FORMULATION AND EVALUATION OF FELODIPINE SOLID DISPERTIONS

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DECLARATION

I hereby declare that the dissertation work entitled "**FORMULATION AND EVALUATION OF FELODIPINE SOLID DISPERSIONS"** is based on the original work carried out by me in Annai Veilankanni's Pharmacy College, Saidapet**,** Chennai & Formulation R&D, AUROBINDO PHARMA LTD, HYDERABAD under the guidance of **Mr.M.PRADEEP** for submission to THE TAMILNADU Dr.M.G.R Medical University in the partial fulfillment of the requirement for the award of Degree Master of pharmacy in Pharmaceutics. The work is original& has not been submitted in part or full for any other diploma or degree of this or any university. The information furnished in this dissertation is genuine to the best of my knowledge and belief.

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LIST OF ABBREVIATIONS

^{o}C	Temperature on celcius scale
DSC	Differential scanning colourimetry
DE	Dissolution efficiency
DP	Percent dissolved
Fig	Figure
FTIR	Fourier transform infrared spectroscopy
G	Gram
HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropyl methyl cellulose
KM	Kneading method
MDT	Mean dissolution time
Min	Minutes
Mg	Milligram
Ml	Millilitres
PEG	polyethylene glycol
PVP	Polyvinyl pyrrolidone
PMs	Physical mixtures
PKa	Dissociation Constant
Ph	Negative logarithm of hydrogen ion concentration
RDR	Relative dissolution rate
SD	Standard deviation
SDs	Solid dispersions
SEM	Scanning electron microscope
XRD	X-ray diffraction
UV	Ultra violet
w/w	Weight by weight
λ max	Wavelength maximum
Vs	Verses
µg	Microgram

ABSTRACT

Objectives: Felodipine is used as an antihypertensive and antianginal drug, widely used orally in the treatment of hypertension. The model drug belongs to BCS class II and undergoes extensive first-pass metabolism with a bioavailability of only about 15%. Hence this work was planned to improve the oral bioavailability of felodipine by increasing its solubility and dissolution characteristics through the solid dispersion technique using polyethylene glycol (PEG 4000) and hydroxypropyl cellulose (HPC) as carriers.

Methods: Solid binary systems of felodipine were prepared with PEG 4000 by solvent deposition (SD) and kneading method (KM) at different drug:carrier ratios of 1:1, 1:3 and 1:5. Then ternary systems were prepared with the addition of different concentrations of HPC to felodipine-PEG 4000 binary systems to investigate the effect of hydrophilic polymer on the solubility and dissolution rate of the felodipine. Solid binary and ternary systems were characterized by drug content, FT-IR, XRD and in vitro dissolution test using USP dissolution test apparatus Type II (paddle method) in dissolution medium of 0.1N HCl. The in vitro dissolution results of all preparations were computed by using dissolution software PCP DISSO V3.

Results: All prepared solid binary and ternary systems were found to be fine and free flowing. Low standard deviation (SD) values (i.e., < 1) indicated uniform drug distribution in all prepared batches. FT-IR studies indicated the possibility of intermolecular hydrogen bonding between amide group of the felodipine and hydroxyl group of the PEG 4000. The XRD results indicated the significant reduction in felodipine crystallinity in the solid binary and ternary systems. The DE_{30} and DE_{60} values of the solid binary systems prepared by the kneading and solvent deposition methods were relatively high ($P < 0.01$) compared to the values rom the physical mixtures (PMs) and felodipine alone. The overall the rank order of improvement in dissolution properties of felodipine with different methods in all ratios was KM > SD > PMs > felodipine. All ternary systems exhibited a significant increase in dissolution

rate with respect to the PMs and the reference drug. The value of T_{50} and MDT of all solid binary and ternary systems were lower than felodipine alone. It was noted that the dissolution was progressively increased with increasing concentration of carriers in both binary and ternary systems. The release pattern in felodipine, PMs and all solid binary and ternary systems showed best fit into first-order with highest 'r' (correlation coefficient) values.

Conclusions: Solid binary and ternary systems of felodipine prepared with PEG 4000 and HPC were found to be effective in improving the solubility and dissolution rate of the model drug. Enhanced dissolution of felodipine from solid binary and ternary systems could be mainly attributed to the particle size reduction as well as decreased drug crystallinity (demonstrated by XRD). The study revealed that optimum ratios of hydrophilic carriers ensure a prompt and complete dissolution of felodipine from solid binary and ternary systems that are used in oral pharmaceutical formulations.

Keywords: Felodipine, polyethylene glycol (PEG 4000) and hydroxypropyl cellulose (HPC), solid binary and ternary systems.

INTRODUCTION

1.1 Drug solubility

Solubility enhancement of poorly water-soluble drugs is a crucial issue to improve their solubility and bioavailability. In recent years, due to application of combinational chemistry and high throughput screening during drug discovery, a majority of new drug candidates exhibits poor aqueous solubility. Such compounds are very challenging for formulation scientists in developing bioavailable dosage forms. Poorly water soluble compound has classically been defined as one dissolving in less than 1 part per 10000 part of water[1]. A poorly water soluble drug, more recently, has been defined in general terms to require more time to dissolve in the gastrointestinal fluid than it takes to be absorbed in the gastrointestinal tract[2]. Thus a greater understanding of dissolution and absorption behaviours of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products.

Consideration of the modified Noyes-Whitney equation provides some hints as to how the dissolution rate of poorly soluble compounds might be improved to minimize the limitations to oral bioavailability.

$$\frac{dc}{dt} = \frac{AD(C_s - C_b)}{hV}$$

Where, dc/dt = Rate of dissolution

A = Surface area available for dissolution

D = Diffusion coefficient of the compound 2

C_s = Solubility of the compound in the dissolution medium

C_b = Concentration of drug in the medium at time

h = Thickness of the diffusion boundary layer adjacent to surface of the dissolving compound

V = Volume of dissolution media

The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound to decrease the boundary layer thickness, to ensure sink conditions for dissolution and last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions.

1.2 Various approaches to improve the solubility[3]

I. Physical modifications

A. *Particle size:* Micronization and Nanosuspensions

B. *Modifications of the crystal habit:* Polymorphs and Pseudopolymorphs (including solvates)

C. *Complexation/solubilization:* Use of surfactants and cyclodextrins

D. *Drug dispersion in carriers:* Eutectic mixtures, solid dispersions (non-molecular) *and* solid solutions

II. Chemical modification

This includes soluble prodrugs**,** salt formation and covalent polymer drug conjugates.

1.3 Solid dispersions (SDs)

The formulation of hydrophobic drugs as SDs is a significant area of research aimed at improving their dissolution and bioavailability. Solid dispersions consisting of two components in the solid state are referred to as binary systems. The two components are a water-soluble carrier and a hydrophobic drug dispersed in the carrier substance[4]. Solid dispersion method of improving the dissolution rate of poorly soluble drugs was first proposed sekiguchi K and Obi N[5]. It is a unique

approach to present a poorly soluble drug in an extremely fine state of subdivision in gastrointestinal fluids. The term 'solid dispersion' has been utilized to describe a family of dosage forms whereby one or more active ingredient is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability.

Chiou and Riegelman[6] defined the term solid dispersion as **'the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method'.** While Corrigan[7] suggested the definition as **'product formed by converting a fluid drug-carrier combination to the solid state'**

Several insoluble drugs have been shown to improve their dissolution character when incorporated into solid dispersion. SDs releases the drug through different mechanisms, and the rate of release of drug to the surrounding fluid is mainly dependent on the type of solid dispersion formed[8,9]. Solid dispersion technique has been widely employed to improve the dissolution rate, solubility and oral adsorption of poorly water soluble drugs[10,11].

1.3.1 Classification of SDs[12]

On the basis of release mechanisms and molecular arrangement in the matrix, SDs are distinguished into following types,

Simple eutectic mixture: Eutectic mixture is prepared by rapid solidification of fused melts of two components that show a complete liquid miscibility with negligible solid-solid solubility. It involves loose atomic or molecular interaction and not on the formation of chemical bond. When the eutectic mixture is exposed to gastrointestinal fluids, both the poorly soluble drug and the carrier may simultaneously crystallize out as a very small particles resulting in increased the surface area and improved dissolution and absorption of drug.

Solid solutions: A solid solution represents a homogenous one phase system, where the solid solution is dissolved in a solid solvent and the two components crystallize together. The solid solution achieves faster dissolution than a eutectic mixture because the drug particles in a solid solution are reduced to molecular size and dissolution of the drug takes place in the solid state prior to the exposure to the liquid medium. According to the extent of miscibility between the two components or the crystalline structure of the solid solution, it is further classified into continuous, discontinuous, substitutional and interstitial solid solution.

Continuous solid solution*:* The two components in this system are miscible in all proportions. The fast dissolution properties of such system may be attributed to the presence of small amount of solute carrier in the crystalline lattice of the poorly soluble drug.

Discontinuous solid solution*:* In this system, there is a limited solubility of a solute in solid solvents. Each component is capable of dissolving the other component to a certain degree above the eutectic temperature.

Substitutional solid solution*:* In this system, the solute molecules substitutes for the solvent molecules in the crystal lattice of the solid solvent. It can form a continuous or discontinuous solid solution.

Interstitial solid solution: In this system, solute molecules occupy the interstitial space of the solvent lattice. Water soluble carrier with higher molecular weight such as PEG 4000, PEG 6000 and PEG 12000 were employed for this purpose. Several scientists have reported faster dissolution of drugs from solid dispersion based on this
method.

Glass solution: It is a homogenous glassy system in which a solute dissolves on glassy solvent results in increased dissolution and absorption of the drug. It is characterized by a transparency and brittleness below the glass forming temperature. Glass solution is a metastable and strength of the chemical bonding is

much less as compared to solid solution. Therefore, the release of the drug was found to be faster than solid solution.

Amorphous precipitations in crystalline carrier: Amorphous form of a drug produces faster dissolution rate. The drug may precipitate out in an amorphous form in a crystalline carrier from solid dispersions prepared by melting or solvent method. A strong interaction between the drug and carrier resulting in the formation of channels with in the matrix seems to be a possible mechanism for improved dissolution of drug.

Compound or complex formation: The formation of complex between the drug and the carrier may either decrease or increase the dissolution and absorption rate of drug. The formation of soluble complex with low association constant resulted in increased rate of dissolution and absorption.

1.3.2 Preparation techniques of SDs [13, 14]

Solvent evaporation method: In this method, physical mixture of two components (drug and carrier) are dissolved in a common solvent and followed by the evaporation of solvent. The advantages of this method are low temperature requirement for the preparation of dispersion and thermal decomposition of drugs and carriers can be prevented. The higher cost of production, incomplete removal of solvent, adverse effects of solvent on the chemical stability of the drug and selection of common solvent are the drawbacks of this method.

Melting method (Fusion method): The physical mixture of drug and water soluble carrier was heated to melt and the molten mixture was then cold and solidified mass was crushed, pulverized and sieved. The melting point of a binary system depends on its composition and proper manipulation of drug carrier ratios. Decomposition should be avoided due to fusion time and rate of cooling.

Kneading method: The physical mixture of drug and carrier were triturated using small quantity of organic solvent and water mixture, usually alcohol and water (1:1w/w). The slurry is kneaded for 45 minutes to 1 h and dried at 45^{o}C. The dried

mass is pulverized and sieved through sieve no 60 and the fraction was collected. The advantages of this method are low temperature requirement for solid dispersion preparation, less usage of organic solvent[11] and avoidance of thermal degradation of the drug.

Melting solvent method: This method involves dissolving the drug in a suitable solvent and incorporation of the solution directly into the molten carrier. This method possesses the advantages of both solvent and melting methods.

Spray drying: Spray drying technique finds more important utility in the pharmaceutical industry due to rapid drying and specific physical characters such as particle size and shape of the product. It consists of dissolving or suspending the drug and carrier, then spraying it into a stream of heated air flow to remove the solvent. It is a cost effective process as compared to that of freeze drying resulting in the production of fine solid particles. The operation conditions and design of the drier depends upon the drying characteristics of the product and powder specifications. Spray drying technique is useful to obtain spherical particles with narrow distribution.

Lyophillization technique: This technique is an alternative to solvent evaporation method. Here the drug and carrier are dissolved in common solvent, frozen and sublimed to obtain lyophilized molecular dispersion.

Melt agglomeration process: This technique is used to prepare solid dispersion where a binder acts as a carrier. The solid dispersion is prepared by heating binder, drug and excipient to a temperature above the melting point or spraying the dispersion of drug in the molten binder on the heated excipients using a high shear mixer. The effect of binder type, method preparation and particle size are the critical factors influencing the solid dispersion preparation by this method. These parameters results in various dissolution rates, mechanism of agglomerate formation and growth, agglomerate size and distribution.

Supercritical fluid methods: Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an anti-solvent. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. This technique does not require the use of organic solvent and since CO_2 is considered environmentally friendly, this technique is referred to as 'solvent free'. This technique is known as Rapid Expansion of Supercritical Solution (RESS). However, the application of this technique is very limited, because the solubility of CO_2 of most pharmaceutical compounds is very low.

Co-precipitation method: In this process, a non-solvent is added drop wise to the drug and carrier solution under constant stirring. In the course of the non-solvent addition, the drug and carrier are co-precipitated to form microparticles. At the end, the resulted microparticles suspension is filtered and dried.

Spin-coated films: This is a new process to prepare SDs by the solvent evaporation method, which consists of dissolving drug and carrier in a common solvent that is dropped onto a clean substrate highly spinned. Solvent is evaporated during spinning. This process is indicated to moisture sensitive drugs since it is performed under dry conditions.

1.3.3 Mechanism of drug release from SDs:

The possible mechanisms of enhanced dissolution from SDs include one or more of the following[6],

Reduction in particle size and agglomeration: Reduction in particle size and agglomeration increases the exposed surface area of the drug. Size reduction has been classically considered to be a result of eutectic or solid solution formation; it is worth noting that this mechanism suggests an intrinsic link between solid state

structure and release. Similarly it has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for SDs may have some wetting properties; hence it is reasonable to suggest that improved wetting may lead to reduced agglomeration and hence increased surface area.

Increased solubility or dissolution rate of the drug: Many of the carriers used may increase the solubility of the drug. Similarly, the carrier and drug may form a soluble complex, as established in case of cyclodextrins. Also, changes to the physical properties of the drug such as degree of crystallinity and polymorphic form may also be considered under this category.

Conversion of crystalline drug into amorphous form: Since the amorphous form is the highest energy form of a pure compound, it produces faster dissolution.

1.3.4. The advantageous properties of SDs[15]

Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability.

Particles with reduced particle size: Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability.

Particles with improved wettability: Strong contribution to the enhancement of drug solubility is related to the drug wettability improvement in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts,

when used, can significantly increase the wettability properties of drugs. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects recently, the inclusion of surfactants in the third generation solid dispersions reinforced the importance of this property.

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. The increased porosity of solid dispersion particles also hastens the drug release profile.

Drugs in amorphous state: Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. 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. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form.

1.3.5 Methods of characterization of SDs[16]

The SDs can be studied and characterized in two ways as follows,

In solution state: Solubility studies, Dissolution studies, UV-spectral studies, and ^{1}H NMR studies.

In solid state: Microscopic methods including polarization microscopy and scanning electron microscopy (SEM), thermo analytical methods which includes differential scanning calorimetry (DSC) and hot stage microscopy (HSM), thermo gravimetric analysis (TGA)**,** spectroscopic methods i.e., fourier transform infrared spectrometry (FTIR) and powder X-ray diffractometry (PXRD).

1.3.6 Carriers used for solid dispersions[16]

A large number of different materials have been examined as potential carriers to prepare solid dispersions. These are summarized in **table1.** All carriers differ widely in their physical and chemical properties. The properties of the carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier chosen for SDs should be freely water soluble, soluble in a variety of solvents, non toxic, chemically, physically and thermally stable, compatible with the drug and pharmacologically inert.

Table1: Various carriers used in SDs

S.No	Nature of carrier	Name of the carrier
1.	Sugars	Dextrose, sorbitol, sucrose, fructose, maltose, galactose, xylitol, mannitol and lactose.
2.	Acids	Citric acid, tartaric acid and succinic acid
3.	Polymorphic materials	Polyvinylpyrrolidone (PVP), polyethylene glycols (PEG4000,6000), hydroxyl propyl methyl cellulose (HPMC), guargum, xanthan gum, sodium alginate, methyl cellulose, pectin, hydroxylethylcellulose (HEC), hydroxyl propyl cellulose (HPC) and dextrins.
4.	Insoluble or enteric polymer	Hydroxypropylmethylcellulosepthalate, Eudragit RL, Eudragit L100, Eudragit S100, Eudragit RS.
5.	Surfactants	Polyethylene stearate, poloxamer 188, tweens and spans.
6.	Miscellaneous	Nicotinic acid, succinamide, dextrin's, gelatin, polyvinyl alcohol,urea,cyclodextrins etc.

2. LITERATURE REVIEW

Pawar S et al[17] studied the SDs of felodipine with polyvinylpyrrolidone (PVP K30) and HPMC K4M prepared by solvent evaporation method. The FTIR study revealed no chemical interaction between felodipine and carriers used. The XRD and DSC studies confirmed the transformation of crystalline form of felodipine into the amorphous form. The *in vitro* dissolution studies showed that the solid dispersion of felodipine:PVP:K30 with the 1:3 ratio enhanced the solubility of felodipine.

Dong-Han W et al[18] studied the SDs of felodipine with HPMC and surfactants by the conventional solvent evaporation (CSE) and supercritical anti-solvent precipitation (SAS) methods. The solid dispersion particles were characterized by particle size, zeta potential, SEM, DSC, powder XRD, solubility and dissolution studies. The effects of the drug:polymer ratios and surfactants on the solubility of felodipine were studied. The SDs from the SAS process showed a high dissolution rate of felodipine about 90% within 2 h.

Mohamed HG et al[19] investigated the effect of different types of carriers on *in vitro* dissolution of meloxicam. Meloxicam SDs were prepared by physical mixing, co-grinding and solvent evaporation methods with PEG 6000. The effect of solubilisation by sodium lauryl sulphate (SLS) was also studied. The maximum *in vitro* dissolution of meloxicam, i.e. 97.45% in 60 min, was observed for SDs containing meloxicam (150 mg), PEG 6000 (350 mg) and SLS (75 mg) prepared by solvent evaporation method.

Kim EJ et el[20] prepared and evaluated felodipine SDs (solvent wetting method) in the presence of various carriers. The results of XRD and thermal analysis indicated that the drug was in the amorphous state when PVP, HPMC, and poloxamer were used as carriers. The dissolution rates of felodipine in PVP, HPMC, or poloxamer SDs were much faster than those for the corresponding PMs. However, dissolution profiles were found to depend on the carrier used. The dissolution rate of felodipine increased slowly for SDs prepared using HPMC,

whereas rapid initial dissolution rates were observed for SDs prepared using PVP or poloxamer. Increases in dissolution rates were partly dependent on the ratios of felodipine to carrier. The results indicated that no significant changes in crystal form were observed by XRD or thermal analysis, and also no significant changes in dissolution rate were observed when sorbitol and mannitol were used as carriers.

Markus V et al[21] prepared and investigated solid dispersion systems of four poorly soluble drugs (EMD 57033, albendazole, danazol and felodipine) by cogrinding with lactose monohydrate, corn starch, PVP, HPMC and SLS using a jet milling technique. A solid state characterization study was done by XRD and DSC. The results suggested that the cogrinding with selected excipients would be a powerful tool to accelerate the dissolution of poorly soluble drugs without converting the drug to the amorphous form or changing the particle size.

Bosca MT et al[22] studied flunarizine SDs prepared with PEG 4000 at different ratios. The physicochemical characterizations of SDs were investigated by FT-IR, XRD, DSC and solubility in equilibrium. The FT-IR results suggested that no chemical interaction between flunarizine and PEG 4000. The XRD patterns confirmed the decrement in crystallinity at certain proportions and DSC indicated the formation of eutectic mixture. Equilibrium solubility studies showed that drug solubility was enhanced as the polymer content in the samples increased.

Moreshwar PP et al[23] studied gliclazide and PEG 4000 SDs by melting or fusion method. The *in vitro* dissolution studies showed that PEG was found to be effective in increasing the dissolution of gliclazide in SDs when compared to pure drug. FT-IR, DSC and XRD studies were carried out in order to characterize the drug in the PMs and SDs. The results indicated that dissolution enhancement was attributed to decreased crystallinity of the drug and also due to the wetting and solubilizing effect of the carrier from the gliclazide SDs.

Vijaya Kumar SG et al[24] prepared solid dispersion systems of meloxicam with PEG 6000 by solvent evaporation method. The formulations were characterized by solubility studies, DSC, FT-IR and *in vitro* dissolution rate studies. FT-IR studies

indicated the possibility of hydrogen bonding with the polymer. The DSC and powder XRD demonstrated the presence of polymer as eutectic (crystalline, amorphous or a mixture of both) mixture. The overall results confirmed that SDs of meloxicam demonstrated higher drug dissolution rates than PMs and meloxicam alone.

Sethia S et al[25] studied carbamazepine (CBZ) solid dispersions prepared by conventional solvent evaporation versus a supercritical fluid method. The SDs of carbamazepine in PVP K30 with Gelucire 44/14 or Vitamin E TPGS, NF (D-α-tocopheryl polyethylene glycol 1000 succinate) were characterized by intrinsic dissolution, DSC, powder XRD and FT-IR. The CBZ/PVP K30 and CBZ/PVPK30/TPGS SDs showed increased dissolution rate. Thermograms of various SDs did not show the melting peak of CBZ, indicating that CBZ was in amorphous form inside the carrier system. This was further confirmed by XRD studies. FT-IR studies showed interaction between CBZ and PVP K30 in solid dispersion.

Masoud RJ et al[26] prepared SDs of miconazole nitrate (MN), using three different water soluble excipients PEG 6000, PVP-10,000 and urea by fusion or coprecipitation from ethanol. A seven-fold increase in the dissolution rate of MN was achieved with both PEG and urea, while the dispersion of MN in PVP resulted in only two fold enhancement.

Venkatesh Kumar K et al[27] attempted to improve the solubility and dissolution rate of a poorly soluble drug, valsartan by solid dispersion method using skimmed milk powder as carrier. Four different formulations were prepared with varying drug: carrier ratios of 1:1, 1:3, 1:5 and 1:9. The formulations were characterized for solubility parameters, drug release studies, phase solubility studies, XRD, FT-IR and TLC analysis. All prepared formulations showed marked improvement in the solubility behavior and improved drug release. Formulation containing drug:polymer ratio of 1: 9 showed the best release as compared the pure drug. The analytical studies confirmed no interaction between the drug and the carrier. It was concluded that skimmed milk powder could be utilized as a carrier to improve the solubility of poorly soluble drugs.

Shinde SS et al[28] investigated SDs of aceclofenac prepared by solvent evaporation method and compared the effectiveness of hydrophilic polymer such as PVP-K30, HPMC E-5 and Aerosil 200. The resultant complexes were evaluated for drug content, FT-IR, XRD and dissolution studies. The present study was successfully utilized the solvent evaporation method for preparation of stable, amorphous SDs of aceclofenac by encapsulation with hydrophilic carrier with adsorbents agent. The results revealed that batch prepared at 1:1:2 ratios of drug: PVPK30:aerosil showed maximum release in phosphate buffer of pH 6.8.

Arora SC et al[29] investigated the cefixime trihydrate solid dispersion prepared with urea by solvent evaporation method to increase its solubility and dissolution rate. Physical mixtures and SDs of cefixime trihydrate were prepared by using urea as water-soluble carrier in various proportions (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7 by weight). The drug release profile was studied and it was found that the dissolution rate and the dissolution parameters of the drug from the physical mixture as well as solid dispersion were higher than those of the intact drug. FT- IR studies revealed no chemical incompatibility between drug and urea.

Ahire BR et al[30] investigated to improve the solubility of nevirapine by solid dispersion techniques using PVP K30 as carrier by physical mixing, solvent evaporation and kneading method. The interaction of the nevirapine with PVP K30 was evaluated by the FTIR spectroscopy, DSC and XRD. The results from the FT-IR and XRD analyses showed that solid dispersion might exist in the amorphous form. A DSC results showed that the sharp melting point was completely disappeared suggested that the nevirapine was molecularly dispersed in an amorphous form. Saturation solubility and dissolution studies indicated that dissolution rate was remarkably increased in solid dispersion as compared to the physical mixture and drug alone.

AIM AND OBJECTIVES OF THE STUDY

Aim of the study

In recent years, the number of poorly soluble drug candidates has increased tremendously and formulation of such poorly soluble drugs for oral delivery presents a great challenge to the formulation scientists. Solubility behaviour of a drug is one of the key determinants of its oral bioavailability. Most useful remedy to overcome the inherent difficulties associated with the formulation and development of a poorly water soluble drug is to enhance its solubility. Different approaches have been developed to enhance the drug release and dissolution rate of poorly water soluble drugs. Among them, the solid dispersion method is the most effective technique to improve the aqueous solubility and the dissolution of poorly water soluble drugs. Hence the present study was planned to improve the solubility and dissolution rate of felodipine (a poorly soluble drugs) through solid dispersion technique.

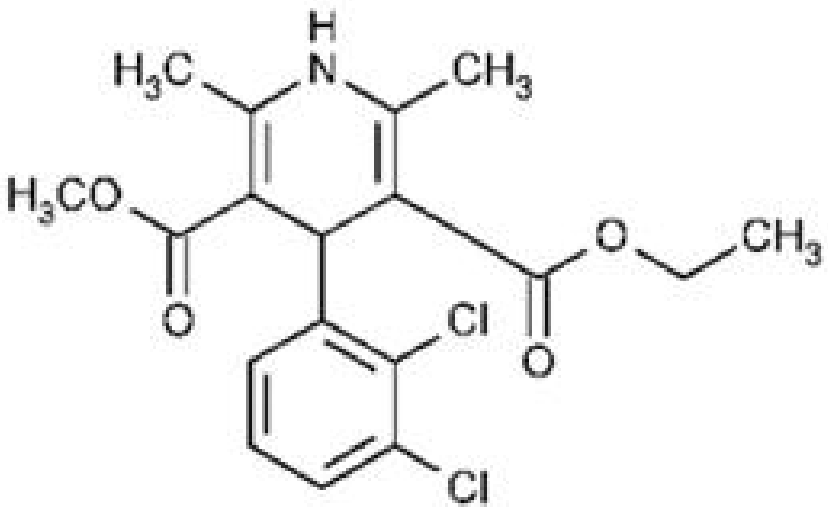
Study objectives

Felodipine is used as an antihypertensive and antianginal drug, widely used orally for the treatment of hypertension. The model drug belongs to BCS class II drug (low solubility and high permeability). It undergoes extensive first-pass metabolism with a bioavailability of only about 15%. The major drawback in the therapeutic application and efficacy of felodipine as oral dosage form is its low aqueous solubility. Hence this work was planned to improve solubility and dissolution characteristics of felodipine using PEG 4000 and HPC as hydrophilic carriers through solid dispersion technique.

DRUG PROFILE[31-35]

Felodipine: Felodipine is a dihydropyridine calcium-channel blocker, used alone or with an angiotensin-converting enzyme inhibitor to treat hypertension, chronic stable angina pectoris and Prinzmetal's variant angina. It lowers blood pressure by reducing peripheral vascular resistance through a highly selective action on smooth muscle in arteriolar resistance vessels.

Physicochemical Properties



Chemical name : (±)-Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5 pyridinedicarboxylate

Molecular formula : $C_{18}H_{19}Cl_2NO_4$

Molecular weight : 384.25

Category : Antihypertensive and antianginal drug

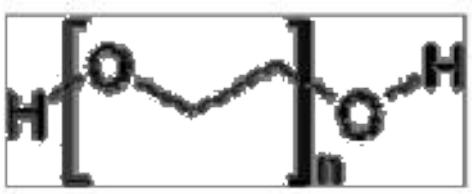
Description : Slightly yellowish and crystalline powder

S**torage** : It should be stored in light resistant container in a cool place.

Solubility	**:**	It is insoluble in water and freely soluble dichloromethane and ethanol
Experimental Log P	**:**	3.8
Predicted Log P	**:**	4.36
Melting point	**:**	142 to145^{o}C
Pharmacokinetic data		
Oral bioavailability	**:**	15%
Urinary excretion	**:**	1%
Plasma protein binding	**:**	99%
Clearance	**:**	0.8 L/min
Volume of distribution	**:**	10 L/Kg
Half-life	**:**	11 h
Dose	**:**	2.5 to 10 mg daily
Mechanism of action	**:**	Felodipine inhibits the influx of extra cellular calcium across the myocardial and vascular smooth muscle cell membranes blocking the calcium channels. The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased after load.

Polymer profile

Polyethylene glycol (PEG 4000)[36-38]: PEG 4000 is a high molecular weight polymer of ethylene oxide and is a blend of polymers with different degrees of polymerisation.



Synonyms **:** Carbowax, macrogol.

Molecular formula **:** $HO\text{-}CH_2\text{-}(CH_2\text{-}O\text{-}CH_2\text{-})_n\text{-}CH_2\text{-}OH$

Molecular weight **:** 3500-4500

Solubility: It is readily soluble in water, soluble in methanol, benzene, and dichloromethane and insoluble in diethyl ether and hexane.

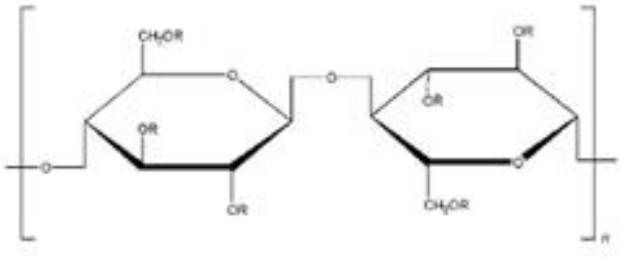
Melting point **:** 53°C to 56°C

Storage **:** It should be stored under dry conditions and in sealed containers

Uses: PEG is used as an excipient in pharmaceutical products**.** It is used as tablet binder, adhesive agent, plasticizer and lubricating agent.

Hydroxylpropyl cellulose (HPC)[39-44]: HPC is partially substituted poly (hydroxy propyl) ether of cellulose. It is non-ionic water-soluble cellulose ether with a versatile combination of properties. It combines dual solubility in aqueous and polar organic solvents, thermoplasticity and surface activity. HPC is used in pharmaceutical formulations for various purposes. Low-viscosity grades are used as

tablet binders in immediate release dosage forms and medium and high viscosity grades are used in sustained release matrix formulations.



R is H or $[CH_2CH(CH_3)O]_mH$

Chemical name: Cellulose, 2 -hydroxy propyl ether

Synonyms: Cellulose, hydroxypropyl ether, hyprolose, Klucel and Methocel.

Molecular weight: 50000 - 1250000

Description: It is a white to slight yellow coloured, odourless and tasteless powder.

Solubility: Freely soluble in water below 38°C and insoluble in water above 45°C, soluble in dimethyl formamide, dimethyl sulfoxide, dioxane, ethanol, methanol and propylene glycol.

Category: Coating agent, emulsifying agent, stabilizing agent, suspending agent, tablet binder, thickening agent, viscosity increasing agent.

Applications: Extended release matrix former, tablet binder, film Coating.

PLAN OF WORK

The present work was planned with the following objectives,

- To prepare felodipine solid binary systems using polyethylene glycol 4000 (PEG 4000) by solvent deposition and kneading method at different drug: carrier ratios of 1:1, 1:3 and 1:5.
- To prepare ternary systems with the addition of different concentrations of HPC to felodipine-PEG 4000 binary systems to investigate the effect of hydrophilic polymer on the solubility and dissolution rate of the felodipine.
- To study the physicochemical characteristics of prepared solid binary and ternary systems by drug content, FT-IR and powder XRD studies.
- To study the *in vitro* drug release profiles of all solid binary and ternary systems of felodipine, to study the effect of the drug-carrier ratios and effect of the preparation methods on drug dissolution characteristics.
- Interpretation of *in vitro* dissolution data by dissolution software PCP DissoV**3** and statistical methods using Graph Pad Instat V3.

MATERIALS AND METHODS

Materials

Table 2: List of chemicals used in the study

Chemical name	Source
Felodipine	Ajantha pharmaceuticals, Mumbai
Methanol	SD Fine chemicals, Mumbai
Ethanol	SD Fine chemicals, Mumbai
PEG 4000	SD Fine chemicals, Mumbai
HPC	SD Fine chemicals, Mumbai

Methodology

Development of UV spectroscopic method

To prevent the photodegradation of felodipine, all the experimental work was carried out under light protected conditions.

Determination of absorption maxima: Absorption maxima are the wavelength at which absorption takes place. For accurate analytical work it is important to determine the absorption maxima of the substance under study. 100 mg of felodipine was dissolved in 100 ml of methanol. 1 ml of this solution was pipetted out in a series of volumetric flask and diluted serially with 0.1N HCl (pH 1.2) to get desired concentration and subjected for UV scanning in the range of 200-800 nm using double beam UV-VIS spectrophotometer (pharmaspec1700, Shimahdzu, Japan). The absorption maxima for felodipine were obtained at 239 nm with a characteristic peak.

Preparation of calibration curve: Using absorption maxima a standard curve was prepared in the concentration range of 2-10 µg/ml. For the preparation of calibration curve, stock solution was prepared by dissolving 100 mg of accurately weighed felodipine in 100 ml of methanol. Further 1 ml of this solution was pippeted into 100 ml of volumetric flask and diluted to 100 ml with phosphate buffer of 0.1 N HCl. From this, 2, 4, 6, 8 and 10 ml pipetted into a series of 10 ml volumetric flask and volume was made up to 10 ml with 0.1N HCl to get 2, 4, 6, 8 and 10 µg/ml of felodipine respectively. The optical density values of resulting solutions were measured at 239 nm in double beam UV-VIS spectrophotometer (pharmaspec-1700, Shimadzu, Japan) and statistical data is given in **table 3.** The concentration versus optical density values are plotted and shown in the **figure 1.**

Table : 3 Calibration curve data of felodipine

Concentration (µg/ml)	Absorbance* ± SD
2	0.051 ± 0.001
4	0.108 ± 0.002
6	0.161 ± 0.175
8	0.216 ± 0.0005
10	0.269 ± 0.001

*Average of three determinations

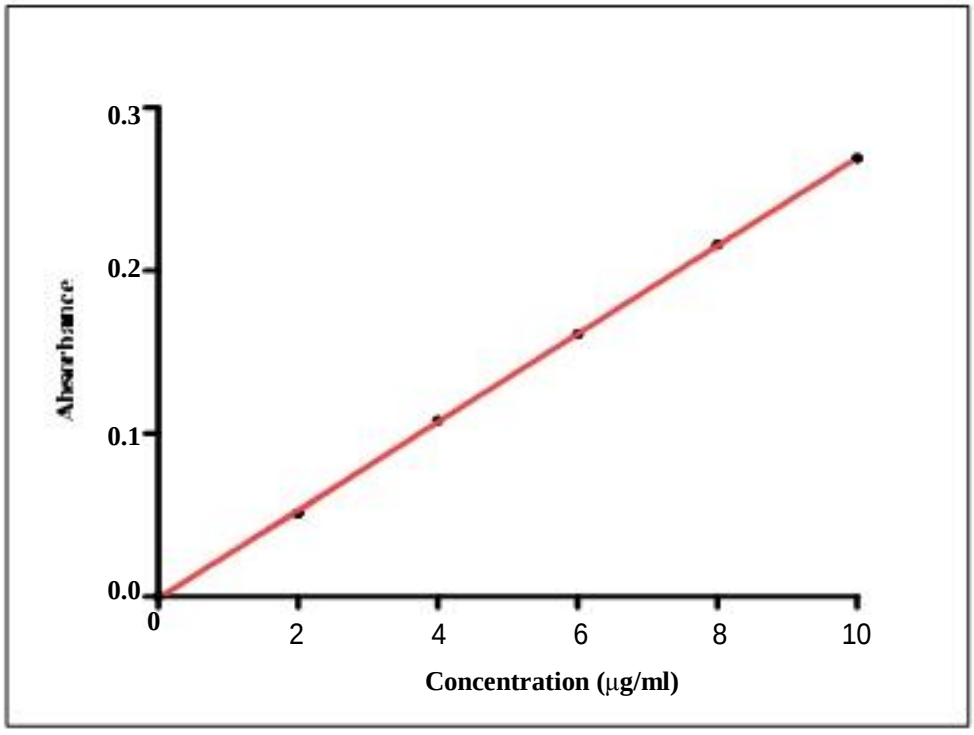


Figure 1: Calibration curve of felodipine

Table 4: Statistical data for calibration curve

Absorption maxima	239 nm
Beer's law limit	1-20 μ/ml
Molar absorptivity ($mol^{-1}cm^{-1}$)	9.807×10^3
Coefficient of correlation	0.9999
Best- fit values	
Slope	0.02704 ± 0.0001547
Y-intercept when X=0.0	-0.001048 ± 0.000937
X-intercept when Y=0.0	0.03874
1/slope	36.98
95% Confidence Intervals	
Slope	0.02661 to 0.02747
P value	< 0.0001

Preparation of solid binary and ternary systems

The solid binary systems of felodipine:PEG 4000 were prepared at 1:1, 1:3 and 1:5 w/w ratios as shown in **table 5.**

Physical mixtures (PMs): The physical mixtures of felodipine and PEG 4000 at 1:1, 1:3 and 1:5 ratios (w/w) were prepared by mixing individual components that had previously been passed through sieve no.120.

Kneading method (KM): The solid binary systems of felodipine with PEG 4000 were prepared by triturating the required quantities in a glass mortar with small volume of solvent blend of water and ethanol. The thick slurry was kneaded for 1 h and then dried at 45^0C until dryness. The dried mass was pulverized and passed through sieve no.120.

Similarly physical mixtures and solid ternary systems of felodipine, PEG 4000 and HPC (**table 6**) were prepared by adding different concentrations of PC (5%, 10% and 15% w/w of the solid binary system) to felodipine-PEG 4000 systems (1:3 ratio).

Solvent deposition method (SD): The aqueous solution of PEG 4000 was dispersed into a solution of felodipine dissolved in methanol. The resulting mixture was stirred for 1 h and evaporated until dry. The dried mass was pulverized and passed through sieve no.120.

Table 5: Formulae of felodipine solid binary system with PEG 4000

Sl. No	Batches	Drug:carrier ratio (w/w)	Method
1	Felodipine:PEG4000	1:1	PM
2	Felodipine:PEG4000	1:1	KM
3	Felodipine:PEG4000	1:1	SD
4	Felodipine:PEG4000	1:3	PM
5	Felodipine:PEG4000	1:3	KM
6	Felodipine:PEG4000	1:5	SD
7	Felodipine:PEG4000	1:3	PM
8	Felodipine:PEG4000	1:5	KM
9	Felodipine:PEG4000	1:5	SD

Table 6: Formulae of felodipine solid ternary system

Sl. No	Felodipine : PEG 4000 ratio (w/w)	% of HPC	Method
1	1:3	5%	PM
2	1:3	5%	KM
3	1:3	10%	PM
4	1:3	10%	KM
5	1:3	15%	PM
6	1:3	15%	KM

Characterization of solid binary and ternary systems

Drug content uniformity: In each case PMs and solid binary/ternary systems, sample equivalent to 10 mg of felodipine was accurately weighed and transferred to 100 ml volumetric flask and extracted in methanol. The volume was made up to 100 ml with 0.1N HCl. From this 1 ml is subsequently diluted to 10 ml with 0.1N HCl and assayed for felodipine content by measuring at 239 nm using 0.1N HCl as blank. The felodipine content was calculated from the calibration curve. The experiments were conducted in triplicate.

Solubility studies: The solubility measurements of felodipine were carried out by adding excess amount of drug (50 mg) to 20 ml of PEG 4000 prepared in 0.1N HCl (pH1.2) in a series of stoppered conical flasks. Then the suspensions were agitated at 37°C ± 1°C until equilibrium was achieved. Then 2 ml aliquots were filtered, diluted suitably and assayed spectrophotometrically at 239 nm for felodipine content. The experiments were conducted in triplicate. The blanks were performed in the same concentrations of PEG 4000 in 0.1N HCl in order to cancel any absorbances that may be exhibited by the PEG 4000 molecules.

Fourier Transform Infrared Spectrometry (FT-IR): Infrared spectra were obtained using a Perkin Elmer 1600 FT-IR spectrophotometer (USA). The spectra were recorded for felodipine, PEG 4000 and HPC, physical mixtures and all solid binary and ternary system. The samples were prepared by the potassium bromide (KBr) disc method. The KBr discs were prepared by compressing the powder and scanning range was kept from 4000 to 450 cm^{-1}.

Powder X-ray diffractometry (PXRD): The powder XRD patterns of felodipine, PEG 4000, HPC, physical mixtures and all solid binary and ternary system were recorded by using Philips X-ray powder diffractometer (model PW 1710) employing Cu-K_α-radiation. The diffractometer were run at 2.4^0/min interms of 2θ angle.

***In vitro* dissolution studies:** The *in vitro* dissolution studies were performed for felodipine alone, PMs and all solid binary and ternary system using the dissolution rate test apparatus USPXXIV Type II by the powder dispersed amount method (powder samples were spread over the dissolution medium). Felodipine 10 mg or physical mixture or solid binary and ternary system equivalent to 10 mg of felodipine was used in each test. The dissolution studies were carried out using 900 ml of 0.1N HCl (pH 1.2), maintained at 37 ± 0.5°C with paddle rotation maintained at 50 rpm. The release of felodipine was measured by withdrawing 5 ml aliquot at regular time intervals, filtered, suitably diluted and assayed spectrophotometrically at 239 nm. Fresh medium was added to maintain a constant volume after each sampling. All dissolution experiments were conducted in triplicate. Dissolution results of pure drug, PMs and solid binary and ternary systems were computed by using dissolution software PCP DISSO V3.

Statistical analysis: Statistical analysis was performed to assess the dissolution of felodipine from PMs, SDs and solid binary systems using Graph Pad Instat V3. The percent dissolution efficiency (DE) values obtained from dissolution studies of solid binary and ternary systems were compared with one-way ANOVA at 95% confidence interval using Dunnett multiple comparision test. A significance level of $P < 0.05$ was used to denote statistically significance in all cases.

4. RESULTS

Table 7: Solubility studies of felodipine in different concentration of PEG 4000

Concentration of PEG 4000 (% w/w)	Concentration of felodipine (µg/ ml)± SD
2	$0.09 \times 10^3 \pm 0.43$
4	$0.15 \times 10^3 \pm 0.33$
6	$0.23 \times 10^3 \pm 0.26$
8	$0.32 \times 10^3 \pm 0.72$
10	$0.40 \times 10^3 \pm 0.18$

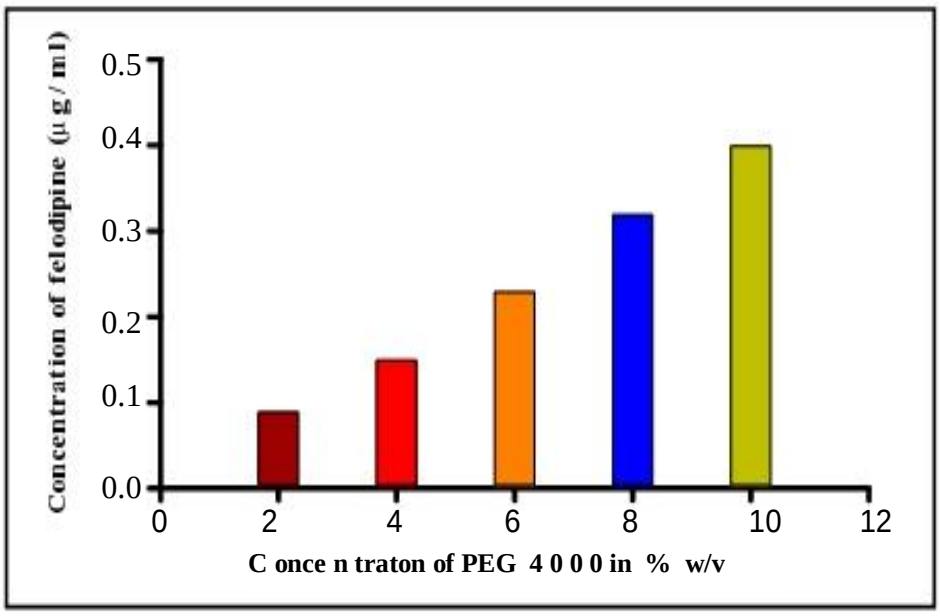


Figure 2: Solubility profile of pure felodipine in different concentration of PEG 4000

Table 8: Percentage drug content in felodipine:PEG 4000 PMs and solid binary systems

Method	Drug : carrier ratio (w/w)	% Drug content ± SD	% Yield
PM	1:1	96.59 ± 0.14	99.56
PM	1:3	98.36 ± 0.22	96.25
PM	1:5	97.74 ± 0.15	98.00
KM	1:1	93.23 ± 0.19	97.42
KM	1:3	95.03 ± 0.13	96.01
KM	1:5	96.54 ± 0.36	95.87
SD	1:1	97.18 ± 0.24	96.89
SD	1:3	96.95 ± 0.30	96.28
SD	1:5	97.21 ± 0.22	95.77

Table 9: Percentage drug content in felodipine:PEG 4000:HPC PMs and solid ternary systems

Felodipine : PEG 4000 ratio (w/w)	% of HPC	Method	% Drug content ± SD	% Yield
1:3	5%	PM	98.72 ± 0.13	97.48
1:3	5%	KM	97.51 ± 0.15	96.76
1:3	10%	PM	97.99 ± 0.21	97.25
1: 3	10%	KM	96.84 ± 0.12	95.99
1:3	15%	PM	98.02 ± 0.23	98.12
1:3	15%	KM	97.98 ± 0.26	96.68

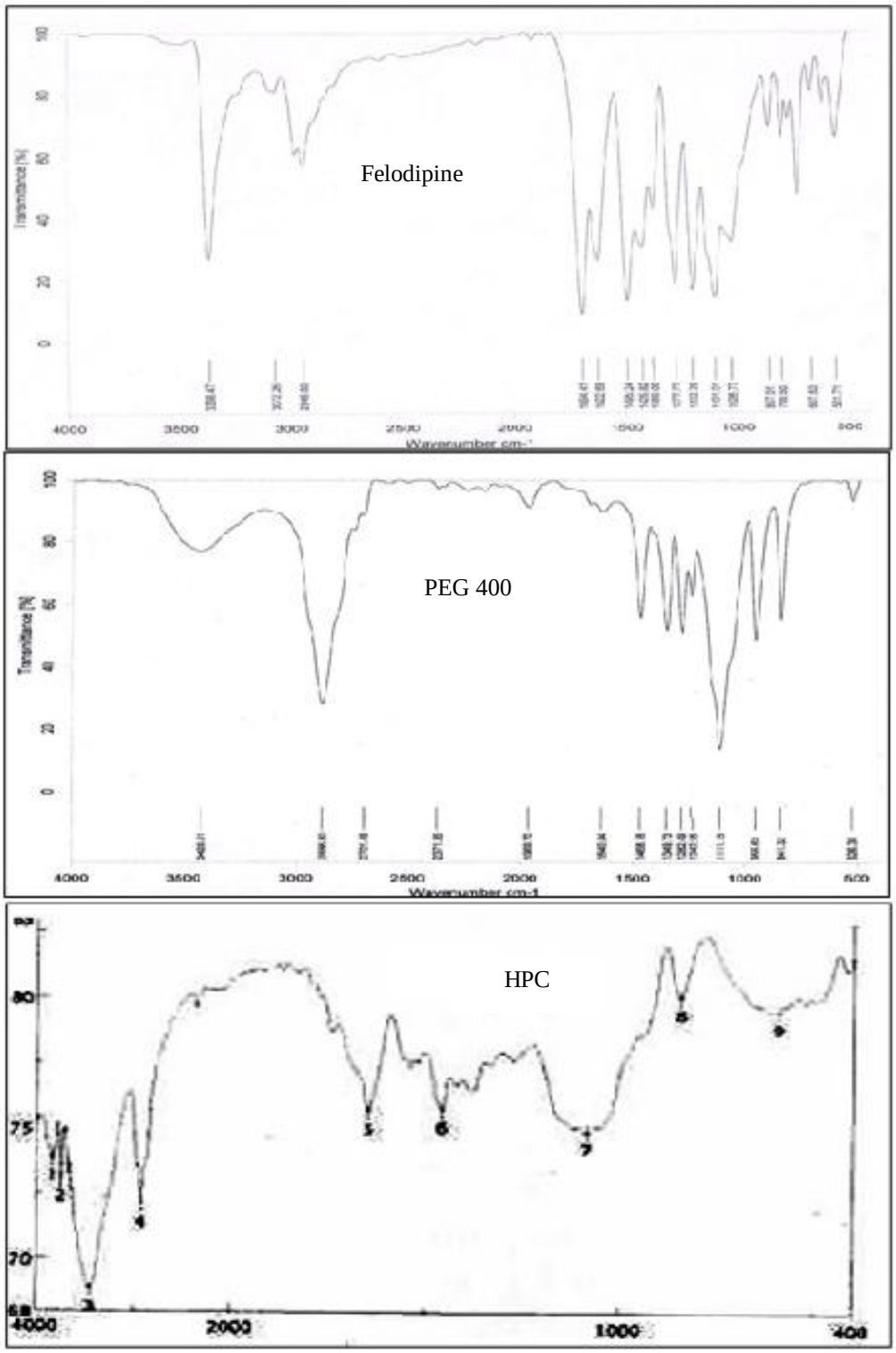


Figure 3: FT-IR spectra of felodipine, PEG 4000 and HPC

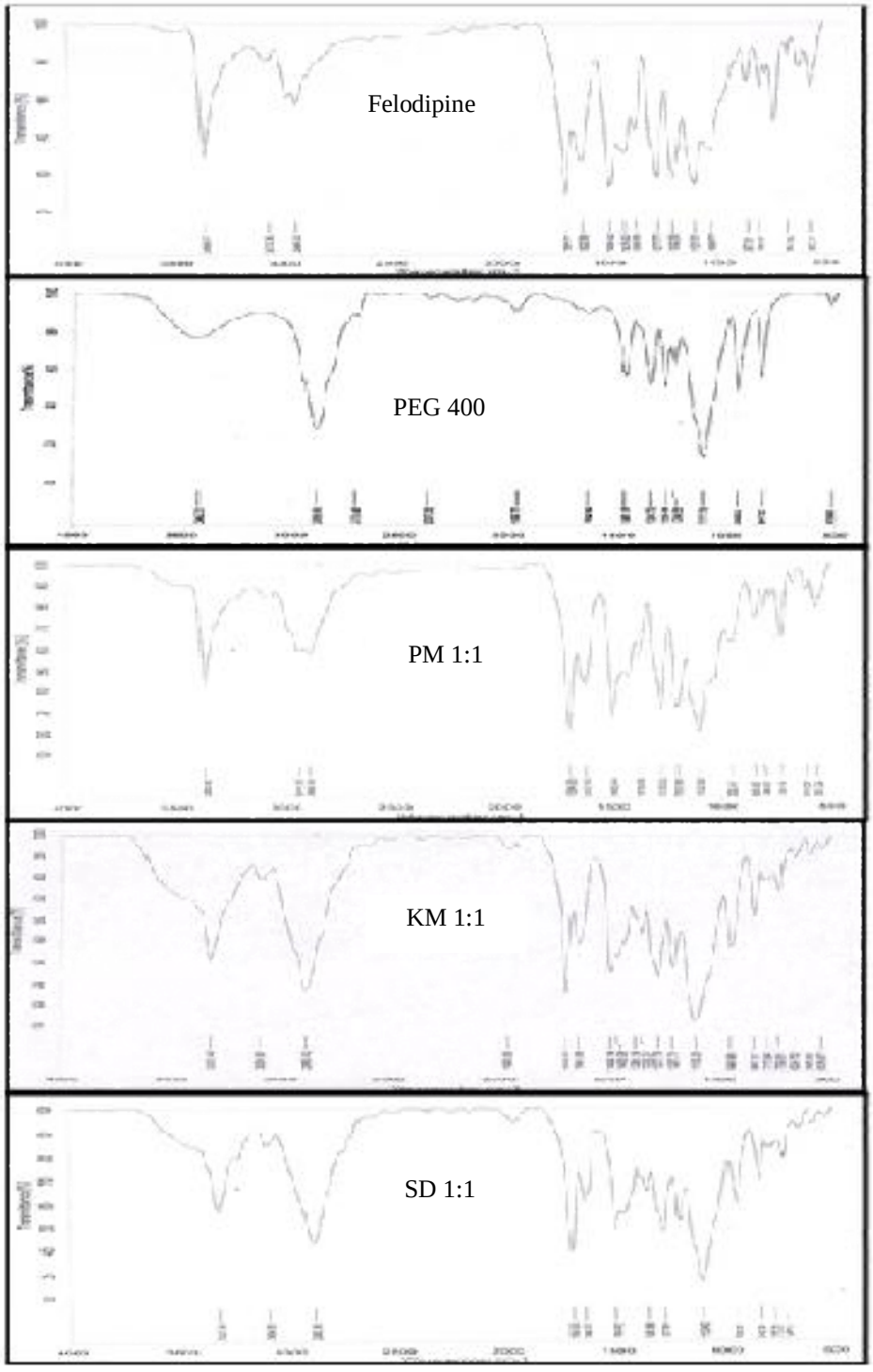


Figure 4: Comparative FT-IR spectra of felodipine, PEG 4000, felodipine:PEG 4000 PMs and solid binary system at 1:1 ratio

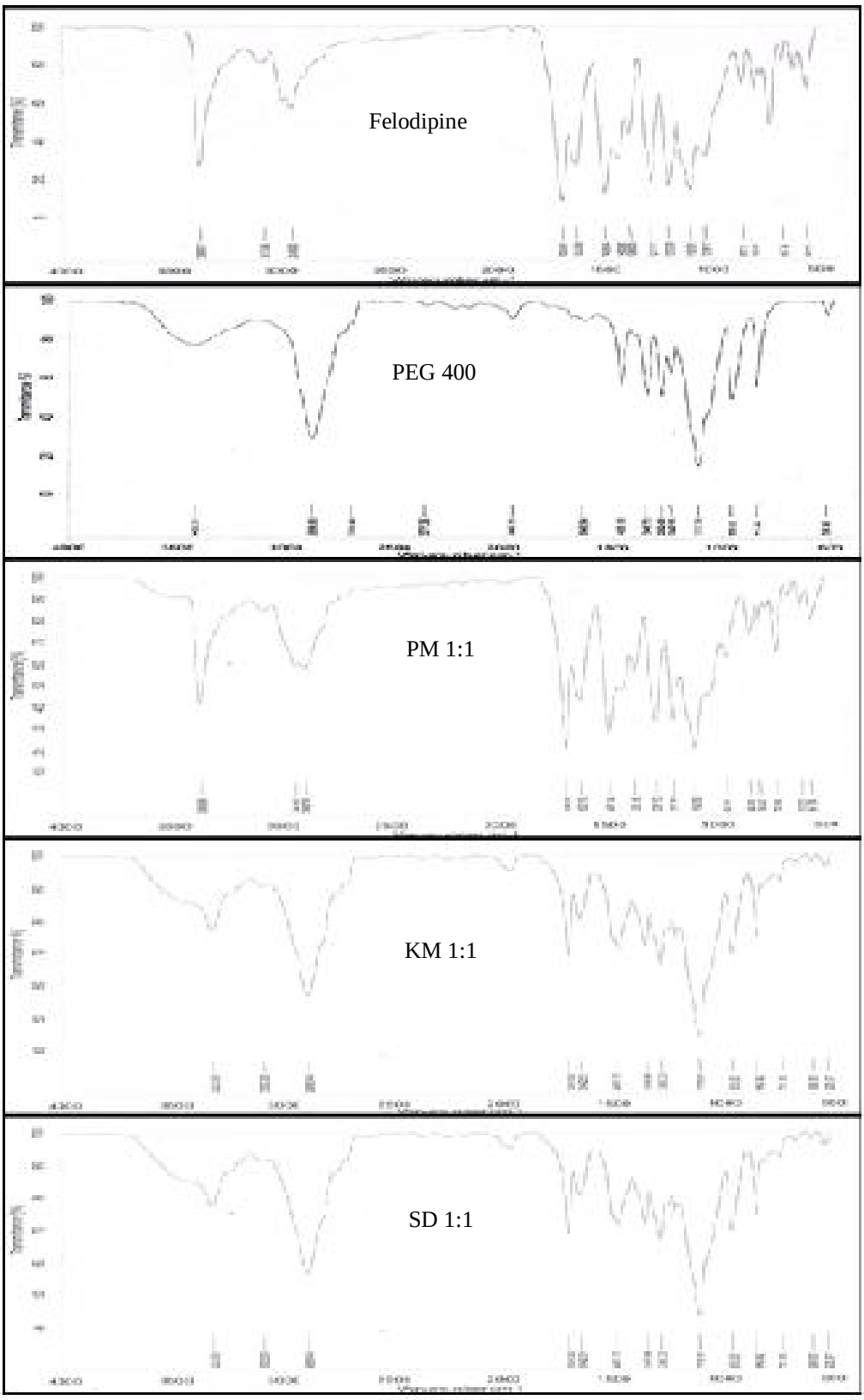


Figure 5: Comparative FT-IR spectra of felodipine, PEG 4000, felodipine:PEG 4000 PMs and solid binary system at 1:3 ratio

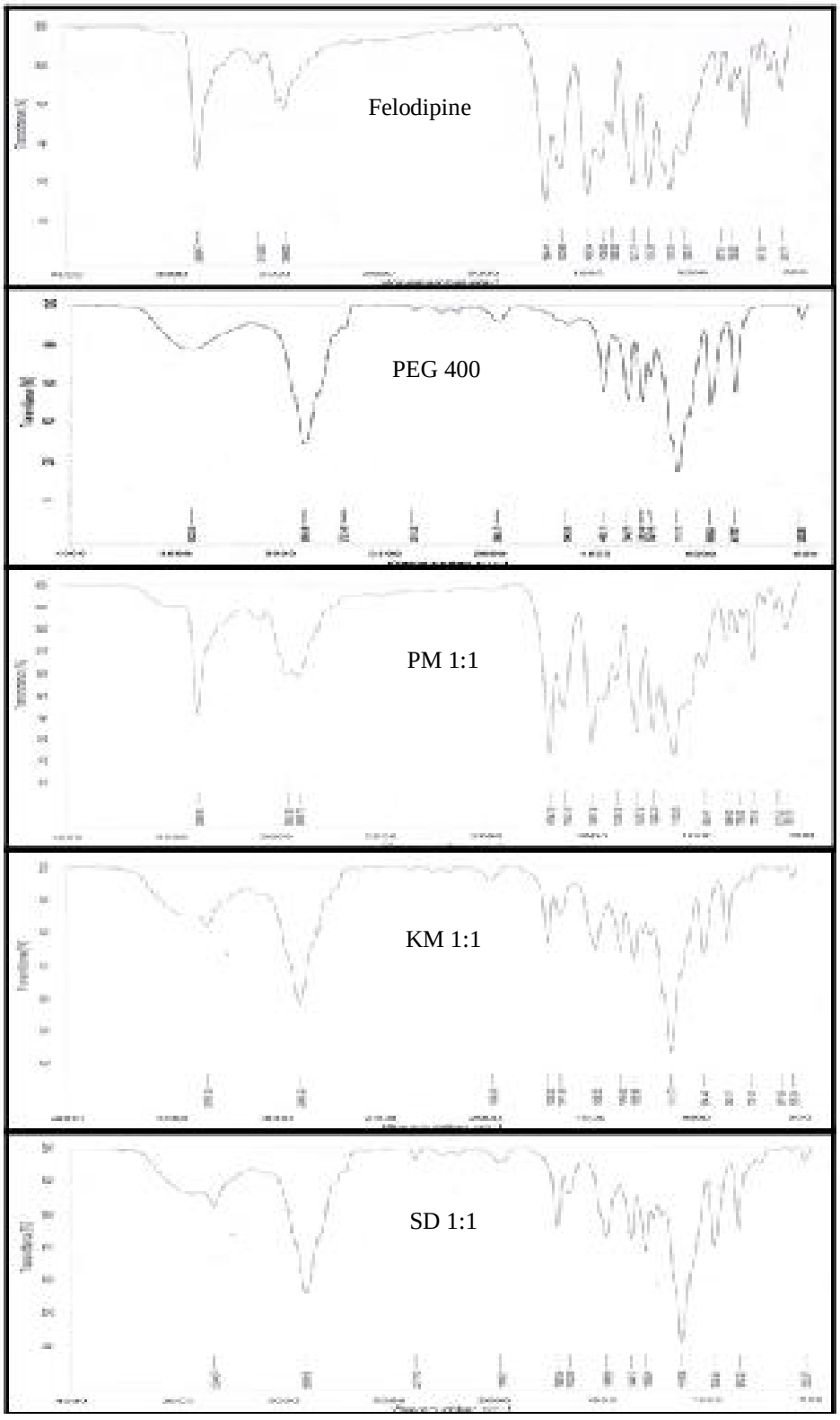


Figure 6: Comparative FT-IR spectra of felodipine, PEG 4000, felodipine:PEG 4000 PMs and solid binary system at 1:5 ratio

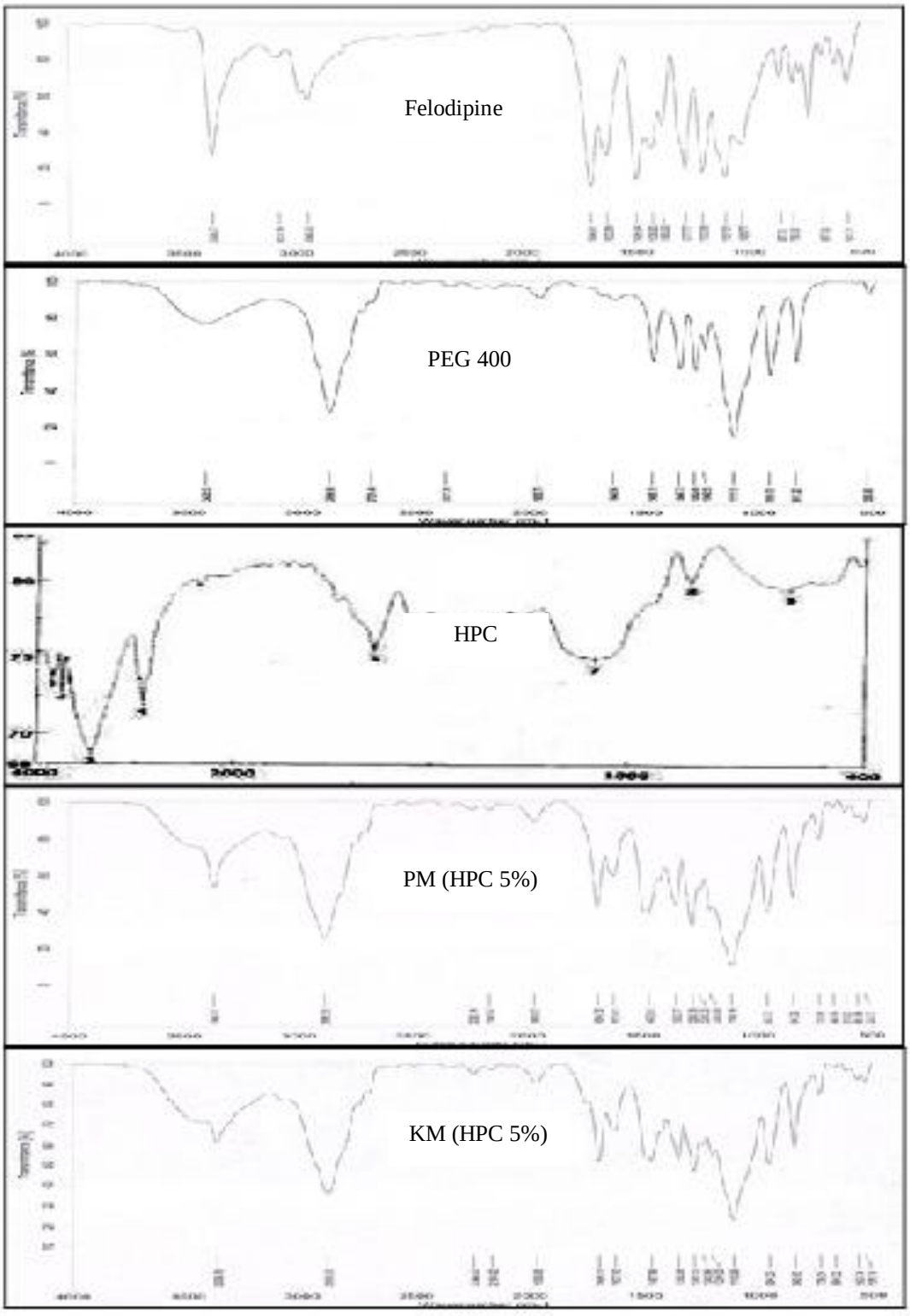


Figure 7: Comparative FT-IR spectra of felodipine, PEG 4000, HPC, felodipine: PEG 4000:HPC (5%) PMs and solid ternary systems

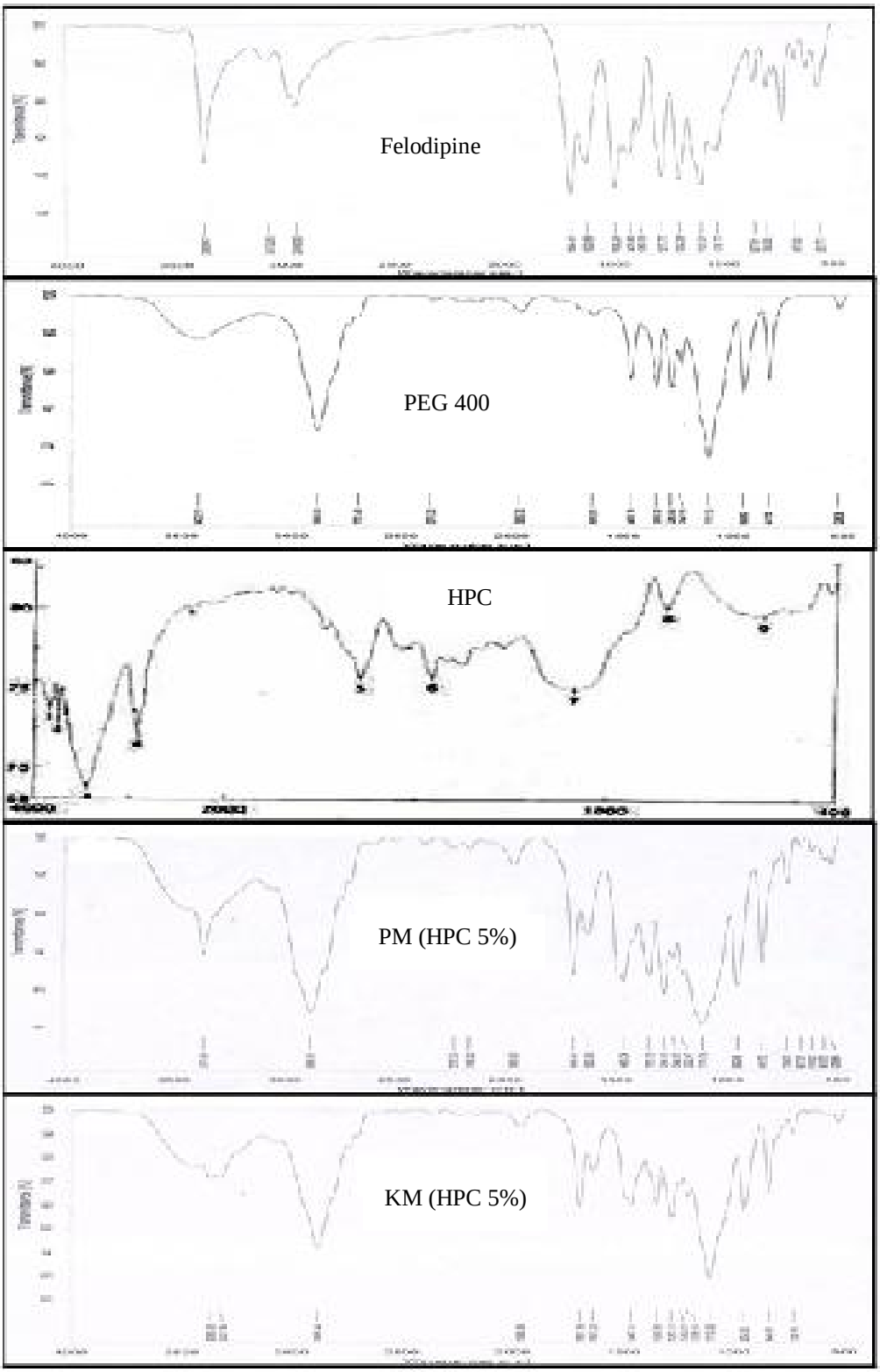


Figure 8: Comparative FT-IR spectra of felodipine, PEG 4000, HPC, felodipine: PEG 4000:HPC (10%) PMs and solid ternary systems

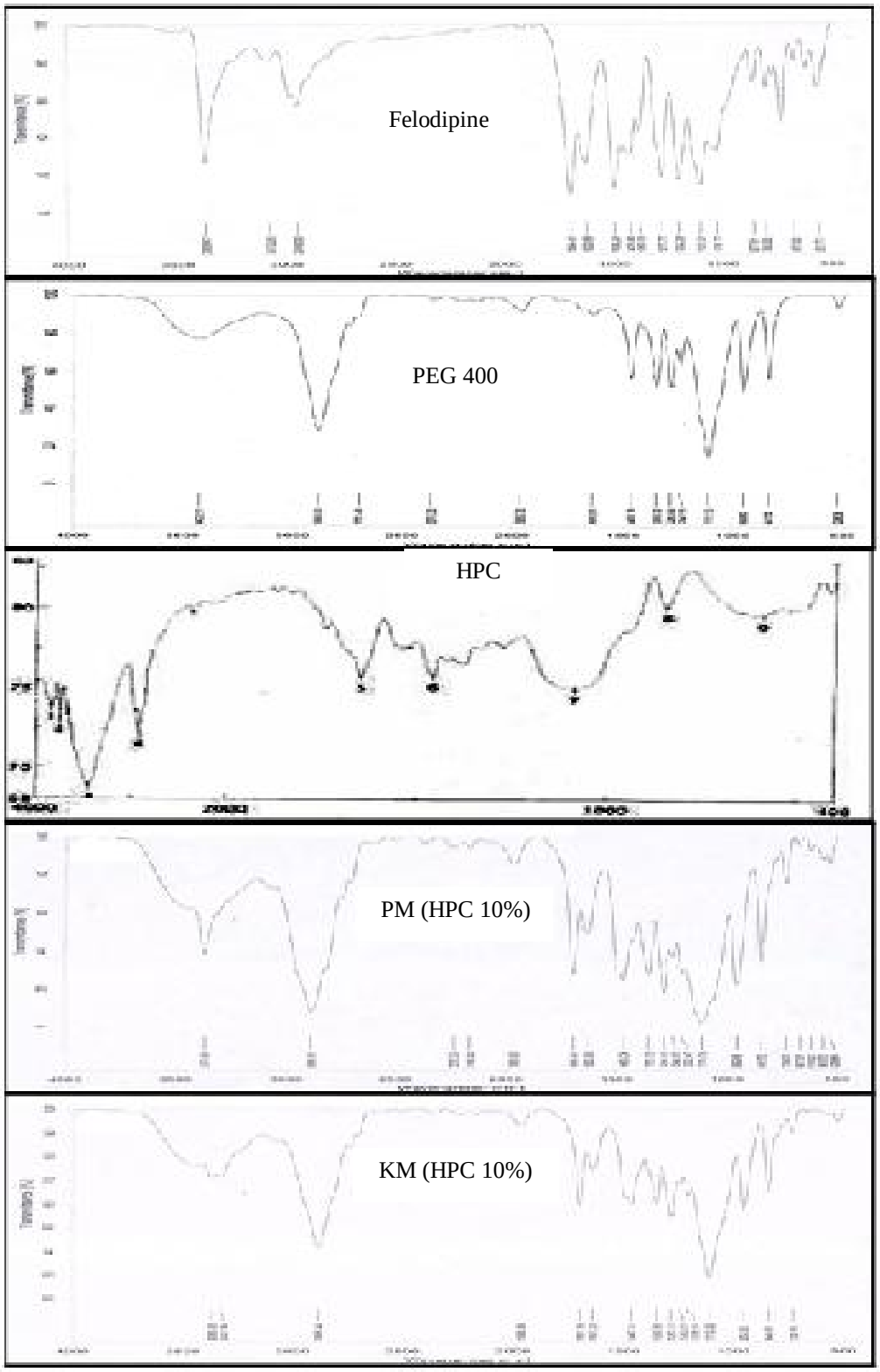


Figure 9: Comparative FT-IR spectra of felodipine, PEG 4000, HPC, felodipine: PEG 4000:HPC (15%) PMs and solid ternary systems

Table 10: Characteristic FT-IR peaks of felodipine in PMs and solid binary systems of felodipine with PEG 4000

Batches	**Characteristic peaks (cm^{-1} of Felodipine**	
	N-H Stretching	**C=O Stretching**
Felodipine	3368.47	1694.41
PM 1:1	3368.68	1694.39
KM 1:1	3322.49	1696.63
SD 1:1	3321.79	1696.33
PM 1:3	3368.88	1694.29
KM 1:3	3322.77	1697.08
SD 1:3	3323.56	1697.02
PM 1:5	3368.58	1694.29
KM 1:5	3325.30	1696.93
SD 1:5	3324.37	1697.54

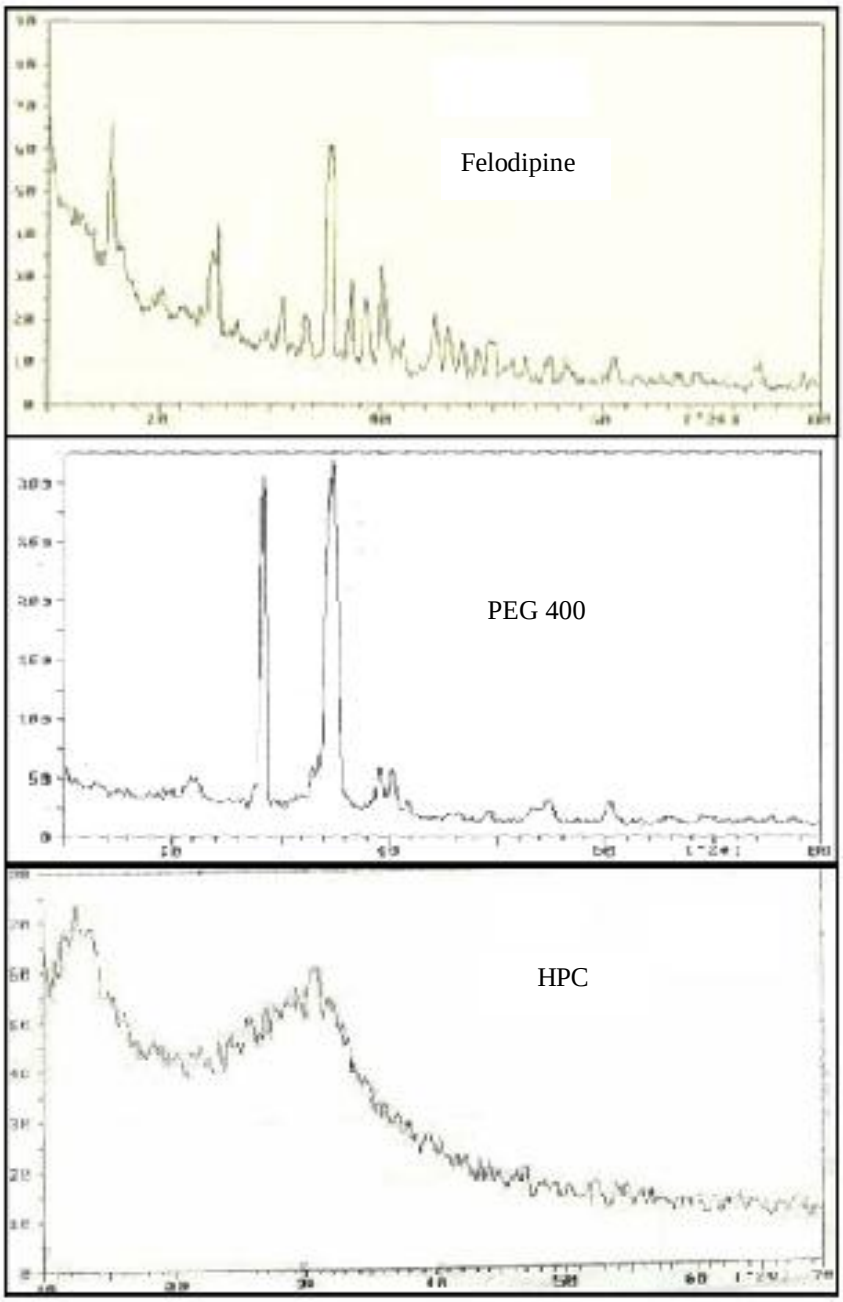


Figure 10: XRD spectra of felodipine, PEG 4000 and HPC

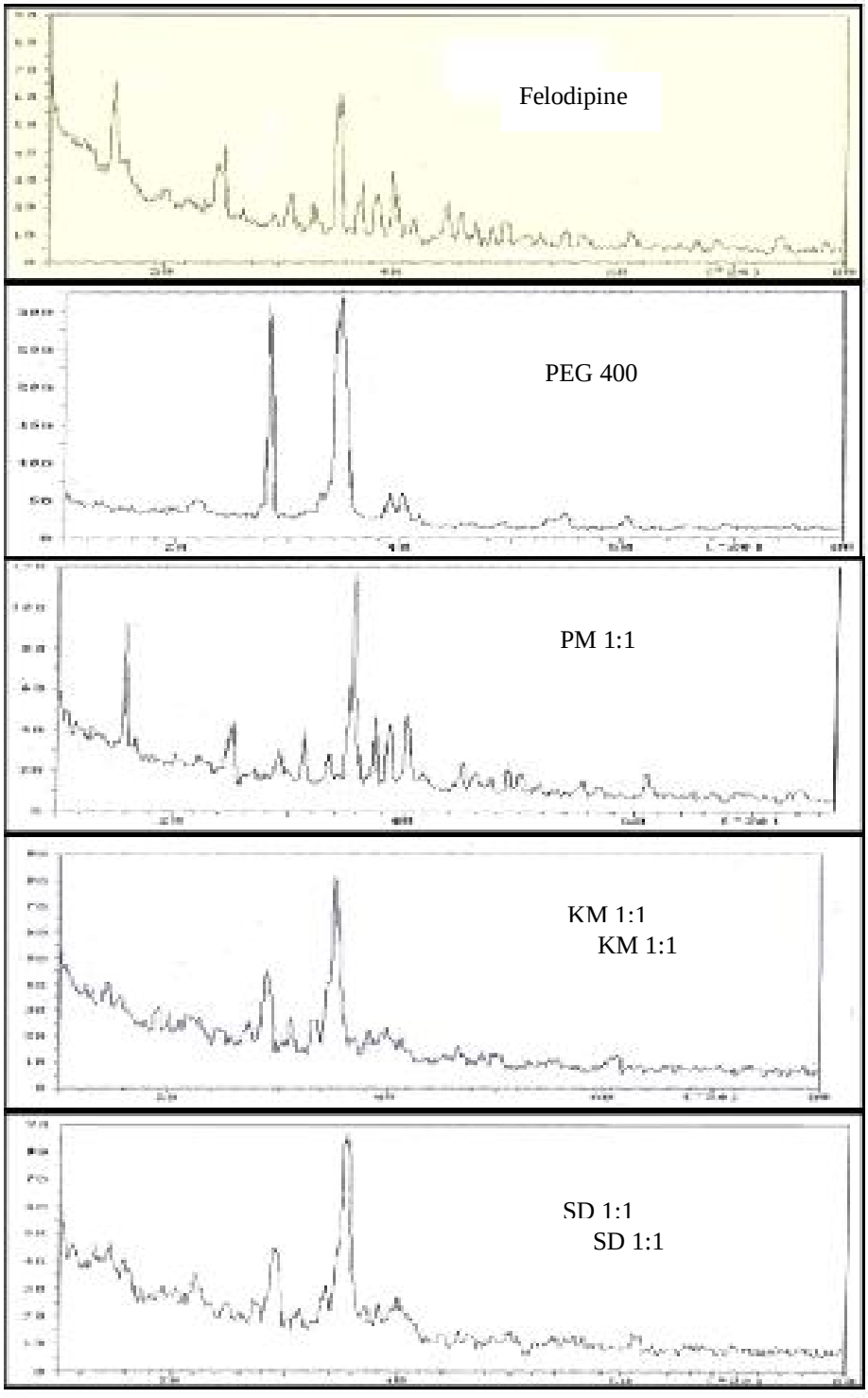


Figure 11: Comparative XRD spectra of felodipine, PEG 4000, felodipine:PEG 4000 PMs and solid binary system at 1:1 ratio

Table 11: XRD values of felodipine, PEG 4000 and felodipine:PEG 4000 PMs at 1:1 ratio

Felodipine			**PEG 4000**			**Felodipine :PEG 4000 1:1 (PM)**		
d(A)	**^{0}2θ**	**I/I_0**	**d(A)**	**^{0}2θ**	**I/I_0**	**d(A)**	**^{0}2θ**	**I/I_0**
8.32	15.8	24	5.92	22.28	11	8.36	15.72	30
6.58	20.02	2	4.66	28.41	222	8.23	15.98	17
5.27	25.08	13	4.04	32.88	28	7.85	16.76	8
5.19	25.45	28	3.87	34.33	231	7.2	18.28	3
4.22	31.44	6	3.84	34.6	279	5.3	24.9	21
3.99	33.29	8	3.79	35.11	234	5.21	25.37	24
3.79	35.11	42	3.41	39.23	42	4.53	29.22	14
3.56	37.46	22	3.33	40.21	44	4.23	31.38	32
3.44	38.78	18	3.21	41.79	14	3.97	33.46	14
3.33	40.2	38	2.91	46.3	5	3.74	35.62	104
3.18	42.06	12	2.74	49.23	10	3.55	37.56	27
3	44.81	15	2.62	51.68	3	3.44	38.78	28
2.93	45.93	12	2.55	53.35	18	3.33	40.18	42
2.85	47.36	13	2.47	55	27	2.98	45.1	18
2.77	48.81	7	2.27	60.37	24	2.92	46.04	11
2.7	50.15	11	2.1	65.92	9	2.84	47.47	15
2.46	55.32	10	2.01	69.28	9	2.76	48.97	18
2.41	56.65	6	1.97	75.48	13	2.7	50.07	14
2.25	60.99	10				2.62	51.74	7
2.07	66.79	5				2.52	53.86	5
2.03	68.56	5				2.45	55.48	9
1.89	74.17	10				2.4	56.88	8
1.81	78.27	7				2.25	60.92	19
						2.02	68.85	7
						1.89	74.18	10

Table 12: XRD values of felodipine, PEG 4000 and felodipine:PEG 4000 (1:1 ratio) solid binary systems prepared by kneading method

Felodipine			**PEG 4000**			**Felodipine :PEG 4000 1:1 (PM)**		
d(A)	**^{0}2θ**	**I/I_0**	**d(A)**	**^{0}2θ**	**I/I_0**	**d(A)**	**^{0}2θ**	**I/I_0**
8.32	15.8	24	5.92	22.28	11	6.94	18.98	4
6.58	20.02	2	4.66	28.41	222	4.84	27.32	7
5.27	25.08	13	4.04	32.88	28	4.57	28.97	23
5.19	25.45	28	3.87	34.33	231	4.26	31.14	9
4.22	31.44	6	3.84	34.6	279	4.02	33.09	10
3.99	33.29	8	3.79	35.11	234	3.78	35.21	62
3.79	35.11	42	3.41	39.23	42	3.48	38.3	6
3.56	37.46	22	3.33	40.21	44	3.33	40.11	8
3.44	38.78	18	3.21	41.79	14	2.89	46.55	7
3.33	40.2	38	2.91	46.3	5	2.24	61.36	7
3.18	42.06	12	2.74	49.23	10	2.09	66.31	4
3	44.81	15	2.62	51.68	3	2.07	66.96	12
2.93	45.93	12	2.55	53.35	18			
2.85	47.36	13	2.47	55	27			
2.77	48.81	7	2.27	60.37	24			
2.7	50.15	11	2.1	65.92	9			
2.46	55.32	10	2.01	69.28	9			
2.41	56.65	6	1.97	75.48	13			
2.25	60.99	10						
2.07	66.79	5						
2.03	68.56	5						
1.89	74.17	10						
1.81	78.27	7						

Table 13: XRD values of felodipine, PEG 4000 and felodipine:PEG 4000 (1:1 ratio) solid binary system prepared by solvent deposition method

Felodipine			PEG 4000			Felodipine :PEG 4000 1:1 (PM)		
d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0
8.32	15.8	24	5.92	22.28	11	9.24	14.22	7
6.58	20.02	2	4.66	28.41	222	8.51	15.46	4
5.27	25.08	13	4.04	32.88	28	4.89	27.05	10
5.197	25.45	28	3.87	34.33	231	4.6	28.8	71
4.224	31.44	6	3.84	34.6	279	4.03	32.99	15
3.996	33.29	8	3.79	35.11	234	3.78	35.2	132
3.79	35.11	42	3.41	39.23	42	3.6	37	8
3.56	37.46	22	3.33	40.21	44	3.39	39.42	17
3.44	38.78	18	3.21	41.79	14	3.26	41.04	10
3.33	40.2	38	2.91	46.3	5	2.7	50.06	7
3.18	42.06	12	2.74	49.23	10	2.47	55.19	10
3	44.81	15	2.62	51.68	3	2.26	60.84	14
2.93	45.93	12	2.55	53.35	18	1.85	76.06	6
2.85	47.36	13	2.47	55	27			
2.77	48.81	7	2.27	60.37	24			
2.7	50.15	11	2.1	65.92	9			
2.46	55.32	10	2.01	69.28	9			
2.41	56.65	6	1.97	75.48	13			
2.25	60.99	10						
2.07	66.79	5						
2.03	68.56	5						
1.89	74.17	10						
1.81	78.27	7						

Table 14: XRD values for felodipine, PEG 4000 and felodipine:PEG 4000 PMs at 1: 3 ratio

Felodipine			**PEG 4000**			**Felodipine:PEG 4000 1:3(PM)**		
d(A)	**$^0 2\theta$**	**c**	**d(A)**	**$^0 2\theta$**	**I/I_0**	**d(A)**	**$^0 2\theta$**	**I/I_0**
8.32	15.80	24	5.92	22.28	11	8.54	15.40	10
6.58	20.02	2	4.66	28.41	222	5.88	22.43	7
5.27	25.08		13	4.04	32.88	28	24.75	12
5.19	25.45	28	3.87	34.33	231	4.55	29.13	61
4.22	31.44	6	3.84	34.60	279	4.28	31.02	5
3.99	33.29	8	3.79	35.11	234	3.83	34.70	98
3.79	35.11	42	33.41	39.23	42	3.74	35.60	112
3.56	37.46	22	3.33	40.21	44	3.59	37.14	7
3.44	38.78	18	3.21	41.79	14	3.47	38.47	4
3.33	40.20	38	2.91	46.30	5	3.35	39.85	22
3.18	42.06	12	2.74	49.23	10	3.26	41.05	12
3.00	44.81	15	2.62	51.68	3	2.99	44.87	10
2.93	45.93	12	2.55	53.35	18	2.70	50.13	6
2.85	47.36	13	2.47	55.00	27	2.47	55.03	16
2.77	48.81	7	2.27	60.37	24	2.25	60.93	15
2.70	50.15	11	2.10	65.92	9	2.09	66.32	6
2.46	55.32	10	2.01	69.28	9	1.82	77.92	9
2.41	56.65	6	1.97	75.48	13			
2.25	60.99	10						
2.07	66.79	5						
2.03	68.56	5						
1.89	74.17	10						
1.81	78.27	7						

Table 15: XRD values of felodipine, PEG 4000 and felodipine:PEG 4000 (1:3 ratio) solid binary system prepared by kneading method

Felodipine			**PEG 4000**			**Felodipine:PEG 4000 1:3(PM)**		
d(A)	**$^0 2\theta$**	**I/I_0**	**d(A)**	**$^0 2\theta$**	**I/I_0**	**d(A)**	**$^0 2\theta$**	**I/I_0**
8.32	15.80	24	5.92	22.28	11	9.13	14.40	3
6.58	20.02	2	4.66	28.41	222	8.31	15.82	3
5.27	25.08	13	4.04	32.88	28	5.91	22.33	4
5.19	25.45	28	3.87	34.33	231	4.53	29.22	40
4.22	31.44	6	3.84	34.60	279	3.98	33.38	7
3.99	33.29	8	3.79	35.11	234	3.76	35.43	121
3.79	35.11	42	3.41	39.23	42	3.36	39.76	14
3.56	37.46	22	3.33	40.21	44	3.26	41.01	12
3.44	38.78	18	3.21	41.79	14	2.71	49.82	21
3.33	40.20	38	2.91	46.30	5	2.51	54.09	7
3.18	42.06	12	2.74	49.23	10	2.45	55.69	15
3.00	44.81	15	2.62	51.68	3			
2.93	45.93	12	2.55	53.35	18			
2.85	47.36	13	2.47	55.00	27			
2.77	48.81	7	2.27	60.37	24			
2.70	50.15	11	2.10	65.92	9			
2.46	55.32	10	2.01	69.28	9			
2.41	56.65	6	1.97	75.48	13			
2.25	60.99	10						
2.07	66.79	5						
2.03	68.56	5						
1.89	74.17	10						
1.81	78.27	7						

Table 16: XRD values of felodipine, PEG 4000 and felodipine:PEG 4000 (1:3 ratio) solid binary system prepared by solvent deposition method

Felodipine			**PEG 4000**			**Felodipine:PEG 4000 1:3(PM)**		
d(A)	**$^0 2\theta$**	**I/I_0**	**d(A)**	**$^0 2\theta$**	**I/I_0**	**d(A)**	**$^0 2\theta$**	**I/I_0**
8.32	15.80	24	5.92	22.28	11	9.97	13.17	3
6.58	20.02	2	4.66	28.41	222	8.28	15.88	3
5.27	25.08	13	4.66	28.41	28	5.96	22.14	7
5.19	25.45	28	4.04	32.88	231	4.83	27.40	6
4.22	31.44	6	3.84	34.60	279	4.55	29.10	22
3.99	33.29	8	3.79	35.11	234	4.25	31.18	6
3.79	35.11	42	3.41	39.23	42	3.98	33.43	22
3.56	37.46	22	3.33	40.21	44	3.79	35.14	6
3.44	38.78	18	3.21	41.79	14	3.7	34.53	12
3.33	40.20	38	2.91	46.30	5	3.79	35.14	62
3.18	42.06	12	2.74	49.23	10	3.7	50.17	71
3.00	44.81	15	2.62	51.68	3	3.49	61.13	6
2.93	45.93	12	2.55	53.35	18	2.70	50.17	4
2.85	47.36	13	53.35	55.00	27	2.25	61.13	6
2.77	48.81	7	55.00	60.37	24			
2.70	50.15	11	60.37	65.92	9			
2.46	55.32	10	65.92	69.28	9			
2.41	56.65	6	1.97	75.48	13			
2.25	60.99	10						
2.07	66.79	5						
2.03	68.56	5						
1.89	74.17	10						
1.81	78.27	7						

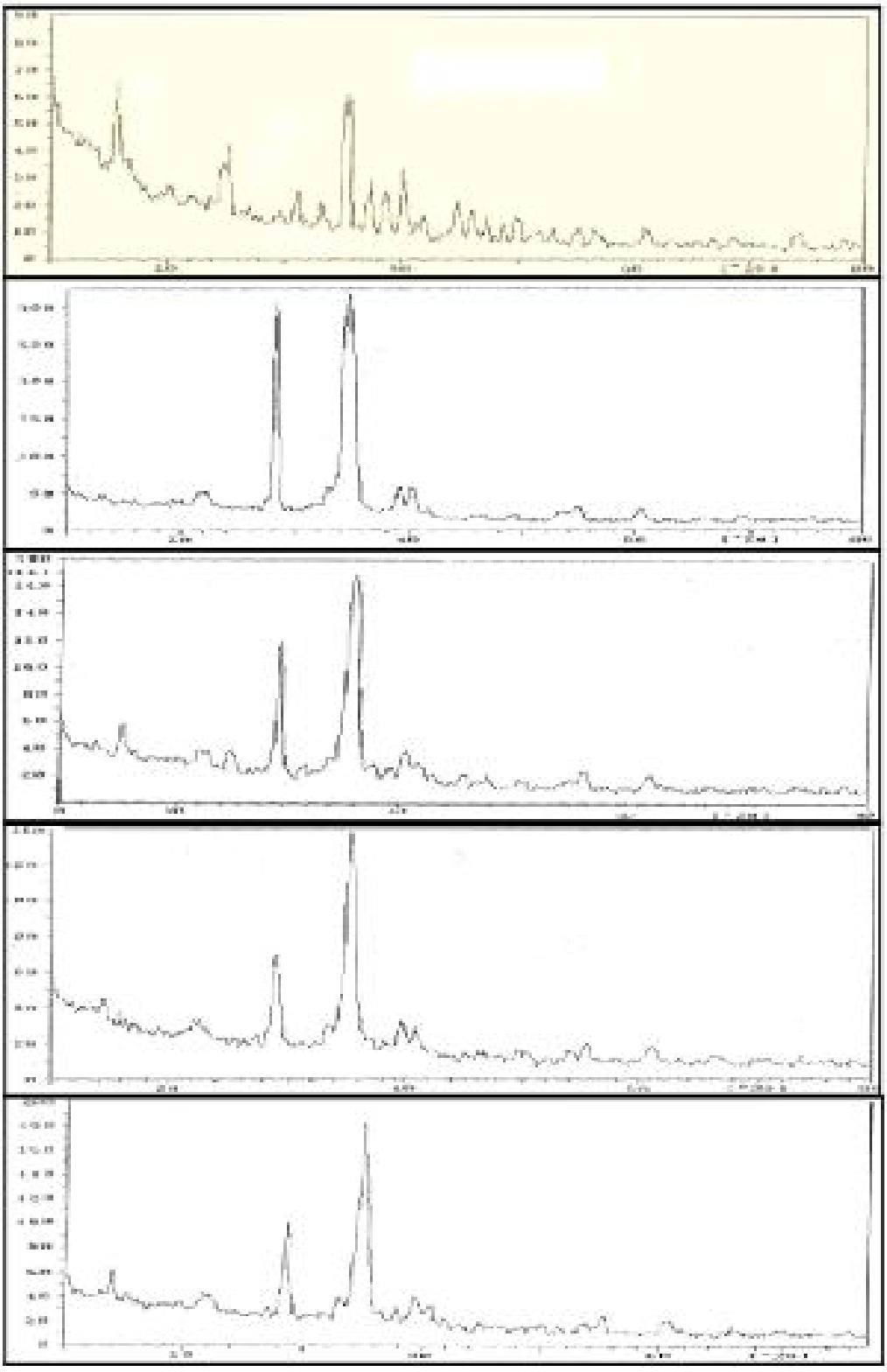


Figure13: Comparative XRD spectra of felodipine, PEG 4000, felodipine:PEG 4000 PMs and solid binary system at 1:5 ratio

Table 17: XRD values for felodipine, PEG 4000 and felodipine:PEG 4000 PMs at 1: 5 ratio

Felodipine			PEG 4000			Felodipine:PEG 4000 1:3(PM)		
d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0
8.32	15.80	24	5.92	22.28	11	9.90	13.27	2
6.58	20.02	2	4.66	28.41	222	8.65	15.20	45
5.27	25.08	13	4.04	32.88	28	8.12	16.19	16
5.19	25.45	28	3.87	34.33	231	6.72	19.61	8
4.22	31.44	6	3.84	35.11	279	6.08	22.53	38
3.99	33.29	22	3.79	35.11	234	5.86	24.30	38
3.79	35.11	42	3.41	39.23	234	5.43	24.72	46
3.56	37.46	22	3.33	40.21	42	5.34	26.37	5
3.44	38.78	18	3.21	41.79	44	5.01	28.59	59
3.33	40.20	38	2.91	46.30	14	4.63	30.72	26
3.18	42.06	12	2.74	49.23	5	4.32	32.96	22
3.00	44.81	15	2.62	51.68	10	4.03	34.80	159
2.93	45.81	12	2.55	55.35	3	3.82	36.81	41
2.85	47.36	13	2.47	55.00	18	3.62	38.12	34
2.77	48.81	7	2.27	60.37	27	3.50	39.85	46
2.70	50.15	11	2.10	65.92	24	3.35	34.64	38
2.46	55.32	10	2.01	69.28	9	3.02	38.95	24
2.41	56.65	6	1.97	75.48	9	3.04	44.55	14
2.25	60.99	10			13	2.95	45.60	19
2.07	66.79	5				2.88	46.81	11
1.89	74.17	10				2.78	48.46	14
1.81	78.27	7				2.73	49.54	17
						2.58	52.62	11
						2.49	54.70	19
						2.43	56.21	4
						2.27	60.44	27
						2.10	66.06	6
						1.91	73.66	6
						1.82	78.10	7

Table 18: XRD values of felodipine, PEG 4000 and felodipine:PEG 4000 (1:5) solid binary system prepared by kneading method

Felodipine			PEG 4000			Felodipine:PEG 4000 1:3(PM)		
d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0
8.32	15.80	24	5.92	22.28	11	8.45	15.56	7
6.58	20.02	2	4.66	28.41	222	6.01	21.95	6
5.27	25.08	13	4.04	32.88	28	5.33	24.76	10
5.19	25.45	28	3.87	34.33	231	4.58	28.93	69
4.22	31.44	6	3.84	34.60	279	4.28	31.00	18
3.99	33.29	8	3.79	35.11	234	3.78	35.25	139
3.79	35.11	42	3.41	39.23	42	3.61	36.96	7
3.56	37.46	22	3.33	40.21	44	3.34	39.95	21
3.44	38.78	18	3.21	41.79	14	2.46	55.30	6
3.33	40.20	38	2.91	46.30	5	2.26	60.83	15
3.18	42.06	12	2.74	49.23	10	2.09	66.39	5
3.00	44.81	15	2.62	51.68	3			
2.93	45.93	12	2.55	53.35	18			
2.85	47.36	13	2.47	55.00	27			
2.77	48.81	7	2.27	60.37	24			
2.70	50.15	11	2.10	65.92	9			
2.46	55.32	10	2.01	69.28	9			
2.41	56.65	6	1.97	75.48	13			
2.25	60.99	10						
2.07	66.79	5						
2.03	68.56	5						
1.89	74.17	10						
1.81	78.27	7						

Table 19: XRD values of felodipine, PEG 4000 and felodipine:PEG 4000 (1:5) solid binary system prepared by solvent deposition method

Felodipine			PEG 4000			Felodipine:PEG 4000 1:3(PM)		
d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0
8.32	15.80	24	5.92	22.28	11	9.41	13.96	9
6.58	20.02	2	4.66	28.41	222	6.09	21.94	8
5.27	25.08	13	4.04	32.88	28	4.88	27.11	4
5.19	25.45	28	3.87	34.33	231	4.63	28.59	64
4.22	31.44	6	3.84	34.60	279	4.03	32.99	16
3.99	33.29	8	3.79	35.11	234	3.80	34.99	164
3.79	35.11	42	3.41	39.23	42	3.53	37.84	10
3.56	37.46	22	3.33	40.21	44	3.40	39.30	26
3.44	38.78	18	3.21	41.79	14	3.29	40.69	21
3.33	40.20	38	2.91	46.30	5	3.20	41.90	8
3.18	42.06	12	2.74	49.23	10	3.00	44.78	6
3.00	44.81	15	2.62	51.68	3	2.71	49.79	5
2.93	45.93	12	2.55	53.35	18	2.54	53.52	10
2.85	47.36	13	2.47	55.00	27	2.47	55.10	22
2.77	48.81	7	2.27	60.37	24	2.26	60.58	17
2.70	50.15	11	2.10	65.92	9	2.15	64.12	3
2.46	55.32	10	2.01	69.28	9	1.86	75.82	8
2.41	56.65	6	1.97	75.48	13			
2.25	60.99	10						
2.07	66.79	5						
2.03	68.56	5						
1.89	74.17	10						
1.81	78.27	7						

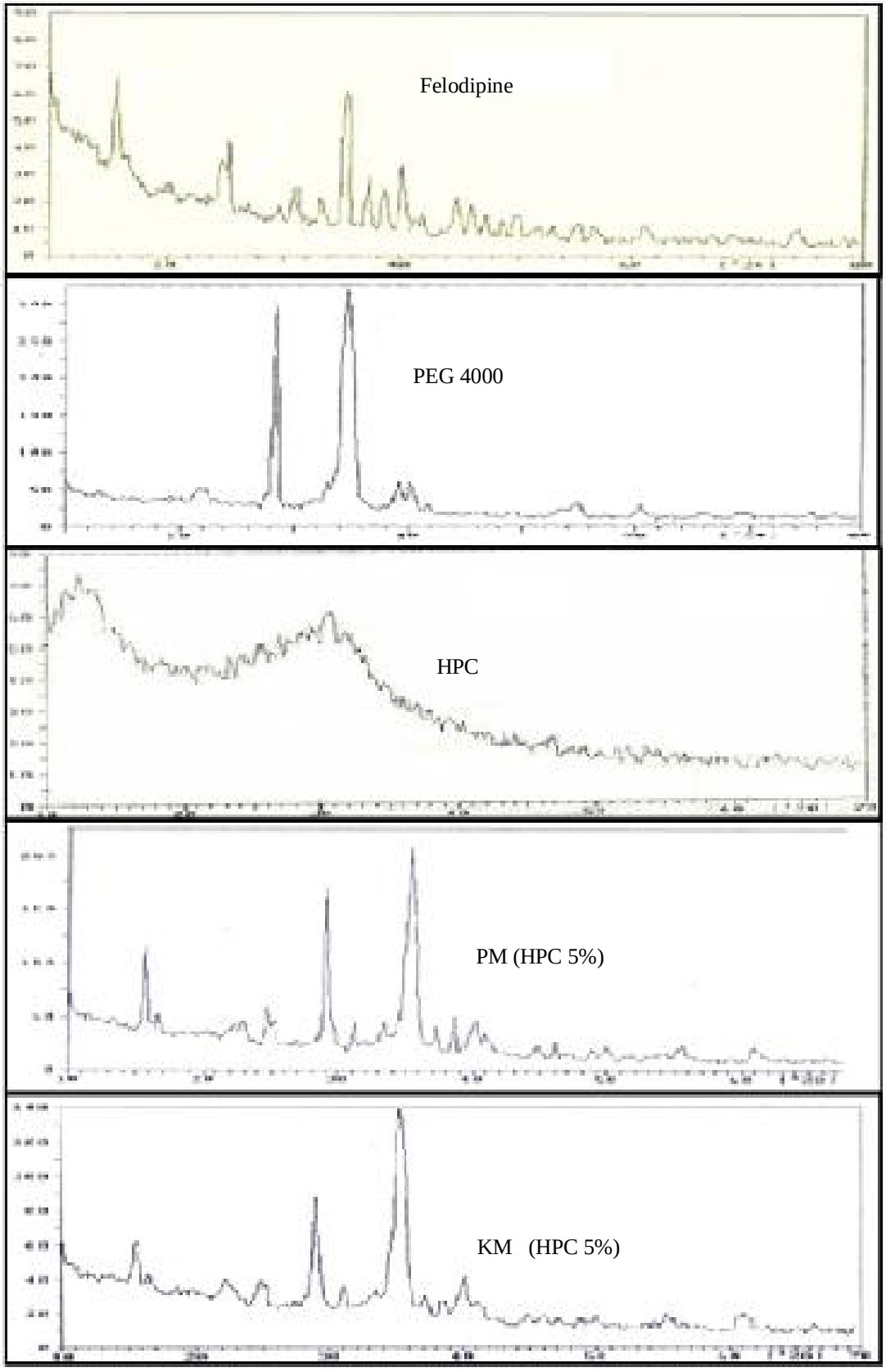


Figure 14: Comparative XRD spectra of felodipine, PEG 4000, HPC and felodipine:PEG 4000:HPC (5%) PMs and solid ternary systems

Table 20: XRD values for felodipine, PEG 4000 and felodipine:PEG 4000:HPC (5%) PMs at 1:3 ratio

Felodipine			PEG 4000			Felodipine:PEG 4000 1:3(PM)		
d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0
8.32	15.80	24	5.92	22.28	11	8.37	15.70	48
6.58	20.02	2	4.66	28.41	222	7.88	16.70	15
5.27	25.08	13	4.04	32.88	2	5.77	22.87	12
5.19	25.45	28	3.87	34.33	231	5.35	24.71	35
4.22	31.44	6	3.84	35.11	279	5.24	25.20	20
3.99	33.29	22	3.79	35.11	234	4.56	29.04	149
3.79	35.11	42	3.41	39.23	234	4.26	31.13	36
3.56	37.46	22	3.33	40.21	42	3.99	33.43	36
3.44	38.78	18	3.21	41.79	44	3.82	34.87	110
3.33	40.20	38	2.91	46.30	14	3.77	35.30	202
3.18	42.06	12	2.74	49.23	5	3.72	35.78	108
3.00	44.81	15	2.62	51.68	10	3.57	37.31	30
2.93	45.81	12	2.55	55.35	3	3.46	38.60	55
2.85	47.36	13	2.47	55.00	18	3.32	40.26	49
2.77	48.81	7	2.27	60.37	27	3.16	42.38	12
2.70	50.15	11	2.10	65.92	24	2.99	44.87	15
2.46	55.32	10	2.01	69.28	9	2.92	46.09	23
2.41	56.65	6	1.97	75.48	9	2.77	48.82	17
2.25	60.99	10			13	2.71	49.94	15
2.07	66.79	5				2.64	51.32	4
1.89	74.17	10				2.46	55.40	12
1.81	78.27	7				2.41	56.65	8
						2.26	60.76	20

*HPC is amorphous in nature

Table 21: XRD values for felodipine, PEG 4000 and felodipine:PEG 4000:HPC (5%) solid ternary systems at 1:3 ratio

Felodipine			PEG 4000			Felodipine:PEG 4000 1:3(PM)		
d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0
8.32	15.80	24	5.92	22.28	11	8.37	15.71	13
6.58	20.02	2	4.66	28.41	222	5.34	24.73	8
5.27	25.08	13	4.66	28.41	28	4.55	29.09	64
5.19	25.45	28	4.04	32.88	231	4.25	31.20	13
4.22	31.44	6	3.84	34.60	279	3.98	33.43	18
3.99	33.29	8	3.79	35.11	234	3.76	35.45	137
3.79	35.11	42	3.41	39.23	42	3.59	37.17	16
3.56	37.46	22	3.33	40.21	44	3.47	38.44	14
3.44	38.78	18	3.21	41.79	14	3.30	40.48	40
3.33	40.20	38	2.91	46.30	5	3.17	42.34	9
3.18	42.06	12	2.74	49.23	10	2.71	49.87	10
3.00	44.81	15	2.62	51.68	3	2.46	55.29	13
2.93	45.93	12	2.55	53.35	18	2.25	61.00	15
2.85	47.36	13	53.35	55.00	27			
2.77	48.81	7	55.00	60.37	24			
2.70	50.15	11	60.37	65.92	9			
2.46	55.32	10	65.92	69.28	9			
2.41	56.65	6	1.97	75.48	13			
2.25	60.99	10						
2.07	66.79	5						
2.03	68.56	5						
1.89	74.17	10						
1.81	78.27	7						

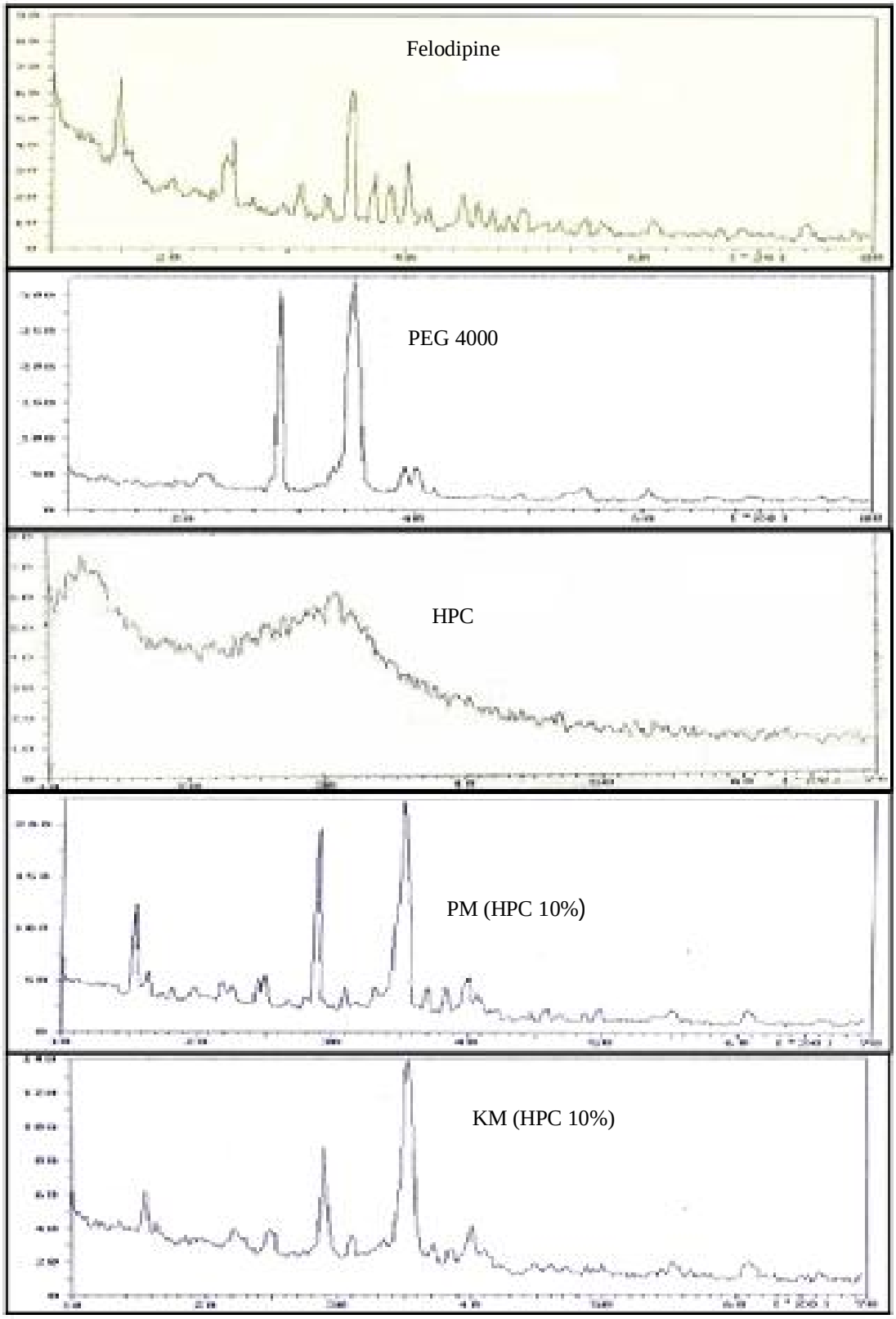


Figure 15: Comparative XRD spectra of felodipine, PEG 4000, HPC and felodipine:PEG 4000:HPC (10%) PMs and solid ternary systems

Table 22: XRD values for felodipine, PEG 4000 and felodipine: PEG 4000:HPC (10%) PMs at 1:3 ratio

Felodipine			PEG 4000			Felodipine:PEG 4000 1:3(PM)		
d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0
8.32	15.80	24	5.92	22.28	11	8.48	15.50	45
6.58	20.02	2	4.66	28.41	222	8.01	16.43	8
5.27	25.08	13	4.66	28.41	28	7.27	18.11	6
5.19	25.45	28	4.04	32.88	231	6.70	19.67	5
4.22	31.44	6	3.84	34.60	279	6.06	21.75	12
3.99	33.29	8	3.79	35.11	234	5.84	22.59	10
3.79	35.11	42	3.41	39.23	42	5.40	24.47	24
3.56	37.46	22	3.33	40.21	44	5.29	24.98	22
3.44	38.78	18	3.21	41.79	14	4.61	28.75	172
3.33	40.20	38	2.91	46.30	5	4.29	30.93	20
3.18	42.06	12	2.74	49.23	10	4.01	33.13	23
3.00	44.81	15	2.62	51.68	3	3.84	34.63	110
2.93	45.93	12	2.55	53.35	18	3.80	35.06	222
2.85	47.36	13	53.35	55.00	27	3.75	35.55	117
2.77	48.81	7	55.00	60.37	24	3.61	36.94	35
2.70	50.15	11	60.37	65.92	9	3.49	38.27	29
2.46	55.32	10	65.92	69.28	9	3.34	40.05	41
2.41	56.65	6	1.97	75.48	13	3.29	40.61	26
2.25	60.99	10				3.18	42.08	10
2.07	66.79	5				3.01	44.65	12
2.03	68.56	5				2.94	45.79	12
1.89	74.17	10				2.88	46.81	9
1.81	78.27	7				2.78	48.59	13
						2.72	49.68	18
						2.47	55.14	13
						2.26	60.83	15
						2.09	66.33	7

*HPC is amorphous in nature

Table 23: XRD values for felodipine, PEG 4000 and felodipine:PEG 4000:HPC (10%) solid ternary system at 1:3 ratio

Felodipine			PEG 4000			Felodipine:PEG 4000 1:3(PM)		
d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0
8.32	15.80	24	5.92	22.28	11	8.43	15.60	10
6.58	20.02	2	4.66	28.41	222	5.92	22.27	7
5.27	25.08	13	4.04	32.88	28	5.28	25.00	9
5.19	25.45	28	3.87	34.33	231	4.59	28.85	44
4.22	31.44	6	3.84	34.60	279	4.28	31.01	10
3.99	33.29	8	3.79	35.11	234	3.76	35.36	112
3.79	35.11	42	3.41	39.23	42	3.58	37.21	7
3.56	37.46	22	3.33	40.21	44	3.47	38.47	6
3.44	38.78	18	3.21	41.79	14	3.32	40.22	23
3.33	40.20	38	2.91	46.30	5	2.47	55.18	10
3.18	42.06	12	2.74	49.23	10	2.26	60.86	13
3.00	44.81	15	2.62	51.68	3	2.09	66.35	7
2.93	45.93	12	2.55	53.35	18			
2.85	47.36	13	2.47	55.00	27			
2.77	48.81	7	2.27	60.37	24			
2.70	50.15	11	2.10	65.92	9			
2.46	55.32	10	2.01	69.28	9			
2.41	56.65	6	1.97	75.48	13			
2.25	60.99	10						
2.07	66.79	5						
2.03	68.56	5						
1.89	74.17	10						
1.81	78.27	7						

*HPC is amorphous in nature

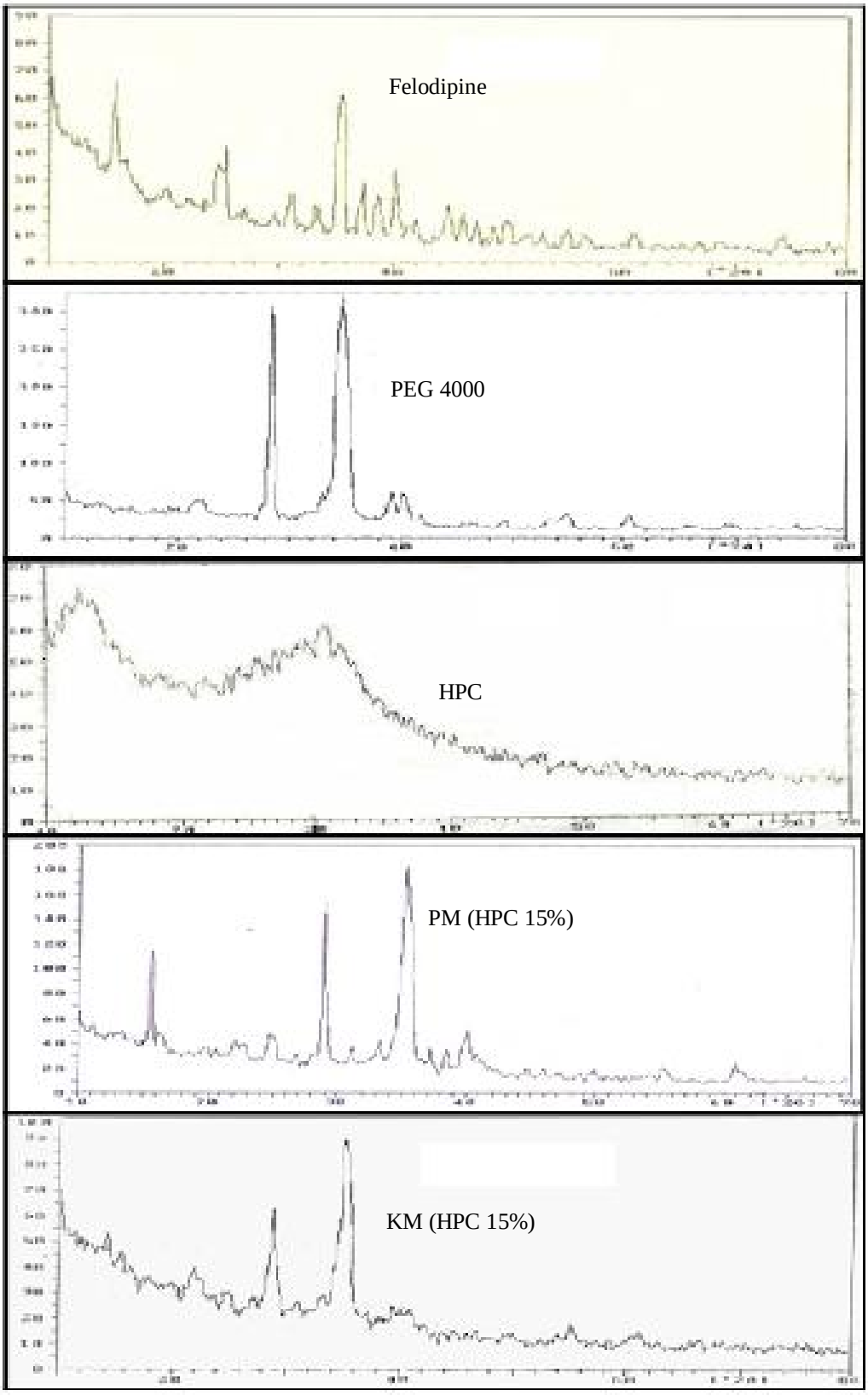


Figure 16: Comparative XRD spectra of felodipine, PEG 4000, HPC and felodipine:PEG 4000:HPC (15%) PMs and solid ternary systems

Table 24: XRD values for felodipine, PEG 4000 and felodipine:PEG 4000:HPC (15%) PMs at 1:3 ratio

Felodipine			PEG 4000			Felodipine:PEG 4000 1:3(PM)		
d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0
8.32	15.80	24	5.92	22.28	11	8.44	15.59	71
6.58	20.02	2	4.66	28.41	222	5.89	22.38	5
5.27	25.08	13	4.66	28.41	28	5.35	24.69	13
5.19	25.45	28	4.04	32.88	231	4.69	28.23	7
4.22	31.44	6	3.84	34.60	279	4.56	31.12	19
3.99	33.29	8	3.79	35.11	234	4.26	33.39	23
3.79	35.11	42	3.41	39.23	42	3.82	34.81	86
3.56	37.46	22	3.33	40.21	44	3.78	35.24	172
3.44	38.78	18	3.21	41.79	14	3.72	34.77	81
3.33	40.20	38	2.91	46.30	5	3.58	37.20	18
3.18	42.06	12	2.74	49.23	10	3.47	38.48	18
3.00	44.81	15	2.62	51.68	3	3.36	39.72	34
2.93	45.93	12	2.55	53.35	18	3.33	40.17	44
2.85	47.36	13	53.35	55.00	27	3.00	44.82	9
2.77	48.81	7	55.00	60.37	24	2.93	45.93	9
2.70	50.15	11	60.37	65.92	9	2.70	50.00	10
2.46	55.32	10	65.92	69.28	9	2.60	54.82	14
2.41	56.65	6	1.97	75.48	13	2.47	55.08	18
2.25	60.99	10				2.26	60.80	23
2.07	66.79	5						
2.03	68.56	5						
1.89	74.17	10						
1.81	78.27	7						

*HPC is amorphous in nature

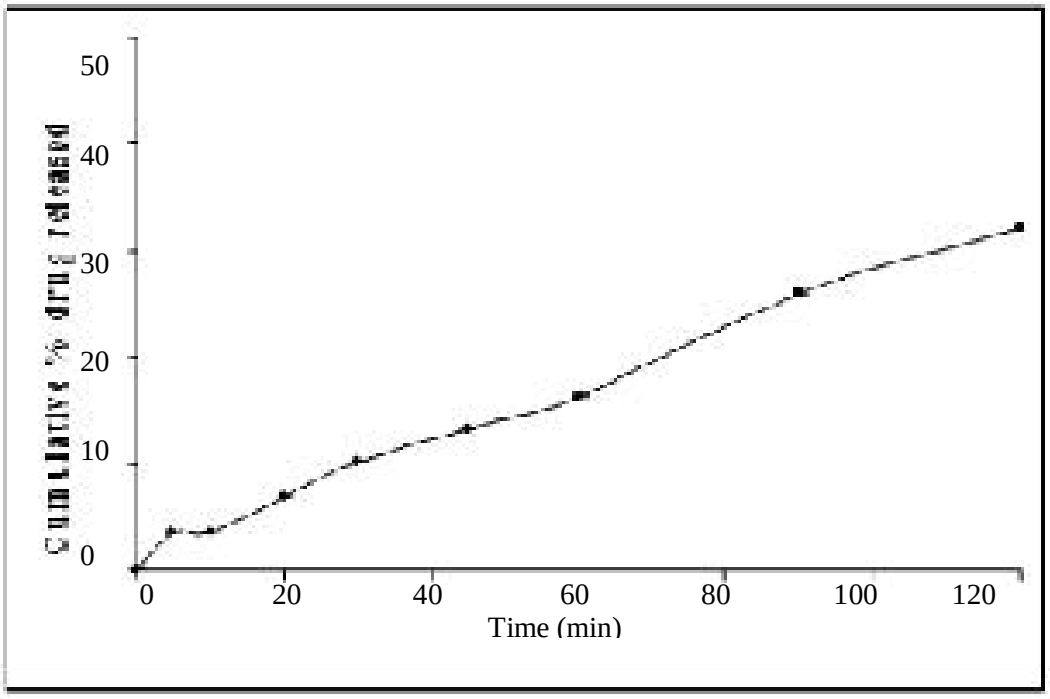
Table 25: XRD values for felodipine, PEG 4000 and felodipine:PEG 4000:HPC (15%) solid ternary system at 1:3 ratio

Felodipine			PEG 4000			Felodipine:PEG 4000 1:3(PM)		
d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0	d(A)	$^0 2\theta$	I/I_0
8.32	15.80	24	5.92	22.28	11	9.28	14.16	4
6.58	20.02	2	4.66	28.41	222	5.97	22.07	6
5.27	25.08	13	4.04	32.88	28	5.33	24.79	4
5.19	25.45	28	3.87	34.33	231	4.59	28.87	34
4.22	31.44	6	3.84	34.60	279	3.80	35.00	71
3.99	33.29	8	3.79	35.11	234	2.47	55.17	9
3.79	35.11	42	3.41	39.23	42	2.11	65.53	8
3.56	37.46	22	3.33	40.21	44			
3.44	38.78	18	3.21	41.79	14			
3.33	40.20	38	2.91	46.30	5			
3.18	42.06	12	2.74	49.23	10			
3.00	44.81	15	2.62	51.68	3			
2.93	45.93	12	2.55	53.35	18			
2.85	47.36	13	2.47	55.00	27			
2.77	48.81	7	2.27	60.37	24			
2.70	50.15	11	2.10	65.92	9			
2.46	55.32	10	2.01	69.28	9			
2.41	56.65	6	1.97	75.48	13			
2.25	60.99	10						
2.07	66.79	5						
2.03	68.56	5						
1.89	74.17	10						
1.81	78.27	7						

*HPC is amorphous in nature

Table 26: *In vitro* dissolution data of solid binary system of felodipine with PEG 4000 at 1:1 ratio

Time (min)	Cumulative percent of drug relased (± SD,n=3)			
	Felodipine	**PM**	**SD**	**KM**
10	3.52 ± 0.01	6.83 ± 0.21	13.45 ± 0.19	13.58 ± 0.33
20	6.79 ± 0.03	10.08 ± 0.17	16.66 ± 0.22	23.24 ± 0.45
30	10.03 ± 0.02	13.30 ± 0.18	19.84 ± 0.21	29.66 ± 0.32
45	13.27 ± 0.06	16.48 ± 0.27	36.00 ± 0.28	42.51± 0.48
60	16.38 ± 0.01	22.85 ± 0.26	48.73 ± 0.30	51.97 ± 0.27
90	25.94 ± 0.01	32.37 ± 0.23	58.11± 0.27	64.54 ± 0.54
120	32.19 ± 0.02	41.76 ± 0.25	70.57 ± 0.26	73.76 ± 0.65



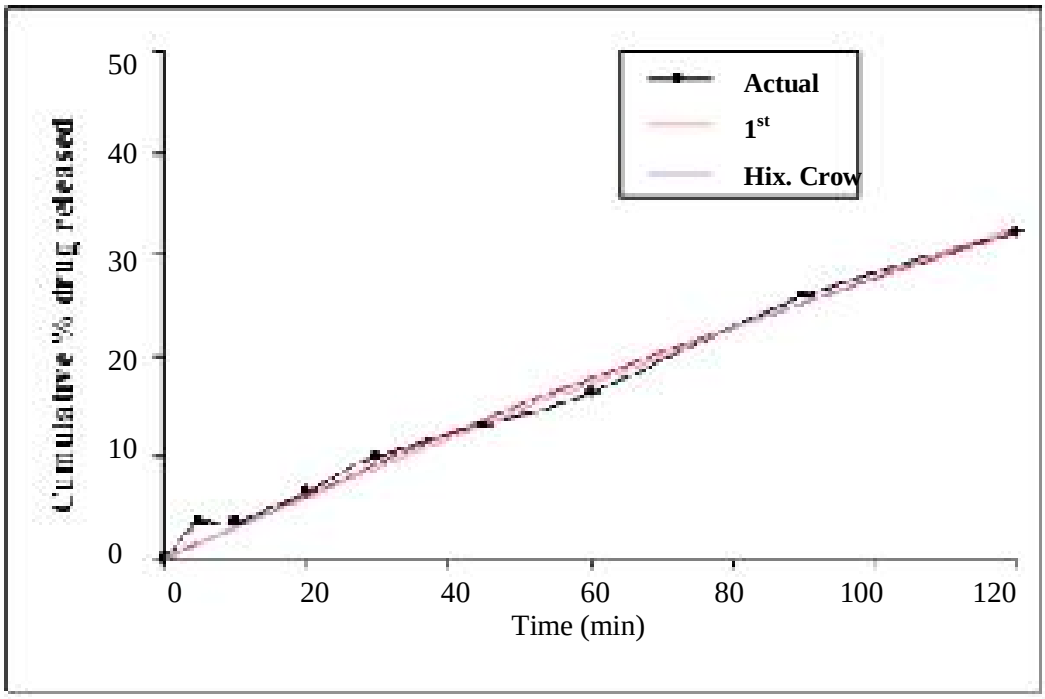
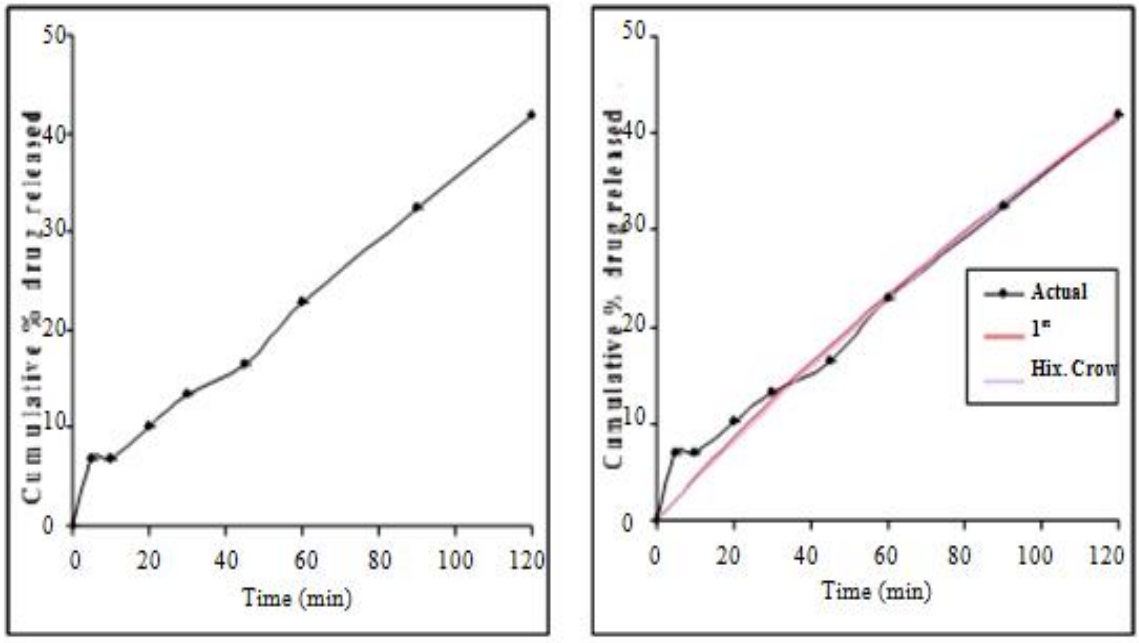
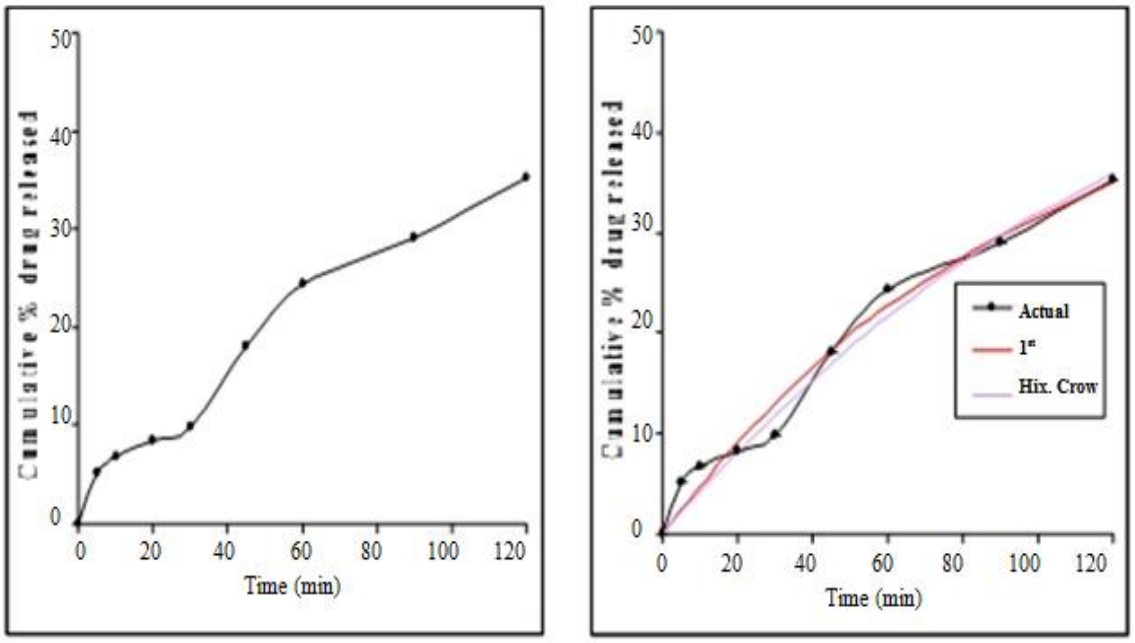


Figure 17: Dissolution profile of felodipine in 0.1N HCl (a) without model fitting (b) with model fitting



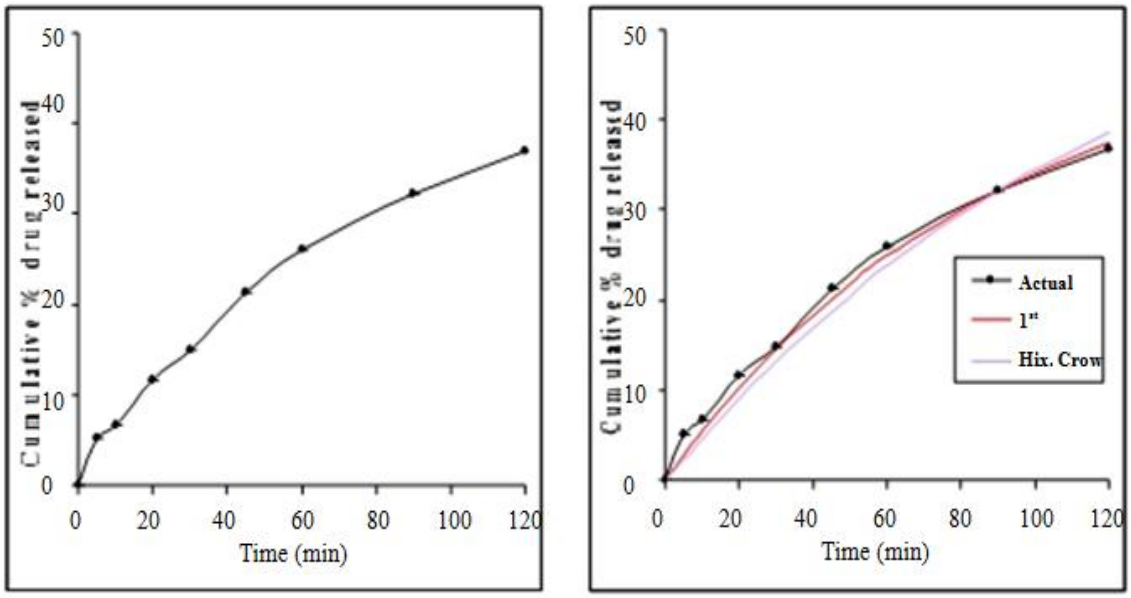
(a) **(b)**

Figure 18: Dissolution profile of felodipine:PEG 4000 PMs at 1:1 ratio (a) without model fitting (b) with model fitting



(a) **(b)**

Figure 19: Dissolution profile of felodipine:PEG 4000 solid binary system (SD) at 1:1 ratio (a) without model fitting (b) with model fitting



(a) **(b)**

Figure 20: **Dissolution profile of felodipine:PEG 4000 solid binary system (KM) at 1:1 ratio (a) without model fitting (b) with model fitting**

Table 27: ***In vitro*** **dissolution data of solid binary system of felodipine with PEG 4000 at 1:3 ratio**

Time (min)	Cumulative percent of drug relased (± SD,n=3)			
	Felodipine	PM	SD	KM
10	3.52 ± 0.01	6.83 ± 0.23	13.45± 0.17	14.54 ± 0.32
20	6.79 ± 0.03	10.08 ± 0.17	26.54 ± 0.24	28.21 ± 0.43
30	10.03 ± 0.02	15.30 ± 0.18	32.93 ± 0.21	36.20 ± 0.30
45	13.22 ± 0.06	22.98 ± 0.27	45.76 ± 0.26	49.01 ± 0.47
60	16.38 ± 0.01	26.09 ± 0.24	55.20 ± 0.30	61.68 ± 0.24
90	25.94 ± 0.01	35.59 ± 0.14	64.54 ± 0.26	67.76 ± 0.56
120	32.19 ± 0.02	44.98 ± 0.25	76.96 ± 0.24	80.16 ± 0.62

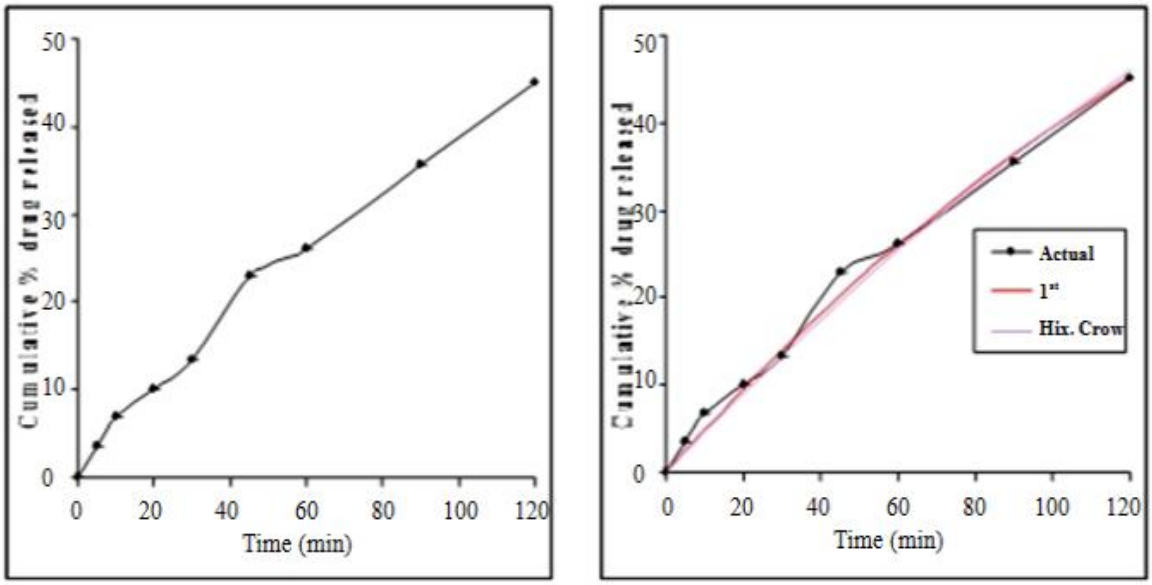


Figure 21: Dissolution profiles of felodipine:PEG 4000 PMs at 1:3 ratio (a) without model fitting (b) with model fitting

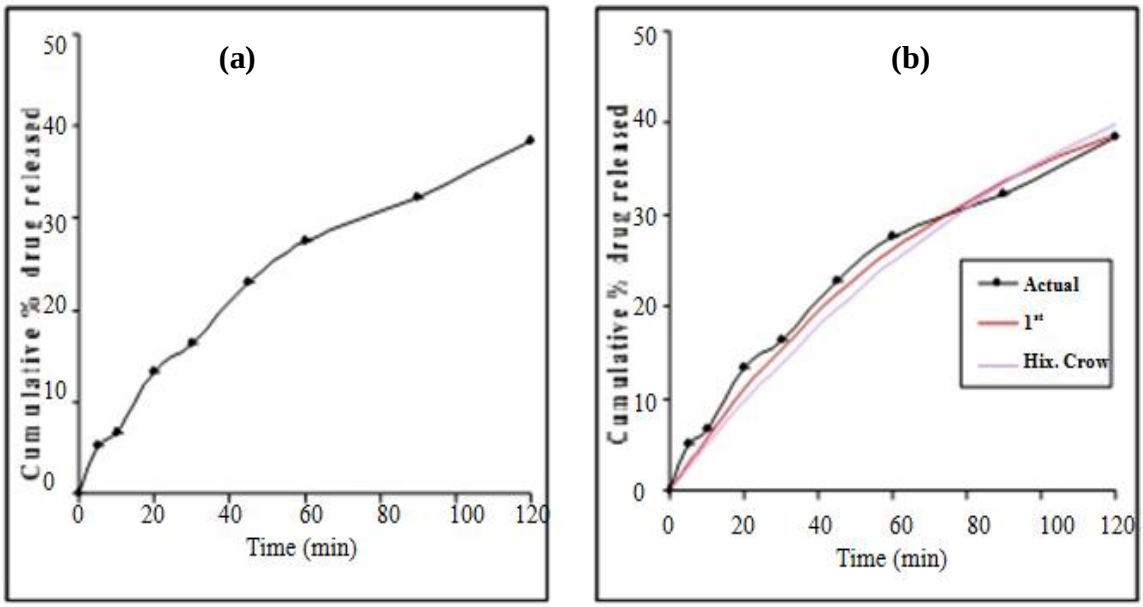
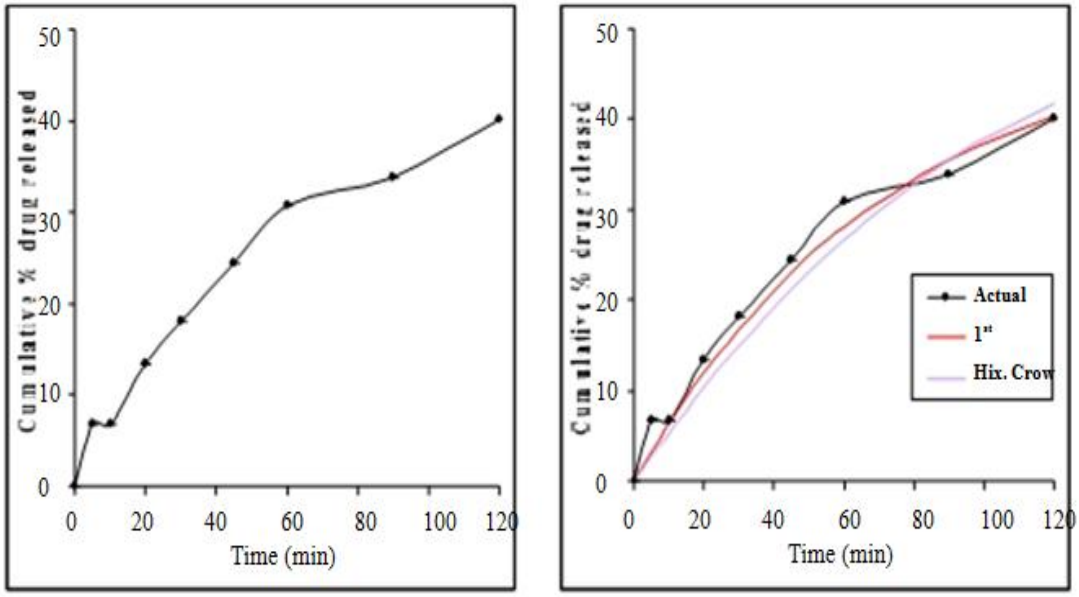


Figure 22: Dissolution profile of felodipine:PEG 4000 solid binary system (SD) at 1:3 ratio (a) without model fitting (b) with model fitting

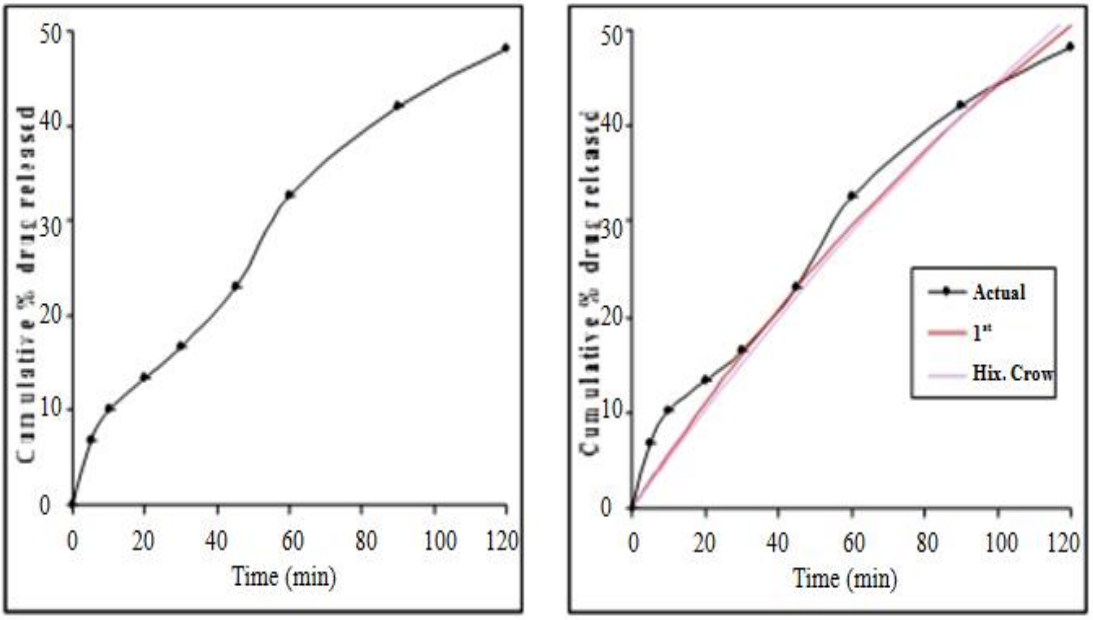


(a) **(b)**

Figure23: **Dissolution profile of felodipine:PEG 4000 solid binary system (KM) at 1:3 ratio (a) without model fitting (b) with model fitting**

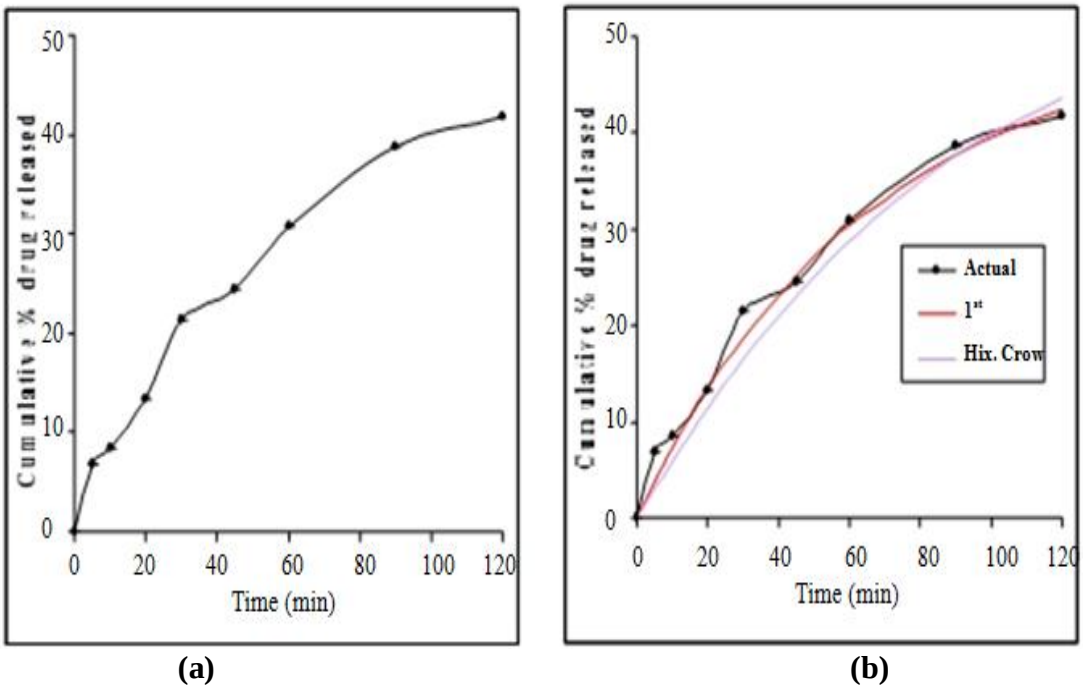
Table 28: ***In vitro* dissolution data of solid binary system of felodipine with PEG 4000 at 1:5 ratio**

Time (min)	Cumulative percent of drug relased (± SD,n=3)			
	Felodipine	PM	SD	KM
10	3.52 ± 0.01	12.12 ± 0.21	16.76 ± 0.19	18.76 ± 0.28
20	6.79 ± 0.03	13.37 ± 0.17	26.54 ± 0.22	28.54 ± 0.24
30	10.03 ± 0.02	16.57 ± 0.18	42.75 ± 0.21	52.75 ± 0.26
45	13.27 ± 0.06	19.73 ± 0.27	49.08 ± 0.28	62.08 ± 0.48
60	16.38 ± 0.01	32.56 ± 0.26	61.60 ± 0.30	71.60 ± 0.27
90	25.94 ± 0.01	42.07 ± 0.11	77.41 ± 0.27	79.41 ± 0.52
120	32.19 ± 0.02	48.12 ± 0.25	83.36 ± 0.26	86.36 ± 0.58



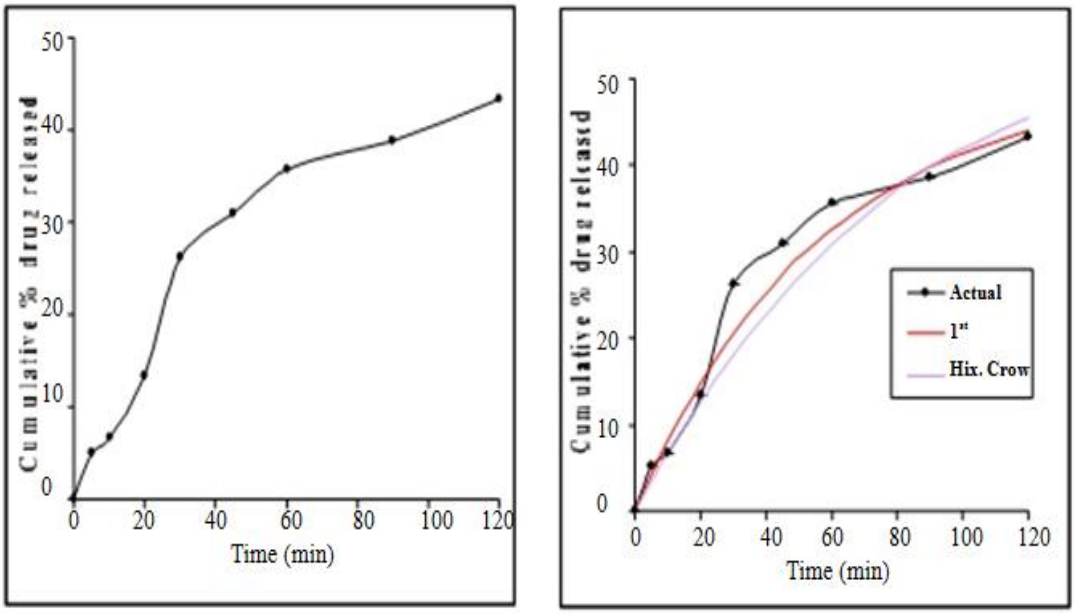
(a) **(b)**

Figure 24: Dissolution profile of felodipine:PEG 4000 PMs at 1:5 ratio (a) without model fitting (b) with model fitting



(a) **(b)**

Figure 25: Dissolution profile of felodipine : PEG 4000 solid binary system (SD) at 1:5 ratio (a) without model fitting (b) with model fitting



(a) **(b)**

Figure 26: **Dissolution profile of felodipine: PEG 4000 solid binary system (KM) at 1:5 ratio (a) without model fitting (b) with model fitting**

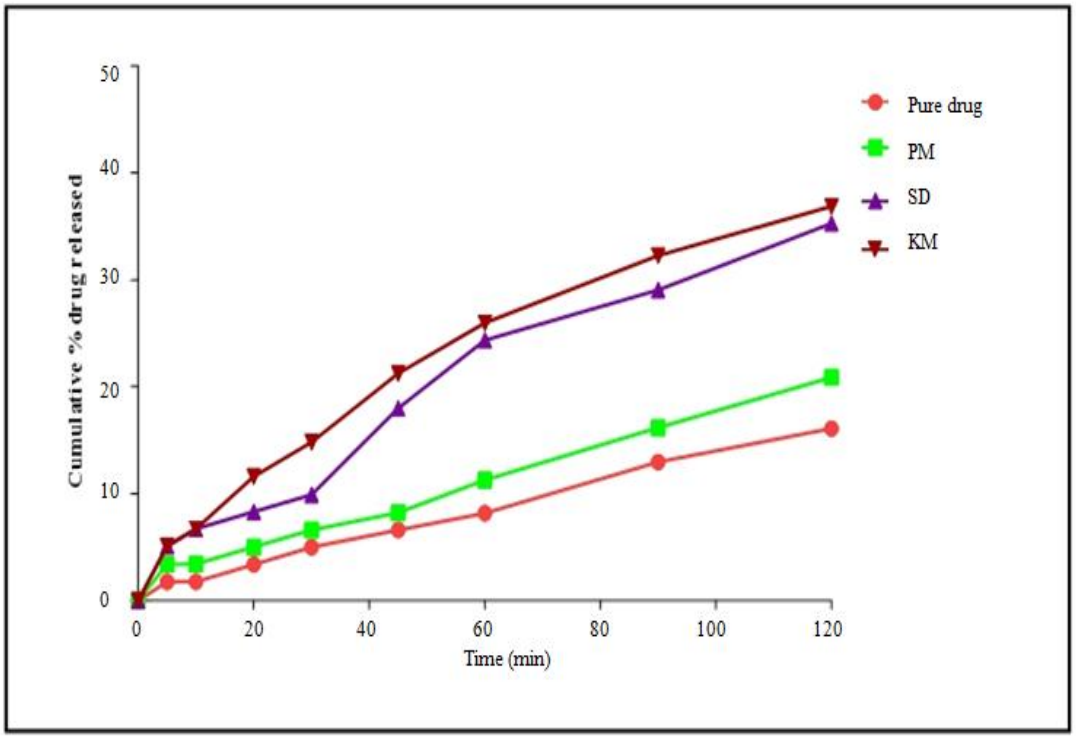


Figure 27: **Comparative dissolution profiles of felodipine:PEG 4000 PMs and solid binary systems at 1:1 ratio**

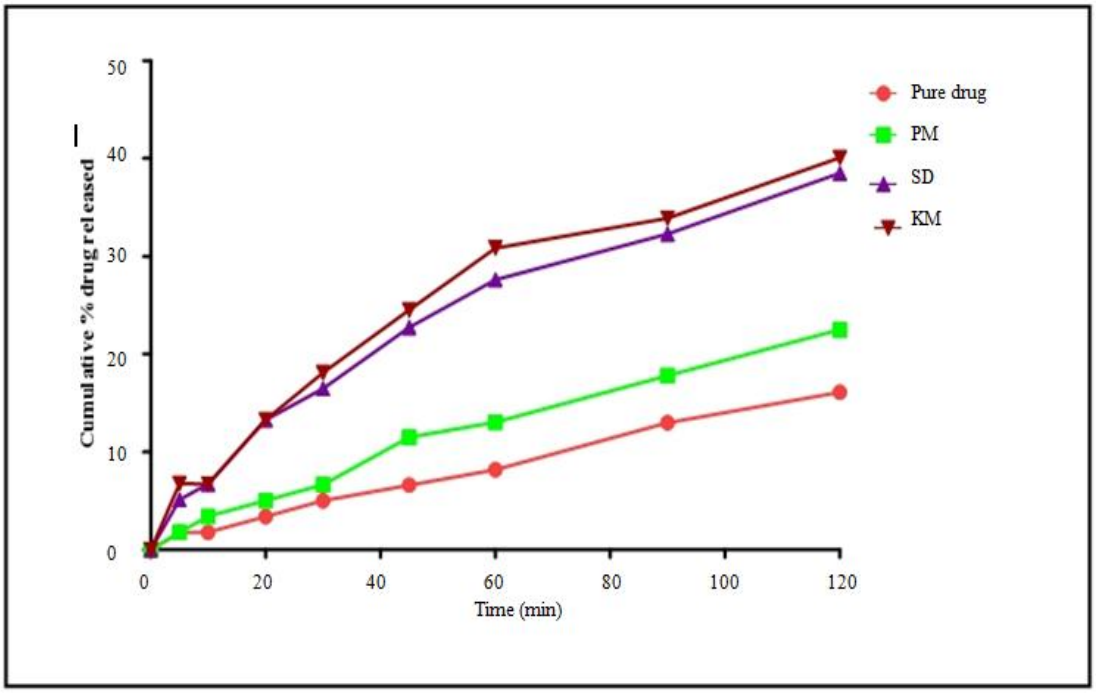


Figure 28: Comparative dissolution profiles of felodipine:PEG 4000 PMs and solid binary systems at 1:3 ratio

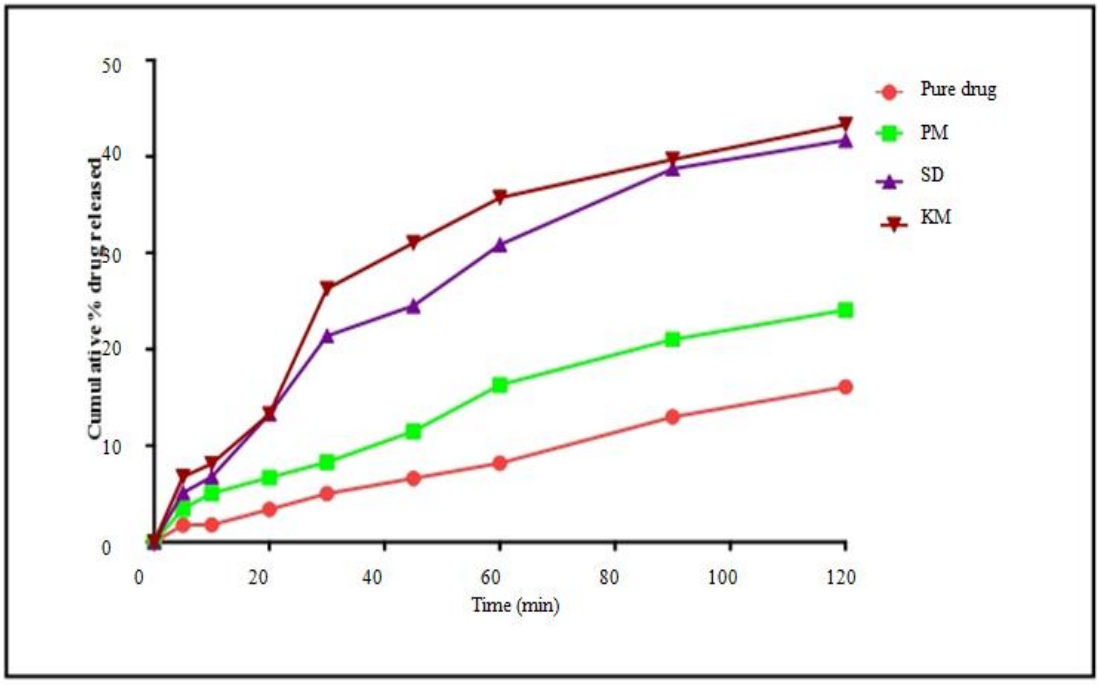


Figure 29: Comparative dissolution profile of felodipine:PEG 4000 PMs and solid binary system at 1:5 ratio

Table 29: Various dissolution parameters of felodipine, felodipine: PEG 4000 PMs and solid binary systems

Methods	Drug: carrier ratio (w/w)	DE_{30} (%)	DE_{60} (%)	DP_{30} (%)	T_{50} (min)	RDR_{30}	MDT_{120}
Felodipine	----	5.41	9.31	10.03	213.6	1	55.83
PM	1:1	8.43	12.86	13.30	156	1.32	55.09
SD	1:1	13.93	24.54	19.84	68.8	1.9	49.07
KM	1:1	17.76	29.71	29.66	60.1	2.95	44.02
PM	1:3	10.90	14.61	15.30	137.9	1.52	53.07
SD	1:3	18.76	32.16	32.93	56.1	3.28	43.72
KM	1:3	20.50	34.02	36.20	50.1	3.60	42.10
PM	1:5	12.12	17.34	16.57	119.6	1.65	47.11
SD	1:5	21.04	36.52	42.75	44.3	4.26	39.76
KM	1:5	22.67	42.4	52.56	39.5	5.24	36.45

Where, DE= Dissolution efficiency after 30 and 60 min, DP= percent of drug dissolved after 30 min (DP), T_{50} = time necessary to dissolve 50% drug and RDR = relative dissolution rate

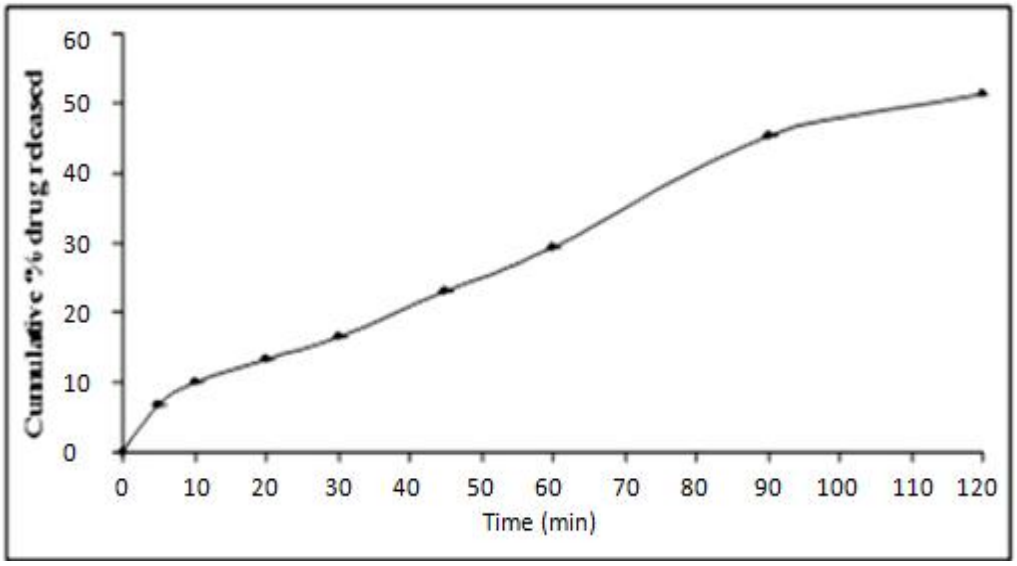
Table 30: Mathematical modeling and comparative kinetic values of felodipine, felodipine:PEG 4000 PMs and solid binary systems

Methods	Drug : carrier ratio (w/w)	First order rates K_1x10^2 (min^{-1})		Hix.Crow K_{HC} x 10^2 ($mg^{1/3}.min^{1}$)	
		r	K_1	r	K_{HC}
Felodipine	----	0.9967	-0.0038	0.9927	-0.0012
PM	1:1	0.9916	-0.0044	0.9897	-0.0014
SD	1:1	0.9934	-0.0101	0.9904	-0.0029
KM	1:1	0.9971	-0.0115	0.9875	-0.0032
PM	1:3	0.9968	-0.0050	0.9945	-0.0016
SD	1:3	0.9947	-0.124	0.9833	-0.0034
KM	1:3	0.9911	-0.00137	0.9771	-0.0037
PM	1:5	0.9966	-0.0058	09815	-0.0018
SD	1:5	0.9955	-0.0157	0.9829	-0.0046
KM	1:5	0.9822	0.0177	0.9572	-0.0041

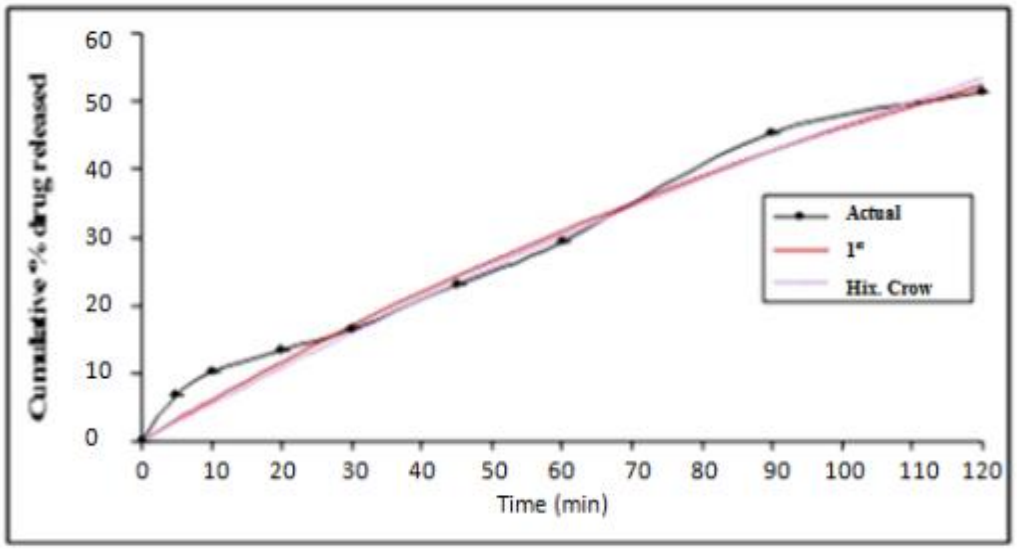
Where, K_1 $K_{HC,}$ = release rate constants for First order and Hixon Crowell's model

Table 31: ***In vitro*** **dissolution data of felodipine and felodipine:PEG 4000:HPC solid ternary system**

Time (min)	Cumulative percent of drug released (±SD, n=3)						
	Felodipine	Felodipine : PEG 4000 : HPC solid ternary systems					
		HPC 5% PM	HPC 5% KM	HPC 10% PM	HPC 10% KM	HPC 15% PM	HPC 15% KM
10	3.52 ± 0.01	6.87 ± 0.48	20.07 ± 0.58	10.14 ± 0.48	26.68 ± 0.52	13.5 ± 0.43	33.30 ± 0.46
20	6.79 ± 0.03	10.14 ± 0.38	29.83 ± 0.57	13.37 ± 0.35	33.12 ± 0.37	15.76 ± 0.54	52.86 ± 0.70
30	10.03 ± 0.02	16.88 ± 0.27	42.75 ± 0.70	18.88 ± 0.47	59.11 ± 0.64	19.04 ± 0.25	72.20 ± 0.41
45	13.27 ± 0.06	22.98 ± 0.58	62.03 ± 0.34	26.24 ± 0.58	68.54 ± 0.36	26.24 ± 0.65	78.30 ± 0.53
60	16.38 ± 0.01	29.32 ± 0.48	68.15 ± 0.26	35.79 ± 0.57	77.85 ± 0.44	35.78 ± 0.70	84.32 ± 0.62
90	25.94 ± 0.01	45.24 ± 0.35	80.62 ± 0.64	47.24 ± 0.64	83.84 ± 0.66	51.67 ± 0.63	93.49 ± 0.42
120	32.19 ± 0.02	51.38 ± 0.28	89.75 ± 0.27	54.57 ± 0.59	92.95 ± 0.73	57.77 ± 0.64	96.15 ± 0.34

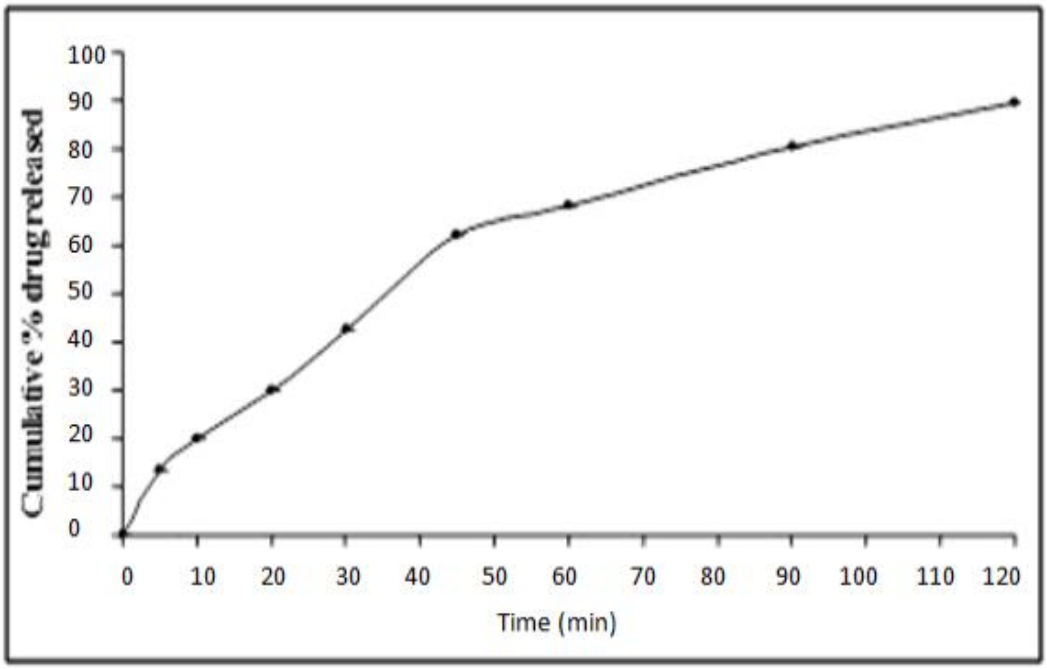


(a)



(b)

Figure 30: Dissolution profile of felodipine:PEG 4000:HPC 5% (PMs) at 1:3 ratio a) without model fitting b) with model fitting



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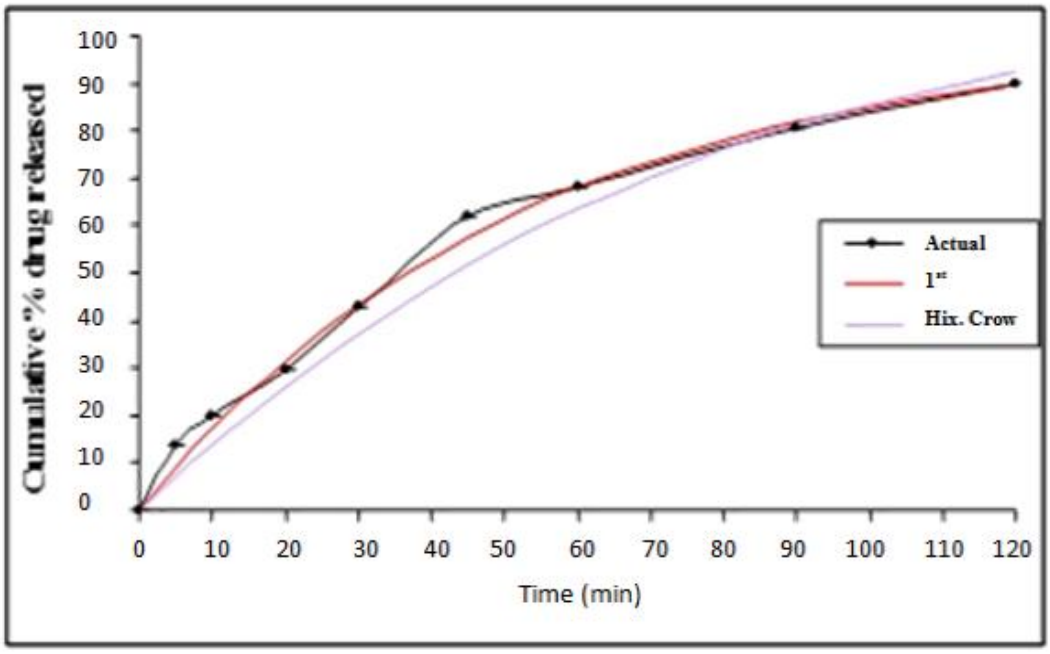
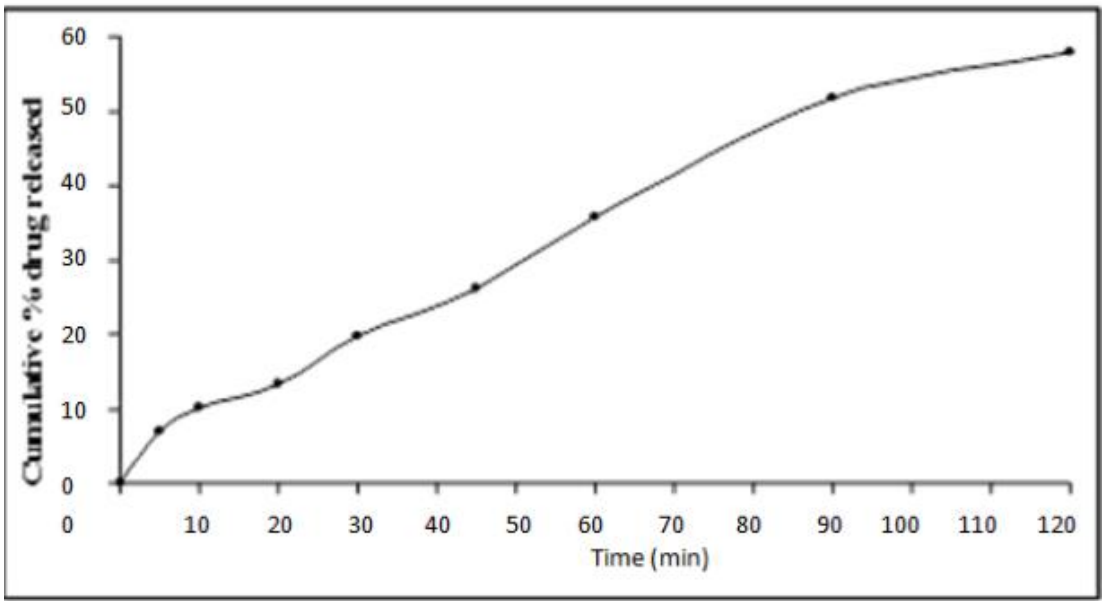
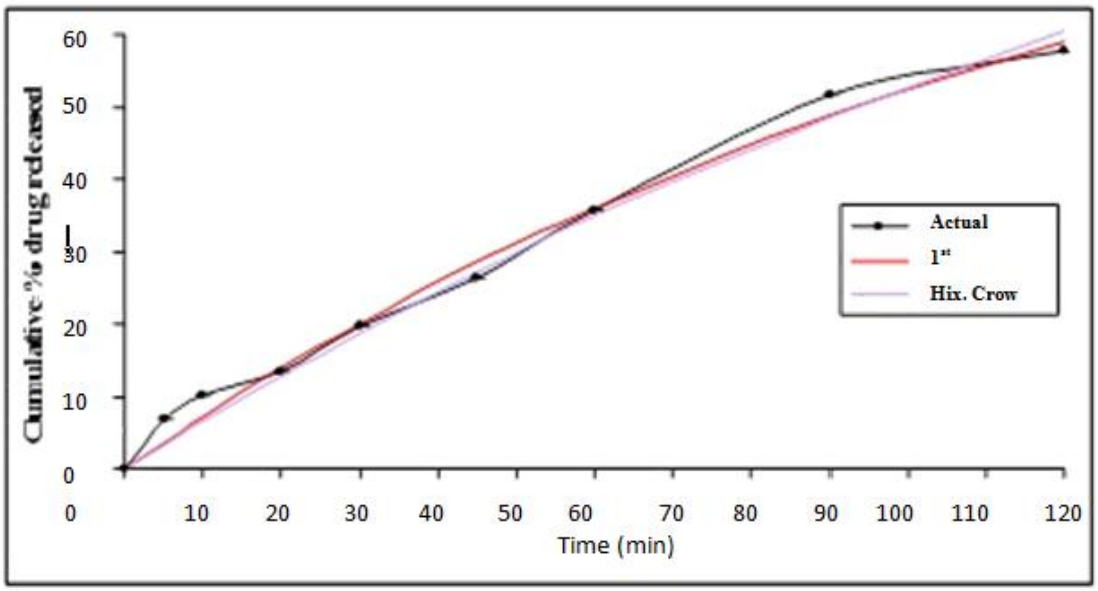


(b)

Figure 31: Dissolution profile of felodipine:PEG 4000:HPC 5% (KM) at 1:3 ratio a) without model fitting b) with model fitting

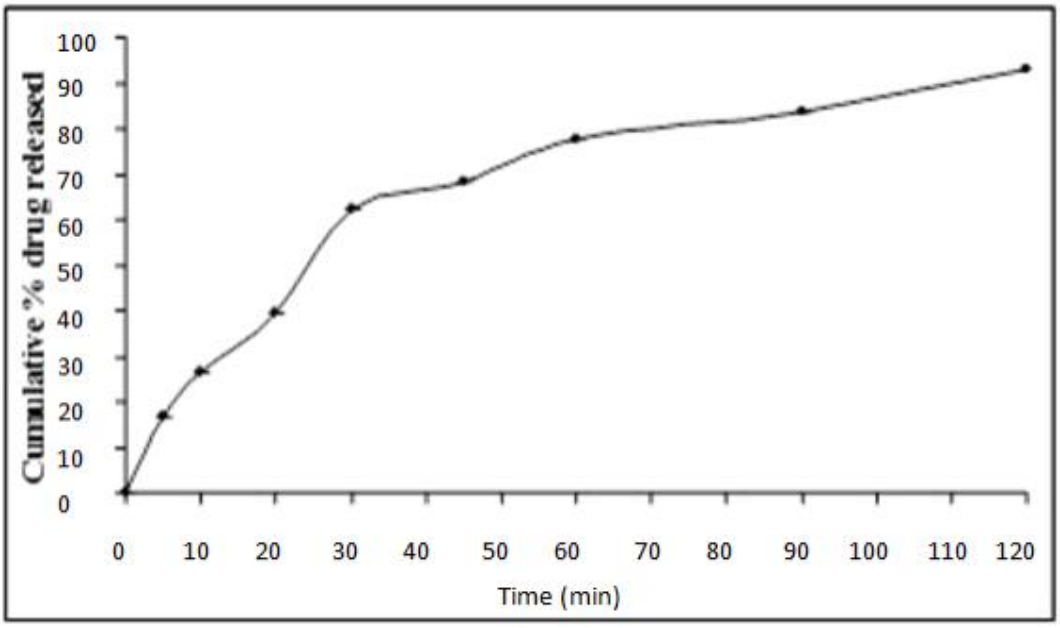


(a)

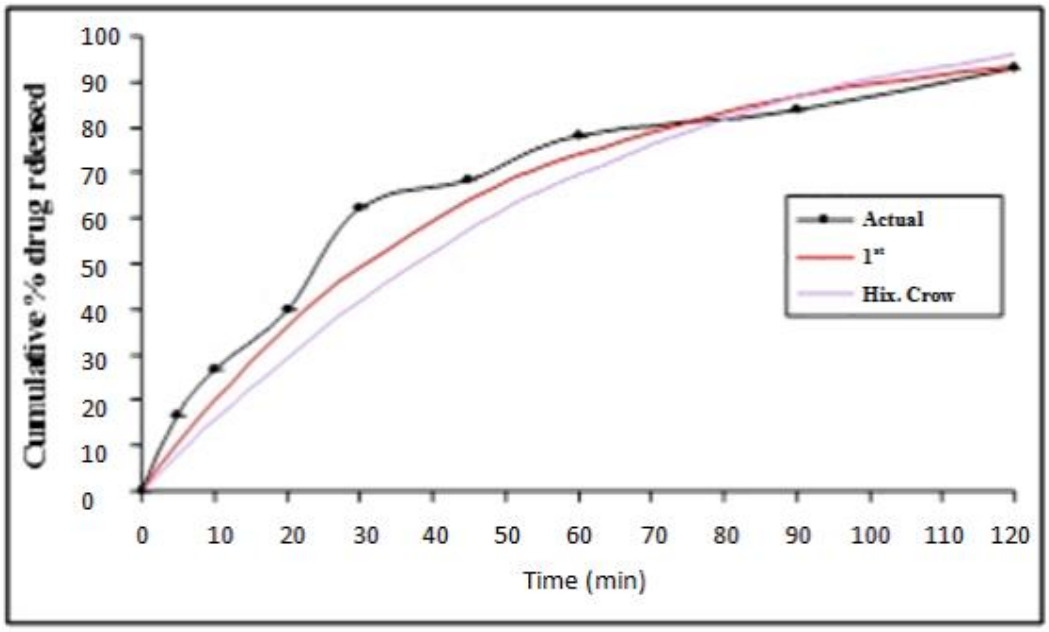


(b)

Figure 32: Dissolution profile of felodipine:PEG 4000:HPC (10%) PMs at 1:3ratio a) without model fitting b) with model fitting

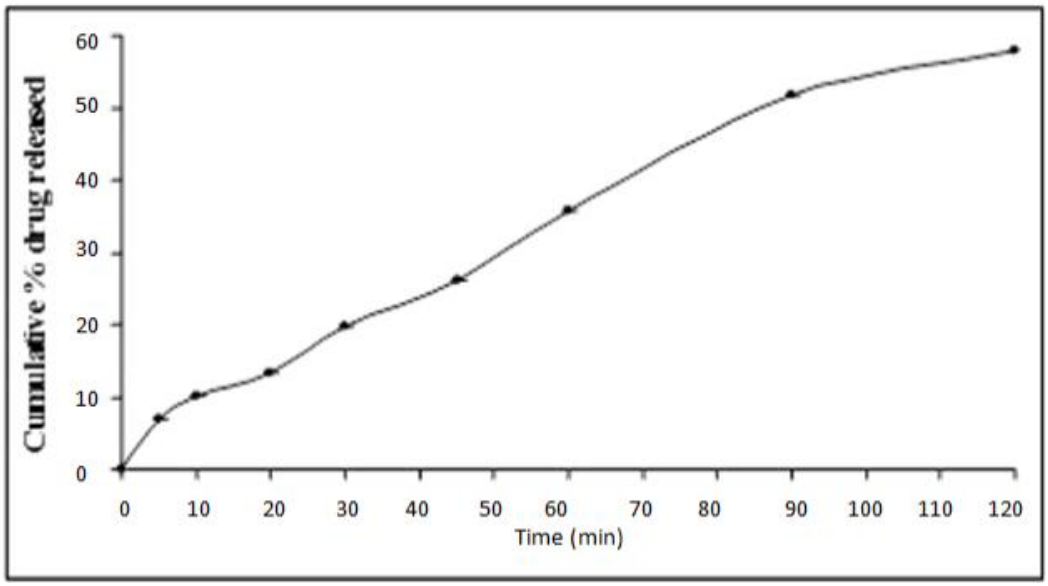


(a)

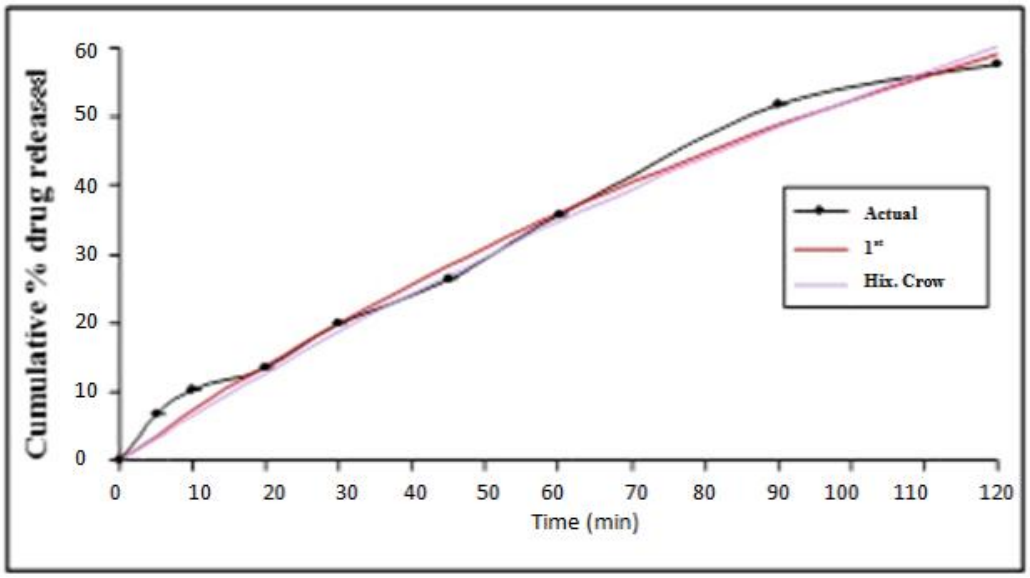


(b)

Figure 33: **Dissolution profile of felodipine:PEG 4000:HPC 10% (KM) at 1:3 ratio a) without model fitting b) with model fitting**

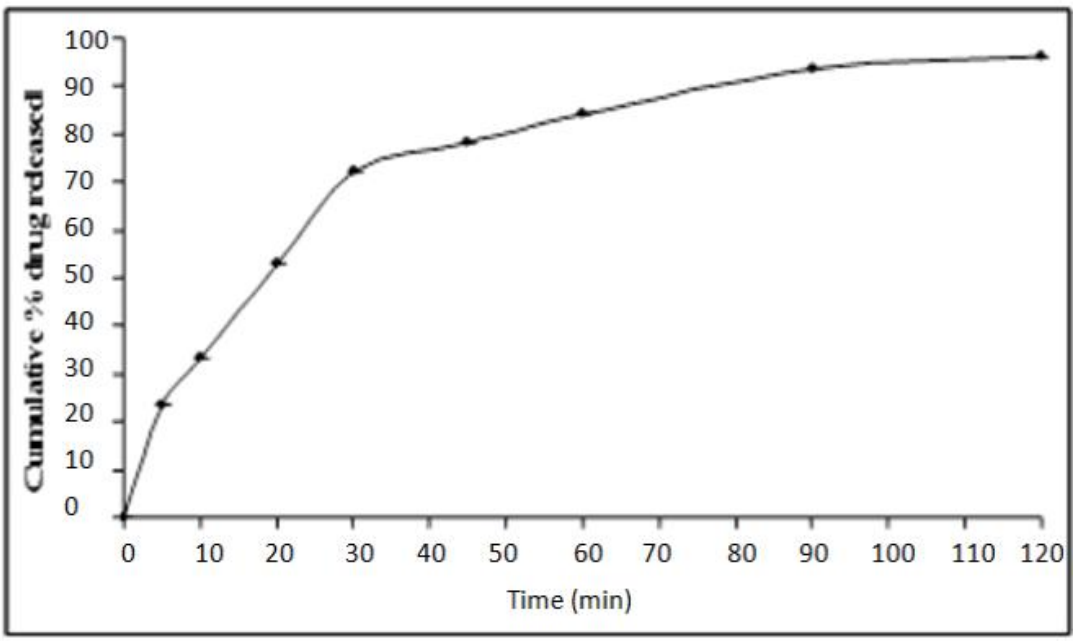


(a)

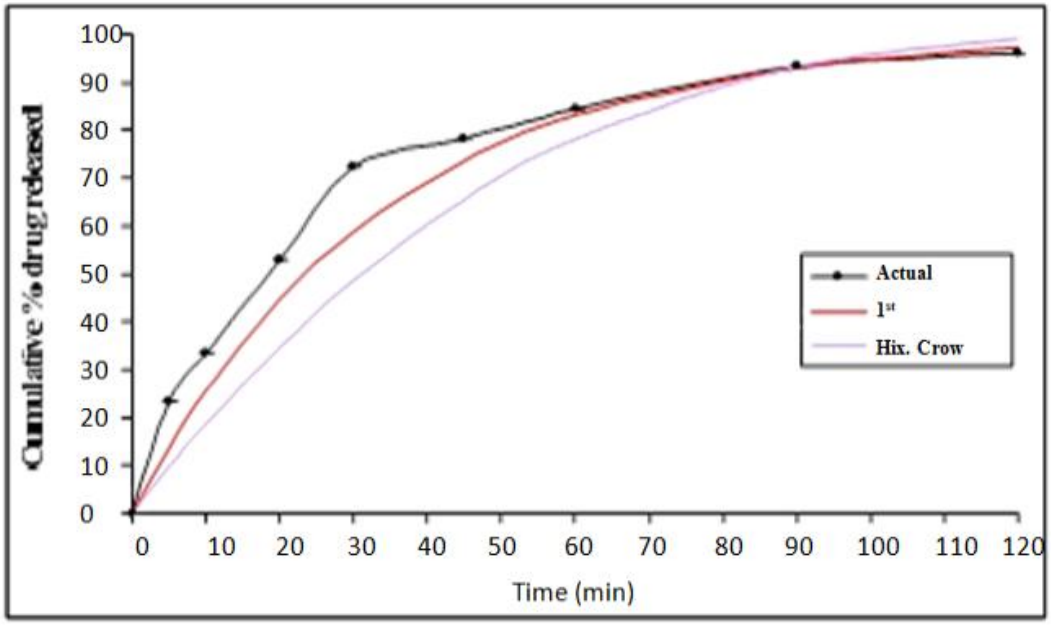


(b)

Figure 34 Dissolution profile of felodipine:PEG 4000:HPC (15%) PMs at 1:3 ratio a) without model fitting b) with model fitting



(a)



(b)

Figure 35: Dissolution profile of felodipine:PEG 4000:HPC 15% (KM) at 1:3 ratio a) without model fitting b) with model fitting

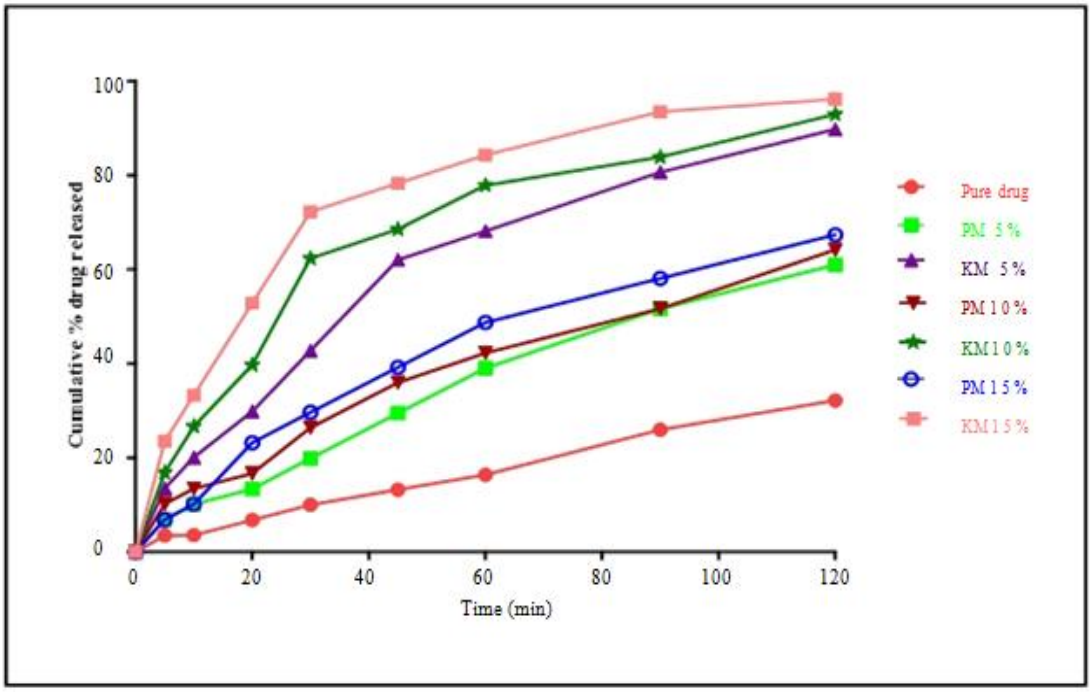


Figure 36: Comparative dissolution profiles of felodipine and PEG 4000 PMs and solid ternary systems at 1:3 ratio

Table 32: Various dissolution parameters of felodipine, felodipine:PEG 4000:HPC PMs and solid ternary systems

Methods	Drug: carrier ratio (w/w)	DE_{30} (%)	DE_{60} (%)	DP_{30} (%)	T_{50} (min)	RDR_{30}	MDT_{120}
Felodipine	----	5.41	9.31	10.03	213.6	1	55.83
PM	5%	11.24	16.94	16.88	111.9	1.68	50.24
KM	5%	24.34	41.54	42.75	36.6	4.15	38.89
PM	10%	12.24	18.56	18.08	103.8	1.8	49.89
KM	10%	33.11	51.22	62.83	30.06	6.21	32.32
PM	15%	13.45	19.24	19.04	93.30	1.89	48.89
KM	15%	41.90	60.09	72.20	23.4	7.19	25.18

Where, DE= Dissolution efficiency after 30 and 60 min, DP= percent of drug dissolved after 30 min (DP), T_{50} = time necessary to dissolve 50% drug and RDR = relative dissolution rate

Table 33: **Mathematical modeling and comparative kinetic values of felodipine, felodipine: PEG 4000:HPC PMs and solid ternary systems**

Methods	Drug : carrier ratio (w/w)	First order rates $K_1 x 10^2$ (min^{-1})		Hix.Crow $K_{HC} \times 10^2$ ($mg^{1/3}.min^1$)	
		r	K_1	r	K_{HC}
Felodipine	-----	0.9967	-0.0038	0.9927	-0.0012
PM	5%	0.9922	-0.0062	0.9897	-0.0019
KM	5%	0.9976	-0.0190	0.9839	-0.0048
PM	10%	0.9952	-0.0067	0.9813	-0.0020
KM	10%	0.9838	-0.0226	0.9438	-0.0055
PM	15%	0.9949	-0.0075	0.9927	-0.0022
KM	15%	0.9830	-0.0296	0.9165	-0.0066

Where, K_1 $K_{HC,}$ = release rate constants for First order and Hixon Crowell's model

DISCUSSION

Felodipine is used as an antihypertensive and antianginal drug, belongs to BCS class II drug (low solubility and high permeability). It undergoes extensive first pass metabolism with a bioavailability of only about 15%. The major drawback in the therapeutic application and efficacy of felodipine as oral dosage form is its low aqueous solubility. Hence this work was planned to improve dissolution characteristics of the model drug by increasing its release and solubility through solid dispersion technique. Solid binary systems of felodipine with PEG 4000 were prepared by kneading and solvent deposition method at different drug:carrier ratios. In the next phase, ternary systems were prepared by kneading method with the addition of different concentrations of HPC to felodipine:PEG 4000 (1:3 ratio) binary systems to investigate the effect of hydrophilic polymer on the solubility and dissolution rate of the felodipine.

All prepared solid binary and ternary systems were found to be fine and free flowing. The characterization of binary and ternary systems was performed by FT-IR and powder X-ray diffractometry. The *in vitro* dissolution results of felodipine, PMs, solid binary and ternary systems were computed by using dissolution software PCP DISSO V3.

Solubility studies of pure felodipine in different concentration of PEG 4000

An effect of PEG 4000 on the solubility of felodipine was studied and the results are summarized in **table 7** and displayed in **figure 2**. The solubility of felodipine was found to be 0.09×10^3, 0.15×10^3, 0.23×10^3, 0.32×10^3 and 0.40×10^3 µg/ml at 2%, 4%, 6%, 8% and 10% (w/v) of PEG 4000 concentration respectively. The solubility studies showed that solubility of felodipine increased linearly as a function of concentration of the carrier. These results are in accordance with the well established formation of weak water soluble complexes between water soluble polymeric carriers and poorly soluble drugs[45].

Percentage drug content

The percentage drug content results of PMs and all binary and ternary systems of felodipine are shown in **table 8** and in **table 9** respectively. The drug content was found to be in the range of 93.23 to 98.36 % for binary systems and 97.51 to 98.72 % for ternary systems. Low standard deviation (SD) values (i.e., < 1) indicated uniform drug distribution in all prepared batches. The overall yield of binary and ternary systems of felodipine was in the range of 95.87 to 99.56 % and 95.99 to 98.12 %.

Fourier transform-IR studies

To study the possible interactions between the felodipine, PEG 4000 and HPC in the solid state, IR spectra of binary and ternary systems were compared with the drug alone. The IR spectrum of felodipine, PEG 4000 and HPC are shown in **figure 3**. The IR spectrum of felodipine exhibit characteristic peaks for amide group (N-H streching) at 3368.47 cm^{-1}, aromatic C-H stretching at 3072.26 cm-^{1} and 1694.41 cm^{-1} due to C=O stretching. A very distinctive peak for PEG 4000 was a broad band at 3426.51 cm^{-1} that represents the stretching vibration for the OH groups. Other important vibrations detected in the spectrum of PEG 4000 were C-H stretching at 2286.80 cm^{-1} and C-O stretching at 1111.15 cm^{-1}.

The comparative FT-IR spectrum of felodipine, PEG 4000, PMs and its solid binary systems prepared by all methods at 1:1, 1:3 and 1:5 ratios are displayed in **figures 4, 5 and 6** respectively. The characteristics peaks of felodipine, PMs and solid binary systems prepared at all ratios are summarized in **table 10.** The PMs showed almost same characteristic peaks of drug indicating no interaction. In the spectra of 1:1, 1:3 and 1:5 ratios prepared by kneading and solvent deposition method, N-H stretching of amide group of the felodipine is shifted towards lower wavelength **table 10.** Similar results were observed with solid the ternary systems. The intensity and shape of these bands changed dramatically in all solid binary and ternary systems. A decrease in the intensity of bands may also be due to the amount of compounds. However, little shifts in the stretching vibration due to -CH_2 groups

of PEG 4000 appeared at wave numbers 2286.80 cm^{-1} suggesting the possible difference in the degree of interaction between drug and carriers in PMs, solid binary and ternary systems. Further, C=O stretching of felodipine in all solid binary systems slightly shifted to higher wavelength. These significant changes indicate the possibility of intermolecular hydrogen bonding between amide group of the felodipine and hydroxyl group of the PEG 4000. In the low frequency region (1500-500 cm^{-1}) of spectra of solid binary and ternary systems, the characteristic peaks of felodipine were almost unchanged. This indicated that overall symmetry of the molecule is not significantly affected even though the drug molecule is hydrogen bonded with the carrier.

Powder X-ray diffraction studies

Crystallinity has a great impact on the solubility and dissolution rate of poorly water soluble drugs. The powder XRD pattern of pure felodipine and PEG 4000 and HPC are shown in **figure 10.** Comparative 2θ peak values of felodipine, PMs and solid binary systems are presented in **tables 11 to 19 and** their XRD pattern of felodipine, PMs and solid binary systems are shown in **figures 11, 12 and 13** respectively. Many diffraction peaks with high intensity were observed in the diffraction pattern of felodipine due to its crystallinity. Few peaks with high intensity were observed in the diffraction pattern of PEG 4000. The spectrum of HPC was characterized by complete absence of any diffraction peaks. All principle peaks of felodipine were present in PMs. On the other hand, the diffraction pattern of all solid binary systems at 1:1, 1:3 and 1:5 ratios showed principle peaks of felodipine with significant decrease in the intensity of peak indicating the reduction in crystallinity. The intensity of felodipine at 15.80, 25.45 and 35.11(2) remarkably reduced in solid binary systems. However in the solid binary systems prepared by kneading method at 1:5 ratios, the crystallinity of felodipne was found to be reduced to a greater extent, evidenced by marked reduction in the number as well as the intensity of peaks.

X-ray diffractograms of felodipine, PMs and solid ternary systems of felodine:PEG 4000:HPC 5%, 10% and 20% prepared by kneading method are shown in **figures 14, 15 and 16** respectively. The XRD pattern of ternary systems differs significantly from that of the PMs. Also, the effect of HPC concentration on the drug crystallinity was evident from the XRD studies. A marked reduction in the number as well as the intensity of peaks was observed in case of ternary systems prepared at 15% HPC. The XRD results of all solid binary and ternary ystems indicated significant reduction in the felodipine crystallinity.

***In vitro* dissolution behaviour of solid binary and ternary systems**

The *in vitro* dissolution studies of felodipine, PMs, solid binary and ternary systems prepared by kneading and solvent deposition method were carried out in 0.1 N HCl (pH 1.2) up to period of 120 min using USP Dissolution apparatus type II. *In vitro* dissolution data was evaluated on the basis of cumulative percentage drug release Vs time profile. The *in vitro* results all solid binary and ternary systems and their corresponding PMs were compared with the pure felodipine. The percentage of felodipine dissolved at 30 min (DP_{30}) and dissolution efficiency 30 min (DE_{30}) and at 60 min (DE_{60}); the characteristic time for 50% dissolution of felodipine (T_{50} min) and mean dissolution time (MDT) were calculated for all solid binary and ternary systems. Khan[47] suggested the 'dissolution efficiency' (DE) as a suitable parameter for the *in vitro* dissolution data. It is defined as the area under the dissolution curve up to a certain time 't', expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

$$\text{Dissolution efficiancy (DE)} = \left[\frac{\int \lambda_{\beta}^{t} \, x \, dt}{\nu \, md \, x \, t} \right] x100$$

The *in vitro* dissolution data of felodipine, PMs and solid binary systems studied in 0.1N HCl are presented in **table 26, 27 and 28** respectively and their dissolution profiles (with and without model fitting) are shown in **figure 17 to 26.** The comparative dissolution profiles of felodipine, PMs and all binary

systems prepared at 1:1, 1:3 and 1:5 are shown in **figure 27, 28** and **29** respectively. Various dissolution parameters such as DE_{30}, DE_{60}, DP_{30}, T_{50}, RDR_{30} and MDT of solid binary systems are summarized in **table 29.** Dissolution profiles were also analysed according to two release models i.e., first order and Hixson-Crowell cube root model. The calculated release rate constants 'K' and `r' values of these models for solid binary systems are summarized in **table 30.**

The dissolution of drug alone was incomplete even after 120 minutes. The *in vitro* dissolution studies indicated higher dissolution rate of felodipine from solid binary systems compared to felodipine alone and the corresponding PMs. The DE_{30} and DE_{60} values of the solid binary systems prepared by kneading and solvent deposition methods were relatively high compared to the values from the PMs and felodipine alone. The value of T_{50} and MDT of all solid binary systems were lower than felodipine alone. Further, it was found that the drug dissolution was higher in 1:5 (drug:carrier ratio) compared to 1:1 and 1:3 ratios. These observations indicated the enhanced dissolution of solid binary systems with increase in the concentration of PEG 4000, possibly due to drug particle size reduction as well as decrease in the crystallinity of drug during course of the solid dispersion preparation. The overall the rank order of improvement in dissolution properties of felodipine with different methods in all ratios was found in the following rank order,

KM > SD >PMs > Felodipine

The DE_{30} and DE_{60} values of the solid binary systems prepared by kneading method were higher compared to solid binary systems prepared by solvent deposition methods. This may be attributed to the less crystallinity of drug in solid binary systems prepared by kneading methods. These results are further supported by other parameters such as XRD and FT-IR studies.

In the next phase, solid ternary systems were prepared by kneading method using HPC in different concentrations (5%, 10% and 15% w/w of the solid binary system) to study the effect of hydrophilic polymer on the drug release. The *in vitro* dissolution data of felodipine, PMs and solid ternary systems are summarized in

table 31. Their respective dissolution profiles and comparative graphs are shown in **figures 30 to 35** and **figures 36** respectively. The slight increase noted in the dissolution rate in the PMs of binary and ternary systems might be due to the 'microenvironment effect' in binary systems and ability of the hydrophilic polymer (HPC) to increase drug wettability in case of ternary systems. All ternary systems exhibited a significant increase in dissolution rate with respect to the PMs and the reference drug. It was noted that the dissolution rate was progressively increased with increasing concentration of HPC in the ternary systems. Ternary system with HPC 15% showed the most significant effect on the dissolution properties of drug. The increase in dissolution rate of felodipine in ternary systems with different concentration of HPC was found in the following order,

HPC 15% > HPC 10% > HPC 5%

In addition to the size reduction of the crystalline felodipine in binary systems, the faster dissolution rate of the drug exhibited in ternary systems might be due to excellent wettability and dispersibility of drug from a solid dispersion system due to the presence of higher concentration of water soluble carrier HPC. Usually in solid dispersions, the drug is partially dissolved in melted or dissolved polymer. After drying of these solid dispersions, the drug will not nucleate to form firm crystals resulting in formation of microcrystals. Drug microcrystals are embedded in the water-soluble matrix, where hydrophilic polymers present the ability of rapid wetting and thereby dissolution of drug[47]. The release pattern in felodipine, PMs and all solid binary and ternary systems were found to be first order (best fit model) compared to Hixson-Crowell's cube root model. These results were observed based on the highest correlation coefficient 'r' values.

To analyse the statistical significance of difference between PMs, solid binary and ternary systems and pure drug, one-way ANOVA with Dunnett multiple comparison test was used. Obtained $p < 0.05$ were considered to be statistically significant. Significant differences in the means of DE_{30} values of felodipine, PMs, solid binary and ternary systems were tested at 95% confidence. The DE_{30} values of PMs, solid binary and ternary systems were significantly higher ($P < 0.01$) compared to the DE_{30} values of felodipine alone.

SUMMARY

The present study was planned to improve solubility and dissolution rate of felodipine (BCS class II drug) through solid dispersion technique using water soluble carriers. Solid binary systems of felodipine with PEG 4000 were prepared by kneading and solvent deposition method at different drug:carrier ratios. In the next phase, ternary systems were prepared by kneading method with addition of different concentrations of HPC to felodipine-PEG 4000 binary systems to investigate the effect of hydrophilic polymer on the solubility and dissolution rate of the felodipine.

Chapter 1 discusses about the drug solubility and various approaches to improve the solubility especially on solid dispersions technology. Then, this chapter presents the method of preparation of solid dispersion systems and their characterization. Later part of this chapter provides the aims, objectives and plan of investigation of the study.

Chapter 2 deals with the literature review related to the past research work on solid dispersions and various carriers used to prepare solid dispersions.

Chapter 3 discusses about materials used, analytical and experimental methods employed in the present investigation. The first part of this chapter provides drug profile and polymer profile. Then later part of this chapter describes the method of preparation of solid binary systems of felodipine with PEG 4000 by kneading and solvent deposition method at different drug:carrier ratios of 1:1, 1:3 and 1:5 w/w. Then ternary systems were prepared by kneading method with addition of different concentrations of HPC (5%, 10% and 15%) to felodipine-PEG 4000 (1:3 ratio). The preceding part of this chapter deals with the methods of characterization of prepared solid binary and ternary systems by drug content uniformity, FT-IR, XRD and *in vitro* dissolution studies.

Chapter 4 summarized all the research results of prepared solid binary and ternary systems of felodipine according to plan of investigations as described in

Chapter 5 provides the discussions on research results of solid binary and ternary systems of felodipine. All prepared solid binary and ternary systems were found to be fine and free flowing. Solubility studies showed that the solubility of felodipine in different concentration of PEG 4000 increased linearly as a function of concentration of carrier. Low standard deviation (SD) values indicated uniform drug distribution in all prepared batches. The percentage yield of all formulations was found to be satisfactory. FT-IR studies indicated the possibility of intermolecular hydrogen bonding between amide group of the felodipine and hydroxyl group of the PEG 4000. XRD results of all solid binary and ternary systems indicated significant reduction in the felodipine crystallinity.

The results of the dissolution rate studies indicated higher dissolution rate of felodipine from solid binary systems compared to felodipine alone and their corresponding PMs. The DE_{30} and DE_{60} values of the solid binary systems prepared by kneading and solvent deposition methods were relatively high compared to the values from the PMs and felodipine alone. The value of T_{50} and MDT of all solid binary systems were lower than felodipine alone. Further, it was found that the drug dissolution was higher in 1:5 drug to carrier ratio compared to 1:1 and 1:3 ratios. The overall the rank order of improvement in dissolution properties of felodipine with different methods in all ratios was found in the following rank order,

KM > SD > PMs > Felodipine

The DE_{30} and DE_{60} values of the solid binary systems prepared by kneading method were higher compared to solid binary systems prepared by solvent deposition methods.

All ternary systems prepared with different concentrations of HPC exhibited a significant increase in dissolution rate with respect to the PMs and the felodipine alone. It was noted that the dissolution rate was progressively

increased with increasing concentration of HPC in the ternary systems. Ternary system prepared with HPC 15% showed the most significant effect on the dissolution properties of drug. The increase in dissolution rate with these systems were found in the following manner,

HPC 15% > HPC 10% > HPC 5%

The release pattern in felodipine, PMs and all solid binary and ternary systems were found to be first order (best fit model) compared to Hixson-Crowell's cube root model. The DE_{30} values of PMs and all solid binary and ternary systems prepared kneading and solvent deposition methods were significantly higher ($P < 0.01$) compared to the DE_{30} values of felodipine alone.

CONCLUSION

The following conclusions were drawn from the present investigations;

- Solubility studies showed that the solubility of felodipine increased linearly as a function of concentration of carrier (PEG 4000).
- All prepared solid binary and ternary systems were found to be fine and free flowing.
- Drug content of solid binary (felodipine:PEG 4000) and ternary systems (felodipine:PEG 4000:HPC) was uniform as indicated by the low SD (i.e., < 1) values.
- The FT-IR studies of binary and ternary systems indicated the possibility of intermolecular hydrogen bonding between amide group of felodipine and the hydroxyl group of the PEG 4000.
- The XRD results of all solid binary and ternary systems indicated significant reduction in the felodipine crystallinity.
- The *in vitro* dissolution studies indicated higher dissolution rate of felodipine from solid binary and ternary systems compared to felodipine alone and the corresponding PMs.
- The DE_{30} and DE_{60} values of the all solid binary systems prepared by kneading and solvent deposition methods were relatively high compared to the values from PMs and felodipine alone.
- The drug dissolution was higher in solid binary systems prepared by kneading and solvent deposition methods at 1:5 drug to carrier ratio compared to 1:1 and 1:3 ratios.

- Comparatively, DE_{30} and DE_{60} values of the solid binary systems prepared by kneading method were higher compared to solid binary systems prepared by solvent deposition methods.
- Ternary systems exhibited a progressive increase in dissolution rate with increasing concentration of HPC. Ternary systems with HPC 15% showed the most significant effect on the dissolution properties of drug.
- The release pattern in felodipine, PMs and all solid binary and ternary systems were found to be first order compared to Hixson-Crowell's cube root model.
- One-way ANOVA was used to analyse significant differences in the means of DE_{30} values felodipine, PMs and all solid binary and ternary systems. The DE_{30} values of PMs and all solid binary and ternary systems prepared by kneading and solvent deposition methods were significantly higher ($P < 0.01$) compared to the DE_{30} values of felodipine alone.
- The overall results showed that dissolution rate of felodipine were considerably improved when formulated in solid binary and ternary systems.

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