PREPARATION AND USAGE OF PRE-GELATINIZED STARCH FOR ENHANCING THE SOLUBILITY OF WATER INSOLUBLE ANTI-INFLAMMATORY AGENT

Dissertation work submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the award of degree of

MASTER OF PHARMACY

(Pharmaceutics)

Submitted by

Ms. ASWATHY K.S

Under the guidance of

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Vice-Principal

Head, Department of Pharmaceutics

March 2009

COLLEGE OF PHARMACY

SRI RAMAKRISHNA INSTITUTE OF PARAMEDICAL SCIENCES

COIMBATORE – 641044

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Certificate

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Dr. M.G.R. Medical University, Chennai, under the direct supervision and guidance of **Dr. M. Gopal Rao, M.Pharm.,Ph.D.,** Department of Pharmaceutics, College of Pharmacy, SRIPMS, Coimbatore.

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Dr. M.G.R. Medical University, Chennai, under my direct supervision and complete satisfaction.

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ACKNOWLEDGEMENT

I consider it as a great honour to express my deep sense of gratitude and indebtedness to **Dr. M.Gopal Rao, M.Pharm.Ph.D.** Vice Principal and Head, Department of Pharmaceutics, who not only guided at every stage of this thesis, but also kept me in high spirits through his valuable suggestions and inspiration.

My sincere gratitude to our beloved Principal **Dr.T.K.Ravi, M.Pharm., Ph.D., FAGE.,** for providing every need from time to time to complete this work successfully.

I am elated to place on record my profound sense of gratitude to **Mr. K. Muthusamy, M.Pharm.,(Ph.D.), Assistant Professor** and **Mr. B. Rajalingam, M.Pharm., (Ph.D),** Assistant Professor for their constructive ideas for my project work

I owe my gratitude and thanks to **Mrs.M Gandhimathi. M.Pharm., (Ph.D), PGDMM, Assistant professor,** Department of Pharmaceutical Analysis for helping me to carry out the spectral studies.

I would like to thank **Mr. Ramakrishnan M.Sc., B.Ed., (Ph.D).**, **Mr. S. Muruganandham, Librarians** for their kind co-operation during this work.

I would like to thank **Ms. Geetha** and **Mrs. Kalaivani** for their kind co-operation during this work.

I wish to extend my thanks to **Sophisticated Test & Instrumentation Centre, Cochin** for timely carrying out the sample analysis.

My sincere thanks to **M/s. Saraswathi Computer Centre** for giving shape to this manuscript.

I submit my sincere thanks to our beloved Managing Trustee **Dr. R. Venkatesalu Naidu** for providing all the facilities to carry out this work.

Word's can't express my sincere gratitude and obligation to my dear batch mates **Shaik Rihana Parveen, Rubina Raichal, Thanu Malayan, Arthur Paul,**

Harikrishnan, Thangamuthu, Venkatesh, Chaitanya Kumar, Veerendra and to all other batch mates who directly or insinuately helped during my work. I would like to thank my room mates **Lini, Dency** and **Sini** who directly or insinuately helped during my work.

I submit my awesome thanks to my Seniors & Juniors for their support and co-operation during the course of my work.

I remain greatly indebted to my beloved **Parents** , **Brother** and **Sister** for their precious love, affection, prayers and moral support which guided me in the right path and are also the backbone for all successful endeavors in my life.

Above all, I humbly submit my dissertation work, into the hands of Almighty, who is the source of all wisdom and knowledge for the successful completion of my thesis.

ASWATHY K.S

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PURPOSE AND PLAN OF THE STUDY

Recent technological innovation of combinatorial chemistry and high-throughput screening can effectively discover the seeds of new drugs, which presents good pharmacological activities. However, since many seeds of new drugs discovered by those techniques are poorly water soluble, it is often difficult to adopt them as a candidate of new drug

Together with the permeability, the solubility behaviour of a drug is a key determinant of its oral bioavailability. It is estimated that more than 35% of the known drugs and more than 25% of the new discovered appear such problems.

In the present study Etodolac is the drug been selected, which is a member of the pyranocarboxylic acid group of non-steroidal anti-inflammatory drugs (NSAIDs). It is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide and aqueous polyethylene glycol.

Problems related to poor water solubility, slow dissolution and concomitantly low bioavailability can be overcome by using solid dispersions, a concept firstly introduced by Sekiguchi and Obi. Solid dispersions consist of a hydrophilic carrier in which a hydrophobic drug is incorporated. The carrier can be either crystalline or amorphous and the drug can be dispersed either molecularly, in amorphous particle or in crystalline particles. [1-3]

The main perspective of the present study aims at overcoming these problems by solid dispersion technology by using traditional carrier such as pregelatinized starch from their respective native starch of Potato, Tapioca and Maize. Pregelatinized starch is a modified starch that has been modified chemically or mechanically to rupture all or part of starch granules.[4] The objective of the present study is to prepare pregelatinized starch from three sources such as Potato, Tapioca and Maize by a known method. It is a low cost carrier. Tapioca is cultivated in many regions of Tamil Nadu. It is very cheap so that we can reduce the cost of production significantly.

The research work envisaged was:

1. Literature survey on Solid dispersion methods and carriers used for solid dispersion
2. Preparation, Characterization and evaluation of solid dispersions of Etodolac with PGS prepared from Potato, Tapioca and Maize.
3. Formulation and evaluation of Etodolac compressed tablets from selected Etodolac solid dispersion

INTRODUCTION

When the drug is administered in a solid dosage form such as tablet and capsule it must be released from the dosage form and dissolved in the gastrointestinal fluids before it can be absorbed. The bioavailability of poorly water soluble drugs is limited by their dissolution rates, which are in turn controlled by the surface area that they are present for dissolution. If the rate of dissolution of the drug is significantly slower than the rate of absorption, the dissolution of the drug becomes the rate limiting step in the absorption process, and the particle size of the drug is of great importance in the transport from the gastrointestinal tract to the site of action[5].

Consideration of the modified Noyes-Whitney equation[6,7] provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability:

$$\frac{dC}{dt} = \frac{AD(C_s - C)}{h}$$

where dC/dt is the rate of dissolution, “A” is the surface are 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 and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound. The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by

decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions.

Of these possibilities, changes in the hydrodynamics are difficult to invoke in vivo and the maintenance of sink conditions will depend on how permeable the gastrointestinal mucosa is to the compound as well as on the composition and volume of the lumenal fluids. Although some research effort has been directed towards permeability enhancement using appropriate excipients, results to date have not been particularly encouraging. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution; the likely magnitude of the food effect can be forecasted from dissolution tests in biorelevant media[8]. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches.

DEFINITION

Solid dispersion is defined as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or the melting-solvent method.

The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. The term

coprecipitate (more accurately *coevaporate)* has also been frequently used when a solid dispersion is prepared by a solvent method.

ADVANTAGES OF SOLID DISPERSIONS:

- Solid dispersion of drugs in solid state is helpful in stabilizing unstable drugs.
- The PEGs may protect certain drug e.g. cardiac glycosides against the decomposition by saliva and allow buccal absorption.
- Solid dispersions may be thermodynamically more active form of drug and directly influence the diffusion and release rate.
- An increased diffusion of steroid from the ointment was obtained. e.g. solid dispersion of prednisolone urea dispersion.
- Solid dispersion technology can be used to solidify liquid drugs.e.g. clofibrate and benzyl benzoate.

DISADVANTAGES OF SOLID DISPERSIONS:

- Tackiness and decommission during preparation and formulation.
- The oral administration of solid dispersions without concomitant reduction in dose may result in higher incidence of adverse effect. E.g. ulceration of indomethacin-PEG 6000 dispersion.
- Difficulty in pulverization of solid dispersion.
- Drug carrier incompatibility.
- Poor flow and mixing properties.
- Sifting of the solid dispersions, which are usually soft and tacky.

CLASSIFICATION OF SOLID DISPERSIONS

1. Simple eutectic mixtures

Solid eutectic mixtures are usually prepared by rapid cooling of a comelt of two components in order to obtain a physical mixture of very fine crystals of the two components. When the preparation is dissolved in aqueous medium the carrier will dissolve rapidly, releasing very fine crystals of drug which offers large surface area thereby improvement in dissolution is effected.[9,10]

2. Solid solutions

Solid solutions of a poorly water soluble drug dissolved in a carrier with relatively good aqueous solubility are of particular interest as a means of improving oral bioavailability. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions [11] and the dissolution rate are determined by the dissolution rate of the carrier. By judicious selection of a carrier, the dissolution rate of the drug can be increased by up to several orders of magnitude. Solid solutions can be classified according to two methods. First, they can be classified according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous).

A) Continuous and discontinuous solid solutions:

1. Continuous solid solutions

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

2. Discontinuous solid solutions

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited.

B) Substitutional crystalline, interstitial crystalline and amorphous solid solutions:

1. Substitutional crystalline solid solutions

Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules[12].

2. Interstitial crystalline solid solutions

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In

the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter[13]. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

3. Amorphous solid solutions

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou and Riegelman[14] were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose.

SOLID DISPERSION TECHNIQUES

1. Melting or fusion method

The melting or fusion method was first proposed by Sekiguchi and Obi[15] to prepare fast release solid dispersion dosage forms. In this method the physical mixture of drug and the water soluble carrier is heated directly until it is melted. The melted mixture is then cooled and solidified in an ice bath under vigorous stirring. The final mass was crushed, pulverized and sieved. The dispersion can also be cooled through the process of spray congealing using spray drying equipment. The melted material is sprayed onto cold metal surfaces, which forms pellet of the dispersion. This does

not require grinding and therefore no alteration of the crystal modification of the drug occurs. E.g. solid dispersion of sulphamethoxazole, acetaminophen, chloramphenicol, tolazamide, steroids.

Advantages

- Simplicity and economy.
- This method also advantageous for compounds, which do not undergo significant thermal degradation
- Super saturation of a solute or drug in a system can often be obtained by quenching of the melt rapidly from high temperature.

Disadvantages

- The main disadvantage of the melt method includes thermal degradation, sublimation and polymeric transformation, which can affect the physicochemical properties of the drug including its rate of dissolution.
- The temperature at which the dispersion solidifies affects crystallization rate and may alter both the size of the crystal and hardness of the dispersion. This may result in tacky or glassy and unmanageable dispersions, which will require storage at elevated temperature to facilitate hardening.

2. Solvent evaporation method

This method involves dissolving the drug and carrier in a suitable organic solvent followed by evaporation of the solvent to form solid dispersion involves dissolving the drug and carrier in a suitable organic

solvent followed by evaporation of the solvent to form solid dispersion. The mass was then stored in dessicator, pulverized and sieved. removal is accomplished by various means. The most common approach is the application of reduced pressure at a fixed temperature to evaporate the organic solvent. Temperatures of 125^0C for 25 minutes, 115^0C for one hour[16], -5^0c and reduced pressure followed by drying for 12 hours in vacuum have been used[17]. Spray drying is another approach by which solvent removal can be accomplished and it is probably the fastest way of removing solvent[18,19]. The freeze drying technique is also employed to prepare solid dispersions by removal of aqueous solutions[20,21]. E.g. solid dispersion of β-carotene-PVP, griseofulvin-PVP and reserpine-deoxy cholic acid.

Advantages

- The procedure is suitable for drugs that are thermo labile.
- The thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of the organic solvents.
- For aqueous system, frozen temperature can be used to evaporate the solvent, which can enhance the integrity of the drug.

Disadvantages

- Difficulty in complete removal of solvent.
- Finding a suitable solvent that will dissolve both the drug and carrier is very difficult.

- Plasticization of some polymers such as poly vinyl pyrrolidone has occurred with the use of some solvents.
- It is important that the rate of evaporation of a solvent is controlled so as to control the particle size of the drug. This in turn will affect the rate of dissolution of the drug in the solid dispersion.

3. Fusion-solvent method

In the fusion solvent method, a carrier(s) is/are melted and the drug(s) is/are incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for removal is eliminated. This method is particularly useful for drugs that have high melting points are that are thermo labile. The feasibility of the method has been demonstrated for spironolactone and griseofulvin dispersions in polyethylene glycol 6000(PEG 6000) [22]. E.g. solid dispersion of clofibrate, methyl salicylate, benzyl benzoate.

MECHANISM OF INCREASED DISSOLUTION RATE BY SOLID DISPERSION SYSTEM

- In the case of glass solutions, and amorphous dispersions, particle size is reduced to a minimum level. This can result in an enhanced dissolution rate due to both an increase in surface area and solubilization.
- The carrier material as it dissolves may have a solubilization effect on the drug.

- The carrier material may also have an enhancing effect on the wettability and dispersibility of the drug in the dissolution medium. Then should retard any agglomeration or aggregation of the particles, which can slow the dissolution process.
- Formation of metastable dispersion that has a greater solubility would result in faster dissolution rates.[23]

APPROACHES TO IMPROVE THE SOLUBILITY OR TO INCREASE THE AVAILABLE SURFACE AREA FOR DISSOLUTION

I. Physical modifications

- Particle size [23]
  - o Micronization
  - o Nanosuspensions
- Modifications of the crystal habit
- Polymorphs
- Pseudo polymorphs (including solvates)
- Complexation/solubilization
  - o Use of surfactants
  - o Use of cyclodextrines
- Drug dispersion in carriers
  - o Eutectic mixtures
  - o Solid dispersions (non-molecular)
  - o Solid solutions

II. Chemical modification

- Soluble prodrugs
- Salts

CARRIERS USED FOR SOLID DISPERSION SYSTEMS

1. Polyethylene glycols (PEGs) [23]
2. Polyvinylpyrrolidone (PVP)
3. Polyvinyl groups

o Polyvinyl alcohol (PVA)

o Crospovidone

o Polyvinylpyrollidone-polyvinylacetate copolymer (PVP-PVA)

4. Cellulose derivatives

o Hydroxypropylmethylcellulose (HPMC)

o Hydroxypropylcellulose (HPC)

o Carboxymethylethylcellulose (CMEC)

o Hydroxypropylmethylcellulose phthalate (HPMCP)

5. Polyacrylates and polymethacrylates

o Eudragit E

o Eudragit L

6. Urea
7. Sugar, polyols and their polymers

o Dextrose

o Sucrose

8. Emulsifiers

- o Sodium Lauryl Sulphate
- o Tween 80

9. Organic acids and their derivatives

- o Succinic acid
- o Citric acid

10. Other carriers

- o Phospholipid
- o Pentaerythritol

11. Modified starches

a) Pregelatinized (pregelled) starch

b) Chemically modified starches

- o Hydroxy ethyl starch
- o Hydroxy propyl starch
- o Sodium starch glycolate

MODIFIED STARCHES

There have been numerous attempts to modify starch to improve different properties, mostly for use in commercial food products. The types of modifications used can be classified as either physical(no new chemical bonds formed) or chemical (new chemical bonds formed).Some types of modified starches may require both chemical and physical modification.[24]

Pregelatinized (Pregelled) Starch

When starch is heated eventually the pressure inside the starch grain will increase to such an extent that the grain ruptures. When the

starch grain is ruptured the inner amylose component of the starch is no longer totally encapsulated by the outer amylopectin layer, and this has significant implications for the physical properties of the starch.

The rupture of the starch grain is referred to a gelatinization, and the temperature at which it occurs is known as gelatinization temperature. This temperature varies according to the botanical source of the starch. It is not a sharp change with temperature but typically occurs over a rang of 10 ^{0}C-15^{0}C.

If starch grains are heated in air to a suitable temperature , the grains will still rupture but, in the absence of a suitable medium to dissolve the amylose, the amylose will remain mostly inside the amylopectin sacs. Such starches are referred to as pregelatinized or pregelled starches. Examined under the microscope the ruptured starch grains will have a characteristic slit in the amylopectin coat. Depending on the temperature used and the time of exposure of the starch grain to the heat, it is possible to obtain starches that are pregelatinized to different extents. The extent of pregelatinization has a major influence on their physical properties and thus their suitability for use in different applications.

One property that is changed and has implications for use in tablet formulations is the solubility of the pregelatinized starch. Fully pregelatinized starches are cold water soluble and have little or no disintegrant activity. Indeed they may retard disintegration and dissolution, particularly after aqueous granulation. The compactilibility of fully pregelatinized starch is also poor. It is used as a wet granulation binder.

By contrast, partially pregelatinized starches have good compaction properties and retain adequate disintegrant activity. They may be used in direct compression formulations as both a filler / binder and as a disintegrant. The typical grades of partially pregelatinized starch used in the pharmaceutical industry are about 20% pregelatinized.

Partially pregelatinized starch may be used as a direct compression binder/filler and as a disintegrant. Use levels as a direct compression disintegrant are typically around 15% by weight. It can be used at higher as a direct compression binder/filler.[24]

Chemically Modified Starches

Three chemically modified starches that are used in pharmaceutical formulations are hydroxyl ethyl starch, hydroxyl propyl starch, and sodium starch glycolate. The permitted modifications are acid-modified, bleached, oxidized, esterified, etherified or modified enzymatically. The stated intent of these modifications is to change the functionality of the starch.[24].

NON – STEROIDAL ANTI-INFLAMMATORY DRUGS

Non- steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used for all therapeutic agents. They are frequently prescribed for 'rheumatic' musculoskeletal complaints and are often taken without prescription for minor aches and pains.

NSAIDS include a variety of different agents of different chemical classes. Most of these drugs have three major types of effect.

- Anti-inflammatory effects: Modification of the inflammatory reaction.
- Analgesic effect: reduction of certain sort of pain
- Antipyretic effect: lowering of a raised temperature.

In general, all of these effects are related to the primary action of the drugs-inhibition of arachidonate cyclooxygenase (COX) and thus inhibition of the production of prostaglandins and thromboxanes, though some aspects of the action of individual drugs may occur by different mechanisms.[25]

ANTIPYRETIC EFFECTS

Normal body temperature is regulated by a centre in the hypothalamus which ensures a balance between heat loss and heat production. Fever occurs when there is a disturbance of this hypothalamic 'thermostat' that leads to the set point of body temperature being raised. NSAIDs reset the thermostat. The mechanisms of the antipyretic action of

the NSAIDs are thought to be due largely to inhibition of prostaglandin production in the hypo-thalamus.

ANALGESIC EFFECT

NSAIDs are mainly effective against pain associated with inflammation or tissue damage because they decrease production of the prostaglandins that sensitive nocicepters to inflammatory mediators such as bradykinin. Therefore they are effective inarthritis, bursitis, pain of muscular and vascular origin, toothache, dysmenorrhoea, the pain of postpariem states and the pain of cancer metastasis in bone, all conditions that are associated with increased prostaglandin synthesis. There is some evidence that they have a central effect by an action mainly in the spinal cord.Clinical data indicate that certain NSAIDs are effective in the control of some types of severe pain unrelated to inflammation.

ANTI – INFLAMMATORY EFFECT

Drugs such as the NSAIDs reduce mainly those components of the inflammatory and immune response in which the products of COX-2 action play a significant part, namely:

- Vasodilatation
- Oedema
- Pain

COX inhibitors, per se, have no effects on those processes that contribute to tissue damage in chronic inflammatory conditions such as rheumatoid arthritis, vasuclitis and nephritis. Infact, because some

prostaglandins decrease lysosomal enzyme release reduces the generation to toxic O_2 products inhibit lymphocyte activation, NSAIDs could actually exacerbate tissue damage in the long term.

CLASSIFICATION OF NSAIDs

The various analgesic –antipyretic anti-inflammatory agents are classified as[26]

1. Acidic Drugs

a. Salicylates:

E.g. Salicylic acid, Apirin

b. Para-amino phenols:

Eg:Paracetamol

c. Pyrazolones:

Eg: Phenylbutazone, Suxibuzone

d. Indole acetic acids:

Eg:Indomethacin, clamidoxic acid

e. Propionic acids:

Eg: Ibuprofen, Diclofenac

f. Aryl anthranilic acids:

Eg: Meclofenamic acid, Tolfenamic acid

g. Miscellaneous agents:

Eg: Piroxicam, Fenoxicam

2. Basic Drugs

Eg: Timegadine, inhibits neutrophil degranulation and superoide production

2. Non-Acidic Drugs:

Eg: Indoxole Nictimodole

CLASSIFICATION OF NSAIDs BY CHEMICAL STRUCTURE:

1. Carboxylic Acid Groups:

- Salicylates (Acetylsalicylate, Choline Salicylate, Diflunisal, Magnesium choline Salicylate, Magnesium Salicylate, Salsa late)
- Acetic Acids (Diclofenac sodium, Diclofenac potassium, Etodolac, Indomethacin, Ketorolac, Nabumetone, Sulindac, Tolmetin)
- Propionic acids (Carprofen, Fenoprofen, Flubiprofen, Ibuprofen, Ketoprofen, Loxoprofen, Naproxen, Naproxen sodium, Oxaprozin, Vedaprofen)
- Anthranilic acids (Meclofenamic acid, Meclofenamate sodium, Tolfenamic acid)
- Phenylacetic acids (Acetaminophen)
- Amino nicotinic acids (Flunixin)
- Indole Analogs (Indomethacin, Nabumetone, Ketorolac, Etodolac,)

2. Enolic Acid Groups (which doesn't have carboxylic group but acid due to the enolic Hydroxy substituent)

- Pyrazolones (Phenylbutazone, Oxyphenbutazone, Dipyrone, Ramifenazone)
- Oxicams (Aceclofenac, Piroxicam, Tenoxicam)

3. Coxibs

Celecoxib, Rofecoxib, Vladecoxib, Parecoxib, Etoricoxib

4. Gold Salts

Auranofin, Gold sodium thiomalate, Aurothioglucose

MECHANISM OF ACTION

The main action of NSAIDs is inhibition of arachidonate cyclo oxygenase. COX is a bifunctional enzyme, having two distinct activities, the main cyclo-oxygenase action which gives PGG2, and a peroxidase action which converts PGG2 to PGH2. Different NSAIDs inhibit the enzyme by different mechanisms.

BIOSYNTHESIS OF PROSTAGLANDINS

The biochemical effect of NSAIDs includes inhibition of lysosomal membrane stabilization, inhibition of the biosynthesis of mucopolysaccharides, uncoupling oxidative phosphorylation, fibrinolytic activity, sulfahydryl disulfide stabilization. Collagenase production and at times suppression of lymphocytic functions.

Cyclooxgenase catalyses two enzymatic process

- The incorporation of oxygen in a dioxygenase step to form PGG2.
- The subsequent peroxidation to PGH2. The reaction is initiated by the stereospecific abstractin of hydrogen at C_{13} followed by oxygen attach at C_{11} and C_{15}.
- Most of NSAIDs act by inhibiting cyclooxygenase by preventing the abstractin of hydrogen from C_{13} and therefore peroxidatin at C_{11} and C_{15}.

Prostaglandins potentiate the early inflammatory response causing vasodilatation, increases permeability, facilitating cellular infiltration land sensitizing the pain receptors to bradykinin. The NSAIDs inhibit both the synthesis and release of prostaglandins.

ADVERSE EFFECTS

1. Side effect that occurs at analgesic dose (0.3-1.5g/day)

Nausea, vomiting, epigastric distress, increased occult blood loss in stools. The most important adverse effect of NSAIds is gastric mucosal damage and peptic ulceration.

2. Hypersensitivity and idiosyncrasy

Though infrequent, there can be serious reactions, which include rashes, urticaria, rhinorrhea, angiodema, asthama and anaphylactic reaction. Profuse gastric bleeding occurs in rare instance.

3. Anti – inflammatory dose (1-2g/day)

It will produce the syndrome called salicylism- dizziness, tinnitus, vertigo, reversible impairment of hearing and vision, excitement and mental confusion, hyperventilation and electrolyte imbalance.

4. Gastric Mucosal Damage

All NSAIDs to varying extent produce gastric pain, mucosal erosion or ulceration and blood loss.

5. Renal effect

Conditions leading to hypovolemia, decreased renal perfusion and Na^+ loss induce renal prostaglandin synthesis which brings about intra renal adjustment by promoting vasodilation, inhibiting tubular reabsorption and opposing ADH action.[26]

DRUG PROFILE

Etodolac

Etodolac is a member of the pyranocarboxylic acid group of nonsteroidal anti-inflammatory drugs (NSAIDS). Etodolac is a racemic mixture of [+] S and [-] R enantiomers.[27]

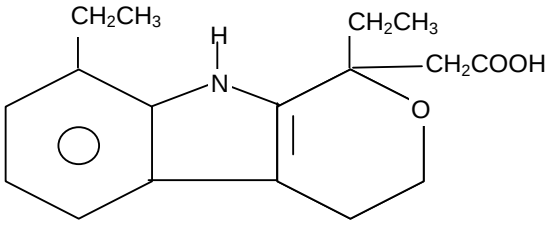
Chemical Name

(±) 1,8- diethyl - 1,3,4,9 - tetrahydropyrano - [3,4 -b] indole - 1-acetic acid.

Molecular Formula

$C_{17}H_{21}NO_3$

Chemical Structure



Characteristics

A white or almost white, crystalline powder,practically insoluble in water, freely soluble in alcohols, acetone, chloroform, dimethyl sulfoxide and aqueous polyethylene glycol.[27]

Table:1 Typical Properties of Etodolac

Melting Point	144 ^{0} C-150 ^{0}C
Molecular Weight	287.36
pKa	4.65
N-octanol: Water partition coefficien	11.4 at pH 7.4
Hygroscopicity	Non-hygroscopic

CLINICAL PHARMACOLOGY

Pharmacodynamics

Etodolac is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic and antipyretic activities in animal models. The mechanism of action of Etodolac, is not completely understood, but may be related to prostaglandin synthetase inhibition.

Etodolac is a racemic mixture of [-] R and [+] S Etodolac. As with other NSAIDs, it has been demonstrated in animals that the [+] S form is biologically active.Both enantiomers are stable and there is no [-] R to [+] S conversion invivo.[28]

PHARMACOKINETICS

Absorption

Based on mass balance studies, the systemic availability of Etodolac from either the tablet or capsule formulation is atleast 80%. Etodolac doesnot undergo significant first-pass metabolism following oral

administration. Mean peak plasma concentration (Cmax) range from approximately 14 ± 4 to 37 ± 9 mcg/ml after 200 to 600 mg single doses and are reached in 80 ± 30 minutes. The extent of absorption of Etodolac is not affected when Etodolac is administered after a meal. Food intake, however reduces the peak concentration reached by approximately one-half and increases the time to peak concentration by 1.4 to 3.8 hours.

Distribution

The mean apparent volume of distribution of Etodolac is approximately 390ml/kg. Etodolac is more than 99% bound to plasma proteins, primarily to albumin. The free fraction is less than 1% and is independent of Etodolac total concentration over the dose range studied.

Metabolism

Etodolac is extensively metabolized in the liver. The metabolites include 6,7 and 8-hydroxylated Etodolac and Etodolac glucuronide.

Excretion

The mean oral clearance of Etodolac following oral dosing is 4 (± 16) ml/h/kg. Approximately 1% of a Etodolac dose is excreted unchanged in the urine with 72% of the dose excreted into urine as parent drug plus metabolite

Etodolac unchanged 1%
Etodolac glucuronide 5%
Hydroxylated metabolites(6,7 and 8-OH) 13 %
Hydroxylated metabolite glucuronides 20%
Unidentified metabolities 33%

The terminal half-life(t½) of Etodolac is 6.4 hours.Fecal excretion accounted for 16% of the dose.[28]

Indications and usage

Etodolac tablets are indicated:

For acute and long term use in the management of signs and symptoms of the following:

1. Osteoarthritis.
2. Rheumatoid arthritis.
3. Juvenile rheumatoid arthritis.

For the management of acute pain

Contraindications

- Treatment of peri-operative pain in setting of coronary artery bypass graft surgery
- Hypersensitivity to Etodolac
- Patients who have experienced asthma,urticaria,or allergic-type reactions after taking Aspirin or other NSAIDs; severe , even fatal anaphylactic like reactions have been reported.

Drug Interactions

Etodolac diminish the antihypertensive effect of ACE inhibitors. Antacids can decrease the peak concentration of Etodolac reached by 15% to 20% but have no detactable effect on the time to peak. When Etodolac is administered with aspirin, its protein binding is reduced,

although clearance of free Etodolac is not altered. Etodolac through effects on renal prostaglandins may cause changes in the elimination of cyclosporine, Digoxin and Methotrexate leading to elevated serum levels and increased toxicity.Nephrotoxicity associated with cyclosporine may also be enhanced. Etodolac can reduce the natriuretic effect of Furosemide and thiazides in some patients, an elevation of plasma lithium levels;phenylbutazone causes increase in the free fraction of Etodolac. The effects of Warfarin and Etodolac on GI bleeding are synergistic.

Adverse drug reactions

Common

1. Cardiovascular: edema
2. Gastro intestinal: Abdominal pain, Diarrhoea, Flatulence, Indigestion, Nausea
3. Neurologic : Dizziness
4. Other: Malaise

Serious

1. Cardiovascular : CHF,hypertension,MI
2. Dermatologic : Scaling eczema,stevens-Johnson syndrome
3. Gastro intestinal : Gastro intestinal haemorrhage,Gastro intestinal perforation,Inflammatory disorder of digestive tract
4. Haematologic : Agranulocytosis,anaemia,thrombocytopenia
5. Hepatic : Hepatitis, Jaundice

6. Immunologic : Anaphylactoid reaction,immune hyper sensitivity reaction.
7. Neurologic : Cerebrovascular accident
8. Renal : papillary necrosis,renal failure.
9. Respiratory : bronchospasm.[28]

DOSE AND ADMINISTRATION

Analgesia

The recommended total daily dose of Etodolac for acute pain is upto 1000mg,given as 200-400 mg every 6 to 8 hours.

Osteoarthritis and Rheumatoid arthritis

The recommended starting dose of Etodolac for the management of the signs and symptoms of osteoarthritis or rheumatoid arthritis is : 300 mg b.i.d, t.i.d or 400 mg b.i.d or 500 mg b.i.d. A lower dose of 600 mg/day may suffice for long-term administration.[28]

Administration : Oral

POLYMER PROFILE

PRE-GELATINIZED STARCH

1. Nonproprietary names

BP: Pregelatinized starch

Ph Eur : Amylum pregelificatum

USPNF : Pregelatinized starch[29]

2. Synonyms

Compressible starch ; Instastarch ; Lycatab C ; Lycatab PGS; Merigel ; National 78-1551 ; Pharma-Gel ; Prejel ; Sepistab ST 200 ; Spress B820 ; Starch 1500 G ; Tablitz ; Unipure LD ; Unipure WG220[29]

3. Chemical Name

Pregelatinized starch

4. Empirical formula Molecular weight

$(C_6H_{10}O_5)_n$ Where n = 300-1000

5. Composition

Free amylose 5%

Free amylopectin 15%

Unmodified starch 80%

6 Functional category

Tablet and capsule diluent, tablet and capsule disintegrant, tablet binder.

7. Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.[29]

8. Table : 2 Types of starch used

Starch	Botanical source	Comments
Maize(corn)	*Zea mays*	The traditional starch used in the formulation of tablets. Widely used
Potato	*Solanum tuberosum*	Has also been used for many years in tablet manufacture. Less widely used than corn starch
Tapioca	*Manihot esculenta*	Appears to be comparable to rice starch in many respects.

9. Typical properties

Acidity/alkalitinity : pH = 4.5-7.0 for a 10% w/v aqueous dispersion.

Angle of repose : 40.7^{0}

Density(bulk) : $0.586 g/cm^3$

Density (tapped) : $0.879 g/cm^3$

Density (true) : $1.516 g/cm^3$

Flowability : 18-23%

Moisture content : Pregelatinized starch is hygroscopic.

Specic surface area : $0.26 m^2/g$

Viscosity (dynamic) : 8-10 mPa s (8-10 cP) for a 2% w/v aqueous dispersion at $25\ ^{0}C$ [29]

10. Solubility

Practically insoluble in organic solvents.Slightly soluble in cold water, depending upon the degree of pregelatinization.Pastes can be prepared by sifting the pregelatinized starch into, stirred ,cold water.Cold water-soluble matter for partially pregelatinized starch is 10-20%.

11. Preparation of pregelatinized starch

An aqueous slurry (100 ml) of starch (40%) w/v containing 1% Tween-80 was heated to 65^0C with continuous stirring until the starch gelatinizes and produces a viscous translucent mucilage. The viscous mucilage was then dehydrated by the addition of acetone while stirring and the solids separated were collected by filtration and further dried at 45^0C for 2 hrs. The dried mass obtained was crushed, pulverized and sifted through mesh no.120.

12. Stability and storage conditions

PGS is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

13. Safety

PGS and starch are widely used in oral solid dosage formulations. PGS is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of massive amounts of PGS may be harmful.

14. .Applications in pharmaceutical formulation or technology

1. PGS is a modified starch used in oral capsule and tablet formulations as a binder, diluent and disintegrant.
2. Grades of pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry-compression process.
3. PGS may also be used in wet granulation processes.[29]

REVIEW OF LITERATURE

- Vijayakumar SG *et al*., [38] (2005) have studied the improvement of aqueous solubility and dissolution rate by preparing physical mixture and solid dispersion with skimmed milk . Enhancement of aqueous solubility of MLX was observed with solid dispersion of the drug with skimmed milk due to amino acids and surface active agents content in the milk, which can be used for the treatment of gastric disturbance. Rotary vacuum evaporation technique was used to prepare solid dispersion. Results showed that the solubility of solid dispersion of the drug was almost three times greater than the pure drug. Similarly, the solid dispersion of the drug indicated a significant improvement in the dissolution of the drug as compared to the physical mixture and the pure drug. Differential scanning calorimetry, X-ray diffraction and scanning electron microscopic analysis revealed the formation of solid dispersion of the drug with skimmed milk.

- Okonogis *et al.,*[39] (2006) have studied the dissolution improvement of high drug loaded solid dispersion system consisting of drug, carrier and surfactant. Solid dispersions of a water-insoluble ofloxacin (OFX) with polyethylene glycol (PEG) of different molecular weights, namely binary solid dispersion systems, were prepared at drug to carrier not less than 5:5. Polysorbate 80, a

nonionic surfactant, was incorporated into the binary solid dispersion systems as the third component to obtain the ternary solid dispersion systems. The powder x-ray diffraction and differential scanning calorimetric studies indicated that crystalline OFX existed in the solid dispersions with high drug loading. However, a decreased crystallinity of the solid dispersions obtained revealed that a portion of OFX was in an amorphous state. The results indicated a remarkably improved dissolution of drug from the ternary solid dispersion systems when compared with the binary solid dispersion systems. This was because of polysorbate 80, which improved wettability and solubilized the non–molecularly dispersed or crystalline fraction of OFX.

- MM Patel and DM Patel [40] (2006) were prepared solid dispersions of Valdecoxib with Mannitol, poly ethylene glycol 4000, and PVP K-12 with a view to increase its water solubility. Valdecoxib solid dispersion with polyvinyl pyrolidone K-12 showed maximum drug release hence, the tablet formulation containing valdecoxib polyvinyl pyrolidone K-12 solid dispersion, was prepared with a view to improve its water solubility. The dissolution profile of best laboratory developed formulation (F1) was compared with marketed tablet products. The drug release profile was studied in 0.1 N HCL. F1 gave far better dissolution than the conventional marketed tablet, which released only 44.3% drug and valdecoxib in

b cyclodextrin, which released 53.4% drug in 20 min, while F1 exhibited almost 100% drug release in 20 min. The dissolution efficiency of F1 was compared with pure drug, conventional market tablet, and valdecoxib in **b** cyclodextrin. F1 showed maximum dissolution efficiency. F1 was considered better than valdecoxib in **b** cyclodextrin, as far as the cost of raw materials used in the product is concerned. F1 was subjected to stability studies. The formulation was found to be stable for 4 weeks at 45°, with insignificant change in the hardness, disintegration time, and in vitro drug release pattern.

- Wang *et al.,*[41] (2006) have studied the oral composition and preparative methods of solid dispersion of glibenclamide. The solid dispersion containing glibenclamide 2-60% and disperse medium 98-40% by the ratio of weight. The glibenclamide disperse in the disperse medium by the form of unformed, molecule or microcrystal. The solid dispersion can be prepared by the methods of triturate, fusion or spray drying. According to the preparative methods of said, the solid dispersion of glibenclamide is harmless and pollution-free. And the operation of methods is conveniently. The solid dispersion can improve the solubility materially, improve the bioavailability and the stability of thermodynamics of preparation of glibenclamide.

- Barakat NS *et al*.,[42] (2006) have studied the formation of melt dispersion as an effective method of increasing the dissolution rate of poorly soluble drugs and of improving the bioavailability. The carrier fusion method was used to prepare different dispersion of etodolac using Gelucire 44/14 and D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). The physical characteristics of the binary systems were determined by differential scanning calorimetry (DSC), infrared spectroscopy (IR). The release rate from the resulting dispersion was determined from dissolution studies by use of USP dissolution apparatus II (paddle method). The dissolution rate of etodolac is increased in all the dispersion systems compared to that of pure drug. A liquid dispersion system of etodolac (20%) and Gelucire 44/14: TPGS blend (80%), in different ratios, was also prepared. The capsule formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines. Physical and chemical properties of the dispersion didn't change during a period of storage at room temperature and at 4 degrees C, 0% RH. It was found that etodolac was chemically stable against the effects of temperature and humidity. However, the relative humidity and storage time exerted an effect on the dissolution behavior of etodolac. The changes in dissolution behavior after storage under conditions of high humidity and temperature might be related to the formation of etodolac

microcrystal and to water absorption by the carrier during storage. It is predicted that acceptable shelf-lives should result when moisture-resistant packaging is used for pharmaceutical formulations of this type.

- Uchino T *et al*.,[43] (2007) were prepared solid dispersions of Spironolactone with porous silica (sylysia 730 and sylysia 350) by the solvent method. The physicochemical properties of the prepared solid dispersions were evaluated by powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and atomic force microscopy (AFM). The results of PXRD and DSC data in the solid dispersion of the Sylysia 350:SPI system (weight ratio of 1:1) indicated that the molecular state of the adsorbed SPI changed from crystalline to amorphous. Although the decrease in the SPI concentration increased with the amorphous fraction in the solid dispersion, the diffraction peaks due to SPI crystals still remained in the solid dispersion of a Sylysia 730:SPI system (weight ratio of 1:1), indicating that the mean pore diameter and specific surface area of an additive are some of the important factors for the amorphization of SPI crystals. The dissolution property of the SPI from the solid dispersions was remarkably improved in comparison with that of SPI crystals. The dissolution rate of the SPI from the solid dispersions with Sylysia 350 was faster than that of the SPI

from the solid dispersions with Sylysia 730. The difference in the dissolution properties of SPI from both the solid dispersions was attributed to the difference in the molecular state of the SPI in both the solid dispersions. In the stability test, the amorphous state of the SPI in the solid dispersion of the Sylysia 350:SPI system (weight ratio of 1:1) was maintained for 2 weeks at 25 degrees C and 0% RH, while the amorphous SPI without Sylysia 350 crystallized under the same conditions.

- Gerrit S. Zijlstra *et al* ., [44] (2007) has been developed a respirable, inulin- based solid dispersion containing cyclosporine for lung transplant patients. The solid dispersions were prepared by spray freezedrying. The solid dispersion was characterized by water vapor uptake, specific surface area analysis, and particle size analysis. Furthermore, the mode of inclusion of CsA in the dispersion was investigated with Fourier transform infrared spectroscopy. Finally, the dissolution behavior was determined and the aerosol that was formed by the powder was characterized. The powder had large specific surface areas (~ 160 m 2). The water vapor uptake was dependant linearly on the drug load. The type of solid dispersion was a combination of a solid solution and solid suspension.

- Minsuk Lee *et al*.,[45] (2007) have studied the enhancement of solubility of Sibutramine free base by preparing the solid dispersion using a fluid-bed granulator. The solid dispersion containing sibutramine freebase was characterized by differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD). After filling the sibutramine solid dispersion in the gelatin hard capsule, we performed *in vitro* dissolution test, the stability test under accelerated conditions and pharmacokinetic study in beagle dogs. The DSC and XRD data showed that sibutramine solid dispersion would be amorphous state. The dissolution rate of sibutramine solid dispersion was significantly increased about 70% than sibutramine freebase. The stability of sibutramine solid dispersion capsules was equivalent or above to commercial product of sibutramine.
- Shah T J *et al*.,[46] (2007) have studied the improvement of dissolution rate of Rofecoxib, a poorly water soluble drug by solid dispersion technique using a water soluble carrier, poloxamer 188 (PXM). The melting method was used to prepare solid dispersions. A 3(2) full factorial design approach was used for optimization wherein the temperature to which the melt-drug mixture cooled (X(1)) and the drug-to-polymer ratio (X(2)) were selected as independent variables and the time required for 90% drug dissolution (t(90)) was selected as the dependent variable. Multiple linear regression analysis revealed that for obtaining higher

dissolution of RXB from PXM solid dispersions, a low level of X(1) and a high level of X(2) were suitable. The differential scanning calorimetry and x-ray diffraction studies demonstrated that enhanced dissolution of RXB from solid dispersion might be due to a decrease in the crystallinity of RXB and PXM and dissolution of RXB in molten PXM during solid dispersion preparation. In conclusion, dissolution enhancement of RXB was obtained by preparing its solid dispersions in PXM using melting technique. The use of a factorial design approach helped in identifying the critical factors in the preparation and formulation of solid dispersion.

- Yogesh Rane *et al.,*[47] (2007) have studied the dissolution rate enhancement efficiency and solid dispersion formation ability of hydrophilic swellable polymers such as sodium carboxymethyl cellulose (Na-CMC), sodium starch glycolate (SSG), pregelatinized starch (PGS), and hydroxypropylmethyl cellulose (HPMC) with carbamazepine using 3^2 full factorial design for each of the polymers. Solid dispersions of carbamazepine were prepared using solvent evaporation method with around 70% solvent recovery. The independent variables were the amount of polymer and organic solvent. The dependent variables assessed were percentage drug dissolved at various time points and dispersion efficiency (ie, in terms of particle size of solid dispersion). Solid dispersions were evaluated for percentage drug dissolved, wettability, differential

scanning calorimetry, scanning electron microscopy, and angle of repose. Multiple linear regression of results obtained led to equations, which generated contour plots to relate the dependent variables.

- Elena Vittadini *et al .,*[48] (2007) were carried out Gelatinization of tapioca starch (25% dry basis) was induced by high hydrostatic pressure processing (HPP) at 600 MPa under different time and temperature regimes (30 °C for 10, 20 and 30 min; 50 °C for 10 min; 80 °C for 10 min). Textural, thermal and structural properties of the gels were studied and their stability was evaluated after 28 days of refrigerated (4 °C) and frozen (−18 °C) storage. Thermally induced gels (90 ± 1 °C, 20 min, gel-T) were used as controls. HPP resulted in the formation of harder gels than thermal processing (more significantly at lower processing temperatures) partially preserving the granular structure of the native starch.
- Thierry Tran *et al.,*[49] (2007) were studied the effect of starch chemical modifications and hydrocolloids on the proportion of freezable water in starch gels at various moisture contents. The proportion of freezable water increased with moisture content, from less than 6.1% to 84.9% (w/w) of the water fraction between 30% and 70% moisture content (wet weight basis, wwb). A transition between limited and excess water conditions was identified in the range 30-40% moisture content (wwb), whereby the proportion of

freezable water markedly increased from 6.1% to 40.4% (w/w) of the water fraction, in the case of the non-modified starch control. At 30 and 40% moisture content (wwb), gels made of acetylated starch and hydroxypropylated starch had a significantly lower amount of freezable water than the control, in particular at 40% moisture content (wwb) the amount of freezable water was reduced from 40.4% to 15.3-25.7% (w/w) of the water fraction. In systems with 50% moisture content (wwb) or higher, modified starches did not show a significant reduction in freezable water compared to the control. Two hydrocolloids, xanthan and carboxymethyl cellulose (CMC) used in a 40% moisture content (wwb) starch system significantly reduced freezable water from 40.4% to 23.9-24.1% of the water fraction (w/w), at a hydrocolloid: starch ratio of 1:14 (w/w). The linear decrease in the freezable water proportion with xanthan and CMC concentration pointed to the absence of interactions between the starch and hydrocolloid fractions.

- Nakhat PD *et al.,*[50] (2007) were prepared silymarin-HP-β-CD solid dispersion and formulate to tablets in order to improve oral bioavailability. Tablet formulations were prepared by direct compression technique using superdisintegrants such as crosscarmellose sodium, sodium starch glycolate and polyplasdone XL in different concentrations. Developed formulations were evaluated for various pharmaceutical characteristics viz. hardness,

% friability, weight variation, drug content, disintegration time and *in vitro* dissolution profiles. Amongst different batches, formulations containing crosscarmellose sodium showed superior disintegration and dissolution profiles compared to other formulations. However all the formulations showed improved dissolution over marketed formulation reflecting vital role of HP-β -CD dispersion in promotion of silymarin oral bioavailability. Moreover, optimized formulation showed stability at varying temperature and relative humidity.

- Murli SV *et al .,* [51] (2007) has been measured solid – phase axial dispersion in 0.15 m.i.d solid-liquid fluidized beds. The solid phase was ion-exchange resin in the size range of 300−1000 μm. The particle size distribution was measured at 34 axial locations ranging from 0.03 to 1.10 m from the bottom. A model describing the particle classification enabled the estimation of axial dispersion coefficient. Based on the experimental results, a correlation has been developed that has been found to be applicable to all the reported data in the published literature over a wide range of Reynolds number.
- Mariarosa Moneghini *et al.,*[52] (2008) have studied the application of attractive technique of the microwaves irradiation for the preparation of solvent free solid dispersions. In particular, the microwave technology has been considered in order to prepare an enhanced release dosage form for the poorly soluble drug

Ibuprofen (IBU), employing PVP/VA 60/40 (PVP/VA 64) and hydroxypropyl-β-cyclodextrin (HP-β-CD) as hydrophilic carriers. Their physico-chemical characteristics and dissolution properties were compared to the corresponding physical mixtures and the drug alone. The results of physico-chemical characterization attested a correspondence of the solid state of the drug before and after irradiation treatment and that an amorphous form of the drug was obtained. This result, together with the presence of the hydrophilic polymers determined a remarkable enhancement of the in vitro dissolution rate of the drug suggesting that the microwave technique could be considered as a new and interesting method to prepare drug–polymer systems.

- Odeku OA *et al.,* [53] (2008) have been investigated the material and tablet formation properties of pregelatinized (thermally modified) forms of four dioscorea starches. *Dioscorea* starches were pregelatinized followed by either oven drying (PS) or freeze drying (FD) and used as excipient in direct compression. The physicochemical, morphological and material properties of the pregelatinized starches have been investigated. The tablet formation properties were assessed using the 3-D modeling parameters, the Heckel equation and the force–displacement profiles. The tablet properties were evaluated using the elastic recovery, compactibility plots and the disintegration test. The results

indicate that pregelatinization improved the compressibility and flowability of the *Dioscorea* starches. The high bulk and tap densities of PS coupled with their good flowability offer a unique possibility of the starches being used as filler in capsule formulations. The modified starches generally showed differences in their time and pressure dependent deformation behaviour. PS exhibited higher elasticity during tableting. FD Chinese and FD Bitter showed higher plasticity and low fast elastic deformation than the PS forms of the starches indicating that the FD starches undergo the highest plastic deformation.

- Aubin HT *et al.,* [54] (2008) have studied the use of modified polysaccharides such as high amylose starch as excipients in controlled drug release technology.Crosslinked high amylose starch is a hydrophilic matrix used for the sustained release of drugs. Tablets using modified hybrid starch as excipient display zero-order release over 2–24 h. A release over 3–4 weeks was observed when the modified starch is used as an implant. The use of starch in controlled release system is appealing because it could be easily metabolized in the human body. We review here the use of NMR imaging and solid state ^{13}C spectroscopy in the study of the various factors influencing drug release in such systems.

- Yongmei Xie *et al.,* [55] (2008) were prepared solid dispersions of esomeprazole Zinc in polyethylene glycol 4000 (PEG 4000) with different EZ to PEG 4000 ratios by solvent method. studies showed that dissolution rate of EZ were distinctively increased in the solid dispersion system compared to that in pure EZ or physical mixtures. The increase of dissolution rate was obviously related to the ratio of EZ to PEG4000. The solid dispersion system (EZ/PEG4000 = 1/8, w/w) gave the highest dissolution rate: about 14.7-fold higher than that of the pure EZ. EZ was proved to be in amorphous state in this solid dispersion by using differential scanning calorimetry (DSC) and scanning electron microscopy (SEM) techniques.
- Biswal S et al .,[56] (2008) were prepared solid dispersions of gliclazide with PEG 6000. The solubility of gliclazide increased with increasing amount of PEG 6000 in water. The SDs of gliclazide with PEG 6000 were prepared at 1:1, 1:2 and 1:5 (gliclazide/PEG 6000) ratio by melting-solvent method and solvent evaporation method. Evaluation of the properties of the SDs was performed by using dissolution, Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies. The SDs of gliclazide with PEG 6000 exhibited enhanced dissolution rate of gliclazide, and the rate increased with increasing concentration of PEG 6000 in SDs. Mean dissolution time (MDT)of gliclazide decreased significantly after preparation of SDs and

physical mixture with PEG 6000. The FTIR spectroscopic studies showed the stability of gliclazide and absence of well-defined gliclazide–PEG 6000 interaction. The DSC and XRD studies indicated the microcrystalline or amorphous state of gliclazide in SDs of gliclazide with PEG 6000.

MATERIALS AND METHODS

Table: 3 Materials used

Name of the materials	Name of company
Etodolac	Dr.Reddys Laboratories Ltd , Hyderabad
Potato starch	Loba chemie pvt.Ltd , Mumbai
Maize starch	Loba chemie pvt.Ltd , Mumbai
Tapioca starch	Loba chemie pvt.Ltd , Mumbai
Tween 80	Qualigens fine chemicals
Methanol	Loba chemie pvt.Ltd , Mumbai
Sodium hydroxide	SD fine chem. Ltd
Potassium dihydrogen phosaphate	Ranchem Ltd
Glacial acetic acid	SD fine chem. Ltd
Toluene	Qualigens fine chemicals
Ethanol	Changshu Yangyuan chemicals
Potassium bromide	Qualigens
Acetone	Ranbaxy fine chemicals Ltd

Table : 4 Equipment used

Name of equipment	Name of company
Vacumm pump	Gelman sciences
Dissolution apparatus	Electrolab TDT – 08L
UV spectrometer	Jasco V 530 UV spectrophotometer
FT IR spectrometer	Jasco-FT-IR 8201 PC
pH testr 1 (water proof)	Oakton instruments.

ANALYTICAL METHODS

Methods available for the identification of etodolac are

a) Examine by infrared absorption spectrophotometry, comparing with the spectrum obtained with the spectrum obtained with Etodolac

b) Melting point: 144°C to 150°C.

c) The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

METHODS AVAILABLE FOR ESTIMATION OF ETODOLAC ARE

a) Spectrophotometric estimation of Etodolac in pure form and pharmaceutical formulation was reported.

b) Spectrofluorimetric determination of Etodolac was reported. The detection limit was reported to be 96 to 640ng/ml.

c) The separation of Etodolac and its metabolites has been reported by the use of Capillary electro – chromatography.

d) HPLC and Mass spectrometry was reported for the determination of Etodolac in human plasma.

METHOD FOR ESTIMATION OF ETODOLAC

A Spectrophotometric method based on the measurement of absorbance at 274 nm in 0.1 M phosphate buffer pH 6.8 was used in the present study for estimation of Etodolac.

MATERIALS

1. Etodolac pure drug.
2. Methanol.
3. Potassium dihydrogen phosphate.
4. Sodium hydroxide
5. Distilled water.

THE METHODOLOGY USED IN THE PRESENT RESEARCH WORK

Preparation of pH 6.8 phosphate buffer:

250 ml of 0.2M potassium dihydrogen phosphate in a 100 ml vessel and 112 ml of 0.2 M NaOH and made up to 1000 ml with water.

Potassium dihydrogen phosphate (0.2M)

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

Sodium hydroxide (0.2M) NaOH

Dissolve 8 g of NaoH in water and dilute to 1000 ml with water.

Preparation of standard stock solution

Stock solutions of Etodolac were prepared by dissolving 100 mg of pure drug in methanol,followed by dilution to 100 ml with pH 6.8 phosphate buffer to obtain 1 mg/ml standard solution.

Procedure for standard graph

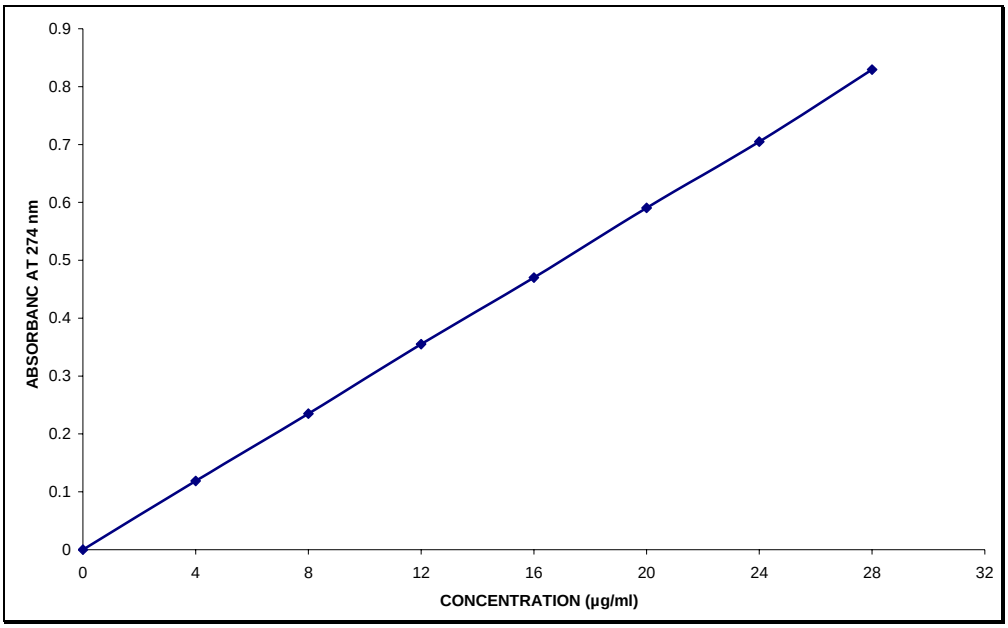
Working solution were prepared by pipetting out 10 ml of stock solution, made upto 100 ml with pH 6.8 phosphate buffer to obtain 100 mcg/ml solution.

From this solution pipette out 0.4,0.8,1.2,1.6, 2,2.4, and 2.8 ml which were transferred into a series of 10 ml volumetric flasks and final volume was brought upto 10 ml with pH 6.8 phosphate buffer to get a concentration of 4-28 mcg/ml. Ablank was also prepared. The absorbance was measured at 274 nm and the standard graph was plotted against concentration (mcg/ml) Vs absorbance.[30-35] The results were given in table. 5 and figure .1

Table : 5 Standard Graph values of Etodolac in 0.1M, pH 6.8 phosphate buffer

Concentration µg/ml	Absorbance at 274 nm
0	0.0000
4	0.1187
8	0.2350
12	0.3550
16	0.4701
20	0.5906
24	0.7050
28	0.8295

Fig : 1 Standard Graph of Etodolac in 0.1M, pH 6.8 phosphate buffer



PREPARATION AND CHARACTERIZATION OF SOLID DISPERSION

In the present study, pre-gelatinized starch is prepared from the native starches such as Potato, Tapioca and Maize. It is low cost carrier widely used in pharmaceutics as diluent, binder, disintegrant and carrier for solid dispersion.

Preparation of pre-gelatinized starch

An aqueous slurry (100 ml) of potato, Tapioca and Maize starch (40%) w/v containing 1% Tween-80 was heated to 65 ^{0}C with continuous stirring until the starch gelatinizes and produces a viscous translucent mucilage. The viscous mucilage was then dehydrated by the addition of acetone while stirring and the solids separated were collected by filtration and further dried at 40^{0} C for 2 hrs. The dried mass obtained was crushed, pulverized and sifted through mesh no.120.[4]

Preparation and characterization of etodolac solid dispersion

The prepared PGS from Potato, Tapioca and Maize are used as carrier in the preparation of solid dispersion of Etodolac. Etodolac is a member of the pyranocarboxylic acid group of drug practically in soluble in water. In the present study Etodolac: PGS solid dispersion are prepared at four different ratios namely 1:1,1:3,1:9 and 1: 19 by two different methods such as kneading and solvent evaporation.

Procedure for preparation of Etodolac solid dispersion by kneading method

Each polymer and solvent were mixed together in a mortar so as to obtain a homogenous paste. Etodolac was then added slowly with constant stirring. The mixture was then ground for 1 hour. During this process, an appropriate quantity of solvent was added to the mixture in order to maintain a suitable consistency. The paste was dried in oven at 40°C for 24 hours. The dried complex was pulverized into a fine power.

Procedure for preparation of Etodolac solid dispersion by solvent evaporation method

In solvent evaporation method, methanol was used as solvent and four different drug: carrier ratios were used (1:1, 1:3, 1:9,1:19) to prepare solid dispersion of Etodolac Respective amount of carrier was dissolved in required amount of methanol taken in a conical flask to get a clear completely soluble polymer methanol solution. Magnetic stirrer was used for this purpose. The weighed amount of Etodolac was added to this solution carefully with constant stirring. Stirring was continued until the drug was completely incorporated in solvent. Then the solvent was removed by evaporation at 40° C under vacuum. The mass obtained was dried crushed, pulverized and shifted through mesh no. 80.

Physical mixture (PM)

Drug: Carrier ratio of 1:1 was used to prepare physical mixture (1000 mg of drug and 1000 mg of carrier). The drug and carrier were

mixed thoroughly in a mortar. This was done by geometric dilution technique to ensure homogenous distribution.

Table : 6 Drug carrier ratio and respective amount taken:

Drug carrier ratio	Drug (mg)	Carrier (mg)
1:1	1000	1000
1:3	500	1500
1:9	200	1800
1:19	100	1900

CHARACTERIZATION AND EVALUATION OF ETODOLAC SOLID DISPERSION

The prepared Etodolac :PGS solid dispersion were characterized and evaluated for:-

a. Thin layer Chromatography

b. IR spectral Analysis

c. Powdered X-ray Diffraction studies

d. Differential Scanning Calorimetry

e. Scanning Electron Microscopy

f. Drug content uniformity

g. Invitro dissolution studies

Thin layer chromatography (TLC)

A thin layer chromatographic method was also carried to study the interaction between the drug and carriers and also to confirm the chemical

satiability of the solid dispersions prepared. For this, the pure drug and the solid dispersions prepared with various carriers by kneading and solvent evaporation method were subjected to chromatographic studies.

The TLC system used for this study is given below.

Precoated TLC Plates	:	Manufactured by SD Fine chemicals Ltd, Mumbai
Adsorbent Layer	:	Silicagel GF 254.
Layer Thickness	:	250 μm
Size	:	10 ×10 cm
Separation technique	:	Ascending
Chamber Saturation	:	The chamber was lined on three sides with filter paper and saturated for 30 minutes.
Mobile phase	:	glacial acetic acid : ethanol: toluene [0.5: 30: 70 % v/v]
Preparation of sample	:	A suitable amount of pure drug or equivalent solid dispersion dissolved in acetone and dilute to 10 ml with the same solvent and used for spotting.
Amount applied	:	10 μl.
Detection	:	Under UV light at 254nm. [31]

The R_f values obtained were given in the table.7-8 and thin layer chromatograms of pure drug avd various solid dispersions were shown in fig.2.

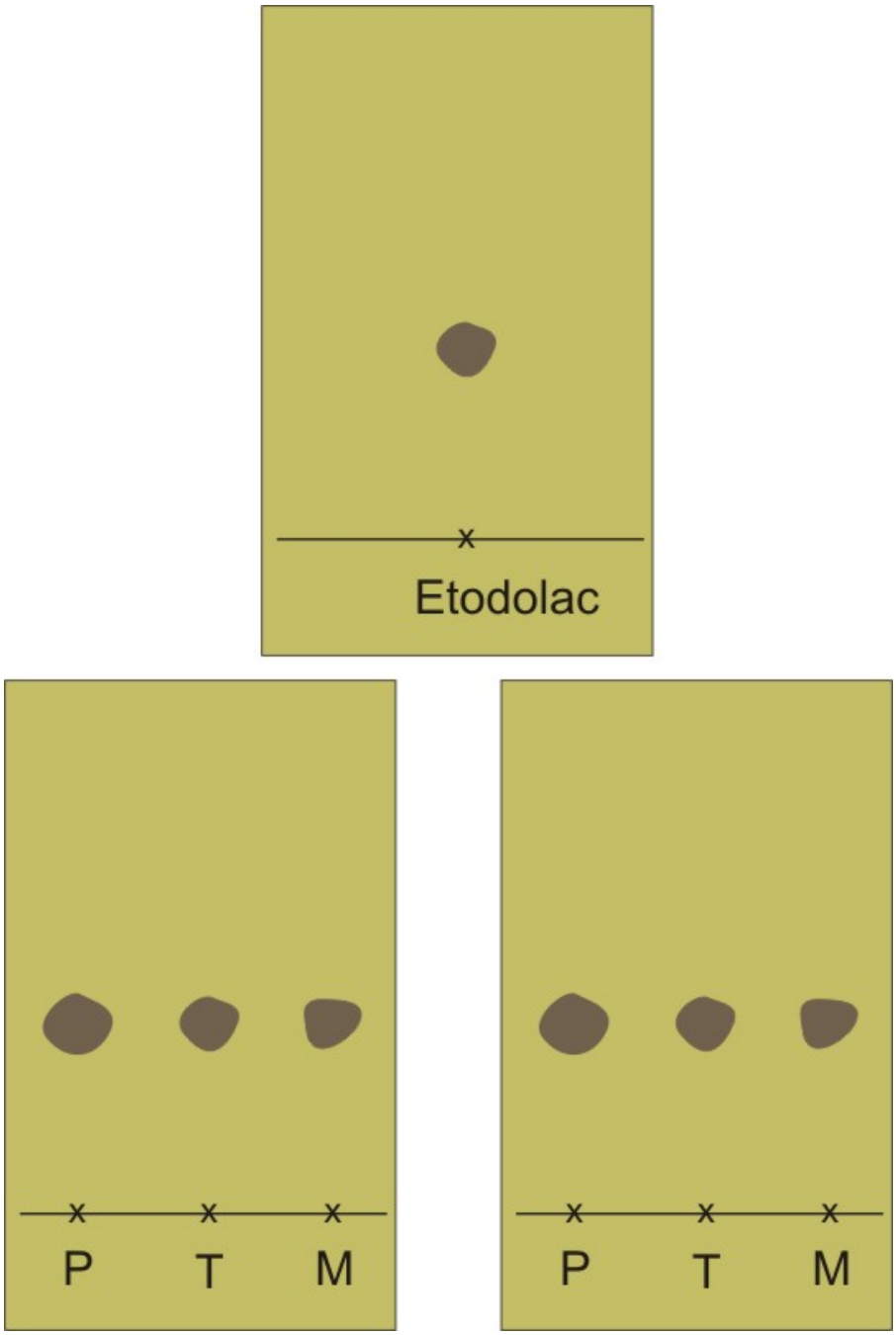
Table : 7 TLC data for pure drug and various solid dispersion systems (kneading method)

Pure drug	Polymer	Ratio	R_f Value
Etodolac	-	-	0.49
Etodolac	PGS(Potato)	1:1	0.40
Etodolac	PGS(Tapioca)	1:1	0.40
Etodolac	PGS(Maize)	1:1	0.40

Table : 8 TLC data for pure drug and various solid dispersion systems (solvent evaporation method)

Pure drug	Polymer	Ratio	R_f Value
Etodolac	-	-	0.49
Etodolac	PGS(Potato)	1:1	0.60
Etodolac	PGS(Tapioca)	1:1	0.60
Etodolac	PGS(Maize)	1:1	0.60

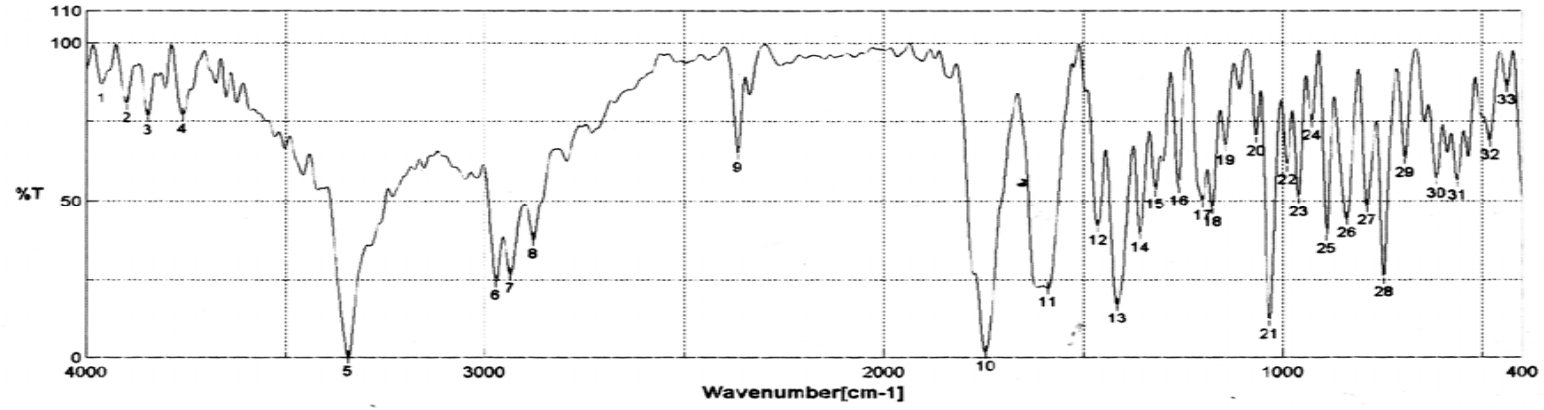
Fig : 2 Thin Lay chromatogram of Pure Drug Etodolac and Solid dispersion by kneading and solvent evaporation method. (1:1) ratio



IR Spectral analysis:

Fourier Transform (FTIR) spectra of the samples were obtained in the range of 400-4000 cm^{-1} using a Jasco-FT-IR 8201 PC Spectrophotometer (Jasco. Essex) by the KBr disc method.[36] The IR Spectra obtained are given in fig. 3-12

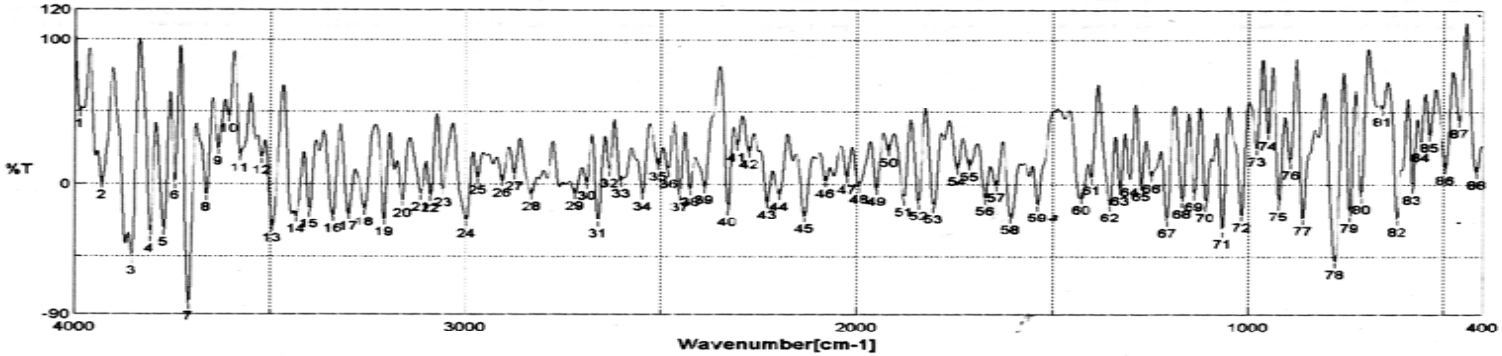
Fig : 3 IR Spectrum Of Pure Drug Etodolac



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	9/29/2008 0:16PM	Update	9/30/2008 10:22AM
Operator	C.Geetha		
File Name	Pure drug -etodolac		
Sample Name	Pure drug -etodolac		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3981.07	86.7111	2	3899.36	80.5063	3	3844.4	76.7063	4	3756.65	77.0734	5	3343	0.220293
6	2970.8	24.513	7	2936.09	26.7931	8	2878.24	37.6298	9	2365.26	85.1328	10	1745.26	1.8992
11	1589.06	22.3477	12	1463.71	41.809	13	1415.49	17.0945	14	1357.64	39.5841	15	1319.07	53.4311
16	1261.22	54.447	17	1201.43	49.8968	18	1176.36	47.7712	19	1142.62	67.3192	20	1065.48	70.1675
21	1031.73	12.0679	22	988.339	61.1587	23	959.412	50.993	24	926.628	74.9799	25	889.987	39.3372
26	840.812	44.2617	27	789.707	48.3889	28	747.281	25.5531	29	693.284	63.521	30	614.217	56.8439
31	562.148	56.3566	32	480.188	68.8925	33	437.762	86.2666						

Fig: 4 IR Spectrum of PGS(Potato)



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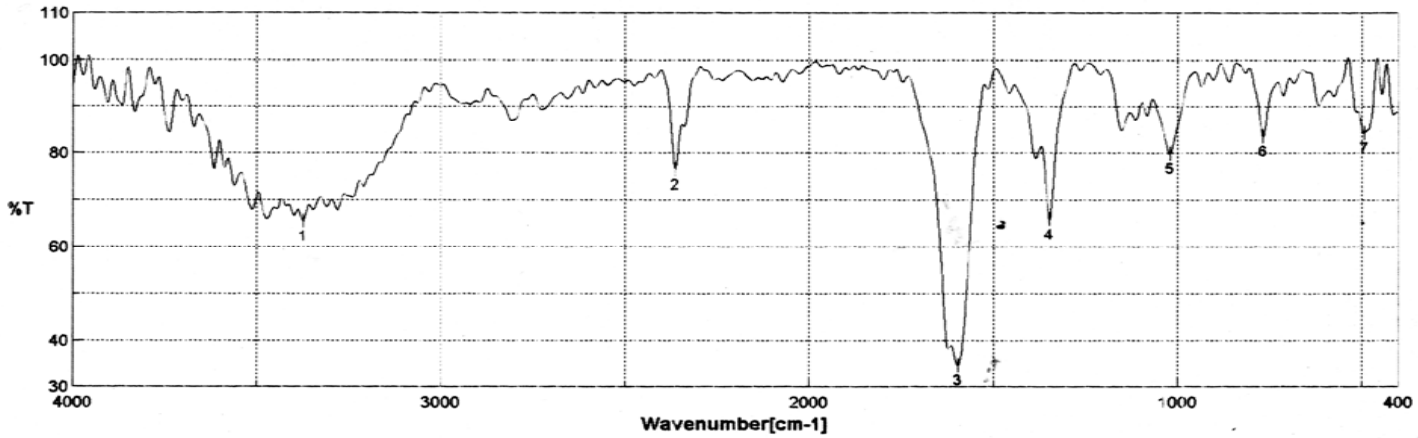
Zero Filling	ON	Apodization	Cosine
Gain	256	Scanning Speed	2 mm/sec
Date/Time	9/29/2008 0:09PM	Update	9/30/2008 10:19AM
Operator	C.Geetha		
File Name	Potato PGS		
Sample Name	Potato PGS		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3987.11	49.5837	2	3931.18	0.839122	3	3854.04	-51.4301	4	3806.79	-36.6068	5	3772.08	-31.9834
6	3744.12	0.395505	7	3708.44	-82.4431	8	3663.12	-7.58565	9	3633.23	24.1873	10	3606.23	46.6251
11	3577.31	19.3332	12	3522.34	18.0119	13	3495.35	-29.1948	14	3433.64	-22.6526	15	3399.89	-19.3473
16	3339.14	-22.4702	17	3299.61	-21.0016	18	3256.14	-17.6786	19	3208.97	-24.7864	20	3161.72	-11.5337
21	3114.47	-7.30863	22	3090.37	-7.92988	23	3058.55	-4.0801	24	2998.77	-25.7633	25	2969.84	4.18
26	2907.16	2.20229	27	2876.31	7.13019	28	2832.92	-6.89146	29	2721.07	-6.36827	30	2691.18	0.556418
31	2662.25	-25.7857	32	2632.36	8.94854	33	2603.43	1.85349	34	2547.5	-6.95572	35	2507.01	13.7237
36	2481.94	8.58409	37	2453.01	-7.13315	38	2426.01	-3.7287	39	2389.37	-2.16099	40	2329.59	-17.835
41	2305.48	26.8805	42	2275.59	22.1931	43	2229.31	-12.7561	44	2198.45	-6.74812	45	2133.85	-22.3569
46	2079.85	2.12306	47	2025.85	4.87858	48	1995	-1.69773	49	1950.64	-3.52177	50	1919.79	23.3016
51	1880.26	-10.9052	52	1842.65	-13.6005	53	1803.12	-15.9723	54	1742.37	10.4959	55	1710.55	13.5968
56	1671.98	-10.154	57	1643.05	-0.696818	58	1606.41	-23.35	59	1537.95	-14.6748	60	1425.14	-9.38375
61	1400.07	4.29129	62	1352.82	-14.5134	63	1326.79	-3.08114	64	1301.72	3.23438	65	1272.79	0.190309
66	1247.72	5.38981	67	1208.18	-25.4277	68	1168.65	-11.8366	69	1137.8	-6.94953	70	1108.87	-14.8221
71	1085.48	-32.7673	72	1016.3	-21.5955	73	976.766	24.1782	74	947.841	34.9248	75	920.843	-14.0279
76	891.916	14.8081	77	860.096	-24.0221	78	778.136	-53.9975	79	739.567	-22.1022	80	710.64	-8.88153
81	658.643	51.8041	82	619.038	-24.9018	83	578.54	-2.24494	84	557.327	27.2325	85	534.185	33.8859
86	494.652	11.3446	87	458.975	43.5117	88	416.549	8.0842						

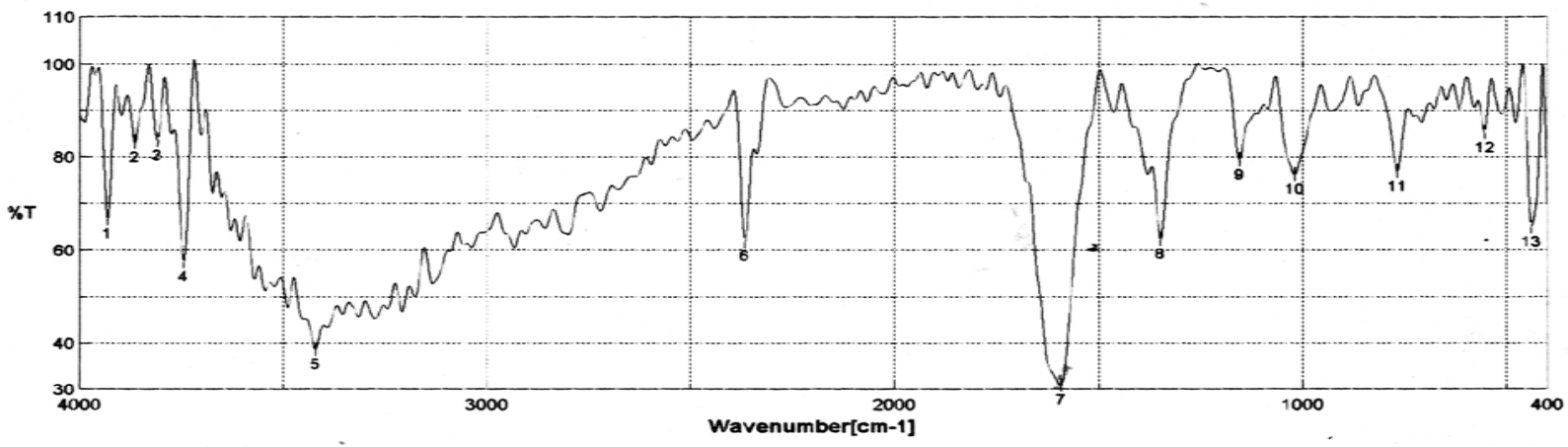
Fig: 5 IR spectrum of PGS (Tapioca)



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	9/29/2008 0:18PM	Update	9/30/2008 10:24AM
Operator	C.Geetha		
File Name	Tapioca PGS		
Sample Name	Tapioca PGS		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3374.82	65.4239	2	2363.34	76.3808	3	1596.77	34.7133	4	1348	85.8732	5	1019.19	79.7742
6	766.566	83.4626	7	493.688	84.2512									

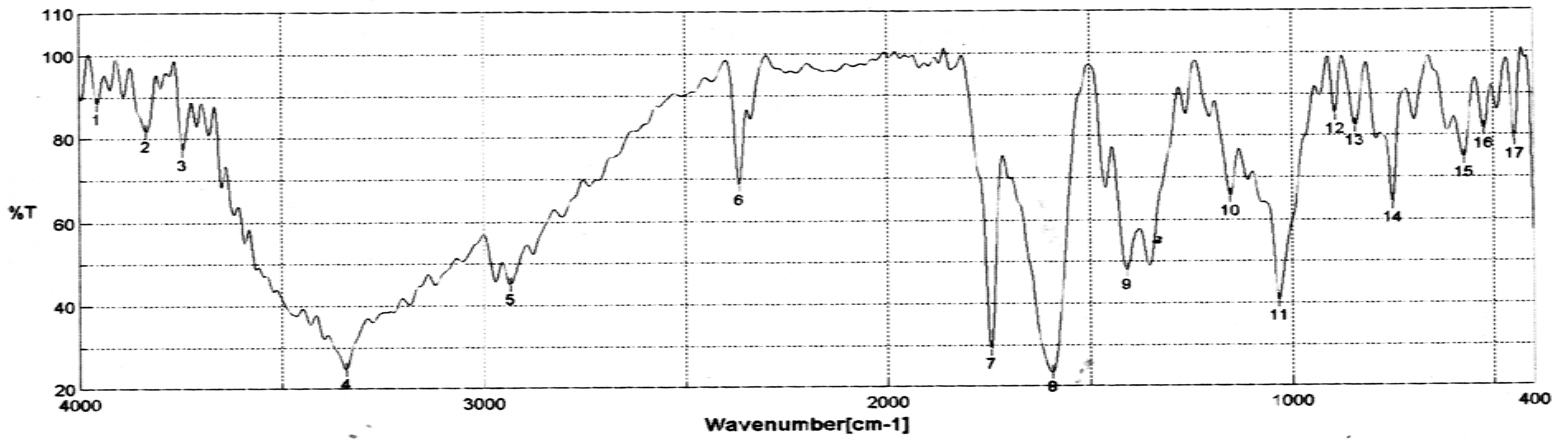
Fig: 6 IR spectrum of PGS(Maize)



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	9/29/2008 0:11PM	Update	9/30/2008 10:16AM
Operator	C.Geetha		
File Name	Maize PGS		
Sample Name	Maize PGS		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3931.18	66.7569	2	3864.65	83.034	3	3808.72	83.5737	4	3743.15	57.5481	5	3421.1	38.658
6	2367.19	61.941	7	1592.91	30.9962	8	1348	62.4178	9	1154.19	79.4428	10	1019.19	76.2542
11	767.53	76.8558	12	553.47	85.1874	13	438.726	65.0876						

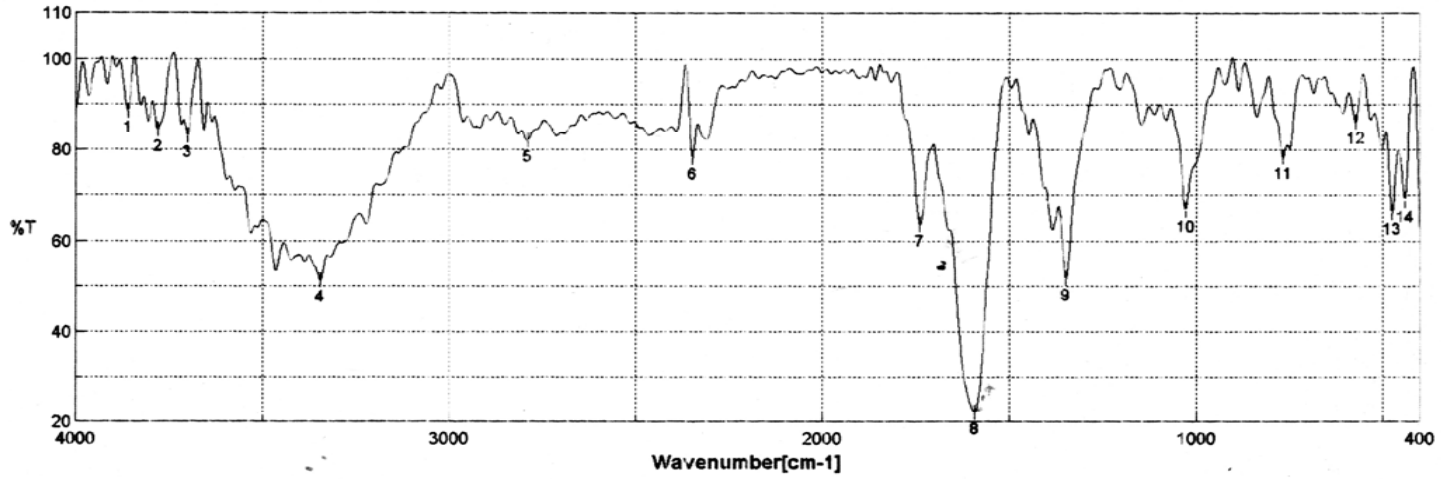
Fig: 7 IR spectrum of solid dispersion of Etodolac with PGS (Potato) (1: 1) KM



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	9/29/2008 0:38PM	Update	9/30/2008 10:00AM
Operator	C.Geetha		
File Name	Drug+PotatoPGS (1;1)KM		
Sample Name	Drug+PotatoPGS (1;1)KM		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3955.29	88.2888	2	3835.72	81.7416	3	3745.08	77.2454	4	3342.03	24.8614	5	2935.13	45.0041
6	2366.23	68.5656	7	1744.3	29.1689	8	1592.91	23.4858	9	1408.75	47.9008	10	1151.29	65.6534
11	1031.73	40.511	12	891.916	85.0157	13	841.776	82.2941	14	749.209	63.8815	15	572.755	74.6293
16	523.579	81.3823	17	447.404	78.9451									

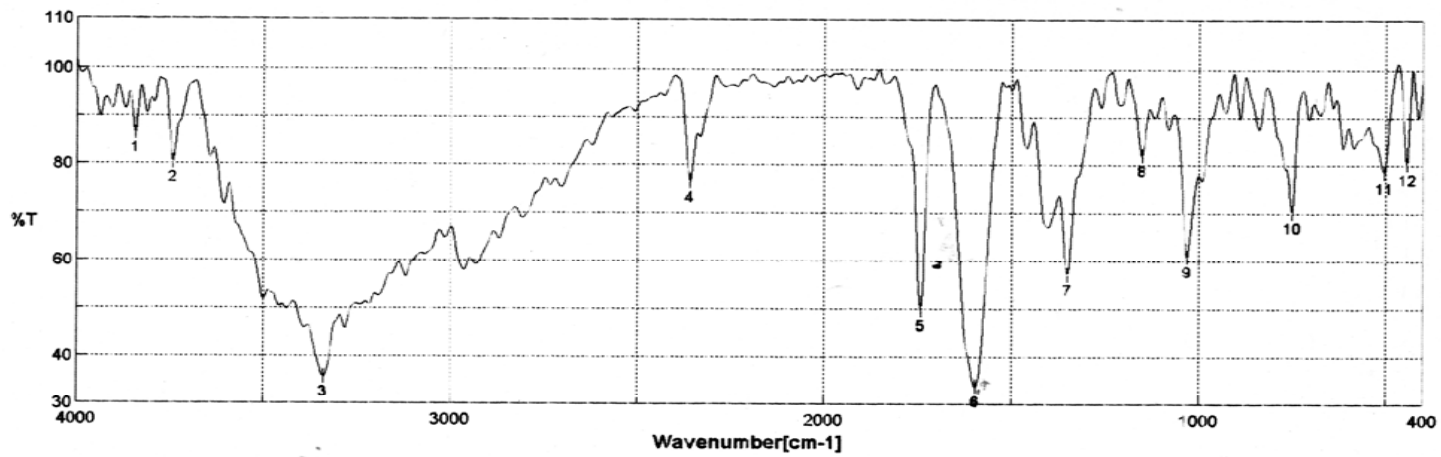
Fig: 8 IR spectrum of solid dispersion of Etodolac with PGS(Tapioca) (1: 1) KM



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	9/29/2008 0:22PM	Update	9/30/2008 10:02AM
Operator	C.Geetha		
File Name	Drug+Tapioca PGS (1:1)KM		
Sample Name	Drug+Tapioca PGS (1:1)KM		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3861.76	88.4577	2	3781.72	84.4443	3	3700.73	83.0915	4	3344.93	51.2099	5	2791.46	81.9795
6	2347.91	78.1747	7	1739.48	63.5108	8	1591.95	22.1986	9	1348	51.5899	10	1027.87	66.8295
11	766.566	78.3702	12	572.755	86.1765	13	474.403	66.1682	14	439.69	68.9837			

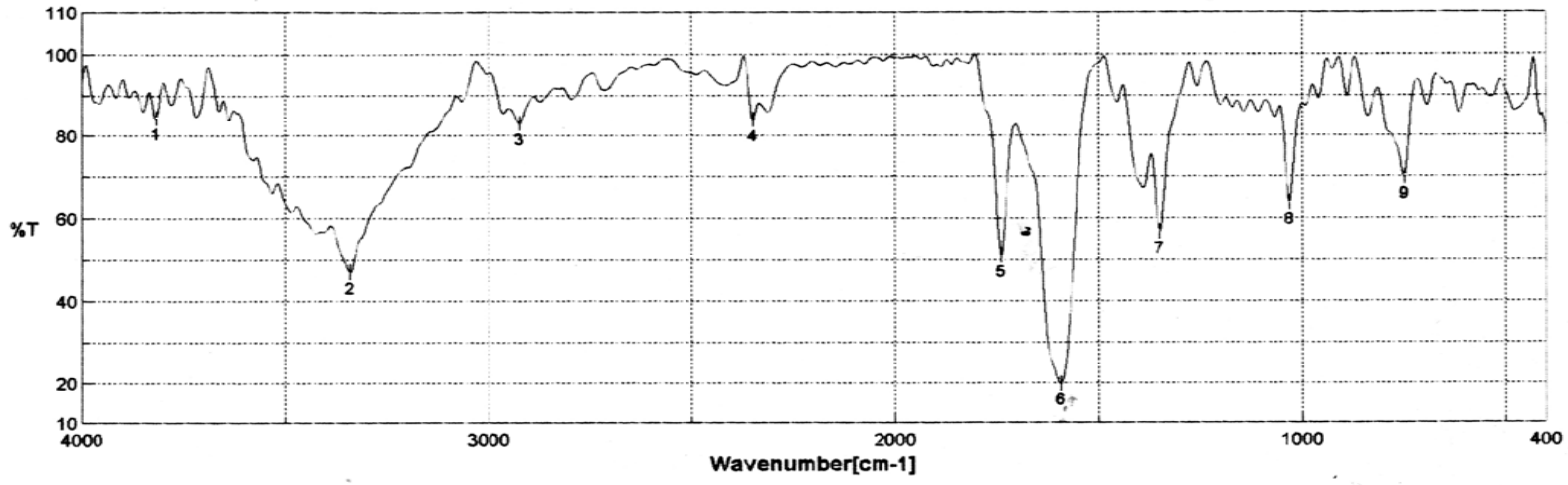
Fig: 9 IR spectrum of solid dispersion of Etodolac with PGS(Maize) (1: 1) KM



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	9/29/2008 0:30PM	Update	9/30/2008 9:53AM
Operator	C.Geetha		
File Name	Drug+MaizePGS (1:1)KM		
Sample Name	Drug+MaizePGS (1:1)KM		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3842.47	86.3667	2	3743.15	80.2889	3	3341.07	35.7535	4	2358.52	76.4328	5	1743.33	49.6747
6	1596.77	33.8005	7	1350.89	57.1337	8	1150.33	81.9307	9	1030.77	60.8728	10	749.209	70.2796
11	504.294	78.3018	12	442.583	80.1676									

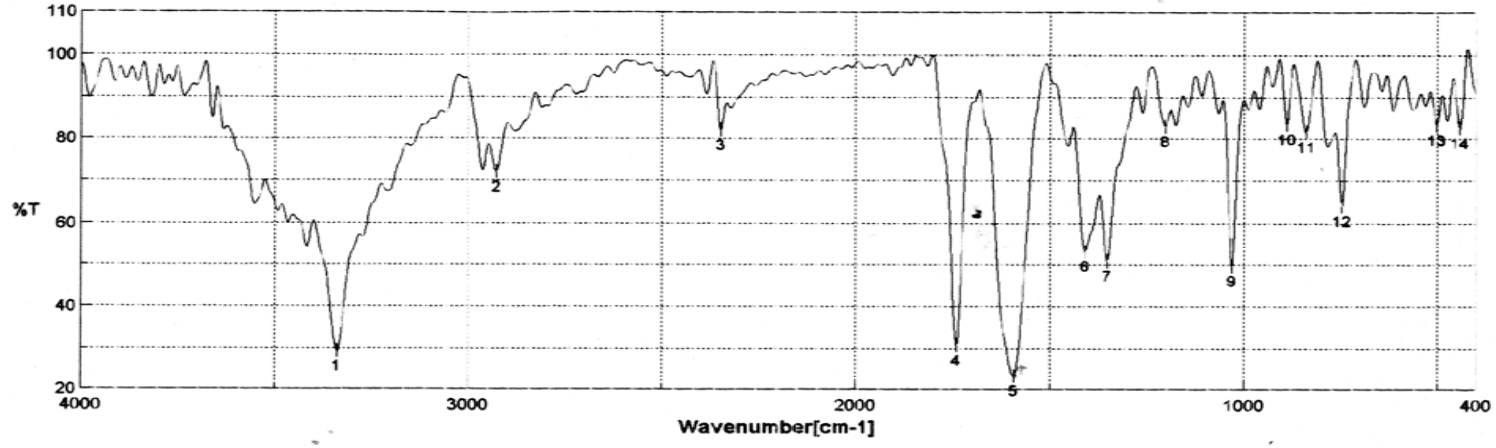
Fig: 10 IR spectrum of solid dispersion of Etodolac with PGS(Potato) (1: 1) SE



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	9/29/2008 0:25PM	Update	9/30/2008 10:28AM
Operator	C.Geetha		
File Name	Drug+PotatoPGS (1;1)SE		
Sample Name	Drug+PotatoPGS (1;1)SE		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3817.4	84.2737	2	3340.1	46.9393	3	2923.56	82.9501	4	2348.87	83.9015	5	1739.48	50.9921
6	1593.88	19.8231	7	1349.93	56.691	8	1030.77	63.8243	9	748.245	69.9084			

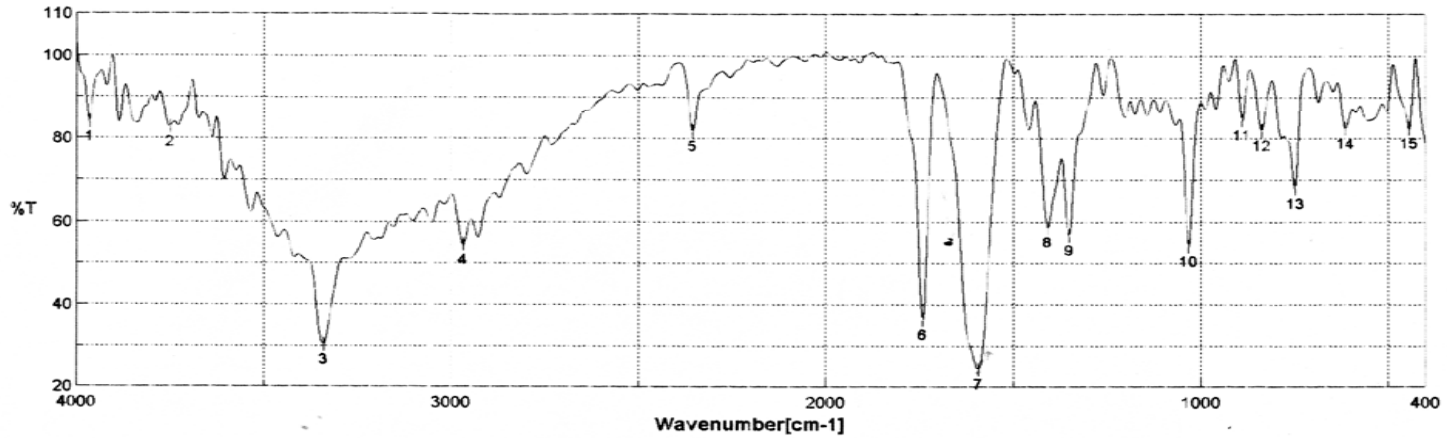
Fig: 11 IR spectrum of solid dispersion of Etodolac with PGS (Tapioca) (1: 1) SE



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	9/29/2008 0:28PM	Update	9/30/2008 10:06AM
Operator	C.Geetha		
File Name	Drug+TapiocaPGS (1;1)SEM		
Sample Name	Drug+TapiocaPGS (1;1)SEM		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3338.18	29.2813	2	2928.38	72.0123	3	2348.87	82.0353	4	1740.44	30.7596	5	1592.91	23.3593
6	1408.75	53.1366	7	1350.89	50.8494	8	1200.47	82.9473	9	1030.77	49.6045	10	889.023	83.3481
11	838.883	81.5474	12	746.317	64.1361	13	501.401	83.2447	14	441.619	82.568			

Fig: 12 IR spectrum of solid dispersion of Etodolac with PGS(Maize) (1: 1) SE



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	9/29/2008 0:20PM	Update	9/30/2008 9:50AM
Operator	C.Geetha		
File Name	Drug+maize PGS (1;1)SEM		
Sample Name	Drug+maize PGS (1;1)SEM		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3984.93	83.901	2	3750.87	82.7045	3	3341.07	30.3952	4	2966.95	54.4251	5	2353.69	81.7945
6	1741.41	36.2563	7	1593.88	24.3344	8	1407.78	58.5722	9	1351.86	56.5444	10	1031.73	53.9972
11	889.987	84.3068	12	837.919	81.8877	13	748.245	67.9029	14	614.217	82.3286	15	443.547	82.3344

Powder X-ray diffractometry

The Powder X-ray Diffraction Patterns were recorded using Bruker AXS D8 Advance model with Cu as anode material and crystal graphite monochromator,wavelength 1.5406A^0 operated at a voltage of 40 kV and a current of 30 mA. The samples were analyzed in the 2θ angle range of 3° to 65° and the process parameters were set as follows: step size of 0.45° (2θ), scan step time of 0.1 seconds and time of acquisition of 2 hours. The results were shown in fig. 13-19.

Fig: 13 X- ray diffraction studies of pure Etodolac

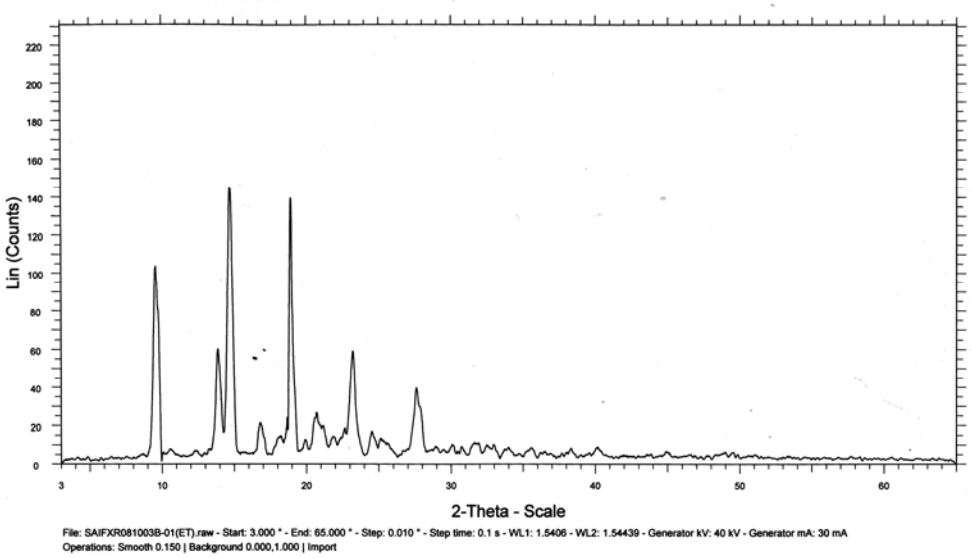


Fig: 14 X-ray diffraction studies of solid dispersion of Etodolac with PGS(Potato) (1: 1) KM

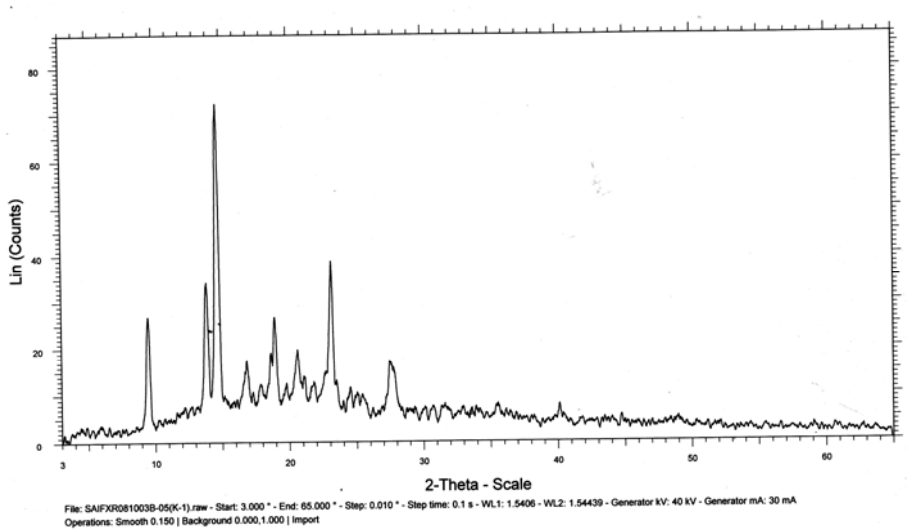


Fig : 15 X-ray diffraction studies of solid dispersion of Etodolac with PGS (Tapioca) (1: 1) KM

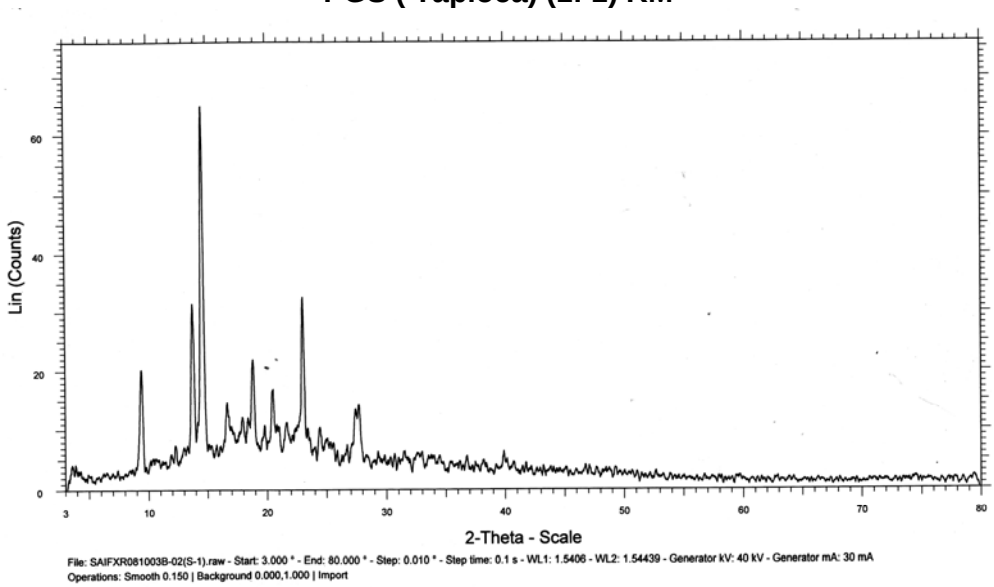


Fig: 16 X-ray diffraction studies of solid dispersion of Etodolac with PGS(Maize) (1: 1) KM

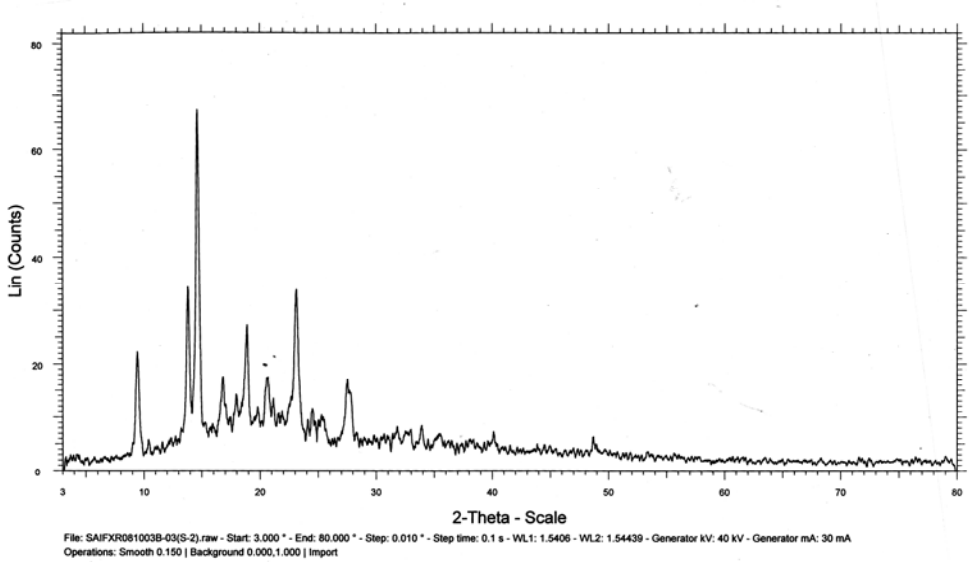


Fig: 17 X-ray diffraction studies of solid dispersion of Etodolac with PGS(Potato) (1: 1) SE

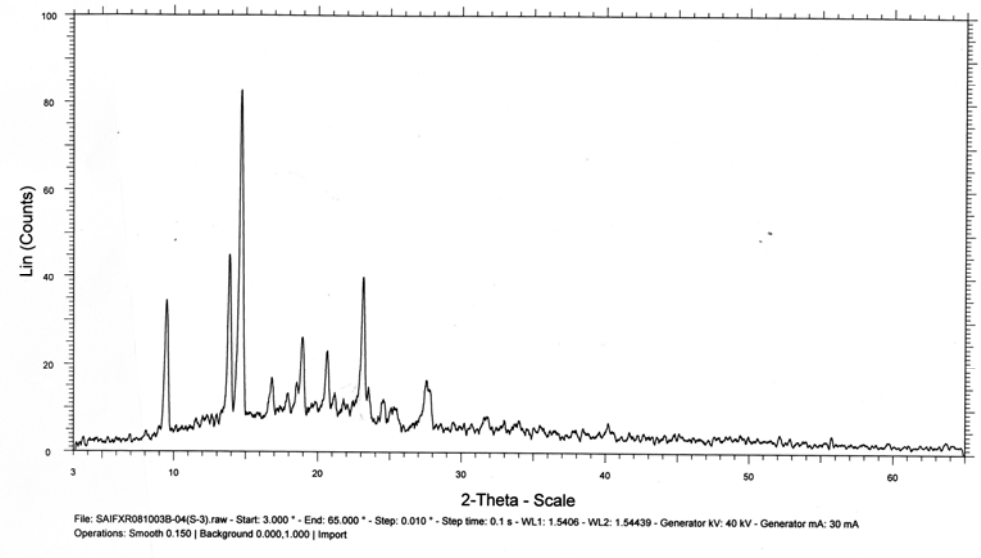


Fig: 18 X-ray diffraction studies of solid dispersion of Etodolac with PGS (Tapioca) (1: 1) SE

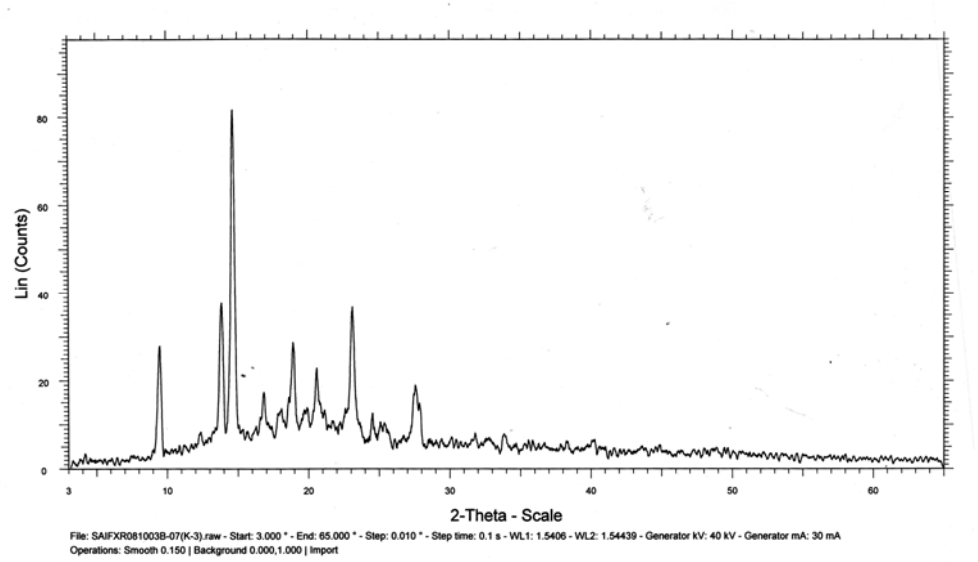
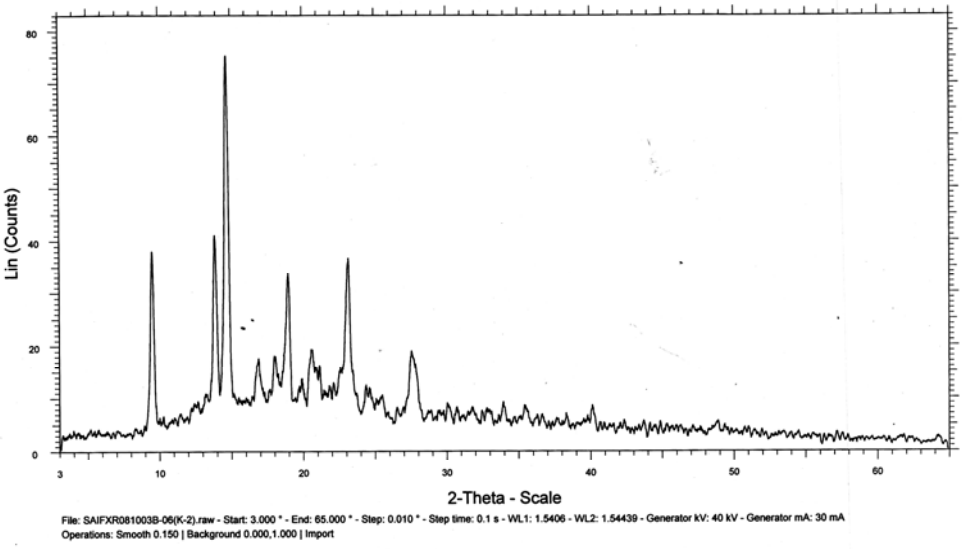


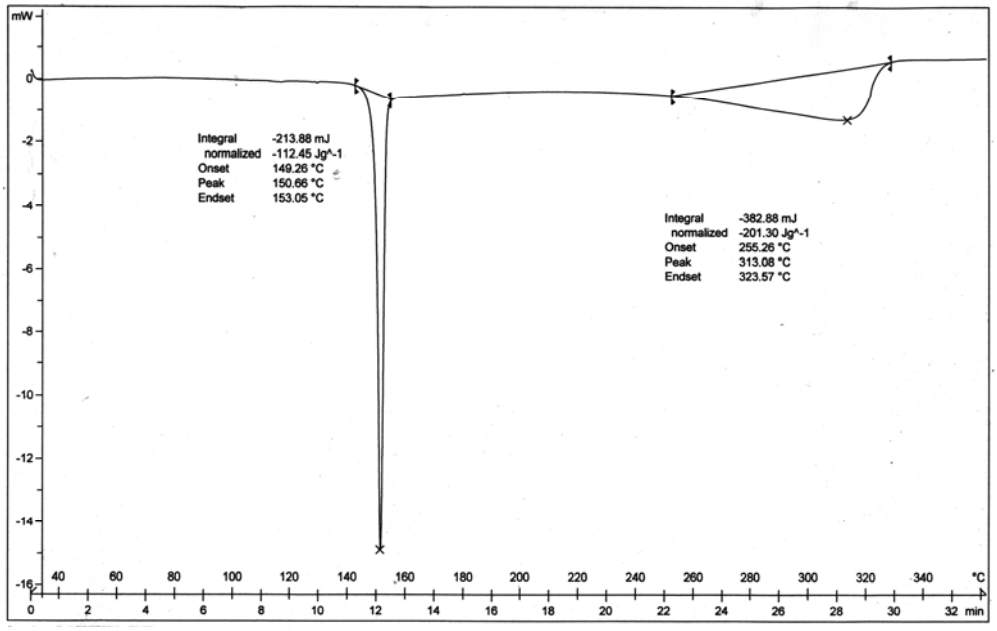
Fig: 19 X-ray diffraction studies of solid dispersion of Etodolac with PGS(Maize) (1: 1) SE



Differential Scanning Calorimetry

The DSC measurements were performed using a Mettleer Toledo DSC 822e model controlled by STAR^e Software (Mettler – Toledo. GmbH, Switzerland). All accurately weighted samples (1 mg of aceclofenac or its equivalent) were placed in seated aluminum pans, before heating under nitrogen flow (20ml/min) at a scanning rate of 10° C min-1, over the temperature range of 30°C to 220°C. An empty aluminum pan was used as reference. The results were shown in fig.20-26.

Fig: 20 DSC thermogram of pure Etodolac



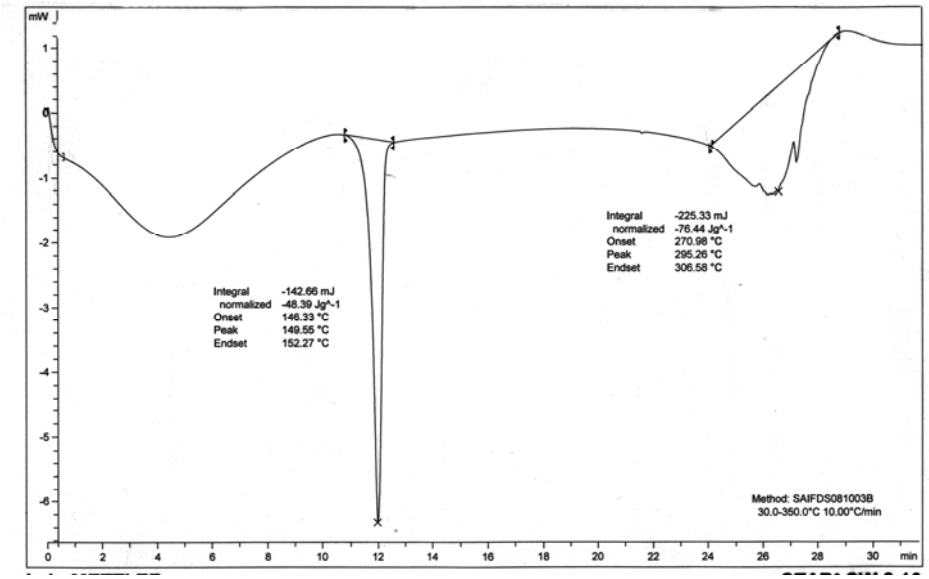


Fig: 21 DSC thermogram of solid dispersion of Etodolac with PGS (Potato) (1: 1) KM

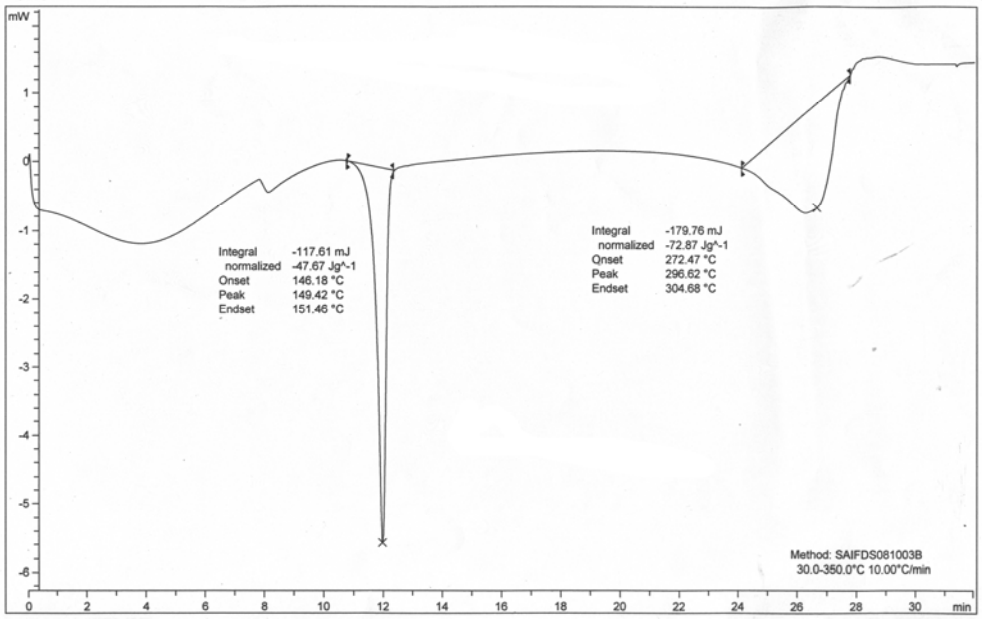


Fig: 22 DSC thermogram of solid dispersion of Etodolac with PGS (Tapioca) (1: 1) KM

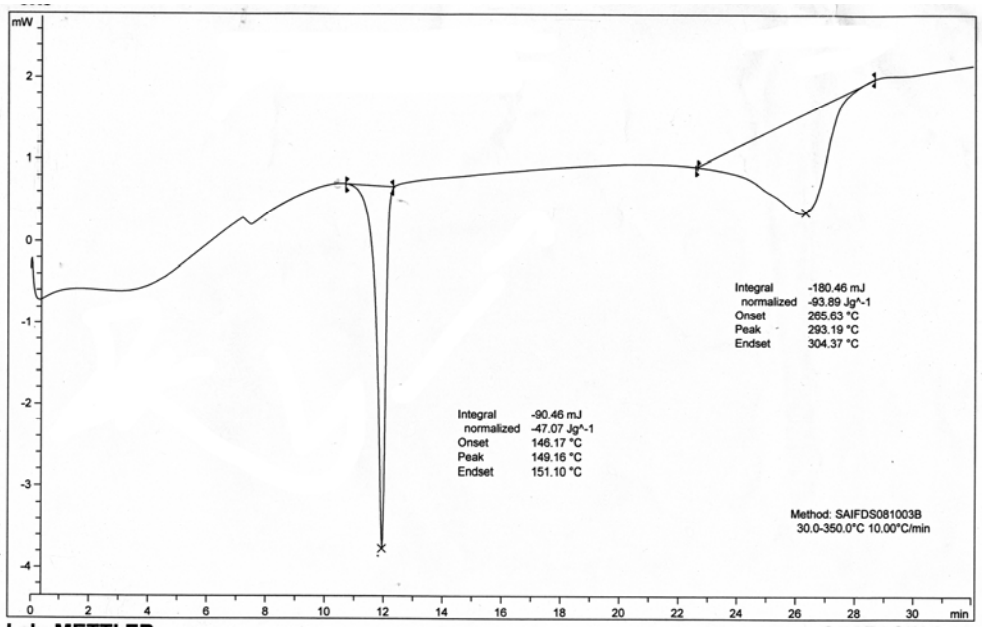


Fig: 23 DSC thermogram of solid dispersion of Etodolac with PGS(Maize) (1: 1) KM

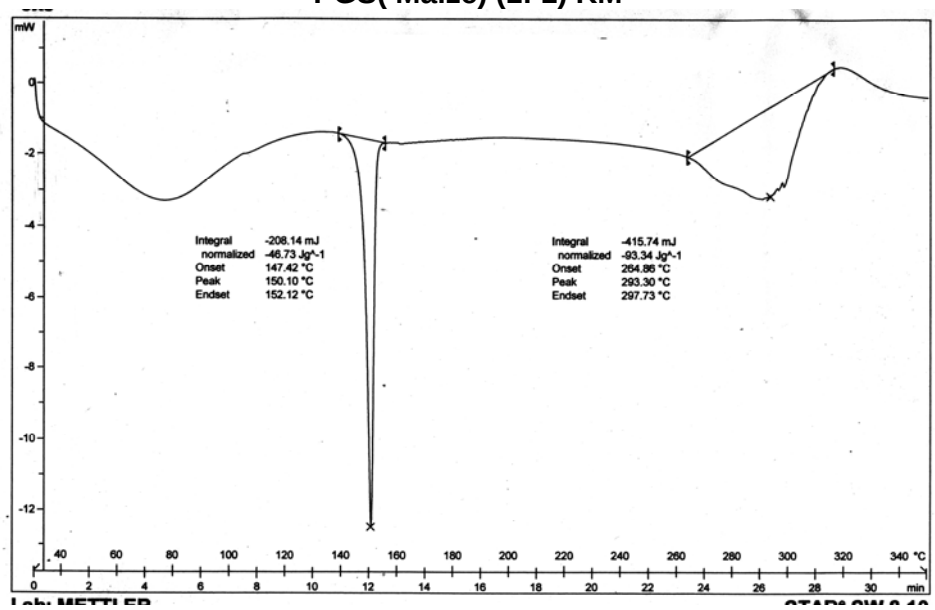


Fig: 24 DSC thermogram of solid dispersion of Etodolac with PGS(Potato) (1: 1) SE

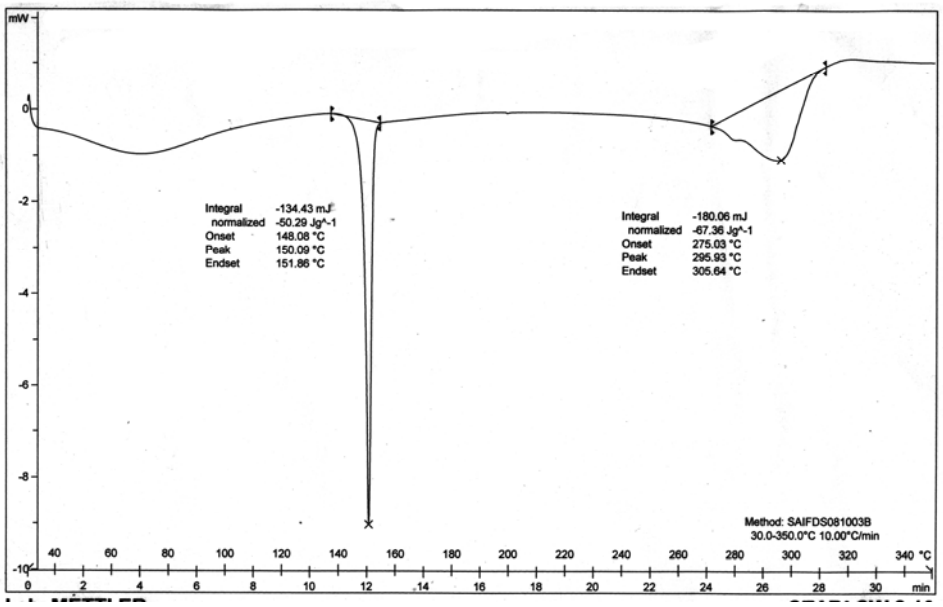


Fig: 25 DSC thermogram of solid dispersion of Etodolac with PGS (Tapioca) (1: 1) SE

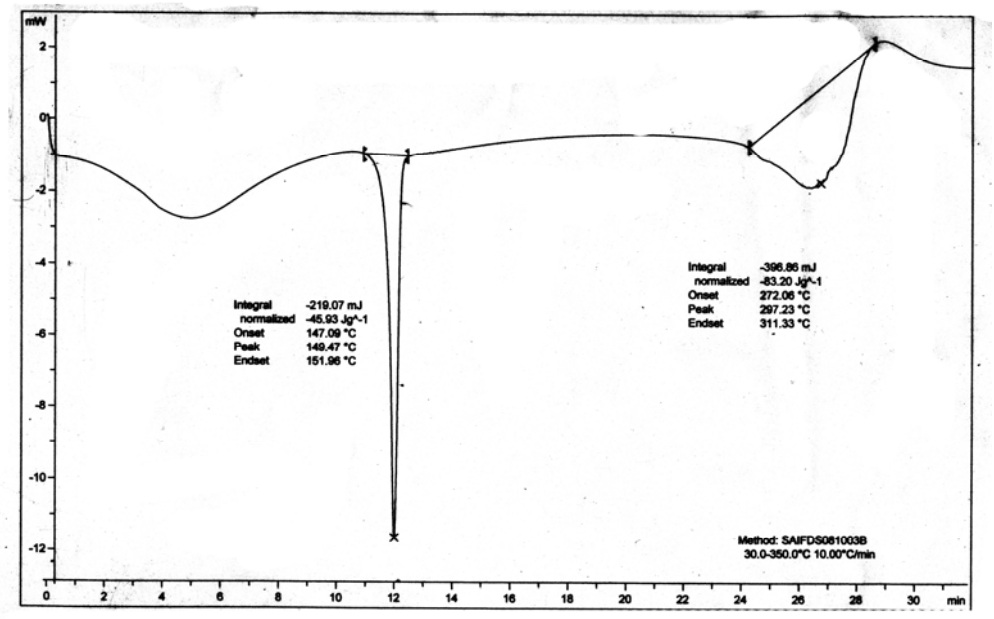


Fig: 26 DSC thermogram of solid dispersion of Etodolac with PGS(Maize) (1: 1) SE

Scanning Electron Microscopy

Particle surface of the prepared solid dispersion were analysed by JSM-6390 instrument.The instrument was operated at a voltage of 20 kV.For pure drug and various solid dispersions the particle surface were observed in the following Fig 27-30.

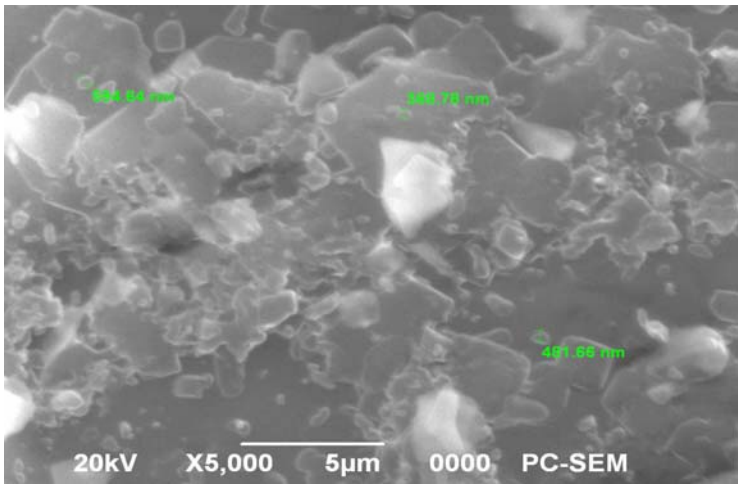


Fig: 27 Scanning Electron Microscopy of Pure drug Etodolac at 5000X

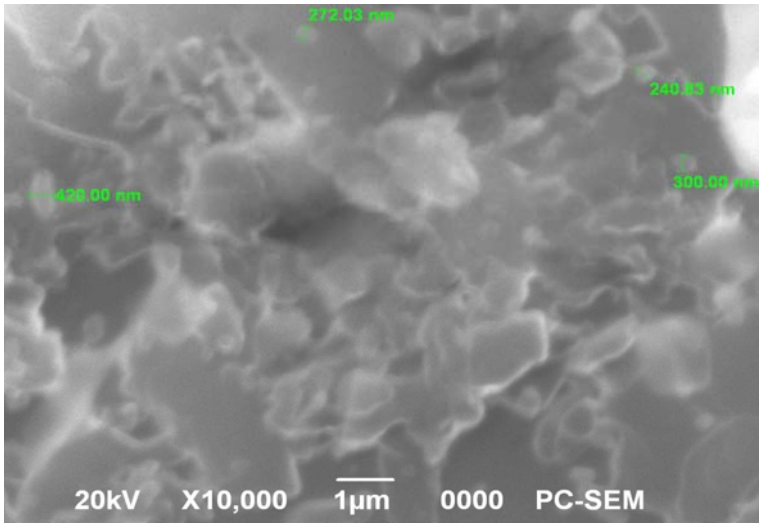


Fig : 28 Scanning Electron Microscopy of Pure drug Etodolac at 10,000X

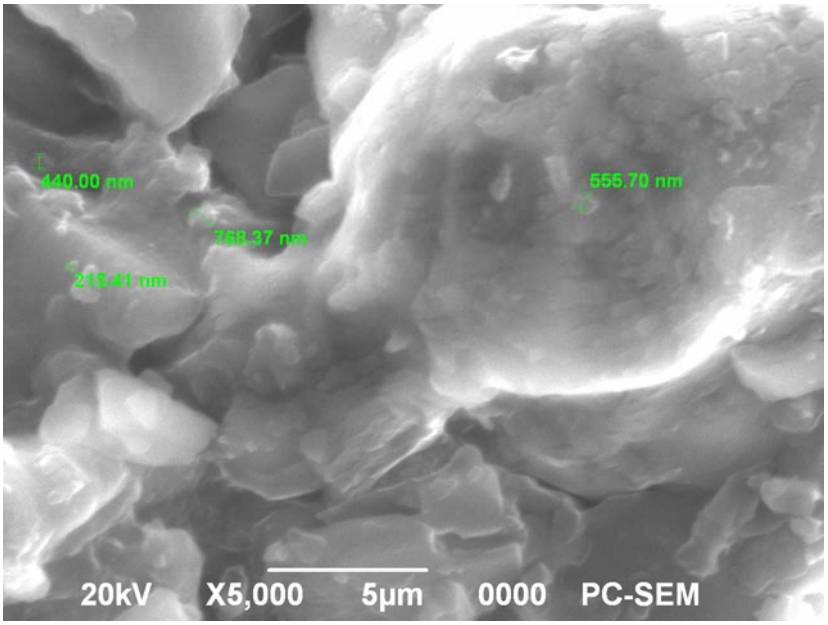


Fig:29 Scanning Electron Microscopy of Etodolac: PGS(Potato) Solid dispersion (1:19) KM at 5000X

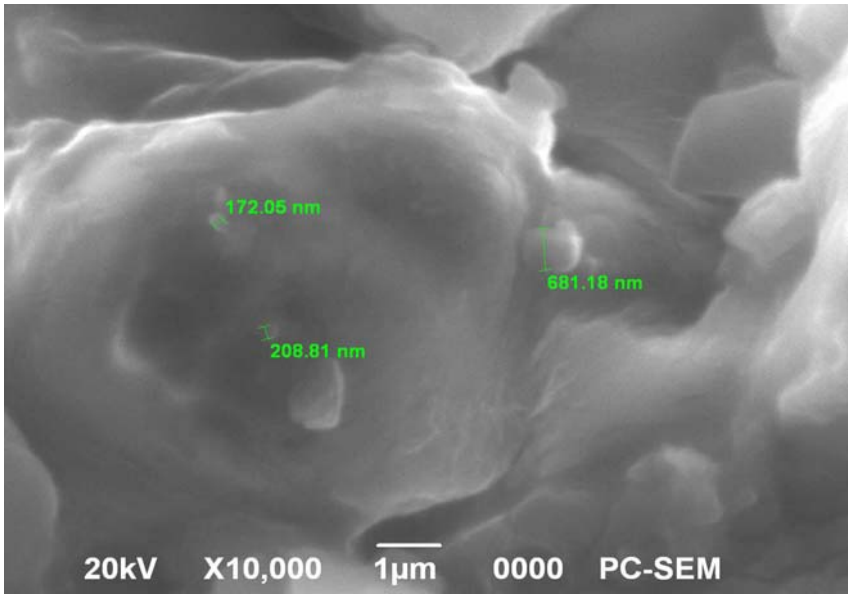


Fig : 30 Scanning Electron Microscopy of Etodolac: PGS(Potato) Solid dispersion (1:19) KM at 10,000X

Drug Content uniformity

The prepared Etodolac solid dispersion was tested for drug content uniformity. From each bach of solid dispersion prepared in different ratios,equivalent to 100 mg of Etodolac solid dispersion were taken and analyzed for drug content uniformity.

Estimation of Etodolac in solid dispersion by UV Spectroscopy:

Accurately weighed amount of solid dispersion was dissolved in 100 ml of pH 6.8 phosphate buffer in 100 ml volumetric flask which was previously clean and dry. This solution after suitable dilution was measured for absorbance at 274 nm in a Jasco V530 UV visible spectrophotometer. The results were shown in table.9,10.

Table : 9 Drug Content Uniformity in solid dispersions (Kneading method)

Solid dispersion	Drug: Carrier	Amount of S.D taken (mg)	Expected Amount of Etodolac in S.D(mg)	Etodolac estimated by spectrophotometer (%)
Etodolac: PGS(Potato)	1:1	200	100	97.8
	1:3	400	100	101.0
	1:9	1000	100	100.8
	1:19	2000	100	97.8
Etodolac PGS(Tapioca)	1:1	200	100	93.0
	1:3	400	100	94.4
	1:9	1000	100	102.8
	1:19	2000	100	99.8
Etodolac: PGS (Maize)	1:1	200	100	98.6
	1:3	400	100	96.2
	1:9	1000	100	93.3
	1:19	2000	100	97.8

Table :10 Drug Content Uniformity in solid dispersions (solvent evaporation method)

Solid dispersion	Drug:Carrier	Amount of S.D taken(mg)	Expected Amount of Etodolac in S.D(mg)	Etodolac estimated by spectrophoto meter(%)
Etodolac: PGS(Potato)	1:1	200	100	94.8
	1:3	400	100	97.3
	1:9	1000	100	95.6
	1:19	2000	100	95.2
Etodolac: PGS(Tapioca)	1:1	200	100	100.0
	1:3	400	100	95.1
	1:9	1000	100	93.6
	1:19	2000	100	98.8
Etodolac: PGS (Maize)	1:1	200	100	98.4
	1:3	400	100	94.8
	1:9	1000	100	96.2
	1:19	2000	100	99.5

***In-vitro* dissolution studies**

The dissolution studies are the most important part of the evaluation of solid dispersion, where the dissolution of pure drug and solid dispersion is carried out. Dissolution rate studies of various solid dispersions were carried out in phosphate buffer of PH 6.8 using USP XXII dissolution apparatus (Electro lab).

Dissolution method

900 ml of phosphate buffer of PH 6.8 was used as dissolution medium. SDs equivalent to 100 mg of Etodolac was taken in a hard gelatin capsule; a stainless steel wire was wound around the capsule to sink. The paddle type stirrer was adjusted to 100 rpm. The temperature was maintained at 37°±0.5°c. 10 ml aliquot dissolution media was

withdrawn at different time intervals and volume withdrawn was replaced with fresh quantity of dissolution medium. The samples were analyzed for Etodolac after suitable dilution by measuring the absorption values at 274 nm using Jasco V 530 UV visible spectrophotometer. Phosphate buffer of pH 6.8 used as a blank. The percentage of Etodolac dissolved at various time intervals was calculated and plotted against time. T_{50}, T_{90} values were calculated from these dissolution curves.[31,37] The results are shown in table.11-16 and fig. 32-37.

Fig: 31 Dissolution apparatus

Table: 11 Dissolution Profile of Etodolac from PGS(Potato) solid dispersion at different drug carrier ratios (kneading method)

Time in minutes	Percentage release of Etodolac from different drug carrier ratios					
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9	1:19
0	0	0	0	0	0	0
5	1.48	1.50	1.52	1.54	1.67	1.99
10	2.99	3.65	3.78	3.69	3.86	3.91
15	4.01	7.49	8.51	9.61	10.25	15.95
30	7.37	15.61	20.97	24.68	34.35	36.40
45	17.39	27.13	63.86	67.83	76.91	86.15

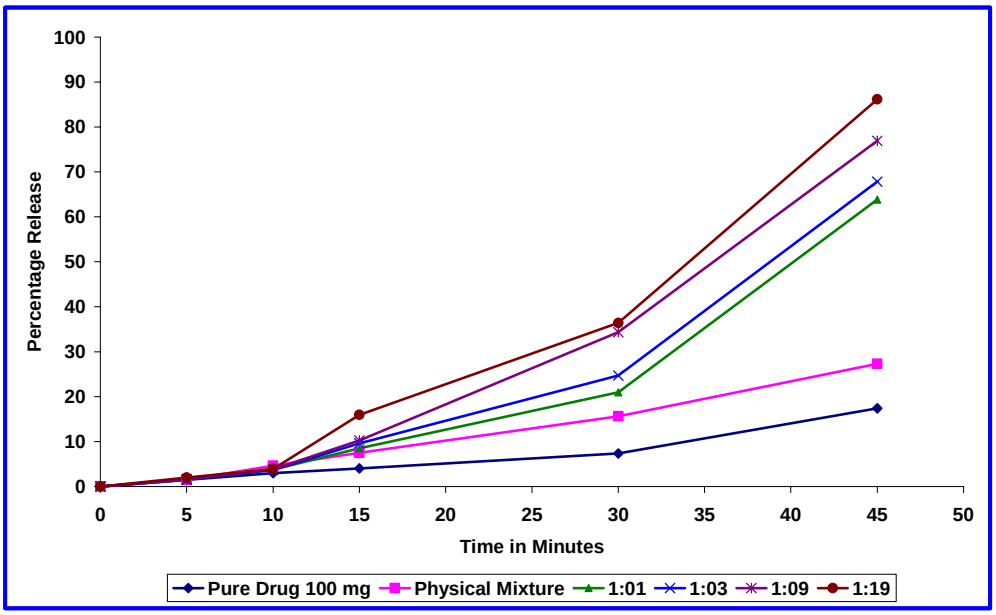


Fig: 32 Dissolution Profile of Etodolac from PGS(Potato) solid dispersion at different drug carrier ratios (kneading method)

Table:12 Dissolution Profile of Etodolac from PGS(Tapioca) solid dispersion at different drug carrier ratios (kneading method)

Time in minutes	Percentage release of Etodolac from different drug carrier ratios					
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9	1:19
0	0	0	0	0	0	0
5	1.48	1.63	1.71	1.83	1.91	1.96
10	2.99	3.01	3.52	3.58	4.01	4.12
15	4.01	6.54	7.41	8.01	8.53	8.71
30	7.37	14.23	20.23	21.45	20.83	24.05
45	17.39	25.15	55.86	60.45	62.93	76.01

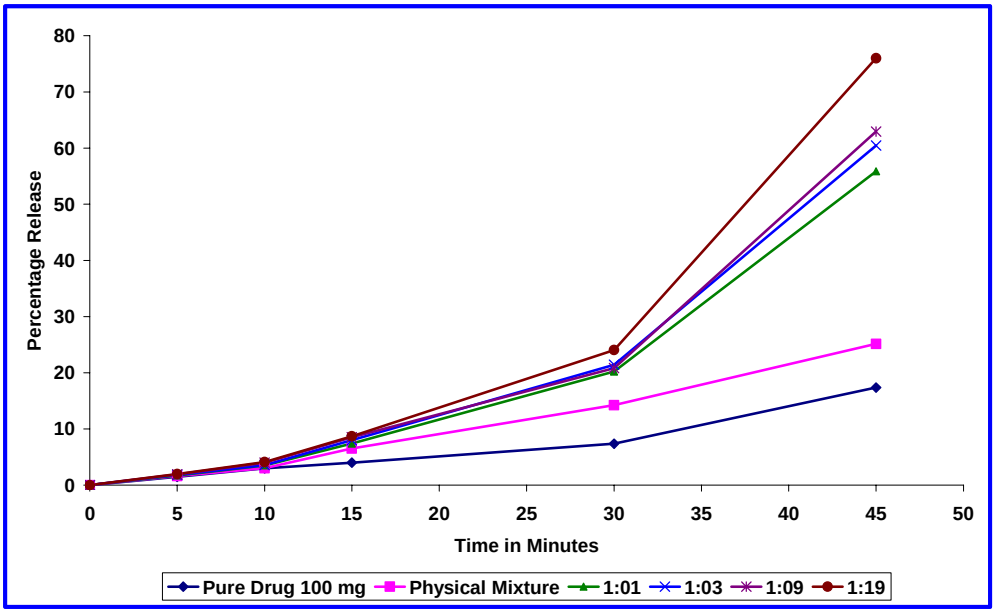


Fig: 33 Dissolution Profile of Etodolac from PGS(Tapioca) solid dispersion at different drug carrier ratios (kneading method)

Table : 13 Dissolution Profile of Etodolac from PGS(Maize) solid dispersion at different drug carrier ratios (kneading method)

Time in minutes	Percentage release of Etodolac from different drug carrier ratios					
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9	1:19
0	0	0	0	0	0	0
5	1.48	1.81	1.91	1.91	1.97	1.98
10	2.99	3.51	3.61	3.72	3.89	3.96
15	4.01	5.85	6.41	7.43	8.59	10.05
30	7.37	17.21	19.25	20.31	21.76	25.48
45	17.39	28.31	44.58	58.51	59.48	75.99

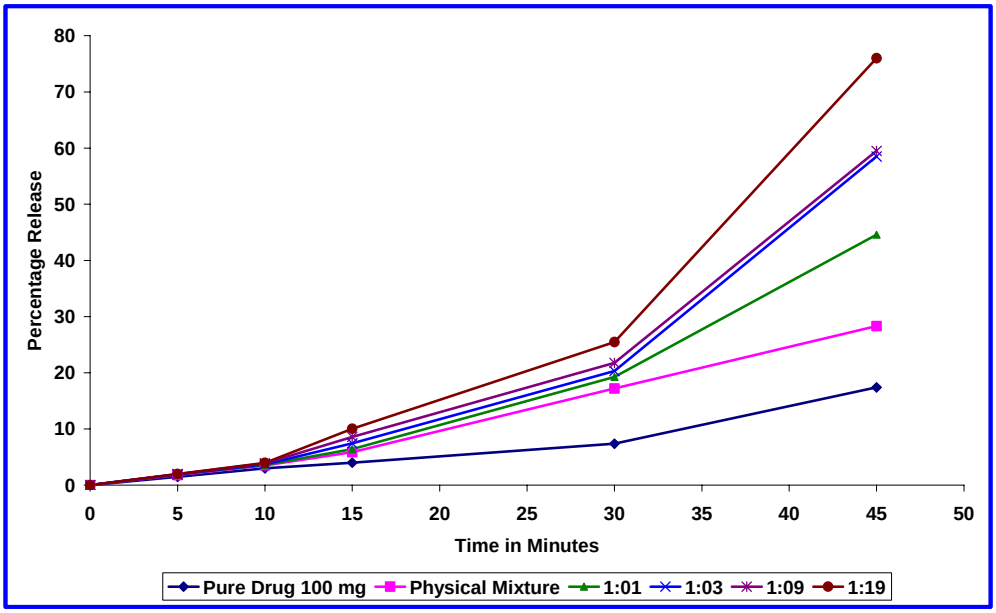


Fig: 34 Dissolution Profile of Etodolac from PGS(Maize) solid dispersion at different drug carrier ratios (kneading method)

Table : 14 Dissolution Profile of Etodolac from PGS(Potato) solid dispersion at different drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage release of Etodolac from different drug carrier ratios					
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9	1:19
0	0	0	0	0	0	0
5	1.48	1.50	1.51	1.53	1.64	1.89
10	2.99	3.65	3.79	4.01	4.18	4.29
15	4.01	7.49	7.99	8.03	8.99	9.23
30	7.37	15.61	19.98	22.09	24.95	25.09
45	17.39	27.13	47.89	58.87	74.98	83.17

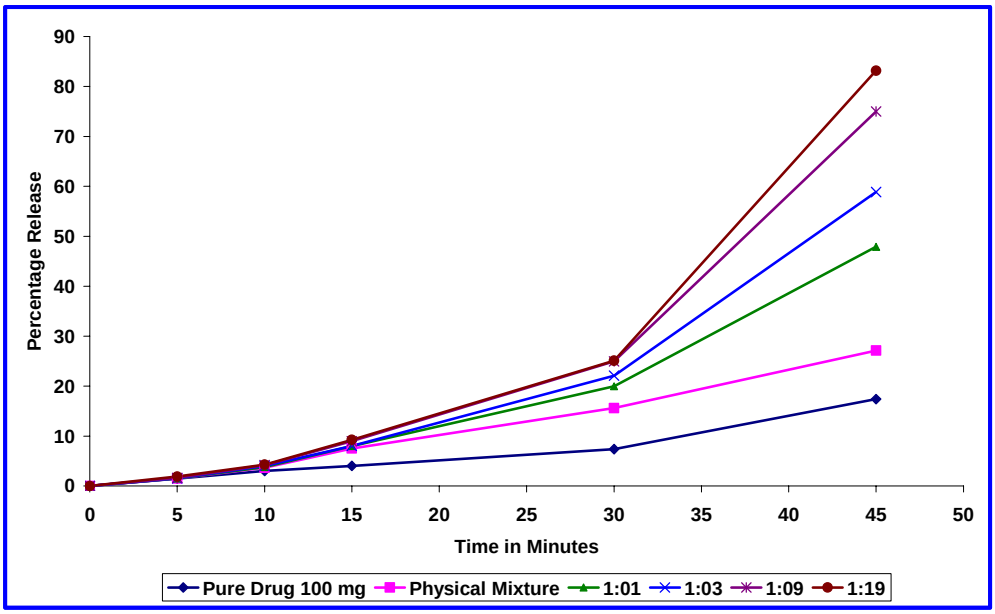


Fig: 35 Dissolution Profile of Etodolac from PGS(Potato) solid dispersion at different drug carrier ratios (solvent evaporation method)

Table: 15 Dissolution Profile of Etodolac from PGS(Tapioca) solid dispersion at different drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage release of Etodolac from different drug carrier ratios					
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9	1:19
0	0	0	0	0	0	0
5	1.48	1.63	1.69	1.73	1.74	1.81
10	2.99	3.01	3.41	3.50	3.89	3.90
15	4.01	6.54	6.94	7.57	8.18	8.19
30	7.37	14.23	22.25	23.68	26.25	27.34
45	17.39	25.15	49.03	63.68	72.58	77.51

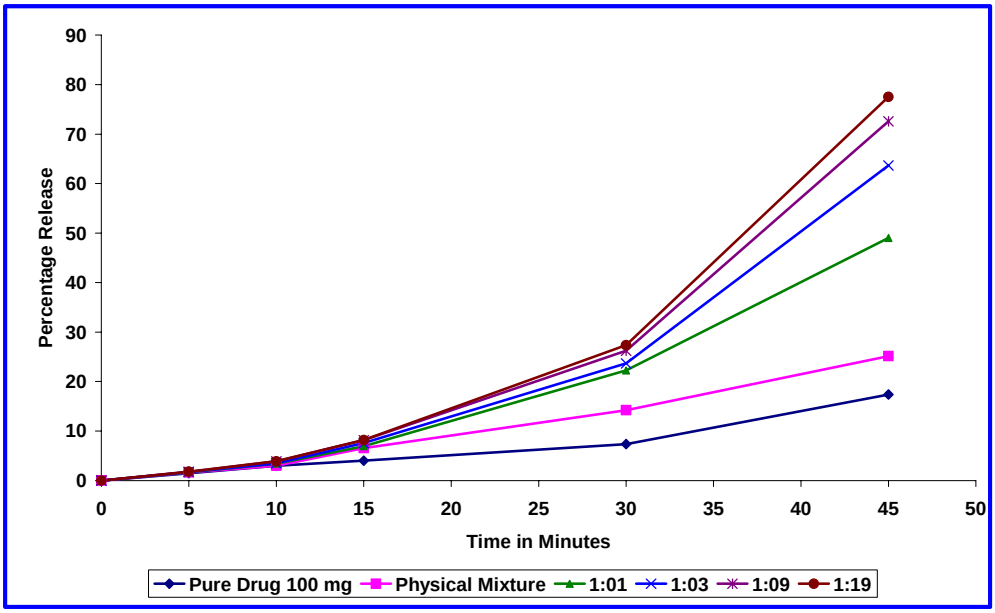


Fig: 36 Dissolution Profile of Etodolac from PGS(Tapioca) solid dispersion at different drug carrier ratios (solvent evaporation method)

Table: 16 Dissolution Profile of Etodolac from PGS(Maize) solid dispersion at different drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage release of Etodolac from different drug carrier ratios					
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9	1:19
0	0	0	0	0	0	0
5	1.48	1.81	1.95	1.96	1.96	1.98
10	2.99	3.51	3.53	3.51	3.54	3.60
15	4.01	5.85	5.99	6.03	7.12	7.35
30	7.37	17.21	17.91	20.15	23.49	29.05
45	17.39	28.31	51.05	63.94	70.47	75.35

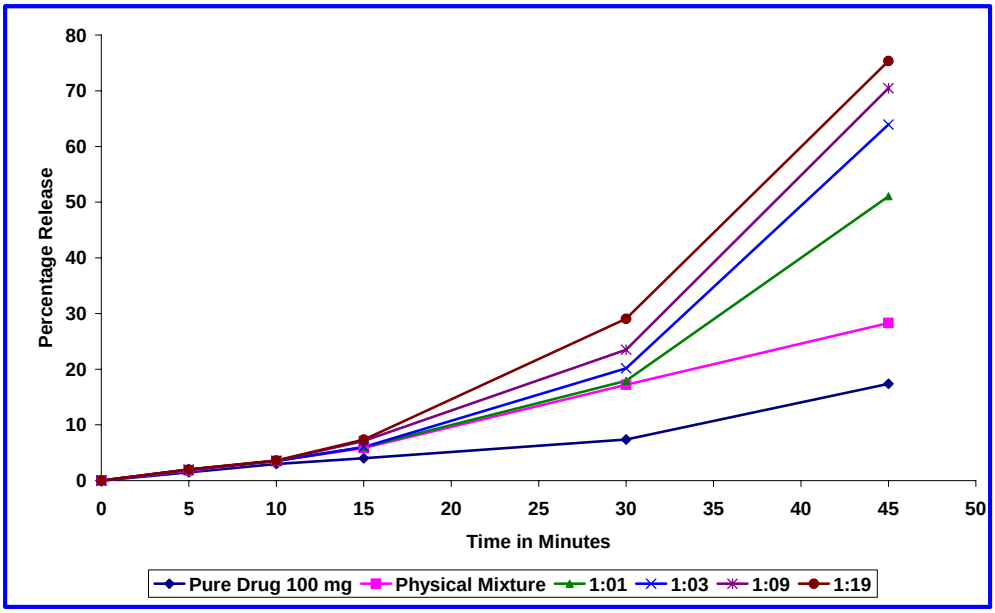


Fig: 37 Dissolution Profile of Etodolac from PGS(Maize) solid dispersion at different drug carrier ratios (solvent evaporation method)

Table : 17 Percentage release of Etodolac from various solid dispersions (kneading method)

Time in minutes	Percentage release of Etodolac from												
	Pure drug	PGS(Potato)				PGS(Tapioca)				PGS(Maize)			
		1:1	1:3	1:9	1:19	1:1	1:3	1:9	1:19	1:1	1:3	1:9	1:19
0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	1.48	1.52	1.54	1.67	1.99	1.71	1.83	1.91	1.96	1.91	1.91	1.97	1.98
10	2.99	3.78	3.69	3.86	3.91	3.52	3.58	4.01	4.12	3.61	3.72	3.89	3.96
15	4.01	8.51	9.61	10.25	15.95	7.41	8.01	8.53	8.71	6.41	7.43	8.59	10.05
30	7.37	20.97	24.68	34.35	36.40	20.23	21.45	20.83	24.05	19.25	20.31	21.76	25.48
45	17.39	63.86	67.83	76.91	86.15	55.86	60.45	62.93	76.01	44.58	58.51	59.48	75.99

Table : 18 Percentage release of Etodolac from various solid dispersions (solvent evaporation method)

Time in minutes	Percentage release of Etodolac from												
	Pure drug	PGS(Potato)				PGS(Tapioca)				PGS(Maize)			
		1:1	1:3	1:9	1:19	1:1	1:3	1:9	1:19	1:1	1:3	1:9	1:19
0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	1.48	1.51	1.53	1.64	1.89	1.69	1.73	1.74	1.81	1.95	1.96	1.96	1.98
10	2.99	3.79	4.01	4.18	4.29	3.41	3.50	3.89	3.90	3.53	3.51	3.54	3.60
15	4.01	7.99	8.03	8.99	9.23	6.94	7.57	8.18	8.19	5.99	6.03	7.12	7.35
30	7.37	19.98	22.09	24.95	25.09	22.25	23.68	26.25	27.34	17.91	20.15	23.49	29.05
45	17.39	47.89	58.87	74.98	83.17	49.03	63.68	72.58	77.51	51.05	63.94	70.47	75.35

Table:19 Relation between % carrier and T_{50}, T_{90} values for Etodolac:PGS(Potato) solid dispersions

% of drug	%of carrier	T_{50} (min)		T_{90} (min)	
		KM	SE	KM	SE
1	1	40.25	-	-	-
1	3	38.00	41.00	-	-
1	9	34.75	37.75	-	-
1	19	33.25	35.75	-	-

Table:20 Relation between % carrier and T_{50}, T_{90} values for Etodolac:PGS(Tapioca) solid dispersions

% of drug	%of carrier	T_{50} (min)		T_{90} (min)	
		KM	SE	KM	SE
1	1	42.50	-	-	-
1	3	41.00	40.00	-	-
1	9	40.00	38.00	-	-
1	19	37.50	37.00	-	-

Table: 21 Relation between % carrier and T_{50}, T_{90} values for Etodolac:PGS(Maize) solid dispersions:

% of drug	% of carrier	T_{50} (min)		T_{90} (min)	
		KM	SE	KM	SE
1	1	-	44.50	-	-
1	3	41.50	40.25	-	-
1	9	41.25	38.50	-	-
1	19	37.50	37.00	-	-

Table : 22 Percentage Etodolac undissolved from pure form and from PGS (Potato) solid dispersions at various drug carrier ratios (kneading method)

Time in minutes	Percentage Etodolac undissolved from (log percentage Etodolac undissolved)					
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9	1:19
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
5	98.52 (1.9935)	98.5 (1.9934)	98.48 (1.9933)	98.46 (1.9932)	98.33 (1.9926)	98.01 (1.9912)
10	97.01 (1.9868)	96.35 (1.9838)	96.22 (1.9832)	96.31 (1.9836)	96.14 (1.9829)	96.09 (1.9826)
15	95.99 (1.9822)	92.51 (1.9661)	91.49 (1.9613)	90.39 (1.9561)	89.75 (1.9530)	84.05 (1.9245)
30	92.63 (1.9667)	84.39 (1.9262)	79.03 (1.8977)	75.32 (1.8769)	65.65 (1.8172)	63.60 (1.8034)
45	82.61 (1.9170)	72.87 (1.8625)	36.14 (1.5579)	32.17 (1.5074)	23.09 (1.3634)	13.85 (1.1414)

Fig: 38 Percentage Etodolac undissolved from pure form and from PGS (Potato) solid dispersions at various drug carrier ratios (kneading method)

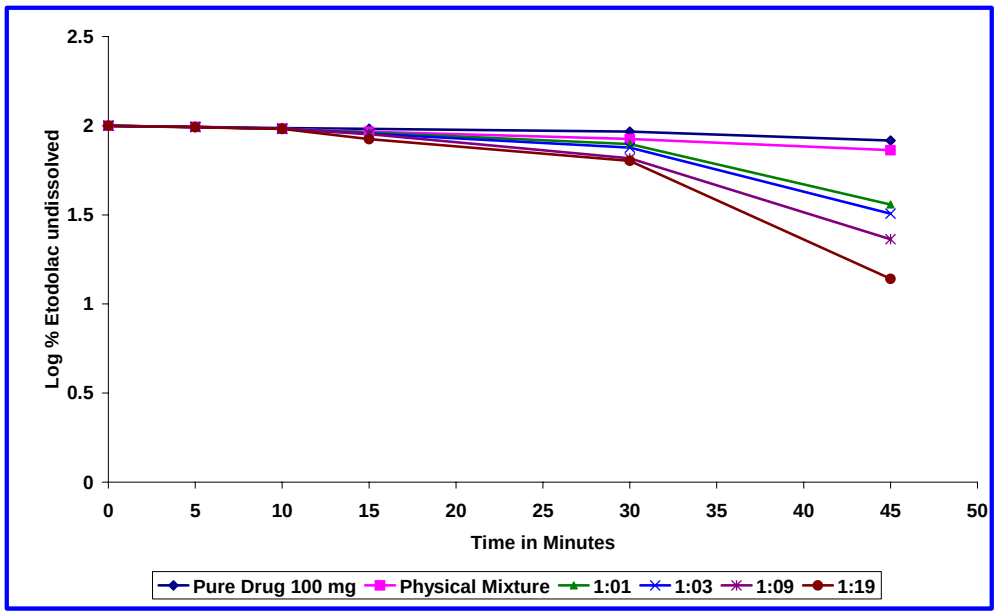


Table : 23 Percentage Etodolac undissolved from pure form and from PGS (Tapioca) solid dispersions at various drug carrier ratios (kneading method)

Time in minutes	Percentage Etodolac undissolved from (log percentage Etodolac undissolved)					
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9	1:19
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
5	98.52 (1.9935)	98.37 (1.9928)	98.29 (1.9925)	98.17 (1.9919)	98.09 (1.9916)	98.04 (1.9914)
10	97.01 (1.9868)	96.99 (1.9867)	96.48 (1.9844)	96.42 (1.9841)	95.99 (1.9822)	95.88 (1.9817)
15	95.99 (1.9822)	93.46 (1.9706)	92.59 (1.9665)	91.99 (1.9637)	91.47 (1.9612)	91.29 (1.9604)
30	92.63 (1.9667)	85.77 (1.9333)	79.77 (1.9018)	78.55 (1.8951)	79.17 (1.8985)	75.95 (1.8805)
45	82.61 (1.9170)	74.85 (1.8741)	44.14 (1.6448)	39.55 (1.5971)	37.07 (1.5690)	23.99 (1.3800)

Fig: 39 Percentage Etodolac undissolved from pure form and from PGS (Tapioca) solid dispersions at various drug carrier ratios (kneading method)

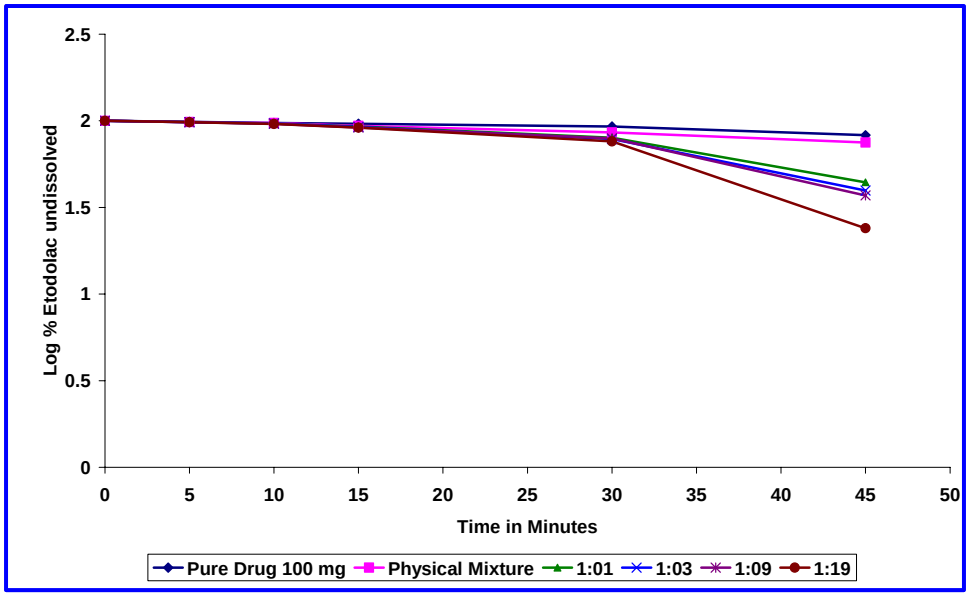


Table :24 Percentage Etodolac undissolved from pure form and from PGS(Maize) solid dispersions at various drug carrier ratios (kneading method)

Time in minutes	Percentage Etodolac undissolved from (log percentage Etodolac undissolved)					
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9	1:19
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
5	98.52 (1.9935)	98.19 (1.9920)	98.09 (1.9916)	98.09 (1.9916)	98.03 (1.9913)	98.02 (1.9913)
10	97.01 (1.9868)	96.49 (1.9844)	96.39 (1.9840)	96.28 (1.9835)	96.11 (1.9827)	96.04 (1.9824)
15	95.99 (1.9822)	94.15 (1.9738)	93.59 (1.9712)	92.57 (1.9664)	91.41 (1.9609)	89.95 (1.9540)
30	92.63 (1.9667)	82.79 (1.9179)	80.75 (1.9071)	79.69 (1.9014)	78.24 (1.8934)	74.52 (1.8722)
45	82.61 (1.9170)	71.69 (1.8554)	55.42 (1.7436)	41.49 (1.6179)	40.52 (1.6076)	24.01 (1.3803)

Fig: 40 Percentage Etodolac undissolved from pure form and from PGS(Maize) solid dispersions at various drug carrier ratios (kneading method)

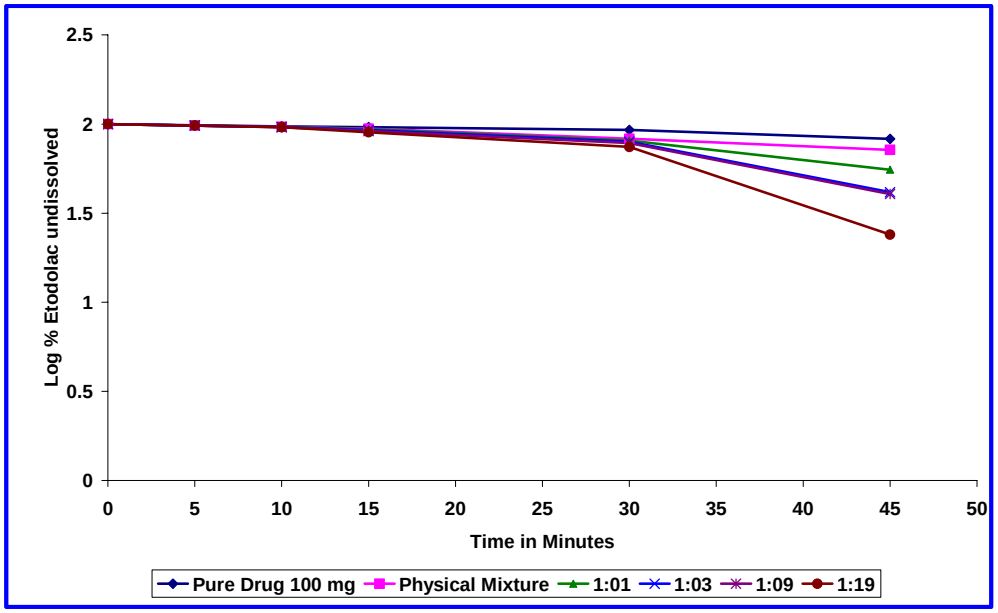


Table :25 Percentage Etodolac undissolved from pure form and from PGS (Potato) solid dispersions at various drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage Etodolac undissolved from (log percentage Etodolac undissolved)					
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9	1:19
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
5	98.52 (1.9935)	98.5 (1.9934)	98.49 (1.9933)	98.47 (1.9933)	98.36 (1.9928)	98.11 (1.9917)
10	97.01 (1.9868)	96.35 (1.9838)	96.21 (1.9832)	95.99 (1.9822)	95.82 (1.9814)	95.71 (1.9809)
15	95.99 (1.9822)	92.51 (1.9661)	92.01 (1.9638)	91.97 (1.9636)	91.01 (1.9590)	90.77 (1.9579)
30	92.63 (1.9667)	84.39 (1.9262)	80.02 (1.9031)	77.91 (1.8915)	75.05 (1.8753)	74.91 (1.8745)
45	82.61 (1.9170)	72.87 (1.8625)	52.11 (1.7169)	41.13 (1.6141)	25.02 (1.3982)	16.83 (1.2260)

Fig: 41 Percentage Etodolac undissolved from pure form and from PGS (Potato) solid dispersions at various drug carrier ratios (solvent evaporation method)

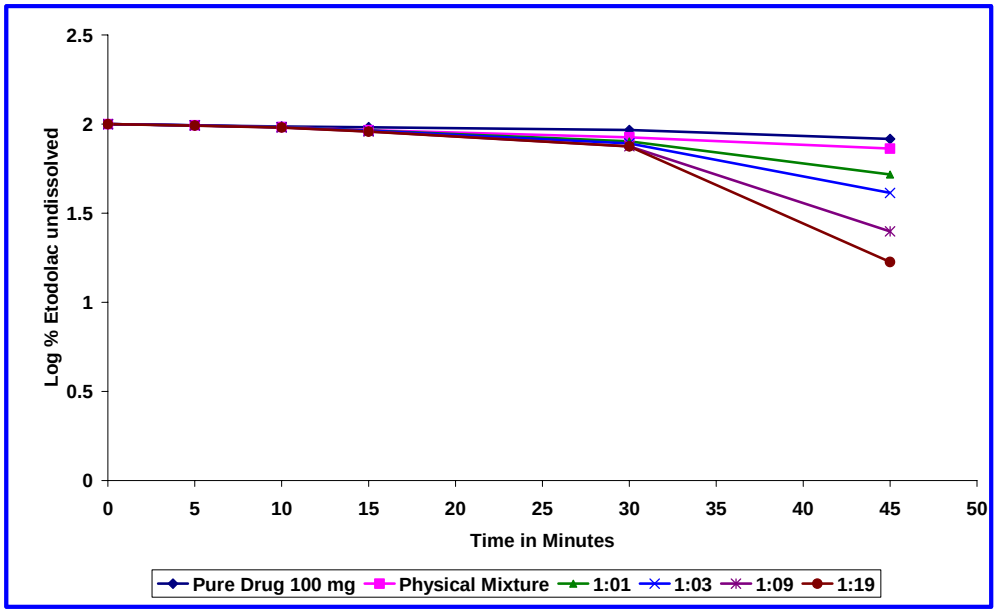


Table : 26 Percentage Etodolac undissolved from pure form and from PGS (Tapioca) solid dispersions at various drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage Etodolac undissolved from (log percentage Etodolac undissolved)					
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9	1:19
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
5	98.52 (1.9935)	98.37 (1.9928)	98.31 (1.9925)	98.27 (1.9924)	98.26 (1.9923)	98.19 (1.9920)
10	97.01 (1.9868)	96.99 (1.9867)	96.59 (1.9849)	96.50 (1.9845)	96.11 (1.9827)	96.10 (1.9827)
15	95.99 (1.9822)	93.46 (1.9706)	93.06 (1.9687)	92.43 (1.9658)	91.82 (1.9629)	91.81 (1.9628)
30	92.63 (1.9667)	85.77 (1.9333)	77.75 (1.8907)	76.32 (1.8826)	73.75 (1.8677)	72.66 (1.8612)
45	82.61 (1.9170)	74.85 (1.8741)	50.97 (1.7073)	36.32 (1.5601)	27.42 (1.4380)	22.49 (1.3519)

Fig: 42 Percentage Etodolac undissolved from pure form and from PGS (Tapioca) solid dispersions at various drug carrier ratios (solvent evaporation method)

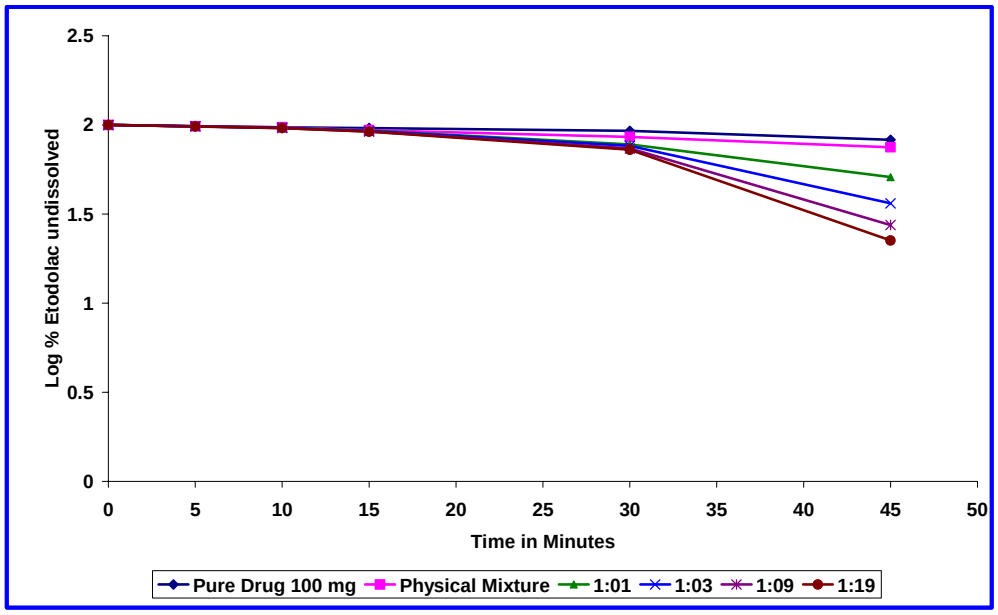


Table : 27 Percentage Etodolac undissolved from pure form and from PGS(Maize) solid dispersions at various drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage Etodolac undissolved from (log percentage Etodolac undissolved)					
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9	1:19
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
5	98.52 (1.9935)	98.19 (1.9920)	98.05 (1.9914)	98.04 (1.9914)	98.04 (1.9914)	98.02 (1.9913)
10	97.01 (1.9868)	96.49 (1.9844)	96.47 (1.9843)	96.49 (1.9844)	96.46 (1.9843)	96.40 (1.9840)
15	95.99 (1.9822)	94.15 (1.9738)	94.01 (1.9731)	93.97 (1.9729)	92.88 (1.9679)	92.65 (1.9668)
30	92.63 (1.9667)	82.79 (1.9179)	82.09 (1.9142)	79.85 (1.9022)	76.51 (1.8837)	70.95 (1.8509)
45	82.61 (1.9170)	71.69 (1.8554)	48.95 (1.6897)	36.06 (1.5570)	29.53 (1.4702)	24.65 (1.3918)

Fig: 43 Percentage Etodolac undissolved from pure form and from PGS(Maize) solid dispersions at various drug carrier ratios (solvent evaporation method)

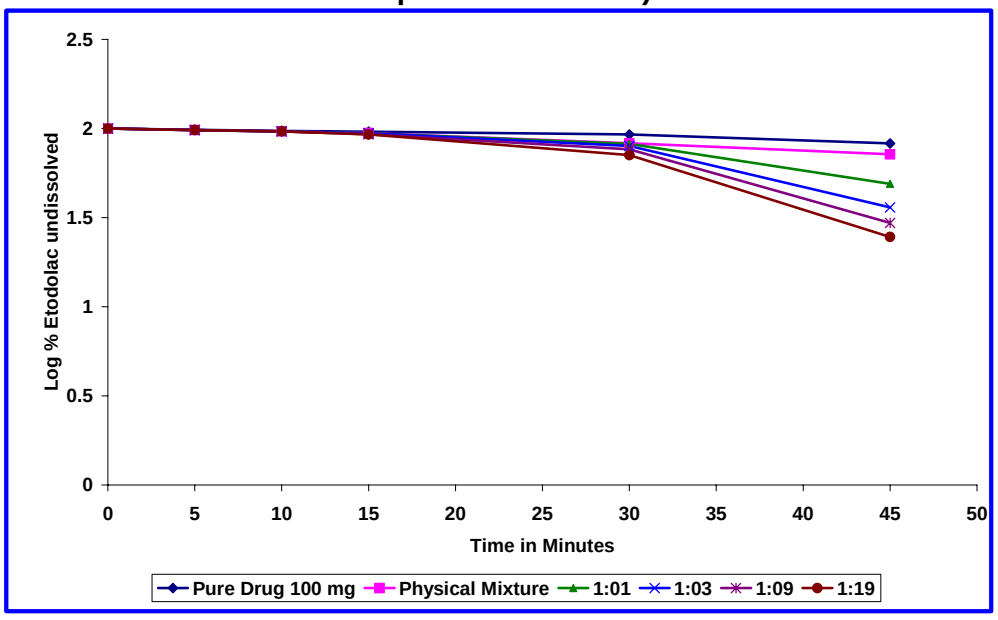


Table : 28 First order rate constant for Etodolac dissolution from various solid dispersions

Sample	K (min $^{-1}$)	
	KM	SE
Pure drug	0.0050	
Physical mixture		
ETD: PGS(Potato)	0.0060	
ETD:PGS(Tapioca)	0.0100	
ETD: PGS(Maize)	0.0053	
Solid dispersion		
ETD: PGS(Potato)		
1:1	0.0233	0.0125
1:3	0.0250	0.0184
1:9	0.0300	0.0350
1:19	0.0454	0.0416
ETD: PGS(Tapioca)		
1:1	0.0181	0.0130
1:3	0.0194	0.0208
1:9	0.0233	0.0291
1:19	0.0333	0.0333
ETD: PGS(Maize)		
1:1	0.0119	0.0145
1:3	0.0194	0.0233
1:9	0.0197	0.0250
1:19	0.0300	0.0333

RESULTS AND DISCUSSION

Solid dispersion of Etodolac were prepared by depositing on the polymers namely PGS (Potato), PGS (Tapioca) and PGS(Maize) by solvent evaporation method and kneading method. Solid dispersions at different drug: carrier ratios (1:1, 1:3, 1:9, 1:19) were prepared . All solid dispersions prepared were found to be fine and free flowing powders. The percent of drug content in the solid dispersions were given in table 9,10. There was no significant loss of drug during the preparation of solid dispersions and the proportion of drug and carrier remained the same as that initially taken. The estimated drug content of the prepared solid dispersions was in the range of 100±7%.

The prepared solid dispersions were characterized by TLC, FTIR, X-ray diffraction, Scanning Electron Microscopy and Differential Scanning Calorimetry

Thin Layer Chromatography

In TLC studies, Etodolac dispersed in various carriers showed the same R_f value as pure compound and no additional spots were detected. TLC studies thus indicated no interaction between Etodolac and carriers in the solid dispersions prepared. This observation also indicated that Etodolac was not decomposed during the preparation of solid dispersions.

FT-IR Spectral Analysis

Compatibility studies of Etodolac and the carriers PGS (Potato), PGS (Tapioca) and PGS(Maize) were carried out by using FT-IR. The IR spectra obtained are given in fig 2-11. In Etodolac IR spectrum, intense peaks were noticed at 1746 cm^{-1} (– C=O stretching),1412 cm^{-1} (– NH bending), 1034 cm^{-1} (C–O stretching) and 748 cm^{-1} (monosubstituted benzene).

IR spectra of Etodolac and its solid dispersions are identical. The principal IR absorption peaks of Etodolac were all observed in the spectra of Etodolac as well as its dispersions. IR spectra indicated no interaction between Etodolac and carriers in the solid dispersions.

Powder X- Ray Diffraction

The X-ray diffraction pattern of pure drug Etodolac showed a numerous distinctive peaks indicating a high crystallinity. Diffraction pattern of solid dispersions showed reduction in intensive peaks .This indicates conformation of changing the nature of the compound from crystalline to amorphous nature shown in fig:13-19.

Differential Scanning Calorimetry

The thermal behaviour of solid dispersions of Etodolac with PGS prepared from Potato, Tapioca and Maize at 1:1 ratio prepared by kneading and solvent evaporation method was studied using DSC to confirm the formation of solid complexes are shown in fig:20-26.The DSC thermogram of pure drug Etodolac exhibited an endothermic peak at

150.66^{0}C corresponding to its melting point. The two peaks in the thermogram is due to different polymorphic form of the drug. For solid dispersion systems such as ETD:PGS(Potato) KM, ETD: PGS (Tapioca) KM, ETD: PGS (Maize) KM, ETD: PGS(Potato) SE, ETD: PGS (Tapioca) SE and ETD: PGS(Maize) SE at 1:1 ratio this peaks are at 149.55^{0}C , 149.42^{0}C, 149.16^{0}C,150.10^{0}C,150.09^{0}C and 149.47^{0}C respectively. A reduction in intensity of endothermic peak is observed in all solid dispersions indicative of amorphous change from crystallinity. Furthermore, the characteristic endothermic peak is slightly shifted to lower temperature, indicating that there is no interaction between drug and carrier.

Scanning Electron Microscopy

Needle shaped crystals were clearly evident from scanning electron microscopy of pure drug indicating high crystallinity of the active moiety under 5000X and 10,000X magnification shown in fig:29-30.Under same magnifications it was found that the surface of the solid dispersion of drug and PGS(Potato) at 1:19 ratio prepared by kneading method were seen as swollen fragmented particles. Resulted picture has been shown in fig : 27-30.

***In- vitro* dissolution Studies**

The dissolution profiles of pure drug, physical mixture and various solid dispersions were given in table11-16 . and fig. 32-37 The dissolution parameters of T_{50} and dissolution rate indicates rapid dissolution of Etodolac from the solid dispersions when compared with the pure drug and physical mixture as the proportion of the polymer in the dispersion was increased the dissolution rate of Etodolac also increased. T_{50} values were found to be decreased and K values found to be increased when the carrier concentration was raised indicating the fast dissolution of Etodolac at higher carrier concentration. Among the solid dispersions prepared Etodolac: PGS(Potato) (1:19) KM dispersions gave the highest dissolution rate.

The order of dissolution of Etodolac from various carriers is `PGS (Potato) KM > PGS (Potato) SE> PGS (Tapioca) SE> PGS (Tapioca) KM> PGS(Maize) KM> PGS(Maize)SE.

FORMULATION STUDIES ON SELECTED SOLID DISPERSION OF ETODOLAC

Tablets may be defined as solid pharmaceutical dosage forms containing drug substance with or without suitable diluents, prepared by either compression or molding.

Formulation of tablets

Etodolac solid dispersion in PGS(Potato) at a drug carrier ratio of 1:19 were formulated into tablets with usual additives and evaluated for drug release characteristics. Tablets containing 30 mg of Etodolac were prepared using the solid dispersions and other additives as per the formula given in table.29 .

Table : 29 Formula of Etodolac tablets

S.No	Ingredients	Formulations (mgs)
1	Etodolac-Potato PGS (1:19)(KM)	600
2	Microcrystalline cellulose	70.0
3	Povidone	12.5
4	Colloidal silicon dioxide	7.00
5	Magnesium stearate	10.5

Table: 30 Materials used for tablet formulation:

Name of the materials	Name of company
Etodolac: Potato PGS (1:19) drug carrier ratio.	Prepared in the laboratory
Etodolac	Dr. Reddy's Laboratories Ltd, Hyderabad
Povidone	SD Fine chemicals Ltd, Mumbai.
Micro crystalline cellulose	Loba chemie, Mumbai
Colloidal silicon dioxide	Himedia Laboratories Pvt Ltd
Magnesium stearate	SD Fine chemicals Ltd, Mumbai.

Table: 31 Equipments used for tablet formulation

Name of equipment	Name of company
Tablet punching machine	Rimek Mini Press 1
Tablet disintegration test apparatus	Remi equipments
Pfizer tablet hardness tester	Scientific engineering corporation
Roche friability tester	Remi equipments
Dissolution apparatus	Electrolab TDT – 08L
UV spectrometer	Jasco V 530 UV spectrophotometer
pH tester 1 (water proof)	Oakton instruments.

Method

The required amount of drug and the other additives were mixed thoroughly in a mortar and the tablets are prepared by direct compression using Rimek Mini Press 1 punching machine. The prepared tablets were stored in screw capped glass bottles. The prepared tablets were evaluated for dissolution characteristics.

EVALUATION OF TABLETS

The formulated tablets were subjected for the following quality control tests.[37,57]

- Weight variation
- Disintegration test
- Friability
- Hardness
- Drug content uniformity
- Dissolution

Weight variation test

Twenty tablets were taken weighed individually. They were evaluated for the weight variations. The weight variation allowed as IP limit is ± 5%. The weight of tablets with in the IP limits. The results were shown in table 32.

Disintegration test

The USP device to test disintegration uses six glass tubes that are three inches long open at the top and held against 10 inch screen at the basket rack assembly. A tablet is placed in

each tube and the basket is positioned in a 1 litre beaker of distilled water at 37±2°C, such that the tablets below the surface of the liquid on their movement and descend not closer than 2.5 cm from the bottom of the tester. The disintegration time is 4 min. 45 sec. The results were shown in table .32

Friability test

Friability test was performed on the formulated tablets. The weight of the tablets after undergoing 100 revolutions was found to be within the limits 0.5 to 1.0%. The results were shown in table. 32

Hardness

Pfizer hardness tester was used for measuring the hardness of formulated Etodolac solid dispersion tablets. Five tablets were taken randomly and subjected to test. The hardness was found to be 4-5 kg/cm^2. The results were shown in table. 32.

Drug content uniformity

The prepared tablets containing Etodolac solid dispersion was tested for drug content uniformity. Tablets were dissolved in 100 ml of pH 6.8 phosphate buffer in 100 ml volumetric flask which was previously clean and dry. This solution after suitable dilution was measured for absorbance at 274 nm in a Jasco V530 UV visible spectrophotometer. The results were shown in table. 32

Table : 32 Weight variation, disintegration time, friability, hardness and drug content uniformity of tablets containing solid dispersions of Etodolac

S. No.	Weight variation(%),weight range of tablets (mg)	Disintegration time (sec)	Friability (%of loss of weight)	Hardness (kg/cm^2)	Drug content uniformity (%)
1	710	285	0.51	4.3	98.1
2	713	270	0.60	4.2	94.5
3	722	300	0.63	4.1	92.4
4	678	303	0.52	4.8	93.6
5	685	280	0.54	4.9	90.6
6	691	288	0.57	4.5	94.5
7	718	290	0.65	4.6	95.4
8	704	294	0.7	4.7	99.3
9	697	298	0.50	4.3	93.0
10	690	301	0.65	4.4	97.2
11	680	305	0.67	4.0	99.0
12	727	309	0.55	4.6	92.4
13	709	299	0.53	4.1	100.2
14	715	291	0.59	4.5	94.5
15	695	289	0.64	4.9	92.4
16	674	296	0.68	4.3	93.6
17	707	295	0.69	4.2	94.5
18	689	306	0.8	4.0	99.0
19	702	310	0.72	4.4	97.4
20	698	293	0.66	4.8	92.5

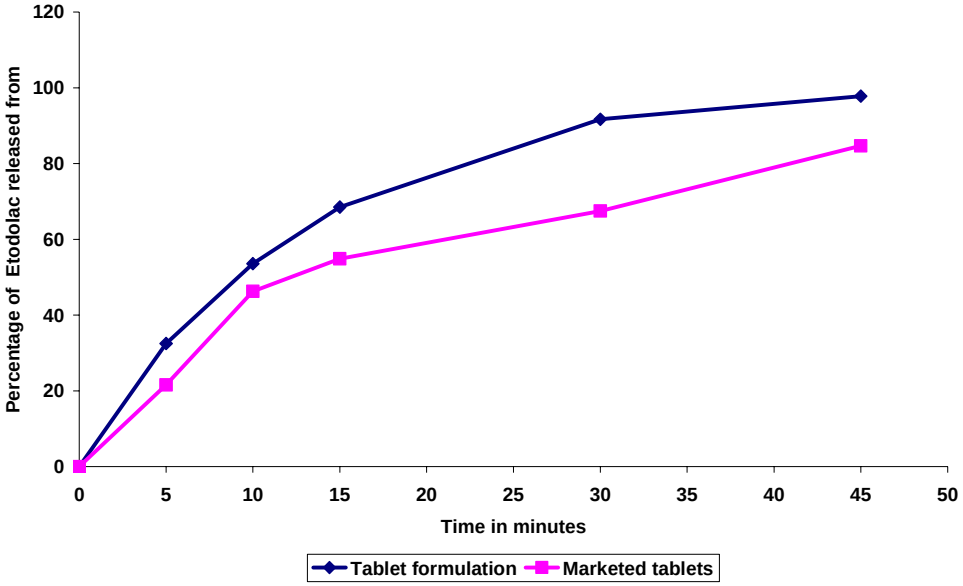
In-vitro Dissolution studies

Dissolution of Etodolac from various tablets was studied in USP dissolution medium. The tablets containing solid dispersions equivalent to 100mg of Etodolac were taken and the paddle type stirrer was adjusted to 100 rpm. The temperature was maintained at 37±0.5°C. 10 ml aliquot dissolution media was withdrawn at different time intervals and volume withdrawn was replaced with fresh quantity of dissolution media. The samples were analyzed for Etodolac by measuring absorbance at 274 nm using Jasco UV visible spectrometer. pH 6.8 phosphate buffer was used as blank.[39] The percentage of Etodolac dissolved at various time intervals was calculated and plotted against time. The results are shown in table 33 and fig.44

Table : 33 Dissolution profile of Etodolac from tablet formulation and from marketed tablets

Time in minutes	Percentage of Etodolac released from	
	Tablet formulation	Marketed tablet
0	0	0
5	32.5	21.6
10	53.6	46.3
15	68.5	54.9
30	91.7	67.5
45	97.8	84.7

Fig: 44 Dissolution profile of Etodolac from tablet formulation and from marketed tablets



RESULTS AND DISCUSSION

The tablets were formulated using solid dispersion at 1:19 ratio with PGS (Potato) by kneading method.

All the batches fulfill the official IP requirements for tablets. Hardness of the tablets in all the batches was found to be 4 to 5 kg/cm^2 and was satisfactory. The percentage weight loss in the friability test was found to be less than 1 % in all batches. Thus the tablets prepared were found to be good quality and fulfilling all the official requirements of compressed tablets.

The dissolution profile of various tablets formulated employing, Etodolac: PGS (Potato) dispersions at 1:19 ratio by kneading method and marketed tablet were shown in table 33. Tablets formulated with solid dispersions gave rapid dissolution of the medicament when compared to the marketed tablets The dissolution rate was found to be high in the case of tablets formulated employing solid dispersions indicating rapid and higher dissolution of the medicament from these tablets when compared to the marketed tablets.

SUMMARY AND CONCLUSION

Studies were under taken on the preparation and evaluation of solid dispersions of Etodolac with view to develop fast release formulation of Etodolac. Three carriers viz PGS(Potato), PGS (Tapioca) and PGS (Maize) were used to prepare the solid dispersions of Etodolac by solvent evaporation and kneading method at various drug: carrier ratios namely (1:1,1:3,1:9 and 1:19). The solid dispersions prepared were found to be fine and free flowing powders. X-ray diffraction studies revealed that crystalline nature of Etodolac in pure form was reduced to amorphous form in the dispersions The thermal behavior of Etodolac: PGS (Potato) solid dispersion was studied using DSC indicating that Etodolac has complexed with PGS (Potato). This phenomenon is indicative of stronger interaction between Etodolac and PGS (Potato) in the solid state. Interaction studies like TLC, FTIR indicated no interaction between drug and polymer used.

Results of dissolution studies showed rapid and fast dissolution of Etodolac from all solid dispersions when compare with pure drug and physical mixture. Good correlation was absorbed between percentage carrier in the solid dispersion and T_{50} and T_{90} values. Among the three carriers PGS (Potato) gave highest dissolution rate in the drug carrier ratio of 1:19.

The order of dissolution of Etodolac from various carriers is PGS (Potato) KM > PGS (Potato) SE> PGS (Tapioca) SE> PGS (Tapioca) KM> PGS(Maize) KM> PGS(Maize)SE.

Etodolac solid dispersion in PGS (Potato) (1:19) was formulated into tablets with usual additives and the tablets were evaluated for dissolution characteristics .The dissolution of Etodolac from tablet formulation based on solid dispersion was found to be fast and rapid when compared to marketed tablet.

The additives added have not hindered the dissolution of Etodolac from solid dispersions. All the tablet formulations based on the solid dispersion fulfilled the official dissolution requirements. Hence the tablet formulations based on solid dispersions are considered as fast release dosage of Etodolac.

In this work it was concluded that the Etodolac tablets formulated employing Etodolac: PGS (Potato) solid dispersion gave comparable dissolution when compared to the marketed samples.Moreover, the carrier used in the present study is pre-gelatinized starch.It is a low cost carrier so that we can reduce the cost of production significantly.

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ABBREVIATIONS

ETD	-	Etodolac
PGS	-	Pre-gelatinized starch
SD	-	Solid Dispersion
PM	-	Physical Mixture
IR	-	Infra Red
DSC	-	Differential Scanning Calorimetry
SEM	-	Scanning Electron Microscopy
SE	-	Solvent Evaporation Method
KM	-	Kneading Method
TLC	-	Thin Layer Chromatography