



Formulation and Evaluation of Aceclofenac Sustained Release Tablets

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ABSTRACT

Increase in complication and expenses involved in marketing of new drug entities has focused greater attention in development of sustained release drug delivery system of existing drugs. NSAID are having short biological half life of 4-4.3 hrs and fluctuation in drug plasma concentration. NSAID are used in symptomatic treatment of rheumatoid arthritis & spondylitis. They have analgesic, anti inflammatory, antipyretics activity. Aceclofenac sustained released tablets was developed using wax and polymer matrix in the different ratio. The evaluation of granules was carried for angle of repose, Hausner's ratio, Carr's compressibility index. Tablets were evaluated for hardness, uniformity of weight, content of active ingredient, thickness, *in-vitro* dissolution studies. The results of hardness showed that as the concentration of wax or polymer increases, the hardness of tablet increases. The *in-vitro* dissolution study showed that for the formulation containing Aceclofenac with highest concentration of wax and polymer showed maximum sustained activity. Formulation containing bees wax and Carnauba wax in ratio 1:0.5 were optimized based on *in-vitro* dissolution and hardness. The dispersion of the drug in the wax and polymer network altered its dissolution profile at pH 6.8, thus making it possible to obtain a gradual and prolonged release, and to modulate the release pattern.

Keywords: Aceclofenac, Bees and Carnauba wax, Ethyl cellulose, HPMC, NSAID, Sustained release.

INTRODUCTION

Over past 30 years, expenses and complication involved in marketing new drug entities have increased. With concomitant recognition of therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained release system. The primary objectives of sustained drug delivery are to ensure safety and enhancement of efficacy of drug with improved patient compliance. For any drug therapy to be successful, the drug must reach the target tissue or systemic circulation in optimum concentration which should be maintained for desired time. So the use of these dosage forms is increasing in treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above minimum effective concentration and below the minimum toxic level for extended period of time.

Aceclofenac is a non steroidal anti-inflammatory drug with balanced COX-1 and COX-2 inhibition reversibly, which decreases production of proinflammatory prostaglandin precursors. It is commonly used for a variety of inflammatory and pain conditions such as musculoskeletal & joint disorders, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.^{1,2} Aceclofenac is administered mainly as oral & in transdermal drug delivery (TDDS). The dose of Aceclofenac is 100 mg/day. It is given in two divided doses. The short biological half-life (about 4-4.3 hrs) and dosing frequency more than one per day make Aceclofenac an ideal candidate for sustained release.

The present study aims to develop sustained release matrix tablets using hydrophobic matrix material as bees

wax, carnauba wax by hot melt extrusion method.^{3,4} Aim was to formulate sustained release formulation using wax and polymers HPMC and ethyl cellulose to study the release effect. These are readily available meltable raw materials which may be helpful to reduce its cost & increase its effectiveness.⁵⁻⁷

MATERIALS AND METHODS

Aceclofenac was obtained as gift sample from Amoli chemicals Ltd, Gujarat, India. Carnauba wax, bees wax and lactose were purchased from Cosmo chemicals Ltd, Mumbai, India. Magnesium stearate was purchased from Vishal chemicals. Ltd. Mumbai, India. All other chemicals used were of analytical grade.

Preparation of stock solution

Accurately weighed quantity of Aceclofenac was transferred to 10ml volumetric flask, dissolved in 5ml methanol and diluted to the mark with the water (stock solution: 100µg/ml).

Dilutions and actual measurements

From the stock solution, working standard solution of Aceclofenac (10µg /ml) was prepared by appropriate dilution and was scanned in entire U.V. range on double beam UV spectrophotometer to determine the maximum absorbance. Aceclofenac showed maximum absorption at 273 nm. A series of standard solution ranging from 4µg – 20 µg/ml were prepared and the absorbance was measured at 273 nm.



Preparation of tablets

Tablets weighing 300mg were prepared containing 100 mg of Aceclofenac. Bees wax; carnauba wax, ethyl cellulose and HPMC were used in ratio 1:1, 1:0.5, 1:1.5. Magnesium stearate was added as lubricant prior to compression. All granules containing wax were prepared by hot melt extrusion method and polymer by direct

compression method. The granules were passed through sieve no.20. The granules were dried at 50°C for 45 minutes and were mixed with magnesium stearate. The tablets were compressed using Rimek mini press II -Tablet compression machine. The different formulations prepared are shown in Table 1.

Table 1: Formulation of Tablet

Ingredients (W/W)	F1 (1:1)	F2 (1:0.5)	F3 (1:1)	F4 (1:0.5)	F5 (1:1)	F6 (1:1.5)	F7 (1:1)	F8 (1:1.5)	F9 (1:1)	F10 (1:0.5)	F11 (1:1)	F12 (1:0.5)
Aceclofenac	100	100	100	100	100	100	100	100	100	100	100	100
Bees wax	100	50	--	--	--	--	--	--	50	25	--	--
Carnauba wax	--	--	100	50	--	--	--	--	50	25	--	--
Ethyl cellulose	--	--	--	--	100	150	--	--	--	--	50	25
HPMC	--	--	--	--	--	--	100	150	--	--	50	25
Magnesium state	40	40	40	40	40	40	40	40	40	40	40	40
Lactose	60	110	60	110	60	10	60	10	60	110	60	110
Total	300	300	300	300	300	300	300	300	300	300	300	300

All weight in mg

Table 2: Micromeritic properties of granule

Formulation no.	Angle of repose	Bulk density	Tap density	Hausner's ratio	Carr's index
F1	28.36	0.4	0.46	1.15	13.04
F2	30.11	0.37	0.43	1.16	13.9
F3	34.6	0.39	0.42	1.07	7.14
F4	29.68	0.38	0.41	1.07	7.14
F5	21.8	0.4	0.46	1.15	13.04
F6	30.96	0.4	0.46	1.15	13.04
F7	34.9	0.37	0.42	1.13	11.9
F8	30.1	0.38	0.41	1.02	7.31
F9	33.3	0.31	0.33	1.06	6
F10	31.4	0.37	0.42	1.13	11.9
F11	29.3	0.37	0.4	1.08	7.5
F12	27.4	0.32	0.36	1.12	11.1

Table 3: Assignment of band

Assignment of bands	Absorption of band for Aceclofenac	Absorption of band for Aceclofenac in bees wax	Absorption of band for Aceclofenac bees and Carnauba wax
N-H(s)	3321	3317	3322
Ar C-H(s)	3026	3209	3074
C=O (s)	1728	1768	1730
Aromatic ring	1589	1562	1534
C-O-C(s)	1256	1243	1148
C-Cl(s)	770	720	720



Evaluation of the flow Properties for granules⁸

Angle of Repose

The angle of repose for the granule was determined by fixed funnel and petri dish method, where the sample powder poured into fixed funnel and allow to flow gently over fixed diameter Petri dish, the angle of repose were calculated as follow :

$$\tan \theta = h/r \quad (1)$$

Where $\tan \theta$ is the tan of the angle of repose, h is the height of the resulted cone after pouring, r is the radius of the fixed petri dish.

Compressibility Index (Carr's index)

A sample of each formula powder was poured into 10 ml graduated cylinder to occupy the initial bulk volume (V_0) which was then subjected to constant standard tapping procedure until a constant volume was achieved (V_t). Compressibility index was then calculated using the following formula 2.⁹

$$\text{Compressibility Index} = \frac{V_0 - V_t}{V_0} \times 100 \quad (2)$$

Bulk density

The bulk density was calculated using the following formula 3,

$$pb = M/V \quad (3)$$

Where, pb = Bulk density

M = Mass of the granules in grams

V = Final untapped volume of granules in ml.

True density

The true density was calculated using the following formula 4,

$$pt = M/Vp \quad (4)$$

Where, pt = true density

M= Mass of granules in grams

Vp= Final tapped volume of granules in ml.

Hausner's ratio¹⁰

Hausner's ratio was calculated using the following formula 5,

$$\text{Hausner's ratio} = \text{Tapped density} / \text{Bulk density} \quad (5)$$

Evaluation of prepared tablets¹¹

Weight variation

Twenty tablets were selected randomly and weighed. Average weight of the tablet was determined. These tablets were weighed individually and the weight variation was determined.

Tablet hardness

The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usages are depends on its hardness. The hardness of tablet of each formulation was checked by using Monsanto hardness tester. The hardness was measured in terms Kg/cm².

Thickness

Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking ten tablets from each formulation.

Percent drug content

The percent drug content of drug was calculated. For the content uniformity, the individual tablets were triturated in mortar and powder was dissolved in methanol. The UV spectroscopic scan was calculated after appropriate dilution of the solution of powder at 273nm. The percent drug content was calculated and content uniformity was further calculated.

Dissolution studies

The *in-vitro* dissolution study was carried out using USP Type I dissolution apparatus. The study was carried out in 900 ml of 0.1N HCl (pH 1.2) for first 2hours and then 900 ml of phosphate buffer (pH 6.8) upto 8 hrs. The dissolution medium was kept in thermostatically controlled water bath, maintained at $37 \pm 0.5^\circ\text{C}$. Basket rotation was adjusted to 50 rpm. At definite intervals, 5 ml sample was withdrawn and analyzed spectrophotometrically at 273 nm for the drug release. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask.^{12,13}

Infra Red Spectroscopy (IR)

IR spectra of pure Aceclofenac and physical mixture of drug and excipients were recorded on Varian-640 IR spectrometer. Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region $400-4000 \text{ cm}^{-1}$ at spectral resolution of 2 cm^{-2} and ratio against background interferogram. Spectra were analyzed by software supplied by Varian.

Assay

The formulation containing 100 mg of Aceclofenac tablet was analyzed. In this procedure, 10 tablets were accurately weighed and powdered. The powder equivalent to 100 mg of Aceclofenac was transferred to 100 ml volumetric flask and 50 ml of methanol is added to it. This mixture was sonicated in bath sonicator for 45 minutes and the volume is made up to 100 ml with methanol. It was then filtered through Whatman filter paper. Then 5 ml of the filtrate was transferred in a 50 ml volumetric flask and the volume was made up to the mark

to give a resultant concentration of 100 µg/ml and absorbance were recorded at 273nm.¹⁴

RESULTS AND DISCUSSION

Micromeritic properties

Granules having good flow property should have angle of repose values ranging from 25-30°. All the prepared granules were within the range 21.80 to 33.30°. This indicates granules have good flow property.⁴ Also, the Carr's compressibility index of all granules was found below 13.9. This also indicates granules have good flow ability. Bulk density, tapped density and Hausner's ratio were observed and were within standard.⁴ It reveals that all the formulation blend have good flow characteristics. Degree of compression is characteristic of compression capability of the granules and the results obtained exhibited good compression capability of the granules (table 2).

Evaluation of prepared tablets

Different batches of tablets were prepared containing wax and polymer matrix material in the ratio 1:1, 1:0.5, 1:1.5 respectively. The tablets of different batches shown hardness within the range of 2.5-4.5 kg/cm². The results of hardness showed that as the concentration of wax or polymer increases the hardness of tablet increases proportionately. Formulation containing ethyl cellulose in ratio 1:1.5 had least hardness. The diameter of all formulation was in the range of 9.50- 8.50 mm. The thickness of tablets was measured by vernier caliper and was range 0.52±0.05 for all formulation. In weight variation test, the pharmacopoeial limit for percentage deviation for tablets of more than 250 mg is ±5% and all the formulations complies with the specifications given in I.P. for weight variation test. For uniformity of content, if each individual content is 85 to 115% of the average content and the prepared formulation complies with I.P. specification. It was also observed that increasing the concentration of wax or polymer material sustains the release of the drug. From the observed evaluation parameters F1 and F10 shows most satisfactory results for hardness and content uniformity.¹³

Dissolution studies

For the formulation containing Aceclofenac, the % drug release in the tablets containing bees wax was observed in the order: F-2> F-1. This indicates that the formulation containing less concentration of bees wax shows lesser drug release after 8 hrs. (Figure 1)

For the formulation containing Aceclofenac, the % drug release in the tablets containing carnauba wax was observed in the order: F-3> F-4. This indicates that the formulation containing more concentration of carnauba wax shows less drug release after 8 hrs. (Figure 1)

The % drug release in the tablets containing ethyl cellulose was observed in the order: F-5> F-6. This indicates that the ethyl cellulose retards the drug release

from formulation. Tablets containing HPMC, the % drug release pattern was observed in the order: F-8 > F-7. Hence, it was observed that the formulation containing less quantity of HPMC shows more drug release within 8 hrs. (Figure 2)

The % drug release in the tablets containing bees wax and carnauba wax was observed in the order: F-9> F-10. This indicates that the bees wax and carnauba in combination retards the drug release from formulation. Formulation F11 and F12 containing ethyl cellulose and HPMC got disintegrated within 3 hrs and the batch fails to control the release of the drug. (Figure 2)

Best fit model was found to be Zero order (F1 and F10). This indicated that rate is independent of the concentration of drug undergoing reaction *i.e.* the rate of reaction cannot be increased further by increasing the concentration.

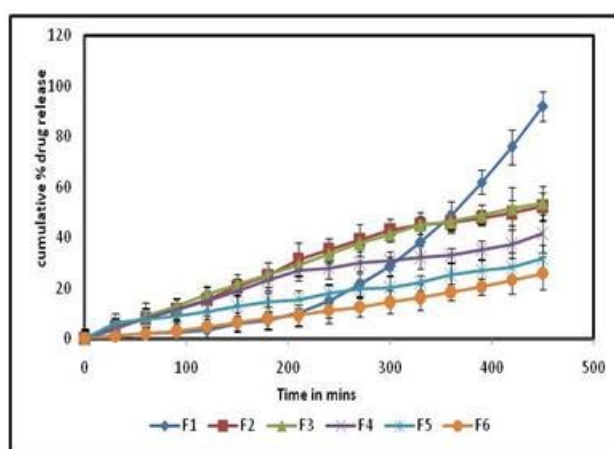


Figure 1: Dissolution of tablets of Aceclofenac of batch F₁-F₆

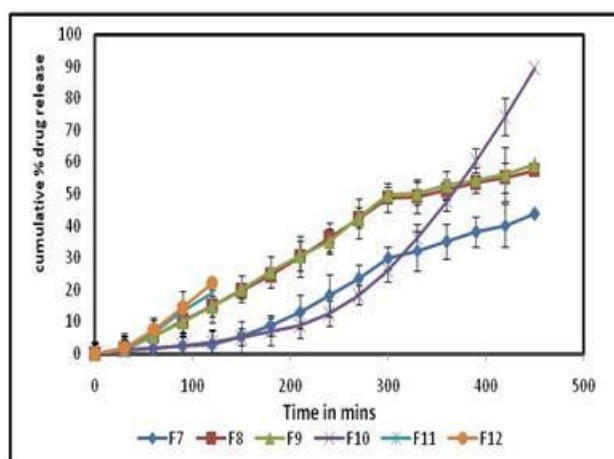


Figure 2: Dissolution of tablets of Aceclofenac of batch F₇-F₁₂

IR spectra

From figure 3, 4 and 5 and table 3 it can be concluded that there is no major change in peak for drug and hence drug remains in its pure state without any physical and chemical interaction with other excipients.

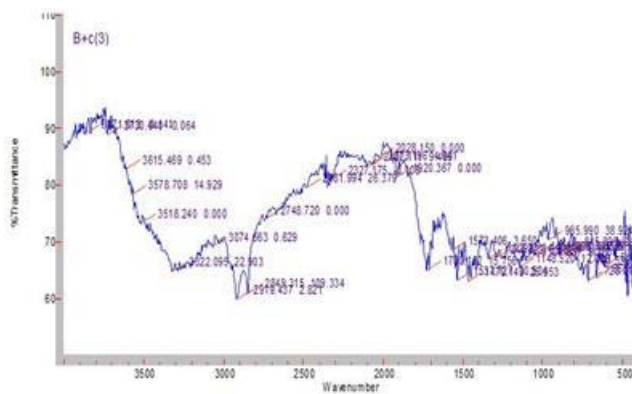


Figure 3: IR spectra of drug with bees wax and Carnauba wax

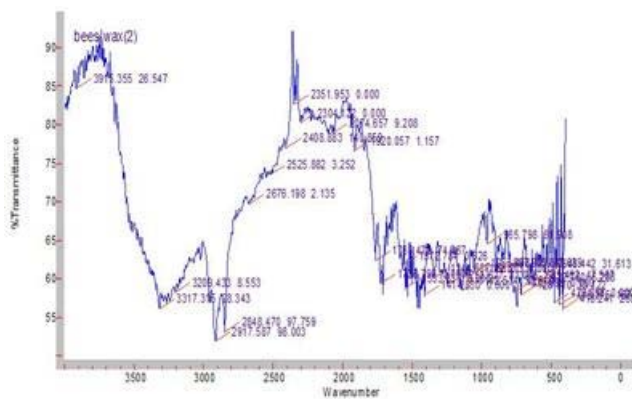


Figure 4: IR spectra of drug with bees wax

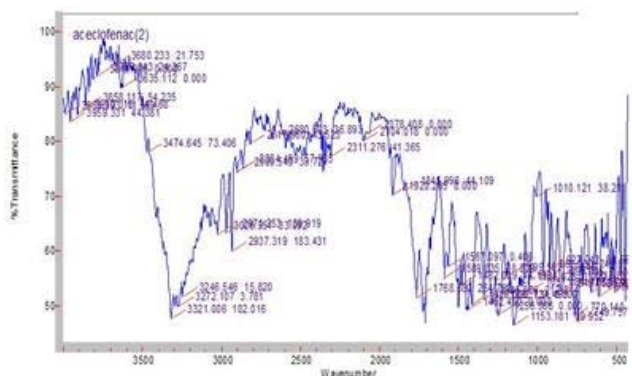


Figure 5: IR spectra of Aceclofenac

CONCLUSION

From present study it can be concluded that the waxy material can be successfully used for the formulation of sustained release dosage form. The waxy material such as carnauba wax and bees wax are efficient matrix forming agent and can control the release of drug from the formulation. From tablets of Aceclofenac containing bees

and combination of beeswax and carnauba wax was observed as the best formulation in regards of evaluation parameters and release pattern. The retarding agents are cheap, readily available safe and easy to handle. The melt granulation method is best suited for wax forming material as melting point of wax is low. The formulation containing beeswax and combination of both carnauba and bees wax showed better sustained release action as compared to other formulation.

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