International Journal of Pharmacy and Pharmaceutical Sciences, Vol. 1, Issue 2, Oct-Dec. 2009

Research Article

# FORMULATION DEVELOPMENT, EVALUATION AND VALIDATION OF SUSTAINED RELEASE TABLETS OF ACECLOFENAC

DR.UMESH.D .SHIVHARE*, NANDKISHOR D.ADHAO, DR.KISHORE.P.BHUSARI, DR.VIJAY.B. MATHUR, MR.DIGVIJAY U. AMBULKAR

Sharad Pawar College of Pharmacy, Wanadongri, Hingna Road, Nagpur-441 110
E-mail*: udshivhare@gmail.com, Mobile No. 09970163246
Received – 18th May, 2009, Revised and Accepted – 12th July 2009

## ABSTRACT

The objective of the present study was to develop "once daily" sustained release tablets of aceclofenac by wet granulation using carboxypolymethylene polymer. The drug excipient mixtures were subjected to preformulation studies while the tablets were subjected to physicochemical studies, *in vitro* drug release, stability studies and validation studies. The physicochemical properties of tablets were found within the limits. Formulation F2 & F9 containing Carbopol 971P and Carbopol 974P were found to release the drug in sustained manner upto 24 hour and were stable under accelerated conditions of temperature for 6 months since there were no significant changes in drug content and physical parameters.

**Keywords:** Aceclofenac, Matrix tablets, Sustained release, Wet granulation, Carboxypolymethylene polymer.

## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be the first-line drugs in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosingspondylitis, aceclofenac is one of them[1]. It is a newer derivative of diclofenac with low gastrointestinal complications. The short biological half-life (about 4 h) and dosing frequency more than one per day make aceclofenac an ideal candidate for sustained release. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained release formulation of aceclofenac is desirable. Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in designing a sustained release system. The present study aims to develop sustained release matrix tablets using hydrophilic matrix materials[2], such as Carbopol 971P and Carbopol 974P along with drug in varying proportions by wet granulation method.

## EXPERIMENTAL

### Materials

Aceclofenac B.P., Carbopol 971P and Carbopol 974P were obtained as gift samples from Amoli organics Ltd., Mumbai and Noveon, Mumbai respectively. Poly vinyl pyrrolidone K – 30, Isopropyl alcohol, Magnesium stearate, Talc, Microcrystalline cellulose, Hydrochloric acid, Methanol, Tween 80 were purchased from S.D. Fine-Chem Limited, Merck, Loba Chemie Mumbai, India respectively. All other chemicals used were of analytical grade.

### Preformulation studies

### Micromeritic properties

The physical mixtures of drug with different excipients were prepared by triturating drug and additives in a dried mortar for 5 min.

The angle of repose of aceclofenac and its physical mixtures with other excipients was determined by fixed funnel method.

The angle of repose (θ), Compressibility index (C.I.), Degree of compression (c) and the Hausner's ratio were calculated using following equations[3]:

$\theta = \tan^{-1} (h/r)$ ---------- (1)

Where, θ=Angle of repose

h=Height of granule above flat surface

r=Radius of circle formed by the granule pile.

C.I. = {($\rho t - \rho_0$) / $\rho_t$} × 100 ------- (2)

Where, $\rho_t$ - tapped density, $\rho_0$ - bulk density

$$c = \frac{H_o - H_p}{H_o} \times 100 \text{ ------- (3)}$$

Where, C - Degree of compression

$H_o$ - height of granule bed in the die before compression

$H_p$ - height of granule bed in the die at a pressure p

Hausner's ratio = TBD / LBD ---------- (4)

Where, TBD - Tapped Bulk Densities

LBD - Loose Bulk Density

**Table 1 : It shows results of study of physical parameters of granules**

| Formulation | Angle of repose (degree) | % Compressibility | Degree of compression | Homogeneity of blend (% w/w) |
|---|---|---|---|---|
| F1 | 28.36 | 18.21 | 41.80 | 98.87± 0.016 |
| F2 | 30.52 | 15.81 | 40.00 | 98.65± 0.761 |
| F3 | 28.76 | 16.14 | 41.60 | 97.34± 0.937 |
| F4 | 29.62 | 17.76 | 41.40 | 97.65± 1.213 |
| F5 | 28.16 | 17.26 | 40.40 | 97.34± 0.827 |
| F6 | 30.14 | 13.00 | 39.0 | 97.23± 1.115 |
| F7 | 30.42 | 18.21 | 40.40 | 98.65± 0.761 |
| F8 | 30.48 | 15.08 | 40.00 | 98.65± 0.721 |
| F9 | 28.81 | 14.82 | 41.80 | 98.64± 0.816 |
| F10 | 31.52 | 16.41 | 40.90 | 97.34± 0.937 |

**Preparation of tablets**

Tablets weighing 250 mg were prepared containing 200 mg of aceclofenac and Carbopol 971P or Carbopol 974P. The above polymers were added to the formulations in quantities ranging from 8.0 to 24.0 mg. polyvinyl pyrrolidone (1%) was used as binder, magnesium stearate (0.5%) and talc (0.5%) was added as lubricant prior to compression. Different tablet formulations were prepared by wet granulation technique. All the powders were passed through ASTM 80 mesh. Required quantity of drug and polymers were mixed thoroughly and a sufficient quantity of binding agent was added slowly. After enough cohesiveness was obtained, the mass was sieved through 16/22 mesh. The granules were dried at 50º for 2 h and were mixed with 15% of fines, talc and magnesium stearate. The tablets were compressed using Mini Press tablet compression machine.

**Table 2 : It Shows composition of sustained release tablet formulations**

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Aceclofenac | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| Carbopol 971P | 8 | 12 | 16 | 20 | 24 | | | | | |
| Carbopol 974P | | | | | | 8 | 12 | 16 | 20 | 24 |
| Microcrystalline cellulose | 42 | 38 | 34 | 30 | 26 | 42 | 38 | 34 | 30 | 26 |
| Magnesium stearate | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 |
| Talc | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 |

**Physicochemical characterization of tablets**

The thickness and diameter of the tablets were determined using digital vernier calipers. The hardness of the tablets was determined by using Monsanto hardness tester. The friability of the tablets was determined using Roche Friabilator. Weight variation test of the tablets was carried out as per the official method. For determining the drug content, three tablets were crushed and powder containing 200 mg of aceclofenac was dissolved in 100 mL of methanol. The solution was passed through a whatmann (No. 1) filter and analyzed spectrophotometrically at 275 nm after sufficient dilution with phosphate buffer (pH 6.8).

**Table 3 : It shows results of study of physical parameters of tablets**

| Formulation | Hardness ($Kg/cm^2$) | % Friability (%w/w) | Weight variation (g) | % Drug content (% w/w) |
|---|---|---|---|---|
| F1 | 5-7 | 0.77 ±0.073 | 252.4± 0.0106 | 98.89± 0.027 |
| F2 | 5-7 | 0.44±0.076 | 247.8± 0.0108 | 98.76± 0.346 |
| F3 | 5-7 | 0.50±0.098 | 248.3± 0.0102 | 98.26± 0.340 |
| F4 | 5-7 | 0.56±0.073 | 250.4± 0.0106 | 97.26± 0.875 |
| F5 | 5-7 | 0.55±0.070 | 248.6± 0.0102 | 97.96± 0.017 |
| F6 | 5-7 | 0.43 ±0.098 | 252.6± 0.0114 | 98.13± 0.112 |
| F7 | 5-7 | 0.72±0.049 | 251.6± 0.0120 | 97.46± 0.741 |
| F8 | 5-7 | 0.75±0.024 | 249.4± 0.0106 | 96.52± 0.872 |
| F9 | 5-7 | 0.46±0.090 | 247.6± 0.0054 | 96.52± 0.765 |
| F10 | 5-7 | 0.76±0.049 | 248.1± 0.0121 | 97.89± 0.215 |

**Dissolution studies**

During the development of a dosage form, the *in-vitro* test serve as a guide in estimating the amount of drug released with respect to time. After every hour, 2.0 ml of sample solution was withdrawn from each vessel and was replaced by same quantity of fresh dissolution medium. The sample solutions withdrawn from each vessel were diluted and analyzed spectrophotometrically at 275 nm for concentration of drug in each vessel. Percentage drug release in each case was calculated using standard calibration curve of drug in same dissolution medium.

**Table 4 : It shows comparative percentage drug release from various formulations of aceclofenac**

| Time in hour / Formula | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| F1 | 27.9± 0.32 | 38.94±0.87 | 45.97±0.65 | 50.61±0.14 | 56.61±0.74 | 59.80±0.98 | 62.76±0.11 | 80.40±0.58 | 90.63±0.32 | 96.69±0.33 | | | |
| F2 | 21.50±0.47 | 28.24±1.22 | 30.66±0.81 | 34.90±0.58 | 38.58±0.65 | 42.41±0.52 | 45.81±0.36 | 48.79±0.25 | 52.00±0.84 | 54.12±0.22 | 58.02±0.87 | 63.60±0.84 | 98.59±047 |
| F3 | 22.00±0.54 | 31.02±0.12 | 35.20±0.32 | 37.79±0.25 | 40.9± 0. 24 | 44.41±0.24 | 47.00±0.47 | 49.72±0.68 | 52.38±0.25 | 55.08±0.54 | 58.45±0.12 | 64.71±0.65 | 98.9± 0.52 |
| F4 | 23.93±0.24 | 34.46±0.58 | 35.26±1.65 | 44.42±0.11 | 49.4± 0.54 | 54.92±0.74 | 60.14±0.22 | 64.95±0.58 | 69.72±0.62 | 79.67±0.87 | 87.53±0.14 | 95.85±0.58 | |
| F5 | 21.09±0.14 | 27.66±0.58 | 29.28±0.34 | 32.98±0.47 | 35.54±0.19 | 39.41±0.16 | 42.53±0.87 | 46.17±0.22 | 50.05±0.44 | 53.44±0.87 | 56.04±0.55 | 62.05±0.54 | 98.4±0.21 |
| F6 | 29.74±0.22 | 32.90±0.58 | 38.05±0.87 | 49.03±0.21 | 55.25±0.47 | 60.95±0.65 | 66.43±0.72 | 71.48±0.58 | 83.10±0.45 | 98.97±0.21 | | | |
| F7 | 26.23±0.14 | 31.76±0.19 | 37.55±0.27 | 46.70±0.56 | 51.74±0.47 | 57.19±0.61 | 62.40±0.87 | 67.21±0.52 | 71.97±0.54 | 81.92±0.21 | 89.77±0.61 | 98.09±0.47 | 26.23±0.14 |
| F8 | 24.02±0.25 | 30.56±0.14 | 37.26±0.87 | 40.54±0.25 | 43.37±0.41 | 46.62±0.46 | 49.57±0.34 | 51.77±0.37 | 54.76±0.53 | 57.45±0.74 | 61.07±0.21 | 66.42±0.54 | 98.64±0.53 |
| F9 | 23.64±0.14 | 28..71± .74 | 34.21±0.52 | 40.04± .59 | 43.09±0.66 | 46.40±0.65 | 49.39±0.76 | 51.46±0.81 | 54.48±0.52 | 57.24±0.47 | 60.57±0.25 | 65.93±0.34 | 98.1± 0.47 |
| F10 | 20.94± 0.5 | 26.5± 0.25 | 32.8± 0.47 | 37.65±0.21 | 42.40±0.21 | 45.27±0.29 | 48.48±0.54 | 50.86±0.57 | 53.55±0.65 | 55.47±0.41 | 59.34±0.57 | 64.26±0.74 | 97.7± 0.46 |

Each value represents mean ± S.D., n=6

**Table 5: It Shows dissolution kinetics of aceclofenac**

| Formulation | Zero order (r) | 1st order (r) | Peppas ( r) | Hix.Crow ( r) |
|---|---|---|---|---|
| **F1** | 0.7784 | 0.8881 | 0.9870 | 0.9649 |
| **F2** | 0.8226 | 0.8959 | 0.9836 | 0.9692 |
| **F3** | 0.8572 | 0.8930 | 0.9739 | 0.9665 |
| **F8** | 0.7754 | 0.9406 | 0.9886 | 0.9718 |
| **F9** | 0.7903 | 0.9455 | 0.9889 | 0.9742 |
| **F10** | 0.8183 | 0.9458 | 0.9899 | 0.9761 |

**Drug release kinetics**

For finding out the mechanism of drug release from tablets, the dissolution data obtained from the above experiments were treated with the different release kinetic equations.

Zero order release equation:

$Q = K_0 t$ ------ (5)

First order equation:

$\ln Q = K_f t$ ------ (6)

Higuchi's square root of time equation:

$Q = K_H t^{½}$ ------ (7)

Korsmeyer and Peppas equation:

$F = (M_t / M) = K_m t^n$ ------ (8)

**Stability studies**

The tablets were exposed for the accelerated stability studies according to ICH guidelines (40±2°C and 75±5% RH) for a period of 6 months in stability chambers. The samples were taken out at 15th, 30th, 60th, 90th and 180th days and evaluated for the drug content and physical parameters like color change, friability and hardness[4].

**RESULTS AND DISCUSSION**

**Micromeritic properties**

The results of Micromeritic properties are given in Table 1.

As a general guide, powders with angle of repose close to 25° correspond to good flow properties whereas angle near to 50°C is characteristics of cohesive powders. The results of angle of repose indicate good flow properties of the granules. Generally, compressibility index values up to 15% result in good to excellent flow. The compressibility indexes of granules were slightly higher this could be because of presence of more fines. Degree of compression is characteristic of compression capability of the granules and the results obtained exhibited good compression capability of the granules. Degree of homogeneity of blend was studied to characterize the mixing process. The observations indicated uniform mixing.

**Evaluation of prepared tablets**

The results of physicochemical evaluation of tablets are given in Table 3. The hardness of tablet is indicative of crushing strength to withstand handling during packaging and transportation. The tablets of different batches were found uniform with respect to hardness within the range of 5-7 kg/cm$^2$. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability of formulation was below 1%, indicating that the friability was within the prescribed limits. In weight variation test, the pharmacopoeial limit for

percentage deviation for tablets of more than 250 mg is ±5% and all the formulations were found to comply with the specifications given in I.P. for weight variation test. Good uniformity in drug content was found among the formulations, and percentage of drug content was more than 95%. All the tablet formulations showed acceptable pharmacotechnical properties.

**Stability studies**

The results of accelerated stability studies, carried out according to ICH guidelines, indicated that the tablets did not show any physical changes (color change, friability and hardness) during the study period.

***In vitro* drug release study**

The results of dissolution studies of formulations composed of Carbopol 971P (F1 to F5) shows that F1, F2 released 38.94 ± 0.87% and 28.24± 1.22% at end of 2 hour and 96.69 ± 0.33% in 10 hour for F1 and 98.59 ± 0.47% of drug at the end of 24 hour for F2. F3, F4 and F5 released 31.02 ± 0.12%, 34.46 ± 0.58% and 27.66± 0.58% at end of 2 hour respectively and 98.9 ± 0.52% in 24 hour for F3, 95.85 ± 0.58% in 12 hour for F4, 98.4± 0.21% of drug at the end of 24 hour for F5.

The results of dissolution studies of formulations composed of Carbopol 974P showed release of 32.90 ± 0.58 %, 31.76± 0.19%, 30.56 ± 0.14%, 28.71 ± 0.74% and 26.5 ± 0.25% at the end of 2 hour respectively and 98.97 ± 0.21% at the end of 10 hour for F6, 98.09 ± 0.47%, 98.64 ± 0.53%, 98.1 ± 0.47% and 97.7 ± 0.46% at the end of 24 hour for F7, F8, F9, F10 respectively. Formulation **F2** containing Carbopol 971P was found to release the drug in sustained manner upto 24 hour and was considered optimum for stability studies. Formulation **F9** containing Carbopol 974P was found to release the drug in sustained manner upto 24 hour and was considered optimum for stability studies.

**Study of drug release kinetics**

**Mechanism of drug release from carbomer matrices**

In dry state, the drug is entrapped in the glassy core of carbomer matrix. On hydration of this surface, a gelatinous layer is formed that consists of discrete micro gels made up of many polymer particles in which the drug is dispersed. When the hydrogel is fully hydrated, it does not dissolve, but osmotic pressure from within works to break up the structure, mainly by sloughing off discrete pieces of the hydrogel. These hydrogel remain intact, and the drug continues to diffuse through the gel layer at a continuous rate. It is postulated that, as the concentration of the drug becomes high within the gel matrix and its thermodynamic potential increases, the gel layer around the tablet core then acts as a rate controlling membrane, resulting in a linear release of the drug. Factors that influence the dissolution rate are the molecular structure of the polymer and the rate of hydration and swelling, which in turn is depends upon the pH of the dissolution medium.

Drugs exhibiting poor solubility tend to partition into more hydrophobic domains of the system. Since the hydrogel layer is stable, it results in linear drug release. On the other hand, in the case of highly soluble drugs, the Fickian diffusion CR rate is due to the fast dissolution of the drug through the water filled interstitial spaces between the hydrogel of such highly cross linked carbomer as 974P and 934P. With lower cross linked carbomer

971P, the drug is more likely to partition preferentially in the hydrophilic matrix of the resin and exhibit nonlinear diffusion.

In order to study the drug release kinetics of the examined tablets, the dissolution profiles of formulations F1, F2, F3, F8, F9 and F10 were analyzed according to zero-order, first order, Higuchi's square root and Peppas Korsmeyer equations (Table 5).

## CONCLUSION

The present study demonstrated the successful preparation of stable, once daily extended release matrix tablets of aceclofenac. Carbopol 971P or Carbopol 974P were found to be suitable as bases for preparing hydrophilic tablet matrices and a stable sustained release dosage form containing the drug aceclofenac.


## ACKNOWLEDGEMENTS

Authors are thankful to Amoli organics Ltd. Mumbai and Noveon, Mumbai for the gift samples of aceclofenac and Carbopol 971P and Carbopol 974P respectively.


## REFERENCES


1. British Pharmacopoeia, Published in the recommendations of the Medicines Commission pursuant to the Medicines Act, London, Vol.I, 33, (1968), 1998.
2. Goodrich BF. Controlled Release Tablets and Capsules. Bulletin no. 17, Brecksville OH. Ed 1995.
3. Aulton ME. Pharmaceutics, The Science of Dosage Form Design, 2nd Ed, ELBS with Churchill living stone. 2002:199-200.
4. Lachman, L, Liberman, HA, and Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd Ed., Lea and Febiger 1987: 297-300.