DISSOLUTION ENHANCEMENT OF ACECLOFENAC SOLID DISPERSION PREPARED WITH HYDROPHILIC CARRIERS BY SOLVENT EVAPORATION METHOD

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Under the Guidance of

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This work is original and has not been submitted earlier for the award of any other degree or diploma of this or any other university.

[**Prof. R. NATARAJAN]**

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CONTENTS

ABSTRACT

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) having anti-inflammatory and analgesic properties, and is widely used in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore, solid dispersions (SDs) of aceclofenac were prepared using PEG6000, PVP and HPMC to increase its aqueous solubility. Aceclofenac SDs was prepared in 1:1, 1:2 and 1:1:1 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 (1:1:1) ratio of drug: PEG6000: PVP. 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 percentage practical yield, drug content, infrared (IR) spectroscopic and differential scanning calorimetry (DSC) studies. Absence of significant drug-carrier interaction was confirmed by infrared spectroscopic (IR) and differential scanning calorimetry (DSC) data. Solid dispersion of formulation (F7) aceclofenac, PEG 6000 and PVP combination prepared in (1:1:1) ratio showed excellent solubility and the dissolution rate was found to be 96.21% was selected as the best formulation in this study.

1.0 INTRODUCTION

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. There were several ways in which bioavailability of the drug can be enhanced all of which aimed at increasing the surface area of the drugs which includes. Micronization, use of salt form, use of metastable polymorphs, solvent deposition, selective adsorption on insoluble carriers, solid dispersion, solute solvent complexation and complexation with cyclodextrins.[1] The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilisation by co solvents and particle size reduction.

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability.[2] Lipophilic molecules, especially those belonging to the bio-pharmaceutics classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence pose serious delivery challenges, like incomplete release from the dosage form, poor bioavailability, increased food effect and high inter-patient variability.[3]

In 1961, Sekiguchi and Obi[4] developed a practical method where by many of the limitations with the bioavailability enhancement of poorly water-soluble drugs just mentioned can be overcome. This method, which was later termed solid dispersion[5,] involved the formation of eutectic mixtures of drugs with water-soluble carriers by the melting of their physical mixtures[6]. Sekiguchi and Obi[4] suggested that the drug was present in a eutectic mixture in a microcrystalline state. Later, Goldberg et al,[7] demonstrated that all the drug in a solid dispersion might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, there by forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high.

The term solid dispersion refers to a group of solid products consisting of at least two different compounds, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particle (clusters) or in crystalline particles.[8]

Solid dispersion can be prepared by various methods such as solvent evaporation and melting method. The mechanism by which the solubility and the dissolution rate of the drug are increased includes: reduction of the particle size of drug to submicron size or to molecular size in the case where solid solution is obtained. The particle size reduction generally increases the rate of dissolution; secondly, the drug is changed from amorphous to crystalline form, the high energetic state which is highly soluble, finally, the wettability of the drug particle is improved by the hydrophilic carrier.[9]

Solid dispersion of drug helps to reduce the particle size of drug due to molecular dispersion.[10] Particle size reduction by micronization or nanonization can enhance the dissolution rate; however, the apparent solubility remains unaltered. At the molecular level, polymorphs offer a limited solubility advantage because of a small difference in free energy. In contrast, amorphous systems with excess thermodynamic properties and lower energetic barrier can offer significant solubility benefits.[11]

Aceclofenac (BCS Class II drug) is an orally effective non-steroidal anti-inflammatory drug (NSAID) which possesses remarkable analgesic, antipyretic and anti-inflammation in osteoarthritis and rheumatoid arthritis. It is a weakly acidic drug (pKa= 4–5), practically insoluble in water and acidic pH conditions, but slightly solubility in basic pH conditions. There are certain problems coming with using aceclofenac as traditional oral tablet which includes bioavailability of aceclofenac is highly variable due to its low aqueous solubility and first pass metabolism. An increased solubilty with enhanced dissolution of the drug will improve its bioavailability. In order to improve the solubility, dissolution rate and bioavailability of the drug, it was attempted to prepare optimized aceclofenac solid dispersion. Previously several solid dispersion systems were prepared for the enhancement of solubility, dissolution rate, absorption rate and hence bioavailability of aceclofenac using Peg6000, Pvp ,Hpmc, Mannitol, Lactose, Urea, sodium citrate, Aeglemarmelos gum, β-cyclodextrins, and Poloxamer[12]. In the present study solid dispersions of aceclofenac were prepared with *PEG 6000, PVP, HPMC* each separately as well as in combination of these polymers and evaluated for physicochemical

and *In-vitro* release characteristics. This study will help understand the beneficial effects of polymers combination in comparison to individual polymers in improving the solubility, dissolution rate and bioavailability of aceclofenac solid dispersion.

2.0 REVIEW OF LITERATURE

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameters to 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.[13]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. In other words the solubility can also be defined as the ability of one substance to form a solution with another substance. 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.[14]The transfer of molecules or ions from a solid state into solution is known as dissolution.

Dissolution of drug is the rate-controlling step which determines the rate and degree of absorption. Drugs with slow dissolution rates generally show erratic and incomplete absorption leading to low bioavailability when administered orally. Since aqueous solubility and slow dissolution rate of BCS class II and class IV drugs is a major challenge in the drug development and delivery processes, improving aqueous solubility and slow dissolution of these Classes of drugs have been investigated extensively[15]. A review of new monograph (1992-1995) in European pharmacopoeia shows that more than 40% of the drug substances have aqueous solubility below 1mg/ml and the 32% have an aqueous solubility below 0.1mg/ml[16, 17]

The dissolution rate of a drug is directly proportional to its solubility as per Noyes-Whitney equation and therefore solubility of a drug substance is a major factor that determines its dissolution rate and hence its absorption and bioavailability eventually[18]

Noyes-Whitney equation illustrates how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral bioavailability:

$$\mathbf{dc/dt = AD. (Cs - C) / h}$$

Where, dc/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, Cs is the solubility of the compound in the dissolution medium, C is the concentration of drug in the medium at time t, h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound[19].

TECHNIQUES OF SOLUBILITY ENHANCEMENT [20]

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are

Micronization

Particle size reduction leads to increase in the effective surface area resulting in enhancement of solubility and dissolution velocity of the drug.

Nanonization

Recently, 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; it might also decrease systemic side-effects.

Nanocrystals

The term drug nanocrystals imply a crystalline state of the discrete particles, but depending on the production method they can also be partially or completely amorphous.

Nanosuspension

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. Nanosuspension technology solved the problem of drugs which are poorly aqueous soluble and less bioavailability.

Nano emulsion

Nanoemulsions are non-equilibrium, heterogeneous system consisting of two immiscible liquids in which one liquid is dispersed as droplets in another liquid.

Sonocrystallization

Sonocrystallization is a novel particle engineering technique to enhance solubility and dissolution of hydrophobic drugs and to study its effect on crystal properties of drug.

Supercritical fluid method

A supercritical fluid (SCF) can be defined as a dense noncondensablefluid is another novel nanosizing and solubilisation technology whose application has increased in recent years.

Spray freezing into liquid and lyophilization

This technique involves atomizing an aqueous, organic, aqueous-organic cosolvent solution, aqueous organic emulsion or suspension containing a drugand pharmaceutical excipients directly into a compressed gas (i.e. carbon dioxide, helium, propane, ethane), or the cryogenic liquids (i.e. nitrogen, argon or hydrofluroethers).

Precipitation into aqueous solution

This process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs.

Use of surfactant

Surface active agents (surfactants) are substances which at low concentrations, adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface or interfacial tension.

Use of co-solvent

Co solvent addition is a highly effective technique for enhancement of solubility of poorly soluble drugs. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs.

Hydrotropy method

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. The term "*Hydrotropy*" has been used to designate the increase in aqueous solubility of various poorly watersoluble compounds due to the presence of a large amount of additives.

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 solubilities than their corresponding acid or base forms.

Solvent deposition

In this technique drug is dissolved in a solvent like methylene 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.

Solubilizing agents

Solubilizing materials like super disintegrants such crospovidone,crosscarmellose sodium and sodium starch glycolate used as solubilizing agents in many formulations which increase the solubilty and dissolution rate of poorly water soluble drugs. The superdisintegrants acts as hydrophilic carrier for poorly water soluble drug.

Modification of the crystal habit

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc.

Co-crystallization

The new approach available for the enhancement of drug solubility is through the application of the co-crystals, also referred as molecular complexes.

Complexation

The most common complexing ligands are cyclodextrins, caffeine, urea, polyethylene glycol, N methylglucamide. Considerable increase in solubility and dissolution of the drug has been achieved by the use of cyclodextrins.

CLASSIFICATION OF SOLID DISPERSION

First generation solid dispersions

First generation solid dispersions were prepared using crystalline carriers such as urea and sugar, which were the first carriers to be employed in solid dispersion. They have the disadvantage of forming crystalline solid dispersion, which were thermodynamically more stable and did not release the drug as quickly as amorphous ones.[21]

Second generation solid dispersions

Generation solid dispersions include amorphous carriers instead of crystalline carriers which are usually polymers. These polymers include synthetic polymers such as povidone (PVP),polyethylene glycols (PEG) and polymethacrylates as well as natural product based polymers such as hydroxy propyl methyl-cellulose (HPMC), , and hydroxypropoylcellulose or starch derivates like cyclodextrins.[21]

Third generation solid dispersions

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties. Therefore, third generation solid dispersions appeared. The use of surfactant such as inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer407 as carriers was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability.[21]

SIGNIFICANT PROPERTIES OF SOLID DISPERSION

There are certain parameters that are given below when successfully controlled, can produce improvements in bioavailability[22].

Particle size reduction

Solid dispersion represents the last state of the size reduction. It includes the principle of drug release by creating a mixture of poorly water soluble drug and highly soluble carriers, and after dissolution of carrier, the drug get molecularly dispersed in dissolution medium.

Wettability

Carriers having surface activity like cholic acid and bile salts, when used, can significantly increase the wettability properties of drug. Recently, in third generation solid dispersion surfactants have been included that is the emerging technique.

Higher porosity

Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate.

Amorphous state of drug particles

Drug particles in amorphous state have higher solubility.

Approaches for avoiding drug recrystallization

Recrystallization is the major disadvantage of solid dispersions, as we are using amorphous drug particles and they are thermodynamically instable and have the tendency to change to a more stable state. Several polymers are being used for improving the physical stability of the amorphous drugs by increasing the Tg of the miscible mixture.

CHARACTERISATION OF SOLID DISPERSION

Solid dispersions are characterized for crystallinity and molecular structure in amorphous solid dispersion. Various different types of analytical methods are available to characterize solid dispersion.[23]

Detection of crystallinity in solid dispersions

Many attempts have been to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. For that purpose many techniques are available which detect the amount of crystalline material in the dispersion. The amount of crystalline material is never measured directly but is mostly derived from the amount of crystalline material in the sample. It should be noted that through the assessment of crystallinity as method to determine the amount of amorphous drug it will not be revealed whether the drug is present as amorphous drug particles or as molecularly dispersed molecule.

1. Powder x-ray diffraction (Xrd)
2. Infrared Spectroscopy (IR)
3. Water Vapoursorption
4. Isothermal Microcalorimetry
5. Dissolution Calorimetry
6. Differential scanning Calorimetry (DSC)

FACTORS AFFECTING SOLUBILITY[24]

Particle size

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases.

Temperature

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased.

Pressure

For gaseous solutes, an increased in pressure increases solubility and a decreases in pressure decreases the solubility.

Nature of the solute and solvent

While only 1 gram of lead chloride can be dissolved in 100gm of water at room temperature, 200gm of zinc chloride can be dissolved.

Molecular size

Molecular size will affect the solubility. The large molecule or the higher its molecular weight the less soluble the substance.

Polarity

Polarity of the solute and solvent molecules will affect the solubility.

Polymorphism

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.[24]

ADVANTAGES OF SOLID DISPERSION

Rapid dissolution rates that result in an increase in the rate and extent of the absorption of the drug, and a reduction in pre systemic 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, avoidance of polymorphic changes and There by bio-availability problems), as in the case of nabilone and PVP dispersion, and protection of certain drugs by PEGs (e.g., cardiac glycosides) against decomposition by saliva to allow buccal absorption.[22.]

DISADVANTAGES OF SOLID DISPERSIONS

The major disadvantages of SDs are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate on ageing. By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place which leads to the reduction of drug solubility .Moisture and temperature have more of deteriorating effect on solid dispersions than on physical mixtures. Sometimes it is difficult to handle because of tackiness.[25]

LIMITATIONS OF SOLID DISPERSION

The major limitation in the development of solid dispersion is the lack of suitable Manufacturing techniques that could be scaled up to commercial production. The various limitations are: [22]

Laborious and expensive methods of preparation,
Reproducibility of physicochemical characteristics,
Difficulty in incorporating into formulation of dosage forms,
Scale-up of manufacturing process,
Stability of the drug and vehicle.

APPLICATIONS OF SOLID DISPERSION

- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize the unstable drug.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.
- To stabilize unstable drugs against hydrolysis, oxidation, recrimination isomerization, photo oxidation and other decomposition procedures.
- To reduce side effect of certain drugs.
- Masking of unpleasant taste and smell of drugs.
- Improvement of drug release from ointment creams and gels.
- To avoid undesirable incompatibilities.[26,]

Table: 1 Classification of carriers enhancing dissolution of drugs[24]

S.NO	CHEMICAL CLASS	EXAMPLES
1	Acids	Citric acid, Tartaric acid, Succinic acid
2	Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
3	Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000, Carboxymethyl cellulose, Hydroxypropyl cellulose, Guar gum, Xanthan gum, Sodium alginate, Methylcellulose, HPMC, Dextrin, Cyclodextrins, Galactomannan
4	Surfactants	Polyoxyethylene stearate, Poloxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14, Vitamin E TPGS NF
5	Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxy alkyl xanthine

Table: 2 Analytic methods for characterization of solid forms

S.NO	METHODS	SIGNIFICANCE
1.	Thermal analysis Cooling Curve Method Thaw Melt Method Thermo microscopic Method Zone Melting Method DSC Studies DTA Studies	To study the morphology and degree of crystallinity. To find out the interaction between drug and carrier and formation of inclusion complex.
2.	X-ray Powder Diffraction Studies	To find out the crystalline or amorphous form of drug.
3.	FTIR, NMR, Raman spectra	To find out the complex formation between drug and carrier.
4.	Scanning Electron Microscopy	To find out the particle size and shape.
5.	Dissolution rate /diffusion rate studies	Rate and extent of dissolution.
6.	Thermodynamic study	Degree of crystallinity

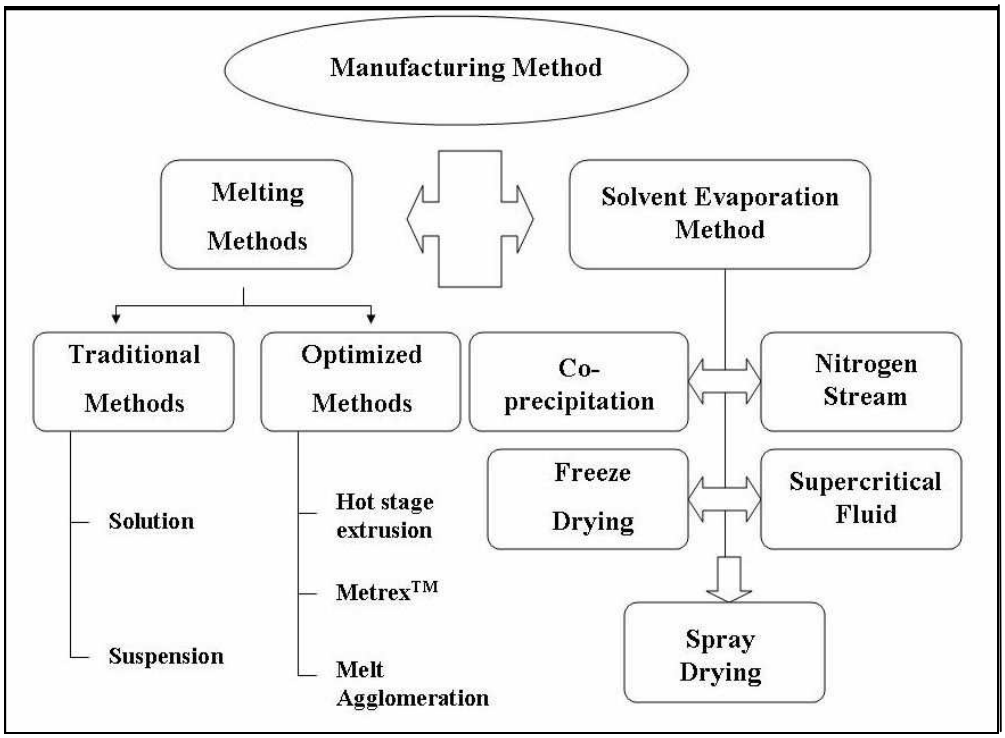


Fig.1 Methods of preparation of solid dispersion[28]

SOLVENT EVAPORATION METHOD

Though different methods have been followed for preparation of solid dispersion, the solvent evaporation method assumes significance in the present study and so a brief review of this method is presented. Commonly used method of preparing a solid dispersion is the dissolution of drug and carrier in a common organic solvent, followed by the removal of solvent by evaporation.[29-31]Because the drug used for solid dispersion is usually hydrophobic and the carrier is hydrophilic, it is often difficult to identify a common solvent to dissolve both compone[3]nts. Large volumes of solvents as well as heating may be necessary to enable complete dissolution of both components. Chiou and Riegelman[29] used 500 mL of ethanol to dissolve 0.5 g of griseofulvin and 4.5g of PEG 6000. Although in most other reported studies the volumes of solvents necessary to prepare solid dispersions were not specified, it is possible that they were similarly large. To minimize the volume of organic solvent necessary, Usui et al.[32] dissolved a basic drug in a hydro alcoholic mixture of 1 N HCl and methanol, with drug to cosolvent ratios ranging from 1:48 to 1:20, because as a protonated species, the drug was more soluble in the acidic cosolvent system than in methanol alone. Some other investigators dissolved

only the drug in the organic solvent, and the solutions were then added to the melted carriers. Vera et al.[33] dissolved 1g of oxodipine per 150mL of ethanol before mixing the solution with melted PEG 6000. In the preparation of piroxicam-PEG 4000 solid dispersion, Fernandez et al.[34] dissolved the drug in chloroform and then mixed the solution with the melt of PEG 4000 at 70°C. Many different methods were used for the removal of organic solvents from solid dispersions. Simonelli et al.[30]evaporated ethanolic solvent on a steam bath and the residual solvent was then removed by applying reduced pressure. Chiou and Riegelman[29] dried an ethanolic solution of griseofulvin and PEG6000 in an oil bath at 115 °C until there was no evolution of ethanol bubbles. The viscous mass was then allowed to solidify by cooling in a stream of cold air. Other investigators used such techniques as vacuum-drying, [34, 35] spray-drying, [36-39] spraying on sugar beads using a fluidized bed-coating system, [40] lyophilization, [41] etc., for the removal of organic solvents from solid dispersions. None of the reports, however, addressed how much residual solvents were present in solid dispersions when different solvents, carriers, or drying techniques were used.

Solvent

Solvent to be included for the formulation of solid dispersion should have the following criteria:

Both drug and carrier must be dissolved.

Toxic solvents to be avoided due to the risk of residual levels after preparation

E.g. chloroform and dichloromethane.

Ethanol can be used as alternative as it is less toxic.

Water based systems are preferred.

Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration. [31]

Class I Solvents (Solvents to be avoided)

Solvents included in this class are not to be taken in to use because of their deleterious environmental effects.

Table: 3 List of some Class I Solvents

Solvent	Concentration limit (ppm)	Effect
Benzene	2	Carcinogen.
Carbon tetrachloride	4	Toxic and environmental Hazards.
1,2-dichloroethane	5	Toxic.
1,1-dichloroethane	8	Toxic.
1,1,1-trichloroethane	1500	Environmental hazards.

Class II Solvents (Solvents to be limited)

These solvent should be limited used in pharmaceutical products because of their inherent toxicity.

Table: 4 Class II Solvents in pharmaceutical products

Solvent	PDE(mg/day)	Concentration limit(ppm)
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-dichloroethene	18.7	1870
Ethylene glycol	6.2	620
Methanol	30.0	3000
Pyridine	2.0	200
Toluene	8.9	890

PDE= Permitted Daily Exposure

Class III Solvents (Solvents with low toxic potential) [19]

Solvents included in this class may be regarded as less toxic and have the low risk to human health.

Table: 5 Class III solvents which should be limited by GMP or other quality based requirements[21]

Acetic acid	Heptane
Acetone	Isobutyl acetate
1-Butanol	Isopropyl acetate
2-Butanol	Methyl acetate
Butyl acetate	3-Methyl-1-Butanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Formic acid	Propyl acetate

Class IV Solvents (Solvents for which no adequate toxicological data was found)

Some solvents may also be of interest to manufacturers of excipients, drug substances or drug products for example Petroleum ether, isopropyl ether. However, no adequate toxicological data on which to base a PDE was found[19].

REVIEW OF PREVIOUS WORKS

Sanjoy Kumar das *et al* developed and improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. The dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form of relatively insoluble drugs. Therefore increase in dissolution of poorly soluble drugs by solid dispersion technique presents a challenge to the formulation scientists. Solid dispersion techniques have attracted considerable interest of improving the dissolution rate of highly lipophilic drugs thereby improving their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. This article reviews historical background of solid dispersion technology, limitations, classification, and various preparation techniques with its advantages and disadvantages. This review also discusses the recent advances in the field of solid dispersion technology. Based on the existing results and authors' reflection, this review give rise to reasoning and suggested choices of carrier or matrix and solid dispersion procedure.[42]

Teresa Marın *et al* (2002) described as Flunarizine is a selective calcium entry blocker poorly water-soluble. In this report, the interactions of this drug with Polyvinylpyrrolidone in solid dispersions, prepared according to the dissolution method using methanol as the solvent, have been investigated. For purposes of comparison physical mixtures were prepared by simple mixture and homogenization of the two pulverized components. Combinations of flunarizine/Polyvinylpyrrolidone of the following percentage proportions were prepared: 10/90, 20/80, 30/70, 40/60, 50/50, 60/40 and 80/20 (mean particle size of 0.175 mm). The physicochemical properties of solid dispersions were investigated with X-ray diffraction, infrared spectroscopy, differential scanning calorimetry and solubility in equilibrium. X-ray patterns and differential scanning calorimetry have shown that Polyvinylpyrrolidone inhibits the crystallization of flunarizine when percentages drug/polymer are 10/90, 20/80 and 30/70. The infrared spectra suggest that there was no chemical interaction between flunarizine and Polyvinylpyrrolidone. Equilibrium solubility studies showed that drug solubility was enhanced as the polymer content increased.[43]

Bikiaris *et al* (2005) developed a Polyvinylpyrrolidone (PVP) and poly (ethylene glycol) (PEG) solid dispersions with Felodipine or Hesperetin having up to 20 wt. % drug were prepared using solvent evaporation method. Solid dispersions in comparison with their physical mixtures were studied using differential scanning calorimetry (DSC), wide-angle X-ray diffraction (WAXD), scanning electron microscopy (SEM) and hot stage polarizing light microscopy (HSM). PVP formulations with low drug load proved to be amorphous, since no crystalline Felodipine or Hesperetin drugs were detected using DSC and WAXD. Low and fast heating rates were applied for DSC study, to prevent changes in the samples caused during heating. Similarity between results of WAXD and DSC was also found in the case of physical mixtures, where the drug was in the crystalline state. However, though specific tests showed the high sensitivity of the DSC technique, it was difficult to arrive to reliable results for PEG solid dispersions or physical mixtures with low drug content by DSC, even by high heating rates. Crystalline drug could not be detected by DSC, leading to erroneous conclusions about the physical state of the drug, in contrast to WAXD. On the other hand, HSM proved the presence of small drug particles in the solid dispersions with PEG and the dissolution of the drug in the melt of PEG on heating. In such systems, in which a polymer with low melting point is used as drug carrier, DSC is inappropriate technique and must be used always in combination with HSM. The coupling of WAXD with thermal analysis, allowed complete physicochemical characterization and better understanding which is essential for a first prediction of dissolution characteristics of such formulations.[44]

Sachin R. Patil *et al* (2009) developed an Aceclofenac is a novel non-steroidal anti-inflammatory drug (NSAID) having anti-inflammatory and analgesic properties and is widely used in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore, solid dispersions (SDs) of aceclofenac were prepared using lactose, mannitol and urea to increase its aqueous solubility. Aceclofenac SDs were 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 SD 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 also due to reduction in drug crystallinity. The prepared SDs was objected for percent practical

yield, drug content and infrared (I.R) spectroscopic studies. Absence of significant drug carrier interaction was confirmed by I.R data.[45]

Ravi Kumar *et al* (2010) reported an Aceclofenac is a novel non-steroidal anti-inflammatory drug (NSAID) having anti-inflammatory and analgesic properties and is widely used in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and pediatrics. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Though aceclofenac is well absorbed after oral dosing, there is a first pass metabolism leading to a reduced bioavailability of the drug (40- 50%). Therefore, the present investigation was concerned to develop Mouth dissolving tablets of aceclofenac by effervescent formulation approach to provide patient friendly dosage form. The effervescent excipient system not only aids rapid disintegration of tablets in the oral cavity but also masks the slight bitter taste of medicament. Sodium bicarbonate, heat treated Sodium bicarbonate, tartaric acid, sodium glycine carbonate and citric acid were used as effervescent agents and their ratio in the formulation was optimized. The study revealed that 10:8 ratio of heat treated Sodium bicarbonate and citric acid (F3) in the Aceclofenac Mouth dissolving tablets gave a soothing fizz, excellent mouth feel, good palatability and quick dissolution profile. The optimized formulation (F3) was found to be stable during the stability studies conducted as per ICH guidelines, as it showed no significant changes ($P<0.05$) in the physicochemical properties, disintegration time and *in vitro* drug release.[46]

Appa Rao. B *et al*, (2010) reported an Aceclofenac is a novel non-steroidal anti-inflammatory drug (NSAID) having anti-inflammatory and analgesic properties, and is widely used in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore, solid dispersions (SDs) of Aceclofenac were prepared 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.[47]

Mohammed Gulzar Ahmed *et al (*2010) reported the present study is aimed at improving the dissolution of poorly water-soluble drug, aceclofenac. It is very slightly soluble in water and hence orally administered drug is less bioavailable. In order to enhance the bioavailability it is necessary to improve its solubility, hence the solid dispersion technique was adopted to enhance solubility. The solid dispersions were prepared in different proportions using hydrophilic carriers like Urea and Mannitol. The dissolution rate studies were performed in both simulated gastric fluid and simulated intestinal fluid. It is observed that the dissolution was affected by the acidity of the medium. Solid dispersions gave faster dissolution rate when compared to corresponding physical mixture and pure drug. In vivo absorption and anti-inflammatory activity studies of solid dispersions also confirmed the above results. The FTIR and DSC studies revealed that there is no interaction between drug and carriers and the drug, aceclofenac is stable in solid dispersions.[48]

Aejaz A *et al* (2010) developed an Aceclofenac, an analgesic and anti-inflammatory drug is used in treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Various compositions of Aceclofenac solid dispersions were prepared by physical mixing, fusion and solvent evaporation methods using. PVP, PEG 6000, mannitol and urea as carrier to enhance the solubility of drug. The formulations evaluated for drug content, *In-vitro* dissolution study and also characterized by IR and DSC studies. There is no interaction between drug and carrier. The general trend indicated that there was a increase in *In-vitro* drug release for solid dispersion prepared in the following order Urea > PEG 6000 > PVP > Mannitol. Based on *In-vitro* drug release pattern, 1:3 drug carrier ratio was selected as ideal dispersion for gels. HPMC selected as ideal gel base for preparation of gels and dispersions are incorporated to gel bases by trituration. Formulations were characterized for rheological studies, drug content estimation and *In-vitro* diffusion study, IR spectroscopy. All these properties were found to be ideal.[49]

Kamal Dua *et al* (2010) developed the objective of the present investigation was to study the effect of various water soluble carriers like urea, mannitol, PVP and PVP/VA-64 on in vitro dissolution of aceclofenac from solid dispersions. Aceclofenac binary solid dispersions (SD) with different drug loadings were prepared using the melting or fusion method. In vitro dissolution of pure drug, physical mixtures and solid dispersions were carried out. Solid dispersion of aceclofenac with all four carriers (urea, mannitol, PVP and PVP/VA-64) showed considerable increase in the dissolution rate in comparison with physical mixture and pure drug in 0.1 N HCl, pH1.2 and phosphate buffer, pH, 7.4. FT-IR spectroscopy and differential scanning calorimetry studies indicated no interaction between aceclofenac and carriers in solid dispersions in solid state. Dissolution enhancement was attributed to decreased crystallinity of the drug and to the wetting, eutectic formation and solubilizing effect of the carrier from the solid dispersions of aceclofenac. In conclusion, dissolution of aceclofenac can be enhanced by the use of various hydrophilic carriers like urea, mannitol, PVP and PVP/VA-64.[50]

Shobhit Kumar *et a*l (2011) reported the aim of this study was to prepare and characterize solid dispersions of aceclofenac, employing a mixed excipient system composed of lactose, corn starch as a carrier and to study the effect of a mixed excipient system on rate of dissolution of drug. The solid dispersions were prepared by physical mixture method and solvent wetting method using 1:1 ratios of drug to mixed excipient system. The formulations were evaluated for % practical yield, drug content, bulk density, tapped density, Hauser's ratio, Carr's index, angle of repose and in vitro drug release. In this study it was concluded that there was considerable increase in in vitro drug release for solid dispersion as compared to the pure drug taken alone. It was observed that the dissolution rate of drug from solid dispersions increases with the increase in lactose amount in comparison to corn starch with the optimum ratio of (1.0) lactose:(0.5) corn starch showing the best result.[51]

Ratna parkhi. M *et al* (2012) developed a Aceclofenac is new non-steroidal anti-inflammatory drug acting by an inhibition of the synthetic of prostaglandins by inhibiting the activity of the enzyme, cyclooxygenase- 2(COX-2). It is more selective for COX –2 than COX-1. Aceclofenac is practically insoluble in water and peak blood level release between 1.25 to 3 hrs after oral administration. It is practically insoluble in aqueous fluids. In the case of poorly -watersoluble drugs, dissolution is the rate-limiting step in the

process of drug absorption. 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. To improve the dissolution of aceclofenac through the formulation of solid dispersion using water soluble carriers like mannitol by melt solvent methods and to convert the optimized solid dispersion in fast dissolving tablet formulation. The formulated tablets showed rapid in vitro drug dissolution and dissolution efficiency with in 30 min.[52]

Reddy B. V *et al* (2012) reported in the present study, the aim was to enhance the oral bioavailability and dissolution rate of Aceclofenac by solid dispersions using polyethylene glycol (PEG-6000) as a carrier and to study the effect of carrier on dissolution rate. Initial studies were carried out using physical mixtures of the drug and carrier. Solid dispersions were prepared by fusion technique using dropping method. Aceclofenac was formulated as physical mixtures and solid dispersions (dropping method) using 1:2, 1:4, 1:6 and 1:8 ratios of drug and carrier (PEG 6000). Saturation solubility study for pure drug, physical mixtures and solid dispersions were carried out in water and pH 6.8 phosphate buffer solutions (PBS). PEG 6000 in 1: 8 drug to carrier ratio exhibited the highest drug release (98.69%) formulated as solid dispersions using dropping method. The FT-IR study shows that drug was stable in solid dispersions and there were no interactions. It is concluded that dissolution rate was improved by solid dispersion of aceclofenac: PEG 6000 prepared as 1:8 ratio by dropping method showed excellent physicochemical characteristics and was found to be described by dissolution release kinetics and was selected as the best formulation.[53]

Aminul Haque Md. ***et al*** (2012) reported the objective of the study was to improve the aqueous solubility and dissolution of carbamazepine, a poorly water soluble anti-epileptic drug by solid dispersion technique, using water soluble polymers. Solid dispersion of drugs was prepared by physical mixing, fusion and solvent evaporation method. The drug along with the polymers was heated first and then hardened by cooling to room temperatures. They were then pulverized, sieved, and then drug release was studied by the USP basket method at 75 rpm and 37±0.5°C. In this experiment sodium lauryl sulfate (SLS), acetone, hydroxy propyl cellulose (HPC), polyethylene glycol (PEG) 6000, PEG 4000, poloxamer 407, hydroxy propyl methyl cellulose (HPMC) 6cps, HPMC 15cps, Polyvinyl pyrrolidone (PVP) K30, PVP K12, and glyceryl monostearete (GMS)

were used as polymers. Distilled water was used as dissolution medium. The amount of drug was measured from the absorbance of UV spectrophotometer at 288 nm. The release of drug was plotted in zero order, 1st order, Hixson Crowell and Higuchi release pattern. The study shows that all the polymers enhanced the release profile of carbamazepine. The polymers are thought to serve as dispersing or emulsifying agents for the liberated drug, thus preventing the formation of any water-insoluble surface layers. The correlation coefficients values of the trend lines of the graphs showed that the formulations best fit in Higuchian release pattern.[54]

Kumari R *et al* (2013) reported one of the favorable strategy to improve the solubility and hence bioavailability of poorly water soluble drugs is the formulation of solid dispersion. It refers to dispersion of an active ingredient in a carrier at solid state which is prepared by solvent evaporation method, melting method; melt solvent method, kneading method, co-grinding method, co-precipitation method, modified solvent evaporation method, spray drying, gel entrapment technique, and co-precipitation with supercritical fluid. On the basis of the carrier used in solid dispersion it is classified as first, second and third generation solid dispersions. As per biopharmaceutical classification system class II drugs are with low solubility and high permeability and are the promising candidates for improvement of bioavailability by solid dispersion. Some of the practical aspects to be considered for the preparation of solid dispersions, such as selection of carrier, molecular arrangement of drugs in solid dispersions are discussed.[55]

Ramana B.V *et al* (2013) developed the aim of this study was to prepare and characterize solid dispersions of aceclofenac, employing a different excipient system composed of PEG6000, Glycine, and PVPk30 and to study the effect of a mixed excipient system on rate of dissolution of drug. The solid dispersions were prepared by physical mixture method and solvent wetting method using 1:1 ratios of drug to mixed excipients system. The formulations were evaluated for % practical yield, drug content, and in vitro drug release. In this study it was concluded that there was considerable increase in *In-vitro* drug release for solid dispersion as compared to the pure drug taken alone. Based on the drug release pattern, the solvent wetting method showed more in vitro drug release as compared to physical mixture method. Finally it could be concluded that solid dispersion of Aceclofenac using hydrophilic polymers would improved the aqueous solubility, dissolution rate and thereby enhancing its systemic availability.

3.0 AIM AND OBJECTIVE

AIM

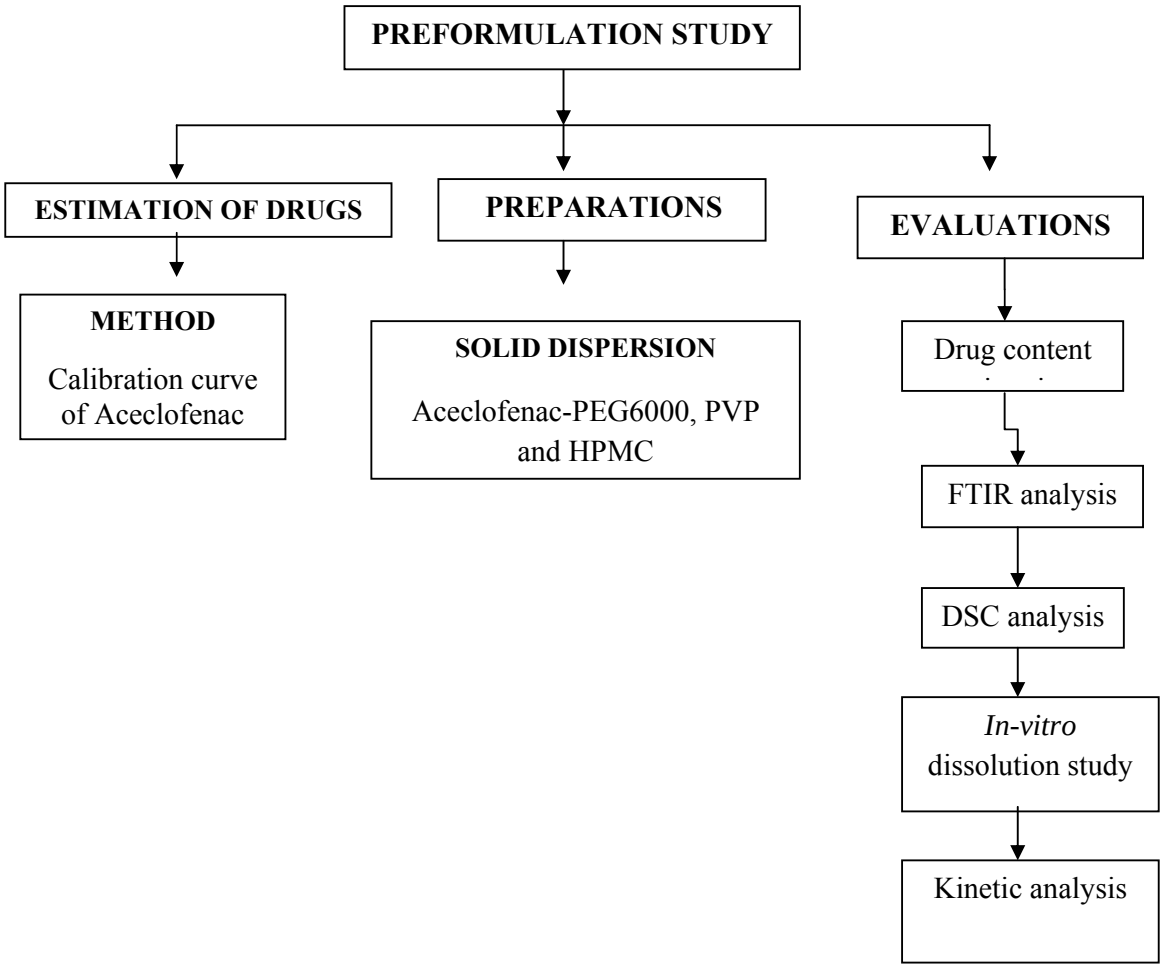
To develop a solid dispersion of aceclofenac and improve the solubility of aceclofenac by using different carriers like PEG6000, PVP & HPMC to enhance the bioavailability of the drug.

OBJECTIVE

To estimate the following parameters.

- Calibration curve of aceclofenac.
- Preparation of solid dispersions (1:1, 1:2 and 1:1:1 ratios).
- FTIR analysis of pure drug and solid dispersions.
- DSC analysis of pure drug and solid dispersion.
- Percentage Practical yield.
- Drug Content estimation.
- Phase solubility study.
- *In-vitro* dissolution of pure drug, and solid dispersions.
- Release kinetic study.

4.0 PLAN OF WORK



5.0 PROFILES

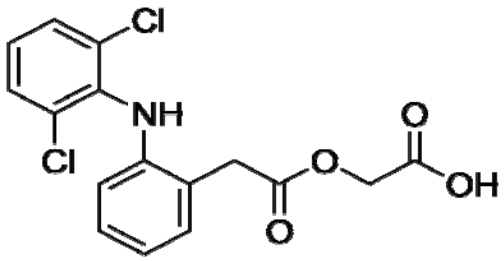
5.1 DRUG PROFILE

ACECLOFENAC[57]

Drug : Aceclofenac

Chemical name : [2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy acetic acid

Structure :



Formula : $C_{16}H_{13}Cl_{12}No_4$

Molecular Weight : 354.2

Characters Appearance : White or almost white, crystalline power.

Melting point : 149-150^{0}C

Solubility : practically insoluble in water, freely soluble in acetone, soluble in alcohol.

Pharmacology

The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase, which is involved in the production of prostaglandins.

The Drugs inhibits synthesis of the inflammatory cytokines interleukin (IL)-1 and tumor necrosis factor and prostaglandin E_2 (PGE2) production. Effects on cell adhesion molecular from neurophils have also been noted. In vitro data indicate inhibition of cyclooxygenase (Cox)-1 and 2 by aceclofenac in whole blood assays, with selectivity for Cox-2 being evident.

Aceclofenac has shown stimulatory effects on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit IL-1 activity. In vitro data indicate stimulation by the drug of synthesis of glycosaminoglycan in osteoarthritic cartilage. There is also evidence that aceclofenac stimulates the synthesis of IL-1 receptor antagonist in human articular chondrocytes subjected to inflammatory stimuli and that 4'-hydroxyacelofenac has chondroprotective properties attributable to suppression of IL-1 mediated promatrix metalloproteinase production and proteoglycan release. In patients with osteoarthritis of the knee, aceclofenac decrease pain reduces disease severity and improves the functional capacity of the knee. It reduces joint inflammation, pain intensity and the duration of morning stiffness in patients with rheumatoid arthritis. The duration of morning stiffness and pain intensity are reduced and spinal mobility improved, by aceclofenac in patients with ankylosing spondylitis.

Pharmacokinetics

Aceclofenac is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3 hours after an oral dose. The drug is highly protein bound (99.7%). The presence of food does alter the extent of absorption of aceclofenac but the absorption rate is reduced. The plasma concentration of aceclofenac was approximately twice that in synovial fluid after multiple doses of the drug in-patient with knee pain and synovial fluid effusion. Aceclofenac is metabolized to a major metabolite, 4'-hydroxyaceclofenac and to a number of other metabolites including 5-hydroxyaceclofenac, 4'-hydroxydiclofenac, diclofenac and 5-hydroxydiclofenac. Renal excretion is the main route of elimination of aceclofenac with 70 to 80% of an administered dose found in the urine, mainly as the glucuronides of aceclofenac and its metabolites of each dose of aceclofenac, 20% is excreted in the faces. The plasma elimination half-life of the drug is approximately 4 hours.

Summary of pharmacokinetics

- Volume of distribution 25lit
- Plasma half-life:2.5-4.0hrs
- Plasma protein binding: 99.7%
- Dose: 100mg twice daily

Drug Interactions

Aceclofenac may increase plasma concentrations of lithium, digoxin and methotrexate, increase the activity of anticoagulant, inhibits the activity of diuretics, enhance cyclosporine nephrotoxicity and precipitate convulsions when co-administered with quinolone antibiotics. Furthermore, hypo or hyper glycaemia may result from the concomitant administration of aceclofenac and antidiabetic drugs, although this is rare. The co administration of aceclofenac with other NSAIDS of corticosteroids may results in increased frequency of adverse event.

Adverse Drug Reaction

Aceclofenac is well tolerated, with most adverse events being minor and reversible and affecting mainly the GI system. Most common events include dyspepsia (7.5%), abdominal pain (6.2%), nausea (1.5%), diarrhea (1.5%), flatulence (0.8%), gastritis (0.6%), constipation (0.5%), vomiting (0.5%), ulcerative stomatitis (0.1%), and pancreatitis (0.1%).

Although the incidence of gastro intestinal adverse events with aceclofenac was similar to those of comparator NSAIDS in individual clinical trials, withdrawal rates due to these events were significantly lower aceclofenac than with ketoprofen and tenoxicam. Other adverse effect, which is not common such as dizziness (1%), vertigo (0.3%), and rare cases: par aesthesia and tremor.

Therapeutic uses

Aceclofenac significantly reduced pain and improves functional capacity and mobility relative to baseline in patients with osteoarthritis, rheumatoid arthritis or ankylosing spondylitis and reduces inflammation in patients with rheumatoid arthritis. No

head to head comparison between Aceclofenac and coxibs have been performed, nor for efficacy neither for tolerance.

Aceclofenac in osteoarthritis

In patients with osteoarthritis of the knee, aceclofenac decreases pain, reduces disease severity and improves the functional capacity of the knee to a similar extent to diclofenac, piroxicam, and naproxen.

Aceclofenac in rheumatoid arthritis

The anti-inflammatory and analgesic efficacy of aceclofenac is similar to that of ketoprofen, indomethacin, tenoxicam and diclofenac in patients with rheumatoid arthritis. In randomized, double blind trials in 169 to 261 patients, aceclofenac (100 mg twice daily for 3 or 6 months) significantly reduced relative to baseline joint inflammation, pain intensity and the duration of morning stiffness and improved handgrip strength.

Aceclofenac in ankylosing spondylitis

The duration of morning stiffness and pain intensity are reduced and spinal mobility improved, by aceclofenac in patients with ankylosing spondylitis, with improvements being similar to those observed with indomethacin, naproxen or tenoxicam. These effects were observed after aceclofenac 100 mg twice daily for 3 months in randomized, double blind trials involving 104 to 308 patients.

Aceclofenac in dental pain

The analgesic efficacy as single doses of aceclofenac has been assessed in patients with moderate to severe tooth pain and in extraction of impacted third molars. The analgesic efficacy of single doses of aceclofenac 50, 100 and 150 mg was greater than that of place in patients with moderate to severe tooth pain or pain caused by extraction of impacted third molars.

Aceclofenac in postoperative pain

The analgesic efficacy of aceclofenac has been shown in comparisons with paracetamol in women undergoing episiotomy. Aceclofenac 100 mg was superior to paracetamol 650 mg in providing relief from post episiotomy pain, particularly 3 to 5 hours after ingestion.

Aceclofenac in Dysmenorrhea

In a more recent non comparative study in 1338 women with dysmenorrhea treated for first 3 days of 2 consecutive cycles.

Aceclofenac in acute lumbago

Aceclofenac (150 mg intramuscularly for 2 days, then 100 mg orally, both twice daily) was superior to diclofenac in alleviating functional impairment in a 7 days study in 100 patients with acute lumbago. Aceclofenac 100 mg twice daily was associated with symptomatic relief of acute low back pain in a non-comparative study in 67 patients.

Aceclofenac in musculoskeletal trauma

Aceclofenac 100 mg twice daily has also been assessed in patients with musculoskeletal trauma, although only non-comparative studies are available.

Aceclofenac Gonalgia (Knee pain)

A controlled double blind study was performed with aceclofenac comparing it with diclofenac in 40 patients with acute or chronic gonalgia. The results of the trial indicate slightly superior activity, although there was no statistically significant difference between two drugs**.**

5.2 POLYMER PROFILE

(A) Polyethylene Glycol (PEG 6000)[58]

Specifications;

Average molecular Weight	**:**	5000-7000
pH of5% Aq. Sol	**:**	4-7
Freezing Point	**:**	56-63^{0}C
Viscosity at100^{0}C	**:**	470-900CST

Properties and Applications

PEG-6000 is a high molecular weight polymer of ethylene oxide and is a blend of polymers with different degrees of polymerization. Like all other PEGs, PEG -6000 is readily soluble in water. So water can be the most economical solvent for this, apart from other organic solvents. PEG-6000 acts as binder and dry lubricant due to its laminar structure and therefore can be used in the manufacture of pills and tablets for certain pharmaceutical preparations. In rubber industry, PEG-6000 can be used as a mould release agent. A solution of PEG 6000 can be used as a mould release agent. A solution of PEG 6000 of 3-20% concentration can be coated or sprayed into the hot mould cavities, thus enabling the solvent to evaporate , the solution is either dried by applying heat or allowed to dry evaporate ,the solution is either dried by applying heat or allowed to dry evaporation of solvent. Other applications of PEG -6000 include as wetting agents to inhibit soap cracking, as binder for facial makeup, as anti-dusting agent for after bath talcum powder, lubricant in paper industry, as a tire mounting agent, as an additive in grease, as plasticizer in synthetic resin, as enhancer of thermal stability in adhesive preparations, as an additional component of galvanization bath etc. for copper and nickel electroplating of steel and iron parts. PEGs being non-ionic products, facilitate the even distribution of electrolytes.PEG6000 dissolved in lower glycols in place of paraffin wax are used for embalming of histological and other medical specimens.

Compatibility

Compatibility of glycols is proved to be good in formulations of Nitrofurazone, Undencanoic acid, Sulphur, Hydrocortisone, Methyl Salicylate, Benzyl Benzoate etc.

Incompatibility

Glycols are not compatible with Penicillin, Bacitracin, Iodine, potassium iodide, Sorbitol, Tannic acid, Bismuth salts. Glycols are also not suitable with Poly ethylene, Backlit and celluloid.

Packing

25 KG Net in pp. woven bags.

Storage

Under dry conditions and at room temperature in sealed containers.

Stability

Stable under ordinary conditions of use and storage.

Hazardous decomposition products:

Carbon dioxide and carbon monoxide may form when heated to decomposition.

Hazardous polymerization

Will not occur.

Incompatibilities

Incompatible with polymerization catalysts (peroxides, per sulfates) and accelerators, strong oxidizers, strong bases and strong acids.

Conditions to avoid

In compatibilities.

(B) Polyvinylpyrrolidone[59]

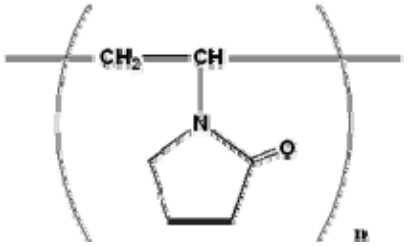
Synonym : Poly [1-(2-oxo-1-pyrrolidinyl) ethylene]; polyvidone; Polyvinylpyrrolidone;pvp;1-vinyl-2-pyrrolidinone Polymer

Chemical name : 1-Ethenyl-2-pyrrolidinone homo polymer.

Empirical Formula : $(C_6H_9NO)n$

Molecular Weight : 40000(approximately)

Structural Formula :



Description : povidone occurs as a fine, white to creamy-white colored, odorless.

Typical properties

Acidity/alkalinity : pH=3.0-7.0(5%w/v aqueous solution).

Flow ability : 20g/s for povidone k-15; 1620g/s for povidone k-29/32.

Melting point : softens at 150^0c.

Moisture content

Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidity.

Solubility

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol and water; practically insoluble in ether hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the polymer.

Viscosity (dynamic)

The viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed.

Functional Category

Disintegrent; dissolution aid; suspending agent; tablet binder

Applications

It is used as a binder in many pharmaceutical tablets It simply through the body when taken orally.

It is used in pleurodesis.

It is used as an adhesive in glue stick and hot-melt adhesive.

As an emulsifier and Disintegrent for solution polymerization

Used in aqueous metal quenching.

As a thickening agent in tooth whitening gels.

(C) Hydroxy Propyl MethylCellulose[60]

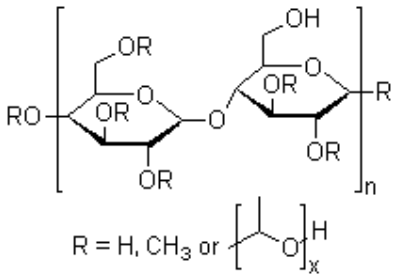
Synonyms : Methyl hydroxypropyl cellulose, methylcellulose propylene glycol ether.

Chemical name : Cellulose, 2- Hydroxy propyl methyl ether

BP : Hypromellose

USP : Hydroxy propyl methyl cellulose

Chemical structure



Molecular weight : Molecular weight is approximately 10,000-1, 50,000.

Empirical Formula

Hydroxypropylmethylcellulose is partly O-methylated and O-(2-hydroxy propylated) cellulose. It is available in several grades which vary in viscosity and extent of substitution.

Functional category

Coating agent, film-former, rate controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Applications

Hydroxy propyl methyl cellulose is widely used in oral and topical pharmaceutical formulation. In oral products, hydroxy propyl methyl cellulose is primarily used as an

extended release tablet matrix. High viscosity grades may be used to retard the release of drugs from a matrix at levels 10-80%w/w in tablets and capsules.

Description

Hydroxy propyl methyl cellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

Typical properties

Bulk Density : 0.341 g/cc

Viscosity : 80,000-1, 20,000 cps

Methyl Content : 19-24%

Tap density : 0.557 g/cc

Specific Gravity : 1.26 g/cc

Hydroxy propyl content **:** 7-12% true density:1.326 g/cc

Melting point : Browns at 190-200^{0}C; chars at 225-230^{0}C.

Moisture Content

Hydroxy propyl methyl cellulose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content and temperature and relative humidity of the surrounding air.

6.0 MATERIALS AND INSTRUMENTS

INGREDIENTS USED

Table: 6 Ingredients used for the experiment

S. No	Name of the ingredient	Manufacturer/Suppliers
1.	Aceclofenac	Dr.Reddy's laboratory (Hyderabad)
2.	Polyethylene glycol(PEG6000)	Yarrow chemicals laboratory (Mumbai)
3.	Polyvinylpyrrolidone	Loba chemie pvt.ltd (Mumbai)
4.	Hydroxypropyl methylcellulose	Loba chemie pvt.ltd (Mumbai)
5.	Methanol	Finar chemicals ltd (Mumbai)

INSTRUMENTS USED

Table: 7 Instruments used for the experiment

S. No	Name of the instrument	Manufacturing company
1.	UV – visible Spectrophotometer	Perkin Elmer lamda25 (USA)
2.	FT-IR Spectrophotometer	Perkin Elmer spectrum RX1 (USA)
3.	Differential Scanning Calorimetry	DSC DA 609 Shimadzu (Japan)
4.	Single pan digital Balance	Schimadzu BL 220H (Japan)
5.	Programmable dissolution Apparatus (USP)	Veego (Mumbai)
6.	Magnetic stirrer	Eltek MS 2012 (Mumbai)

7.0 METHODOLOGY

7.1 CONSTRUCTION OF STANDARD CURVE FOR ACECLOFENAC

This method was adapted to pure aceclofenac 100mg was accurately weighed and dissolved in phosphate buffer (pH 6.8). Further, dilutions were made to get 2,4,6,8 &10µg/ml the sample point 275 nm. A standard curve was constructed by plotting the absorbance vs. concentration of the drug taken[47].

Preparation of PH 6.8 phosphate buffer

Placed 50 ml of 0.2 M Potassium dihydrogen phosphate in a 200 ml volumetric flask, added specified volume of 22.4 ml of 0.2 M NaOH and then added water to make the volume.

0.2 M Potassium dihydrogen phosphate

Dissolve 27.218 gm of potassium dihydrogen phosphate in distilled water and dilute to 1000 ml with distilled water.

0.2 M NaOH solution

Dissolved 8 gm of NaOH in distilled water and diluted to 1000 ml with distilled water.

7.2 PREPARATION OF SOLID DISPERSION

Aceclofenac solid dispersion were prepared by using hydrophilic carriers like polyethylene glycol (PEG6000) Polyvinylpyrrolidone and Hydroxypropyl methylcellulose in proportions viz .1:1 (drug: carrier) (50mg:50mg), 1:2 (50mg: 100mg) and 1:1:1 (drug:carrier:carrier) (50mg: 50mg: 50mg) was prepared by solvent evaporation method. Aceclofenac and carriers were dissolved in methanol and mixed with magnetic stirring. Solvent was evaporated at reduced pressure at 40^{o}C in a rotatory evaporation apparatus. Subsequently solid dispersion was stored under vacuum over silica gel for 12 hrs at room temperature. After drying the solid dispersion was passed through a 250µm sieve. Sample was stored in a desiccator and used for further investigation[61].

Table: 8 Formulation of aceclofenac solid dispersion

S.NO	FORMULATION	COMPOSITION	DRUG : CARRIER
1	F1	Aceclofenac+ polyethyleneglycolate(PEG6000)	1:1
2	F2	Aceclofenac+ Polyvinylpyrrolidone (PVP)	1:1
3	F3	Aceclofenac+ Hydroxypropylmethylcellulose (HPMC)	1:1
4	F4	Aceclofenac+ polyethylene glycol(PEG6000)	1:2
5	F5	Aceclofenac+ Polyvinylpyrrolidone (PVP)	1:2
6	F6	Aceclofenac+ Hydroxypropylmethylcellulose (HPMC)	1:2
7	F7	Aceclofenac+polyethyleneglycol+ Polyvinylpyrrolidone	1:1:1
8	F8	Aceclofenac+Polyethylene glycol+ Hydroxypropylmethylcellulose	1:1:1
9	F9	Aceclofenac+ Polyvinylpyrrolidone Hydroxypropylmethylcellulose	1:1:1

7.3 EVALUATION OF FORMULATIONS

The prepared formulations of solid dispersions were evaluated for the following

Physico chemical characterization

In-vitro dissolution studies

7.3.1 PHYSICO CHEMICAL CHARACTERIZATION

Compatibility study

Fourier transform infrared spectroscopy was employed to characterize the possible interactions between the aceclofenac and carriers. In this study pure drug, solid dispersions were studied by FTIR spectrophotometer.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) curve of aceclofenac, PEG6000, PVP, HPMC, physical mixture and solid dispersions were measured with a DSC instrument (Mettler Tolero Model). The samples were accurately weighed and heated in closed aluminum crimped cells at a rate of $10^{o}C.min^{-1}$ between 30 and $300^{o}C$ temperature under a nitrogen gas flow of $40mL.min^{-1}$during study.

Drug content estimation

Solid dispersions equivalent to 10 mg of aceclofenac were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 275 nm by UV spectrophotometer. The Actual Drug Content was calculated using the following equation as follows[62]:

$$\% \text{ Drug content} = \frac{M_{act}}{M_{ss}} \times 100$$

$$\frac{\text{Actual amount of drug in solid dispersion}}{\text{Theoretical amount of drug in solid dispersion}} \times 100$$

Percentage Practical Yield

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation [63].

$$PY\,(\%) = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + carrier)}} \times 100$$

7.3.2 Determination of phase solubility of Aceclofenac

Drug solubility studies were performed in triplicate by adding excess amount of aceclofenac to methanol and buffer solutions having different pH (6.8). Solutions containing flasks were kept on a Rotary Shaking Incubator for 24 hrs. After 24 hrs, solutions were analyzed using UV spectrophotometer[64].

7.3.3 *In-vitro* Dissolution study

In-vitro dissolution studies of the pure drug (aceclofenac), the selected ratios of solid dispersions (equivalent to 50mg aceclofenac filled in hard gelatin capsules using stainless steel sinkers) were performed using USP type II (Paddle) apparatus with paddle rotating at 50 rpm in 900ml of phosphate buffer pH 6.8 at 37 ± 0.5ºC. At fixed time intervals, 5ml samples were withdrawn, filtered and replaced with phosphate buffer pH 6.8. Concentration of aceclofenac in each sample was determined by UV spectrophotometer[47].

KINETIC ANALYSIS OF *IN -VITRO* RELEASE RATES OF FORMULATIONS[65, 66]

The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

Zero-order kinetic model-cumulative percentage drug release versus time.

First- order kinetic model-log cumulative percentage drug release remaining versus time.

Higuchi's model-cumulative percentage drug released versus square root of time.

Korsmeyer's equation/peppa's model-log cumulative percentage drug released versus log time.

1. Zero-order kinetics

Zero order release would be predicted by the following equation:-

$$\mathbf{A_t = A_0 - K_0 t}$$

Where,

A_t = Drug release at time't'

A_0 = Initial drug concentration

K_0 = Zero order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

2. First- order kinetics

First-order release would be predicted by the following equation:-

$$\mathbf{Log\ C = log\ C_0 - K_t /2.303}$$

Where,

C=Amount of drug remained at time't'

C_0=Initial amount of drug

K=First-order rate constant (hr^{-1}

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant K can be obtained by multiplying 2.303 with slope values.

3. Higuchi's model

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = [D\varepsilon / \tau(2A - \varepsilon Cs)\, Cst]^{1/2}$$

Where,

Q=Amount of drug released at time‘t’

D=Diffusion coefficient of drug in the matrix

A=Total amount of drug in unit volume of matrix

Cs= The solubility of drug in the matrix

ε= Porosity of the matrix

τ= Tortuosity

t= Time (hrs) at which Q amount of drug is released

Above equation may be simplified if one assumes that D, Cs, and A, are constant. Then equation becomes:

$$Q = K\, t^{½}$$

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

4. Korsmeyer’s equation/ peppa's model

To study the mechanism of drug release from the solid dispersions, the release data were also fitted to the well-known exponential equation (Korsmeyer’s equation/peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$M_t/M_a = Kt^n$$

Where,

M_t/M_a = The fraction of drug released at time‘t’

K= Constant incorporating the structural and geometrical characteristics of the drug/polymeric

N= Diffusion exponent related to the mechanism of release

Above equation can be simplified by applying log on both sides, and we get:

$$\textbf{Log } M_t/M_a = \textbf{Log K +n Log t}$$

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y-intercept. For Fickian release 'n' =0.5 while for anomalous (non-Fickian) transport 'n' ranges from 0.5 to 1.0 as shown below.

Table: 9 Mechanism of drug release as per korsemeyer equation/peppa's model

S.No	n Value	Drug release
1.	n < 0.5	Fickian release
2.	0.5<n<1	Non- Fickian release
3.	n>1	Case II transport

8.0 RESULTS AND DISCUSSION

COMPATABILITY STUDY

The FTIR spectra of pure aceclofenac, carriers, physical mixture of drug and carriers and solid dispersion of drug and carrier are shown in Tables- 10-15 and Figures 2-7. The spectra exhibited presence of characteristic peaks of drugs in physical mixture and indicate that there was no chemical interaction between the drugs.

Fig.2 FTIR SPECTRA OF PURE ACECLOFENAC

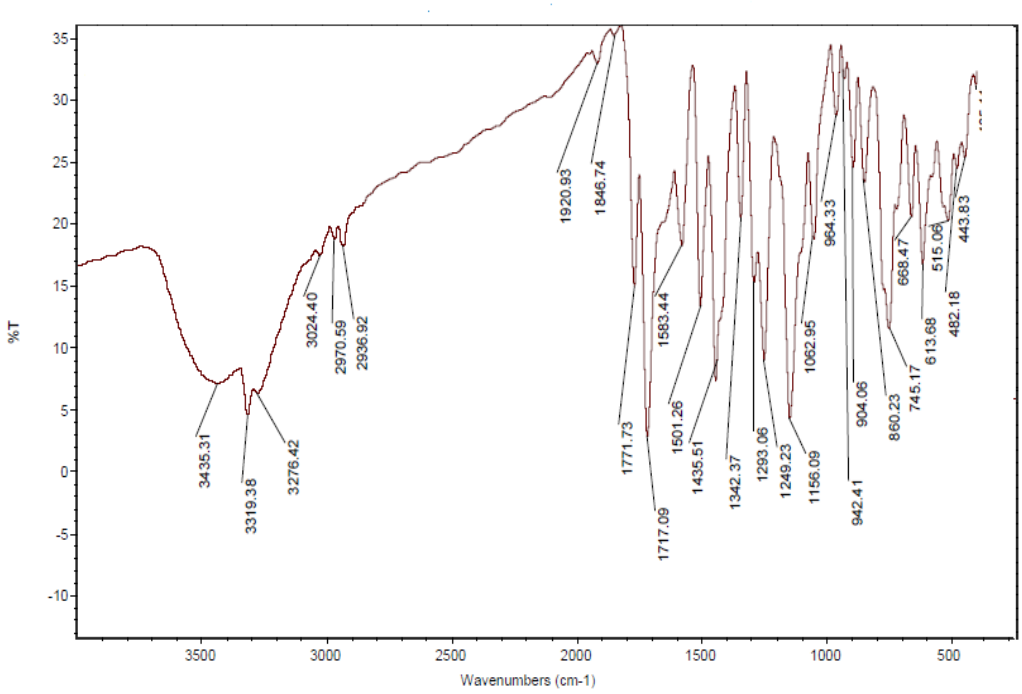


Table: 10

S.no	IR Spectrum	Peaks(cm^{-1})	Groups	Stretching /Deformation
1	ACECLOFENAC	3319.38	O-H(Alcohol)	Stretching
		1717.09	C=O(Carbonyl)	Stretching
		1158.09	C-N(Amine)	Stretching
		745.17	C-Cl(Alkyl halide)	Stretching

Fig.3 FTIR SPECTRA OF PURE POLYETHYLENE GLYCOL 6000

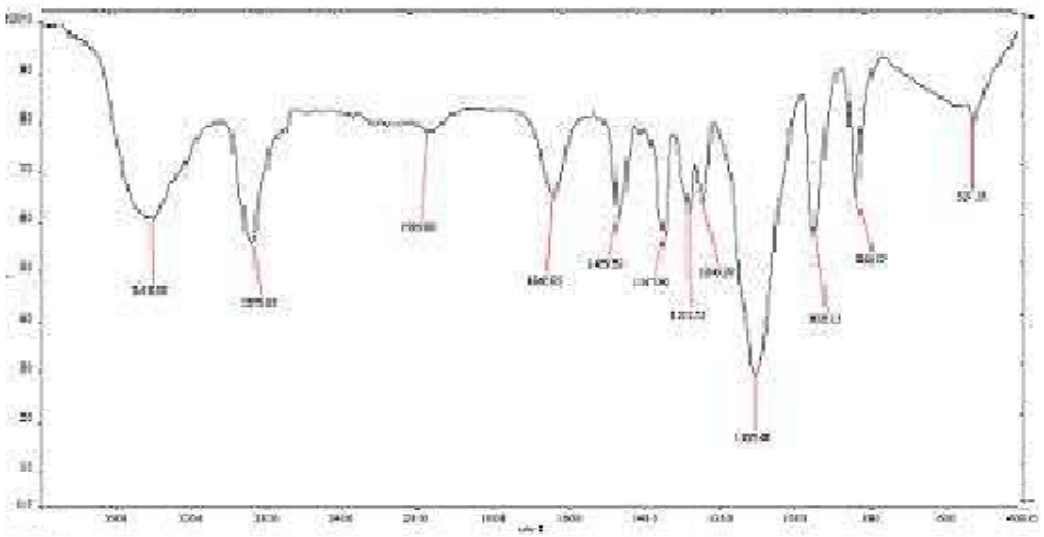


Table: 11

S.no	IR Spectrum	Peaks(cm^{-1})	Groups	Stretching /Deformation
1	PEG6000	3446.54	O-H(Alcohol)	Stretching
		2889.37	C-H(Alkane)	Stretching
		1640.10	C=O(Amide)	Stretching
		542.79	C-BR(Alkyl halide)	Stretching

Fig.4 FTIR SPECTRA OF PURE POLYVINYL PYRROLIDONE

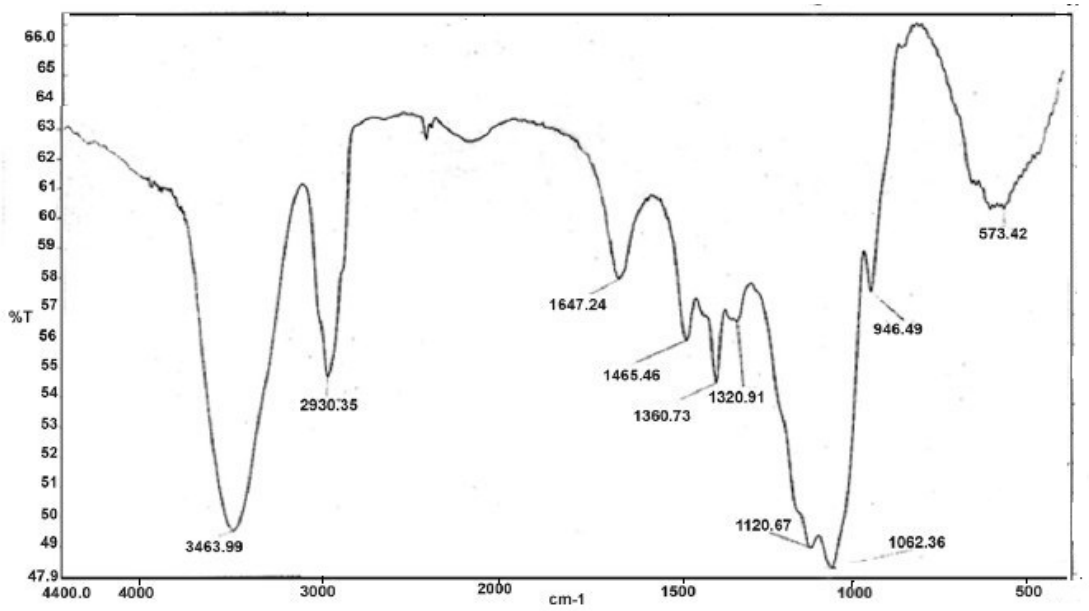


Table: 12

S.no	IR Spectrum	Peaks(cm^{-1})	Groups	Stretching /Deformation
1	PVP	3463.99	O-H(Alcohol)	Stretching
		1674.24	C=C(Alkene)	Stretching
		1062.36	C-F(Alkyl halide)	Stretching
		573.42	C-Br(Alkyl halide)	Stretching

Fig.5 FTIR SPECTRA OF PURE HYDROXYPROPYL METHYLCELLULOSE

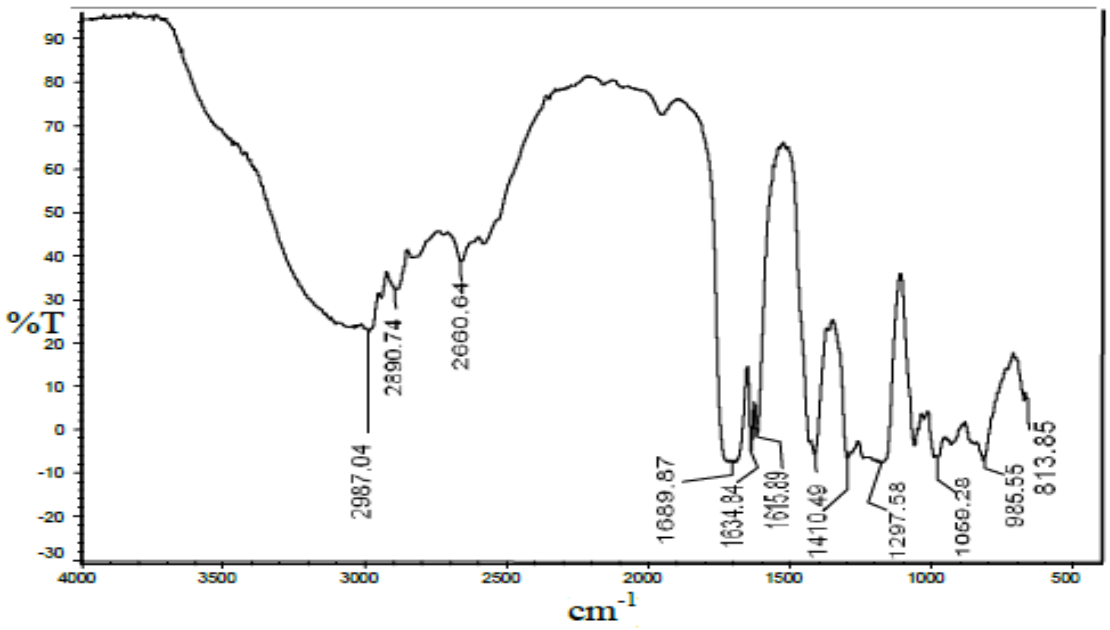


Table: 13

S.no	IR Spectrum	Peaks(cm^{-1})	Groups	Stretching /Deformation
1	HPMC	2987.04	C-H(Alkane)	Stretching
		1689.87	C=O(Carbonyl)	Stretching
		1297.58	C-F(Alkyl halide)	Stretching
		1059.28	C-F(Alkyl halide)	Stretching

Fig.6 FTIR SPECTRA OF PHYSICAL MIXTURE OF ACECLOFENAC, PEG6000, PVP AND HPMC

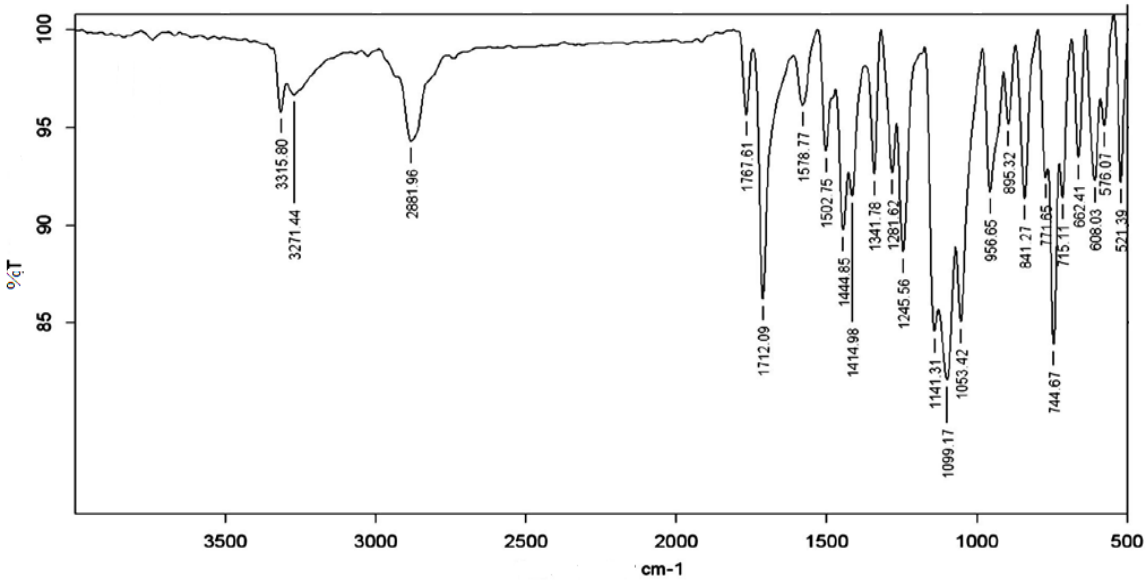


Table: 14

S.no	IR Spectrum	Peaks(cm^{-1})	Groups	Stretching /Deformation
1	Physical mixture	3271.44	O-H (Alcohol)	Stretching
		1712.09	C=o (Carbonyl)	Stretching
		1099.17	C-N(Amine)	Stretching
		744.67	C-Cl(Alkyl halide)	Stretching

Fig.7 FTIR SPECTRA OF SOLID DISPERSION OF ACECLOOFENAC, PEG6000, PVP AND HPMC

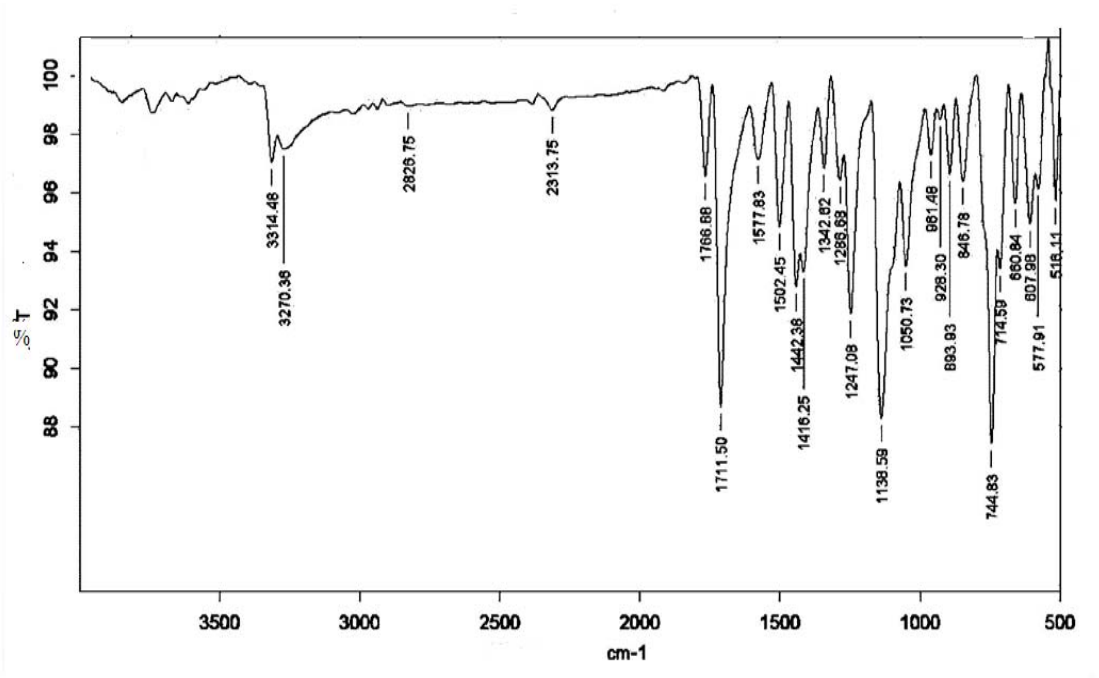


Table: 15

S.no	IR Spectrum	Peaks(cm^{-1})	Groups	Stretching /Deformation
1	Solid dispersion	3270.38	O-H (Alcohol)	Stretching
		1711.50	C=o (Carbonyl)	Stretching
		1138.58	C-F(Alkyl halide)	Stretching
		744.83	C-Cl(Alkyl halide)	Stretching

DIFFERENTIAL SCANNING CALORIMETRY

In the DSC studies of pure aceclofenac showed a sharp endotherm at 152.51^{o}C, PEG6000 at 62.50^{o}C, PVP at 218.76 ^{o}C, Hpmc at 122.8^{o}C and physical mixture at 160^{o}C to its melting point. There was no appreciable change in the melting endotherm of spherical agglomerates compared to that of pure drug (F7 agglomerates =153.27^{0}C) the DSC results also revealed little amorphization of aceclofenac when compared in the form of agglomerates with PEG6000 and PVP combination.

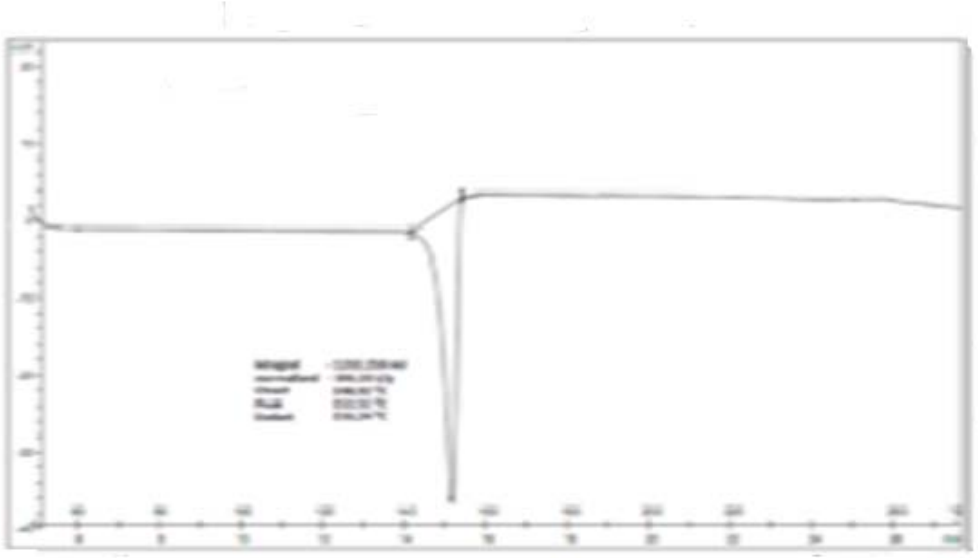


Fig.8 DSC THERMO GRAM OF PURE ACECLOFENAC

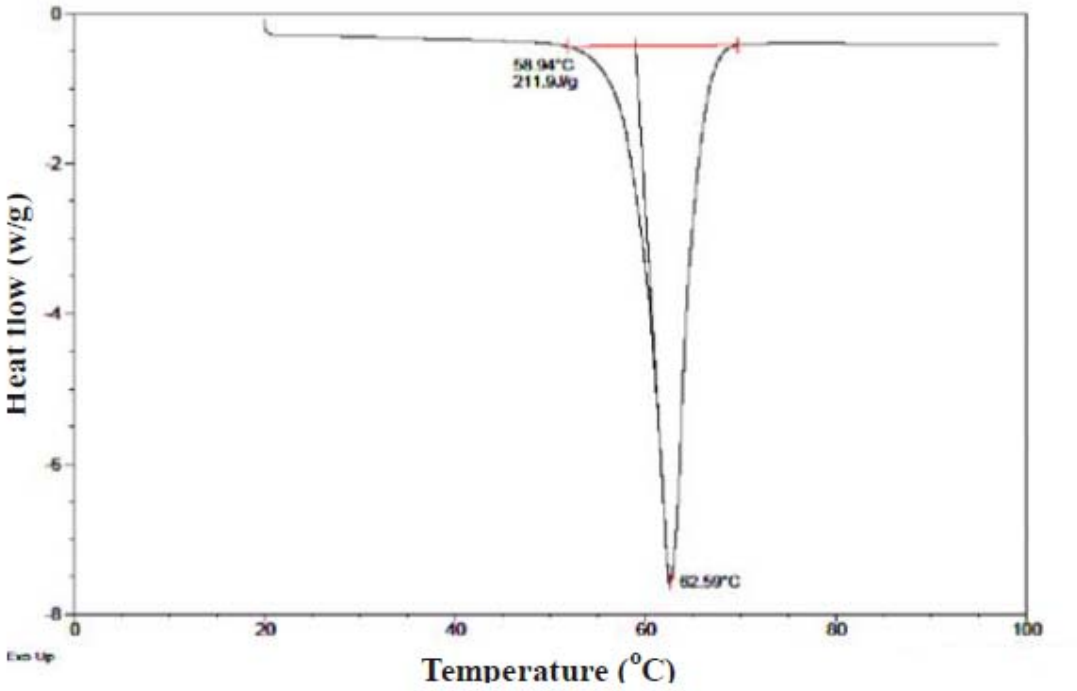


Fig.9 DSC THERMO GRAM OF PURE PEG6000

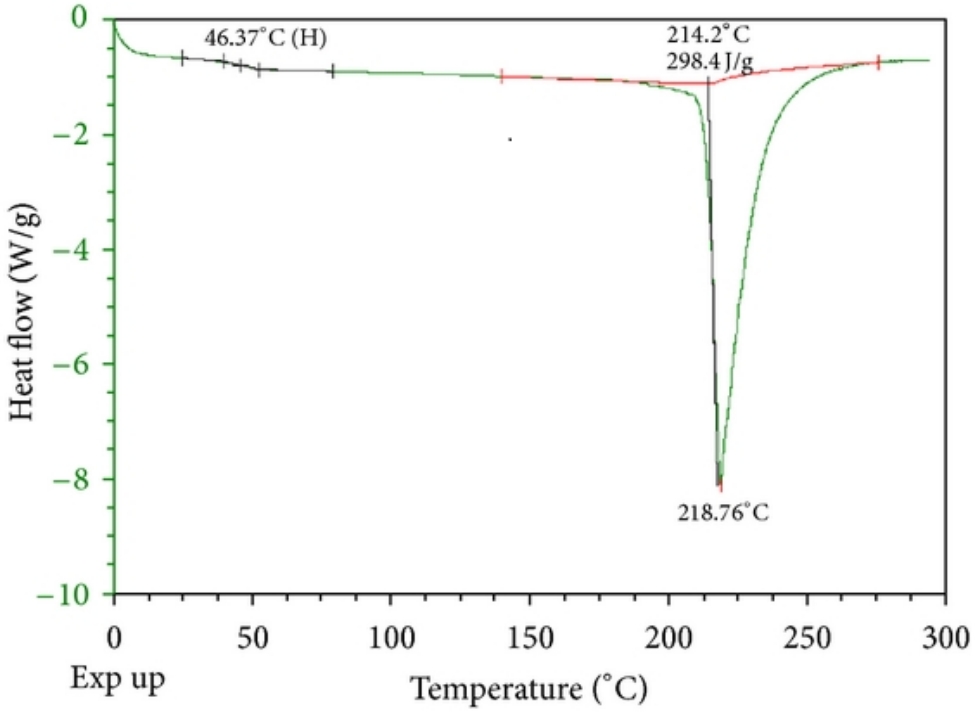


Fig.10 DSC THERMO GRAM OF PURE PVP

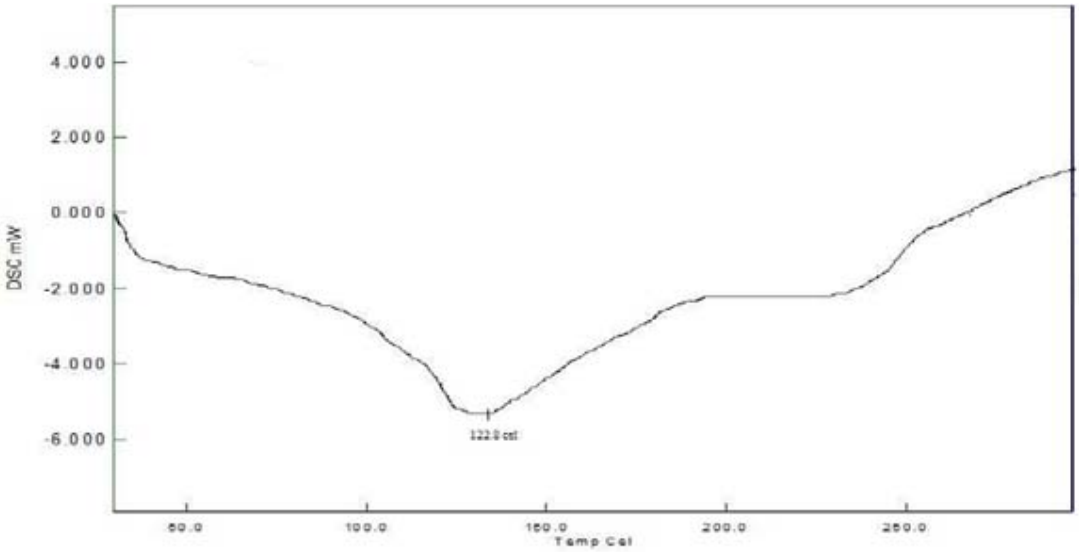


Fig.11 DSC THERMO GRAM OF PURE HPMC

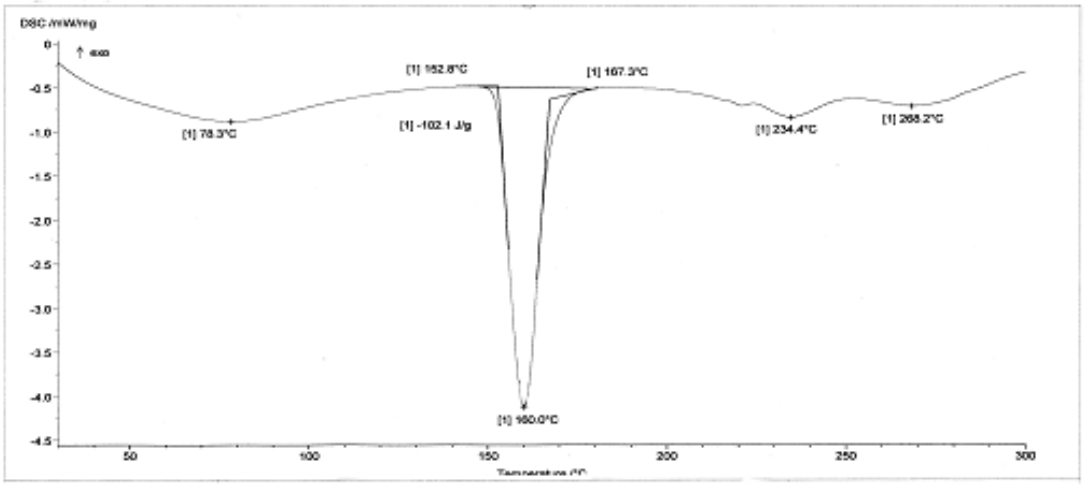


Fig.12 DSC THERMO GRAM OF PHYSICAL MIXTURE

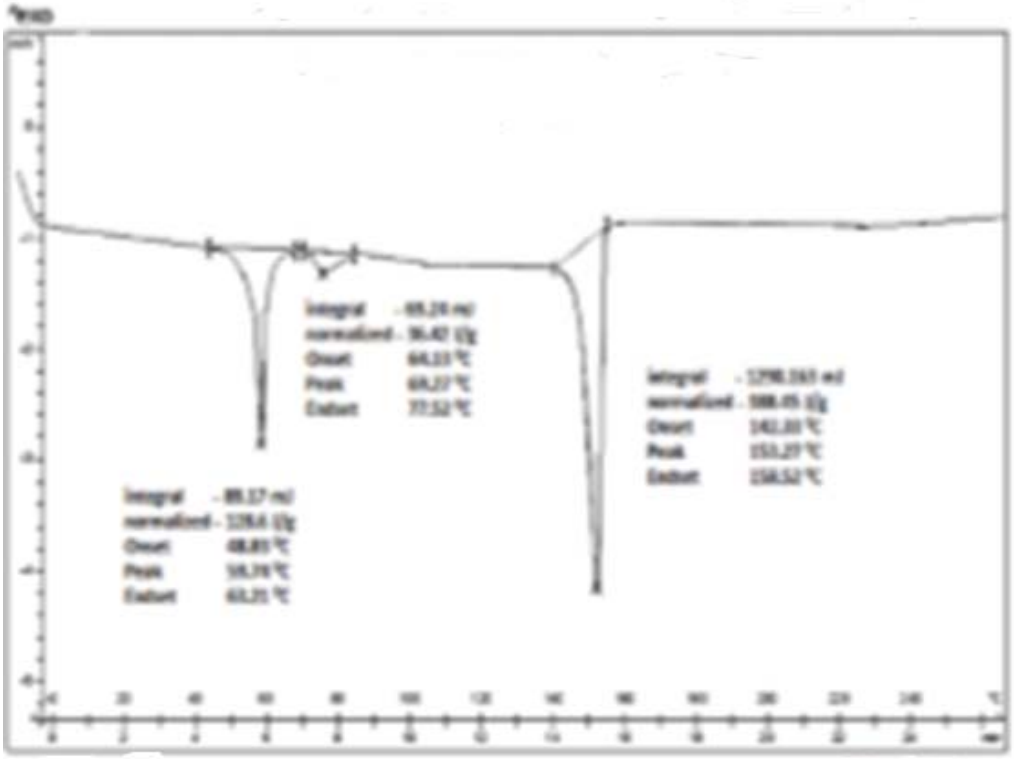


Fig.13 DSC THERMO GRAM OF F7 FORMULATION

CALIBRATION CURVE OF ACECLOFENAC

The calibration curve of aceclofenac was determined in pH 6.8 phosphate buffer by using UV-Visible spectrophotometer at 275 nm. Graph was plotted by taking absorbance (nm) on X-axis verses concentration (µg/ml) on Y-axis and it is follows the Beer's law. The results were shown in table: 16.

Table: 16 Calibration curve of aceclofenac

Sl.no	Concentration of aceclofenac(µg/ml)	Absorbance at 275nm
0	0	0
1	2	0.05541
2	4	0.1047
3	6	0.1564
4	8	0.2019
5	10	0.2624
R^2 value		0.9988

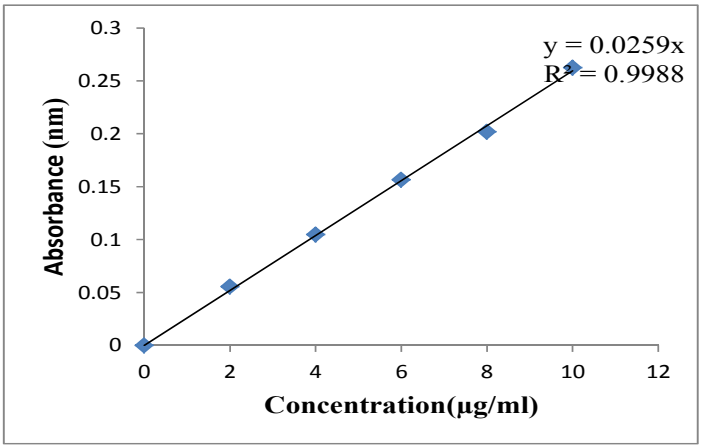


Fig. 14 Calibration curve of aceclofenac

DRUG CONTENT ESTIMATION

Drug content uniformity of aceclofenac solid dispersion in all the formulations (F1 to F9) were shown from 66.5±0.7071 to 87.09±3.7390 respectively.[62]As shown in table 17.

Table: 17 Drug content of aceclofenac in all formulations

Formulation code	Drug content (in %)
F1	76.89±0.7128
F2	66.5±0.7071
F3	70.55 ±0.7805
F4	67.68±1.2583
F5	72.14±1.1185
F6	74.20±1.1145
F7	87.09±3.7390
F8	82.5±2.121
F9	78.37±1.4913

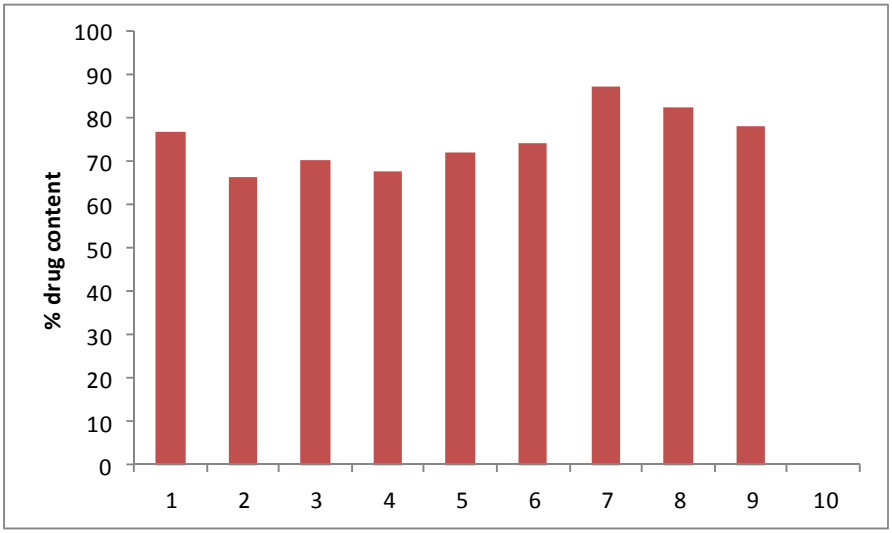


Fig. 14 Drug content of aceclofenac in all formulations

PERCENTAGE PRACTICAL YIELD

Percentage practical yield of aceclofenac in all the formulations (F1 to F9) were shown from 89.09±0.291 to 95.46±0.9799 respectively. [63] As shown in table 18.

Table: 18 Drug content of aceclofenac in all formulations

Formulation code	% Practical yield
F1	92.71±1.0651
F2	89.09±0.291
F3	94.7±0.6420
F4	91.08±0.305
F5	90.12±1.307
F6	90.82±0.3614
F7	95.46±0.9799
F8	93.51±0.1937
F9	92.77±0244

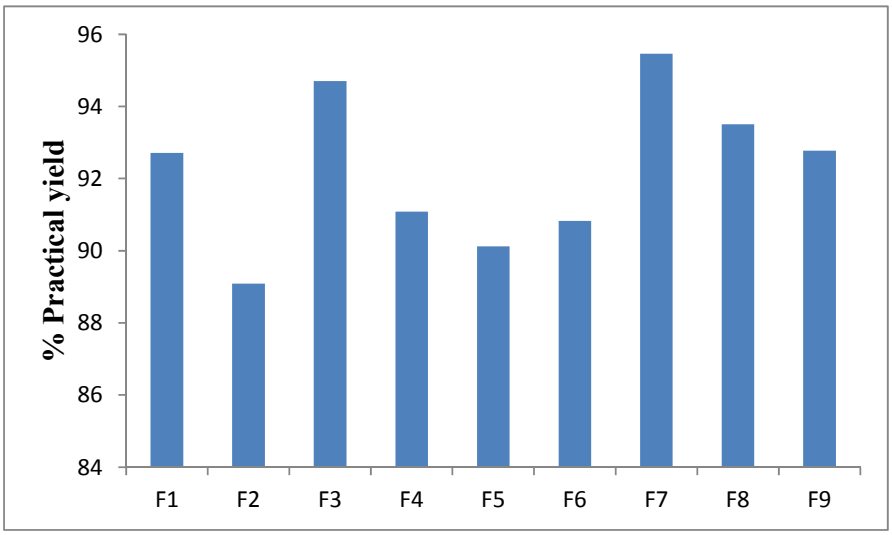


Fig. 15 Drug content of aceclofenac in all formulations

PHASE SOLUBILITY STUDY

Table: 19 Solubility of aceclofenac in PEG6000 solution

Sl.no	Concentration of PEG6000 (%w/v)	Solubility of aceclofenac in PEG6000 solution (mg/ml)
1	0	0.2125
2	0.0025	0.3621
3	0.0050	0.5410
4	0.010	1.6539

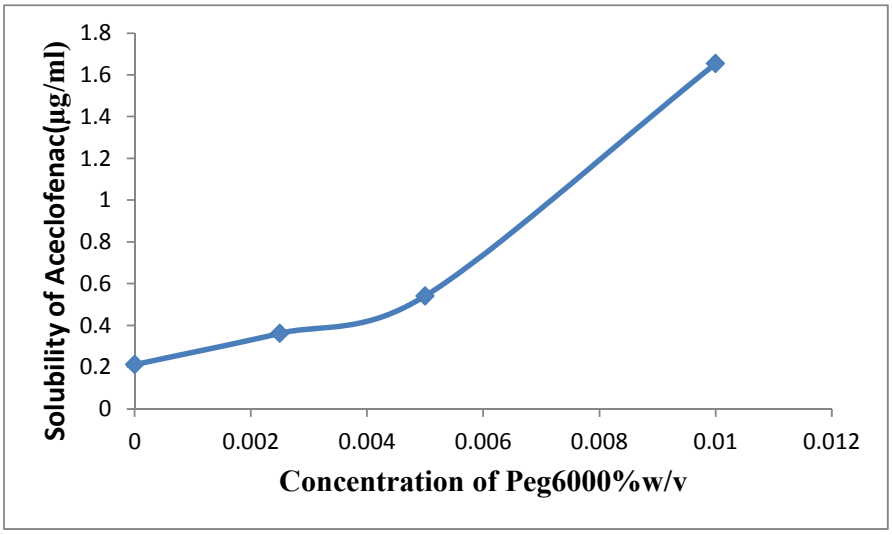


Fig.17 Solubility of aceclofenac in PEG6000 solution

Table: 20 Solubility of aceclofenac in PVP solution

S.no	Concentration of PVP (%w/v)	Solubility of aceclofenac in PVP solution (mg/ml)
1	0	0.1965
2	0.0025	0.3365
3	0.0050	0.5110
4	0.010	1.6393

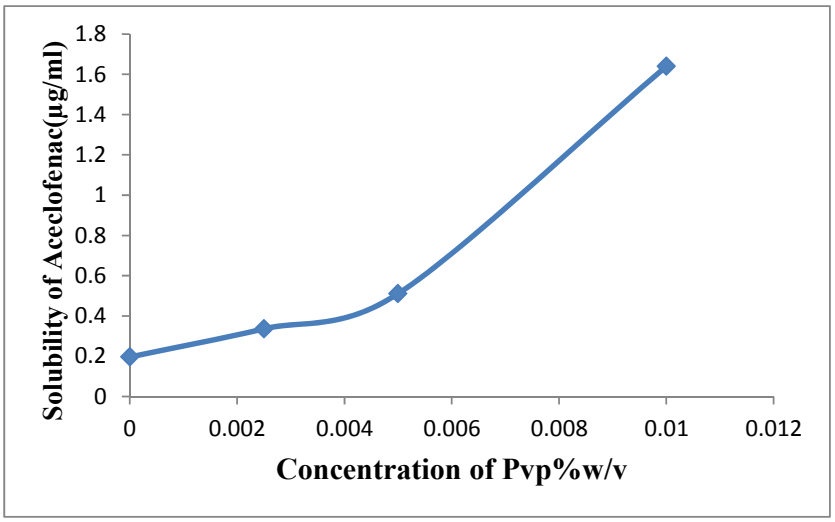


Fig.18 Solubility of aceclofenac in PVP solution

Table: 21 Solubility of aceclofenac in HPMC solution

S.no	Concentration of HPMC (%w/v)	Solubility of aceclofenac in HPMC solution (mg/ml)
1	0	0.1652
2	0.0025	0.2899
3	0.0050	0.4753
4	0.010	1.5861

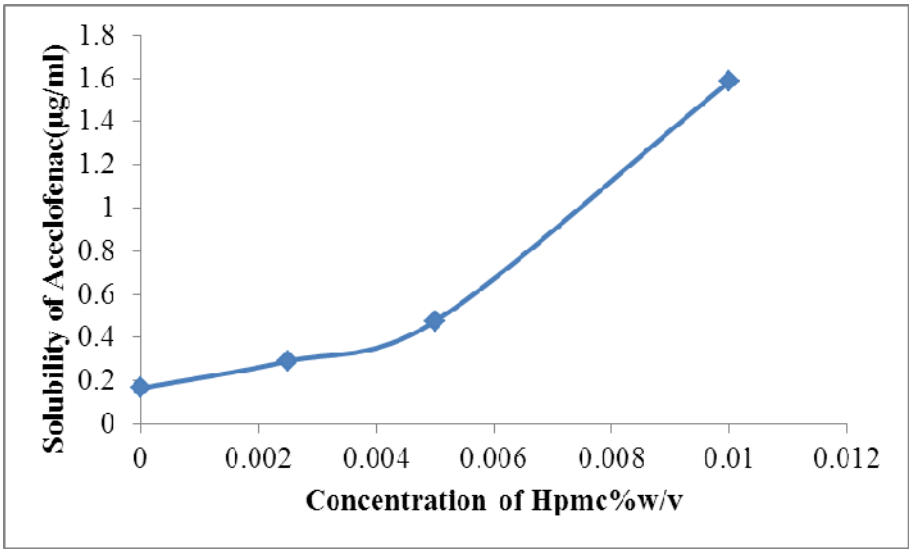


Fig.19 Solubility of aceclofenac in HPMC solution

COMPARATIVE PHASE SOLUBILITY

Phase solubility study was carried out in order in to ascertain effect of carriers on the solubility characteristics of aceclofenac. Solubility of aceclofenac was increased as the concentration of carriers increased[64]. The solubility of aceclofenac was minimal in methanol and increased approximately eight fold at 0.01%w/v of PEG6000 in methanol. These data indicates that PEG6000 in methanol solubility of aceclofenac was greatly enhanced possibly due to the solvent effect of PEG6000.

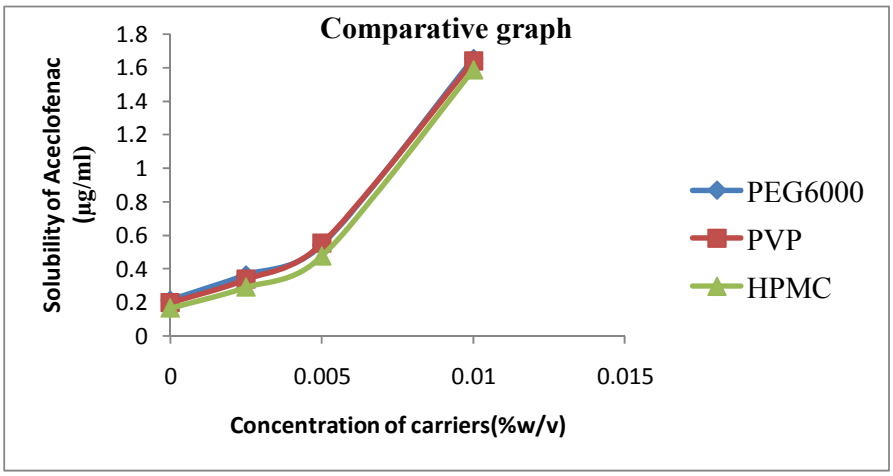


Fig.20 Comparative phase solubility

IN-VITRO DISSOLUTION STUDIES

The aceclofenac solid dispersions were prepared by using with hydrophilic carriers like PEG6000, PVP and HPMC, *in-vitro* drug release studies were carried out in trail (n=3) basis for total 9 formulations.

The release of aceclofenac solid dispersions was studied in 900 ml of pH 6.8 phosphate buffer upto 90 min as dissolution medium using USP II (paddle) dissolution apparatus at 50 rpm and $37^0 \pm 0.5\ ^0C$. Drug content was determined by UV-Spectrophotometer at 275 nm. Cumulative percentage of drug release was calculated by using an equation obtained from a standard curve. The dissolution studies were performed 3 times for a period of 90 min, where Mean±S.D values were calculated. The results of studies were shown in Tables 22-41.

Table: 22 *In-vitro* dissolution profile for solid dispersion pure aceclofenac

Time (min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	4.71	4.70	4.78	4.73±0.0435
20	11.03	10.50	10.56	10.69±0.2902
30	12.34	12.42	12.52	12.42±0.0901
40	14.12	14.19	14.09	14.13±0.0513
50	17.64	17.62	17.39	17.55±0.1389
60	25.73	24.15	25.15	25.01±0.7992
70	29.07	28.93	29.10	29.03±0.0907
80	33.58	33.34	34.09	33.67±0.3830
90	37.59	36.14	38.19	37.30±1.0539

Table: 23 Kinetic data for *in-vitro* release rates solid dispersion pure aceclofenac

Time (min)	square root of time	log time	cumulative % drug release	log cumulative % drug release	cumulative % drug remaining	log cumulative %drug remaining
0	0	0	0	0	100	2
10	3.16227	1	4.73	0.67486	95.27	1.97895
20	4.47213	1.30102	10.69	1.02897	89.31	1.95090
30	5.47722	1.47712	12.42	1.09412	87.58	1.94240
40	6.32455	1.60205	14.13	1.15014	85.87	1.93384
50	7.07106	1.69897	17.15	1.23426	82.85	1.91829
60	7.74596	1.77815	25.01	1.39811	74.99	1.87500
70	8.36660	1.84509	29.03	1.46284	70.97	1.85107
80	8.94427	1.90308	33.67	1.52724	66.33	1.82170
90	9.48683	1.95424	37.30	1.57170	62.7	1.79726

Fig.P (a)

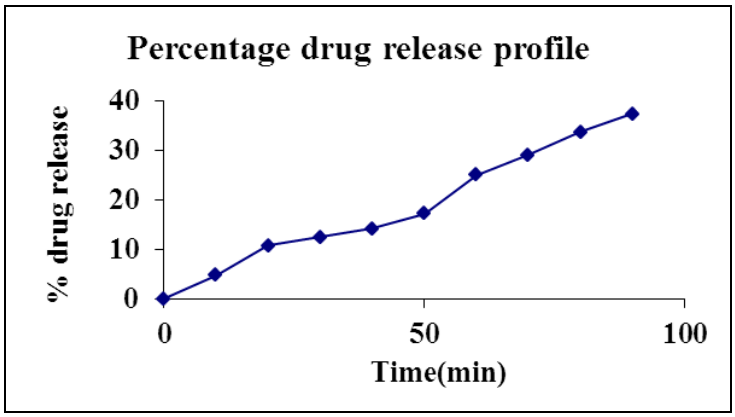


Fig.P (b)

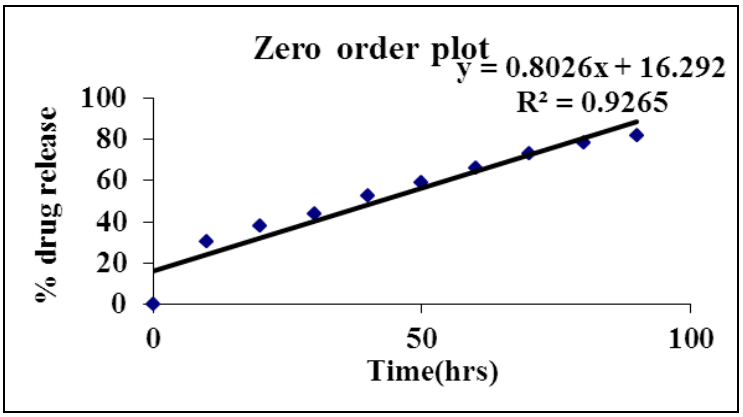


Fig.P (c)

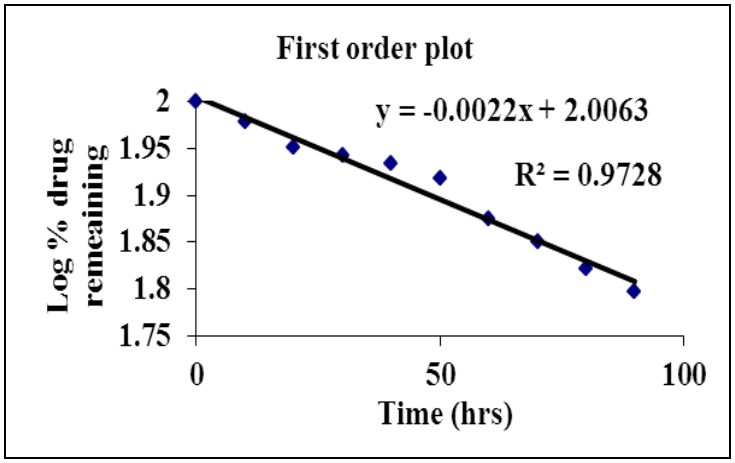


Fig. P (d)

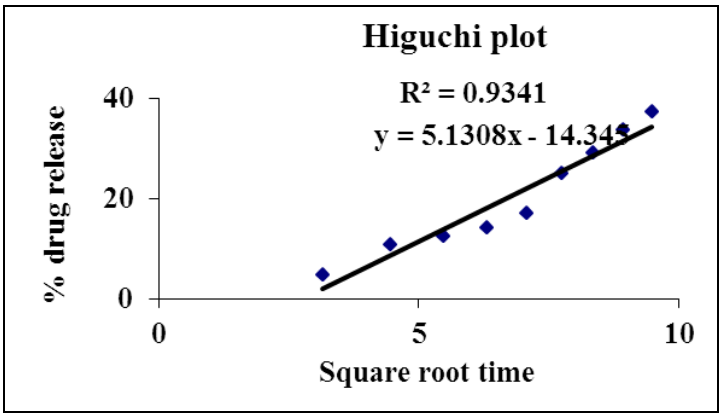

Higuchi plot
R² = 0.9341
y = 5.1308x - 14.345
% drug release
40
20
0
0
5
10
Square root time

Fig.P (e)

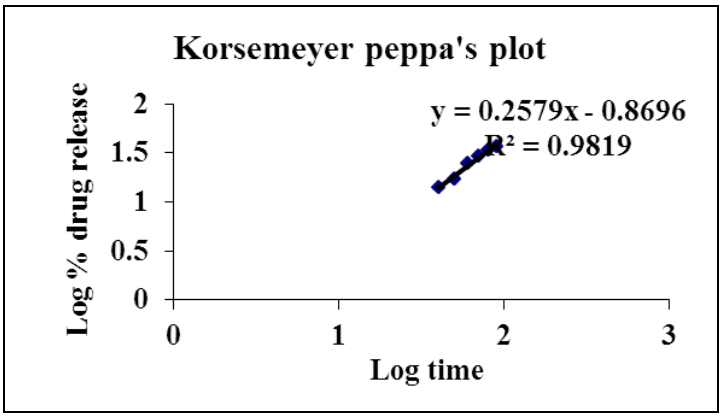

Korsemeyer peppa's plot
y = 0.2579x - 0.8696
R² = 0.9819
Log % drug release
2
1.5
1
0.5
0
0
1
2
3
Log time

Table: 24 *In-vitro* dissolution profile for solid dispersion F1 formulation

Time (min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	30.15	29.70	30.90	30.25 ± 0.606
20	38.20	38.15	37.92	38.09±0.1493
30	45.25	44.51	42.35	44.03 ±1.506
40	53.84	52.09	51.89	52.60±1.0727
50	59.57	58.95	59.00	59.17±0.3443
60	67.25	65.70	66.31	66.42±0.7808
70	74.09	72.12	73.15	73.12±0.9853
80	79.23	78.15	77.15	78.17±1.1784
90	84.29	79.13	83.25	82.22±2.7289

Table: 25 Kinetic data for *in-vitro* release rates of solid dispersion F1 formulation

Time (min)	square root of time	log time	cumulative % drug release	log cumulative % drug release	cumulative % drug remaining	log cumulative % drug remaining
0	0	0	0	0	100	2
10	3.16227	1	30.25	1.48072	69.75	1.8435
20	4.47213	1.30102	38.09	1.58081	61.91	1.79176
30	5.47722	1.47712	44.03	1.64374	55.97	1.74795
40	6.32455	1.60205	52.60	1.72098	47.4	1.67577
50	7.07106	1.69897	59.17	1.77210	40.83	1.61097
60	7.74596	1.77815	66.42	1.82229	33.58	1.52608
70	8.36660	1.84509	73.12	1.86403	26.88	1.42942
80	8.94427	1.90308	78.17	1.89276	21.83	1.33905
90	9.4683	1.95424	82.22	1.91497	17.78	1.24993

Fig.1 (a)

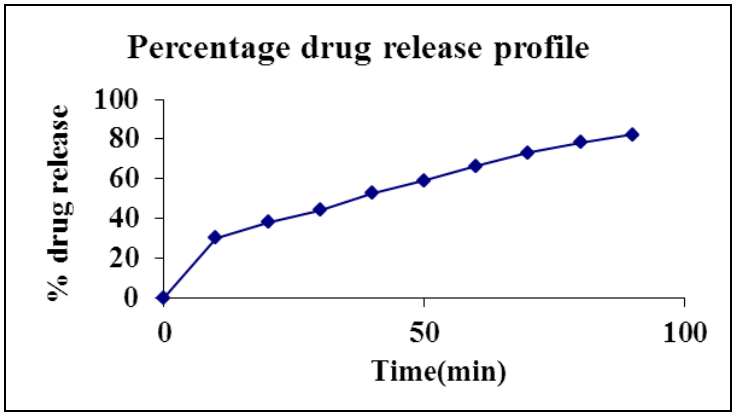


Fig.1 (b)

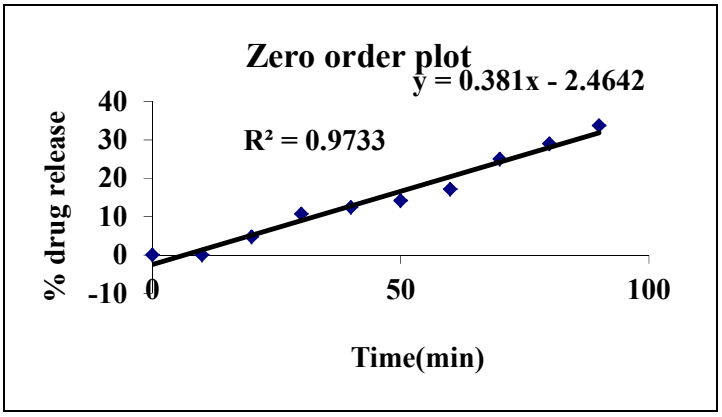


Fig.1 (c)

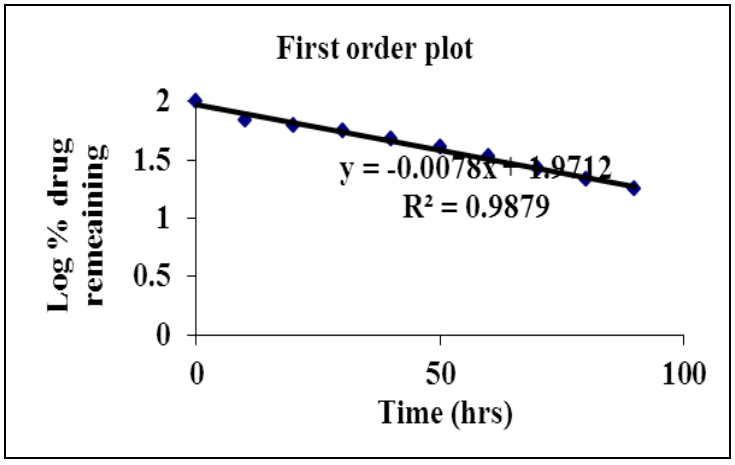


Fig.1 (d)

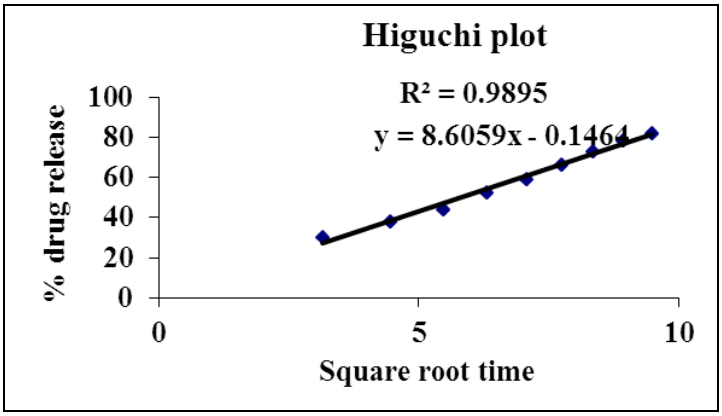

Higuchi plot
R² = 0.9895
y = 8.6059x - 0.1464
% drug release
100
80
60
40
20
0
0
5
10
Square root time

Fig.1 (e)

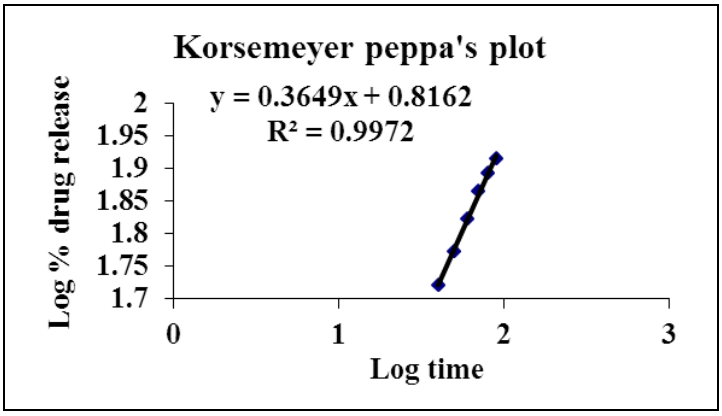

Korsemeyer peppa's plot
y = 0.3649x + 0.8162
R² = 0.9972
Log % drug release
2
1.95
1.9
1.85
1.8
1.75
1.7
0
1
2
3
Log time

Table: 26 *In-vitro* dissolution profile for solid dispersion F2 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	40.08	41.23	42.19	41.16 ±1.0564
20	51.90	50.98	49.67	50.85±1.1206
30	54.01	53.19	54.23	53.81±0.5480
40	57.38	56.29	55.55	56.40±0.9205
50	58.38	57.09	58.09	57.85±0.6767
60	61.38	61.08	59.15	60.53±1.2102
70	70.81	69.15	68.34	69.43±1.2591
80	73.15	72.12	74.09	73.12±0.9853
90	76.39	75.19	76.16	75.91±0.6368

Table: 27 Kinetic data for *in-vitro* release rates of solid dispersion F2 formulation

Time (min)	square root of time	log time	cumulative % drug release	log cumulative % drug release	cumulative % drug remaining	log cumulative % drug remaining
0	0	0	0	0	100	2
10	3.16227	1	41.16	1.61447	58.84	1.76967
20	4.47213	1.30102	50.85	1.70629	49.15	1.69152
30	5.47722	1.47712	53.81	1.73086	46.19	1.66454
40	6.32455	1.60205	56.40	1.75127	43.6	1.63948
50	7.07106	1.69897	57.85	1.76230	42.15	1.62479
60	7.74596	1.77815	60.53	1.78197	39.47	1.59626
70	8.36660	1.84509	69.43	1.84154	30.57	1.48529
80	8.94427	1.90308	73.12	1.86403	26.88	1.42942
90	9.48683	1.95424	75.91	1.88029	24.09	1.38183

Fig.2 (a)

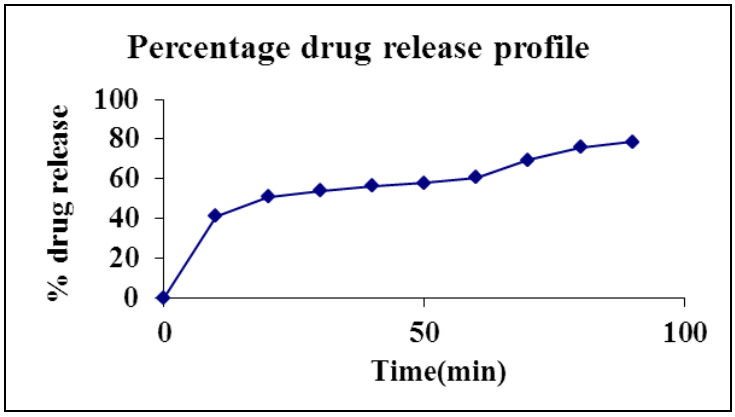


Fig.2 (b)

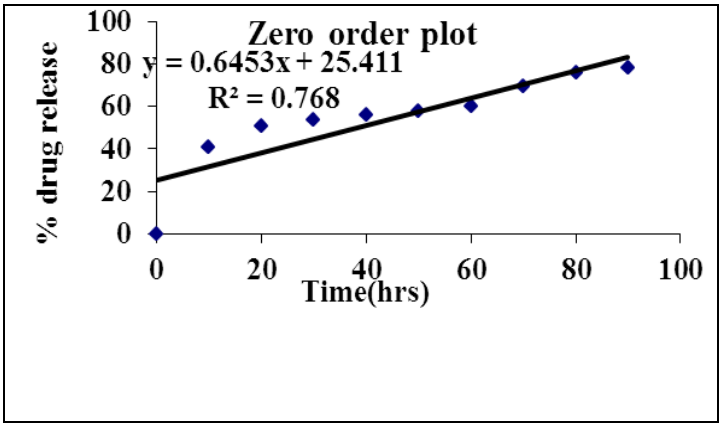


Fig.2 (c)

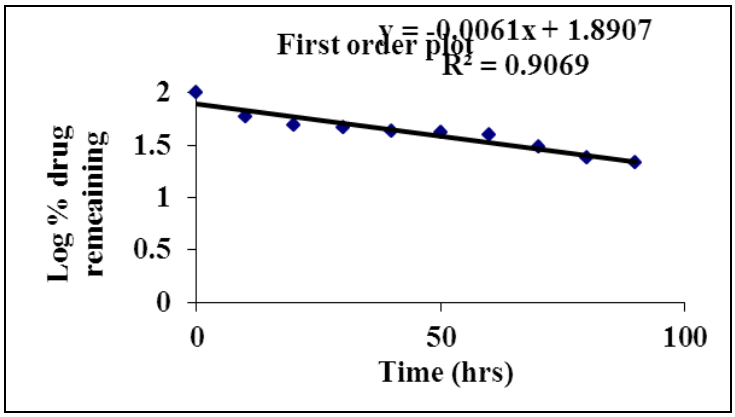


Fig.2 (d)

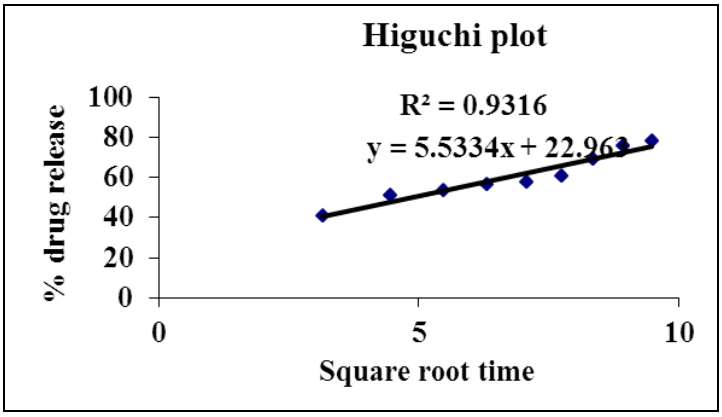

Higuchi plot
R² = 0.9316
y = 5.5334x + 22.963
% drug release
100
80
60
40
20
0
0
5
10
Square root time

Fig.2 (e)

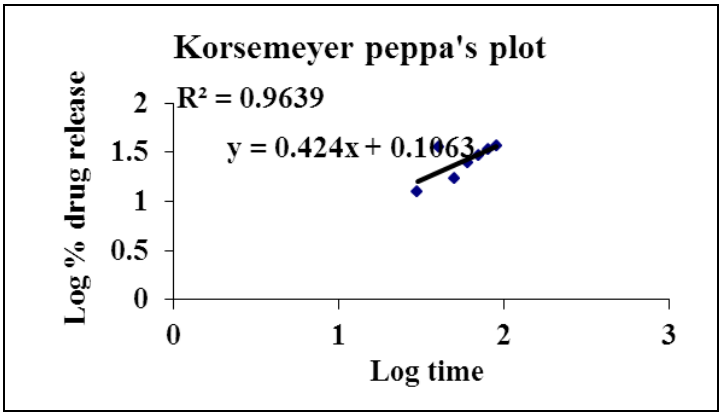

Korsemeyer peppa's plot
R² = 0.9639
y = 0.424x + 0.1063
Log % drug release
2
1.5
1
0.5
0
0
1
2
3
Log time

Table: 28 *In-vitro* dissolution profile for solid dispersion F3 formulation

Time (min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	25.30	24.90	25.95	25.38±0.5299
20	37.29	38.51	38.91	38.23±0.8438
30	39.70	40.75	39.15	39.86±0.8129
40	42.78	43.04	42.80	42.87±0.1446
50	49.10	49.81	48.75	49.22±0.5400
60	55.37	55.25	54.65	55.09±0.3857
70	59.43	58.50	59.85	59.26±0.6908
80	64.80	64.34	65.01	64.71±0.3426
90	69.15	69.95	70.03	69.71±0.4866

Table: 29 Kinetic data for *in-vitro* release rates of solid dispersion F3 formulation

Time (min)	square root of time	log time	cumulative %drug release	log cumulative % drug release	cumulative % drug remaining	log cumulative % drug remaining
0	0	0	0	0	100	2
10	3.16227	1	25.38	1.40277	74.72	1.87343
20	4.47213	1.30102	38.23	1.58240	61.77	1.79077
30	5.47722	1.47712	39.86	1.60053	60.14	1.77916
40	6.32455	1.60205	42.87	1.63215	57.13	1.75686
50	7.07106	1.69897	49.22	1.69214	50.78	1.70569
60	7.74596	1.77815	55.09	1.74107	44.91	1.65234
70	8.836660	1.84509	59.26	1.77276	40.74	1.61002
80	8.94427	1.90308	64.71	1.81097	35.29	1.54765
90	9.48683	1.95424	69.71	1.84329	30.29	1.48129

Fig.3 (a)

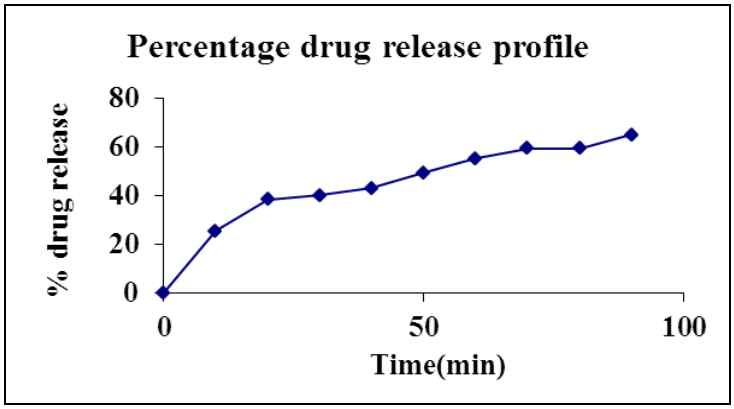


Fig.3 (b)

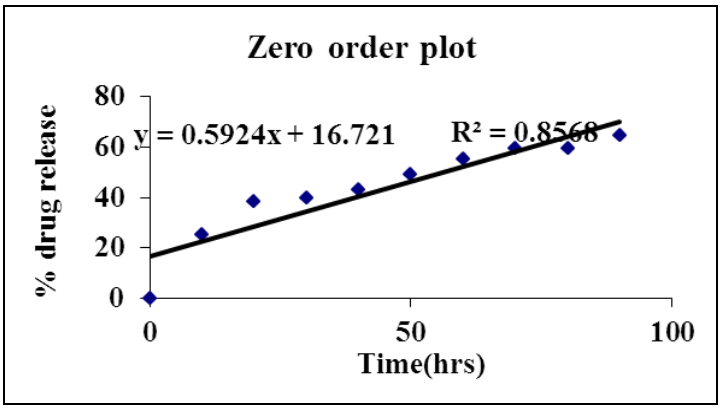


Fig.3 (c)

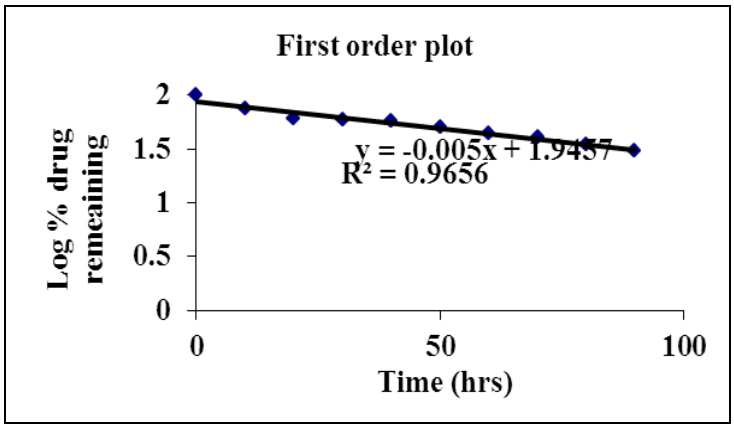


Fig.3 (d)

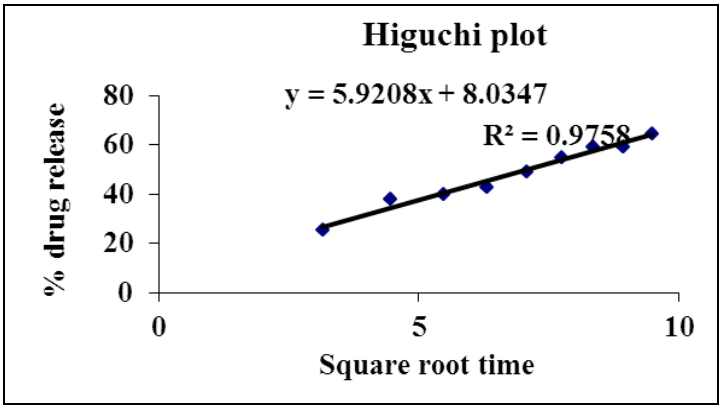

Higuchi plot
y = 5.9208x + 8.0347
R² = 0.9758
% drug release
80
60
40
20
0
0
5
10
Square root time

Fig.3 (e)

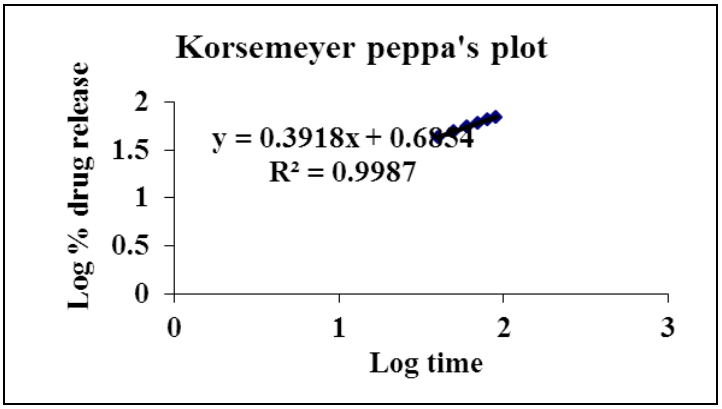

Korsemeyer peppa's plot
y = 0.3918x + 0.6854
R² = 0.9987
Log % drug release
2
1.5
1
0.5
0
0
1
2
3
Log time

Table: 30 *In-vitro* dissolution profile for solid dispersion F4 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	14.92	14.70	15.44	15.02±0.3810
20	24.67	24.42	24.55	24.55±0.1245
30	38.66	37.13	37.65	37.81±0.7792
40	41.14	38.88	41.23	40.51±1.4081
50	51.37	46.75	48.20	48.77±2.3599
60	58.54	54.62	56.01	56.39±1.9864
70	62.60	60.48	61.91	61.66±1.0828
80	69.02	66.52	67.50	67.68±1.2583
90	72.37	70.92	73.12	72.14±1.1185

Table: 31 Kinetic data for *in-vitro* release rates of solid dispersion F4 formulation

Time (min)	square root of time	log time	cumulative % drug release	log cumulative % drug release	cumulative % drug remaining	log cumulative % drug remaining
0	0	0	0	0	100	2
10	3.16227	1	15.02	1.17666	84.98	1.92931
20	4.47213	1.30102	24.55	1.39005	75.45	1.87765
30	5.47722	1.47712	37.18	1.57030	62.82	1.79809
40	6.32455	1.60205	40.15	1.60368	59.85	1.77706
50	7.07106	1.69897	48.77	1.68815	51.23	1.70952
60	7.74596	1.77815	56.39	1.75120	43.61	1.63958
70	8.36660	1.84509	61.66	1.79000	38.34	1.58365
80	8.94427	1.90308	67.68	1.83046	32.32	1.50947
90	9.48683	1.95424	72.14	1.85817	27.86	1.44498

Fig.4 (a)

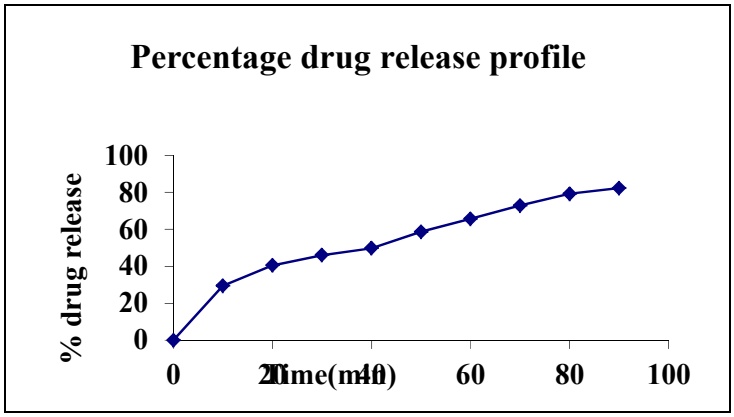


Fig.4 (b)

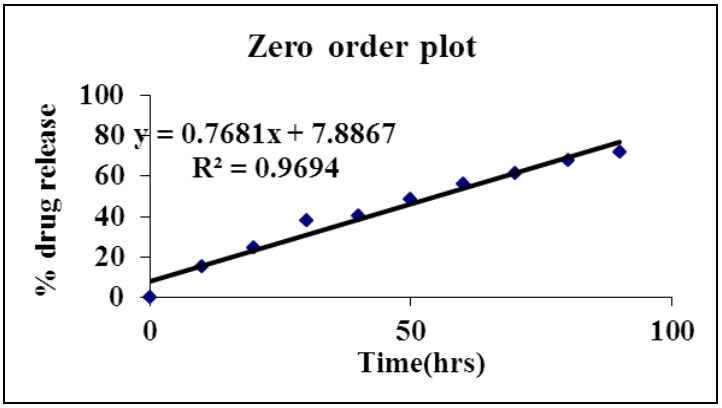


Fig.4 (c)

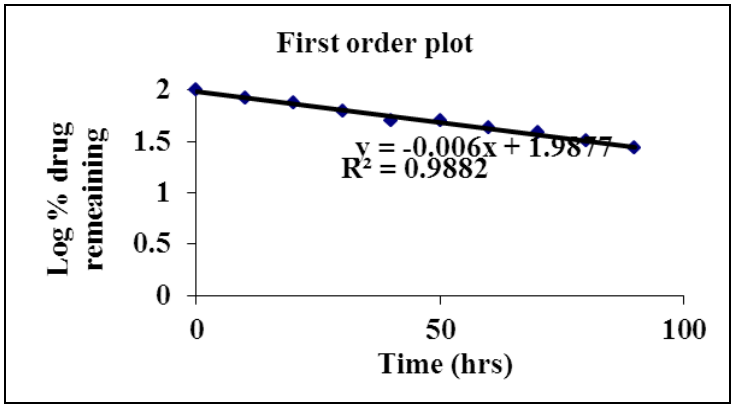


Fig.4 (d)

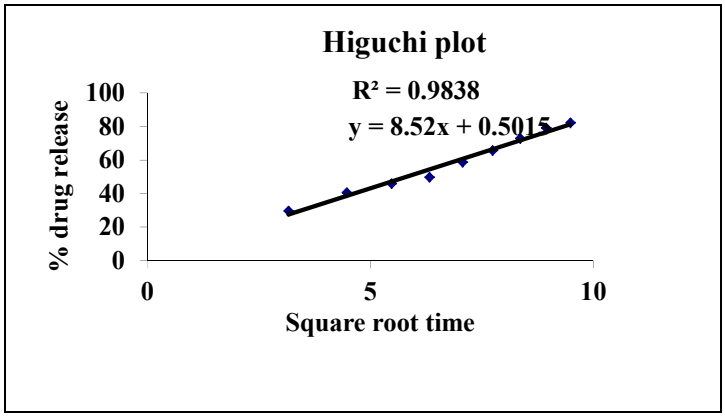

Higuchi plot
R² = 0.9838
y = 8.52x + 0.5015
% drug release
100
80
60
40
20
0
0
5
10
Square root time

Fig.4 (e)

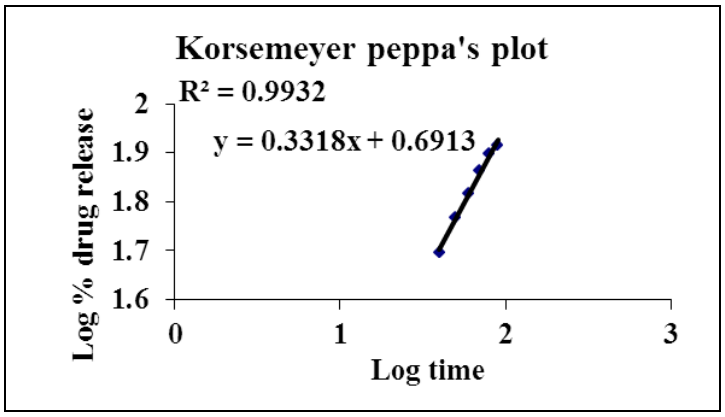

Korsemeyer peppa's plot
R² = 0.9932
y = 0.3318x + 0.6913
Log % drug release
2
1.9
1.8
1.7
1.6
0
1
2
3
Log time

Table: 32 *In-vitro* dissolution profile for solid dispersion F5 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	30.78	28.35	29.51	29.55± 1.21541
20	41.41	38.88	41.23	40.51±1.4116
30	46.29	45.68	46.17	46.05±0.3231
40	51.02	48.84	49.49	49.78±1.1192
50	60.24	57.52	58.21	58.66±1.4149
60	66.49	64.51	66.07	65.69±1.0432
70	74.14	72.76	71.82	72.90±1.1688
80	80.71	77.45	79.56	79.24±1.16568
90	82.40	81.43	83.04	82.29±0.8078

Table: 33 Kinetic data for *in-vitro* release rates of solid dispersion F5 formulation

Time (min)	square root of time	log time	cumulative % drug release	log cumulative % drug release	cumulative % drug remaining	Log cumulative % drug remaining
0	0	0	0	0	100	2
10	3.16227	1	29.55	1.47055	70.45	1.84788
20	4.47213	1.30102	40.51	1.60756	59.49	1.77444
30	5.47722	1.47712	46.05	1.66322	53.95	1.73199
40	6.32455	1.60205	49.78	1.69705	50.22	1.700087
50	7.07106	1.69897	58.66	1.76834	41.34	1.61637
60	7.74596	1.77815	65.69	1.81749	34.31	1.53542
70	8.36660	1.84509	72.90	1.86272	27.1	1.43296
80	8.94427	1.90308	79.24	1.89894	20.76	1.31722
90	9.48683	1.95424	82.29	0.35983	17.71	1..24821

Fig.5 (a)

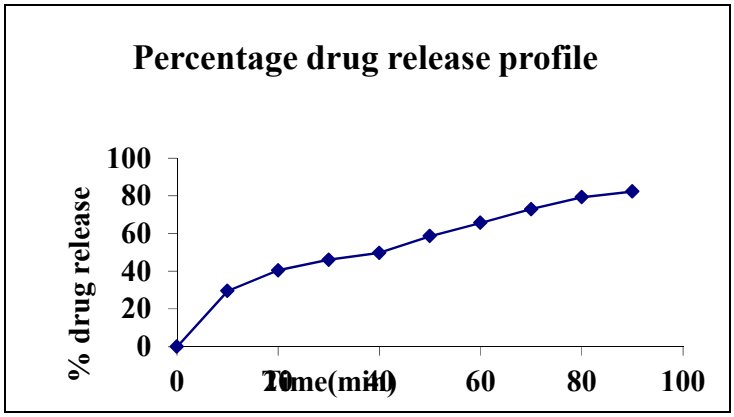


Fig.5 (b)

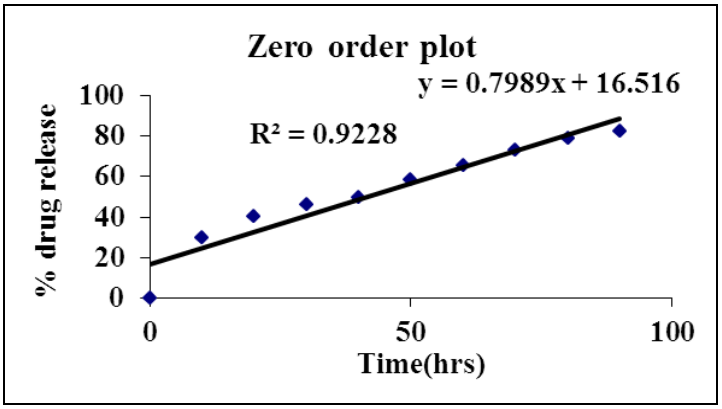


Fig.5 (c)

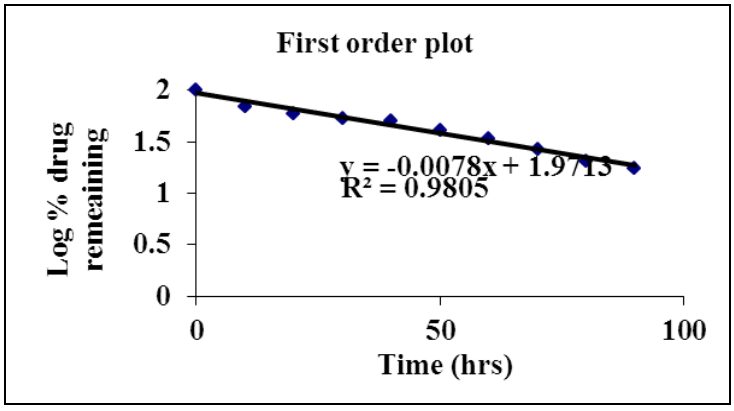


Fig.5 (d)

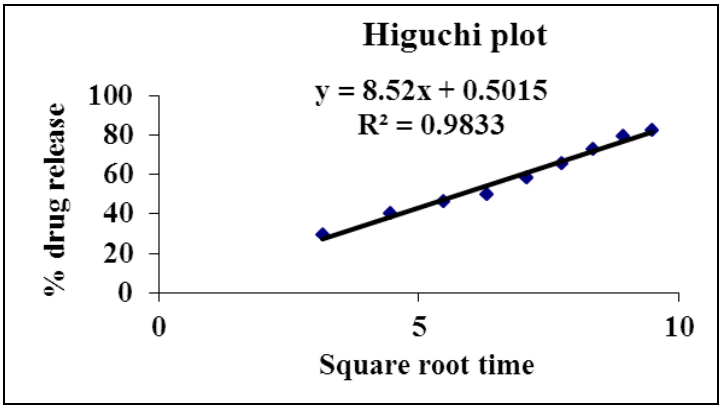

Higuchi plot
y = 8.52x + 0.5015
R² = 0.9833
% drug release
100
80
60
40
20
0
0
5
10
Square root time

Fig.5 (e)

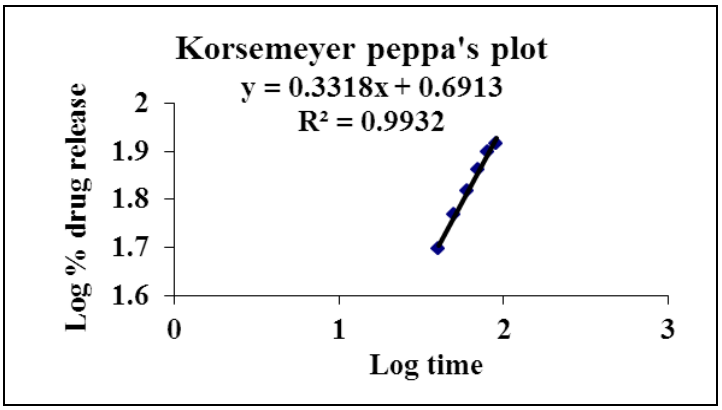

Korsemeyer peppa's plot
y = 0.3318x + 0.6913
R² = 0.9932
Log % drug release
2
1.9
1.8
1.7
1.6
0
1
2
3
Log time

Table: 34 *In-vitro* dissolution profile for solid dispersion F6 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	37.30	38.01	37.15	37.48±0.4593
20	42.78	42.10	43.45	42.77±0.6750
30	46.04	44.99	45.94	45.65±0.5795
40	49.10	49.34	48.15	48.86±06293
50	55.37	54.19	55.90	55.15±0.8753
60	59.43	58.19	59.59	59.07±0.7662
70	64.13	64.09	65.32	64.51±0.6988
80	69.17	68.15	68.99	68.77±0.5444
90	76.51	77.41	76.44	76.79±0.5437

Table: 35 Kinetic data for *in-vitro* release rates of solid dispersion F6 formulation

Time (min)	square root of time	log time	cumulative % drug release	log cumulative % drug release	cumulative % drug remaining	Log cumulative % drug remaining
0	0	0	0	0	100	2
10	3.16227	1	37.48	1.57379	62.52	1.79601
20	4.47213	1..30102	42.77	1.63113	57.23	1.75762
30	5.47722	1.47712	45.65	1.65944	54.35	1.73519
40	6.32455	1.60205	48.86	1.68895	51.14	1.70876
50	7.07106	1.69897	55.15	1.74154	44.85	1.65176
60	7.74596	1.77815	59.05	1.77121	40.95	1.61225
70	8.36660	1.84509	64.51	1.80962	35.49	1.55010
80	8.94427	1.90308	68.77	1.83739	31.23	1.49457
90	9.48683	1.95424	76.79	1.88530	23.21	1.36567

Fig.6 (a)

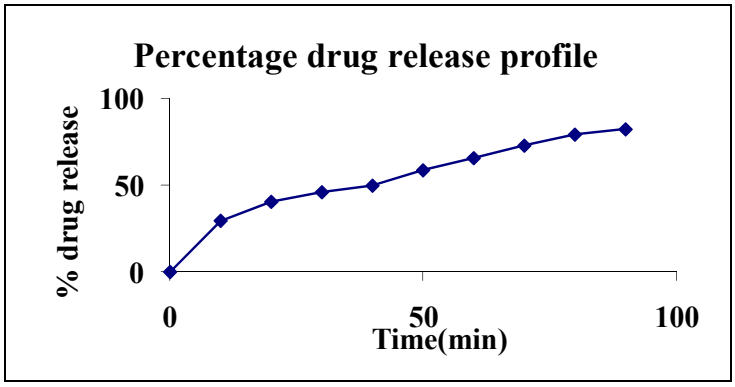


Fig.6 (b)

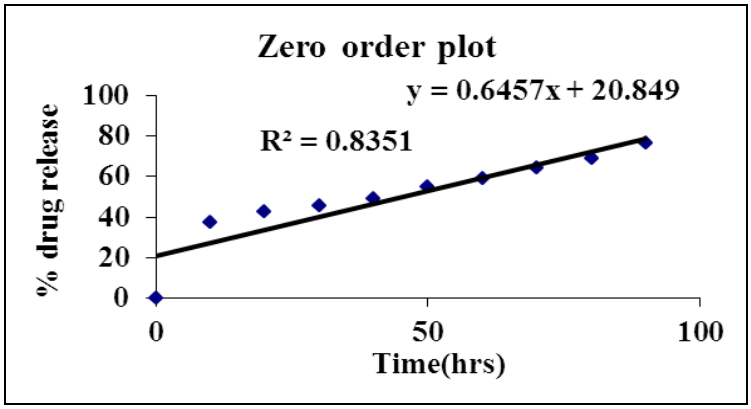


Fig.6 (c)

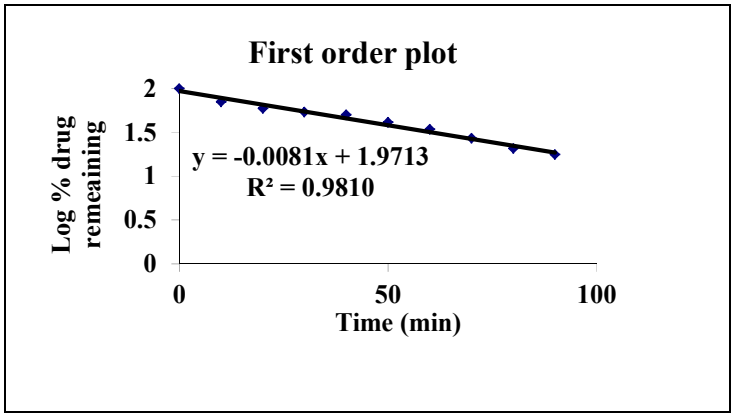


Fig.6 (d)

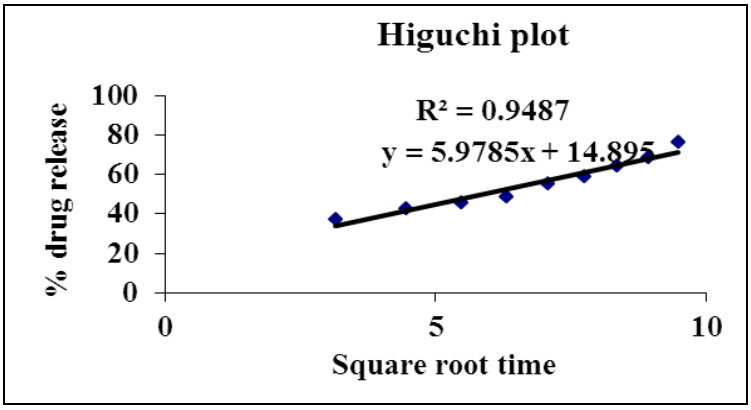

Higuchi plot
R² = 0.9487
y = 5.9785x + 14.895
% drug release
100
80
60
40
20
0
0
5
10
Square root time

Fig.6 (e)

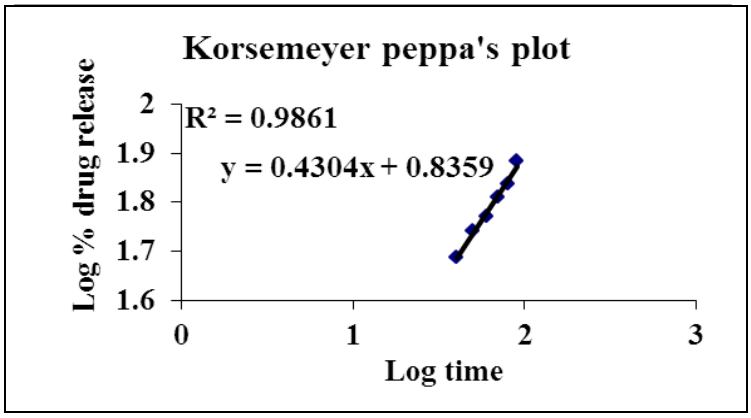

Korsemeyer peppa's plot
R² = 0.9861
y = 0.4304x + 0.8359
Log % drug release
2
1.9
1.8
1.7
1.6
0
1
2
3
Log time

Table: 36 *In-vitro* dissolution profile for solid dispersion F7 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	33.42	34.20	33.06	33.56±0.5827
20	39.70	39.15	40.45	39.86±0.8129
30	47.14	46.50	47.82	47.15±0.6601
40	55.93	56.02	54.29	55.41±0.9738
50	6.70	62.04	63.15	62.29±0.7583
60	69.28	69.32	71.32	69.96±1.1664
70	78.90	77.13	76.23	77.42±0.3584
80	84.24	84.32	85.14	84.56±0.4981
90	97.53	96.25	96.85	96.21±0.6404

Table: 37 Kinetic data for *in-vitro* release rates of solid dispersion F7 formulation

Time (min)	square root of time	log time	cumulative % drug release	Log cumulative % drug release	cumulative % drug remaining	log cumulative % drug remaining
0	0	0	0	0	100	2
10	3.16227	1	33.56	1.52582	66.44	1.82242
20	4.47213	1.30102	39.86	1.60053	60.14	1.77916
30	5.47722	1.47712	47.15	1.67348	52.85	1.72304
40	6.32455	1.60205	55.41	1.74358	44.59	1.64923
50	7.07106	1.69897	62.29	1.79441	37.71	1.57645
60	7.74596	1.77815	69.96	1.84484	30.04	1.47769
70	8.36660	1.84509	77.42	1.88885	22.58	1.35372
80	8.94427	1.90308	84.56	1.92716	15.44	1.18864
90	9.48683	1.95424	96.21	1.98322	3.79	0.57863

Fig.7(a)

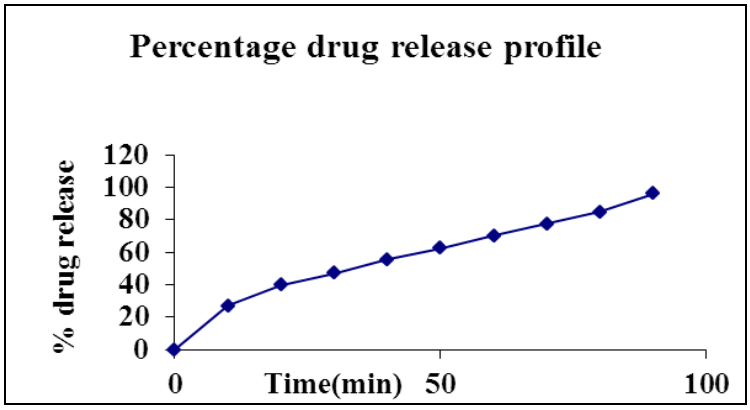


Fig.7(b)

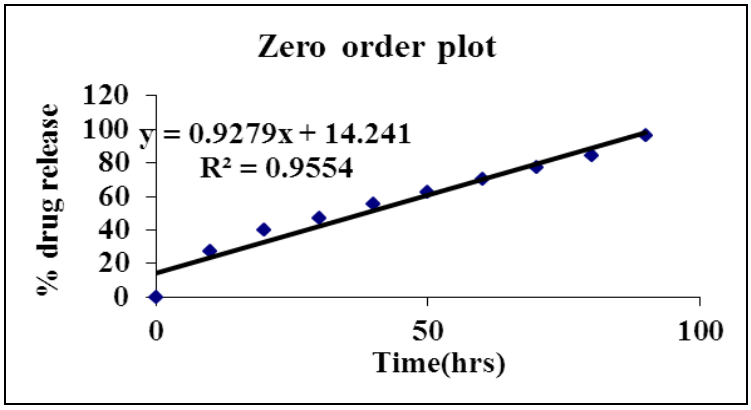


Fig.7 (c)

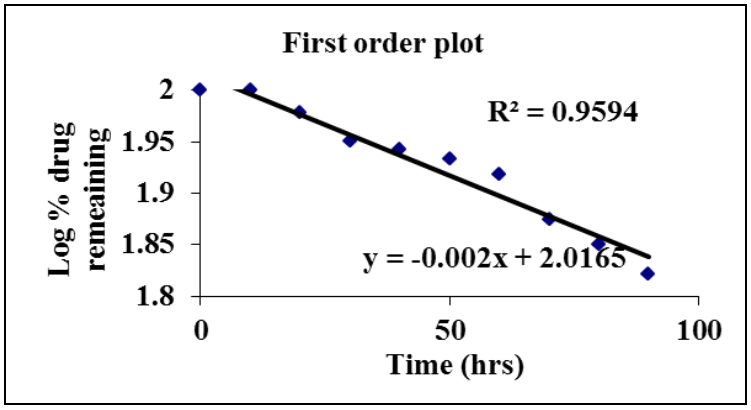


Fig.7 (d)

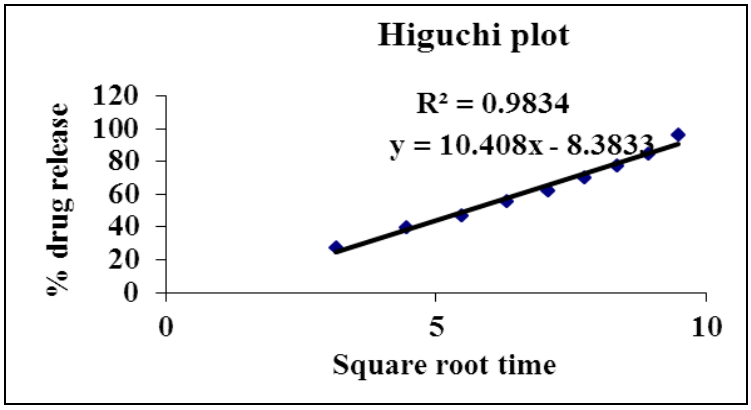

Higuchi plot
R² = 0.9834
y = 10.408x - 8.3833
% drug release
120
100
80
60
40
20
0
0
5
10
Square root time

Fig.7 (e)

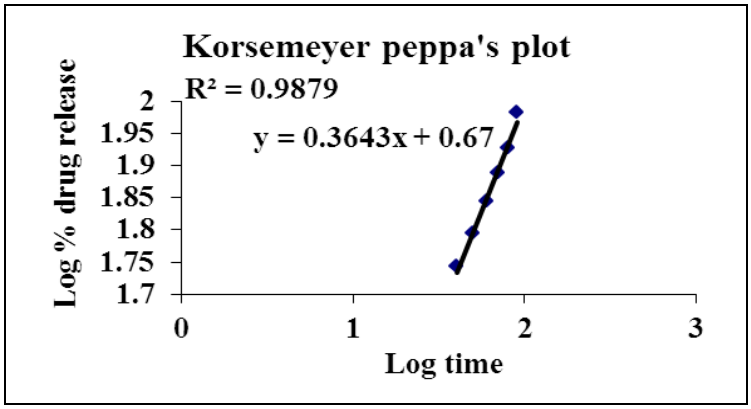

Korsemeyer peppa's plot
R² = 0.9879
y = 0.3643x + 0.67
Log % drug release
2
1.95
1.9
1.85
1.8
1.75
1.7
0
1
2
3
Log time

Table: 38 *In-vitro* dissolution profile for solid dispersion F8 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	44.44	42.29	45.37	44.03±1.5828
20	49.23	46.97	50.49	48.90±1.7853
30	55.20	54.32	55.76	55.10±0.7248
40	61.70	60.28	60.60	60.86±0.7413
50	68.94	68.23	70.31	69.16±1.0576
60	76.51	77.41	76.44	76.79±0.5437
70	83.52	87.02	85.46	85.33±0.7578
80	89.80	89.01	91.56	90.12±0.3077
90	93.14	93.67	93.76	93.52±.3384

Table: 39 Kinetic data for *in-vitro* release rates of solid dispersion F8 formulation

Time (min)	square root of time	log time	cumulative % drug release	log cumulative % drug release	cumulative % drug remaining	log cumulative % drug remaining
0	0	0	0	0	100	2
10	3.16227	1	44.03	1.64374	55.97	1.74795
20	4.47213	1.30102	48.90	1.68930	51.1	1.70842
30	5.47722	1.47712	55.10	1.74115	44.9	1.65224
40	6.32455	1.60205	60.86	1.78433	39.14	1.59262
50	7.07106	1.69897	69.16	1.83985	30.84	1.48911
60	7.74596	1.77815	76.79	1.88530	23.21	1.36567
70	8.36660	1.84509	85.33	1.93110	14.67	1.16643
80	8.94427	1.90308	90.12	1.95482	9.88	0.99475
90	9.48683	1.95424	93.52	1.97090	6.48	0.81157

Fig.8 (a)

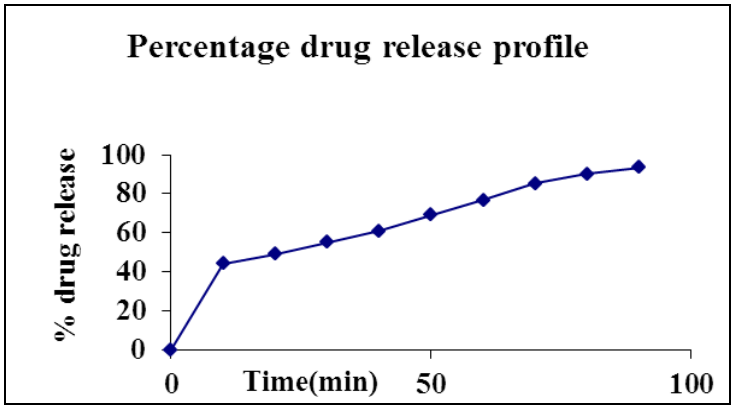


Fig.8 (b)

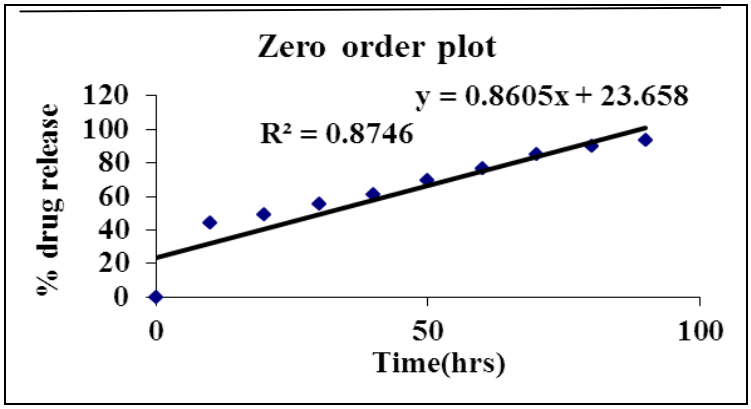


Fig.8 (c)

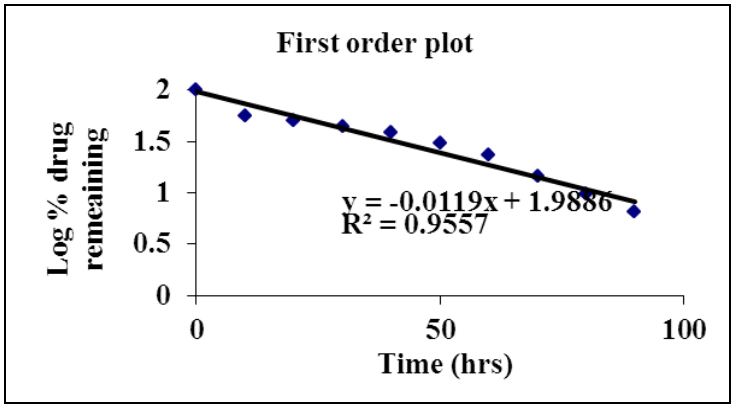


Fig.8 (d)

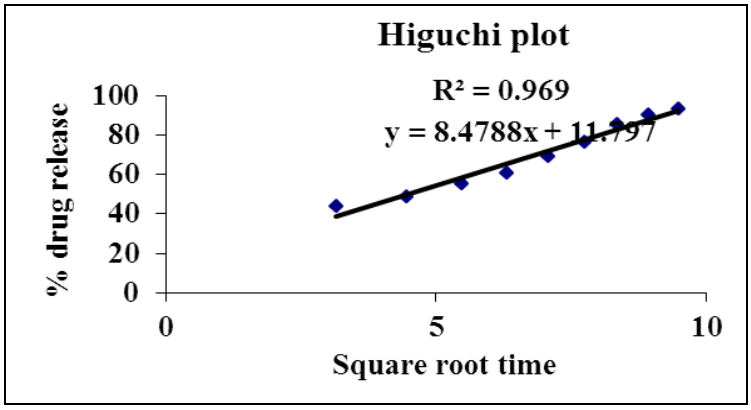

Higuchi plot
R² = 0.969
y = 8.4788x + 11.797
% drug release
100
80
60
40
20
0
0
5
10
Square root time

Fig.8 (e)

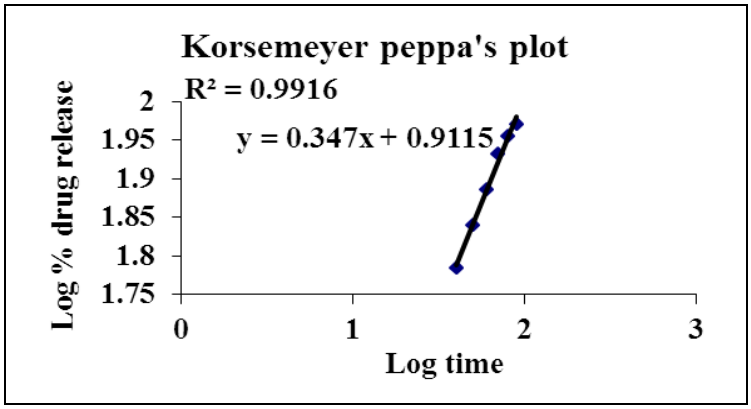

Korsemeyer peppa's plot
R² = 0.9916
y = 0.347x + 0.9115
Log % drug release
2
1.95
1.9
1.85
1.8
1.75
0
1
2
3
Log time

Table: 40 *In-vitro* dissolution profile for solid dispersion F9 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	30.82	31.14	30.77	30.91±0.200
20	36.55	35.98	37.08	36.53±0.550
30	42.91	44.05	43.35	44.43±0.574
40	64.46	64.08	63.80	64.11±0.331
50	70.24	69.63	70.16	70.01±0.331
60	75.22	74.81	75.39	75.14±0.296
70	80.08	79.77	80.29	82.04±0.261
80	86.88	87.30	87.74	87.30±0.430
90	91.09	90.77	91.38	91.08±0.305

Table: 41 Kinetic data for *in-vitro* release rates of solid dispersion F9 formulation

Time (min)	square root of time	log time	cumulative %of drug release	log cumulative %of drug release	cumulative %of drug remaining	log cumulative %of drug remaining
0	0	0	0	0	100	2
10	3.16227	1	30.91	1.40099	69.09	1.83941
20	4.47213	1.30102	36.53	1.56264	63.47	1.80256
30	5.47722	1.47712	44.43	1.64767	55.57	1.74484
40	6.32455	1.60205	64.11	1.80692	35.89	1.55497
50	7.07106	1.69897	70.01	1.84516	29.99	1.47697
60	7.74596	1.77815	75.14	1.87587	24.86	1.39550
70	8.36660	1.84509	82.04	1.91402	17.96	1.25430
80	8.94427	1.90308	87.30	1.94101	12.7	1.10380
90	9.48683	1.95424	91.08	1.9594	8.92	0.95036

Fig.9 (a)

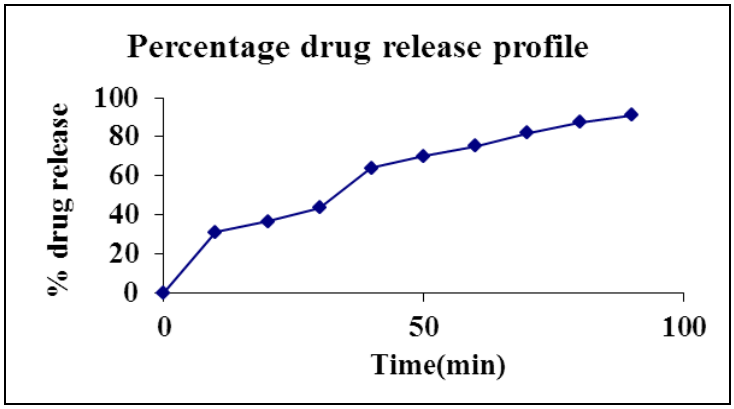


Fig.9 (b)

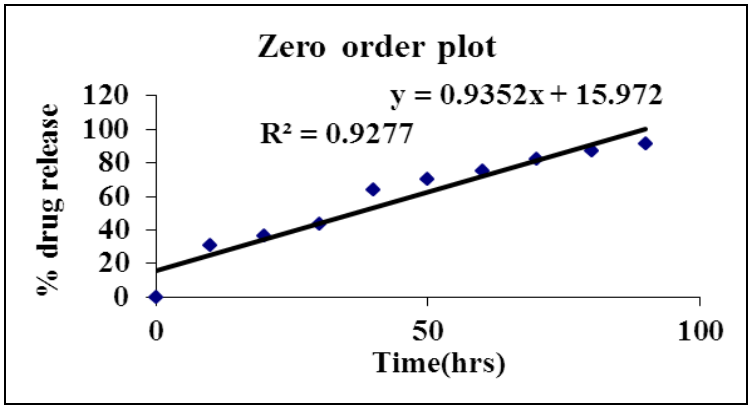


Fig.9 (c)

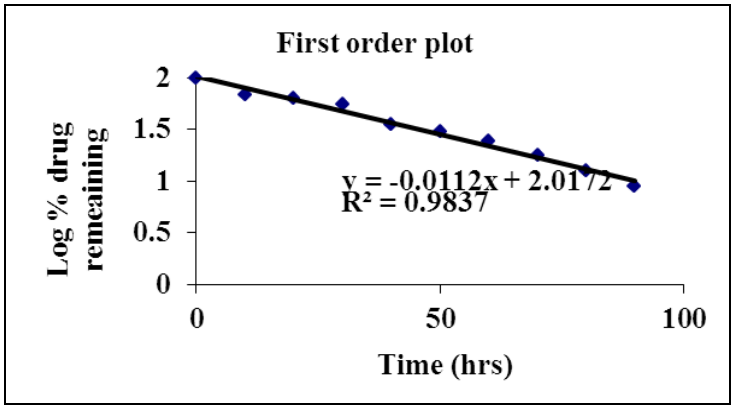


Fig.9 (d)

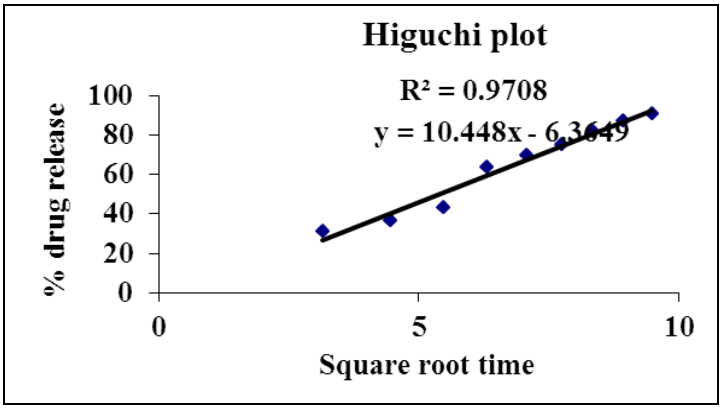

Higuchi plot
R² = 0.9708
y = 10.448x - 6.3649
% drug release
100
80
60
40
20
0
0
5
10
Square root time

Fig.9 (e)

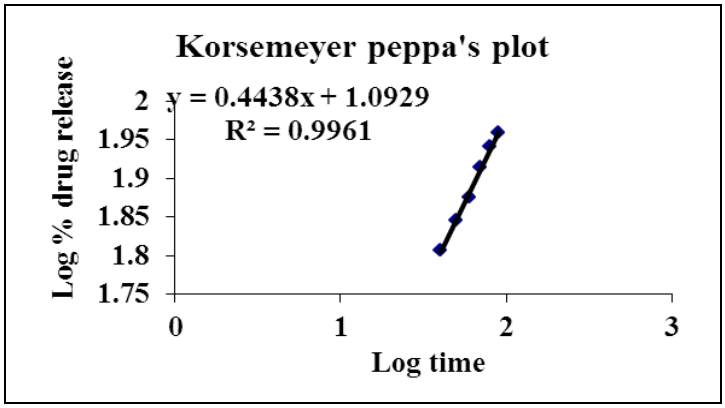

Korsemeyer peppa's plot
y = 0.4438x + 1.0929
R² = 0.9961
Log % drug release
2
1.95
1.9
1.85
1.8
1.75
0
1
2
3
Log time

Table: 42 *In-vitro* cumulative percentage of drug release of F1 to F9 formulations

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
10	30.25	41.16	25.38	15.02	29.55	37.48	33.56	44.03	30.91
20	38.09	50.85	38.23	24.55	40.51	42.77	39.86	48.90	36.53
30	44.03	53.81	39.86	37.81	46.05	45.65	47.15	55.10	44.43
40	52.60	56.40	42.87	40.51	49.78	48.86	55.41	60.86	64.11
50	59.17	57.85	49.22	48.77	58.66	55.15	62.29	69.16	70.01
60	66.42	60.53	55.09	56.39	65.69	59.07	69.96	76.79	75.14
70	73.12	69.43	59.26	61.66	72.24	64.51	77.42	85.33	82.04
80	78.17	73.12	64.71	67.68	79.24	68.77	84.56	90.12	87.30
90	82.22	75.19	69.71	72.14	82.29	76.79	96.21	93.52	91.08

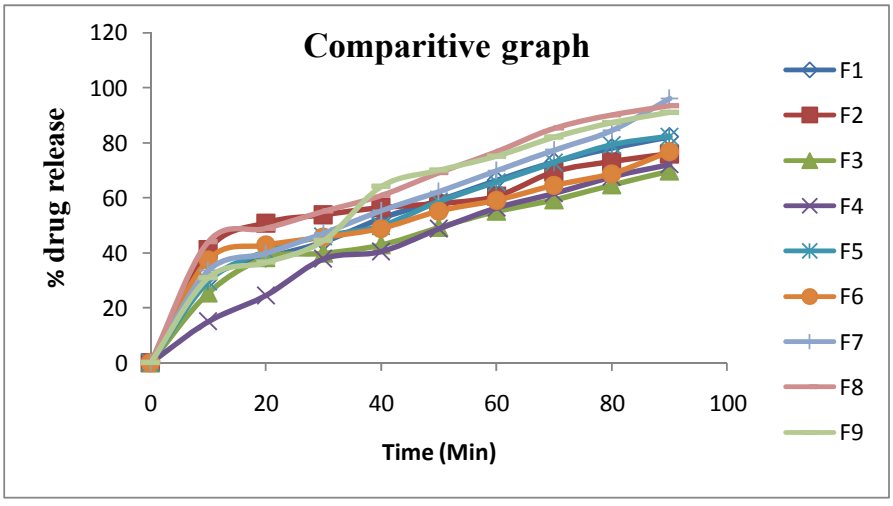


Fig.21

Table: 43 Kinetics of aceclofenac solid dispersions

Formulation code	Zero order ("r"values)	First order ("r" values)	Higuchi ("r" values)	Korsemeyar-Peppas	
				("r" values) values	"n"
Pure drug	0.9265	0.9728	0.9341	0.9819	0.2579
F1	0.9733	0.9879	0.9895	0.9972	0.3649
F2	0.768	0.9069	0.9316	0.9639	0.424
F3	0.8568	0.9656	0.9758	0.9987	0.3918
F4	0.9694	0.9882	0.9838	0.9932	0.3318
F5	0.9228	0.9805	0.9833	0.9932	0.3318
F6	0.8351	0.9810	0.9487	0.9961	0.4304
F7	0.9554	0.9594	0.9834	0.9879	0.3643
F8	0.8746	0.9557	0.969	0.9916	0.347
F9	0.9277	0.9837	0.9708	0.9961	0.4438

In- vitro release studies reveal that there is marked increase in the dissolution rate of aceclofenac from all the solid dispersions when compared to pure aceclofenac itself. From the *in-vitro* drug release profile, it can be seen that formulation F-7 containing PEG6000 and PVP (1:1:1 ratio of drug: PEG6000: PVP) shows higher dissolution rate compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier. The increase in dissolution rate is in the order of PEG6000:PVP > PEG6000:HPMC > PVP:HPMC. In the case of solid dispersions of aceclofenac with PEG6000, PVP, and HPMC ratio of 1:1:1, the dissolution rate of drug increased while in the case of those prepared in the ratio of 1:1 and 1:2 the dissolution rate of drug was decreased. This might be due to formation of viscous layer around the drug particles leading to decrease in the dissolution rate. The increase in dissolution rate is in the order of F7 >F8>F9 >F1>F5>F6>F2 >F4>F3. The regression coefficient (r) values for formulations F1 to F9 model that gave higher 'r' value was considered as best fit model. The r values were found to be higher in the first order model (0.9804, 0.9805, 0.9569, 0.9656, 0.9805, 0.9865, 0.9850, 0.9849, 0.9557, 0.9837) than those in the zero order model (0.9794,0.9265,0.868,08568,0.9228, 0.9328,0.9252,0.9454,0.8746,0.9277) with all the solid dispersion (pure aceclofenac, F1, F2, F3, F4, F5, F6, F7, F8 and F9 respectively) indicating that the dissolution of aceclofenac as such and from all the solid dispersion followed first order kinetics. Based on 'r' values (greater than 0.9527) it was also observed that all the solid dispersion followed Higuchi matrix suggesting the drug release is by diffusion. Korsemeyar-Peppa's suggest Fickian diffusion release which shows that the formulations also appear to release the drug by erosion mechanism and the release is drug dissolution limited. FTIR spectroscopic studies conducted for possible drug: carrier interactions FTIR spectra of pure drug aceclofenac, PEG6000, PVP, HPMC and aceclofenac with its solid dispersion were obtained which shows all the characteristic peaks of aceclofenac and carriers were present in the solid dispersions; thus indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its solid dispersion.

The solid dispersions of the water- insoluble drug aceclofenac were successfully prepared by solvent evaporation technique using hydrophilic carriers. The *in-vitro* dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure aceclofenac. Mechanisms involved are solubilization and improved

wetting of the drug in the hydrophilic carriers rich microenvironment formed at the surface of drug crystals after dissolution rate. The crystallinity of the drug was reduced in solid dispersion formulation with polymers i.e. PEG6000 and PVP combination.

9.0 CONCLUSION

Aceclofenac solid dispersions were prepared using PEG 6000, PVP and HPMC as carriers to improve the solubility of aceclofenac. Solid dispersion technique found to be effective in increasing the aqueous solubility of aceclofenac. *In-vitro* dissolution studies showed that in the dispersion systems containing the carriers, dissolution of aceclofenac were retarded, which attributed to ionic interaction and gel forming respectively. But solid dispersion containing as a carrier, gave faster dissolution rates than the pure drug. Solid dispersion of formulation (F7) aceclofenac, PEG 6000 and PVP combination prepared in (1:1:1) ratio showed excellent solubility and the dissolution rate found to be 96.21% was selected as the best formulation in this study. All the formulations described by the first order kinetics and the "n" values of peppa's suggest Fickian release mechanism. More ever , the crystallinity of the drug was reduced in solid dispersion formulation with carriers, results from FTIR spectroscopy concluded that there was no well-defined interaction between aceclofenac and carriers .Finally it could be concluded that solid dispersion of aceclofenac using hydrophilic carriers would improve the aqueous solubility, dissolution rate and thereby enhancing its systemic availability.

10.0 REFERENCES

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