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FORMULATE AND EVALUATE KETOPROFEN FOR ADEQUATE MECHANICAL STRENGTH, RAPID DISINTEGRATION & FAST ACTION

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ABSTRACT

Ketoprofen is a non-steroidal anti-inflammatory drug which is mainly used for osteoarthritis and rheumatoid arthritis. The major problem with this drug was it is of having very low solubility in biological fluids, which results in poor solubility after oral administration. Therefore, solid dispersion of Ketoprofen with PEG-6000 and PVP K30 in different weight ratios (1:1, 1:2, 1:3) were prepared in a view to increase the water solubility. The solid dispersions were evaluated to solubility study, drug content, in-vitro drug release study, dissolution efficiency. The Ketoprofen SD with PVP K30 (1:3) ratio was showed maximum amount of drug release hence it was selected for Fast Dissolving Tablets formulation. The Fast-Dissolving Tablets of Ketoprofen was prepared by direct compression technique by addition of super disintegrant like Sodium starch glycolate, Cross caramellose sodium, and Cross povidone in different concentration (1-5% w/w) and by effervescence technology by using combination of (2:3 ratio) Citric acid and sodium bicarbonate in different concentration (1-5% w/w) in a view to enhance the patient compliance. The prepared batches of tablets were evaluated for hardness, friability, disintegration time, wetting time, dispersion time, drug content uniformity and *in-vitro* drug release in 6.8 pH Sorenson's buffer measured at 260 nm. Among all formulations, F15 containing 5% w/w of Cross Povidone is best having least disintegration time 25.68 seconds and release 99.55% of drug in 20 minutes. The formulation F4, F10, F18 and best formulation F15 at 40^0 C (75% RH) confirms there is not significantly change in hardness,

friability, disintegration time, drug content and *in-vitro* drug release pattern.

KEYWORDS: *Ketoprofen, Solid dispersion, Direct compression, Fast dissolving Tablets, Super disintegrants, Effervescent method, Stability Study.*

INTRODUCTION

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage forms. For many decades treatment of an acute disease or chronic illness has mostly accomplished by delivery of drugs to patients using conventional drug delivery system. Even today these conventional drug delivery systems are the primary pharmaceutical products commonly seen in the prescription. Conventional oral drug products are formulated to release the active principle immediately after oral administration to obtain rapid and complete systemic drug absorption. Drug absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation.[1] Systemic drug absorption from a drug product consists of a succession of rate process for solid oral, immediate release drug products.

The rate process include

- Dissolution of the drug in an aqueous environment.
- Absorption across cell membranes into systemic circulation.

For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step and therefore exhibits a rate limiting effect on drug bioavailability. In contrast, for a drug that has a high aqueous solubility the dissolution rate is rapid the rate at which the drug crosses or permeates cell membrane is the slowest or rate limiting step.[2,3]

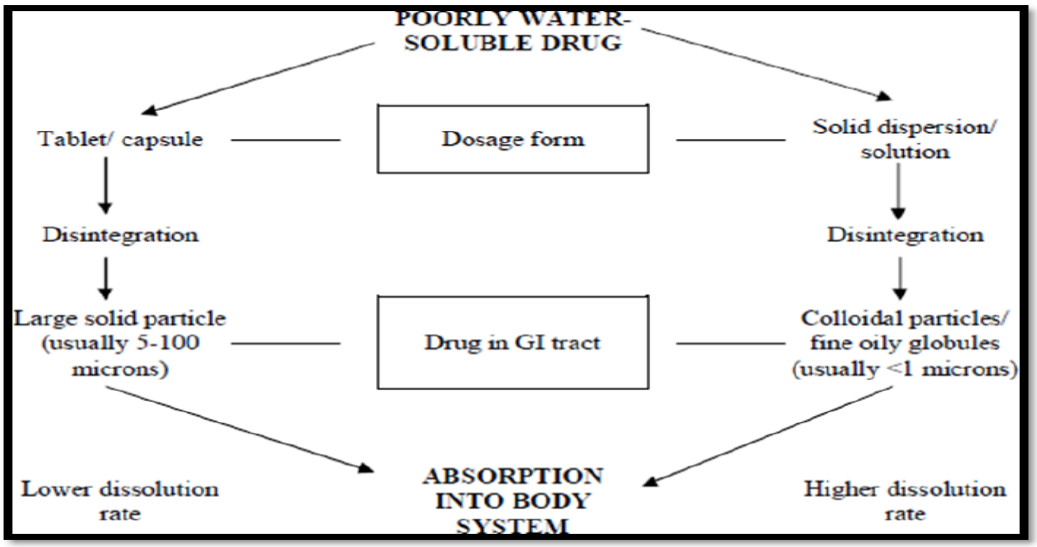
Together with the permeability, the solubility behavior of a drug is a key determinant of its oral bioavailability. They have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole & chloramphenicol come immediately to mind. With the recent advent of high through put screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most

frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

Introduction to solid dispersion technology

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs, there are practical limitations of these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the GIT may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and cosolvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability.

In 1961, Sekiguchi and Obi developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs can be overcome, which was termed as “Solid Dispersion”.



A schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersion compared with conventional tablet or capsules

Types of solid dispersions[5]

a. Simple eutectic mixture

A eutectic mixture of a sparingly water soluble drug and a highly water soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline component. The increase in surface area is mainly responsible for increased rate of dissolution. This led to a conclusion that the increase in dissolution was mainly due to decreased particle size.

b. Solid solutions

Solid solutions consist of a solid solute dissolved in a solid solvent. A mixed crystal is formed because the two components crystallize together in a homogenous one-phase system. Hence, this system would be expected to yield much higher rates of dissolution than simple eutectic systems.

c. Glass solution of suspension

A glass solution is a homogenous system in which a glassy or a vitreous of the carrier solubilizer drug molecules in its matrix. PVP dissolved in organic solvents undergoes a transition to a glassy state upon evaporation of the solvent.

d. Compound or complex formation

This system is characterized by complexation of two components in a binary system during solid dispersion preparation. The availability of the drug from the complex is dependent on the solubility dissociation constant and the intrinsic absorption rate of the complex.

e. Amorphous precipitation

Amorphous precipitation occurs when drug precipitates as an amorphous form in the inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug.

Mechanism of increased dissolution rate[6]

The enhancement in dissolution rate as a result of solid dispersion formulation, relative to pure drug varies from as high as 400 folds to less than two-fold. Corrigan reviewed the current understanding of the mechanism of release from solid dispersion. The increase in dissolution rate for solid dispersion can be attributed to a number of factors. It is very difficult to show experimentally that any one particular factor is more important than another. The main reasons postulated for the observed improvements in dissolution of these systems are as follows:

a. Reduction of particle size

In case of glass, solid solution and amorphous dispersions, particle size is reduced to a minimum level. This can result in an enhanced dissolution rate due to an increase in both the surface area solubilization.

b. Solubilization effect

The carrier material, as it dissolves may have a solubilization effect on the drug. This was shown to be the case for acetaminophen and chlorpropamide in urea as well as for numerous other drugs.

c. Wettability and dispersibility

The carrier material may also have an enhancing effect on the wettability and dispersibility of the drug in the dissolution media. This should retard any agglomeration or aggregation of the particles, which can slow the dissolution process.

d. Metastable forms

Formation of metastable dispersions with reduced lattice energy would result in faster dissolution rates. It was found that the activation energies for dissolution for furosemide was 17 K Cal per mol, whereas that for 1:2 furosemide: PVP coprecipitate was only 7.3 K Cal per mol.

Methods of preparing solid dispersions[4,5,7]

The basic methods used to prepare solid dispersions are

1. Melting method or fusion method
2. Solvent evaporation method
3. Kneading method
4. Supercritical Fluid Process

Evaluation of solid dispersions[5]

Various methods are available which can give information regarding the physical nature of solid dispersion system. The commonly used methods are the following-

1. Thermal methods

This method is most commonly used to observe the Physico-chemical interactions of two or more compounds. It utilizes the principle of change of thermal energy as a function of temperature and can be performed by the following techniques.

- **Cooling curve method**

Physical mixtures of components in various properties are heated to a homogenous melt.

During the cooling process temperature of each mixture is plotted as a function of time. Critical temperatures are noted and plotted against composition to provide the phase diagram. The method is time consuming, requires relatively larger amounts of samples and is not applicable to samples that decompose after melting. Moreover, changes in slope can be mixed, especially if cooling takes place rapidly.

- **Thaw melt method**

A solidified sample in a capillary tube is heated gradually and the thaw and melting points are noted by visual observation. Since the method depends on visual observation the results are not reproducible.

- **Thermo microscopic method**

Physical mixtures of drug and carrier placed in a slide covered with a cover slip and scaled with silicone grease to prevent sublimation. The mixture is heated until it completely liquefies. After cooling, the mixture is reheated. The have and melting points are noted and a phase diagram is constructed.

- **Differential thermal analysis (DTA), differential scanning calorimetry (DSC)**

It is effective for studying phase equilibrium of pure compounds as well as their mixtures. This method is limited to compounds with high thermal stability and low volatility. In addition to thaw and melting points, polymorphic transitions, evaporation, sublimation, dissolution and other types of decomposition can also be detected by thermal analysis. The greatest advantage lies in constructing phase diagrams of high reproducibility.

2. X-ray diffraction method (XRD)

It is very important and efficient tool in studying physical nature of solid dispersions. In simple eutectic systems, diffraction peaks of each crystalline compound can be found in the diffraction spectra. In substitutions solid solutions, the lattice parameter of the solvent crystal is either increased, remains unchanged or decreased depending on the relative size of the solute atom or molecule. In continuous solid solutions, there is a shift from the positions of the peaks in one pure component to those in other. In interstitial solid solutions the diffraction pattern of solvent component may or may not change while that of the solute component disappears. The X-ray diffraction method can be applicable in detecting compound or complex formation. Since the spectra of lattice parameters of a complex are different from those of pure compound.

3. Dissolution rate determination

This method can be used to study degree or crystallinity in solid-solid equilibria. This method

involves comparison of *in-vitro* dissolution rates of solute component from a constant surface tablet with the physical mixture of same composition. The technique is simple to perform except that in some binary systems, the tablet may not be constant due to the leaching of particulars into dissolution media. It has been shown to be applicable to simulated systems of indomethacin- PEG-6000 and sulphathiazole-urea.

4. Electron microscopy

Often used to get primary information of the systems and to detect amorphous and crystalline structures.

5. Thermodynamic methods

The phase diagrams of eutectic and solid solution systems can be evaluated by phase thermodynamic parameters. The knowledge of heats of fusion, entropies and partial pressure at various compositions enables the determination of the solubility gap below the solid-liquid equilibrium temperature.

Introduction fast dissolving tablets

Recent advances in Novel Drug Delivery System (NDDS) aims to enhance safety and efficacy of already used drug molecule by formulating a convenient dosage forms for administration and to achieve better patient compliance. To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects.[8]

The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance.[9] The most popular dosage forms being tablets and capsules, one important drawback of these dosage forms however is the difficulty to swallow.[10] It is estimated that 50% of the population is affected by this problem which results in a high incidence of non-compliance and ineffective therapy. The difficulty is experienced in particular by pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water and also in following conditions like: Parkinsonism, Motion sickness, Unconsciousness and Mentally disabled persons.[11] To fulfill these medical needs, the pharmaceutical technologists have developed a novel type of dosage form for oral administration, the Fast-Dissolving Tablets (FDT), tablets that disintegrate and dissolve

rapidly in saliva without water.

Fast dissolving tablets

The fast-dissolving tablets usually dissolve in the oral cavity within 15 seconds to 3 minutes. In another words a fast-dissolving tablet is tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing.

Fast dissolving tablets are also called as Orodispersible tablets, Quick disintegrating tablets, Mouth dissolving tablets, Oral rapid disintegrating tablets, Rapid dissolving tablets, Porous tablets and Rapimelts. However, of all the above terms, United States Pharmacopoeia (USP) approved those dosage forms as Orally Disintegrating Tablets (ODTs). Recently European Pharmacopoeia has used the term Orodispersible tablet for tablets that disperses readily and within three minutes in mouth before swallowing.

United States Food and Drug Administration (USFDA) define ODT as "A solid dosage form containing medicinal substances or an active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon tongue". The disintegration time for fast dissolving tablets generally ranges from several seconds to about a minute.[12]

Advantages of fast dissolving drug delivery system

- Ease of administration to pediatric, geriatric patients and psychiatric patients.
- Free of the risk of suffocation due to physical obstruction when swallowed.
- Convenience of administrate accurate dose as compared to liquids.
- Having good mouths feel property.

Challenges to develop fast dissolving tablet[19,20]

I. Mechanical strength and disintegration time

ODTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge. Many ODTs are fragile and there are many chances that such fragile tablet will break during packing, transport or handling by the patients. Tablets based on technologies like Zydis need special type of packaging. It is very natural that increasing the mechanical strength will delay the disintegration time. So a good compromise between these two parameters is always essential.

II. Taste masking

Many drugs are bitter in taste. A tablet of bitter drug dissolving/ disintegration in mouth will

seriously affect patient compliance and acceptance for the dosage form. So effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity.

III. Mouth feel

The ODT should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the ODT should be as small as possible. ODT should leave minimal or no residue in mouth after oral administration. Morever addition of flavours and cooling agents like menthol improve the mouth feel.

IV. Sensitivity to environmental conditions

ODT generally should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in an ODT are meant to dissolve in minimum quantity of water.

V. Amount of drug

For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs.

VI. Aqueous solubility

Water-soluble drugs form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process.

VII. Size of tablet

It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

VIII. Cost

The technology used for an ODT should be acceptable in terms of cost of the final product. Methods like Zydis and Orasolv that require special technologies and specific packaging increase the cost to a remarkable extent.[8]

MATERIALS AND METHODS

List of materials

S. no.	Name of the Material
1	Ketoprofen
2	Polyvinylpyrrolidone K-30
3	Polyvinylglycol-6000
4	Ac-Di-Sol
5	Sodium Starch Glycolate
6	Cross Povidone
7	Sodium Bicarbonate
8	Citric Acid
9	Avicel PH 102
10	Lactose
11	Dextrose
12	Magnesium Stearate
13	Talc
14	Cardamom Flavor
15	Sodium Phosphate
16	Sodium Hydroxide
17	Methanol LR
18	Acetone LR
19	Aluminum Foil

Preparation of physical mixtures of ketoprofen

Physical mixtures of Ketoprofen were prepared using Polyvinylpyrrolidone k- 30 and Polyvinylglycol-6000 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 motor and pestle (Table 9 & 10).

Composition of ketoprofen-PVP K-30 physical mixture.

Sr. No.	Formulation Number	Drug : Carrier Weight Ratio
1	KP1	1:1
2	KP2	1:2
3	KP3	1:3

Composition of Ketoprofen-PEG-6000 Physical Mixture.

Sr. No.	Formulation Number	Drug : Carrier Weight Ratio
1	KPG1	1:1
2	KPG2	1:2
3	KPG3	1:3

Preparation of solid dispersions of ketoprofen[100]

Ketoprofen solid dispersions were prepared by solvent evaporation method using carriers (i.e.

PVP K-30, PEG-6000) in proportions, viz. 1:1, 1:2, 1:3 (Drug: Carrier). Methanol is selected as common solvent for solid dispersion. The respective amount of carrier was dissolved in methanol 20 ml and ketoprofen was added in parts with continuous stirring. The solvent was then removed by evaporation. The prepared solid dispersion were pulverized and shifted through sieve no. 100 and stored over a fused calcium chloride in a desiccator for further use.

Composition of Ketoprofen-PVP K-30 Solid Dispersions.

Sr. No.	Formulation Number	Drug : Carrier Weight Ratio
1	KPVP1	1:1
2	KPVP2	1:2
3	KPVP3	1:3

Composition of Ketoprofen-PEG-6000 Solid Dispersions.

Sr. No.	Formulation Number	Drug : Carrier Weight Ratio
1	KPEG1	1:1
2	KPEG2	1:2
3	KPEG3	1:3

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 using different techniques.

By addition of super disintegrants[102]

The superdisintegrants (Croscarmallose sodium, Sodium starch glycolate and Crospovidone) in varying concentration (1-5%) were used to develop the tablets. All the ingredients were shown in Table 13-15 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.

Formulation of fast dissolving tablet using cross caramellose sodium.

Ingradient	F1	F2	F3	F4	F5
Kpvp3	200	200	200	200	200
Croscarmellose sodium	5	10	15	20	25
Lactose	70	70	70	70	70
Dextrose	70	70	70	70	70
Avicel PH 102	135	130	125	120	115
Talc	10	10	10	10	10
Mg. Stearate	10	10	10	10	10
Cardamom flavor	QS	QS	QS	QS	QS

Formulation of fast dissolving tablet using sodium starch glycolate.

Ingradient	F6	F7	F8	F9	F10
Kpvp3	200	200	200	200	200
Sodium starch glycolate	5	10	15	20	25
Lactose	70	70	70	70	70
Dextrose	70	70	70	70	70
Avicel PH 102	135	130	125	120	115
Talc	10	10	10	10	10
Mg. Stearate	10	10	10	10	10
Cardamom flavor	QS	QS	QS	QS	QS

Formulation of fast dissolving tablet using crospovidone.

Ingradient	F11	F12	F13	F14	F15
Kpvp3	200	200	200	200	200
Crospovidone	5	10	15	20	25
Lactose	70	70	70	70	70
Dextrose	70	70	70	70	70
Avicel PH 102	135	130	125	120	115
Talc	10	10	10	10	10
Mg. Stearate	10	10	10	10	10
Cardamom flavor	QS	QS	QS	QS	QS

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* wetting property**

***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.

***In-vitro* disintegration property.**

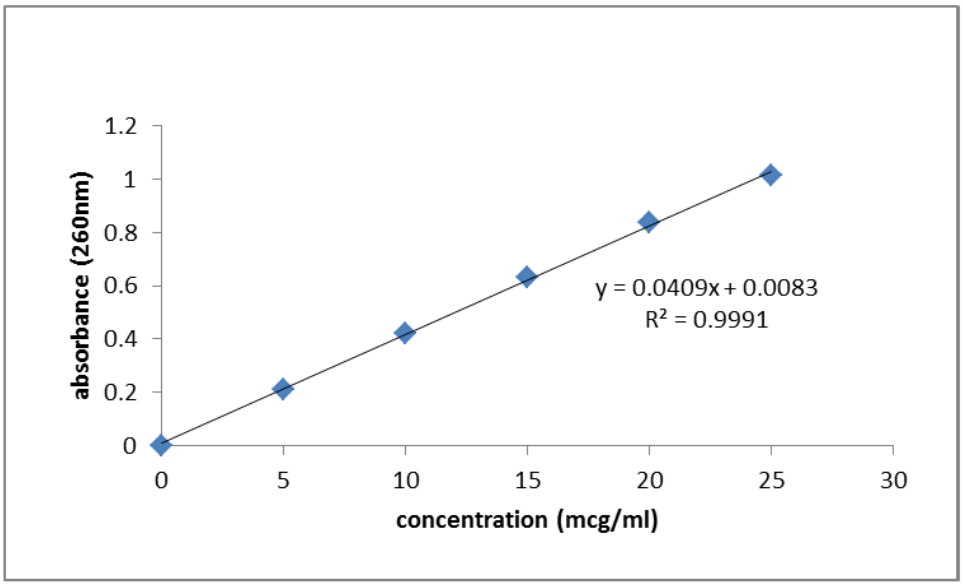
RESULTS AND DISCUSSION

Result of calibration curve data

The calibration curve of Ketoprofen was prepared in Sorenson's buffer (pH 6.8). The plot of different concentrations of Ketoprofen versus absorbance was found to be linear in the concentration range of 5-25 µg/ml at 260 nm. The absorbances at different concentrations were shown in Table 24. The data of standard curve were linearly regressed. The slope and correlation coefficient values were found to be 0.0198 and 0.9979 respectively. The intercept on Y-axis found to be 0.1361. The calibration curve was shown.

Calibration curve data of Ketoprofen

Sr. no.	Concentration	Absorbance
1	0	0
2	5	0.211
3	10	0.422
4	15	0.633
5	20	0.837
6	25	1.013



Calibration curve of ketoprofen.

Evaluation of solid dispersion

Prepared polymer drug conjugates were evaluated by

1. Determination of solubility of solid dispersion
2. Estimation of drug content
3. *In- vitro* dissolution studies
4. Dissolution efficiency of solid dispersion
5. FT-IR
6. X-ray diffraction (XRD)
7. Differential scanning calorimeter (DSC)
8. Scanning electron microscopy (SEM)

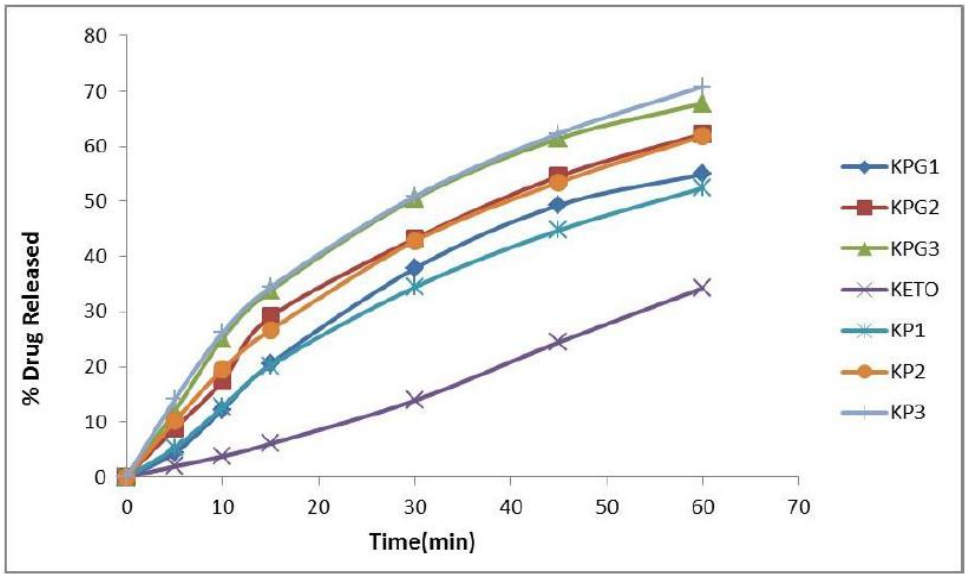
Determination of solubility of solid dispersion

Solubility data of Ketoprofen, physical mixture and solid dispersion in Sorenson's buffer pH 6.8 at 25°C and 37°C.

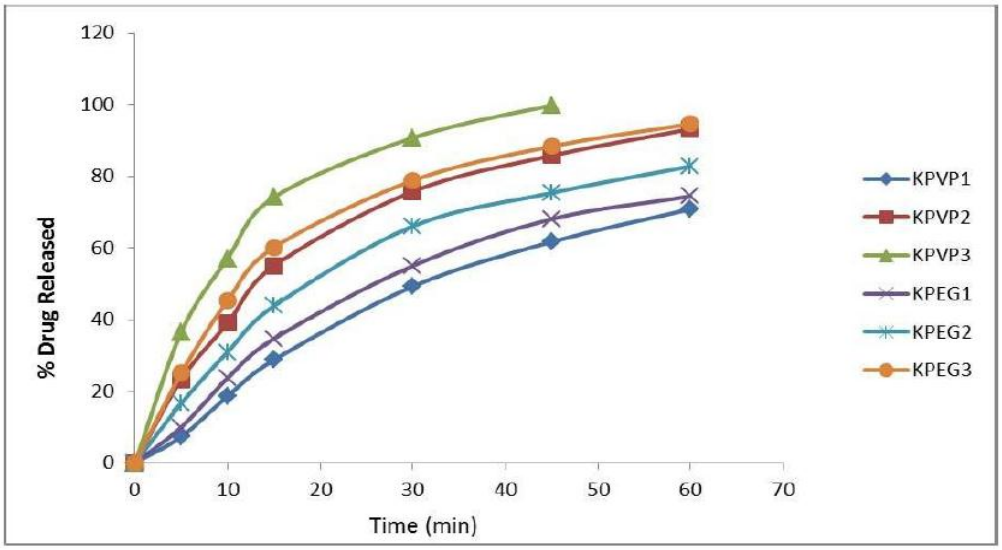
Formulation code	Ketoprofen solubility (mg/ml) at 25° C	Ketoprofen solubility (mg/ml) at 37° C
Pure Drug	0.014333 ± 0.003086	0.018417 ± 0.001809
KP1	0.28825 ± 0.002883	0.316167 ± 0.00527
KP2	0.383333 ± 0.002765	0.438917 ± 0.001665
KP3	0.46675 ± 0.003	0.564917 ± 0.002082
KPG1	0.2275 ± 0.002537	0.251833 ± 0.001507
KPG2	0.331 ± 0.002634	0.388333 ± 0.001127
KPG3	0.444917 ± 0.004856	0.501083 ± 0.001127
KPVP1	0.533083 ± 0.002126	0.603833 ± 0.001258
KPVP2	0.6775 ± 0.002537	0.751 ± 0.001146
KPVP3	0.803833 ± 0.003263	0.894417 ± 0.000878
KPEG1	0.481333 ± 0.00366	0.575333 ± 0.001127
KPEG2	0.620167 ± 0.006385	0.715417 ± 0.008098
KPEG3	0.71125 ± 0.005074	0.80475 ± 0.00522

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

Cumulative Percent Release of Ketoprofen from Physical Mixtures of Ketoprofen-PVP K-30 and Ketoprofen-PEG-6000 Systems



Cumulative Percent Release of Ketoprofen from Solid Dispersions of Ketoprofen-PVP K-30 and Ketoprofen-PEG-6000 Systems



Dissolution efficiency

Dissolution Efficiency of Ketoprofen-PVP K30 &/ Ketoprofen-PEG 6000 Physical Mixtures and Solid Dispersions.

Formulation	Dissolution Efficiency (%)	
	DE 15	DE 30
Pure drug	2.92	6.46
KP1	9.58	18.13
KP2	13.33	23.96
KP3	18.75	30.42
KPG1	8.33	18.95
KPG2	12.91	24.58
KPG3	17.92	29.17
KPVP1	12.91	25.83
KPVP2	30	47.92
KPVP3	44.16	63.33
KPEG1	17.50	31.67
KPEG2	23.33	39.17
KPEG3	34.17	52.08

Characterization of blends for fast dissolving tablets

Characterization of Blends.

Formulation	Bulk Density	Tapped density	Hausners ratio	Compressibilit y Index	Angle repose
F1	0.681092 ±0.001094	0.783293 ±0.001873	1.150054 ±0.000933	13.04752 ±0.070577	23.99959 ±0.520574
F2	0.591251 ±0.001069	0.673251 ±0.001386	1.13869 ±0.000285	12.17977 ±0.022013	23.14928 ±0.50656
F3	0.61501 ±0.002005	0.704891 ±0.002071	1.146146 ±0.000411	12.75107 ±0.031322	23.2435 ±0.485106
F4	0.670249 ±0.002695	0.75873 ±0.002303	1.132016 ±0.001117	11.66196 ±0.087151	23.82844 ±0.837309
F5	0.598567 ±0.001802	0.680278 ±0.002444	1.13651 ±0.001053	12.01126 ±0.081509	22.40116 ±0.719261
F6	0.677508 ±0.000918	0.755288 ±0.001141	1.114806 ±0.002766	10.29793 ±0.222876	23.7341 ±0.591321
F7	0.567537 ±0.000644	0.641849 ±0.000824	1.130937 ±0.000168	11.57776 ±0.013142	23.70906 ±0.491507
F8	0.61535 ±0.00239	0.697039 ±0.003689	1.132748 ±0.001647	11.71899 ±0.128243	23.05747 ±0.747942
F9	0.553101 ±0.001621	0.630258 ±0.00243	1.139499 ±0.001186	12.24204 ±0.091409	24.26282 ±0.744986
F10	0.608027 ±0.001129	0.68151 ±0.00142	1.120855 ±0.000871	10.78234 ±0.069326	23.69731 ±0.999613
F11	0.612746 ±0.000751	0.700609 ±0.001501	1.143392 ±0.001105	12.54091 ±0.084452	20.72383 ±0.51672
F12	0.560748 ±0.000363	0.656169 ±0.000861	1.170168 ±0.002224	14.5419 ±0.16249	23.11178 ±0.676691
F13	0.608027 ±0.001129	0.699304 ±0.001956	1.150119 ±0.001191	13.05239 ±0.089995	25.66395 ±0.45653
F14	0.594061 ±0.001079	0.691291 ±0.006953	1.163659 ±0.009671	14.0602 2±0.71082	25.01529 ±0.541887
F15	0.666076 ±0.001356	0.75567 ±0.001746	1.134509 ±0.000311	11.85616 ±0.024141	23.78599 ±0.471261
F16	0.585941 ±0.001727	0.66756 ±0.001783	1.139296 ±0.000485	12.22651 ±0.037362	23.81718 ±0.730814
F17	0.609016 ±0.001484	0.694448 ±0.001929	1.140278 ±0.00039	12.30212 ±0.029969	23.70906 ±0.491507
F18	0.624222 ±0.001559	0.722552 ±0.003132	1.157521 ±0.002128	13.60825 ±0.158823	24.3578 ±0.714602
F19	0.657607 ±0.001	0.751127 ±0.000652	1.142213 ±0.000744	12.45062 ±0.057075	23.79845 ±0.661456
F20	0.634788 ±0.001232	0.741109 ±0.001679	1.167491 ±0.000379	14.34621 ±0.027839	26.10666 ±0.462065

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

Characterization of fast dissolving tablets

Characterization of fast dissolving tablets.

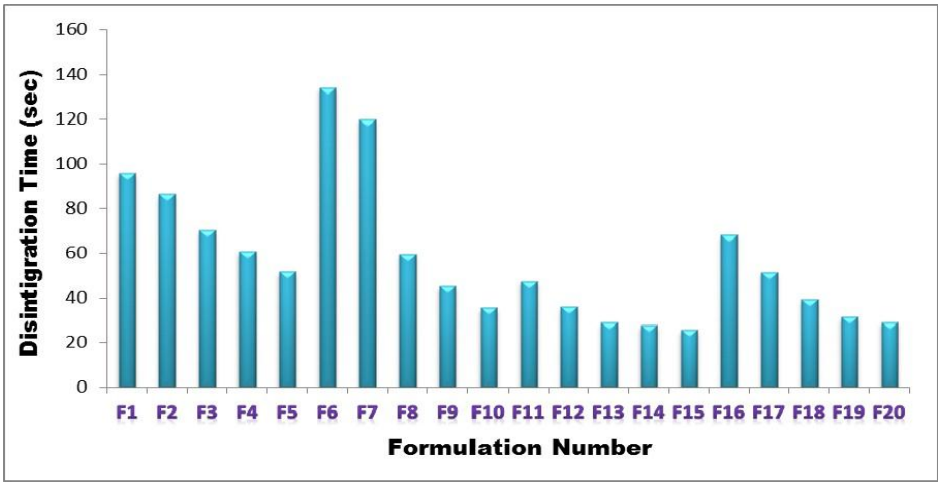
Formulation	Thickness (mm)	Weight (mg)	Friability (%)	Hardness (Kg/cm^2)
F1	6.325±0.014	500.6667 ±1.527525	0.478151 ±0.000291	3.166667 ±0.057735
F2	6.342±0.026	496.6667 ±3.785939	0.440411 ±0.000269	3.133333 ±0.057735
F3	6.343±0.034	497.3333 ±0.57735	0.639744 ±0.000256	2.8 ±0.1
F4	6.325±0.004	501.3333 ±2.081666	0.781955 ±0.045364	2.8 ±0.1
F5	6.349±0.037	496.6667 ±1.527525	0.876262 ±0.000533	2.733333 ±0.152753
F6	6.342±0.029	502.6667 ±1.527525	0.719904 ±0.0006	3 ±0.173205
F7	6.348±0.043	500.3333 ±1.527525	0.519308 ±0.000432	3.6 ±0.1
F8	6.349±0.021	500.3333 ±2.309401	0.800108 ±0.00103	3 ±0.173205
F9	6.334±0.034	499.3333 ±1.527525	0.638808 ±0.00039	3.266667 ±0.057735
F10	6.325±0.008	498.6667 ±2.081666	0.519654 ±0.000523	3.533333 ±0.11547
F11	6.345±0.016	499.3333 ±3.21455	0.519792 ±0.000208	3.433333 ±0.11547
F12	6.372±0.031	498.6667 ±0.57735	0.719138 ±0.000994	3.133333 ±0.152753
F13	6.346±0.034	501.6667 ±2.081666	0.76132 ±0.000466	3.166667 ±0.152753
F14	6.335±0.031	499.3333 ±1.527525	0.519662 ±0.002573	3.066667 ±0.208167
F15	6.348±0.031	501.3333 ±1.527525	0.478151 ±0.000396	3.3 ±0.2
F16	6.344±0.034	498.6667 ±0.57735	0.760102 ±0.000978	2.666667 ±0.152753
F17	6.363±0.035	498.6667 ±1.527525	0.67991 ±0.000415	2.8 ±0.173205
F18	6.343±0.016	499.3333 ±2.081666	0.840785 ±0.000514	2.566667 ±0.208167
F19	6.366±0.041	498.6667 ±3.05505	0.919755 ±0.000212	2.5 ±0.173205
F20	6.321±0.339	500.6667 ±1.527525	0.958467 ±0.000383	2.7 ±0.264575

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

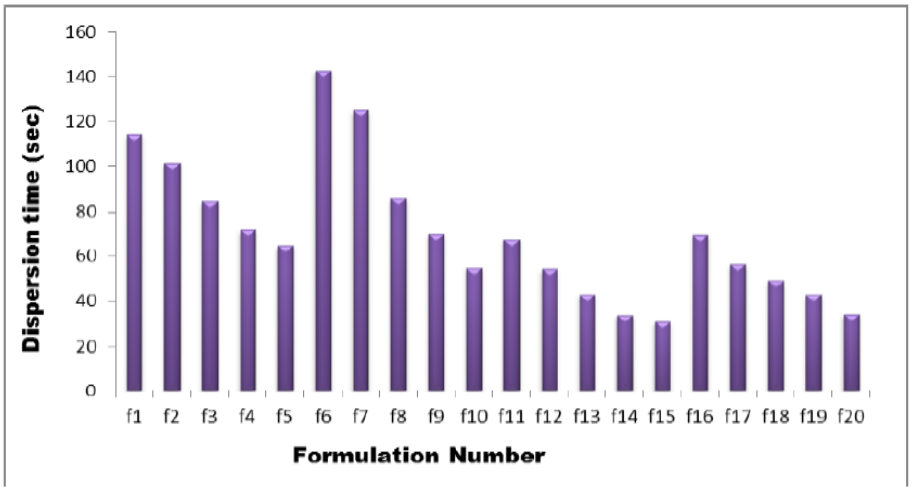
Characterization of fast dissolving tablets.

Formulation	Disintegration time (Seconds)	Wetting time (Seconds)	Dispersion time (Seconds)
F1	95.53333 ±1.507459	87.37 ±1.770339	114.3467 ±3.381262
F2	86.50333 ±2.360452	80.13667 ±3.928897	101.4433 ±2.408513
F3	70.25667 ±3.769726	65.34333 ±3.674647	84.76 ±4.26522
F4	60.65 ±1.85696	55.04 ±3.125972	71.81 ±3.404453
F5	51.94667 ±3.34403	49.22333 ±3.511885	64.70667 ±4.265024
F6	134.2233 ±5.162183	125.6633 ±5.760046	142.7133 ±4.83864
F7	119.93 ±4.994207	110.2733 ±3.544014	124.9033 ±4.639874
F8	59.48 ±1.509073	80.09333 ±4.400231	86.23333 ±2.717174
F9	45.11333 ±2.155327	62.69 ±2.507349	69.72333 ±1.804476
F10	35.60667 ±1.471915	48.98333 ±3.493799	55.07333 ±3.127944
F11	47.48333 ±1.878546	60.04333 ±3.823354	67.46667 ±2.541679
F12	36.01333 ±1.651676	42.94 ±3.040049	54.35 ±2.626385
F13	29.02333 ±1.708489	31.83667 ±2.848233	42.83667 ±1.180777
F14	27.71 ±1.141753	29.67 ±1.477329	33.69667 ±2.080993
F15	25.68 ±1.411063	27.44667 ±1.404754	30.91 ±1.681547
F16	68.31333 ±2.26809	59.38333 ±1.8037	69.56 ±1.915385
F17	51.65667 ±2.110126	49.47333 ±2.941451	56.48 ±3.137276
F18	39.41 ±2.201704	43.66333 ±2.033749	49.44667 ±3.786322
F19	31.52667 ±3.023183	36.40667 ±1.420047	42.74333 ±2.555902
F20	29.16 ±1.746396	31.11667 ±2.146214	34.19 ±1.93

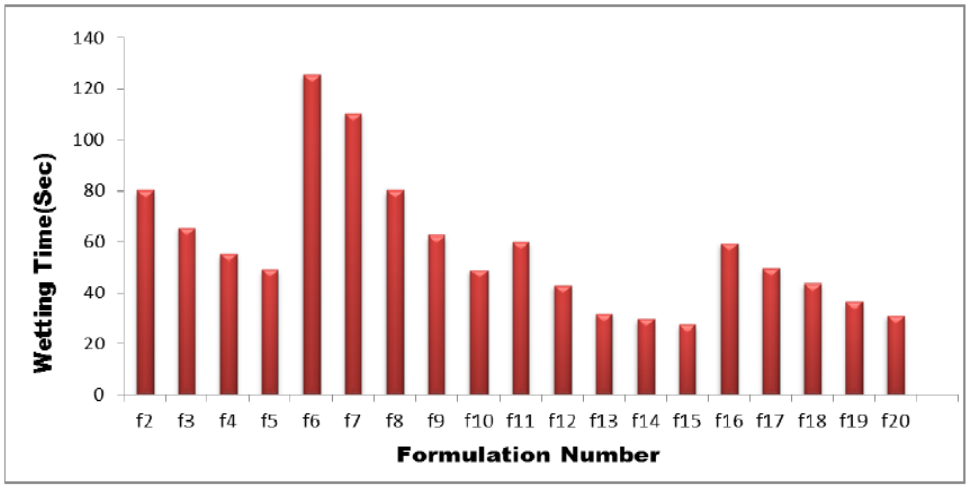
Data are expressed as mean ±S.D. (n = 3)



Effect of Concentration of Super disintegrant and Effervescent Agent on Disintegration Time.



Effect of Concentration of Super disintegrant and Effervescent Agent on Dispersion Time.



Effect of Concentration of Super disintegrant and Effervescent Agent on Wetting Time

DISCUSSION

In the present project FDT of Ketoprofen were prepared and evaluated for achievement of fast action of active moiety. The tablets were prepared by direct compression method by using solid dispersion technology. Fast disintegration of tablets was achieved by using superdisintegrants and effervescent agents. The Ketoprofen is water insoluble drug so this is necessary to increase the water solubility of the drug for that purpose firstly the solid dispersion of Ketoprofen were prepared with PVP K-30 and PEG-6000 and evaluated. The optimized solid dispersion was incorporated in FDTs. These prepared tablets were evaluated for there quality control parameter.

The gift sample of Ketoprofen was analyzed by various organoleptic, physicochemical and spectrophotometric methods. The sample of Ketoprofen possesses similar color, odor, taste and texture as given in officials. The melting point of procured sample was analyzed by capillary fusion method and found 95^0 C. The FT-IR spectrum of drug sample was concordant with reference spectra as given in IP 1996. The IR spectra of reference and sample are shown in Figure 10 (A) and 11 (B) respectively. The FT-IR spectra verified the authenticity of the procured sample, characteristics peak of Ketoprofen are present at 1700 cm^{-1} and 1650 cm^{-1} in sample spectra. The absorption maxima of Ketoprofen was observed at 260 nm in 5% methanolic Sorenson's buffer, which is concordant with the value given in IP 1996. The UV spectra of Ketoprofen were shown. The DSC of drug sample shows a sharp endothermic peak at 94.54^0C, which further support the authenticity of the procure sample.

In-vitro drug release experiments were performed at 37±1^{o}C in eight basket dissolution apparatus. The results of dissolution profile are shown in Table 36-39 and Figure 42-45. The maximum drug release was found in formulation F15 (99.56%).

The order of drug release was found to be:

F15>F20>F14>F10>F13>F5>F19>F9>F4>F12>F3>F8>F18>F11>F2>F17>F16> F7>F1>F6

Formulations F5, F10, F15 and F20 which contains 5% of Croscarmellose sodium, Sodium starch glycolate, Crospovidone and citric acid + sodium bicarbonate respectively. The release was estimated after twenty minutes was 90.559%, 91.293%, 99.548% and 94.751% respectively. The formulation with Crospovidone shows more release than the tablets with Citric acid, Croscarmellose sodium and Sodium starch glycolate.

SUMMARY AND CONCLUSION

Compounds with poor aqueous solubility are extremely challenging to be developed as new formulations. It is well known that drug dissolution rather than permeation through the epithelia of the gastrointestinal tract is responsible for a low oral absorption. One of the pharmaceutical strategies to improve the oral bioavailability that is solid dispersions. Ketoprofen was selected a model drug for the research work because it has a poor aqueous solubility and low dissolution rate, while high permeability.

The Ketoprofen was formulated as physical mixture and solid dispersions with PVP K30 & PEG-6000 in different ratios in order to improve the drug dissolution. Ketoprofen-PVP K30 solid dispersions & Ketoprofen- PEG-6000 solid dispersions were prepared by solvent evaporation technique.

Solid dispersions were evaluated for solubility, percent drug content, dissolution efficiency (DE15 and DE30), *in-vitro* drug release studies and characterized by FT-IR, DSC, XRD, SEM.

Formulations containing Ketoprofen-PVP K30 solid dispersions in 1:3 ratio (KPVP3) prepared by solvent evaporation technique showed better dissolution rate and dissolution efficiency. And on the basis of *in-vitro* drug release study formulation (KPVP3) was selected for preparation of FDT.

Fast dissolving tablets were prepared dissolution might be due to the easy and fast breakdown of tablet and rapid absorption of drug into the dissolution media.

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