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Enhancing the Solubility and Dissolution of Ketoprofen by Recrystallization Method

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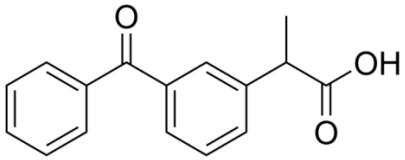
ABSTRACT
Poor solubility poses a significant challenge in drug development, leading to reduced bioavailability and therapeutic inefficacy. Ketoprofen, a poorly water-soluble drug with oral bioavailability around 50%, was selected for solubility improvement using solvates. Two solvate forms were obtained by recrystallization in chloroform and ethanol, both showing superior solubility and dissolution compared to pure Ketoprofen, with chloroform solvate outperforming ethanol solvate. Stability studies revealed that solvates may convert to more crystalline forms over time, impacting dissolution profiles. Tablets prepared from fresh and aged chloroform solvates via direct compression confirmed solvate suitability for pharmaceutical dosage forms. This study concludes that solvates present a viable approach to enhance solubility and dissolution of poorly soluble drugs like Ketoprofen, potentially improving bioavailability.

Keywords: Ketoprofen, poor solubility, solvates, chloroform solvate, ethanol solvate, recrystallization, dissolution enhancement, stability, direct compression tablets, bioavailability improvement.

INTRODUCTION



Chemical Name: 2-(3-benzoylphenyl) propanoic acid
Molecular Formula: C16H14O3
Molecular Weight: 254.28 g/mol
Category: Nonsteroidal anti-inflammatory drug (NSAID), propionic acid derivative
Physical Description: White, crystalline, odorless solid powder
Melting Point: 152-154°C (typical reported value 153°C)
Solubility: Highly soluble in ethanol and methanol; soluble in phosphate buffer pH 7.4; slightly soluble in water and 0.1 N HCl
Mechanism of Action: Inhibits cyclooxygenase-1 and -2 enzymes (COX-1 and COX-2), reducing prostaglandin synthesis that mediates inflammation, pain, and fever
Absorption: Well absorbed orally
Half-life (t1/2): Approximately 1.8 to 2 hours
Volume of Distribution (Vd): Variable, generally moderate tissue distribution
Protein Binding: High (approximately 99%) primarily to albumin
Metabolism: Extensively metabolized in the liver mainly via glucuronidation and cytochrome P450 enzymes (CYP3A4, CYP2C9)
Elimination: Primarily renal excretion of metabolites
Clearance: Variable depending on hepatic and renal function
Therapeutic Indication: Management of pain, inflammation, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and dysmenorrhea
Drug Interactions: May interact with anticoagulants, other NSAIDs, antihypertensives, and corticosteroids
Contraindications:
Hypersensitivity to ketoprofen or NSAIDs, active peptic ulcer, severe heart failure, and during late pregnancy (third trimester)
Route/Dosage: Oral, topical, or parenteral; doses vary by indication and formulation
Precautions: Gastrointestinal irritation risk, renal impairment caution, and use with caution in cardiovascular disease
Adverse Effects: Gastrointestinal discomfort, ulceration, bleeding, renal toxicity, hypersensitivity reactions, and photosensitivity

MATERIALS AND METHODS

Table 1: List of chemicals

S.No	Materials	Suppliers
1	Ketoprofen	Yarrow
2	Ethanol	Sisco research laboratory
3	Chloroform	Sisco research laboratory
4	Microcrystalline Cellulose	Sisco research laboratory
5	Talc	Sd fine Chemicals, Mumbai
6	Sodium Starch Glycolate	Sd fine Chemicals, Mumbai
7	Magnesium Stearate	Sd fine Chemicals, Mumbai

Table 2: List equipment's used

S.No	Name of the Equipments	Suppliers
1	Digital Balance	SHIMADZC ELB 300
2	UV- visible spectrometer	SHIMADZC UV -1700
3	FTIR	SHIMADZU

4	SEM Analyser	ZEISS-5200 SEM
5	Hot air oven	ELCON
6	Magnetic stirrer	REMI
7	Dissolution Apparatus	LAB INDIA
8	Disintegration apparatus	INCO
9	Tablet Punching Machine	REMEK
10	Hardness Tester	PFIZER
11	Friability Apparatus	INCO

FTIR spectroscopy:

As physical mixes, FTIR spectrum analysis of pure drug and polymer was performed. It was observed whether changes in the chemical composition of the medicine happened after mixing it with the polymer. The spectrum's absorption maxima were compared to the reference spectrum.

Preparation of Ketoprofen Solvates:

Ketoprofen solvate was created by recrystallizing the raw material from Solvent (Chloroform, Ethanol). In a magnetic stirrer, 5 g of Ketoprofen was added to 50 mL of Solvent while swirling continuously and heating the solution to about 60°C for 4 hours. A thick mass was produced after gradual evaporation of the Solvent. This substance was dry, yet it adhered to the surfaces of containers. The desolvated solid was created by soaking the Ketoprofen solvate in a Dessicator for 48 hours at room temperature. It was then triturated and kept in an airtight container.

Table 3: Formulation Code for Ketoprofen Solvate

Material	Formulation code
Ketoprofen	F1
Ketoprofen Chloroform Solvate	F2
Ketoprofen Ethanol Solvate	F3

Evaluation of odt tablets:

Tablets from all the formulations were subjected to following process in quality control.

Weight Variation test:

The IP technique was used for the weight variation test. Twenty pills were weighed individually and collectively using a single pan electronic balance (AR 0640, Ohaus Corp. USA). The aggregate weight was used to calculate the average weight of the pills. The range and % standard deviation were computed based on the weight of the individual pills. There should be no more than two pills that depart from the average weight of tablets, with a maximum percentage of variation permitted. consistent weight of tablets in direct compression reflects proper powder flow and consistent die filling. Table no.7.8 lists the official weight uniformity values.

Table 4: Standard values for uniformity of weight

Average weight of tablets (mg)	Maximum percentage of deviation allowed
80 or less	10
80 – 250	7.5
More than 250	5

Thickness:

Thickness is a significant factor in both duplicating look and counting with filling equipment. Take 20 pills and measure their thickness using digital vernier callipers.

Hardness: The hardness of a tablet is determined by the weight of the material used, the gap between the upper and lower punches during compression, and the pressure used during compression. The kind and quantity of excipients employed during formulation also influence hardness.

If the completed tablet is too hard, it may not dissolve in the requisite time, and if the tablet is too soft, it may not endure hardening during packaging and transportation. As a result, when compressing tablets, it is required to verify their hardness and adjust the pressure on the tablet machine correspondingly.

The hardness of a tablet can be roughly assessed by holding it between the fingers of one's hand and throwing it lightly on the floor; if it does not shatter, the required hardness has been reached. A variety of hardness tests are used to determine tablet hardness, although the Monsanto harness tester and the Pfizer hardness tester are the most often used. A Monsanto hardness tester was used to determine the tablet's hardness. It is measured in kilogrammes per square centimetre.

Friability test

The friability test determines the physical strength of compressed tablets. Tablets are subjected to pressures during handling as a consequence of collisions and tablets sliding towards one another and other solid surfaces, which can result in the removal of minute pieces and particles from the tablet surface. As a result, the tablet's weight will gradually decrease and its look will alter. Tablet examination Friability was tested in accordance with I.P 2007, which states that friability less than 1% passes the test. The Roche Friabilator (Rolex Scientific Engineers Limited) was used to examine the friability of tablets from each formulation. Initially, twenty pills were weighed and passed to the Friabilator. For 4 minutes, the instrument was set to 25 rpm. The pills were reweighed, and the percentage loss was determined using a formula.

$$\% \text{ Friability} = \text{Initial } \frac{\text{Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Drug Release Kinetics

The data from the in vitro release research was applied to various motor circumstances. Zero request (aggregate level of medication discharge versus time), first request (log total level of medication remaining versus time), Higuchi model (total level of medication discharge versus square base of time), and Korsmeyer-Peppas (log combined percent sedate delivery versus log of time) were the active models used. Relapse (r2) values were calculated for the direct bends obtained from relapse research.

Kinetic analysis: The grid frameworks were accounted for in order to follow the zero-request discharge rate and the Diffusion component for pharmaceutical arrival. The information obtained was fitted into the Zero request, First request, Higuchi lattice, and Peppa's model to break down the system for the delivery and delivery rate energy of the measurements structure. The best fit model was picked in this case based on the r Values obtained.

a. Kinetics of zero order: The following equation can be used to depict drug dissolution from pharmaceutical dosage forms

that do not disaggregate and release the medication slowly, provided that the area does not change and no equilibrium conditions are established.

$$Qt = Q0+K0t$$

Where Qt represents the quantity of drug dissolved in time t, Q0 represents the starting amount of drug in the solution, and Ko represents the zero order release constant. To investigate first order release kinetics, the release rate data were fitted to the following equation.

$$Qt = \log Q0 + k1t/2.303.$$

Where Qt represents the quantity of drug released in time t, Qo represents the initial amount of drug in the solution, and K1 represents the first order release constant.

Higuchi model: Higuchi created many theoretical models to investigate the release of water-soluble and low-soluble medicines integrated in semisolids and/or solid matrices. For drug particles distributed in a uniform matrix acting as a diffusion medium, mathematical formulas were developed. And the formula is Qt = KH.t1/2.

Where Qt represents the quantity of medication released in time t and KH represents the Higuchi Dissolution constant.

The Korsmeyer and Peppa model: To investigate this concept, the following equation is fitted to the release rate data.

$$Mt/M = Ktn$$

Where Mt/M is the drug release percentage, K is the release constant, t is the release period, and n is the drug release diffusion exponent that depends on the geometry of the matrix dosage form.

RESULTS AND DISCUSSION

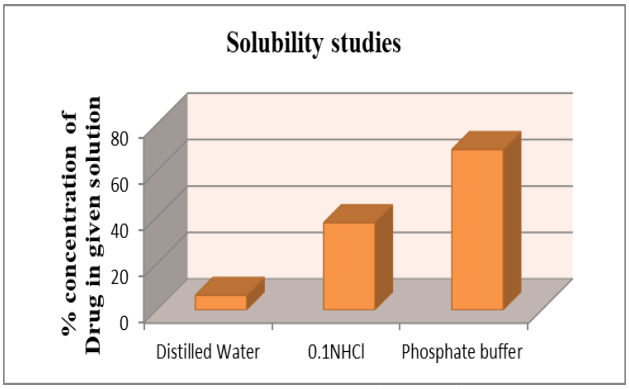


Fig.1: Solubility studies of Ketoprofen

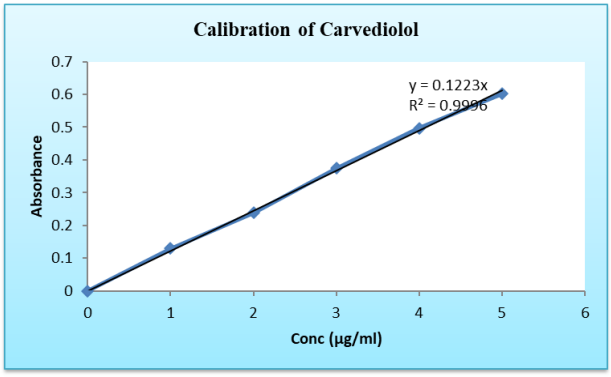


Fig.2: Calibration graph of Ketoprofen in pH 6.8 phosphate buffer

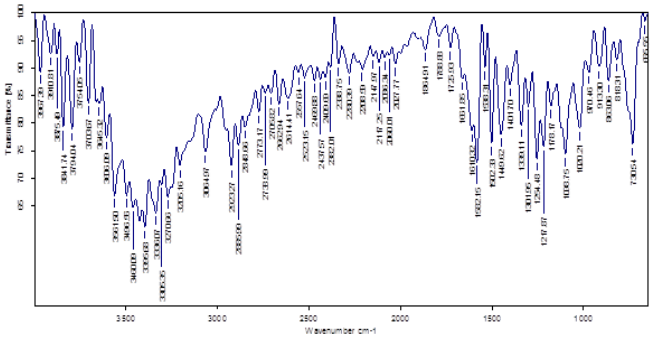


Fig.3: FTIR graph of Ketoprofen

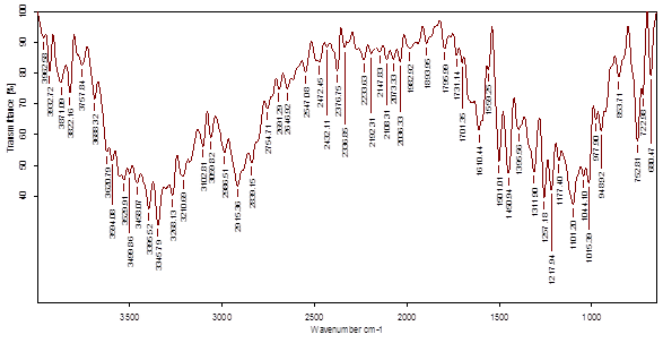


Fig.4: FTIR graph of Ketoprofen with Chloroform solvates

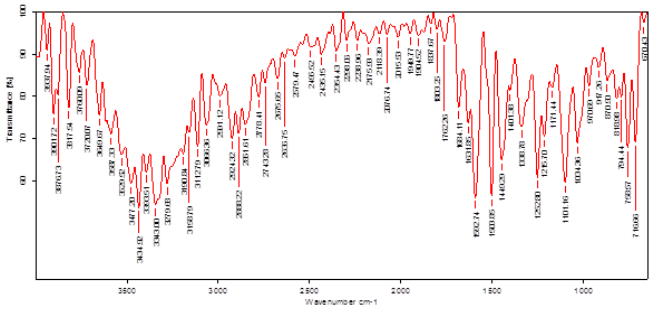


Fig.5: FTIR graph of Ketoprofen with Ethanol solvates

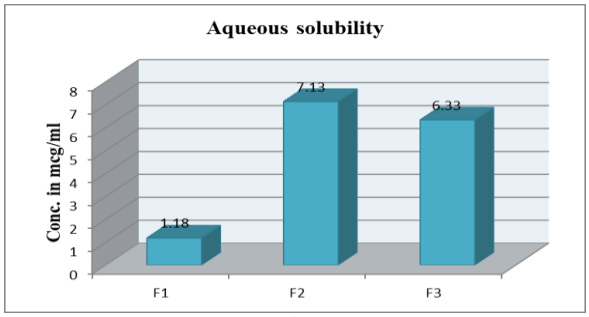


Fig6: Aqueous solubility of Formulation F1, F2 and F3

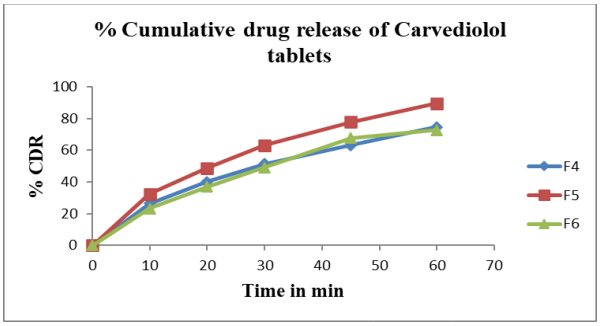


Fig.7: % Cumulative drug release of Ketoprofen tablets

Table 1: Solubility of Ketoprofen in various solvents

% concentration of Drug in given solution	Distilled Water	0.1NHCl	Phosphate buffer 6.8
1 test	6.10	31.15	69.14
2 test	6.23	42.23	68.85
3 test	6.51	39.21	69.25
Average	6.28	37.53	69.08

Table 1: In-Vitro drug release studies

S.No	Time in minutes	% Cumulative drug release		
		F4	F5	F6
1	10	26.32	32.49	23.15
2	20	40.14	48.69	36.87
3	30	51.25	63.14	49.13
4	45	63.11	77.67	67.68
5	60	74.67	89.46	72.69

Table 2: In vitro Drug release kinetics of Ketoprofen Tablets

Formulation code	Zero order		First order		Higuchi model		Korsmeyer-peppas		Release Mechanism transport
	Slope	R^2	Slope	R^2	Slope	R^2	n	R^2	
F5	0.895	0.775	-0.015	0.99	7.998	0.955	1.085	0.945	Super Case II transport

CONCLUSION

Recent estimates indicate that roughly 40% of novel chemical entities are rejected because to poor solubility, i.e. biopharmaceutical characteristics. Poor medication solubility can lead to insufficient bioavailability and, as a result, unsatisfactory treatment regimens. Ketoprofen has a similar poor solubility profile, and the most common form available on the market is the stable, crystalline monohydrate, with an oral bioavailability of 50%. The goal of this study is to improve the solubility and dissolution of Ketoprofen utilising solvates. Recrystallisation of Ketoprofen solvates in chloroform and ethanol yielded two solvate forms. When compared to Ketoprofen, the Solvates demonstrated superior solubility and dissolution profiles. Choloroform solvate outperformed Ethanol solvate in terms of solubility and dissolution characteristics. By comparing freshly prepared choloroform solvates to 1 month old choloroform solvate, the tablets of choloroform solvates were produced by direct compression technique to determine the appropriateness of Solvates in the formation of Pharmaceutical Dosage form. Solvate variations were utilised to determine the stability of solvates. Based on the study of tablets, it was discovered that the solvates converted into a more crystalline material during storage, which may impact the dissolving profile of the dose.
According to the findings of the study, Solvates can be utilised to improve the solubility and dissolution of poorly soluble medicines.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL: Not applicable

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AI TOOL DECLARATION

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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