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Original Research Article

Preformulation Studies of Aceclofenac: Major Part of Formulation Strategy

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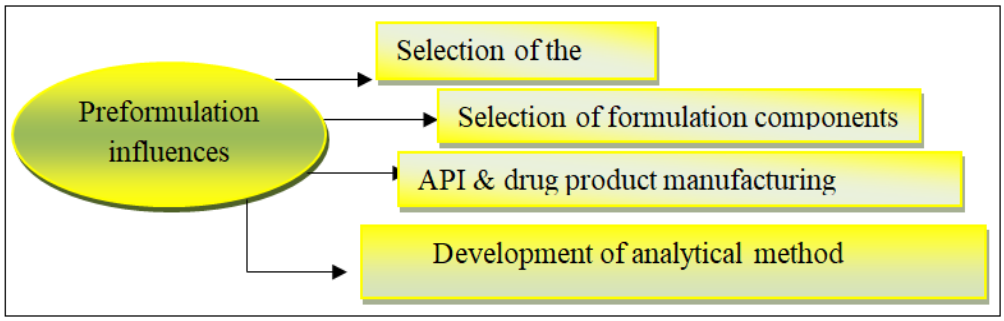
Abstract: Preformulation studies are fractions that are initiated once new molecules are seeded. In a broader sense, it deals with the study of physical, chemical, analytical, and pharmacological properties associated with molecules, providing ideas for appropriate modifications of molecules for better performance. The study of pre-formulation parameters can lead to the production of effective, safer, stable and reliable drug formulations. Aceclofenac is an analgesic. It relieves pain, stiffness and swelling caused by various conditions of bones and joints. It is also used to relieve headaches, toothaches, back pain, menstrual cramps, sprains and muscle strains. Aceclofenac works by preventing the body from releasing chemicals that cause pain and swelling. In the current work, the overall goal of aceclofenac preformulation research is to generate information useful for the development of stable bioavailable dosage forms.

Keywords: Preformulation study, Aceclofenac, Solubility & Analytical methods.

INTRODUCTION

Pre-formulation testing is a key step in the rational development of drug substance dosage forms. This study includes examination of the physical and chemical properties of drugs alone and in combination with excipients. The general goal of preformulation testing is to generate information that will help formulators in developing stable, bioavailable dosage forms that can be mass produced. Pre-formulation studies should provide all the necessary data, especially the physico-chemical, physico-mechanical and biopharmaceutical properties of drugs, excipients and packaging materials [1]. These studies should focus on the physicochemical properties of new compounds that may influence drug performance and the development of effective dosage forms. Finally, a systematic understanding of these properties can provide a rationale for formulation design or support the need for molecular modifications. The aim of this study was to determine several physicochemical properties such as solubility, melting point, pKa, dissolution, assay development and stability in solution [2, 3].



Aceclofenac works by preventing the body from releasing chemicals that cause pain and swelling.

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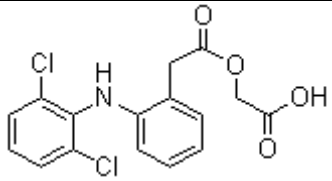
Description of Drug [4]

IUPAC Name	2-[2-[2-(2,6-Dichlorophenyl)amino phenyl]acetyl]oxyacetic acid		
Molecular structure		**Molecular Weight** 354.184 g/mol	**Molecular Formula** $C_{16}H_{13}Cl_2NO_4$
Appearance, color:	White, crystalline powder		
Density 1.455g/cm^3	**Refractive index** 1.639	**Melting point** 149-153℃	**Boiling point** 486°C at 760 mmHg
Solubility	Practically insoluble in water, soluble in alcohol and methyl alcohol, freely soluble in acetone and dimethyl formamide		
Indication	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.		
Absorption	Aceclofenac is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3 hours after an oral dose.		
Pharmacokinetics	Quickly and completely absorbed after oral administration, peak plasma concentrations are reached 1-3 hrs, after an oral dose. The drug is highly protein bound (7.99%). The plasma concentration of aceclofenac was approximately twice that in synovial fluid after multiple doses of the drug in-patient with knee pain and synovial fluid effusion. Renal excretion is the main route of elimination of aceclofenac with 70 to 80% of an administered dose found in the urine, mainly as the glucuronides of aceclofenac and its metabolites of each dose of aceclofenac, 20% is excreted in the faeces. The plasma elimination half-life of the drug is approximately 4 hours.		
Drug interactions	Aceclofenac may increase plasma concentrations of lithium, digoxin and methotrexate, increase the activity of anticoagulant, inhibits the activity of diuretics, enhance cyclosporine nephrotoxicity and precipitate convulsions when co-administered with quinolone antibiotics.		
Adverse effects	GI discomfort, heart burn, nausea and pruritis.		

In the present works an attempt was made to study preformulation parameters of Aceclofenac which helps to generate information useful in developing stable and Bioavailable dosage forms.

MATERIAL AND METHODOLOGY

Procurement of Drug: Drug (Aceclofenac) was obtained as a gift sample from Milton Drugs Pvt. Limited Puducherry.

Organoleptic properties

Organoleptic properties of the drug sample were studied by visual inspection.

Preformulation studies [5-10]

Identification of Drug

Melting Point Determination

Melting point determination by DSC.

Solubility

The solubility of Aceclofenac 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 25 ℃. The solutions were examined physically for the absence or presence of drug.

Partition coefficient

10 mg of the Aceclofenac was accurately weighed and dissolved in 10 ml of distilled water and 10 ml of n- octanol in separating funnel. This mixture was shaken for 10 minutes interval for 1 hour and left it for 24 hours. The two layers were separated out using separating funnel. The aqueous phase was filtered with the help of filter paper and was diluted 100 times with distilled water. The absorbance of aqueous phase was taken at 276 nm using distilled water as a blank in 1700 Shimadzu UV spectrophotometer and the concentration was determined with the help of standard curve of drug and the partition coefficient was determined by following formula:

$P_{o/w} = C_{oil}/C_{aq}$

Here,

$P_{o/w}$= partition coefficient,

C_{oil}= concentration of drug in organic phase,

C_{aq}= concentration of drug in aqueous phase.

pH Determination

This was carried out by shaking a 1%w/v dispersion of the sample in water for 5min and the pH determined using a digital pH meter.

FTIR spectroscopy studies

FTIR (ATR Bruker, Germany) was used. The IR spectrum was obtained by scanning it in the range 4000-500nm and compared with the reference pharmacopoeia (IP-2014).

Analytical Method

UV spectroscopy was selected as the suitable analytical method for estimation of the drug.

Standard Stock Solution

The standard stock solutions of Aceclofenac was prepared by dissolving accurately weighed 100 mg of drug in 100 ml of distilled water in two 100 ml volumetric flasks to get a concentration of 1000 µg/mL. The Solution was diluted with distilled water, to get a concentration of 100 µg/mL, and was kept as the stock solutions.

Determination of λmax

1 ml of standard stock solution of Aceclofenac was taken in 10 ml standard volumetric flask diluted to 10 ml with distilled water to get the concentration of 10 µg/ml. The absorbance of resulting solution was measured against respective blank solution (distilled water) in the UV region of 200-400 nm, which shows maximum absorbance at 276 nm.

Preparation of calibration curve

100mg of Aceclofenac was dissolved in phosphate buffer 7.4 in a 100ml standard flask and filled up to the mark using phosphate buffer 7.4. Serial dilutions were made in phosphate buffer pH 7.4 in order to obtain 0µg/ml-12 µg/ml. Absorbance of these solutions were measured at 276nm using UV-Visible Spectrophotometer (Schimadzu 159) and standard graph was plotted.

RESULTS AND DISCUSSION

The overall objective of the present work was to investigated preformulation studies of Aceclofenac is to generate information useful in developing stable and Bioavailable dosage forms. The partition coefficient of Aceclofenac was found 1.86, which confirms the lipophilicity of the drug (Table 4). The solubility of Aceclofenac with different solvent was tabulated in table 3. The melting point was determined by DSC the result was shown in Fig 2 and it was found to be 153.3^0C. The analytical method for determination of drug was UV spectroscopy. The absorption spectral analysis showed the λ_{max} of Aceclofenac at 276 nm (Fig 3 & Table 2). The calibration curve was obtained for a series of concentration in the range of 0-12 µ g/mL. The FTIR spectrum, there was no variation in the Aceclofenac peaks from the standard spectrum of IP 2014 (Fig 1 & Table).

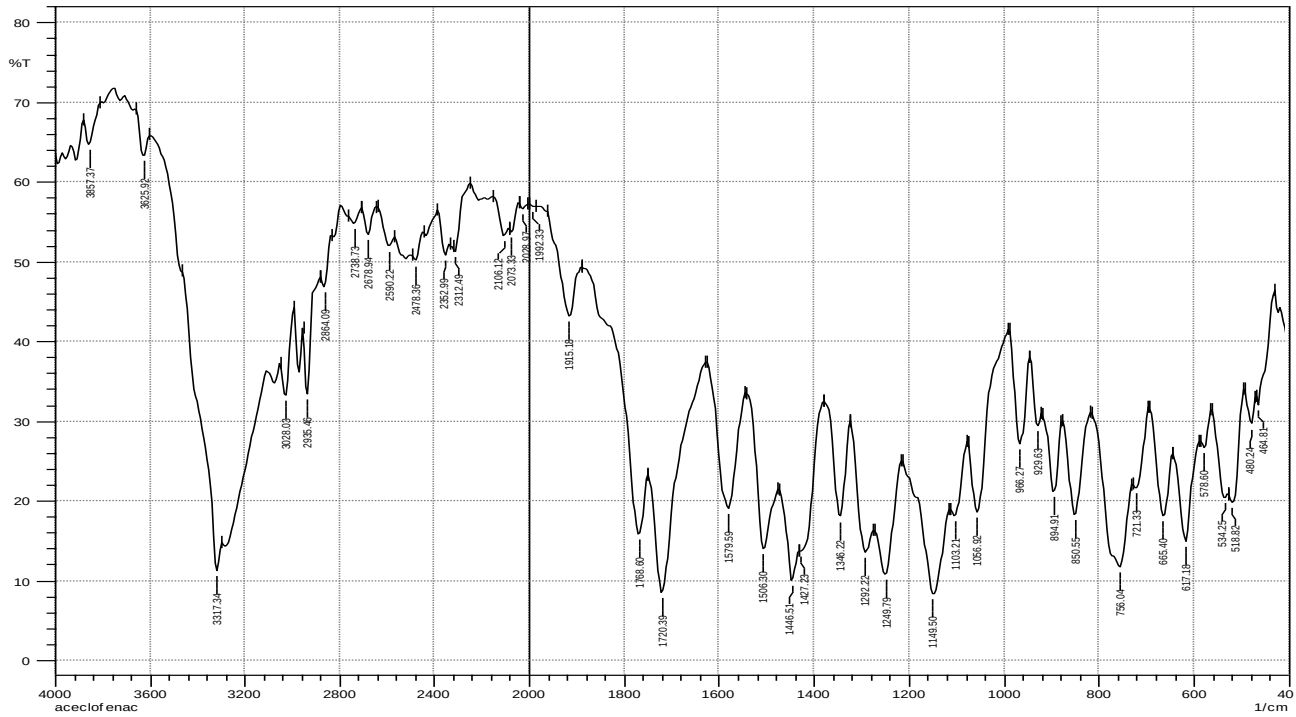


Fig 1: FTIR Spectra of Aceclofenac

Table 1: IR Interpretation Peaks for Aceclofenac

Functional Group	Reference value/ Theoretical value cm^{-1}	Observed value/ Practical value cm^{-1}
N-H stretch	3370-3310	3375.20
C-Cl Stretch	1096-1089	1089.71
C-H Stretch	2926-2853	2906.53
C=0 Stretch	1650-1550	1652.88-1396.37
C=C stretch	1400	1456.16-1396.37
C-H stretch	3100-3000	3083.96-3026.10
C-H Bend	900-675	943.13-684.68

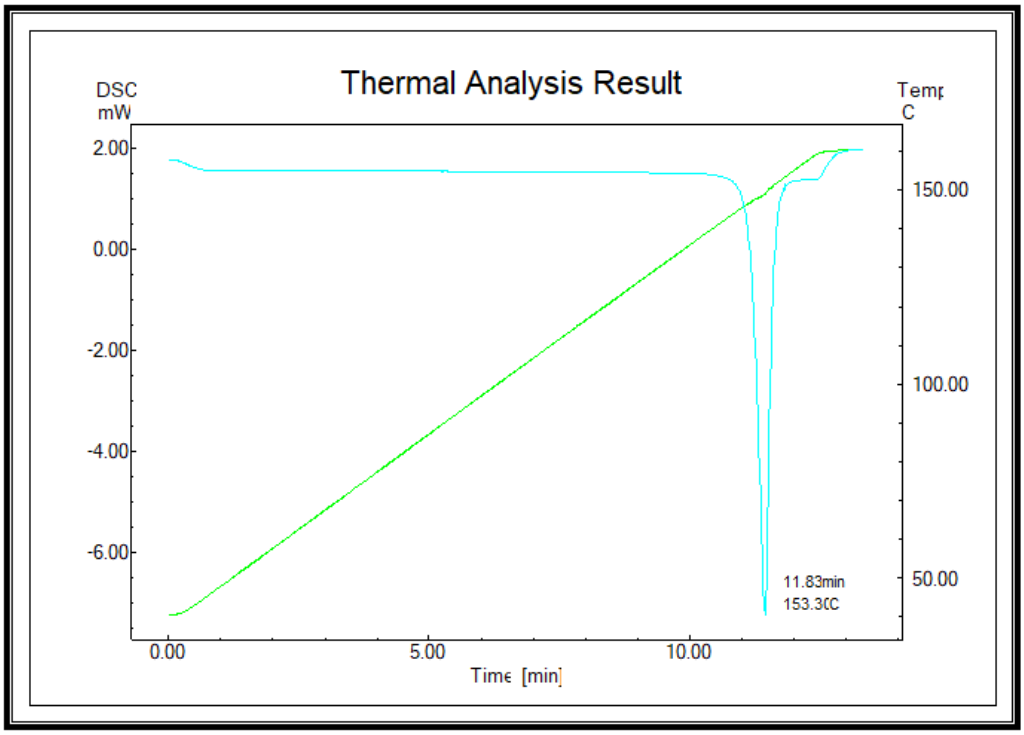


Fig 2: DSC of Aceclofenac

Table 2: Absorbance data for calibration curve of Aceclofenac in phosphate buffer 7.4 at 276nm

S. No	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.083
3	4	0.159
4	6	0.235
5	8	0.297
6	10	0.364
7	12	0.430

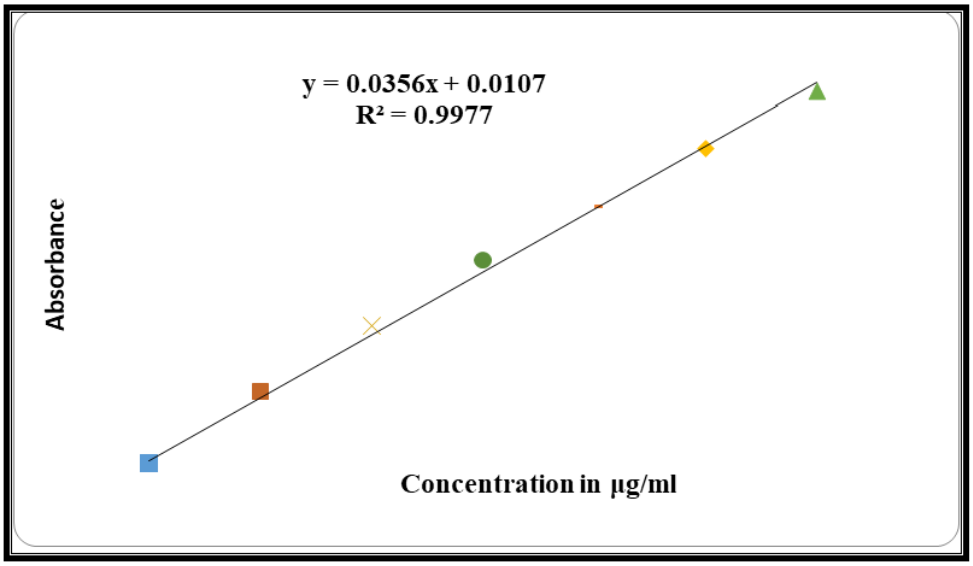


Fig 3: Calibration curve of Aceclofenac in phosphate buffer at 276nm

Table 3: Solubility of Aceclofenac in different solvents

Solubility	It is very soluble in acetone and chloroform

Table 4: Partition coefficient of Aceclofenac

S. No.	Solvent system	Partition coefficient
1.	n-octanol:distilled water	1.86

CONCLUSION

The pre-formulation stage is an integral part of identifying the properties of a drug product to enable proper risk assessment for development. It usually starts in the lead optimization phase and progresses through dominance to early development. Therefore, it is imperative that the pre-formulation be done as carefully as possible to facilitate rational decisions. Pre-formulation studies of Aceclofenac are expected to provide useful information for the development of stable and Bioavailable dosage forms.

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