Advance Journal of Pharmaceutical Research & Review
Volume 1, Issue 4, October 2024, PP: 29-37, ISSN No: 3048-491X

Pre-Fabrication Comparision Studies of Two Cox-2 Inhibitors (Diclofenac & Acecofenac)

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ABSTRACT: The current aim of the study was to systematically investigate some of the important physicochemical properties of Acceclofenac & Diclofenac . Before the development of any dosage form, it is essential to find some fundamental physical and chemical properties of the drug molecule and other divided properties of the drug powder are determined. It helps to decide many of the approaches in formation and development. Thus before selection of excipients, the Pre-formulation study of any API should be completed for any successful formulation
The Evaluation of API's is involved the Prefabrication studies such as compressibility index, bulk density, angle of repose. All the physical characters of the API's were within acceptable limits.
In this article I focused only on pre-formulation study of API's with comparision with two COX-2 inhibitors.

KEYWORDS: *Diclofenac sodium, Acceclofenac sodium*

I. INTRODUCTION

Preformulation is the stage of development during which the physicochemical properties of the drug substance are characterized and established. Knowledge of the relevant physiochemical and biopharmaceutical properties determines the appropriate formulation and delivery method for Pre-Clinical and Phase 1 studies. The purpose of the pre-formulation research is to provide the basis for the design of the formulation process, and to provide a mechanism-specific and targeted solution to the problems arising in the formulation process research.

Non steroidal anti-inflammatory drugs

NSAIDs are drugs having analgesic, antipyretic and anti inflammatory property that are used to reduce pain, fever and showing anti inflammatory action. These drugs are different from steroids drugs, which having a wide range of effect different from NSAID's have a similar eiconoside depressing, anti inflammatory action.

Mechanism of action

NSAID's are act by inhibiting he enzyme Cyclooxygenaseive inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2(COX-2) iso-enzymes. There is overwhelming evidence pointing to the inhibition of cyclooxygenase enzyme as the main mechanism of NSAIDs' analgesic, antipyretic, and anti-inflammatory properties. Inhibition of Cyclooxygenase (COX) results in inhibition prostaglandin synthesis and other eicosanoid thereby reducing, fever, and inflammation. The cyclooxygenase (COX) enzyme also known as prostaglandin endoperoxide H synthase (PGHS) which is exists in two isoforms: PGHS-1 or COX-1 and PGHS-2 or COX-2. Both isoforms are able to membrane glycoprotein's catalyzing the formation of prostaglandin from arachidonic acid.[4]

Classification of NSAIDs

Table 1: Classification of NSAIDs.[5]

Sr. No.	Category	Drug
1.	**Nonselective COX inhibitors (traditional NSAIDs)**	
	Salicylates	Aspirin
	Propionic acid erivatives	Diclofenac Sodium, Naproxen, Ketoprofen, Flurbiprofen.
	Fenamate	Mephenamic acid.
	Enolic acid derivatives	Piroxicam, Tenoxicam
	Pyrazolone derivatives	Phenylbutazone, Oxyphenbutazone

	Acetic acid derivatives	Ketorolac, Indomethacin, Nabumetone
2.	**Preferential COX-2 inhibitors**	Nimesulide, Diclofenac, Acceclofenac, Meloxicam,Etodolac
3.	**SelectiveCOX-2inhibitors**	Celecoxib, Etoricoxib, Parecoxib.
4.	**Analgesic-antipyretics with poor antiinflammatory action**	
	Para amino phenol derivative	Paracetamol (Acetaminophen).
	Pyrazolone derivatives	Metamizol (Dipyrone), Propiphenazone.
	Benzoxazocine derivative	Nefopam.

II. MATERIALS AND METHOD

Material Source:

Following materials were gifted from different sources.

Table 2: List of materials with source.

Sr.No.	Nameof Ingredients	Nameof supplier
1	Diclofenac	Amoli Organics
2	Acceclofenac	Amoli Organics

Diclofenac

It is an analgesic-antipyretic anti inflammatory drug, similar in efficacy to naproxen. It acts by inhibiting Prostaglandin synthesis and is somewhat COX-2 selective. The also having the short antiplatelet action. The reactions like Neutrophil chemotaxis and production of superoxides are reduced. It is well absorbed orally, 99% protein bound, metabolized and excreted both in urine and bile. The plasma t½ is ~2 hours. However, Penetration into the tissue is good and synovial fluid concentration in is maintained for 3 times more period than in plasma, Producing long lasting therapeutic action in arthritis.

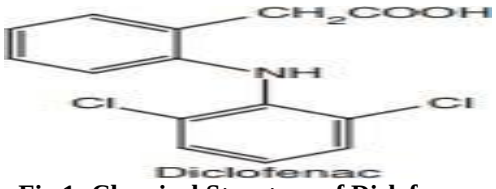

Fig.1: Chemical Structure of Diclofenac.

Metabolism

There are four major metabolites that are produced by aromatic hydroxylation, that is, 4- hydroxy derivative, 5-hydroxy, 3-hydroxyl, and 4, 5-dihydroxy metabolites. Remaining metabolites are excreted as sulphate conjugates.

Properties and uses

Diclofenac sodium occurs as white or slightly yellowish crystalline, mild hygroscopic powder, sparingly soluble in water, soluble in methanol and alcohol, slightly soluble in acetone. Used in the treatment of rheumatic arthritis.

Advers eeffects

Epigastric distress, nausea, headache, Gastric ulceration, rashes. Dizziness and bleeding are less common. Reversible rise of serum amino transferases has been reported more commonly; kidney damage is rare.

Assay

Anhydrous acetic acid is used to Dissolve the sample and titrate it with 0.1M perchloric acid. Determine the end point by using calibrated potentiometer.

Dose

The normal dose of Diclofenac is 20–50mg three times a day. It can also be given as a suppository to treat pain caused by piles.

Dosage forms

Diclofenac tablets I.P., Diclofenac injection I.P., Prolonged-release Diclofenac tablets B.P., Gastro-resistant Diclofenac tablets B.P., Prolonged-release Diclofenac injection B.P., Prolonged-release Diclofenac capsules B.P.[7]

Acceclofenac:

Acceclofenac is a potent analgesic, anti-pyretic and anti-inflammatory agent used in the management of moderate to severe pain and in rheumatoid disorder, rheumatoid arthritis and ankylosing spondylitis. Almost all drugs are marketed as tablets, capsules or both. The current aim of the study was to systematically investigate some of the important physicochemical properties of Acceclofenac. Before the development of any dosage form, it is essential to find some fundamental physical and chemical properties of the drug molecule and other divided properties of the drug powder are determined. It helps to decide many of the approaches in formation and development. Thus before selection of excipients,

the Preformulation study of any API should be completed for any successful formulation. Preformulation Studies like solubility, pKa, dissolution, melting point, stability in solid state; bulk density, flow properties, were investigated and reported. Acceclofenac is a nonsteroidal anti-inflammatory drug (NSAID) analog of Diclofenac. It is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It was patented in 1983 and approved for medical use in 1992.

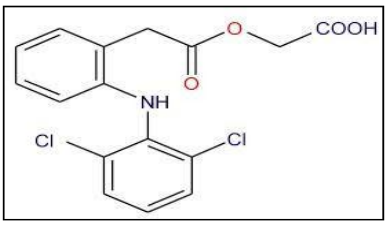

Figure-2 Acceclofenac

Physical properties: Acceclofenac ($C_{16}H_{13}Cl_2NO_4$), chemically [(2-{2, 6-dichlorophenyl) amino} phenyl aceto oxyacetic acid], is a crystalline powder with a molecular weight of 354.19. It is practically insoluble in water with good permeability.

Metabolism: Acceclofenac is metabolized in human hepatocytes and human microsomes to form [2-(2',6'-dichloro-4'-hydroxy-phenylamino)phenyl]acetoxyacetic acid as the major metabolite, which is then further conjugated.

Mechanism of action: Acceclofenac is a phenyl acetic acid derivative having potent analgesic and anti-inflammatory properties. Acceclofenac is a novel NSAIDs which exhibit multifactor mechanism of action. It is known for directly blocking PG2secretion of the site of inflammatory cells (intracellular action) it is Cox inhibitor.

Adverse drug reaction: dyspepsia, abdominal pain, nausea and diarrhea other rare side- effects include dizziness, constipation, vomiting, ulcer of mouth and tongue, rash, dermatitis, headache, fatigue.

Drug interaction: The plasma concentrations of lithium, digoxin and methotrexate may increase with Acceclofenac therapy. It may increase the clotting time of anticoagulant drugs and decrease the diuretic drugs effect. Acceclofenac should not be co-administered with other NSAIDs and corticosteroids which may due to chance of incidence of side-effects. Acceclofenac also increase cyclosporine renal toxicity and precipitate convulsion when co- administered with ciprofloxacin, levofloxacin antibiotics.

Therapeutic uses:

Osteoarthritis, Rheumatoid arthritis, Low back pain, Dental pain, Inflammation and pain in conditions of ear, nose & throat infection.

Characterization of Powdered Bulk density:

It is characterized as the angle of heapto the horizontal plane. Angle of repose was controlled by utilizing fixed funnel technique. Specific amount of powder medication was moved to the funnel keeping the opening of the funnel hindered by thumb. Powder was cleared from funnel at that point estimated its angle of repose. Obvious bulk density (pb) was dictated by pouring the mix in to a graduated cylinder.

The bulk volume (vb) and weight of the powder (M) was calculated utilizing the formula.[8]

Pb=M/Vb

Tapped density

Tapped density was calculated by Tapping the known amount of powdered drug for a specific time by using a graduated measuring cylinder. The tapped density (Pt) was calculated by using formula:

Pt=M/Vt

Where,

Vt=minimum volume occupied in the cylinder

M= weight of the blend was measured.[8]

Carr'sindex

It is also known as compressibility index, it is simple method to measure the compressibility index, indicating easiness of material free flowing, it is calculated by.[8]

I=(Vo-Vt/Vo)×100

Where,

Vo is the bulk volume Vt=tapped volume.

Table 3: Car's Index.

Carr's index%	Flow ability
5-15	Excellent
12-16	Good
18-21	Fairly acceptable
23-35	Poor
33-38	Very poor
<40	Very very poor

Hausner'sratio

Hausner's ratio was ease of indirect index of powder flow measurement. Hausner's ration is indirectly proportional to flow properties of powder means if Lower is Hausner's ratio(<1.25) indicates better flow properties than higher Hausner's ratio (>1.25).[9]

It was calculated by. **Hausner ratio=Pt/Pd** Where,

Pt=tapped density

Pd=bulk density lower Hausner's ratio

(<1.25) indicates better flow properties than higher ones(> 1.25)

Angle of repose

Angle of repose (θ) is defined as the angle between surface of a pile formed by powder and horizontal plane. It is measured by using a funnel method.

The powder blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was formed. After passing of poured powder from funnel the maximum height of cone is obtained and radius of the heap (r) was measured and angle of repose (θ) was calculated by use of the following formula.

θ=tan-1(h/r)

Table 4: Angle of Repose.

Sr. No.	Flowability	Angle of repose
1	Excellent	<25
2	Good	25-30
3	Passable	30-40
4	Poor	37-45
5	Very poor	>45

III. RESULTS AND DISCUSSION

Table 5: Characterization of powder Blend of Diclofenac & Acceclofenac.

Fabrication Code	Bulk density Gm/ml	Tapped density Gm/ml	Hausner's ratio	Car's Index	Angle of repose
Characterization of powder Blend of Diclofenac					
F1	0.67	0.74	1.15	11.53%	34.25
F2	0.64	0.74	1.14	12.19 %	28.23
F3	0.62	0.78	1.22	15.22%	32.40
F4	0.63	0.74	1.18	14.16%	34.16
F5	0.61	0.72	1.21	15.02%	28.45
Characterization of powder Blend of Acceclofenac					
F1	0.67	1.72	2.55	60.81	39.25
F2	0.95	1.31	1.58	27.18	38.25
F3	0.93	1.40	1.60	33.29	33.21
F4	0.95	1.42	1.58	32.96	33.23
F5	0.95	1.32	1.59	27.73	34.25

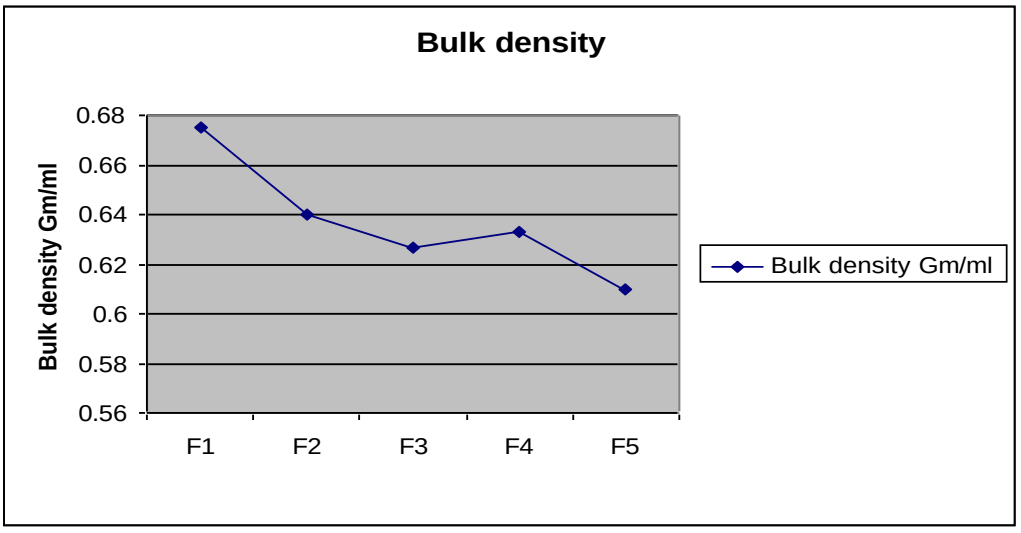

Fig.3: Bulk Density.

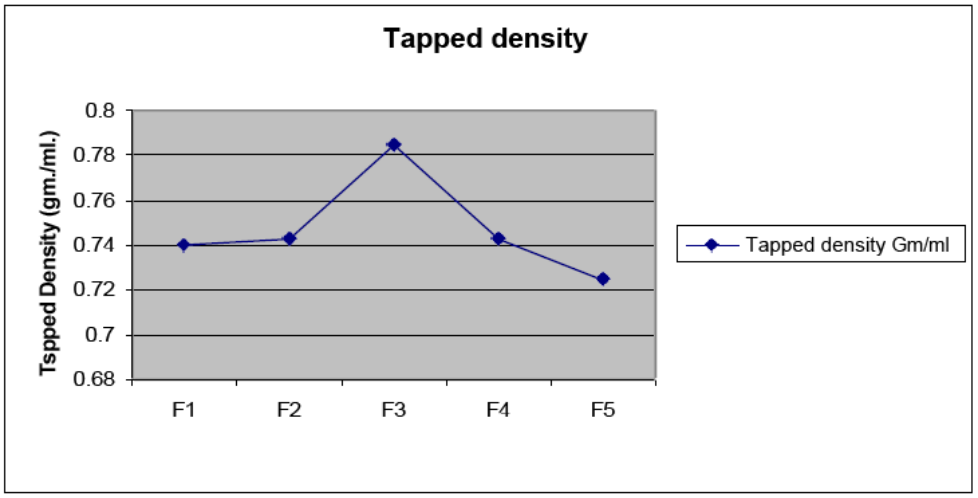

Fig.4: Tapped Density.

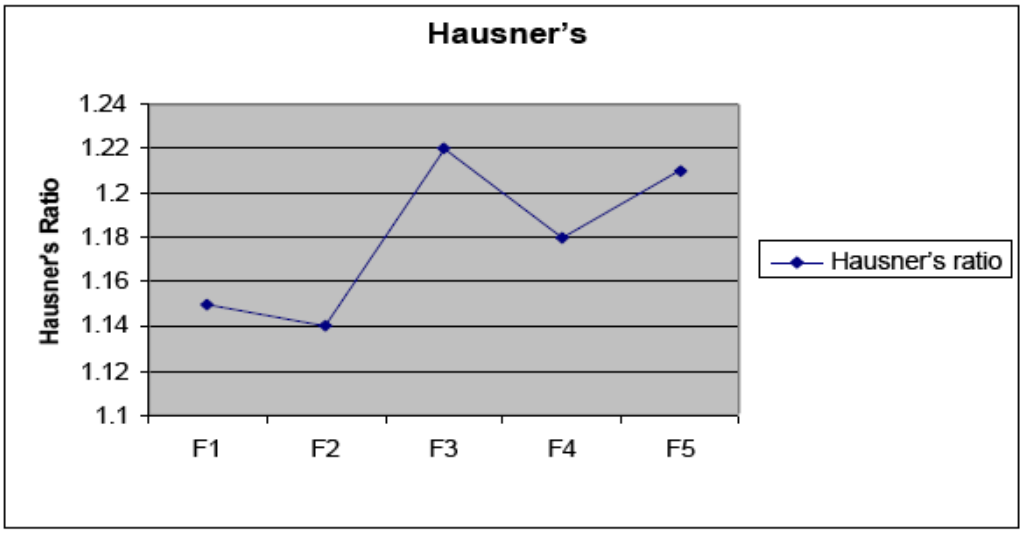

Fig.5: Hausner'sRatio.

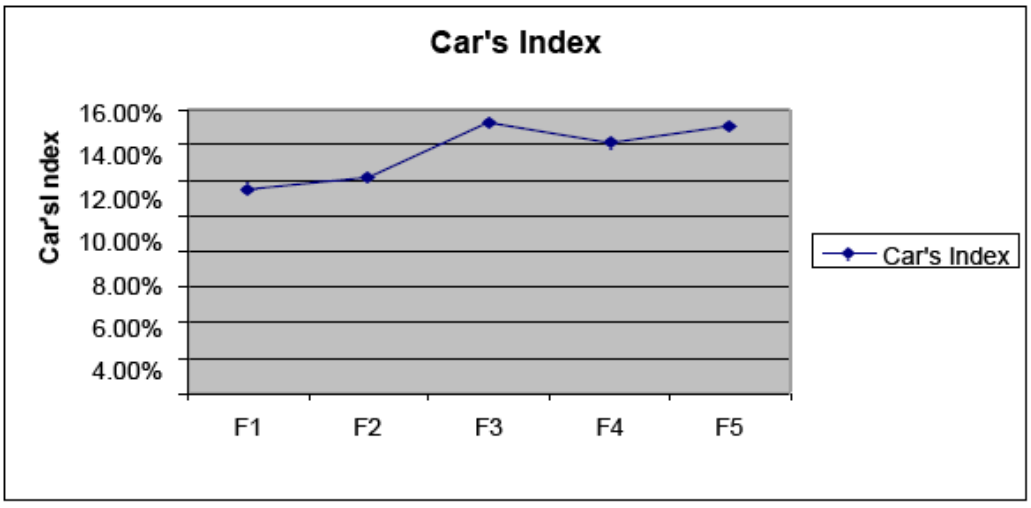

Fig.6: Car's Index.

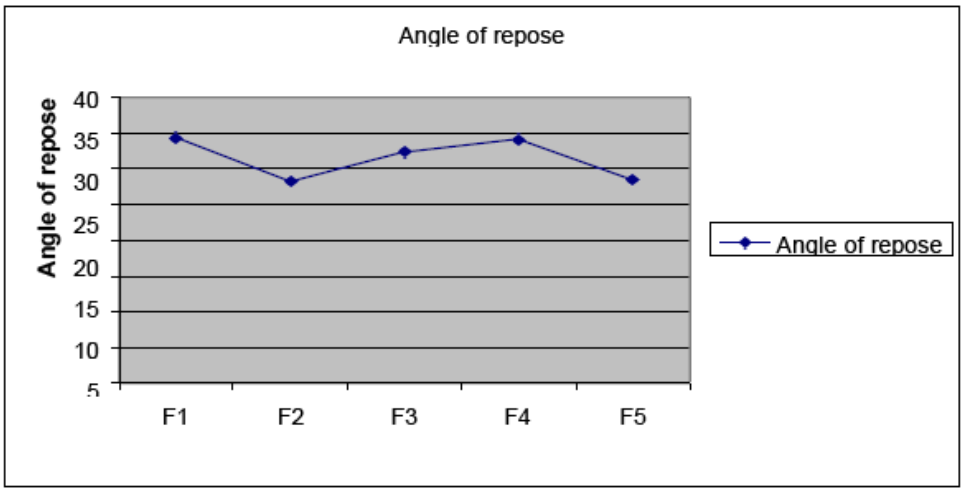

Fig.7: Angle of Repose.

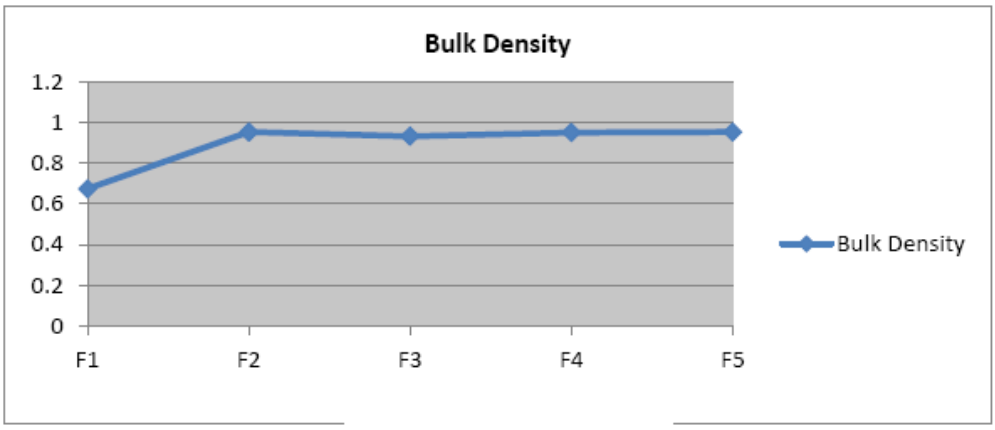

Figure 8: Bulk density of Aceclofenac

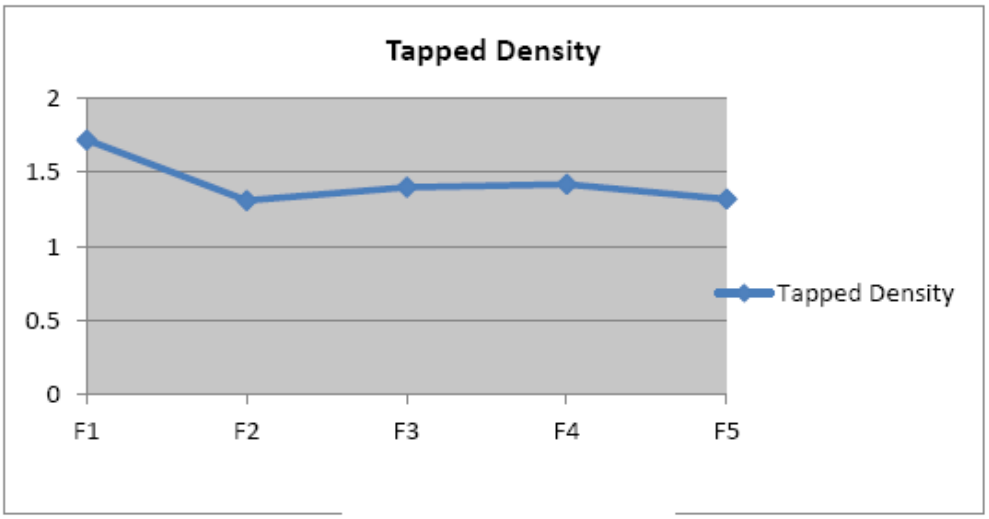

Figure 9 : Tapped density of Acceclofenac

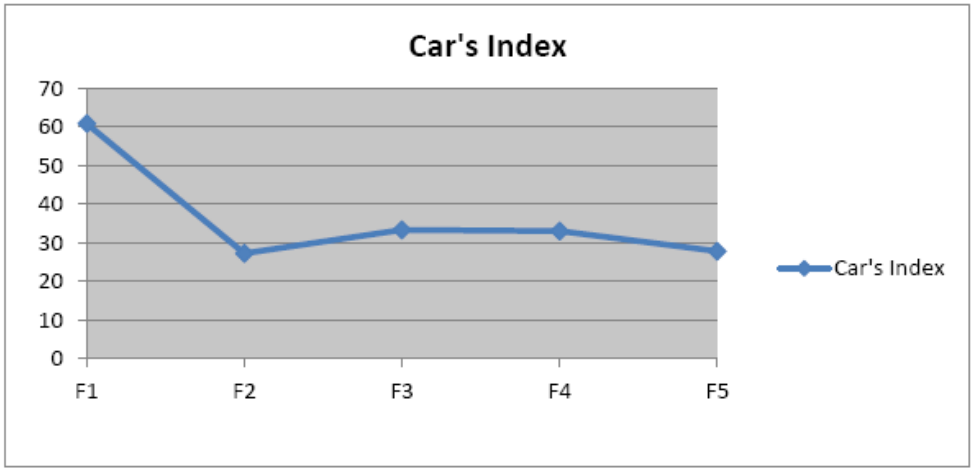

Figure 10 Car's Index of Acceclofenac

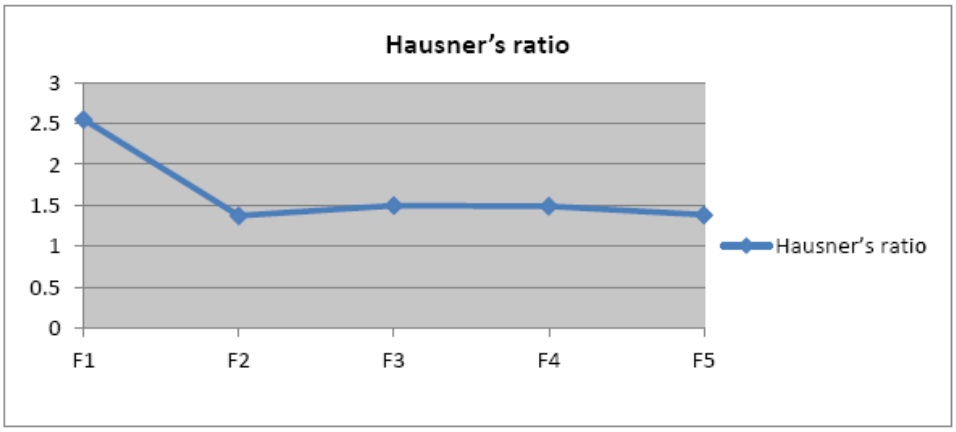

Figure 11 Hausner's Ratio of Acceclofenac

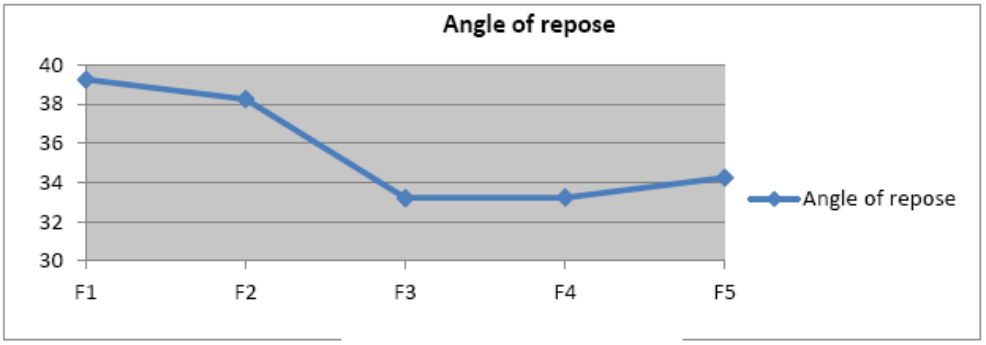

Figure 12 Angle of Repose of Acceclofenac

IV. RESULT & DISCUSION

Acceclofenac & Diclofenac API's were compared for their pre-formulation studies included Compressibility index, Bulk density, Tapped density, Hausner ratio, Angle of repose. On Both the API studied were preformed for their individual 5 batches. This is shown in figure no. 1 to7 for Diclofenac and figure no. 8 to12 for Acceclofenac. All 5 batch of Diclofenac found good in Hausner ratio i.e. below 1.25 and show good flow properties as compared to Acceclofenac. Good Compressibility index found with Diclofenac while Accleclofenac batch F1 show very very poor, and F2, F5 batch show poor and F3, F4 shows good response in compressibility index. Angle of repose response shown by Diclofenac is passable while Acceclofenac show poor response.

V. CONCLUSION

The current aim of the work was to perform various physicochemical characteristic Pre-formulation test for Acceclofenac & Diclofenac API and it was found that the API had variable solubility and other physicochemical properties that could be used for incorporating it in various dosage forms for oral, route of administration the drug was also found to be stable at various conditions.

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