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PREPARATION AND EVALUATION OF SOLID DISPERSIONS OF OFLOXACIN

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ABSTRACT

The aim of the study was to develop and physico-chemically characterized solid dispersions of Ofloxacin by using hydrophilic polymers. Ofloxacin is quinolone derivate used for the treatment of fungal infection. Ofloxacin is belongs to the category of poorly water soluble drug. For this drug, dissolution is the rate determining step. We have to increase the solubility of the drug by preparing the solid dispersions. Ofloxacin is an appropriate model drug for formulation of solid dispersions forms due to its poor solubility it is a BCS class II drug, which affects its solubility. Therefore development of solid dispersions of ofloxacin can be advantageous that can provide increase efficacy. In the present study solid dispersions of ofloxacin were prepared by physical mixture method. Prepared dispersions were studied for drug polymer compatibility, characterized for powder blend properties and in vitro drug release studies. Different types of polymers were used poloxomer PEG and Urea were used for the preparation of solid dispersions of ofloxacin. The in vitro release profile of solid dispersions of ofloxacin suggests that formulation containing polaxomer (F8) which consisted of the drug: polymer ratio of 1:1 showed satisfactory drug release 98% at the end of 45 minutes among all formulations.

KEYWORDS: ofloxacin, solid dispersions, polymer, poloxomer, in vitro, compatability.

INTRODUCTION

Oral drug delivery: Oral drug delivery is by far the most preferable route of drug administration due to ease of administration, patient compliance, flexibility in formulation, etc. However in case of the oral route there are several challenges such as limited drug

absorption resulting in poor bioavailability and poor pharmacological response resulting into inadequate and erratic oral absorption.[1]

Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include enhancing solubility and dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly permeable drugs. This article focuses on the former, in particular, the use of solid dispersion technologies to improve the dissolution characteristics of poorly water-soluble drugs and in turn their oral bioavailability. Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs.[2]

Bioavailability: The term bioavailability is defined as the rate and extent (amount) of absorption of unchanged drug from its dosage form.

Factors influencing drug bioavailability

Biopharmaceutic considerations in the dosage from design

To achieve the desired therapeutic objective, the drug product must deliver the active drug at an optimal rate and amount. By proper biopharmaceutic design, the rate and extent of drug absorption or the systemic delivery of the drug to the body can be varied from rapid and complete absorption to slow and sustained absorption depending upon the desired therapeutic objective. The chain of events that occur following administration of a solid dosage form such as a tablet or a capsule until its absorption into systemic circulation are depicted in figure 1.

The process consists of four steps

1. Disintegration of the drug product
2. Deaggregation and subsequent release of the drug

3. Dissolution of the drug in the aqueous fluids at the absorption site.
4. Absorption i.e. movement of the dissolved drug through the GI membrane into the systemic circulation and away from the absorption site.[3]

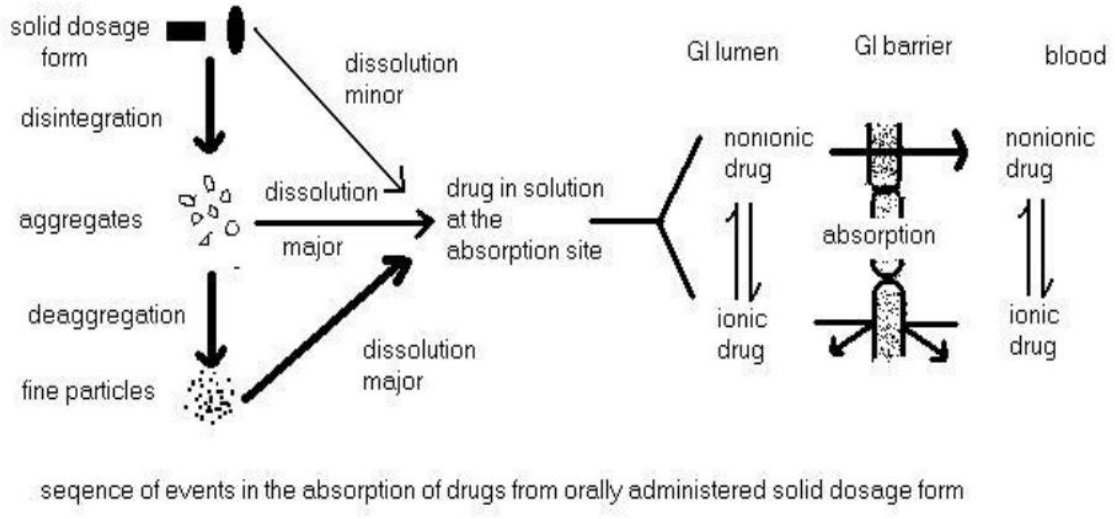

Fig no. 1.

The two critical slower rate determining processes in the absorption of orally administered drugs are

1. Rate of dissolution.
2. Rate of drug permeation through the biomembrane.

Dissolution is the rate determining step for hydrophobic, poorly aqueous soluble drugs like griseofulvin and spiranolactone; absorption of such drugs is often said to be dissolution rate-limited. If the drug is hydrophilic with high aqueous solubility for example, cromolyn sodium or neomycin, then dissolution is rapid and RDS in the absorption of such drugs is rate of permeation through the biomembrane. In other words absorption of such drugs is said to be permeation rate limited or transmembrane rate limited fig-2.

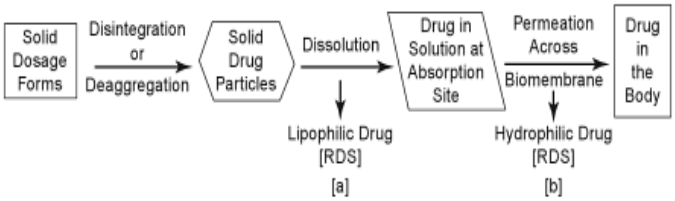

Fig no. 2: The two rate determining steps in the absorption of drugs from orally administered formulations.

Based on the intestinal permeability and solubility of drugs, Amidon *et al* Developed Biopharmaceutic Classification system (BCS) which classifies the drugs into one of the 4 groups as shown in table 1.[3]

Tab no-1: The Biopharmaceutic classification System for Drugs.

Class	Solubility	Permeability	Absorption Pattern	Rate-Limiting step in absorption	Examples
I	High	High	Well absorbed	Gastric emptying	Diltiazem
II	Low	High	Variable	Dissolution	Nifedipine
III	High	Low	Variable	Permeability	Insulin
IV	Low	Low	Poorly absorbed	Case by case	Taxol

Methods to increase dissolution rate: There are several ways by which drug dissolution rate can be enhanced. Some of the widely used methods are discussed briefly.

Micronization[4]: Particle size reduction leads to increase in the effective surface area resulting in enhancement of solubility and dissolution velocity of the drug. Micronization technique is used to improve dissolution rates of drugs into the biological environment, in order to improve the oral bioavailability. Particle size reduction methods include re crystallization of the solute particles from solutions using liquid anti solvents, along with labor intensive techniques like crushing, milling, grinding and freeze drying and spray-drying. Micronization has some limitations; micronization of sparingly or poorly soluble drugs is by no means a guarantee of better dissolution and absorption. A hydrophobic powder with small particle size leads to aggregation, making it difficult to disperse. The particles float on the dissolution medium because of entrapped air.

Nanonization[5]

Various nanonization strategies have emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water. Nanonization broadly refers to the study and use of materials and structures at the nano scale level of approximately 100 nm or less. Nanonization can result in improved drug solubility and pharmacokinetics, and it might also decrease systemic side-effects. For many new chemical entities with very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has the tendency to agglomerate, which leads to decrease effective surface area for dissolution, the next step is nanonization.

There are different techniques currently in use to prepare nanoparticles

- Homogenization in water (Wet milling as in a colloid mill)
- Pear milling
- Homogenization in non-aqueous media or in water with water –miscible liquids.

Solvent deposition

In this technique drug is dissolved in a solvent like ethylene chloride to produce a clear solution. The carrier is then dispersed in the solution by stirring and the solvent is removed by evaporation under temperature and pressure. The resultant mass is then dried, pulverized, and passed through a sieve. The increase in the dissolution rate is ascribed to the reduced particle size of the drug deposited on the carrier and enhanced wettability of the particles brought about by the carrier. Successfully solubility of nifedipine has increase by solvent deposition technique using lactose.[6]

Use of salt forms

A major improvement in solubility and dissolution rate can be achieved by forming a salt. Salts of acidic and basic drugs have, in general, higher solubility's than their corresponding acid or base forms. For solid dosage forms, dissolution rates of salt forms of several weakly acidic compounds under gastrointestinal (GI) pH conditions were much higher than those of their respective free acid forms. This may be attributed the higher dissolution rate of a salt to its higher solubility (relative to the free acid form) in the aqueous diffusion layer surrounding the solid. Alkali metal salts of acidic drugs like penicillin's and strong acid salts of basic drugs like atropine are more water soluble than the parent drug.

Salt formation does have limitations

- It is not feasible to form salts of neutral compounds.
- It may be difficult to form salts of very weal bases or acids
- The salt may be hygroscopic, exhibit polymorphism or has poor processing characteristics
- Conversion of salt to free acid or base of the drug on surface of solid dosage form that prevents or retards drug release
- Precipitation of unionized drug in the GI milieu that has poor solubility.

Evaporative precipitation into aqueous solution

This process utilizes rapid phase separation to nucleate and grow nanoparticles and micro particles of lipophilic drugs. The solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution on the aqueous solution to optimize particle formation and stabilization.

Alteration of pH of the drug microenvironment

This can be achieved in two ways- *in situ* salt formation and addition of buffers tothe formulation e.g. Buffered aspirin tablets.[7]

Use of Amorphous, Anhydrates, Solvates and Metastable Polymorphs

Depending upon the internal structure of the solid drug, selection of proper form of drug with greater solubility is important. In general, amorphous more soluble than Metastable polymorphs, anhydrates are more soluble than hydrates and solvates are more soluble than non –solvates**.**

Precipitation

In this method, the poorly aqueous soluble drug such as cyclosporine is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nanosize particles. The product so prepared is also called as hydrosol.

Selective adsorption on Insoluble Carriers: A highly active adsorbent such as the inorganic clays like bentonite can enhance the dissolution rate of poorly water soluble drugs such as griseofulvin, indomethacin and prednisone by maintaining the concentration gradient at its maximum. The two reasons suggested for the rapid release of drugs from the surface of clays are the weak physical bonding between the adsorbate and adsorbent, and hydration and swelling of the clay in the aqueous media**.**

Solid solutions

The three means by which the particle size of a drug can be reduced to submicron level are

- **Use of solid solutions**
- **Use of eutectic mixtures, and**
- **Use of solid dispersions.**

In all these cases, the solute is frequently a poorly water-soluble drug acting as the guest and the solvent is a highly water soluble compound or polymer acting as a host or carrier.

A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent. Since the two compartments crystallize together in a homogeneous one phase system, solid solutions are also called as molecular dispersion or mixed crystals. Because of reduction in particle size to molecular level, solid solutions show greater aqueous solubility and faster dissolution than eutectics and solid dispersion. They are generally prepared by fusion method whereby physical mixture of solute and solvent are melted together followed by rapid solidification. Such systems, prepared by fusion are called as melts e.g. griseofulvin-succinic acid. The griseofulvin from such solid solution dissolves 6 to 7 times faster than pure griseofulvin.[8]

Definition of solid dispersions

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage to achieve an increased dissolution rate or sustained release of drug, altered solid state properties and improved stability.[9]

Solid dispersions are generally prepared by solvent or co-precipitation method whereby both are guest solute and the solid carrier solvents are dissolved in a common volatile liquid solvent such as alcohol. The liquid solvent is removed by evaporation under reduced pressure or by freeze-drying which results in amorphous precipitation of guest in a crystalline carrier. Thus the basic difference between solid dispersions and solid solutions is that the drug is precipitated out in an amorphous form in the former as opposed to crystalline form in the latter: e.g amorphous sulphathiazole in crystalline urea. Such dispersions are often called as co-evaporates or co-precipitates. The method is suitable for thermo labile substances but has a number of disadvantages like higher cost of processing, use of large quantities of solvent, difficulty in complete removal of solvent, etc. The carriers used are same as for eutectics or solid solutions. With glassy materials, the dispersions formed are called as glass dispersions or glass suspensions.

Polymers such as PEG, HPMC are also employed to prepare solid dispersions of poorly water soluble drugs such as nifedipine and itraconazole.

Preparation of solid dispersions also presents several limitations

- Since the carrier is hydrophilic and the drug is hydrophobic, it is difficult it find a common solvent to dissolve both components.
- The product is often soft, waxy and possesses poor compressibility and flow ability.
- Physical instability of the solid dispersion.
- Difficulty in preparation of reproducible product.

Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly water-soluble drugs. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution.

Introduction to Solid Dispersion

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, co- solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs there are practical limitations of these techniques. The salt formation technique is not feasible for neutral compounds and also the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co solvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to size reduction achieved by commonly used methods as controlled crystallization, grinding, pearl milling etc. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability due to charge development.

In 1961, Sekiguchi and Obi developed a practical method whereby most of the limitations with the bioavailability enhancement of poorly water-soluble drugs can be overcome, which was termed as solid dispersion.[10]

From conventional capsules and tablets, the dissolution rate is limited by the size of the primary particles formed after disintegration of dosage forms. In this case, an average particle size of 5 µm is usually the lower limit, although higher particle sizes are preferred for ease of handling, formulation and manufacturing.

Types of Solid Dispersions: There are several types of solid dispersions those are discussed below.[11]

A) Simple Eutectic Mixture: Eutectic mixture of a sparingly water-soluble drug and a highly water-soluble Carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline components (Fig. 3). These systems are usually prepared by melt fusion method. When the eutectic mixture is exposed to water, the soluble carrier dissolves leaving the drug in a microcrystalline state which gets solubilized rapidly. The increase in surface area is mainly responsible for increased rate of dissolution.

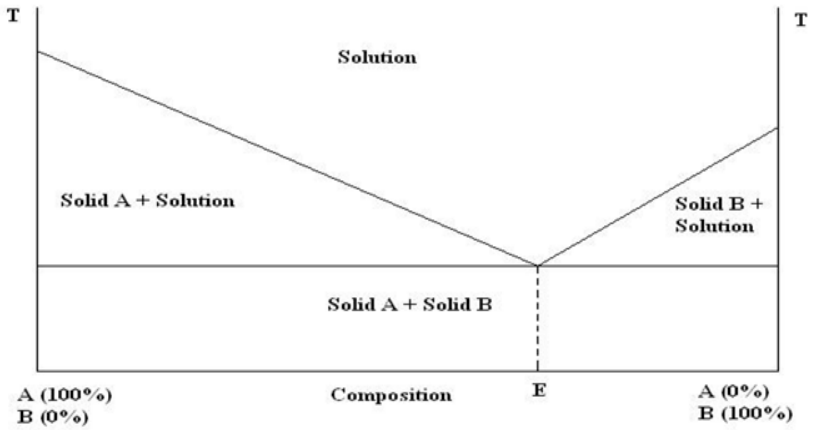

Fig.3: Hypothetical Phase Diagram of Eutectic Mixture.

Solid Solutions: Solid solutions consist of a solid solute dissolved in a solid solvent. These systems are generally prepared by solvent evaporation or co-precipitation method, whereby guest solute and carrier are dissolved in a common volatile solvent such as alcohol. The solvent is allowed to evaporate, preferably by flash evaporation. As a result, a mixed crystal containing amorphous drug in crystalline carrier is formed because the two components crystallize together in a homogenous single phase system. Such dispersions are also known as Co-precipitates or Co-evaporates. This system would be expected to yield much higher rates of dissolution than simple eutectic systems. Because, the basic difference between solid

solution and eutectic mixture is that the drug is precipitated out in an amorphous form in solid dispersion/solution while it is in crystalline form in eutectics.[12]

Solid solution can generally be classified according to the extent of miscibility between the two components or the crystalline structure of the solid solution.

(i) Continuous solid solutions

(ii) Discontinuous solid solution

(iii)Substitutional solid solution

(iv)Interstitial solid solution

***i)* Continuous Solid Solutions**

In this system, the two components are miscible or soluble at solid state in all proportions (Fig. 4). No established solid solution of this kind has been shown to exhibit faster dissolution properties, although it is theoretically possible. It is obvious that a faster dissolution rate would be obtained if the drug were present as a minor component. However, the presence of a small amount of the soluble carrier in the Crystalline lattice of the poorly soluble drugs may also produce a dissolution rate faster than the pure compound with similar particle size.[13]

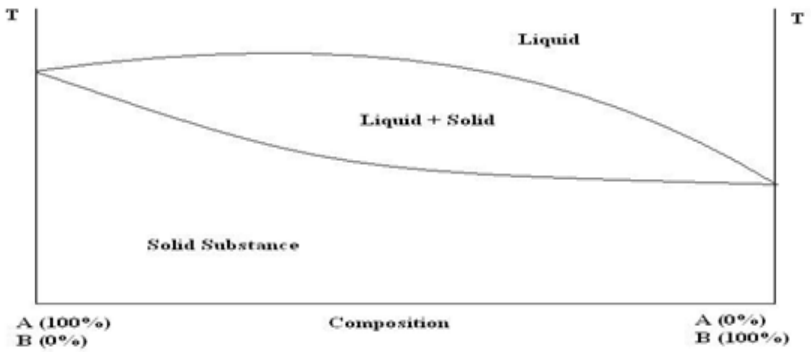

Fig no. 4: Hypothetical Phase Diagram of Continuous Solid Solution.

***ii)* Discontinuous Solid Solution:** In this system (Fig. 5), in contrast to the continuous solid solution, there is only a limited solubility of a solute in a solid solvent. Each component is capable of dissolving the other component to a certain degree above the eutectic temperature. However, as the temperature is lowered, the solid solution regions become narrower. The free energy of stable and limited solid solutions is also lower than that of pure solvent.

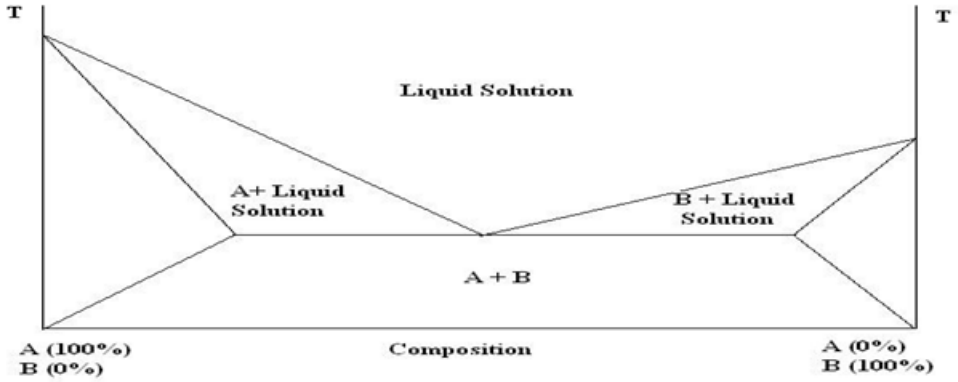

Fig no. 5: Hypothetical Phase Diagram of Discontinuous Solid Solution.

***iii*) Substitutional Solid Solution:** As shown in Fig. 6, in this type of solid solution, the solute molecule substitutes for the solvent molecules in the crystal lattice of the solid solvent. It can form a continuous or discontinuous solid solution. The size and stearic factors of the solute molecules play a decisive role in the formation of solid solution. The size of the solute and the solvent molecule should be as close as possible.[14]

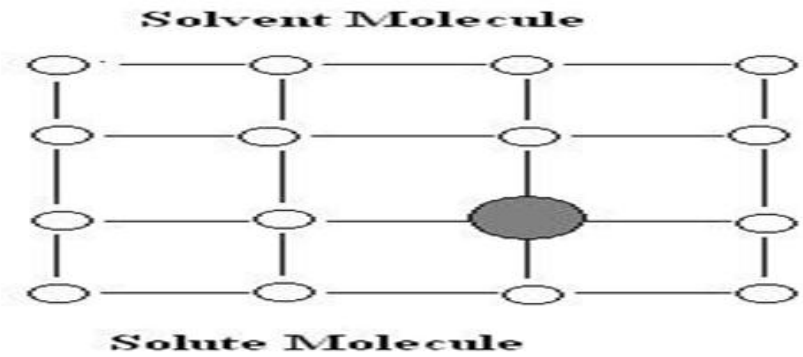

Fig no. 6: Substitutional Solid Solution.

***iv)* Interstitial Solid Solution**

The solute (guest) molecule occupies the interstitial space of the solvent (host) lattice (Fig. 7). It usually forms only a discontinuous (limited) solid solution. The size of the solute is critical in order to fit into the interstices. It was found that the apparent diameter of the solute molecules should be less than that of the solvent in order to obtain an extensive interstitial solid solution of metals.[15]

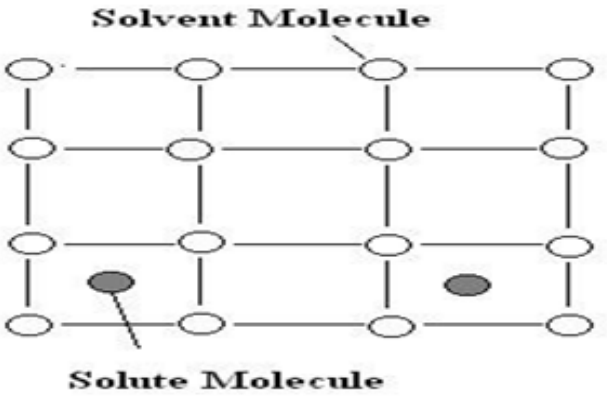

Fig no. 7: Interstitial Solid Solution.

C) Glass Solution

A glass solution is a homogenous system in which a glassy or a vitreous carrier Solubilized drug molecules in its matrix. PVP dissolved in organic solvents undergoes a transition to a glassy state upon evaporation of the solvent. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperature (T_g). On heating, it softens progressively without a sharp melting point.

D) Compound or Complex Formation

This system is characterized by complexation of two components in a binary System during solid dispersion preparation. The availability of drug from complex or compound depends on the solubility, association constant and intrinsic absorption rate of complex. Rate of dissolution and gastrointestinal absorption can be increased by the formation of a soluble complex with low association constant.[16]

E) Amorphous Precipitation

Amorphous precipitation occurs when drug precipitates as an amorphous form in the inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug. It is postulated that a drug with high super cooling property has more tendency to solidify as an amorphous form in the presence of a carrier. Hence, amorphous precipitation is rarely observed.

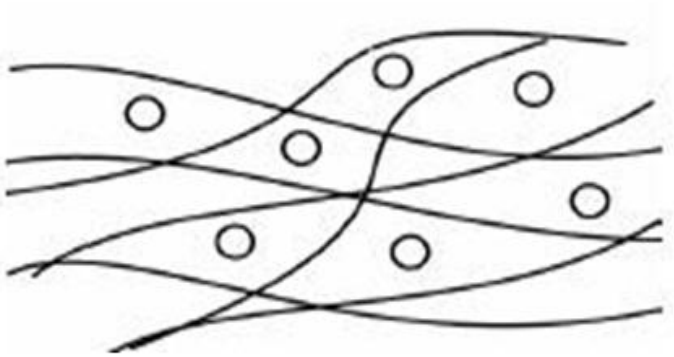

Fig no 8: Amorphous precipitation.

Mechanism of Dissolution Rate Enhancement

Corrigan reviewed the understanding of the mechanism of release from solid dispersion. The increase in drug dissolution rate from solid dispersion system can be attributed to a number of factors like particle size, crystalline or polymorphic forms and wettability of drug etc. It is very difficult to show experimentally that any one particular factor is more important than another. The main reasons postulated for the observed improvements in dissolution from these systems are as follows.[17]

a) Reduction of Particle Size

In case of glass solution, solid solution and amorphous dispersions, particle size is reduced. This may result in enhanced dissolution rate due to increase in the surface area. Similarly, it has been suggested that the presentation of particles to dissolution medium as physically separate entities may reduce aggregation.

b) Solubilization Effect:

The carrier material, as it dissolves, may have a solubilization effect on the drug.

Enhancement in solubility and dissolution rate of poorly soluble drugs is related to the ability of carrier matrix to improve local drug solubility as well as wettability.

c) Wettability and Dispersibility: The carrier material may also have an enhancing effect on the wettability and dispersibility of the drug due to the surfactant action reducing the interfacial tension between hydrophobic drug particle and aqueous solvent phase, increasing the effective surface area exposed to the dissolution medium. This also retards agglomeration or aggregation of the particles, which can slow down the dissolution.

d) Conversion of Polymorphic Nature of Solute: Energy required to transfer a molecule from crystal lattice of a purely crystalline solid is greater than that required for non-crystalline (amorphous) solid. Hence amorphous state of a substance shows higher dissolution rates. But the amorphous solids also demonstrate lack of physical stability due to natural tendency to form crystals. Thus formation of metastable dispersions with reduced lattice energy would result in faster dissolution rate and comparatively acceptable stability.

Selection of Carrier

One of the most important steps in the formulation and development of solid dispersion for various applications is selection of carrier. The properties of carrier have a major influence on dissolution characteristics of the drug. A material should possess following characteristics to be suitable carrier for increasing dissolution

i. Freely water-soluble with intrinsic rapid dissolution properties
ii. Non-toxic nature and pharmacologically inertness
iii. Thermal stability preferably with low melting point especially for melt method
iv. Solubility in a variety of solvents and should pass through a vitreous state upon solvent evaporation for the solvent method
v. Ability to increase the aqueous solubility of the drug
vi. Chemical compatibility and not forming a strongly bonded complex with drug.[18]

Polymers used in solid dispersions

A variety of polymers is offered as carriers for formulation of solid dispersion. Table 2 represents various categories and examples of carriers. Some polymers used in solid dispersions are as follows:

A) Polyethylene Glycols (PEG)

The term polyethylene glycols refer to compounds that are obtained by reacting ethylene glycol with ethylene oxide. PEGs with molecular weight more than 300,000 are commonly termed as polyethylene oxides.

B) Polyvinyl Pyrrolidone (PVP)

PVPs have molecular weights ranging from 10,000 to 700,000. It is soluble in solvents like water, ethanol, chloroform and isopropyl alcohol. PVP is not suitable for preparation of solid dispersions prepared by melt method because it melts at a very high temperature above 275ºC, where it gets decomposed.

C) Polymers and Surface Active Agent Combinations

The addition of surfactants to dissolution medium lowers the interfacial tension between drug and dissolution medium and promotes the wetting of the drug thereby they enhance the solubility and dissolution of drug. Ternary dispersion systems have higher dissolution rates than binary dispersion systems.[19]

D) Cyclodextrin

Cyclodextrin are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment of hydrophobic solute in hydrophilic cavity of CD. Advantages of CD include increasing the stability of the drug, release profile during gastrointestinal transit through modification of drug release site and time profile, decreasing local tissue irritation and masking unpleasant taste.

E) Phospholipids

Phospholipids aremajor structural components of cell membranes. Phosphotidylcholine was first isolated from egg yolk and brain. In phosphatidyl ethanolamine and phosphatidyl serine, the choline moiety is replaced by ethanolamine and serine respectively. Other phospholipids that occur in tissues include phosphotidyl ethanolamide, phosphotidyl serine and phosphotidyl glycerol. Naturally occurring lecithin's contain both a saturated fatty acid and unsaturated fatty acids with some exceptions.

Table no 2: Materials used as carrier for solid dispersion.

Sr. No.	Category	Examples
		Dextrose, Sucrose, Galactose, Sorbitol,
1	Sugars	Maltose, Xylitol, Mannitol, Lactose
2	Acids	Citric acid, Succinic Acid
		PVP, PEG, Celluloses like HPMC
3	Polymeric materials	HEC, HPC, Pectin, Galactomannan, CDs
4	Insoluble/ enteric polymer	HPMC, Phthalate, Eudragits
		Polyoxyethylene stearate, Renex,
5	Surfactants	Poloxamers, texafor, Deoxycholic acid,
		Tweens, Spans
		Pentaerythritol, Pentaerythrityl tetra acetate,
6	Miscellaneous	Urea, Urethane, Hydroxy alkyl xanthins

Methods of preparation of solid dispersions

A)Fusion Process: The fusion process is technically less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. Drug and carrier mixture of eutectic composition is molten at temperature above its eutectic temperature. Then molten mass is solidified on an ice bath and pulverized to a powder. Since a super saturation of the drug can be obtained by quenching the melt rapidly (when solute molecules are arrested in solvent matrix by instantaneous solidification), rapid congealing is favored. The solidification is often performed on stainless steel plates to facilitate rapid heat loss. A modification of the process involves spray congealing from a modified spray drier onto cold metal surfaces.[20]

Decomposition should be avoided during fusion but is often dependent on composition and affected by fusion time, temperature and rate of cooling. Therefore, to maintain drug content and physicochemical stability of formulation at an acceptable level, fusion must be effected at a temperature only just in excess of that which completely melts both drug and carrier.

B) Solvent Evaporation Process

Solid dispersion prepared by solvent removal process was termed by Bates et al. as Coprecipitates. But these systems should more correctly, be designated as Coevaporate,a term that has been recently adopted.

The solvent evaporation process uses organic solvents, the agent to intimately mix the drug and carrier molecules and was initially used by Tachibana and Nakamura, where, chloroform was used to co-dissolve -carotene and PVP to form Co-evaporate.

The choice of solvent and its removal rate are critical parameters affecting the quality of the solid dispersion. Since the chosen carriers are generally hydrophilic and the drugs are hydrophobic, the selection of a common solvent is difficult and its complete removal, necessitated by its toxic nature, is imperative. Vacuum evaporation may be used for solvent removal at low temperature and also at a controlled rate. More rapid removal of the solvent may be accomplished by freeze-drying. The difficulties in selecting a common solvent to both drug and carrier may be overcome by using an azeotropic mixture of solvent in water.[21,22]

C) Fusion Solvent Method

This method consists of dissolving the drug in a suitable solvent and incorporating the solution directly in the melt of carrier. If the carrier is capable of holding a certain proportion of liquid yet maintains its solid properties and if the liquid is innocuous, then the need for solvent removal is eliminated. This method is particularly useful for drugs that have high melting points or they are thermo-labile.

D) Supercritical Fluid Process

Supercritical CO_2 is a good solvent for water-insoluble as well as water-soluble compounds under suitable conditions of temperature and pressure. Therefore, it has potential as an alternative for conventional organic solvents used in solvent based processes for forming solid dispersions due to its favorable properties of being non-toxic and inexpensive.[23]

The process consists of the following steps

i. Charging the bioactive material and suitable polymer into the autoclave.

ii. Addition of supercritical CO_2 under precise conditions of temperature and pressure, that causes polymer to swell

iii. Mechanical stirring in the autoclave.

The temperature condition used in this process is fairly mild (35-75°C), which allows handling of heat sensitive biomolecules, such as enzymes and proteins.

Importance of Solid Dispersions: Despite issues a vast amount of research is still being conducted. Investigations have shown that using SD can increase the bioavailability of API's, as seen in the cases of docetaxel and paclitaxel. Based on concerns about stability, studies are currently being explored into choosing the best method of preparation as shown in research conducted by Agrawal et al. and analyzing the molecular interactions between the API and its carrier.12 Due to the high level of interest in this topic, this review intends to evaluate the properties and methodologies involved in SD, to ascertain the impact this is having in current pharmaceutical research spanning the last five years.

Advantages and disadvantages of solid dispersions

The advantages of solid dispersion include the rapid dissolution rates that result in increased bioavailability and a reduction in pre-systemic metabolism. The latter advantage may occur due to saturation of the enzyme responsible for biotransformation of the drug or inhibition of

the enzyme by the carrier, as in the case of morphine-tristearin dispersion both can lead to the need for lower doses of the drug. Other advantages include transformation of the liquid form of the drug into a solid form (e.g. clofibrate and benzoyl benzoate can be incorporated into PEG 6000 to give a solid, avoiding polymorphic changes and thereby bioavailability problems and protection of certain drugs by PEGs against decomposition by saliva to allow buccal absorption.[24,25]

The disadvantages of solid dispersion are related mainly to stability issue. Several systems have shown changes in crystalline and a decrease in dissolution rate with aging Moisture and temperature have a more prominent deteriorating effect on solid dispersions than on physical mixtures. Some solid dispersion may not lend them to easy handling because of tackiness.[25]

Applications of solid dispersions: To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.

1.To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerisation, photo oxidation and other decomposition procedures.

2.To reduce side effect of certain drugs.

3.Masking of unpleasant taste and smell of drugs.

4.Improvement of drug release from ointment creams and gels.

5.To avoid undesirable incompatibilities.

6.To obtain a homogeneous distribution of a small amount of drug in solid state.

7.To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.

8.To formulate a fast release primary dose in a sustained released dosage form.

To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

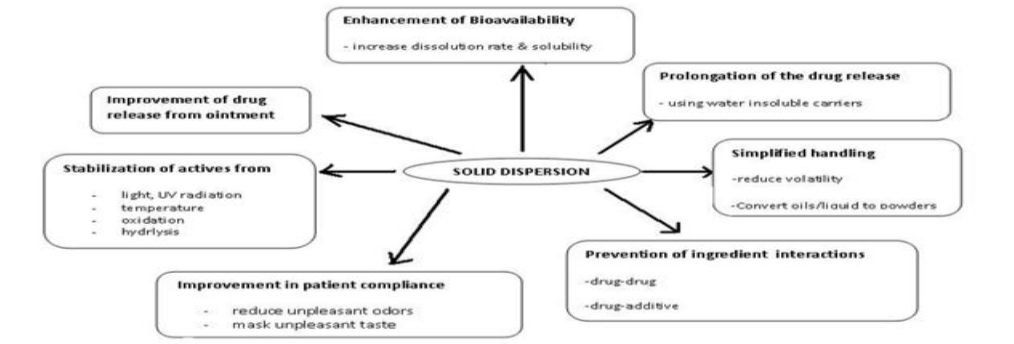

Fig no 9: Pharmaceutical Applications of solid dispersions.

Future Prospects

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up and stability has limited its use in commercial dosage forms for poorly water-soluble drugs. Successful development of solid dispersion systems for preclinical, clinical and commercial use has been feasible in recent years due to the availability of surface active and self-emulsifying carriers with relatively low melting points. The preparation of dosage forms involves the solubilization of drug in melted carriers and the filling of the hot solutions into hard gelatin capsules because of the simplicity of manufacturing and scale-up processes, the physicochemical properties and as a result, the bioavailability of solid dispersions are not expected to change significantly during the scale-up. For this reason, the popularity of the solid dispersion system to solve difficult bioavailability issues of poorly water-soluble drugs will grow rapidly. As the dosage form can be developed and prepared using small amount of drug substance in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques such as micronization and soft gelatin encapsulation.

One major focus of the future research will be the identification of new surface active and self-emulsifying carriers for solid dispersion. Only a small number of such carriers are currently available for oral use. Some carriers that are used only for topical applications of drug may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion systems is inadequate drug solubility in carrier, so a wider choice of carriers will increase the success of dosage form development.

Research should also be directed towards identification and synthesis of new possibilities of vehicles or excipients that would retard or prevent crystallization of drugs from super-saturated systems. Attention must be given to any physiological, pharmacological and toxicological effects of carriers. Many of the surface active and self-emulsifying carriers are lipoidal in nature, so potential roles of such carriers on drug absorption, especially on their inhibitory effects on CYP-3 based drug metabolism and *p*-glycoprotein mediated drug efflux will require careful consideration.[26]

In addition to bioavailability enhancement, much recent efforts and advances in the research on solid dispersion systems are directed towards the development of extended release dosage forms.

Physical and chemical stability of both drug and carrier in a solid dispersion are major developmental issues, so future research needs to be directed to address various stability issues. The semisolid and waxy nature of solid dispersions poses unique stability problem that might not be seen in other types of solid dosage forms. Predictive methods are necessary for the investigation of any potential drug crystallization and its impact on dissolution and bioavailability. Also possible drug-carrier interactions must also be investigated.

AIM AND OBJECTIVE

The main aim of the present work is to prepare and evaluate the solid dispersions of Ofloxacin.

OBJECTIVES

The major objectives of the present work are as follows

1. To study the compatibility between drug and physical mixture of drug, polymer by using FTIR method.
2. To formulate solid dispersions of Ofloxacin by physical mixture method using different polymers like poloxomer 407, PEG-6000 and Urea.
3. To study in-vitro drug release profile of different solid dispersions.s
4. To ascertain the release mechanism and kinetics of drug release from solid dispersions.

REVIEW LITERATURE

Pintu k De et al., (2013): The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin were formulated by using PEG-6000, Tween-80. The solid dispersions were prepared fusion method, freeze drying method, solvent evaporation method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations PEG-6000 shows better percentage drug release 89%.[2]

Anjuman Ara Alam et al., (2013): The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin were formulated by using CCS, SSG, poloxomer 407, PEG 4000 and PEG 6000 in the ratios of 1:1, 1:5 and 1:10. The solid dispersions were prepared by physical mixture method (1:1), solvent evaporation method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations PEG 6000 1:5 (solvent evaporation method) ratio shows better percentage drug release that is 94.68%.[3]

G Nisha Shetty et al., (2013): objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin was formulated by using poloxomer 188, aerosil was used as an adsorbent. The solid dispersions were prepared by using hot melt method. All the dispersions showed better dissolution compared to the pure drug. The dispersions are prepared in the ratio of 1:1:1(drug: polymer: adsorbent).[4]

Bankar p.v et al., (2013): The objective of the present work was to develop and evaluate the solid dispersions of glipizide. The solid dispersions of the glipizide were formulated by using Beta- cyclodextrin. The solid dispersions were prepared by solvent evaporation method in the ratios of 1:1, 1:3. All the dispersions showed better dissolution compared to the pure drug. Among these preparations Beta cyclodextrin 1:3 ratio shows better percentage drug release.[5]

Rajnikant M. Suthar et al.,(2013): The objective of the present work was to develop and evaluate the solid dispersions of ondansetron. The solid dispersions of the ondansetron was formulated by using CP, L-HPC, CCS. The solid dispersions were prepared by solvent method, physical mixture method in the ratios of 1:1, 1:2, 1:3. All the dispersions showed better dissolution compared to the pure drug. Among these preparations CP shows better percentage drug release that is 98%.[6]

Anne Ramu et al., (2013): The objective of the present work was to develop and evaluate the solid dispersions of irbesartan. The solid dispersions of the irbesartan were formulated by using PEG 6000, SSG and CCS. The solid dispersions were prepared by kneading method, physical mixture method and solvent evaporation method in the ratios of 1:2. All the dispersions showed better dissolution compared to the pure drug. Among these preparations SSG 1:2 (kneading method) shows better percentage drug release.[7]

Kantamaneni Rama Devi et al., (2013): the objective of the present work was to develop and evaluate the solid dispersions of telmisartan. The solid dispersions of the telmisartan were formulated by using CP, SSG and CCS. The solid dispersions were prepared by physical mixture method, solvent evaporation method in the ratios of 1:4. All the dispersions showed better dissolution compared to the pure drug. Among these preparations CP 1:4 shows better percentage drug release that is 98.4%.[8]

Lende Lalita K et al., (2013): The objective of the present work was to develop and evaluate the solid dispersions of diclofenac. The solid dispersions of diclofenac were formulated by

using CP, CCS, and SSG. The solid dispersions were prepared by solvent evaporation method in the ratios of 1:1, 1:3, 1:5, 1:7 and 1:9. All the dispersions showed better dissolution compared to the pure drug. Among these preparations SSG1:7 shows better percentage drug release that is nearly 100%.[9]

Mahmoud EI Badry et al., (2013): The objective of the present work was to develop and evaluate the solid dispersions of nimesulide. The solid dispersions of the nimesulide were formulated by using poloxomer 407. The solid dispersions were prepared by kneading method, melting method, solvent method in the ratios of 1:1, 1:2 and 1:4. All the dispersions showed better dissolution compared to the pure drug. Among these preparations kneading method shows better percentage drug release.[10]

Md.Abdullah Al Masum et al., (2013): The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin was formulated by using poloxomer 407, SSG,CCS,PEG4000,PEG 6000,HPMC 5cps in the ratios of 1:1,1:5,1:10. The solid dispersions were prepared by solvent evaporation method, physical mixture method in the ratio of 1:1. All the dispersions showed better dissolution compared to the pure drug. Among these preparations PEG 6000 1:5 ratio (solvent evaporation) shows better percentage drug release that is 94%.[11]

Swati changdeo Jagdale et al., (2012): The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin were formulated by using CCS, SSG and Beta-cyclodextrin in the ratios of 1:1. The solid dispersions were prepared by physical mixture method, kneading method, freeze drying method, melting method, co grounding method, inclusion complexation method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations Beta-cyclodextrin 1:1 (inclusion complexes with ofloxacin) ratio shows better percentage drug release that is 86.70%.[12]

Rakesh Singh et al., (2012): The objective of the present work was to develop and evaluate the solid dispersions of telmisartan. The solid dispersions of the telmisartan were formulated by using PEG 6000, Beta-cyclodextrin in the ratios of 1:1. The solid dispersions were prepared by physical mixture method, kneading method, Fusion method, solvent evaporation method. All the dispersions showed better dissolution compared to the pure drug. Among

these preparations kneading method 1:1 ratio shows better percentage drug release that is 86.70%.[13]

Irin dewan et al., (2012): The objective of the present work was to develop and evaluate the solid dispersions of carvediol. The solid dispersions of carvediol were formulated by using poloxomer 407, HPMC, SSG. The solid dispersions were prepared by fusion method, solvent evaporation method in the ratios of 1:1, 1:2, 1:4. All the dispersions showed better dissolution compared to the pure drug. Among these preparations 1:4 shows better percentage drug release.[14]

Mogal S.A et al., (2012): The objective of the present work was to develop and evaluate the solid dispersions of paracetamol. The solid dispersions of the paracetamol was formulated by using PEG4000,PEG 6000, pvp in the ratios of 1:1,1:2,1:3,1:4. The solid dispersions were prepared by solvent evaporation method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations 1:4 ratio (solvent evaporation) shows better percentage drug release that is 63.59%.[15]

V.N.V Vinay et al., (2012): The objective of the present work was to develop and evaluate the solid dispersions of fenofibrate. The solid dispersions of the fenofibrate was formulated by using PEG4000,PEG 6000 in the ratios of 1:1,1:2,1:3,1:4. The solid dispersions were prepared by solvent evaporation method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations 1:4 ratio (solvent evaporation) shows better percentage drug release that is 99%.[16]

Abhishek Datta et al., (2011): The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin was formulated by using Hydroxy propyl beta-cyclodextrin, with drug and increasing the different SLS percentages, in the ratios of 1:2,1:3,1:4. The solid dispersions were prepared by solvent evaporation method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations hydroxy propyl beta-cyclodextrin1:4 ratios shows better percentage drug release that is 86.32 %.[17]

Ashwini kumar et al., (2011): The objective of the present work was to develop and evaluate the solid dispersions of irbesartan. The solid dispersions of the irbesartan were formulated by using SSG, CP, CCS and MCC. The solid dispersions were prepared by

solvent evaporation method, physical mixture method in the ratios of 1:1, 1:2, 1:4. All the dispersions showed better dissolution compared to the pure drug. Among these preparations CP shows better percentage drug release.[18]

Ramana G et al., (2011)

The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin was formulated by using CCS,SSG in the ratios of 1:1,1:2,1:4. The solid dispersions were prepared by solvent evaporation method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations CCS 1:4 ratio shows better percentage drug release that is 90.24.%.[19]

Abhishek Datta et al., (2011): The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin was formulated by using poloxomer 407 was tried with different proportion with drug and increasing the different SLS percentages. in the ratios of 1:2,1:3,1:4. The solid dispersions were prepared by solvent evaporation method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations poloxomer 1:4 ratio shows better percentage drug release that is 100.13%.[20]

Gohel MC et al., (2011): The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin were formulated by using poloxomer 407, hydroxy propyl beta cyclodextrin in the ratios of 1:10. The solid dispersions were prepared fusion method, freeze drying method, solvent evaporation method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations poloxomer 407 shows better percentage drug release.[21]

K.Nagarajan et al., (2010): The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin was formulated by using PEG4000 in the ratios of 9:1,3:1,1:1,1:3,1:9. The solid dispersions were prepared by solvent evaporation method, melting fusion method, physical mixture method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations PEG 4000 1:9 ratio (solvent evaporation) shows better percentage drug release that is 94.95%.[22]

Uddin et al., (2010): The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin was formulated by using poloxomer 407, poloxomer 188. The solid dispersions were prepared by fusion method, in the ratios of 1:2, 1:4, 1:1. All the dispersions showed better dissolution compared to the pure drug. Among these preparations poloxomer 1:4 shows better percentage drug release.[23]

Appa Rao et al., (2010): The objective of the present work was to develop and evaluate the solid dispersions of acelofenac. The solid dispersions of the acelofenac was formulated by using lactose, mannitol. The solid dispersions were prepared by solvent evaporation method, in the ratios of 9:1, 7:3, 4:1. All the dispersions showed better dissolution compared to the pure drug. Among these preparations 9:1 ratio shows better percentage drug release.[24]

Vikrant Vyas et al., (2009): The objective of the present work was to develop and evaluate the solid dispersions of tadalafil. The solid dispersions of the tadalafil were formulated by using poloxomer 407. The solid dispersions were prepared by melting method, in the ratios of 1:0.5, 1:1.5 and 1:2.5. All the dispersions showed better dissolution compared to the pure drug. Among these preparations 1:0.5 ratio shows better percentage drug release.[25]

Kanagale et al., (2008): The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin were formulated by using poloxomer 188 in the ratios of 1:1, 1:5 and 1:10. The solid dispersions were prepared by hot melt method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations poloxomer 1:10 ratio shows better percentage drug release that is 84.95%.[26]

Siriporn Okponogi et al., (2005): The objective of the present work was to develop and evaluate the solid dispersions of OFLOXACIN. The solid dispersions of the ofloxacin were formulated by using PEG-4000, Tween-80'PEG-20000 in the ratios of 5:5:1 and 7:3:1 The solid dispersions were prepared by physical mixture method, solvent evaporation method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations PEG-4000, Tween-80 5:5:1 (solvent evaporation method) ratio shows better percentage drug release that is 81.68%.[1]

Emara LH et al., (2002): The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin were formulated by

using PEG 6000, Beta-cyclodextrin in the ratios of 1:1. The solid dispersions were prepared fusion method, freeze drying method, solvent evaporation method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations Beta cyclodextrin shows better percentage drug release.[27]

Chutimaworapan et al., The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin were formulated by using poloxomer 407, PEG4000, PEG 6000, HPCD in the ratios of 1:10. The solid dispersions were prepared by melting method. All the dispersions showed better dissolution compared to the pure drug. Among these preparations poloxomer 1:10 ratio shows better percentage drug release that is 80.60%.[28]

Weiym et al., The objective of the present work was to develop and evaluate the solid dispersions of ofloxacin. The solid dispersions of the ofloxacin were formulated by using pvp. The solid dispersions were prepared fusion method, freeze drying method, solvent evaporation method. All the dispersions showed better dissolution compared to the pure drug.[29]

Mowafaq M et al., The objective of the present work was to develop and evaluate the solid dispersions of meloxicam. The solid dispersions of meloxicam were formulated by using poloxomer. The solid dispersions were prepared by kneading method, physical mixture method in the ratios of 1:2, 1:5 and 1:8. All the dispersions showed better dissolution compared to the pure drug. Among these preparations kneading method shows better percentage drug release that is 86.15%.[30]

Plan of Work

1 Selection of Ofloxacin drug based on its solubility.

1 Selection of polymers. Analysis of drug and physical mixture containing drug, polymers by using FTIR method to know the interaction among drug, polymers and other excipients.

2 Construction of standard graph of selected drug in suitable medium.

3 Development of solid dispersions by using polymers at various concentrations.

Evaluation: Evaluation of prepared dispersions for in-vitro drug release profile.

5 Selection of best solid dispersion based on the result of physicochemical parameter and in vitro drug release.

MATERIALS

Materials: The list of materials used in this present work was shown in table no-3.

Table. no. 3: List of materials.

S. NO	Materials	Supplied by
1	Ofloxacin	Aman scientific products
2	Poloxomer 407	Aman scientific products
3	PEG-6000	Aman scientific products
4	Urea	Aman scientific products
5	HCL	Aman scientific products

Equipments

Equipments

The equipments used in the formulation and evaluation of solid dispersions were shown in Table no-4.

Table no-4: List of Equipments.

S. NO	Equipments	Company
1	Electronic digital balance	Shimadzu
2	Double beam UV spectrophotometer	Lab India
3	Dissolution tester(USP apparatus-2)	DBK Electro labs
4	FT-IR	Shimadzu

Experimental Procedures

A. Selection of drug, polymers

B. Compatibility studies.

C. Preparation of calibration curve of Ofloxacin using 0.1 N HCL buffer.

D. Preparation of solid dispersions of Ofloxacin

E. Evaluation of the solid dispersions by in-vitro drug release studies using pH 0.1 N HCL

A. Selection of drug, polymers

1. Ofloxacin was selected as model drug for the preparation of solid dispersions.
1. PEG-6000, Urea and Poloxomer 407 were selected as the polymers for the preparation of solid dispersions.

B. Compatibility studies: FT-IR spectra were taken in IR-Prestige 21, Shimadzu, Japan by scanning the sample in potassium bromide (KBr) discs. Before taking the spectrum of the sample, a blank spectrum of air background was taken.SD were scanned over the frequency

range 2000 to 4000 cm^{-1} The IR spectra of SD were compared with standard IR spectra of pure ofloxacin and respective carrier.

C. Standard graph of Ofloxacin

1 100 mg of ofloxacin was weighed accurately and transferred to 100 ml volumetric flask.

2 The drug was dissolved in 100ml of 0.1N HCL. This was the standard stock solution of ofloxacin-1

3 10 ml of ofloxacin solution took from stock 1 solution and transferd in to 100ml of volumetric flask and make up the volume with 0.1N HCL. This solution was reffered as stock 2 solution.

4 From the stock 2 solution appropriate quantities of aliquots (0.4, 0.8, 1.2, 1.6 ml) of the standard solution were taken in 10ml volumetric flasks. These were diluted with 0.1N HCL make solutions of concentration of 4, 8, 12, 16 µg/ml.

5 The absorbance of solutions were recorded at 294 nm.[7,8]

Preparation of Solid dispersion of ofloxacin with Poloxomer 407, PEG-6000 and Urea Solid Dispersion of ofloxacin in Poloxomer 407, PEG-6000,Urea containing three different weight ratios (1:0.5, 1:1 1:2) was prepared by the physical mixture method. PMs in the ratio of 1:0.5, 1:1, and 1:2 were prepared by mixing the appropriate amounts of ofloxacin and carrier for 10 min in a mortar. The mixtures were coded as per Table 5. The mixtures were sieved through a '60'mesh screen and stored in glass vials surrounded by aluminum foil in a desiccators

Table No. 5: Formulation Of Solid Dispersions.

S. No	Drug: carrier (ratio)	Carrier
1	1:0.5(F1)	UREA
2	1:1(F2)	UREA
3	1:2(F3)	UREA
4	1:0.5(F4)	PEG-6000
5	1:1(F5)	PEG-6000
6	1:2(F6)	PEG-6000
7	1:0.5(F7)	POLAXOMER 407
8	1:1(F8)	POLAXOMER 407
9	1:2(F9)	POLAXOMER 407

RESULTS AND DISCUSSION

Fourier transforms infrared (FT-IR) spectroscopy

FT-IR spectra were taken in IR-Prestige 21, Shimadzu, Japan by scanning the sample in potassium bromide (KBr) discs. Before taking the spectrum of the sample, a blank spectrum

of air background was taken. Pure ofloxacin, SD was scanned over the frequency range 2000 to 4000 cm^{-1}. The IR spectra of SD were compared with standard IR spectra of pure ofloxacin and respective carrier.

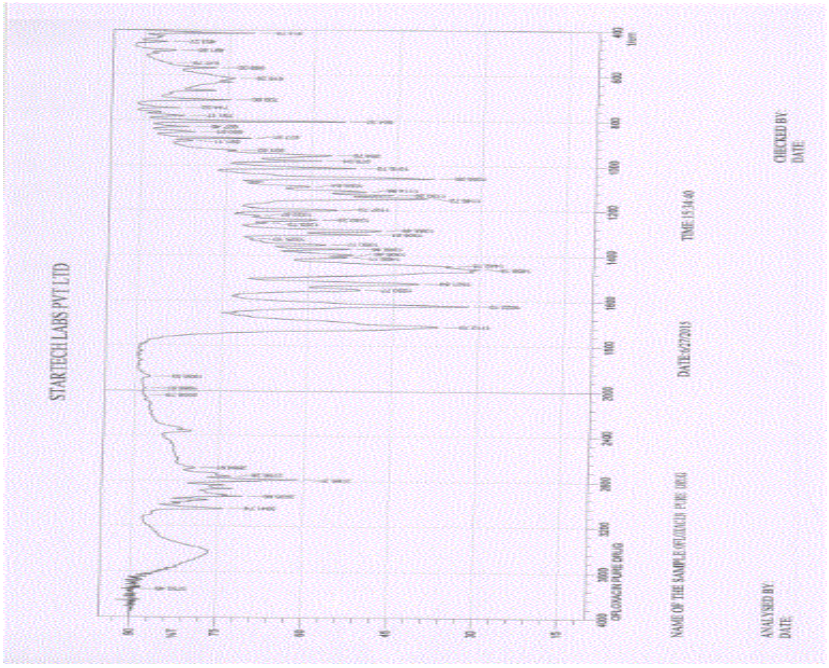

Fig. no. 10: FT-IR Spectrum of pure Ofloxacin.

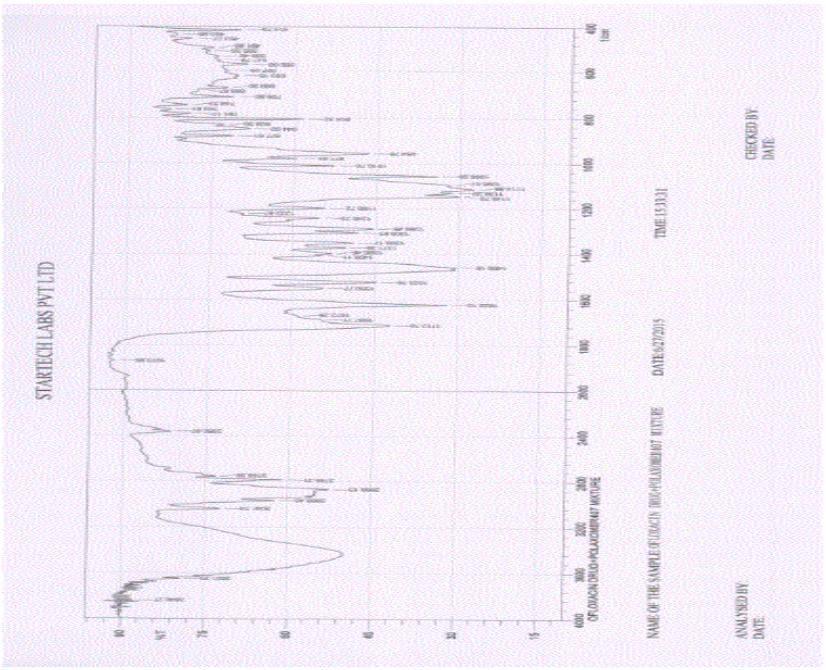

Fig. no. 11: FT-IR Spectrum of Ofloxacin and polaxomer.

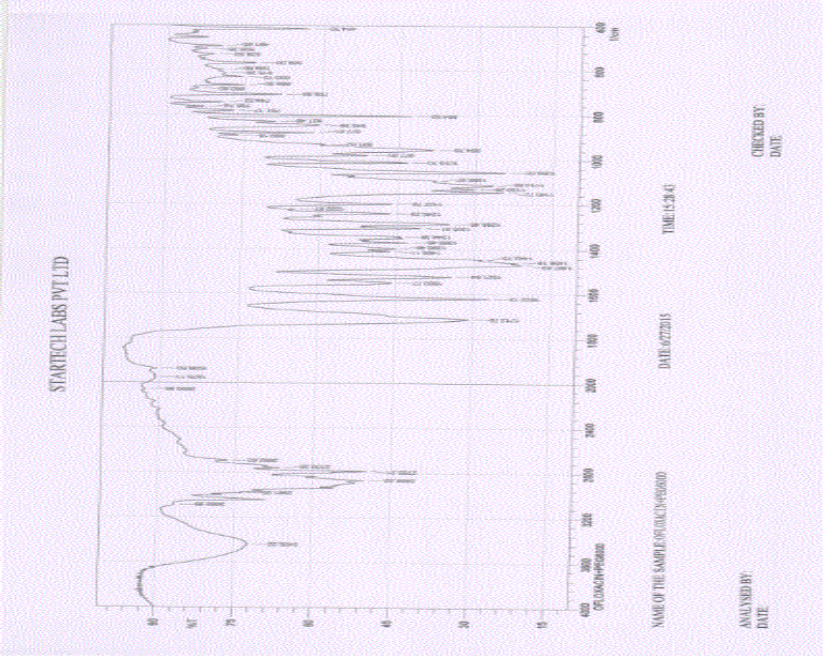

Fig. no. 12: FT-IR Spectrum of Ofloxacin and PEG-6000.

Table no: 6 Interpretation of Ofloxacin FT-IR spectrum.

S. no	Functional group and type of vibration	Characteristic peaks(cm^{-1})	Observed peaks (cm^{-1})in pure drug	Observed peaks (cm^{-1})in drug with poloxomer	Observed peaks (cm^{-1})in drug with PEG-6000
1	C=C (str) of aromatic	1400-1600	1450	1458	1458
2	C-O (str) of Carboxylic	1210-1320	1288	1288	1288
3	C=O (str) of Cyclic	1665-1680	1687	1687	1686
4	C=O (str) of carboxylic	1705-1725	1712	1712	1712
5	O-H(str) carboxilyc	2500-3300	2968	2968	2968
6	C-H (str)of aliphatic	2850-3000	2951	2951	2951

FTIR techniques have been used to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that the characteristic absorption peaks of Ofloxacin were obtained at different wave numbers in different samples. From the results it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no chemical interactions between drug and polymers.

Preparation of Standard Graph

A standard graph of pure drug in suitable medium was prepared by plotting the concentrations on X – axis and absorbance on Y – axis.

Procedure for preparation of standard graph of Ofloxacin

Accurately weighed amount of 100mg of Ofloxacin is taken in a 100ml volumetric flask. The volume was made up to 100 ml with 0.1N Hcl, which constitutes the stock solution of 1mg/ml. by further diluting the stock solution suitably with 0.1N Hcl solutions of 2,4,6,8 and 10µg/ml concentrations were prepared. These solutions were checked for their absorbance using UV – Visible spectrophotometer at λ_{max} 294 nm against 0.1N Hcl as blank and a standard graph was plotted.

Table no. 7: Calibration curve of Ofloxacin.

S. No	Concentration (µg/ml)	absorbance
1	0	0
2	4	0.259
3	8	0.493
4	12	0.737
5	16	0.962

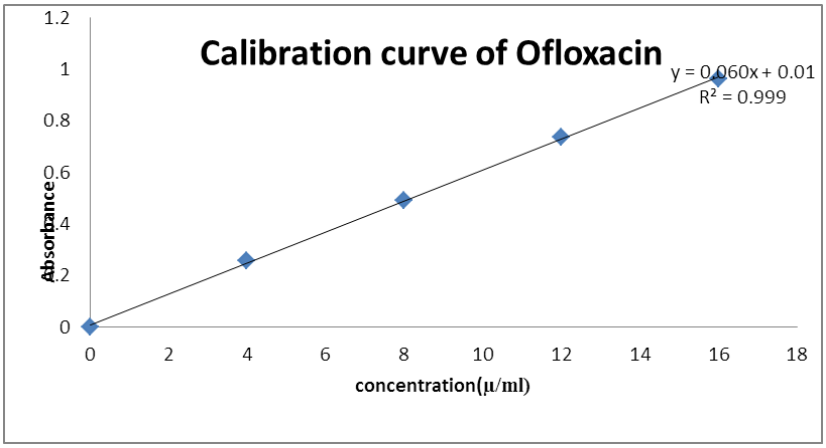

Fig. no. 13 Calibration curve of Ofloxacin.

The linear regression analysis was done on absorbance data points. The correlation Coefficient, slope (m) and intercept (c) were found to be 0.06, 0.01 and 0.01 in 0.1 N HCL buffer.s

Dissolution of Ofloxacin solid dispersions

The *in-vitro* dissolution studies of all the formulations of solid dispersions of Ofloxacin were carried out in pH 0.1N HCL for 1 hour. The results of *in-vitro* dissolution studies of all formulations were shown in table no-14.The plot of % drug release v/s time (hrs) were plotted for formulations containing ofloxacin with PEG-6000, ofloxacin with Urea, ofloxacin with POLOXOMER 407.

Table no: 8 In vitro drug release studies of Ofloxacin solid dispersions.

	%Drug release								
Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
5	48.12	49.12	45	34.57	49.37	31.12	70.89	77.25	30.75
10	55.12	57.31	49.5	44.06	61.87	38.51	76.98	80.87	36.45
15	57.23	67.32	51.71	49.05	69.37	44.12	80.67	81.5	39.12
20	69.76	79.76	52.75	56.94	73.5	48	82.20	87	40.58
25	71.25	81.34	60.12	62.15	76.87	52.18	87.45	90.50	42
30	73.42	85.54	61.57	65.57	80.25	56.75	90.56	94.75	42.75
35	80.62	87	69.27	68	85.75	61.25	91.26	95.17	44.25
40	87	94.54	73.5	75.08	89.79	65.75	93.87	96.08	46.5
45	91.12	105	83.2	76.59	94.12	68.12	94.5	98	59.25

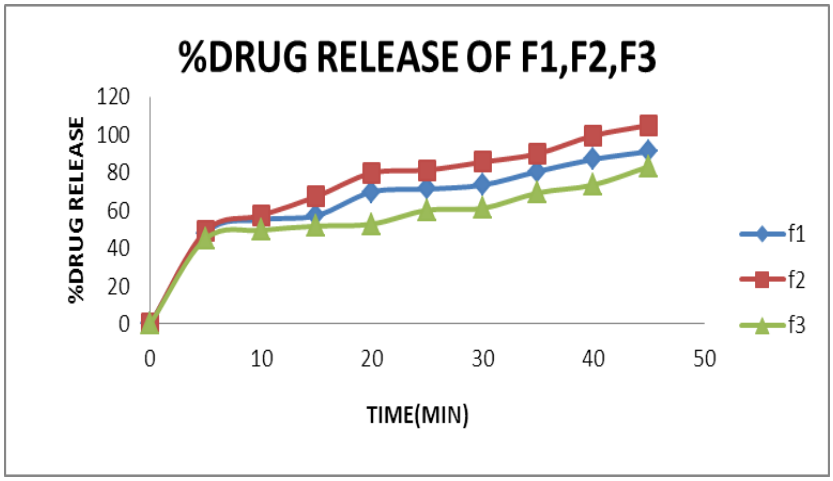

Fig. no. 14: In-vitro drug release profile of Ofloxacin solid dispersions containing urea as polymer.

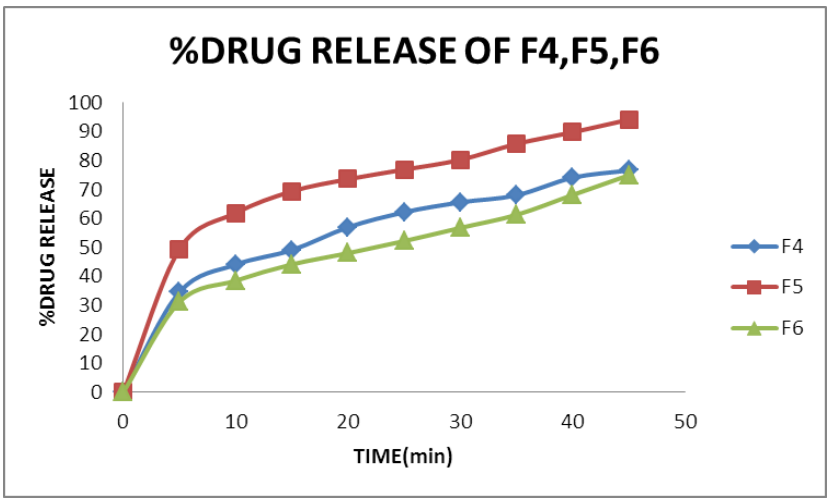

Fig. no. 15: In-vitro drug release profile of Ofloxacin solid dispersions containing PEG 6000as polymer.

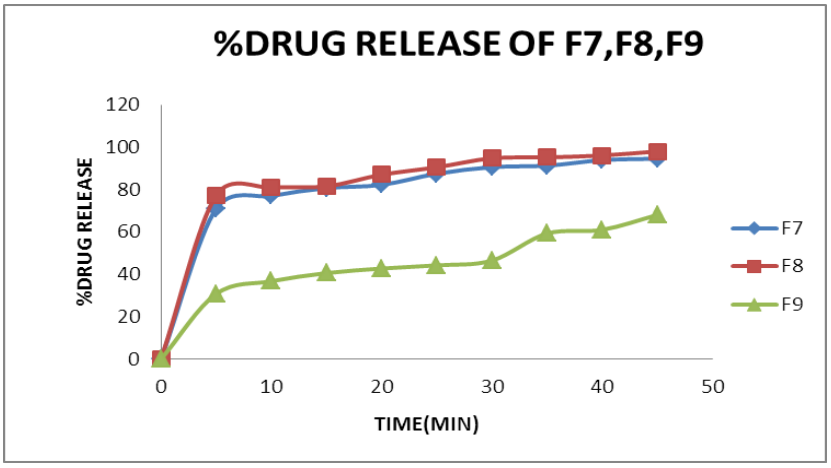

Fig. no. 16: In-vitro drug release profile of Ofloxacin solid dispersions containingPolaxomr 407 as polymer.

It was observed that the higher amount of %drug release obtained from dispersions containing Polaxomer 407 polymer.

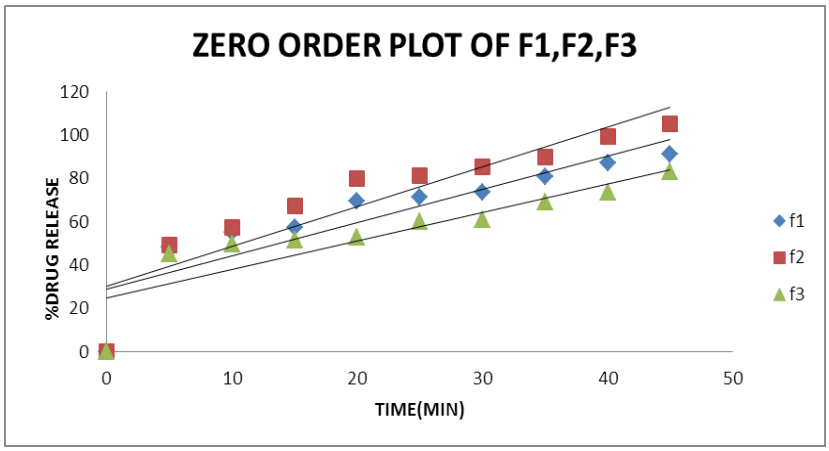

Fig. no. 17: zero order plot of Ofloxacin solid dispersions containing Urea as polymer.

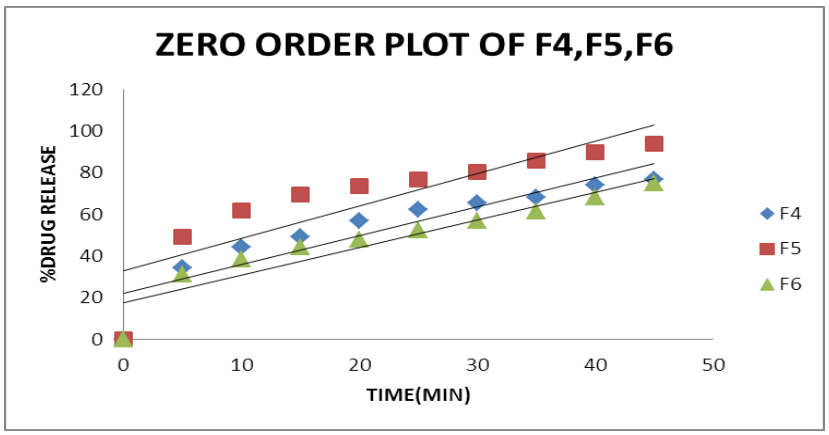

Fig. no. 18: zero order plot of Ofloxacin solid dispersions containing PEG 6000 as polymer.

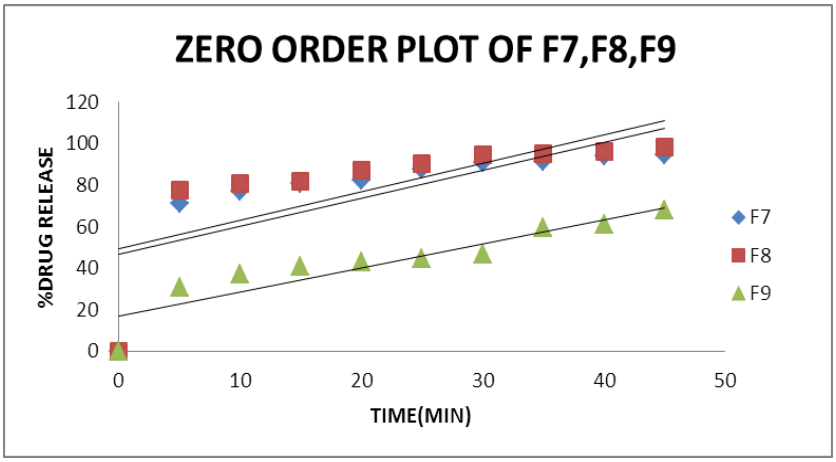

Fig. no. 19: zero order plot of Ofloxacin solid dispersions containing Polaxomr 407 as polymer.

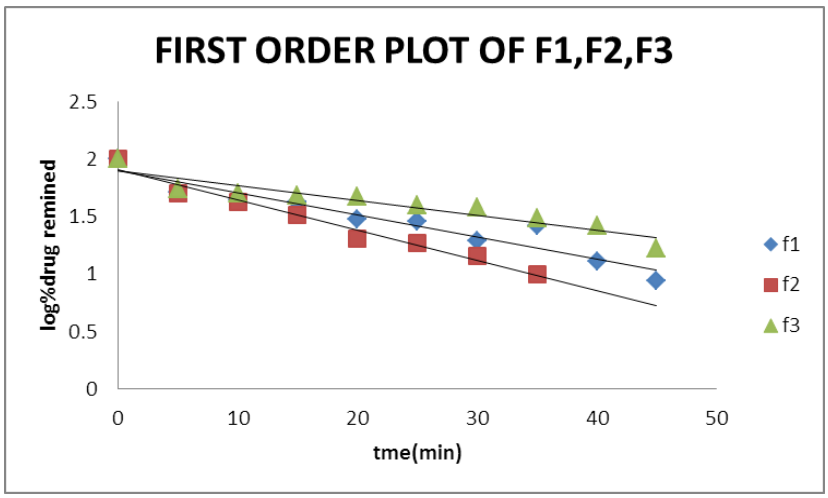

Fig. no. 20: First order plot of Ofloxacin solid dispersions containing urea as polymer.

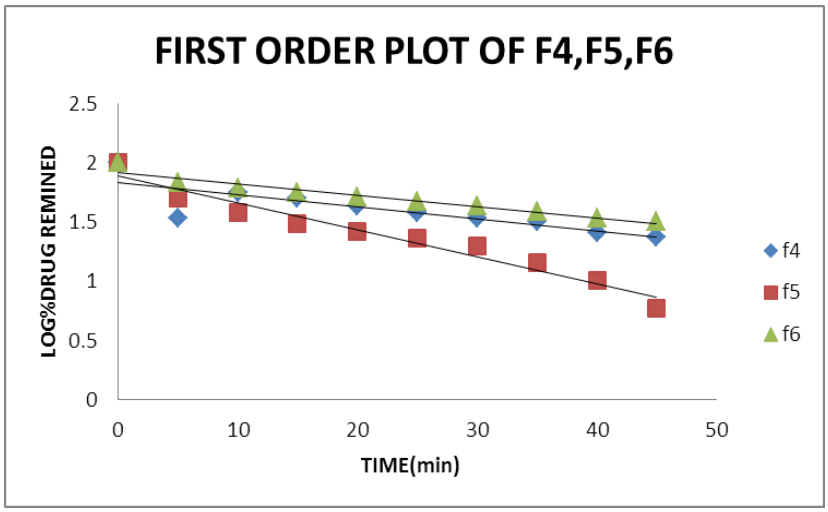

Fig. no. 21: First order plot of Ofloxacin solid dispersions containing PEG 6000 as polymer.

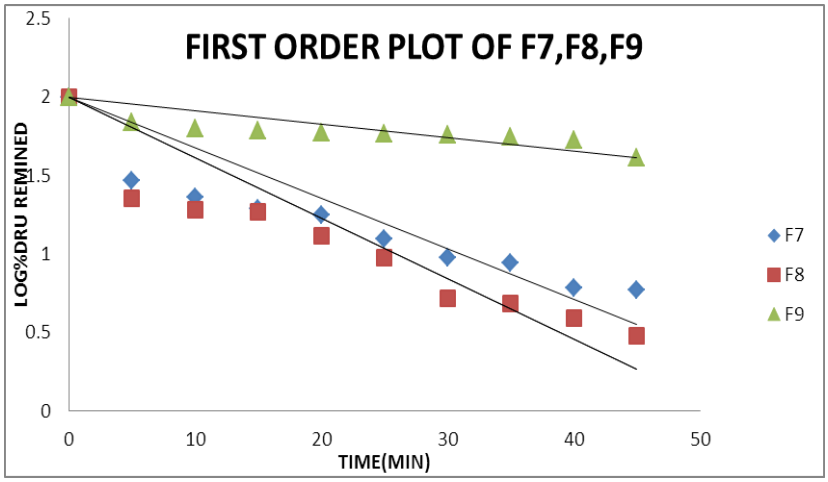

Fig. no. 22: First order plot of Ofloxacin solid dispersions containing Polaxomer 407 as polymer.

Table no. 9: Curve fitting results of release data for all formulations.

Formulation	Zero order	First order
	R^2	R^2
F1	0.79	0.907
F2	0.826	0.970
F3	0.776	0.889
F4	0.833	0.701
F5	0.742	0.953
F6	0.878	0.950
F7	0.533	0.961
F8	0.507	0.965
F9	0.845	0.876

The kinetic treatment reflected that release that data of solid dispersions (F2, F5 AND F8) was showed higher R^2 values for First order kinetics, plot indicating that release of drug follows First order kinetics.

CONCLUSION

Solid dispersions of Ofloxacin were prepared by using poloxomer, PEG-6000, Urea by physical mixture method. FT-IR spectral analysis showed that characteristic peak of Ofloxacin pure drug was retained in the spectra of all the formulations indicating the compatibility of the drug in all the formulations. The prepared dispersions, evaluated for, in vitro drug release studies. Almost all the formulations showed acceptable values for all parameters evaluated. The formulation (F8) contained drug: polymer ratio of 1:1, showed 98% of drug release at the end of 45 minutes, is considered as best formulation.

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