



RESEARCH ARTICLE

Formulation Development and evaluation of ibuprofen sustained release matrix tablet using *Lepidium Sativum* mucilageSachin S. Salunkhe^{*1}, Sachin S. Mali², Neela M. Bhatia¹, Sachin S. Gadkari¹, Manish S Bhatia¹, Ashok A. Hajare²¹Department of Quality Assurance, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India.²Department of Pharmaceutical Technology, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India.**Received 07 March 2014; Accepted 13 March 2014****ABSTRACT**

Ibuprofen is one of the safest and most potent non-steroidal anti-inflammatory drugs (NSAID) available in the market. The objective of present study was to prepare and evaluate sustained release matrix tablets of ibuprofen using mucilage *Lepidium sativum*. Granules were prepared by wet granulation technique and were evaluated for angle of repose, bulk density, tapped density, Hausner's ratio and Carr's compressibility index. Tablets were evaluated for hardness, thickness, weight variation, drug content and *in-vitro* release characteristics. The results were found to be satisfactory and within acceptable limits. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. The drug release data fits well to the Korsmeyer-Peppas expression. The retarding system of mucilage with drug provides prolong duration of treatment and reduced adverse effect in patients. An attempt has been made to achieve a better therapeutic profile through tablets with the use of mucilage *Lepidium sativum* and wet granulation technique. The results of present study demonstrated that hydrophilic *Lepidium sativum* polymer could be successfully employed for formulating sustained release matrix tablets of ibuprofen.

Keywords: Ibuprofen, *Lepidium sativum*, wet granulation technique, matrix tablets, sustained release., etc.

INTRODUCTION:

Ibuprofen is chiral propionic acid derivative belonging to the class of NSAID drugs. Due to its analgesic, antipyretic and anti-inflammatory actions it is used in the treatment of inflammatory conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, mild and moderate pain, dysmenorrhea, vascular headaches and fever.¹ Ibuprofen has the more COX-2 specificity than other non-steroidal anti-inflammatory drugs (NSAIDs), as it is active only in inflammatory cells with less gastrointestinal (GI) stress than other NSAIDs. It has biological half-life of 4 h, and the usual oral dosage regimen is 100 mg taken twice a day.² It may be tolerated better than other NSAIDs. Due to rapid excretion of ibuprofen in the urine, large amount of drug is required for conventional dosage form.³ The basic goal of therapy is to achieve a steady state blood or tissue level that is therapeutically effective and non-toxic for an extended period of time. Sustained release drug delivery systems, with an aim of improved patient compliance, better therapeutic efficacy, less side effects and reduced

dosage regimen with less toxicity for treatment of many acute and chronic diseases.²

Ibuprofen is one of the NSAIDs used for arthritis treatment due to numerous advantages such as reduced dosing frequency, prolonged pharmacological effects and improved patient compliance. Thus a sustained release formulation of Ibuprofen is very much desirable.

Among the many techniques used for modulating the drug release profile, the most commonly used method is embedment of the drug into a polymer matrix. The matrix may be formed by either dissolving or dispersing the drug uniformly in the polymer mass. Such polymer matrices can give desirable release profiles, cost effective manufacturing method and broad regulatory acceptance.² *Lepidium sativum*, known as Pepper cress or Elrashad, belongs to the family *Brassicaceae* (*cruciferae*) and it is an erect, annual herb grows up to 50 cm height. The leaves are variously lobed and entire, flowers are white small and found in racemes and fruits are obovate pods, about 5 mm long, with two seeds per pods. The

seeds and leaves of the plant contain volatile oils.⁴ The plant is eaten and seed oils are used in treating dysentery, diarrhoea.⁵ and migraine.⁶ The plant was found to contain glucosinolate and glucotropaeolin.⁴⁻⁷

Studies reported indicate that a gel forming husk powder obtained from *Lepidium sativum* seeds were used to prepare solid sustained release oral unit dose pharmaceutical composition, comprising one or more of therapeutic agent. This powder is used in the range of 10 to 70% of the total weight of dosage form along with the cross-linking enhancer selected from xanthan gum, karaya gum in amounts between 3 to 10 % by weight of the dosage form to give a release profile between 4 to 20 h. The total excipients employed between 10 to 40 % by weight of the total dosage form.⁸

Mucilage are often found in different parts of plants for example, in the epidermal cells of leaves (senna), in seed coats (linseed, psyllium), roots (marshmallow), barks (slippery elm) and middle lamella (aloe)⁹ and are physiological products with variety of applications in pharmacy due to its various characteristics like binding, disintegrating, gelling etc.¹⁰

In the present work an attempt has been made to develop sustained release matrix tablets of ibuprofen by using mucilage of *Lepidium sativum* for sustaining the effect.²



a)



b)

Figure 1: *Lepidium sativum* a) plant b) seeds

Tablet Preparation:

Granules for ibuprofen matrix tablets were prepared by wet granulation technique using various percentages of *Lepidium sativum* mucilage powder and microcrystalline cellulose, Table 2. All the remaining powders were passed through 30# sieve. The required quantity of drug, polymers and other ingredients were mixed thoroughly and a sufficient volume of granulating agent (ethanol) was added slowly. After achieving enough cohesiveness

MATERIALS AND METHODS:

MATERIALS:

Ibuprofen was procured from Sun Pharma Pvt. Ltd. Mumbai, India as a gift sample. *Lepidium sativum* seed extract was prepared in lab. Microcrystalline cellulose obtained from S.D. Fine Chemicals, Mumbai, India. Talc and Magnesium stearate obtained from Loba Chem. Pvt. Ltd. Mumbai, India. All other materials and chemicals used were of either pharmaceutical or analytical grade.

METHODS:

Extraction of mucilage:

Methodology for extraction of mucilage *Lepidium sativum*:

The seeds of *Lepidium sativum* contain the mucilage around the outer layer. The major problem in isolation of mucilage is that it swells but does not separate from the seeds. Because of this, general methods of separation of mucilage are not applicable to separate the seed mucilage. The 100 g seeds were soaked for 12 h in distilled water (1L). Mucilage was separated by filtration applying vacuum. Remaining particulate matter was separated by passing through the muslin cloth and was treated with acetone. Precipitated mucilage powder was separated by filtration and dried at 45-50°C for 6 h. Then powder was sifted through 80# and weighed to calculate the yield.¹¹

the wet mass was sieved through 30# sieve. Granules were dried at 60°C for 30 minutes and were passed through 60# sieve. At the end Talc I.P. and Magnesium stearate I. P. were added as a glidant and lubricant, respectively.

Prepared blends were compressed using multi rotary tablet machine (Type: Patel services Pvt. Ltd, Ahmadabad). Each tablet contained 500 mg of ibuprofen and other pharmaceutical ingredients, Table 1.

Table 1: Different formulation for Ibuprofen sustained release tablet

Ingredients	Formulations				
	F1	F2	F3	F4	F5
Ibuprofen	200	200	200	200	200
<i>Lepidium sativum</i>	0	60	120	180	240
Microcrystalline cellulose	300	240	180	120	60
Magnesium stearate	1	1	1	1	1
Talc	1	1	1	1	1
Ethanol	q.s.	q.s.	q.s.	q.s.	q.s.

*All values are in mg

EVALUATION OF POWDER AND POWDER BLEND:

Angle of Repose:

Angle of repose of powder and powder blend were determined by the funnel method. Accurately weight powder blend were taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation¹

$$\tan\theta = h/r$$

where, h is the height of heap of pile and r is radius of base of pile.

Bulk density:

Accurately weighed 10 g powder and powder blend which were previously passed through 20# sieve were transferred to 100 ml graduated cylinder. Carefully powder was leveled without compacting and unsettled apparent volume (V_0) was noted. The apparent bulk density was calculated in g/ml by the following formula¹

$$\text{Bulk density} = \text{weight of powder} / \text{Bulk volume}$$

Tapped Density:

Tapped density was determined by USP method II. Tablet blend was filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume reached a minimum. It was calculated by formula given below.

$$Dt = M/V_b$$

where, m is weight of powder taken and V_b is tapped volume.¹²

Carr's Compressibility Index:

Carr's compressibility index (CCI) was calculated by using values of bulk density and tapped density as given below.¹³

$$\%CCI = [(TD-BD)*100] / TD$$

Hausner's Ratio¹:

Hausner's ratio is a number that is correlated to the flowability of powder and powder blend. It was calculated using equation given below.

$$\text{Hausner's ratio} = TD / BD$$

EVALUATION OF TABLETS:

Thickness:

The thickness of the tablet was measured by using digital Vernier Caliper. A total of 20 tablets from each batch were randomly selected and thickness were measured.¹²

Weight variation test:

Accurately 20 tablets of each formulation were weighed using an electronic balance (Digital weighing balance, Purvi Enterprise Pvt. Ltd Ahmedabad India) and the test was performed as per specifications.¹

Hardness:

Hardness in kg/cm^2 for tablets from each batch was measured using Pfizer hardness tester.¹⁴

Friability:

Friability of the tablet was determined using friability tester made by Electro Lab (India) rotated at 25rpm for 4 min. Percentage friability was determined by following equation¹⁵,

$$\% \text{ Friability} = [(\text{Initial weight} - \text{Final weight}) / \text{Initial weight}] \times 100$$

Drug content:

Randomly three tablets from each batch were selected, weighed and powdered. A quantity equivalent to 5 mg of ibuprofen was placed in a 100 ml volumetric flask and dissolved in distilled water, sonicated for 5 min and the volume was made up to the mark followed by filtration through membrane filter. After appropriate dilutions with solvent, the drug content was determined by UV spectrophotometer at 237 nm. (Shimadzu 1800, Tokyo, Japan).¹⁶

RESULTS AND DISCUSSION:

For the calibration curve of ibuprofen a concentration range of 5 to 25 µg/ml was selected as drug obeys Beer-Lambert's law in this range. The ibuprofen showed λ_{max} at 264 nm in phosphate buffer of pH 7.2. The slope and

intercepts of the calibration curve were 0.041208 and 0.1393, respectively. The results of granule and tablet characterization are given in Table 2 and Table 3. In-vitro release kinetic models for ibuprofen sustained release matrix tablets are given in table 4.

Table 2: Characterization of Ibuprofen granules

Parameter	F1	F2	F3	F4	F5
Angle of repose	28.09±0.96	27.29±1.10	26.78±0.87	27.42±0.91	29.11±1.04
Bulk density (g/ml)	0.543±0.098	0.589±0.054	0.511±0.085	0.512±0.086	0.534±0.089
Tapped density (g/ml)	0.673±0.056	0.698±0.061	0.692±0.071	0.681±0.074	0.731±0.064
Hausner's ratio	1.239±1.20	1.185±1.10	1.353±0.98	1.327±1.40	1.360±1.46
Carr's index	19.31±0.46	15.61±0.67	26.11±0.87	24.68±0.89	26.85±0.91

Table 3: Physico-chemical characterization of Ibuprofen SR tablets

Formulation Code	Thickness(mm)*	Hardness(kg/cm ²)*	Friability (%)	Weightvariation(mg)	Drug content (%w/w)**
F1	4.44±0.02	6.31±0.05	0.676±0.01	396.25±1.28	98.95±0.69
F2	4.38±0.06	6.66±0.01	0.503±0.04	397.25±2.39	99.59±1.05
F3	4.41±0.09	6.75±0.03	0.412±0.02	397.65±1.94	99.83±0.87
F4	4.39±0.07	6.46±0.01	0.568±0.06	395.05±1.75	99.72±0.87
F5	4.55±0.02	6.54±0.03	0.515±0.03	392.05±1.94	99.45±0.66

Table 5: In- vitro Release Kinetic models for Ibuprofen sustained release Matrix tablets

Formulation Code	Zero order	First order	Higuchi	Korsemeyer-Peppas		Best fit model
	R ²	R ²	R ²	R ²	Slope(n)	
F1	0.938	0.809	0.900	0.875	0.136	Zero order
F2	0.963	0.829	0.976	0.985	1.491	Korsemayer-Peppas
F3	0.980	0.829	0.983	0.986	1.210	Korsemayer-Peppas
F4	0.955	0.952	0.901	0.950	0.917	Zero order
F5	0.968	0.833	0.939	0.943	1.462	Korsemeyer-peppas

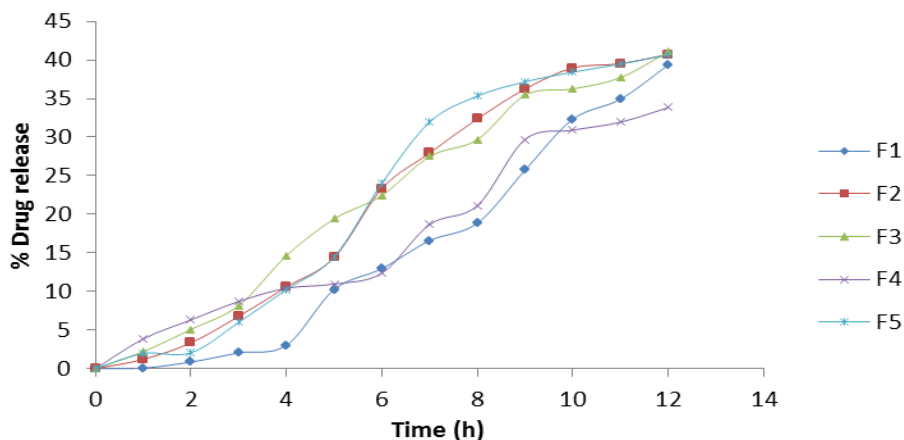


Figure 2: In vitro drug release of formulations (F1-F5)

The blended granules of abovementioned formulations were evaluated for angle of repose, bulk density, tapped density, Hausner's ratio and CCI. Angle of repose for formulations under study was ranged from 26.78 ± 0.87 to 29.11 ± 1.04 . The results were observed to be less than 30° and hence the blends under investigation have good flowability. The Hausner's ratio was observed in the range from 1.185 ± 1.10 to 1.360 ± 1.46 which indicates the granules are of free flowing nature. The Carr's index (%) ranged from 15.61 ± 0.67 to 26.85 ± 0.91 which implies that the blend have excellent flowing property as shown in Table 3. The drug content in the formulations was observed to be in the range of 98.95 ± 0.69 to $99.83 \pm 0.87\%$ w/w, as in specified limit of Indian Pharmacopoeia 1996 (i.e. 90-110% w/w). The hardness of tablets was observed to be in the range of 6.31 ± 0.05 to $6.75 \pm 0.03 \text{ kg/cm}^2$ indicates tablet have good strength. Friability and weight variation were also found to be within specified limit as shown in Table 4. Drug release from matrix signifies the controlling behavior in release from prepared formulations. Formulations under study were formulated using release retardant polymer as *Lepidium sativum* mucilage, microcrystalline cellulose as binder and magnesium stearate as a lubricant. *In vitro* drug release at the end of 12 hour from formulations F1 to F5 were found to be $39.36 \pm 2.14\%$, $40.73 \pm 1.34\%$, $41.05 \pm 1.82\%$, $33.84 \pm 2.10\%$, $40.66 \pm 1.30\%$ respectively as shown in Fig.2.

Mechanism of release can be indicated according to Korsmeyer where 'n' is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case-II relaxational release are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. $0.5 < n < 1$ means a non-Fickian release model and $n = 0.5$ indicates Fickian diffusion. Formulations F1 and F4 follows zero order release whereas F2, F3 and F5 follows Korsmeyer-Peppas model as shown in Table 5. The formulations following Korsmeyer-Peppas model and having higher correlation coefficient deemed to be fit for sustained release of drug. For formulations F2, F3 and F5 the calculated regression coefficients were observed as 0.985, 0.986, 0.943 respectively whereas 'n' value were found to be 1.491, 1.210 and 1.462 respectively. The 'n' value of F3 is near to 1. The formulation F3 has shown maximum drug release of $41.05 \pm 1.82\%$ at the end of 12 hour. Therefore, formulation F3 is best suited for

sustained release of drug by use of release retardant polymer *Lepidium sativum* mucilage. So from this, it should predict its release kinetics.

CONCLUSION:

Mucilage of *Lepidium sativum* has been successfully used in preparing matrix type sustained release tablets of ibuprofen. The drug release from such tablet is usually by diffusion-controlled mechanism. Ibuprofen sustained release matrix tablet was prepared successfully using *Lepidium sativum* mucilage as polymer to retard release and achieve required dissolution profile. Drug release kinetics of this formulation corresponds to Korsmeyer-Peppas model. But the release kinetics cannot be predicted clearly as it appears to be a complex mechanism of swelling, diffusion and erosion. Tablet formulation (F3) containing 24% mucilage of *Lepidium sativum* showed non-Fickian release kinetics of ibuprofen with highest release of ibuprofen at the end of 12 h and is thus a best suited. The study deals with the investigation of release retardant effect of *Lepidium sativum* mucilage when formulated as a matrix tablet. The mucilage exhibited an appreciable physicochemical properties and suited best for the development of sustained release tablets as indicated by the drug release studies. This can be used as a potential natural source over the synthetic release retardant. Hence, *Lepidium sativum* could be employed as a release rate retardant for sustaining the drug release from the formulation.

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