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A Study on Fixed Dose Combination Tablets of Cytokine Inhibitor and Thiocolchicoside

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ABSTRACT

Fixed-dose combination drug products may be developed by a pharmaceutical company as a way to extend the marketability of a drug product. Since FDCs may be protected by patents, a company may obtain exclusive rights to sell the FDC, even though the individual active ingredients may be off-patent The World Health Organization (WHO) lists nearly 325 essential drugs, including only 19 of such drug combinations. Whereas, the national list of essential medicines has 354 essential drugs, including 14 drug combinations. FDCs available for the treatment of various ailments range from nutritional deficiency to cardiovascular diseases. Maximum FDC preparations comprise vitamins, cough suppressants, anti-diarrheal, iron preparations, antacids, analgesics and tonics**.** The cumulative % drug release was found that Trial No. 01 Thiocolchicoside in present in Fixed dose combination Aceclofenac and Thiocolchicoside in 0.1N HCl in first 10 minutes was 61% and the after 50 minutes 93 %., Trial No. 05 contained % drug release was found that Thiocolchicoside in present in Fixed dose combination Aceclofenac and Thiocolchicoside in 0.1 N HCl in first 10 minutes was 62% and the after 50 minutes 93 %, Trial No. 06 contained the percentage of Thiocolchicoside /tablet 99.60% and percentage of Aceclofenac / tablet 100.20%.

Keywords: Fixed-dose; Thiocolchicoside; Aceclofenac; FDCs; Antacids; Analgesics.

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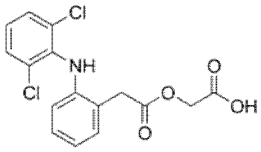
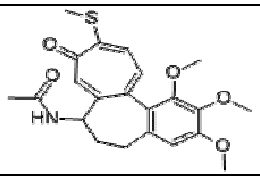
INTRODUCTION

A Fixed-Dose Combination (FDC) is a formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses. Fixed-dose combination drug products may improve medication compliance by reducing the pill burden of patients. Typically, fixed-dose combination drug products are developed to target a single disease (such as with antiretroviral FDCs used against AIDS). However, FDCs may also target multiple diseases, such as Caduet or EXFORGE. Caduet contains atorvastatin to treat hypercholesterolemia and amlodipine to treat hypertension. Since FDCs are reviewed by the Food and Drug Administration, the active ingredients used in the FDC are unlikely to exhibit adverse drug interactions with each other. However, FDCs may interact with other drugs that a patient is taking. While FDCs may reduce pill burden, there are some disadvantages.Enteric film should have an apparent pKa value between 4—6. At a pH two units below the pKa only 1% of the acid groups will be ionized and film will be poorly soluble in gastric fluid. When pH exceeds the pKa by two units the % of acid group approaches 100%. Ionization causes the charge repulsion with in the polymer leading to stretching of the polymer chain, water penetration into the dosage form, and disintegration in the intestine[1]. Healey (1989) states that the pH of empty stomach should be considered to be in region of 0.8 to 2.0 with variation due to food ingestion causing transient rises in the region of 4 to 5 or higher. The dissolution of the enteric coating depends on the intrinsic solubility's and pKa's of the drug and polymer and the medium properties[2]. The release rate of the drug is depending on the intrinsic solubility's and pKa's of drug and polymer, the medium properties, i.e., pH and buffer capacity, and a mass transfer coefficient. Explicit relationships between the release rates and all these factors are derived. Successful prediction of experimental data indicates that the model provides an adequate description of release from enteric-coated tablets.[3] Non-steroidal anti-inflammatory drugs, usually abbreviated to NSAIDs, are drugs with analgesic, antipyretic and anti-inflammatory effects - they reduce pain, fever and inflammation. The term "Non-steroidal" is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic. NSAIDs are sometimes also referred to as non-steroidal anti-inflammatory agents/analgesics (NSAIAs) or non-steroidal anti-inflammatory medicines (NSAIMs). The most prominent members of this group of drugs are aspirin, ibuprofen, and naproxen partly because they are available over-the-counter in many areas. Most NSAIDs are weak acids, with a pKa of 3-5. They are absorbed well from the stomach and intestinal mucosa. They are highly protein-bound in plasma (typically >95%), usually to albumin, so that their volume of distribution typically approximates to

plasma volume. The term "muscle relaxant" is used to refer to two major therapeutic groups: neuromuscular blockers and spasmolytics. Neuromuscular blockers act by interfering with transmission at the neuromuscular end plate and have no CNS activity. They are often used during surgical procedures and in intensive care and emergency medicine to cause paralysis.

MATERIAL AND METHODS

Table No: 1. DRUG PROFILE

NAME	ACECLOFENAC (Cytokine Inhibitor)	THIOCOLCHICOSIDE
CHEMICAL FORMULA	$C_{16}H_{13}C_{l2}NO_4$	$C_{27}H_{33}NO_{10}S$
MOLECULAR STRUCTURE		
PHYSICAL STATE	Solid	Solid
MOLECULAR WEIGHT	354.18472 g/mole	563.62 g/mole
COLOR	white crystalline	Yellow crystalline solid
SOLUBILITY	Partially insoluble in Water & Alcohol	Soluble in Water & Alcohol
THERAPEUTIC CATEGORY	Anti-inflammatory, analgesic	central acting muscle relaxant

Material Used:

Table No: 2. List of materials which are used for formulation of FDC tablet.

S.No.	Formulation Ingredients	Used As
1	Aceclofenac	Active pharmaceutical ingredient
2	Thiocolchicoside	Active pharmaceutical ingredient
3	Starch	Disintegrant
4	Microcrystalline Cellulose	Diluent
5	Sodium Methyl paraben	Binder
6	Sodium Propyl paraben	Binder
7	Starch	Binder
8	Polyvinyl Pyrrolidone K- 30	Binder
9	Talc	Glidant
10	Dicalcium phosphate	Glidant
11	Silicondioxide (Aerosil)	Lubricant
12	Sodium starch glycolate	Glidant
13	Magnesium stearate	Lubricant

METHODS FOR FORMULATION OF TABLETS

Wet granulation: is a process of using a liquid binder or adhesive to the powder mixture. The amount of liquid can be properly managed, and over wetting will cause the granules to be too hard and under wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvents.[4]

PROCEDURE

Step1: Weighing, Sifting/Dry Mixing: Weight & sifting the active ingredients& the diluents through sieve & Mix sifted material for 15 to 20 minutes. **Step2:** Binder solution preparation**:** The purified water is added with preservative & dissolves with stirring & heating. Add binder in this with stirring, leave it to soak completely. **Step3:** The purified water is added in diluents with stirring to form starch slurry. Heat binder solution up to boiling temperature & add diluents slurry to it with stirring to form binder solution. **Step4: Granulation**: Granulate the dry mix by adding binder solution.**Step5: Drying the granulation. Step6: Dry screening**: After the granules are dried, pass through a screen of smaller size than the one used for the wet mass to select granules of uniform size to allow even fill in the die cavity. **Step7: Lubrication**: A dry lubricant, the taste masking agent, glidant & disingredient added to the granules either by dusting over the spread-out granules or by blending with the granules. Its reduces friction between the tablet and the walls of the die cavity. **Step8: Compression:** The lubricated granules were compressed by using 8mm round concave plane punches.

EXPERIMENTAL WORK

- **Preparation of 0.1 N HCl:** 8.5 ml of concentrated HCl GR was added slowly to about 200 ml of distilled water with constant stirring. Final volume was made up to 1000 ml with distilled water to get 0.1 N HCl.
- **Preparation of standard stock solution:** 100 mg of NSAID drug was weighed accurately and transferred to 100 ml of volumetric flask containing pH 6.8 phosphate buffer solution, sonicated it for 10 minutes. Volume was adjusted up to 100 ml by the same buffer.
- **Determination of analytical wavelength:** For selection of λ_{max} a working solution of 20 µg/ml was prepared and scanned over complete UV range (i.e.200-400nm) using UV1700 Pharmaspec Shimadzu -Visible spectrophotometer. Then according to sensitivity broad range of different dilution i.e. 4, 8, 12, 16, 20, 24, 28µg/ml was prepared and scan for UV range. λ_{max} were observed and regression coefficient (R^2) was calculated.[5,6]

FORMULATION TRIALS CHART

Table: 3. Comparative Formulation Ingredients for all 6 Formulations (All quantities are indicated in mg)

S.NO.	Ingredients	F1	F2	F3	F4	F5	F6
1	Aceclofenac	100	100	100	100	100	100
2	Thiocolchicoside	8	8	8	8	8	8
3	Starch	45.84	45.84	45.84	42.3	42.3	42.3
4	Microcrystalline Cellulose	12	12	12	15	15	15
5	Sodium Methyl paraben	0.12	0.12	0.12	0.14	0.14	0.14
6	Sodium Propyl paraben	0.04	0.04	0.04	0.06	0.06	0.06
7	Polyvinyl Pyrrolidone K- 30	3	3	3	3.5	3.5	3.5
8	Starch	5	5	5	5	5	5
9	Dicalcium Phosphate	3	3	3	3	3	3
10	Sodium starch Glycolate	4	4	4	4	4	4
11	Talc	5	5	5	5	5	5
12	Aerosil	3	3	3	3	3	3
13	Magnesium stearate	3	3	3	3	3	3
14	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
15	Average weight of Tablet	200	200	200	200	200	200

EVALUATION OF FORMULATION

Uniformity of weight: Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of twenty tablets were calculated. The batch passes the test for weight variation if not more than two of the individual weight of tablet deviate from the average weight by more than the % shown in table and none deviate by more than twice the % shown.[7]

Table No: 4. Allowable limit for weight variation

Average weight of tablet (X mg)	Percentage deviation
X≤ 130 mg	10
130< X <324 mg	7.5
X≥324 mg	5

Average weights of Tablets: Dedust the twenty tablets. Weigh accurately and note down the weights of twenty tablets. Calculate by the formula:

$$\text{Average weight} = \frac{\text{Weight of 20 tablets}}{20}$$

Hardness Test: Hardness was measured using Pfizer hardness tester. For each batch three tablets were tested. Select five tablets randomly, place one tablet at a time in the hardness tester, which is already set to 0.Apply pressure by pressing the start button of hardness tester apparatus, till the tablet breaks. Note down the reading on the tester i.e. the hardness of the tablet in Newtons. Take the average of five such tablets and calculate the average hardness of the tablet.

Friability Test: is performed to assess the effect of friction and mechanical shocks, which may often cause tablet to chip, cap, laminate or break. Roche friabilator is generally used for the purpose. This device subjects the tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a distance of 6 inches with each revolution. Pre weighed tablets weighing equivalent to 6.5 gm are placed in the friabilator, which is then operated for 100 revolutions. Tablets are dedusted and reweighed.[8]

Friability is expressed in percentage (%). If the initial weight of the tablets is (W_O) and the weight of tablets after the test is (W) then % friability can be calculated by,

$$\% F = \{1- (W/Wo)\} \times 100$$

Where, % F = Friability in %

Thickness Test: Three samples were selected randomly from each batch and thickness was measured using Verniercalliper**.**

Disintegration Test: The disintegration time was measured by using USP disintegration test apparatus. Six tablets were placed in the tubes and the basket was kept positioned in a 1-litre beaker of water maintained at 37 ± 2^0C. The tablets remained 2.5 cm from the bottom of water. A standard motor driven device moves the basket containing tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. When all six tablets have disintegrated, time is noted.

Dissolution Test: In vitro dissolution testing of oral dosage forms is an important tool, not only to assure product uniformity, but also to screen and optimize formulation during product development. It

is used as an indirect measurement of drug availability, especially in preliminary assessments of formulation factors and manufacturing methods that are likely to influence bioavailability. Stressed conditions are encouraged in the latter case to detect possible critical formulation variables. The objectives in the development of in vitro dissolution tests are to show that the release of the drug from the dosage form is as close as possible to 100 % and that the rate of drug release is uniform from batch to batch.[9,10,11]

USP Apparatus: II paddle

As per USP Dissolution parameters Dissolution Medium	: Water 900ml
Apparatus	: USP Type II (Paddle type)
Speed	: 100 rpm
Time point	: 10, 20,30,40,50 minutes
Temperature	: 37°C
Wavelength	: (A) 275 nm ,(B)370 nm

For Drug Aceclofenac (A) and Thiocolchicoside (B)

Acid Stage:

Temperature	: 37ºC ± 0.5º
Speed	: 100 RPM
Medium	: 0.1 N HCl
Volume	: 900 ml
Recommended sampling Points	: 10, 20, 30, 40, 50 minutes.

Standard preparation

Weigh accurately about 30mg of drug working standard into 50ml volumetric flask. Add 30 ml of methanol, sonic ate to dissolve and dilute to volume with methanol. Further dilute 1.0ml of this solution to 100ml with dissolution medium. Transfer one tablet into each vessel containing 900ml of water. Determine the amount of drug released, by estimating the drug using the method given bellow: Estimation of Drug dissolved :(By UV/VIS spectrophotometer)

Test Aliquots: After completion of specified time intervals of Dissolution test, remove the aliquots and filter. Further dilute 2 ml of these aliquots to 50 ml with water. Measure the absorbance of the resulting solution at the maximum at about 275 nm for Aceclofenac and 370 nm Thiocolchicoside using water as a blank.[12, 13]

Calculate the content by using the following formula.

$$\% \text{ of drug Released} = \frac{A_T \quad W_{std} \quad 1 \quad 900 \quad 50 \quad P}{As \quad 50 \quad 100 \quad L.C \text{ (in mg)} \quad 2 \quad 100} \quad 100$$

Here- $A_{T:}$ Absorbance of test, As: Absorbance of standard , $W_{std:}$ weight of standard, L.C: label claim of tablet, P: Potency of drug.

ASSAYS BY HPLC

Aceclofenac and Thiocolchicoside

Reagents Used:

1) HPLC grades water (Milli Q or equivalent)

2) Methanol (HPLC grade)

- **Buffer preparation (pH3.0):** Weigh accurately 13.6 g of Sodium acetate dissolved in one liter of water.
- **Mobile phase**: Prepare a mixture of 400 volume of buffer and 600 volume of methanol. Filter and degas before use.
- **Standard Preparation (A):** Weigh accurately about 50 mg of Thiocolchicoside dissolved and dilute with 100 ml of mobile phase.
- **Standard Preparation (B):** Weigh accurately about 75 mg of Aceclofenac dissolved and dilute with 25 ml of mobile phase. Solution C: Taken solution (**A)** 2.5 ml and 5.0 ml solution (**B)** diluted with 50 ml mobile phase.

Sample preparation: Taken a powder sample equivalent to 300 mg of Aceclofenac and 25 mg Thiocolchicoside, add mobile phase, and sonic ate for 5 minutes and make up to 100 ml with mobile phase. In this solution, taken 5 ml diluted with mobile phase 50 ml. [14] separately inject 20 micro l of the assay preparation into the liquid Chromatography and record the chromatogram. Measure the peak response for major peak. Calculate the quantity of Aceclofenac and Thiocolchicoside in % from the mean peak areas of standard and Assay preparation and potency of working standard used.[15, 16]

Calculation for Thiocolchicoside:

$$\% \text{ of drug in tablet} = \frac{Ru}{Rs} \times \frac{Wstd}{100} \times \frac{2.5}{50} \times \frac{50}{spl.wt} \times \frac{100}{5} \times \frac{P}{L.C} \times Avg.Wt\ (mg)$$

Here- Ru/Rs: Peak response ratios of Thiocolchicoside to the internal standard obtained from the assay (sample) preparation and standard preparation, respectively. $W_{stand:}$ Weight of Standard preparation in mg, Spl.wt: Weight of Sample preparation in mg, L.C.: Label claim of Thiocolchicoside in mg, P: Potency of Thiocolchicoside working standard in %, Avg.wt. : Average weight of tablet.

Calculation for Aceclofenac :

$$\% \text{ of drug in tablet} = \frac{Ru \quad W_{std} \quad 5 \quad 50 \quad 100 \quad P}{Rs \quad 100 \quad 50 \quad spl.wt \quad 5 \quad L.C} \text{ Avg. Wt (mg)}$$

Here- Ru/Rs: Peak response ratios of Aceclofenac to the internal standard obtained from the assay (sample) preparation and standard preparation, respectively. W_{stand}: Weight of Standard preparation in mg, Spl.wt: Weight of Sample preparation in mg, L.C.: Label claim of Aceclofenac in mg, P: Potency of Aceclofenac working standard in %, Avg.wt. : Average weight of tablet.

DRUG IDENTIFICATION TEST

FT-IR spectrum of pure drug: The infra red spectrum of Thiocolchicoside and Aceclofenac are taken and which is compared with the reference spectra of Thiocolchicoside and Aceclofenac. The functional group value of Thiocolchicoside and Aceclofenac is observed closer to the reference infra red spectra value of Thiocolchicoside and Aceclofenac. FT – IR is used to determine the degradation of the active compound in polymeric carrier system. The surface of the granules is investigated measuring alternated total reflectance. The IR beam passing through the ATR cell reflected many times through the sample to provide IT spectra mainly of surface materials. The FT – IR indicated that no chemical interaction between drug and excipients. It is also confirmed the stability of drug during compressed of the tablets.

DIFFERENTIAL SCANNING COLORIMETER

Differential Scanning analysis measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. It is a micro technique and depends on the thermal equilibration within the sample. Significant variables in these methods include sample homogeneity, sample size, particular size, and heating rate sample atmosphere. **Application** - It is used to determine drug degradation, compatibility of excipients with drug analysis of coating and polymorphism, moisture content and characterization of drug loaded microcapsules. **Procedure:** The instrument works on the temperature control of two similar specimen holders assembly. In its left half, there is a circuit for differential temperature control while in its right half there is a circuit for average temperature control. In the average temperature control circuit. Signals representing the temperatures

of the sample and reference are compared. If no reaction is taking place in the sample and reference heater is almost zero. However if a reaction is taking place a differential power is fed to the heaters. A signal proportional to this differential power is transmitted to the recorder pen. The integral of the peak so obtained gives the internal energy change of the sample.

RESULTS AND DISCUSSION

DRUG RELEASE PROFILE OF ACECLOFENAC IN ACECLOFENAC AND THIOCOLCHICOSIDE

Table No: 5 Comparative dissolution data of Aceclofenac (F1-F6). Aceclofenac 100 mg and Thiocolchicoside 8 mg tablet

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
10	60	58	60	62	63	65
20	68	67	68	70	71	71
30	71	70	72	83	84	84
40	85	84	86	89	91	91
50	90	90	92	92	94	95

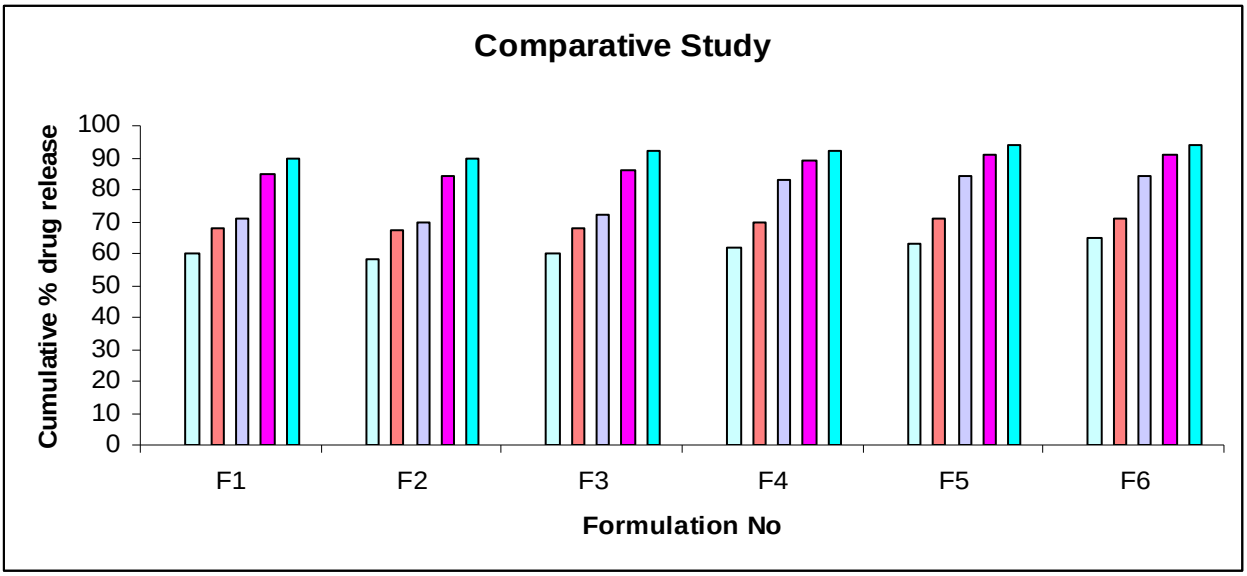


Figure No 1: Comparative dissolution data of Aceclofenac (F1-F6). Aceclofenac 100 mg and Thiocolchicoside 8 mg tablet

Table No: 6 Comparative dissolution data of Aceclofenac (F1-F6). Drug release profile of Thiocolchicoside in Aceclofenac and Thiocolchicoside

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
10	61	60	58	61	62	63
20	68	68	66	65	68	68
30	72	71	70	72	75	76
40	86	86	75	87	89	89
50	91	91	90	93	93	94

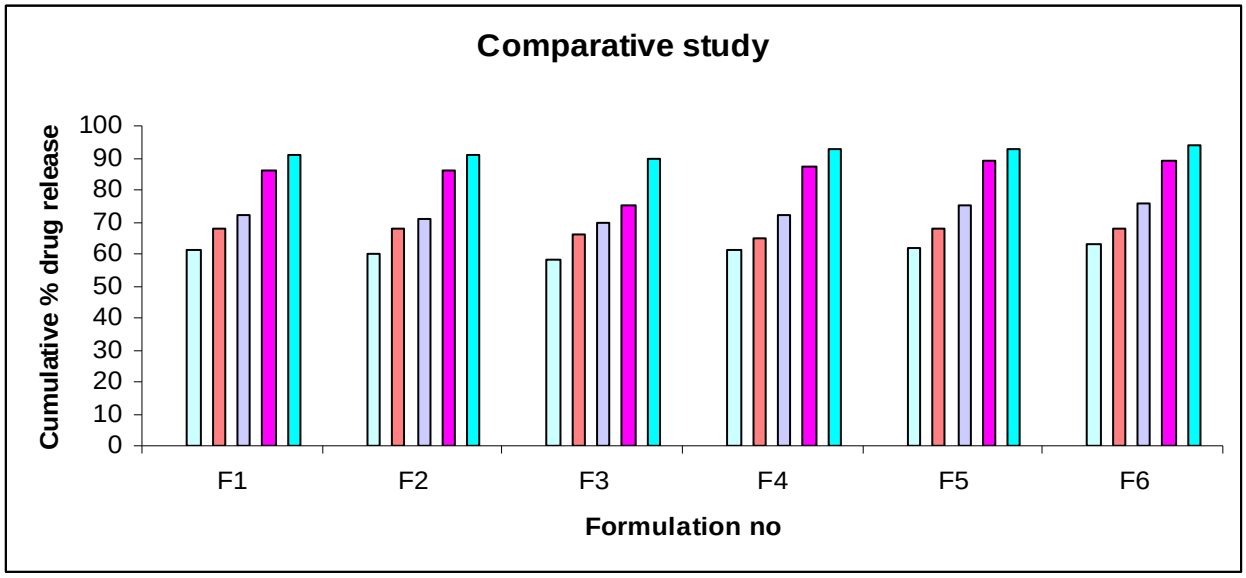


Figure No: 2. Comparative dissolution data of Thiocolchicoside (F1-F6)

FT-IR spectrum of pure drug:

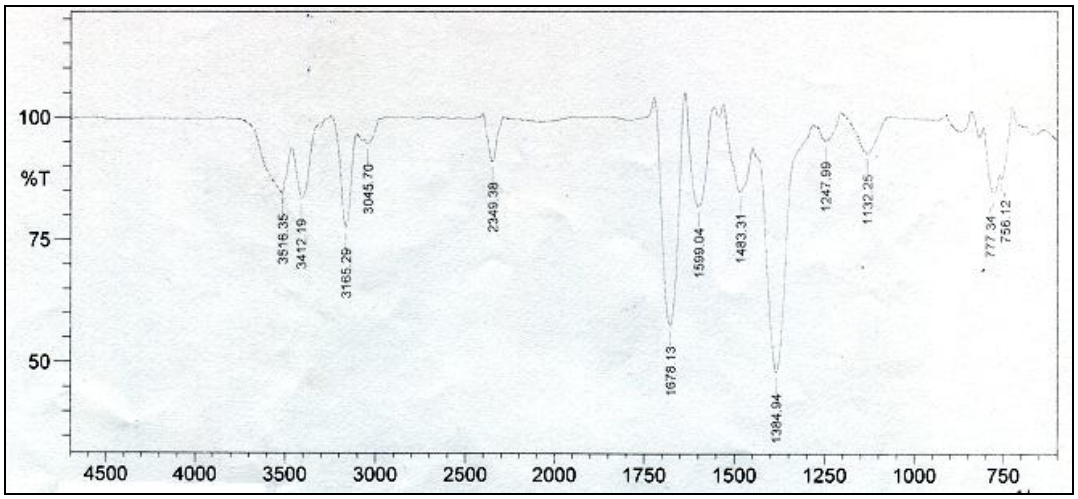


Figure No.3: Graph showing the FT-IR spectrum of Thiocolchicoside drug

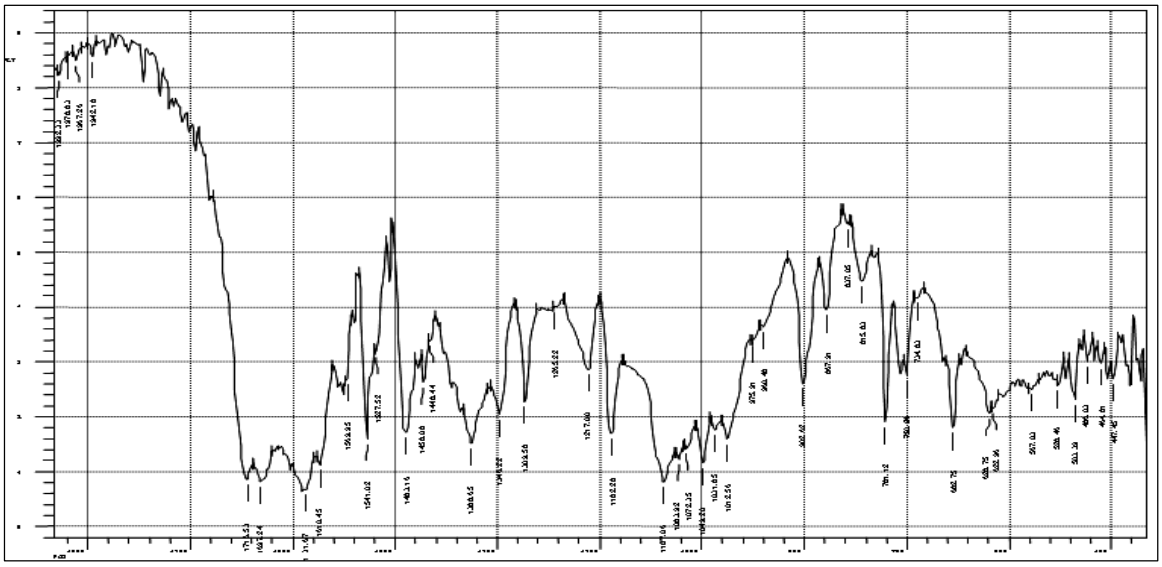


Figure No.4: Graph showing the FT-IR spectrum of Aceclofenac

DIFFERENTIAL SCANNING COLORIMETER

For checking the melting point of pure Thiocolchicoside drug, DSC is taken and is observed near about the 194^{0}C.

For checking the melting point of pure Aceclofenac drug, DSC is taken and is observed near about the 150 ^{0}C.

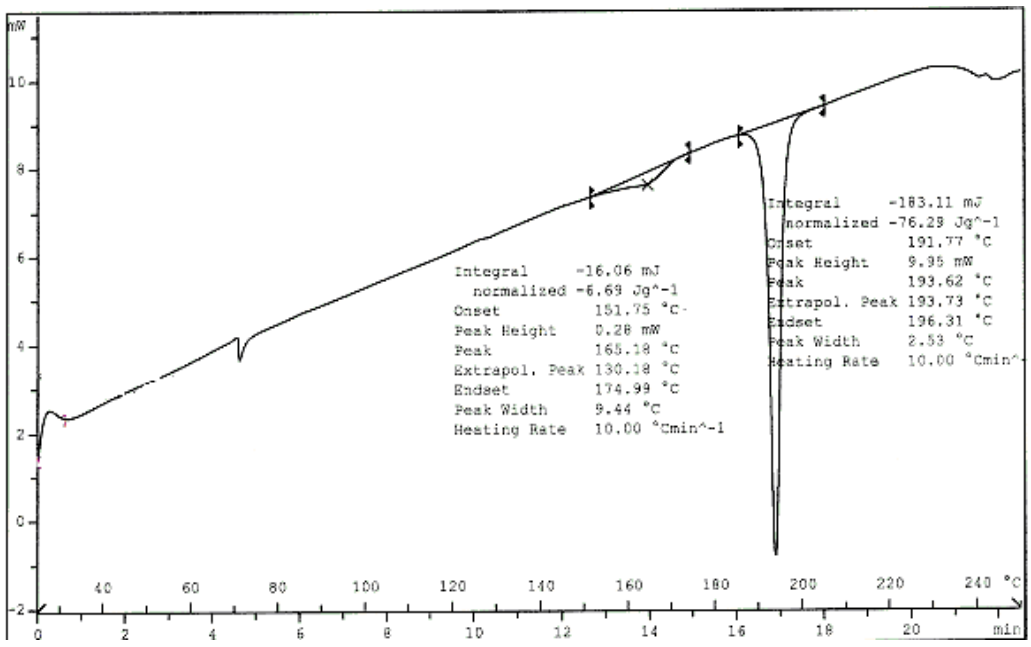


Figure No 5: Graph showing the DSC of Thiocolchicoside drug

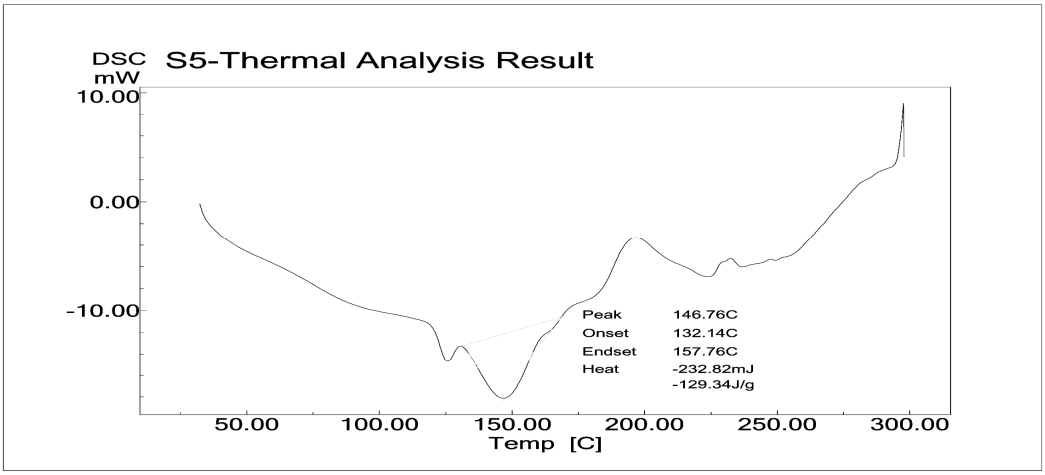


Figure No 6: Graph showing the DSC of Aceclofenac drug

Calibration Curve – Standard Graph

50 mg of standard drug was accurately weighed and transferred to a 50 ml of volumetric flask. To this small quantity of methanol is used and kept for sonication for dissolving the drug, then make up the volume up to 50ml with same solvents. This solution was considered as stock solution of 1000 mcg/ml. From the stock solution 10 ml solution was pipette out to 100 ml of volumetric flask and make up the volume up to 100 ml with Millipore water and this solution considered as a 100 mcg/ml solution of drug. From this solution pipette out 1, 2, 3, 4, and 5ml to each 10 ml of volumetric flask and make up the volume up to 10 ml with Millipore water and these all solution was considered as a 10, 20, 30, 40, and 50 mcg/ml of drug solution. Measure the absorbance at specific in UV/VIS Spectrophotometer. Graph is plotted as Concentration vs. Absorbance and determined the Regression coefficient i.e. $R^{2.}$

Table No: 7. Table Showing the Standard value of Aceclofenac

S.No.	Concentration mcg/ml	Absorbance
1	10	0.253
2	20	0.51
3	30	0.754
4	40	1.02
5	50	1.253

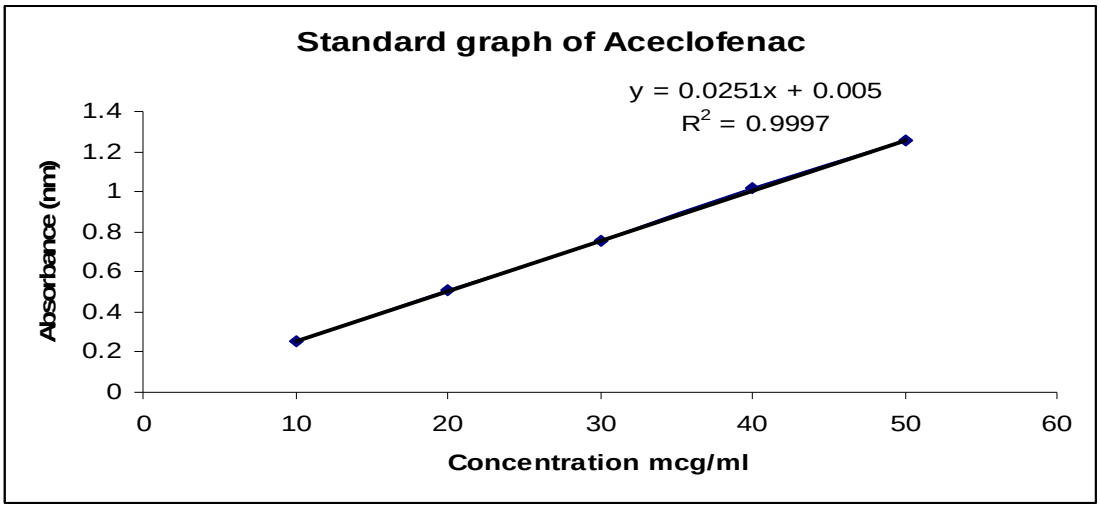


Figure No 7: Standard Graph of Aceclofenac

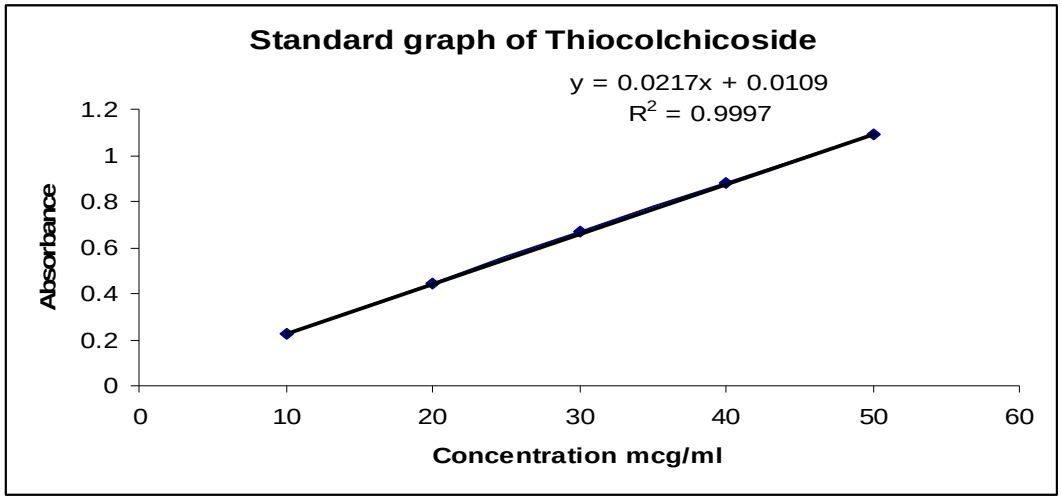


Figure No 8: Standard Graph of Thiocolchicoside

Table No: 8. Table Showing the Standard value of Thiocolchicoside

S.No.	Concentration mcg/ml	Absorbance
1	10	0.225
2	20	0.441
3	30	0.671
4	40	0.878
5	50	1.09

The granules of drug were prepared and they are carried out for different physical Characterization of Drug as shown in table.

Table No: 9. Table Showing the Physical Characterization of Drug and Granules of it for all 6 formulation trials

S.No.	Formulation No.	Bulk Density gm/ml	Tap Density gm/ml	Compressibility Index %	Hausner Ratio
1	F1	0.31	0.428	27.52	1.38
2	F2	0.31	0.435	27.58	1.38
3	F3	0.4	0.485	20.67	1.18
4	F4	0.39	0.44	21.36	1.12
5	F5	0.24	0.327	26.6	1.36
6	F6	0.31	*0.42*	*25.01*	*1.33*

Prior to formulation of granules, the active drug undergoes preformulation studies. In the preformulation studies of active drug, evaluate the physical characterization parameters such as its melting point, Infra Red spectrum of active drug and also parameters like its bulk density, tap density, compressibility Index and Hausner Ratio. After the formulation of granules of drug from all the respective batches, the granules are analyzed for their density parameter such as bulk density, tap density, compressibility index and Hausner Ratio.

Quality Control Parameters

After the compression of granules for all 6 formulation trials, it is necessary to check the post compression parameters such as Tablet Hardness (N), Tablet thickness (mm) and % Friability for all 6 formulation trials. The all post compression parameters are indicated in the table No. 10.

Table No: 10. Table showing the post compression parameters for all 6 formulation trials of tablets.

S.No.	Formulation No.	Tablet Diameter (mm)	Hardness (kg/cm^2)	Tablet Thickness (mm)	Friability %
1	F1	8.05	5	3.33	0.862
2	F2	8.02	4.5	3.32	0.835
3	F3	8.05	4.5	3.33	0.621
4	F4	8	5	3.34	0.102
5	F5	8.03	5	3.34	0.103
6	F6	8.02	5	3.32	0.098

CONCLUSION

In trail no 1 the capping occurs and flow property is not proper so trial no 1 is fail. In trail no 2 friability , compressibility index % does not pass the test and flow property is not proper so trial no 2 is fail. In trail no 3and 4 the disintegration time is more and hardness is also high due to high compression . In trail no 5and 6 pass the all test but trial no 5 disintegration time and friability is high compare to trial no 6. The Assay of Formulation Trial No. 06 contained the percentage of Thiocolchicoside /tablet 99.60% and percentage of Aceclofenac / tablet 100.20%. Trial no 6 pass the all test so trial no 6 is the best formulation.

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