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# Combination of Allopurinol' and Sustained Release Diclofenac Sodium for Treatment of Gout

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**Abstract:** ***The present investigation concern with the combination of the two drugs for the treatment of gout. One of these drug is pain killer which is sustain their action within the body for 12 hours and the other drug is antigout which will release as conventional dosge.After oral administration the Diclofenac sodium prolong up to 12 hours and increase patient compliance .6 batches of tablet were developed and evaluate .For the sustain release action of Diclofenac sodium Kollicoat® SR 30 and Sicovit® 30 combination used with other inactive ingredients. In 1st method only Diclofenac sodium pellets which were sustained released prepared. Pellets of the Diclofenac sodium developed with wet granulation method. This method is easy and cost effective, the evaluation of granules and tablets were done at the end, all prepared material mixed together and form tablet. The tablets were evaluated for all test like appearance, friability, dissolution, hardness, assay, weight variation and in-vitro release profile which is for both API. The result obtained were satisfactory and complies with USP specification .The formulation containing combination of Kollicoat® SR 30 and Sicovit® 30 showed good sustain release profile for 12 hours. Seperate granules were prepared of both API and check the flow property of these granules and then mixed them for compression.***

**Keywords:** Kollicoat® SR 30 and Sicovit® 30, Diclofenac sodium, Allopurinol and sustain release

## 1. Introduction

Combination therapy is new technique for the treatment of the disease. Sustain release technology is relatively modern field and combination of two drug which have different release profile is also new concept of dosage form. With many drugs, the basic purpose is to achieve a steady state blood level. In this research the design of two different release profiles was critical thing and was important element to complete this research. The success of a therapy depends on selection of the appropriate delivery system as much as drug itself.[1] Allopurinol is specifically indicated for the treatment of acute gouty arthritis. The usual dose to relieve or abort an attack is 100 to 300 mg [2]. Diclofenac Sodium is pain killer and indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, bursitis and acute gout. It is also indicated in the relief of mild to moderate pain and the treatment of primary dysmenorrhea. The recommended starting dose of Diclofenac sodium in adults is (100 mg) once daily[2].

## 2. Material and Method

### 2.1 Materials

Allopurinol and Diclofenac sodium were obtained as a gift sample from Ameer & Adnan pharmaceuticals Lahore Pakistan .kollicoate, sicovit 30 and PG also obtain from this company. Lactose, kolidon30,mag sterate, aerosol, avicel, talc and titanium dioxide were purchased from local market. Double distilled water was used throughout the research. Other materials used for analysis were also purchased from local market and these were all analytical grade.

### 2.2 Diclofenac sodium sustained-release pellet[3]

**a) Formulation**
The formulation is designed for 100g of pure Diclofenac sodium pellets (Spherofillin diameter 0.8-1.3mm)

***Polymer suspension***

| |
|---|
| Kollicoat® SR 30 D 223.67g |
| Propylene glycol 6.71g |
| Water 149.86g |

***Pigment suspension***

| |
|---|
| Kollidon® 30 2.24g |
| Titanium dioxide 2.24g |
| Sicovit® 30 2.24g |
| Talc 15.66g |
| Water 44.73g |

**b) Preparation of the spray suspension**

***Polymer suspension***
Add propylene glycol followed by Kollicoat® SR 30 D to the given quantity of water with stirring.

***Pigment suspension***
Dissolve Kollidon® 30 in the given quantity of water. Add Sicovit® Red 30, titanium dioxide and talc with vigorous stirring and homogenize the mixture in a corundum disk mill.

**API Mixing**
Diclofenac sodium mixes in the suspension and converted into pellets shape by using the pellet mill/machine

**c) Coating**

The pellets were coated in an Aeromatic Strea-1 (Aeromatic AG). The suspension was sprayed continuously onto the fluidized, pre-heated pellets from the top.

***Process parameters***

| |
|---|
| Inlet air temperature 60°C |
| Outlet air temperature 37°C |
| Product temperature 38°C |
| Air flow 80m³/h |
| Nozzle diameter 0.8mm |
| Spraying rate approx. 11.5g/min |
| Spraying time 39 min |
| Atomizing pressure 1.0bar |
| Drying 45°C/ 5min |
| Coating weight 2mg film former/cm² |

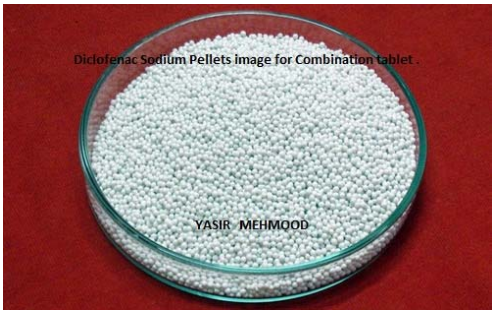


**Figure 1**

**2.3 2nd step**

**2.3.1 Method**

Tablets were prepared by direct compression technique.

**2.3.2 Procedure**

1. Diclofenac Sodium pellets and Allopurinol after passing it through 20 SS mesh for 30-45 minutes in horizontal mixer.
2. Add kollidon 30 in this mixture as binder.
3. Add this to the content of the mixer and Knead for 15-20 minutes..
4. Load this granular powder in horizontal mixer and add Avicel PH 102 after sieving SS mesh # 40 mix for 30 minutes then add Mg. Stearate, & Aerosil after screening mesh # 40 and mix for 10 minutes.
5. Shift the material in containers containing Poly bags with proper identification, to the in process quarantine.
6. When the batch is passed for compression, shift it to compression section when required.
7. After the compression is completed intimation for release for coating is given to QA. After getting sampled shift the Tablets to the in process quarantine.
8. When passed for coating, shift it to coating section when required.
9. After the batch is coated give intimation to QA for release of batch for blistering and shift the coated tablets in airtight containers to in process quarantine.
10. After the batch is approved for blistering, shift the batch to blistering section if required.

**Important study**: compatibility evaluation was carried out using infra-red spectra. Infrared spectrum of formulated granules and drug alone were recorded and observed between 400 nm and 5000 nm. Infra - red spectrum of pure drug was also run individually.

**Compatibility studies:** Fourier Transform Infrared Spectroscopy (FTIR) spectrums of Diclofenac sodium and Allopurinol individual and with mixture were obtained for compatibility study .the scanning range was from 400 to 5000 $cm^{-1}$.

**2.3.3 Drug Content of Diclofenac sodium pellets**

**Assay: (DICLOFENAC SODIUM)**

**Assay**

Dissolve 6.8 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water* and adjust the pH to 6.8 with 1M *sodium hydroxide* (solution A). To a quantity of the mixed contents pellets containing 100 mg of Diclofenac Sodium add 10 mL of *ethanol (96%)* and mix with the aid of ultrasound for 20 minutes or until completely dispersed. Add 150 mL of solution A and mix with the aid of ultrasound for a further 20 minutes or until completely dispersed. Cool to room temperature, dilute to 250 mL with solution A and shake thoroughly. Filter the resulting solution and dilute 5 mL to 100 mL with solution A. Prepare a reference standard in the following manner. Dissolve 50 mg of *diclofenac sodium BPCRS* in 10 mL of *ethanol (96%)* with the aid of ultrasound for 5 minutes. Add 150 mL of solution A and mix with the aid of ultrasound for a further 5 minutes. Cool to room temperature, dilute to 250 mL with solution A and shake thoroughly. Dilute 5 mL of the resulting solution to 50 mL with solution A. Measure the *absorbance*, of the solutions at 275 nm using in the reference cell a 0.4% v/v solution of *ethanol (96%)* in solution A. Calculate the content of $C_{14}H_{10}Cl_2NNaO_2$ in the capsules using the absorbances at the maximum at 275 nm and the declared content of $C_{14}H_{10}Cl_2NNaO_2$ in diclofenac sodium .

**Limits:** 95% - 105 %

**2.3.4 Drug Content of Allopurinol in tablet** BP2013

**ASSAY**

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.1 g of Allopurinol with 20 mL of 0.05M *sodium hydroxide* for 20 minutes, add 80 mL of 0.1M *hydrochloric acid* , shake for 10 minutes, add sufficient 0.1M *hydrochloric acid* to produce 250 mL, filter and dilute 10 mL of the filtrate to 250 mL with 0.1M *hydrochloric acid* . Measure the *absorbance* of the resulting solution at the maximum at 250 nm, using 0.1M *hydrochloric acid* in the reference cell. Calculate the content of $C_5H_4N_4O$ taking 563 as the value of A (1%, 1 cm) at the maximum at 250 nm.

**Limits: 95% - 105 %**

**2.4Evaluation of Tablets**

**Thickness**

The thickness of the tablets was determined using a thickness gauge. Five tablets from each batch were used, and average values were calculated.

**Weight Variation Test**

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (srtorius MA45), and the test was performed according to the official method.6

**Hardness and Friability**

For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester

(Monsanto tester) and the roche friabilator (labsonic electronics, Lahore), respectively.

**Table 1:** Formulation of each combination tablet :

| *Sr No* | *Ingredients* | *F1* | *F2* | *F3* | *F4* | *F5* | *F6* |
|---|---|---|---|---|---|---|---|
| 1 | Diclofenac sodium | 100 | 100 | 100 | 100 | 100 | 100 |
| 2 | Allopurinol | 100 | 100 | 100 | 100 | 100 | 100 |
| 3 | Kolidol 30 | 10 | 10 | 15 | 15 | 25 | 15 |
| 4 | Mg sterate | 0.5 | 1.5 | 0.5 | 1.0 | 1.5 | 0.5 |
| 5 | Avicel | 20 | 30 | 10 | 5 | 15 | 10 |
| 6 | Aerosol | 0.2 | 0.5 | 0.8 | 0.5 | 0.2 | 0.5 |
| 7 | Lactose | 50 | 60 | 50 | 10 | 30 | 50 |
| Total weight | | 280.7 | 302 | 276.3 | 231.5 | 271.7 | 276 |

*All quantities are in mg.*Weight Diclofenac sodium pellets equivalent to 100mg Diclofenac sodium.

**2.5 In vitro dissolution studies of Diclofenac sodium**

In vitro dissolution study was carried out using USP I apparatus (basket apparatus) in 900 ml of phosphate buffer pH 7.4 for 12 hours. The temperature of the dissolution medium was kept at 37± 0.50C and the basket was set at 50 rpm. 1 ml of the sample solution was withdrawn with micropipette at specified interval of time. The absorbance of the withdrawn samples was measured at λmax 275 nm using UV visible spectrophotometer. The concentration was determined from the standard curve of Diclofenac sodium prepared in distilled water at λ max 275 nm. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

**2.6 Swelling index**

Swelling of the tablets involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles or hydration of macromolecules. The liquid enters the particles through pores and bind to large molecule; breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of %weight gain by the tablet. The swelling index of tablets was determined in 0.2 N HCl (pH 1.5) at 25c temperature. After each interval the tablet was removed from the beaker and remove the excess buffer by using filter paper and weighed again upto 6 hrs. The swelling index was calculated by the following equation:

$$\text{Swelling index (SI)} = \frac{(Wt - W0)}{W0} \times 100$$

Where,
Wt= Weight of tablet at time t.
W0 = Initial weight of tablet

**2.7 Mathematical models7,8&9**

**2.7.1 Zero Order Kinetics:**
Drug dissolution from pharmaceutical dosage forms that do not disintigrate and release the API slowly according to time and this can be represented by the following equation;

$$Qt = Qo + ko\ t$$

Where,
Qt = amount of drug released in time‘t’,
kt = zero order release constant
Qo = initial amount of drug in the solution,

The pharmaceutical dosage forms following this profile, release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage form, as in the case of some transdermal system, as well as matrix tablets with low soluble drugs, coated form, osmotic systems, etc.

**2.7.2 First Order Kinetics**
The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman. The following relation can express this model:

$$\text{Log } Qt = \text{Log } Qo + ktt/2.303$$

Where, Qo = initial amount of drug in the solution,
kt = first order release constant
Qt = amount of drug released in time‘t’,
.
The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in porous matrices, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amounts of drug released by unit of time diminish.

**2.7.3 Higuchi Model**
Higuchi developed several theoretical models to study the release of water soluble drugs incorporated in semisolid and/or solid matrixes. Simplified Higuchi model can be expressed by following equation:

$$ft = kH\ t1/2$$

Where, kH = Higuchi diffusion constant,
ft = fraction of drug dissolved in time‘t’.

Higuchi describes drug release as a diffusion process based in the Fick’s law, square root time dependent. This relation can be used to describe the drug dissolution from several types modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs.

**2.7.4 Korsmeyer-Peppas Model**

Korsmeyer et al. developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time (t);

$$ft = atn$$

Where,
a = constant incorporating structural and geometric characteristics of the drug dosage form,
n = release exponent
ft = Mt/M∞ = fraction release of drug.

### 2.7.5 Comparison of dissolution profiles

We found the dissolution profile and release profile of the F4 and F5 very suitable and according to time line. The dissolution profile of F5 is between 0 to 90,the dissolution profile for both formulation were as similar to reference drug of sustain release.

### 2.7.6 Stability studies

The stability study of the formulation is also so important and is need for producing the effective formulation. We carry both stability study for our formulation, accelerated and normal study. We found F4 formulation best in this time frame of stability; we have checked its safety and efficiency during stability study. This stability study was for 3months at 40c and 75% RH.

## 3. Results and Discussion

### 3.1 Compatibility studies

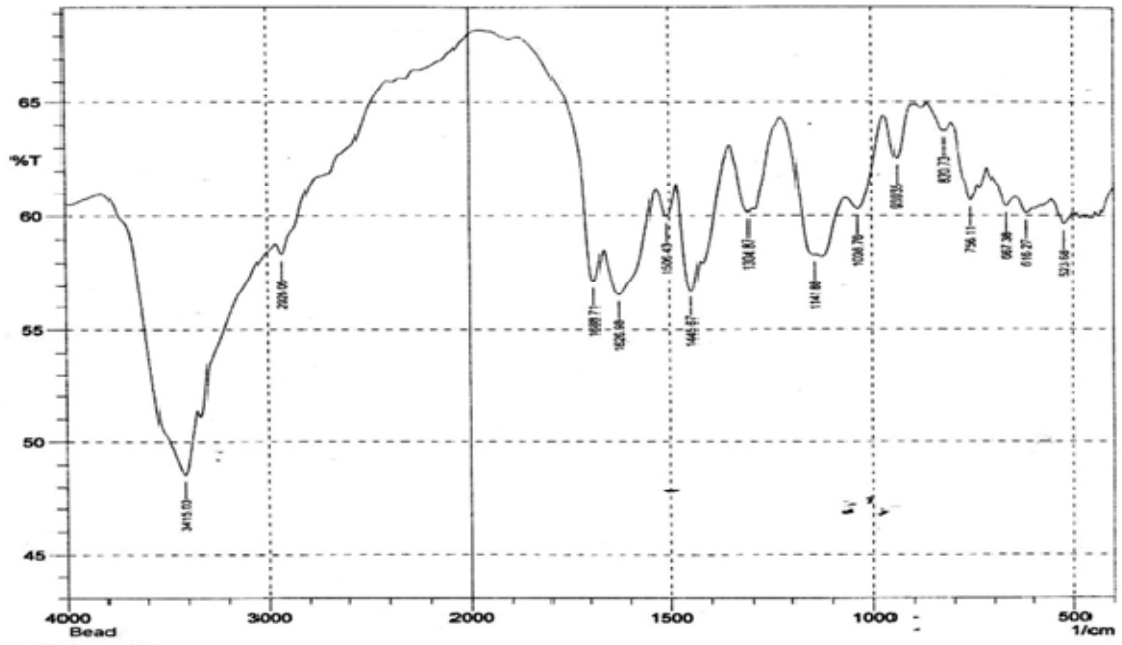


**Figure 2:** IR image of pure Diclofenac sodium

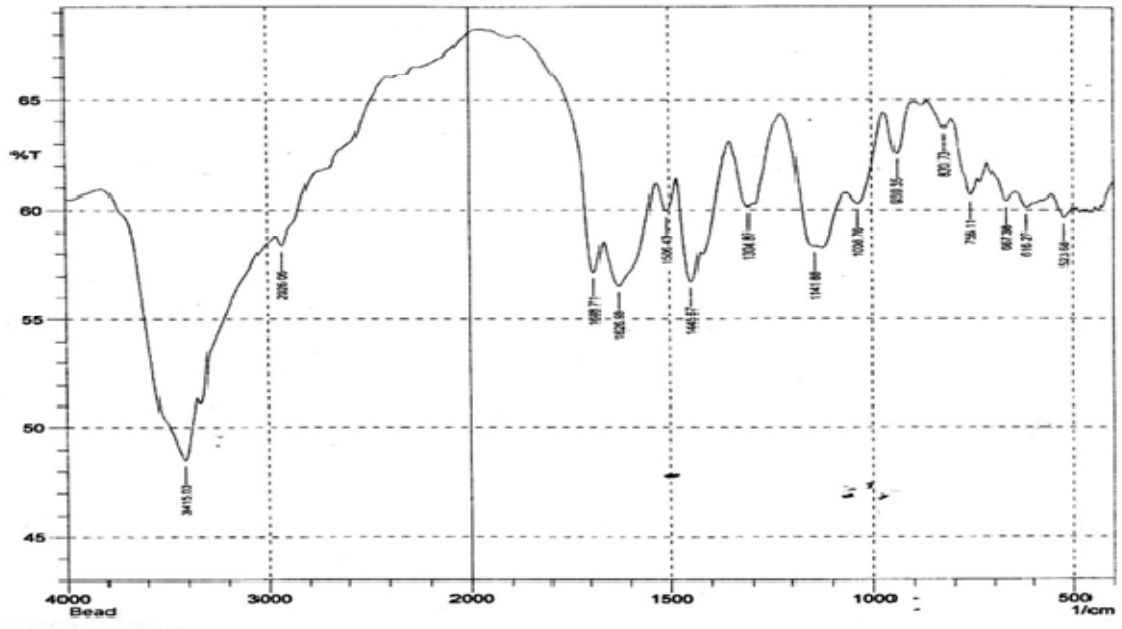


**Figure 3:** IR image of pure Diclofenac sodium pellets.

**Table 2:** Calibration curve of Diclofenac Sodium

| Concentration mcg/ml | Absorbance |
|---|---|
| 2 | 0.067 |
| 4 | 0.137 |
| 6 | 0.194 |
| 8 | 0.260 |
| 10 | 0.323 |

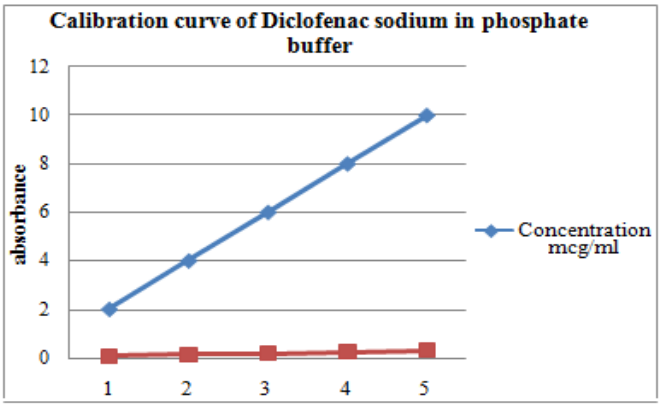


**Figure 4**

**Drug-Excipients Compatibility Studies**

The pure drug and along with formulation excipients were subjected to compatibility studies and studies were carried out by mixing definite proportions of drug and excipients and kept on glass vials which are stored at 40°c±2°c & 75±5%RH for one month

**Physico – Chemical Evaluation of Matrix Tablets:**

The results of the thickness, Hardness, weight variation, drug content, friability, disintegration time of tablet are shown in Table.

**Table 3:** Results of Thickness, weight variation, Hardness and Friability

| *Formulation* | *Hardness (Kg/cm2)* | *Thickness (mm)* | *Friability (%)* | *Weight variation (mg)* |
|---|---|---|---|---|
| F1 | 7.0 | 4.5 | 0.45 | pass |
| F2 | 6.4 | 4.9 | 0.54 | pass |
| F3 | 7.5 | 4.7 | 0.34 | pass |
| F4 | 6.5 | 5.3 | 0.59 | pass |
| F5 | 6.9 | 4.5 | 0.68 | pass |
| F6 | 5.8 | 5.1 | 0.75 | pass |

**Drug content uniformity of Diclofenac sodium in tablet. We found drug % is between 87-98**

**Table 4:** drug content in each formulation (Diclofenac sodium)

| *Formulation* | *Drug %* |
|---|---|
| F1 | 94.34 |
| F2 | 98.55 |
| F3 | 98.48 |
| F4 | 87.78 |
| F5 | 92.48 |
| F6 | 95.49 |

**Drug content uniformity of Allopurinol in tablet**

We found drug % is between the 92-97.

**Table 5:** Drug content in each formulation (Allopurinol)

| *Formulation* | *Drug %* |
|---|---|
| F1 | 92.34 |
| F2 | 93.45 |
| F3 | 95.48 |
| F4 | 94.78 |
| F5 | 97.48 |
| F6 | 95.49 |

**Table 6:** In-vitro Release study of tablet about Diclofenac sodium

| *Sr No* | *Time (h)* | *F1* | *F2* | *F3* | *F4* | *F5* | *F6* |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 12.5 | 13.5 | 14.5 | 12.4 | 15.3 | 13.4 |
| 2 | 2 | 20.5 | 20.4 | 23.4 | 18.4 | 23.4 | 18.9 |
| 3 | 3 | 34.5 | 27.4 | 29.4 | 27.4 | 29.2 | 25.6 |
| 4 | 4 | 48.4 | 31.3 | 36.4 | 32.4 | 37.1 | 31.3 |
| 5 | 5 | 58.4 | 42.4 | 41.4 | 40.4 | 42.4 | 39.5 |
| 6 | 6 | 72.9 | 52.4 | 56.5 | 46.4 | 53.4 | 43.6 |
| 7 | 7 | 79.8 | 64.2 | 61.4 | 52.4 | 61.2 | 54.5 |
| 8 | 8 | 85.4 | 71.4 | 68.6 | 62.3 | 69.4 | 63.7 |
| 9 | 9 | 91.3 | 79.4 | 78.3 | 71.3 | 78.2 | 69.0 |
| 10 | 10 | 94.3 | 87.4 | 85.4 | 78.3 | 83.4 | 73.7 |
| 11 | 11 | - | 91.3 | 94.2 | 82.3 | 89.3 | 81.3 |
| 12 | 12 | - | 95.5 | 98.4 | 94.4 | 99.4 | 83.5 |
| 13 | 13 | | | | | | 88.9 |
| 14 | 14 | | | | | | 95.4 |

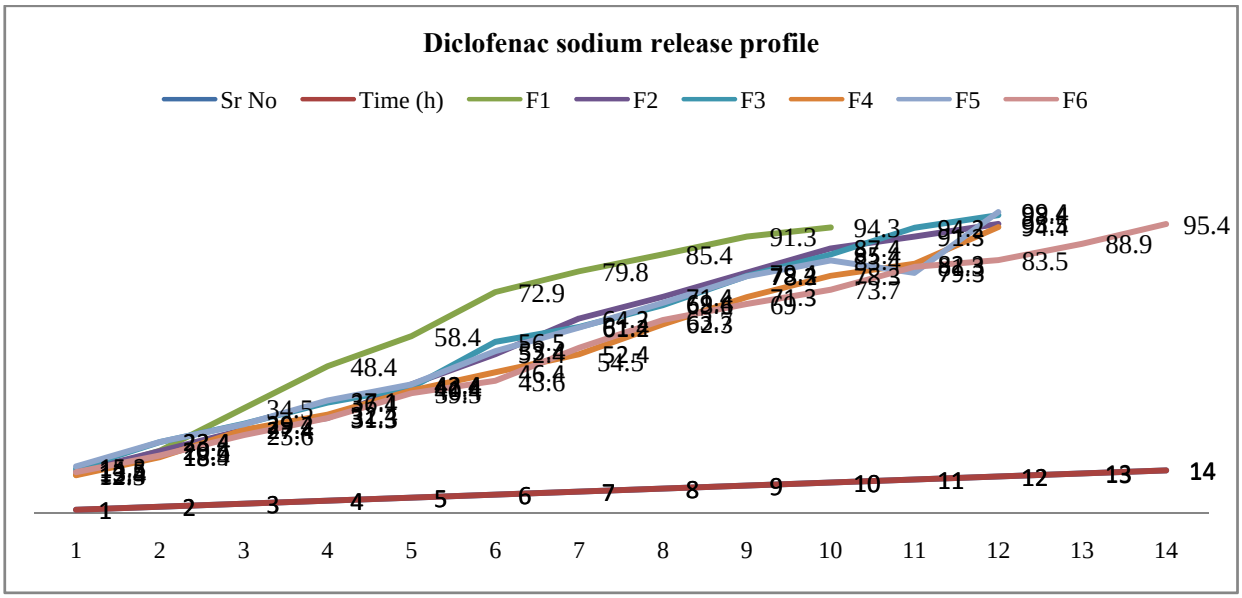


**Figure 5**

**Table 7:** Stability studies of formulation F4 and F5 at room temperature

| *Time (hr)* | *Cumulative % drug release* | |
|---|---|---|
| | *Initial* | *3months* |
| 1 | 15.3 | 16.3 |
| 2 | 23.4 | 26.4 |
| 3 | 29.2 | 29.9 |
| 4 | 37.1 | 37.1 |
| 5 | 42.4 | 42.4 |
| 6 | 53.4 | 55.4 |
| 7 | 61.2 | 61.9 |
| 8 | 69.4 | 69.4 |
| 9 | 78.2 | 77.2 |
| 10 | 83.4 | 83.4 |
| 11 | 89.3 | 91.3 |
| 12 | 99.4 | 98.4 |

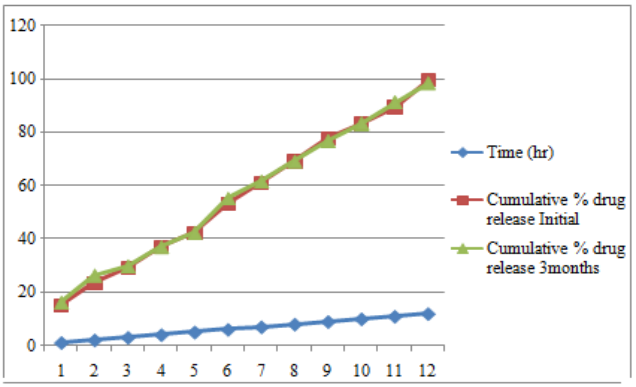


**Figure 5**

**Table 8:** Stability studies of formulation F5 at 40ºC

| Time (hr) | Cumulative % drug release | |
|---|---|---|
| | Initial | 3months |
| 1 | 14.3 | 16.3 |
| 2 | 23.4 | 26.4 |
| 3 | 28.2 | 29.9 |
| 4 | 37.1 | 37.1 |
| 5 | 42.0 | 42.4 |
| 6 | 53.4 | 55.4 |
| 7 | 61.2 | 61.9 |
| 8 | 67.4 | 69.4 |
| 9 | 78.2 | 77.2 |
| 10 | 84.4 | 86.4 |
| 11 | 89.3 | 91.3 |
| 12 | 99.4 | 98.4 |
| | | |
| Hardness | 6.81 | 6.83 |
| Friability | 0.85 | 0.84 |
| Drug contents | Pass | Pass |

**Table 9:** Kinetics of Drug Release Study of $F_5$

| Formulation | Zero order ($R_2$) | First order ($R_2$) | Higuchi's P lot (R 2) | Hixison Crowell (R 2) | Korsmeyer- peppas model | | |
|---|---|---|---|---|---|---|---|
| F5 | 0.9886 | 0.1375 | 0.9792 | 0.8843 | (R 2) | (n) | Order release |
| | | | | | 0.8210 | 0.765 | Non - Fickian |

**Table 10:** Swelling Index of Tablets of Batch $F_1$ to$F_6$

| Formulation | Time (hr) | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| F1 | 54.5 | 67.3 | 75.4 | 93.4 | 104 | 111 |
| F2 | 34.4 | 54.4 | 71.4 | 87.5 | 98.5 | 103 |
| F3 | 44.5 | 65.4 | 77.5 | 92.4 | 101.3 | 112 |
| F4 | 35.4 | 55.2 | 68.5 | 79.1 | 93.2 | 98.3 |
| F5 | 35.4 | 65.3 | 78.4 | 89.3 | 102.3 | 114 |
| F6 | 51.3 | 63.3 | 73.2 | 82.1 | 93.3 | 101 |

## 4. Conclusion

From the above formulation study we concluded that formulation of combinational drug of Diclofenac sodium and Allopurinol is well optimized formulation and can be use for the gout treatment, all the trial batches give good result for this combinational drug. Now a day the combinational therapy is very successful and has good synergistic effect and this is easy to take only one time for the patient. In this research we estimate the in-vitro release profile for two different drugs with different release profile one was sustain release and other was conventional release. There was no incompatibility for both drugs during release and action in this study we found that F5 has best result and good release profile.

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