SOLID DISPERSION AS AN APPROACH FOR SOLUBILITY AND DISSOLUTION ENHANCEMENT OF IBUPROFEN AND PIROXICAM

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AUGUST, 2014

DECLARATION

I declare that the work in this thesis entitled, 'Solid dispersion as an approach for solubility and dissolution enhancement of ibuprofen and piroxicam' has been carried out by me in the Department of Pharmaceutics and Pharmaceutical Microbiology, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, under the supervision of Dr (Mrs.) T.S. Allagh, Prof. (Mrs.) A.R. Oyi and Prof. M.U Adikwu. The information derived from the literature have been duly acknowledged in the text and a list of references provided. No part of this thesis was previously presented for another degree or diploma at this or any other institution.

SOPHIE ISHAYA NOCK

…….. …… …….

NAME Signature Date

CERTIFICATION

This thesis entitled 'SOLID DISPERSION AS AN APPROACH FOR SOLUBILITY AND DISSOLUTION ENHANCEMENT OF IBUPROFEN AND PIROXICAM' by Sophie Ishaya Nock meets the regulations governing the award of the degree of Master of Science (Pharmaceutics) of the Ahmadu Bello University, and is approved for its contribution to knowledge and literary presentation.

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DEDICATION

The work is dedicated to the Almighty God, my ever present help and to my dearest parents, Prof. and Mrs. I. H. Nock

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I ascribe all glory and adoration to God Almighty for bringing me thus far in life; I am a product of His amazing grace and mercy.

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ABSTRACT

The aim of this study was to enhance the solubility and hence dissolution rate of two poorly soluble drugs: ibuprofen and piroxicam using Eudragit RS 100 and hydroxymethylpropylcellulose (HPMC) as carriers, by solid dispersion technique and to evaluate the effect of trona (sodium sesquicarbonate) on the dispersions . Solid dispersions of ibuprofen and piroxicam were prepared using HPMC or Eudragit RS 100 and their combinations by the solvent evaporation method. The prepared dispersions were characterized with respect to drug content, production yield, moisture sorption and desorption, Fourier Transform Infrared (FT-IR) spectroscopy and differential scanning calorimetry (DSC). The solubilities of the pure drug, solid dispersions and their physical mixtures were studied using standard method. *In vitro* drug release of ibuprofen and piroxicam from the solid dispersions was evaluated in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) without enzymes in a sequential fashion. Anti-inflammatory effects of the solid dispersions were investigated in comparison to the pure drug using the egg albumin induced paw odema in rats. Stability studies at 75% relative humidity and room temperature (28^{o}C) was carried out on the prepared solid dispersions. Results indicate that the solid dispersions with HPMC entrapped greater amount of drug in comparison to those with Eudragit RS 100. Moisture sorption studies indicate the amorphous state of drugs in the solid dispersions. Solubility studies revealed marked increase in solubility of drugs from solid dispersions when compared to pure drugs and physical mixtures. Solid dispersions of ibuprofen with HPMC containing 1:2 drug : polymer ratio had 8 fold increase in solubility when compared to pure drug . Solid dispersions of piroxicam with Eudragit and HPMC (ratio 0.1:1:1) gave a 3 fold increase in solubility when compared to the pure drug. Solid dispersion of the drugs with HPMC gave a faster drug release in simulated gastric fluid while Eudragit RS 100 based solid

dispersions exhibited a delayed release of ibuprofen in the fluid. Solid dispersions of piroxicam incorporating trona showed enhanced solubility and dissolution when compared to dispersions without it, but trona was seen to decrease solubility and dissolution of ibuprofen. The FT-IR spectroscopic studies revealed that there was no chemical interaction between the drug and the polymers, while the DSC scans showed changes from crystalline to amorphous form of the drug. Solid dispersions were seen to have enhanced anti-inflammatory effect relative to the pure drug. Stability studies of these solid dispersions revealed that the formulations were stable.

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LIST OF ABBREVIATIONS

DSC……Differential scanning calorimetry

EUD……Eudragit RS 100

FT-IR……..Fourier Transform Infrared spectroscopy

HPMC……Hydroxypropyl methylcellulose

SD ……Solid dispersion

PM……Physical mixture

CHAPTER ONE

1.0 INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery owing to convenience and ease of ingestion (Kumar *et al.*, 2012). From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications when compared with other routes of administration, for example, parenteral (Dhirendra *et al.*, 2009).

Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in the gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. The poor dissolution of water insoluble drugs is a substantial problem confronting the pharmaceutical industry.

A poorly water soluble drug, more recently, has been defined in general terms as a drug which requires more time to dissolve in the gastrointestinal fluid than it may take to get absorbed in the gastrointestinal tract (Reena and Vandana, 2012). The absorption rate of a poorly water –soluble drug formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid at the absorption site. The dissolution rate is often the rate determining step in drug absorption. Therefore, the solubility and dissolution behavior of a drug are the key determinants

of the oral bioavailability (Kumar *et al.,* 2012). A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate-limited absorption.

With recent advances in molecular screening methods for identifying potential drug candidates, an increasing number of poorly water-soluble drugs are being identified as potential therapeutic agents. In fact, it has been estimated that 40% of new chemical entities currently being discovered are poorly water-soluble (Lipinski, 2001). Unfortunately, many of these potential drugs are abandoned in the early stages of development owing to solubility concerns.

One of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs (Ueda *et al.,* 2006). It is therefore becoming increasingly more important that methods for overcoming solubility limitations be identified and applied commercially such that the potential therapeutic benefits of these active molecules can be realized.

Various approaches available to improve drug solubility as well as drug dissolution of poorly aqueous soluble drugs include micronisation, formation of inclusion complexes with cyclodextrins, formation of amorphous drugs, and formulation of solid dispersions of drugs using various hydrophilic carriers. Among them, formulation of solid dispersions is one of the most successful strategies to improve drug release of poorly water- soluble drugs (Hasnain and Nayak, 2012). In the Biopharmaceutics Classification System (BCS), drugs with low aqueous solubility and high membrane permeability are categorized as class II drugs. Solid dispersions technologies are particularly promising for improving the oral absorption and bioavailability of BCS class II drugs (Dhirendra *et al.,* 2009).

1.1 Solubility

Solubility is defined as the amount of a substance that passes into solution in order to establish equilibrium at constant temperature and pressure to produce a saturated solution (Behera *et al.*, 2010). Thermodynamically, it is the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. Of the various states of matter that exist and the corresponding solutions that they can possibly form, the solutions of solids in liquids are the most frequently encountered type in pharmaceutical formulations. The solubility of a solid in an ideal solution depends upon a number of factors such as the temperature of the system, nature of the solvent, the melting point of the solid and the molar heat of fusion.

Solubility is an intrinsic material property that can be altered only by chemical modification of the molecule, in contrast to dissolution which is an extrinsic material property that can be influenced by various chemical, physical or crystallographic means such as complexation, particle size and surface properties (Florence and Attwood, 1998).

1.1.1 Importance of solubility

The major challenge with the design of oral dosage forms lies with their poor bioavailability. Oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability. Solubility also plays a major role for other dosage forms like parenteral formulations as well (Edward and Li, 2008). Drug absorption, sufficient and reproducible bioavailability, pharmacokinetic profile of orally administered drug substances are highly dependent on solubility of that compound in aqueous medium. Solubility is one of the most important parameters to achieve desired concentration of drug in systemic circulation for

achieving required pharmacological response (Vemula *et al.*, 2010). Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration which may lead to increased side effects. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. For any drug to be absorbed, it must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility. The improvement of drug solubility and thereby its oral bio-availability remains one of the most challenging aspects of the drug development process especially for oral-drug delivery systems. There are numerous approaches available and reported in literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen on the basis of certain factors such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form.

1.1.2 Techniques for enhancing solubility

Solubility improvement techniques can be categorized into physical modification, chemical modification of the drug substance, and other techniques.

1.1.2.1 Physical modification

Particle size reduction: The solubility of a drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction with the solvent which causes an increase in solubility (Sandip *et al.*, 2013). Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction thus permits an efficient, reproducible and economic means of solubility enhancement. The

mechanical forces inherent in comminution, such as milling and grinding, however, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermosensitive or unstable active compounds. Using traditional approaches for nearly insoluble drugs may not be able to enhance the solubility up to the desired level. Particle size reduction can be achieved by micronization and nanosuspension (Kumari *et al.,* 2013)

Micronization: Micronization is a conventional technique for particle size reduction. Micronization increases the dissolution rate of drugs through increased surface area, but does not increase equilibrium solubility (Satish *et al.,* 2011). Decreasing the particle size of drugs, which causes increase in surface area, improves their rate of dissolution. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills and so on. Micronization is not suitable for drugs having a high dose because it does not change the saturation solubility of the drug (Blagden *et al.,* 2007). These processes were applied to griseofulvin, progesterone, spironolactone, diosmin and fenofibrate. For each drug, micronization improved their digestive absorption, and consequently their bioavailability and clinical efficacy. Micronized fenofibrate exhibited more than 10-fold (1.3 % to 20 %) increase in dissolution at 30 minutes in biorelevant media (Chaumeil *et al.*,1998 ;Vogt *et al.,* 2008)

Nanosuspension: Nanosuspension technology has been developed as a promising technique for efficient delivery of hydrophobic drugs. This technology is applied to poorly soluble drugs that are insoluble in both water and oil. A pharmaceutical nanosuspension is a biphasic system consisting of nanosized drug particles stabilized by surfactants for either oral and topical use or

parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm (Muller *et al.,* 2000 and Nash, 2002). Various methods utilized for preparation of nanosuspensions include precipitation technique, media milling, high-pressure homogenization in water, high pressure homogenization in non-aqueous media, and combination of precipitation and high-pressure homogenization (Patravale *et al.,* 2004)

Inclusion Complex Formation-Based Techniques: Among all the solubility enhancement techniques, inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate and bioavailability of poorly water soluble drugs. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins (CDs). Three naturally occurring CDs are α-Cyclodextrin, β-Cyclodextrin and γ-Cyclodextrin (Satish *et al.,* 2011).

Cryogenic Technique: Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with high degree of porosity at very low-temperature conditions. Cryogenic inventions can be defined by the type of injection device (capillary, rotary, pneumatic and ultrasonic nozzle) location of nozzle (above or under the liquid level) and the composition of cryogenic liquid (hydrofluoroalkanes, N_2, Ar, O_2 and organic solvents). After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze (Kaur *et al.,* 2012).

1.1.2.2 Chemical modification

Salt Formation: Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Acidic or basic drug converted into salt has higher solubility than the parent drug. Alkali metal salts of acidic drugs like penicillin and strong acid salts of basic drugs like atropine are more water soluble than the parent drug (Deepshikha *et al.,* 2012).

Co-crystallisation: Co-crystals may be defined as crystalline materials that consist of two or more molecular and electrically neutral species held together by non-covalent forces. They can be prepared by evaporation of a heteromeric solution or by grinding the components together or by sublimation, growth from the melt and slurry preparation. It is increasingly important as an alternative to salt formation, particularly for neutral compounds (Satish *et al.,* 2011).

Co-solvent: It is well-known that the addition of an organic co-solvent to water can dramatically change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility which can be improved by altering the polarity of the solvent. Solvents used to increase solubility are known as cosolvents the process is also commonly referred to as solvent blending.

Hydrotropy: This is designed to increase solubility in water due to presence of large amount of additives. It improves solubility by complexation involving weak interaction between hydrophobic agents (sodium benzoate, sodium alginate urea) and solute. Example is sublimation of theophylline with sodium acetate and sodium alginate (Satish *et al.,* 2011)

Solubilising Agents: The solubility of poorly soluble drugs can also be improved by various solubilizing materials. The aqueous solubility of the antimalarial agent halofantrine is increased by the addition of caffeine and nicotinamide (Satish *et al.*, 2011).

1.2 Solid dispersions

According to Chiou and Riegelman (1971), a solid dispersion is, "the dispersion of one or more active ingredient in an inert carrier at solid state prepared by melting (fusion), solvent or the melting-solvent method". Solid dispersion is a common strategy by which to improve the dissolution rate and absorption of poorly water soluble drugs using hydrophilic polymer carriers as dispersing agent. Solid dispersions using insoluble carriers loaded with hydrophilic drugs lead to a delivery system aimed at optimizing pharmacokinetics and reducing side effects such as gastric irritation due to non-steriodal anti-inflammatory drugs (Pignatello *et al* .,2001).

1.2.1 Advantages of solid dispersions

1.2.1.1 Reduced drug particle size

When solid dispersions consisting of poorly soluble drug and highly soluble carrier are exposed to water or gastro -intestinal fluid, the soluble carrier dissolves, leaving the drug in very fine crystalline state that will rapidly go into solution. Due to increased surface area of insoluble compound, an enhanced dissolution rate and hence increased oral absorption is obtained (Sandip *et al.,* 2013).

Solid dispersions are more efficient than all other particle size reduction techniques, since the latter have a particle size reduction limit around 2 - 5 mm which frequently is not enough to

improve considerably the drug solubility or drug release in the small intestine and consequently, to improve the bioavailability (Gaurav *et al.,* 2009). Molecular dispersions, as solid dispersions, represent the last state of particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium (Sharma *et al.,* 2011). Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers in which, a high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability (Leuner and Dressman, 2000).

1.2.1.2 Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions (Karavas *et al.*, 2006). It has been reported that the presentation of particles to the dissolution medium as separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions such as cholic acid and bile salts may have some wetting properties, however even carriers without any surface activity such as urea, improved drug solubility (Daisy *et al.,* 2009).

1.2.1.3 Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate (Sharma *et al*., 2011). The increased porosity of solid dispersion particles has been found to hasten the drug release profile (Leuner and Dressman, 2000).

1.2.1.4 Drugs in amorphous state

The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. Poorly water soluble crystalline drugs, when in the amorphous state, tend to have higher solubility (Daisy *et al.,* 2009). In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if a drug precipitates, it is as a metastable polymorphic form with higher solubility than the most stable crystal form (Leuner and Dressman, 2000; Karavas *et al*., 2006). For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.

1.2.1.5 Drugs with improved dissolution rate

Solid dispersions produce rapid dissolution rates that result in an increase in the rate and extent of absorption of the drug, and a reduction in presystemic metabolism. This latter advantage may occur due to saturation of the enzyme responsible for biotransformation of the drug, as in the case of 17-β-estradiol or inhibition of the enzyme by the carrier, as in the case of morphine-tristearin dispersion (Daisy *et al.,* 2009).

1.2.2 Disadvantages /limitations of solid dispersion

Solid dispersion technique has been extensively confirmed to enhance the dissolution characteristics of sparingly soluble drugs although, the practical applicability of the system has remained limited mainly due to difficulties in manufacturing processes. Only a few products have been marketed so far. Amongst these are griseofulvin in polyethylene glycol (Gris-PEG® by Novartis), nabilone in polyvinylpyrrolidone solid dispersions (Cesamet® by Lily) and itraconazole in hydroxypropyl methylcellulose and polyethylene glycol 20,000 sprayed on sugar spheres (Sporanox® by Janseen).

The main problems limiting the commercial application of solid dispersions involve the following.

1.2.2.1 Instability of solid dispersions

Physical instability of solid dispersions occurs mainly because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress), the amorphous state may undergo crystallization and dissolution rate decreases with ageing. Similarly, certain carriers may exist in thermodynamically unstable states in a solid dispersion and undergo changes with time. Ritonavir capsules (Norvir®, Abbott) was withdrawn from the market because of crystallization (Serajuddin *et al.,* 1999).

The effect of moisture on the storage stability of amorphous pharmaceuticals is also of significant concern, because it may increase drug mobility and promote drug crystallization. Most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a

metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate (Gaurav *et al.,* 2009)

1.2.2.2 *Processing variability*

Manufacturing conditions may greatly influence the physicochemical properties of solid dispersions. The heating rate, maximum temperature used, holding time at a high temperature, cooling method and rate and method of pulverization might affect the properties of solid dispersions prepared by the melting method including particle size distribution (Serajuddin *et al.*, 1999). In addition the nature of solvent used, ratio of drug/solvent or carrier/solvent as well as rate and method used to evaporate the solvent may significantly influence the physicochemical properties of solid dispersions formed (Ruchi *et al.,* 2009).

1.2.2.3 Method of preparation

Total removal of toxic organic solvents used in the preparation of the dispersions is the main problem associated with the solvent method. When fusion method is used, high melting temperature may chemically decompose drugs and / or carriers (Reena and Vandana, 2012).

1.2.2.4 Dosage form development

It is usually very difficult to develop solid dispersions into a suitable dosage form because pulverizing, sieving, mixing and compressing of solid dispersions, which are usually soft and tacky are difficult. Solid powders with low particle size have poor flowability and may stick to the tabletting machines, making it difficult to handle (Sharma *et al.,* 2011).

The physicochemical properties and stability of solid dispersions may be affected by scale-up processes because heating and cooling rates of solid dispersions prepared in a large scale may differ from that of a small scale. It is also expensive and not practical to evaporate hundreds and even thousands of liters of organic solvents to prepare solid dispersions for kilogram quantities of drug (Serajuddin *et al,*. 1999).

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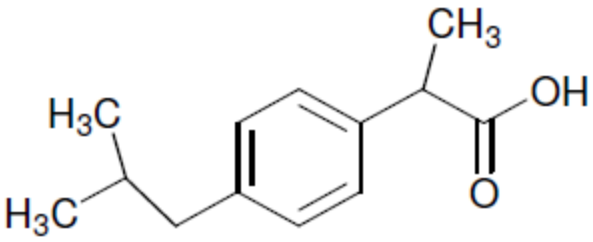
1.2.3 Pharmaceutical applications of solid dispersions

Solid dispersions could be utilized for the following;

1. To obtain a homogenous distribution of small amount of drug in the solid state.
2. To transform liquid forms of a drug into solid formulations such as powders, capsules or tablets. Examples, prostaglandin, unsaturated fatty acids, nitroglycerin, clofibrate and benzaldehyde can be incorporated into PEG-6000 to give a solid.
3. To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization and photo-oxidation as in the case of nabilone and PVP dispersions.
4. To formulate a fast release priming dose in sustained release dosage forms.
5. To reduce presystemic inactivation of drugs like morphine and progesterone.
6. To avoid undesirable incompatibilities.
7. To mask unpleasant taste and smell of drugs as in the case of famoxetine. The bitter taste of famoxetine was greatly suppressed when the solid complex was formulated as aqueous suspension.

8. To reduce the side effects of certain drugs. The damage to the stomach mucous membrane by certain non-steriodal anti-inflammatory drugs (NSAIDs) can be reduced by administration as an inclusion complex.
9. To improve drug release from ointments, gels and creams.
10. To formulate a sustained release preparation of soluble drugs by dispersing drug in poorly soluble and insoluble carrier.
11. To enhance bioavailability, dissolution rate and absorption of drugs by increasing the solubility of poorly water soluble drugs **(** Sharma *et al.*, 2011**).**

1.3 Ibuprofen



Scheme1: structure of ibuprofen

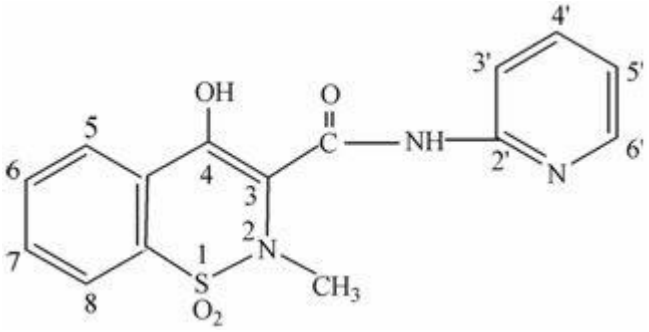
Ibuprofen a weakly acidic, non-steroidal anti-inflammatory drug (NSAID) that has been widely used in the treatment of mild to moderate pain. Ibuprofen is used in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache (including migraine) postoperative pain, dental pain, musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis, peri-articular disorders such as bursitis and tenosynovitis, and soft-tissue disorders such as sprains and strains. It is also used to reduce fever (Kumar *et al.,* 2012)

Ibuprofen is a white crystalline powder or colourless crystals with a slight characteristic odour. British Pharmacopoea (BP) solubilities are; practically insoluble in water, very soluble in alcohol, acetone, chloroform, and in methyl alcohol, slightly soluble in ethyl acetate. The drug has been classified as class II drug as par the Biopharmaceutical Classification System (BCS) having low solubility and high permeability through the stomach as it remains 99.9% unionized in the stomach, because of its solubility limitation and fast emptying time from stomach to intestine (30 min to 2 h) the required quantity cannot enter into systemic circulation. After this time, it goes to the small intestine where it is solubilized but cannot permeate through its membrane because of its pH dependent solubility and permeability.

Thus solubility and dissolution become the rate limiting steps for absorption. Drugs with low dissolution rates generally show erratic and incomplete absorption leading to low bioavailability when administered orally. To enhance solubility and improve dissolution rate of ibuprofen is challenging and rational because its serum concentration and therapeutic effects are correlated; rapid ibuprofen absorption is a prerequisite for quick onset of action.

Pharmacokinetics: Ibuprofen is absorbed from the gastrointestinal tract and peak plasma concentration is attained about 1 to 2 h after ingestion. Ibuprofen is absorbed following rectal administration. There is some absorption following topical application to the skin. Ibuprofen is 90 to 99 % bound to plasma proteins and has a plasma half life of about 2 h. It is rapidly excreted in the urine mainly as metabolite and their conjugates; about 1% is excreted in urine as unchanged ibuprofen and about 4% as conjugated ibuprofen. There appears to be little, if any, excreted in breast milk. However, the bioavailability of ibuprofen is relatively low after oral administration, since it is practically insoluble in water (Patel *et al.*, 2010).

1.4 Piroxicam



Scheme 2: structure of piroxicam

Piroxicam is an oxime derivated non steroidal anti-inflammatory drug with low solubility and high permeability classified as class II in the Biopharmaceutical Classification System. It is used as an analgesic in acute and long time treatment of rheumatoid arthritis, osteoarthritis and in a variety of other chronic musculoskeletal disorders such as dysmenorrhea. Piroxicam is practically insoluble in water, sparingly soluble in alcohol but soluble in methylene chloride. After oral administration piroxicam is completely but slowly and gradually absorbed through the GIT and reaches the maximum blood concentration after 2-4 h. Since the drug is slightly soluble in biological fluid, piroxicam dissolution rate turns is the absorption rate limiting step and consequently, it critically affects its analgesic effect onset (Kulkarni *et al.*, 2012).

1.5 Eudragit RS 100

Eudragit RS 100 is a neutral copolymer of polyethylacrylate, methylmethacrylate and trimethylammonium ethylmethacrylate chloride. The ammonium groups are present as salts and make the polymers permeable. It is a solid substance in form of colourless, clear to cloudy granules with a faint amine-like odour. Eudragit RS 100 is inert to the digestive tract content, pH independent and at the same time capable of swelling. Eudragit is used mainly to form

controlled release formulations, but also shows stabilizing effects. Eudragit can be used to mask taste and color (Pignatello *et al.,* 2001).

Eudragit RS 100 has been employed in previous studies to improve the dissolution rate of a wide range of drugs via solid dispersions. Ofokansi *et al*. (2012) reported that the dissolution rate of trandolapril was increased in solid dispersions based on Eudragit RS 100 and PEG 8000.

1.6 Hydroxypropyl methylcellulose (HPMC)

HPMC is a semi synthetic inert viscoelastic polymer used as an ophthalmic lubricant, as well as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products. HPMC is a solid, and is a slightly off-white to beige powder in appearance and may be formed into granules. The compound forms colloids when dissolved in water. This non-toxic ingredient is combustible and can react vigorously with oxidizing agents. The high interest in HPMC as an excipient is mainly due to the fact that it is non-toxic, easy to handle, relatively cheap, easy to compact and compatible with numerous drugs. HPMC consists of a backbone of cellulose with methyl and hydroxypropyl moieties substituted onto the glucose units HPMC is commercially available in many different viscosity grades. When used at high concentration, HPMC forms a gelatinous layer around the drug particles upon contact with aqueous media which can act as a barrier to drug release; the drug is released slowly from such matrix by diffusion processes. Usually higher molecular weight HPMC are used for sustained releasase in tablet formulation while lower molecular weight HPMC is employed in solid dispersions to enhance drug release (Rahman *et al.,* 2011).

1.7 Trona

Trona is a compound of sodium chemically called sodium sesquicarbonate or sodium monohydrogen dicarbonate (Na_2Co_3. $NaHCO_3$) $2H_2O$). Trona is a Swedish term, deriving ultimately from the Arabic "natrum", native salt. Trona is a commonly used salt in several countries in east, west and central Africa. In Nigeria trona is commonly called “Kaun” in Yoruba, “Kanwa” in Hausa and “Akanwu” in Igbo language. The main use of trona in homes is as a tenderizer in preparing tough food like beans, maize and meat, utilizing its ability to facilitate or speed up the softening of food during cooking. It is used as a source of sodium compounds. In Nigeria, trona is escavated or minced in northern part of the country particularly in Kano and Maiduguri areas extending to border countries like Chad and Niger. Attama *et al.* (2007) have shown that trona could enhance the permeation of ointments.

1.8 Statement of research problem

Poorly water soluble drugs present a problem in pharmaceutical formulation. More than 90 % of drugs approved since 1995 have poor solubility (Satish *et al.*, 2011). With recent advances in molecular screening methods for identifying potential drug candidates, an increasing number of poorly water soluble drugs are being identified as potential therapeutic agents. According to recent estimates, nearly 40-50 % of new chemical entities are rejected because of poor solubility (Satish *et al.*, 2011). Poor solubility would lead to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality. This frequently results in potentially important products not reaching the market or not achieving their full potential. Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration (Reena and Vandana, 2012). The enhancement of dissolution rate and oral bioavailability is one of the greatest challenges in the development of poorly water soluble drugs.

For orally administered drugs, solubility is the most important rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientists (Sharma *et al.,* 2009). Any process, technology or excipient that improves solubility could therefore be useful in:

1. Bringing more new products to the market.
2. Reducing development timelines
3. Reducing production cost.
4. Bringing new life to old products and with improved therapeutic outcomes

1.9 Justification

Ibuprofen and piroxicam are poorly water soluble drugs. The efficacy of these drugs can be severely limited by poor aqueous solubility, leading to low dissolution rate and thus low absorption in the gastrointestinal tract following oral administration hence compromising oral biovailability (Tapan *et al.*, 2010). Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy (Reena and Vandana, 2012). Any compatible additive that could therefore, enhance the solubility of these drugs would enhance their bioavailability and reduce their side effects.

1.10 Hypothesis

Null hypothesis

Solid dispersions cannot be used to improve the aqueous solubility and dissolution of ibuprofen and piroxicam.

Alternate hypothesis

Solid dispersions technique can improve the aqueous solubility and dissolution of ibuprofen and piroxicam.

1.11 Aim

The aim of the study is to enhance the solubility, dissolution and ultimately bioavailability of ibuprofen and piroxicam using solid dispersion technique.

1.12 Objectives

1. To formulate solid dispersions of ibuprofen and piroxicam using Eudragit RS100, hydroxypropyl methylcellulose (HPMC) as carriers by the solvent evaporation method.
2. To formulate solid dispersions of ibuprofen and piroxicam incorporating trona in addition to the two inert carriers above.
3. To characterize the prepared solid dispersions of ibuprofen and piroxicam using DSC and FT-IR.
4. To determine the compatibility of ibuprofen and piroxicam with trona, Eudragit RS 100 and hydroxypropyl methylcellulose using FT-IR.
5. To evaluate the potential of solid dispersions to enhance the solubility and dissolution of ibuprofen and piroxicam.
6. To evaluate the effect of trona on solubility and dissolution of ibuprofen and piroxicam in the solid dispersions.
7. To evaluate the anti-inflammatory properties of the formulated solid dispersions in an animal model.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Solid dispersions

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. The concept of solid dispersions was originally proposed by Sekiguchi and Obi (1964), who demonstrated that the eutectic melts of sulfathiazole and a physiologically inert water-soluble carrier urea exhibited higher absorption and excretion after oral administration than sulfathiazole alone (Bhawana *et al*., 2012).

Recently, there been increased interest in solid dispersion in order to improve biopharmaceutical properties of poorly soluble drugs. The objective is usually to provide a system in which the crystallinity of the drug is so altered in order to change its solubility and dissolution rate, and to surround the drug intimately with a water-soluble material (Florence and Attwood, 1998). When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailabity of poorly water-soluble drugs.

The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization by cosolvents and particle size reduction (Hamsaraj *et al.,* 2006).

In addition to the improvement of bioavailability, most of the recent studies on solid dispersion systems have been directed towards their application to the development of extended-release dosage forms using water insoluble carriers (Filippis *et al.,* 1995).

2.2 Classification of solid dispersions

Solid dispersions are classified based on their molecular arrangement into four representative types

1. Simple eutectic mixtures
2. Amorphous precipitations in crystalline matrix.
3. Solid solutions
    a. Continuous solid solutions
    b. Discontinuous solid solutions
    c. Substitutional solid solutions
    d. Interstitial solid solutions

4 . Glass suspensions and solutions (Singh *et al*., 2011)

2.2.1 Simple eutectic mixtures

These are prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solubility. Thermodynamically, such a system is an intimately blended physical mixture of its two crystalline components. When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously (Figure 2.1), whereas when other compositions are cooled, one of the components starts to crystallize out before the other (Daisy *et al.*, 2009). Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting

suspension should result in an enhanced dissolution rate and thereby improved bioavailability. This technique has been applied to several poorly soluble drugs such as griseofulvin. A griseofulvin-succinic acid (soluble carrier) system has a eutectic point at 0.29 mole fraction of the drug (55 % w/w griseofulvin). The eutectic mixture consists here of two physically separate phases; one is almost pure griseofulvin, while the other is a saturated solid solution of griseofulvin in succinic acid. The solid solution contains about 25 % griseofulvin; the eutectic mixture, which has a fixed ratio of drug to carrier, thus comprises 60 % solid solution and 40 % almost pure griseofulvin, the solid solution dissolves 6 to 7 times faster than pure griseofulvin. Other systems that form eutectic mixtures are chloramphenicol-urea (Attur *et al*., 1966), sulfathiazole-urea (Win and Sarfaraz, 1971) and niacinamide-ascorbic acid. In addition to the reduction in crystalline size, the following factors may contribute to faster dissolution rate of drugs in eutectic mixtures:

1. An increase in drug solubility because of the extremely small particle size of the solid
2. A possible solubilisation effect by the carrier, which may operate in the diffusion layer immediately surrounding the drug particle.

2.2.2 Amorphous precipitation in crystalline matrix

This type of solid dispersion is distinguished from a simple eutectic mixture by the fact that the drug is precipitated out in an amorphous form. Using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties (Reena and Vandana, 2013). Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose.

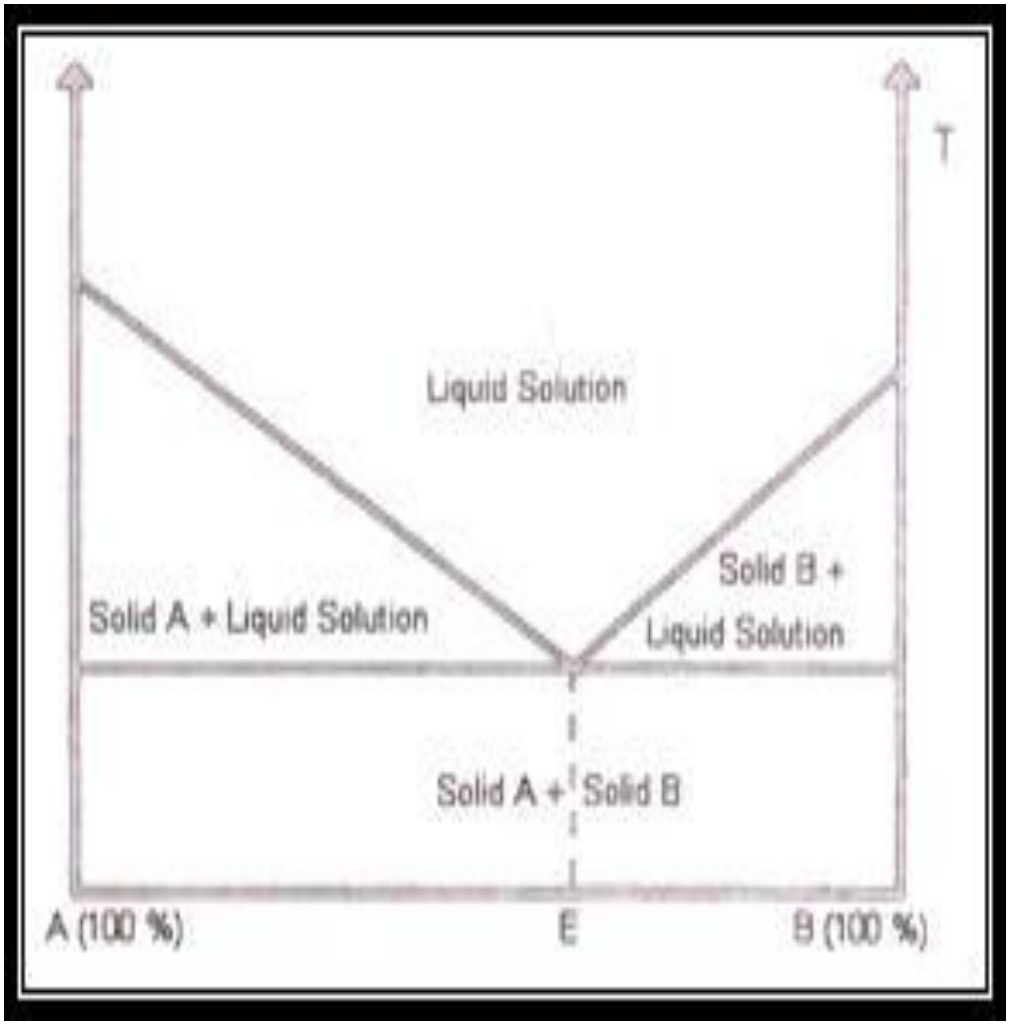


Figure 2.1: Phase diagram of an eutectic system (Daisy *et al.*, 2009)

More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose. Polymer carriers are particularly likely to form amorphous solid solutions as the polymer itself is often present in the form of an amorphous polymer chain network (Figure 2.2). In addition, the solute molecules may serve to plasticize the polymer, leading to a reduction in its glass transition temperature (Kapoor *et al*., 2012)

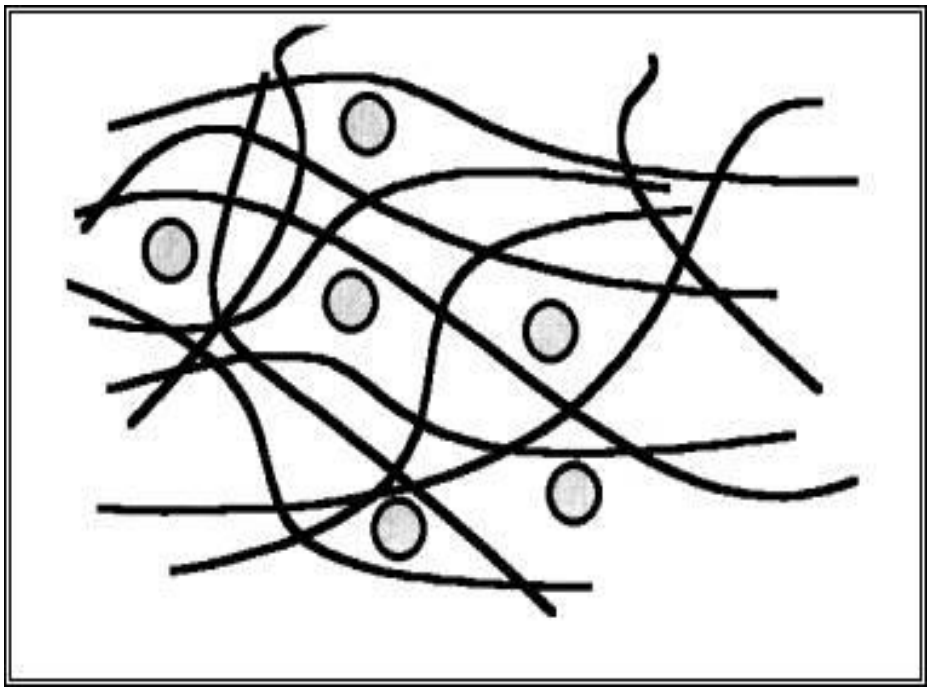


Figure 2.2: Phase diagram of amorphous solid solutions (Daisy *et al.*, 2009)

2.2.3 Solid solutions

In a solid solution, the two components crystallize together in a homogeneous one -phase system. The particle size of the drug in the solid solution is reduced to it's molecular size. Thus a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture (Sharma *et al.,* 2012). They are further classified according to their miscibility and order in which the solute molecules are dispersed in solvendum (Kaur *et al.,* 2012).

2.2.3.1. According to the extend of miscibility

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 (Rahul *et al.,* 2011; Kaur *et al.,* 2012).

Discontinuous solid solutions: In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram shows the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Below a certain temperature, the mutual solubilities of the two components start to decrease. Due to practical considerations it has been suggested that the term "solid solution" should only be applied when the mutual solubility of the two components exceeds 5 % (Sharma *et al*., 2012).

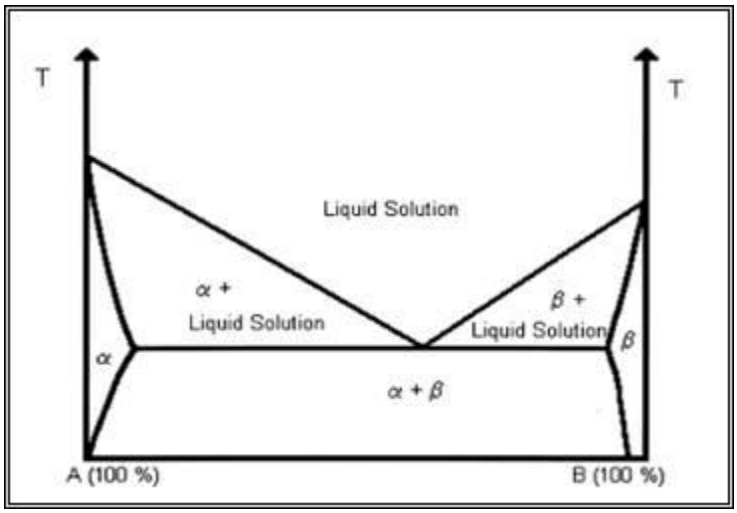


Figure 2. 3: Phase diagram of discontinuous solution (Daisy *et al.*, 2009)

2.2.3.2 According to how solute molecules are dispersed in solvendum

Substitutional 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 into the

interstices between the solvent molecules. Substitution is only possible when the size of the solute molecules differs by less than 15 % from that of the solvent molecules**.** In this solvent molecules in the crystal lattice of the solid solvent are substituted by the solid molecules in substitutional solid solutions (Reena and Vandana, 2012)

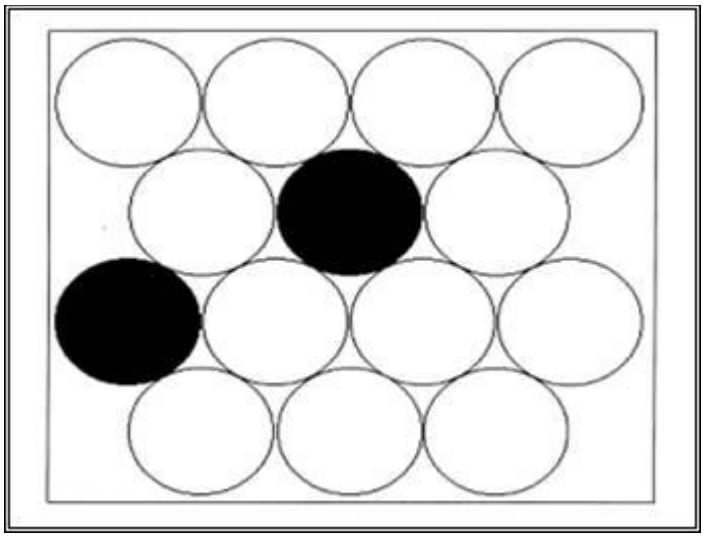


Figure 2. 4: Phase diagram of substitutional solid solutions (Daisy *et al.*, 2009)

Interstitial solid solutions: An interstitial solid solution is obtained when the solute 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 this 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. Furthermore, the volume of the solute molecules should be less than 20% of the solvent. (Dixit *et al.*, 2012).

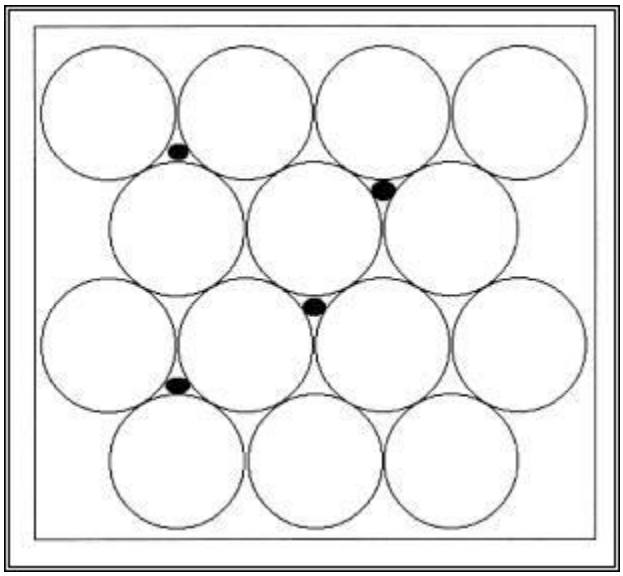


Figure 2.6: Phase diagram of interstitial solid solution (Daisy *et al.*, 2009)

2.2.4 Glass suspensions and solutions

A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent (Singh *et al.*,2010). A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. The familiar term glass however, can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperature. On heating, it softens progressively and continuously without a sharp melting point (Dixit *et al.*, 2012). Many compounds like glucose, sucrose, citric acid, PVP and ethanol form glasses when their liquid state is cooled. Linear and flexible chain polymers show glassy state of transparency and brittleness as they freeze (Singh *et al.*, 2010).

2.3 Methods of preparing solid dispersions

Various preparation methods for solid dispersions have been reported in literature. These methods deal with the challenge of mixing a matrix and a drug, preferably on molecular level, while matrix and drug are generally poorly miscible (Gaurav *et al.*, 2009). Techniques for preparations of solid dispersions are as follows:

2.3.1. Solvent method

This method involves dissolving the drug and the carrier in a common organic solvent, followed by evaporating the solvent at various temperatures resulting in formation of solid dispersion. The choice of solvent and its removal rate are critical to quality of the dispersion (Gaurav *et al.,* 2009). The major advantage of the solvent method is that thermal decomposition of drugs and carriers associated with the fusion method can be avoided. The disadvantages include the higher cost of preparation, the use of large quantities of solvent, the difficulty in complete removal of solvent, the possible adverse effect of residual solvent, the difficulty of reproducing crystal forms and the inability to attain a supersaturation of the solute in the solid system unless the system goes through a highly viscous phase (Daisy *et al.*, 2009). This technique has been used to study solid dispersion of meloxicam, naproxen, and nimesulide using solvent evaporation technique. These findings suggest that the solvent technique can be employed successfully for improvement and stability of solid dispersions of poorly water soluble drugs (Sharma *et al*., 2011).

2.3.2 Fusion / Melt method

In this method, a physical mixture of the drug and the carrier is heated until it is melted. The melt is then cooled, and the resultant solid dispersion is pulverized and sieved. By using this

method, the structure of the drug particles remains largely unchanged during the manufacturing process. Nevertheless, the cooling rate used may significantly affect the aging behavior of solid dispersions. It has been reported that the crystallinity of drug in solid dispersion is less affected by aging when a slow cooling rate is used because thermodynamically more stable systems are produced. On the other hand, rapid cooling of molten mixtures is desirable because it leads to instantaneous solidification, resulting in the drug molecule being trapped in the carrier matrix (Dhirendra *et al*., 2009).

The advantages of the fusion method are: it's simplicity and economy method for drugs stable below 100 ^{o}C, it precludes the use of an organic solvent and dissolution of dispersions obtained by melting technique are much faster than those prepared using solvent technique (Bhawana *et al.,* 2012).

Although frequently applied, the fusion method has serious limitations. Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible, two liquid phases or a suspension can be observed in the heated mixture, which results in an heterogeneous solid dispersion. This can be prevented by using surfactants. Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In this case, phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline dispersions occurred, whereas fast cooling yielded amorphous solid dispersions. Thirdly, degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug (Goldberg *et al*., 1996).

2.3.3 Melting-solvent method (melt evaporation)

This is a combination of two methods, fusion method and solvent method. In this method, the drug is dissolved in a minimum amount of an organic solvent, and then it is added to the molten carrier. As it uses less temperature, it offers advantage for thermolabile drugs. This technique possesses unique advantages over both the fusion and solvent evaporation methods (Goldberg *et al*., 1996).

2.3.4 Hot melt extrusion

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms (Dhirendra *et al.,* 2009). Just like the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are investigated to predict the solid state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder can be a problem for heat-sensitive materials. Compared to the traditional fusion method however, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding. (Narang and Shrivastav*a,* 2002; Breitenbach, 2002). This method has already been used to prepare solid dispersion of itraconazole and hydroxypropylmethylcellulose, indomethacin and polyvinylpyrrolidine, piroxicam and polyvinylpyrrolidine to improve dissolution rate of the poorly soluble drugs (Bhawana *et al.,* 2012).

2.3.5 Supercritical fluid process

This process includes dissolving the drug and carrier in supercritical carbon dioxide under precise conditions of temperature and pressure, followed by rapid depressurization. Supercritical carbon dioxide is non toxic, non inflammable, inexpensive and has the potential as an alternative for organic solvents (Bhawana *et al.*, 2012). The technique does not require the use of organic solvents and since carbon dioxide is considered environmentally friendly, this technique is referred to as solvent free. Another name for this technique is rapid expansion of supercritical solution (RESS). The application of this technique is very limited, because the solubility in carbon dioxide of most pharmaceutical compounds is very low and decreases with increasing polarity and because high capital investment for equipment (Dhirendra *et al.,* 2009).

2.3.6 Electrostatic spinning method

The electrostatic spinning method technology used in the polymer industry combines solid dispersion with nanotechnology (Hamsaraj *et al*., 2006). In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. As the solvent evaporates, the formed fibers can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandril. The fiber diameters depend on surface tension, dielectric constant, feeding rate and electric field strength. Electrospun samples dissolved is dependent on the type of formulation and the drug: polymer ratio. The technique has been successfully used in the pharmaceutical industry for the preparation of solid dispersions. Water-soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble (both biodegradable and non biodegradable) polymers are useful in controllable dissolution properties. Fabrics generated by

water-soluble carriers could be used in oral dosage formulations by direct incorporation of materials into a capsule (Sharma *et al.,* 2011).

2.3.7 Effervescent method

In this technique, sodium bicarbonate and organic acids (tartaric, succinic and citric acid) are incorporated in solid dispersions. The combination of organic acids in poorly water soluble drugs yield effervescent solid dispersions which leads to increased dissolution and absorption of poorly water soluble drugs (Dhiman *et al.,* 2012).

2.3.8 Kneading method

Drug and carrier mixture is prepared in a mortar which is moistened in methanol. This mass is then kneaded for 30 minutes and then dried under vacuum for 24 h (Saindane *et al*., 2011).

2.3.9 Lyphilization technique

Lyophilization has been thought of as a molecular mixing technique where the drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion (Dhiman *et al*., 2012). This technique was proposed as an alternative technique to solvent evaporation. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion and the risk of phase separation is minimized (Sharma *et al.,* 2012).

2.4 Properties of carriers used for dispersions

The properties of a carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug

1. Should be pharmacologically inert and non-toxic.

2. Should be water soluble with intrinsic rapid dissolution properties

3. should be soluble in a variety of solvents.

4. Should be chemically compatible with the drug.

5. Should increase the aqueous solubility of drug.

6. Should be heat stable.

7. Should form only weak bound complex.

8. Should have good flow and compressibility.

9. should have high glass transition point.

10. Should form solid solution in presence of drug.

11. Should have ability of protecting drug from moisture (Kumari *et al.*, 2013).

2.5 Detection of crystallinity in solid dispersions

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Many attempts have been made to investigate the molecular arrangement in solid dispersions. Discrimination between amorphous and crystalline has been the goal of most effort. Consequently, for that purpose many techniques are available which detect the amount of crystalline material in the dispersion. The amount of amorphous material can not be measured

directly but can be derived from the amount of crystalline material in a sample (Saindane *et al.*, 2011). The following techniques can be used to detect the degree of crystallinity:

2.5.1 X-ray diffraction

Powder X-ray diffraction analysis is used in the characterization of crystalline structure. A comparison of the diffractograms of the assumed complex with a physical mixture of guest and carrier, in pure form has to be made. In powder X-ray diffraction analysis, a characteristic fingerprint region in the diffraction pattern reflects the crystallinity of the sample. A reduction in, or the disappearance of the characteristic maxima in the powder diagram of the guest molecule and carrier with the new peaks in the diffraction pattern of the complex are the indications of formation of complex (Lian, 2001).

2.5.2 Infrared spectroscopy

Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix (Dhirendra *et al.*,2009). Sharp vibrational bands indicate crystallinity. Fourier Transform Infrared Spectroscopy (FTIR) was used to accurately detect crystallinities ranging from 1 to 99 % in pure material. IR spectroscopy is used to assess the interaction between carrier or complexing agent and guest molecule in solid state. As a result of their high structural resolution this technique is valuable for characterization of an amorphous system. Bands, which could be assigned to the included part of the guest molecules, are easily masked by the band of complexing agent (Saindane *et al*., 2011).

2.5.3 Water vapour sorption

Water vapour sorption can be used to discriminate between amorphous and crystalline materials when the hygroscopicity is different. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples (Buckton and Darcy, 1995) In some studies, amorphous materials were plasticized by water sorption and crystallized during the experiment. Crystallization can however be accompanied by expulsion of water depending on the degree of hydration of the crystalline material. In this case, the loss of water is used to calculate the amount of amorphous material. Water vapour sorption in a binary mixture, such as solid dispersions, can however be much more complicated than in pure materials, firstly because water vapour sorption is not always proportional to the composition of a binary intimately mixed system. The second complication is that matrix or drug crystallization during water vapour sorption is often not complete within the experimental time scale due to steric hindrance and proceeds to an unknown extent.

2.5.4 Isothermal microcalorimetry

Isothermal microcalorimetry measures the crystallization energy of an amorphous material that is heated above its glass transition temperature (Kumar *et al.,* 2011). This technique however, has some limitations. Firstly, it can only be used if stability and crystallization takes place during measurement. Secondly, it has to be assumed that all amorphous materials crystallize. Thirdly, in a binary mixture of two amorphous compounds, distinction between crystallization energies of drug and matrix is difficult (Dhirendria *et al.,* 2009)

2.5.5 Dissolution calorimetry

Dissolution calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample. Usually, dissolution of a crystalline material is endothermic, whereas dissolution of an amorphous material is exothermic. The dissolution energies of the two components in both crystalline and amorphous state should be determined in separate experiments in order to use this technique quantitatively (Kumar *et al.*, 2011).

2.5.6 Macroscopic technique

Macroscopic techniques that measure mechanical properties that are different for amorphous and crystalline material can be indicative of the degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity and viscosity and thus are affected by the degree of crystallinity. These techniques however, requires knowledge about the additivity of these properties in intimately mixed binary solids (Reena and Vandana, 2012)

2.5.7 Differential scanning calorimetry

A frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC). DSC is used for measuring the differences in heat flow between a sample and a reference during a controlled change of temperature (Ranee and Vandana, 2012).

DSC analysis allows quantitative and qualitative information to be obtained about the physical and chemical changes that occur in the sample. DSC is used extensively in the pharmaceutical industry to determine the melting points, purity and glass transition temperatures of materials. In the area of solid dispersion, DSC is a powerful tool in evaluating the drug-carrier interactions,

determining the solubility of a drug in a polymeric carrier, detecting polymorphic modifications and examining age-induced changes. The absence of the drug melting peak in the DSC thermal profile of solid dispersion indicates that the drug is dispersed molecularly, or it exists in the amorphous form. Moreover, since polymorphs generally have different melting points, DSC can be used to detect polymorphism. This property is extremely important when long-chain organic compounds are studied, because nearly all these compounds exhibit polymorphism (Serajuddin *et al*., 1999).

2.6 Dissolution

Dissolution is the process by which a solid enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Dissolution is considered one of the most important quality control tests performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability, and in some cases, replacing clinical studies to determine bioequivalence. Dissolution behaviour of drugs has a significant effect on their pharmacological activity. In fact, a direct relationship between *in vitro* dissolution rate of many drugs and their bioavailability has been demonstrated and is generally referred to as *in vitro – in vivo* correlation (IVIVC).The dissolution of drugs from a solid dispersion is dependent on the underlying solubility of the polymers (Craig, 2002). This is partially due to the mechanism whereby polymers dissolve due to the diffusion of solvent into the polymer matrix which results in the polymer altering from glassy to the rubbery state. The release process is complex and different factors such as the properties of drug- solubility, physical state, particle size, dissolution of the polymer, molecular weight and the possible drug-

polymer interaction can affect the release process. Craig (2002) presented a drug release model distinguishing between carrier-controlled and drug-controlled dissolution, depending on the solubility of drug in the concentrated polymer layer (Craig, 2002). In dispersions having low drug content, there are two methods for controlling the drug release: carrier-controlled dissolution and drug-controlled dissolution. In the former, the dissolution of carrier controls the dissolution of drug while in the later, the physical properties of the drug itself seem to affect the rate of dissolution (Craig, 2002). The first step for both mechanisms involves the formation of a carrier-rich dissolving surface. The drug has to pass through this surface so that it can be released into the bulk phase. The next phase involves the dissolution of the drug into the carrier diffusion layer, and then the drug is released into the bulk medium. The second phase is vital in stating which mechanism will follow. Craig (2002) proposed that in case of carrier-controlled dissolution, the drug dissolves in the carrier very quickly, causing the drug to disperse molecularly within the diffusion layer. The viscosity of the dissolving surface is sufficient to cause the diffusion of drug through this layer to be very gradual. The dissolution of the polymer is therefore, the controlling factor in the release of drug. In drug-controlled dissolution, particles dissolve slowly into diffusion layer, so are released as solid particles into the bulk medium. The properties of the drug such as the particle size and physical form are therefore, vital in the drug-controlled dissolution mechanism.

2.7 Physical stability of amorphous solid dispersions

The dissolution behaviour of solid dispersions must remain unchanged during storage. The best way to guarantee this is by maintaining their physical state and molecular structure. For optimal stability of amorphous solid dispersions, the molecular mobility should be as low as possible.

Solid dispersions, partially or fully amorphous, however, are thermodynamically unstable. In solid dispersions containing crystalline particles (glass suspension), these particles form nuclei that can be the starting point for further crystallization. It has been shown that such solid dispersions show progressively poorer dissolution behaviour during storage. In solid dispersions containing amorphous drug particles (amorphous precipitate in crystalline matrix and glass suspension), the drug can crystallize, but a nucleation step is required prior to that. In homogeneous solid dispersions (solid solution and glass suspension) the drug is molecularly dispersed, and crystallization requires another step. For nucleation to occur, drug molecules have to migrate through the matrix. Physical degradation is therefore, determined by both diffusion and crystallization of drug molecules in the matrix. It should be noted that in this respect, it is better to have a crystalline matrix, because diffusion in such a matrix is much slower.

The physical stability of amorphous solid dispersions should be related not only to crystallization of drug but also to any change in molecular structure including the distribution of the drug (Sandip *et al.*, 2013)

2.8 Recent studies on solid dispersions

Shukla *et al*. (2010) prepared solid dispersions of glipizide and reported the solubility enhancement of the drug by different solubilization techniques. The solid dispersion was prepared by solvent evaporation method; PEG 4000, mannitol and urea were used as carriers. Hydrotropic studies were carried out using different hydrotropic agents (sodium acetate, sodium benzoate and salicylate) and micellar solubilization was carried out using different surfactant solutions (sodium lauryl sulphate, Tween 80 and cetrimide). The solubility enhancement of

glipizide by different solubilization techniques was observed in decreasing order as: hydrotropic solubilization > solid dispersion > micellar solubilization.

Nadia *et al*. (2011) studied the dissolution profile of ibuprofen solid dispersion prepared with HPMC, HPC, icing sugar, dextrose, mannitol and lactose using the fusion method. The result obtained showed that the rate of dissolution of ibuprofen was considerably improved with HPMC and HPC while dispersions with icing sugar, dextrose, mannitol and lactose showed drug dissolution retardation capability.

Solubility and dissolution rate of clonazepam were improved in a study carried out by Minhaz *et al.* (2012). Clonazepam was used as a model drug to evaluate its release characteristics from different matrices using polyethylene glycol 600, HPMC, HPC and poloxamer in different drug to carrier ratio. Solid dispersions prepared with polyethylene glycol 600 and poloxamer showed the highest improvement in wettability and dissolution.

Ofokansi *et al.* (2012) evaluated trandolapril solid dispersions based on Eudragit RS 100 and PEG 8000. The *in vitro* release studies revealed that there was marked increase in the dissolution rate of trandolapril from the solid dispersion when compared to pure drug.

Meka *et al.* (2012) reported an increase in the therapeutic effectiveness of ibuprofen by increasing the solubility via solid dispersion using beta cyclodextrin and 2 hydroxypropyl beta cyclodextrins as carrier.

Hasnain and Nayak. (2012) studied the saturated solubility and *in vitro* dissolution of ibuprofen solid dispersion using PEG 600- PVPK 30 combination carrier by solvent evaporation technique. They attributed the improvement in solubility as well as drug dissolution of ibuprofen solid dispersion using PEG 6000-PVPK 30 to improved wettability, and reduction in drug crystallinity which can be modulated by appropriate level of hydrophilic carriers.

Sachin *et al.* (2013) reported a faster decrease in paw oedema with solid dispersions of ibuprofen and PEG than pure ibuprofen, signifying that the dissolution and absorption rate of ibuprofen from solid dispersion was more than in marketed preparation.

Poovi *et al*. (2013) investigated the solid dispersions of domperidone using sodium alginate as carrier and reported a marked improvement in solubility and dissolution rate of domperidone solid dispersions.

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Materials

Ibuprofen (BASF, Germany)

Piroxicam, Ethanol, low molecular weight hydroxypropyl methylcelluose HPMC (Sigma Aldrich, Germany)

Eudragit RS 100 (Evonik Pharma, Germany)

Monobasic potassium phosphate (Sigma Chemical Co, USA)

Sodium hydroxide (Merck, USA)

Hydrochloric acid, sodium chloride, calcium chloride, potassium chloride, potassium thiocynate (BDH Chemicals, England)

Trona , was purchased from Sabon Gari market, Zaria, Nigeria

3.2 Methods

3.2.1 Identification, purification and recrystallisation of trona

Trona was identified in the Department of Geology, Ahmadu Bello University, Zaria. It was then purified and recrystallized using the method described by Attama *et al.* (2007) with little modification.

A 500 g quantity of raw crushed solid trona was dissolved in 500 ml of water and boiled with continuous stirring until a dark brown supernatant was formed. This was filtered while hot with Whatman filter paper, 0.45 µm. The filtrate obtained was evaporated to dryness on a water bath and the crystals recovered. Which were then pulverized using mortar and pestle.

3.2.2 Preparation of simulated gastric fluid (SGF) without pepsin pH 1.2

A 2 g quantity of sodium chloride was dissolved in 7 ml of conc. hydrochloric acid and the volume was made up to 1000 ml with distilled water. The pH was adjusted to 1.2 using Oaklon pH meter (pH 1100 series, Eutech Instrument Singapore) by adding drops of conc. hydrochloric acid .

3.2.3 Preparation of simulated intestinal fluid (SIF) without pancreatin pH 7.4

A 6.8 g quantity of monobasic potassium phosphate was dissolved in 77 ml of 0.2 N sodium hydroxide and the volume was made up to 1000 ml. The pH was adjusted to 7.4 using Oaklon pH meter (pH 1100 series, Eutech Instrument Singapore) by adding drops of 0.2 N sodium hydroxide .

3.2.4 Construction of Beer Lambert's plot

A stock solution of ibuprofen (1 mg/ml) was prepared by weighing accurately 100 mg of ibuprofen into a 100 ml volumetric flask. A 50 ml aliquot of 0.1 M NaOH was measured and transferred into the flask containing ibuprofen with intermittent shaking to dissolve the drug. The flask containing ibuprofen was made up to 100 ml mark with 0.1 M NaOH. Serial dilutions of the stock solution were made to give the following concentrations 0.005, 0.01, 0.015, 0.20, 0.25, 0.30, 0.35 mg/ml in aqueous NaOH (0.1M). The absorbance of each concentration was measured at 221 nm using UV-VIS spectrophotometer (Jenway 6405). The graph of absorbance was plotted against the concentration to give the standard curve using Microsoft excel, 2007.

The same procedure above was used for piroxicam by dissolving 100 mg in 100 ml methanol, and the volume made up to 500 ml with distilled water. The absorbance was measured at 334 nm and the Beer's curve plotted.

3.2.5 Preparation of solid dispersions and physical mixtures

Ibuprofen and piroxicam solid dispersions were prepared using Eudragit RS 100 and HPMC by the solvent evaporation method. A 1 g quantity of both ibuprofen and Eudragit RS 100 were dissolved in 100 ml of absolute ethanol. The solution was stirred for 1 h and the solvent was allowed to evaporate at room temperature. The solid dispersion obtained (IB1) was pulverized, sieved through 22 mesh and then stored in screw cap vials at room temperature pending further use. The same procedure was carried out for all the formulations presented in Tables 3.2 and 3.3.

Physical mixtures of the drug and carriers, having the same composition of the solid dispersions were prepared by simply triturating the drugs and the polymers in a porcelain mortar. The mixtures were sieved and stored in screw cap vials at room temperature pending further use.

3.2.6 Preparation of solid dispersions incorporating trona

Solid dispersions containing trona were prepared by incorporating trona into the drug and polymer mixtures using the ratios 1:1:1 (ibuprofen: Eudragit RS 100: HPMC) and 0.1:1:1 (piroxicam:Eudragit RS 100:HPMC) with stirring for 1 h on a magnetic shaker, prior to solvent evaporation

Table 3.1: Composition of ibuprofen solid dispersions

Formulation code	ibuprofen:Eudragit RS 100:HPMC Ratios	Quantities (g)
IB 1	1:1:0	2: 2:0
IB 2	1:2:0	2:4:0
IB 3	1:3:0	2:6:0
IB 4	1:0:1	2:0:2
IB 5	1:0:2	2:0:4
IB 6	1:0:3	2:0:6
IB 7	1:1:1	2:2:2
IB 8	1:2:1	2:4:2
IB 9	1:1:2	2:2:4

Table 3.2: Compositions of piroxicam solid dispersions

Formulation code	piroxicam:Eudragit RS100: HPMC Ratios	Quantities (g)
PR 1	0.1:1:0	0.2:2:0
PR 2	0.1:2:0	0.2:4:0
PR 3	0.1:3:0	0.2:6:0
PR 4	0.1:0:1	0.2:0:2
PR 5	0.1:0:2	0.2:0:4
PR 6	0.1:0:3	0.2:0:6
PR 7	0.1:1:1	0.2:2:2
PR 8	0.1:2:1	0.2:4:2
PR 9	0.1:1:2	0.2:2:4

Table 3.3: Compositions of ibuprofen solid dispersions containing trona

Formulation code	ibuprofen:Eudragit RS100:HPMC:Trona Ratios	Quantities (g)
IBT 1	1:1:1:0.1	2:2:2:0.2
IBT 2	1:1:1:0.2	2:2:2:0.4
IBT 3	1:1:1:0.3	2:2:2:0.6
IBT 4	1:1:1:0.4	2:2:2:0.8

Table 3.4: Compositions of piroxicam solid dispersions containing trona

Formulation code	piroxicam:Eudragit RS100:HPMC:Trona Ratios	Quantities (g)
PRT 1	0.1:1:1:0.1	0.2:2:2:0.2
PRT 2	0.1:1:1:0.2	0.2:2:2:0.4
PRT 3	0.1:1:1:0.3	0.2:2:2:0.6
PRT 4	0.1:1:1:0.4	0.2:2:2:0.8

3.2.7 Determination of percent yield

The percent yield of ibuprofen and piroxicam solid dispersions was determined according to method described by Poovi *et al*.(2013) using the following expression

$$\% \text{ yield} = \frac{Weight\ of\ prepared\ Solid\ dispersion}{Weight\ of\ drug+carrier} x\ 100 \qquad \text{Eq. 1}$$

3.2.8 Estimation of drug content and encapsulation efficiency

An amount (100 mg) of solid dispersion was weighed accurately and dissolved in 100 ml of ethanol. Then 1 ml of the stock was diluted to 50 ml with simulated intestinal fluid (SIF) without pancreatin (pH 7.4) for ibuprofen solid dispersions and simulated gastric fluid (SGF) without pepsin (pH 1.2) for piroxicam solid dispersions. The solution was shaken vigorously and filtered and the filtrate analysed spectrophotometrically (Jenway 6405 UV-VIS spectrophotometer) for drug content at 221 nm for ibuprofen and 334 nm for piroxicam.

The amount of drug encapsulated in the solid dispersion was calculated with reference to a standard Beer's plot for ibuprofen and piroxicam to obtain the encapsulation efficiency (%) using the formula below (Ofokansi *et al.*, 2012).

$$\text{EE} = \frac{Actual\ drug\ content}{Theoretical\ drug\ content} x\ 100 \qquad \text{Eq. 2}$$

3.2.9 Fourier Transform Infra Red (FT-IR) studies

Compatibility studies of each drug (ibuprofen and piroxicam) with HPMC, Eudragit RS 100 and trona were carried out using Fourier Transform Infrared (FT-IR) spectroscopy. Sample from each of drug alone, carrier alone and solid dispersion was prepared in potassium bromide disk in a hydostatic press at 6-8 ton pressure. FT-IR spectra of these prepared samples were recorded at scanning range of 500-4000 cm. Appearance, disappearance or broadening of absorption

band(s) on the spectra of the solid dispersions and the polymeric carriers in comparison with the spectrum of drug were used to determine possible interactions between pure drugs and polymers (Poovi *et al.*, 2013).

3.2.10 Determination of moisture sorption/desorption over saturated salt solution

One gram of each drug-loaded solid dispersion was placed in an aluminium foil and kept in a desiccator with a guaze-holding tray containing saturated solution of different salts to provide the required relative humidity (water 100%, sodium chloride 75%, magnesium nitrate 53% and magnesium chloride 33%). Saturated salt solutions were prepared as shown in Table 3.5. An assembly of sample and saturated solution all contained in a desiccator was made such that the salt solution is placed at the bottom while the sample contained in aluminum foil was placed on top of the separator plate. The assembly was allowed to stand for 7 days after which the dishes containing the powders were brought out and weighed to monitor the mass changes as a function of time according to the method described by Li and Chen, (2005) The equilibrium moisture sorption (EMS) was determined using the formula.

$$EMS=Me/Md \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots Eq\ 3$$

Where:

Me is the amount of moisture sorped at equilibrium

Md is the dry weight of the material

Table 3.5: Composition of saturated salt solution

Salt	Humidity (%)	Salt (g)	Water (ml)
magnesium chloride	33	200	25
magnesium nitrate	53	200	30
sodium chloride	75	200	60

3.2.11 Determination of solubility of various solid dispersions

Ibuprofen loaded-solid dispersions, ibuprofen solid dispersion incorporating trona, physical mixtures and pure ibuprofen equivalent to 500 mg were weighed and transferred to a flask containing 50 ml of simulated intestinal fluid (SIF) without pancreatin (pH 7.4). The sample was agitated at 80 rpm in thermostated shaking water bath (CS 200G) at $37 \pm 0.5\ ^{0}C$ for 8 h. The supernant solution was then filtered through a Whatman filter paper. The filtrate was diluted and the absorbance was measured using Jenway 6405 UV-Vis spectrophotometer.

The procedure was repeated with piroxicam-loaded solid dispersions, piroxicam solid dispersions incorporating trona, pure piroxicam and physical mixtures equivalent to 30 mg piroxicam in simulated gastric fluid (SGF) without pepsin, pH 1.2 as described by Mohammed and Behzed, 2007.

3.2.12 Thermal analysis using Differential Scanning Calorimetry (DSC)

DSC was performed on the samples using Mettler differential scanning calorimeter (Perkin Elmer Pyris 6 DSC model, Germany). Samples (5 mg) used for FT-IR studies were weighed and placed on flat-bottomed aluminum pans. The thermograms were recorded at a heating rate of $5\ ^{0}C$/min from 0 to 300 ^{0}C. Holes were made in the lids in order to allow dehydratioin of samples. Melting peaks, glass transition and enthalpies were calculated using the Mettler Star software. The thermograms obtained were used to determine any possible interaction between pure drugs (ibuprofen and piroxicam) with Eudragit RS 100, HPMC and purified trona. The thermograms obtained were also used to ascertain whether solid dispersions of ibuprofen and piroxicam with Eudragit RS 100, HPMC and purified trona alone and in combination, affected the integrity of the drugs. The appearances or disappearances of peak(s) in the thermograms would indicate the formations or otherwise, of new bonds/structures (Kumar *et al.*, 2011)

3.2.13 Dissolution studies

The dissolution test of best formulations of ibuprofen and piroxicam solid dispersions based on solubility studies was determined as described in the USP (USP 2011) using dissolution apparatus type II. For this 500 ml volume of simulated gastric fluid (SGF) without pepsin (pH 1.2) was used as dissolution medium for the first 2 h after which the sample was transferred to another medium of simulated intestinal fluid (SIF) without pancreatin (pH 7.4) for another 6 h at 37± 0.5 ^{0}C and stirred at a rate of 50 rpm. Samples were placed in a polycarbonate dialysis membrane which was pretreated by soaking in distilled water for 24 h prior to commencement of each release experiment. In each case, samples equivalent to 200 mg ibuprofen and 20 mg piroxicam was placed in the dialysis membrane and securely tied with a thermo-resistant thread and then immersed in the dissolution medium as described by Ofokansi *et al.,* 2012. At predetermined time intervals, 2 ml portions of the dissolution medium were withdrawn. An equivalent volume of the fresh medium maintained at the same temperature was added to maintain sink conditions throughout the study period. Withdrawn samples were filtered through a 0.45 µm Whatman filter paper and assayed spectrophotometerically at 222 nm for ibuprofen and 334 nm for piroxicam . For the purpose of comparisons, the dissolution of physical mixtures of the optimal formulations of ibuprofen and piroxicam solid dispersion was studied alongside that of commercial preparations of ibuprofen tablet and piroxicam capsule.

3.2.14 Anti-inflammatory study

Egg albumin-induced paw oedema as described by Winter *et al.* (1962) was used. Wistar rats weighing 120-200 g were used. Nine groups consisting of five rats each were used. Groups 1-4 received 50 mg/kg of the best solid dispersion of ibuprofen with HPMC, ibuprofen solid

dispersion with Eudragit RS 100, ibuprofen solid dispersion with HPMC and Eudragit RS 100 and pure ibuprofen respectively, suspended using compound tragacanth. Group 5 received the best formulation of piroxicam solid dispersion with HPMC, while solid dispersions of piroxicam with Eudragit RS 100 was given to group 6. Group 7 received solid dispersion of piroxicam with HPMC and Eudragit RS 100 while group 8 received pure piroxicam at a dose of 10 mg/kg suspended using compound tragacanth. The ninth group served as control and was given 0.5 ml normal saline. After a period of 30 min, the rats in each group were administered 0.5 ml of fresh raw egg albumin subcutaneously to the sub-plantar surface of the left hind paw. The paw diameter was measured with the aid of a Vernier caliper 0, 1, 2, 3, 4, 5 h after the injection of the egg albumin. The difference between the readings at time zero and the different time intervals was taken as the oedema diameter.

3.2.15 Stability Studies

Stability studies were carried out on the best formulation in terms of solubility at room temperature (28^{o} C) in a humidity chamber having 75 % relative humidity for 3 months. After 3 months, the sample was examined for drug content.

3.2.16 Statistical Analysis

The results obtained were statistically analysed and expressed as mean ± standard error of mean (SEM). The differences between means were considered significant at P-values <0.05 using the analysis of variance (ANOVA) or student t-test. All statistical analysis were carried out using the SPSS (version 20)

CHAPTER FOUR

4.0 RESULTS

4.1 Percentage Yield of Solid dispersions

Figures 4.1 and 4.3 summarize the percentage yield of the prepared solid dispersions. The production yield ranged between 59.0 - 92.0 % for ibuprofen solid dispersions and 72.5 – 98.2 % for piroxicam dispersions.

Ibuprofen solid dispersion with HPMC had a yield of 80.5, 84.6, and 92.8 % for the ibuprofen:HPMC combination ratios of 1:1, 1:2 and 1:3 respectively. The yield recorded for ibuprofen: Eudragit RS100 solid dispersions at ratios of 1:1, 1:2 and 1:3 were 91.2, 76.5 and 59.4 % respectively. Solid dispersion of ibuprofen with HPMC and Eudragit RS 100 at a ratio of 1:1:1 had a yield of 81.0 %. Increasing the amount of trona in the formulation led to a corresponding increase in the yield of the solid dispersion up to a maximum of 87.8 % as shown in Figure 4.2

Piroxicam solid dispersion with HPMC gave a yield of 98.2, 93.5 and 95.8 % for the Piroxicam:HPMC combination ratios of 0.1:1, 0.1:2 and 0.1:3 respectively. Piroxicam solid dispersion with Eudragit RS 100 on the other hand, gave a yield of 92.7, 90.4 and 74.2 % for weight ratios of 0.1:1, 0.1:2 and 0.1:3 respectively. Solid dispersion of piroxicam with HPMC and Eudragit RS 100 weight ratio of 0.1:1:1 gave a yield of 90.2 % a slight increase in yield was observed when trona was incorporated into the solid dispersion as seen in Figure 4.4

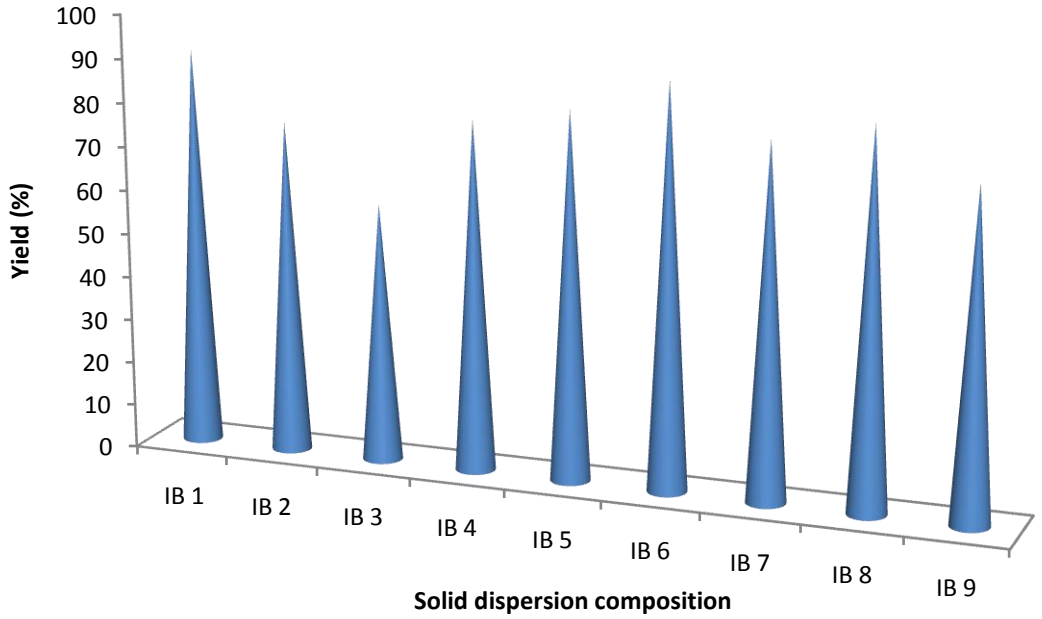


Figure 4.1: Effect of composition of polymers on production yield of ibuprofen solid dispersion

Keys:

IB 1- Ibuprofen:Eud (1:1)

IB 2 - Ibuprofen :Eud (1:2)

IB 3 - Ibuprofen:Eud (1:3))

IB 4 - Ibuprofen:HPMC (1:1))

IB 5 - Ibuprofen:HPMC (1:2)

IB 6 - Ibuprofen:HPMC (1:3)

IB 7-Ibuprofen:Eud:HPMC (1:1:1)

IB 8 - Ibuprofen:Eud:HPMC (1:2:1)

IB 9 - Ibuprofen:Eud:HPMC (1:1:2)

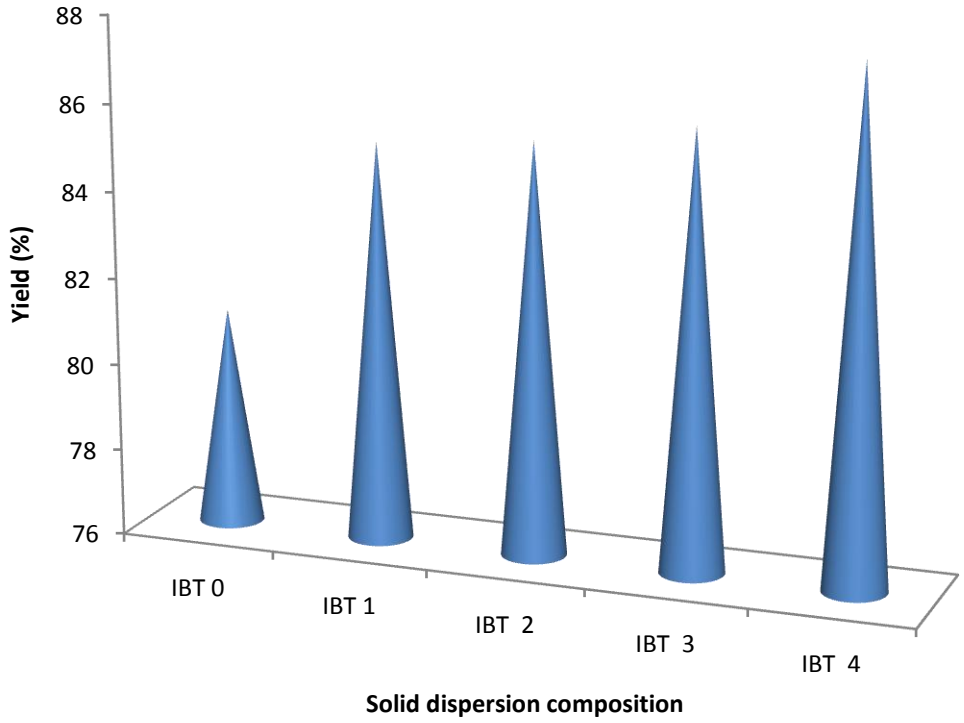


Figure 4.2: Effect of Trona on production yield of ibuprofen solid dispersion

Keys:

IBT0- Ibuprofen:Eud:HPMC:trona (1:1:1:0)

IBT1- Ibuprofen:Eud:HPMC:trona (1:1:1:0.1)

IBT2- Ibuprofen:Eud:HPMC:trona (1:1:1:0.2)

IBT3- Ibuprofen:Eud:HPMC:trona (1:1:1:0.3)

IBT4- Ibuprofen:Eud:HPMC:trona (1:1:1:0.4)

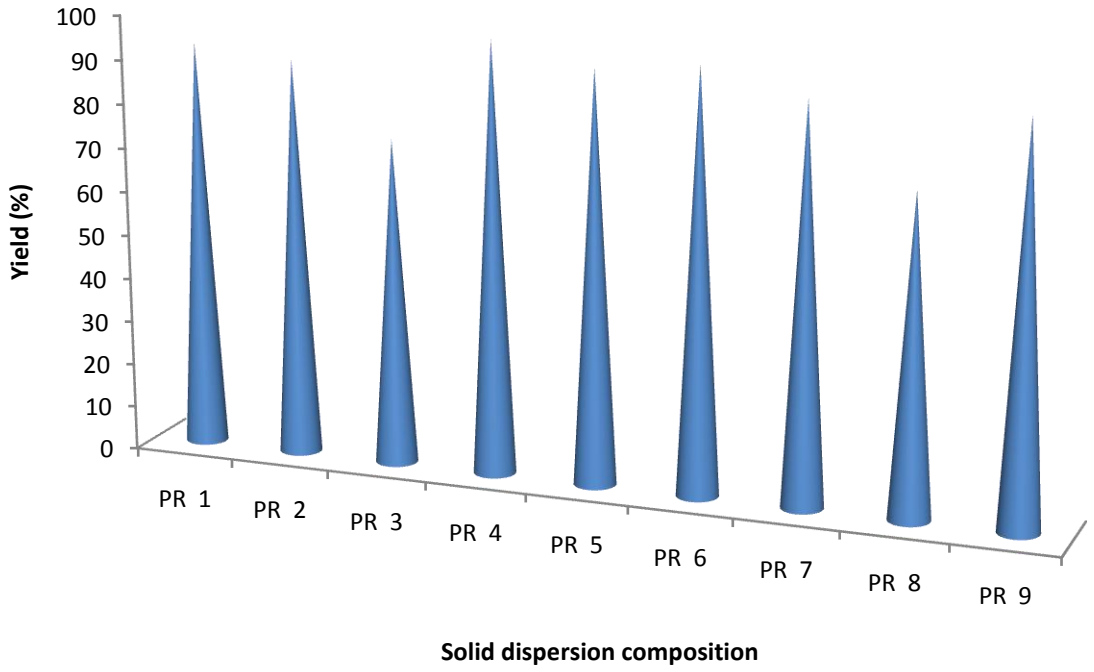


Figure 4.3: Effect of composition of polymer on production yield of piroxicam solid dispersion

Keys:

PR 1- Piroxicam:Eud (1:1)

PR 2 - Piroxicam:Eud (1:2)

PR 3 - Piroxicam:Eud (1:3)

PR 4 - Piroxicam:HPMC (1:1)

PR 5 - Piroxicam:HPMC (1:2)

PR 6 - Piroxicam:HPMC (1:3)

PR 7- Piroxicam:Eud:HPMC (1:1:1)

IB 8 - Piroxicam:Eud:HPMC (1:2:1)

IB 9 - Piroxicam:Eud:HPMC (1:1:2)

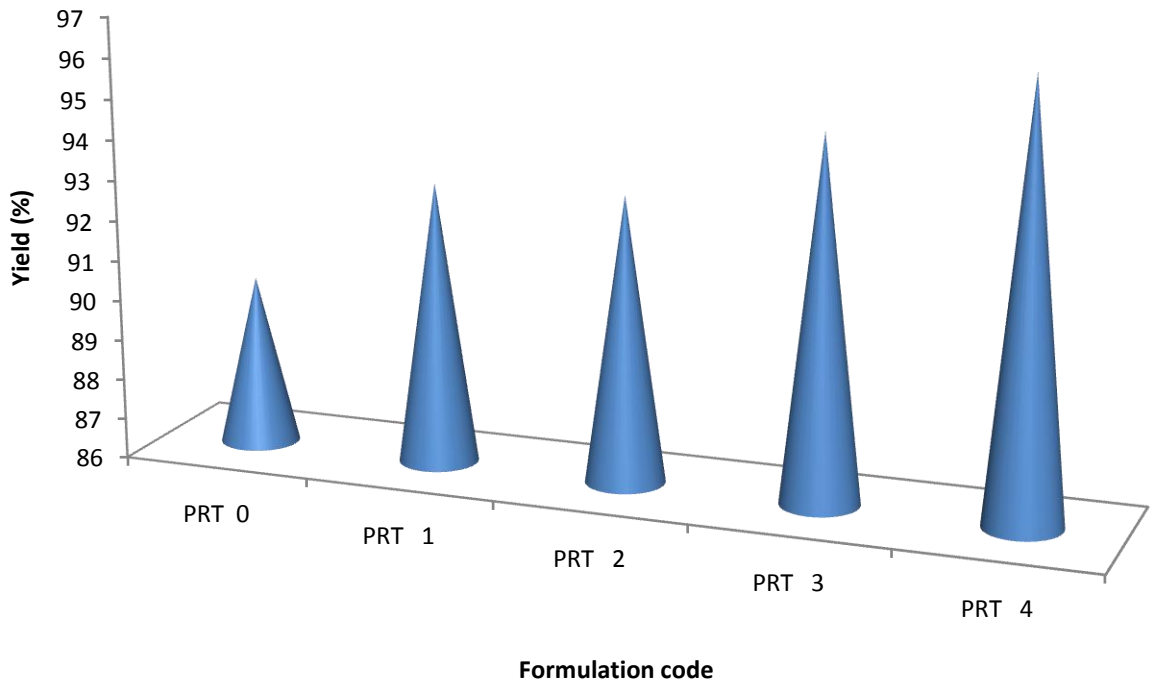


Figure 4.4: Effect of trona on production yield of piroxicam solid dispersion

Keys:

PRT0- Piroxicam:Eud:HPMC:trona (0.1:1:1:0)

PRT1- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.1)

PRT2- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.2)

PRT3- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.3)

PRT4- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.4)

4.2 Drug content of solid dispersion

The absolute drug contents of the solid dispersions are presented in Table 4.1 for ibuprofen solid dispersions and Table 4.2 for piroxicam solid dispersions. Solid dispersions of ibuprofen with HPMC entrapped the highest amount of drug. The amount of drug entrapped increased with increase in polymer concentration and ranged from 64.63 - 85.00 % for ibuprofen solid dispersions with Eudragit RS 100, 75.05 - 90.88 % for ibuprofen solid dispersion with HPMC and 84.32 - 90.88 % for ibuprofen solid dispersion containing HPMC and Eudragit RS 100 in combination.

Piroxicam solid dispersion of HPMC entrapped greater amount of drug (83.34 - 95.24 %) in comparison to solid dispersion in Eudragit RS 100 (75.72 - 85.45%). The ternary system with ratio 0.1:1:1 (piroxicam:Eudragit RS 100:HPMC) entrapped the greatest amount of drug when compared to the binary system containing only Eudragit RS 100 or HPMC with piroxicam

Table 4.1 : Percentage drug content of ibuprofen solid dispersions

Formulation	% drug content± SD
IB 1	64.63 ± 0.30^{f}
IB 2	76.23 ± 0.54^{d}
IB 3	85.00 ± 0.61^{c}
IB 4	75.05 ± 0.74^{e}
IB 5	84.53 ± 0.83^{c}
IB 6	90.88 ± 0.41^{a}
IB 7	84.32 ± 0.89^{c}
IB 8	86.83 ± 0.41^{b}
IB 9	90.88 ± 0.41^{a}

Values are expressed as mean ± standard deviation. Means having different superscripts along the column are significantly different at $p < 0.001$.Mean values were separated using Duncan's multiple range test (DMRT).

Keys:

IB 1- Ibuprofen:Eud (1:1)

IB 2- Ibuprofen :Eud (1:2)

IB 3- Ibuprofen:Eud (1:3)

IB 4- Ibuprofen:HPMC (1:1)

IB 5 - Ibuprofen :HPMC (1:2)

IB 6- Ibuprofen:HPMC (1:3)

IB 7- Ibuprofen :Eud:HPMC (1:1:1)

IB 8- Ibuprofen:Eud:HPMC (1:2:1)

IB 9- Ibuprofen:Eud:HPMC (1:1:2)

Table 4.2: Percentage drug content of ibuprofen solid dispersions containng trona

Formulations	% drug content± SD
IBT0	83.98 ± 0.18^{a}
IBT1	82.81 ± 0.035^{b}
IBT2	82.25 ± 0.082^{c}
IBT3	81.85 ± 0.060^{cd}
IBT4	81.39 ± 0.029^{d}

Values are expressed as mean ± standard deviation. Means having different superscripts along the column are significantly different at $p < 0.001$.Mean values were separated using Duncan's multiple range test (DMRT).

Keys:

IBT0 - Ibuprofen:Eud:HPMC:trona (1:1:1:0)

IBT1 - Ibuprofen:Eud:HPMC:trona (1:1:1:0.1)

IBT 2- Ibuprofen:Eud:HPMC:trona (1:1:1:0.2)

IBT3 - Ibuprofen:Eud:HPMC:trona (1:1:1:0.3)

IBT4 - Ibuprofen:Eud:HPMC:trona (1:1:1:0.4)

Table 4.3: Percentage drug content of piroxicam solid dispersions

Formulation	% drug content± SD
PR 1	75.72 ± 3.14^{d}
PR 2	72.57 ± 2.23^{d}
PR 3	85.45 ± 2.93^{bc}
PR 4	83.34 ± 1.50^{c}
PR 5	87.85 ± 0.30^{b}
PR 6	95.24 ± 2.25^{a}
PR 7	97.29 ± 1.27^{a}
PR 8	89.58 ± 4.78^{b}
PR 9	76.87 ± 1.62^{d}

Values are expressed as mean ± standard deviation. Means having different superscripts along the column are significantly different at $p < 0.001$.Mean values were separated using Duncan's multiple range test (DMRT).

Keys:

PR 1- Piroxicam: Eud (0.1:1)

PR 2- Piroxicam:Eud (0.1:2)

PR 3 Piroxicam:Eud (0.1:3)

PR 4- Piroxicam:HPMC (0.1:1)

PR 5- Piroxicam: HPMC (0.1:2)

PR 6- Piroxicam:HPMC (0.1:3)

PR 7- Piroxicam:Eud: HPMC (0.1:1:1)

PR 8- Piroxicam: Eud: HPMC (0.1:2:1)

PR 9- Piroxicam:Eud:HPMC (0.1:1:2)

Table 4.4: Percentage drug content of piroxicam solid dispersion incorporating trona

Formulation	% drug content± SD
PRT0	97.28 ± 0.73
PRT1	97.31 ± 0.035
PRT2	97.32 ± 0.034
PRT3	97.38 ± 0.024
PRT4	97.42 ± 0.018

Values are expressed as mean ± standard deviation. Means having different superscripts along the column are significantly different at $p < 0.001$.Mean values were separated using Duncan's multiple range test (DMRT).

Keys:

PRT0- Piroxicam:Eud:HPMC:trona (0.1:1:1:0)

PRT1- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.1)

PRT2- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.2)

PRT3- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.3)

PRT4- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.4)

4.3 Fourier transform infrared (FT-IR) spectral studies

Figure 4.5 shows the FT-IR spectrum of pure ibuprofen showing characteristics peaks at 3029.31 cm^{-1} indicating O-H stretching , 2892.36 cm^{-1} 2636.78 cm^{-1} and 2720.69 cm^{-1} indicating C-H stretching in alkanes and a broad band peak at 1718.63 cm^{-1} indicating C=O band in carboxylic acid, 1433.16 cm^{-1} C-H bending frequency in Alkenes and 936.47 cm^{-1} C-H in disubstituted aromatic ring. Figure 4.6 is the FT-IR spectrum of pure piroxicam showing characteristics peaks at 3562.64 cm^{-1} and 3465.23 cm^{-1} corresponding to N-H stretching in amines and amides and a slight broad peak at 3334.07 cm^{-1} indicating O-H band and N-H overlap, 3079.4 cm^{-1} indicating C-H stretching in Alkenes and 2773.73 cm^{-1} indicating C-H band in Alkane.

Figure 4.7 is the FT-IR spectrum of Eudragit RS 100 showing broad peaks at 3592.54 cm^{-1}, 3425.69 $cm^{-1}$and 2972.4 cm^{-1} representing OH band, N-H stretching in amine and C-H stretching frequencies in alkane. Peak at 1730.21 cm^{-1} is characteristics C=O band in ketones. Figure 4.8 shows the FT-IR spectrum of HPMC showing characteristic broad band at 3460.41 cm^{-1} and 2918.4 cm^{-1} indicating OH band and C-H stretching frequency in Alkane. Peaks at 1646.30 cm^{-1} 1436.05 cm^{-1} , and 1361.79 cm^{-1} representing C=O, C-H bending and C-O stretching. Figure 4.9 is the FT-IR spectrum of purified trona showing prominent peaks 3465.23 $cm^{-1,}$ 3314.78 cm^{-1}, 3227.02 cm^{-1} and 3081.39 cm^{-1} representing H-O-H bending and stretching. Figures 4.10 to Figure 4.19 show the FT-IR spectra of various ibuprofen solid dispersions showing similar absorption bands as those of the pure ibuprofen but with weak intensity. Figures 4.20 to Figure 4.29 are the FT-IR spectra of various piroxicam solid dispersions showing characteristic peaks of pure piroxicam, but of very weak intensity.

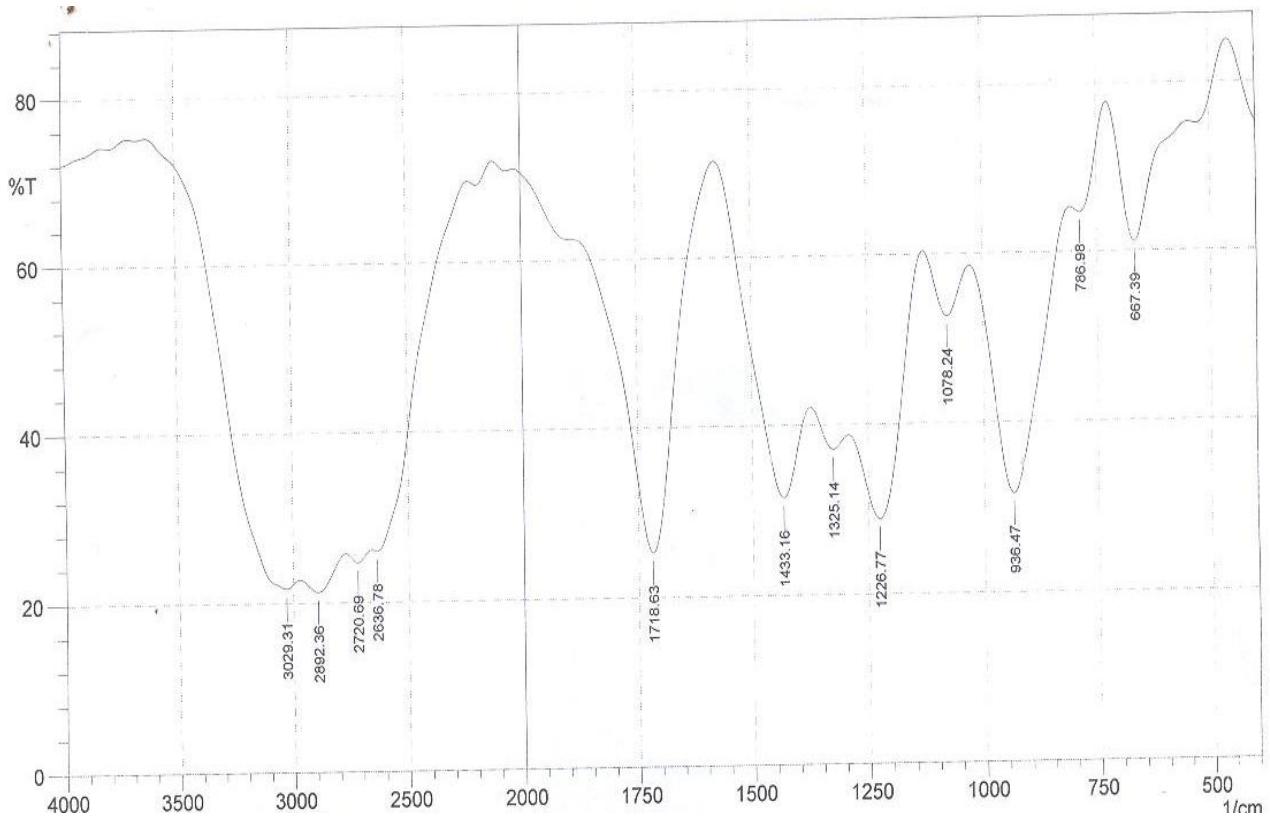


Figure 4.5: FT-IR spectra of pure ibuprofen

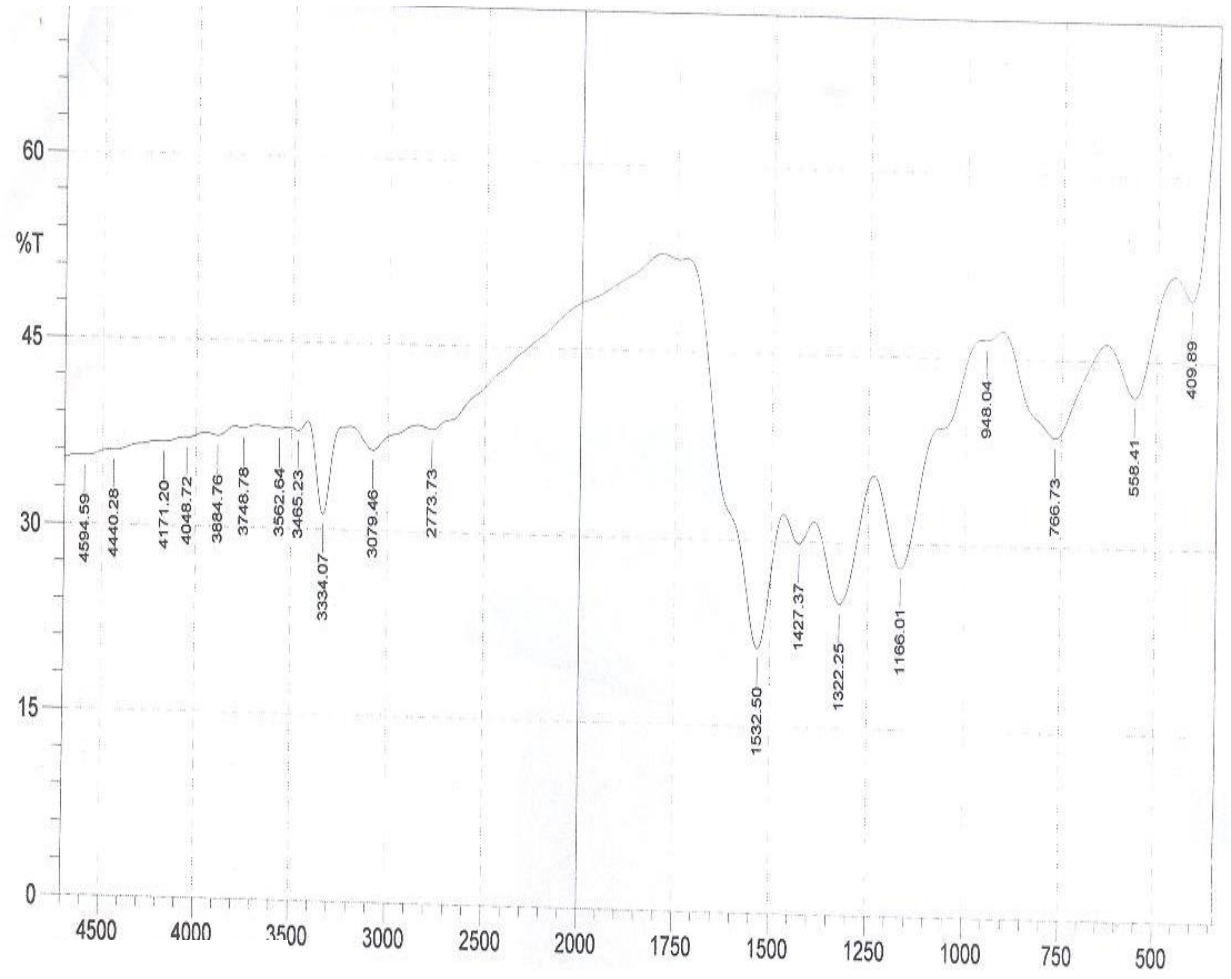


Figure 4.6: FT-IR spectra of pure piroxicam

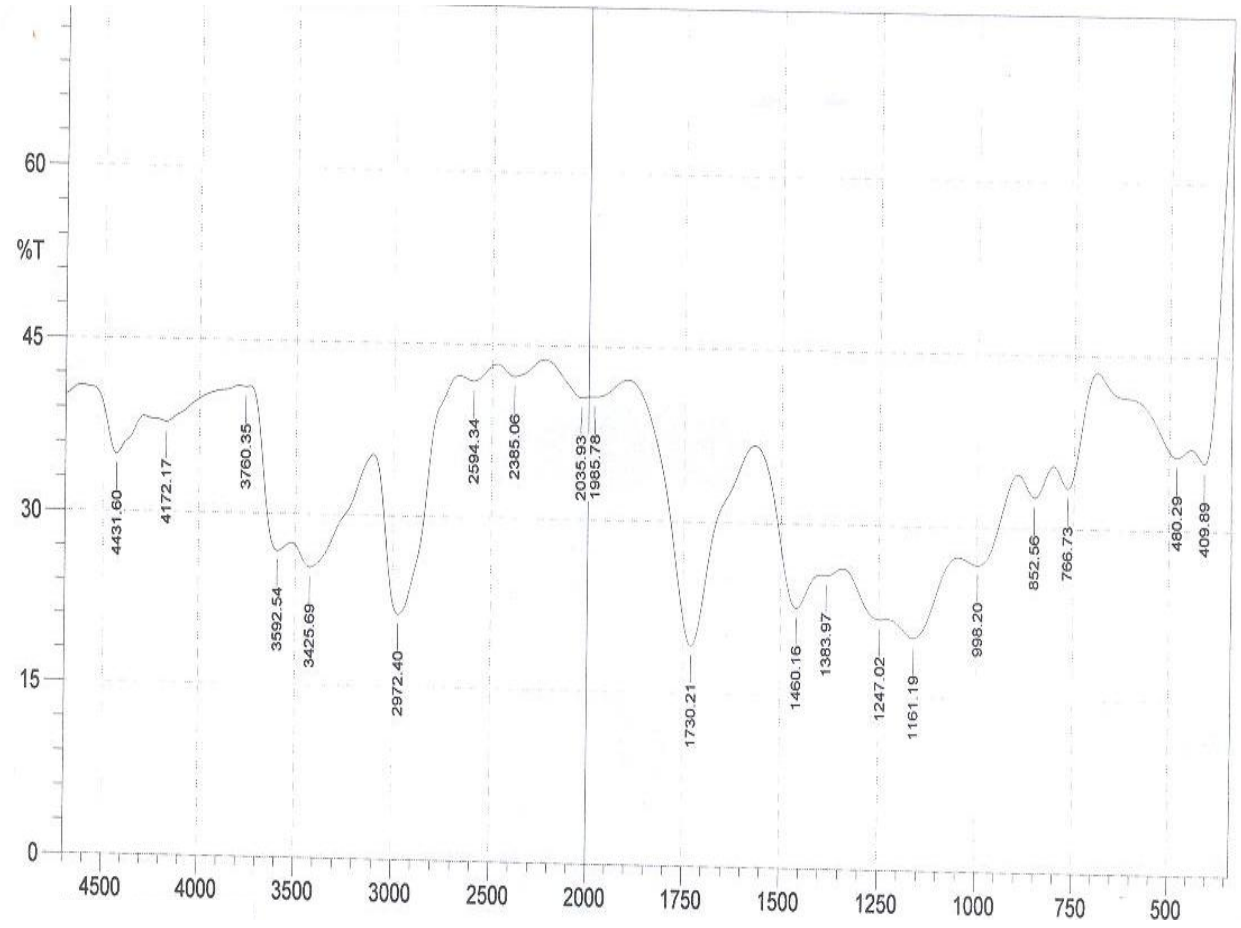


Figure 4.7: FT-IR spectra of pure Eudragit RS 100

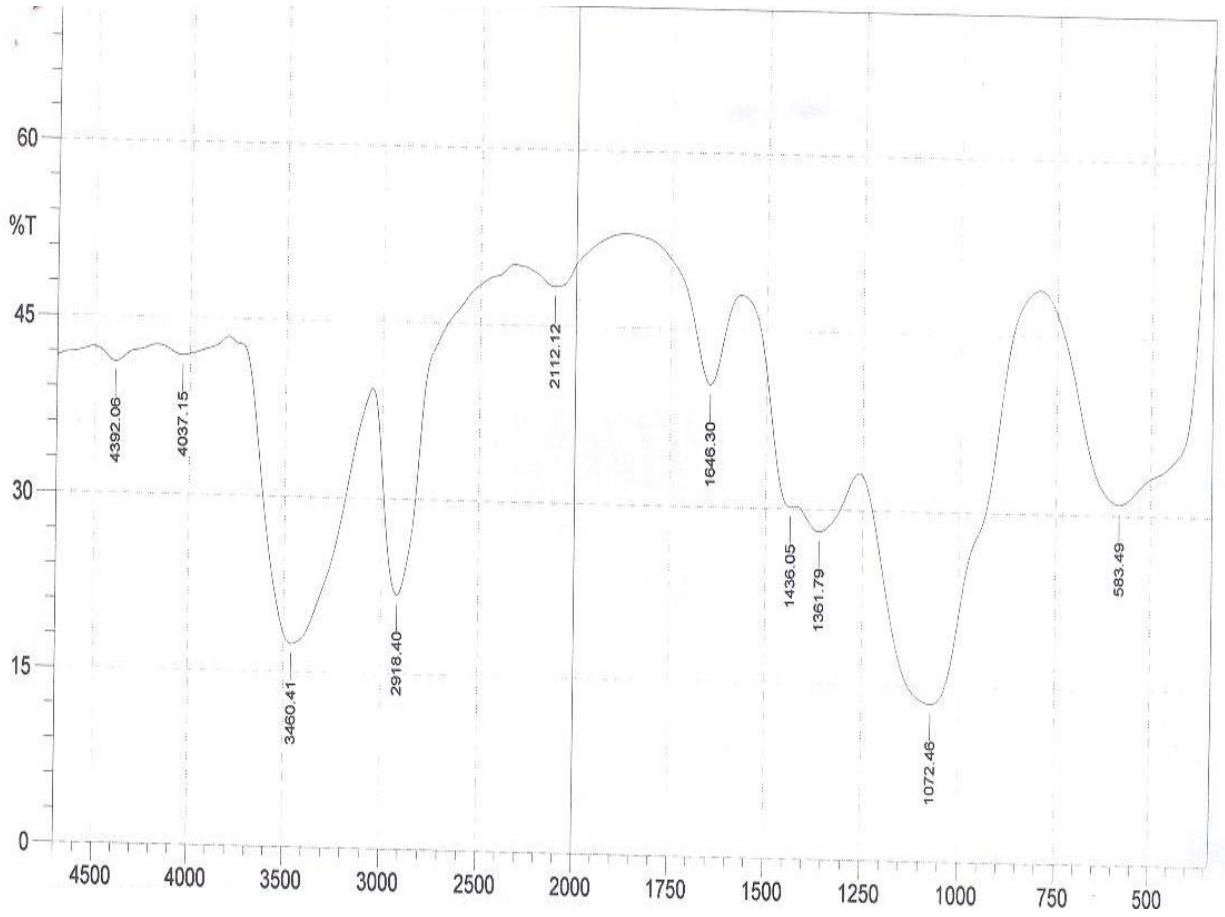


Figure 4.8: FT-IR spectra of pure HPMC

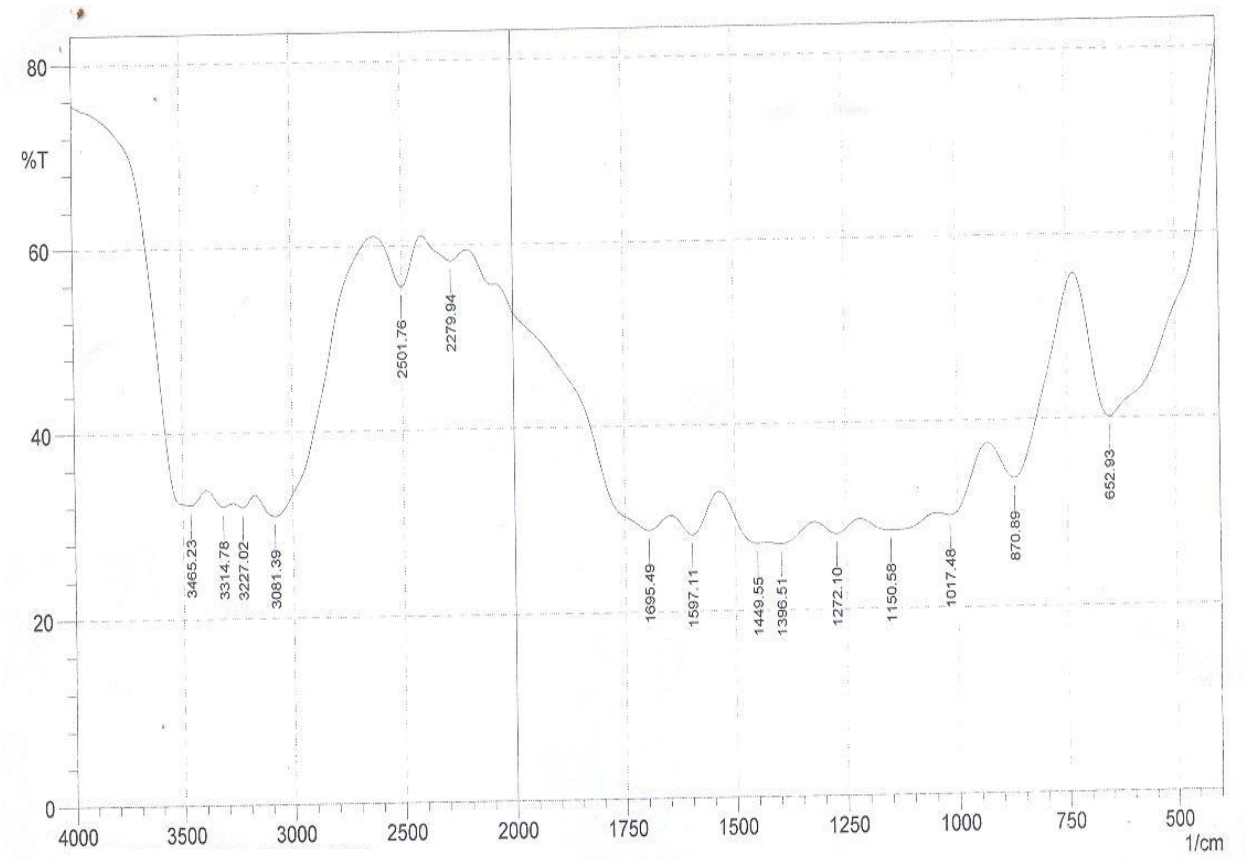


Figure 4.9: FT-IR spectra of purified trona

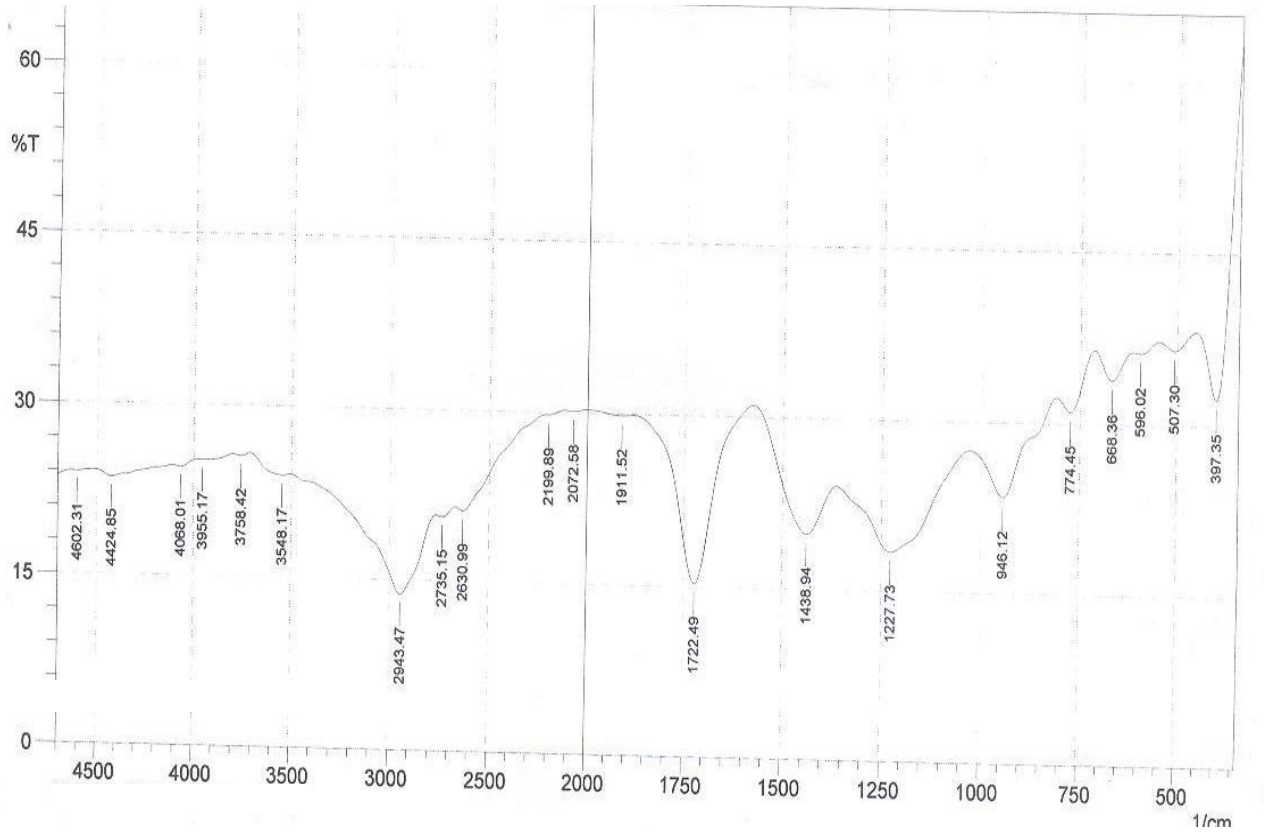


Figure 4.10 : FT-IR of ibuprofen solid dispersion with Eudragit RS 100 (IB1)

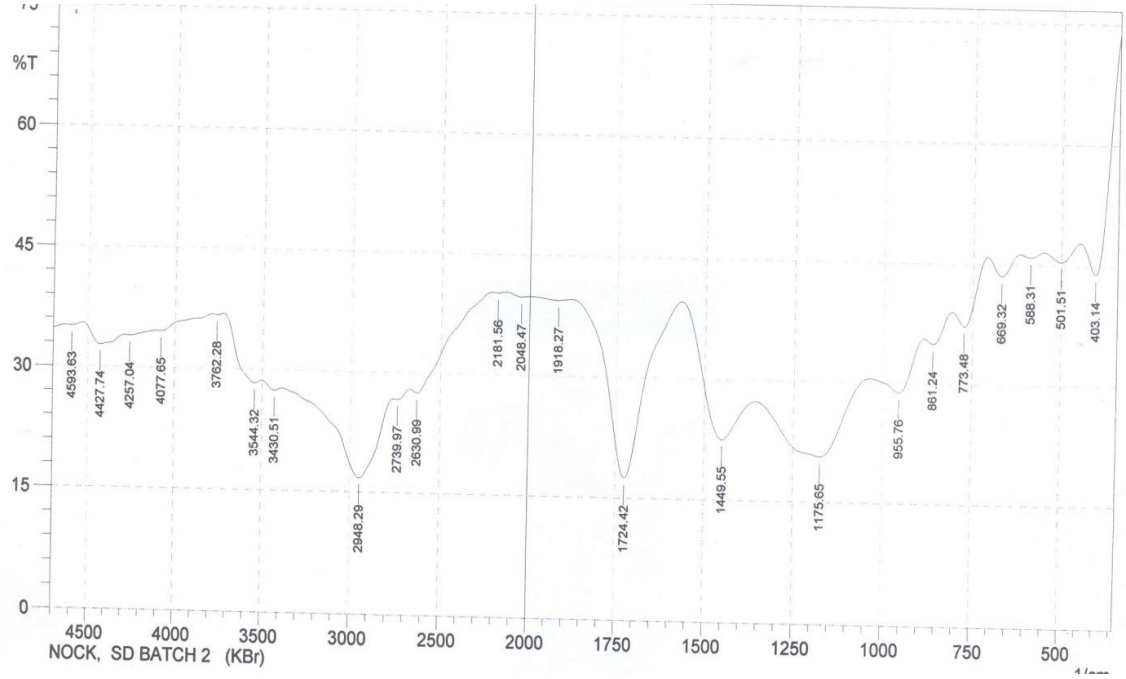


Figure 4.11: FT-IR of ibuprofen solid dispersion with Eudragit RS 100 (IB2)

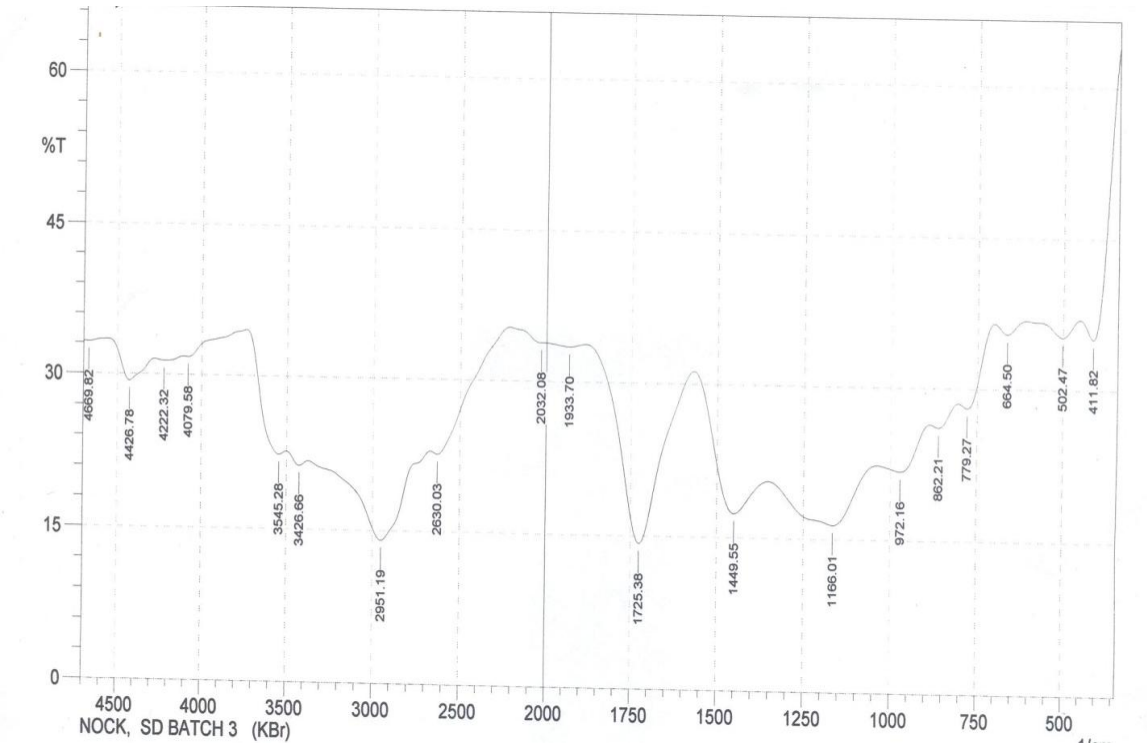


Figure 4.12: FT-IR of ibuprofen solid dispersion with Eudragit RS 100 (IB3)

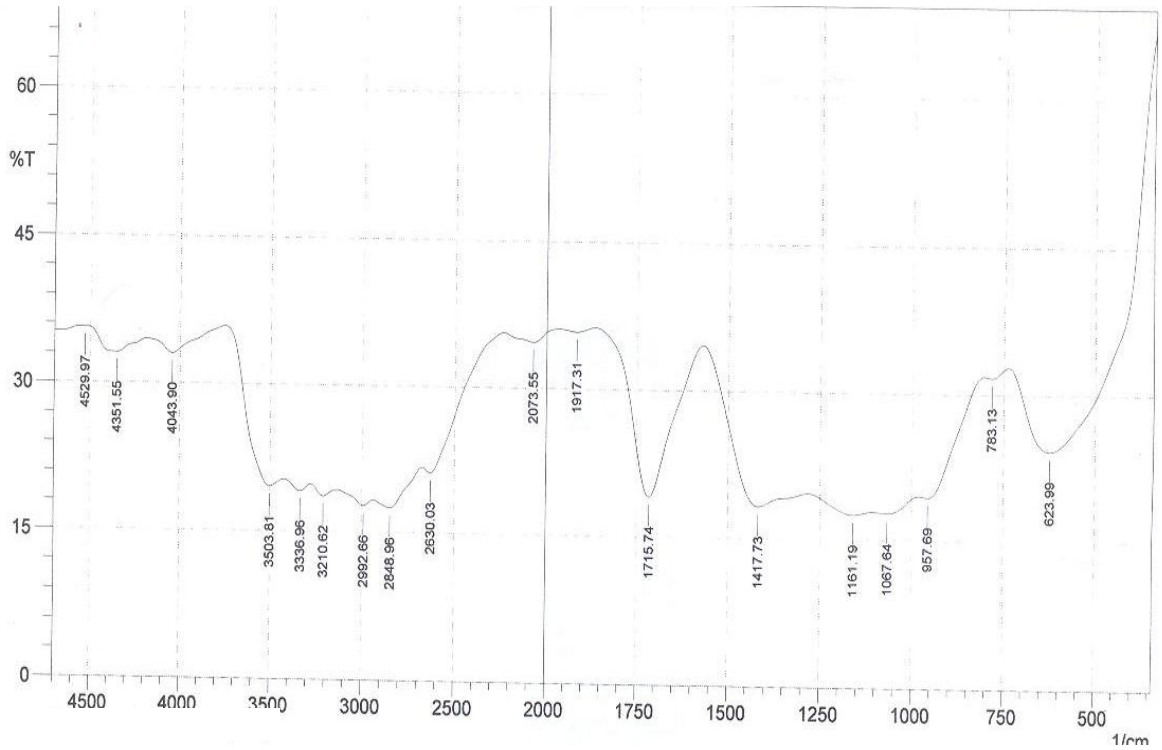


Figure 4.13: FT-IR spectra of ibuprofen solid dispersion with HPMC (1B4)

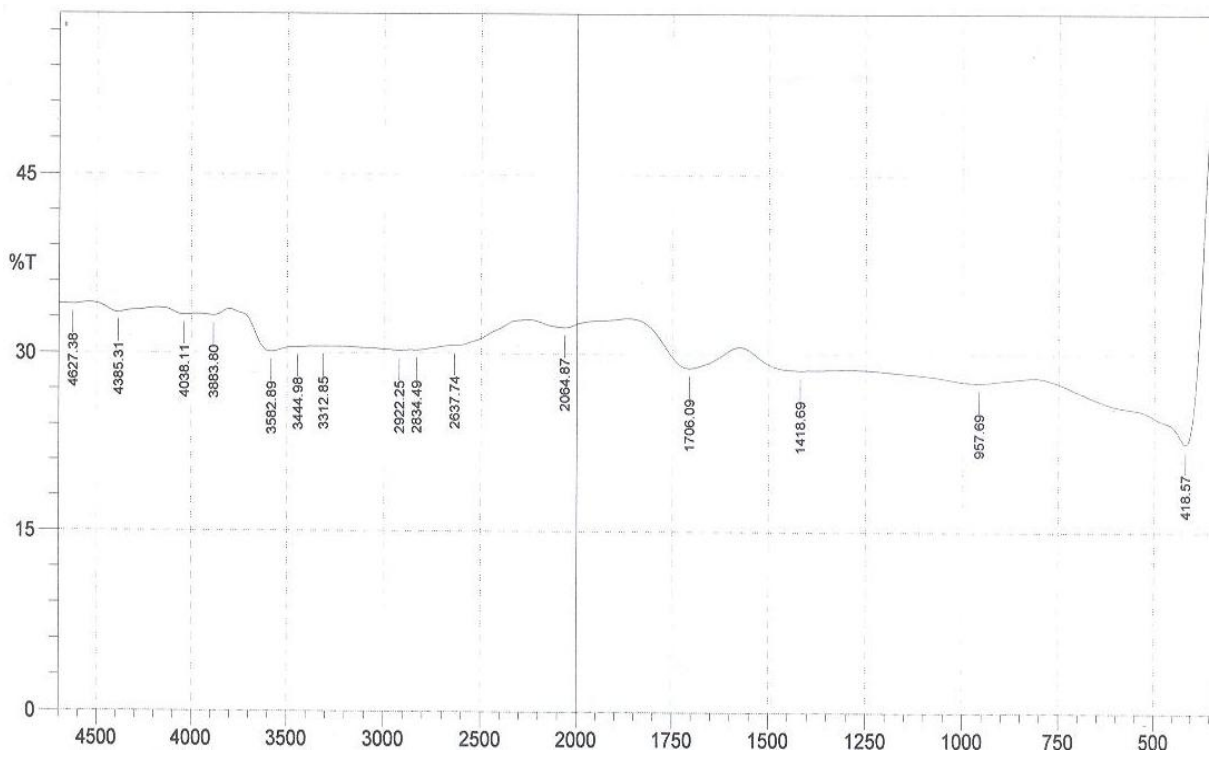


Figure 4.14: FT-IR spectra of ibuprofen solid dispersion with HPMC (1B5)

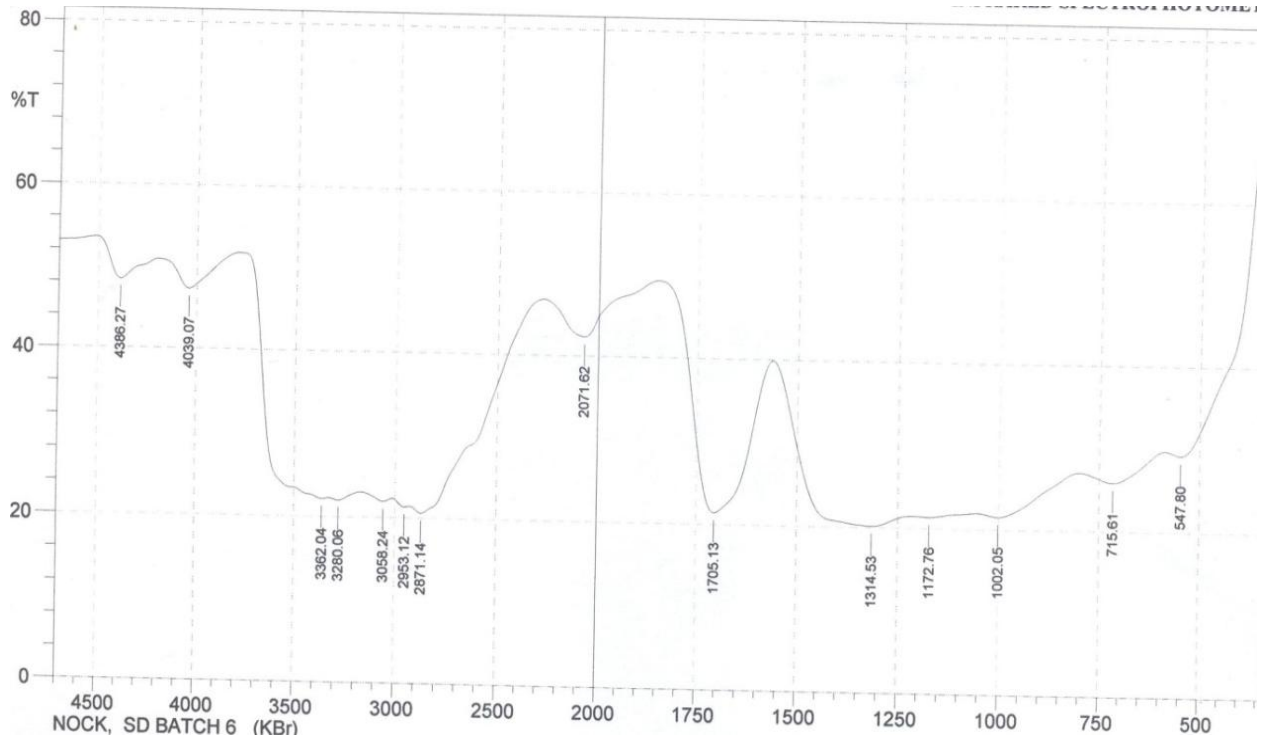


Figure 4.15: FT-IR spectra of ibuprofen solid dispersion with HPMC (1B6)

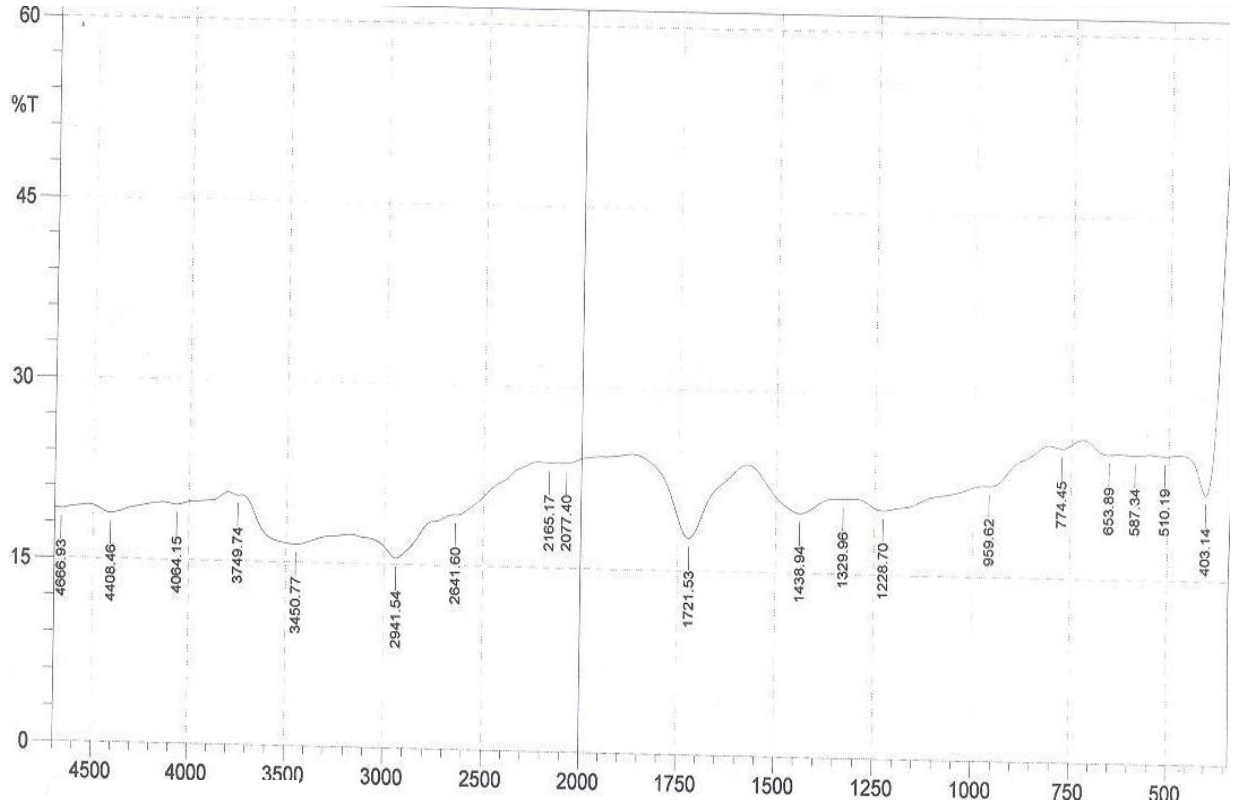


Figure 4.16: FT-IR spectra of ibuprofen solid dispersion with Eudragit RS 100 and HPMC (IB7)

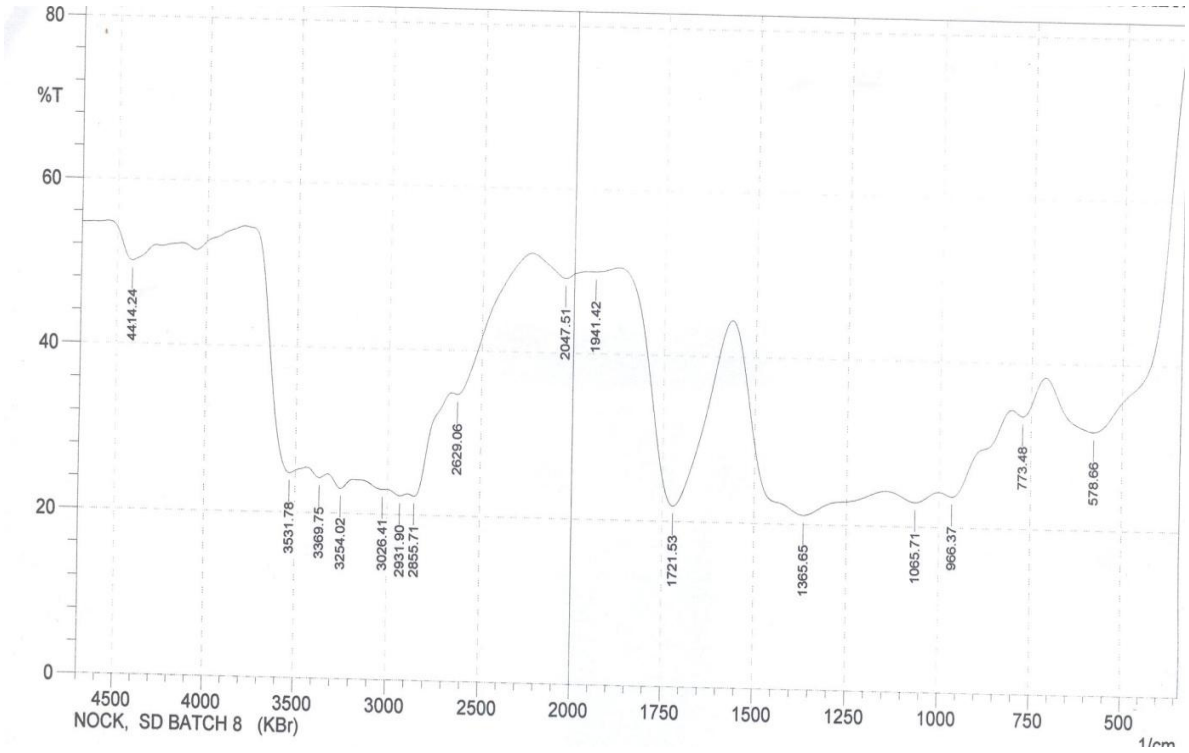


Figure 4.17: FT-IR spectra of ibuprofen solid dispersion with Eudragit RS 100 and HPMC (IB8)

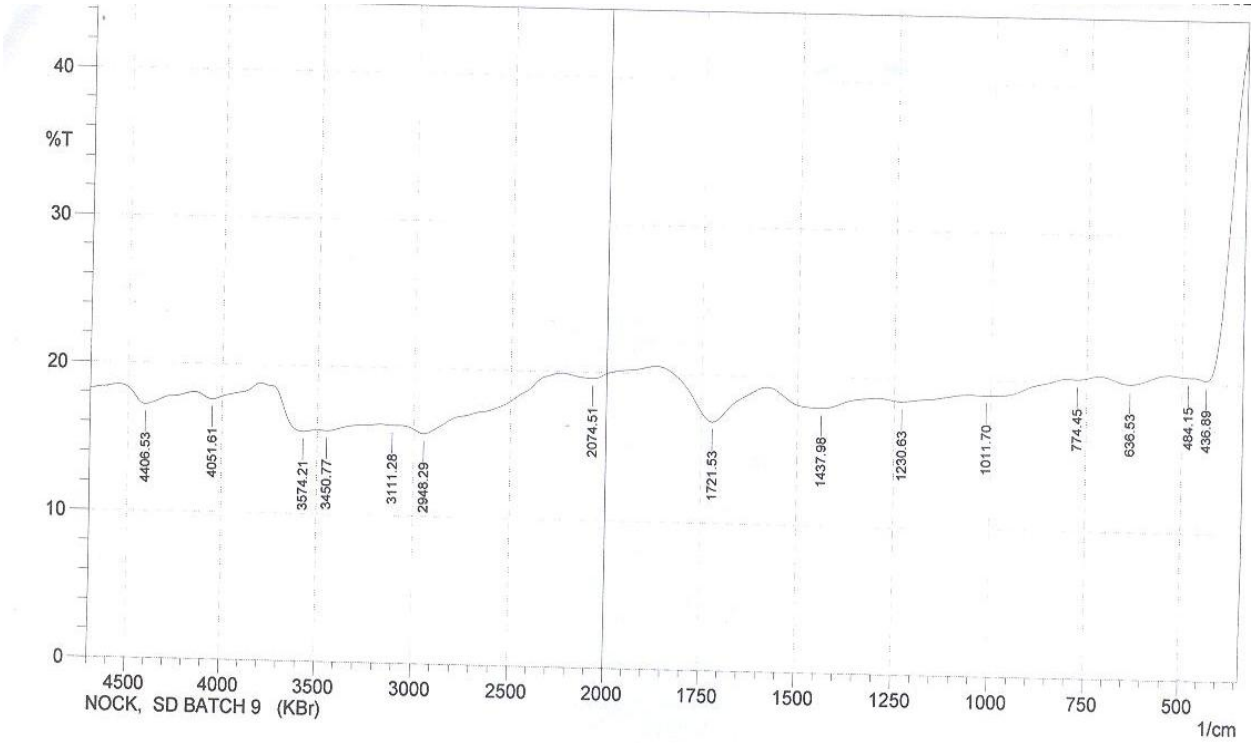


Figure 4.18: FT-IR spectra of ibuprofen solid dispersion with Eudragit RS 100 and HPMC (IB9)

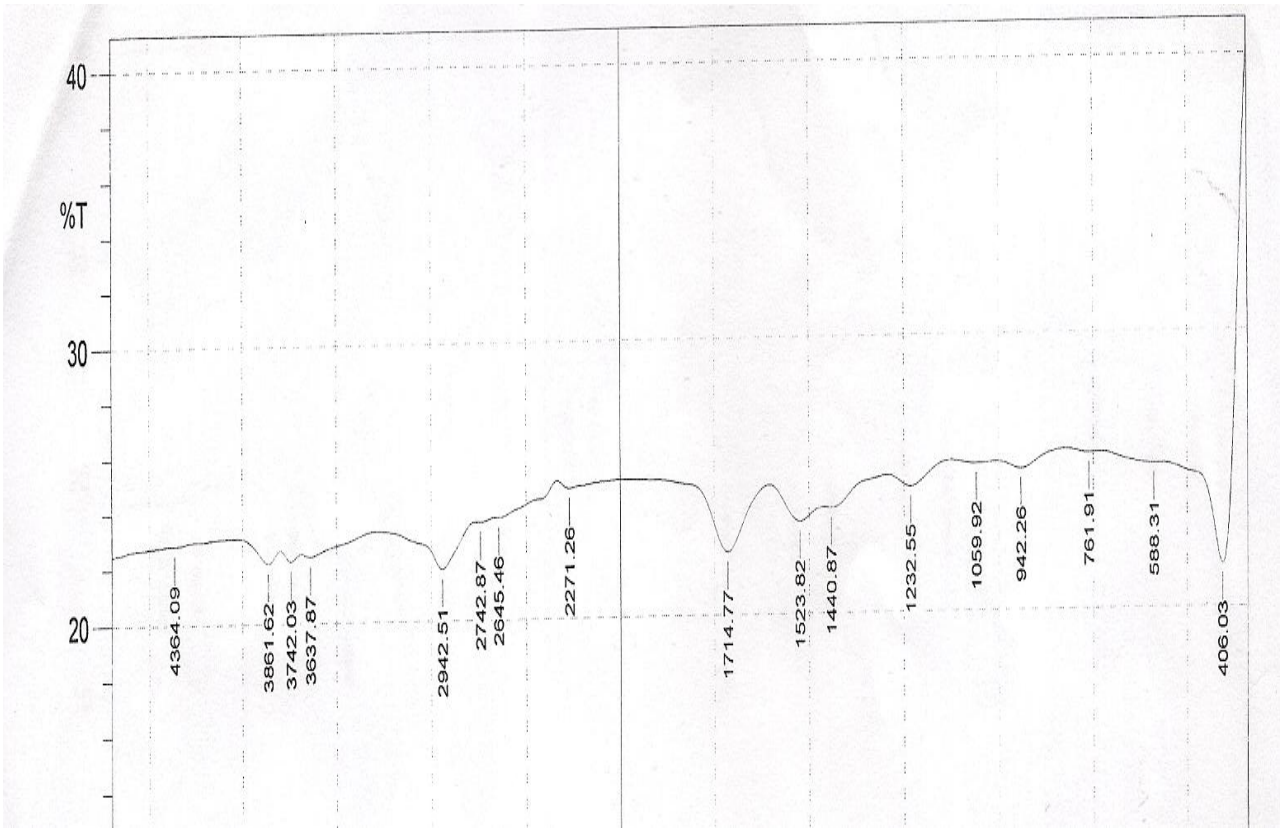


Figure 4.19: FT-IR spectra of ibuprofen solid dispersion with Eudragit RS 100 and HPMC incorporating trona (IBT3)

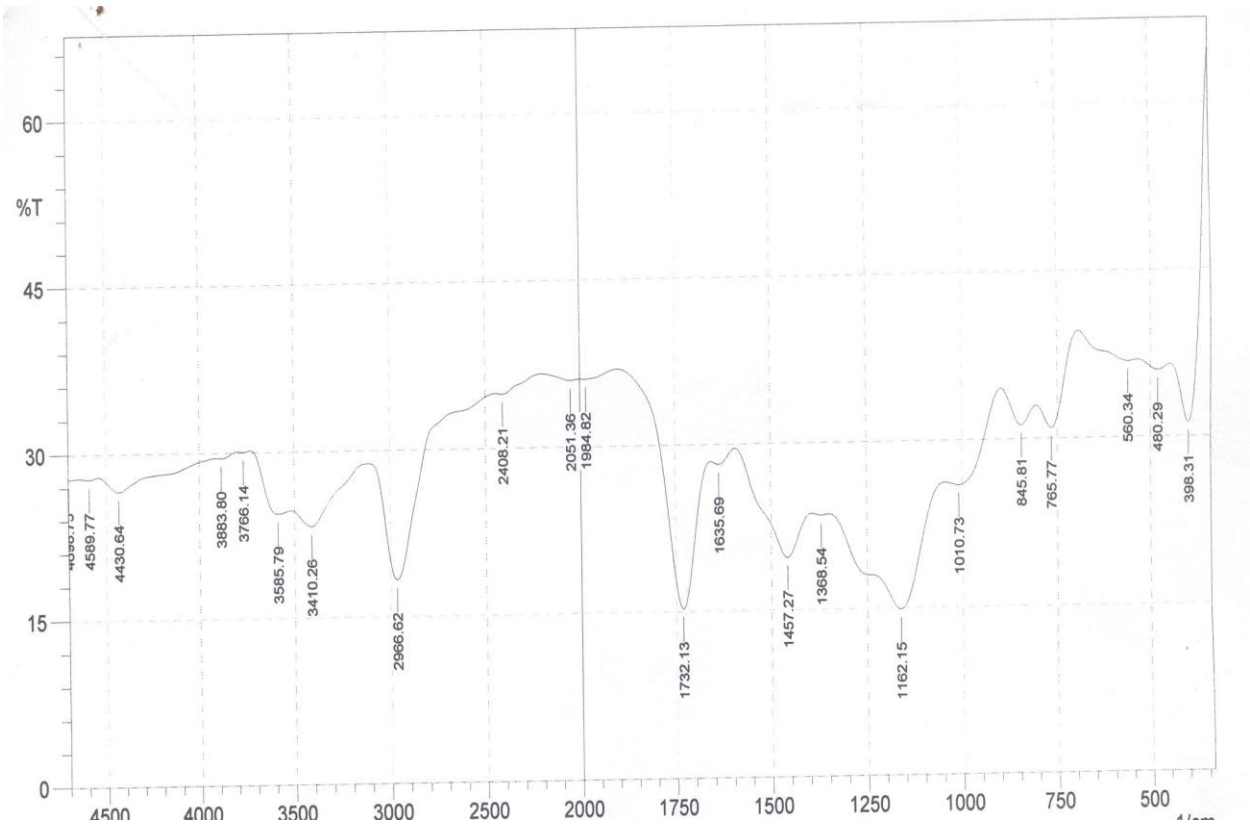


Figure 4.20: FT-IR spectra of piroxicam solid dispersion with Eudragit RS 100 (PR1)

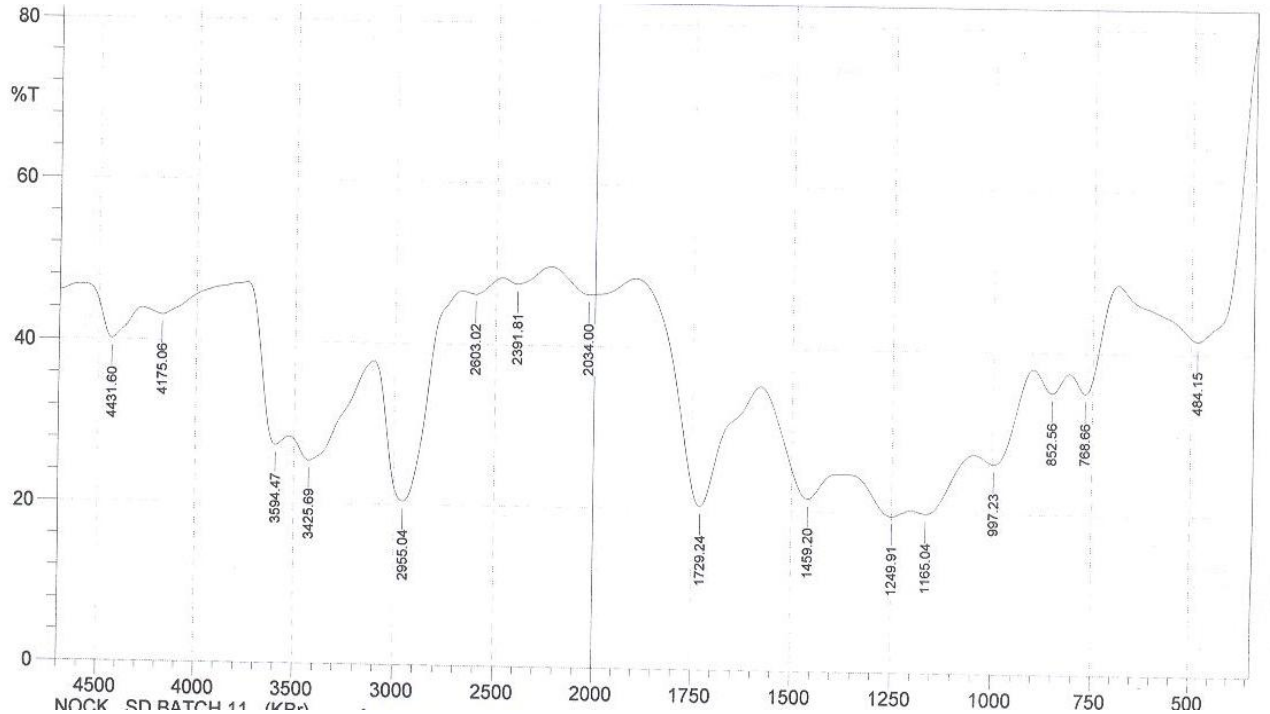


Figure 4.21: FT-IR spectra of piroxicam solid dispersion with Eudragit RS 100 (PR2)

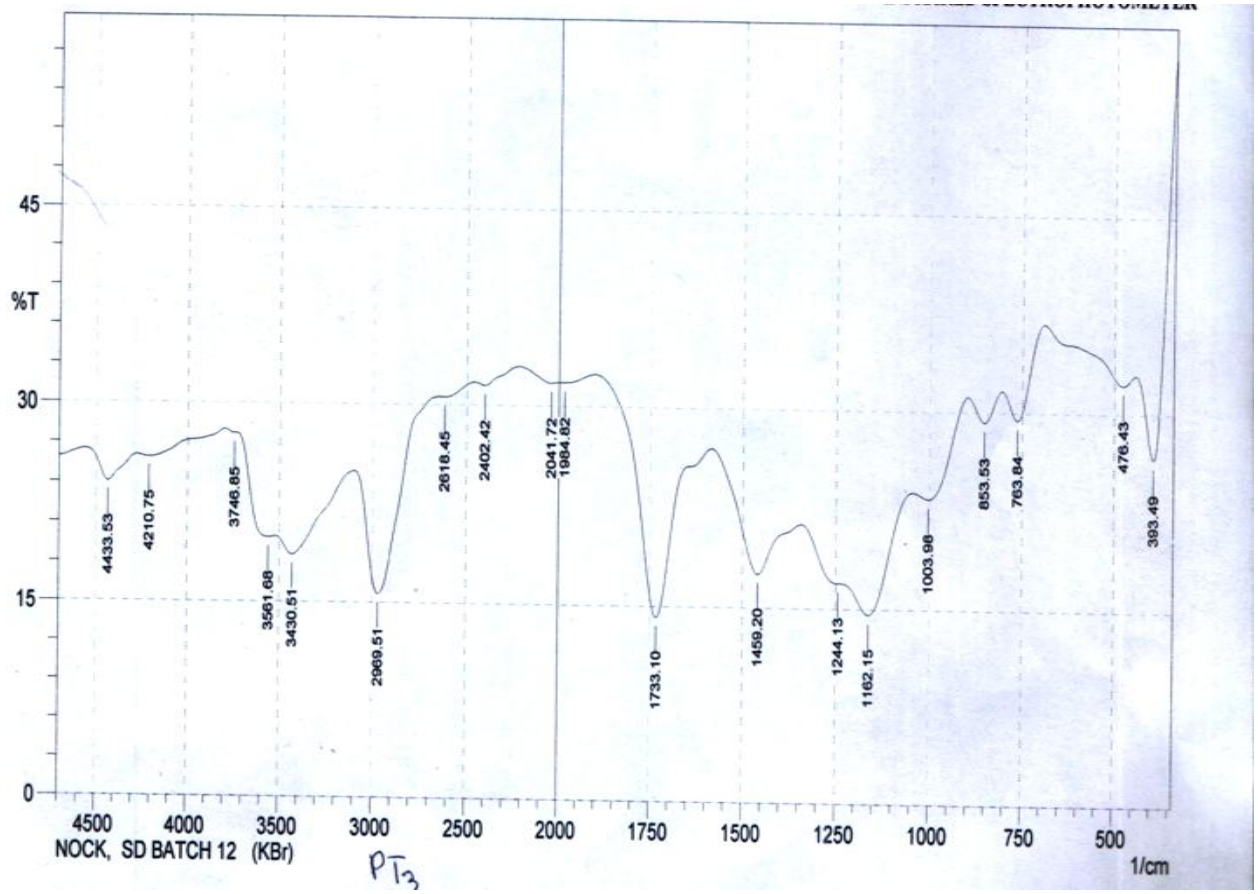


Figure 4.22: FT-IR spectra of piroxicam solid dispersion with Eudragit RS 100 (PR3)

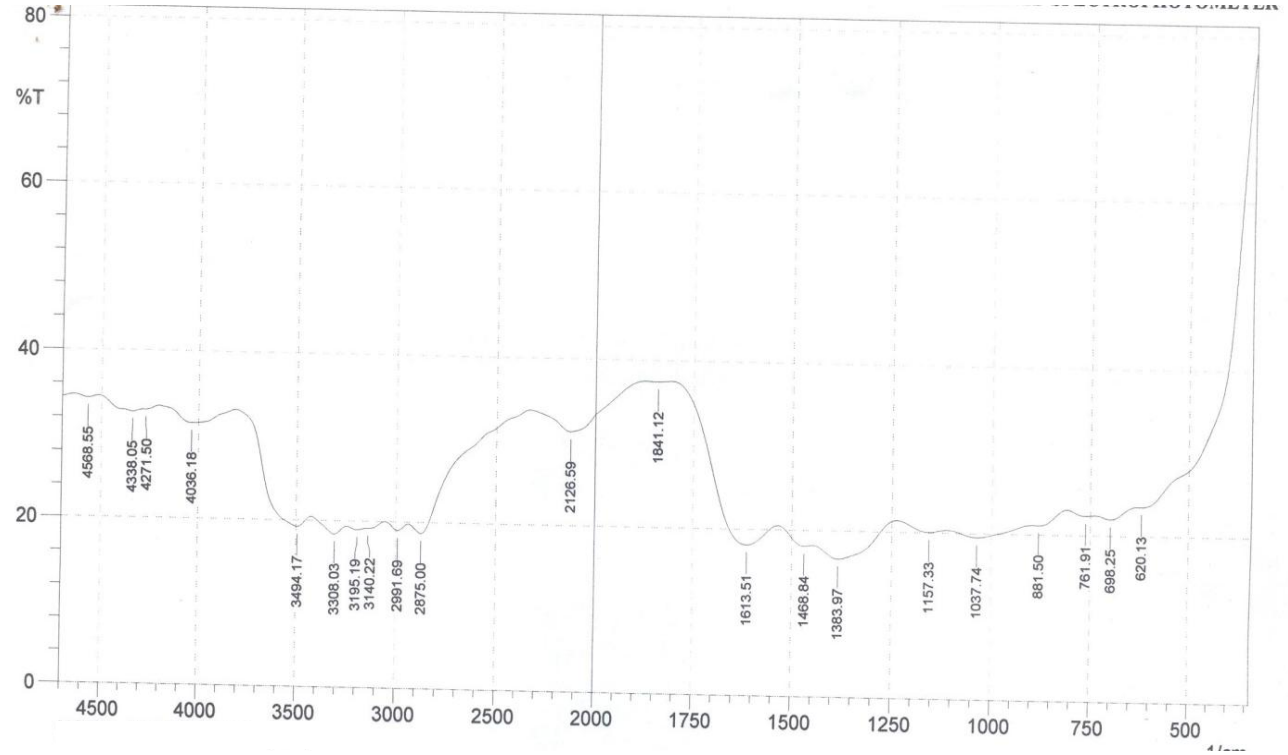


Figure 4.23: FT-IR spectra of piroxicam solid dispersion with HPMC (PR4)

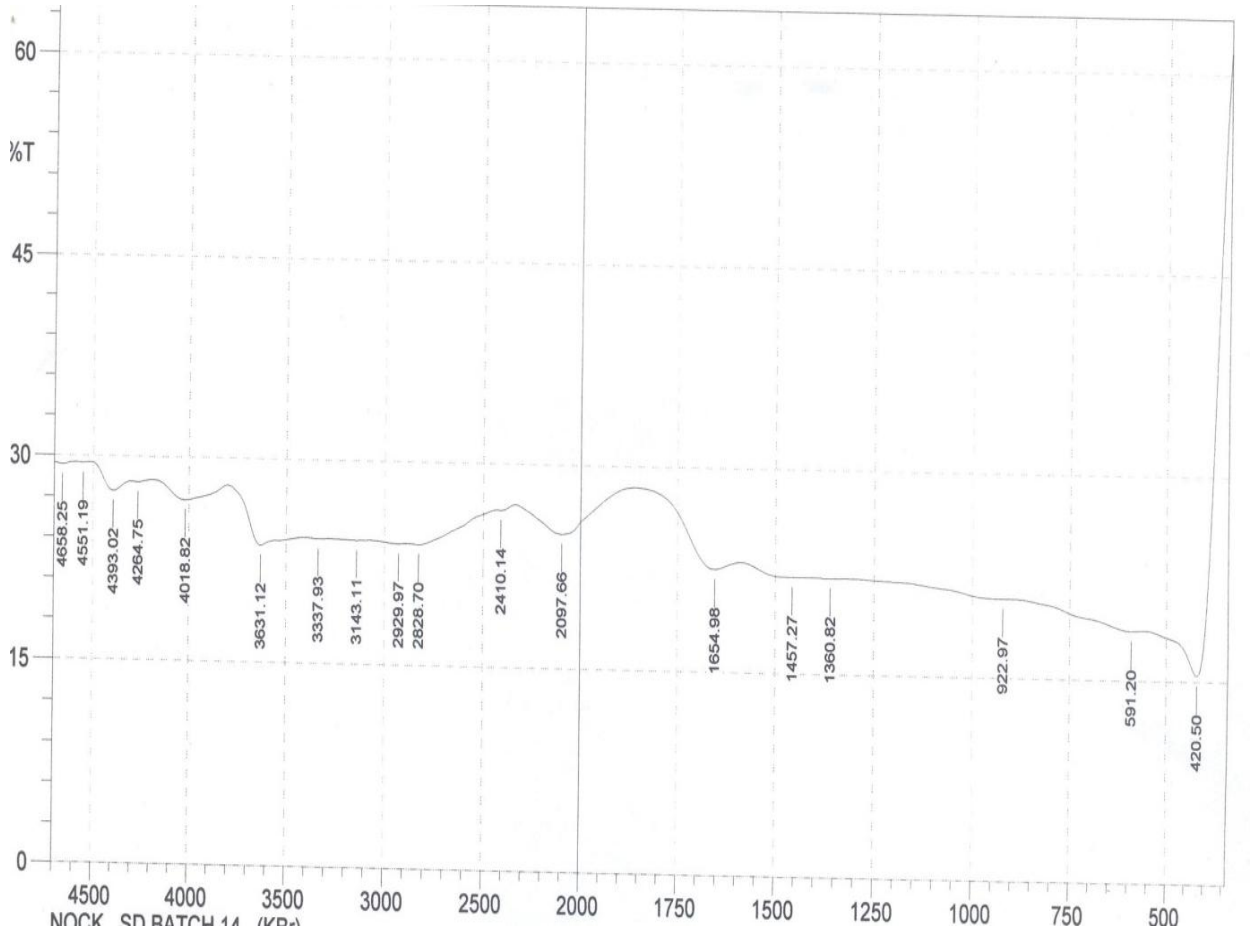


Figure 4.24: FT-IR spectra of piroxicam solid dispersion with HPMC (PR5)

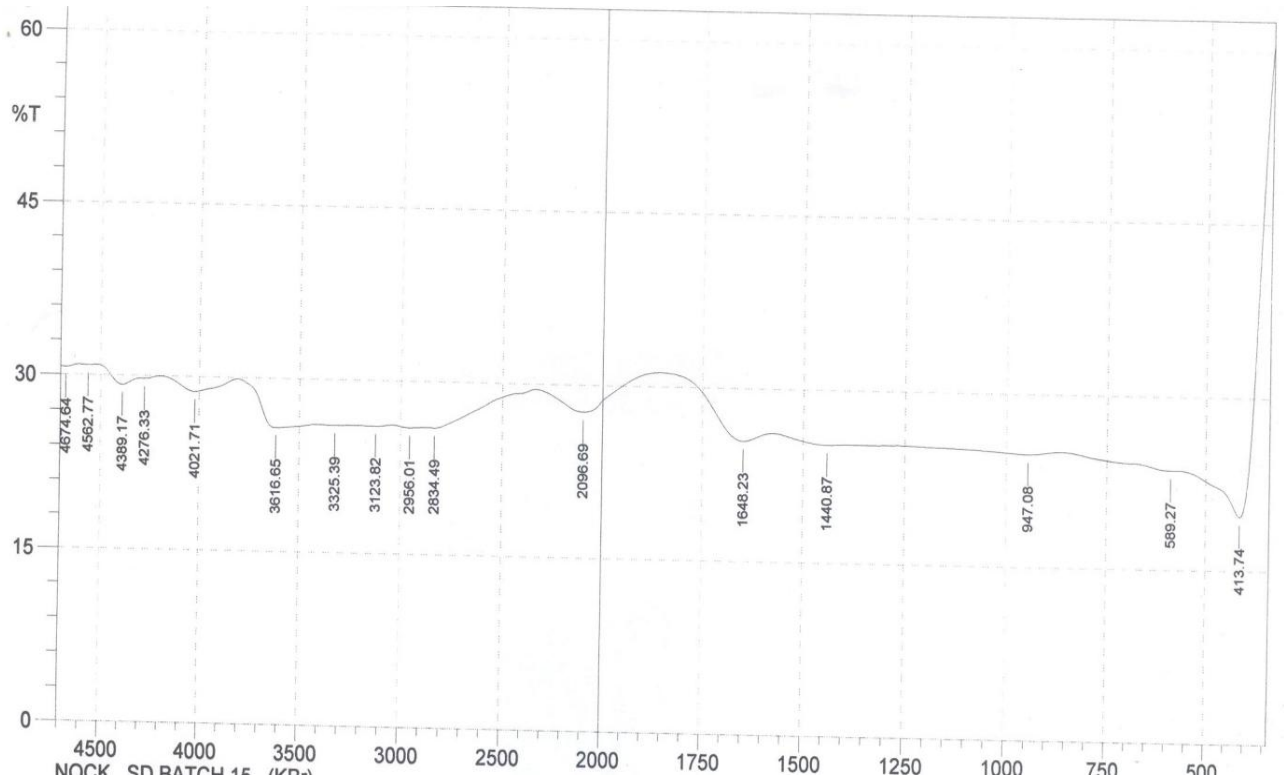


Figure 4.25: FT-IR spectra of piroxicam solid dispersion with HPMC (PR6)

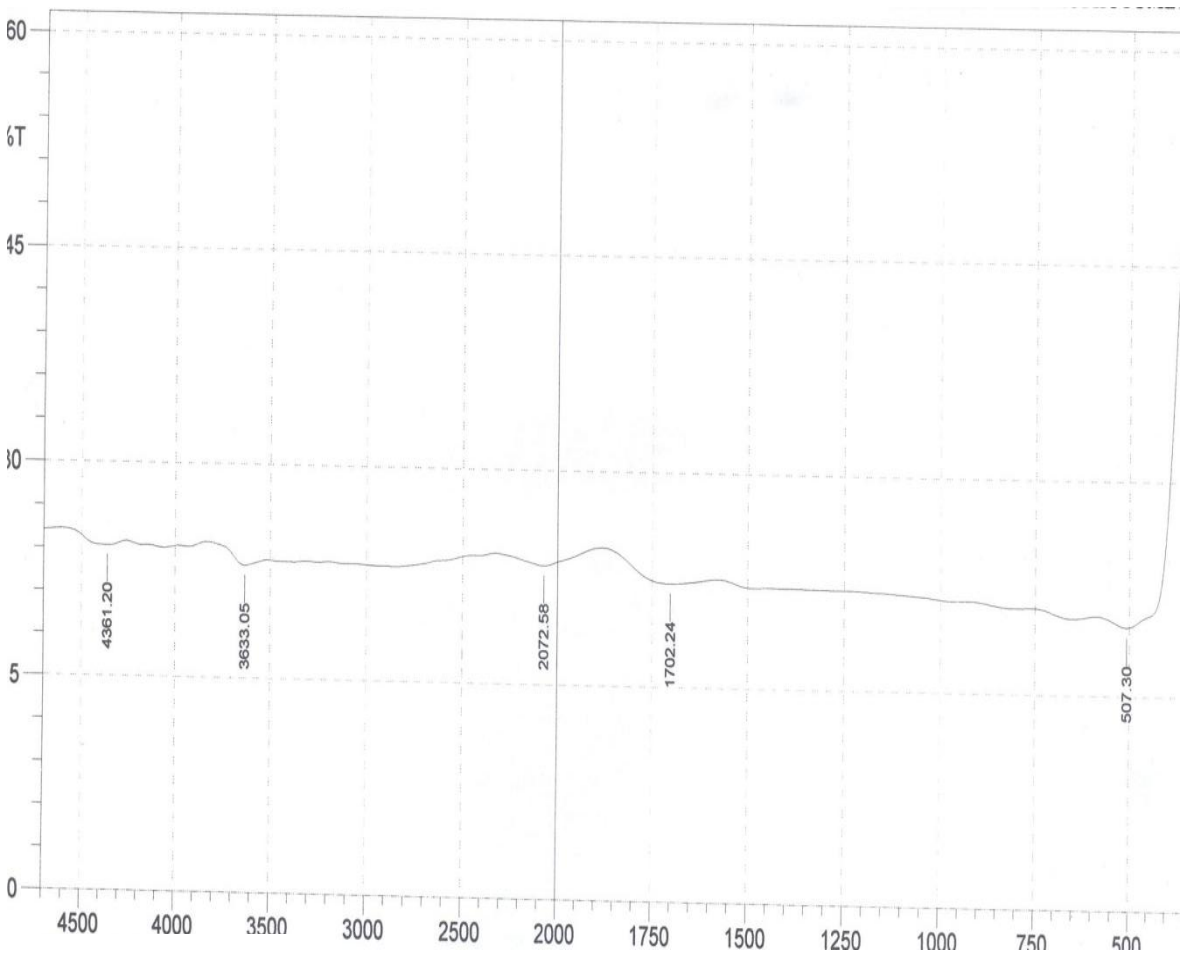


Figure 4.26: FT-IR spectra of piroxicam solid dispersion with Eudragit RS 100 and HPMC (PR7)

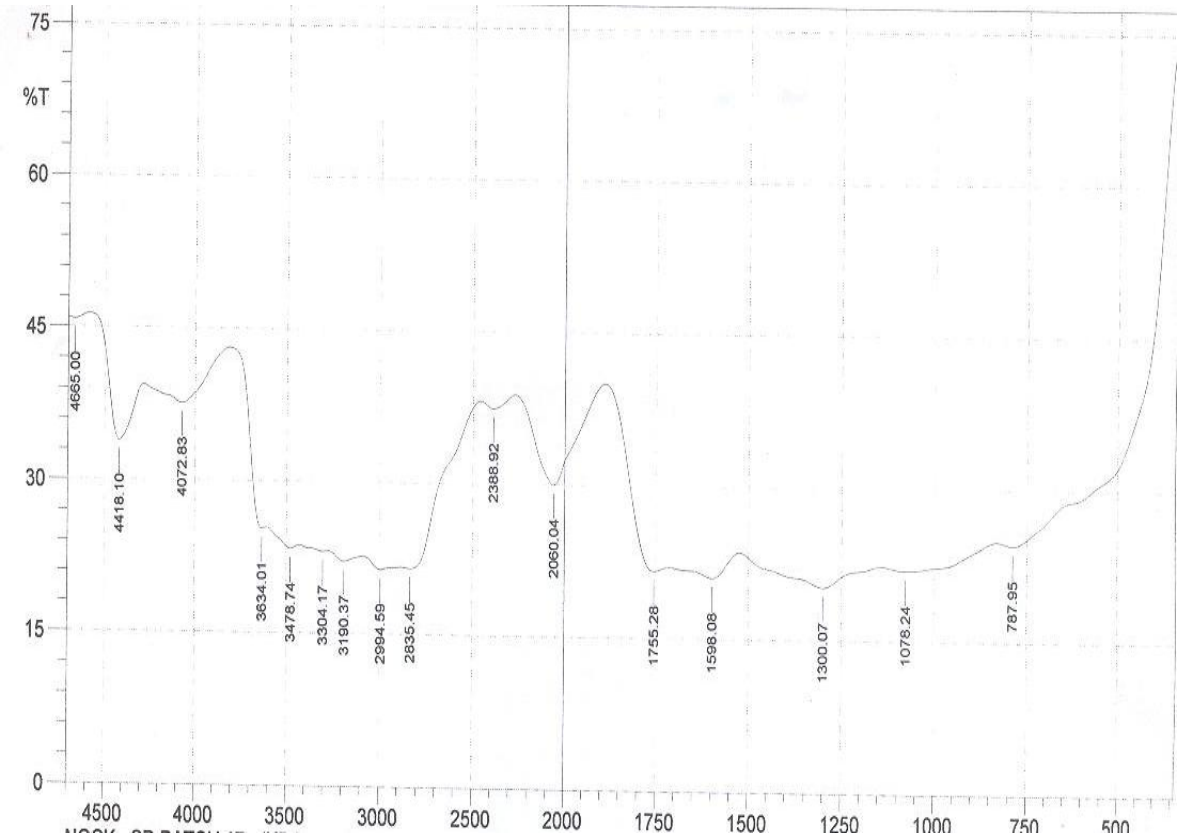


Figure 4.27: FT-IR spectra of piroxicam solid dispersion with Eudragit RS 100 and HPMC (PR8)

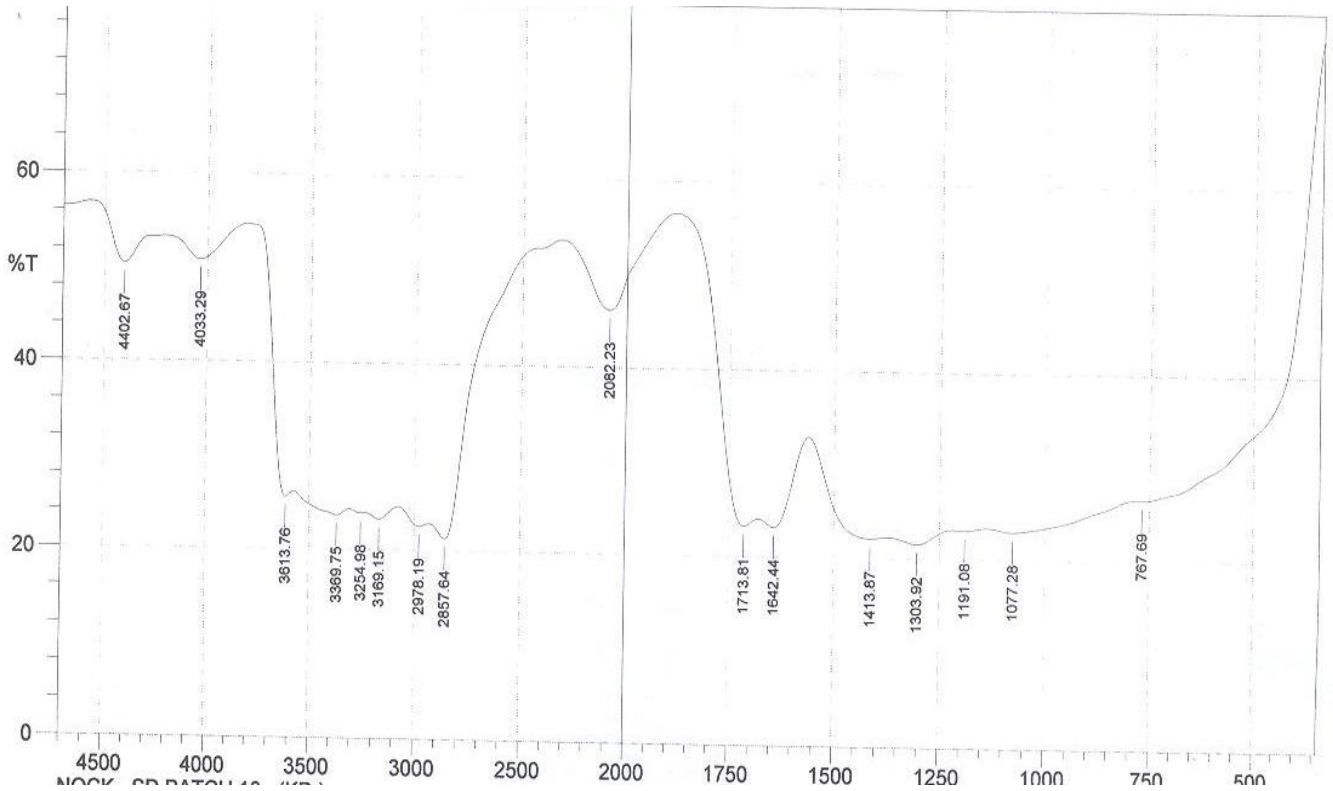


Figure 4.28: FT-IR spectra of piroxicam solid dispersion with Eudragit RS 100 and HPMC (PR 9)

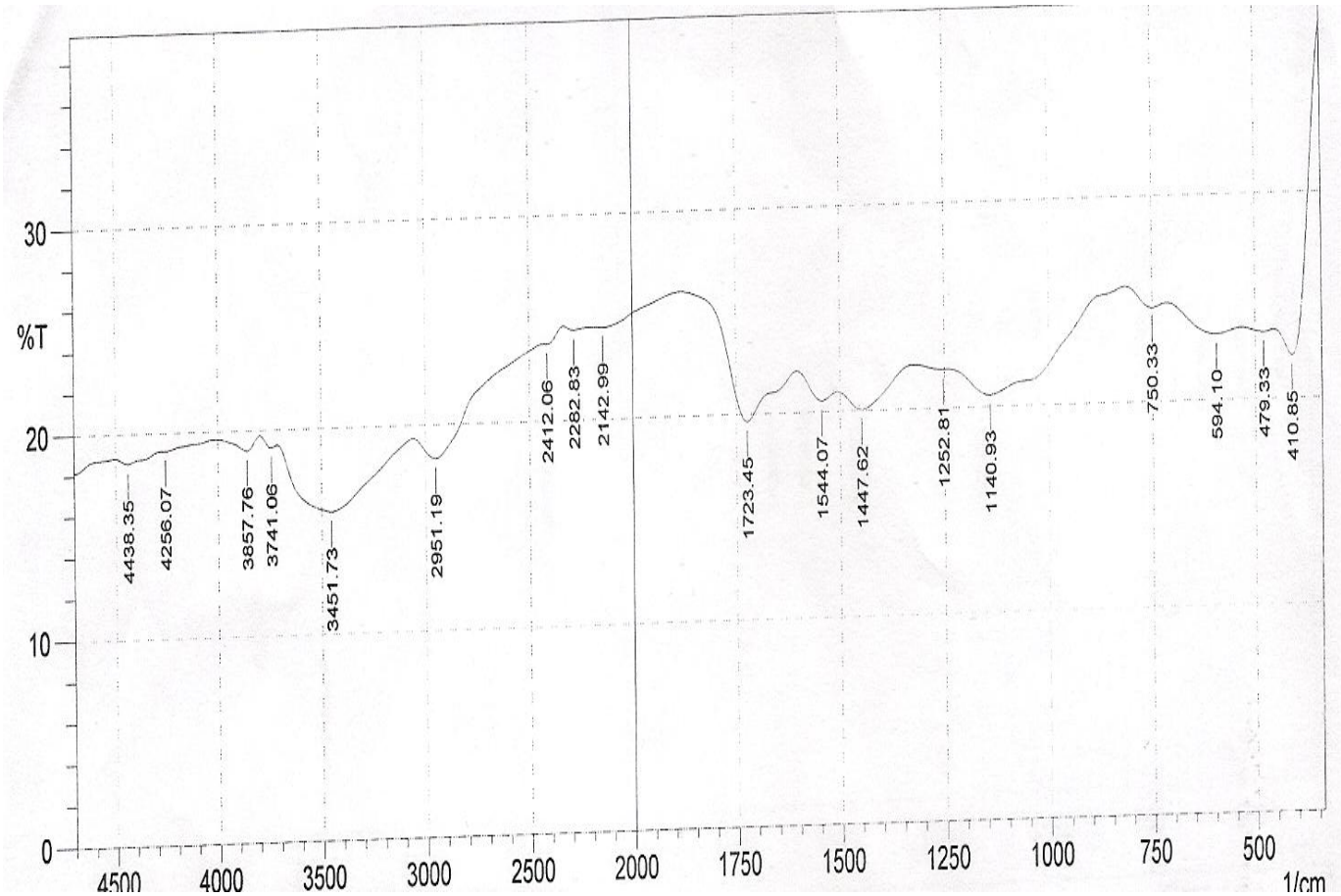


Figure 4.29: FT-IR spectra of piroxicam solid dispersions with Eudragit RS 100 and HPMC incorporating trona (PRT4)

4.4 Moisture sorption / Desorption determination

Figure 4.30 shows the moisture sorption /desorption isotherm of 1 g each of solid dispersions of ibuprofen subjected to various humidity changes. Figure 4.32 shows the moisture sorption /desorption isotherm of various piroxicam solid dispersions.

All the samples were found to sorp moisture to a maximum on the 4^{th} week, corresponding to exposure to distilled water. The samples sorped least quantities of water at weeks 1 and 7 corresponding to sorption and desorption equivalents respectively, following exposures to magnesium chloride.

Solid dispersion of ibuprofen with HPMC (ratio 1:2) sorped a maximum of 0.864 g at week 4. A similar result was obtained with piroxicam solid dispersion with HPMC (ratio 1.1) which sorped a maximum of 0.685 g of water. Formulations containing both Eudragit RS 100 and HPMC sorped more moisture than solid dispersions made with only Eudragit RS 100.

Solid dispersion of ibuprofen incorporating trona sorped less moisture than solid dispersion without trona as seen in Figure 4.31. Piroxicam solid dispersion incorporating trona on the other hand, sorped more moisture than that without trona as seen in Figure 4.33.

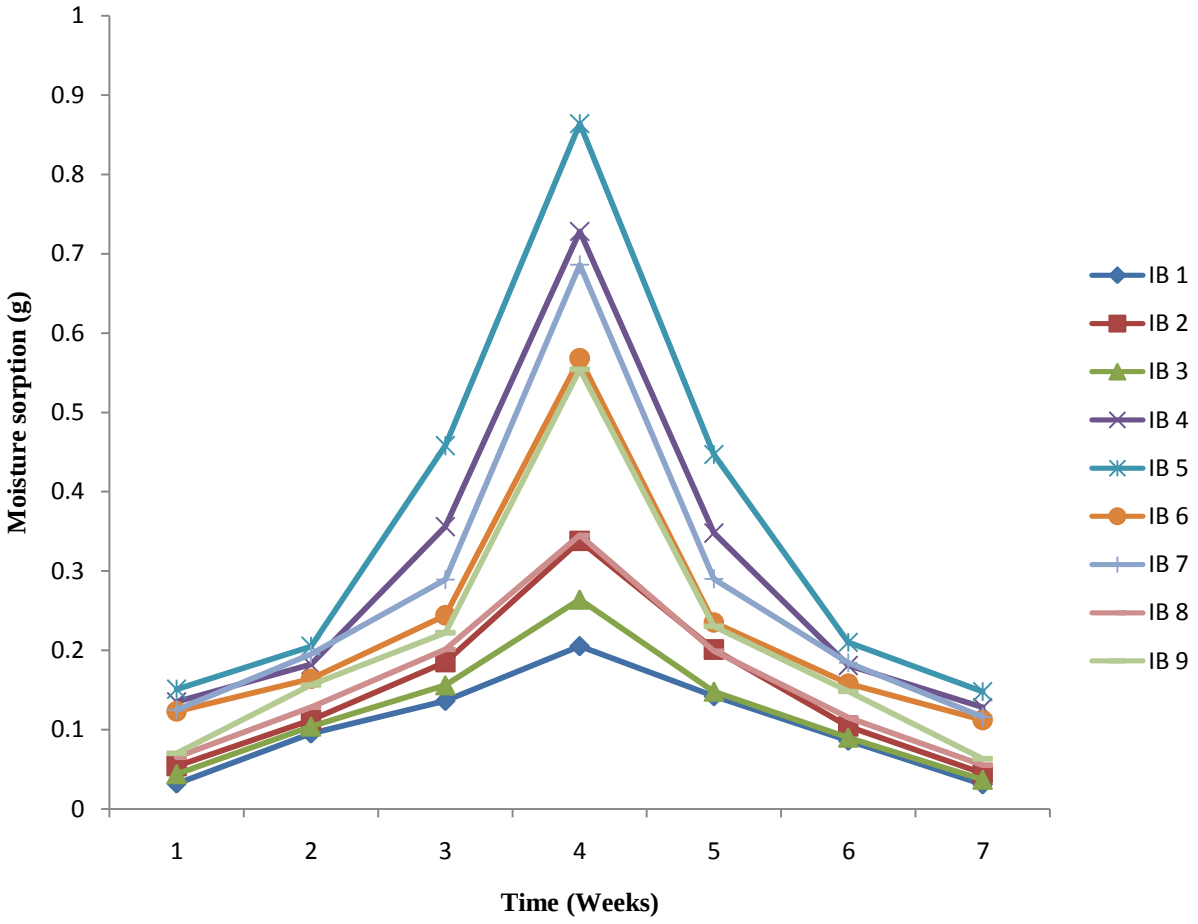


Figure 4.30: Moisture sorption and desorption of ibuprofen solid dispersions

Keys:

IB 1- Ibuprofen:Eud (1:1)

IB 2- Ibuprofen :Eud (1:2)

IB 3- Ibuprofen:Eud (1:3)

IB 4- Ibuprofen:HPMC (1:1)

IB 5- Ibuprofen :HPMC (1:2)

IB 6- Ibuprofen:HPMC (1:3)

IB 7- Ibuprofen :Eud:HPMC (1:1:1)

IB 8- Ibuprofen:Eud:HPMC (1:2:1)

IB 9- Ibuprofen:Eud:HPMC (1:1:2)

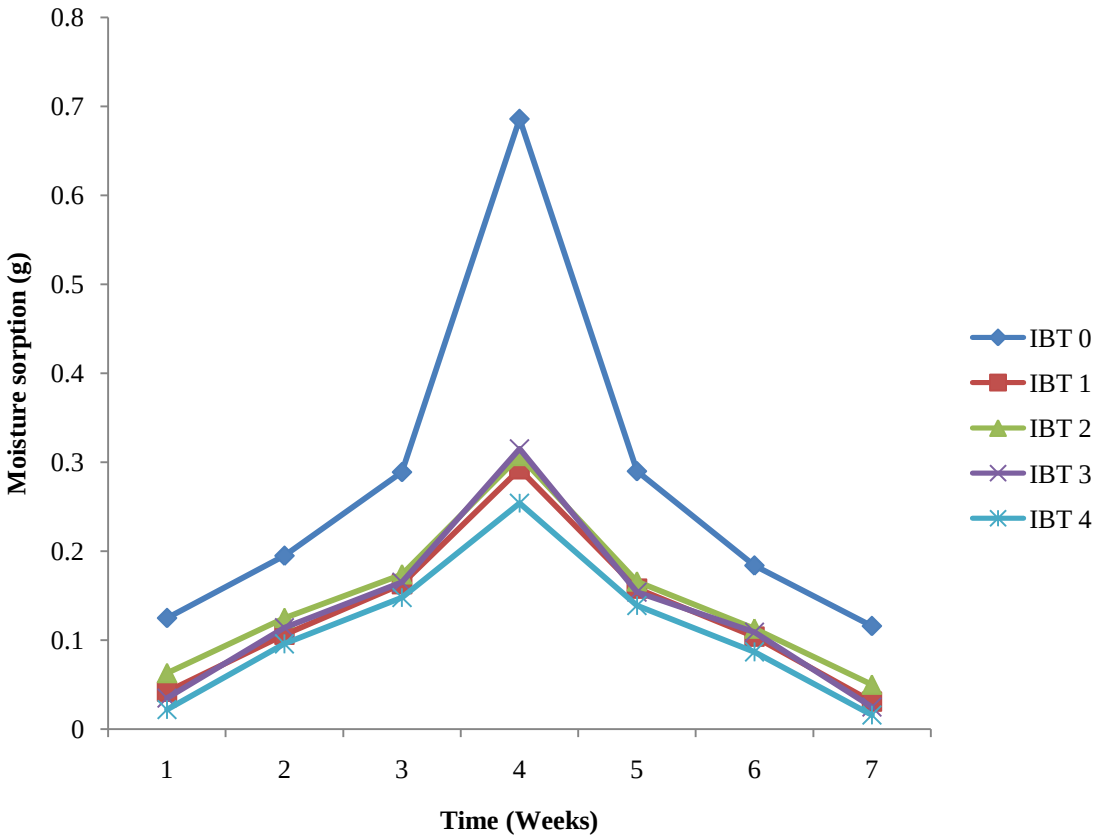


Figure 4.31: Moisture sorption and desorption of ibuprofen solid dispersions incooporating trona

Keys:

IBT0- Ibuprofen:Eud:HPMC:trona (1:1:1:0)

IBT1- Ibuprofen:Eud:HPMC:trona (1:1:1:0.1)

IBT2- Ibuprofen:Eud:HPMC:trona (1:1:1:0.2)

IBT3- Ibuprofen:Eud:HPMC:trona (1:1:1:0.3)

IBT4- Ibuprofen:Eud:HPMC:trona (1:1:1:0.4)

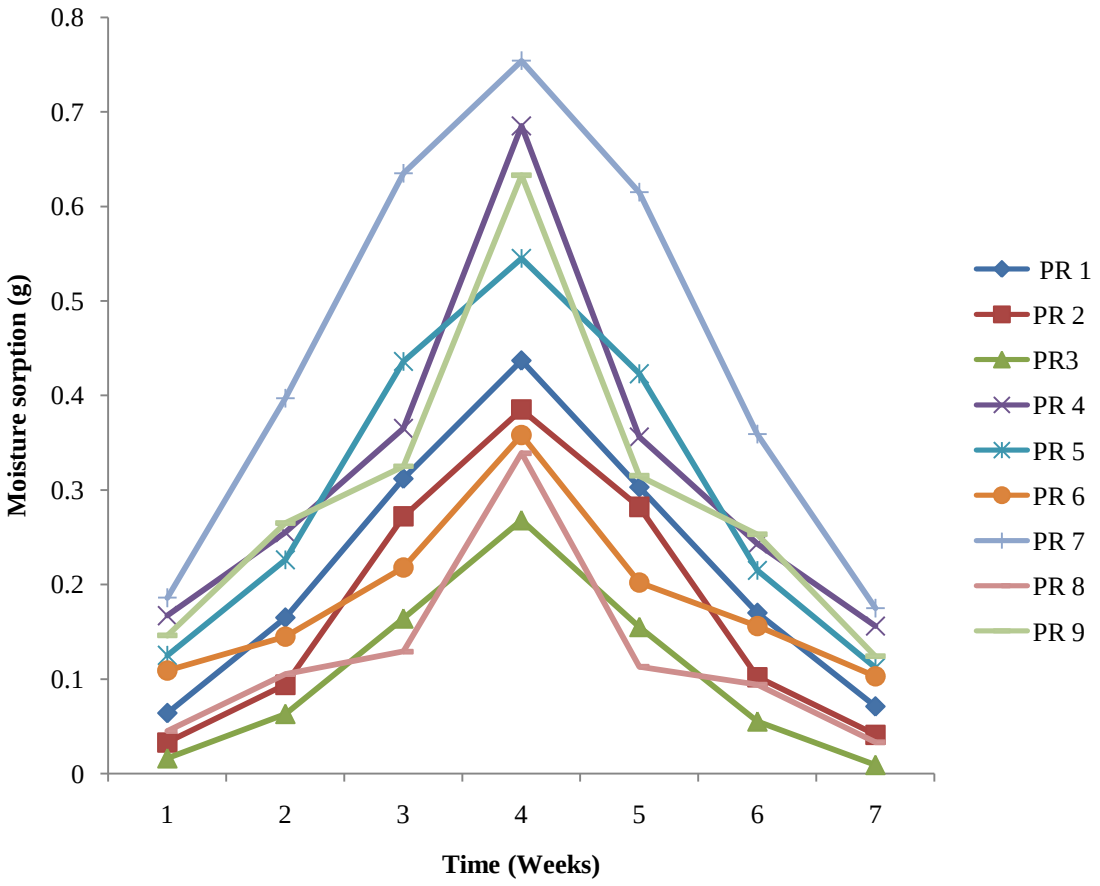


Figure 4.32: Moisture sorption and desorption of piroxicam solid dispersions

Keys:

PR 1- Piroxicam: Eud (0.1:1)

PR 2 - Piroxicam:Eud (0.1:2)

PR 3 - Piroxicam:Eud (0.1:3)

PR 4 - Piroxicam:HPMC (0.1:1)

PR 5 - Piroxicam: HPMC (0.1:2)

PR 6 - Piroxicam:HPMC (0.1:3)

PR 7 - Piroxicam:Eud: HPMC (0.1:1:1)

PR 8 - Piroxicam: Eud: HPMC (0.1:2:1)

PR 9 - Piroxicam:Eud:HPMC (0.1:1:2)

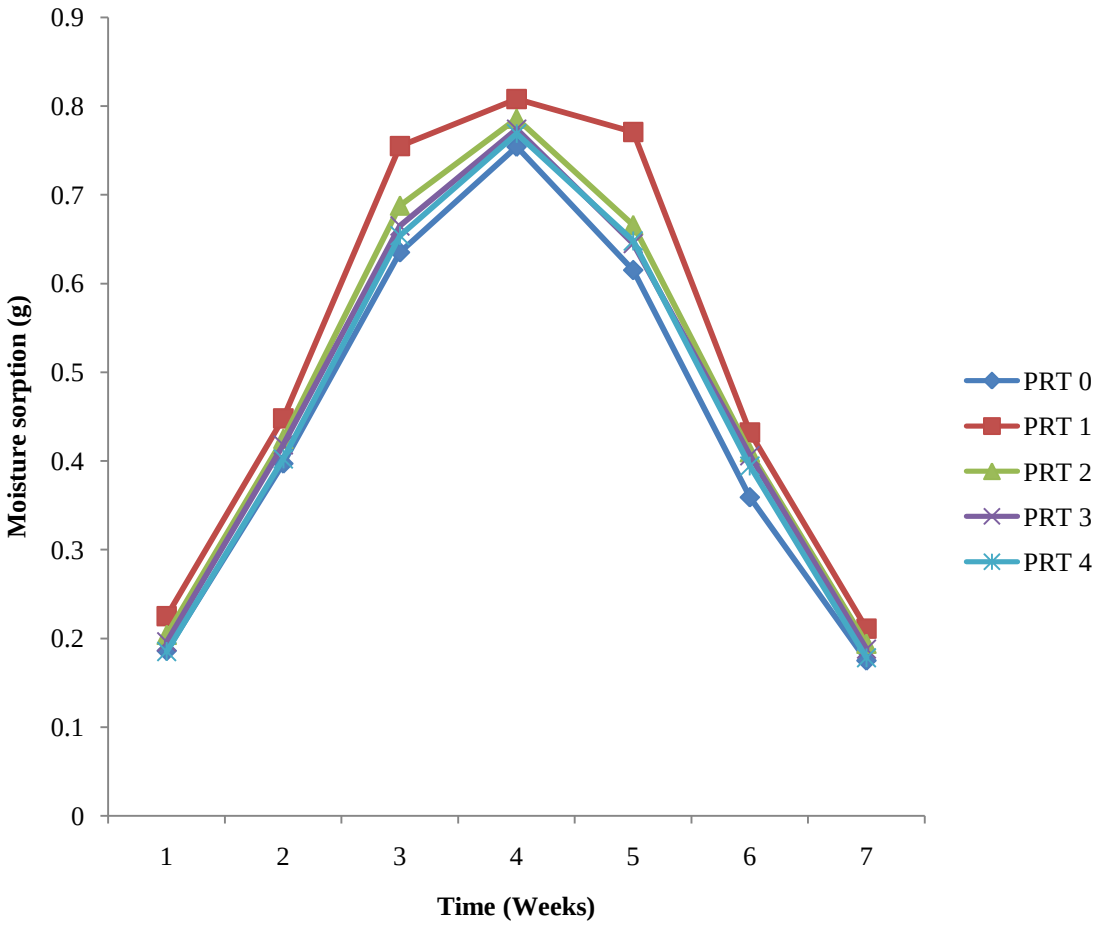


Figure 4.33: Moisture sorption and desorption of piroxicam solid dispersion incorporating trona

Keys:

PRT0- Piroxicam:Eud:HPMC:trona (0.1:1:1:0)

PRT1- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.1)

PRT1- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.2)

PRT3- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.3)

PRT4- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.4)

4.5 Solubility Determination

The saturated solubility of pure ibuprofen and various formulated ibuprofen solid dispersions using Eudragit RS 100 and HPMC in combination as well as individually is shown in Figure 4.34, while Figure 4.36 shows the solubility of ibuprofen solid dispersion containing trona. Pure ibuprofen was seen to have a saturated solubility of 0.31 mg/ml. Solid dispersion of ibuprofen with HPMC showed distinctly superior improvement in solubility. The dispersion of ibuprofen with HPMC containing 1:2 drug : polymer ratio had 8 fold increase in solubility when compared to the pure drug. There was no significant improvement in solubility of ibuprofen with Eudragit RS 100 alone. Incorporating trona into solid dispersion of ibuprofen with HPMC and Eudragit RS 100 gave a decrease in the solubility when compared to solid dispersion without trona. Physical mixture of ibuprofen and the polymer also increased solubility of ibuprofen (Figure 4.35)

Figure 4.38 shows the solubility of pure piroxicam and various solid dispersions using Eudragit RS 100 and HPMC in combination as well as individually. The solubility of pure piroxicam was found to be 0.0114 ± 0.0009 mg/ml. Solid dispersion of piroxicam with HPMC and Eudragit RS 100 in combination (ratio 0.1:1:1) gave the highest solubility of 0.0290 mg/ml, while solid dispersion with Eudragit RS 100 alone (ratio 0.1:3) gave the lowest solubility of 0.0148 mg/ml. Figure 4.40 shows the solubility of piroxicam solid dispersion incorporating trona. Trona was seen to improve the solubility of piroxicam when compared to solid dispersion without trona. Physical mixtures of piroxicam also increased solubility but to a less extent than the solid dispersion (Figure 4.39)

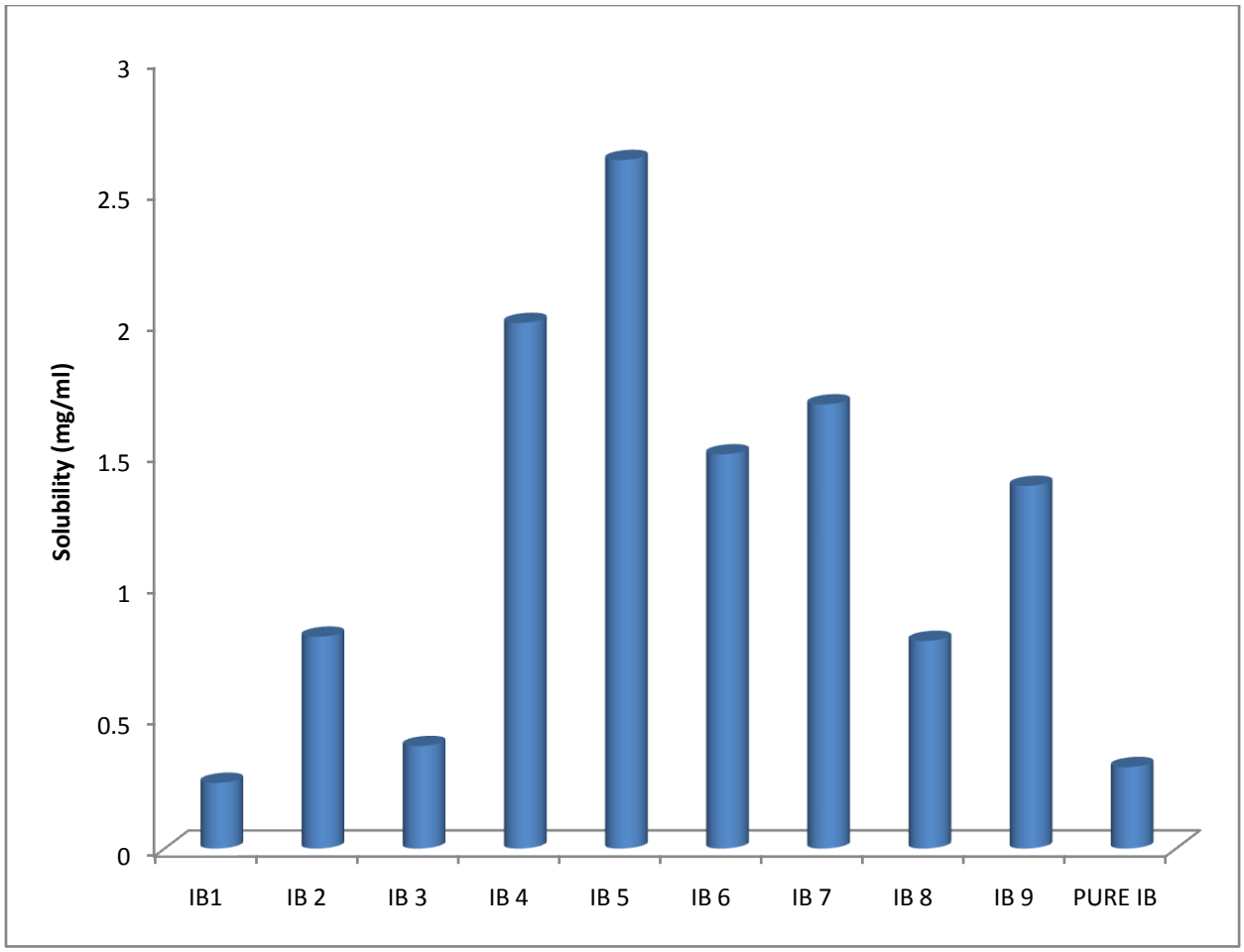


Figure 4.34: Effect of composition of solid dispersions on solubility of ibuprofen

Keys:

IB 1- Ibuprofen:Eud (1:1)

IB 2- Ibuprofen:Eud (1:2)

IB 3- Ibuprofen:Eud (1:3)

IB 4- Ibuprofen:HPMC (1:1)

IB 5- Ibuprofen :HPMC (1:2)

IB 6- Ibuprofen:HPMC (1:3)

IB 7- Ibuprofen :Eud:HPMC (1:1:1)

IB 8- Ibuprofen:Eud:HPMC (1:2;1)

IB 9- Ibuprofen:Eud:HPMC (1:1:2)

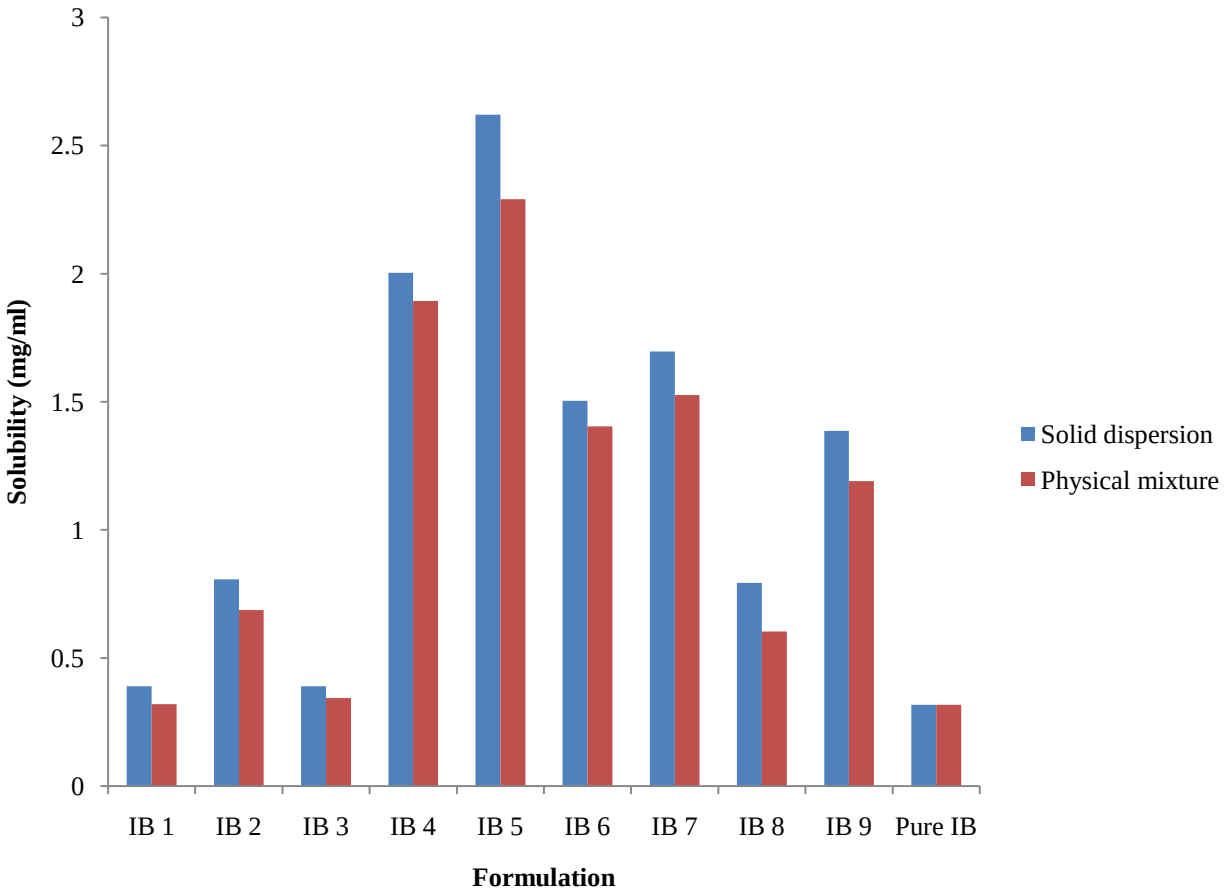


Figure 4.35: Solubility of ibuprofen solid dispersion and physical mixtures

Keys:

IB 1- Ibuprofen:Eud (1:1)

IB 2- Ibuprofen :Eud (1:2)

IB 3- Ibuprofen:Eud (1:3)

IB 4- Ibuprofen:HPMC (1:1)

IB 5- Ibuprofen:HPMC (1:2)

IB 6- Ibuprofen:HPMC (1:3)

IB 7- Ibuprofen :Eud:HPMC (1:1:1)

IB 8- Ibuprofen:Eud:HPMC (1:2:1)

IB 9- Ibuprofen:Eud:HPMC (1:1:2)

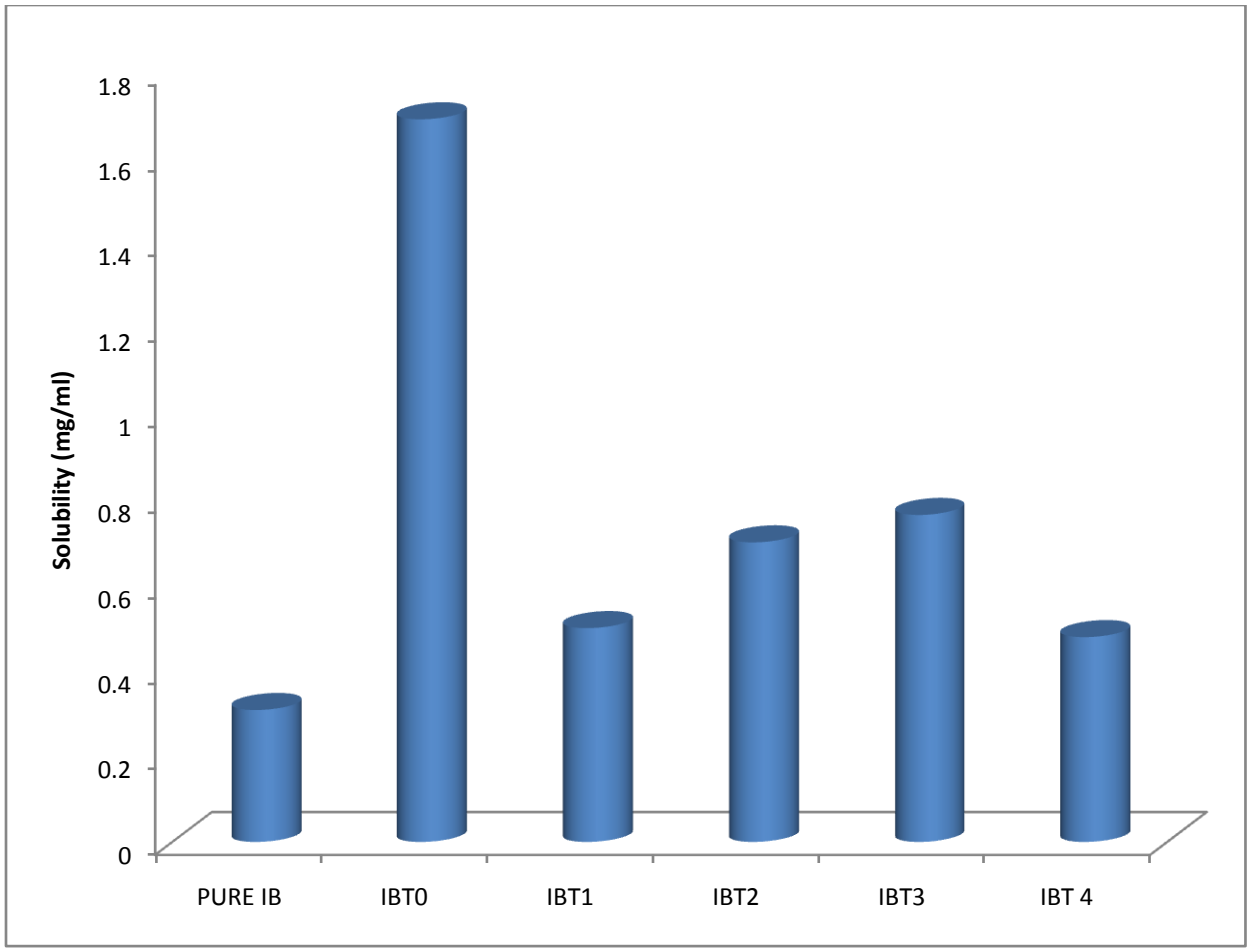


Figure 4.36: Effect of trona on solubility of ibuprofen solid dispersion with Eudragit RS 100 and HPMC

Keys:

Pure IB - pure ibuprofen

IBT0- Ibuprofen:Eud:HPMC:trona (1:1:1:0)

IBT1- Ibuprofen:Eud:HPMC:trona (1:1:1:0.1)

IBT2- Ibuprofen:Eud:HPMC:trona (1:1:1:0.2)

IBT3- Ibuprofen:Eud:HPMC:trona (1:1:1:0.3)

IBT4- Ibuprofen:Eud:HPMC:trona (1:1:1:0.4)

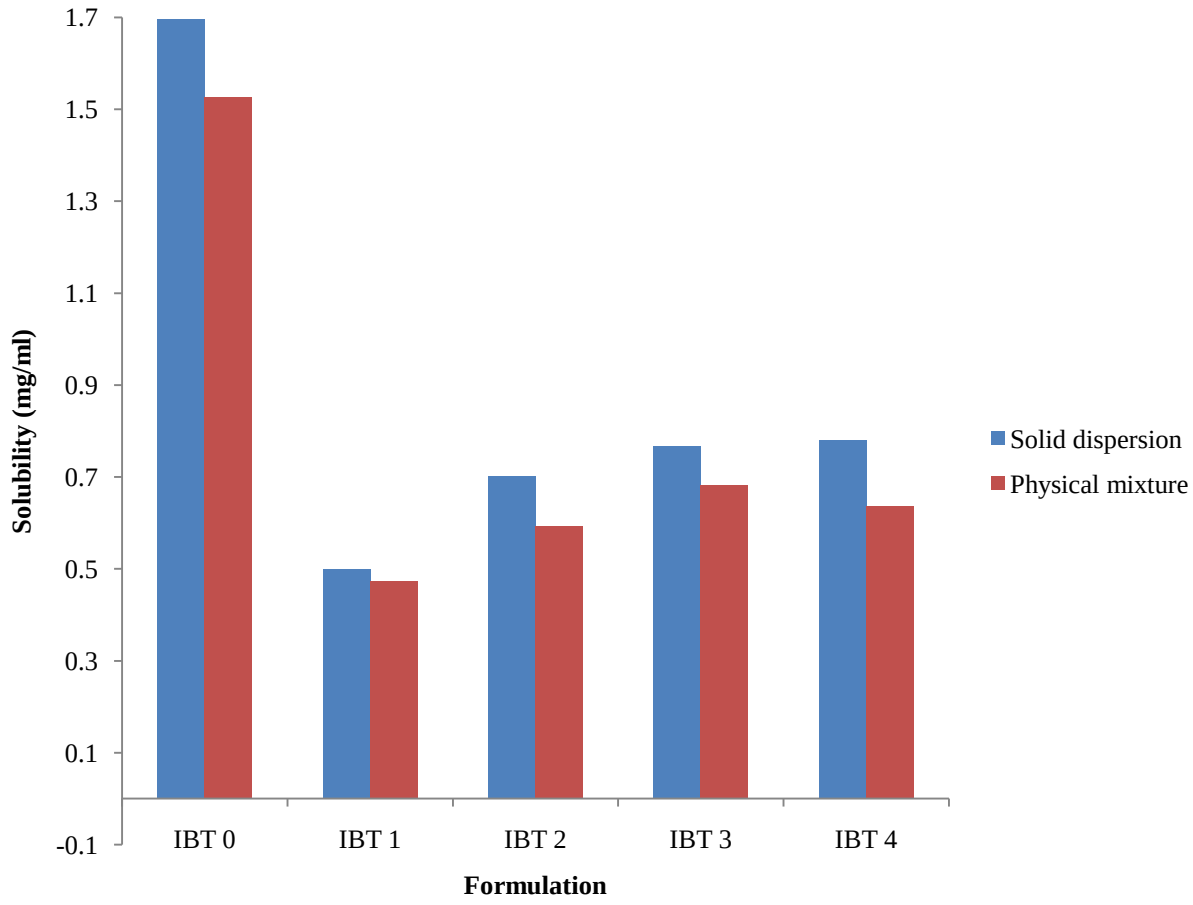


Figure 4.37: Effect of formulation technique on solubility of ibuprofen in the presence of trona

Keys:

IBT0- Ibuprofen:Eud:HPMC:trona (1:1:1:0)

IBT1- Ibuprofen:Eud:HPMC:trona (1:1:1:0.1)

IBT2- Ibuprofen:Eud:HPMC:trona (1:1:1:0.2)

IBT3- Ibuprofen:Eud:HPMC:trona (1:1:1:0.3)

IBT4- Ibuprofen:Eud:HPMC:trona (1:1:1:0.4)

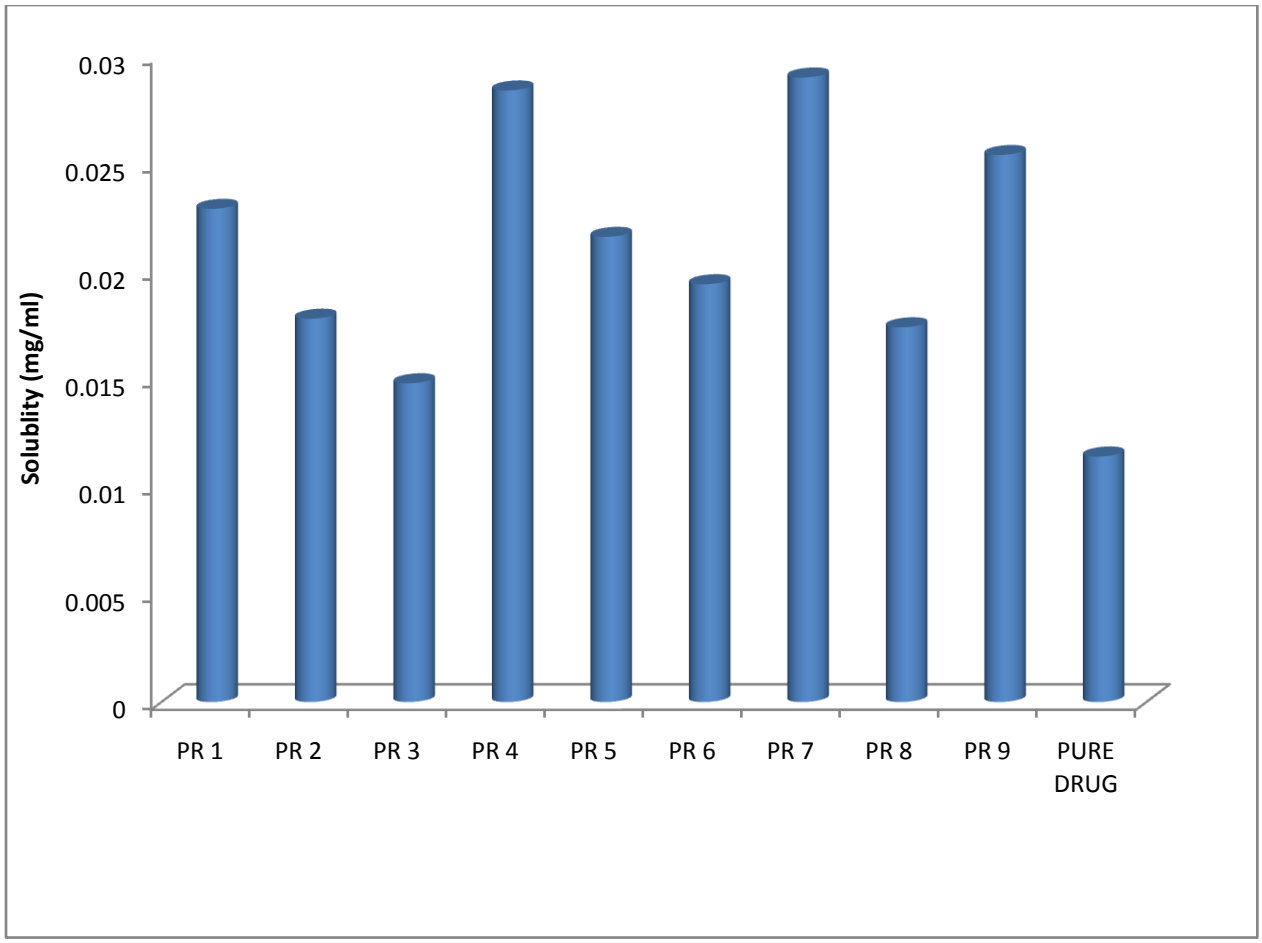


Figure 4.38 : Effect of composition of solid dispersions on solubility of piroxicam

Keys:

PR 1- Piroxicam: Eud (0.1:1)

PR 2- Piroxicam:Eud (0.1:2)

PR 3 -Piroxicam:Eud (0.1:3)

PR 4- Piroxicam:HPMC (0.1:1)

PR 5- Piroxicam: HPMC (0.1:2)

PR 6- Piroxicam:HPMC (0.1:3)

PR 7- Piroxicam:Eud: HPMC (0.1:1:1)

PR 8- Piroxicam: Eud: HPMC (0.1:2:1)

PR 9- Piroxicam:Eud:HPMC (0.1:1:2)

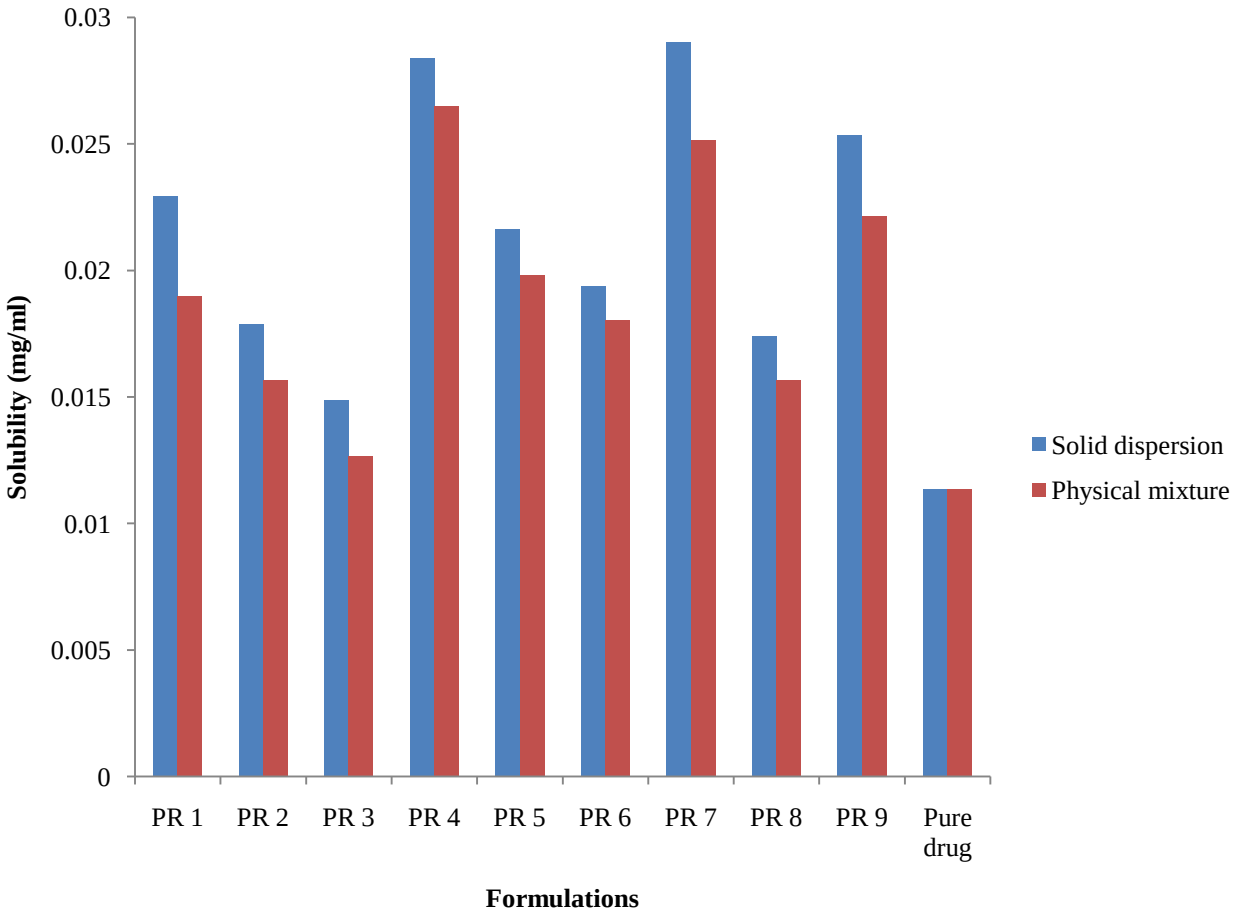


Figure 4.39: Effect of formulation technique on solubility of piroxicam

Keys:

PR 1- piroxicam: Eud (0.1:1)

PR 2- piroxicam:Eud (0.1:2)

PR 3 piroxicam:Eud (0.1:3)

PR 4- piroxicam:HPMC (0.1:1)

PR 5- piroxicam: HPMC (0.1:2)

PR 6- piroxicam:HPMC (0.1:3)

PR 7- piroxicam:Eud: HPMC (0.1:1:1)

PR 8- piroxicam: Eud: HPMC (0.1:2:1)

PR 9- piroxicam:Eud:HPMC (0.1:1:2)

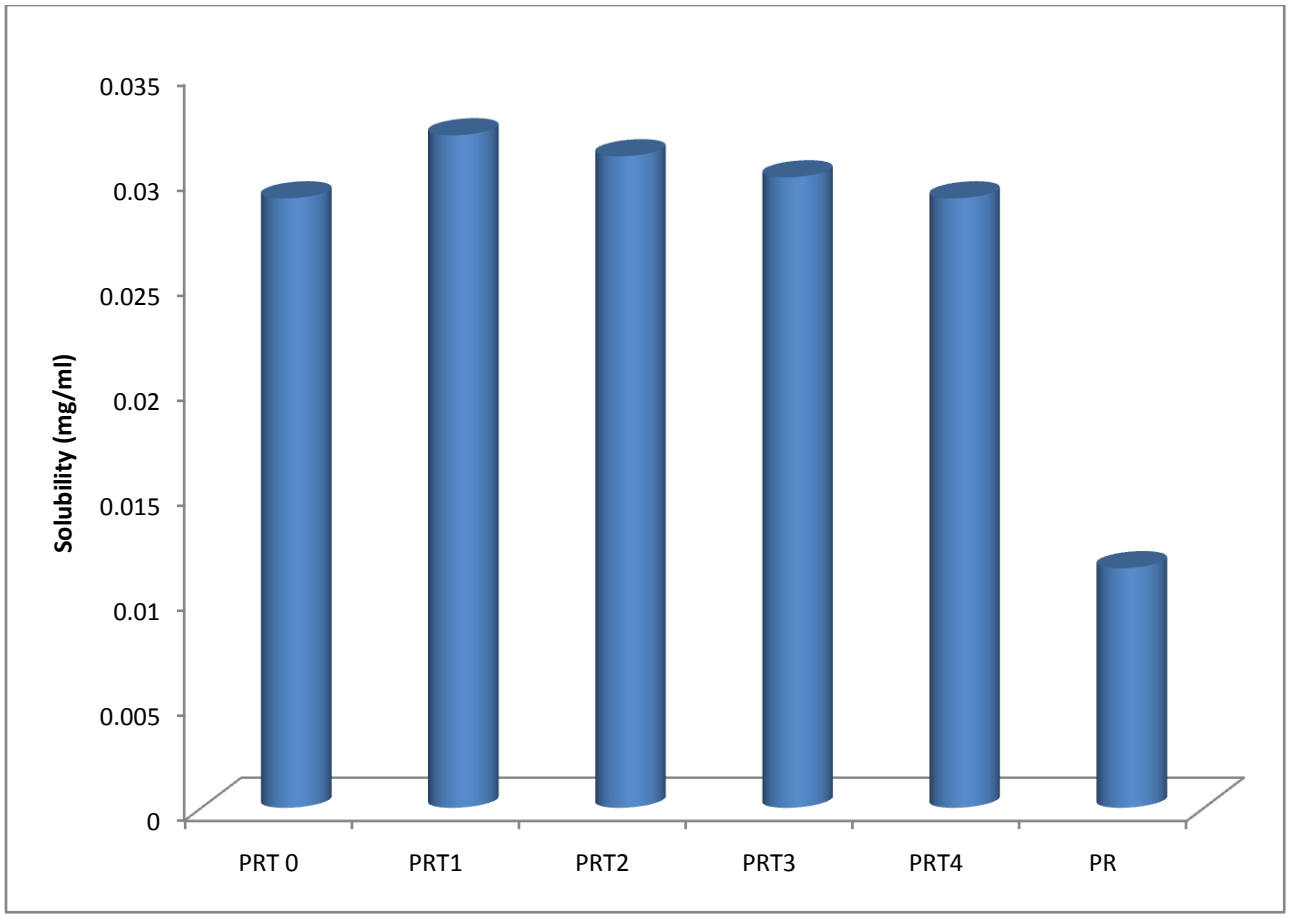


Figure 4.40 : Effect of trona on solubility of piroxicam solid dispersions with Eudragit RS 100 and HPMC

Keys:

PR- Pure piroxicam

PRT0- Piroxicam:Eud:HPMC:trona (0.1:1:1:0)

PRT1- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.1)

PRT2- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.2)

PRT3- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.3)

PRT4- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.4)

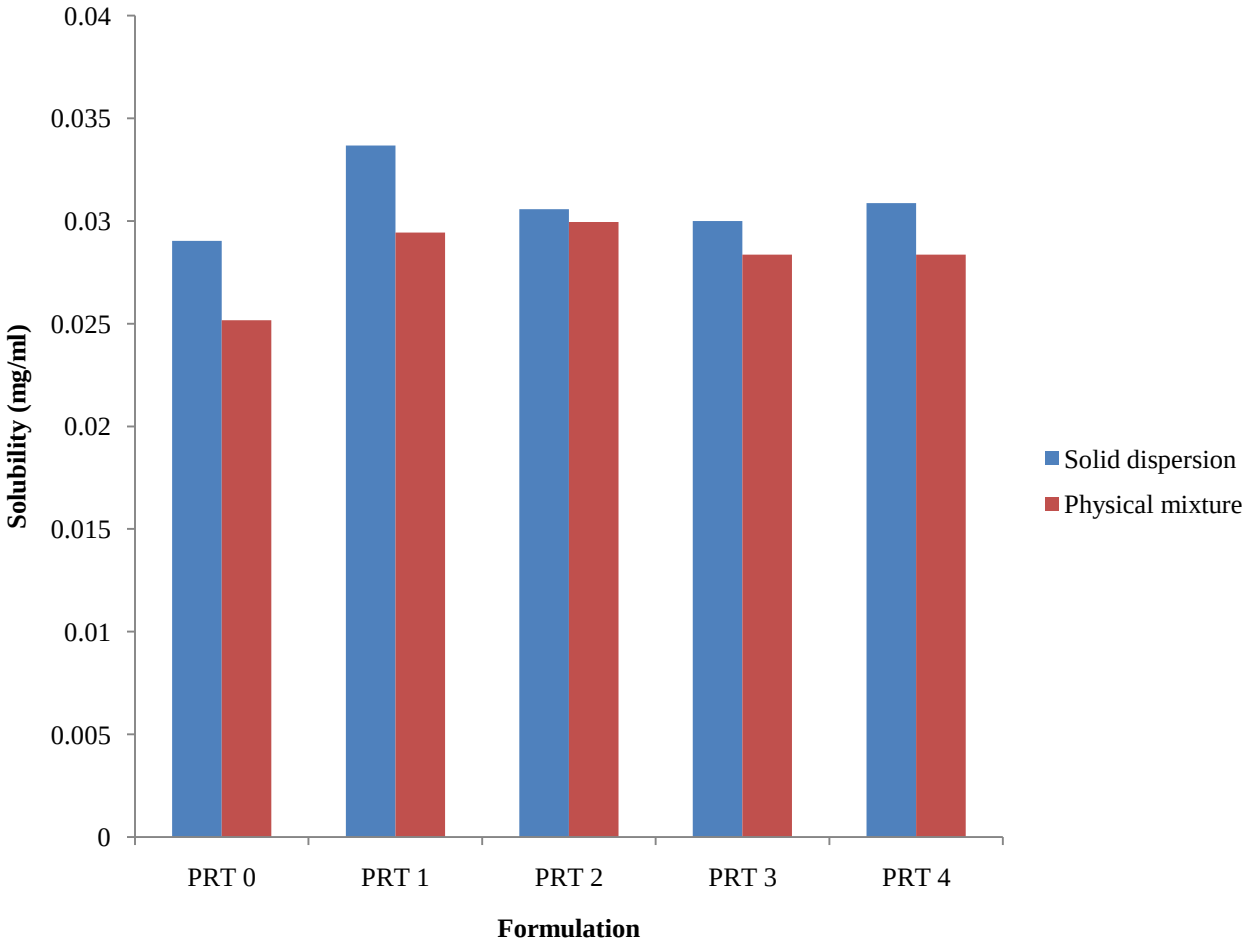


Figure 4.41 : Effect of formulation on solubility of piroxicam in the presence of trona

Keys:

PRT0- Piroxicam:Eud:HPMC:trona (0.1:1:1:0)

PRT1- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.1)

PRT2- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.2)

PRT3- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.3)

PRT4- Piroxicam:Eud:HPMC:trona (0.1:1:1:0.4)

4.6 Drug polymer compatibility studies with DSC

Figures 4.42 to 4.46 show the DSC thermograms of pure ibuprofen, pure piroxicam, HPMC, Eudragit RS 100 and purified trona respectively. Ibuprofen displayed an endothermic peak at 81.3 ^{o}C corresponding to its melting peak. Piroxicam displayed an endothermic peak at 203.7 ^{o}C corresponding to its melting peak. The melting peak for Eudragit RS 100, HPMC and trona was found to be 66.9 ^{o}C, 176.9 ^{o}C and 105.9 ^{o}C respectively.

Figures 4.47 to Figure 4.50 show the DSC thermograms of ibuprofen solid dispersion with HPMC, Eudragit in individually and in combination and solid dispersion incorporating trona. Solid dispersions showed some level of variations in the DSC curve compared to pure ibuprofen. The DSC thermogram of various ibuprofen solid dispersions showed a decrease in the temperature.

Figures 4.51 to Figure 4.53 show the DSC thermograms of piroxicam solid dispersion with HPMC and Eudragit RS 100 individually and in combination respectively. Figure 4.52 shows the thermogram of the dispersion in the presence of trona. The sharp melting peak of piroxicam at 203.7 ^{o}C was completely absent in all the solid dispersions of piroxicam and a decrease is the melting peak was observed.

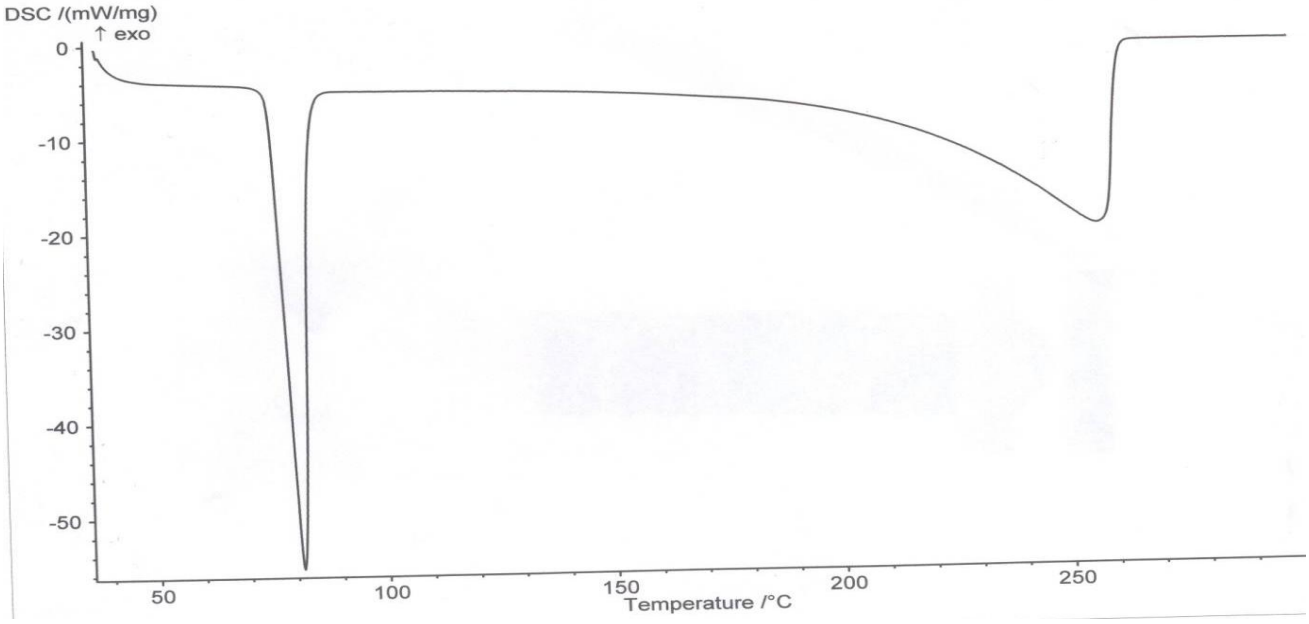


Figure 4.42 : DSC spectra of pure ibuprofen

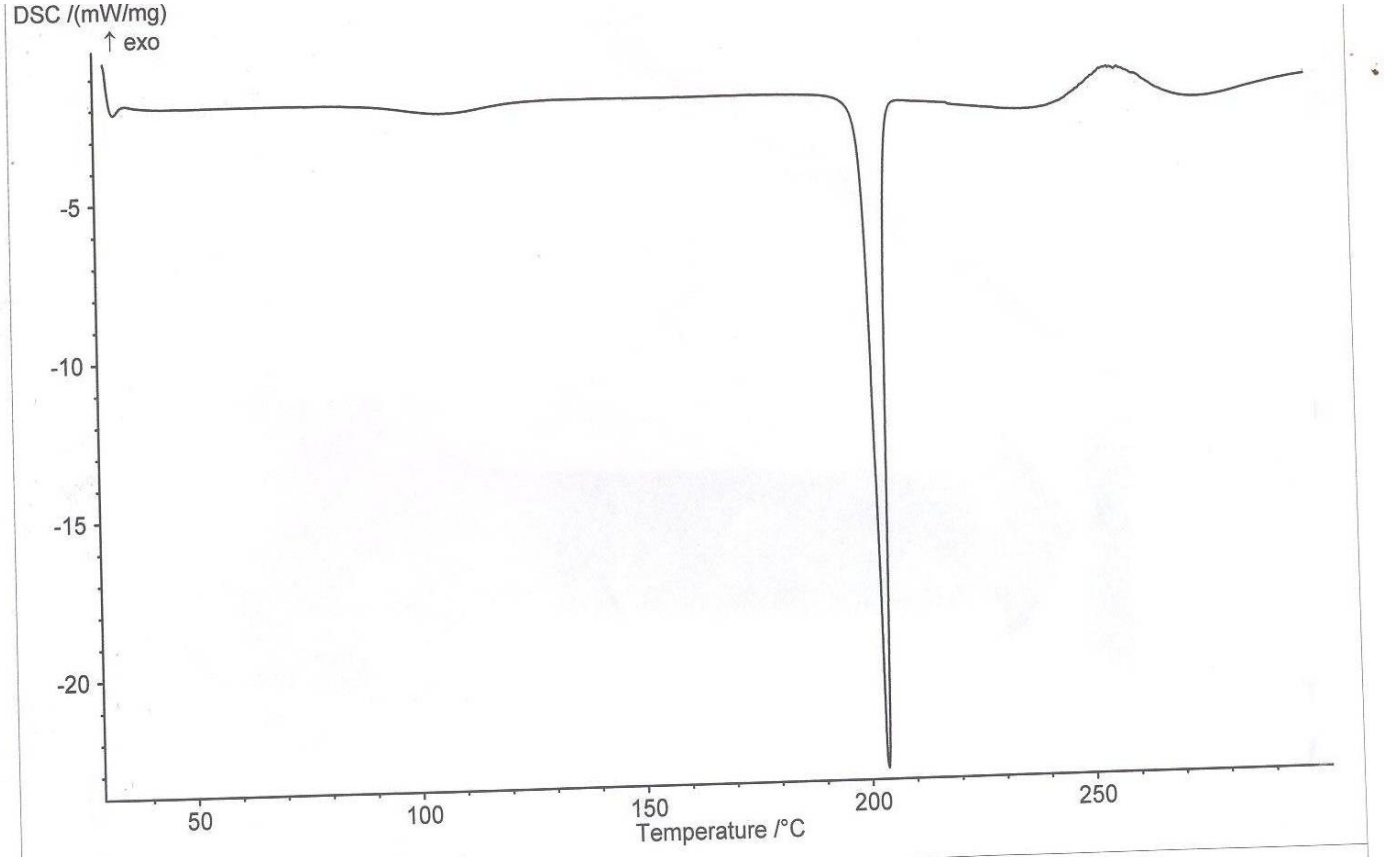


Figure 4.43: DSC spectra of pure piroxicam

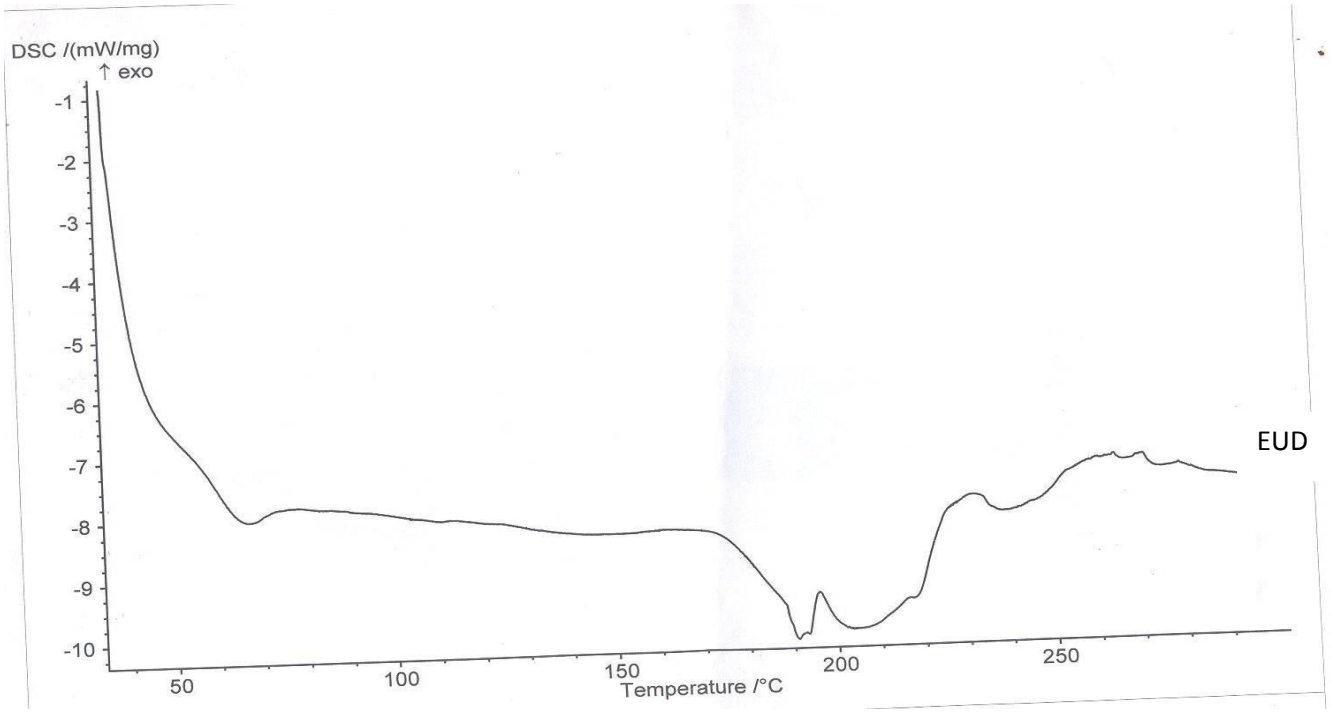


Figure 4.44 DSC spectra of pure Eudragit RS 100

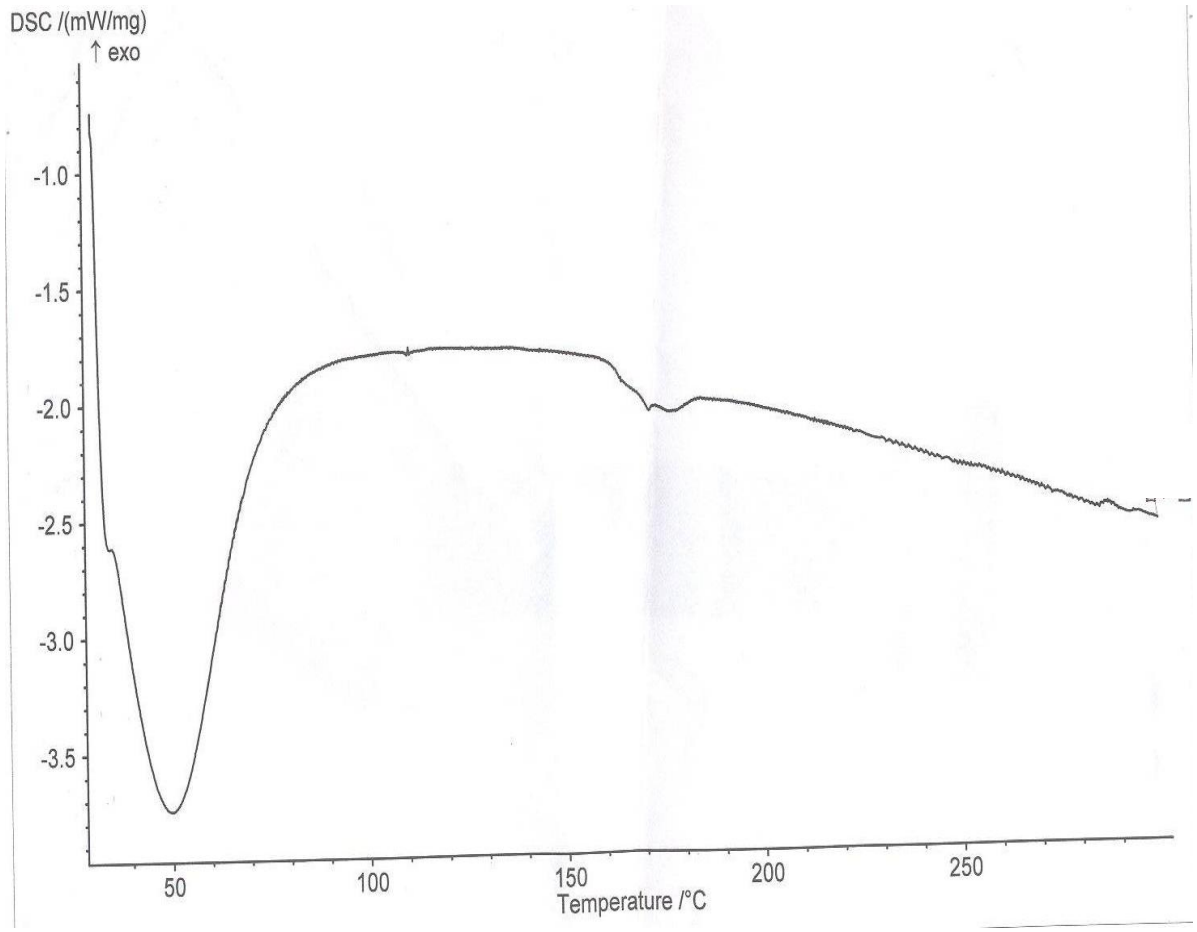


Figure 4.45 : DSC spectra of HPMC

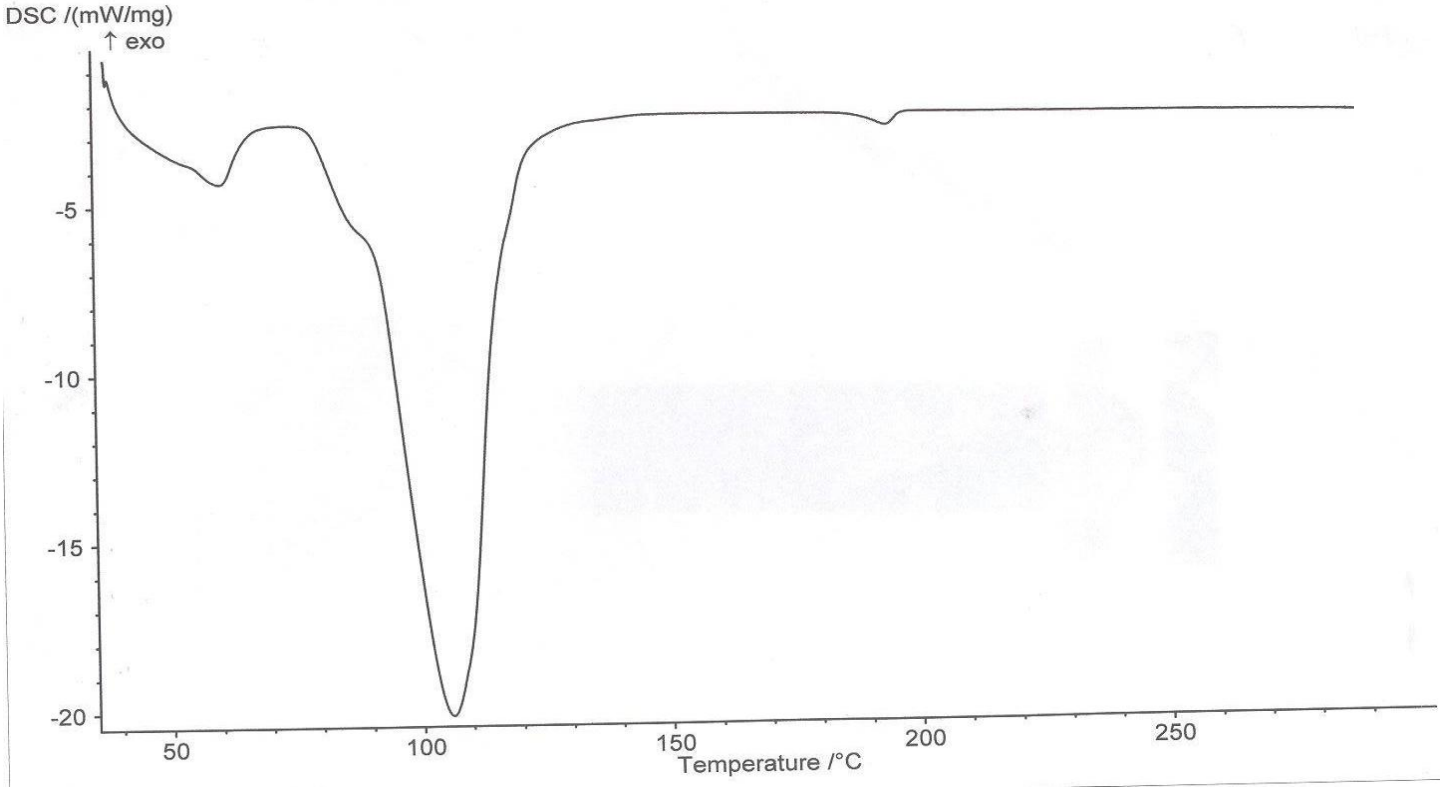


Figure 4.46 : DSC spectra of purified trona

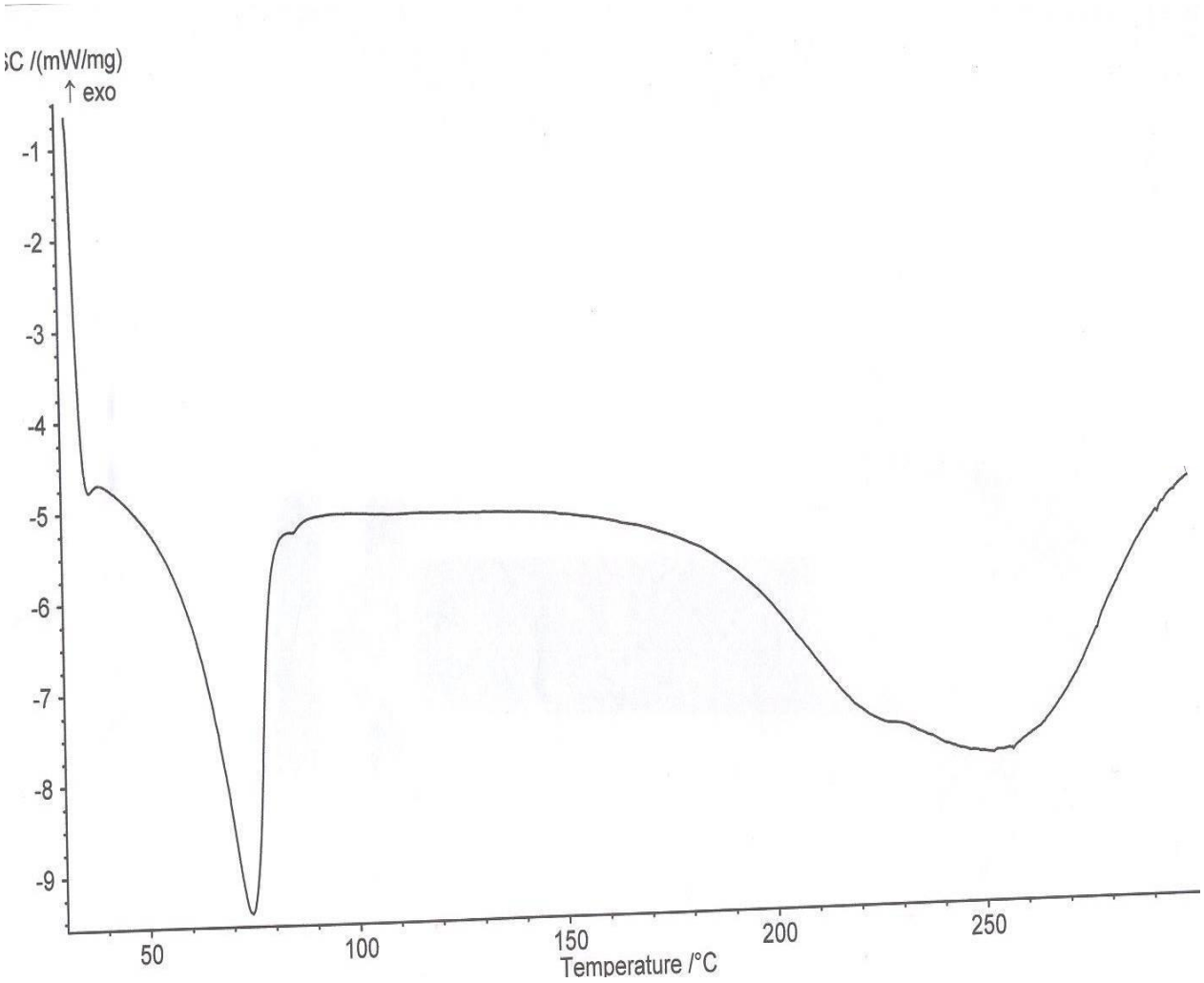


Figure 4.47: DSC spectra of ibuprofen solid dispersion with Eudragit RS 100 (IB2)

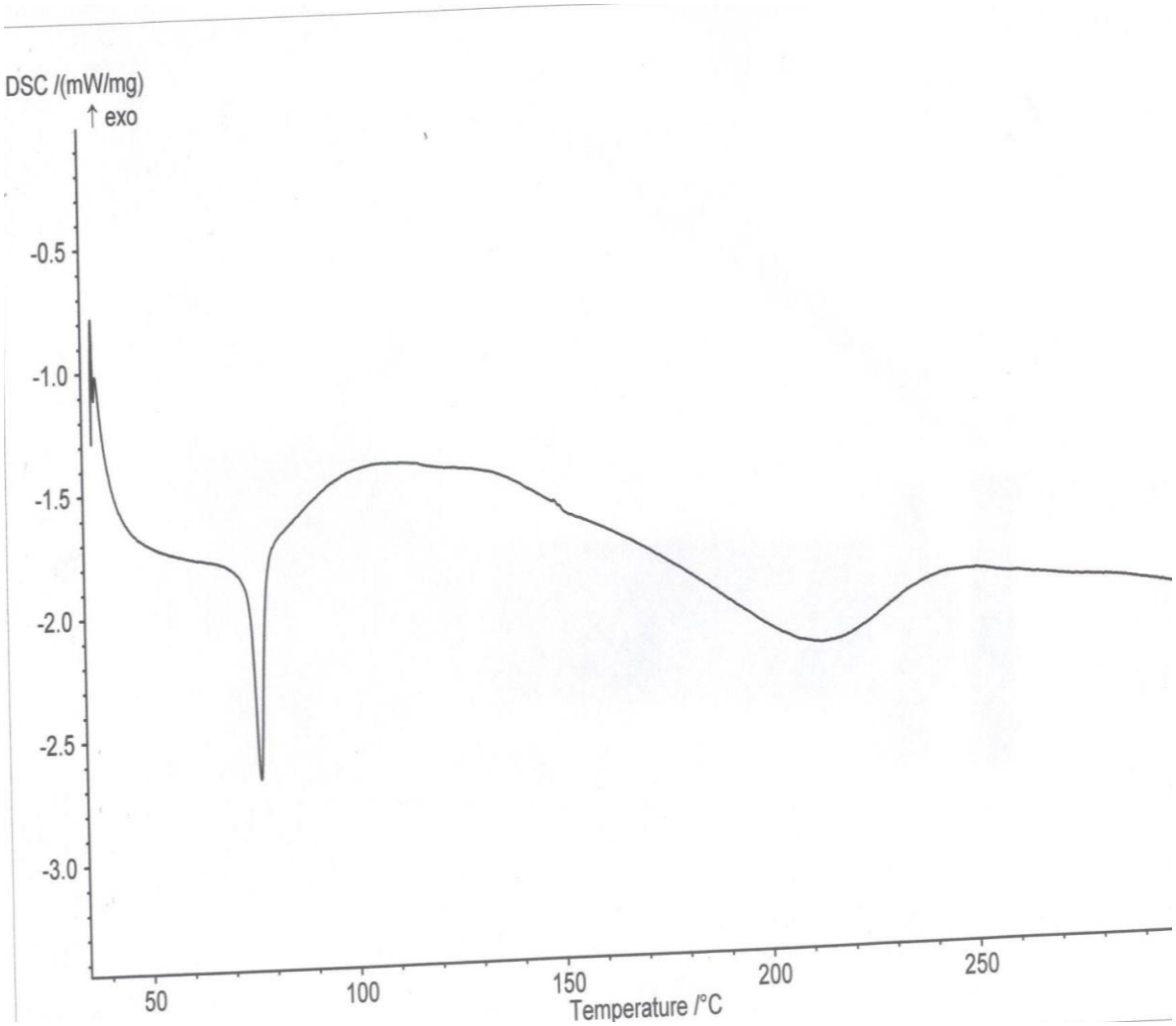


Figure 4.48: DSC spectra of ibuprofen solid dispersion with HPMC (IB5)

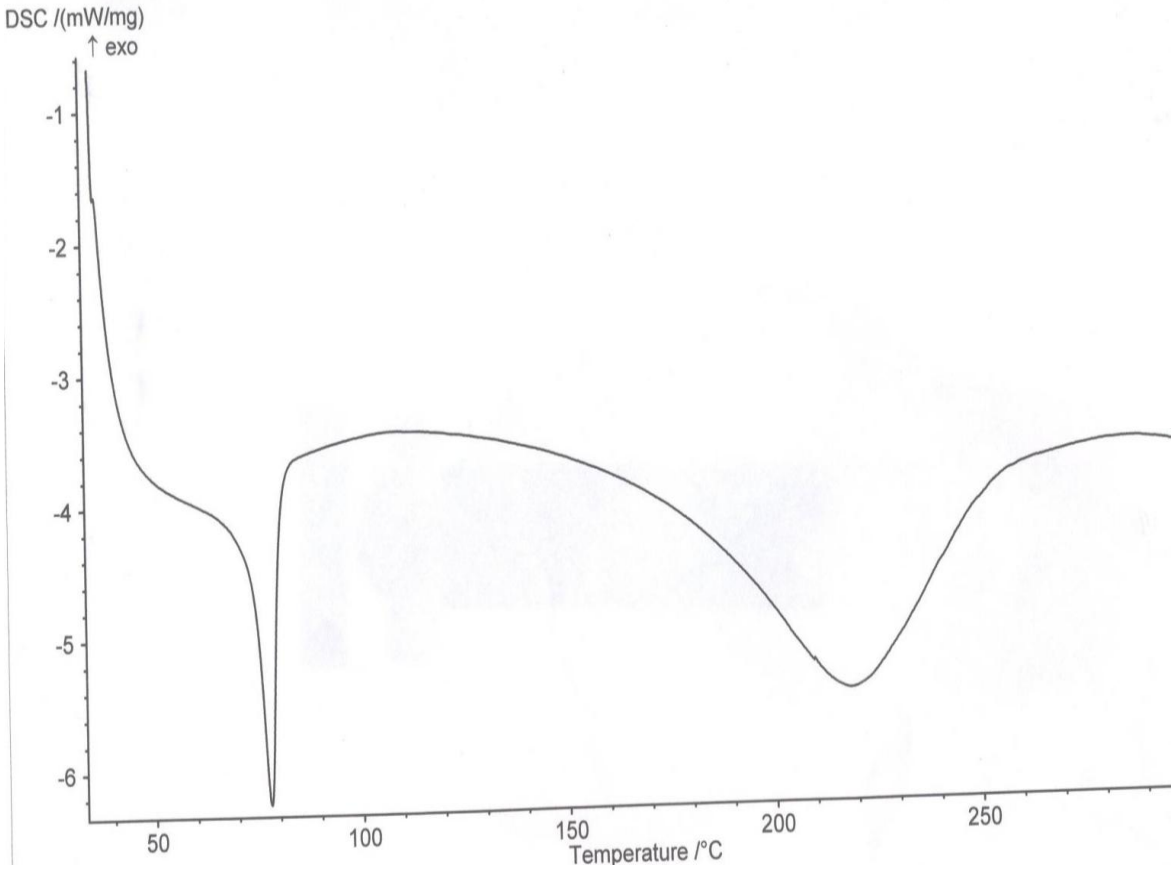


Figure 4.49: DSC spectra of ibuprofen solid dispersion with Eudragit RS 100 and HPMC (IB7)

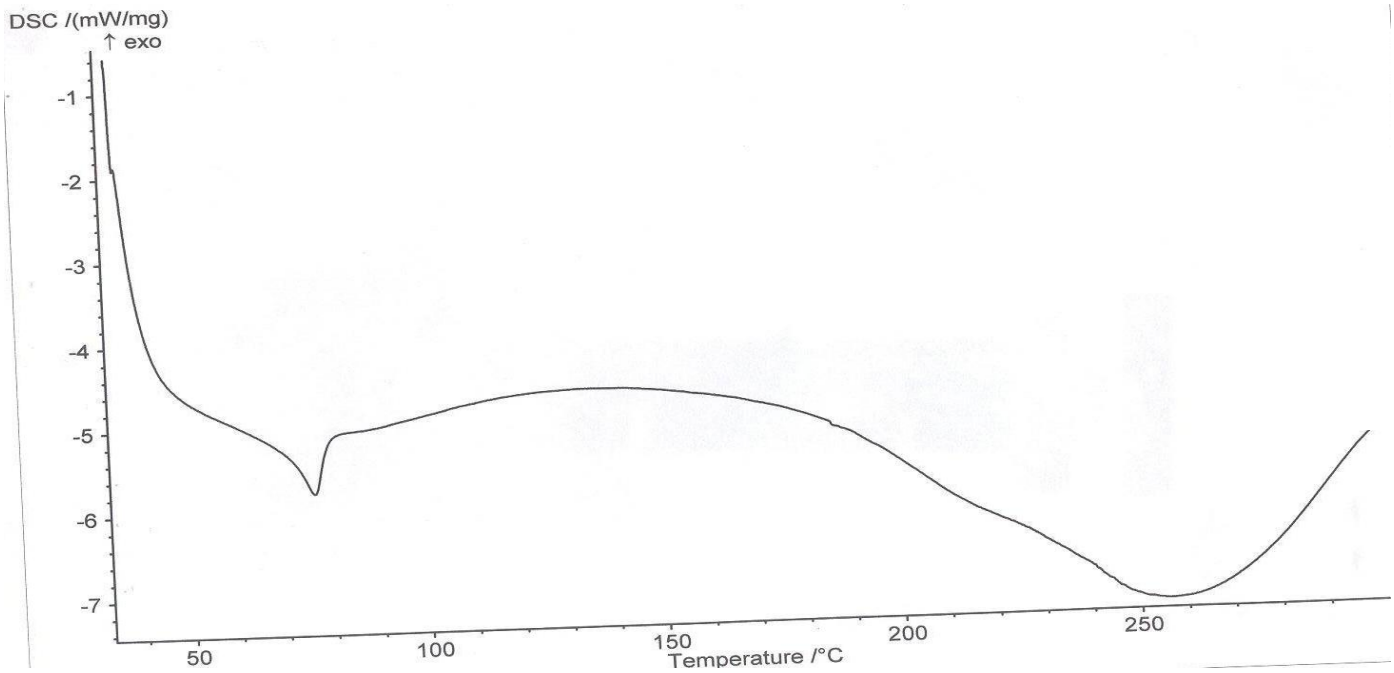


Figure 4.50: DSC spectra of ibuprofen solid dispersion incorporating trona(IBT3)

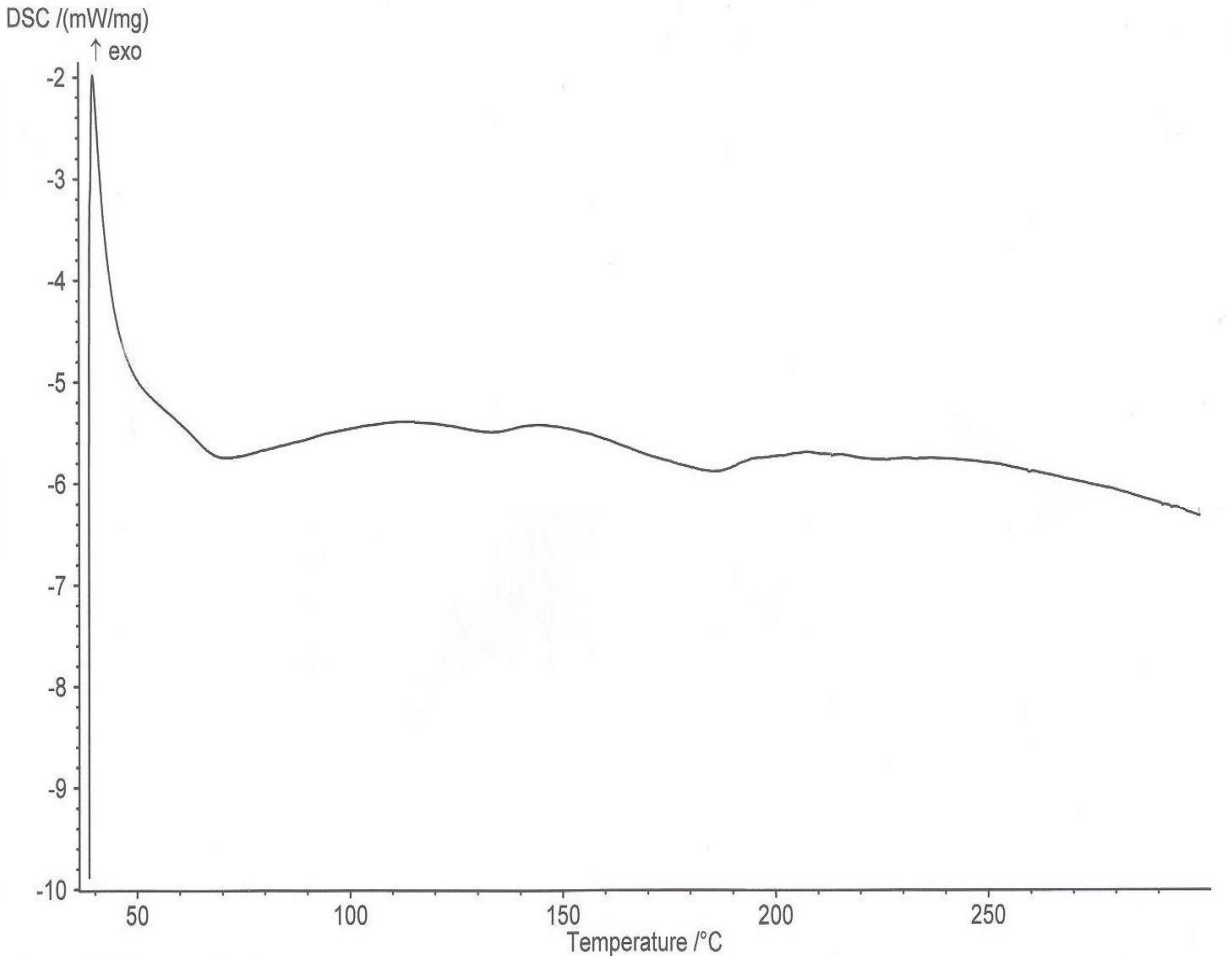


Figure 4.51: DSC spectra of piroxicam solid dispersion with Eudragit RS 100 (PR1)

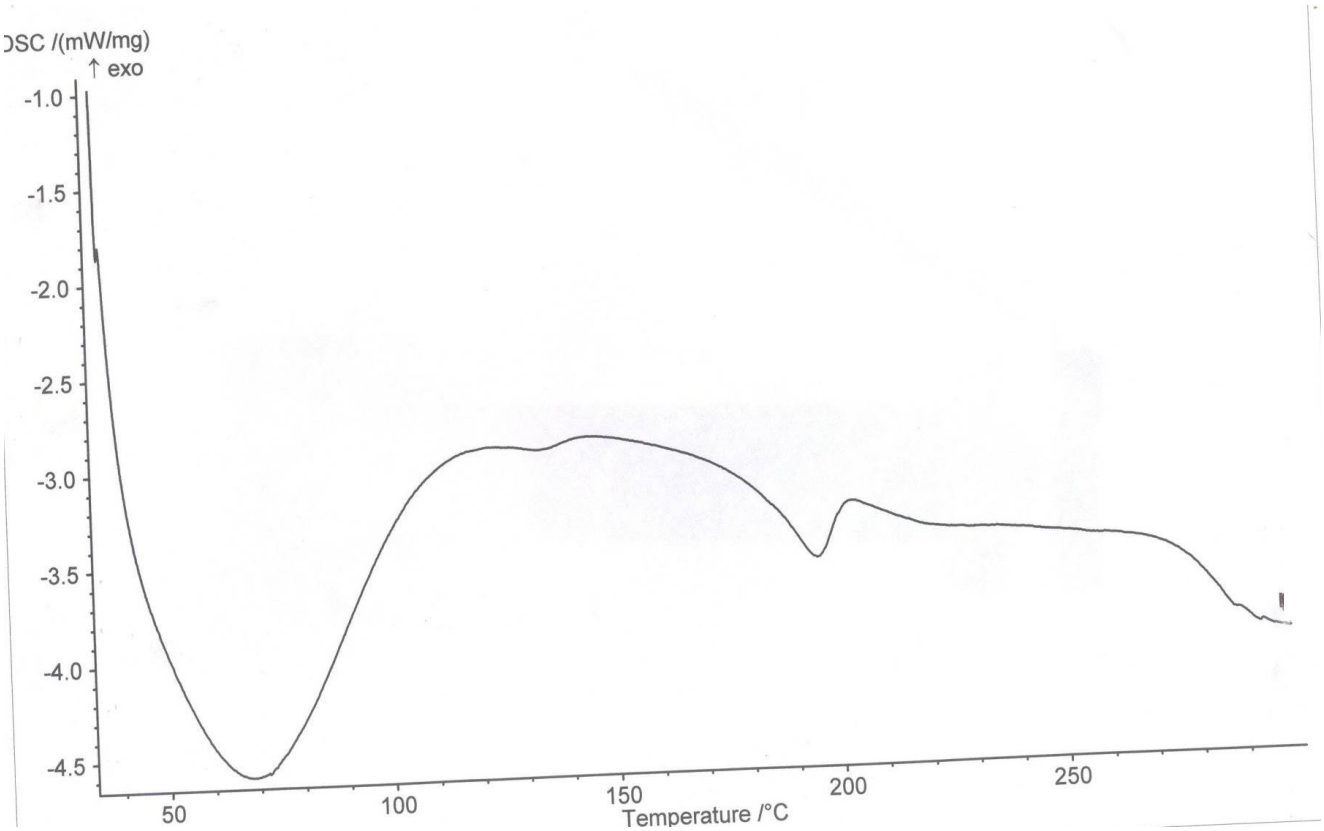


Figure 4.52: DSC spectra of solid dispersion of piroxicam with HPMC (PR1)

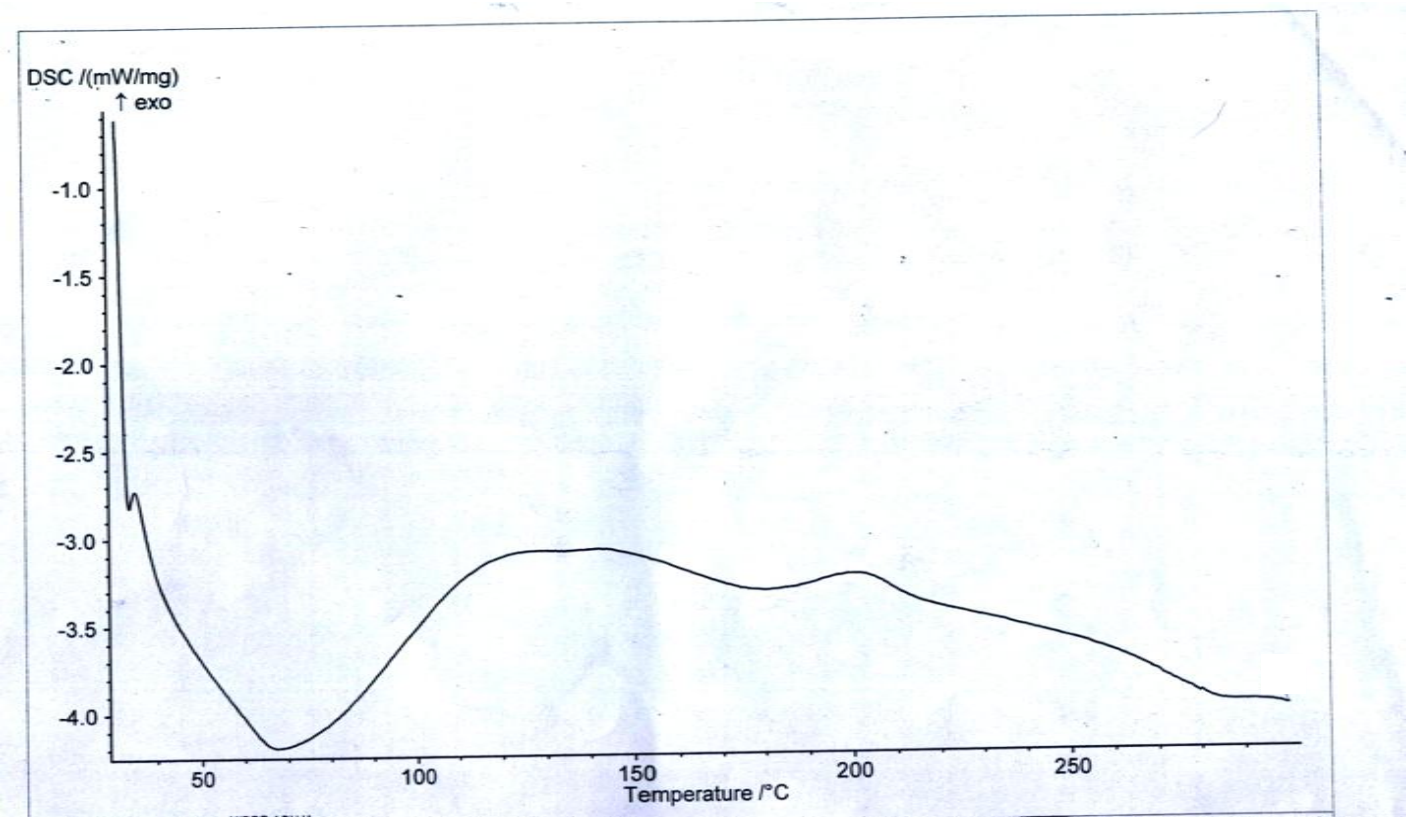


Figure 4.53: DSC spectra of piroxicam solid dispersion with Eudragit RS 100 and HPMC (PR7)

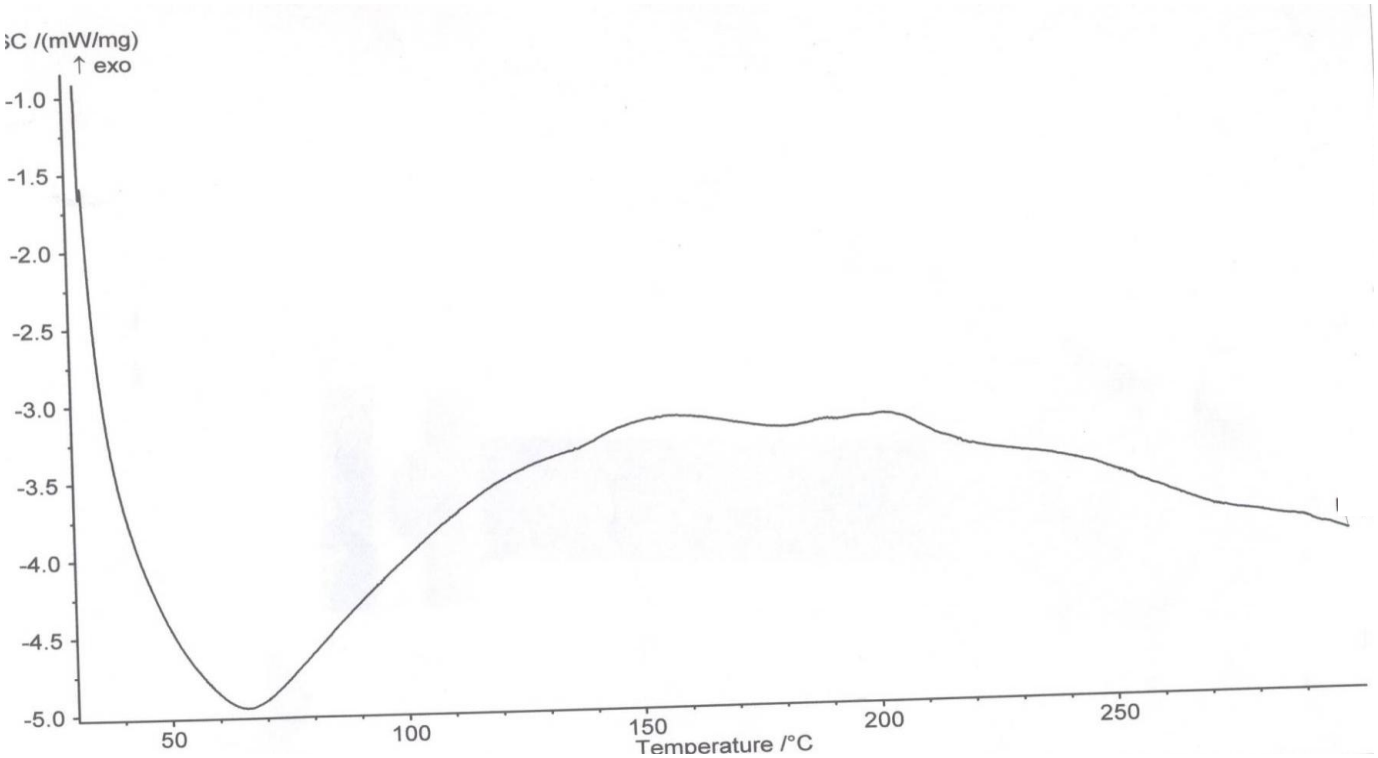


Figure 4.54: DSC spectra of piroxicam solid dispersion in the presence of trona (PRT4)

4.7 Dissolution

The drug release profile from pure sample of ibuprofen and various ibuprofen solid dispersions is showed in Figure 4.55. Solid dispersion of ibuprofen with HPMC gave a four-fold increase in dissolution when compared with the pure drug while solid dispersion with Eudragit RS 100 retarded the release of ibuprofen in the first 2 h. After 8 h of dissolution solid dispersion of ibuprofen with HPMC released about 90.30 % of drug while solid dispersion with Eudragit RS 100 released only about 65.50 % of drug. In comparison, solid dispersions of ibuprofen with Eudragit RS 100 and HPMC without trona showed better performance and drug release (75.80 %) than solid dispersions incorporating trona which released 68% of the drug.

Figure 4.57 shows the drug release profile of pure sample of piroxicam and it's various solid dispersions. The dispersion with HPMC gave the fastest dissolution rate which was about 3 times faster than pure drug within the first 2 h. After 8 h, the solid dispersion with HPMC showed distinctly superior release (78.05 %) of drug, while Eudragit RS 100 solid dispersion showed retarded release (41.85 %) of drug . Solid dispersion of piroxicam incorporating trona released the drug faster (56.78%) than solid dispersion without trona (55.20%). Figure 4.56 showed the drug release from ibuprofen solid dispersion and physical mixtures, while Figure 4.58 showed the drug release from piroxicam physical mixtures and solid dispersion. Solid dispersion released the drugs faster than their corresponding physical mixtures. Solid dispersion of ibuprofen and piroxicam with HPMC also released the drugs faster than commercial preparations.

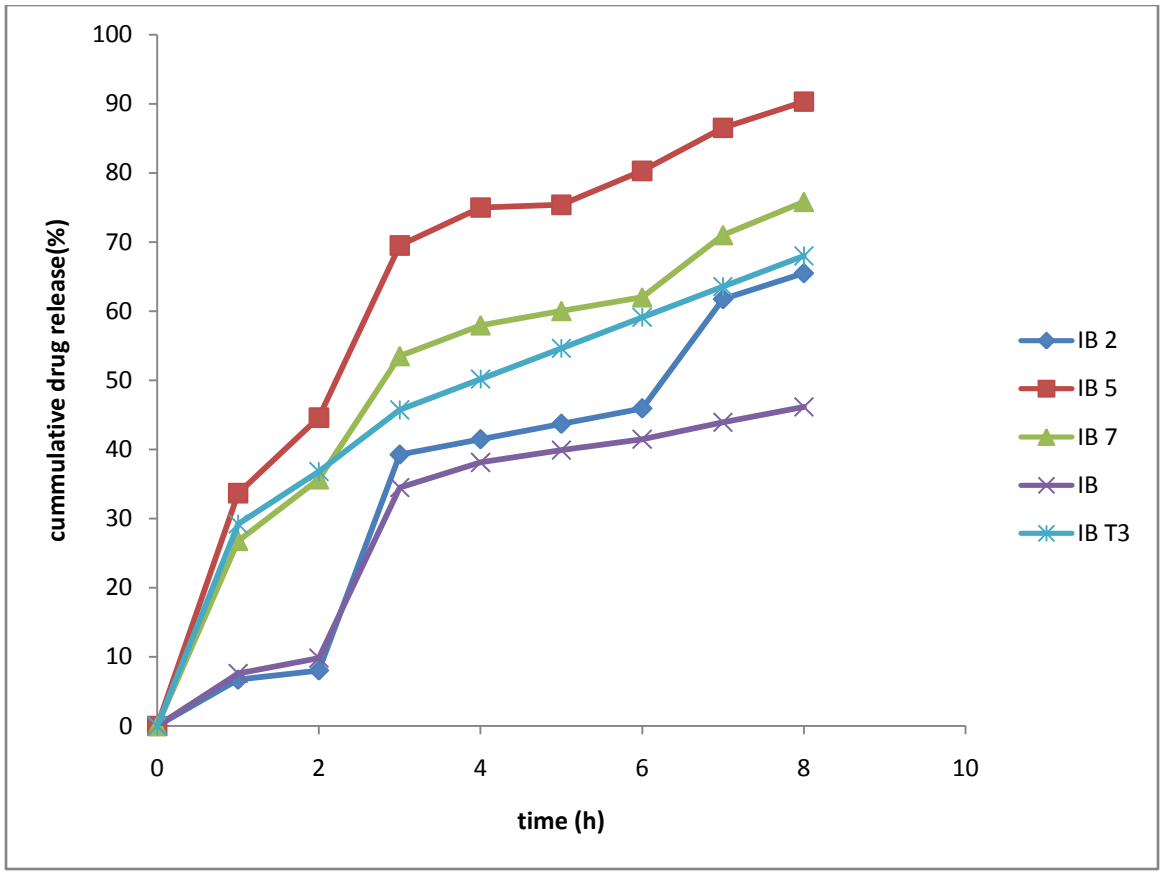


Figure 4.55: Dissolution profile of ibuprofen and various ibuprofen solid dispersions

Keys:

IB –Pure ibuprofen

IB2- Ibuprofen:Eudragit RS 100(1:2)

IB5- Ibuprofen:HPMC (1:2)

IB 7-Ibuprofen:Eud RS 100:HPMC (1:1:1)

IBT3 –Ibuprofen :Eudragit RS 100:HPMC: Trona (1:1:1:0.3)

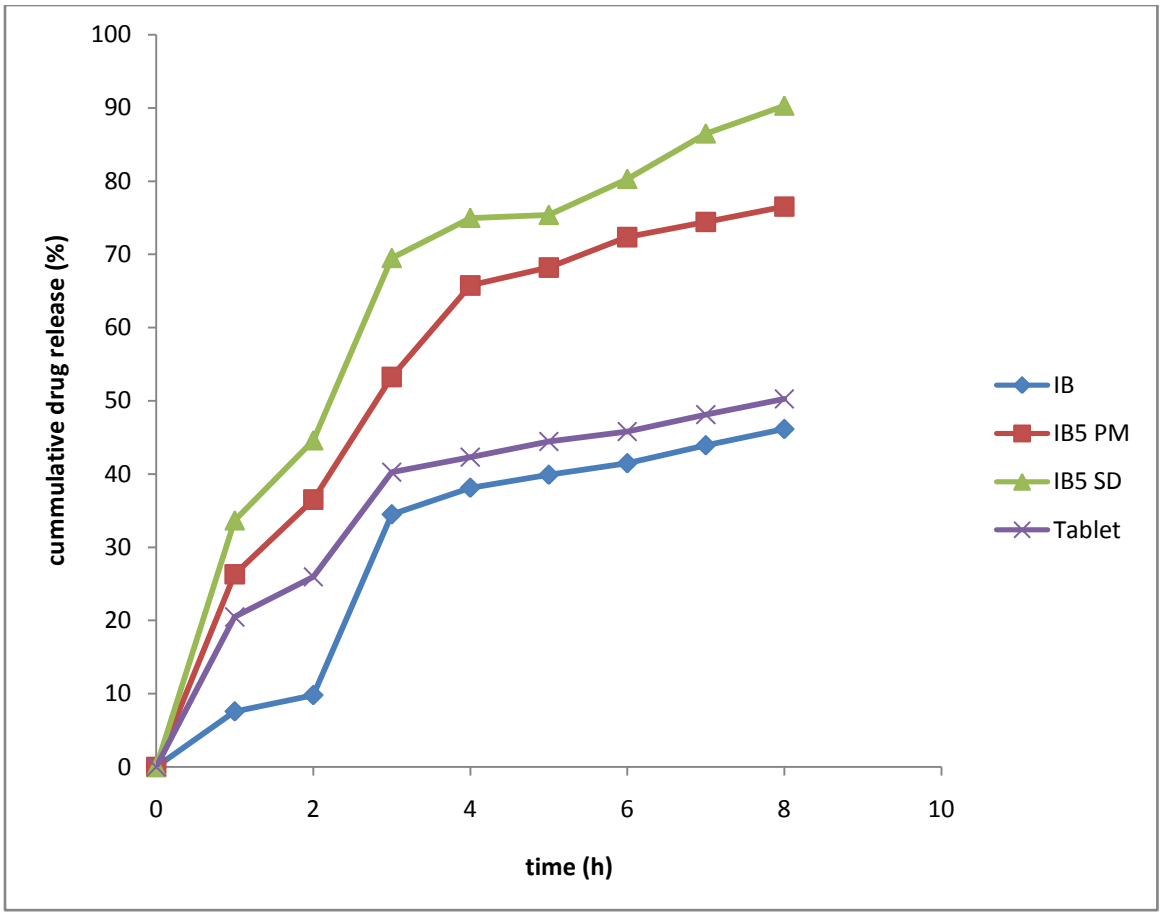


Figure 4.56 : Effect of formulation technique on ibuprofen dissolution

Keys:

IB –Pure ibuprofen

IB5- Ibuprofen:HPMC (1:2) solid dispersion

IB5 PM-Ibuprofen:HPMC (1:2) physical mixture

Tablet -Ibuprofen commercial tablet

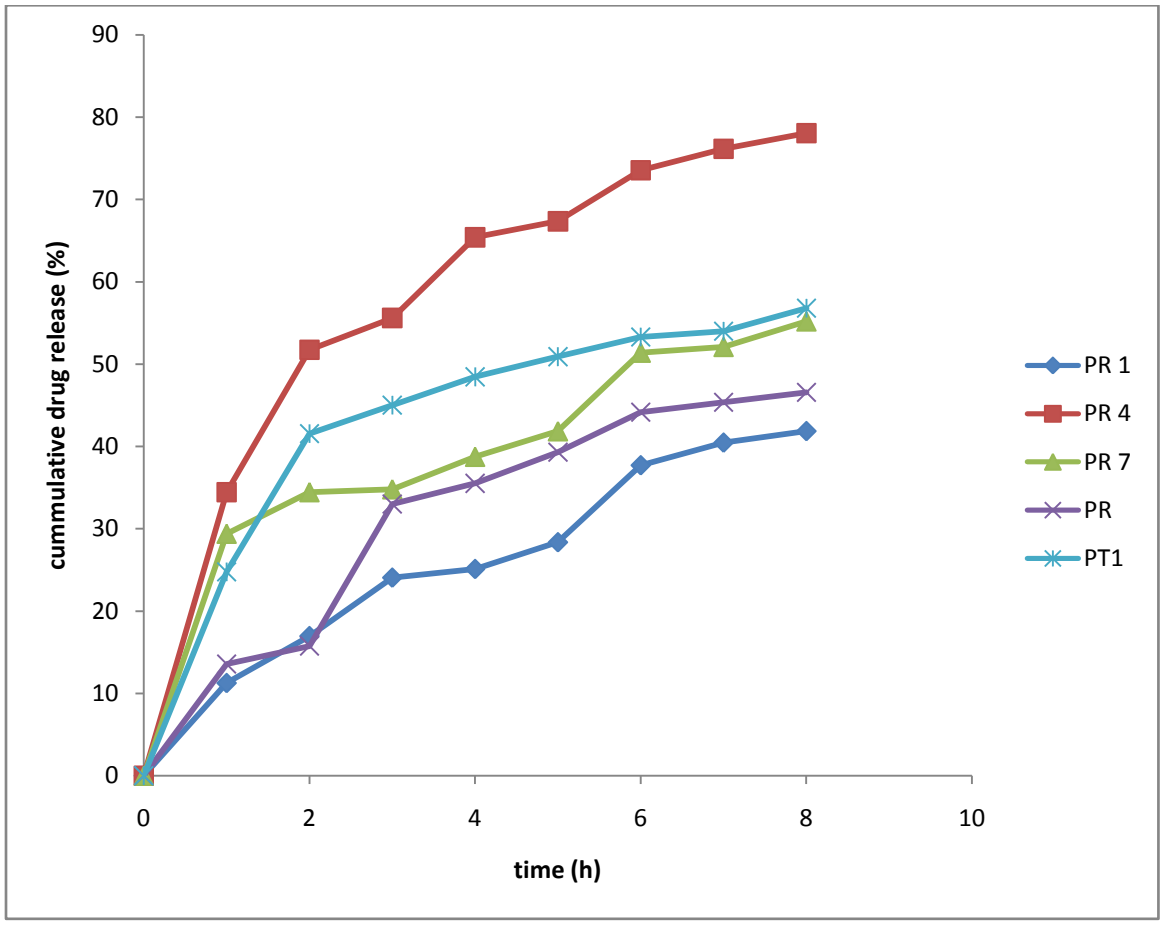


Figure 4.57: Dissolution profile of piroxicam and various piroxicam solid dispersions

Keys:

PR–Pure piroxicam

PR1- Piroxicam:Eudragit RS 100 (0.1:1)

PR4-Piroxicam:HPMC (0.1:1)

PR7- Piroxicam:Eudragit RS 100:HPMC (0.1:1:1)

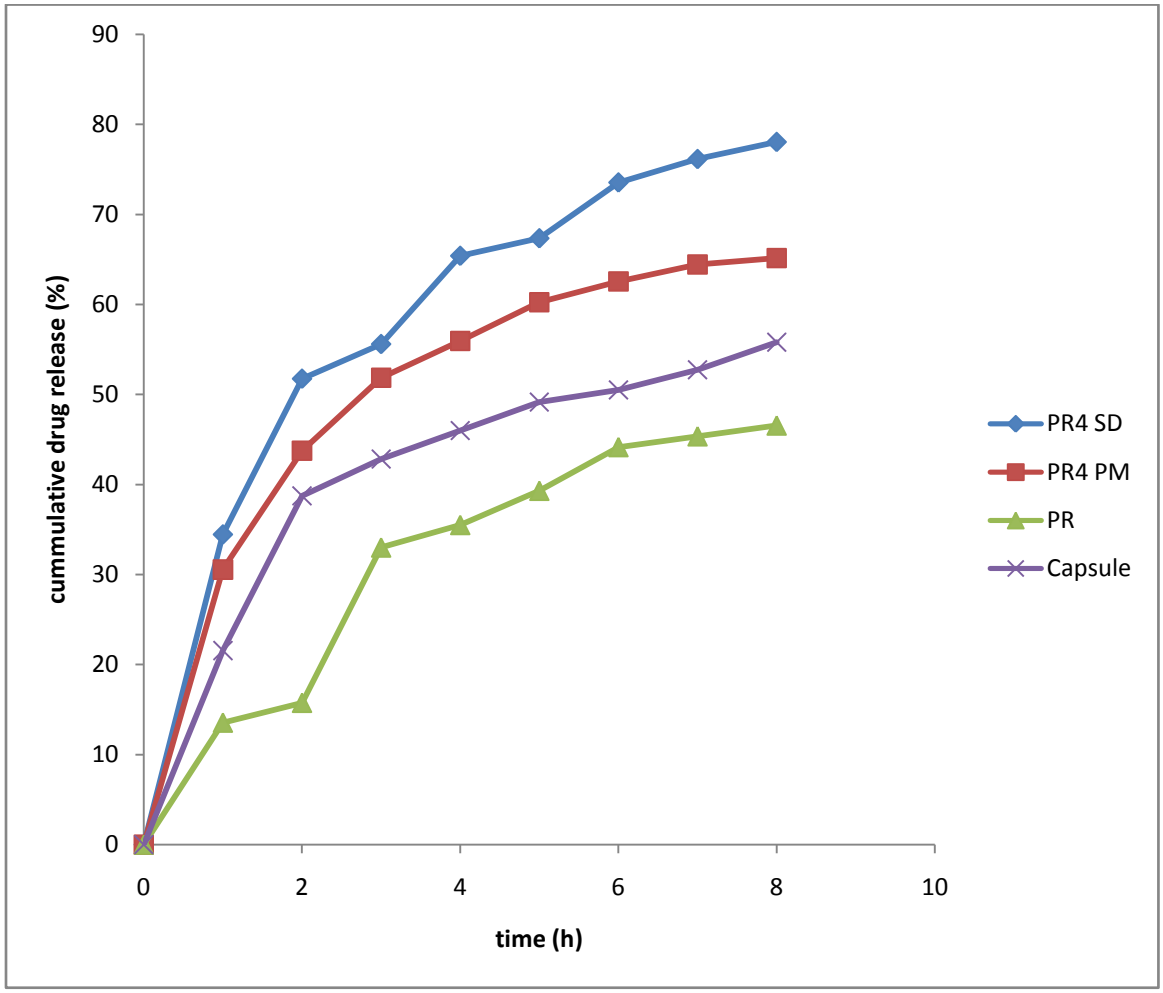


Figure 4.58 : Effect of formulation technique on the dissolution of piroxicam

Keys:

PR–Pure piroxicam

PR4-Piroxicam:HPMC (0.1:1)

PR4 PM-Piroxicam:HPMC (0.1:1) physical mixture

Capsule- Piroxicam commercial capsule

4.8 Anti-inflammatory studies

Figure 4.59 shows the anti inflammatory effect of pure ibuprofen and the solid dispersions. The results show that all the solid dispersions exerted inhibitory effect on the egg-albumin induced oedema. Solid dispersions exhibited a significant increase in anti-inflammatory effect compared to the pure drug. Formulation IB5 exhibited a more rapid onset of anti inflammatory effect with 28 % inhibition in 1 h when compared to pure drug which had 20 % inhibition. Formulation IB 2 had a slower onset of action but at 5^{th} h exhibited the highest anti inflammatory effect with 47 % inhibition.

Figure 4.60 shows the anti-inflammatory effect of pure piroxicam and the solid dispersions. All formulations showed significant increase in anti-inflammatory effect in egg albumin induced paw oedema compared to the pure drug.The highest anti inflammatory activity of solid dispersion was shown by formulation PR1 after 5 h with 49 % inhibition, while formulation PR4 showed fastest onset of action with 28 % inhibition in 1 h as compared to the pure drug (19 % inhibition).

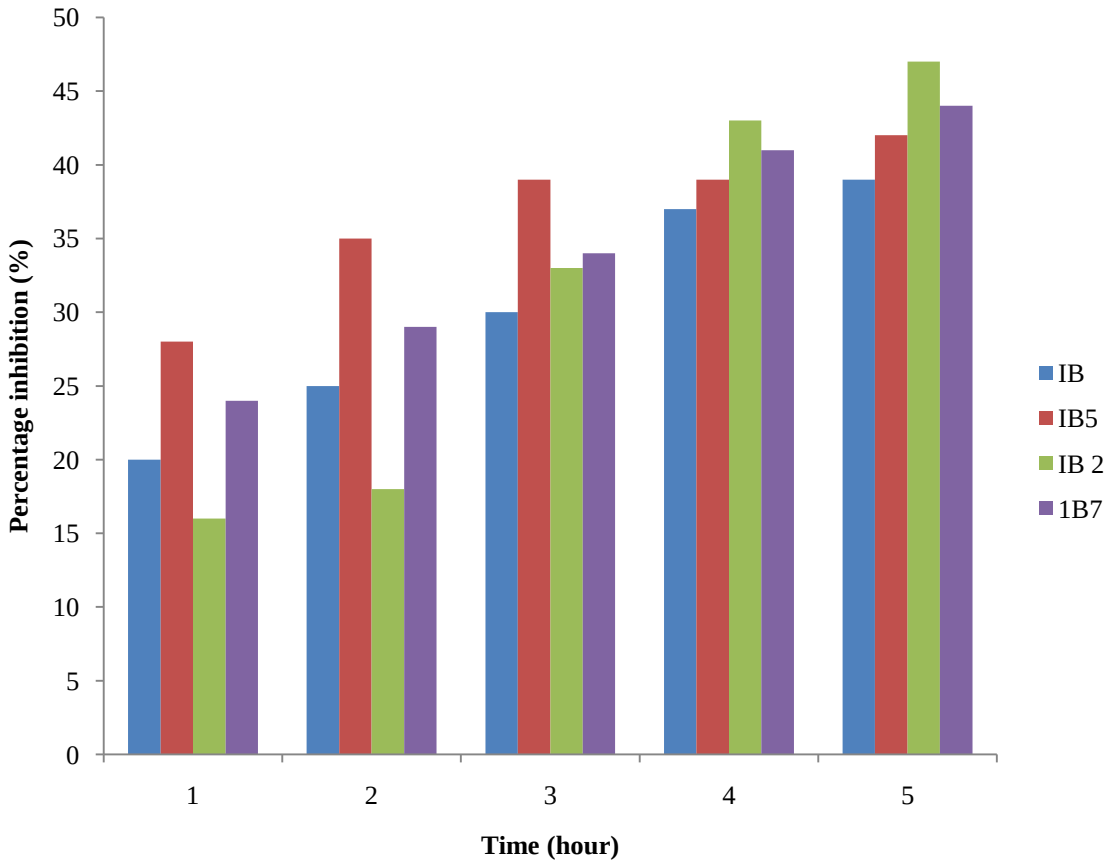


Figure 4.59: Percentage inhibition of egg albumin-induced paw oedema by solid dispersion of ibuprofen

keys:

IB –Pure ibuprofen

IB2- Ibuprofen:HPMC (1:2)

IB5- Ibuprofen:Eudragit RS100 (1:2)

IB7- Ibuprofen:Eud RS 100:HPMC (1:1:1)

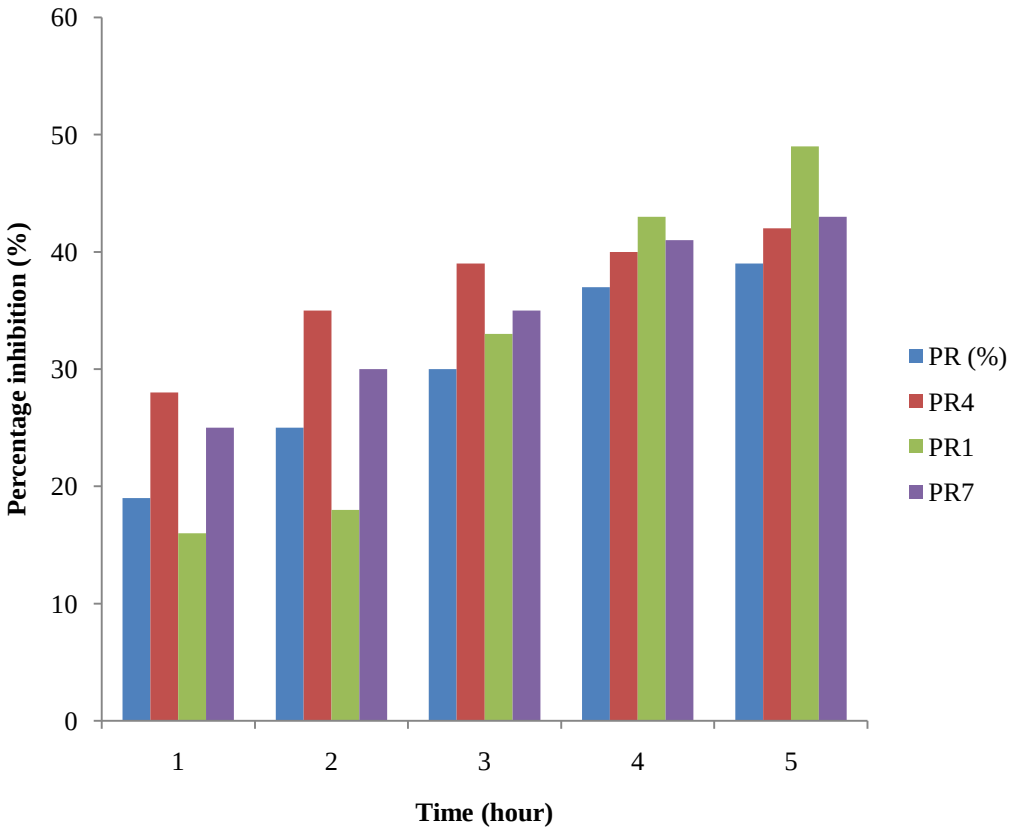


Figure 4.60: Percentage inhibition of egg albumin-induced paw oedema by solid dispersion of piroxicam

Keys:

PR–Pure piroxicam

PR1-Piroxicam:Eudragit RS 100(0.1:1)

PR 4-Piroxicam:HPMC (0.1:1)

PR7-Piroxicam:Eud RS 100:HPMC (0.1:1:1)

4.9 Stability studies

The results of the stability studies carried out on the solid dispersions of ibuprofen and piroxicam are presented in Table 4.5. The results show that the original properties of the solid dispersions at the time of production were preserved and sustained after three months of storage.

Table 4.5: Stability of ibuprofen and piroxicam solid dispersions

Drug	Amount of drug (mg)	
	Initial	Final
IB 2	76.03 ± 0.38	74.67 ± 0.06
IB 5	83.81 ± 0.41	82.37 ± 0.44
IB 7	82.87 ± 0.56	81.94 ± 0.22
PR 1	75.72 ± 3.14	74.03± 1.39
PR 4	82.34 ± 1.50	81.93 ± 1.39
PR 7	97.29 ± 1.27	96.87 ± 0.20

Values are expressed as mean ± standard deviation. Means having different superscripts along the column are significantly different at $p < 0.05$. Mean values were separated using Duncan's multiple range test (DMRT).

CHAPTER FIVE

5.0 DISCUSSION

5.1. Preliminary investigations

The percentage yield of ibuprofen and piroxicam solid dispersions were determined to ascertain the losses incurred during solvent evaporation. A relatively lower yield of dispersions was obtained when Eudragit RS 100 was used at a higher concentration, compared to the yield obtained with HPMC. The lower yield may be due to the fact that Eudragit RS 100 at a higher concentration, forms a rubbery residue after ethanol evaporation which is very sticky and difficult to pulverize and sieve. Pignatello *et al.*(2001) reported a yield of 41-93% when Eudragit RS 100 and RL 100 were used to formulate solid dispersion of diflunisal, because of the difficulty in collecting all the solid materials from the dish after ethanol evaporation.

The absolute drug content of the solid dispersions are presented in Table 4.1 for ibuprofen and Table 4.2 for piroxicam . It is evident from both tables that the drug contents were dependent on the composition of the solid dispersions. Batch IB7 to IB9 containing HPMC in addition to Eudragit RS 100, entrapped the greatest amounts of ibuprofen in comparison to the binary systems (batch IB1 to IB3) containing Eudragit RS 100. For piroxicam solid dispersions, the ternary system containing both Eudragit and HPMC entrapped the greatest amount of drug followed by dispersion containing HPMC. This may be due to increase in the core material of the solid dispersions. Drug entrapment efficiency is an important variable for assessing the drug loading capacity of solid dispersions and their drug release profiles, thus suggesting the amount of the drug that would be available at the absorption site. This parameter is dependent on the formulation variables (Ofokansi *et al.,* 2012). All the solid dispersions showed high drug contents implying that the drugs are uniformly dispersed in the solid dispersions and the solvent

evaporation method is reproducible for development and preparation of solid dispersions. This is consistent with earlier findings on terbinafine hydrochloride solid dispersion prepared using solvent evaporation method by Prasad *et al.* (2010)

5.2 FT-IR STUDIES

The vibrational spectrum of a molecule is considered to be a unique physical property and is characteristic of the molecule. The FT-IR absorption spectrum of pure piroxicam showed bands similar to those noticed on other spectra of piroxicam (Fatty and El-bady, 2003). FT-IR spectra of piroxicam solid dispersions showed no significant shift and no disappearance of characteristic peaks found in pure piroxicam, suggesting that there is no interaction between the drug and polymers or no degradation in the drug molecule. This was similar to finding of Shah *et al.* (2012) that FT-IR spectra of solid dispersions showed decrease in the number of peaks due to overlapping of peaks corresponding to drug and polymer.

Pure ibuprofen showed sharp characteristic peaks at 1706 cm^{-1} which correspond to the carboxylic acid (COOH) present in ibuprofen. Other smaller peaks in the region of 1200 – 1000 cm^{-1} are indication of presence of benzene ring (Kumar *et al*., 2011). These peaks can also be seen in the ibuprofen solid dispersions, but in this case, IR spectrum for ibuprofen solid dispersions shows overlapping of carboxylic acid group. The absence of generation of new peak in any solid dispersions confirm absence of strong chemical interaction (Shah *et al.*, 2012).

5.3 Moisture sorption and desorption

Moisture sorption characterization has been reported to be the most sensitive technique for assessing variation in the amorphous content of polymers as well as predicting some physicochemical and functional properties of polymers (Lin and Chen, 2005). A host of pharmaceutical excipients are affected by moisture. The amount of water adsorbed is dependent on the affinity between the surface and water molecules, temperature and relative humidity, as well as on the amount of surface area exposed. The rate and extent of moisture sorption were found to be almost equivalent to the rate and extent of moisture desorption, following exposure of solid dispersions to varying relative humidity conditions.

The differences in the moisture sorption characteristics between the different batches of solid dispersions could be due to the differences in the polar groups available for intermolecular interaction with water molecule. The result obtained shows a relationship between the sample nature and the amount of moisture sorped. Solid dispersions with HPMC were found to sorp greater amount of water than solid dispersions with Eudragit RS 100

A sharp rise in moisture uptake at between 92 % and 100 % relative humidities corresponds to the total saturation of monomolecular layer and subsequent diffusion of excess moisture into the bulk powder bed or formation of a multimolecular layer (Ofokansi *et al.*, 2012). Amorphous forms of a polymeric materials exhibit a higher shift in the moisture uptake profile when compared to that of crystalline form. The solid dispersions of ibuprofen and piroxicam with HPMC are more amorphous in that of Eudragit RS 100. Solid dispersions of ibuprofen incorporating trona was less amorphous than those without trona, whereas trona enhanced the amorphous nature of piroxicam solid dispersion

5.4. Solubility studies

The solubility studies indicated that the drug solubility increased in the presence of carriers when compared to the solubility of the drugs alone. Even though the carriers are present in physical mixtures, the solubility was less than in the corresponding solid dispersions. Solubility attained with solid dispersions of ibuprofen and piroxicam was higher than the one achieved with physical mixtures. The increase in solubility from physical mixture could be due to the solubilizing effect of carriers and molecules used in the formulations (Kulkarni *et al.,* 2012). The solid dispersions have the advantage of increasing solubility due to decreased crystallinity of the drug and also highly dispersed state of the drug resulting in its higher wettability. Hasnain and Nayak (2012) reported that both physical mixtures and solid dispersions of ibuprofen showed an increase in drug solubility in the presence of PEG 6000-PVP K-30 combination as carriers, but the solid dispersions showed higher saturated solubility than the respective physical mixtures of drug and carrier which might be attributed to an improvement in wetting of the drug particles and localized solubilization by polymeric carriers in the dispersion.

The solubility of piroxicam was improved more in the presence of the hydrophilic polymer-HPMC than in the presence of the hydrophobic Eudragit RS 100. This might be attributed to an improvement in the wetting of drug particles and localized solubilization by the hydrophilic polymer carriers (Rosario *et al.,* 2002). The results in Figure 4.36 shows that increasing the amount of Eudragit RS 100 results in decreasing the solubility of Piroxicam. Figure 4.41 show that the saturated solubility of solid dispersions of piroxicam with Eudragit RS 100 and HPMC was enhanced in the presence of trona. This might be due to the solubilizing effect of trona. Solubility of ibuprofen decreased in the solid dispersions with Eudragit RS 100 this might be due to ionic interaction between ibuprofen and Eudragit RS 100 (Heun *et al.,* 1998). Poorly

soluble crystalline drugs when in the amorphous state tend to have higher solubility because they have higher free energy, entropy and specific volume.

5.5 Thermal Analysis by DSC

There was a sharp endothermic peak of ibuprofen at 81.3^{o}C corresponding to the melting point of ibuprofen, similar to the finding of Kumar *et al*. (2011). The DSC thermogram of the pure ibuprofen and the carriers-HPMC and Eudragit RS 100 showed sharp endothermic peaks. The endothermic peak of pure ibuprofen and piroxicam were of very high intensity, showing the crystalline form of ibuprofen and piroxicam. Pure piroxicam had an endothermic peak at 233^{0}C that corresponded to the melting point of piroxicam similar to findings of Kulkani *et al.* (2012). The DSC thermograms of ibuprofen and piroxicam solid dispersions showed the endothermic peaks with some changes in the characteristics of the peaks shown by individual components (Nayak and Jain, 2011). The peaks were progressively reduced in area and appeared with decreased intensity. No peak corresponding to the melting point of the pure drugs was observed in the thermograms of solid dispersions indicating amorphous form of the drug (Itishree *et al.,* 2011). As the intensity of the endotherm was markedly decreased in the HPMC solid dispersion, the faster dissolution rate of the drug from solid dispersions was obtained which was attributed to the reduction in the crystallinity of the drug. Crystallization inhibition is attributed to the entrapment of drug molecules in the polymer matrix during solvent evaporation.

The endothermic peaks of solid dispersions lost their sharpness and distinctive appearance, an indication that no possible interaction was found between drug and carrier and that a homogenous dissolution of drug in polymer occured (Kulkarni *et al.*,2012).

5.6 Dissolution studies

Pure piroxicam displays a dissolution behaviour typical of acidic molecules, with only a little amount of drug dissolved in the external medium during the first two hours at pH 1.2 when the pH changed to 7.4, the curve showed an instantaneous increase in dissolution of the drug.

Piroxicam possesses a basic group that becomes protonated at the acid pH and makes the drug readily soluble in pH 1.2. Solid dispersions containing Eudragit RS 100 displayed a retarded dissolution of the drug, making piroxicam almost independent of the pH of the external medium. The Eudragit RS 100 system reduced the massive initial drug dissolution observed immediately after the pH change for pure piroxicam (Rosario *et al.,* 2002). Such a behaviour is due to the fact that the dissolved drug becomes ionized in the neutral dissolution medium and is readsorbed onto the polymer particles because of the presence of opposite electrical charges. Rosario *et al.* (2002) reported that the release of non-steroidal anti inflammatory drugs from Eudragit RS and RL polymers was shown to be strongly dependent on the acidic nature of the drugs, which allows chemical interactions, physical interactions, or both, with the ammonium group on the Eudragit RS and RL backbone.

Piroxicam solid dispersions containing HPMC released over fifty percent of the drug within the first two hours. Dissolution of piroxicam from solid dispersions of HPMC was shown to be faster than that of the pure drug and even other solid dispersion as shown in Figure 4.42. In a similar study, Hsiu *et al*. (1996) revealed that the dissolution of nifedipine increased as more HPMC was added to the solid dispersions. Pure piroxicam remained as agglomerates in the dissolution medium and floated on the surface of dissolution medium, but HPMC improved the wetting of the particles which would prevent aggregation of particles when exposed to the aqueous medium

and subsequently allows the particles to present a large surface area thereby leading to enhanced dissolution (Eman, 2012).

The rate of dissolution of pure ibuprofen was slow in acidic medium but increased at pH 7.4. This is favourable for ibuprofen as its absorption was known to occur mainly from the intestine and to a lesser, extent the stomach (Nadia *et al.*, 2011). The results showed that pure ibuprofen has the slowest dissolution rate, the fastest being recorded with formulation IB5 made up of one part of ibuprofen to two parts of HPMC. At 2 h, solid dispersions containing HPMC showed high release compared to other solid dispersions containing different polymers. This is mainly attributed to increased wettability and consequently, solubility of ibuprofen due to the high level of hydrophilicity of HPMC (Rahman *et al.,* 2011). The high rate of dissolution of HPMC component of solid dispersions would pull along more insoluble but finely mixed drug particles into the dissolution medium, leading to enhanced dissolution. In order to dissolve a crystalline drug, energy is required to break up the crystalline lattice and this energy is often considered as a barrier (Howlader *et al.,* 2012). Eudragit RS 100 is only slightly permeable to water and exhibits a pH dependent swelling. It was able to slow down the diffusion of the drug leading to retarded release of ibuprofen. Solid dispersion systems have a potential usage as controlled release drug delivery system with careful use of hydrophobic polymers such as Eudragit RS 100 as reported by Nadia *et al.* (2011). Eudragit RS 100 is only slightly permeable to water hence drug release is relatively retarded compared to freely permeable HPMC. In solid dispersions, a drug forms a complex with an inert soluble carrier in solid state. The availability of the drug depends on the solubility of the polymer and the absorption rate of the drug, therefore, the dissolution rate and oral absorption can be enhanced by using a water-soluble polymer.

The fast and rapid dissolution rate of ibuprofen and piroxicam from solid dispersions compared to that of their corresponding physical mixtures may be due to the presence of the drugs in amorphous form which is revealed by the of DSC results. Ghosh *et al.* (1998) observed that increased dissolution of ibuprofen from solid dispersions was due to presence of drug in amorphous state. The amorphous form is the highest energy state of pure compound and it produces faster dissolution (Prasad *et al.,* 2010). This was similar to the findings of Abdul *et al.* (2013) that solid dispersions of ibuprofen and glucosamine showed considerably higher dissolution rate than corresponding physical mixtures and pure ibuprofen.

5.7 Anti-inflammatory Studies

Solid dispersions of ibuprofen and piroxicam showed better anti-inflammatory properties, compared to the pure drugs. Vijayak *et al.* (2006) and Mohammed *et al.* (2010) reported that solid dispersions of meloxicam showed increased anti-inflammatory activity when compared to pure meloxicam. There was no loss of anti- inflammatory activity in all the solid dispersion formulations. This agrees with similar studies by Sahin and Librowski (2003) that investigated the anti inflammatory and analgesic effects of prednisolone and found that the drug maintained its pharmacologic activity even after formulation into solid dispersions.

A sustained activity was observed in solid dispersions with Eudragit RS 100, while solid dispersions with HPMC gave a faster onset of anti-inflammatory effect. This may be due to increased wettability, solubility and enhanced dissolution rate of solid dispersion with HPMC as revealed by the DSC results. Sachin *et al*. (2013) reported a faster decrease in paw oedema with solid dispersion of ibuprofen and PEG, than the pure drug. All these findings indicate that solid dispersion formulations of ibuprofen and piroxicam with Eudragit RS 100 and HPMC have a

potential to be used as oral dosage forms since the drugs formulated in these preparations did not lose their pharmacological activities.

5.8 Stability studies

The stability studies showed that there was no change in the state of the various solid dispersion after three month of storage, this shows that solid dispersion would show good dissolution characteristics with storage.

CHAPTER SIX

6.0 SUMMARY

Solid dispersion has been the most promising method used to enhance the solubility and dissolution rate of poorly soluble drugs. Solid dispersions are of immense importance now-a-days in the development of poorly water soluble drugs into oral solid dosage forms with enhanced dissolution rate and thus improved oral bioavailability (Huda *et al.,* 2010). Solid dispersions of ibuprofen and piroxicam were formulated using solvent evaporation method. The method was found to be reproducible and the drug content of all formulations was within acceptable limits indicating homogeneity and accuracy of the process. Solid dispersions of both piroxicam and ibuprofen were seen to enhance the solubility of the drugs and their corresponding physical mixtures.

The DSC showed absence of interaction between the drugs and the polymers and a change from crystallinity to amorphous form of the drug. In comparison with the pure drug, the absorption peaks in the FT-IR spectra for ibuprofen, piroxicam and their solid dispersion, showed no significant shift and no disappearance of characteristic peak suggesting that there was no interaction between drug and polymers and no degradation in ibuprofen and piroxicam molecule.

The better dissolution rate of solid dispersions may be due to an improved wettability of drug particles, a significant reduction in particle size during formation of solid dispersions and dissolution due to increase in the surface area of drug, proper dispersions and increase in the amorphousity of drug. *In-vitro* dissolution of the solid dispersions with HPMC showed higher dissolution and than marketed preparation while solid dispersions with Eudragit RS 100 showed delayed dissolution.

6.1 Conclusion

It can be concluded that solid dispersions of ibuprofen and piroxicam using Eudragit RS 100 and HPMC enhanced the aqueous solubility and dissolution rate of ibuprofen and piroxicam thereby enhancing their systemic availability. Trona can be used to increase the aqueous solubility and dissolution of piroxicam solid dispersion and can reduce the aqueous solubility and dissolution rate of ibuprofen. In addition, the results indicate that solid dispersion technique can effectively be used to modify drug release by using hydrophobic carriers such as Eudragit RS 100.

6.2 Recommendations

There is need to prepare the solid dispersions using different techniques like fusion and kneading to determine which gives optimium release and best compressibility properties.

Further work may be required to study the stability of solid dispersions of prepared dosage forms like capsules and tablets to investigate its expiration

REFERENCES

Abdul W., Amjad K. and Gul M.K. (2013). Preperation and evaluation of solid dispersion of ibuprofen using glucosamine HCl as carrier. *British Journal of Pharmacy. Research*,3 (4) :722-733.

Attama A.A., Mbah C.C. and Adikwu M.U. (2007). Trona as a permeation enhancer. *Journal of Pharmaceutical and Allied Sciences,* 4(2):467-480.

Attur H.G., Milo G., Joseph L.K. and Micheal M. (1966). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixture IV;chloramphenicol-urea system. *Journal of Pharmaceutical sciences,* 55(6):581-583.

Behera A.L., Sahoo S.K. and Pahl S.V. (2010). Enhancement of solubility: A pharmaceutical overview. *Scholar Research library*, 2(2):310-318.

Bhawana K., Ramandeep K., Sukhdeep K., Himani B. and Sukhkaran K. (2012). Solid dispersion: an evolutionary approach for solubility enhancement of poorly water soluble drugs. *International Journal of Recent Advances in Pharmaceutical Research*, 2(2): 1-16.

Blagden N., De-Matas M, Gavan P.T. and York P. (2007). Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Advanced Drug Delivery Reviews*, 59(7):617–630.

Breitenbach J. (2002). Melt extrusion from process to drug delivery technology. *European Journal of Pharmaceutics Biopharmaceutics*, 54:107-117.

Buckton G. and Darcy P. (1995). The use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powders. *International Journal of Pharmaceutical Sciences* ,123 :265-271

Chaumeil J.C. (1998). Micronization; a method of improving the bioavailability of poorly soluble drugs.methods and findings in experimental and clinical pharmacology, *Public Medicine* 20(3): 211-215.

Chiou W.L. and Rigelmen S. (1971). Pharmaceutical application of solid dispersions systems. *Journal of Pharmaceutical Sciences*, 60:1281-1302.

Craig, D.Q. (2002). The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics*, 231:131-144.

Daisy S., Mohit S., Sandeep K. and Gupta G.D. (2009). Solubility enhancement-Eminent role in Poorly soluble drugs. *Research Journal of Pharmacy and Technology*, 2(2): 220-224.

Dua k., Pabreja K. and Ramana M.V.(2010). Preparation ,characterization and *in vitro* evaluation of aceclofenac solid dispersions. *ARS Pharmaceutica*, 51(1):57-76.

Deepshikha S., Vaibhav S., Ankit A.K. and Chatterjee D.P. (2012). Technique for solubility enhancement of poorly soluble drugs an overview. *Journal of Medical Pharmaceutical and Allied Sciences,*1:1-22

Dhiman S., Parmjit K. and Sandeep A. (2012). Solid dispersions: opportunity in drug delivery System. *Drug Invention Today* 4, (10): 478-486.

Dhirendra K., Lewis S., Udupa N. and Atin K. (2009). Solid dispersion: A review. *Pakistan. Journal of Pharmaceutical Sci*ences, 22(2): 234-246.

Dixit A.K., Singh R.P. and Singh S. (2012). Solid Dispersion- A Strategy for Improving the Solubility of Poorly Soluble Drugs. *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 3(2). 25-34.

Edward K.H. and Li D. (2008). Drug Like Properties: Concept, Structure, Design and Methods, from ADME to Toxicity Optimization. *Elsevier; Solubility*; (2) 56-57.

Eman Al-Khedairy (2012). Effect of additives on the solubility and dissolution of piroxicam from prepared hard gelatin capsule. *Iraqi Journal of Pharmaceutical Sciences,* 2(1):117-122.

Fatty M. and El B. (2003). Preparationand evaluation of piroxicam pluronic solid dispersions. *Bulletin of Pharmaceutical Sciences*, 26(2):97-108.

Filippis D.P., Guglielmo Z., Merio G., Fulvio R. and Paola R. (1995). Dissolution rates of different drugs from solid dispersions with Eudragit RS. *European Journal of Pharmaceutical Sciences,*3(5):265-271

Florence, A.T. and Attwood D.(1998). The Solubility of Drugs. In Physicochemical Principles of Pharmacy, 3rd Ed.; Florence, A.T., Attwood, D. Eds**.;** *Macmillan Press Ltd.: London,* 152-155.

Gaurav T., Ruchi T., Birendra S. and Awani K.R. (2009). Solid dispersions: An overview to modify bioavailability of poorly water soluble drugs. *International Journal of Pharmtechnology Research,* 4 :1338-1349.

Ghosh L.K., Ghosh N.C., Chatterjee M. and Gupta B.K. (1998). Product development studies on the tablet formulation of ibuprofen bioavailability. *Drug Development Industrial Pharmacy*, 24:473-477

Goldberg A.H., Gibald M. and Kanig J.L (1966). Increasing dissolution rates and gastrointestinal absorption via solid solution and eutectic mixtures, experimental evaluation of griseofulvin-succinic acid solution. *Journal of Pharmaceutical Sciences*, 55:487-492.

Hamsaraj K.,Vikram S.S. and Rayasa R.M. (2006). Industrial feasible alternative approaches in the manufacture of solid dispersions:A technical report. *America Association of Pharmaceutical Scientist; Pharmaceutical Science Technolgy,*31-38

Hasnain.M.S. and Nayak A.K. (2012). Solubility and dissolution enhancement of ibuprofen by solid dispersion technique using PEG 6000-PVP K30 Combination carrier. *Bulgarian Journal of Science Education*,21(1):118-132

Heun G., Lambor N. and Groning R. (1998). Experimental and molecular modeling studies on interactions between drugs and Eudragit RL/RS resins in aqueous environment. *Pharmaceutica Acta Helvetica* 73:57-62.

Howlader T.S, Chakarbarty K.J., Faisal S.K., Kumar U., Sarkar R. and Khan F.M. (2012). Enhancing dissolution profile of diazepam using hydrophilic polymers by solid dispersions technique. *International Current Pharmaceutical Journal*, 1(2):423-430.

Hsiu-O.H., Hue L.S., Tsuimin T., Ming T.S. (1996). The preparation and characterization of solid dispersions on pallets using a fluidized-bed system. *International Journal of Pharmaceutics*,139 (2):223-229

Huda N.H., Saffon N. and Jhanker Y.M. (2010). Dissolution enhancement of ibuprofen solid dispersions prepared with vinyl polymers by fusion method. *Stamford Journal of Pharmaceutical Sciences*,3(20:7-12

Itishree J.D., Hmansu B.S. and Suddhasaltya D. (2011). Enhancement of dissolution rate of piroxicam using solid dispersion with PEG 600 and Eudragit RL100. *Journal of Pharmacy Research*, 4(5):1473-1479

Kapoor B., Kaur R., Kour S. and Behl H.(2012) Solid Dispersion: An evolutionary approach for solubility enhancement of poorly water soluble drugs. *International Journal of Recent Advances in Pharmaceutical Research*, 2(2):1-16

.

Karavas E., Ktistis G., Xenakis A. and Georgarakis E. (2006). Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinylpyrrolidone. *European journal of Pharmaceutics and Biopharmaceutics,* 63:103-114.

Kaur J., Aggarwal G., Singh G. and Rana A.C. (2012). Improvement of drug solubility using solid dispersion. *International Journal Of Pharmaceutical Sciences*, 4(2): 47-53.

Kulkarni P.K., Dixit M., Panner S. and Achin J. (2012). Improvement of solubility and dissolution rate of Piroxicam by solid dispersion in PEG 4000. *International Research Journal of Pharmacy*, 3(4): 231-235.

Kumar A., Sahoo S.K., Padhee K., Kochar P.S., Sathapathy A. and Pathak N.(2011). Review on solubility enhancement techniques for hydrophobic drugs. *Pharmacie Globale*, 3(3): 1-7

Kumar S.D., Gupta V.B., Purohit S. (2012). Solubility improvement using solid dispersion strategy, mechanism and characterization: responsiveness and prospective way out. *International Research Journal of Pharmacy*, 2:55-60.

Kumari R., Chandel P. and Kapor A.(2013). Paramount role of solid dispersions in enhancement of solubility. *Indonesia Global Journal of Pharmaceutical sciences,* 3(1):78-89.

Leuner C and Dressman J (2000). Improving drug solubility for oral delivery using solid dispersions. *European Journal of Pharmaceutics and Biopharmaceutics,* 50: 47-60.

Lian Y. (2001). Amorphous pharmaceutical solids preparation, characterization and stabilization. *Advanced Drug Delivery Research*, 48:27-42

Li-Ping R., Bo Y.Y., Guang-Miao F. and Dan-ni Z. (2005). Improving the solubility of ampelopsin by solid dispersions and inclusion complexes. *Journal of Pharmaceutical and Biomedical Analysis*. 38:457-464.

Lin Y.C. and Chen X. (2005). Moisture sorption/ desorption/ resorption characteristics and its effects on the mechanical behaviour of the epoxy system. *Polymers,* 46:11994-12003

Lipinski C.A (2001). Avoiding investment in doomed drugs, is poor solubility an industry wide problem? *Current Drug Discovery,* 4: 17-19.

Meka A.K., Kumar K.M., Lakshmi P.K and Prasad G.S. (2012). Development and evaluation of solid dispersions formulated using cyclodextrins as carriers. *International Journal of Pharmaceutial Research and Development*, 3 (11):93-110.

Minhaz A., Rahman M., Ahsan Q.,Rahman H. and Chowdhury R. (2012). Enhancement of solubility and dissolution properties of clonazepam by solid dispersions. *Interanational Journal of Pharmacy and Life Science,* 3(3): 1510 – 1518.

Mohammed A.D. and Behzad T. (2007). Investigation of solid dispersion technique in improvement of physicochemical characteristics of ibuprofen powder. *Iranian Journal of Pharmaceutical Sciences,* 3(2):69-76.

Mohammed J., Dehghen M.H.G. and Shareef A. (2010). Enhancement of dissolution and anti inflammatory effect of meloxicam using solid dispersion. *International Journal of Applied Pharmaceutics,* 2(1) :22-28.

Muller R.H, Bohm B.H. and Grau J.(2000). Nanosuspensions: a formulation approach for poorly soluble and poorly bioavailable drugs. In: Wise D, editor. *Handbook of Pharmaceutical Controlled Release Technology*, 345–357.

Nadia S., Marzan J. and Naz H.H. (2011). Dissolution profile of ibruprofen solid dispersion prepared with cellulosic polymers and sugar by fusion method. *Stamford Journal of Pharmaceutical Sciences*.4(1) :31-37

Nash RA. Suspensions. In: Swarbrick J, Boylan JC, editors (2002). *Encyclopedia of Pharmaceutical Technology*. 2nd edition. Vol. 3. New York, NY, USA: Marcel Dekker; pp. 2045–303

Narang A. and Shrivastava A. (2002). Melt extrusion solid dispersion technique. *Drug Development Industrial Pharmacy,* 26(8):111-115

Nayak A. and Jain A. (2011). *In-vitro* and *in-vivo* study of poly(ethylene glycol) conjugated ibuprofen to extend the duration of action. *Scientia Pharmaceutica,* 79:359-363

Ofokansi K.C., Kenechukwu F.C., Isah A.B., Allagh T.S. and Anumeka O.O.(2012). Formulation and evaluation of solid dispersions based on Eudragit RS 100 and PEG 8000 for improved delivery of trandolapril. *African Journal of Pharmaceutical Research and Development*. 4(1): 38-42.

Parsad K.A., Narayanan N. and Rajalakshmi G. (2010) Preparation and evaluation of solid dispersion of terbinafine hydrochloride. *International Journal of Pharmaceutical Science,* 3:130-134.

Patel R., Patel N., Patel N.N. and Patel M.N. (2010). A novel approach for dissolution enhancement of Ibuprofen by preparing floating granules. *International Research Journal of Pharmaceutical Sciences,* 1(1): 57-64 .

Patravale V.B., Date A.A. and Kulkarni R.M. (2004). Nanosuspensions: a promising drug delivery strategy. *Journal of Pharmacy and Pharmacology,* 56(7):827–840.

Pignatello R., Marinella F., Guido G., Gabriella S., Maria A.V., Salvatore G., Marco G., Claudia F. and Giovanni P. (2001). Preparation, characterization and photosensitivity studies of solid dispersion of Diflunisal and Eudragit RS100 and RL 100. *International Journal of Pharmaceutics,* 218:27-42.

Poovi G., Umamahaswari M., Sharmila S., Kumar S. and Rajalakshmi N. (2013). Development of domperidone solid dispersions powders using sodium alginate as carrier. *European Journal of Applied Sciences,* 5(2):36-42.

Rahman M., Minhaz A., Ahsa Q., Rahman H. and Chowdhary R. (2011).Enhancement of solubility and dissolution properties of clonazepam by solid dispersions. *International Journal of Pharmacy and Life Sciences,* 3(3):1510-1518

Rahul M. P., Ajim H.M., Mangesh T. K., Anup M. A.and Dheeraj T. B. (2011) Solid dispersion: strategy to enhance solubility. *International Journal of Pharmaceutical Sciences Review and Research,* 8(2):12-16

Reena T. and Vandana D. (2012). Solid dispersion a fruitful approach for improving the solubility and dissolution rate of poorly soluble drugs. *Journal of Drug Delivery and Therapeutics,* 2(4):5-14

Rosario P., Maranilla F . and Giovanni P. (2002). Preparation of solid dispersions of NSAIDs with acrylic polymers and studies on mechanism of drugs polymer interactions. *America Association of Pharmaceutical Scientist; Pharmaceutical Science Technolgy,* 3(2): 1-11

Ruchi T., Gaurav T., Birendra S. and Avani K.R. (2009). Solid dispersion: an overview to modify bioavailability of poorly water soluble drugs. *International Journal of Pharmaceutical Technology Research* ,1(4): 1338-1349.

Sachin K.G., Subhash V.D., Purohit R.N., Kailas R.B. (2013). In vito –invitro evaluation of solid dispersions containing ibuprofen. *American Journal of Advanced Drug Delivery*, 1(1): 66-72

Saffon N., Uddin R., Huda H.N. and Kumar B.S. (2013). Enhancement of oral bioavailability of solid dispersions a review. *Journal of Applied Pharmaceutical Sciences*, 1(7):13-20

Sahin N.O. and Librowsk T. (2003). Investigations of anti inflammatory and analgesic activities of prednisolone solid dispersions prepared with skimmed milk. *Polish Journal of Pharmacology*, 55: 261-265

Saindane D.S., kulkarni A.S., Khande T.S and Patil M.D. (2011). Enhancing drug solubility and oral bioavailability using solid dispersions. A review. *International Journal of Biopharmaceutics*, 2(1):22-30

Sandip S., Mukesh B., Ashish R., Gutam M. and Mahesh N. (2013). An overview on the mechanism of solubility and dissolution rate enhancement in solid dispersions. *International Journal of Pharmaceutical Technology Research*, 5 (1):31-39

Satish P.K., Kalpesh S.W., Venkatesh B.P, Anup M.A. and Dheeeraj T.B. (2011). Strategies for solubility enhancement of poorly soluble drugs. *International Journal of Pharmaceutical Sciences Review and Research*, 8(2):74-80.

Shah S., Joshi S., Lin S. and Medan P.L. (2012). Preparation and characterization of spironolactone and solid dispersions using hydrophilic carriers. *Asian Journal of Pharmaceutical Sciences*, 7(1):40-49

Sekiguchi K. and Obi N.(1964). Studies on absorption of eutectic mixtures. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. *Chemical and Pharmaceutical Bulletin*, 9 : 866-872.

Serajuddin A.T. (1999). Solid dispersion of poorly water soluble drugs, early promises, subsequent problems and recent breakthrough. *Journal of Pharmaceutical Science*, 88(10):1058-1066

Sharma D., Soni M., Kumar S. and Gupta G.D. (2009). Solubility enhancement—eminent role in poorly soluble drugs. *Research Journal of Pharmacy and Technology*, 2(2):220–224.

Sharma D.K., Gupta V.B. and Purohit S. (2011). Solubility improvement using solid dispersion; strategy, mechanism and characterization:responsiveness and prospect way out. *International Research Journal of Pharmacy*, 2(1):55-60

Sharma P., Kapoor A. and Bhargava S. (2012). A Review on: Solubility Enhancement by Implementing Solid Dispersion Technique for Poorly Water Soluble Drug *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 3(1):23-28

Shukla M., Priyanka R., Ashish J. and Satish N. (2010). Enhanced solubility study of Glipizide using different solubilization techniques. *International Journal of Pharmaceutical Sciences,* 2(2):46-48

Singh D.P, Dhaked U. and Mishra A. M.(2010) Solid dispersions: promising future : A review. *International Journal of Drug Formulation and Research,* 1 (2): 65-82.

Singh S., Baghel R.S. and Yadav L. (2011). A review on solid dispersion. *International Journal of Pharmaceutical and Life Sciences,* 2(9): 1078-1095

Tachibana T. and Nakamura A. (1965). A method for preparing an aqueous colloidal dispersion of organic materials by using water-soluble polymers: dispersion of *β*-carotene by polyvinylpyrrolidone. *Colloid and Polymer Science*. 203(2):130–133.

Tapan K.G., Hemant B., Amit A. and Dulal K. (2010). Solubility enhancement of ibuprofen in the presence of hydrophilic polymer and surfactant. *International Journal Applied Biology and Pharmaceutical Technology*, 1:793-800

Ueda S., Tokunaga Y., Ibuki R. and Higaki k. (2006). Development of novel sustained-release system,disintegration controlled matrix tablet (DCMT) with solid dispersion granules of Nilvadipine(II): *In vivo* evaluation. *Journal of Controlled Release*, 112: 51-56.

Vemula V.R, Lagishetty V. and Lingala S. (2010). Solubility enhancement techniques *International Journal of Pharmaceutical Sciences Review and Research*, 5(1):41–51.

Vijayak S.G and Dinanath M. (2006) Analgesic, anti-inflammatory and ulcerogenic studies of meloxicam solid dispersions in rodents. *Iranian Journal of Pharmacology and Therapeutics,* 5(1) ;77-79.

Vogt M., Kunath K. and Dressman J.B. (2008). Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: comparison with commercial preparations. *European Journal of Pharmaceutics and Biopharmaceutics*, 68 (2):283–288.

Win L.C. and Sarfaraz N. (1971). Phase diagram and dissolution–rate studies on sulfathiazole – urea solid dispersions. *Journal of Pharmaceutical Science* 60 (9):1333-1338

Winter C.A., Risley E.A. and Nuss G.W. (1962). Carrageenan-induced oedema in hnd paw of rats as an assay for anti-inflammatory drugs. *Proceeding of the Society for Experimental Biology and Medicine*, 111:544-547.

APPENDICES

Appendix 1 : Calibration curve for ibuprofen

Conc (µg/ml)	Absorbance (nm)
0.1	0.567
0.05	0.277
0.025	0.125
0.0125	0.0626
0.00625	0.0312

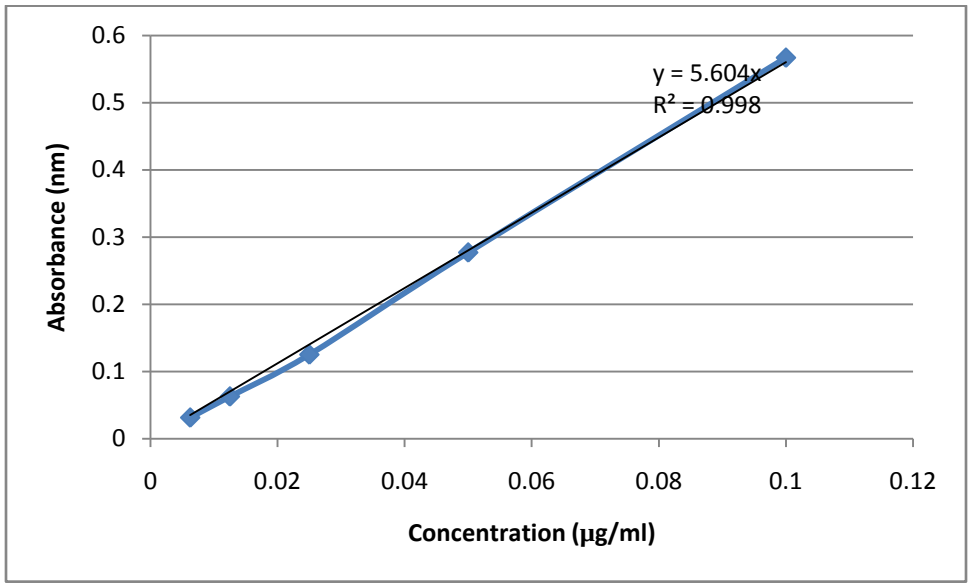


Figure A1: Calibration curve for ibuprofen

Appendix 2: Calibration curve for piroxicam

Conc (µg/ml)	Absorbance (nm)
0.02	2.76
0.01	1.638
0.005	0.822
0.0025	0.404
0.00125	0.188
0.000625	0.088
0.000313	0.031
0.000156	0.005

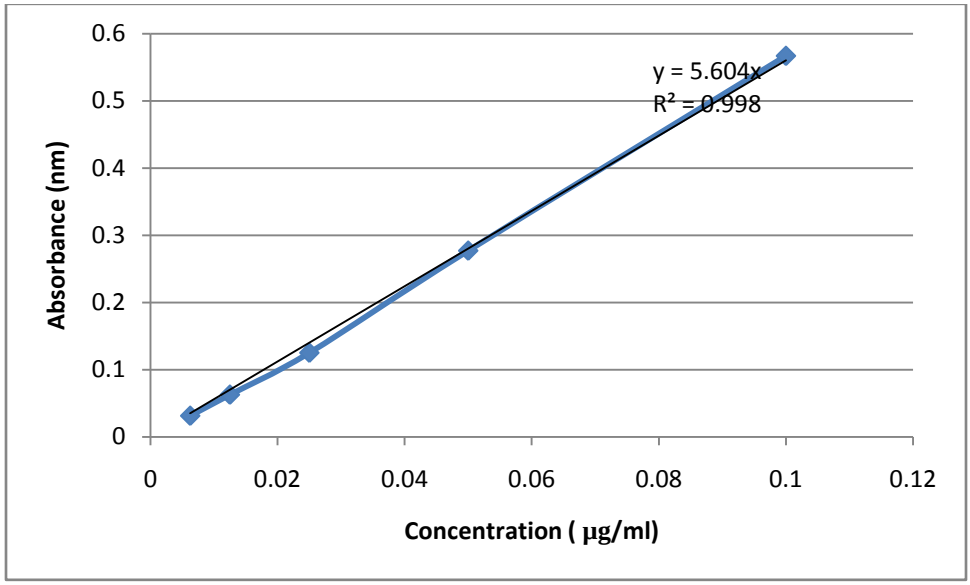


Figure A 2: Calibration curve for piroxicam

Appendix 3: Properties of ibuprofen/Eudragit RS 100 and HPMC solid dispersions

Code	Drug/polymer ratio	Loading	efficiency	Percentage of drug incorporated (%w/w)	Production yield (%)
		Theoretical drug content (% w/w)	Actual drug content (%w/w)		
IB 1	1:1:0	50.0	32.31	64.63 ± 0.30^{f}	91.0
IB 2	1:2:0	33.0	25.15	76.23 ± 0.54^{d}	76.0
IB 3	1:3:0	25.0	21.24	85.00 ± 0.61^{c}	59.0
IB 4	1:0:1	50.0	37.53	75.05 ± 0.74^{e}	80.0
IB 5	1:0:2	33.0	27.89	84.53 ± 0.83^{c}	84.0
IB 6	1:0:3	25.0	22.7	90.88 ± 0.41^{a}	92.0
IB 7	1:1:1	33.0	27.71	84.32 ± 0.89^{c}	81.0
IB 8	1:2:1	25.0	21.70	86.83 ± 0.41^{b}	86.0
IB 9	1:1:2	25.0	22.71	90.88 ± 0.41^{a}	75.0

Values are expressed as mean ± standard deviation. Means having different superscripts along the column are significantly different at $p < 0.001$.

Mean values were separated using Duncan's multiple range test (DMRT).

Appendix 4 : Properties of ibuprofen /Eudragit RS100 and HPMC solid dispersions incorporating trona

Code	Drug /polymer ratio (w/w)	Loading efficiency		Percentage of drug incorporated (%w/w)	Production yield (%)
		Theoretical drug content (%w/w)	Actual drug content (%w/w)		
IBT 0	1:1:1: 0	33.00	27.71	83.98 ± 0.18^{a}	81.00
IBT 1	1:1:1:0.1	32.70	26.51	82.81 ± 0.03^{b}	85.20
IBT 2	1:1:1:0.2	32.30	27.87	82.25 ± 0.08^{c}	85.50
IBT 3	1:1:1:0.3	31.70	28.08	81.85 ± 0.06^{cd}	86.10
IBT 4	1:1:1:0.4	31.25	28.68	81.39 ± 0.03^{d}	87.80

Values are expressed as mean ± standard deviation. Means having different superscripts along the column are significantly different at $p < 0.001$.

Mean values were separated using Duncan's multiple range test (DMRT).

Appendix 5 : Properties of piroxicam/Eudragit RS 100 and HPMC solid dispersions

Code	Drug/polymer ratio	Loading efficiency		Percentage of drug incorporated (%w/w)	Production yield (%)
		Theoretical drug content (% w/w)	Actual drug content (%w/w)		
PR 1	0.1:1:0	9.10	6.89	75.72 ± 3.14^{d}	92.7
PR 2	0.1:2:0	4.8	3.48	72.57 ± 2.23^{d}	90.4
PR 3	0.1:3:0	3.2	2.73	85.45 ± 2.93^{bc}	74.2
PR 4	0.1:0:1	9.1	7.58	83.34 ± 1.50^{c}	98.2
PR 5	0.1:0:2	4.8	4.21	87.85 ± 0.30^{b}	93.5
PR 6	0.1:0:3	3.2	3.04	95.24 ± 2.25^{a}	95.8
PR 7	0.1:1:1	4.8	4.66	97.29 ± 1.27^{a}	90.2
PR 8	0.1:2:1	3.2	2.86	89.58 ± 4.78^{b}	72.5
PR 9	0.1:1:2	3.2	2.45	76.87 ± 1.62^{d}	90.0

Values are expressed as mean ± standard deviation. Means having different superscripts along the column are significantly different at $p < 0.001$.

Mean values were separated using Duncan's multiple range test (DMRT).

Appendix 6: Properties of piroxicam/Eudragit RS 100 and HPMC solid dispersions incorporating trona

Code	Drug/polymer ratio (w/w)	Loading efficiency		Percentage of drug incorporated (%w/w)	Production yield (%)
		Theoretical drug content (% w/w)	Actual drug content (%w/w)		
PRT 0	0.1:1:1:0	4.80	4.60	97.28 ± 0.73	90.2
PRT 1	0.1:1:1:0.1	4.75	4.59	97.31 ± 0.03	93.0
PRT 2	0.1:1:1:0.2	4.74	4.60	97.32 ± 0.03	93.1
PRT 3	0.1:1:1:0.3	4.73	4.61	97.38 ± 0.02	95.0
PRT 4	0.1:1:1:0.4	4.72	4.60	97.42 ± 0.01	96.7

Values are expressed as mean ± standard deviation. Means having different superscripts along the column are significantly different at $p < 0.001$.

Mean values were separated using Duncan's multiple range test (DMRT).

Appendix 7: Moisture sorption and desorption of ibuprofen solid dispersions

Code	Weekly	changes	in mass	(g± SD)			
	1	2	3	4	5	6	7
IB 1	0.032	0.095	0.136	0.205	0.142	0.086	0.031
IB 2	0.054	0.112	0.185	0.338	0.201	0.104	0.045
IB 3	0.044	0.104	0.156	0.264	0.148	0.090	0.037
IB 4	0.135	0.182	0.356	0.728	0.348	0.181	0.128
IB 5	0.151	0.205	0.458	0.864	0.447	0.210	0.148
IB 6	0.123	0.164	0.244	0.568	0.235	0.158	0.112
IB 7	0.125	0.195	0.289	0.686	0.290	0.184	0.116
IB 8	0.065	0.128	0.201	0.345	0.199	0.115	0.055
IB 9	0.070	0.156	0.222	0.554	0.230	0.148	0.063

Appendix 8: Moisture sorption and desorption of ibuprofen solid dispersions containing trona

	Weekly	changes	in mass	(g± SD)			
Code	1	2	3	4	5	6	7
IBT 0	0.125	0.195	0.289	0.686	0.290	0.184	0.116
IBT 1	0.042	0.106	0.163	0.292	0.158	0.104	0.031
IBT 2	0.063	0.125	0.174	0.307	0.166	0.113	0.050
IBT 3	0.035	0.114	0.165	0.315	0.154	0.109	0.025
IBT 4	0.022	0.096	0.148	0.254	0.139	0.087	0.016

Appendix 9: Moisture sorption and desorption of piroxicam solid dispersions

Code	Weekly changes in mass (g± SD)						
	1	2	3	4	5	6	7
PR 1	0.064	0.165	0.312	0.437	0.303	0.170	0.071
PR 2	0.033	0.094	0.272	0.385	0.282	0.102	0.041
PR3	0.016	0.063	0.164	0.268	0.155	0.055	0.009
PR 4	0.167	0.255	0.365	0.685	0.356	0.243	0.156
PR 5	0.125	0.226	0.436	0.545	0.423	0.215	0.112
PR 6	0.109	0.145	0.218	0.358	0.202	0.156	0.103
PR 7	0.186	0.397	0.635	0.754	0.615	0.359	0.175
PR 8	0.045	0.105	0.129	0.339	0.113	0.094	0.033
PR 9	0.146	0.265	0.325	0.633	0.315	0.253	0.124

Appendix 10: Moisture sorption and desorption of piroxicam solid dispersion containing trona

Code	Weekly changes in mass (g± SD)						
	1	2	3	4	5	6	7
PRT 0	0.186	0.397	0.635	0.754	0.615	0.359	0.175
PRT 1	0.225	0.448	0.755	0.808	0.771	0.432	0.211
PRT 2	0.204	0.425	0.688	0.786	0.666	0.410	0.194
PRT 3	0.196	0.418	0.665	0.774	0.645	0.406	0.188
PRT 4	0.185	0.402	0.654	0.769	0.648	0.394	0.178

Appendix 11: Solubility of ibuprofen solid dispersions and Physical mixtures

Code	Solubility (mg/ml)		t-test	p-value
	solid dispersion	physical mixture		
IB 1	0.39 ± 0.023	0.32 ± 0.015	2.528	0.065
IB 2	0.80 ± 0.029	0.68 ± 0.020	3.343	0.029*
IB 3	0.39 ± 0.023	0.34 ± 0.006	1.941	0.124
IB 4	2.00 ± 0.16	1.89 ± 0.008	0.681	0.533
IB 5	2.62 ± 0.11	2.29 ± 0.005	2.898	0.044*
IB 6	1.50 ± 0.05	1.40 ± 0.008	1.882	0.133
IB 7	1.69 ± 0.06	1.52 ± 0.008	2.596	0.060
IB 8	0.79 ± 0.013	0.60 ± 0.012	10.585	< 0.001**
IB 9	1.38 ± 0.11	1.19 ± 0.005	1.722	0.160
Pure IB	0.31 ± 0.02	0.31 ± 0.020	0.000	1.000

* = significant difference exists at $p \leq 0.05$

Appendix 12 : Solubility of ibuprofen solid dispersion and physical mixture containing trona

Code	Solubility (mg/ml)		t-test	p-value
	solid dispersion	physical mixture		
IBT 0	1.69 ± 0.064	1.52 ± 0.008	2.596	0.060
IBT 1	0.49 ± 0.004	0.47 ± 0.003	4.382	0.012*
IBT 2	0.70 ± 0.005	0.59 ± 0.037	2.865	0.046*
IBT 3	0.76 ± 0.002	0.68 ± 0.012	6.651	0.003*
IBT 4	0.78 ± 0.003	0.63 ± 0.01	15.27	< 0.001**

* = significant difference exists at $p \leq 0.05$

Appendix 13: Solubility of piroxicam solid dispersion and physical mixture

Code	Solubility (mg/ml)		t-test	p-value
	solid dispersion	physical mixture		
PR 1	0.022 ± 0.0005	0.019 ± 0.0005	4.754	0.009**
PR 2	0.017 ± 0.0004	0.015 ± 0.0003	4.070	0.015*
PR 3	0.014 ± 0.0004	0.012 ± 0.0003	4.191	0.014*
PR 4	0.028 ± 0.0003	0.026 ± 0.0002	4.214	0.014*
PR 5	0.021 ± 0.0002	0.019 ± 0.0001	6.277	0.003**
PR 6	0.019 ± 0.0004	0.0180 ± 0.0001	3.370	0.028*
PR 7	0.029 ± 0.0006	0.0251 ± 0.0007	4.086	0.015*
PR 8	0.017 ± 0.0004	0.0156 ± 0.0003	2.911	0.044*
PR 9	0.025 ± 0.0006	0.0221 ± 0.0006	3.475	0.025*
Pure Drug	0.011 ± 0.0005	0.0113 ± 0.0005	0.000	1.000

* = significant difference exists at $p \leq 0.05$

Appendix 14 : Solubility of piroxicam solid dispersion and physical mixture containing trona

Code	Solubility (mg/ml)		t-test	p-value
	solid dispersion	physical mixture		
PRT 0	0.029 ± 0.001	0.025 ± 0.001	4.086	0.015*
PRT 1	0.033 ± 0.001	0.029 ± 0.002	3.420	0.027*
PRT 2	0.030 ± 0.002	0.029 ± 0.001	0.409	0.721
PRT 3	0.030 ± 0.003	0.028 ± 0.004	3.398	0.027*
PRT 4	0.030 ± 0.003	0.028 ± 0.004	4.450	0.011*

* = significant difference exists at $p \leq 0.05$

Appendix 15: Release profile of ibuprofen solid dispersion

	% Drug released				
Time (mins)	IB 2	IB 5	IB 7	IB	IB T3
0	0.00	0.00	0.00	0.00	0.00
15	5.10	24.50	20.53	6.20	22.52
30	5.35	29.44	24.53	6.60	27.80
60	6.69	33.67	26.76	7.58	29.20
90	7.58	40.14	31.22	8.25	32.10
120	8.02	44.60	35.68	9.80	36.80
180	39.25	69.50	53.50	34.5	45.72
240	41.48	74.98	57.95	38.13	50.18
300	43.71	75.38	60.02	39.90	54.64
360	45.94	80.29	62.00	41.48	59.11
420	61.75	86.50	71.00	43.93	63.55
480	65.50	90.30	75.80	46.15	68.00

Appendix 16: Release profile of piroxicam solid dispersions

Time (mins)	% Drug release				
	PR 1	PR 4	PR 7	PR	PRT1
0	0.00	0.00	0.00	0.00	0.00
5	5.70	21.30	7.60	4.30	19.00
15	8.40	21.80	11.75	7.60	19.50
30	9.00	28.55	15.25	9.85	20.95
60	11.25	34.45	29.40	13.55	24.75
90	14.85	41.75	32.20	14.50	30.10
120	16.95	51.75	34.45	15.75	41.55
180	24.05	55.60	34.80	33.00	45.00
240	25.10	65.40	38.75	35.50	48.45
300	28.35	67.35	41.85	39.30	50.90
360	37.70	73.55	51.40	44.15	53.30
420	40.45	76.15	52.10	45.35	54.00
480	41.85	78.05	55.20	46.55	56.78

Appendix 17: Release profile of piroxicam from various formulations

Tme (mins)	% drug release			
	PR 4 SD	PR	PR4 PM	Capsule
0	0.00	0.00	0.00	0.00
5	21.30	4.30	18.20	16.25
15	21.80	7.60	19.05	18.00
30	28.55	9.85	22.05	19.40
60	34.45	13.55	30.55	21.55
90	41.75	14.50	36.56	33.65
120	51.75	15.75	43.75	38.75
180	55.60	33.00	51.85	42.82
240	65.40	35.50	55.95	46.00
300	67.35	39.30	60.25	49.15
360	73.55	44.15	62.55	50.50
420	76.15	45.35	64.45	52.75
480	78.05	46.55	65.15	55.80

Appendix 18: Release profile of ibuprofen from various formulations

	% drug release			
Time (mins)	IB	IB5 PM	IB5SD	Tablet
0	0.00	0.00	0.00	0.00
15	6.20	17.00	24.50	11.20
30	6.60	20.25	29.44	15.35
60	7.58	26.30	33.67	20.48
90	8.25	32.46	40.14	23.85
120	9.80	36.51	44.60	25.98
180	34.5	53.25	69.50	40.25
240	38.13	65.75	74.98	42.31
300	39.90	68.20	75.38	44.47
360	41.48	72.35	80.29	45.82
420	43.93	74.42	86.50	48.12
480	46.15	76.52	90.30	50.27

Appendix 19: Anti inflammatory test of ibuprofen solid dispersion

	1 hr	2 hrs	3 hrs	4 hrs	5 hrs
Normal saline	1.59 ± 0.06^{a}	1.71 ± 0.06^{a}	1.73 ± 0.05^{a}	1.62 ± 0.11^{a}	1.56 ± 0.10^{a}
Pure ibuprofen	1.26 ± 0.02^{bc}	1.28 ± 0.02^{b}	1.21 ± 0.03^{b}	1.01 ± 0.03^{b}	0.97 ± 0.03^{b}
IB 5	1.13 ± 0.04^{c}	1.11 ± 0.04^{c}	1.04 ± 0.04^{c}	0.98 ± 0.04^{b}	0.92 ± 0.04^{b}
IB 2	1.32 ± 0.01^{b}	1.37 ± 0.02^{b}	1.15 ± 0.03^{bc}	0.92 ± 0.03^{b}	0.84 ± 0.03^{b}
IB 7	1.19 ± 0.12^{bc}	1.22 ± 0.02^{bc}	1.16 ± 0.02^{bc}	0.99 ± 0.07^{b}	0.88 ± 0.04^{b}

Values are expressed as mean ± standard deviation. Means having different superscripts along the column are significantly different at $p < 0.001$. Mean values were separated using scheffe post hoc test.

Appendix 20: Percentage inhibition of egg albumin induced oedema by ibuprofen solid dispersions

Time (hr)	IB	IB5	IB 2	1B7
1	20	28	16	24
2	25	35	18	29
3	30	39	33	34
4	37	39	43	41
5	39	42	47	44

Appendix 21: Anti inflammatory test of piroxicam solid dispersion

	1 hr	2 hrs	3 hrs	4 hrs	5 hrs
Normal saline	1.59 ± 0.06^{a}	1.71 ± 0.06^{a}	1.73 ± 0.05^{a}	1.62 ± 0.11^{a}	1.56 ± 0.10^{a}
Pure Piroxicam	1.18 ± 0.03^{b}	1.20 ± 0.03^{c}	1.13 ± 0.04^{b}	0.96 ± 0.05^{b}	0.90 ± 0.05^{b}
PR 1	1.30 ± 0.03^{b}	1.39 ± 0.02^{b}	1.16 ± 0.03^{b}	0.93 ± 0.03^{b}	0.82 ± 0.03^{b}
PR 4	1.13 ± 0.04^{b}	1.11 ± 0.04^{c}	1.04 ± 0.04^{b}	0.98 ± 0.04^{b}	0.92 ± 0.03^{b}
PR 5	1.18 ± 0.02^{b}	1.20 ± 0.01^{c}	1.13 ± 0.01^{b}	0.96 ± 0.04^{b}	0.91 ± 0.03^{b}

Values are expressed as mean ± standard deviation. Means having different superscripts along the column are significantly different at $p < 0.001$. Mean values were separated using scheffe post hoc test.

Appendix 22: Percentage inhibition of egg albumin induced oedema by piroxicam solid dispersions

TIME (HR)	PR	PR4	PR1	PR7
1	19	28	16	25
2	25	35	18	30
3	30	39	33	35
4	37	40	43	41
5	39	42	49	43