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Formulation And Invitro Evaluation Of Sustained Release Matrix Tablets Of Ibuprofen

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ABSTRACT

The objective of present study to prepare and evaluate sustained release matrix tablets of ibuprofen. The granules were prepared by wet granulation method. The prepared granules were evaluated for angle of repose, bulk density, tapped density and carr's index. The results were found to be satisfactory and within acceptable limits.The results of present study demonstrated that hydrophilic polymer could be successfully employed for formulating sustained release matrix tablets of ibuprofen. Stability study it was found that there was no significant change.

Keywords: Ibuprofen, Sustained release, Hydroxy propyl methyl cellulose, Stability studies.

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INTRODUCTION

Ibuprofen is a non-steroidal anti-inflammatory, analgesic and antipyretic agent. It is a prodrug of diclofenac, in the inflammatory cells it gets converted into diclofenac and 4-hydroxy diclofenac. Ibuprofen has the more COX-2 specificity than diclofenac, as it is active only in inflammatory cells it has less GI stress than diclofenac. It has short biological half-life (4 hours), and the usual oral dosage regimen is 100 mg taken 2 times a day.

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 for many acute and chronic diseases.

Non–Steroidal Anti-Inflammatory Drugs (NSAIDs) are considered to be the first line drug in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Ibuprofen is one of the emerging NSAIDs molecules for arthritis treatment.

- To minimize the frequent dosing
- To prolong the pharmacological effect and
- To improve patient compliance, 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 also

- Broad regulatory acceptance.

Hence, in the present work, an attempt is made to develop sustained-release matrix tablets of Ibuprofen, with the use of various hydrophilic polymers for their sustaining effect. Wet granulation technique is used for tablet formulation along with the addition of suitable additives by using of hydrophilic polymers of HPMC K100M and ethyl cellulose.

MATERIALS AND METHODS

Materials: Ibuprofen HPMC and ethylcellulose were obtained from Tristar formulation, Puducherry. IPA and polyvinyl pyrrolidone was supplied by Nickon laboratories, Puducherry. Magnesium stearate and talc was purchased from Loba chemie (Pvt) Ltd, Mumbai.

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Preparation of Ibuprofen matrix tablet

Granules for Ibuprofen matrix tablets were prepared by wet granulation technique using various percentages of HPMC K100M and ethyl cellulose as release retardant polymers. All the powders passed through sieve No.80. The required quantity of drug, various polymers and other ingredients were mixed thoroughly and a sufficient volume of granulating agent (isopropyl alcoholic solution of polyvinyl pyrrolidone) was added slowly. After enough cohesiveness was obtained, the wet mass was sieved through sieve No.8. The granules were dried at 60°C for 30 minutes and then the dried granules were passed through sieve No.16. Talc and magnesium stearate were finally added as a glidant and lubricant respectively.

Evaluation of Granules

Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the granules cone was measured and angle of repose was calculated using the following equation.

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

Where, h and r are the height and radius of the granules cone respectively.
* Adding Glidant for improving flow

Loose bulk density

An accurately weighed granules from each formulation was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the granules was measured which gave bulk volume. The loose bulk density of granules was determined using the following formula.
Loose bulk density = Total weight of granules / Total volume of granules

Tapped bulk density

An accurately weighed granules from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TBD of granules was determined by the following formula.

Tapped bulk density = Total weight of granules/ Tapped volume

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Hausner ratio

Hausner ratio is the ratio between tapped density and bulk density. Hausner ratio less than 1.25 indicates good flow properties while Hausner ratio greater than 1.25 shows poor flow of granules.

Carr's compressibility index

It is a simple index that can be determined on small quantities of granules. In theory, the less compressible a material the more flowable it is. The compressibility index of the granules was determined using following formula.

Carr's compressibility index (%) = [(TBD-LBD)/ TBD] ×100

Evaluation of Sustained release matrix tablet of Ibuprofen

Appearance

The tablets were visually observed for capping, chipping, and lamination.

Physical characteristics

The physical characteristic of Ibuprofen sustained release matrix tablets (F1 to F9) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and results of the formulations (F1 to F9) found to be within the limits specified in official books.

Thickness

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined using a vernier caliper. Ten tablets from each type of formulation were used and average values were calculated.

Weight variation

For weight variation, 20 tablets of each type of formulation were weighed individually on an electronic balance, average weight was calculated and individual tablet weight was then compared with the average value to find out the deviation in weight.

Hardness

For each type of formulation, the hardness value of 10 tablets was determined using Monsanto hardness tester.

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Friability

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows.

$$\%F = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Content uniformity

Content uniformity was determined by accurately weighing 20 tablets and crushing them in mortar with the help of a pestle. Then an accurately weighed quantity of powder equivalent to 25 mg of drug was transferred to a 50 ml volumetric flask. Then added few ml of methanol and made upto 50ml with methanol. The solution was filtered through whatmann filter paper. 5 ml of the filtrate was diluted to 50 ml with Methanol. Then 3 ml of the resulting solution was again diluted to 10 ml with Methanol. The absorbance of the resulting 15 µg/ml solution was recorded at 274nm.

Invitro dissolution study

The *in-vitro* dissolution studies were performed using USP type I dissolution apparatus at 50rpm. Dissolution test was carried out for a total period of 8 hours using 0.1N HCl (pH 1.2) solution (900 ml) as dissolution medium at 37 ± 0.5° for first 2 h, and pH 7.4 phosphate buffer solution (900 ml) for the rest of the period An aliquot (5ml) was withdrawn at specific time intervals and absorbance was determined by U.V. spectrophotometer at 274nm. The release studies were conducted in triplicate.

Stability study

Stability studies were carried out at accelerated condition (40°C ± 2°C at 75% RH ± 5% RH) for the optimized formulation F9. The matrix tablets were stored at 40°C ± 2°C at 75% RH ± 5% RH for accelerated temperature in closely packed with aluminium foil for 3 months. The samples were withdrawn after periods of 1st month, 2nd month and 3rd month. The samples were analyzed for its hardness, drug content and *in vitro* drug release.

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RESULT AND DISCUSSION

DSC thermogram showed that there was no any major difference in onset temperature and peak temperature, when compared with pure drug's thermogram interaction was found between drug and polymers.

The blended granules of different formulation were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner ratio.

Angle of repose ranged from 28.3±0.92 to 37.4±0.06. The results were found to be below 30^{o} and hence the blend was found to have good flowability.

The compressibility index (%) ranged from 8.44±0.93 to 10.38±0.82. The blend was found to have excellent flowing property as the result were found to be below 15%.

The Hausner ratio ranged from 4.76±1.22 to 5.73±1.31. The result indicates the free flowing properties of the granules.

A difference in tablet hardness reflects difference in tablet density and porosity. In which turn are supposed to result in different release pattern of the drug by affecting the rate of penetration of dissolution fluid at the surface of the tablet and formation of gel barrier. The hardness of tablets was found to be in the range of 6.32±0.05 kg/cm^2 to 6.75±0.01kg/cm^2. This indicates good tablet strength..

The content of active ingredients in the formulation was found to be between 97.55 ±0.42 to 99.98 ± 0.65% w/w, which is within the specified limit as per Indian Pharmacopoeia 1996 (i.e. 90-110% w/w).

Ibuprofen is a water insoluble drug; its release from the matrix is largely controlling the drug release. Various sustained release formulations were formulated with HPMC K100M, ethyl cellulose, polyvinyl pyrrolidone as granulating agent and magnesium stearate as a Lubricant.

In vitro release studies of formulations F1, F2 and F3 prepared by HPMC K100M with concentrations of 10%, 20% & 30% respectively. The drug released from formulation F1 to F3 were found to be 93.7± 0.25, 92.9 ± 0.66, and 93.9 ± 0.64% for Ibuprofen respectively. *In vitro* release studies of formulations F4, F5 and F6 prepared by ethyl cellulose with concentrations of 10%, 20%& 30% respectively. The drug released from formulation F4 to F6 were found to be 90.8 ± 0.07, 93.9 ± 0.09, and 95.8 ± 0.26% for Ibuprofen respectively.

In vitro release studies of formulations F7, F8 and F9 prepared by wet granulation method.

The drug released from formulation F7 to F9 were found to be 94.9 ± 0.15, 95.6 ± 0.35, and 96.2 ± 0.65% for Ibuprofen respectively.

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The release rate of F9 was found to be higher when compared to other formulations this is due to increase in the concentration of polymer.

The overall release rate of Ibuprofen from ethyl cellulose and HPMC K100M matrices are significantly higher than that from matrices. These results are indicating that has higher drug retarding ability for long duration than ethyl cellulose and HPMC K100M.

To know the kinetics of the best formulations, the release data was treated according to different models. Drug release data of tablets was fitted in peppas equation and found release mechanism to be diffusion.

The results of dissolution data fitted to various drug release kinetic equations. Model was found to be the best fitted in all dissolution profile having higher correlation coefficient followed by the Peppas release equation. Optimized formulation F9 shows the Super case II transport Mechanism.

Table 1: Formulation of Ibuprofen sustained release matrix tablets: Composition of Ibuprofen matrix tablets

Ingredients(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ibuprofen	200	200	200	200	200	200	200	200	200
HPMC K100M	40	80	120	-	-	-	-	-	-
Ethyl cellulose	-	-	-	40	80	120	-	-	-
HPMC+EC	-	-	-	-	-	-	40	80	120
IPA+PVP	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Lactose	150	110	70	150	110	70	150	110	70
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total weight	400	400	400	400	400	400	400	400	400

Table 2: Physico-Chemical Characterization of Ibuprofen SR Tablets

F. Code	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Weight variation (mg)	Drug content (%w/w)**
F1	4.44±0.02	6.32±0.05	0.679±0.01	398.25±.139	99.83±0.69
F2	4.37±0.06	6.65±0.01	0.503±0.04	397.25±2.39	99.59±1.05
F3	4.40±0.09	6.75±0.03	0.417±0.02	397.65±1.94	98.95±0.87
F4	4.38±0.07	6.46±0.01	0.568±0.06	395.05±1.75	99.72±0.87
F5	4.54±0.02	6.54±0.03	0.515±0.03	397.05±1.94	99.65±0.66
F6	4.27±0.06	6.74±0.02	0.667±0.03	396.75±2.04	99.61±0.65
F7	4.60±0.06	6.36±0.01	0.655±0.02	396.55±1.75	98.86±1.55
F8	4.27±0.05	6.74±0.01	0.601±0.01	398.09±1.94	97.55±0.42
F9	4.32±0.06	6.85±0.03	0.414±0.02	398.55±2.04	99.98±0.63

*All the values are expressed as mean± SD, n=3

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Table 3: In- vitro Release Kinetic models for Ibuprofen sustained release Matrix tablets

F. Code	Zero order	First order	Higuchi	Korsemeyer- Peppas		Best fit model
	R^2	R^2	R^2	R^2	Slope(n)	
F1	0.989	0.965	0.862	0.992	1.268	Peppas
F2	0.986	0.943	0.836	0.994	1.302	Peppas
F3	0.984	0.932	0.815	0.991	1.376	Peppas
F4	0.986	0.982	0.894	0.987	1.186	Peppas
F5	0.983	0.955	0.890	0.989	1.279	Peppas
F6	0.981	0.932	0.876	0.994	1.342	Peppas
F7	0.986	0.971	0.831	0.991	1.197	Peppas
F8	0.977	0.926	0.899	0.993	1.279	Peppas
F9	0.964	0.989	0.893	0.995	1.262	Peppas

Table 4:Stability study of best formulation F9

Characteristic	Initial	1st Month	2nd Moth	3rd Month
Hardness (kg/cm^2)*	6.85±0.03	6.82±0.26	6.80±0.28	6.77±0.29
Drug content (%)*	99.9±0.63	99.5±0.79	99.04±0.63	98.9±0.58
In vitro* drug release at 10th hour	96.2±0.65	95.9±0.56	95.8±0.59	95.2±0.57
Appearance	White	No change	No change	No change

*All the values are expressed as mean± SD, n=3

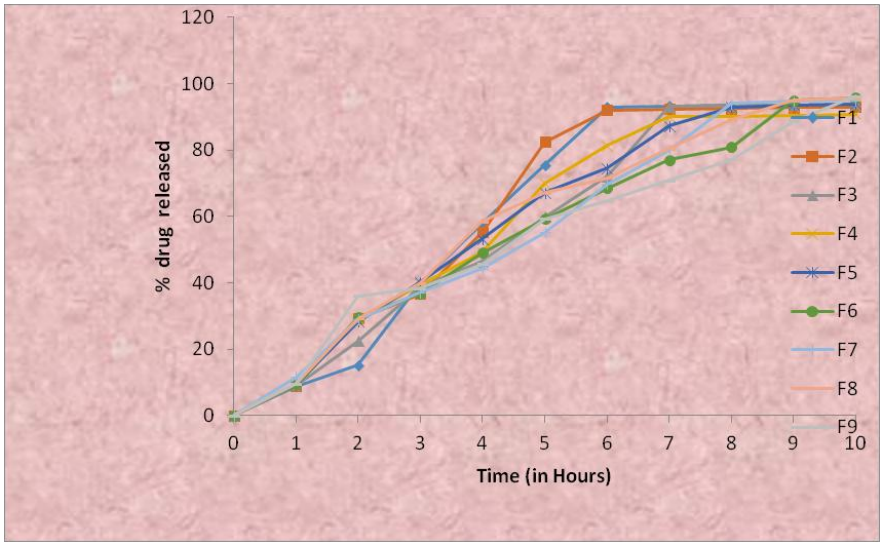

Figure1:Invitro drug release profile of all nine Formulation (F1 to F9)

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