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STABLE FORMULATION OF ACECLOFENAC AND THIOCOLCHICOSIDE TABLETS

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Key words:

Aceclofenac, Thiocolchicoside, Diclofenac, Magnesium stearate, Incompatibility, Tablet

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ABSTRACT: The present study relates to the stable fixed dose combination comprising of Aceclofenac as a glycolic acid ester of Diclofenac is having analgesic and anti-inflammatory action and Thiocolchicoside, as a glycosulfurated analogue of colchicine which is well known centrally acting muscle relaxant in unit dosage form and to the preparation method thereof. Aceclofenac is very susceptible to decomposition under hydrolytic, oxidative stress and exposure to light. The major degradation product identified was diclofenac, which was detected as an impurity in the formulation. Many of the marketed formulation of Aceclofenac tablets having problem of high content of diclofenac impurity. Diclofenac having more gastrointestinal adverse effects such as gastritis, gastrointestinal haemorrhage, haemorrhagic diarrhoea, gastrointestinal ulcer than that of Aceclofenac. It was challenge to develop Aceclofenac tablet formulation having diclofenac impurity within compendial limit. The compatibilty of Aceclofenac with various tableting excipients was investigated physically and by means of Differential Scanning Calorimetry (DSC). Aceclofenac alone and with other excipients in 1:1 binary mixtures were investigated before and after accelerated storage. An interaction was observed between Aceclofenac and magnesium stearate. It was also observed that conversion of Aceclofenac to diclofenac was decreased when used in combination of Thiocolchicoside by using specific method of manufacture. Hydroxypropyl cellulose as a binder also play important role to prevent the conversion of Aceclofenac to diclofenac.

INTRODUCTION: Non Steroidal Anti-Inflammatory Drugs (NSAIDs) are among the most frequently prescribed categories of drugs worldwide in the treatment of pain and inflammation in many conditions. Traditionally NSAIDs account for 70% of the total prescription for pain. NSAIDs help in relieving pain in patients by blocking cyclooxygenase (COX) enzymes that lead to secretion of prostaglandins, which causes pain and inflammation [1, 2].

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Though NSAIDs are widely used for long-term care, it is now well established that they are associated with development of upper gastrointestinal damage, including mucosal erosions, ulcers and life threatening conditions like perforation and hemorrhage. This life threatening consequences led to the development of cyclo-oxygenase-2 inhibitors. The potential advantage of Cyclooxygenase-2 (COX-2) inhibitors is that they have fewer adverse effects on the gastrointestinal tract as a result of having less inhibitory effect on the gastro-protective prostanoids produced by COX-1 enzyme in the Gastrointestinal tract (GIT). This advantage of COX-2 selective NSAIDs has been demonstrated in many trials [3-5].

Aceclofenac is an effective analgesic and anti-inflammatory agent; through these properties it

provides greater symptomatic relief in a variety of painful conditions [6]. It has also shown to exert effects on a variety of mediators of inflammation. The drug inhibits synthesis of inflammatory cytokines like interleukin (IL)-1β and tumor necrosis factor (TNF) and inhibits prostaglandin E2 (PGE2) production [7]. Aceclofenac selectively block COX-2 enzyme and thus reduces the risk of peptic ulceration. Aceclofenac is white to almost white, crystalline powder practically insoluble in water, freely soluble in acetone, soluble in ethanol (96 percent). Chemically it is [[[2-[(2,6-chlorophenyl) amino] phenyl]acetyl]oxy] acetic acid.

Although Aceclofenac is having less gastrointestinal adverse effect, but it is very susceptible to decomposition under hydrolytic stress (acidic and alkaline) and oxidative stress to its analog diclofenac, a major degradation product. Degradation reaction is given below in **Fig 1**.

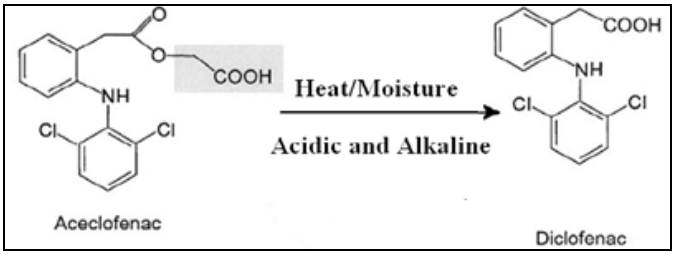


FIG. 1 DEGRADATION REACTION FOR ACECLOFENAC

Diclofenac a analog of Aceclofenac is an already established Non-Steroidal Anti-Inflammatory drug with analgesic and antipyretic properties. Diclofenac exerts its action via inhibition of prostaglandin synthesis by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) with relative equipotency. COX-1 play important role in housekeeping such as it protects gastric mucosa, regulate gastric acid and maintain normal functions of the kidney by stimulating prostaglandins. COX-2 is involved in the synthesis of prostaglandins that causes pain and inflammation in the body [1, 8]. Due to non selectivity Diclofenac has shown increased incidence of adverse effects like abdominal pain, dyspepsia, diarrhoea, heartburn and GI ulcer. Detail Pharmacological action of COX-1 and COX-2 enzymes are diagrammatically demonstrated below in **Fig. 2**.

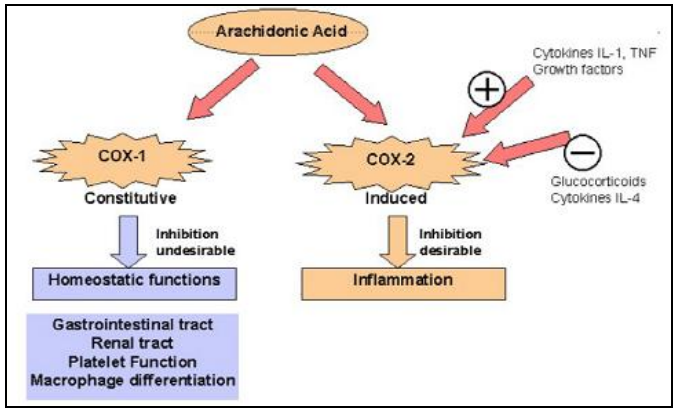


FIG. 2: PHARMACOLOGICAL ACTION OF COX-1 AND COX-2 ENZYMES

Due to high degradation susceptibility of Aceclofenac, many of the marketed formulation of Aceclofenac tablets are having problem of high content of diclofenac impurity. Official compendium have fix limit of diclofenac in Aceclofenac Tablets to 5.0 %, but in investigation many of the marketed formulation shows content of diclofenac on higher side i.e. more than 5.0 %.

Compatibility of an active pharmaceutical ingredient (API) with excipients is one of the key factor influencing the stability of a formulation, because excipients can interact with API both chemically and physically. Chemical interactions between API and excipients result in a reduction of the quantity of the API, which can influence the absorption and therapeutic effect. Physical interactions can alter the physicochemical parameters of the components, e.g. the solubility, the dissolution rate and finally the bioavailability. Adsorption of drug molecules onto the surface of excipients can render the drug unavailable for dissolution and diffusion, which can result in reduced bioavailability. For example, antibacterial activity of cetylpyridinium chloride was decreased when magnesium stearate was used as lubricant in tablet containing cetylpyridinium chloride; this was due to adsorption of cetylpyridinium cation by stearate anion on magnesium stearate particle [9].

In one of the investigation, it was observed that dissolution of drug was decreased due to adsorption of drug on the surface of microcrystalline cellulose. In a similar context, adsorption of novel k-opoid agonist by microcrystalline cellulose led to incomplete drug release from the capsules. Adsorption may also initiate chemical breakdown.

Colloidal silica was shown to catalyze nitrozepam degradation in tablet dosage form, possibly by adsorptive interactions altering electron density in the vicinity of the labile azo group and thus facilitating attack by hydrolyzing entities[10]. Investigation of the incompatibility between the components of the dosage form is critical in the early stages of the development of a stable dosage form. Differential scanning calorimetry (DSC) has been widely used to assess incompatibility between formulation components, because the method is fast and versatile and requires very small quantity of sample [11].

Most commonly used muscle relaxants are central nervous system depressants. Although these groups of drugs usually help to reduce spasticity, but decrease in muscle tone elsewhere, may lead to a decrease in the mobility of the patient. Also the development of sedation, is found to be a major limiting factor in the use of muscle relaxants for the treatment of Acute Low Back Pain (LBP), as they can affect daily activities and decrease working capabilities [12, 13]. Hence, these limiting factors in the use of muscle relaxants raised a need for an ideal muscle relaxant devoid of effects on psychomotor performance, free of sedation and higher tolerability.

Thiocolchicoside is a semi-synthetic derivative of colchicine, a natural glycoside of Superba gloriosa. It's *in- vitro* profile shows affinity for the inhibitory glycine and GABA A receptors and therefore the compound is endowed with glycinomimetic activity and is being used in rheumatology and orthopaedic field for its myorelaxant property [14, 15]. It has been reported that thiocolchicoside produces muscle relaxation without any sedative side effects. It is indicated for the adjunctive treatment of muscle spasm in acute low back pain (LBP) [16].

Thiocolchicoside is yellow crystalline powder. It is soluble in water, slightly soluble in ethanol and insoluble in chloroform. It is a glycosulfurated analogue of colchicine and is a well known centrally acting muscle relaxant used in the treatment of musculoskelatel disorders. Chemically it is N-[(7S)-3-(β-D-Glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl) – 9 – oxo - 5, 6,7,9 tetrahydrobenzo[a]heptalen-7-yl] acetamide.

The primary objective of the study was to develop stable Aceclofenac, Aceclofenac and Thiocolchicoside tablets formulation with minimum diclofenac impurity so that it will comply with all the regulatory requirements.

Many of the marketed formulation of Aceclofenac tablets use common tableting excipients such as microcrystalline cellulose, croscarmellose sodium, povidone, maize starch and magnesium stearate, but in literature survey it was reported that these formulations have problem of high content of diclofenac impurity in stability or during shelf life. Incompatibility of Aceclofenac and magnesium stearate is also reported in the literature. So to find out route cause and for the selection of the appropriate excipients in the formulation it was decided to carry out the drug-excipients compatibility study. Commonly used excipients such as microcrystalline cellulose as a diluent, croscarmellose sodium, crospovidone and sodium starch glycolate as a disintegrants, maize starch, povidone, hydroxypropyl cellulose as a binder and magnesium stearate, stearic acid, glyceryl palmitostearate and sodium stearyl fumarate as a lubricant were subjected to the compatibility study.

MATERIAL AND METHOD:

Material:

Aceclofenac was obtained from Amoli organics Pvt. Ltd. Vapi, Gujarat, India. Thiocolchicoside was obtained from Alchem International Ltd. Mumbai, India. Microcrystalline Cellulose (NB entrepreneurs), Crospovidone (Ashland, U.S.A.), Croscarmellose Sodium (FMC Biopolymer, U.S.A.), Sodium starch glycolate (Amishi drugs and chemicals Pvt. Ltd., Ahmedabad, Gujarat, India), Hydroxypropyl Cellulose (Ashland, U.S.A.), Maize starch (Universal starch chem allied Ltd., Mumbai), Povidone K-30 (ISP, India), Colloidal silicon dioxide (Evonic Ind., Germany), Glyceryl palmitostearate (Gattefosse, France), Stearic Acid (Cognis, Germany), Sodium stearyl fumarate (JRS Pharma., Germany), Opadry White YS-1R-7003 (Colorcon, India), Opadry Yellow 13B520019 (Colorcon, India).

Pre-formulation Study:

Drug-excipient compatibility study was performed using Aceclofenac with the excipients to be used in

the formulations. Aceclofenac alone and with other excipients in 1:1 binary mixtures were physically investigated before and after accelarated storage. It was also confirmed by the differential scanning calorimetry (DSC).

Hydroxypropyl cellulose was chosen as a binder, as it is a nonionic water-soluble cellulose ether with a remarkable combination of properties. It combines organic solvent solubility, thermoplasticity and surface activity with the aqueous thickening and stabilizing properties.

Crospovidone and Croscarmellose sodium were selected as a disintegrants for the development of tablet formulation as they have less pH dependent disintegration profile.

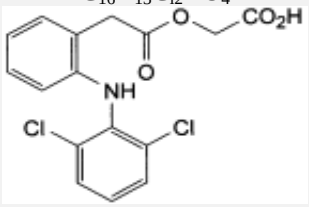
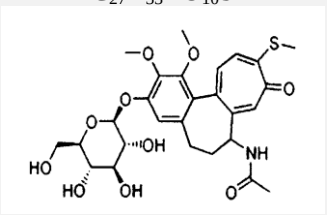
For selection of suitable lubricant out of the choice available, magnesium stearate, glyceryl palmitostearate, sodium stearyl fumarate and stearic acid were investigated for compatibility study with Aceclofenac at normal room temperature and acceletated stability condition with and without moisture and from the DSC analysis it was concluded that along with magnesium stearate, sodium stearyl fumarate was also incompatible with Aceclofenac. Hence it was decided to use glyceryl palmitostearate and stearic acid as lubricant. Proposed list of excipients for development of Aceclofenac, Aceclofenac and Thiocolchicoside tablets formulation were given below in **Table 1.**

TABLE 1: PROPOSED LIST OF INGREDIENTS TO BE USED FOR DEVELOPMENT

Sr. No.	Name Ingredients	Uses
1	Aceclofenac	Active pharmaceutical ingredient
2	Thiocolchicoside	Active pharmaceutical ingredient
3	Microcrystalline Cellulose	Diluent
4	Crospovidone	Disintegrant
5	Hydroxypropyl Cellulose	Binder
6	Croscarmellose Sodium	Disintegrant
7	Glyceryl palmitostearate	Lubricant
8	Stearic Acid	Lubricant
9	Opadry White (YS-1R-7003)	Coating agent
10	Opadry Yellow (13B520019)	Coating agent

Drug profiles are given in **Table 2**

TABLE 2: DRUG PROFILE

Name	Aceclofenac	Thiocolchicoside
Chemical Formula	$C_{16}H_{13}Cl_2NO_4$	$C_{27}H_{33}NO_{10}S$
Molecular Structure		
Molecular weight	354.18 g/mole	563.62 g/mole
Physical State	Solid	Solid
Description	White crystalline powder	Yellow crystalline powder
Solubility	Partially insoluble in Water and Alcohol	Soluble in Water and Alcohol
Therapeutic category	Anti-inflammatory, analgesic	Central muscle relaxant

Method of Manufacture:

In this study following three different formulation trials were conducted based on the observations from DSC studies.

1. Aceclofenac Tablet 100 mg
2. Aceclofenac 100 mg and Thiocolchicoside 4 mg Tablet

3. Aceclofenac 100 mg and Thiocolchicoside 8 mg Tablet

Detail composition is given in **Table 3**.

TABLE 3: DETAIL COMPOSITION OF FORMULATIONS

Sr. No.	Name of ingredients	Aceclofenac Tablets 100 mg	Aceclofenac 100 mg and Thiocolchicoside 4 mg Tablets	Aceclofenac 100 mg and Thiocolchicoside 8 mg Tablets
Dry mixing				
1	Aceclofenac	100.0	100.0	100.0
2	Microcrystalline Cellulose PH101	40.0	40.0	40.0
3	Crospovidone (Polyplasdone XL-10)	7.0	7.0	7.0
Granulation				
4	Thiocolchicoside	--	4.0	8.0
5	Hydroxypropyl Cellulose (Klucel LF)	2.0	2.0	2.0
6	Purified Water*	q.s.	q.s.	q.s.
Lubrication				
7	Microcrystalline Cellulose PH102	73.6	24.3	64.4
8	Croscarmellose Sodium (Ac-Di-Sol)	15.0	--	15.0
9	Glyceryl palmitostearate (Precirol ATO-5)	2.4	1.8	2.4
10	Stearic Acid	--	0.9	1.2
Weight of uncoated tablet		**240.0**	**180.0**	**240.0**

Sr. No.	Name of ingredients	Aceclofenac Tablets 100 mg	Aceclofenac 100 mg and Thiocolchicoside 4 mg Tablets	Aceclofenac 100 mg and Thiocolchicoside 8 mg Tablets
Film Coating				
11	Coating Readymix Opadry White (YS-1R-7003)	4.0	--	--
12	Coating Readymix Opadry Yellow (13B520019)	--	4.5	6.0
13	Isopropyl Alcohol*	q.s.	q.s.	q.s.
14	Dichloromethane*	q.s.	q.s.	q.s.
Weight of coated tablet		**244.0**	**184.5**	**246.0**

* Does not form the part of final product.

Wet granulation approach was used for the manufacturing of tablet formulation. In first trial aceclofenac, microcrystalline cellulose and crospovidone were dry mixed and granulated with hydroxypropyl cellulose binder solution. Granules were dried and sifted through appropriate sieve and finally blended with microcrystalline cellulose, croscarmellose sodium and glyceryl palmitostearate. In combination products Aceclofenac 100mg and thiocolchicoside 4mg tablets and Aceclofenac 100mg and thiocolchicoside 8mg tablets, thiocolchicoside is dissolved along with hydroxypropyl cellulose in purified water and added as binder solution. Aceclofenac along with microcrystalline cellulose and crospovidone were granulated using thiocolchicoside-hydroxypropyl cellulose binder solution. Granules were dried and sifted through appropriate sieve and finally blended with microcrystalline cellulose, croscarmellose sodium, glyceryl palmitostearate and stearic acid. Lubricated blend from all the three batches were compressed into the tablet dosage form and film coated using the coating ready mix material. Finished tablet formulation was then packed in aluminium strip pack and accelerated stability study of each batch along with the reference product of same strength were conducted for six months.

Evaluation of formulation:

1. Weight variation:

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation. (IP, BP and USP Limit ± 7.5% of average weight).

2. Hardness:

Ten tablets were randomly selected from each batch and hardness of tablets was determined by using Monsanto hardness tester.

3. Friability:

Friability indicates the ability of a tablet to withstand mechanical shocks while handling. Friability of the tablets were determined using Electrolab Friabilator and is expressed in percentage (%). Tablets weighed equivalent to 6.5 gm were initially weighed (*W1*) and placed into the friabilator. The friabilator was operated at 25 rpm for 4 minutes and then the tablets were weighed again. The loss in tablet weight due to abrasion or fracture (*W2*) was the measure of tablet friability. Percent friability (*F*) was calculated by using the following formula.

$$F = \frac{W1 - W2}{W1} X\ 100$$

4. Disintegration Time:

The disintegration time for all batches were carried out in water (37 ± 2°C) according to USP using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and noted the time taken for the entire tablet to disintegrate completely (IP, BP and USP limit NMT 30 mins for coated tablets).

5. Related Substances:

Determination of related substances is important tool to judge the safety, efficacy and stability of product. In this study content of diclofenac in three tablet formulation along with their respective marketed formulations were determined initially and after 6M accelerated stability study by using High performance liquid chromatography (HPLC).

RESULTS AND DISCUSSION:

Pre-formulation results:

Results of preformulation study are given in **Table 4** and **5.**

TABLE 4: COMPATIBILITY STUDY OF ACECLOFENAC WITH EXCIPIENTS

Compatibility study of Aceclofenac with excipients										
Sr. No.	Composition details	Initial	Room temperature				40°C/75%RH			
			5 days	10 days	15 days	30 days	5 days	10 days	15 days	30 days
1	Aceclofenac	White powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC
2	Aceclofenac + Microcrystalline Cellulose	White to off white powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC
3	Aceclofenac +Hydroxypropyl Cellulose	White to off white powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC
4	Aceclofenac + Maize starch	White to off white powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC
5	Aceclofenac + Povidone	White to off white powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC
6	Aceclofenac + Croscarmellose sodium	White to off white powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC
7	Aceclofenac+Sodium starch glycolate	White to off white powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC
8	Aceclofenac + Crospovidone	White to off white powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC
9	Aceclofenac + Colloidal anhydrous silica	White to off white powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC
10	Aceclofenac+ Magnesium stearate	White to off white powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC
11	Aceclofenac+ Sodium stearyl fumarate	White to off white powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC
12	Aceclofenac+ Stearic acid	White to off white powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC

13	Aceclofenac + Glyceryl palmitostearate	White to off white powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC
14	Aceclofenac + Opadry White (YS-1R-7003)	White to off white powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC
15	Aceclofenac + Opadry Yellow (13B520019)	Pale Yellow powder	NCC	NCC	NCC	NCC	NCC	NCC	NCC	NCC

NCC– No Characteristic Change

TABLE 5: THERMOANALYTICAL DATA OF ACECLOFENAC AND ACECLOFENAC WITH DIFFERENT LUBRICANTS IN PHYSICAL MIXTURE (1:1 RATIO)

Sr. No.	Sample	Condition	DSC DATA		
			T_{onset}	T_{peak}	Enthalpy
1	Aceclofenac	Room Temperature	151.65°C	153.4°C	139.5J/g
2	Aceclofenac	12 days, 40°C/75%RH	151.82°C	153.41°C	140.2J/g
3	Aceclofenac with 0.5% Moisture	12 days, 40°C/75%RH	151.55°C	153.33°C	137.4J/g
4	Aceclofenac + Mg Stearate	Room Temperature	75.64°C	88.73°C	79.38J/g
			177.73°C	189.98°C	4.799J/g
5	Aceclofenac + Mg Stearate	12 days, 40°C/75%RH	76.48°C	88.9°C	79.08J/g
			179.57°C	188.15°C	3.313J/g
6	Aceclofenac + Mg Stearate with 0.5% Moisture	12 days, 40°C/75%RH	94.76°C	98.38°C	94.25J/g
			117.3°C	129.45°C	17.91J/g
			174.48°C	183.97°C	5.475J/g
7	Aceclofenac + Glyceryl Palmitostearate (1:1)	Room Temperature	51.72°C	57.99°C	81.37J/g
			128.53°C	144.54°C	45.43J/g
8	Aceclofenac + Glyceryl Palmitostearate	12 days, 40°C/75%RH	49.82°C	53.27°C	19.96J/g
			58.02°C	62.43°C	16.6J/g
			131.55°C	147.01°C	39.27J/g
9	Aceclofenac + Glyceryl Palmitostearate with 0.5% moisture	12 days, 40°C/75%RH	51.19°C	54.68°C	24.03J/g
			58.85°C	62.17°C	16.6J/g
			136.6°C	147.69°C	45.53 J/g
10	Sodium stearyl fumarate	Room Temperature	57.17°C	57.64°C	5.551J/g
			95.33°C	112.85°C	77.58 J/g
			127.29°C	134.02°C	52.00J/g
			195.76°C	197.03°C	28.52J/g
11	Aceclofenac + Sodium stearyl Fumarate	Room Temperature	56.65°C	57.48°C	2.978J/g
			94.96°C	104.08°C	117.6 J/g
			229.16°C	248.41°C	44.85J/g
			268.79°C	274.30°C	17.97J/g
12	Aceclofenac + Sodium stearyl Fumarate (1:1)	12 days, 40°C/75%RH	56.33°C	58.33°C	6.292J/g
			94.26°C	104.56°C	102.1 J/g
			234.86°C	248.37°C	34.58J/g
			269.52°C	276.63°C	14.76J/g
13	Aceclofenac + Sodium stearyl Fumarate with 0.5% Moisture	12 days, 40°C/75%RH	56.54°C	57.65°C	3.117J
			93.7°C	105.94°C	93.03 J/g
			230.09°C	250.38°C	63.83J
			270.19°C	276.94°C	17.35J
14	Stearic acid	Room Temperature	51.2°C	67.8°C	16.6J/g
15	Aceclofenac + Stearic acid	Room Temperature	49.0°C	69.8°C	17.6J/g
			151.55°C	160.5°C	141.2J/g
16	Aceclofenac + Stearic acid	12 days, 40°C/75%RH	45.0°C	65.8°C	14.8J/g
			145.12°C	155.5°C	137.2J/g
17	Aceclofenac + Stearic acid with 0.5% Moisture	12 days, 40°C/75%RH	44.9°C	62.8°C	16.2J/g
			99.3°C	110.2°C	19.8J/g
			144.55°C	156.8°C	139.2J/g

DSC data interpretation:

Aceclofenac:

1. The DSC curve of Aceclofenac showed endothermic event between 151.65°C and 153.4°C (ΔH_{fusion} = -139.51J).
2. The DSC curve of Aceclofenac stored at 40°C/75% RH for 12 days showed endothermic event between 151.82°C and 153.41°C (ΔH_{fusion} = -140.21J). This demonstrates that there are no remarkable

alteration in thermo-analytical profile of drug when stored under stress condition.

3. The DSC curve of Aceclofenac with 0.5% moisture stored at 40°C/75% RH for 12 days showed endothermic event between 151.55°C and 153.33°C (ΔH_{fusion} = -137.4J). This demonstrates that there are no remarkable alteration in thermo-analytical profile of drug when stored under stress condition with 0.5% moisture.

Aceclofenac + Magnesium Stearate (1:1)

1. The DSC curve of Aceclofenac + Magnesium Stearate (1:1) stored at room temperature showed two endothermic event

- Between 75.64°C and 88.73°C (ΔH_{fusion} = -79.38J)
- Between 177.73°C and 189.98°C (ΔH_{fusion} = -4.799J)

This demonstrates that there is a shift in peak due to interaction between Aceclofenac and Magnesium Stearate.

3. The DSC curve of Aceclofenac + Magnesium Stearate (1:1) stored at 40°C/75% RH for 12 days showed two endothermic event

- Between 76.48°C and 88.9°C (ΔH_{fusion} = -79.08J)
- Between 179.57°C and 188.15°C (ΔH_{fusion} = -3.313J)

This demonstrates that there is a shift in peak due to interaction between Aceclofenac and Magnesium Stearate.

4. The DSC curve of Aceclofenac + Magnesium Stearate (1:1) with 0.5% moisture stored at 40°C/75% RH for 12 days showed three endothermic event as given below:

- Between 94.76°C and 98.38°C (ΔH_{fusion} = -94.25J)
- Between 117.3°C and 129.45°C (ΔH_{fusion} = -17.91J)
- Between 174.48°C and 183.97°C (ΔH_{fusion} = -5.475J)

This demonstrates that there is a shift in peak due to interaction between Aceclofenac and Magnesium Stearate. The reaction is accelerated in presence of moisture.

Aceclofenac + Glyceryl Palmitostearate (1:1)

1. The DSC curve of Aceclofenac + Glyceryl Palmitostearate (1:1) stored at Room Temperature showed two endothermic event

- Between 51.72°C and 57.99°C (ΔH_{fusion} = -81.37J) (due to Glyceryl Palmitostearate)
- Between 128.53°C and 144.54°C (ΔH_{fusion} = -45.43J). (due to Aceclofenac)

This demonstrates that there are no remarkable alteration in thermo-analytical profile of Aceclofenac when stored with Glyceryl Palmitostearate

2. The DSC curve of Aceclofenac + Glyceryl Palmitostearate (1:1) stored at 40°C/75% RH for 12 days showed three endothermic event (split in the peak due to Glyceryl Palmitostearate)

- Between 49.82°C and 53.27°C (ΔH_{fusion} = -19.96J)
- Between 58.02°C and 62.43°C (ΔH_{fusion} = -16.6J)
- Between 131.55°C and 147.01°C (ΔH_{fusion} = -39.27J) (due to Aceclofenac)

This demonstrates that though the stress condition has affected the thermo-analytical profile of Glyceryl Palmitostearate, there are no remarkable

alteration in thermo- analytical profile of Aceclofenac when stored with Glyceryl Palmitostearate

3. The DSC curve of Aceclofenac + Glyceryl Palmitostearate (1:1) with 0.5% moisture stored at 40°C/75% RH for 12 days showed three endothermic event (split in the peak due to Glyceryl Palmitostearate)

- Between 51.19°C and 54.68°C (ΔH_{fusion} = - 24.03J)
- Between 58.85°C and 62.17°C (ΔH_{fusion} = - 16.6J)
- Between 136.6°C and 147.69°C (ΔH_{fusion} = - 45.53J) (due to Aceclofenac)

This demonstrates that though the presence of moisture and the stress condition has affected the thermo-analytical profile of Glyceryl Palmitostearate, there are no remarkable alteration in thermo-analytical profile of Aceclofenac when stored with Glyceryl Palmitostearate.

Aceclofenac + Sodium Stearyl Fumarate (1:1)

1. The DSC curve of Aceclofenac + Sodium Stearyl Fumarate (1:1) stored at Room Temperature showed four endothermic event.

- Between 56.65°C and 57.48°C (ΔH_{fusion} = - 2.978J)
- Between 94.96°C and 104.08°C (ΔH_{fusion} = - 117.6J)
- Between 229.16°C and 248.41°C (ΔH_{fusion} = -44.85J)
- Between 268.79°C and 274.30°C (ΔH_{fusion} = -17.97J)

This demonstrates that there is a shift in peak due to interaction between Aceclofenac and Sodium Stearyl Fumarate.

2. The DSC curve of Aceclofenac + Sodium Stearyl Fumarate (1:1) stored at 40°C/75% RH for 12 days showed four endothermic event

- Between 56.33°C and 58.33°C (ΔH_{fusion} = - 6.292J)
- 94.26ºC and 104.96ºC (ΔH_{fusion} = - 102.1J)
- Between 234.86°C and 248.37°C (ΔH_{fusion} = -34.58J)
- Between 269.52°C and 276.63°C (ΔH_{fusion} = -14.76J)

The thermo-analytical profile is similar to that of sample stored at room temperature.

This demonstrates that there is a shift in peak due to interaction between Aceclofenac and Sodium Stearyl Fumarate.

3. The DSC curve of Aceclofenac + Sodium Stearyl Fumarate (1:1) with 0.5% moisture stored at 40°C/75% RH for 12 days showed four endothermic event.

- Between 56.54°C and 57.65°C (ΔH_{fusion} = - 3.117J)
- 93.7ºC and 105.94ºC (ΔH_{fusion} = - 93.03J)
- Between 230.09°C and 250.38°C (ΔH_{fusion} = -63.83J)
- Between 270.19°C and 276.94°C (ΔH_{fusion} = -17.35J)

The thermo-analytical profile is similar to that of sample stored at room temperature as well as under stress condition. This demonstrates that there is a shift in peak due to interaction between Aceclofenac and Sodium Stearyl Fumarate.

Aceclofenac + Stearic acid (1:1):

The DSC curve of Aceclofenac + Stearic acid (1:1) stored at Room Temperature showed two endothermic event.

- Between 49.0°C and 69.8°C (ΔH_{fusion} = -17.6J) (due to Stearic acid)

- Between 151.55°C and 160.5°C (ΔH_{fusion} = -141.2J). (due to Aceclofenac)

This demonstrates that there are no remarkable alteration in thermo-analytical profile of Aceclofenac when stored with Stearic acid.

2. The DSC curve of Aceclofenac + Stearic acid (1:1) stored at 40°C/75% RH for 12 days showed two endothermic event

- Between 45°C and 65.8°C (ΔH_{fusion} = -14.8J) (due to Stearic acid)

- Between 145.12°C and 155.5°C (ΔH_{fusion} = -137.2J) (due to Aceclofenac)

This demonstrates that there are no remarkable alteration in thermo-analytical profile of Aceclofenac when stored with Stearic acid in accelerated stress condition.

3. The DSC curve of Aceclofenac + Stearic acid (1:1) with 0.5% moisture stored at 40°C/75% RH for 12 days showed three endothermic event

- Between 44.9°C and 62.8°C (ΔH_{fusion} = -16.2J) (due to Stearic acid)

- Between 99.3°C and 110.2°C (ΔH_{fusion} = -19.8J)

- Between 144.5°C and 156.8°C (ΔH_{fusion} = -139.2J) (due to Aceclofenac)

This demonstrates that though the presence of moisture and the stress condition has affected the thermo-analytical profile of Stearic acid, there are no remarkable alteration in thermo-analytical profile of Aceclofenac when stored with Stearic acid.

Formulation results:

Physical parameters of the tablet formulations are given in **Table 6.**

TABLE 6: PHYSICAL PARAMETERS OF TABLET

Sr. No.	Name of Product		Average weight (mg)	Diameter (mm)	Length (mm)	Width (mm)	Disintegration time (mins)
1	Aceclofenac Tablets 100 mg	Reference product	190.0	8.16	--	--	45.0 sec.
		Trial Batch (Tulip)	247.0	--	11.59	5.58	25.0 sec.
2	Aceclofenac 100 mg and Thiocolchicoside 4 mg Tablets	Reference product	225.0	9.0	--	--	6.0 mins, 12 sec.
		Trial Batch (Tulip)	185.8	8.18	--	--	1.0 mins,
3	Aceclofenac 100 mg and Thiocolchicoside 8 mg Tablets	Reference product	227.0	9.0	--	--	6.0 mins
		Trial Batch (Tulip)	245.9	--	11.62	5.62	2.0 mins, 21 sec.

Related Substances:

Contents of Diclofenac Impurity in trial batches and their respective reference product were given in **Table 7** and graphically represented in **Fig. 3.**

TABLE 7: CONTENT OF DICLOFENAC IMPURITY (%)

Sr. no.	Condition	Aceclofenac Tablets 100 mg		Aceclofenac 100 mg and Thiocolchicoside 4 mg Tablets		Aceclofenac 100 mg and Thiocolchicoside 8 mg Tablets	
		Trial Batch (Tulip)	Reference product	Trial Batch (Tulip)	Reference product	Trial Batch (Tulip)	Reference product
1	Initial	0.097	1.64	0.14	0.42	0.04	0.15
2	6M accelerated stability	0.43	5.71	0.45	2.8	0.22	0.52

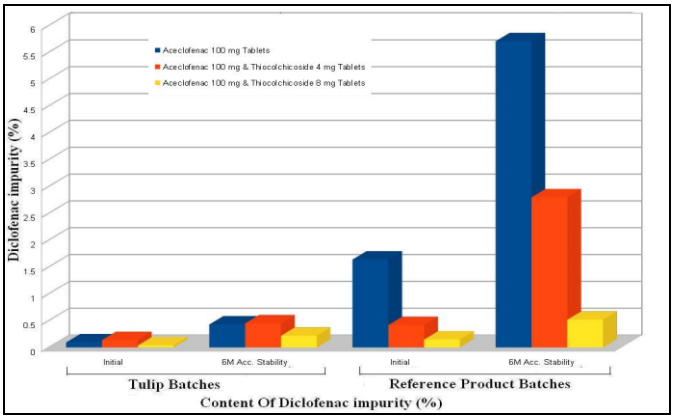


FIG. 3: CONTENT OF DICLOFENAC IMPURITY (%)

CONCLUSION: From the above thermoanalytical data it was concluded that Aceclofenac is incompatible with magnesium stearate and sodium stearyl fumarate. Aceclofenac is very susceptible to degradation to its analog diclofenac which is having many gastrointestinal side effects. Degradation of aceclofenac can be reduced by using specific method of manufacturing. Thiocolchicoside along with hydroxypropyl cellulose help in controlling the degradation of Aceclofenac and it acts as a barrier that inhibits degradation of Aceclofenac to its analog diclofenac. It was also proved that concentration of the thiocolchicoside have effect on the degradation of Aceclofenac, as concentration of the thiocolchicoside increases degradation of aceclofenac to diclofenac decreases.

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