]

The relative solubility of solute in solvent is as follows

| **Definition** | **Parts of solvent required for one part of solute** |
|---|---|
| Very soluble | < 1 |
| Freely soluble | 1 – 10 |
| Soluble | 10 – 30 |
| Sparingly soluble | 30 – 100 |

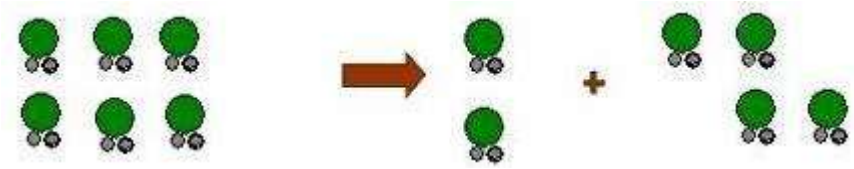
| | |
|---|---|
| Slightly soluble | 100 – 1000 |
| Very slightly soluble | 1000 - 10,000 |
| Insoluble | > 10,000 |

### 1.1.1 PROCESS OF SOLUBILISATION

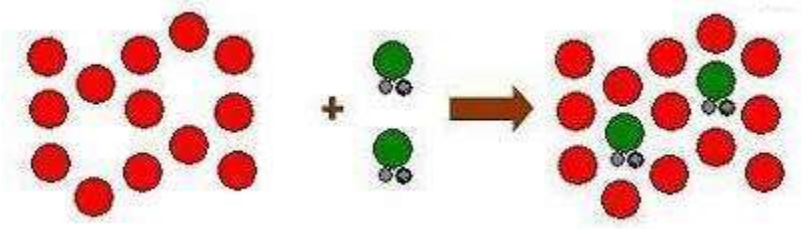
The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

**Step 1: Holes opens in the solvent**

**Step 2: Molecules of the solid breaks away from the bulk**



**Step 3:The freed solid molecule is intergrated into the hole in the solvent**



### 1.1.2 FACTORS AFFECTING SOLUBILITY

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system.

#### 1.1.2.1 PARTICLE SIZE

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be described by

$$\log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$

Where,

**S** is the solubility of infinitely large particles
**So** is the solubility of fine particles
**V** is molar volume
***g*** is the surface tension of the solid
**r** is the radius of the fine particle

#### 1.1.2.2 TEMPERATURE

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased. If the solution process releases energy then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases.

#### 1.1.2.3 PRESSURE

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility.

### 1.1.2.4 NATURE OF THE SOLUTE AND SOLVENT

While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubility's of these two substances is the result of differences in their natures.

### 1.1.2.5 MOLECULAR SIZE

Molecular size will affect the solubility. The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance . In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent

### 1.1.2.6 POLARITY

Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative

electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules.

### 1.1.2.7 POLYMORPHS

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of both polymorphs. The two polymorphs cannot be converted from one another without undergoing a phase transition. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

### 1.1.2.8 SIZE OF THE PARTICLES

When the total surface area of the solute particles is increased, the solute dissolves more rapidly because the action takes place only at the surface of each particle. Breaking a solute into smaller pieces increases its surface area and hence its rate of solution.

### 1.1.2.9 STIRRING

With liquid and solid solutes, stirring brings fresh portions of the solvent in contact with the solute, thereby increasing the rate of solution.

### 1.1.3.1 PHYSICAL MODIFICATIONS

**A. Particle size reduction**

*a. Micronization*

*b. Nanosuspension*

**B. Modification of the crystal habit**

*a. Polymorphs*

*b. Pseudopolymorphs*

**C. Drug dispersion in carriers**

*a. Eutectic mixtures*

*b. Solid dispersions*

*c. Solid solutions*

**D. Complexation**

*a. Use of complexing agents*

**E. Solubilization by surfactants**

*a. Microemulsions*

*b. Self microemulsifying drug delivery systems*

### 1.1.3.2 CHEMICAL MODIFICATIONS

For organic solutes that are ionizable, changing the pH of the system may be simplest and most effective means of increasing aqueous solubility. Under the proper conditions, the solubility of an ionizable drug can increase exponentially by adjusting the pH of the solution. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa. Similar to the lack of effect of heat on the solubility of non-polar substances, there is little effect of pH on nonionizable substances. Nonionizable, hydrophobic substances can have improved solubility by changing the dielectric constant (a ratio of the capacitance of one material to a reference standard) of the solvent by the use of co-solvents rather than the pH of the solvent.

The use of salt forms is a well known technique to enhanced dissolution profiles. Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. An alkaloid base is, generally, slightly soluble in water, but if the pH of medium is reduced by addition of acid, and the solubility of the base is increased as the pH continues to be reduced. The reason for

this increase in solubility is that the base is converted to a salt, which is relatively soluble in water (e.g. Tribasic calcium phosphate).The solubility of slightly soluble acid increased as the pH is increased by addition of alkali, the reason being that a salt is formed (e.g. Aspirin, Theophylline , Barbiturates).

### 1.1.4 BIOPHARMACEUTICAL CLASSIFICATION SYSTEM[6]

Depending upon solubility and bioavailability drugs are classified into four types

| Class | Dissolution in aqueous environment | Permeation over (intestinal) Membrane |
|---|---|---|
| I | Fast | Fast |
| II | Slow | Fast |
| III | Fast | Slow |
| IV | Slow | Slow |

## 1.2 SOLID DISPERSIONS

### DEFINITION

The term solid dispersions refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting method, solvent method or fusion solvent-method.

### 1.2.1 CLASSIFICATION OF SOLID DISPERSIONS

Based upon their molecular arrangement, solid dispersions are classified into 6 type

| SOLID DISPERSION TYPE | MATRIX * | DRUG ** | REMARKS | NO PHASES |
|---|---|---|---|---|
| I eutectics | C | C | The first type of solid dispersions prepared | 2 |
| II amorphous Precipitations In crystalline matrix | C | A | Rarely encountered | 2 |
| III solid Solutions | | | | |
| Continuous Solid Solutions | C | M | Miscible at all compositions, never prepared. | 1 |
| discontinuous solid solution | C | M | Partially miscible, 2 phases even though drug is molecularly dispersed | 1 |
| Substitution Solid | C | M | Molecular diameter of drug(solute) differs less than | 1 or 2 |

| | | | | |
|---|---|---|---|---|
| solutions | | | 15% from matrix(solvent) diameter. In that case the drug and matrix are substitutional. can be continuous or discontinuous. When discontinuous:2 phases even though drug is molecularly dispersed | |
| Intestinal solid solution | C | M | Drug(solute) molecular diameter less than 59% of matrix(solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug in intestinal spaces of PEG | 2 |
| IV glass suspension | A | C | Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix | 2 |
| V glass suspension | A | A | Particle size of dispersed phase dependent on cooling/ evaporation rate many solid dispersions are of this type | 2 |
| VI glass solutions | A | M | Requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during | 1 |

| | | | | |
|---|---|---|---|---|
| | | | preparation, many(recent) examples especially with PVP | |

## 1.2.2 METHODS OF PREPARATION OF SOLID DISPERSIONS

1.2.2.1 Hot Melt Method
1.2.2.2 Solvent Evaporation Method
1.2.2.3 Modified Solvent Evaporation Method
1.2.2.4 Hot-Melt Extrusion Method
1.2.2.5 Melting-Solvent Method
1.2.2.6 Common Solvent Method
1.2.2.7 Solvent Deposition
1.2.2.8 Solvent Method
1.2.2.9 Fusion Method
1.2.2.10 Super Critical Fluid Methods

1.2.2.11 Other Methods

a. Evaporative ppt. Method
b. Supercritical Fluid impregnation Method
c. Electrostatic Spinning Method
d. Kneading method

### 1.2.2.1 HOT MELT METHOD

It is used to prepare solid dispersions. Drug and Polymer were melted together & then cooled in an ice bath. The resultant solid mass was obtained and then milled to reduce the particle size. Cooling leads to super saturation, but due to solidification the

dispersed drug becomes trapped with in the carrier matrix. Molecular dispersion depends on the degree of super saturation and rate of cooling.

An important requisite for the formation of solid dispersion by the Hot melt method is

- Miscibility of drug & carrier in Molten form
- Thermo stability of the drug & carrier.

### 1.2.2.2 SOLVENT EVAPORATION METHOD

In this method both the drug & carrier are dissolved in a common solvent then this solution is transferred to Petri dish and then evaporate at room temperature and then dried at 65 degree c for 6hrs in hot air oven. Then the resultant mass is crushed & sieved (#80)

Temperature used for solvent evaporation generally lie in the range of 23-65$^0$c.

The solvent can be removed by spray drying or freeze drying.

An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug & carrier are sufficiently soluble in the solvent.

This method has negative effects of the solvents on the environment and high cost of production due to extra facility for the removal of solvents.

Due to the toxicity potential of organic solvents employed in the solvent evaporation method, hot melt extrusion methods is preferred in preparing solid solutions.

### 1.2.2.3 MODIFIED SOLVENT EVAPORATION METHOD

In this method the drug is dissolved in a suitable solvent with continuous stirring up to 30 min. swell able polymers like Sodium carboxy methyl cellulose, Starch, HPMC are selected and water is added up to the wet of polymer. Then the drug solution is poured at once in to polymer and the solution is allowed to evaporate at 60-70oC. The solid dispersions obtained are dried at 70-80oC and are stored in (desecrator) for 24hrs.

### 1.2.2.4 HOT MELT EXTRUSION METHOD

Melt extrusion is essentially the same as the fusion method except that the intense mixing of the components is induced by the extruder. When compared to melting in a

vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug matrix mixture in to implants, ophthalmic insects (or) oral dosage forms .The process has been useful in the preparation of solid dispersions in a single step so, this offers continuous production which makes it suitable for large scale production.

### 1.2.2.5 MELTING SOLVENT METHOD

Drug is dissolved in a suitable liquid solvent and then this solution is incorporated in to the melt of polymer, obtained below 70oC without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of PEG. Also polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used.

### 1.2.2.6 COMMON SOLVENT METHOD

In this method the drug and the polymer are taken in a beaker containing solvent and then mixed well until they get dissolved. Then the solvent is evaporated by heating on water bath with continuous stirring. Then the mass is stored in dessicator for 2days to (haiden) and then sieved (#60).

### 1.2.2.7 SOLVENT DEPOSITION

In this method of preparation the drug is dissolved in a suitable solvent to produce a clear solution. Then the carrier was dispersed in the solution by stirring at $38^0$ C. Then the solvent is removed at $61^0$ C with continuous stirring. Then the obtained mass is dried at $40^0$c for 24hrs and sieved (#120).

### 1.2.2.8 SOLVENT METHOD

The first step in the preparation of solid dispersions through solvent method is the preparation of a solution containing both matrix material and drug. The second step

involves the removal of solvent resulting in the formation of a solid dispersion. Mixing at the molecular level is preferred because this leads to optimal dissolution properties.

### 1.2.2.9 FUSION METHOD

Fusion method is sometimes referred to as the melt method. Here the starting materials must be crystalline. The dispersion consisted of drug and polymer as a matrix which were melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was choosen to obtain simultaneous crystallization of drug and matrix during cooling. This procedure resulted in solid dispersions formation.

The major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature.

When the drug & matrix are incompatible 2 liquid phases or a suspension can be observed in the heated mixture, which results in an on homogeneous solid dispersions. This can be prevented by using surfactants. A problem can arise during cooling when the drug-matrix miscibility changes.

Degradation of drug & matrix can occur during heating to temperatures necessarily to fuse matrix and drug.

### 1.2.2.10 SUPER CRITICAL FLUID METHOD

Super critical fluid methods are mostly applied with CO2 which is used as either a solvent for drug and matrix or as an anti solvent. When super critical CO2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, in to an expansion vessel with lower pressure and particles are immediately formed. The Adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since the CO2 is considered environmentally friendly, this technique is referred to as “Solvent free”. The application of this technique is very limited because the solubility in CO2 of most pharmaceutical compounds is very low and decreases with increasing polarity.

### 1.2.2.11 OTHER METHODS

a) Evaporative precipitation in to aqueous solutions (EPAS) is used to coat a colloidal suspension of drug with block-copolymers as stabilizing surfactants. A solution of drug was sprayed in as aqueous solution containing polymeric surfactants as stabilizers. The obtained colloidal suspension was spray dried, freeze dried it spray freeze dried resulting in solid dispersions. The Amorphous state of the drop was best preserved, with the spray freeze drying process.

b) In another process called supercritical fluid impregnation, the drug is dissolved in a supercritical fluid and exposed to solid matrix material that swells and absorbs the supercritical solution.

c) In an electrostatic spinning process a drug matrix solution is pumped through an orifice and then subjected to an electrical field to form fibres with a diameter of micro or nano scale this process is restricted to a limited amount of matrices because only a high few molecular weight materials are fibre forming materials. After rapid evaporation of solvent the fibres can be directly used or willed and further processed.

d) In kneading method, the drug and the polymer was triturated in a glass mortar by using sodium hydroxide as solvent. This slurry was kneaded for 45min and then evaporated at $50^0$c to constant weight. The dried mass was pulverized and sifted through sieve #100 and stored in a dessicator.

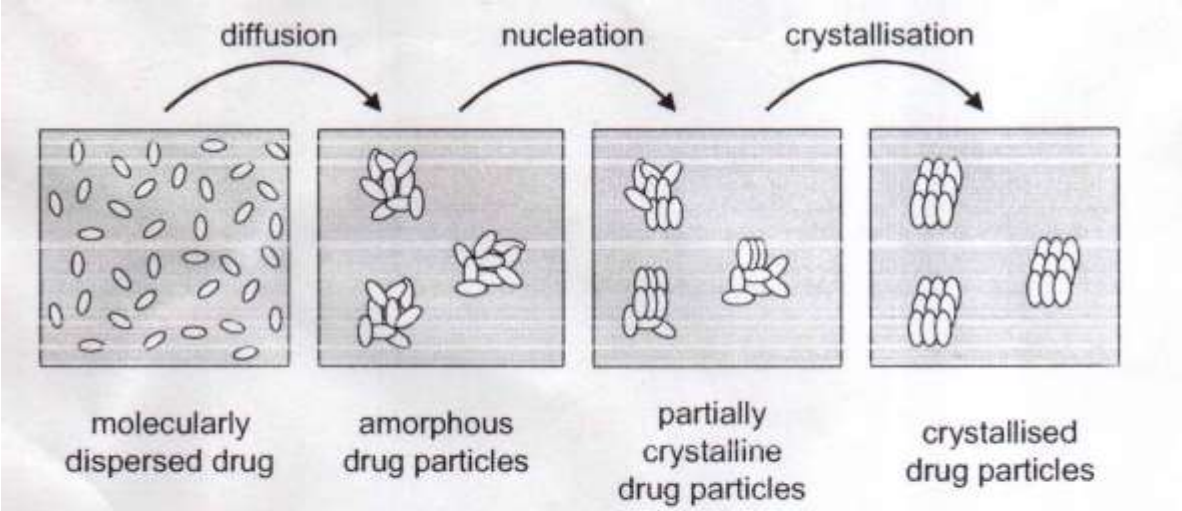



*Figure 6: Physical changes in solid dispersions resulting in crystallization*

## APPLICATION OF SOLID DISPERSIONS IN DOSAGE FORMS

The formulation of solid dispersions into drug administration forms also presents a great challenge.

- To mask the bitter taste of drugs.
- In design of fast release and rapid release dosage forms.
- To reduce gastric and other GIT irritation.
- Stabilization of drugs sensitive to oxygen ,moisture or light.
- Elimination of incompatibilities among drugs.
- Reduction of toxicity.
- To reduce hygroscopicity.

# CHARACTERISATION OF SOLID DISPERSIONS

- **SEM ANALYSIS** [7]

The particle size, shape and surface morphology of solid dispersions were examined by scanning electron microscopy. (LEO, 435VP, UK) prior to examination, samples were mounted on an aluminum stub using a double sided adhesive tape and then making it electrically conductive by coating with a thin layer of gold (approximately 20nm) in vacuum. The scanning electron microscope was operated at an acceleration voltage of 15KV.

- **SIEVE ANALYSIS**

Different sizes in a batch are separated by sieving using a range of standard sieves 10/22, 22/44, 44/60, 60/85, 85/100 and the amounts retained on different sieves were weighed. Studies were carried out in triplicate. The average size of the solid dispersions were calculated by using the equation.

$$D\ ave = \Sigma xifi/fi$$

Where

xi = the mean size of the range
fi = the percent material retained on the smaller sieve in the size range.

- **ESTIMATION OF DRUG CONTENT IN SOLID DISPERSION**

50ml solid dispersions or physical mixture were weighed accurately and transferred in to a 50ml volumetric flask. The volume was made up to the mark with methanol and kept for 2hrs with occasional shaking and filtered. Then the drug content was analyzed spectrophotometrically at 475nm using a single beam visible U.V Spectrophotometer.

- **INVITRO DISSOLUTION STUDIES**

The release of gatifloxacin from solid dispersion was investigated in phosphate buffer of PH 7.4 as a dissolution medium (900ml) using the paddle method specified in

USP **X** XIV (model TD T6P-Electrolab).sample of 100mg solid dispersions were taken in the dissolution flask. A speed of 75rpm and temperature 37+ 0.5 C was maintained through out the experiment. At fixed intervals, aliquots (5ml) were with drawn and replaced with fresh dissolution media.

The concentration of drug released at different time intervals was then determined by measuring the absorbance using visible spectrophotometer at 286nm against blank.The studies were carried out in triplicate.

The basic *invitro* release data was tabulated and graphed as

- Cumulative percent drug released Vs time.
- Log cumulative percent drug retained Vs * T
- Log cumulative percent drug released Vs log time.

- **IR STUDIES**[8]

FTIR Spectroscopy was performed on each at the samples to determine the structure of the organic compounds and to identify the presence of specific functional groups with in a sample. Further more drug polymer interactions were examine using the resulting spectra. The infrared spectra were obtained using a scale of wave numbers (cm-1). The analysis were performed by using a thermo nicolet nexus 470 FTIR ESP.3-5mg of sample was added to approximately 100mg of KBr. The mixture was then ground to a fine powder using a mortar & pestle and transparent discs formed using a pellet press. The discs were placed in FTIR spectroscopy apparatus and spectra were collected. The range of the collected spectra was 40000-400cm

- **WETTABILITY STUDIES**[9]

Pure drug approximately 1gm was placed in sintered glass funnel with the heap of cotton plug. The funnel was held in upright position in a beaker filled with water level in the beaker just touched the cotton plug. The time required to raise the water

through the drug for the colorings of water was recorded. Same procedure was followed for all solid dispersions.

- **SOLUBILITY STUDIES[10]**

Pure drug (20mg), its physical mixture and solid dispersion with PEG 6000 (40 mg, 60mg, 80mg= 20mgdrug (1:1, 1:2, 1:3) under test was placed in a test tube containing 1ml distilled water. The samples were shaken at room temperature until equilibrium was achieved and the aliquots were filtered. The filtered samples were diluted suitably and assayed spectrophotometrically at 286nm.

- **ANGLE OF REPOSE** [11]

To get an idea about flow ability properties of the solid dispersion, angle of repose for all the batches are determined.

### 1.2.6 KINETICS OF DRUG RELEASE[12]

Release of the active constituent is an important consideration in case of solid dispersions. Many theoretically possible mechanisms may be considered for the release of drug from solid dispersions.

i) Liberation due to polymer erosion or degradation.
ii) Self diffusion through the pore.
iii) Release form the surface of the polymer.
iv) Pulsed delivery initiated by the application of an oscillating or sonic field.

In most of the cases, a combination of more than one mechanism for drug release may operate so the distinction amongst the mechanism is not always trivial. The release profile from the solid dispersion depends on the nature of the polymer used in the prep ration as on the nature of the active drug.

Attempts to model drug release from solid dispersions have been reported and in the treatment of their data, it was assumed that drug release was confined to any of the

order such as zero of mechanism can be obtained using a plot of cumulative percentage of drug remaining in the matrix against time.

First order release would be linear as predication by following equation.

Log c = log Co-kt/2.303→(1)

Where

C = Amount of drug left in the matrix
Co = Initial amount of drug in the matrix
K = First order rate constant (time-1)
T = Time (hours/minutes)

The in-vitro drug release date obtained from selected batch of solid dispersions was treated according to equation (1) by plotting log of cumulative % of drug remaining against time. Next, an attempt was made to see who there the drug by diffusion, were proposed by Higuchi.

Q =[DE/T(2A-ECs)t]→(2)

Q = Weight in grams of drug released per unit surface.
D = Diffusion coefficient of drug in the release medium
E = Porosity of the matrix
Cs = solubility of drug in the solid dispersion expressed as gm/ml.

The assumption made in the deriving equation (2) is as follows.

- A pseudo steady state is maintained during release.
- A>>Cs i.e., excess solute is present.
- C = 0 solution at all times (perfect sink condition)
- Drug particles are much smaller than those in the matrix
- The diffusion coefficient remains constant.
- No interaction between the drug and the matrix occurs.

For the purpose of data treatment, equation is usually reduced to,

Q = k t1/2-→(3)

Therefore a plot amount of drug released Vs square root of time should be linear if the drug release from the matrix is diffusion controlled.

Precisely, to know the exact mechanism of drug release, whether it is by diffusion or with combination of diffusion and erosion control, the data has also been plotted according to equation as suggested by korsemeyer, they used a simple empirical equation to describe the general solute release behavior from control release polymer matrices.

$$Mt/M\alpha = k\ tn \rightarrow (4)$$

Where

Mt/Mα = The fraction of drug release
K = Kinetic rate constant
T = release time
N = Diffusional exponent for drug release.

The value of 'n' gives an indication of the release mechanism. For non-fickian release, the 'n' value falls between 0.5 and 1.0 while in the case of fickian diffusion n < 0.5, zero order release (case 2 Trans port ), n=1 and for super case 2 transport, n >1.

The in-vitro drug release date obtained from solid dispersion was treated according to equation (4) By plotting log cumulative percentage of drug release Vs log time.

## 2. AIM AND OBJECTIVE

The rate and extent of dissolution of the drug from any solid dosage form determines the rate and extent of absorption of the drug. In the case of poorly soluble drugs, dissolution is the rate limiting step in the process of drug absorption. Potential bioavailability problems are prevalent with extremely hydrophobic drugs due to incomplete absorption from GIT. The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly water soluble drugs.

Solid dispersions are dosage forms where the drug is dispersed in a biologically inert matrix. They can be used to increase the dissolution rate of a drug with low aqueous solubility, thereby improving its oral bioavailability. Higher drug dissolution rates from a solid dispersion can be facilitated by optimizing the wetting characteristics of the compound surface as well as increasing the interfacial surface area available for drug dissolution. Gatifloxacin has been selected as a model drug because it exhibits all the

pharmacokinetic and physico-chemical properties. Gatifloxacin is well absorbed from GIT after oral administration. It is about 20% bound to proteins. It has biological half life of 7-14 hours and is slowly eliminated from the body. It is usually administered orally or intravenous route containing 400 mg of drug. The effect of drug lasts for few hours and also it undergoes decomposition in solution form and also it is poorly soluble in water and gastric medium. Hence to improve therapeutic efficacy, to reduce decomposition, to increase solubility and to reduce adverse effects, solid dispersions of gatifloxacin are essential.

The present study is planned with the following objectives.

- To prepare the solid dispersions of gatifloxacin using mannitol employing common solvent method, kneading method, physical mixture method.
- To study the influence of polymer concentration on drug release.
- To evaluate the solid dispersions for sieve analysis, drug content, IR studies, wettability studies, angle of repose and *in-vitro* studies.

# . 3. REVIEW OF LITERATURE

## 3.1 SOLID DISPERSIONS

**Mallick, Asahoo et al.,**[13] prepared solid dispersions of Albendazole by co-dissolvation of and solvent evaporation techniques using water soluble carrier such as PEG and PVP to improve the aqueous solubility of the drug and thus enhancing its bio availability. The physicochemical characteristics of these solid dispersions were performed by scanning electron microscopy and X-Ray diffraction. Fourier Transform infrared spectroscopy and dissolution rate analysis. SEM was used to clarify the surface and shape characteristics of different samples. No significant changes in the frequency and shape of Albendazole were noticed by FTIR studies which leads to the conclusion that no strong interaction between the drug and the polymer exists in the solid dispersion particles. The degree of Crystallinity of Albendazole decreased and also differed with the solid dispersions of different polymers. Dissolution rate and % dissolution efficiency

was significantly increased in the solid dispersions in comparison with drug alone. The drug release kinetics was ascertained by using F-Test statistics using kinetic models of zero order, first orders. Higuchi and Hixson Crowell formed solid dispersions of Albendazole with water soluble polymers like PVP& PEG and the dissolution rate of the drug in the solid dispersion system was faster when the ratio of polymer to drug was greater .First order model may be used for explaining the kinetics of drug release from all the solid formulations as suggested by F-Test.

**Patel MM, Patel DM et al**.,[14] developed solid dispersions of valdecoxib with mannitol, poly ethylene glycol 4000 and polyvinyl pyrrolidone K-12, with a view to increase its water solubility. Valdecoxib solid dispersion with polyvinyl pyrolidine K-12 showed maximum dry release hence, the tablet formulation containing valedecoxib polyvinyl pyrolidine. K-12 solid dispersion, was prepared with a view to improve its water solubility. The dissolution profile of best laboratory developed formulation (f1) was compared with marketed tablet products. The drug release profile was studies in 0.1 N HCL. F1 gave far better dissolution than the conventional marketed tablet. Which released only 44.3% drug and valdecoxib in b cyclodextrin, which released 53.4% drug in 20 min, while f1 exhibited almost 100% dmg release in 20 min. The dissolution efficiency of f1 was compared with pure drug, conventional marked tablet, and valdecoxib in b cyclodextrin, f1 showed maximum dissolution efficiency. F1 was considered better than valdecoxib in b cyclodextrin, as far as the cost of raw materials used in the product is concerned. F1 was subjected to stability studies. The formulation was found to be stable for 4 weeks at 45 degrees, with insignificant change in the hardness, disintegration time, and in vitro drug release pattern.

**Manjunatha KM, R V amana M[15] et al**; developed a sustained release dosage form of diclofenac sodium containing immediate and controlled release components. Solid dispersion of immediate release component was prepared using polyvinyl pyrrolidone and mannitol carriers by common solvent method. Controlled release component was prepared in form of spherical beads by ionotropic gelation technique. The beads were prepared based on dispersing drug in solutions of ionic polysaccharides

such as chitosan and sodium alginate. There dispersions were dropped into solutions of counter ions such as tetra sodium pyrophosphate and calcium chloride respectively. The beads were also prepared using agae by dropping agae-drug hot solution into a mixture of chilled liquid paraffin and water. Then, diclofenac sodium controlled release drug delivery systems were prepared by combining the immediate release and controlled release components in different ratios. The formulations were found to be effective in providing controlled release of drug for a longer period of time. The beads were characterized by SEM and X-Ray diffraction studies.

**Dhirendra k, lewis s et al.,[16] developed** Solid dispersions of considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs. This article reviews the various preparation techniques for solid dispersion and compiles some of the recent technology transfers. The different types of solid dispersions based on the molecular arrangement have been highlighted. Some of the practical aspects to be considered for the preparation of solid dispersions, such as selection of carrier and methods of physicochemical characterization, along with an insight into the molecular arrangement of drugs in solid dispersions are also discussed. Finally, an in-depth rationale for limited commercialization of solid dispersions and recent revival had been considered.

**AppaRao., M. R. Shivalingam et al[17]** ; formulated solid dispersions (SDs) of Aceclofenac using lactose, mannitol and urea to increase its aqueous solubility. Aceclofenac SDs was prepared in 9:1, 7:3 and 4:1 ratios of the drug to polymer (by weight). *In vitro* release profiles of all SDs (F-1 to F-9) were comparatively evaluated and also studied against pure Aceclofenac. Faster dissolution was exhibited by solid dispersion containing 9:1 ratio of drug: lactose. The increase in dissolution rate of the drug may be due to increase in wettability, hydrophilic nature of the carrier and due to reduction in drug crystallinity. The prepared solid dispersion was subjected for % practical yield, drug content and infrared (IR) spectroscopic studies. Absence of significant drug-carrier interaction was confirmed by infrared spectroscopic (IR) data.

**Punitha s, vedha hari bn, karthikeyan d et al [18];** Preapared solid dispersions of celecoxib a poorly water soluble drug by forming dispersion with mannitol as water soluble carrier. The solid dispersion of celecoxib by physical triturating, solvent evaporation and fusion method were prepared using 1:1, 1:3 and 1:5 ratios of drug and polymer (mannitol). The prepared dispersions showed marked increase in the saturation solubility and dissolution rate of celecoxib than that of pure drug. The dispersions with mannitol (1:5) by fusion method showed faster dissolution rate (82.46%) as compared to other solid dispersions with mannitol (1:1 and 1:3) whichever prepared by physical mixture And solvent evaporation method. The FT-IR shows the complexation and there were no interactions. Finally, solid dispersions of celecoxib: mannitol prepared as 1:5 ratio by fusion method showed excellent physicochemical characteristics and was found to be described by dissolution kinetics and was selected as the best formulation in the study.

**K R Bobe, C R Subrahmanya, Sarasija Suresh** et al [19]; prepared Atorvastatin solid dispersion was prepared with mannitol, PEG 4000 and PVP-K30. These solid dispersions were analysed for the solubility and Invitro dissolution profile, solid dispersion of drug with PEG 4000 had shown enhanced solubility with improved dissolution rate. Further FTIR, DSC, SEM studies were carried out. Solid dispersion prepared with PEG 4000 shows the presence of amorphous form confirmed by the characterization study .The study also shows the that dissolution rate of Atorvastatin can be enhanced to considerable extent by solid dispersion technique with PEG.

**Eun-Jung Kim, Myung-Kwan Chun et al[20] ;** prepared felodipine solid dispersions in the presence of various carriers. Dichloromethane is not needed when HPMC solid dispersions were produced using the solvent wetting method. The amount of ethanol used to prepare solid dispersions did not have a significant effect on the dissolution rate of felodipine. The results of X-ray diffraction and thermal analysis indicated that the drug was in the amorphous state when PVP, HPMC, and poloxamer were used as carriers. The dissolution rates of felodipine in PVP, HPMC, or poloxamer solid dispersions were much faster than those for the corresponding physical mixtures. However, dissolution profiles were found to depend on the carrier used; the dissolution rate of felodipine increased

slowly for solid dispersions prepared using HPMC, whereas rapid initial dissolution rates were observed for solid dispersions prepared using PVP or poloxamer. Increases in dissolution rates were partly dependent on the ratios of felodipine to carrier. No significant changes in crystal form were observed by X-ray diffraction or thermal analysis, and no significant changes in dissolution rate were observed when sorbitol and mannitol were used as carrier.

**Dehghan M H G , Saifee M**[21] , discussed solid dispersion of glipizide using water soluble carriers such as polyethylene glycol (PEG) and mannitol by fusion method and PVP K 30 by solvent evaporation method in an attempt to increase the solubility and dissolution rate of Glipizide- a practically insoluble drug in water. IR spectroscopy and in-vitro dissolution studies were used to characterize the solid dispersion. FTIR studies show no chemical interaction between Glipizide and PEG 6000, mannitol and PVP K 30. The solid dispersion prepared in this study was found to have higher dissolution rate and solubility compared to plain drug and physical mixture of drug and carriers. It was found that the optimum weight ratio 1.5 for PEG-6000 shows higher solubility and dissolution rate. Finally it was concluded that PEG-6000 shows greater dissolution enhancing capacity than mannitol and PVP K 30.

**Omaima A. Sammour, Mohammed A. Hammad et al**[22]; prepared rofecoxib solid dispersion with polyvinyl pyrrolidone K30 (PVP K30) using solvent evaporation method. Drug-polymer interactions were investigated using differential scanning calorimetry (DSC), x-ray diffraction (XRD), and Fourier transform infrared spectroscopy (FTIR). For the preparation of rofecoxib mouth dissolve tablets, its 1:9 solid dispersion with PVP K30 was used with various disintegrants and sublimable materials. In an attempt to construct a statistical model for the prediction of disintegration time and percentage friability, a $3^2$ randomized full and reduced factorial design was used to optimize the influence of the amounts of superdisintegrant and subliming agent. The obtained results showed that dispersion of the drug in the polymer considerably enhanced the dissolution rate. The drug-to-carrier ratio was the controlling factor for dissolution improvement. FTIR spectra revealed no chemical incompatibility between the drug and

PVP K30. As indicated from XRD and DSC data, rofecoxib was in the amorphous form, which explains the better dissolution rate of the drug from its solid dispersions. Concerning the optimization study, the multiple regression analysis revealed that an optimum concentration of camphor and a higher percentage of crospovidone are required for obtaining rapidly disintegrating tablets. In conclusion, this investigation demonstrated the potential of experimental design in understanding the effect of the formulation variables on the quality

**B.Stephen Rathinaraj , Ch. Rajveer et al[23] ;** prepared and evaluated sustained release solid dispersions of Nimodipine using retarding polymers. Solid dispersions were prepared by solvent evaporation techniques as described in the literature using EVA, EU (RL) – 100 and EC. Solid state and drug polymer interaction were studied by I.R. In – vitro drug release were studied in U.S.P XXIII Electrolab six basket dissolution apparatus using 900 ml of dissolution media (Acetate buffer pH 4.5) at 75 RPM at 37 ± $0.5^0$c. The IR studies confirmed absence of any possible interaction. The dissolution studies indicated that about 99.2% with EC, 95.2% with EU RL 100 & 89.34% with EVA, of Nimodipine dissolved in 12 hours in PH 4.5. It is also seen that the incorporation of PEG 6000 in solid dispersions increases the release of Nimodipine. However, the release of Nimodipine was retarded with an increasing the concentration of EC, EU RL 100 and EVA. The mathematical treatment of the data indicates Fickian diffusion controlled release from the matrix. The use of PEG improved the release of Nimodipine in acidic pH while EC, EVA, EU RL 100 retarded its release.

**Sivert, A., Bérard, V. and Andrès, C**. et al[24] ; prepared solid dispersions containing a poor water-soluble drug, indomethacin (IND), and a new surfactant polymer, polyoxyethylene 32 distearate (POED). Solid dispersions were prepared by the melting method and characterized by DSC, hot-stage microscopy (HSM), X-ray diffraction (XRD) and scanning electron microscopy (SEM). DSC and HSM analyses performed on IND/POED physical mixtures indicated that IND could dissolve in liquid POED. The materials showed complete miscibility at liquid state. Combination of DSC, XRD, and SEM revealed that these materials had limited miscibility at the solid state. Up to 20%

w/w IND in POED, we did not detect significant modification of physical properties of the polymer. It supports the formation of a solid solution of IND in solid POED. Above 20% w/w, the solid dispersions presented particular behavior upon heating (recrystallization of IND) and at the solid state (presence of some IND crystallites). Under 3-month storage at 25°C/53% RH, the solid dispersions demonstrated a good stability of the samples. Finally, *in vitro* dissolution studies showed that IND release was greatly improved (5.5–12 times as fast) by formation of solid dispersion. This enhancement was principally attributed to the high dispersion of IND in POED and to the polymer surfactant properties.

**Darío Leonardi, María Gabriela Barrera**, et al[25] ; prepared. Solid-dispersion systems using PVP, PEG and mannitol as drug carrier matrices. Characterizations of these dispersions were done by differential scanning calorimeter (DSC) and X-ray diffraction (XRD). The glass transition ($T_g$) temperature of PVP was only recorded in the DSC thermograms of PVP solid-dispersions of both flavanone glycosides and their aglycones, while in case of PEG and mannitol solid-dispersions endotherms of both glycosides and aglycones were noticed with low peak intensity, indicating that high percent of drug is in amorphous state. The XRD patterns of all PVP solid-dispersions of aglycones show typical amorphous materials, but XRD patterns of their glycosides reveal the presence of crystalline material. However, in all solid dispersions shifts in $T_g$ of PVP as well as $T_m$ of PEG were observed, indicating the existence of some interactions between drugs and matrices. SEM and TEM microscopy revealed that PVP/aglycone flavanone compounds are nanodispersed systems while all the other solid dispersions are microcrystalline dispersions. The solubility of both flavanone glycosides and their aglycones was directly affected by the new physical state of solid dispersions. Due to the amorphous drug state or nano-dispersions in PVP matrices, the solubility was enhanced and found to be 100% at pH 6.8 in the nano-dispersion containing 20 mass% of aglycones. Also solubility enhancement was occurred in solid dispersions of PEG and mannitol, but it was lower than that of PVP nano-dispersions due to the presence of the drug compounds in crystalline state in both matrices.

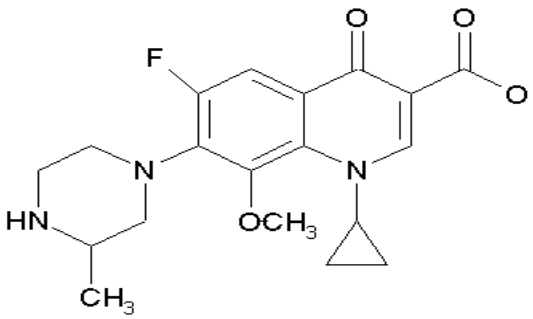
**Natalija Zajca, Aleš Obrezaa, Marjan Bele** et al[26] ; prepared solid dispersions of nifedipine (NIF) with mannitol in preparations containing 10 and 50% (w/w) of drug were manufactured by the hot melt method. Physical properties and the dissolution behaviour of binary systems as physical mixtures and solid dispersions were investigated. In all samples, the crystal structure of NIF was confirmed using differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). Fourier transform infrared spectroscopy (FTIR) revealed, there was no interaction between drug and carrier, however, FTIR spectra indicated formation of thermodynamically less stable polymorph of mannitol. The dissolution rate of NIF from solid dispersions was markedly enhanced, the effect being stronger at higher drug loading (50%, w/w, NIF). The dissolution rate enhancement was attributed to improved wetting of NIF crystals due to mannitol particles, attached on the surface, as inspected by means of SEM. Thermal stability of NIF, mannitol and two other potential carbohydrate carriers (lactose and saccharose) during the hot melt procedure was investigated using 1H NMR. NIF was found to be thermically stable under conditions applied. As expected, among carriers only mannitol demonstrated suitable resistance to high temperature used in experiments.

**Ruchi Tiwari , Birendra Srivastava, Gaurav Tiwari** et al[27] ; formulated solid dispersions of promethazine hydrochloride (PHC) with acrylic polymers Eudragit RL100 and Eudragit S100 in different weight ratios (1:1 and 1: 5), and in combination (0.5+1.5), using freeze-drying and spray-drying techniques. Solid dispersions were characterized by Fourier-transformed infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), Powder X-ray diffractometry (PXRD), Nuclear magnetic resonance (NMR), Scanning electron microscopy (SEM), as well as solubility and in vitro dissolution studies in 0.1 N HCl (pH 1.2), double-distilled water and phosphate buffer (pH 7.4). Adsorption tests from drug solution to solid polymers were also performed. A selected solid dispersion system was developed into capsule dosage form and evaluated for in vitro dissolution studies. The progressive disappearance of drug peaks in thermotropic profiles of spray-dried dispersions were related to increasing amount of polymers, while SEM studies suggested homogenous dispersion of drug in polymer. Eudragit RL100 had a greater adsorptive capacity than Eudragit S100, and thus its combination in (0.5+1.5)

for S100 and RL 100 exhibited a higher dissolution rate with 97.14% drug release for twelve hours. Among different formulations, capsules prepared by combination of acrylic polymers using spray-drying (1:0.5 + 1.5) displayed extended release of drug for twelve hours with 96.87% release followed by zero order kinetics (r2= 0.998)

# 4 DRUG PROFILE

## 4.1 STRUCTURAL FORMULA OF GATIFLOXACIN[28]




**Class** : broad-spectrum fluoroquinolone

**Chemical name** : (±)-1-cyclopropyl-6-fluoro-1,4- dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylicacid sesquihydrate

| Chemical data | |
|---|---|
| **Formula** | $C_{19}H_{22}FN_3O_4$ 1.5 $H_2O$ |
| **Mol. mass** | 402.42 daltons |

| Physical data | |
|---|---|
| **colour** | Pale yellow |
| **state** | Crystalline powder |

**Solubility**: Solubility of gatifloxacin is pH dependent, with maximum aqueous solubility (40-60 mg/ml) occurring in a pH range of 2-5

.

**Dosage**: Doses of 400 mg orally or intravenously 10.7-12.5 hours

**Pharmacokinetics**[29] :

Bioavailability(%) - 96%

Protein binding(%) - 20%

Elimination half life(hrs) - 8hrs

Routes of administration - oral,I.V

Dosage - 400 mg once a day

**Absorption:** gatifloxacin is well absorbed after oral administration. . The drug is rapidly absorbed from the gastrointestinal tract, with maximum plasma concentrations ($T_{max}$) of 0.75-2.0 hours.

**Distribution** : Gatifloxacin protein binding is over 20%

**Mechanism of action**[30] : DNA gyrase and topoisomerase IV are thought to be essential for replication of DNA and partition of replicated chromosomal DNA. DNA gyrase, a tetrameric enzyme consisting of two A and two B subunits, is a primary target of gatifloxicin in Escherichia coli and is the only enzyme capable of introducing negative superhelical twists into bacterial DNA The two subunits of gyrase are encoded by gyrA and gyrB, which are also potential sites of mutation and subsequent quinolone resistance. Topoisomerase IV, a recently characterized topoisomerase, seems to be a primary target of gatifloxicin in gram-positive bacteria such as Staphylococcus aureus and Streptococcus pneumoniae. Bacterial topoisomerase IV appears to be the principal enzyme that resolves or decatenates interlocked daughter DNA circles occurring at the completion of a round of DNA replication, allowing segregation of daughter chromosomes into daughter cells. Topoisomerase IV, like DNA gyrase, is composed of four subunits, two each of the parC and parE gene products.

As part of the topoisomerase reaction mecha-nism, DNA gyrase and topoisomerase IV transiently break the DNA backbone and pass a double strand of DNA through those breaks, thus introducing a negative supercoil into the strand. Gatifloxicin antibiotics target DNA gyrase and topoisomerase IV while these enzymes are functionally attached to the DNA strand, resulting in a drug-enzyme-DNA complex in which DNA probably

remains broken. Cell death apparently results from release of double-stranded DNA breaks from numerous drug-enzyme-DNA complexes throughout the chromosome.

**Excretion** : Gatifloxacin's major route of excretion is urinary excretion of unchanged drug With renal clearance ($Cl_R$) accounting for 82-88% of ($Cl_S$).

**Pregnancy** : Gatifloxacin, like other fluoroquinolones, is contraindicated in pregnant or nursing women due to arthropathies and cartilage damage associated with this drug class.

**Drug interactions** : Like other orally administered fluoroquinolones, gatifloxacin can form stable coordination compounds with many metal ions. The potential for chelation with various cations occurs in the following approximate formation order: $Al^{3+} > Fe^{2+} > Cu^{2+} > Zn^{2+} > Mg^{2+} > Ca^{2+}$. Antacids containing divalent or trivalent metal cations (aluminum, magnesium, calcium) may cause significantly decreased bioavailability (30-94%) of oral fluoroquinolones through formation of nonabsorbable metal-quinolone chelates in the stomach or small intestine.

**Side effects** : the most common side effects are abdominal discomfort , nausea , vomiting , diarrhea , and loss of appetite. Vaginitis was reported in 6% of women.

**Usuage** : Gatifloxacin is approved for the treatment of acute sinusitis, ABECB, community-acquired pneumonia, complicated and uncomplicated urinary tract infections, pyelonephritis, uncomplicated urethral and cervical gonococcal infections, and acute uncomplicated rectal gonococcal infections in women caused by susceptible pathogens.

**Diet** : Gatifloxacin may be administered orally without regard to food.

## 4.2 POLYMER PROFILE

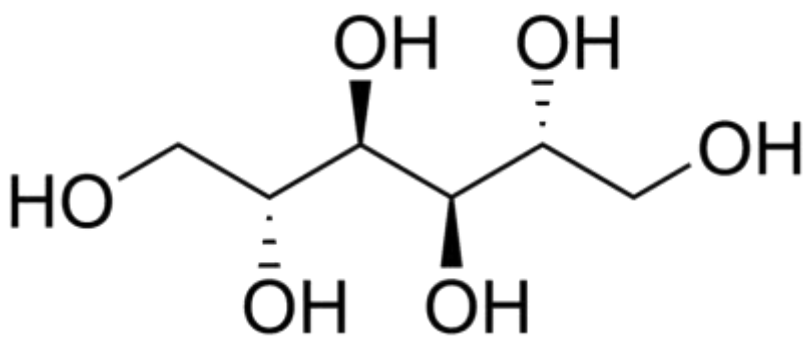
### MANNITOL[31] :

**Synonyms** : cordycepic acid, manita, manna sagar, D-mannite, mannite, mannogem pearlitol

**Molecular weight** : 182.17

**Emperical formula** : $C_6 H_{16} 0_6$

**Structural formula** :



**Functional category** : Tablet and capsule diluent , sweetening agent , tonicity agent , vehicle(bulking agent) for lyophilised prepartion.

**Application in pharmaceutical formulations (or) technology** :

Mannitol is widely used in pharmaceutical formulation and food products. In pharmaceutical preparation it is particularly used as diluent (10-90%w/w) in tablet formulation. Mannitol is commonly used as excipient in the manufacture of chewable tablets formulation because of its negative heat of solution , sweetness and mouth feel. Mannitol has also been used to prevent thickening in aqeous antacid suspensions of aluminium hydroxide( <7%w/v).

**Description** : white , odorless , crystalline powder (or) free flowing granules.

**TYPICAL PROPERTIES** :

Bulk density : 0.430 $g/cm^3$ for powder ;
0.7 $g/cm^3$ for granules.

Tapped density : 0.734 $g/cm^3$ for powder ;
0.8 $g/cm^3$ for granules.

True density : 1.514 $g/cm^3$

Melting point : 166 – 168$^0$C

$P_{Ka}$ : 13.5 at 18$^0$C

**SOLUBILITY** :

Solvent ---------- solubility at 20$^0$c

Ethanol (95%) -------- 1 in 83

Ether ---------- practically insoluble

Glycerin ---------- 1 in 18

Propanol ---------- 1 in 100

Water ---------- 1 in 5.5

Refractive index : 1.33

Specific surface area : 0.37 to 0.39 $m^2/g$

**Safety** : Mannitol is naturally occuring sugar alcohol found in animals and plants . It is present in small quantities in almost all vegetables . Laxative effects may occur if mannitol is consumed orally in large quantities.

# 5 METHODOLOGY

## 5.1 MATERIAL

All the materials and its source used in the formulation evaluation and other experiments are listed below. Distilled water is used in all experiment

| S.NO. | CHEMICALS | SOURCE |
|---|---|---|
| | | |

| | | |
|---|---|---|
| 1. | Gatifloxacin | Reddy's laboratories, Hyderabad. |
| 2. | Mannitol | Universal laboratories Mumbai |
| 3. | Hydrochloric acid | Universal laboratories Mumbai |
| 4. | Sodium hydroxide | Burgoyne burbidges & co Mumbai |
| 5. | Methanol | Sd fine-chem. Limited Mumbai |

## 5.2. EQUIPMENTS

All the equipments and its source used in the formulation and evaluation are listed below

| S.NO | EQUIPMENTS | MANUFACTURER |
|---|---|---|
| 1. | Dissolution apparatus | Secor laboratories instrument Mumbai. |
| 2. | Electronic balance | United technician corp. Delhi. |
| 3. | Sieves | Sethi standard test sieves Mumbai. |
| 4. | UV/Visible Spectrophotometer | Elico[sh 150], Hyderabad. |
| 5. | Infrared spectrophotometer | Thermo Nicolet nexus 470 FTIR ESP,Mumbai. |
| 6. | Remimotors Limited, Mumbai | Remimotors Limited, Mumbai. |

## 5.3 CALIBRATION CURVE OF GATIFLOXACIN

Spectrophotometric method based on measurement of absorbance at 286 nm of UV of 0.1N HCL was used in study for estimation of Gatifloxacin.

**PREPARATION OF 0.1N Hydrochloric acid :**

| S.No. | Concentration (µg /ml) | Absorbance |
|---|---|---|

0.1N Hcl was prepared by placing 8.5ml of hydrochloric acid in 1000ml of volumetric flask .Make up to the mark with distilled water.

**PREPARATION OF STANDARD GRAPH**

Standard solution was prepared by dissolving 100mg of Gatifloxacin in 100ml of 0.1N HCL. From the standard solution a series of dilution containing 2,4,6,8 &10µgm/ml of drug were prepared. The absorbance of those dilutions were measured in a spectrophotometer at 286 nm using 0.1N HCL as blank.

The absorbance of Gatifloxacin for corresponding concentrations are given in table1.The absorbance was plotted against concentration of Gatifloxacin as shown in figure1.

This calibration curve was used for estimation of Gatifloxacin in solid dispersions in present study.

**TABLE 1 STANDARD VALUES OF GATIFLOXICIN PURE DRUG IN 0.1N HCL**

| | | |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 2 | 0.096 |
| 3 | 4 | 0.237 |
| 4 | 6 | 0.309 |
| 5 | 8 | 0.420 |
| 6 | 10 | 0.516 |

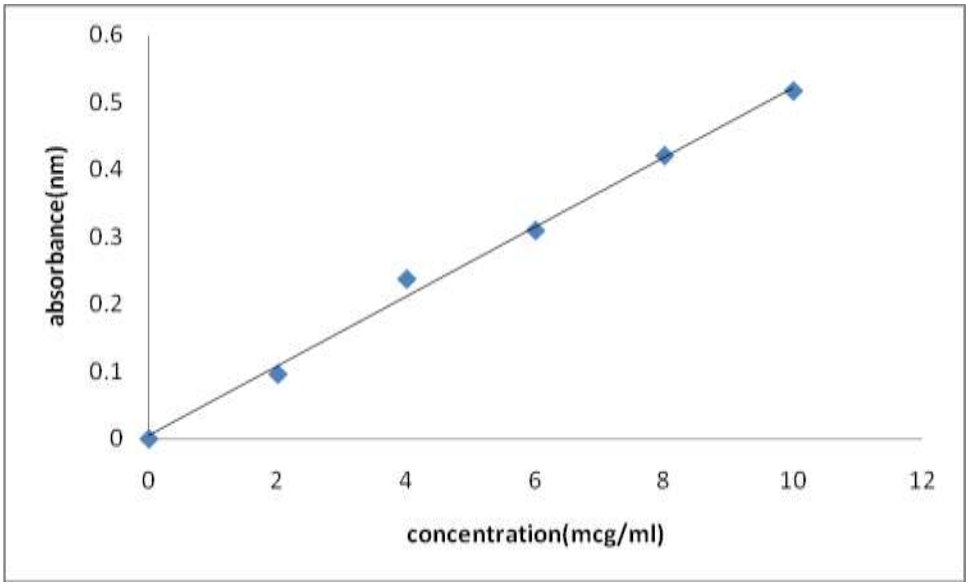



FIG.1 CALIBRATION CURVE FOR THE ESTIMATION OF GATIFLOXACIN IN 0.1N HCL

**TABLE 2 LIST OF MANNITOL SOLID DISPERSIONS OF GATIFLOXACIN**

| S.No | Formula code | Core:coat Ratio | Batch size(mg) Drug+polymer |
|---|---|---|---|
| 1 | $M_1$ | 1:1 | 1000+1000 |
| 2 | $M_2$ | 1:2 | 1000+2000 |
| 3 | $M_3$ | 1:3 | 1000+3000 |
| 4 | $M_4$ | 1:4 | 1000+4000 |

## 5.4 PREPARATION OF SOLID DISPERSSIONS BY SOLVENT EVAPORATION, PHYSICAL MIXTURE & KNEADING METHOD

### 5.4.1 PREPARATION OF SOLID DISPERSIONS BY SOLVENT EVAPORATION

Solid dispersions containing gatifloxicin were prepared by using mannitol as coat material employing common solvent method. Four batches with drug to carrier (mannitol) ratio at different ratios namely 1:1,1:2,1:3 and 1:4 were prepared for the preparation solid dispersions. The respective amount of carrier was dissolved in 10ml sodium hydroxide taken in conical flask to get a clear complete soluble polymer solution. The weighed amount of gatifloxicin was added to this solution with constant stirring until the drug is completely incorporated in solvent. The solvent was removed by evaporation at room temperature. The mass obtained were further dried in desiccator for overnight, crushed and pulverized .

### 5.4.2 PREPARATION OF SOLID DISPERSIONS BY PHYSICAL MIXTURE

Drug carrier ratio of 1:1,1:2,1:3,1:4 was used to prepare physical mixture. The drug and carrier were mixed thoroughly in a mortor. This was done by geometric dilution technique to ensure homogenous distribution**.**

### 5.4.3 PREPARATION OF SOLID DISPERSIONS BY KNEADING

The weighed quantities of drug and carrier were triturated in a glass mortar using a small amount of sodium hydroxide. The thick slurry was kneaded for 45 min and then evaporated at $50^0$c to constant weight. The dried mass was pulverized and sifted through sieve #100 and stored in dessicator.

## 5.5 EVALUATION OF SOLID DISPERSIONS

### 5.5.1 SIZE ANALYSIS

Particle size determination was carried out using optical microscopy with a calibrated eye piece micrometer and stage micrometer by taking a small quantity of formulation on slide. About 100 microcrystal size was measured individually, average was taken and their size range and mean diameter frequency was calculated. The data was shown in Table 3.

Average Particle size is calculated by the formula,

Average Particle size= εnd/ n

### 5.5.2 ESTIMATION OF DRUG CONTENT IN SOLID DISPERSION

50ml solid dispersions or physical mixture were weighed accurately and transferred in to a 50ml volumetric flask. The volume was made up to the mark with sodium hydroxide and kept for 2hrs with occasional shaking and filtered. Then the drug content was analyzed spectrophotometrically at 286 nm using a single beam visible U.V Spectrophotometer.

### 5.5.3 WETTABILITY STUDIES

Pure drug approximately 1gm was placed in sintered glass funnel with the heap of cotton plug. The funnel was held in upright position in a beaker filled with water level in the beaker just touched the cotton plug. The time required to raise the water through the drug for the colorings of water was recorded. Same procedure was followed for all solid dispersions..

### 5.5.4 ANGLE OF REPOSE

To get an idea about flow ability properties of the solid dispersion, angle of repose for all the batches was determined, suitable for solid dosage form preparation.

### 5.5.5 INVITRO DISSOLUTION STUDIES

The release of gatifloxacin from solid dispersion was investigated in 0.1N HCL as a dissolution medium (900ml) using the paddle method specified in USP **X** XIV (model TD T6P-Electrolab).sample of 100mg solid dispersions were taken in the basket. A speed of 75rpm and temperature 37+ $0.5^0$C was maintained through out the experiment. At fixed intervals, aliquots (5ml) were withdrawn and replaced with fresh dissolution media .The concentration of drug released at different time intervals was then determined by measuring the Absorbance using UV spectrophotometer at 286 nm against blank. The studies were carried out in triplicate.

### 5.5.6 IR STUDIES

FTIR Spectroscopy was performed on each at the samples to determine the structure of the organic compounds and to identify the presence of specific functional groups with in a sample. Further more drug polymer interactions were examine using the resulting spectra. The infrared spectra were obtained using a scale of wave numbers (cm-1). The analysis were performed by using a thermo nicolet nexus 286 FTIR ESP.3-5mg of sample was added to approximately 100mg of KBr. The mixture was then ground to a fine powder using a mortar and pestle and transparent discs formed using a pellet press. The discs were placed in FTIR spectroscopy apparatus and spectra were collected. The range of the collected spectra was 4000-400cm-1.

# 6 .RESULTS

**TABLE 3 PARTICLE SIZE DETERMINATION OF GATIFLOXACIN SOLID DISPERSIONS**

| S.NO. | Ratio | Kneading method | Physical mixture | Solvent evaporation |
|---|---|---|---|---|
| 1 | 1:1 | 38.8 | 45.3 | 43.4 |
| 2 | 1:2 | 41.2 | 49.47 | 49.6 |
| 3 | 1:3 | 49.24 | 55.7 | 57.6 |
| 4 | 1:4 | 49.97 | 64.6 | 62.9 |

***$D_{average}$ = Average particle size**

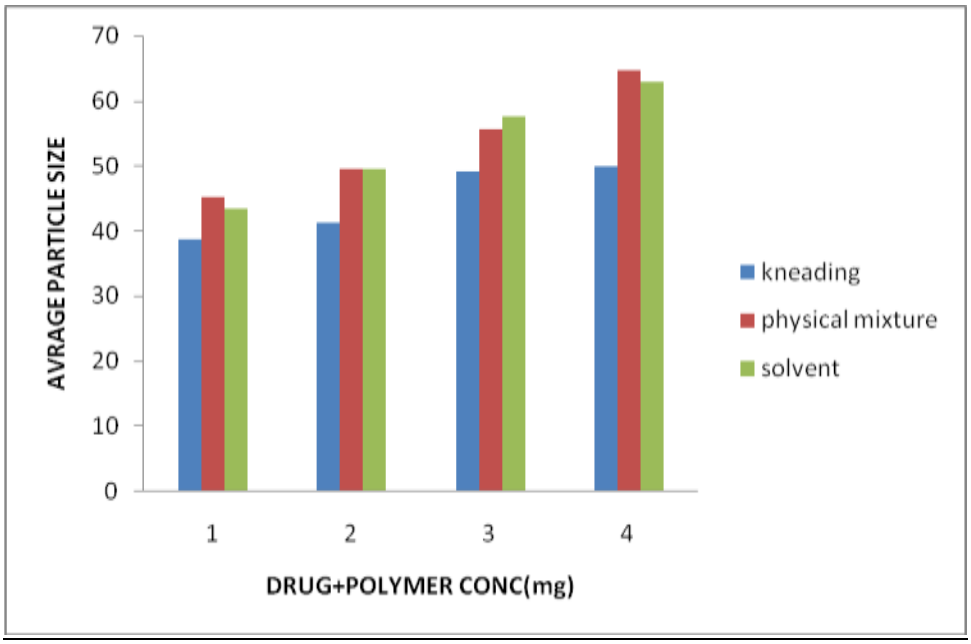



**FIG.2 SIZE ANALYSIS OF GATIFLOXACIN SOLID DISPERSIONS**

**TABLE 4 PERCENTAGE DRUG CONTENT OF GATIFLOXACIN SOLID DISPERSIONS**

| S.NO. | Ratio | Kneading method(%) | Physical mixture(%) | Solvent evaporation(%) |
|---|---|---|---|---|
| 1 | 1:1 | 87.6 | 82.03 | 84.42 |
| 2 | 1:2 | 94.03 | 89 | 90.19 |
| 3 | 1:3 | 96.5 | 94.42 | 95.76 |
| 4 | 1:4 | 100.19 | 97.6 | 99.42 |

**TABLE 5 PERCENTAGE YIELD OF GATIFLOXACIN SOLID DISPERSIONS**

| S.NO. | Ratio | Kneading method (%) | Physical mixture (%) | Solvent evaporation(%) |
|---|---|---|---|---|
| 1 | 1:1 | 94.5 | 96 | 94.3 |
| 2 | 1:2 | 93 | 95.43 | 92.6 |
| 3 | 1:3 | 91.125 | 94.72 | 90.7 |
| 4 | 1:4 | 89.78 | 89.78 | 89.78 |

**TABLE 6 WETTING STUDIES OF GATIFLOXACIN SOLID DISPERSIONS**

| S.NO. | Ratio | Kneading method(min) | Physical mixture(min) | Solvent evaporation(min) |
|---|---|---|---|---|
| 1 | 1:1 | 6.20 | 6.10 | 6.25 |
| 2 | 1:2 | 5.30 | 5 | 5.20 |
| 3 | 1:3 | 4 | 3.25 | 3.25 |
| 4 | 1:4 | 2 | 1.30 | 1.35 |

*Average of 3 determinations

**TABLE 7 ANGLE OF REPOSE OF GATIFLOXACIN SOLID DISPERSIONS**

| S.NO. | Ratio | Kneading method($^0$) | Physical mixture ( $^0$) | Solvent evaporation($^0$) |
|---|---|---|---|---|
| 1 | 1:1 | 20.55 | 26.56 | 21.80 |
| 2 | 1:2 | 21.06 | 27.02 | 22.24 |
| 3 | 1:3 | 21.30 | 27.47 | 22.587 |
| 4 | 1:4 | 21.80 | 27.87 | 23.46 |

*Average of 3 determinations

**TABLE 8 IN-VITRO RELEASE OF GATIFLOXACIN SOLID DISPERSIONS BY KNEADING METHOD(1:1)**

| S.No. | Time (min) | Absorbance | Conc in 5ml | Conc in 900ml | Loss of drug | Cumulative loss of drug | %cumulative drug release |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 2 | 0.289 | 0.243 | 43.85 | 0 | 43.85 | 17.54 |
| 3 | 4 | 0.696 | 0.586 | 105.61 | 0.289 | 105.899 | 42.35 |
| 4 | 6 | 0.847 | 0.714 | 128.52 | 0.875 | 129.39 | 51.75 |
| 5 | 8 | 1.103 | 0.929 | 167.36 | 1.589 | 168.94 | 67.57 |
| 6 | 10 | 1.375 | 1.1591 | 208.64 | 2.518 | 211.158 | 84.46 |
| 7 | 12 | 1.588 | 1.338 | 240.96 | 3.677 | 244.63 | 97.80 |

*Average of 3 determinations

**TABLE 9 IN-VITRO RELEASE OF GATIFLOXACIN SOLID DISPERSIONS**

**BY KNEADING METHOD(1:2)**

| S.No. | Time (min) | Absorbance | Conc in 5ml | Conc in 900ml | Loss of drug | Cumulative loss of drug | %cumulative drug release |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 2 | 0.064 | 0.0539 | 9.711 | 0 | 9.711 | 5.849 |
| 3 | 4 | 0.098 | 0.0826 | 14.870 | 0.0539 | 14.924 | 8.990 |
| 4 | 6 | 0.161 | 0.135 | 24.43 | 0.1365 | 24.566 | 14.79 |
| 5 | 8 | 0.342 | 0.288 | 51.895 | 0.2715 | 52.1665 | 31.42 |
| 6 | 10 | 0.675 | 0.569 | 102.42 | 0.5595 | 102.979 | 62.03 |
| 7 | 12 | 1.078 | 0.908 | 163.56 | 1.128 | 164.688 | 99.20 |

*Average of 3 determinations

**TABLE 10 IN-VITRO RELEASE OF GATIFLOXACIN SOLID DISPERSIONS BY KNEADING METHOD(1:3)**

| SNo. | Time (min) | Absorbance | Conc in 5ml | Conc in 900ml | Loss of drug | Cumulative loss of drug | %cumulative drug release |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 2 | 0.092 | 0.077 | 13.96 | 0 | 13.96 | 11.25 |
| 3 | 4 | 0.167 | 0.140 | 25.34 | 0.077 | 25.417 | 20.49 |
| 4 | 6 | 0.289 | 0.243 | 43.85 | 0.217 | 44.067 | 35.53 |
| 5 | 8 | 0.366 | 0.308 | 55.53 | 0.46 | 55.99 | 45.15 |
| 6 | 10 | 0.594 | 0.500 | 90.02 | 0.768 | 90.768 | 73.2 |
| 7 | 12 | 0.807 | 0.680 | 122.45 | 1.268 | 123.71 | 99.77 |

*Average of 3 determinations

**TABLE 11 IN-VITRO RELEASE OF GATIFLOXACIN SOLID DISPERSIONS**

**BY KNEADING METHOD(1:4)**

| SNo. | Time (min) | Absorbance | Conc in 5ml | Conc in 900ml | Loss of drug | Cumulative loss of drug | %cumulative drug release |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 2 | 0.103 | 0.0868 | 15.62 | 0 | 15.62 | 15.62 |
| 3 | 4 | 0.298 | 0.251 | 45.21 | 0.0868 | 45.30 | 45.30 |
| 4 | 6 | 0.468 | 0.394 | 71.014 | 0.3378 | 71.35 | 71.351 |
| 5 | 8 | 0.527 | 0.444 | 79.966 | 0.7318 | 80.69 | 80.69 |
| 6 | 10 | 0.599 | 0.5049 | 90.892 | 1.1758 | 92.067 | 92.067 |
| 7 | 12 | 0.647 | 0.545 | 98.17 | 1.680 | 99.85 | 99.85 |

*Average of 3 determinations

**FIG.3 IN-VITRO RELEASE OF GATIFLOXACIN SOLID DISPERSIONS BY KNEADING METHOD**

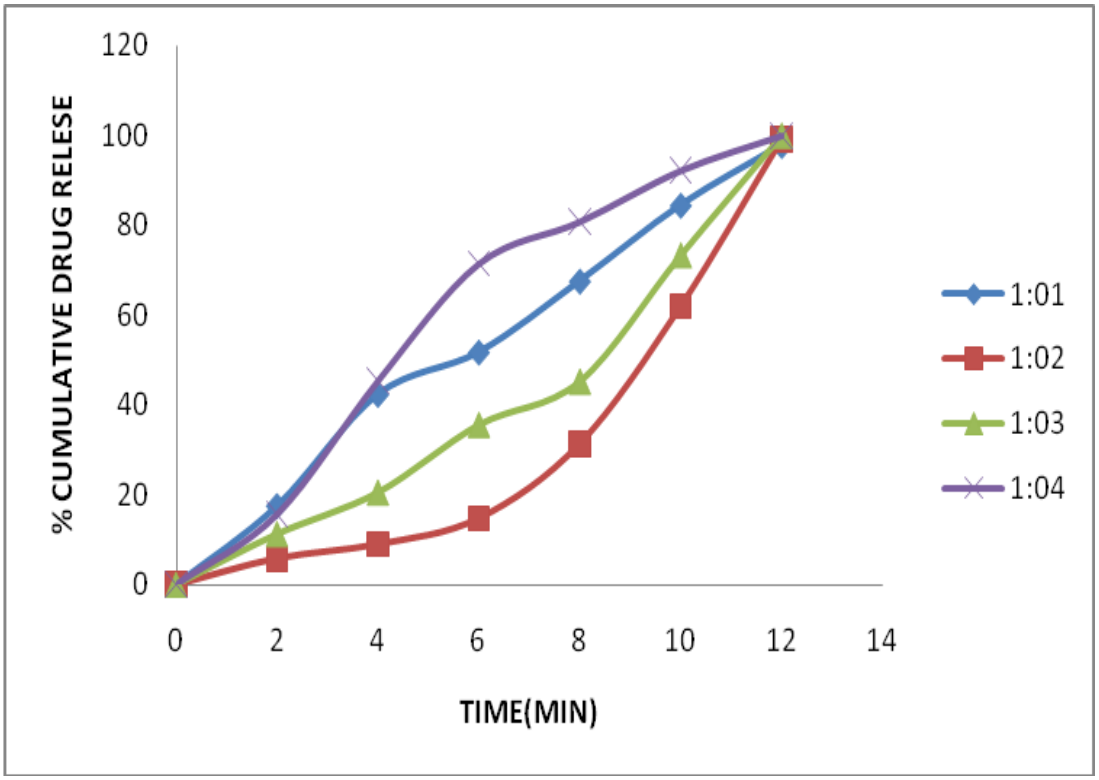



**TABLE 12 IN-VITRO RELEASE OF GATIFLOXACIN SOLID DISPERSIONS**

**BY PHYSICAL MIXTURE(1:1)**

| S.No. | Time (min) | Absorbance | Conc in 5ml | Conc in 900ml | Loss of drug | Cumulative loss of drug | %cumulative drug release |
|---|---|---|---|---|---|---|---|
| 1. | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2. | 2 | 0.773 | 0.6516 | 117.288 | 0 | 117.288 | 39.09 |
| 3. | 4 | 0.829 | 0.698 | 125.79 | 0.6516 | 126.44 | 42.14 |
| 4. | 6 | 1.065 | 0.8977 | 161.60 | 1.3496 | 162.94 | 54.31 |
| 5. | 8 | 1.362 | 1.148 | 206.66 | 2.247 | 208.90 | 69.63 |
| 6. | 10 | 1.587 | 1.337 | 240.81 | 3.395 | 244.20 | 81.40 |
| 7. | 12 | 1.706 | 1.438 | 258.86 | 4.732 | 263.60 | 87.82 |

*Average of 3 determinations

**TABLE 13 IN-VITRO RELEASE OF GATIFLOXACIN SOLID DISPERSION BY PHYSICAL MIXTURE(1:2)**

| S.NO. | Time (min) | Absorbance | Conc in 5ml | Conc in 900ml | Loss of drug | Cumulative loss of drug | %cumulative drug release |
|---|---|---|---|---|---|---|---|
| 1. | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2. | 2 | 0.486 | 0.409 | 73.74 | 0 | 73.74 | 44.42 |
| 3. | 4 | 0.689 | 0.580 | 104.54 | 0.409 | 104.94 | 63.2 |
| 4. | 6 | 0.724 | 0.610 | 109.85 | 0.989 | 110.839 | 66.77 |
| 5. | 8 | 0.878 | 0.740 | 133.22 | 1.599 | 134.81 | 81.21 |
| 6. | 10 | 0.932 | 0.785 | 141.42 | 2.339 | 143.75 | 86.66 |
| 7. | 12 | 0.997 | 0.840 | 151.28 | 3.124 | 154.404 | 93.01 |

*Average of 3 determination

**TABLE 14 IN-VITRO RELEASE OF GATIFLOXICIN SOLID DISPERSION BY PHYSICAL MIXTURE (1:3)**

| S.NO. | Time (min) | Absorbance | Conc in 5ml | Conc in 900ml | Loss of drug | Cumulative loss of drug | %cumulative drug release |
|---|---|---|---|---|---|---|---|
| 1. | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2. | 2 | 0.389 | 0.327 | 59.02 | 0 | 59.02 | 47.60 |
| 3. | 4 | 0.456 | 0.384 | 69.19 | 0.327 | 69.57 | 56.06 |
| 4. | 6 | 0.534 | 0.450 | 81.02 | 0.711 | 81.731 | 65.91 |
| 5. | 8 | 0.645 | 0.543 | 97.87 | 1.161 | 99.03 | 79.86 |
| 6. | 10 | 0.721 | 0.607 | 109.40 | 1.704 | 111.104 | 89.80 |
| 7. | 12 | 0.767 | 0.676 | 116.38 | 2.311 | 118.169 | 95.71 |

*Average of 3 determinations

**TABLE 15 IN-VITRO RELEASE OF GATIFLOXICIN SOLID DISPERSION BY PHYSICAL MIXTURE(1:4)**

| S.No | Time (min) | Absorbance | Conc in 5ml | Conc in 900ml | Loss of drug | Cumulative loss of drug | %cumulative drug release |
|---|---|---|---|---|---|---|---|
| 1. | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2. | 2 | 0.267 | 0.225 | 40.51 | 0 | 40.51 | 40.51 |
| 3. | 4 | 0.389 | 0.327 | 59.02 | 0.225 | 59.25 | 59.25 |
| 4. | 6 | 0.456 | 0.384 | 69.12 | 0.552 | 69.67 | 69.67 |
| 5. | 8 | 0.589 | 0.496 | 89.37 | 0.936 | 90.306 | 90.306 |
| 6. | 10 | 0.602 | 0.507 | 91.34 | 1.432 | 92.772 | 92.772 |
| 7. | 12 | 0.622 | 0.524 | 94.382 | 1.939 | 96.321 | 96.321 |

*Average of 3 determinations

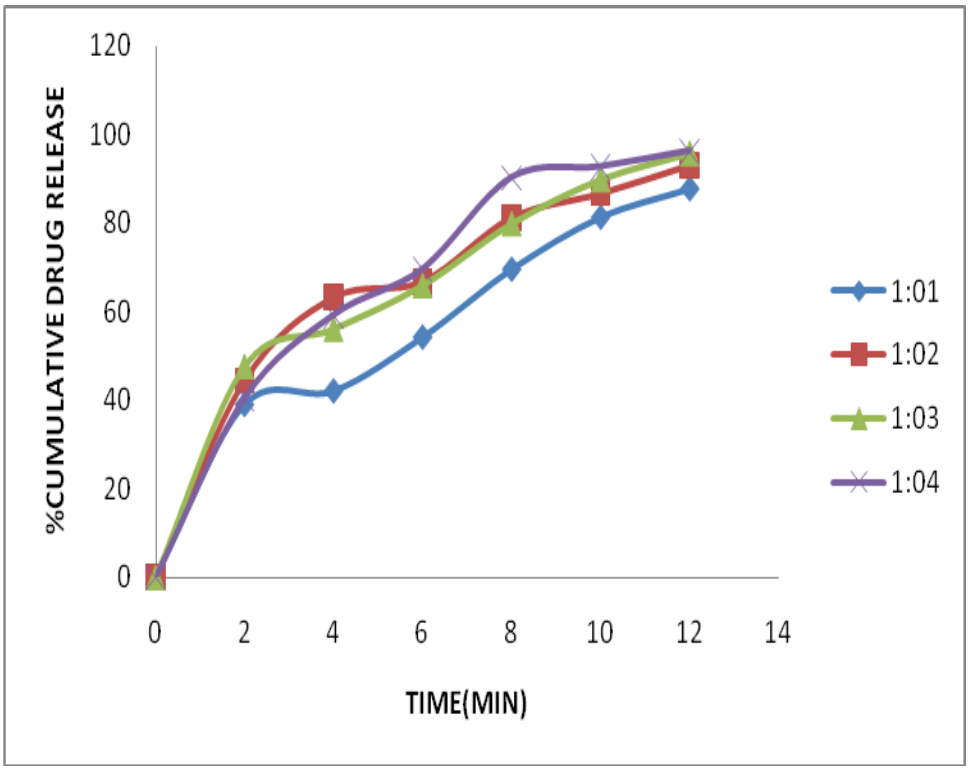



**FIG.4 IN-VITRO RELEASE OF GATIFLOXACIN SOLID DISPERSIONS BY PHYSICAL MIXTURE**

**TABLE 16 IN-VITRO RELEASE OF GATIFLOXICIN SOLID DISPERSION BY SOLVENT EVAPORATION (1:1)**

| S.NO. | Time (min) | Absorbance | Conc in 5ml | Conc in 900ml | Loss of drug | Cumulative loss of drug | %cumulative drug release |
|---|---|---|---|---|---|---|---|
| 1. | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2. | 2 | 0.682 | 0.574 | 103.48 | 0 | 103.48 | 41.3 |
| 3. | 4 | 0.826 | 0.696 | 125.337 | 0.574 | 125.91 | 50.3 |
| 4. | 6 | 1.004 | 0.846 | 152.34 | 1.27 | 153.61 | 61.44 |
| 5. | 8 | 1.128 | 0.950 | 171 | 2.116 | 173.116 | 69.2 |
| 6. | 10 | 1.247 | 1.051 | 189.2 | 3.066 | 192.266 | 76.90 |
| 7. | 12 | 1.465 | 1.234 | 222.29 | 4.117 | 226.40 | 90.56 |

*Average of 3 determinations

**TABLE 17 IN-VITRO RELEASE OF GATIFLOXICIN SOLID DISPERSION BY SOLVENT EVAPORATION (1:2)**

| S.NO. | Time (min) | Absorbance | Conc in 5ml | Conc in 900ml | Loss of drug | Cumulative loss of drug | %cumulative drug release |
|---|---|---|---|---|---|---|---|
| 1. | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2. | 2 | 0.439 | 0.3700 | 66.6 | 0 | 66.6 | 40.120 |
| 3. | 4 | 0.647 | 0.545 | 98.1 | 0.3700 | 98.47 | 59.31 |
| 4. | 6 | 0.698 | 0.588 | 105.91 | 0.915 | 106.82 | 64.35 |
| 5. | 8 | 0.742 | 0.625 | 112.59 | 1.503 | 114.09 | 68.73 |
| 6. | 10 | 0.898 | 0.757 | 136.26 | 2.128 | 138.38 | 83.36 |
| 7. | 12 | 1.004 | 0.846 | 152.340 | 2.885 | 155.23 | 93.50 |

*Average of 3 determinations

**TABLE 18 IN-VITRO RELEASE OF GATIFLOXICIN SOLID DISPERSION BY SOLVENT EVAPORATION (1:3)**

| S.no | Time(min) | Absorbance | Conc in 5ml | Conc in 900ml | Loss of drug | Cumulative loss of drug | %cumulative drug release |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 2 | 0.428 | 0.360 | 64.94 | 0 | 64.94 | 51.95 |
| 3 | 4 | 0.503 | 0.424 | 76.32 | 0.360 | 76.68 | 61.344 |
| 4 | 6 | 0.552 | 0.465 | 83.76 | 0.784 | 84.54 | 67.63 |
| 5 | 8 | 0.627 | 0.528 | 95.14 | 1.249 | 96.38 | 77.112 |
| 6 | 10 | 0.699 | 0.589 | 106.06 | 1.777 | 107.83 | 86.26 |
| 7 | 12 | 0.782 | 0.659 | 118.66 | 2.366 | 121.02 | 96.821 |

*Average of 3 determinations

**TABLE 19 IN-VITRO RELEASE OF GATIFLOXICIN SOLID DISPERSION BY SOLVENT EVAPORATION (1:4)**

| S.NO. | Time (min) | Absorbance | Conc in 5ml | Conc in 900ml | Loss of drug | Cumulative loss of drug | %cumulative drug release |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 2 | 0.289 | 0.243 | 43.85 | 0 | 43.85 | 43.85 |
| 3 | 4 | 0.391 | 0.329 | 59.33 | 0.243 | 59.57 | 59.57 |
| 4 | 6 | 0.449 | 0.378 | 68.131 | 0.572 | 68.703 | 68.703 |
| 5 | 8 | 0.523 | 0.440 | 79.36 | 0.95 | 80.31 | 80.31 |
| 6 | 10 | 0.594 | 0.5007 | 90.133 | 1.473 | 91.606 | 91.606 |
| 7 | 12 | 0.639 | 0.538 | 96.84 | 1.973 | 98.813 | 98.813 |

*Average of 3 determinations

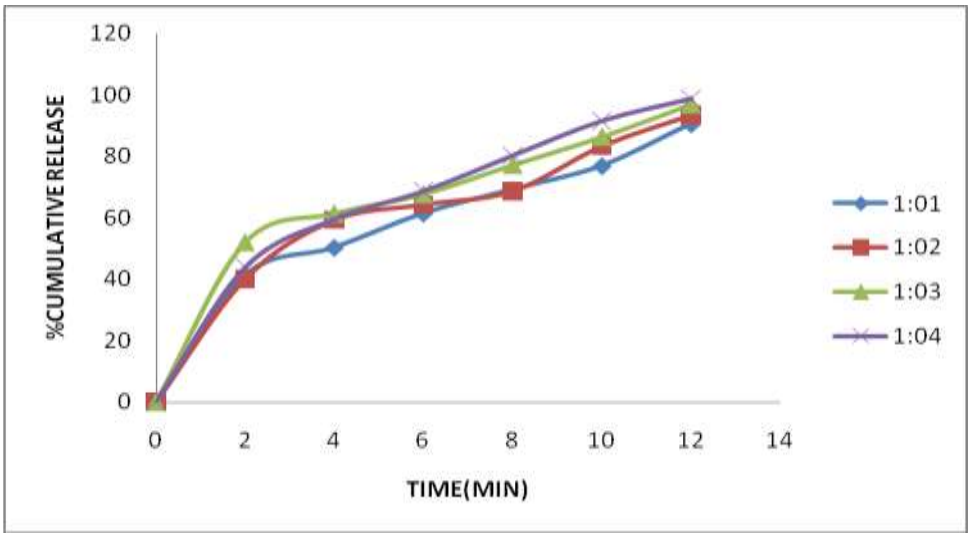



**FIG.5 IN-VITRO RELEASE OF SOLID DISPERSIONS BY SOLVENT EVAPORATION**

**TABLE 20 KINETICS VALUE OBTAINED FOR MANNITOL SOLID DISPERSIONS BY KNEADING (1:4)**

| S.No. | % Drug release Vs time Zero order equation | | Log % Drug retained Vs time First order equation | | Cumulative %drug release Vs square of time Higuchi's equation | | Log cumulative %drug release Vs time Korsemeyer's equation | |
|---|---|---|---|---|---|---|---|---|
| | Slope | Regression coefficient | slope | Regression coefficient | slope | Regression coefficient | slope | Regression coefficient |
| 1 | 8.711 | 0.944 | 0.229 | -0.34 | 27.05 | 0.924 | 2.139 | 0.807 |

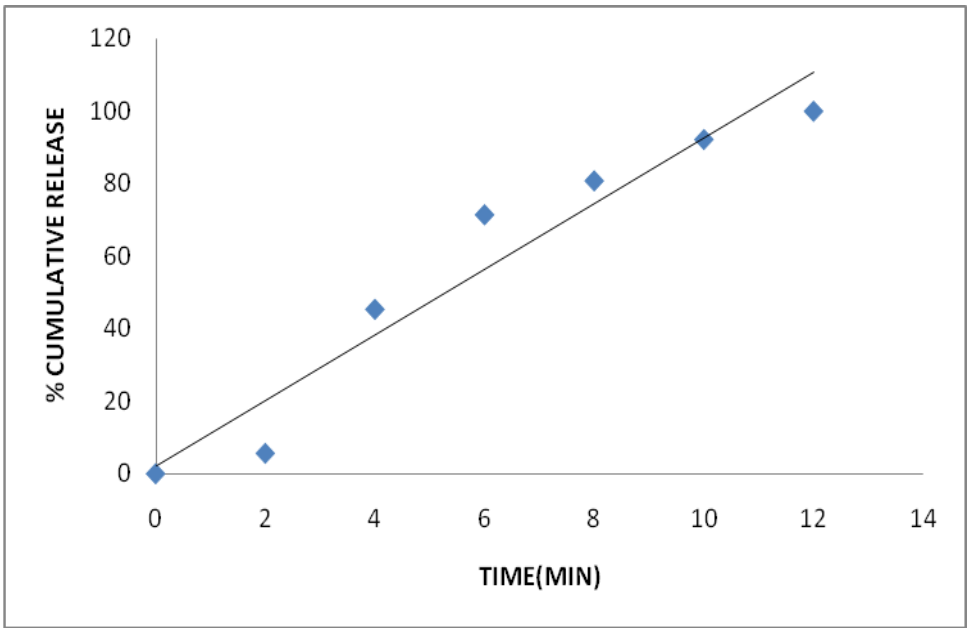



**FIG.6 CUMULATIVE % RELEASE VS TIME PLOT OF GATIFLOXACIN SOLID DISPERSIONS BY KNEADING (1:4)**

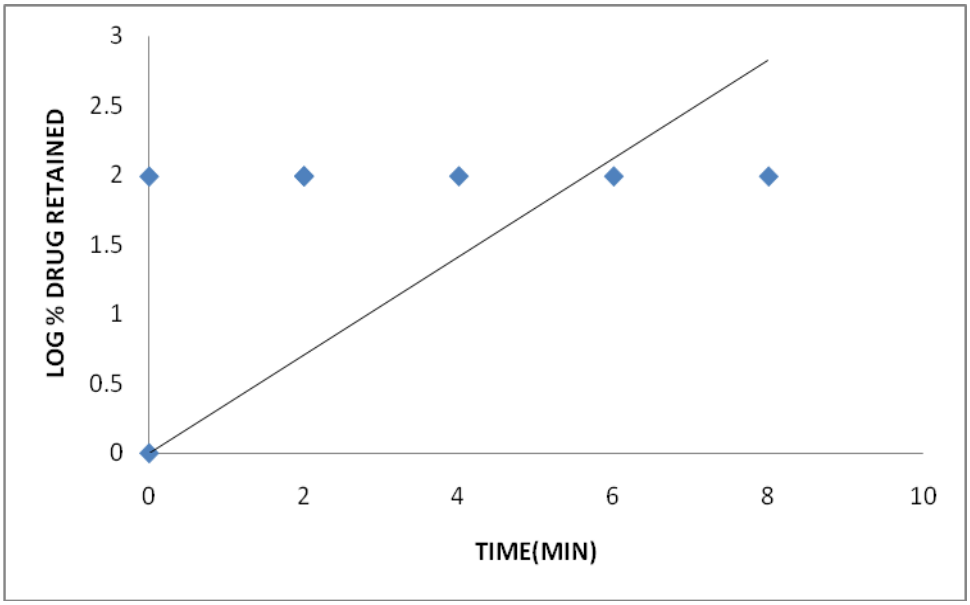



**FIG.7 LOG CUMULATIVE DRUG REMAINING VS TIME PLOT OF GATIFLOXACIN SOLID DISPERSIONS BY KNEADING (1:4)**

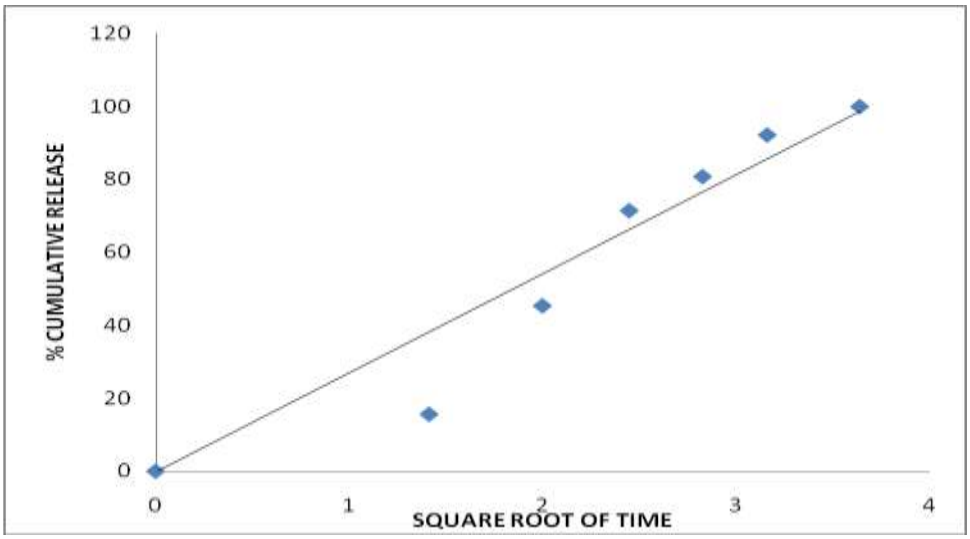



**FIG.8 PERCENTAGE DRUG RELEASE VS TIME PLOT OF GATIFLOXACIN SOLID DISPERSIONS BY KNEADING (1:4)**

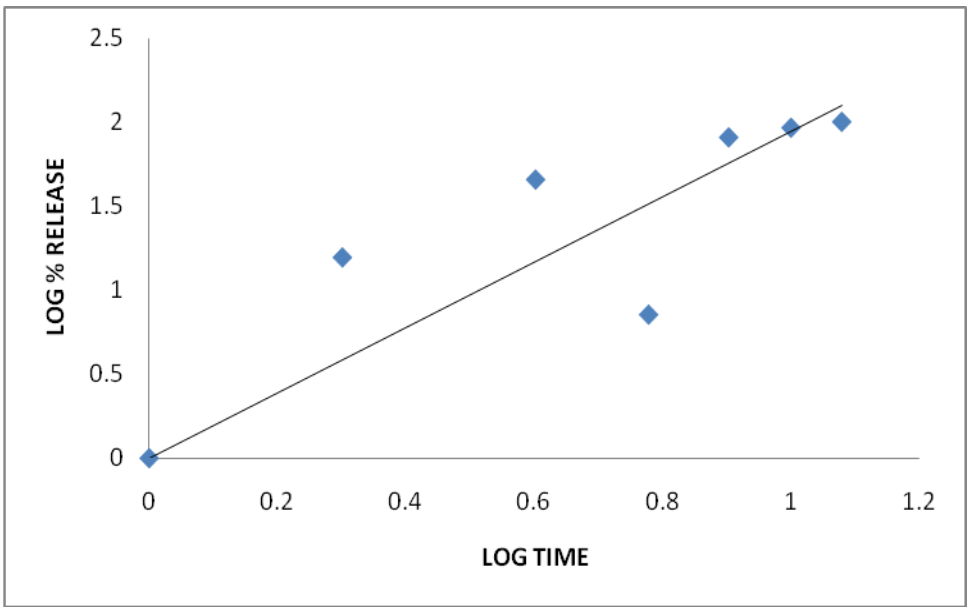



**FIG.9 LOG % DRUG RELEASE VS LOG TIME OF GATIFLOXACIN SOLID DISPERSIONS BY KNEADING (1:4)**

# 7. DISCUSSION

The objective of the study was to develop and evaluate mannitol solid dispersions of gatifloxacin. For core:coat ratios namely 1:1,1:2,1:3 and 1:4 were used to prepare mannitol solid dispersions by common solvent method, physical mixture, kneading method.

**SIZE ANALYSIS**

Particle size is directly proportional to surface area and this effects is the drug release from solid dispersions.

Particle size analysis was carried out using standard sieve 100. The size analysis of solid dispersions with different ratios formulated by using kneading method, physical mixture, solvent evaporation method showed enhanced particle size for 1:4 ratio of physical mixture method. With an increase in the concentration of core:coat ratio the size of solid dispersions prepared was increased , this is due greater amount of coat material containing in the same volume of solvent and drug concentration.

**DRUG CONTENT**

Drug content of solid dispersions determines the amount of drug present in the solid dispersions. The drug content estimated in each 50 mg of various solid dispersions[1:1,1:2,1:3 and 1:4] were found in the range of 82-100.1% in methanol.

The results of drug content are given in table 4

**WETTABILITY STUDIES**

Wettability studies are done to know the wetting nature of the solid dispersions .The time required for rising water through capillary action to wet the drug was found to be in the range of 2-6.25 min. For all the solid dispersions which was significantly less when compared with 2 min's for 1:4 ratio of kneading method and 1.30 min's for 1:4 of physical mixture and 1.35 min's for 1:4 ratio of solvent evaporation method. The wetting

time increases as the polymer ratio increases this was due to more soluble nature of polymer.

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**ANGLE OF REPOSE**

Angle of repose for all the solid dispersions were determined to know the flow properties of the solid dispersions. It was found to be in the range of 20.55-21.80 for kneading method, 26.56-27.87 for physical mixture and 21.80-23.46 for solvent evaporation method. This range indicates that all the solid dispersions has good flow properties. The free flow ability of solid dispersions indicates that they can be used for formulation in to solid dosage form.

**IN-VITRO DISSOLUTION STUDIES**

To assess the influence of coat concentration (mannitol), four batches of solid dispersions were prepared with core:coat ratio 1:1, 1:2, 1:3, and 1:4. *In-vitro* release studies were performed in 0.1N HCL for 12 min. The release rate of solid dispersions were 97.8%, 99.20%, 99.77% and 99.85% for kneading method,87.8% ,93.01%, 95.71% and 96.321% for physical mixture,90.56%, 93.50%, 96.821% and 98.831% solvent evaporation respectively. It indicates that increase in concentration of coat material (mannitol) resulted in increase in the release rate. This may be attributed to the fact that in the case of solid dispersions it may be due to the absences of aggregation of drug particles, and reduced size particles.

Also increased dissolution rate solid dispersions, may be due to the presence of drug in partially dissolved in melted or dissolved polymer. After drying the solid dispersions, the drug will not nucleate to form firm crystals resulting in formation of micro crystals which are embedded in the water soluble matrix. Hydrophilic polymers present the wetting and there by increases the dissolution of drug.

**KINETICS**

In order to elucidate the release mechanism, the data of gatifloxacin solid dispersions by kneading (1:4) were fitted into the models representing zero order, first order, Higuchi and korsemeyer's equations.

When data was plotted according to first order kinetics, a linear plot was obtained with their high regression coefficient value -0.34, suggesting that the rate of release from solid dispersions was followed as per “first order kinetics”.

The data fitted with higuchi equation yields a linear plot with their high regression coefficient values 0.924,indicating that mechanism of release from solid dispersions was diffusion controlled .To know precisely whether fickian’s or non fickian’s diffusion exsits the data was plotted according to Korsemeyer equation . The plot showed the slope value n=0.807,this shows that mechanism of relese was “super case 11”

# 8. CONCLUSION

The following conclusions can be drawn from the results obtained.

1. kneading method of solid dispersions give good batch yield and uniform drug content.
2. The size analysis of solids dispersions showed that about 32.8-64.6% were in the size mesh of 100
3. Solid dispersions size was proportionate with the concentration of core: coat ratio
4. Drug content of solid dispersions showed the range of 84.42-99.42%
5. Wetting time was decreased with increased proportion of coat composition.
6. As the sold dispersions shows free flow property, so suitable for tablet dosage from.
7. *In-vitro* drug release showed fast and complete release over a period of 12 min in 0.1N HCL release profile of solid dispersions were compared between different methods (kneading, physical mixture and solvent evaporation).
8. The sold dispersions flowed the drug release of super case 11
9. Studies have shown promising results these exits a scope for further *in-vivo* evaluation.

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