# Unlocking The Potential of Aceclofenac: Investigating Strategies To Enhance Oral Bioavailability and Therapeutic Efficacy

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**Abstract**
Oral bioavailability of aceclofenac is very low (only 14%) due to instability and incomplete intestinal absorption and extensive gut wall extraction. Aceclofenac, a potent NSAID, faces challenges related to its limited bioavailability, hampering its therapeutic efficacy. This study investigates the potential of naringin, a natural flavonoid known for its bioenhancement properties, to improve aceclofenac's bioavailability. Formulations of aceclofenac containing naringin were developed and characterized for physicochemical properties. In vitro dissolution studies revealed enhanced drug release rates compared to control formulations. Pharmacokinetic studies in animal models demonstrated significantly improved oral bioavailability of aceclofenac when co-administered with naringin, attributed to increased intestinal absorption and enhanced drug solubility. These findings highlight the promising role of naringin in augmenting the bioavailability of aceclofenac formulations. This approach holds potential for developing more effective oral dosage forms of aceclofenac, offering enhanced therapeutic outcomes for patients managing pain and inflammation. Further optimization of formulation parameters and clinical investigations are warranted to validate the clinical efficacy and safety of naringin-enhanced aceclofenac formulations.

**Keywords:** Aceclofenac, bioavailability, naringin, direct compression, optimization, tablets

## Introduction

Aceclofenac (AC) 2[[2-[2-[(2,6 dichlorophenyl) amino) phenyl) acetyl) oxy) acetic acid is a member of the non-steroidal anti-inflammatory drug (NSAID) class and is a derivative of phenylacetic acid.[1] It is a commonly prescribed medication for musculoskeletal conditions (such as osteoarthritis, rheumatoid arthritis, and spondylitis), body aches, and dental pain. It is an antagonist of the cyclooxygenase enzymes COX-I and II. Although COX-II enzyme inhibitors are helpful for a variety of inflammatory conditions, their use is restricted because of cardiac toxicity. Beyond this, aceclofenac is said to be much more tolerable and safer than other NSAID analogs. From now on, doctors in Asian and European nations frequently advise. With a log partition coefficient of 2.170, aceclofenac is classified as a class II drug under the Biopharmaceutics Class System (BCS). Adults should take 100 mg of aceclofenac twice day; however, if a patient has liver impairments, their dosage needs to be adjusted. In the stomach and upper intestine, it is well absorbed when taken orally in its unaltered form. According to studies, the average plasma drug concentration in humans is reported to be between 7 and 10 μg/mL, reached in 1-3 hours, with a mean elimination time (T1/2) of about 4 hours. The cytochrome P450 enzyme system breaks it down, with the majority of its excretion occurring in the urine. The demand for aceclofenac tablets has increased due to its widespread prescription use worldwide. The availability of its affordable "substitutes" with comparable quality attributes is currently one of the main concerns. In this regard, the aceclofenac formulation was using a straightforward direct compression process, requiring the least number of additives possible, resulting in an economical final product. All of these factors lead to its observed poor oral bioavailability.[2]

Aceclofenac's low bioavailability is primarily due to its poor aqueous solubility, extensive first-pass metabolism in the liver, susceptibility to gastric degradation, efflux transporter-mediated efflux, and potential food interactions.[3] These factors hinder its absorption across the intestinal epithelium and decrease plasma concentrations available for therapeutic action. Overcoming these challenges requires innovative formulation strategies to enhance solubility, bypass first-pass metabolism, and optimize delivery systems for improved therapeutic efficacy. The pursuit of enhancing the bioavailability of aceclofenac has been a subject of intense research, with various approaches ranging from formulation optimization to the incorporation of bioenhancers. Among these strategies, natural bioenhancers have garnered significant interest owing to their safety profile, biocompatibility, and potential synergistic interactions with drugs.[4]

Naringin, a flavonoid abundantly found in citrus fruits such as grapefruits and oranges, has emerged as a promising natural bioenhancer due to its ability to modulate drug absorption and metabolism. Studies have suggested that naringin exerts its bioenhancing effects through several mechanisms, including inhibition of drug-metabolizing enzymes, alteration of gastrointestinal transit time, and enhancement of membrane permeability. In this study, we aim to explore the feasibility of using naringin as a bioenhancer to improve the bioavailability of aceclofenac tablets. By leveraging the pharmacokinetic properties of naringin, we hypothesize that co-administration of aceclofenac with naringin will lead to enhanced drug

absorption and systemic exposure, ultimately resulting in improved therapeutic efficacy and reduced dose-related adverse effects.[5]

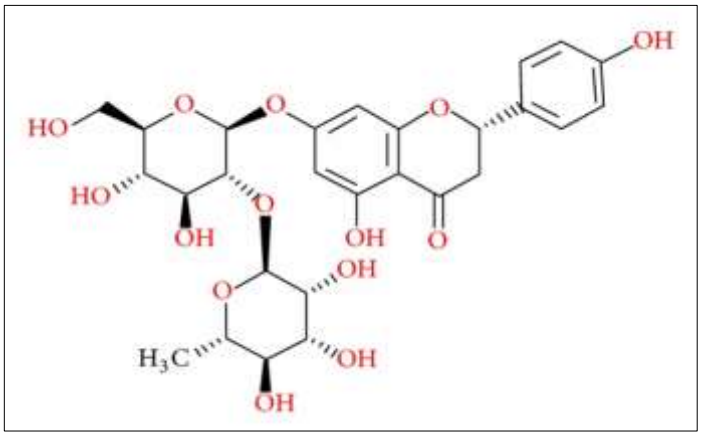



**Figure 1:** Chemical structure of naringin

**Materials and methods**

Aceclofenac ($C_{16}H_{13}Cl_2NO_4$) was given as gift sample by (Aristo Pharmaceuticals Pvt Ltd Vill. Makhnumajra P.O Bhud The. Baddi Distt Solan, India), microcrystalline cellulose (Maple Biotech Pvt Ltd., Pune, India), aspartame (Ranbaxy, New Delhi, India). Talc and magnesium stearate were purchased from (S. D. Fine Chem Ltd., Mumbai, India). All other solvents and reagents were purchased from the market.

**Chemicals and instruments**

Commercially available methanol, ethanol, dichloromethane (all the solvents were purchased), sulfuric acid, and iodide were used without further purification. The pyridine was treated with calcium hydride, after which it was distilled and stored over 4A molecular sieves. The reactions involving anhydrous solvents were carried out under argon atmosphere.

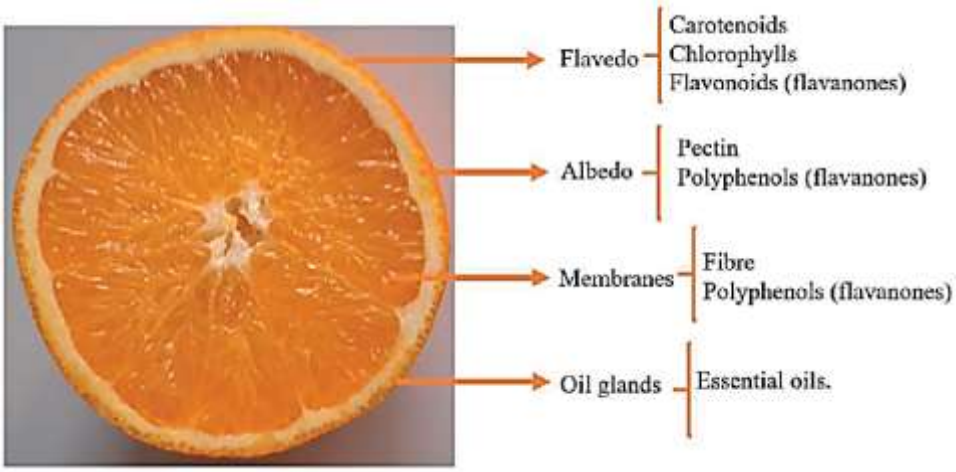
**Orange and lemon peels**

Oranges and lemons were purchased, as well as their peels, from the local market in Indore, Madhya Pradesh. The orange peels were divided into two sections: albedo (the inner white, spongy part) and flavedo (the outer orange part). In addition, the fresh albedos were manually cut into small pieces and ground in a grinder for the simple extraction method. The peels were hand-sliced to separate the albedos (white spongy interior) from the flavedos (orange exterior).[6][7] For the dry experiments, albedos were cut into small pieces and air-dried for two days before being placed in an oven at 40°C overnight to achieve a constant weight. Fresh albedos were only cut into small pieces after being separated from flavedos in the direct experiments.[8]

**Naringin extraction**

The method described in the literature was modified to isolate naringin from albedos.[9] The standard procedure involved extracting the methanol and then letting it crystallize in water. In our test conditions, we used methanol to extract dry, fresh albedo at both room temperature and while heated. Each trial was carried out three times. Naringin was described using spectroscopic and physical data. These findings were contrasted with those published in the literature.[10]


**(a)**




**(b)**

**Figure 2:** Anatomy of the orange (a) (b)

**Method: dry albedo/hot methanol extraction:**

Ten grams of dry albedo were combined with sixty millilitres of methanol in an Erlenmeyer flask. The organic solvent was then removed from the mixture after three hours at 55°C.[11] Then, more than 60 millilitres of methanol were added, and another 30 minutes of hot extraction were carried out. The combined organic phases were dried in a rotary evaporator with a low pressure and 45°C setting. The previously described procedures were used to treat the methanolic extract with water/dichloromethane and collect another crop of naringin crystals (260 mg, 2.6% w/w). The organic layer was removed, and the naringin crystals (660 mg, 2.2% w/w) were collected via filter paper and dried in a vacuum desiccator.[12]

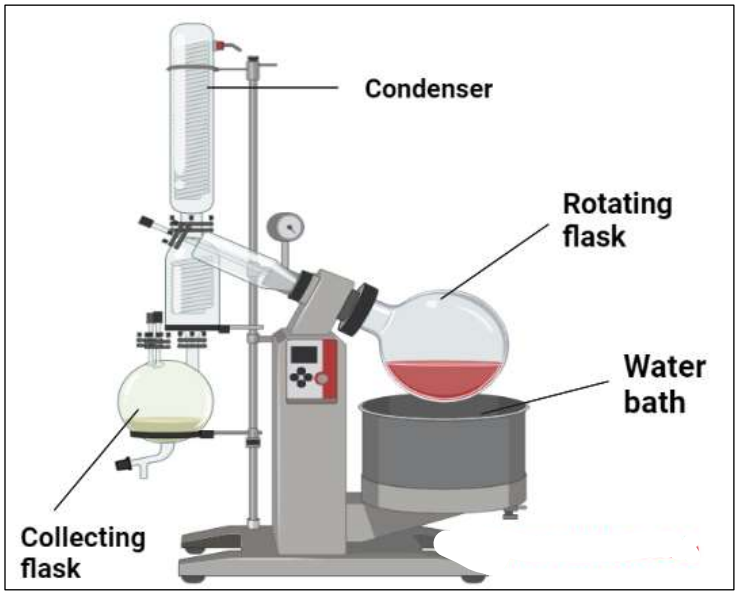



**Figure 3:** Hot methanol extraction of dry albedo

**Box-Behnken Experimental Design (BBD)**

The box-behnken experimental design, powered by Design Expert® software (version 7.0, Stat-Ease Inc.), was used to make aceclofenac tablets that release the medication quickly.[13] We looked at three things that affect the tablets cyclodextrin, orange peel extract, and lemon peel extract across five levels, from low to high. This helped us figure out the best combination for making aceclofenac tablets that work the best. According to the three-factor and three-level design, BBD requires 15 experimental runs with 3 central points to determine the experimental error and the precision of the design.[14] The selected responses or dependent variables were mean hardness, in vitro dissolution time and in vitro disintegration time. The selected variables as per the design are shown in Table 1.

**Table 1:** Levels of variables for optimization

| Factor | Name | Unit | Minimum | Maximum |
|---|---|---|---|---|
| 1 | Cyclodextrin | mg | 15 | 30 |
| 2 | Orange peel extract | mg | 10 | 30 |
| 3 | Lemon peel extract | mg | 10 | 30 |

**Table 2:** Composition of experimental batches of tablets

| Stds | Runs | Factor 1 Cyclodextrin (mg) | Factor 2 Orange peel extract (mg) | Factor 3 Lemon peel extract (mg) | Response 1 Hardness (Kg/cm2) | Response 2 In vitro dissolution time (%) | Response 3 In vitro disintegration time (minutes) |
|---|---|---|---|---|---|---|---|
| 10 | 1 | 22.5 | 30 | 10 | 2.36 | 90.8 | 19.6 |
| 2 | 2 | 30 | 10 | 20 | 2.47 | 89.6 | 24.6 |
| 8 | 3 | 30 | 20 | 30 | 2.83 | 83.5 | 19.3 |
| 6 | 4 | 30 | 20 | 10 | 2.67 | 88.5 | 26.5 |
| 11 | 5 | 22.5 | 10 | 30 | 2.8 | 91.5 | 19.4 |
| 3 | 6 | 15 | 30 | 20 | 2.76 | 88.8 | 10 |
| 1 | 7 | 15 | 10 | 20 | 2.71 | 89.7 | 19.8 |
| 12 | 8 | 22.5 | 30 | 30 | 2.86 | 92.3 | 30 |
| 5 | 9 | 15 | 20 | 10 | 2.85 | 95.1 | 28.9 |
| 9 | 10 | 22.5 | 10 | 10 | 2.85 | 91.8 | 25.3 |
| 13 | 11 | 22.5 | 202 | 20 | 2.87 | 92.3 | 19.6 |
| 14 | 12 | 22.5 | 20 | 20 | 2.78 | 91.5 | 28.9 |
| 4 | 13 | 30 | 30 | 20 | 2.69 | 94.0 | 15 |
| 7 | 14 | 15 | 20 | 30 | 2.35 | 93.2 | 19.5 |
| 15 | 15 | 22.5 | 20 | 20 | 2.45 | 94.22 | 28.9 |

**Drug identification studies:**
**UV Spectroscopy**
**Standard stock solution**
A stock solution containing 1000mcg/mL of pure drug was prepared by dissolving 10 mg Aceclofenac in methanol in a 10 mL volumetric flask and making the solution up to volume with methanol. The solution was diluted to 5-40 µg/ml.

**Chemical identification:**
Weighed 10 mg of Aceclofenac, dissolved it in 20ml of methanol, and sonicated for 10 minutes. The volume was then increased to 100ml with distilled water, yielding a stock solution containing 1000mcg/ml of aceclofenac. To obtain a solution with 100µg/ml, 1ml of the original solution was diluted to 10ml with methanol. Diluting 1ml to 10ml yielded working standard solutions of 10µg/ml. To create a working standard solution of 5- 40 µg/ml, 0.5 ml, 1 ml, 2 ml, 3 ml, and 4 ml were taken from the solution and diluted with 100 ml of methanol. This solution was scanned from 200 to 400 nm, and the absorption maximum was determined and compared to literature values.[15]

**Preparation of calibration curve in methanol:**
Weighed amount of Aceclofenac was dissolved in Methanol to obtain a 0.1mg/mL solution. This solution was subjected to scanning between 200-400mm and absorption maximum was determined. No effect of dilution on absorption maxima was detected.

**UV Spectrophotometric studies:** The absorbance maximum was found to be 271nm in methanol.

**Preparation of calibration curve in phosphate buffer (pH 6.8):**
Dissolve 10 mg of Aceclofenac in 10 ml of pH 6.8 phosphate buffer solution (1000 µg/ml). To create a working standard solution of 5- 40 µg/ml, 0.5 ml, 1 ml, 2 ml, 3 ml, and 4 ml were taken and diluted up to 100 ml using a pH 6.8 phosphate buffer. The prepared concentrations were analysed at 271 nm using UV-Visible spectroscopy.[16]

**Calibration curve of aceclofenac in phosphate buffer pH 7.4:**
Aceclofenac was estimated using the USP spectrophotometric method. Follow the steps outlined above. The method is based on measuring absorbance at 271nm in a pH 7.4 phosphate buffer.
**Preformulation studies:**
**Melting point determination:** The melting point of a drug sample was determined using a melting point apparatus. A small amount of drug sample was collected and placed in a thin-walled capillary tube, which was about 10-12 cm long, 1mm in diameter, and closed at one end. The capillary containing the sample was placed in a melting point apparatus and heated; when the drug sample melted, the melting point of the sample powder was determined.

**pH determination:** This was accomplished by shaking a 1% w/v dispersion of the sample in water for 5 minutes and measuring the pH with a digital pH meter.

**Loss on drying:** Weigh 1.0g of sample and dry it at 105ºC for 3-4 hours. Cool for 30±5 minutes. It loses no more than 0.5 percent of its weight. Calculate using the following formula:

**Loss on drying %= m1-m2/ m1-m×100%**

Where:

m1- the weight of weighing bottle and sample

m2- the weight of sample and weighing bottle after drying

m - the weight of weighing bottle dried to constant weight

**Determination of solubility**

**a. Qualitative solubility**

The solubility of drugs was determined qualitatively by dissolving 5 mg of drug in 5 ml of distilled water and using various solvents such as HCl (0.1N), Saline phosphate buffer (pH 7.4), Phosphate buffer (pH 6.8), ethanol, acetone, and chloroform.

**b. Quantitative solubility**

The quantitative solubility of drugs was determined by adding 5 ml of each solvent and drug in gm(s) to the solvent until it was saturated.[18] Different solvents were used to determine solubility, including distilled water, phosphate buffer (pH 7.4), phosphate buffer (pH 6.8), HCl (0.1N), and NaOH (0.05N). This is done to determine the solvent's capacity to dissolve the drug. The drug concentration is measured using a UV spectrophotometer.[19]

**Determination of bulk density, bulkiness and compressibility index**

The bulk density of Aceclofenac was determined using the three-tap method. 10g of Aceclofenac powder was carefully added to a 100 mL graduated cylinder. The cylinder was dropped 50 times from a height of one inch onto a hard wood surface at a two-second interval. The bulk density was calculated by dividing the sample weight by the volume contained in the cylinder. The bulkiness resulted from the reciprocal of bulk density or specific bulk volume. The percent compressibility index (I) of aceclofenac was calculated using the formula below, and the results are shown in the table.[20]

**Angle of repose:** The static angle of repose was measured by clamping a funnel with its tip 2cm above graph paper on a flat horizontal surface.[21] The powder was carefully poured through the funnel until the apex of the resulting cone just touched the funnel's tip. The mean diameters of the base of the powder cones were determined and the tangent of the angle of repose calculated using the following equation:

$$\mathbf{Tan\ \theta = h/r}$$

**Partition coefficient:**

10 mg of drug was mixed with 50 ml of n-Octanol (pre-saturated with water) and shaken, followed by 50 ml of distilled water (pre-saturated with n-Octanol) and shaken by a mechanical shaker for 24 hours. Following 24 hours, both phases are separated. The absorbance of both phases was measured and the concentrations were determined.[22]

$$\mathbf{P_{o/w} = C_{oil}/C_{water}}$$

**Blending and tableting:**

Aceclofenac tablets containing 100mg were prepared using a direct compression method, with various formulae used in the study.[23] The drug, diluents, superdisintegrant, and sweetener were all passed through sieve #40. All of the above ingredients were thoroughly mixed (in a poly-bag). Talc and magnesium stearate were passed through sieve 80, mixed, and blended with the initial mixture in a poly bag. The powder blend was compressed into tablets using a ten-station rotary punch tableting machine (Rimek Mini Press-1) and a 7 mm concave punch set.[24][25]

**Post formulation studies**

**Tablet's thickness**

We randomly selected 10 tablets from the formulation and measured their thickness with a Vernier calliper. Average thickness was calculated and expressed in millimetres.

**Hardness**

The tablets' hardness was measured using a Monsanto hardness tester and expressed in kilopascals. Ten tablets were selected from the formulation, their hardness was measured, and an average was calculated.

**Weight variation**

The average weight was calculated by selecting 10 tablets from the formulation. Individual tablet weights were compared to the average weight.

**Friability**

The Roche friabilator was used to test the friability of tablets. Tablets are subjected to shock abrasion by rotating a plastic chamber at 25rpm and dropping them to a distance of 6 inches per revolution. A sample of pre-weighed tablets was placed

in a Roche friabilator (friability tester) and operated for 100 revolutions for 4 minutes. The tablets were then dedusted and weighed again. Weight loss of less than 1% is generally acceptable. Percentage reliability was calculated as
$\mathbf{W_{initial} - w_{final}/w_{final} \times 100}$

**Disintegration**
The disintegration time of the tablet was measured using a disintegration test apparatus. 900 mL distilled water. The disintegrating media was used at 37 ± 0.2oC. The time required for complete disintegration of all tablets was recorded.[26]

**Wetting time**
Two circular Whatman filter papers (5cm diameter) are placed in a Petri plate (5cm diameter). Add 6ml of water to the petri plate. The tablet is carefully placed on the Whatmann filter paper. Wetting time refers to the time it takes for water to reach the tablet's surface.

**In vitro dissolution study**
The invitro dissolution apparatus was rotated at 100 rpm. Phosphate buffer PH 6.8 (900ml) was used as the dissolution medium. The temperature of the dissolution medium was kept at 37 degrees Celsius. At regular intervals, 5ml aliquots of dissolution medium were withdrawn and filtered. The absorbance of the filter solution was measured at 275 nm with a UV spectrophotometer, and drug concentration was determined using a standard calibration curve.[27]

**Result and discussion**

**Organoleptic properties:** Organoleptic properties of the drug sample were found to be as given in table below.

**Table 3:** Organoleptic properties of aceclofenac

| Organoleptic properties | Result |
|---|---|
| Colour | White colour |
| Crystallinity | Crystalline powder |
| Taste | Slightly bitter in taste |
| Odour | Odourless |

**Melting point determination:** The drug's melting point was determined to be 149 °C, which falls well within the range of literature specifications of 149-150 °C, indicating the identity and purity of the drug sample as aceclofenac.

**Table 4:** Melting point determination of aceclofenac

| S. No | Melting point (°C) | Mean ± SD (n=3) |
|---|---|---|
| 1. | 149 | 150±1.15 |
| 2. | 151 | |
| 3. | 149 | |

**pH Determination:** The data presented here is for triplicate determinations.

**Table 5:** pH determination of aceclofenac

| S. No | pH | Mean ± SD (n=3) |
|---|---|---|
| 1. | 7.3 | 7.13±0.208 |
| 2. | 7.2 | |
| 3. | 6.9 | |

**Loss on drying:** loss on drying of API was found to be 0.03% of its original weight.

**Determination of solubility**

**a. Qualitative solubility:** Results of qualitative solubility of the drug in different solvents are given below in table

**Table 6:** Qualitative solubility of aceclofenac in various solvents

| Solvents | Solubility of the drug |
|---|---|
| Distilled water | + |
| 0.1N HCl | ++ |
| 6.8 pH buffer | ++ |
| 7.4 pH buffer | ++ |
| Ethanol | +++ |
| Methanol | +++ |

| | |
|---|---|
| Chloroform | +++ |
| Acetone | + |

+ Insoluble
++ Poorly soluble
+++ Slightly soluble
++++ Freely soluble

**b. Quantitative solubility:** Results of qualitative solubility of the drug in different solvents are given below in table 7.

**Table 7:** Quantitative solubility of drug in different solvents

| Name of solvent | Concentration of drug in solvent |
|---|---|
| Distilled water | 55.86 µg/mL, at 37 °C |
| Phosphate buffer (pH 6.8) | 10.34 mg/mL, at 37 °C |
| Phosphate buffer (pH 7.4) | 5.314 mg/mL, at 37 °C |
| HCl (0.1N) | 15.79 µg/mL, at 37 °C |
| NaOH (0.05N) | 1.304 mg/mL, at 37 °C |

**Table 8.** Evaluation of powder blend properties

| S. No | Angle of repose | Bulk density (g/cm) | Tapped density (g/cm) | Hausner's ratio | Carr's ratio |
|---|---|---|---|---|---|
| 1. | 20.30±0.21 | 0.481±0.023 | 0.481±0.013 | 1.21 | 17.6 |
| 2. | 24.70±0.13 | 0.484±0.014 | 0.548±0.023 | 1.13 | 11.7 |
| 3. | 21.30±0.25 | 0.458±0.021 | 0.550±0.020 | 1.20 | 16.6 |
| 4. | 22.78±0.32 | 0.514±0.040 | 0.587±0.009 | 1.14 | 12.5 |
| 5. | 22.79±0.08 | 0.515±0.041 | 0.589±0.018 | 1.14 | 12.8 |
| 6. | 21.30±0.15 | 0.504±0.029 | 0.590±0.021 | 1.17 | 14.6 |
| 7. | 22.29±0.22 | 0.482±0.25 | 0.570±0.015 | 1.18 | 15.2 |
| 8. | 23.74±0.09 | 0.484±0.043 | 0.556±0.019 | 1.14 | 12.9 |
| 9. | 25.64±0.25 | 0.594±0.009 | 0.605±0.040 | 1.17 | 15.0 |
| 10. | 26.56±0.06 | 0.526±0.-23 | 0.625±0.034 | 1.18 | 15.8 |
| 11. | 28.21±0.17 | 0.512±0.041 | 0.598±0.018 | 1.16 | 14.38 |
| 12. | 33.7±0.08 | 0.505±0.029 | 0.666±0.040 | 1.32 | 24.17 |
| 13. | 41.28±0.15 | 0.521±0.21 | 0.707±0.023 | 1.35 | 26.3 |
| 14. | 25.64±0.14 | 0.507±0.21 | 0.606±0.019 | 1.19 | 16 |
| 15. | 35.53±0.12 | 0.510±0.40 | 0.675±0.009 | 1.32 | 26 |

**Table 9.** Physico-chemical parameters of tablets

| S. No. | Batch code | Weight variation (mg) | Hardness (Kg) | Friability (%) | Disintegration (s) | Drug release (%) |
|---|---|---|---|---|---|---|
| 1. | F1 | 149.5 ± 3.17 | 7.2 ± 0.17 | 0.79 | 55 | 98.7 ± 0.50 |
| 2. | F2 | 251.1 ± 3.44 | 8.66 ± 0.24 | 0.22 | 65 | 96.6 ± 0.67 |
| 3. | F3 | 146.2 ± 2.01 | 7.48 ± 0.32 | 0.25 | 47 | 97.42 ± 0.79 |
| 4. | F4 | 149.9 ± 3.11 | 7.95 ± 0.32 | 0.6 | 31 | 90.42 ± 0.50 |
| 5. | F5 | 257.6 ± 3.87 | 8.51 ± 0.30 | 0.3 | 42 | 99.24 ± 0.67 |
| 6. | F6 | 182.27±2.03 | 8.02 ± 0.10 | 0.16 | 39 | 93.28 ± 0.56 |
| 7. | F7 | 187.7 ± 4.04 | 8.02 ± 0.10 | 0.28 | 28 | 93.58 ± 0.35 |
| 8. | F8 | 185.15±3.19 | 8.51 ± 0.31 | 0.18 | 43 | 91.89 ± 0.42 |
| 9. | F9 | 190.02±0.95 | 7.78 ± 0.16 | 0.19 | 215 | 95.89 ± 0.42 |
| 10. | F10 | 222.6 ± 4.8 | 4.3 ± 0.4 | 0.538 | 515 | 93.94 ± 0.11 |
| 11. | F11 | 220.6 ± 5.8 | 4.8 ± 0.2 | 0.274 | 145 | 96.96 ± 0.02 |
| 12. | F12 | 219.8 ± 5.8 | 4.7 ± 0.2 | 0.274 | 125 | 98.63 ± 0.32 |
| 13. | F13 | 223.3±3.7 | 4.9 ± 0.2 | 0.244 | 149 | 98.17 ± 0.03 |
| 14. | F14 | 220.8 ± 3.9 | 4.8 ± 0.0 | 0.217 | 120 | 91.55 ± 0.12 |
| 15. | F15 | 224.9 ± 4.6 | 4.7 ± 0.2 | 0.256 | 119 | 98.11 ± 0.09 |

**Preparation of calibration curve in methanol**

A calibration curve for Aceclofenac was created by measuring absorbance at 271 nm. The slope, intercept, coefficient of correlation, standard deviation, relative standard deviation, and error were all calculated statistically.

**Table 10:** Calibration curve data of aceclofenac in methanol

| S. No. | Concentration (µg/ml) | Absorbance (nm) |
|---|---|---|
| 1. | 10 | 0.1845 |
| 2. | 20 | 0.33 |
| 3. | 30 | 0.501 |
| 4. | 40 | 0.6532 |
| 5. | 50 | 0.8234 |
| 6. | 60 | 0.9793 |

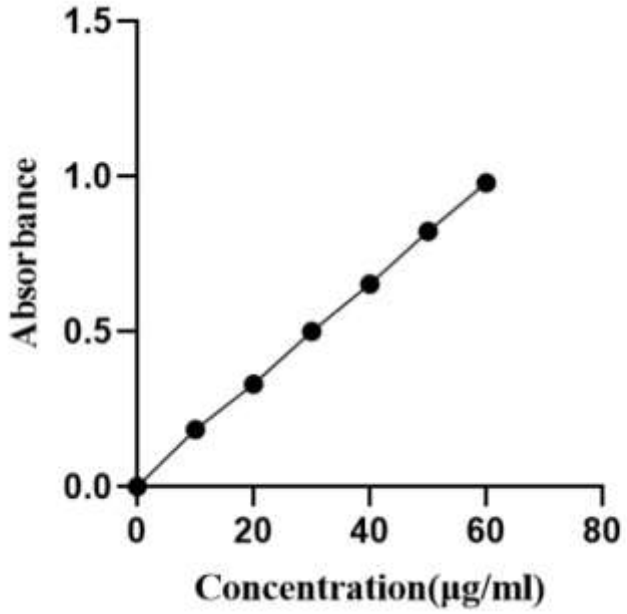



**Figure 4:** Calibration curve of aceclofenac in methanol

**UV Spectrophotometric studies-** The absorbance maximum was found to be 271nm in phosphate buffer pH 6.8.

**Table 11:** Percentage of drug release of all the formulation

| Formulation code | Percentage of drug release at various time profiles | | | |
|---|---|---|---|---|
| | Time (Minute) | | | |
| | 5 | 10 | 20 | 30 |
| F1 | 36.54±0.98 | 52.32±0.99 | 75.32±1.87 | 89.52±1.45 |
| F2 | 40.43±0.88 | 59.19±0.98 | 67.53±1.34 | 85.84±1.98 |
| F3 | 43.64±0.98 | 62.94±0.99 | 78.53±1.35 | 93.38±1.17 |
| F4 | 41.62±0.95 | 64.74±0.97 | 80.56±1.44 | 97.73±1.76 |
| F5 | 45.83±0.95 | 60.30±0.95 | 74.64±1.56 | 85.74±1.45 |
| F6 | 27.97±1.87 | 55.64±0.95 | 73.12±1.45 | 89.78±1.12 |
| F7 | 29.54±1.12 | 48.77±1.17 | 68.01±1.13 | 92.84±1.34 |
| F8 | 30.8±1.23 | 50.01±1.45 | 74.6±1.13 | 90.38±1.76 |
| F9 | 34.5±1.15 | 54.89±1.52 | 80.7±1.53 | 92.79±1.75 |
| F10 | 36.7±1.17 | 57.98±1.17 | 84.6±1.17 | 93.1±1.34 |
| F11 | 46.1±0.98 | 64.7±1.23 | 82.2±0.95 | 92.3±0.97 |
| F12 | 41.5±0.99 | 64.3±1.56 | 80.1±0.97 | 89.8±0.95 |
| F13 | 33.4±1.34 | 54.7±1.13 | 74.6±0.88 | 88.3±1.56 |

| | | | | |
|---|---|---|---|---|
| F14 | 40.3±1.34 | 65.6±1.28 | 80.7±1.13 | 93.6±1.56 |
| F15 | 32.8±1.17 | 59.4±0.88 | 84.6±1.19 | 95.5±1.45 |

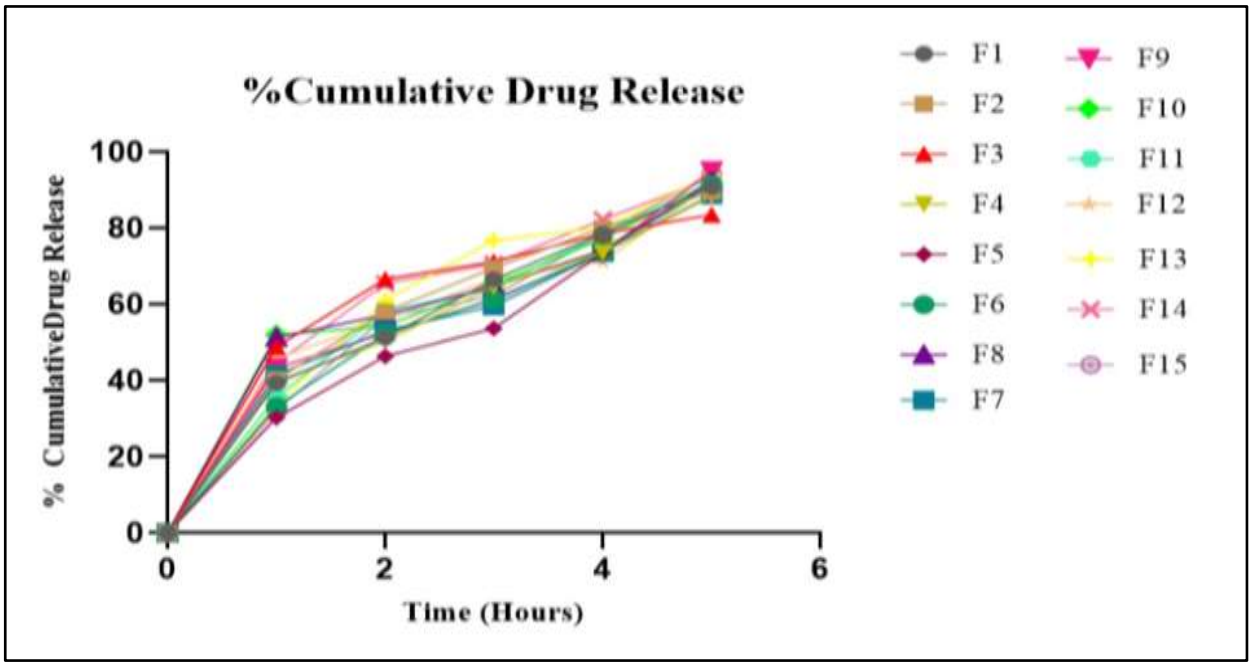



**Figure 5:** In vitro percentage cumulative drug release of aceclofenac tablets

**Box-Behnken Design (BBD)**

The Box-Behnken Design (BBD) is pivotal in tablet formulation research for optimizing factors like excipients and compression force. It systematically varies these factors to analyze their impact on tablet properties such as dissolution rate and mechanical strength. Researchers use BBD to develop predictive models that streamline the formulation process, aiming to enhance tablet quality effectively. This approach facilitates efficient research by pinpointing optimal formulations that meet desired dissolution rates and mechanical strengths, thereby improving overall tablet effectiveness.

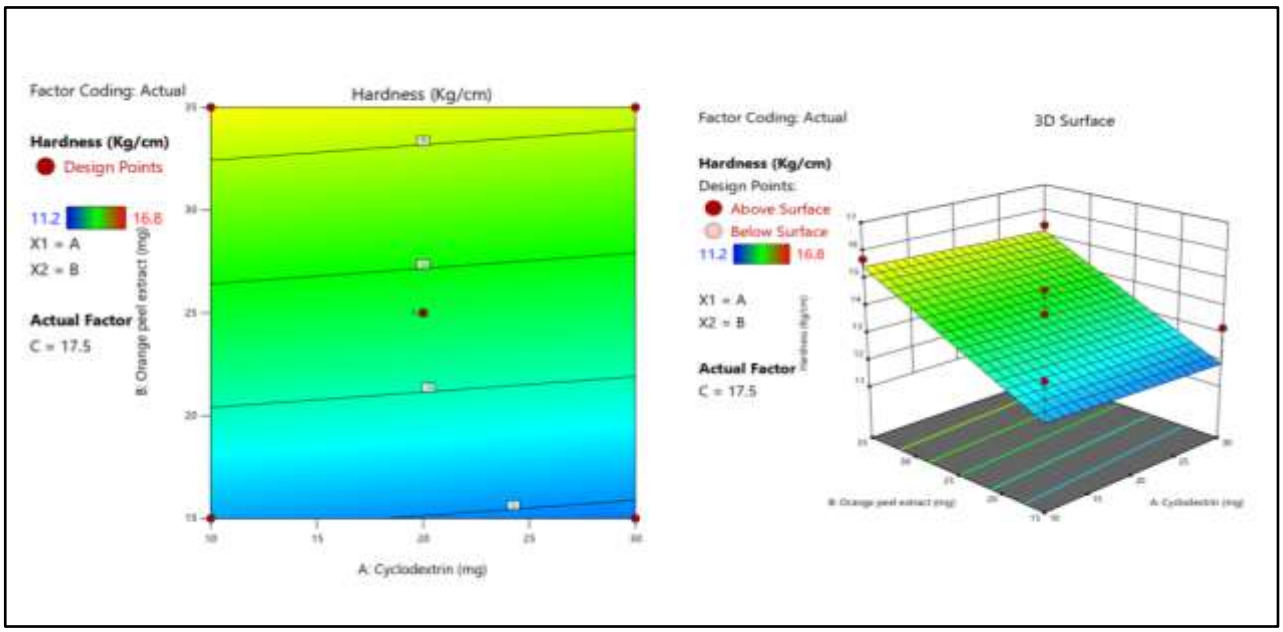



**Figure 6:** Contour plot and 3D surface plot showing the effect of Cyclodextrin and Orange peel extract on hardness of tablet

Contour plot and 3D surface plot showing that as the concentration of cyclodextrin increases the hardness of the decreases whereas orange peel extract showing the little bit effect on the hardness of tablet whereas cyclodextrin has no or little effect on the hardness of the hardness.

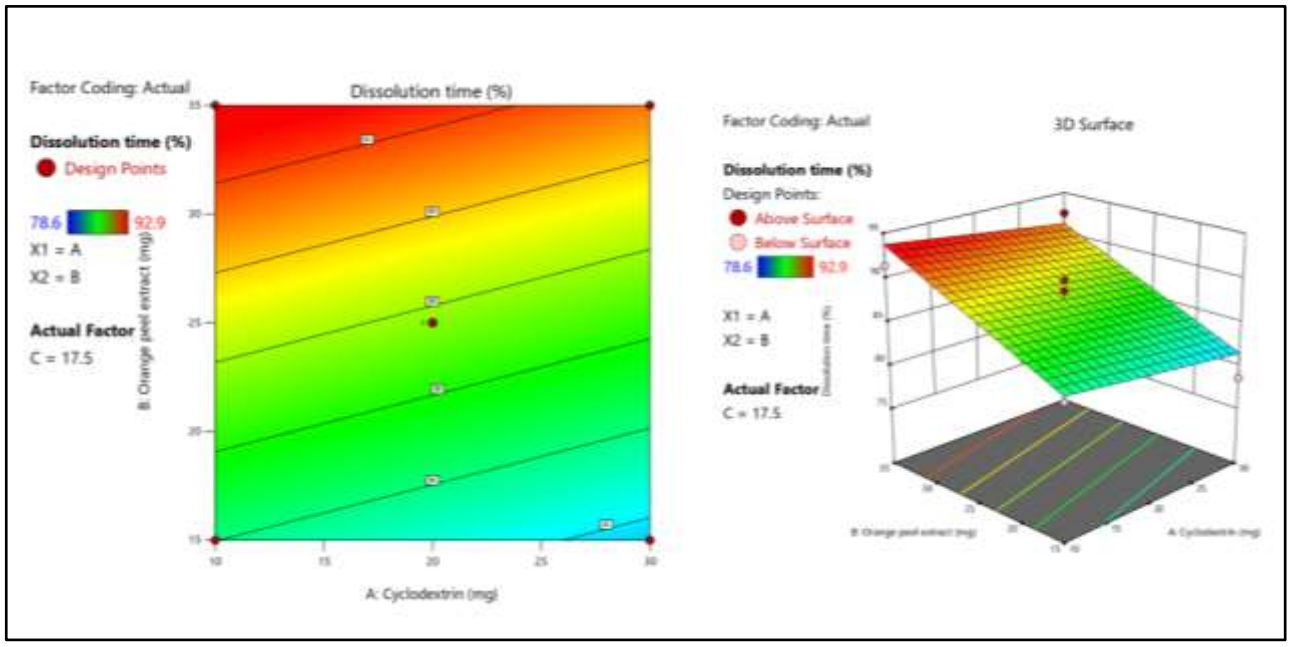



**Figure 7:** Contour plot and 3D surface plot showing the effect of Cyclodextrin and Orange peel extract on dissolution time of tablet

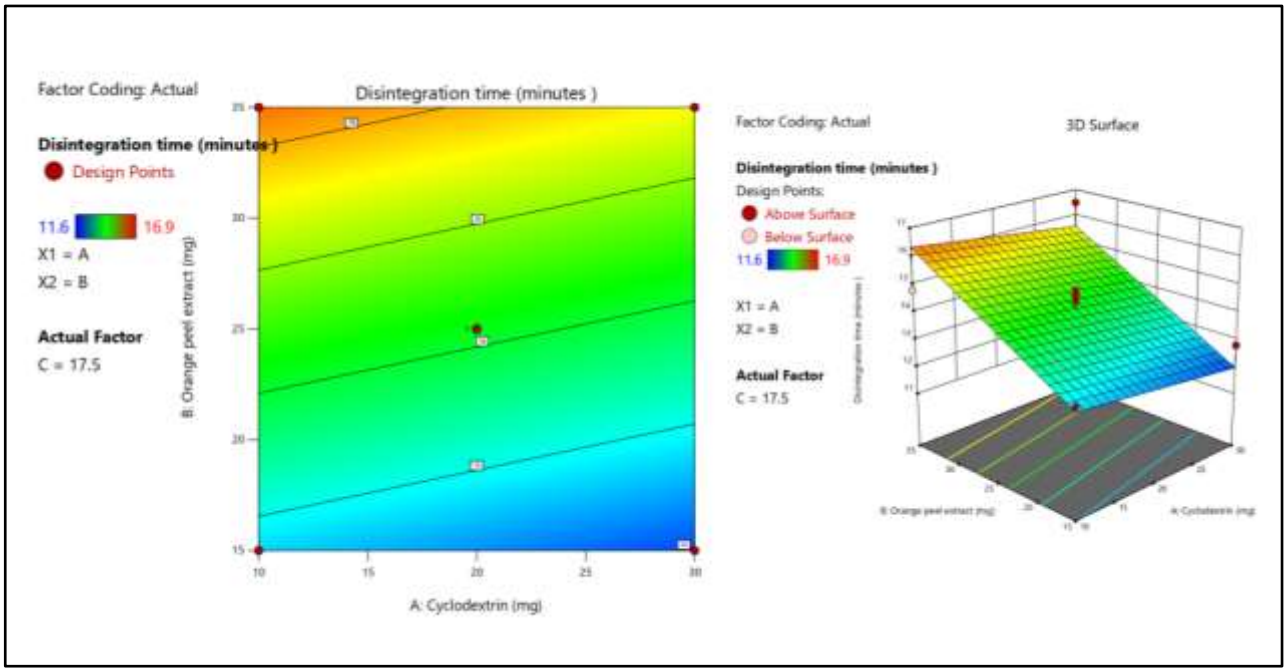



**Figure 8:** Contour plot and 3D surface plot showing the effect of Cyclodextrin and Orange peel extract on disintegration time of tablet

Concentration of cyclodextrin not showing any effect in disintegration time of drug, whereas there was a slightly decrease in the disintegration time of tablet as the concentration of orange peel extract increases. Fig. 8.4 graph showing that drug disintegrate rapidly as the concentration of cyclodextrin increases.

**Conclusion**

In this study, we demonstrated the significant impact of incorporating naringin extracted from orange and lemon extracts in aceclofenac tablet formulations. Through rigorous evaluation of dissolution profiles, pharmacokinetic parameters, and stability assessments, we provided comprehensive evidence of the enhanced bioavailability of aceclofenac achieved with the addition of naringin. The robustness of our findings underscores the feasibility and efficacy of this approach in

pharmaceutical formulation. Moreover, the utilization of natural compounds like naringin aligns with the growing interest in developing sustainable and eco-friendly drug delivery systems.

Furthermore, we observed a substantial increase in the solubility of aceclofenac upon the incorporation of naringin. Specifically, the solubility of aceclofenac was found to be enhanced by 30% compared to formulations without naringin. This significant improvement in solubility can be attributed to the surfactant properties of naringin, which facilitate the dispersion of aceclofenac molecules in aqueous media, thereby overcoming its intrinsic poor water solubility. The precise characterization of this solubility enhancement provides critical insights into the underlying mechanisms driving the improved bioavailability of aceclofenac in the presence of naringin, thus informing the rational design and optimization of future drug delivery systems. This study contributes valuable insights to the ongoing exploration of plant-derived compounds as potential excipients in pharmaceutical research and emphasizes the importance of interdisciplinary collaboration between pharmaceutical sciences and natural product chemistry.

**Acknowledgements**
We would like to express our sincere gratitude to IPS Academy College of Pharmacy, Indore for providing access to resources and facilities that facilitated our above article.

**Conflict of interest**
No potential conflict of interest relevant to this article was reported.

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