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BILAYER TABLETS OF PARACETAMOL AND ACECLOFENAC: FORMULATION AND EVALUATION

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Abstract

The objective of the study was to formulate bilayer tablets consisting of paracetamol and aceclofenac for immediate drug release. Bilayer tablets are prepared by wet granulation technique by using sodium starch glycolate (SSG) as super disintegrant sodium lauryl sulphate (SLS) as surfactant to promote drug release. 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 paracetamol 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 all the tablet formulations were analyzed with dissolution efficiency (% DE). These results indicated that release of the drug from the tablet was influenced by content of super disintegrants and surfactants. Maximum drug release was found in tablets containing 4% SSG with 4% SLS. So, bilayer tablets could be a potential dosage form for delivering paracetamol and aceclofenac.

Keywords: Acetaminophen, bi layer tablet, extended drug release, 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 bi layer 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.

Paracetamol 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 suppositories¹. The drug is official in different pharmacopeia²⁻³. Paracetamol is often prescribed with aceclofenac for greater patient acceptability, increased potency, multiple activity, fewer side effects and quick relief.

Aceclofenac , [(2-{2,6-dichlorophenyl)amino} phenylacetooxyacetic acid] is a non-steroidal anti-inflammatory drug (NSAID) indicated for the symptomatic treatment of pain and inflammation with a reduced side effect profile, especially gastro-intestinal events that are frequently experienced with NSAID therapy. 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)⁴. Therefore, aceclofenac shows dissolution rate limited absorption that gives rise to difficulties in pharmaceutical formulations for oral delivery, which may lead to variable bioavailability.

Aceclofenac in combination with acetaminophen is now available in the market and indicated in pain, fever etc. Comparative dissolution study of some of the 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 paracetamol and aceclofenac by using sodium starch glycolate as super surfactants to promote drug release.

Material and Methods

Materials:

Paracetamol and acetaminophen were kind gift from Incepta Pharmaceuticals Ltd, Bangladesh. Other excipients, avicell pH 101, lactose, magnesium stearate, purified talc and aerosil-200 were procured commercially and were used

as received. Potassium di-hydrogen phosphate, sodium hydroxide and other reagents were of analytical-reagent grade and purchased from E. Merck, Darmstadt, Germany. Water was deionised and double distilled.

Preparation of paracetamol and aceclofenac granules:

Granules of paracetamol and aceclofenac were prepared separately by using wet granulation technique. The composition of granules is summarized in Table 1 and 2. Calculated amount (required to prepare a 50 tablet batch) of the drug was mixed with excipients thoroughly. 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 separately prior to compression.

Compression of bilayer tablets:

Paracetamol layer was compressed first followed by aceclofenac layer. The quantity of granules for the Paracetamol part was compressed lightly using 13 mm-diameter die of an infrared hydraulic press. Over this compressed layer, required quantity of aceclofenac granules 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.

Table 1: Composition of paracetamol granules (mg/tablet)

| Ingredients | F1 | F2 | F3 | F4 | F5 |
|-----------------------------------------------|-----|-----|-----|-----|-----|
| Paracetamol BP | 500 | 500 | 500 | 500 | 500 |
| Microcrystalline Cellulose (Avicel PH 101) BP | 54 | 54 | 54 | 54 | 39 |
| Povidone (K-30) BP | 15 | 15 | 15 | 15 | 15 |
| Methylparaben BP | 1 | 1 | 1 | 1 | 1 |
| Sodium Starch Glycollate BP | - | 10 | 15 | 20 | 25 |
| Colloidal Anhydrous Silica (Aerosil-200) BP | 3 | 3 | 3 | 3 | 3 |
| Magnesium Stearate BP | 6 | 6 | 6 | 6 | 6 |

Table 2: Composition of aceclofenac granules (mg/tablet)

| Ingredients | F1 | F2 | F3 | F4 | F5 |
|---------------------------------------------|-----|-----|-----|-----|-----|
| Aceclofenac BP | 100 | 100 | 100 | 100 | 100 |
| Maize Starch BP | 19 | 19 | 19 | 19 | 19 |
| Microcrystalline Cellulose (Avicel PH 101) | 22 | 22 | 22 | 22 | 22 |
| Povidone K-30 BP | 3 | 3 | 3 | 3 | 3 |
| Sodium Starch Glycollate BP | - | 2 | 4 | 4 | 4 |
| Colloidal Anhydrous Silica BP (Aerosil-200) | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 |
| Magnesium Stearate BP | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Sodium Lauryl Sulphate BP | - | - | - | 2 | 4.0 |

Evaluation of Granules:*Bulk Density*

LBD (Loose Bulk Density) and TBD (Tapped Bulk Density) were determined by packing 2 g of powder from each formula (previously lightly shaken to break any agglomerates formed) into a 10-ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. 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:

$$\text{Carr's index (\%)} = \{(TBD - LBD) \times 100\} / TBD$$

Angle of Repose

The angle of repose of granules was determined by the funnel method. 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:

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

Where, h = Height of the powder cone.

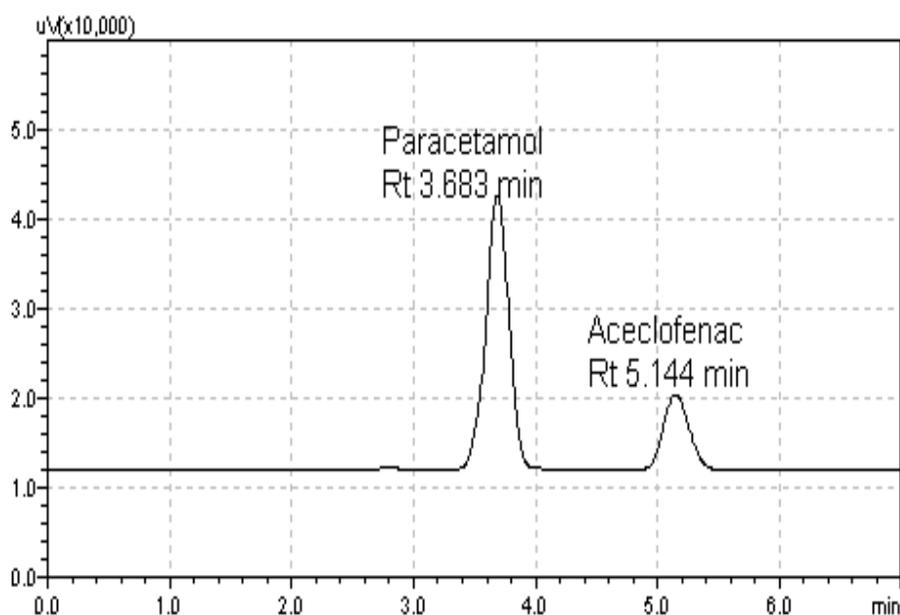
r = Radius of the powder cone

EVALUATION OF TABLETS

HPLC analysis of drugs:

Various HPLC methods for the analysis of paracetamol and aceclofenac have been reported⁵⁻⁶. A modified reported HPLC method was used for the analysis of drugs. A Shimadzu (Japan) HPLC system consisting of a CMB-20 Alite system controller, two LC-20AT pumps, SIL-20A auto-sampler and CTO-10ASVP column oven were used. Ultraviolet detection was achieved at 273 nm with a SPD-20A UV-VIS detector (Shimadzu, Japan). The drug analyses data were acquired and processed using LC solution (Version 1.3, Shimadzu, Japan) software running under Windows XP on a Pentium PC. The mobile phase, water (pH 3.5 with acetic acid) : methanol (50:50 v/v) pumped at a flow rate of 1.0 ml/min through the column (C₁₈; 250 mm X 4.6 mm, 5 μ shim-pack, Japan) at 30⁰C. The mobile phase was filtered through a 0.2 μ nylon membrane filter and degassed prior to use under vacuum. Elutions were analyzed by UV detector at a sensitivity of 0.0001. The method was validated for the parameters like system suitability, selectivity, linearity, accuracy, precision and robustness. The retention time was 3.683 minutes for paracetamol and 5.144 minutes for aceclofenac (Figure I). Similar retention time proves the selectivity of the method. The calibration curves were linear over the concentration range of 80% to 120% ($R^2 > 0.999$). The proposed method is accurate with 100.165% recovery, precise (% RSD < 0.5) and robust.

Figure I: chromatogram of standard paracetamol and aceclofenac.



Assay

Average weight of paracetamol and aceclofenac tablet was calculated. Then the tablets were grinded to fine powder with the help of mortar and pestle. Powder containing 50 mg paracetamol and 10 mg aceclofenac was dissolved in mobile phase, shaken for about 10 minutes and filtered through filter paper. The filtered solution was further diluted so that diluted solution contains 50 mcg/ml paracetamol and 10 mcg/ml aceclofenac. Solutions were injected in Shimadzu (Japan) HPLC system. Potency was calculated from peak area.

Determination of uniformity of weight:

20 tablets from each of the 5 brands were weighed individually with an analytical weighing balance (Model: AY-200, SHIMADZU Corporation, JAPAN). The average weights for each brand as well as the percentage deviation from the mean value were calculated.

Hardness test:

Automatic Tablet Hardness Tester (8M, Dr Schleuniger, Switzerland) was used to determine the crushing strength. 6 tablets were randomly selected from each brand and the pressure at which each tablet crushed was recorded.

Friability test:

20 tablets of each brand were weighed and subjected to abrasion by employing a Veego friabilator (VFT-2, India) at 25 rev/min for 4 min. The tablets were then weighed and compared with their initial weights and percentage friability was obtained.

Disintegration test:

6 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 to pass 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, Electrolab, India) in 5 replicates for each brand. Aceclofenac is soluble in phosphate buffer pH 6.8⁷. 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

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 experiments, 5 ml of dissolution sample was withdrawn at 0, 10, 20, 30, 40, 50 and 60 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 paracetamol and aceclofenac.

Stability studies:

Stability studies were done according to ICH guidelines to assess the drug and formulation stability⁸. All the formulations were subjected to stability study at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for 90 days. The samples were evaluated for physical changes, hardness, friability, drug content and percentage drug release during the stability studies.

Results and Discussion

Characterization of granules:

Paracetamol and aceclofenac granules of different formulations were evaluated for LBD, TBD, compressibility index and angle of repose (Table 3). The bulk density of aceclofenac granules of the proposed formulation was quite higher than those of paracetamol granules. This may be due to the presence of more fine granules. The results of compressibility index (%) ranged from 12.5-13.26 for paracetamol granules and 13.20-13.61 for aceclofenac granules. 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 27. The results of angle of repose ($<30^\circ$) 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 3: Physical properties of the prepared granules.

| Granules | LBD (g/cm ³) | TBD (g/cm ³) | Compressibility Index (%) | Angle of Repose |
|----------------------|--------------------------|--------------------------|---------------------------|-----------------|
| Paracetamol Granules | 0.410-0.418 | 0.475-0.483 | 12.5-13.26 | 21-23 |
| Aceclofenac Granules | 0.413-0.421 | 0.482-0.491 | 13.20-13.61 | 25-27 |

Physicochemical evaluation of matrix tablets:

The results of physical parameters (weight, hardness, thickness and friability) and drug content of the prepared bi-layer tablets are shown in Table 3. The thickness of the tablets were found between 4.33 ± 0.10 mm to 4.43 ± 0.09 mm, hardness of the tablets ranged from 205 ± 6.38 N to 217 ± 6.82 N and friability ranged from 0.15% to 0.24%. SD of weight variations of prepared tablets was 1.88 to 3.18. The drug content (paracetamol and aceclofenac) of every formulation was found about to 100% of labeled content that complied with the pharmacopoeial specifications. So it can be said that physical properties and drug content of the compressed bi-layer tablets were satisfactory.

Table 4: Physical properties of the prepared tablets of different formulations.

| Formulations | Thickness (mm) \pm SD (n = 5) | Hardness (N) \pm SD (n = 6) | Friability (%) (n = 20) | Weight (mg) \pm SD (n = 20) | Paracetamol % \pm SD (n = 5) | Aceclofenac % \pm SD (n = 5) |
|--------------|---------------------------------------|-------------------------------------|-------------------------------|----------------------------------|-----------------------------------|-----------------------------------|
| F-1 | 4.33 ± 0.10 | 217 ± 6.82 | 0.22% | 725.14 ± 3.11 | 99.23 ± 0.57 | 100.41 ± 0.58 |
| F-2 | 4.35 ± 0.14 | 215 ± 7.56 | 0.17% | 736.19 ± 3.18 | 99.57 ± 0.61 | 99.64 ± 0.62 |
| F-3 | 4.39 ± 0.09 | 200 ± 8.93 | 0.15% | 748.15 ± 2.53 | 97.92 ± 0.82 | 99.50 ± 0.47 |
| F-4 | 4.41 ± 0.08 | 210 ± 7.62 | 0.19% | 750.43 ± 1.88 | 100.42 ± 0.58 | 99.93 ± 0.99 |
| F-5 | 4.43 ± 0.09 | 205 ± 6.38 | 0.24% | 755.62 ± 2.13 | 100.28 ± 0.81 | 100.47 ± 0.19 |

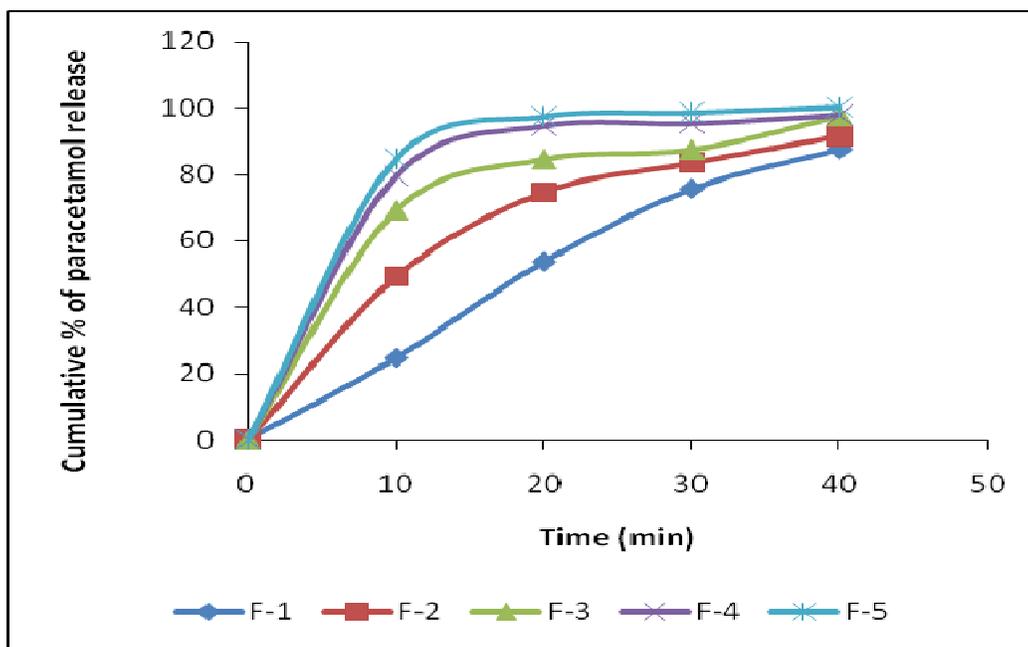
SD- Standard deviation; n- Number of replicates

***In vitro* release study:**

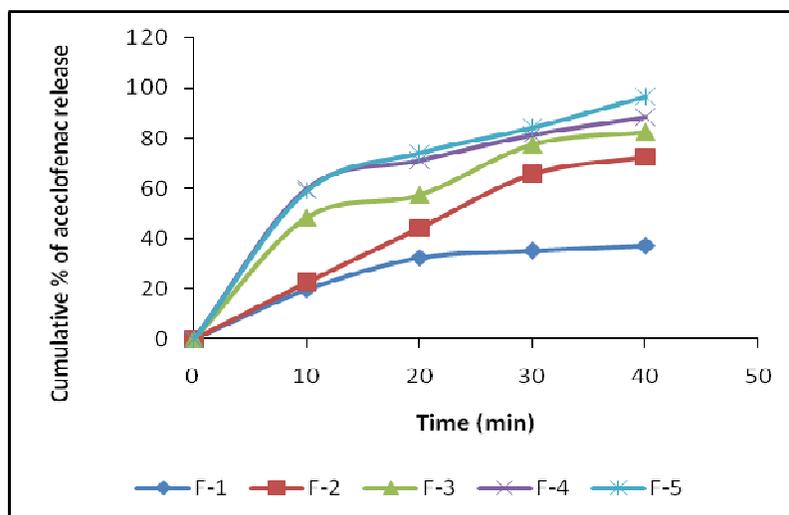
Drug release from different formulations (F-1 to F-5) of bi-layer tablets are shown in Figure II and III. All dissolution data are based on the actual drug content of the test tablets as calculated from the assay results. Formulation 1(F-1) does not contain sodium starch glycolate or sodium lauryl sulphate. Drug release was very poor from this formulation. Only 37% aceclofenac was released within 40 min from this formulation. This is because

aceclofenac is poorly water soluble drug. Release of paracetamol from this formulation was slow initially but it increased after 10 min but finally it did not comply USP specification (Not less than 80% in 30 min).

Figure II: Paracetamol release from bi-layer tablets (F-1 to F-5).



Formulation 2(F-2) contains SSG both in paracetamol layer (3% of drug) and aceclofenac layer (2% of drug). Drug release was found increased. Release of paracetamol complied USP specification but release of aceclofenac was still lower (72% in 40 min). The amount of SSG in paracetamol layer of F-3, F-4 and F-5 was 3%, 4% and 5% respectively. Paracetamol released was increased with increased of SSG. SSG is a super disintegrating agent. It disintegrates the tablet rapidly as a result paracetamol dissolves after disintegration. Use of 4% SSG in formulation 3 further increased aceclofenac release from this formulation. But addition of 2% SLS along with 4% SSG released 80% within 30 min. Aceclofenac tablet is not official in USP or BP till now. So, official tolerance for drug release is not available. Further increase in aceclofenac release was found (F-5) for increase of SLS. So use of sodium starch glycolate and sodium lauryl sulphate in bi layer tablet is helpful to obtain higher drug release in case of water insoluble drugs. Sodium starch glycolate disintegrates the tablets quickly. On the other hand, sodium lauryl sulphate increases the pH of the dissolution media which is helpful for the quick drug release of aceclofenac. Similar result was also reported by Srivastav et al., 2011 in case of gliclazide, a poorly water soluble drug⁹.

Figure III. Aceclofenac release from bi-layer tablets (F-1 to F-5).**Comparison of dissolution data:**

Dissolution efficiency (%DE) was calculated to compare the dissolution profile of different formulation.

Dissolution efficiency is the area under the dissolution curve within a time range ($t_1 - t_2$). DE was calculated by using the following equation:

$$AUC = \sum_{i=1}^{i=n} \frac{(t_i - t_{i-1}) (y_{i-1} + y_i)}{2}$$

Where y is the percentage dissolved at time t

Products can be said to be equivalent if the difference between their dissolution efficiencies is within appropriate limits ($\pm 10\%$, which is often used)¹⁰. Formulation F-4 and F-5 may be considered similar due to the close % DE (Table 5).

Table 5: Dissolution Efficiency (% DE) of different formulations (F-1 to F-5)

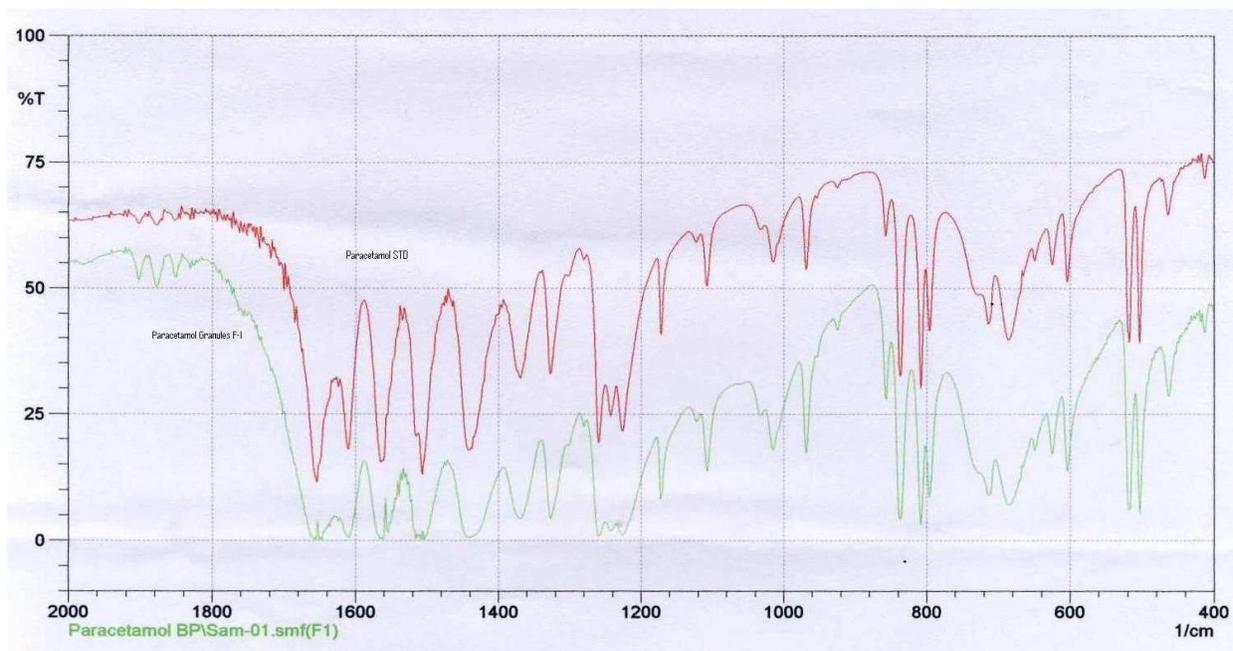
| Formulation | %DE | |
|-------------|-------------|-------------|
| | paracetamol | Aceclofenac |
| F-1 | 61.84 | 31.99 |
| F-2 | 76.01 | 52.37 |
| F-3 | 85.01 | 66.77 |
| F-4 | 92.97 | 75.55 |
| F-5 | 96.11 | 78.76 |

Stability study:

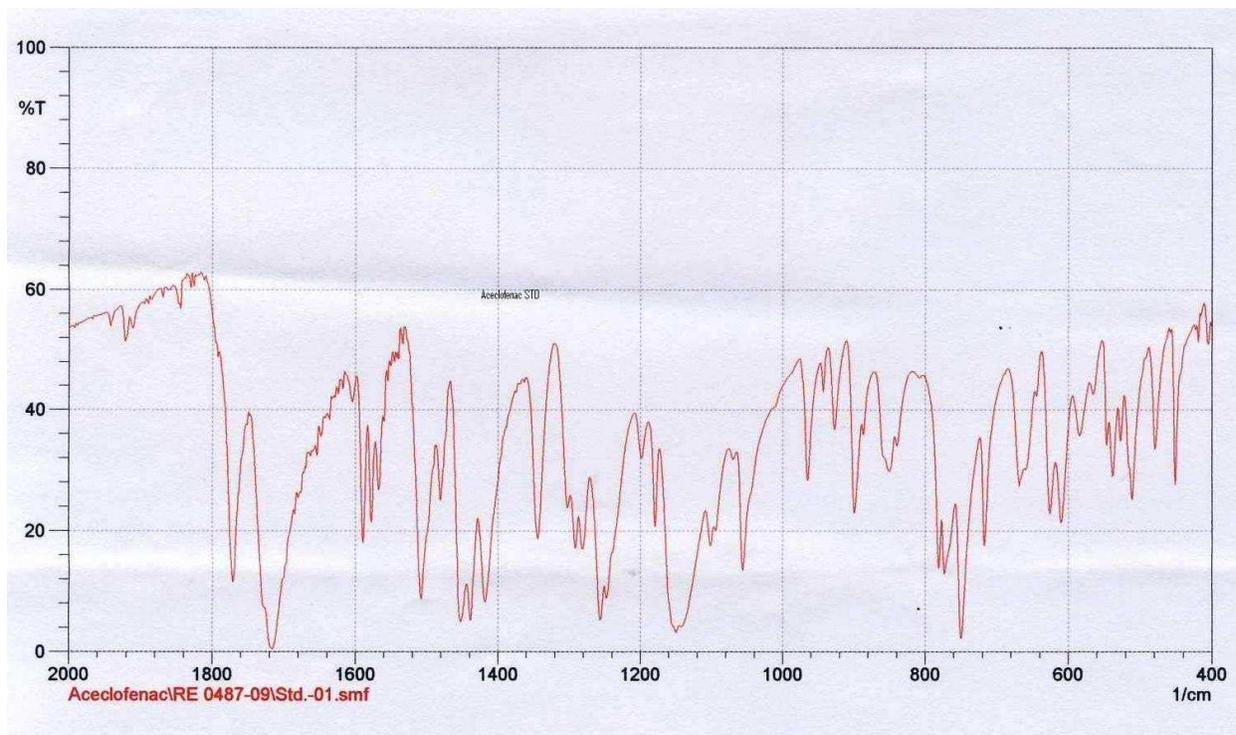
Drug release and potency of different formulations (F-1 to F-5) after 90 days are summarized in table 6. Potency and drug release were almost similar with the initial values which indicates that there is no interaction between drug and polymer. Initial potency and potency after 90 days were compared by paired *t* Test. As the *p* value is greater than the level of significance there is no difference between the potency and the formulations are stable. Stability of formulations was also confirmed by FTIR study. FTIR spectrums of standard samples were similar with the formulation samples (Figure IV).

Table 6: Potency from different formulations (F-1 to F-5) initial and after 90 days.

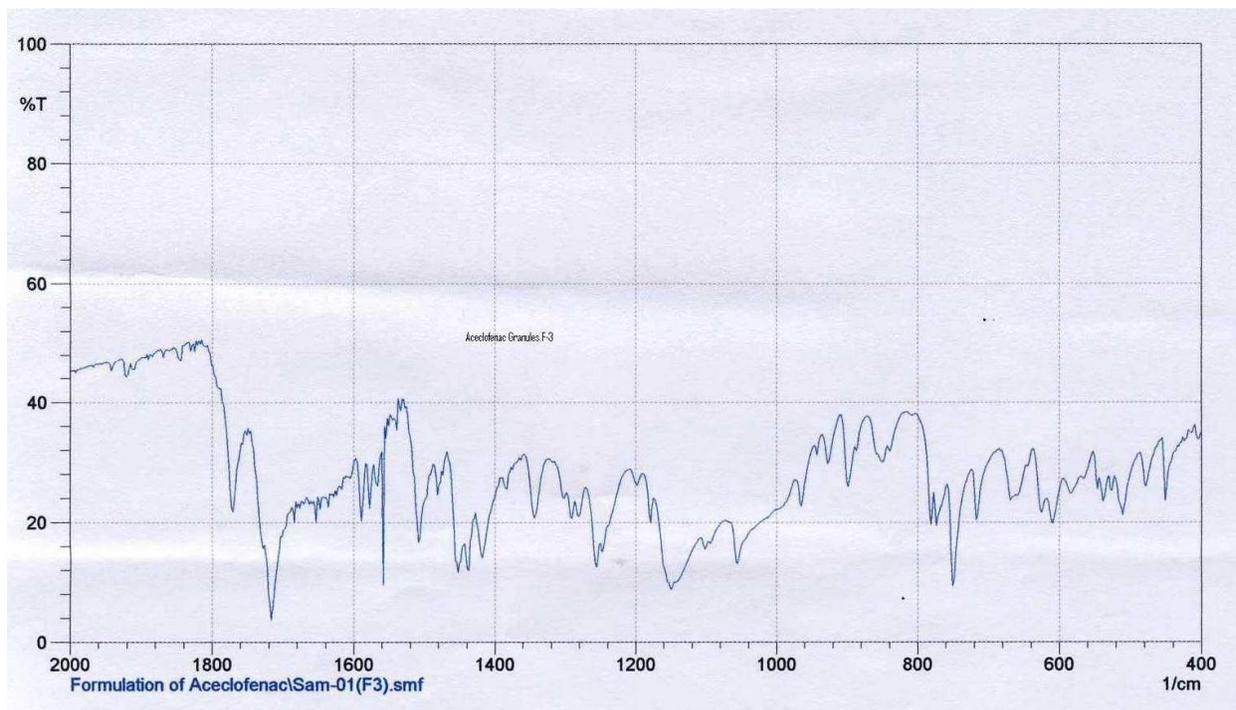
| Formulation | Paracetamol | | | | Aceclofenac | | | |
|-------------|-----------------|-----------------------|--------|------|-----------------|-----------------------|--------|------|
| | Initial Potency | Potency after 90 days | t-test | p | Initial Potency | Potency after 90 days | t-test | p |
| F-1 | 99.23 | 99.14 | | | 100.41 | 99.35 | | |
| F-2 | 99.57 | 99.37 | | | 99.64 | 99.35 | | |
| F-3 | 99.92 | 99.72 | 2.42 | 0.07 | 99.5 | 99.82 | 1.91 | 0.13 |
| F-4 | 100.42 | 99.36 | | | 99.93 | 99.53 | | |
| F-5 | 100.28 | 99.59 | | | 100.47 | 99.42 | | |

Figure IV: FTIR spectrum of paracetamol, aceclofenac standard and granules.**a) Paracetamol STD and granules F-1**

b) Aceclofenac STD



c) Aceclofenac Granules F-3



Conclusion

The present study was undertaken with an aim to design oral immediate release tablet of paracetamol and aceclofenac. Results indicated that release of the drug from the tablet was influenced by content of super disintegrants and surfactants. Formulation containing 4% SLS with 4% SSG showed maximum drug release. So, bilayer tablets could be a potential dosage form for delivering paracetamol and aceclofenac. Success of the *In vitro* drug release studies recommends the product for further in vivo studies.

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