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RESEARCH ARTICLE

# Formulation Development and Evaluation of Bi-Layer Tablet Containing Acetaminophen and Aceclofenac Layer by Solid Dispersion Technique

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## ABSTRACT

The objective of the study was to formulate bilayer tablets consisting of Acetaminophen and aceclofenac for immediate drug release. Bilayer tablets were prepared by using granules of Acetaminophen and solid dispersion of aceclofenac. Granules of Acetaminophen were prepared by wet granulation technique by using sodium starch glycolate (SSG) as super disintegrant, and sodium lauryl sulphate (SLS) used as surfactants to promote drug release in solid dispersion of aceclofenac. Bilayer tablets were evaluated for hardness, friability, weight variation, thickness and drug content uniformity and subjected to in vitro drug release studies. The amount of Acetaminophen and aceclofenac released at different time intervals were estimated by HPLC method. The bilayer tablets showed no significant change either in physical appearance, drug content or in dissolution pattern after storing at 40 °C/75% relative humidity (RH) for 3 months. Dissolution results of the entire tablet were analyzed with dissolution efficiency (% DE). These results indicated that release of the drug from the tablet was increased by content of super disintegrants and surfactants in solid dispersion technique.

## KEYWORDS

Acetaminophen, Aceclofenac, bi layer tablet, dissolution comparison.

## INTRODUCTION

Bilayer tablets concept has long been utilized to develop both immediate release and sustained release formulation. Immediate release bilayer tablets generally contain two layers for two drugs. After administration such a bilayer tablet breaks down into granules and small fragments that facilitate dissolution by increasing the surface area for both the drug. But many existing drugs are poorly soluble and they do not dissolve quickly in GIT. These poorly soluble compounds lead to poor bioavailability, high intra- and inter-subject variability and lack of dose proportionality[1].

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Aceclofenac, a widely prescribed anti inflammatory analgesic drug belongs to BCS class II and exhibit low and variable oral bioavailability due to its poor solubility and dissolution rate. Achieving higher dissolution rate is a key factor in its formulation development especially solid dosage forms like tablets[2]. Aceclofenac is practically insoluble in water with good permeability (calculated log P = 2.170) and belongs to biopharmaceutics classification system (BCS) class II (low solubility, high permeability)[3]. Aceclofenac in combination with acetaminophen is now available in the market and indicated in pain, fever etc. Comparative dissolution study with some brands revealed that tablets containing acetaminophen and aceclofenac released

acetaminophen easily but high intra- and inter-subject variability in aceclofenac release was observed. This is due to the low water solubility of aceclofenac. So in this study initiative was taken to design bilayer tablets of Acetaminophen and aceclofenac by using sodium starch glycolate as super disintegrant, and sodium lauryl sulphate as surfactants to promote drug release[4].

Acetaminophen is one of the most popular over-the-counter drugs. It has analgesic and antipyretic properties with weak anti-inflammatory activity and it is used in the symptomatic management of moderate pain and fever. When taken at recommended doses it has an excellent safety profile. It is available in different dosage forms: tablet, capsules, drops, elixirs, suspensions and suppositories[5]. Acetaminophen is often prescribed with aceclofenac for greater patient acceptability, increased potency, multiple activity, fewer side effects and quick relief [6].

## MATERIALS AND METHOD

### Materials

Table 1: List of ingredients used in experiment

| Name of the material | Justification |
|---|---|
| Acetaminophen | Active Ingredient |
| Aceclofenac | Active Ingredient |
| Avicel PH 101 Grade | Diluent |
| Povidone K-30 | Binder |
| Sodium Lauryl Sulphate | Surfactant |
| Sodium Starch Glycolate | Disintegrant |
| Magnesium Stearate | Lubricant |
| Aerosil-200 | Glidant |

Table 2: List of Reagents and Solvents used in experiment

| Name | Source | Country of Origin |
|---|---|---|
| Potassium Dihydrogen orthophosphate | E. Merck | Germany |
| Sodium Hydroxide | E. Merck | Germany |
| Distilled Water | Research Laboratory of The University of Asia Pacific | Bangladesh |
| Methanol | E. Merck | Germany |

Table 3: List of machine & apparatus used in the experiment

| Name | Source | Country of origin |
|---|---|---|
| UV-Visible Spectrophotometry | Shimadzu Corporation. | Japan |
| USP Type II Dissolution Apparatus. | VEEGO | India |
| Electronic balance | Shimadzu Corporation. | Japan |
| Hot Air Oven | Binger | Germany |
| PH meter Cyberscan500$^{pH}$ | Eutech Instruments Ltd. | Singapore |
| Double rings Filter paper | Hangzhou Xinhua paper industry co. Ltd. | China |

| | | |
|---|---|---|
| KBr Hydraulic Press, Mogel M-15 | Technosearch Instruments. | India |
| VTAP/ MATCO-II, | VEEGO | India |
| Automatic Tablet Hardness Tester (8M) | Dr Schleunider | Switzerland |
| Friabilator (VFT-2) | VEEGO | India |
| Tablet Disintegration Test Apparatus | VEEGO | India. |

**Preparation and Composition of Bilayer Tablet**

***Preparation of Acetaminophen Granules***

Granules of Acetaminophen were prepared by using wet granulation technique. The composition of granules is summarized in Table-4 Calculated amount (required to prepare a 50 tablet batch) of the drug was mixed with excipients thoroughly[7]. Povidone solution was added slowly and mixed. When enough cohesiveness was obtained, the granules were dried at 60°C for 2 hours in a tray dryer and there after kept in desiccators for 24 hours at room temperature. The LOD of the granules was kept between 2.5 to 3.0%. The dried granules were collected and screened through a #20 mesh sieve. Granules were blended with magnesium stearate and aerosil-200 separately prior to compression

***Preparation of Solid Dispersion of Aceclofenac***

Solid dispersion of aceclofenac was prepared by solvent evaporation method using sodium lauryl sulphate as a carrier. The SD was prepared at weight ratio of 1:1, 1:3 and 1: 5 (drug: carrier). In this method, the required amount of drug was taken in a beaker and then methanol added gradually until transparent solution was formed and then sodium lauryl sulphate was dissolved in this solution, which was evaporated[8]. After solvent evaporation the SD of Aceclofenac and SLS was stored in a screw-cap vial at room temperature and kept in a desiccator for further use. The main advantage of the solvent evaporation method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents[9].

Table 4: Composition of Acetaminophen Part (mg/tablet)

| **Ingredients** | **F1** |
|---|---|
| Acetaminophen BP | 500 |
| Microcrystalline Cellulose (Avicel PH 101) BP | 54 |
| Povidone (K-30) BP | 15 |
| Methylparaben BP | 1 |
| Sodium Starch Glycollate BP | 10 |
| Colloidal Anhydrous Silica (Aerosil-200) BP | 3 |
| Magnesium Stearate BP | 6 |

Table 5: Composition of Aceclofenac Part

| **Ingredients** | **F1 (mg) SD 1:1** | **F1 (mg) SD 1:3** | **F1 (mg) SD 1:5** |
|---|---|---|---|
| Aceclofenac | 100 | 100 | 100 |
| Sodium Lauryl Sulphat0065 | 100 | 300 | 500 |
| methanol | 7.5 | 12 | 15 |

**Compression of Bi-layer Tablets**

Acetaminophen layer was compressed first followed by aceclofenac layer. The quantity of granules for the Acetaminophen part was compressed lightly using 13 mm-diameter die of an infrared hydraulic press. Over this compressed layer, required amount of solid dispersion of aceclofenac was placed and compressed with a compression force of 4 ton to obtain hardness in the range of 180-220 N. All compressed tablets were stored in an airtight container at room temperature for further study [10-11].

Figure 1: Prepared Bi-layer Tablet containing Acetaminophen layer and Aceclofenac layer

**Evaluation of Physical Parameters of Granules**

***Bulk Density***

Loose Bulk Density (LBD) and Tapped Bulk Density (TBD) were determined by Digital Automatic Tap Density Test Apparatus (Vegoo, VTAP/ MATCO-II, India). 2 g of powder from each formula (previously lightly shaken to break any agglomerates formed) were taken into a 10 ml measuring cylinder. After the initial volume was observed, the equipment was on and the cylinder was allowed to fall under its own weight onto a hard surface. The reading of tapping was continued until no further change in volume was noted. Using the following equation LBD and TBD was calculated:

LBD = Weight of the powder / volume of the packing.

TBD = Weight of the powder / Tapping volume of the packing

***Compressibility Index***

The compressibility index of the granules was determined by Carr's compressibility index

Carr's index (%) = {(TBD – LBD) X 100}/TBD

***Angle of Repose***

Funnel method was used to measure the angle of repose of granules. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

Angle of Repose $\theta = \tan^{-1} h/r$

Where, h = Height of the powder cone.

r = Radius of the powder cone.

***Uniformity of Weight***

20 tablets from each of the formulation were weighed individually with an analytical weighing balance (Model: AY-200, SHIMADZU Corporation, Japan). The Average weights for each formulation as well as the percentage deviation from the mean value were calculated. The same procedure was also applied to evaluate each of the market products.

***Hardness Test***

Automatic Tablet Hardness Tester (8M, Dr Schleunider, Switzerland) was used to determine the crushing strength. 6 tablets were randomly selected from each formulation and the pressure at which each tablet crushed was recorded. The same procedure was also applied to determine the hardness of the market products.

***Disintegration Test***

2 tablets from each brand were employed for the test in distilled water at 37°C using Tablet Disintegration Tester (Model: VDT-2, Veego, India). The disintegration time was recorded as the time required passing the tablet completely

through the sieve and no particle remained on the basket of the system.

***Dissolution Test***

The dissolution test was undertaken using tablet dissolution tester, apparatus 2 (TDT-08L, Veego, India) in 5 replicates for each brand. Aceclofenac is soluble in phosphate buffer pH 6.8. So USP buffer solutions at pH 6.8 (phosphate buffer solution) was used as dissolution media. The medium was maintained at 37 ± 0.5°C. In all the experiments, 5 ml of dissolution sample was withdrawn at 2, 5, 10, 20, 30, and 40 min and replaced with equal volume to maintain sink condition. Samples were filtered and assayed by RP-HPLC method. The concentration of each sample was determined from a calibration curve obtained from pure samples of acetaminophen and aceclofenac.

***Kinetic Modeling of Drug Release***

The dissolution profile of all the batches was fitted to zero order, first-order, Higuchi and Korsmeyer to ascertain the kinetic modeling of drug release. After linear transformation of dissolution curves, the results were tested with the following mathematical models

**Zero Order Plot:** The Zero order equation assumes that drug release is constant[12]:

$$M = M_o - K_o t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

In this equation,

M = the amount of drug remaining undissolved at time t

$M_o$ = the amount of drug undissolved at t=0 and

$K_o$ = the corresponding release rate constant.

Zero order plot of drug release is obtained by plotting percent release of drug versus time in hour.

**Higuchi Plot:** A form of the Higuchi Square Root Law is given by equation[13]:

$$Q = K_H \sqrt{t} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (II)$$

Where, Q= (Q = 100 - M) is the amount of drug dissolved at time t and

$K_H$ = the corresponding rate constant.

Higuchi plot of this impact that is obtained by plotting percent release of drug versus square root of time.

**First Order Plot:** Release behavior generally follows the following first order release equation[14]:

$$\text{In } M = \text{In } M_o - K_1 t \quad \ldots\ldots\ldots\ldots\ldots\ldots (III)$$

Where, M = the amount of drug undissolved at time t,

$M_o$ = the amount of drug undissolved at t=0 and

$K_1$ = the corresponding release rate constant.

Log % remaining is plotted as a function of time to demonstrate the first order release profile.

**Korsmeyer Plot:** The Korsmyer's equation is[15]:

$$M_t / M_\alpha = K_k t^n \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (IV)$$

Where $K_k$ = the Korsmeyer release rate constant

n = the diffusion exponent.

Log fraction release as a function of log of time (hour) gives the Korsmeyer release pattern from various formulations of bilayer tablets.

***Preparation of Phosphate Buffer Solution pH 6.8***

6.805 grams of potassium dihydrogen phosphate and 1.5 grams of sodium hydroxide were dissolved in 1 liters of distilled water.

***Preparation of Standard Curve***

An accurately weighed quantity of 100 mg of Aceclofenac was transferred to clean and dried 100 ml standard flasks. It is dissolved in 100 ml phosphate buffer pH – 6.8. From this primary stock solution, 10 ml was pipette out, transferred into a separate standard flask and diluted to 100 ml with phosphate buffer pH – 6.8. From this secondary stock solution, 1ml, 2ml, 3ml, 4ml, 5ml, 6ml, 7ml, 8ml, 9ml, and 10ml were pipette out and diluted up to 10ml with phosphate buffer pH 6.8 to give a concentration of 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20µg/ml. The absorbance of the resulting solutions were measured at 273nm using the buffer solutions blank by UV-

spectrophotometer. A calibration curve was drawn by plotting absorbance and concentration of drug. This standard curve was used to estimate the concentration of the drug released from the solid dispersion formulations of aceclofenac.

## RESULTS AND DISCUSSION

Table 6: Concentration and Absorbance of Aceclofenac for preparation of Standard Curve.

| SL. No. | Concentration (µg/ml) | Absorbance (273 nm) |
|---|---|---|
| 1 | 2 | 0.049 |
| 2 | 4 | 0.086 |
| 3 | 6 | 0.139 |
| 4 | 8 | 0.198 |
| 5 | 10 | 0.246 |
| 6 | 12 | 0.298 |
| 7 | 14 | 0.341 |
| 8 | 16 | 0.401 |
| 9 | 18 | 0.456 |
| 10 | 20 | 0.501 |

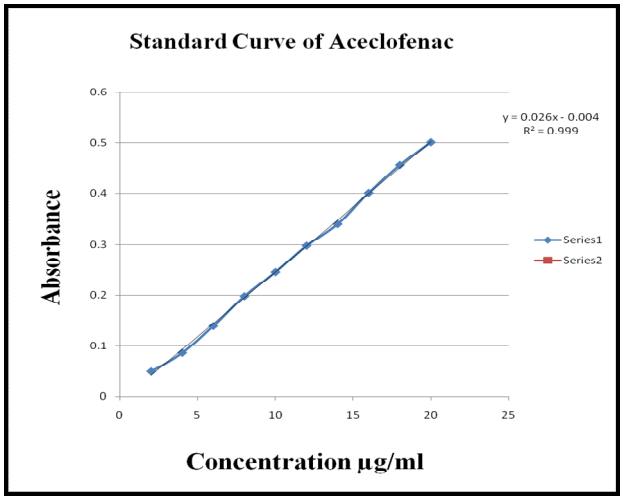



Figure 2: Standard Curve of Aceclofenac

### Potency Test for Prepared Solid Dispersion

Prior to in-vitro dissolution study the prepared solid dispersions were subjected to potency test. For this purpose from each solid dispersion 10 mg equivalent amount of aceclofenac was taken and dissolved in 100ml of dissolution medium of phosphate buffer pH 6.8. Then the solution was filtered and finally assayed by Shimadzu UV/Visible double beam spectrophotometer at 273 nm. The potency of these solid dispersions were,

Solid Dispersion 1:1—87.5%

Solid Dispersion 1:3—91.6%

Solid Dispersion 1:5—93.49%

### Physicochemical Evaluation of Prepared Bi-layer Tablets

The results of physical parameters (Weight, Hardness, Thickness, Diameter and DT) of the prepared bi-layer tablets are shown in Table 7.The thickness of the tablets were found between 7.35mm, 7.51mm, 7.45mm, hardness of the tablets ranged from 145 N to 217 N. The DT of three prepared bi-layer tablet were 2.25, 4.21and 2.54.

Table 7: Weight, Thickness, Hardness and DT of prepared bi-layer tablets

| SL. No. | Weight (mg) | Thickness (mm) | Hardness (N) | DT (min) |
|---|---|---|---|---|
| 1 | 1170 | 7.35 | 217 | 2.25 |
| 2 | 1158 | 7.51 | 129 | 4.21 |
| 3 | 1163 | 7.45 | 145 | 2.54 |

### *In-vitro* Dissolution Rate Studies

The in-vitro dissolution tests were performed for the pure aceclofenac solid dispersions and tablet formulations using USP dissolution test apparatus type II (paddle type) using 9000 ml of dissolution medium. Phosphate buffer pH 6.8 was used as dissolution medium. The temperature of the medium was maintained at

$37^0C \pm 0.5^oC$ throughout the experiment. The samples containing 100 mg of aceclofenac or its equivalent in solid dispersions were placed in the dissolution medium. Paddle was used at a stirring rate of 100 rpm. A 10 ml aliquot was withdrawn at predetermined time intervals of at 2, 5, 10, 15, 20,25, 30, 35, and 40 minutes and then 10 ml of fresh dissolution medium was replaced to maintain the constant volume of dissolution medium then measured at 273nm using Shimadzu UV-1700 UV/Visible double beam spectrophotometer (Shimadzu, Japan) against dissolution medium as blank. Percentage of drug release was calculated using the equation obtained from the standard curve prepared in the media.

Table 8: Weight, Thickness, Diameter, Hardness and DT of market product bi-layer tablet Dolokind Plus

| Wt. (mg) | Thickness (mm) | Diameter (mm) | Hardness (N) | DT (min |
|---|---|---|---|---|
| 669 | 5.85 | 16.61/8.70 | 144 | 1.18 |
| 681 | 5.72 | 16.59/8.68 | 243 | 1.38 |
| 668 | 5.72 | 16.57/8.69 | - | - |
| 682 | 5.81 | 16.63/8.73 | - | - |
| 677 | 5.76 | 16.58/8.66 | - | - |

Table 9: Weight, Thickness, Diameter, Hardness and DT of market product bi-layer tablet Zerodol-P

| Wt (mg) | Thickness (mm) | Diameter (mm) | Hardness (N) | DT (min) |
|---|---|---|---|---|
| 772 | 6.19 | 18.24/8.21 | 209 | 1.45 |
| 769 | 6.16 | 18.28/8.17 | 166 | 1.40 |
| 763 | 6.2 | 18.19/8.15 | - | - |
| 762 | 6.22 | 18.23/8.19 | - | - |
| 786 | 6.17 | 18.19/8.19 | - | - |

**_In-vitro_ Dissolution Rate Studies of Aceclofenac (Pure Drug)**

100 mg of pure Aceclofenac powder was used for dissolution study. It was found 94.62% was release after 10 minutes, 103.96% was released after 30 minutes.

Figure 3: Prepared Bi-layer Tablet

**Dissolution Profile for Solid Dispersion of Aceclofenac in 3 ratio of SD1:1, SD 1:3, SD 1:5 with Sodium Lauryl Sulphate**

Solid dispersion of aceclofenac with SLS as a carrier in mass ratio of 1:1, 1:3, 1:5 were prepared by solvent evaporation method. The prepared solid dispersions were used for dissolution study. It was found that 52.79% from SD1:1, 72.02% from SD 1:3, 86.13% from SD 1:5 after 2 minutes. 60.40% from SD 1:1 %, 76.15from SD 1:3 and 89.75% from SD 1:5 were released after 5 minutes. Drug released from SD were much higher than pure drug. So, SD is an effective method to enhance dissolution of aceclofenac.

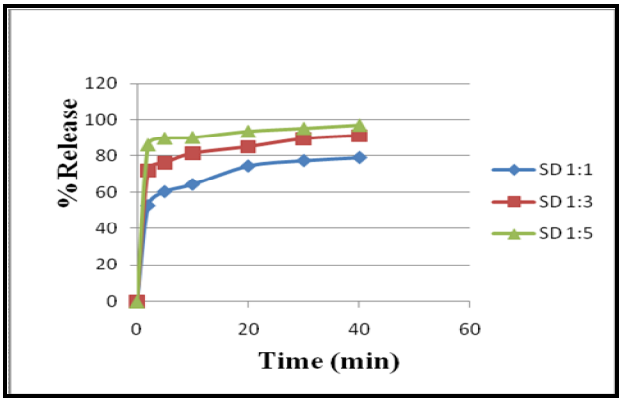



Figure 4: Comparison of Percent Release of Solid Dispersion of Aceclofenac with SLS in mass ratio of 1:1, 1:3, 1:5

**Physicochemical Evaluation of Aceclofenac Powder Form**

The results of physical parameters (Bulk density, Car's index, Angle of repose) of aceclofenac are shown in Table 10

Table 10: The results of physical parameters of Aceclofenac

| Parameter | SD 1:1 | SD 1:3 | SD 1:5 |
|---|---|---|---|
| **Bulk Density (mg/ml)** | 417.08 | 405 | 407 |
| **Compressibility Index** | 16.66 | 40 | 47 |
| **Angle of Repose** | 27.16 | 29.25 | 29.67 |

**Characterization of Granules**

Acetaminophen granules of F1 were evaluated for LBD, TBD, compressibility index and angle of repose (Table 11). The results of compressibility index (%) ranged from 12.5-13.26. Generally, compressibility index values up to 15% result in good to excellent flow properties. So the granules showed good flow properties. The results of angle of repose ranged from 21 to 23.

The results of angle of repose (<30°) indicate good flow properties of granules which was supported the results found from compressibility index. All these results indicate that the granules possessed satisfactory flow properties and compressibility.

Table 11: Physical properties of the prepared granules

| Granu. | LBD (g/cm3) | TBD (g/cm3) | Compressibility Index (%) | Angle of Repose |
|---|---|---|---|---|
| Acetaminophen granules | 0.410-0.418 | 0.475-0.483 | 12.5-13.26 | 21-23 |

**Physicochemical Evaluation of Formulated Bi-layer Tablets**

The results of physical parameters (Weight, Hardness, Thickness, Diameter and DT) of the formulated bi-layer tablets are shown in Table 7. The thickness of the tablets were found between 7.35mm, 7.51mm, 7.45mm, hardness of the tablets ranged from 145 N to 217 N. The DT of three prepared bi-layer tablet were 2:25, 4:21and 2:54 min.

Table 12: The average percent release of two sample of formulated bi-layer tablet

| Time | % Release | |
|---|---|---|
| | Acetaminophen | Aceclofenac |
| 0 | 0 | 0 |
| 2 | 79.95 | 13.46 |
| 5 | 81.99 | 76.43 |
| 10 | 84.86 | 91.54 |
| 20 | 90.43 | 92.02 |
| 30 | 93.85 | 94.15 |
| 40 | 96.18 | 95.69 |

So dissolution rate and extend of dissolution of our formulated product were higher than the marketed product.

**Different Types of Release Kinetics for Formulated Bi-layer Tablet**

Aceclofenac is poorly water-soluble drug and the present study was aimed to enhance the dissolution property of aceclofenac. So this study was designed to observe release pattern of drug from the solid dispersion of aceclofenac and compared with market products, pure drug. In this study solvent evaporation method was used for the preparation of solid dispersion aceclofenac. Then SD of aceclofenac was used to prepare bi-layer tablet with acetaminophen and drug release from bi-layer tablet. Consequently release kinetics was determined by using various kinetics equations.

Table 13: Comparison of percent release of formulated product and market product.

| Time (min) | % Release | | | | | |
|---|---|---|---|---|---|---|
| | Formulated product | | Market product X | | Market product Y | |
| | Acetaminophen | Aceclofenac | Acetaminophen | Aceclofenac | Acetaminophen | Aceclofenac |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 79.95 | 13.46 | 53.76 | 11.14 | 32.08 | 10.65 |
| 5 | 81.99 | 76.43 | 69.80 | 69.96 | 69.41 | 52.41 |
| 10 | 84.86 | 91.54 | 75.85 | 75.56 | 77.30 | 63.34 |
| 20 | 90.43 | 92.02 | 80.87 | 80.09 | 80.39 | 64.84 |
| 30 | 93.85 | 94.15 | 86.30 | 82.66 | 86.09 | 71.95 |
| 40 | 96.18 | 95.69 | 90.29 | 87.14 | 88.36 | 80.36 |

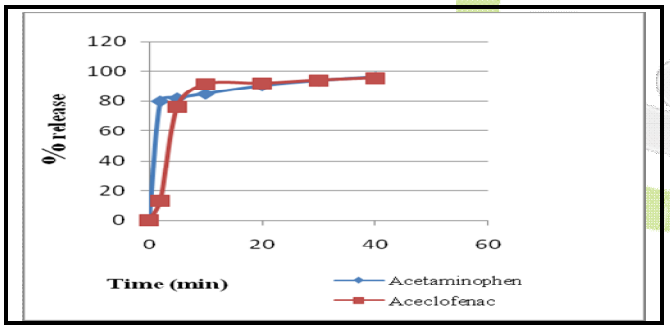



Figure 5: Zero order plot of release kinetics of Acetaminophen and Aceclofenac from bi-layer tablets

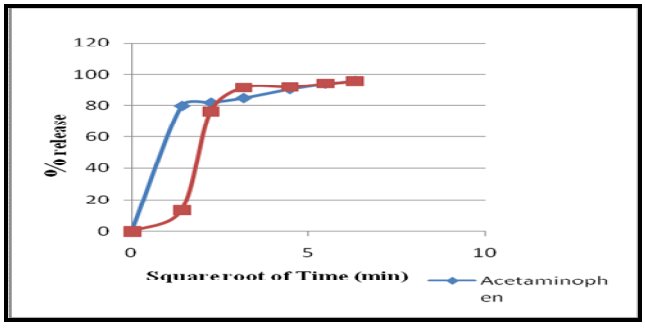



Figure 6: Higuchi plot of release kinetics of Acetaminophen and Aceclofenac from Bi-layer tablets

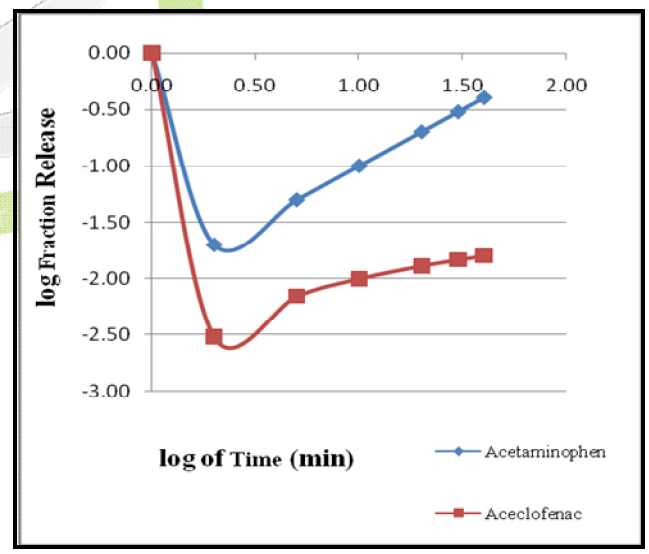
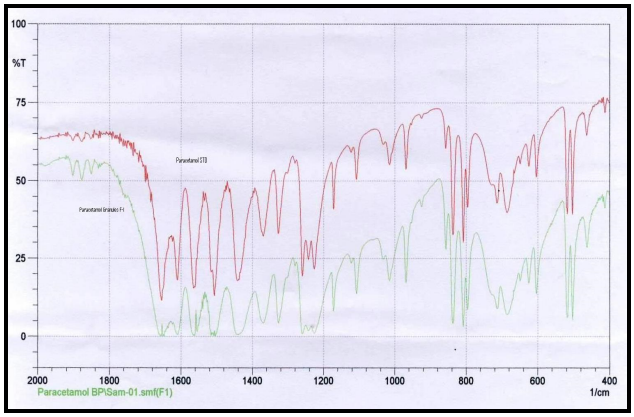



Figure 7: Korsmeyer plot of release kinetics of Acetaminophen and Aceclofenac from Bi-layer tablets

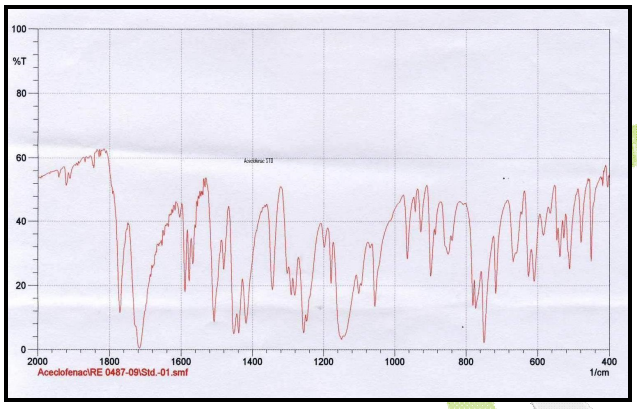
### Drug Excipients Interaction Study by FTIR

FTIR study proves that there was no interaction in acetaminophen granules and SD of aceclofenac as peaks in standard were similar with that in granules and SD.

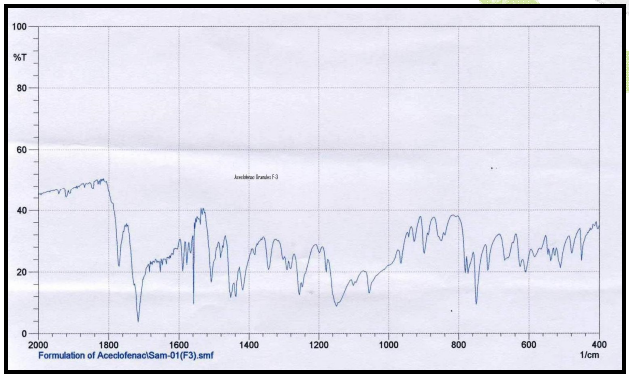
Figure 8: FTIR spectrum of Acetaminophen, aceclofenac standard and granules




8a) Acetaminophen STD and granules F-1




8b) Aceclofenac STD




8c) Aceclofenac SD

## CONCLUSION

The present study was undertaken with an aim to design oral immediate release tablet of acetaminophen and aceclofenac with solid dispersion technology. The formulations of acetaminophen and aceclofenac bi-layer tablets by solid dispersion technique showed good results in case of physicochemical parameters. They showed uniform weight, thickness crushing strength and uniformity of content. Drug release was also higher that the pure drug and market product. Solid dispersion system acts as an effective tool to enhance the dissolution rate. In recent years, a great deal of knowledge has been collected about solid dispersion technology, but commercial application of solid dispersion is limited.

The result generated in this study showed that the profile and kinetics of drug release were functions of excipient present in the formulation. However in-vivo test is required to correlate the release data with the in-vitro data to achieve a perfect bi-layer formulation for maximum therapeutic effectiveness and for final selection of formulation. Success of the In vitro drug release studies recommends the product for further in vivo studies.

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