Development and Evaluation of Fast-Dissolving Tablets ofFlurbiprofen-Cyclodextrin Complexes

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ABSTRACT

The aim of the present study was to develop a tablet formulation based on flurbiprofen-cyclodextrin system that allows rapid and complete dissolution of Flurbiprofen an insoluble drug practically. For the development of tablets, three different cyclodextrins: the parent β-cyclodextrin and two amorphous derivatives i.e., methyl-β-cyclodextrin and hydroxyethyl-β-cyclodextrin were evaluated. Equimolar drug-cyclodextrin binary systems were prepared according to five different techniques i.e., physical mixing, kneading,sealed-heating, coevaporation, and colyophilization. All these binary systems were characterized by Differential Scanning Calorimetry, x-ray powder diffractometry, infrared spectroscopy, and optical microscopy and evaluated for solubility and dissolution rate properties. The drug solubility improvement observed in the different binary systems varied from a minimum of 2.5 times up to a maximum of 120 times, depending on the type of cyclodextrin and the preparation method employed. Tablets were prepared suing direct compression method employing the selected binary systems. Chitosan and spray-dried lactose, were used as excipients in the formulation. All formulations containing drug-cyclodextrin systems showed greater dissolution compared to the drug alone. However, the drug dissolution behavior of the drug-cyclodextrin system was strongly influenced by the formulation factors. Tablets containing the drug mixed with methyl-β-cyclodextrin or colyophilized with β-cyclodextrin and spray-dried lactose satisfied the requirements laid down by the Food and Drug Administration (FDA) for fast dissolving tablets.

Keywords: Fast dissolving,Cyclodextrins, Rapid dissolution, Solid dosage form, Flurbiprofen

INTRODUCTION

Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs show good bioavailability. The solubility and dissolution properties of drugs play an important role in the process of formulation development. Solubility is the phenomenon of the dissolution of solid in a liquid phase to give a

homogenous system. Solubility is one of the important parameters to achieve the desired concentration of drug in systemic circulation for pharmacological response to be shown. Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration[1-2]. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities. Hence a number of methodologies can be adapted to improve solubilization of poorly water-soluble drugs and further to improve its bioavailability[3]. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complication, co-solvency, micellar solubilization, hydrotropy etc[4-6]. Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development

For physical modifications, various excipients such as cyclodextrins, carbohydrates, hydrotropes, polyglycolized glycerides, and dendrimers are utilized[7].

Fast dissolving tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in the technology have prompted scientists to develop FDTs with improved patient compliance and convenience. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. FDTs or orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. Orally disintegrating tablets are also called as oral disperse, mouth dissolving, rapidly disintegrating, fast melt, and quick dissolve system[8-10].

Flurbiprofen, a propionic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAIDs) with analgesic and antipyretic properties. Its elimination half-life is usually 4.7-5.7 hours. This compound belongs to the diphenyl derivatives. It is widely used for symptomatic treatment of acute and chronic rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, primary dysmenorrhea and mild to moderate pain associated with musculotendinous trauma (sprains and strains), postoperative (including dental surgery) or postpartum pain.Flurbiprofen has pharmacologic actions similar to those of other prototypical NSAIDs, which inhibit prostaglandin synthesis.The anti-inflammatory effects of Flurbiprofen are believed to be due to inhibition cylooxygenase-2 (COX-2), an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. This results in decreased levels of prostaglandins that mediate pain, fever and inflammation. Flurbiprofen is a non-specific cyclooxygenase inhibitor and inhibition of COX-1 is thought to confer some of its side

effects, such as GI upset and ulceration. Flurbiprofen is thought to have anti-bradykinin activity, as well as lysosomal membrane-stabilizing action. Antipyretic effects may be due to action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation.Flurbiprofen is rapidly and well-absorbed orally, with peak plasma levels occurring within 0.5 to 2 hours[11-13].

The present study was aimed at developing a tablet formulation based on an effective flurbiprofen-cyclodextrin system, able to allow a rapid and complete dissolution of this practically insoluble drug. It aimed to enhance the solubility and bioavailability of Flurbiprofen by solid dispersion technique and evaluate the potential of PEG 4000, PEG 6000, Xanthan gum & Guar gum as suitable drug carrier system for delivery of Flurbiprofen.

MATERIALS AND METHODS

MATERIALS:

Flurbiprofen was obtained from Ningbo Hi-Tech Biochemicals Co., Ltd., China. PEG 4000 was procured from S.D.FinePvt.Ltd., Mumbai. Guar gum, xanthan gum and PVP K-30 were obtained from Neelkanth Chemicals, Jodhpur. Croscarmellose sodium, Sodium starch glycolate and Crospovidone XL-10 were obtained from M/s Healer's LabPvt.Ltd. Baddi. All other chemicals were of analytical grade.

METHODS:

Physical Appearance

Physical appearance of drug was examined by various organoleptic properties.

Melting Point Determination

Melting point of flurbiprofen was determined by capillary fusion method one sided closed capillary filled with drug and put into the Melting Point Apparatus. The temperature was noted at which solid drug changed into liquid.

Solubility

The solubility of flurbiprofen was determined in different solvent systems and buffers. An excess quantity of the drug was mixed with 10 ml of each solvent in screw capped glass tubes and shaken on constant water bath shaker for 24 hours at 25ºC. The solutions were examined physically for the absence or presence of drug particles and also by spectrophotometrically for quantitative determination of drug in buffers.

Infrared Spectral Assignment

The pellet of approximately 0.1 mm diameter of the drug was prepared grinding 3-5 mg of sample with 100-150 mg of Potassium Bromide using hydrostatic press. The sample pellet was mounted in IR compartment and scanned at wavelength 4000 cm^{-1} to 500 cm^{-1}.

Differential Scanning Calorimetry (DSC)

DSC analysis was performed on 5 mg sample. Samples were heated in an open aluminum pan at a rate of 100 per min–1 in a 30 to 300^0C temperature range under a nitrogen flow of 40 ml/min.

Ultraviolet Absorption Maxima

Ultraviolet absorption in the range 200 to 400 nm of a 5µg/ml solution in 5% (v/v) methanolic Sorenson's Buffer (pH 6.8) was measured.

Preparation of Calibration Curve

Preparation of Sorenson's Buffer (pH 6.8):

24.5 ml of 0.2 M dibasic sodium phosphate and 25.5 ml of 0.2 M monobasic sodium phosphate was placed in 100 ml volumetric flask and make up the volume 100 ml with water.

Calibration Curve:

50 mg of flurbiprofen was weighed accurately and dissolved in 5 ml of methanol in a 100 ml of volumetric flask and volume was made up to 100 ml with the Sorenson's buffer (pH 6.8). 10 ml of this solution was diluted with 100 ml Sorenson's buffer (pH 6.8) to obtain a stock solution of 50µg/ml. From this stock solution, aliquots of 1 ml, 2 ml, 3 ml, 4 ml and 5 ml were taken transferred to 10 ml volumetric flask and volume was made up to 10 ml with Sorenson's buffer (pH 6.8). The absorbance of these solutions was measured at 260 nm against a blank Sorenson's buffer (pH 6.8). The calibration curve was plotted between concentration and absorbance[14].

DRUG- EXCIPIENT COMPATIBILITY STUDY

Drug-excipient compatibility study was carried out using mixture of drug and excipients. Selected excipients and drug were taken in appropriate ratio 1:1. The prepared mixture are placed in glass vials, sealed and stored in an oven at a temperature of 50 ^{0}C $\pm1^0$C for 15 days.

At the end of 7 and 15 days compatibility was evaluated by observing physical changes and chemical changes. Physical changes: such as discoloration, caking, and liquifaction. Chemical changes: evaluated by λ_{max}determination (UV spectrophotometer).

PREPARATION OF PHYSICAL MIXTURES OF FLURBIPROFEN

Physical mixtures of Flurbiprofen were prepared using PEG-4000, Guar Gum, Xanthan Gum & PVP K-30 as a carrier in a weight ratio. First drug and carrier were passed through a 40 mesh screen and then weighed and mixed by using a motor and pestle. The composition of the physical mixture is given in Table 1.

Table 1: Composition of Physical Mixture

S.NO.	Drug + Carrier	Drug: carrier weight ratio	Solid dispersion code
1	Flurbiprofen + PEG 4000	1:1	KPEG4-1
2	Flurbiprofen+ PEG 4000	1:2	KPEG4-2
3	Flurbiprofen + PEG 4000	1:3	KPEG4-3
4	Flurbiprofen+ Guar Gum	1:1	KGG-1
5	Flurbiprofen + Guar Gum	1:2	KGG-2
6	Flurbiprofen + Guar Gum	1:3	KGG-3
7	Flurbiprofen + Xanthan Gum	1:1	KXG-1
8	Flurbiprofen+ Xanthan Gum	1:2	KXG-2
9	Flurbiprofen+ Xanthan Gum	1:3	KXG-3
10	Flurbiprofen + PVP K-30	1:1	KPVP-1
11	Flurbiprofen+ PVP K-30	1:2	KPVP-2
12	Flurbiprofen+ PVP K-30	1:3	KPVP-3

EVALUATION OF PHYSICAL MIXTURES AND SOLID DISPERSIONS

The prepared physical mixtures and solid dispersions were evaluated for solubility studies; percent drug content, in-vitro drug release.

Determination of Solubility of Solid Dispersions

Flurbiprofen, physical mixtures or solid dispersions equivalent to 10 mg of Flurbiprofenwere added to 10 ml of Sorenson's buffer pH 6.8 in a 10 ml volumetric flask. The volumetric flasks were capped properly and shaken at 25 and 37^0 C in a temperature-controlled water bath (Shaking water bath) for 48 h. Resultant samples containing undissolved solid

dispersions suspended in the volumetric flask were filtered through 0.45µm filters, suitably diluted with Sorenson's buffer pH 6.8 and analyzed by UV spectrophotometer at 260 nm[15-16].

Determination of Drug Content

Drug content was calculated by dissolving solid dispersions equivalent to 100 mg Flurbiprofen in 10 ml of methanol, filtered using0.45µm Whatman filter paper, suitably diluted with Sorenson's buffer (pH 6.8) and analyzed by using UV spectrophotometer against Sorenson's buffer as blank.

In-vitro Drug Release

Accurately weighed preparations equivalent to 100 mg of Flurbiprofenwere added to 900 ml of dissolution medium in USP II Paddle type apparatus and stirred at speed of 50 rpm at 37 ± 0.5ºC. 5 ml aliquots were withdrawn at 5, 10, 15, 30, 45, 60 minutes and replaced by 5 ml of fresh dissolution media. The collected samples were analyzed after filtration and dilution at 260 nm using UV-visible spectrophotometer against the blank. Drug release studies were carried out in triplicate. The dissolution of pure flurbiprofenwas done similarly. The release profile data was analyzed for cumulative percent dissolved at different time intervals.

FORMULATION OF FAST DISSOLVING TABLETS

Fast dissolving tablets containing selected solid dispersion were prepared by direct compression method using single punch tablet machine to produce convex faced tablets weighing 500 mg each with a diameter of 11 mm. A minimum of 100 tablets were prepared for each batch. The formulations were developed by addition of super disintegrants.

The superdisintegrants (Croscarmallose sodium, Sodium starch glycolate and Crospovidone XL-10) in varying concentration (2-5%) were used to develop the tablets (by Margret Chandira R 2010). All the ingredients were passed through sieve no. 60 and were co-grounded in a glass pestle motor. These blends were evaluated for mass-volume relationship (Bulk Density, Tapped Density, Hausners Ratio, Compressibility Index) and flow properties (Angle of Repose). The mixed blend of excipients was compressed using a single punch tablet machine (Cadmach, Ahmedabad) to produce convex faced tablets weighing 500 mg each with a diameter of 11 mm. Various compositions of fast dissolving tablets have been mentioned in Table 2.

Table 2: Various compositions of Fast Dissolving Tablets

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**

KPVP-3	200	200	200	200	200	200	200	200	200	200	200	200
Croscarmellose sodium	10	15	20	25	-	-	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	10	15	20	25	-	-	-	-
Crospovidone XL-10	-	-	-	-	-	-	-	-	10	15	20	25
Dextrose	70	70	70	70	70	70	70	70	70	70	70	70
Lactose	70	70	70	70	70	70	70	70	70	70	70	70
Avicel PH 102	130	125	120	115	125	115	105	95	105	95	85	75
Purified Talc	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10	10	10	10	10	10	10
β (beta)-cyclodextrin	0	0	0	0	5	10	15	20	25	30	35	40
Cardamom (Flavour)	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs

CHARACTERIZATION OF BLENDS

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing step and all these can affect the characteristics of blend produced. The characterization of mixed blend done for the flow properties of powder that are bulk density, tapped density, Hausner's ratio, Compressibility index, and angle of repose[17-18].

Bulk density

It is the ratio of total weight of powder to the bulk volume of powder. 10g of granules were weighed separately and transferred into a graduated measuring cylinder via a large funnel and measure the volume of the powder. The bulk density of the prepared granules was calculated by given formula:

Bulk density = Weight of powder/ Bulk volume

Tapped density

It is the ratio of total weight of powder to the tapped volume of powder. After measuring the bulk density, tapped density was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between bulk volume and tapped volumes should be less than 2%). The tapped density was calculated by the following formula:

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume}}$$

FLOW PROPERTIES

Hausner's ratio

It is measurement of frictional resistance of the granules. The ideal range should be 1.2 – 1.5, Hausner's ratio is an important character to determine the flow property of powder and granules. This can be calculated by the following formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Value < 1.25 indicate good flow (=20% CI)

Value > 1.50 indicate poor flow (=35% CI)

Carr's index (Compressibility index)

The flowability of powder can be evaluated by comparing the bulk density and tapped density. It can be calculated from the following equation.

$$\text{Carr's index} = \frac{\text{(Tapped density- bulk density)}}{\text{Tapped density}} \times 100$$

Angle of repose

The angle of repose is defined as the maximum angle possible between the surface of piles of powder and the horizontal plane. Angle of repose of granules is done by fixed funnel method and is calculated by using following formula.

$$\theta = \tan^{-1} h/r$$

Where, h= height of the pile; r= radius of the pile

The tangent of the angle is equal to the coefficient of friction (M) between the particles.the value of angle of repose indicates the type of flow of granules as mentioned in Table 3.

Table 3: Angle of repose as an indication of granule flow property

S.No	**Angle of repose**	**Type of flow**
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

CHARACTERIZATION OF FAST DISSOLVING TABLETS

After compression of powder, the tablets were evaluated for organoleptic characteristics like color, odor, taste, diameter, thickness and physical characteristics like hardness, friability, disintegration time, wetting time, dispersion time and dissolution studies.

General Appearance

Visual identification and over all 'elegance' were performed such as color, presence or absence of an odour, taste, surface texture and physical flaws.

Tablet Thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by suing filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Uniformity of Weight

As per IP, twenty tablets were taken and weighted individually and collectively using digital balance. The average weight of one tablet was calculated. The weight variation test would be

satisfactory method of determining the drug content uniformity. The weight variation limits of tablets as per IP in mentioned in Table 4.

Table 4: Weight variation limit of tablet as per IP

Average of tablet (mg)	**Maximum % difference allowed**
130 or less	10
130-324	7.5
More than 324	5

Hardness

Hardness of the tablet of each formulation was determined using Pfizer hardness tester.

Friability

Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inch in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed.

Disintegration Test

Disintegration of fast disintegrating tablets is achieved by saliva in the mouth, however amount of saliva inthe mouth is limited and no tablet disintegration test was found inUSP and IP to simulate in vivoconditions. A modifiedmethod was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10-meshscreen was placed in such way that only 2 ml of disintegrating ordissolution medium would be placed below the sieve. Todetermine disintegration time, 6 ml of Sorenson's buffer (pH 6.8), was placed inside the vessel in such way that 4 ml of the mediawas below the sieve and 2 ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve wastaken as a disintegration time of the tablet. Six tablets were chosenrandomly from the composite samples and the average value wasdetermined.

Wetting Time

The method was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small Petri dish (ID = 65 cm) containing 6 ml of

Sorenson's buffer (pH 6.8), A tablet was put on the paper, and the time for the complete wetting was measured. Three trials for each batch were performed and the standard deviation was also determined.

In-vitro Dispersion Time

In-vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of Sorenson's buffer (pH 6.8). Three tablets from each formulation were randomly selected and in-vitro dispersion time was performed.

Content Uniformity

Ten randomly selected tablets were weighed and powdered in a glass mortar pestle. The weight equivalent to 10 mg Flurbiprofen was weighed and dissolved in 5 ml of methanol in volumetric flask using magnetic stirrer, the volume was adjusted to 100 ml with Sorenson's buffer (pH 6.8) and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml Sorenson's buffer (pH 6.8) in separate volumetric flask. The content in was determined spectrophotometrically at 260 nm.

In-Vitro Dissolution Studies

In-vitro dissolution studies of formulation were carried out using USP paddle method at 50 rpm in 900 ml of Sorenson's buffer (pH 6.8) as dissolution media, maintained at 37±0.5ºC. 5 ml of aliquot was withdrawn at the specified time intervals, filtered through whatmann filter paper and analysedspectorphotometrically at 260 nm. An equal volume of fresh medium, which was prewarmed at same condition, was replaced into the dissolution media after each sampling to maintain the constant volume throughout the test.

STABILITY STUDIES

Deterioration of drug may take several forms arising from changes in the chemical, physical and microbiological properties. These changes may affect therapeutic value of dosage form or increases toxicity. Such a study is important to prevent economic repercussion of marketing an unstable product. Consideration must be taken to the relevant legal requirements concerned with the identity, strength, purity, and quality of the drug.

Prediction of shelf-life

Shelf-life is a period during which a dosage form keeps it qualities. The prediction of shelf-life is based on applying the Arrhenius equation, which gives the effect of temperature on rate

constant, K of a chemical reaction. Considering a preparation whose instability is measured in terms of color disappearance when subjected to different elevated temperatures and a plot is drawn with absorbance v/s time.

The reaction velocity constant K for the decomposition at each of the elevated temperature can be calculated from the slope of line. The most satisfactory method for expressing the influence of temperature on reaction velocity is the quantitative relation proposed by Arrhenius:

$$K = A\, e^{-Ea/RT}$$

Where,

K = Specific rate constant,

R= Gas constant (1.987cals/day/mol)

T= Absolute temperature,

Ea=Energy of activation.

Types of Stability Studies

Long term, intermediate and accelerated studies are the main types of stability studiesconducted.

The storage conditions according to ICH guidelines are given in Table 5.

Table5: Storage conditions according to ICH guidelines

Study	**Storage condition**		**Minimum time**
	Temperature	**Relative humidity**	
Long term	25±2ºC	60±5% RH	12 months
Intermediate	30±2ºC	65±5% RH	6 months
Accelerated	40±2ºC	75±5% RH	3 months

Stability study was carried out at 39ºC / 76% RH for the optimized formulations. The procedure was divided into two parts,

Part I:

Achieving of 60% RH:

26.66 gm. of sodium hydroxide was weighed and dissolved in 100 ml of distilled water to get 26.66% sodium hydroxide solution. The solution was placed in the desiccator over which a wire mesh was placed, over which the dosage form was placed and the desiccator was sealed.

The desiccator was placed in the oven maintained at 25^0C to create the Relative Humidity of 60%.

Achieving of 76% RH:

Saturated solution of sodium chloride was prepared and placed in the desiccators over which a wire mesh was placed, over which the dosage form was placed and the desiccator was sealed. The desiccator was kept in oven maintained at

39ºC to create the relative humidity of 78%.

Part II

The sealed formulation were placed in amber colored bottles, tightly plugged with cotton and capped. They were then stored at 25ºC /60% RH and 39ºC / 76% RH for two months and evaluated for their physical appearance and drug content.

RESULT AND DISCUSSION

Identification Tests:

Physical Appearance

Physical appearance of drug was examined by various organoleptic properties are given in Table 6 below:

Table 6: Physical appearance of Flurbiprofen

S.NO.	CHARACTERISTICS	RESULT
1	Color	White or almost white
2	Odor	Odorless
3	Taste	Tasteless
4	State	Fine to granular powder

Result: Results were satisfactory according to their specification

Melting Point

Melting point of the Flurbiprofen was determined by capillary fusion method; one sided closed capillary filled with drug and put into the Melting Point Apparatus. Temperature was noted at which solid drug changed into liquid. It was found to be 95°C. The melting point of Flurbiprofen has been mentioned in Table 7.

Table 7: Melting point of Flurbiprofen

Standard Value	**Observed Value**	
	CAPILLARY FUSION METHOD	**DIFFERENTIAL SCANNING CALORIMETRY**
94-97ºC	95	95.54

Infrared Spectrum

The pellet of approximately 01 mm diameter of the drug was prepared grinding 3-5 mg of sample with 100-150 mg of Potassium Bromide using hydrostatic press. The sample pellet was mounted in IR compartment and scanned at wavelength 4000 cm^{-1} to 500 cm^{-1}. On analysis of the IR spectra of the reference spectra given in Indian Pharmacopoeia (2014) and pure drug, no major differences were observed in the characteristic absorption peak (1696, 1655) pattern. The IR spectra obtained has been shown in Figure 1.

Figure 1: IR Spectra Sample of Flurbiprofen

Differential Scanning Calorimetry (DSC)

DSC analysis was performed on 5 mg sample. Samples were heated in an open aluminum pan at a rate of 100 per min^{-1} in a 30 to 300ºC temperature range under a nitrogen flow of 40

ml/min. It shows endothermic peak at about 95.54ºC. The DSC of flurbiprofen has been shown in Figure 2.

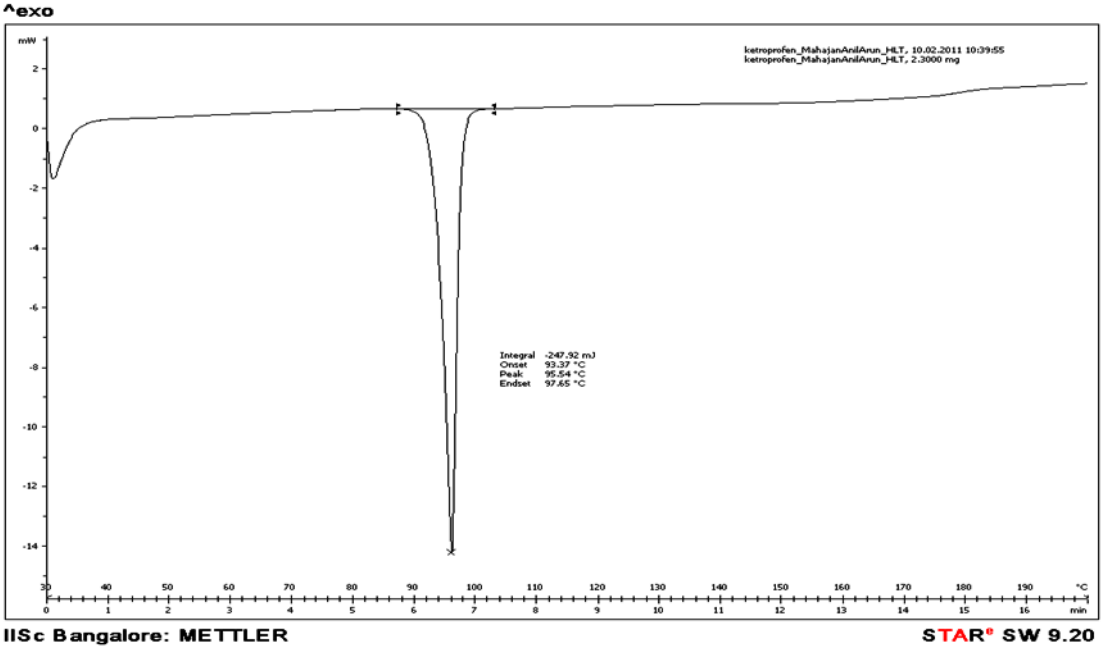

Figure 2: DSC of Flurbiprofen

UV- Visible spectroscopy

Ultraviolet absorption in the rage 200 to 400 nm of a 5µg/ml solution in 5% (v/v) methanolic Sorenson's Buffer (pH 6.8) was measured. The absorption maxima (λmax) of Flurbiprofen (5 µg/ml) in this solution was found to be 260 nm which is concordant with the Indian Pharmacopoeia (2014). The UV curve has been shown in Figure 3.

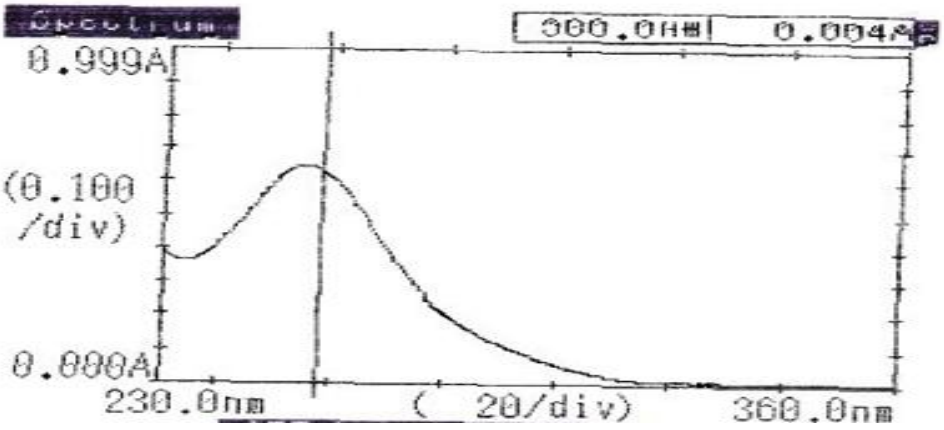

Figure 3: λ- Max of Flurbiprofen

Preformulation Studies

Solubility

The solubility of Flurbiprofen was determined in different solvent systems and buffers. An excess quantity of the drug was mixed with 10 ml of each solvent in screw capped glass tubes and shaken on constant water bath shaker for 24 hours at 25ºC. The solutions were examined physically for the absence or presence of drug particles and also by spectrophometrically for quantitative determination of drug in buffers. The Solubility of Flurbiprofen in Different Solvents and buffers are given in Table 8 and 9.

Table 8: Solubility of Flurbiprofen in Different Solvents

S.No.	Solvents	Solubility
1	Distilled water	-
2	Sorenson's buffer pH 6.8	-
3	0.1N HCl	+
4	0.1N NaOH	+
5	Ethanol	++
6	Methanol	++

Practically insoluble (-) slightly soluble (+) soluble (++)

Table9: Solubility of Flurbiprofen in Various Buffer Solutions

S.No.	Buffer (pH)	Solubility (mg/ml)
1	6.8 (Sorenson's buffer)	0.014±0.002
2	7.0 (Water)	0.016±0.003
3	7.4 (Buffer)	0.016±0.002

Data are expressed as mean ± S.D. (n = 3)

Result of calibration curve data

The calibration curve of Flurbiprofen was prepared in Sorenson's buffer (pH 6.8). The plot of different concentrations of Flurbiprofen versus absorbance was found to be linear in the concentration range of 5-25 µg/ml at 260 nm. The absorbance at different concentrations was shown below. The data of standard curve were linearly regressed. The Calibration curve data of Flurbiprofen is given in Table 10 and the calibration curve is shown in Figure 4.

Table 10: Calibration curve data of Flurbiprofen

S.No.	Concentration (µg/ml)	Absorbance
1	Blank	0
2	10	0.312
3	15	0.467
4	20	0.624

5	25	0.777
6	30	0.932

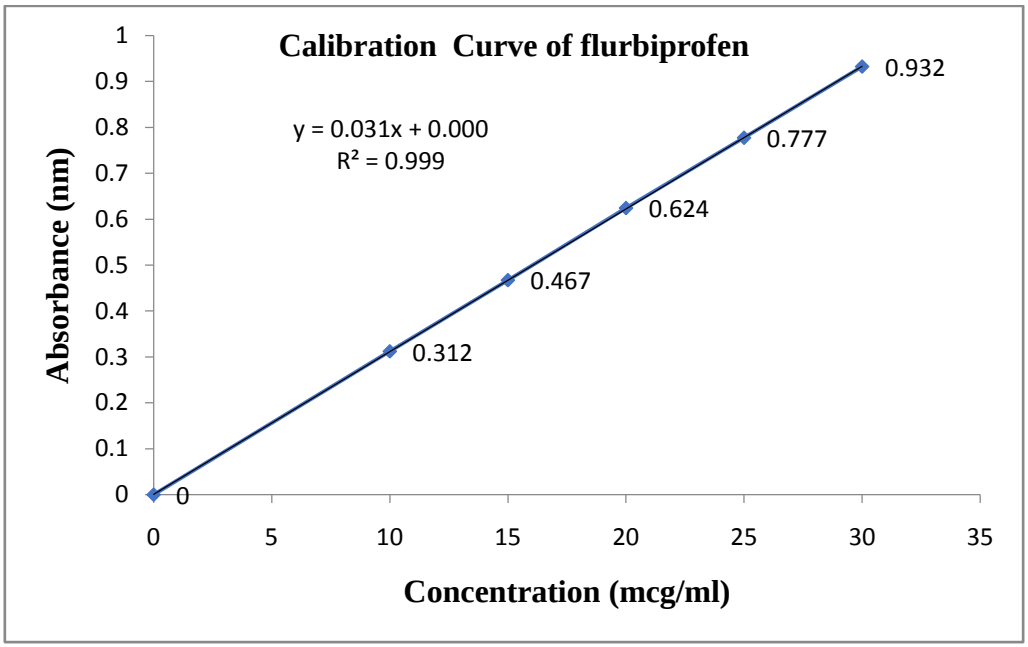

Figure 4: Calibration curve of Flurbiprofen

Drug excipients compatibility study

The Physical and Chemical Changes during Drug-Carrier Compatibility Screening are summarized in Table 11.

Table 11: Observation Table for Physical and Chemical Changes During Drug-Carrier Compatibility Screening

Mixture	**7days**			**15days**			
Physical changes			**Chemical changes**	**Physical changes**			**Chemical changes**
D	**C**	**L**	**λmax.**	**D**	**C**	**L**	**λmax.**
–	–	–	260 nm	–	–	–	260 nm

D = Discoloration

C = Caking

L = Liquification

Determination of solubility of solid dispersion

The solubility data of Flurbiprofen, physical mixture and solid dispersion in Sorenson's buffer pH 6.8 at 25ºC and 37ºC has been summarized in Table 12.

Table 12: Solubility data of Flurbiprofen, physical mixture and solid dispersion in Sorenson's buffer pH 6.8 at 25ºC and 37ºC.

Solid dispersion Code	Flurbiprofen Solubility mg/ml at 25ºC	Flurbiprofen Solubility mg/ml at 37ºC
KPEG4-1	0.014333±0.003086	0.018417±0.001809
KPEG4-2	0.28825±0.002883	0.316167±0.00527
KPEG4-3	0.383333±0.002765	0.0438917±0.001665
KGG-1	0.2275±0.002537	0.251833±0.001507
KGG-2	0.331±0.002634	0.38833±0.001127
KGG-3	0.415±0.006589	0.426±0.0488
KXG-1	0.526±0.00369	0.526±0.00369
KXG-2	0.658±0.111	0.613±0.00786
KXG-3	0.589±0.00569	0.575±0.00321
KPVP-1	0.533083±0.002126	0.603833±0.001258
KPVP-2	0.6775±0.002537	0.751±0.001146
KPVP-3	**0.803833±0.003263**	**0.894417±0.000878**

Data are expressed as mean ± S.D. (n=3

Estimation of drug content

Percent drug content of solid dispersions has been given in Table 13.

Table 13: Percent drug content of solid dispersions

S.No.	Solid dispersion Code	% Drug content
1	KPEG4-1	96.25±0.543
2	KPEG4-2	96.90±0.245
3	KPEG4-3	96.99±0.554
4	KGG-1	96.99±0.589
5	KGG-2	97.03±0.012
6	KGG-3	97.00±0.02

7	KXG-1	97.11±0.146
8	KXG-2	97.28±0.003
9	KXG-3	97.36±0.986
10	KPVP-1	97.95±0.236
11	KPVP-2	98.02±0.545
12	KPVP-3	**98.96±0.726**

Data are expressed as mean ± S.D. (n=3)

In-vitro dissolution studies

The In-vitro dissolution release profiles of flurbiprofen from physical mixture is given in Table 14.

Table 14: Dissolution Release Profile of Flurbiprofen from Physical Mixture

Cumulative mean %DR±SD %DR±SD	**Drug: polymer ratio**	**Time (min)**						
		0	**5**	**10**	**15**	**30**	**45**	**60**
	Pure Drug	0	1.89±0.20	3.70±0.25	6.02±0.23	13.92±0.23	24.35±0.23	34.28±0.22
	KPEG4-1	0	5.26±0.24	12.73±0.22	20.18±0.22	34.43±0.43	44.66±0.23	52.37±0.24
	KPEG4-2	0	10.2±0.22	19.52±0.21	26.68±0.22	42.73±0.29	53.42±0.36	61.87±0.45
	KPEG4-3	0	14.10±0.10	26.19±0.35	34.46±0.98	50.85±0.48	62.36±0.21	70.82±0.87
	KGG-1	0	4.38±0.21	12.27±0.54	20.53±0.36	37.80±0.54	49.23±0.36	54.94±0.48
	KGG-2	0	8.87±0.59	17.46±0.48	29.07±0.78	43.16±0.12	54.54±0.12	62.32±0.48
	KGG-3	0	12.03±0.68	25.08±0.89	33.82±0.48	50.43±0.96	61.44±0.55	67.83±0.88
	KXG-1	0	9.93±0.33	23.62±0.96	34.35±0.54	54.52±0.44	68.02±0.98	74.58±0.55
	KXG-2	0	16.59±0.48	30.94±0.64	43.74±0.88	66.06±0.65	75.34±0.48	82.78±0.64
	KXG-3	0	25.02±0.48	45.32±0.56	60.93±0.48	78.79±0.34	88.33±0.44	94.59±0.98
	KPVP-1	0	7.29±0.22	18.61±0.22	28.70±0.20	49.23±0.24	61.69±0.21	70.81±0.22
	KPVP-2	0	23.27±0.20	38.98±0.98	54.93±0.20	75.75±0.17	85.75±0.75	93.16±0.22
	KPVP-3	0	36.46±0.21	57.04±0.24	74.11±0.23	90.71±0.71	99.81±0.17	99.95±0.73

The percentage drug release of pure drug and various excipients of PEG 4000, guar gum, xanthan gum and PVP K-30 have been shown in Figure 5-8 respectively.

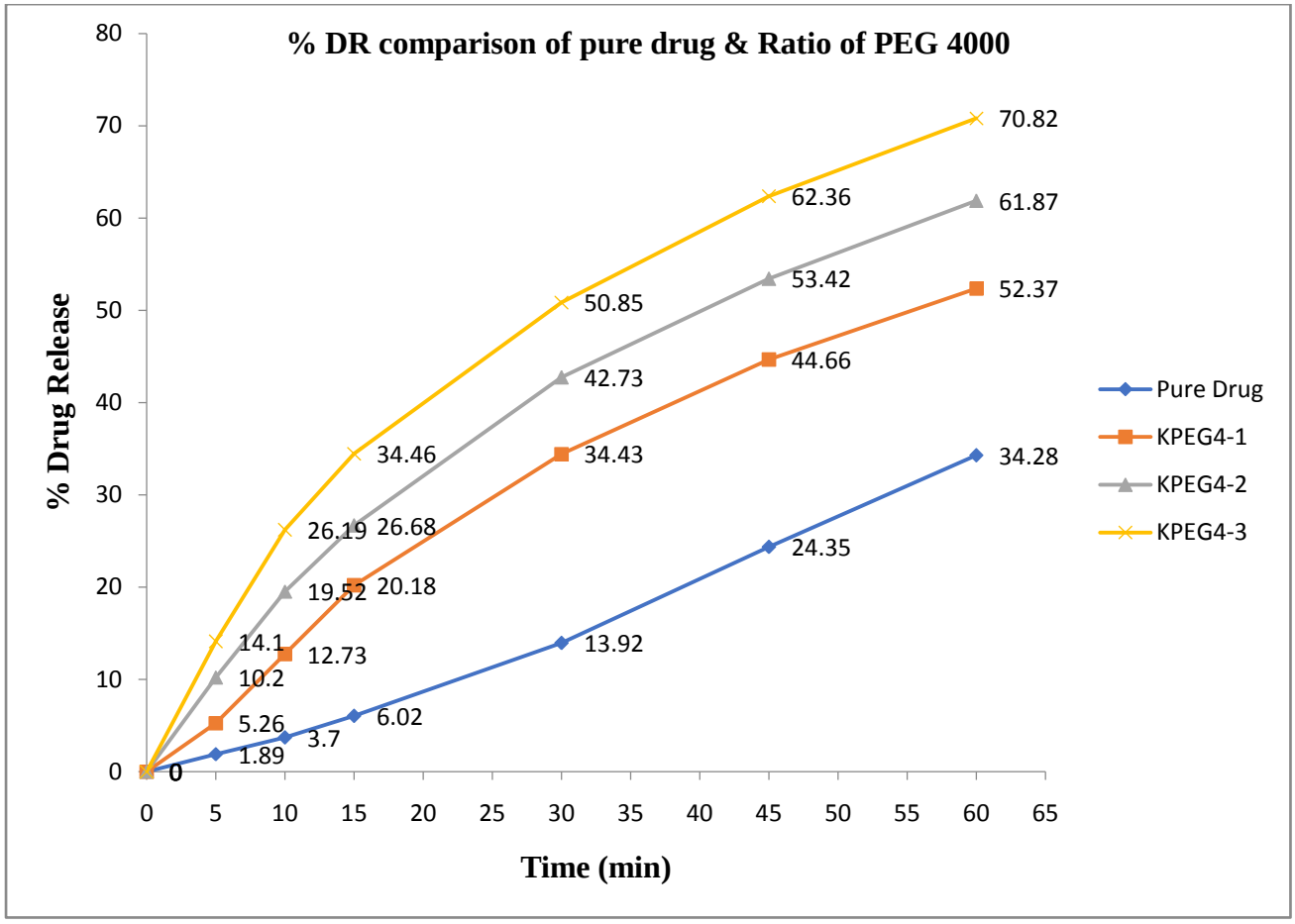

Figure 5: Graph of % DR comparison of pure drug & Ratio of PEG 4000

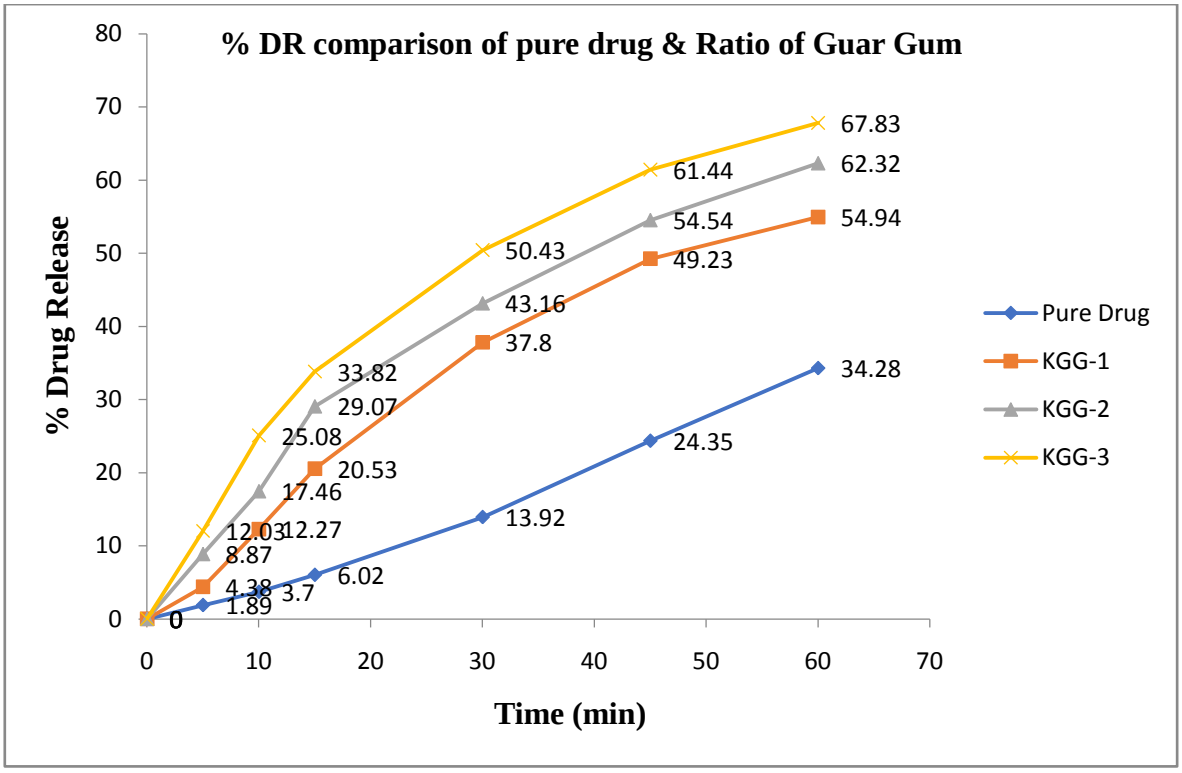

Figure 6: Graph of % DR comparison of pure drug & Ratio of Guar Gum

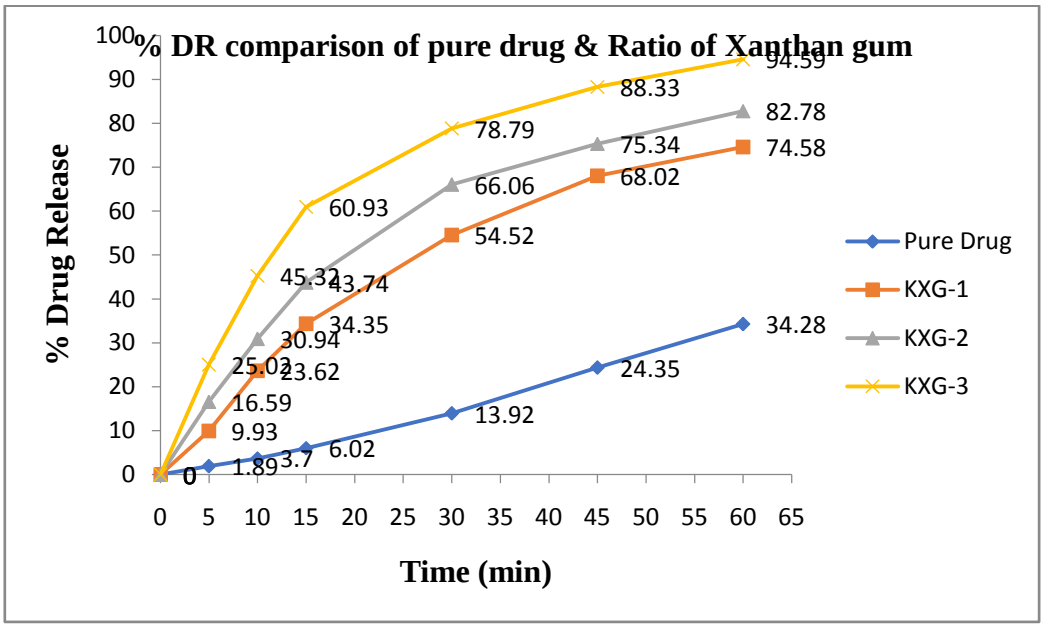

Figure 7: Graph of % DR comparison of pure drug & Ratio of Xanthan gum

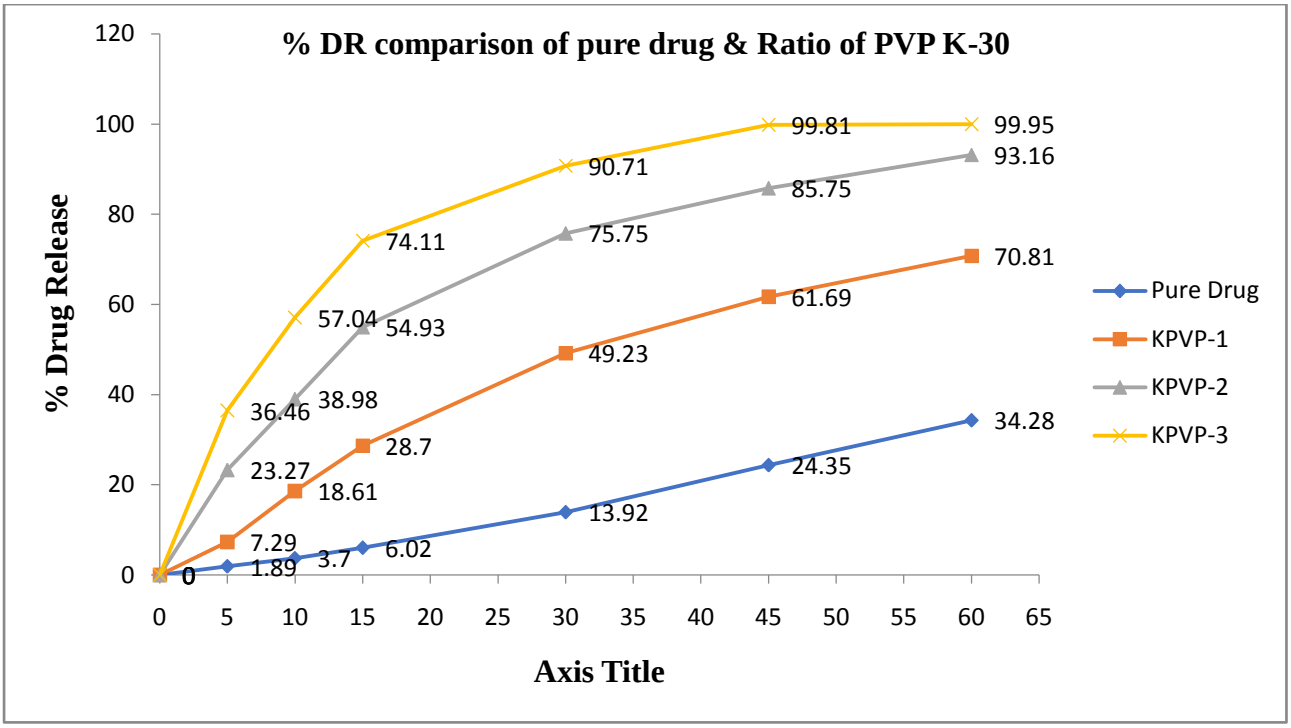

Figure 8: Graph of % DR comparison of pure drug & Ratio of PVP K-30

Characterization of Blends for Fast Dissolving Tablets

The various characterization parameters of blends for fast dissolving tablets have been summarized in Table 15-19. The dissolution profile curve is shown in Figure 9.

Table 15: Characterization of Blends.

Formulation	Bulk Density	Tapped density	Hausners ratio	Compressibility Index	Angle repose
F 1	0.681±0.0010	0.783±0.0018	1.150±0.009	13.047±0.070	23.999±0.520
F 2	0.591±0.0024	0.673±0.0013	1.138±0.002	12.179±0.220	23.149±0.506
F 3	0.615±0.0021	0.704±0.0020	1.146±0.0004	12.751±0.031	23.243±0.485
F 4	0.670±0.0026	0.758±0.0023	1.132±0.0011	11.661±0.087	23.828±0.837
F 5	0.598±0.0018	0.680±0.0024	1.136±0.0010	12.001±0.081	22.401±0.719
F 6	0.677±0.0009	0.755±0.0011	1.114±0.0027	10.297±0.222	23.734±0.591
F 7	0.567±0.0064	0.641±0.0008	1.130±0.0001	11.577±0.013	23.709±0.491
F 8	0.615±0.0023	0.697±0.0036	1.132±0.0016	11.718±0.128	23.057±0.747
F 9	0.553±0.0016	0.630±0.0024	1.139±0.0011	12.242±0.091	24.262±0.744
F 10	0.608±0.0011	0.699±0.0019	1.150±0.0011	13.052±0.089	25.663±0.456
F 11	0.594±0.0010	0.691±0.0069	1.163±0.0096	14.060±0.710	25.015±0.541

F 12	**0.666±0.0013**	**0.755±0.0017**	**1.134±0.0003**	**11.856±0.241**	**23.785±0.471**

Table 16:Characterization of fast dissolving tablet

Formulation	**Thickness (mm)**	**Weight (mg)**	**Friability (%)**	**Hardness (kg/cm^2)**
F 1	6.325±0.014	500.666±1.527	0.478±0.0002	3.0
F 2	6.342±0.026	496.667±3.785	0.440±0.0002	3.0
F 3	6.343±0.034	497.333±0.577	0.639±0.0002	3.0
F 4	6.325±0.004	501.333±2.081	0.781±0.045	3.0
F 5	6.349±0.037	496.666±1.527	0.8765±0.0005	3.0
F 6	6.342±0.029	502.666±1.527	0.719±0.0006	3.0
F 7	6.348±0.043	500.333±1.527	0.519±0.0004	3.5
F 8	6.349±0.021	500.333±2.309	0.800±0.0010	3.0
F 9	6.334±0.034	499.333±1.527	0.638±0.0003	3.0
F 10	6.346±0.034	501.666±2.081	0.761±0.0004	3.0
F 11	6.335±0.031	499.333±1.527	0.519±0.002	3.0
F 12	**6.348±0.031**	**500.123±0.001**	**0.478±0.0003**	**3.0**

Table 17: Characterization of fast dissolving tablet

Formulation	**Disintegration time (Seconds)**	**Wetting time (Seconds)**	**Dispersion time (Seconds)**
F 1	95.533±1.507	87.37±1.770	114.346±3.381
F 2	86.503±2.360	80.13±3.928	101.443±2.408
F 3	70.256±3.769	65.34±3.674	84.76±4.265
F 4	60.65±1.856	55.04±3.125	71.81±3.404
F 5	51.94±3.344	49.223±3.511	64.706±4.265
F 6	1345.223±5.162	125.663±5.760	142.713±4.838
F 7	119.93±4.994	110.273±3.544	124.903±4.639
F 8	59.48±1.509	80.093±4.400	86.233±2.717
F 9	45.113±2.155	62.69±2.507	69.723±1.804
F 10	29.023±1.708	31.836±2.848	42.836±1.180

F 11	27.710±1.141	29.670±1.477	33.696±2.080
F 12	**25.680±1.411**	**27.446±1.404**	**30.910±1.681**

Table 18:Drug content in fast dissolving tablet of Flurbiprofen:

Formulation	**Drug Content (mg)**	**Drug Content (%)**
F 1	49.341±0.339	98.683±0.678
F 2	48.883±0.440	97.766±0.880
F 3	49.466±0.398	98.933±0.797
F 4	48.658±0.146	97.316±0.292
F 5	49.591±0.177	99.183±0.354
F 6	49.066±0.330	98.133±0.660
F 7	49.65±0.139	99.30±0.278
F 8	49.108±0.473	98.216±0.946
F 9	49.225±0.229	98.450±0.458
F 10	49.191±0.357	98.383±0.714
F 11	49.716±0.177	99.433±0.354
F 12	**50.366±0.028**	**100.733±0.057**

Table 19: Dissolution release Profile:

Time (Min)	Cumulative mean percentage drug release ± SD											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12

0	0	0	0	0	0	0	0	0	0	0	0	0
4	38.655 ±0.311	44.565 ±0.340	50.34 ±0.432	54.78 ±0.578	59.655 ±0.343	27.855 ±0.324	32.085 ±0.384	41.805 ±0.450	54.195 ±0.687	54.345 ±0.936	59.91 ±0.687	63.54 ±0.54
8	48.087 ±0.289	52.324 ±0.289	60.610 ±0.332	68.925 ±0.579	73.491 ±0.375	35.295 ±0.595	41.720 ±0.306	53.626 ±0.382	70.935 ±0.663	67.425 ±0.708	72.126 ±0.688	82.345 ±0.473
12	55.446 ±0.254	59.672 ±0.290	65.388 ±0.350	73.142 ±0.268	81.162 ±0.426	46.585 ±0.375	51.666 ±0.350	67.110 ±0.450	81.048 ±0.451	76.545 ±0.901	81.101 ±0.451	91.692 ±0.708
16	61.087 ±0.239	68.648 ±0.364	78.090 ±0.325	82.088 ±0.580	86.862 ±0.358	52.756 ±0.344	56.434 ±0.325	76.665 ±0.687	84.993 ±0.342	84.325 ±0.452	87.101 ±0.689	94.793 ±0.768
20	64.350 ±0.275	73.314 ±0.458	83.382 ±0.389	86.304 ±0.327	90.559 ±0.477	56.4003 ±0.307	61.011 ±0.474	82.945 ±0.676	88.268 ±0.483	94.138 ±0.633	93.858 ±0.475	99.548 ±0.452

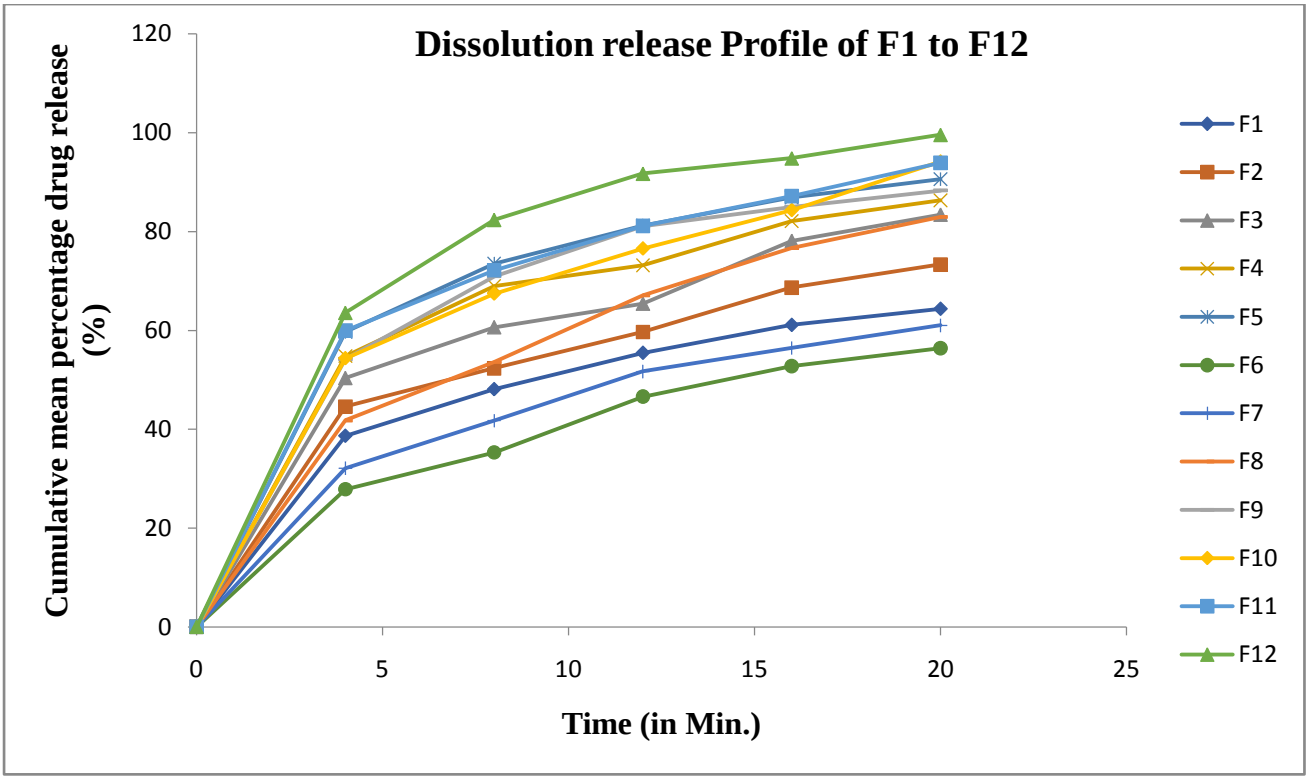

Figure 9: Graph of Dissolution release Profile

STABILITY STUDY:

The effect of various storage conditions on various parameters of Tablet F12 is given in Table 20-21.

Table 20: Effect of Storage Condition (39°C/76%RH) of Trial of Tablet F-12

Stability	**Weight (mg)**	**Friability (%)**	**Hardness (kg/cm^2)**
Initial	**500.123±0.001**	**0.478±0.0003**	**3.0**
1 month	**500.001±0.012**	**0.478±0.0012**	**3.0**
2 month	**499.983±0.036**	**0.476±0.0056**	**3.0**
3 month	**499.663±0.008**	**0.475±0.0023**	**2.9**

Table 21: Effect of Storage Condition (39°C/76%RH) of Trial of Tablet F-12

Stability	**Disintegration time (Second)**	**Drug Content (mg)**	**Drug release (%)**
Initial	25.680±1.411	50.366±0.028	100.733±0.057
1 month	24.966±0.329	50.152±0.015	100.316±0.152
2 month	23.190±0.621	49.933±0.011	99.866±0.062
3 month	21.512±551	49.541±0.089	99.083±0.112

The cumulative percent drug release from the formulation is given in Table 22. The drug release curve after stability study of Tablet F12 is shown in Figure 10.

Table 22: Cumulative % drug release

Time (Min)	Cumulative percentage drug release			
	Initial	1 Month	2 Month	3 Month
0	0	0	0	0
4	63.54 ±0.54	63.360 ±0.54	62.505 ±0.433	62.505 ±0.433
8	82.345 ±0.473	82.165 ±0.473	81.264 ±0.468	81.264 ±0.468
12	91.692	91.346	90.234	90.234

	±0.708	±0.708	±0.522	±0.522
16	94.793 ±0.768	94.357 ±0.768	92.839 ±0.6454	92.839 ±0.644
20	99.548 ±0.452	99.202 ± 0.452	98.837 ±0.314	98.837 ±0.314

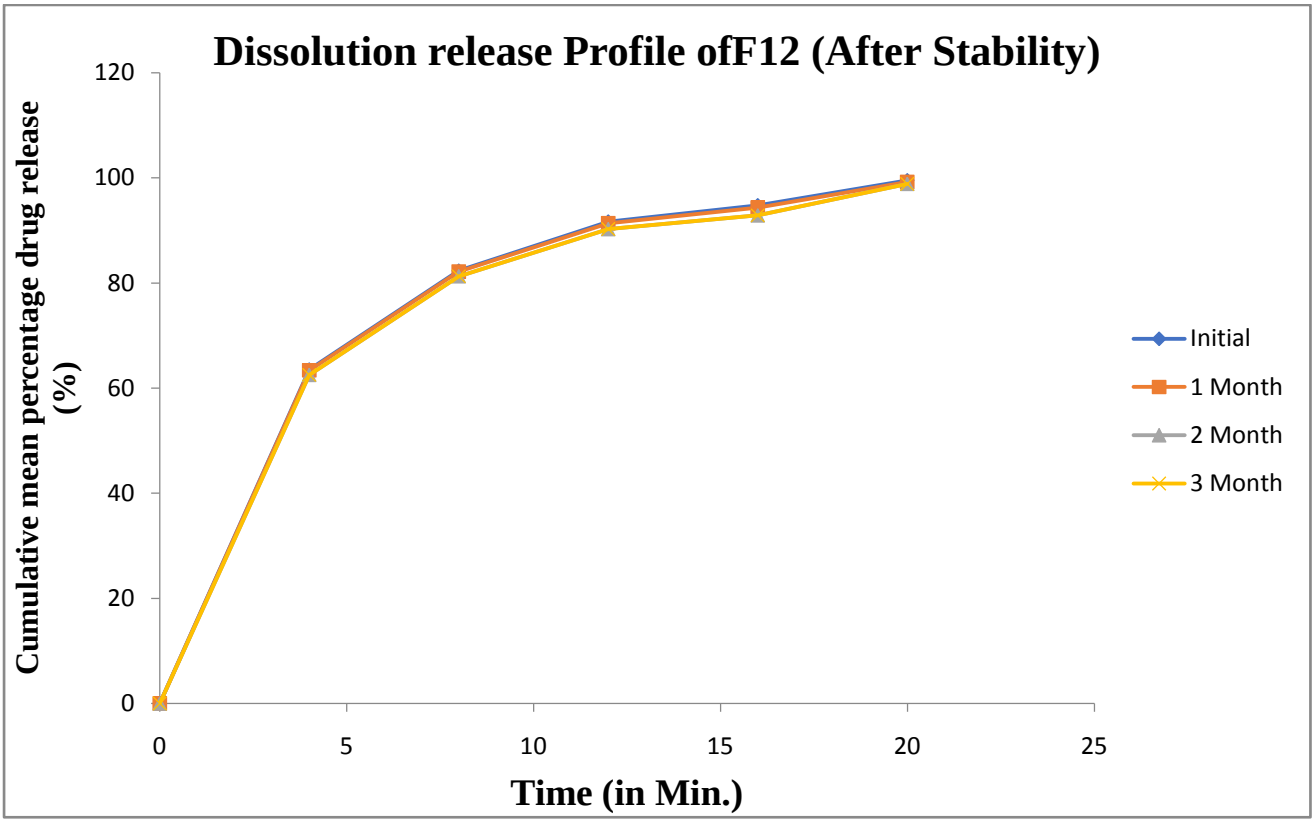

Figure 10: Graph of Dissolution release Profile

Result: Stability studies were conducted for the formulations F12. The reasons for selection is, this formulation has shown best results in term of weight, hardness, friability, in-vitro disintegration, drug content, in-vitro drug release studies. Stability studies of the prepared fast dissolving tablets were performed at different temperatures (39ºC/76%RH). The tablets were analyzed for weight, hardness, friability, in-vitro disintegration time, and for drug content in each formulation at a time interval of one month for the period of three months shown better result.

CONCLUSION

For improving the solubility of Flurbiprofen solid dispersion was prepared by using PEG 4000, Guar Gum, Xanthan Gum and PVP K-30 by using ratio(1:1 to 1:3) by physical mixture

method, in which PVP K-30 ratio 1:3 given better solubility results in all solid dispersion ratios. The characterization of mixed blend was carried out for all formulations, all having value between specified limit.Fast dissolving tablet F12 having Flurbiprofen and PVP K-30 in ratio 1:3 have better results, and contain 5% Crospovidone XL-10 shown most satisfactory results in all formulations. On the basis of in-vitro release of dispersion KPVP-3 was chosen for Fast dissolving tablet.Stability study for F12 (Cyclodextrin)was performed at temperature (39ºC/76%RH). The formulation did not show any significant variation in all parameters evaluated under the test period conditions.From the above study it was concluded that the F12 is best formulation for Fast dissolving tablet of flurbiprofen.

Conflict of Interest: None

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