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Research Article

FORMULATION AND EVALUATION OF ACECLOFENAC MATRIX TABLETS USING HYDROPHOBIC WAXES FOR SUSTAINED RELEASE

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ABSTRACT

The aim of the present investigation was to develop a suitable matrix tablets for sustained release drug delivery of aceclofenac in order to overcome their side effects by conventional dosage form. A total of 14 matrix tablets were prepared by melt granulation method using Hydrophobic waxes. The formulations were characterized including uniformity of weight, drug content, hardness, thickness, and swelling index to study the stability of the formulations and *in vitro* dissolution of the experimental formulations were also performed to determine the drug distribution in the matrix. Drug–excipient interaction studies were carried out using Fourier transform infrared (FTIR) spectroscopic technique. Optimized formulations (A13andA14) were found to be suitable for formulating in development of sustained release matrix tablets in terms of physicochemical characteristics and there was no significant interaction noticed between the drug and blend of waxes used.

INTRODUCTION

Sustained Release drug delivery System

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time (Wadher *et al.*2013). The primary objectives of sustained release drug delivery are to ensure safety and enhancement of efficacy of drug with improved patient compliance. 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 (Chugh *et al*. 2012). Thus, sustained drug delivery results in optimum drug therapy with reduced frequency of dosing and side effect (Gaikwad *et al.* 2011).Matrix system is widely used for the purpose of Sustained release. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has focused on the designation of SR system for poorly water soluble drugs (Srivastava et al. 2012). Hydrophobic waxes have been extensively investigated for sustained release of drug. Because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance and provides good stability at varying pH and effective retarding blending used (Bharathi *et al.* 2011 and Shende *et al.* 2009). Waxes, lipids and related materials form matrices that control release through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to the totally

insoluble polymer matrix. Total release of drug from wax-matrix lipids matrices is not possible, since a certain fraction of the dose is coated with impermeable wax films. Release is more controlled by the addition of surfactants or wicking agent in the form of hydrophilic polymers, which promote water penetration and subsequent matrix erosion (Lachman *et al.* 1987). Aceclofenac are one of the most widely used new generations NSAID used in the treatment of osteoarthritis, rheumatoid arthritis and other joint diseases. It is chemically designated as 2-[[2-[2-[(2, 6 dichlorophenyl) amino] phenyl] acetyl] oxy] acetic acid. Usual therapeutic dose is 100 mg twice daily and half-life is 3-4 hrs, thus it is necessary to be administered frequently in order to maintain the desired concentration. The absorption of AC following oral administration is almost complete. However, it has a very high first pass metabolism and plasma protein binding leading to low oral bioavailability. Therefore, Aceclofenac is an ideal candidate for sustained release formulation, resulting in more reproducible drug absorption and reducing the risk of local irritations compared to single dosage forms. These dosage forms reduce fluctuations in plasma concentration of drug and they provide favourable efficacy (Raj, 2013). The objective of the present work are to design, formulate and evaluate matrix tablets of Aceclofenac using Hydrophobic waxes for sustained release dosage form is to provide and maintain adequate concentration of drug at the site of action.

MATERIALS AND METHODS

Aceclofenac was procured from Parek Pharmaceutical Company, (Baddi, India).Beeswax, Paraffin wax, Stearic acid were kind gift from S.D Fine chemicals Ltd., Mumbai. Talc, MCC, was purchased from S.D Fine chemicals Ltd., Mumbai. All other regents were used of analytical grade.

Compatibility studies by IR- Spectroscopy

Desired quantity of drug with specified excipients (Beeswax, Paraffin wax, Stearic acid, MCC and Talc) in 1:1 w/w ratio were taken and mixed thoroughly. The infrared absorption spectra of physical mixture of excipients and drug were run for drug excipients compatibility studies between 400 cm^{-1} - 4000 cm^{-1} by using Perkin Elmer FTIR spectrophotometer (RXIFT-IR system, USA).

Formulation of matrix tablets

The Matrix tablets were prepared by melting the waxes in porcelain dish on a water bath maintained at constant temperature. The drug was gradually added to the molten wax with continuous stirring. The molten mixture was allowed to cool and solidified at room temperature. The drug was present in its solid form within the molten mixture. The solidified mass was sieved through a 22# screen. Then granule were lubricated with MCC and Talc and directly compressed by direct compression method (Raj, 2013). The composition of prepared matrix tablets is given in Table 1.

Table 1 Composition of Aceclofenac Matrix Tablets

Formulation Code	Ingredients (mg)						
	Drug	Beeswax	Paraffin wax	Stearic acid	MCC	Talc	Total Weight
A1	100	97.5	-	-	97.5	5	300
A2	100	130	-	-	65	5	300
A3	100	-	97.5	-	97.5	5	300
A4	100	-	130	-	65	5	300
A5	100	-	-	97.5	97.5	5	300
A6	100	-	-	130	65	5	300
A7	100	45	45		5	5	200
A8	100	30	60		5	5	200
A9	100	45	-	45	5	5	200
A10	100	30		60	5	5	200
A11	100	-	45	45	5	5	200
A12	100	-	30	60	5	5	200
A13	100	30	30	30	5	5	200
A14	100	22.5	22.5	45	5	5	200

Drug Excipient interaction studies: FTIR spectra of pure Aceclofenac drug, mixture of drug and excipients (Beeswax, paraffin wax, stearic acid, MCC and Talc) were taken using Perkin Elmer FTIR spectrophotometer (RXIFT-IR system (Asija *et al.* 2013).

CHARACTERIZATION OF MATRIX TABLET

Precompression parameters

Prior to compression, granules were evaluated for their characteristic parameters

Angle of repose

Angle of repose is the maximum angle possible between the surface of a pile of powder and the horizontal plane (Barnabas *et al.* 2013). Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, h, was obtained. Diameter of heap, D, was measured. The angle of repose, Ɵ, was calculated by formulas- tan Ɵ = h / r, Ɵ = tan-1 (h / r), Where, Ɵ is the angle of repose, h is the height in cm and r is the radius (Kumar *et al.* 2009).

Bulk density and tapped density

Both LBD (Loose Bulk Density) and TBD (Tapped Bulk Density) were determined by taking 2 g of powder from each formula, previously lightly shaken to break any agglomerates and pouring into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The reading of tapping was continued until no further change in volume was noted. LBD = Weight of the powder/initial volume of the packing. TBD = Weight of the powder / Tapping volume of the packing (Kabir *et al.* 2012).

Compressibility index

The compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down (Kabir *et al.* 2012 and Banker *et al.* 2012). Carr's index (%) = [(TBD-LBD) x 100]/TBD

Hausner's ratio

This value was calculated by making use of bulk and tap densities of powder samples. Hausner's ratio = TBD / LBD (Mahajan *et al.* 2011).

Post compression Parameters

Weight variation

Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated. According to IP standards, the requirements are met if the weights of not more than 2 of the tablets differ by more than the percentage listed in table1 and no tablets differ in weight by more than double that percentage (Mohiuddin *et al.* 2008).

Thickness

Thickness and diameter of tablets was measured using a Calibrated dial calipers. Three tablets of each formulation were picked randomly and dimensions determined were measured in mm. This was done in triplicate and standard deviation was calculated. The tablet thickness was controlled within ±5%variations of a standard (Mohiuddin *et al.* 2008).

Friability

Friability test will be conducted on the tablets using Roche friabilated and ten tablets were weighed placed in the friabilator, which was then operated for 25 revolutions per minute. After 100 revolutions the tablets were dusted and reweighed. The percentage friability can be measured using the formula (Umarunnisha et al. 2010). %F= 1-(Loss in weight/Initial weight) ×100

Tablet Hardness

The tablets to be tested and held between a fixed and a moving jaw of hardness test apparatus (Monsanto) and reading of the indicator is adjusted to zero. The screw knob was moved forward until tablet breaks and the force required to break the tablet was noted (Umarunnisha et al. 2010).

Swelling Characterstics

The extent of swelling was measured in terms of % weight gain by the tablet. Swelling is a phenomenon involving imbibitions of water in to the matrix tablet forming a gel layer and thus controlling the release profile of drug (Misra *et al.* 2008).

Measurement of weight gain on swelling (Jain *et al.* 2011)

The extent of the swelling was measured in terms %weight gain by the tablet. One tablet from each formulation was kept in a beaker containing ph 7.4 phosphate buffers. At the end of 0.5 hrs, the tablet was withdrawn, soaked with tissue paper and weighed. Then for every o.5 hrs, weights of the tablet were noted and the process was continued till the end of 3. %weight gain by the tablet was calculated by formula;

$S.I = [(M_t - M_0)/M_0] \times 100$

Where, S.I= swelling index, Mt= weight of tablet at time t and M_0= weight of tablet at time t=0

Drugs content

To evaluate a tablet potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet, and batch to batch. To perform the test, 10 tablets were crushed using mortar pestle. Quantity equivalent to 100 mg of drug was dissolved in 100 ml phosphate buffer pH 7.4, filtered and diluted up to 50µg/ml, and analyzed spectrophotometrically at 275 nm. The concentration of drug was determined using standard calibration curve (Saha *et al.* 2013).

In-vitro Dissolution studies

The *in-vitro* drug release studies of Aceclofenac from the tablets were carried out using USP dissolution test apparatus type-II (Paddle type) in 900 ml of dissolution medium (Phosphate buffer pH 7.4) at 37±0.5°C temperature and rotated at 50 rpm. In this test, single tablet from each formulation was used for the studies. At specified time intervals, 5 ml samples were collected from each vessel at 0.5, 1, 2, 4, 6, 8, 10and 24 hour interval and immediately replaced with an equal volume of fresh medium. The release study was conducted in triplicate. The sample was assayed for Aceclofenac using UV-VIS spectrophotometer at 275nm (Kabir *et al.* 2012). Dissolution study of Aceclofenac Marketed conventional tablets (Flam-ace 100mg) were also done in order to compare the percent release of the drug from the matrix tablets.

To establish a relationship between the release kinetics of the dissolution study, data obtained from *in vitro* dissolution study was fitted into various kinetic models: zero order as cumulative percent of drug dissolved *vs.* time, first order as log cumulative percentage of drug remaining *vs.* time and Higuchi's model as cumulative percent drug dissolved *vs.* square root of time. To determine the mechanism of drug release, the data were fitted into Korsmeyer and Peppas equation as log cumulative percentage of drug released *vs.* log time, and the exponent n was calculated from slope of the straight line. For slab matrix, if exponent is 0.5, then diffusion mechanism is fickian; if 0.5<n <1.0, mechanism is non- fickian, n = 1 to Case II (relaxational) transport, and n > 1 to super case II transport (Siepmann and Peppas; 2011), (Singh et al. 2010) and (Costa &lobo; 2011).

Stability Studies

Stability study of Aceclofenac matrix tablets based waxes were studied at different temperature conditions according to ICH guidelines at 25 ºC ± 2 ºC / 60 % ± 5 % RH for real and at 40 ºC ± 2 ºC / 75 % RH ± 5 % for accelerated stability studies. The formulation was stored at different storage conditions. The samples were withdrawn at different time intervals as 0, 7, 15, 30 days. Formulation equivalent to 25 mg of the drug was dissolved in methanol, diluted approximately and estimated for

the drug content spectrophotometrically at 272 nm using methanol as blank. Effect of storage conditions on drug release was also studied (Mahajan et al. 2011).In the present study, stability studies were carried out at for a specific time period up to 30 days for selected formulations.

Statistical analysis

All experimental measurements were performed in triplicates. Result values were expressed as mean value ± standard deviation (SD). The level of significance was taken p value < 0.05.

RESULT

Physicochemical characterization of matrix tablets: The average weights of matrix tablets ranged between 200 to 328mg. The thickness of the films was measured by micrometer and the film thickness was found to lie between 5.2to 6.9 mm in all the cases (Table 1). The drug content among the batches was observed with all formulations and ranged from 96 to 99%. The results indicated that the process employed to prepare matrix tablets in this study was capable of producing formulations with uniform drug content. Hardness was observed from 5.2to 7.9kg/mm^2. Swelling index indicated the increase in the concentration of hydrophobic waxes was inversely proportional to the increase in moisture content in the tablets. Moisture content was found to be 191±0.28 to 453±0.44in all formulations.

Swellling Index

Swelling characterstics were observed by measuring the weight of all the formulations and change in weight after hydration in PBS 7.4.The swelling index varied in range from 191±0.28 to 453±0.44 in all formulation.

The formulation A5, A6 containing stearic acid were shows more swelling characterstics. Increasing amount of stearic acid caused increasing amount of swelling up to certain limit (10%) which might reduce the drug diffusion pathways from the tablet matrix. Swelling characterstics of formulations indicated that swelling index decreased with increasing the concentration of waxes as shown in figure

In vitro release studies

In vitro release studies were conducted as per USP procedure using phosphate buffer saline PBS pH 7.4 as dissolution medium.

Effect of combination of two waxes on release of Aceclofenac:

The release of Aceclofenac from combination of both waxes at different ratio (A7-A12) showed that drug release was very slower and it gets more retarded than that of individual waxes used This may be due higher lipophilicity provided by combination of both wax. The formulation A7, A8, are the combination of Beeswax and Paraffin wax showed more than 80% release at the end of 24hr. Drug release decreased as the content of beeswax and paraffin wax in the tablet increased. The formulations A11, A12 are the combination of paraffin wax and stearic acid showed less release compared to the formulation A7, A8, A9, A10 due to paraffin wax shows more retarding property than stearic acid. The formulation A9, A10 are the combination of Beeswax and stearic acid shows high release rate at the end of 24hr compared to A7, A8, A11, A12 due to carboxylic acid group (-COOH) present in stearic acid which enhanced the formation of H-bonding with surrounding dissolution medium and facilitated wetting of matrices.

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Effect of combination of three waxes on release of Aceclofenac:

The formulations A13, A14 are the combination of beeswax, paraffin wax and stearic acid showed less release (less than 60%). It has been observed that when the concentration of waxes increases, the rate of drug release tends to be slower. The rate of drug release from combination of three waxes get more retarded due to higher lipophilicity offered by combination of three waxes. Formulation A14 shows release rate of drug much slower than other formulations. Hence formulations A14 was selected as the optimized formulation for development of sustained release matrix tablets of Aceclofenac.

The order of drug release from the wax based matrices decreasing in following order

Stearic acid> Beeswax> Paraffin wax> Beeswax and Stearic acid> Beeswax and Paraffin wax > Paraffin wax+ Stearic acid > Beeswax, Paraffin wax and Stearic acid.

Comparative Analysis with marketed product:

The formulation A13, A14 was compared with marketed product of Aceclofenac Conventional tablets by conducting comparative *in vitro* dissolution study. The marketed product (Flamace-100mg) showed 99.75% drug release at end of 12hrs while formulation A13, A14 showed drug release less than 60% in 24 hrs. *In vitro* dissolution profile of marketed product and formulated batch in reported in table: 5, 6, 7. Results of the present study demonstrated that Hydrophobic waxes and their combination could be successfully employed for formulating sustained release matrix tablets of Aceclofenac. The sustained release tablets can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional Aceclofenac.

The applicability of all of these equations was tested. Drug release process was not zero order in nature. The dissolution data of all formulations when fitted in accordance with first order equation, a linear results relationship was obtained with higher r^2 value (0.904-0.956) in A1-A8 formulation. In all the formulations A9-A14 were expressed by Higuchi's model, as the plot show high linearity (r^2- 0.908 to 0.977). The linearity of the plot indicated that the release process was diffusion controlled. The amount of drug released was dependent on the matrix drug load. As concentration reduced on drug release, the diffusional path increased resulting in drug release at comparatively slower rate in later phase. To confirm the diffusion mechanism, the data were fitted to Koresmeyer-peppas model. All the formulations (A1-A14) showed n value ranging from 0.237-0.439. Stability studies Stability studies of selected matrix tablets (A13 and A14) were carried out according to ICH guidelines. The revealed no physical alterations of the formulation after 3 months storage. The drug content of optimized formulations was determined and it was found to be 98.14% and 99.15% after 3 month storage respectively.

DISCUSSION

From these results, it can be concluded that the prepared and optimized matrix formulations of Aceclofenac using such as hydrophobic waxes as demonstrated their ability to give sustained release. These studies have shown promising results, hence there is feasibility of delivering Aceclofenac for sustained release delivery by using waxes and in their combination. The developed sustained release delivery of anti-

inflammatory may prove to be a better alternative to conventional dosage forms. These studies can help industry to scale up for commercial production.

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