Research Article **CODEX: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

PREPARATION AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE TABLETS OF ACECLOFENAC

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ABSTRACT

The objective of the present investigation was to design and develop sustained release of Aceclofenac tablets. Aceclofenac sustained release tablets were developed different natural polymers like Guar gum and Xanthan gum and Chitosan. Sustained release tablets of Aceclofenac were prepared by direct compression technique. The prepared tablets evaluated in terms of their Pre-compression studies, Post-compression studies, *in vitro* study and bioequivalence studies. The results of *in vitro* drug release studies showed that formulation-7 (FAS-7) has better sustained over release of drug (98.47%) when compared to marketed product (73.52%) for 24hrs.

KEY WORDS

Aceclofenac, Guar gum, Xanthan gum, Chitosan, *In vitro* study and Bioequivalence studies.

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INTRODUCTION

Oral sustained release dosage form by direct compression technique is a very simple approach in the pharmaceutical area for its ease, compliance, faster production, avoids hydrolytic or oxidative reactions occurred during processing of dosage forms and also economics. Sustained or controlled drug delivery occurs while a drug embedded within a polymer that may be natural or semi-synthetic or synthetic in nature. The polymer is judiciously

combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predetermined fashion and released drug at constant rate for desired time period. There are number of techniques applied in the formulation of sustained release dosage form. However, the matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems[1]. Aceclofenac is a newer derivative of the Diclofenac group of non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic and anti-inflammatory activities. It directly blocks the prostaglandin synthesis. It has less gastrointestinal complications. It is considered to be the first-line drug in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis[2]. Non-steroidal anti-inflammatory drugs (NSAIDs) are highly effective in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. But their long term use has lead to gastrointestinal (GI) complications like ulceration, perforation and obstruction. Due to its short biological half life (about 4 hrs) and dosing frequency (200 mg daily in 2 divided doses) of more than one per day, Aceclofenac is an ideal candidate for sustained release formulation. Several matrixes based sustained release products of Aceclofenac have been reported based on their use as either a hydrophilic or hydrophobic polymers. The reported sustained release formulations of Aceclofenac did not involve any attempt to prevent drug release in the upper GI tract.

MATERIALS AND METHODS

Materials

Aceclofenac was obtained from Cadila Health Care Pvt.Ltd, Ahmedabad, India. Chitosan were purchesed from Paras Chem suppliers, Pune, India. Xanthangum and Polyvinyl pyrrolidone K_{30} was a Gift sample from Apex Laboratories Pvt. Ltd, Chennai. Guar gum, Lactose, Methyl paraben, Talc and Magnesium Stearate were purchased from Qualigens fine chemicals, Mumbai, India. All other chemicals and ingredients were used for study are of Analytical grade.

Methods

Preparation of Aceclofenac sustained release tablets

The composition of different formulations of Aceclofenac SR matrix tablets is shown in Table No.1. Different tablet formulations were prepared by direct compression technique. All the powders passed through 40/60 mesh sieve. The required quantity of pure drug, various polymers and other ingredients were mixed thoroughly. Talc and magnesium stearate were finally added as a glidant and lubricant respectively. The blend was directly compressed (10 mm diameter, round flat faced punches) using multiple punch tablet compression machine (Cad mach Machinery Ltd., Ahmedabad, India). Each tablet containing 200 mg of pure Aceclofenac[1].

Evaluation Parameters[3-5]

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy

The fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug, polymers and formulations were recorded by using BOMENMB SERIES FTIR instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade KBr, samples were scanned in the IR range from 500 to 3500 cm^{-1}, with a resolution of 4 cm^{-1}.

Pre-compression studies of sustained release tablet granules

Bulk density

3gm of granules were weighed separately and transferred into 100ml measuring cylinder, initial volume was measured and calculated according to the formula,

Bulk density = Mass / Volume

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the granules in the cylinder and this minimum volume, the tapped density may be computed.

Tapped density = Weight of granules/Tapped volume of granules

Angle of Repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The most commonly used of this in angle of repose, which may be determined experimentally by number of methods. The method used to find the angle of repose is to pour the powder a conical on a level, flat surface and measure the included angle with the horizontal.

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

Where, θ = Angle of repose, h = Height of the powder cone, r = Radius of the powder con.

Compressibility Index or Carr's Index

Carr's Index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where, TD = Tapped density**,**
BD = Bulk density

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

Hausner's Ratio = Tapped density/Bulk density

Post-compression studies of Aceclofenac sustained release tablets

Hardness or Crushing strength Test

Hardness of the tablet was determined using the Monsanto hardness tester (The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets have a hardness of 3 kg and some sustained release tablets have a hardness of 10-20 kg[5].

Thickness Test

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Vernier calliper and the reading was recorded in millimeters.

Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The Conventional compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where,

I - Initial weight, F - Final weight

Weight variation test

Weights of 20 individual tablets were noted and their mean weight also calculated. The percentage deviation was calculated by using the following formula,

$$\text{Percentage deviation} = [X-X^*/ X] \times 100$$

X - Actual weight of the tablet,

X^*- Average weight of the tablet

Estimation of Drug Content

An accurately weighed amount of powdered Aceclofenac (100 mg) was extracted with water and the solution was filtered through 0.45 µ membrane filter paper. The absorbance was measured at 275 nm after suitable dilution[6].

Calculation

The amount of Aceclofenac present in tablet can be calculated using the formula

$$A_t/As \times S_w/100 \times 100$$

Where,

A_t = Absorbance of sample preparation,

A_s = Absorbance of Standard preparation,

S_w = weight at Aceclofenac working standard (mg)

***In vitro* Drug Release Studies**

The *in vitro* drug release study was carried out for 24 hours using USP paddle type dissolution

apparatus in phosphate buffer (pH 6.8) at 75 rpms maintaining temperature at 37±0.5^{0}c. A 10ml of samples were collected from each vessel at 0, 2, 4, 8, 12, 16 and 24 hours and analyzed by UV spectrophotometer at 275 nm. The withdrawn sample was immediately replaced by equal volume of fresh buffer. The dissolution data obtained were plotted as percentage drug release versus time[6].

Bioequivalence studies

The bioequivalence study (FAS-7 and ARRESTIN SR TAB) was carried out for 24 hours using USP paddle type dissolution apparatus in phosphate buffer (pH 6.8) at 75 rpms maintaining temperature at 37±0.5^{0}c. A 10ml of samples were collected from each vessel at 0, 2, 4, 8, 12, 16 and 24 hours and analyzed by UV spectrophotometer at 275 nm. The withdrawn sample was immediately replaced by equal volume of fresh buffer. The dissolution data obtained were plotted as percentage drug release versus time.

RESULTS AND DISCUSSIONS

Pre-formulation studies

Compatibility studies (Fourier Transform Infrared Spectroscopic studies)

The Fourier transform infra-red analysis was conducted for the surface structure characterization. FTIR spectrum of the pure drug, polymers and formulations was recorded. The Fourier transform infrared spectroscopy study reveals that there is no interaction between the pure drug, polymers and formulations. Then all the functional groups found in the IR spectrum of pure drug, polymers and formulations.

Pre-compression studies of sustained release tablet granules

Bulk density

The packing properties of the drugs and their formulations widely depend upon bulk density. It has been stated that bulk density values less than 1.2gm/cm^3 indicate good flow and values greater than 1.5 gm/cm^3 indicate poor flow. From the result it can be seen that the bulk density values are less than 1.2gm/cm^3. This indicates good flow characteristics of the granules. The results are shown in Table No.6.

Tapped density

The tapped density was determined by cylindrical method. The tapped density values indicate good flow characteristics of the granules. The results are shown in Table No.6.

Angle of Repose

The angle of repose for various batches of the granules is found to be less than 40^0, it indicates good flow properties of the granules. The results shown in Table No.6.

Compressibility Index or Carr's Index

The Carr's Index for various batches of the granules is found to be less than 15, it indicates good flow properties of the granules. The results are shown in Table No.6.

Hausner's Ratio

Hausner's Ratio for various batches of the granules is found to be less than 1.18; it indicates good flow properties of the granules. The results are shown in Table No.6.

Post-compression studies of sustained release tablets

Hardness Test

The hardness of the sustained release tablets various batches were determined. The various batches of the sustained tablets of hardness values are found within limits and it indicates good strength of the sustained tablets. The results shown in Table No.7.

Thickness Test

The sustained release tablets mean thicknesses were almost uniform in the all formulations and were found to be in the range of 4.2mm. The results are shown in Table No.7.

Friability Test

The sustained release tablets friability values are found to be less than 1% in all cases and considered to be satisfactory. The results are shown in Table No.7.

Weight variation test

All this sustained release tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. The weight of the all tablets was found to be uniform with low standard deviation values. The results are in Table No.7.

Estimation of Drug Content

Drug content of all the batches are within the acceptable range which shows the proper mixing of the drug with the excipients. The results are shown in Table No.7.

DISCUSSION

Sustained release tablets of Aceclofenac were prepared by direct compression method. The prepared sustained release tablets are round in shape. FTIR spectrum of the pure drug, polymers and formulations was recorded. The Fourier Transform Infrared Spectroscopy study reveals that there is no interaction between the pure drug and individual, composition of polymers. The pre-compression studies values are within the limits, indicating that the powder blends have the required flow property for direct compression and the post compression studies values have within the acceptable range such as hardness, friability, thickness, weight variation profile of sustained release tablets from each batch was carried in phosphate buffer pH (6.8) for 24 hours by using the *in vitro* dissolution data, FAS-7 formulation was found that the drug release is best (formulation containing combination of Guar gum: Xanthan gum: Chitosan) and the cumulative % of drug release was 98.47% respectively. The promising formulation FAS-7 was found by evaluation studies were compared with Marketed available product (Aceclofenac 200mg SR tablets (ARRESTIN SR)), the FAS-7 formulation gave 98.47% of the drug release and the Marketed product gave 73.52 % of drug release in 24 hours of dissolution study. The result of formulation FAS-7 drug release has better sustained release of drug when it is compared to marketed product.

Table No.1: Formulation of different batches of Aceclofenac sustained release Tablets (mg/tab)

S.No	Formulations	FAS-1	FAS-2	FAS-3	FAS-4	FAS-5	FAS-6	FAS-7
1	Drug	200	200	200	200	200	200	200
2	Guar gum	180	—	—	90	—	90	60
3	Xanthan gum	—	180	—	90	90	—	60
4	Chitosan	—	—	180	—	90	90	60
5	Lactose	20	20	20	20	20	20	20
6	Poly Vinyl Pyrrolidine K_{30}	15	15	15	15	15	15	15
7	Methyl Paraben	5	5	5	5	5	5	5
8	Magnesium stearate	20	20	20	20	20	20	20
9	Talc	10	10	10	10	10	10	10

Table No.2: Angle of Repose I.P limits

S.No	Angle of Repose	Powder flow
1	< 25	Excellent
2	25 – 30	Good
3	30 – 40	Passable
4	> 40	Very poor

Table No.3: Carr's Index I.P limits

S.No	Carr's Index	I.P Limits value
1	Excellent	<10
2	Good	11 – 15
3	Fair	16 – 20
4	Possible	21 – 25
5	Poor	26 – 31
6	Very poor	32 – 37
7	Very very poor	>38

Table No.4: Hausner's Ratio I.P Limits

S.No	Hausner's Ratio	I.P Limits value
1	Excellent	1.00 – 1.11
2	Good	1.01 – 1.18
3	Fair	1.19 – 1.25
4	Possible	1.26 – 1.34
5	Very poor	1.35 –1.45
6	Very very poor	>1.60

Table No.5: Weight variation Tolerances for uncoated Tablets

S.No	Average weight of Tablets(mg)	Maximum % difference allowed
1	130 or less	± 10
2	130-324	±7.5
3	More than 324	±5

Table No.6: Pre-compression studies of sustained release tablet granules

S.No	Formulations	Bulk Density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of repose (θ)	Carr's Index (%)	Hausner's ratio
1	FAS-1	0.370	0.412	34.86	10.19	1.113
2	FAS-2	0.370	0.412	35.54	10.19	1.113
3	FAS-3	0.317	0.364	32.48	12.91	1.148
4	FAS-4	0.294	0.327	35.14	10.09	1.112
5	FAS-5	0.287	0.323	35.57	11.14	1.125
6	FAS-6	0.333	0.374	36.42	10.96	1.123
7	FAS-7	0.384	0.446	38.26	13.90	1.161

Table No.7: Post-compression studies of Aceclofenac sustained release tablets

S.No	Formulations	Hardness Test (kg/cm)	Thickness Test (mm)	Friability Test (%)	% of Weight variation test	Estimation of Drug Content (%)
1	FAS-1	12.45	4.2	0.524	100.0	97.53
2	FAS-2	13.46	4.2	0.576	99.8	95.42
3	FAS-3	14.52	4.2	0.623	100.0	96.25
4	FAS-4	15.54	4.2	0.664	99.9	96.86
5	FAS-5	15.34	4.2	0.718	99.8	95.93
6	FAS-6	14.12	4.2	0.784	99.9	96.64
7	FAS-7	15.68	4.2	0.812	100.0	98.25

Table No.8: Comparative dissolution study of different formulations with various ratios of polymers

S.No	Time (hrs)	% of drug release (FAS-1)	% of drug release (FAS-2)	% of drug release (FAS-3)	% of drug release (FAS-4)	% of drug release (FAS-5)	% of drug release (FAS-6)	% of drug release (FAS-7)
1	0	00.00	00.00	00.00	00.00	00.00	00.00	00.00
2	1	02.12	02.43	03.45	03.98	04.23	04.59	04.96
3	3	05.53	06.24	06.87	07.23	07.86	08.23	09.54
4	6	10.76	12.56	13.24	15.03	15.74	17.34	21.27
5	12	18.63	20.15	22.35	24.38	26.28	28.54	34.76
6	15	31.41	33.25	35.16	37.20	39.17	43.62	53.32
7	18	50.28	52.45	54.96	57.38	60.08	62.25	64.92
8	21	62.34	65.98	68.38	70.31	73.94	75.96	78.36
9	24	79.26	82.43	84.52	86.02	89.59	93.16	98.47

Table No.9: Comparative dissolution study of formulation-7 and Marketed sample (ARRESTIN SR)

S.No	Time (hrs)	% of drug release (FAS-7)	% of drug release Marketed sample
1	0	00.00	00.00
2	1	04.96	02.47
3	3	09.54	05.23
4	6	21.27	15.57
5	12	34.76	24.62
6	15	53.32	36.46
7	18	64.92	47.29
8	21	78.36	59.64
9	24	98.47	73.52

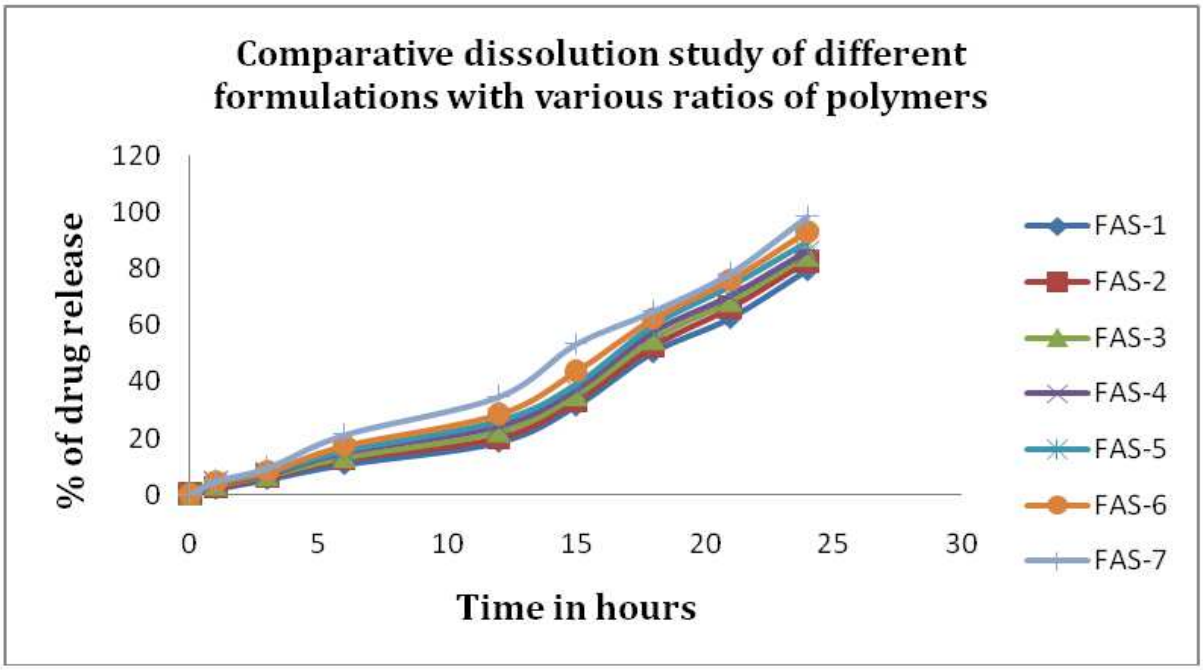

Figure No.1: Comparative dissolution study of different formulations with various ratios of polymers

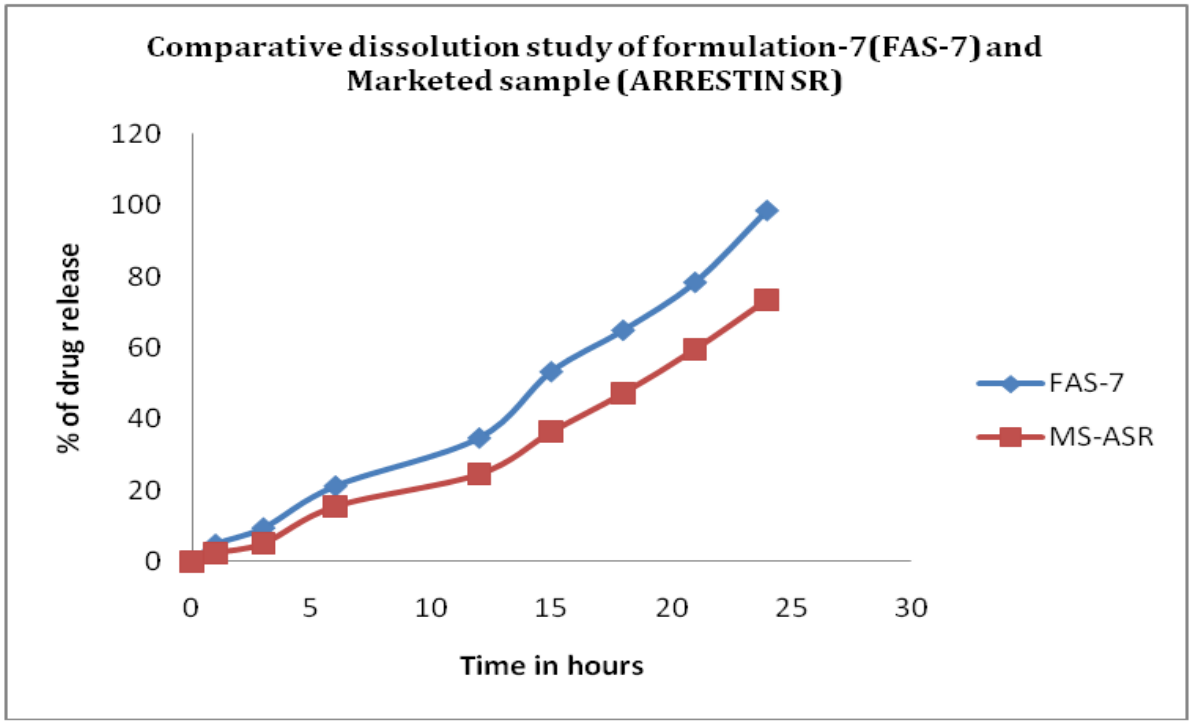

Figure No.2: Comparative dissolution study of formulation-7 and Marketed sample (ARRESTIN SR)

CONCLUSION

The sustained release tablets of Aceclofenac were successfully formulated by direct compression technique. The sustained release tablets of Aceclofenac containing combination of formulation-7 (Guar gum: Xanthan gum: Chitosan (FAS-7)) showed satisfactory results more than 24 hrs and the drug release (FAS-7) has better sustained release of drug when it is compared to marketed product.

ACKNOWLEDGEMENT

The authors are sincerely thanks to the A.M. Reddy Memorial College of Pharmacy, Petlurivaripalem, Guntur (Dt), Andhra Pradesh, India for providing the facilities to complete this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Arunachalam A *et al*. Preparation and *In Vitro* Evaluation of Sustained Release Tablets of Aceclofenac, *International Journal of Research in Pharmaceutical and Nano Sciences,* 1(1), 2012, 1-10.