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Development, Evaluation, and Characterization of Fast Disintegrating Tablets of Ketoprofen Solid Dispersion Prepared by Co-Precipitation Technique

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Muhamed Haris V A.

Qatar Red Crescent, QATAR College of Pharmaceutical Sciences, Govt. Medical College, Kozhikode.

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ABSTRACT

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) having poor water solubility and low bioavailability. The purpose of the present study is to increase the solubility and dissolution rate of Ketoprofen by preparing solid dispersions with β-CycloDextrin and Polyethylene Glycol (PEG 6000) at various ratios by Co-Precipitation method. The solid dispersions are evaluated for solubility, drug content, in-vitro drug release study, surface morphology by scanning electron microscopy (SEM). The Fast Disintegrating Tablets of Ketoprofen was prepared by direct compression technique by addition of superdisintigrantCrospovidone in different concentration (1-5% w/w). The prepared batches of tablets were evaluated for hardness, friability, disintegration time, wetting time, dispersion time, drug content uniformity and in-vitro drug release. It may be concluded that Fast Disintegrating Tablets of Ketoprofen formulated with ketoprofen solid dispersion prepared by co-precipitation technique using β-cyclodextrin as a carrier can be a promising approach for enhancing solubility and bioavailability of poorly water-soluble drugs.

INTRODUCTION

The solubility of active pharmaceutical ingredients (API) is always a concern for formulators, since poor aqueous solubility may limit the use of oral products. Drugs that have a very poor aqueous solubility, the rate of drug release is often the slowest step and exhibits a rate limiting effect on drug bioavailability.

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) having poor water solubility and low bioavailability. The purpose of the present investigation is to increase the solubility and dissolution rate of ketoprofen by preparing solid dispersions with β-CycloDextrin and Polyethylene Glycol (PEG 6000) at various ratios by Co-Precipitation method.

In the present study, Ketoprofen solid dispersion prepared by co-precipitation method is formulated as fast disintegrating tablet employing crospovidone as a super disintegrant.

OBJECTIVE:

Thus the objectives of the work are:

To enhance the solubility and bioavailability of Ketoprofen by preparing Solid dispersions using co-precipitation technique.

Evaluate the potential of β-cyclodextrin, Polyethylene glycol-6000 as suitable drug carrier systems for delivery of Ketoprofen.

Determine the effect of the change in polymer and polymer composition and Drug-polymer ratio on the solubility of Ketoprofen.

Study of *in-vitro* dissolution kinetics of Ketoprofen from the formulated Solid dispersion systems.

To formulate Fast disintegrating tablets of Ketoprofen using optimized solid dispersion of ketoprofen.

MATERIALS

Ketoprofen (Concept Pharmaceuticals, Aurangabad),β-Cyclodextrin (A – One Chemicals, Ahmedabad), Polyethylene Glycol 6000(S.D. Fine Chem. Ltd, Mumbai, India), Crospovidone (Jasmin Trade Link, Ahmedabad, India)

Equipment

Electronic Balance (Shimadzu,Japan),

Tablet Compression Machine (Cadmach Machinery Ltd, Ahmedabad), Disintegration Test Apparatus (Electrolab (Ed-2l), Bangalore).

METHOD:

Preparation of Solid Dispersions of Ketoprofen

The solid dispersion of ketoprofen was prepared using carriers PEG-6000 and β-cyclodextrin at various ratios by co-precipitation method and evaluated.

Co-precipitation method

SDs was prepared by dissolving accurately weighed amounts of a carrier in 20 ml of water and drug in 20 ml of methanol. After complete dissolution, the aqueous solution of the carrier was then poured into the methanolic solution of the drug. The solvents were then heated and evaporated under reduced pressure at room temperature. Subsequently, the solid dispersions were passed through sieve no. 40 and stored.

Table: 1 Formulation ingredients of ketoprofen Solid Dispersions.

INGREDIENTS	**QUANTITY**								
	DP1	**DP2**	**DP3**	**DC1**	**DC2**	**DC3**	**DC4**	**DC5**	**DC6**
Ketoprofen(mg)	1	1	1	1	1	1	1	1	1
PEG 6000(mg)	0.5	1	1.5	-	-	-	-	-	-
β-cyclodextrin(mg)	-	-	-	0.5	1	1.5	2	2.5	3
Methanol (ml)	20	20	20	20	20	20	20	20	20
Water (ml)	20	20	20	20	20	20	20	20	20

EVALUATION OF SOLID DISPERSIONS:

Determination of Solubility of Solid Dispersions:

Ketoprofen solid dispersions equivalent to 10 mg of Ketoprofen were added to 10 ml of phosphate buffer pH 6.8 in a 10 ml volumetric flask. The volumetric flasks were capped properly and shaken at room temperature in a temperature controlled water bath for24 hr. Resultant samples containing undissolved solid dispersions were filtered through 0.45µm filters, suitably diluted with phosphate buffer pH 6.8 and analyzed by UV spectrophotometer at 260 nm.

In vitro Drug Release:

Accurately weighed preparations equivalent to 100 mg of Ketoprofen were added to 900 ml of dissolution medium (phosphate buffer PH 6.8) in USP II Paddle type apparatus and stirred at speed of 50 rpm at 37 ± 0.5^0C. 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 after filtration and dilution were analyzed at 260 nm using UV-visible spectrophotometer against the blank. The dissolution of pure Ketoprofen was done similarly.

Scanning Electron Microscopy (SEM):

The external morphology of solid dispersions was analyzed by Scanning Electron Microscope (SEM). The samples were examined under a scanning electron microscope.

FORMULATION OF FAST DISINTEGRATING TABLETS:

FDTwere formulated with optimized solid dispersion (DC4) by direct compression technique using 16 stations multiple punch tablet compression machines (Cadmech) to produce tablets weighing 500 mg each with a diameter of 85mm. A minimum of 30 tablets was prepared for each batch. The formulation was developed by the following method.

Preparation of Fast disintegrating tablets by direct compression method:

FDT of ketoprofen was prepared by direct compression method, according to the proportions given in the table-7. All the ingredients were passed through 60 mesh sieve prior to mixing. Solid dispersion (DC4) equivalent to 100mg of ketoprofen was mixed with microcrystalline cellulose employing cross-povidone as a super disintegrant. Talc and magnesium stearate

were used as glidant and lubricant. After uniform mixing, it was compressed using Cadmech Tablet Compression Machine equipped with flat faced punches.

Table 2: Formulation of Fast Disintegration Tablets

INGREDIENTS	AMOUNT (mg)		
	F_1	F_2	F_3
Ketoprofen Solid Dispersion(DC4)	300	300	300
Microcrystalline Cellulose	180	172.5	160
Crosspovidone	5	12.5	25
Magnesium Stearate	5	5	5
Talc	10	10	10

Evaluation Parameters for Fast Disintegrating Tablets

Preformulation Parameters Such As Angle of repose, Bulk Density, Tapped Density, Carr's Compressibility Index, Hausners Ratiowere evaluated.

Post-compression Parameters Such As Weight Variation, Thickness, Hardness, Friability were evaluated.

FAST DISINTEGRATING TABLETS CHARACTERIZATION

***In-vitro* disintegration test**

One tablet was placed in each tube of disintegration test apparatus and a disc was placed on each tube. The water was maintained at a temperature of 37±0.5ºC and time taken for complete disintegration of the tablet was measured in seconds.

Wetting time

A piece of tissue paper folded twice was placed in a Petri dish (i.d. = 6.5 cm) containing 10 ml of 6.8 pH phosphate buffer solution, a tablet was placed on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and the standard deviation was determined.

Drug content uniformity

Ten tablets were weighed and triturated. The tablet triturates equivalent to 100 mg of the drug was weighed accurately and taken into a 100 ml volumetric flask and dissolved in methanol. One ml of the filtrate was diluted to 100 ml with 6.8 phosphate buffer and assayed for drug content using a double beam UV/Vis spectrophotometer at 260 nm.

***In vitro* dissolution studies**

In vitro dissolution study was performed by using USP Dissolution Test Apparatus Type-2 (Paddle method). Weighed tablets from different batches were kept in the dissolution apparatus containing 900 ml of 6.8 phosphate buffer dissolution medium maintained at 37 ± 0.5ºC and at a speed of 50 rpm. Five ml of the aliquot was withdrawn at specific time intervals and filtered through a 0.45-micron membrane filter. The samples were replaced with fresh dissolution medium. The samples were suitably diluted and analyzed at 260 nm against blank using UV spectrophotometer.

RESULTS AND DISCUSSION:

Preformulation Studies – Solubility

Table: 3 Solubility of Ketoprofen in Different Solvents

S.No.	Solvents	Solubility
1	Distilled water	-
2	Ethanol	++
3	Methanol	++
4	0.1 HCl	+

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

Table: 4 Pre-formulation studies of pure drug:

Drug	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausners ratio	Compressibility Index	Angle of repose
Ketoprofen	0.053±0.015	0.71±0.045	1.33±0.075	25.35±0.084	$31^0.52`$±0.0824

EVALUATION OF SOLID DISPERSION

Determination of solubility of solid dispersions

The solubility study was carried out in pH 6.8 phosphate buffer. All the prepared solid dispersions exhibited better solubility when compared to pure drug. The solubility of ketoprofen was increased by using different carriers (PEG-6000 and β-cyclodextrin). The maximum solubility was found with DC_4 solid dispersion which was prepared by using ketoprofen and β-cyclodextrin (1:2 ratio) by co-precipitation method. It was observed that saturation solubility of a drug was increased by 20 to 25 folds by converting the drug into a solid dispersion.

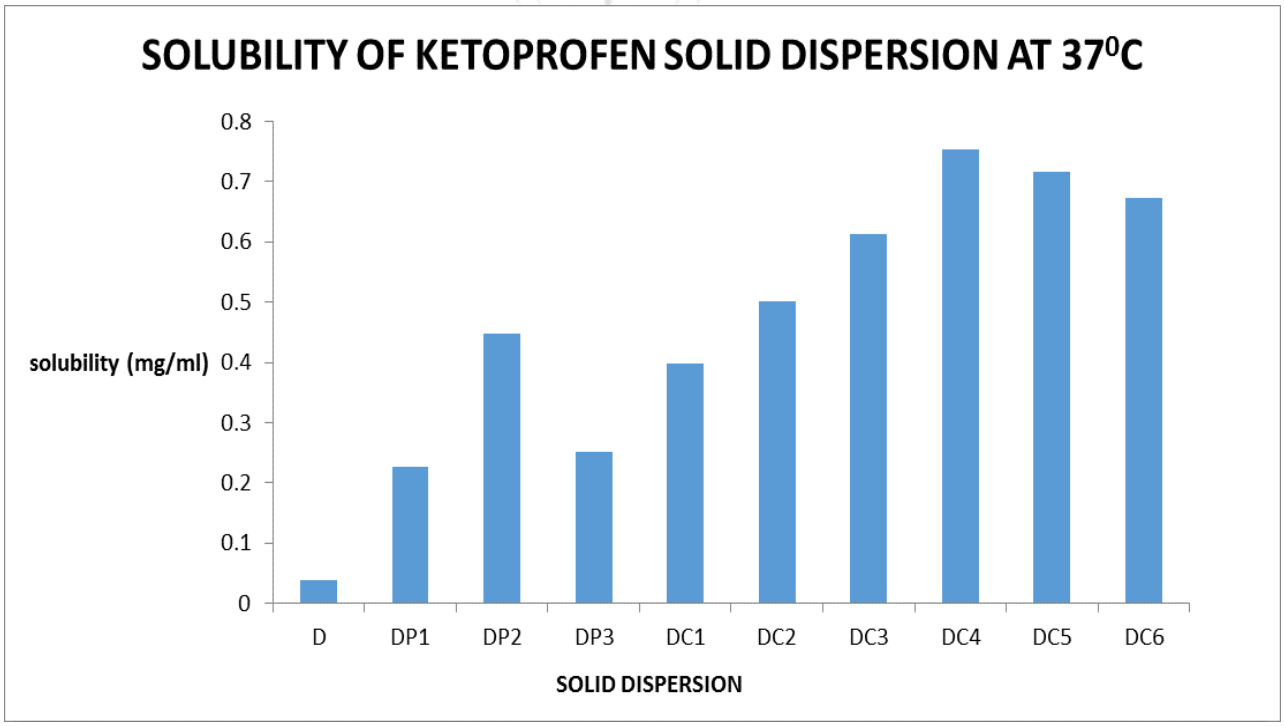

Figure 1: Solubility of Ketoprofen Solid Dispersions

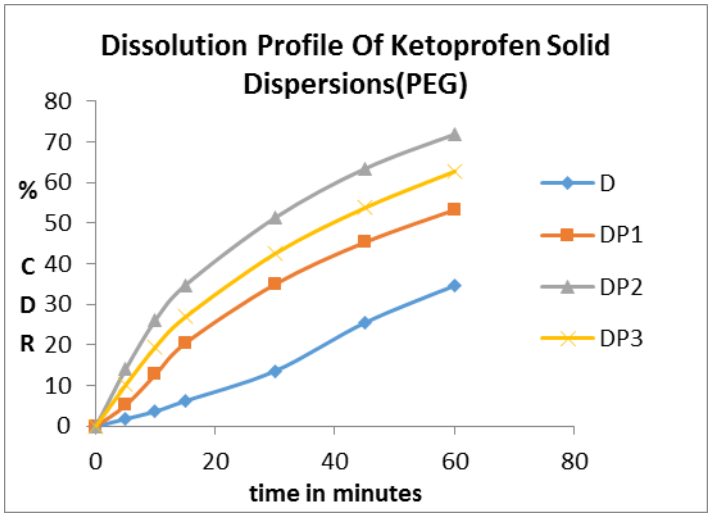

Figure 2: *In vitro* Dissolution study

***In vitro* Dissolution characteristics of Ketoprofen Solid Dispersions**

Initially, SDs of ketoprofen was prepared using PEG 6000 as the carrier by co-precipitation technique. *In-vitro* Dissolution studies were carried out for 60 minutes. Pure ketoprofen has shown a % CDR of 34.5% in 60 minutes. Formulation DP1 with PEG 6000 in 1:0.5 drug-polymer ratio has shown a %CDR of 53.9%

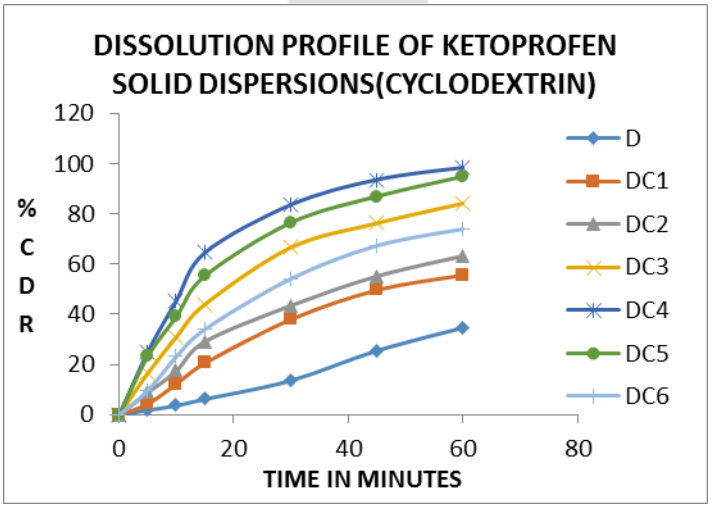

Figure 3: *In vitro* Dissolution study

In order to improve the drug release, further formulations DP2 and DP3 were prepared by increasing the amount PEG 6000. Formulation DP2 shown an increase in percentage cumulative drug release when compared to DP1 but a further enhancement in the amount of PEG(DP3) has retarded the percentage cumulative drug release when compared to DP2.(table

18, fig 8). All the formulations have shown an increase in %CDR when compared to the pure drug.

Among the formulations, DP2 has exhibited better release rate. The enhancement of drug dissolution with PEG 6000 may be due to the entrapment of drug in the helical interstitial space of hydrophilic PEG molecules and also due to the reduction in the particle size.

Further studies were carried out to enhance the drug release using β-cyclodextrin as a carrier. More formulations (DC1-DC6) were prepared by varying the drug-polymer ratios. *In-vitro* release studies showed that increase in the amount of β-cyclodextrin increased the drug release up to a drug-polymer ratio of 1:2 (DC4). It showed a % CDR of 98.28% in 60 minutes. Further formulations were prepared by increasing the amount of β-cyclodextrin (DC5and DC6). But the release rate was found to be declining above a ratio of 1:2 (drug: polymer).

All the formulations have shown increased drug release when compared to pure drug. Formulation (DC4) showed better %CDR (98.28%) when compared to the pure drug (34.5%) and all other formulations. Formulation DC4 prepared with β-cyclodextrin also showed a significant improvement in drug release when compared with that of PG 6000. This may be attributed to the fact that β-cyclodextrin formed the inclusion complex with lipophilic ketoprofen and enhanced the solubility and finally *in-vitro* dissolution.

Scanning Electron Microscopy (SEM):

The SEM of pure Ketoprofen and Ketoprofen-B Cyclodextrin solid dispersion (DC4) were shown. Formulation DC4 was selected based on *in-vitro* dissolution and solubility analysis. It was found that Ketoprofen was highly crystalline in nature. In formulation DC4 it can be observed that the crystallinity of ketoprofen is decreased and the crystals were found to be entrapped in β-cyclodextrin inclusion complex. The rough surface of prepared SD (DC4) also enhanced the wettability of the drug and overall improvement in solubility.

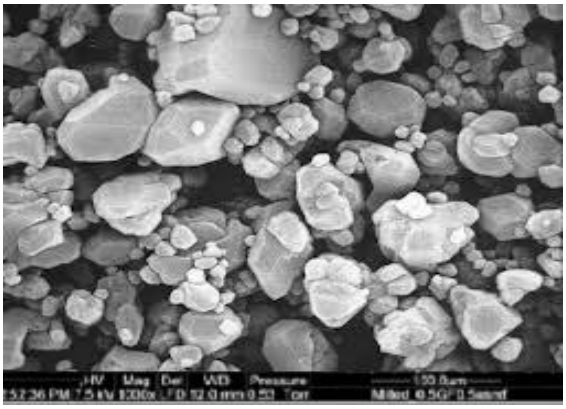

Figure 4: SEM of Ketoprofen sample.

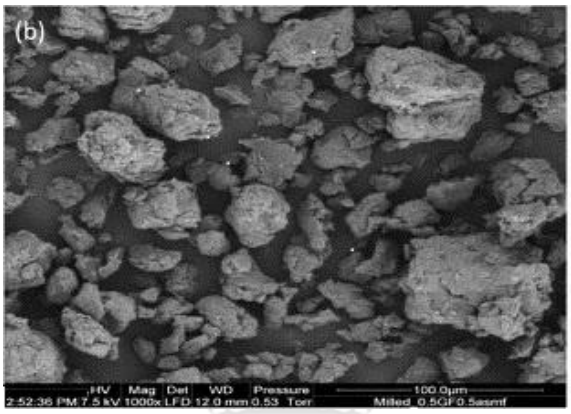

Figure 5: SEM of Ketoprofen Solid

Dispersion

PREPARATION OF FAST DISINTEGRATING TABLETS

Fast disintegrating Tablets of ketoprofen was prepared using DC4 solid dispersion by direct compression method employing super disintegrant crospovidone in various concentrations (1-5%w/w).

FAST DISINTEGRATING TABLETS CHARACTERIZATION.

Table 5: Post-compression parameters of tablets prepared by direct compression method.

Formulation	Thickness(mm)	Weight(mg)	Friability (%)	Hardness
F1	6.325±0.245	500.77±1.23	0.47±0.045	5.2±0.212
F2	6.342±0.142	501.82±0.985	0.74±0.052	4.8±0.124
F3	6.48±0.263	498.31±0.653	0.51±0.036	5.6±0.451

In- vitro disintegration time:

The tablets prepared by direct compression method undergo *in-vitro* disintegration within 48.14 seconds. The formulation F_3 containing 5 % of superdisintegrant (crospovidone) was found to disintegrate faster (25.12 sec) when compared to other formulations.

Wetting time:

The wetting time of ketoprofen tablets prepared by direct compression method was found to be in the range of 24.58 to 42.45 sec. Promising formulations was found to be F_3 which contain 5 % of super disintegrant.

Table 6: Characterization of Fast Disintegrating Tablets

Formulation Code	Disintegration Time (Sec)	Wetting Time (Sec)
F1	48.14±0.856	42.45±0.542
F2	38.42±1.265	32.48±0.947
F3	25.12±0.895	24.58±1.264

IN- VITRO DISSOLUTION STUDIES:

FDT prepared with the varying amount of superdisintegrant (crospovidone) were subjected to *in-vitro* drug release study. Three formulations were prepared (F1, F2, and F3) with increasing amounts of crospovidone 1, 2.5, 5 % respectively. The dissolution studies reveal that formulation F3 prepared with 5% of crospovidone released 98.45% of the drug in 40

minutes. The release rate of formulation F3 was found better when compared with other formulations.

SUMMARY AND CONCLUSION

The concept of formulating fast disintegrating tablets using superdisintegrants offers an appropriate and practical approach of faster disintegration and dissolution characteristics.

Ketoprofen, a non-steroidal anti-inflammatory agent, is widely used as the first-line drug in the symptomatic relief of rheumatoid arthritis and osteoarthritis. One of the major problems with this drug is its very poor solubility in biological fluids, which results in low bioavailability after oral administration. Therefore, there is a strong need to formulate Ketoprofen as solid dispersions and to formulate into suitable dosage forms like fast disintegrating tablets.

Solid dispersions with ketoprofen were prepared by co-precipitation technique using carriers PEG 6000 and β-cyclodextrin. The prepared solid dispersions were subjected to various evaluation parameters and *in-vitro* dissolution studies.

Solubility analysis showed that the solubility of ketoprofen was enhanced by PEG 6000 andβ-cyclodextrin. Formulation DC4 prepared with β-cyclodextrin (1:2 drug-polymer ratio) exhibited maximum solubility.

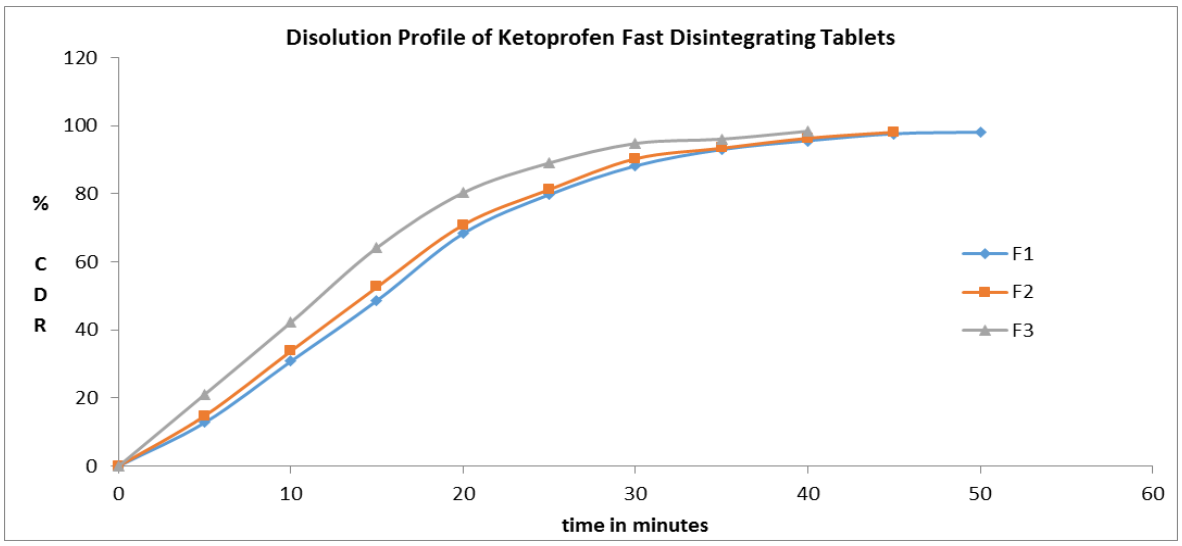

Figure 6: Dissolution Profile of Ketoprofen Fast Disintegrating Tablets.

In-vitro drug release studies also showed formulation DC4 with drug polymer ratio 1:2 exhibited maximum percentage drug release when compared to pure drug and other formulations.SEM analysis confirms the reduction in crystallinity and formation of inclusion complex, which might have contributed to the enhancement of solubility of the formulation DC4.

Optimized solid dispersion (DC4) was used for the preparation of fast disintegrating tablet.

FDT were prepared by direct compression technique employing crospovidone as a super disintegrant.

In-vivo disintegration and wetting time of formulation F3 employing 5% of crospovidone has shown enhanced wettability and disintegration.

i, drug release studies showed formulation F3 exhibited maximum percentage drug release.

It may be concluded that Fast Disintegrating Tablets of Ketoprofen formulated with ketoprofen solid dispersion prepared by co-precipitation technique using β-cyclodextrin as a carrier can be a promising approach for enhancing solubility and bioavailability of poorly water-soluble drugs.

Long-term stability analysis and bioavailability have to be performed for ensuring the biological activity of the prepared formulation.

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