DESIGN AND IN VITRO EVALUATION STUDIES OF DICLOFENAC SODIUM FLOATING MATRIX TABLETS BY MELT GRANULATION TECHNIQUE

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ABSTRACT

The purpose of this study was to formulate diclofenac sodium floating matrix drug delivery system by melt granulation technique. These tablets were developed to prolong gastric residence time and increase its bio availability. The diclofenac sodium tablets of 100mg were developed by using different bees wax combinations which are prepared by melt granulation technique by using polymers such as Hydroxy propyl methyl cellulose (HPMC K15M), ethyl cellulose, bees wax alone or in combination with cetyl alcohol, sodium bicarbonate as a gas generating agent and other standard excipients. The prepared granules are subjected to pre compression studies such as angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. The optimized formulation produced monolithic tablets with optimum hardness, uniform thickness, consistent weight uniformity and low friability. The results of dissolution studies, floating lag time indicates that formulations F6 exhibited good and controlled drug release.

Key words: Diclofenac sodium, Melt granulation, Dissolution, 0.1N HCl

INTRODUCTION

Floating drug delivery systems were first described by Davis in 1968. These systems were used to prolong the gastric residence time of drug delivery systems. They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents. A floating dosage form is useful for those drugs that act locally in the proximal gastro intestinal tract are unstable in lower parts of gut or are poorly absorbed in the intestine¹⁻³. Diclofenac sodium is a nonsteroidal anti inflammatory drugs having chemical name sodium 2-[(2,6-dichlorophenyl)-amino] Phenyl acetate. The most frequent adverse side effects occurring with diclofenac sodium are gastro intestinal disturbances, peptic ulceration and gastro intestinal bleeding, hence there is potential need for a floating matrix dosage form for this drug to minimize gastric erosion side effect. It's biological half life on the other hand is very short, sustaining its anti inflammatory activity only for a few hours and associated adverse effects; it is considered as an ideal model drug for floating matrix drug delivery⁴⁻¹⁰. The present study is to formulate rate controlled floating drug delivery system of diclofenac sodium which is primarily absorbed from stomach, so by increasing the GRT of the drug, the bio availability can be increased. As the moderately weekly acidic drug, so the stomach is the major absorption site for the drug. So basing on this fact the drug is made to float in the stomach using mechanism of buoyancy by using gas generating agent and the drug is delivered in the sustained release dosage form by using HPMC as swell able polymer to formation of gel layer for controlled release. Ethyl cellulose is used to retard the disintegration and also dissolution. Microcrystalline cellulose is used as diluents¹¹. The study also includes various evaluation studies of diclofenac sodium tablet and the effect of processing variables on it. A possible interaction between drug and polymers are also investigated by FTIR study.

The objective of this study is to formulate diclofenac sodium floating matrix tablets using hydrophobic wax materials, sodium bicarbonate as gas generating agent and to evaluate

the in vitro release characteristics and to predict and correlate the release behavior of diclofenac from the matrix

MATERIALS AND METHODS

Materials

Diclofenac sodium as a gift of hetero chemicals Ltd, Hyderabad, HPMC K15M by SD fine chemicals, Mumbai, Ethyl cellulose from Loba chemicals Pvt Ltd, Mumbai, Micro crystalline cellulose and talc from Yarrow chemicals Ltd, Mumbai. Sodium bicarbonate, Magnesium stearate for Thomas bakers Ltd, Mumbai

Methods

Preparation of standard curve of diclofenac sodium

Solutions ranging from 2 to 10 microgram per ml were prepared by using ethanol and 0.1N HCl absorbance was measured for each solution at lambda max of 276nm, using Shimadzu spectrophotometer. Correlation coefficient was found to be 0.9996 in 0.1N HCl.

Preparation of floating tablets by melt granulation technique

Floating tablets, each containing 100mg diclofenac were formulated by a conventional melt technique. The composition of various formulations of the tablets with their codes is listed in table. The composition with respect to polymer combination was selected on the basis of trial preparation of tablets. The amount of bees wax was decreased gradually and the reduced amount of bees wax was replaced by cetyl alcohol. As per each formulation batch code required quantity of bees wax and cetyl alcohol were weighed and melted separately in a large china dish over a water bath. The drug was added to molten wax and mixed well. Previously weighed quantities of ethyl cellulose, HPMC, Micro crystalline cellulose and sodium carbonate were added to the drug wax mixture and mixed well. After thorough mixing china dish was removed from water bath and cooled. The coherent mass was then scrapped from the china dish and was passed through sieve no 30. The amount of ingredients that are added for each tablet is given in following table 1.

Evaluation of granules**Angle of repose**

Flowability of different batch of granules was determined by calculating angle of repose by fixed height method. A funnel with 10mm inner diameter of stem was fixed at a height of 2 cm over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the stem of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured.

Angle of repose was calculated from the average radius using the following formula.

$$\Theta = \tan^{-1}(h/r)$$

Where, Θ = Angle of repose, h = height of the pile, r = average radius of the powder cone

Bulk density

Apparent bulk density was determined by pouring preserved drug excipient blend in to graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/ml and is given by

$$D_b = M / V_o$$

Where, M is the mass of powder and V_o is the bulk volume of the powder

Tapped density

It was determined by placing a graduated cylinder, containing a known mass of drug excipients blend, on mechanical tapping apparatus. the tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by

$$D_t = M/V_t$$

Where M is the mass of powder and V_t is the tapped volume of the powder

Powder flow properties

The flow properties were determined by

Carr's index(i)

It is expressed in percentage and is expressed by

$$I = D_t \cdot D_b / D_t$$

Where D_t is the tapped density of the powder and D_b bulk density of the powder

Hausner's ratio

It is expressed in percentage and is expressed by

$$H = D_t / D_b$$

Where D_t is the tapped density of the powder and D_b is the bulk density of the powder

Compression of tablets

After evaluation of granules were then compressed in to the tablet by direct compression technique using 10 punches tablet punching machine

Evaluation of tablets**Weight variation**

20 tablets were selected at random and average weights were determined. The individual tablets weighed the individual weight was compared with the average.

Thickness and diameter

The thickness and diameter of the tablets was measured by Vernier calipers. It is expressed in mm.

Hardness

The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed in kg/cm².

Friability (f)

The friability of the tablet was determined using roche friabilator. The friabilator was operated at 25 Rpm per min for 4 min (100 revolutions). The tablets were weighed again(W_{final}). The % friability was then calculated by

$$F = W_{initial} - W_{final} / W_{initial} * 100$$

Content uniformity

20 tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 5ml of methanol and make up to volume with 0.1N HCl. The sample was mixed thoroughly and filtered through 0.45 μ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer at lambda max of 276nm using 0.1N HCL as blank.

In vitro buoyancy studies

The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as a floating lag time. the duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time.

In vitro dissolution studies

The dissolution test was performed using 900ml of 0.1N HCL at 37 $\pm$ 0.5 $^{\circ}$ c and 75 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly and samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 microns membrane filter and diluted to a suitable concentration with 0.1N HCL. Absorbance of these solutions were measured at 276nm using a Shimadzu UV spectrophotometer.

RESULTS AND DISCUSSION

Diclofenac sodium is a water insoluble drug. Its poor inherent compressibility coupled with associated side effect possess a significant challenge for developing floating tablets. For developing floating tablets with desirable drug release profile, cost effectiveness and broader regulatory acceptance combination of HPMC, Ethyl cellulose, Bees wax and Cetyl alcohol was chosen as release controlling polymers, sodium bicarbonate was added as a gas generating agent.

The formulated granule blends of different formulations (F1 to F10) were evaluated for angle of repose, tapped density, bulk density, Carr's index and Hausner's ratio.

TABLE 1: FORMULATION INGREDIENTS FOR FLOATING MATRIX TABLETS OF DICLOFENAC SODIUM

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Diclofenac sodium	100	100	100	100	100	100	100	100	100	100
Bees wax	90	90	90	90	90	70	60	50	40	35
Cetyl alcohol	-	-	-	-	-	20	30	40	50	55
HPMC K15M	64	64	64	64	64	64	64	64	64	64
Ethyl cellulose	30	30	30	30	30	30	30	30	30	30
Microcrystallinecellulose	60	50	40	35	30	30	30	30	30	30
Sodium bicarbonate	-	10	20	25	30	30	30	30	30	30
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
talc	3	3	3	3	3	3	3	3	3	3
Total weight of tablet in mg	350	350	350	350	350	350	350	350	350	350

TABLE 2: PRE COMPRESSION PARAMETERS OF FORMULATED GRANULES

Formulation code	Angle of repose in degree	Bulk density	Tapped density	Carr's index	Hausner's ratio
F1	15.2	0.57	0.71	19.0	1.24
F2	12.4	0.55	0.67	16.9	1.22
F3	10.2	0.55	0.70	19.9	1.27
F4	14.0	0.54	0.73	21.5	1.35
F5	17.7	0.53	0.67	20.8	1.26
F6	16.6	0.57	0.74	23.1	1.29
F7	19.2	0.56	0.74	23.7	1.30
F8	18.7	0.57	0.73	22.8	1.32
F9	20.8	0.58	0.72	18.7	1.24
F10	20.3	0.55	0.71	18.9	1.24

TABLE 3: POST COMPRESSION PROPERTIES OF FORMULATED FLOATING TABLETS

Formulation code	%of weight variation	Thickness (mm)	Diameter	hardness	Friability	Drug content	% Drug release
F1	350±4	5.3±0.01	9.9±0.01	4.0±0.01	0.28±0.01	96.6	69.02
F2	350±5	5.5±0.01	9.9±0.01	4.9±0.01	0.22±0.01	96.1	70.20
F3	350±4	5.3±0.01	9.9±0.01	4.9±0.01	0.18±0.01	97.0	71.13
F4	350±3	5.3±0.01	9.9±0.01	4.9±0.01	0.44±0.01	96.1	72.23
F5	350±2	5.4±0.01	9.9±0.02	4.4±0.01	0.38±0.01	96.1	72.21
F6	350±4	5.2±0.01	9.9±0.01	5.0±0.01	0.49±0.01	95.6	75.02
F7	350±3	5.5±0.01	9.9±0.02	5.0±0.01	0.41±0.01	97.0	59.85
F8	350±4	5.3±0.01	9.9±0.01	5.0±0.01	0.28±0.01	96.6	58.52
F9	350±3	5.4±0.01	9.9±0.02	5.0±0.01	0.25±0.01	95.6	58.07
F10	350±4	5.3±0.01	9.9±0.01	5.0±0.01	0.28±0.01	96.6	57.96

TABLE 4: IN VITRO BUOYANCY STUDIES RESULTS OF DICLOFENAC SODIUM FLOATING MATRIX TABLETS

Formulation code	Amount of sodium bicarbonate in mg	Buoyancy lag time in min	Total floating time in hrs
F1	0	Did not float	did not float
F2	10	30	>4
F3	20	18	>6
F4	25	10	>8
F5	30	5	>12
F6	30	5	>12
F7	30	5	>12
F8	30	5	>12
F9	30	4	>12
F10	30	4	> 12

Figure 1

Figure 2

The results of angle of repose ($<25^\circ$) indicated good flow properties of the entire granule blend. The compressibility index value were recorded, result in good excellent flow properties.

Formulated powder blends density; Porosity and hardness are often interrelated properties and are likely to influence compressibility, porosity, dissolution profile and properties of tablets made from it. The results of percentage porosity indicating that packaging of the granule blend may range from close to loose packaging and also confirming that particle are not of greatly different sizes. All the results indicate that the formulated granule blend possessing satisfactory flow properties and compressibility.

The tablets of different formulations (F1 to F10) were evaluated for various parameters they are thickness, diameter, hardness, friability, percentage weight variation percentage drug content and dissolution studies. All the formulations showed uniform thickness and diameter. In a weight variation test, the pharmacopeias limit for the percentage deviation for the tablets of more than 350 mg is $\pm 5\%$. The average percentage deviation of all tablet formulations was found to be within the above limit and hence all formulations passed the test for uniformity of weight as per official requirements. Drug content was found to be uniform among different batches of the tablets and the percentage of the drug content was more than 96%. The hardness of all the formulation was between 4.0 to 5.5 kg/cm². The Percentage friability for all formulations was below 1% indicating that the friability is within the prescribed limits. The percentage drug release is found to be 75.02%. All the tablet formulations showed pharmacotechnical properties and complied with specifications for weight variation, drug content, hardness and friability shown in the table 2 & 3.

In vitro buoyancy studies

The floating behavior studies it was found that as the concentration of effervescent mixture increase, the floating lag time, floating duration and matrix integrity decreased and

vice versa were observed through results. A reverse trend was observed on increasing the polymer concentration. The Initial batch is prepared without sodium bicarbonate did not show any sign of floating. Therefore, sodium bicarbonate was used as a gas generating agent in order to float the tablet. The sodium bicarbonate induces CO₂ generation in the presence of dissolution medium (0.1N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1gm/ml, and the tablet become buoyant. To study the effect of sodium bicarbonate concentration on floating lag time batches F1 to F10 were selected. It was found that as the amount of sodium bicarbonate increases the floating lag time decreases. Thus sodium bicarbonate 30 mg was essential to achieve optimum in vitro buoyancy (i.e floating lag time of 4-5 minutes and floating duration of 12 hrs). Further increase in the concentration of sodium carbonate does not show any significant effect of floating behavior. The increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid drug release. Thus 30mg concentration of sodium bicarbonate was kept constant for batches F5 to F10, which showed floating lag time between 4 and 5 minutes and remained floating for more than 12 hours. The relationship between the amounts of gas generating agents and floating lag time as well as the duration of floating are shown in table. It was observed that floating lag time for this system in the range of 4 to 15 min and flotation was achieved maximum at gas generating quantity of 30 mg with in 4 min. Therefore the formulation F5 to F10 was selected for In-vitro Dissolution study of floating matrix tablet. as shown in the table 4.

In vitro dissolution studies

Depending on floating lag time and total floating time formulation F5 to F10 were selected for in vitro dissolution study. In formulations F5 to F10 were showed 72.21%, 75.02%, 59.85%, 58.52%, 58.07% and 57.96% at the end 12th hour. Incorporation of higher amounts of cetyl alcohol in

formulation F7, F8, F9 and F10 was found to be less drug release characteristics due to excess of cetyl alcohol in comparison F5 and F6. The drug released from the formulations diffusion coupled with erosion. Formulation F6 is selected as optimized formulation among all the formulations showing 75 % sustained release at the end of 12 hours as shown in following figures 1&2.

Compatibility studies of infra red

IR spectra of drug diclofenac sodium and optimized formulation F5 (drug and Polymer mixture) were shown in tables and figures. The studies revealed that there was no significant interaction between drug and polymer.

CONCLUSION

The present study was to develop an floating system of diclofenac sodium with the use of wax materials, swell able polymer, release retardant and alkalizing agent which proved to be an ideal formulation, as it released the drug in a controlled manner for extended period of time by maintaining the buoyancy. The optimized formulation F5 reveals that in terms of floating lag time (5minurtes) and floating duration of 12 hours and drug release more than 75 % at the end of 12 hrs. This results in developing, because a longer gastric residence time is an important condition for higher bioavailability of the drugs included in floating matrix dosage forms.

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