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# STABILITY STUDIES OF FORMULATED CONTROLLED RELEASE ACECLOFENAC TABLETS

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## ABSTRACT

Stability studies were performed on various formulations of aceclofenac tablets prepared by wet granulation method and solid dispersions using Eudragit RS 100 as a rate controlling polymer. The *in vitro* drug release was found to be 89% for aceclofenac from solid dispersion formulation (**B7**) compared with 83% from wet granulation formulation (**B1**). Selected formulation (**B7**) was packed and stored at 40 ± 2°C with 75 ± 5% RH for a period of six months and 25 ± 2°C with 60 ± 5% RH for a period of 9 months. At every 1, 2, 3, 6 and 9 months, samples were evaluated for appearance, hardness, friability, weight variation, drug content and drug release studies. A slight variation occurred in above parameters periodically in aceclofenac content. Drug release rate was good, when stored under accelerated conditions.

**Key words**: Aceclofenac, Wet granulation, Solid dispersions, Stability studies, Controlled release

## INTRODUCTION

Aceclofenac is a non-steroidal anti-inflammatory drug useful in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis[1,2]. The maintenance of effective drug concentration level in the body for a constant and uniform supply of drug is desired for the successful treatment of arthritis. It is rapidly and effectively absorbed after oral administration but has short biological half life of 4 hr[3].

The stability of a drug product refers to the chemical and physical integrity of the dosage unit and when appropriate, the ability of the drug product to maintain protection against environmental conditions. An ideal drug product must be fully characterized physically, chemically at the start of study and throughout the intended shelf-life period[4].

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Eudragit RS 100 is a hydrophobic polymer and it is used extensively as a coating material, as a tablet binder in the preparation of microcapsules and microspheres and in the preparation of matrix type controlled release tablets. Hydrophobic polymers provide several advantages, ranging from good stability at varying pH values and moisture levels established safe applications[5].

The major objective of this paper is to disclose our work of preparing a stable, controlled release formulation of aceclofenac with amino methacrylate copolymer (Eudragit RS-100). The use of an amino methacrylate copolymer to form a controlled release formulation of aceclofenac can improve and enhance two important physical and chemical properties of aceclofenac. First, the solid dispersion matrix formed by the copolymer can protect aceclofenac from being degraded by water so that the stability of aceclofenac is improved. Second, aceclofenac can be slowly released by diffusion from the copolymer matrix. The primary advantage of a controlled release dosage form should also be addressed here; the dosing frequency for the oral administration of aceclofenac can be greatly reduced to a once-daily form.

## EXPERIMENTAL

### Materials and methods

### Material

Aceclofenac, Eudragit RS 100 and aerosil were gift samples from M/s Seeks Biotech Ltd., Vijayawada. Lactose (anhydrous), ethanol and magnesium stearate were purchased from S.D. Fine Chemicals, Mumbai.

### Methods

### Preparation of tablets by wet granulation method

Different formulations were prepared by wet granulation method. The amount of drug was kept constant at 200 mg/tablet, or 66.67% w/w. The amount of polymers in these formulations varies from 6, 8, 10, 12, 16 and 20% w/w. The final tablet weight was adjusted to 300 mg by adding lactose as filler. The different composition of the tablet formulations are given in Table 1.

Required quantity of aceclofenac, Eudragit RS-100 and lactose were mixed thoroughly and transferred into mortar and ethyl alcohol was added with constant mixing. The wet mass was passed through sieve No. 10 and the obtained granules dried for 2 hrs in an oven at $40^0$C. The dried granules were passed through a sieve No. 12. Finally magnesium

stearate (1%w/w) and Aerosil (1%w/w) was mixed for lubrication and glidant for granules. The obtained granules were then compressed with single punch tablet compression machine (Cadmach, Ahmedabad, India) using 9 mm punches and dies.

**Table 1: Formulation of tablets prepared by wet granulation method**

| Ingredients | Quantities mg/tablet | | | | | |
|---|---|---|---|---|---|---|
| | **B1** | **B2** | **B3** | **B4** | **B5** | **B6** |
| Aceclofenac | 200 | 200 | 200 | 200 | 200 | 200 |
| Eudragit RS100 | 18 | 24 | 30 | 36 | 48 | 60 |
| Lactose | 76 | 70 | 64 | 58 | 46 | 34 |
| Ethyl alcohol | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 |
| Aerosil | 3 | 3 | 3 | 3 | 3 | 3 |

## Preparation of tablets by solid dispersion

The amount of polymers used in these formulations varies from 4, 8, 10, 12, 16 and 20% w/w and the final tablet weight was adjusted to 300 mg by adding lactose as filler, maintaining the drug in each tablet as 200 mg or 66.67% w/w. The different compositions of the tablet formulations are given in Table 2.

**Table 2: Formulation of tablets prepared by solid dispersions**

| Ingredients | Quantity mg/tablet | | | | | |
|---|---|---|---|---|---|---|
| | **B7** | **B8** | **B9** | **B10** | **B11** | **B12** |
| Aceclofenac | 200 | 200 | 200 | 200 | 200 | 200 |
| Eudragit RS100 | 12 | 24 | 30 | 36 | 48 | 60 |
| Lactose | 82 | 70 | 64 | 58 | 46 | 34 |
| Ethyl alcohol | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 |
| Aerosil | 3 | 3 | 3 | 3 | 3 | 3 |

Required quantity of drug and polymer were transferred into a beaker; ethyl alcohol was added to the beaker and stirred for 15 min until dissolved. Lactose was then added and mixed for 10 min. The beaker containing the dispersion was then incubated at $40^0$C and stirred constantly until complete evaporation of the solvent. After evaporation of the solvent, the mass was passed through sieve No. 10. The obtained granules were then dried in an oven at $40^0$C for 2 hrs. The dried granules were passed through sieve No. 12. Magnesium stearate (1%w/w) and aerosil (1%w/w) were added to the above mass and blended for 2 min. The final blend was then compressed into tablets by using a single punch tablet compression machine (Cadmach, Ahmedabad, India) using 9 mm punches and dies.

## Physicochemical characterization of tablets[6]

The thickness of the tablets was determined by using vernier calipers. The hardness of the tablets was determined by using Pfizer hardness tester. The friability of the tablets was determined by using Roche friabilator. Weight variation of the tablets was carried out as per the official method of IP.

## Estimation of drug content[7]

Three tablets of each formulation were collected and powdered. Powder equivalent to 100 mg of aceclofenac was weighed and added to sufficient quantity of methanol and diluted with 6.8 phosphate buffer to make up the volume to 100 mL. It was allowed to sonicate for 15 min. The solution was filtered and the absorbance was measured after suitable dilutions by using Shimazdu UV spectrophotometer at 275 nm.

## *in vitro* Dissolution studies

The *in vitro* dissolution study was carried out using USP Type 2 dissolution apparatus. The study was carried out in 900 mL of 2% SLS in 0.1N HCl for first 2 hours and then 900 mL of phosphate buffer (pH 6.8) from 3 to 24 h. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37 ± $0.5^0$C. The pre-weighed tablet was then introduced into the dissolution jar and the paddle was rotated at 75 rpm. At different time intervals, 5 mL sample was withdrawn and analyzed spectrophotometrically at 275 nm for the drug release. At each time of withdrawal, 5 mL of fresh corresponding medium was replaced into the dissolution flask.

## Stability studies

After determining drug content, the tablet was charged for the accelerated stability studies according to ICH guidelines (40 ± $2^0$C / 75 ± 5% RH) for a period of 6 months and (25 ± $2^0$C / 60 ± 5% RH) for a period of 9 months in stability chambers (Thermolab,

Mumbai, India). They were placed in USP type-1 flint vials and hermetically sealed with bromobutyl rubber plugs and aluminum caps. The samples were taken out and evaluated for the drug content and physical parameters like color change, friability and hardness.

## RESULTS AND DISCUSSION

The results of physicochemical evaluation of tablets for the formulations **B1**, **B2**, **B3**, **B4**, **B5**, **B6**, **B7**, **B8**, **B9**, **B10**, **B11** and **B12** are shown in Table 3. All the formulations showed uniform hardness of the tablets, which was satisfactory and the percentage friability for all the formulations were below 1% indicating that friability was within the prescribed limits. Good and uniform drug content (>98%) was observed within the batches of different tablet formulations. All the tablets complied with I.P weight variation test requirements.

**Table 3: Evaluations of tablets prepared by wet granulation method and solid dispersions**

| Formulations code | Thickness* (mm) | Hardness* (kg/cm$^2$) | Friability** (%) | Weight variation*** (%) | Drug content* (%) |
|---|---|---|---|---|---|
| **B1** | 4.72 ± 0.03 | 4.8 ± 0.158 | 0.71 ± 0.041 | 2.469 ± 0.127 | 97.78 ± 0.173 |
| **B2** | 4.71 ± 0.02 | 5.0 ± 0.315 | 0.68 ± 0.054 | 2.494 ± 0.066 | 98.59 ± 0.173 |
| **B3** | 4.69 ± 0.01 | 4.9 ± 0.214 | 0.55 ± 0.025 | 3.095 ± 0.071 | 96.99 ± 0.051 |
| **B4** | 4.72 ± 0.02 | 4.2 ± 0.132 | 0.81 ± 0.028 | 2.585 ± 0.053 | 99.76 ± 0.069 |
| **B5** | 4.72 ± 0.03 | 4.3 ± 0.161 | 0.67 ± 0.016 | 3.199 ± 0.064 | 98.78 ± 0.259 |
| **B6** | 4.69 ± 0.03 | 4.5 ± 0.102 | 0.77 ± 0.019 | 4.151 ± 0.053 | 98.14 ± 0.219 |
| **B7** | 4.69 ± 0.03 | 4.9 ± 0.204 | 0.82 ± 0.037 | 3.239 ± 0.066 | 98.96 ± 0.035 |
| **B8** | 4.68 ± 0.02 | 4.2 ± 0.103 | 0.61 ± 0.031 | 2.221 ± 0.028 | 99.12 ± 0.143 |
| **B9** | 4.68 ± 0.03 | 4.3 ± 0.152 | 0.62 ± 0.042 | 2.885 ± 0.051 | 98.68 ± 0.105 |
| **B10** | 4.70 ± 0.04 | 4.5 ± 0.102 | 0.68 ± 0.022 | 2.549 ± 0.013 | 97.92 ± 0.047 |
| **B11** | 4.71 ± 0.02 | 4.0 ± 0.109 | 0.62 ± 0.035 | 2.841 ± 0.155 | 99.45 ± 0.113 |
| **B12** | 4.75 ± 0.02 | 4.7 ± 0.141 | 0.73 ± 0.062 | 4.109 ± 0.017 | 98.48 ± 0.042 |

All values are expressed as Mean ± S.d; * n = 3; ** n = 10, and *** n = 20

**Dissolution profile of controlled release aceclofenac tablets**

The dissolution profiles of the aceclofenac controlled release tablets **(**Figs. 1 and 2**)**, prepared by wet granulation and solid dispersion techniques using Eudragit as a rate controlling polymer, were carried out in 900 mL of 2% SLS in 0.1N HCl for first 2 hr and then 900 mL of phosphate buffer (pH 6.8) up to 12 hr.

The *in vitro* drug release was found to be 89% for aceclofenac from solid dispersion formulation **(B7)** compared with 83% from wet granulation formulation **(B1)**.Thus solid dispersions require less quantity of polymer, when compared to wet granulation method.

As the solid dispersion formulation **B7** was found to be the best in a drug release among the formulated ones, accelerated stability studies were determined on those tablets by storing them at various temperatures for different time periods.

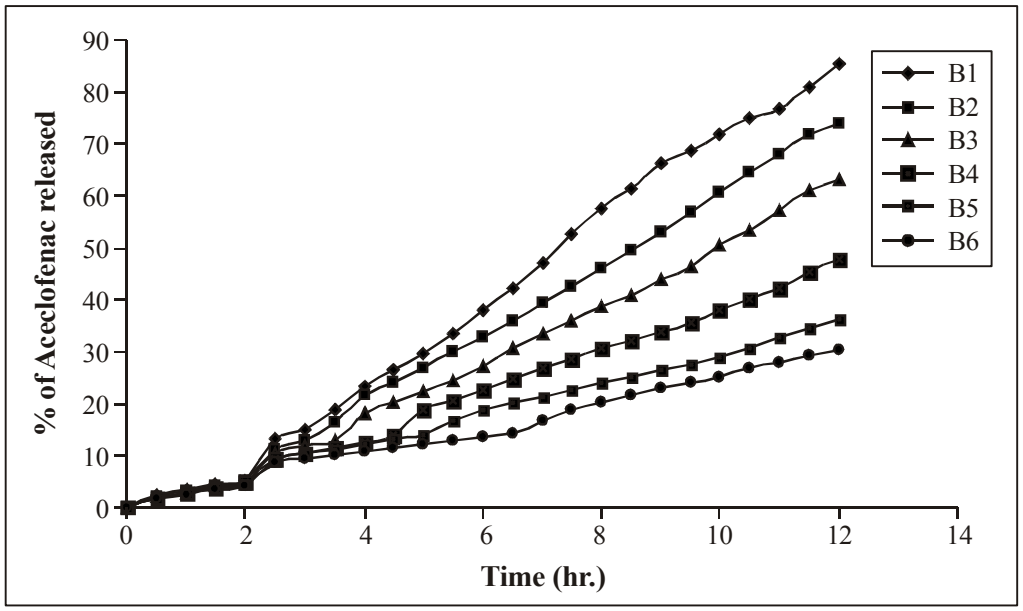


**Fig. 1: Dissolution profiles of aceclofenac tablets prepared with Eudragit RS-100 by wet granulation method**

**B1**: Tablets prepared with ERS 6%; **B2**: Tablets prepared with ERS 8%; **B3**: Tablets prepared with ERS 10%; **B4**: Tablets prepared with ERS 12%; **B5**: Tablets prepared with ERS 16%; **B6**: Tablets prepared with ERS 20% .

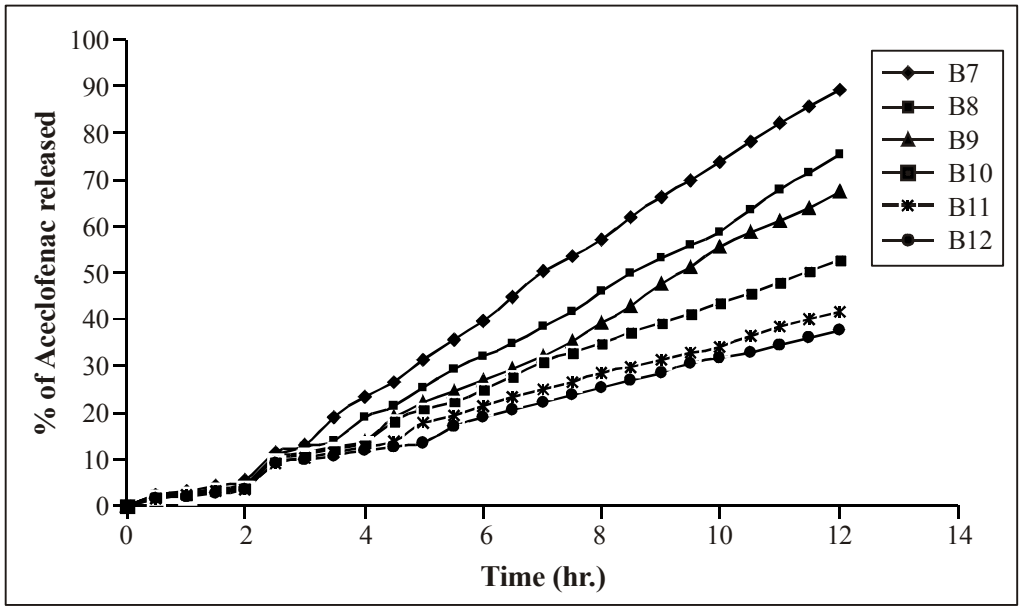


**Fig. 2: Dissolution profiles of aceclofenac tablets prepared with Eudragit RS-100 by solid dispersions**

**B7**: Tablets prepared with ERS 4%; **B8**: Tablets prepared with ERS 8%; **B9**: Tablets prepared with ERS 10%; **B10**: Tablets prepared with ERS 12%; **B11**: Tablets prepared with ERS 16%: **B12**: Tablets prepared with ERS 20%

## Stability studies on formulated tablet (B7)

The results of stability studies, carried out according to ICH guidelines, indicated that the tablets hardly showed physical changes (colour change, friability, and hardness) during the study period Table 4.

**Table 4: Stability studies of physical and chemical prameters of formulated aceclofenac tablets**

| Formulation (B7) | Time | Appearance | Hardness* (kg\|cm$^2$) | Friability** (%) | Weight variation *** (%) | Drug Content* (%) |
|---|---|---|---|---|---|---|
| Stability chamber (40 ± 2$^0$C/ | Initial | No change | 4.9±0.204 | 0.82±0.037 | 3.239±0.066 | 99.76±0.069 |
| | 1 month | No change | 4.8±0.302 | 0.80±0.455 | 3.237±0.122 | 99.69±0.202 |

Cont…

| Formulation (B7) | Time | Appearance | Hardness* (kg\|cm$^2$) | Friability** (%) | Weight variation *** (%) | Drug content* (%) |
|---|---|---|---|---|---|---|
| 75 ± 5% RH) | 2 months | No change | 4.75±0.451 | 0.85±0.266 | 3.235±0.147 | 99.35±0.073 |
| | 3 months | No change | 4.73±0.372 | 0.79±0.567 | 3.233±0.245 | 99.09±0.061 |
| | 6 months | No change | 4.70±0.465 | 0.81±0.385 | 3.231±0.211 | 98.75±0.421 |
| Stability chamber (25± 2$^0$C/ 60 ±5%RH) | Initial | No change | 4.9±0.204 | 0.82±0.037 | 3.239±0.066 | 99.76±0.069 |
| | 1 month | No change | 4.9±0.204 | 0.80±0.037 | 3.239±0.143 | 99.62±0.259 |
| | 2 months | No change | 4.85±0.502 | 0.08±0.135 | 3.238±0.324 | 99.48±0.219 |
| | 3 months | No change | 4.80±0.502 | 0.79±0.567 | 3.236±0.242 | 99.31±0.035 |
| | 6 months | No change | 4.70±0.108 | 0.86±0.432 | 3.234±0.109 | 99.25±0.173 |
| | 9 months | No change | 4.68±0.603 | 0.83±0.368 | 3.232±0.177 | 99.01±0.051 |

All values are expressed as Mean ± S.d; * n = 3; ** n = 10, and *** n = 20

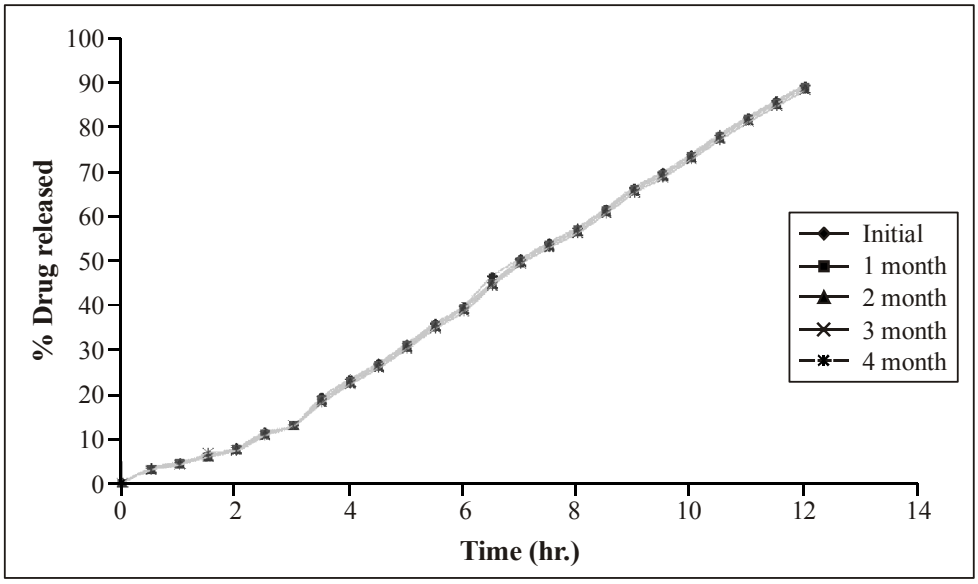


**Fig. 3: Dissolution profiles of aceclofenac matrix tablets (B7) stored at different times of storage**

The formulation **B7** stored at 40 ± 2$^0$C with 75 ± 5% RH for a period of 6 months and the

drug content was found >98.75 ± 0.421% at the end of 6 months (40°C ± 2°C with 75% RH ± 5% RH) and 99.01 ± 0.051% at the end of 9 months (25°C ± 2°C with 60%RH ± 5%RH).This indicates that **B7** tablet is fairly stable at storage condition, The dissolution profiles as shown in Fig. 3 and 4. However, real time stability studies for a period of 2 years are required to establish the stability of developed product.

The stability of aceclofenac prepared using 4% Eudragit RS-100 by solid dispersion techniques (**B7**) was significantly improved.

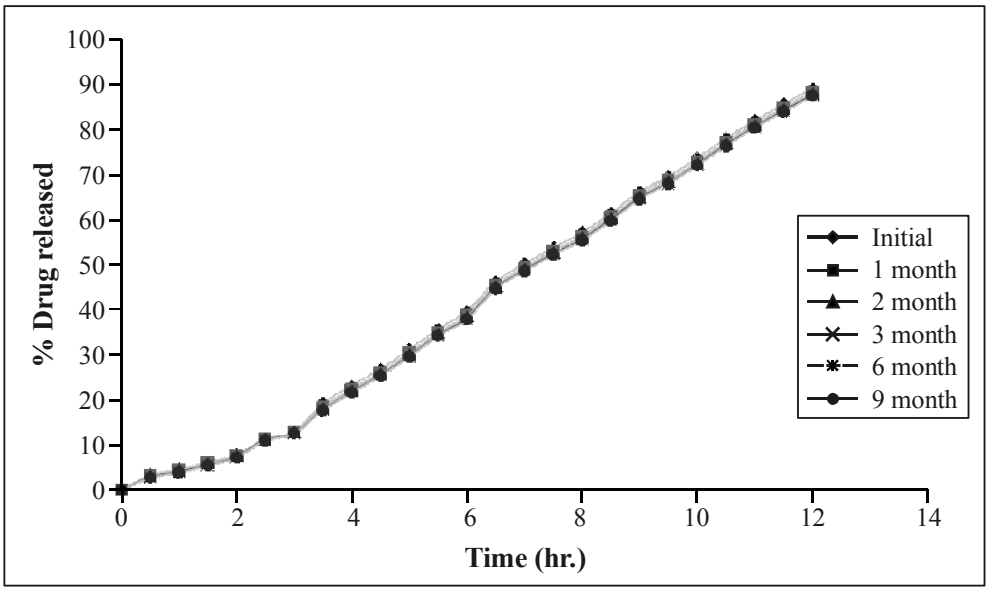


**Fig. 4: Dissolution profiles of aceclofenac matrix tablets (B7) stored at different times of storage**

The formulation **B7** stored at 25 ± 2°C with 60 ± 5%RH for a period of 9 months.

## CONCLUSIONS

Eudragit RS-100 can be used successfully to formulate controlled release aceclofenac tablets by wet granulation and solid dispersion techniques. The release rate of drug from matrix tablet can be governed by manufacturing processes and concentration of polymer employed in the preparation of tablets. A controlled release tablet formulation containing Eudragit RS-100 exhibits stable characteristics, when stored under stress condition.

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