International Journal of Pharmaceutical Research and Development (IJPRD)
Platform for Pharmaceutical Researches & Ideas
www.ijprd.com

FORMULATION AND EVALUATION OF DICLOFENAC SODIUM FLOATING TABLET MANUFACTURED BY MELT GRANULATION TECHNIQUE

Harshad Asodiya[1*],
Aniket Asodiya[1], Krunal sameja[1], Ami Makwana[1], Nayana M.Bhatt[1], Nimish L.Pathak[1]

[1]C.U.Shah College of Pharmacy and Research, Wadhwan.

ABSTRACT

The purpose of this research was to prepare floating matrix drug delivery system of Diclofenac sodium. Diclofenac sodium is a traditional non-steroidal anti inflammatory (NSAIDS) drug. Floating matrix tablets of Diclofenac sodium were developed to prolong gastric residence time which were developed using combination of different polymers such as hydroxylpropylmethylcellulose (HPMC K4M) and bees wax. The tablets were prepared by melt granulation technique, using dicalcium phosphate as diluents; Sodium bicarbonate and citric acid were incorporated as gas-generating agents. The effects of gas generating agents on floating properties of tablets were investigated. The formulation was optimized on the basis of acceptable tablet properties, floating lag time, and total duration of floating and in vitro drug release. The resulting formulation produced monolithic tablets with optimum hardness, uniform thickness, consistent weight uniformity, low friability showing more than 12 hours of total in vitro floating time.

Correspondence Author

Harshad Asodiya

[1]C.U.Shah College of Pharmacy and Research, Wadhwan.

Email: harshadasodiya@gmail.com

KEYWORDS : *Diclofenac Sodium, floating tablets, melt granulation, in vitro release.*

INTRODUCTION

The high cost involved in the development of a new drug molecule has diverted the pharmaceutical companies to investigate various strategies in the development of new drug delivery system[1] .Retention of drug delivery system in the stomach prolongs the overall gastrointestinal transit time, thereby resulting in improved bioavailability. Scientigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications, that is

short gastric residence time and unpredictable gastric emptying rate[2]. Floating drug delivery systems have various advantageous like sustained release, site specificity, absorption enhancement, maintenance of constant blood level etc[3]. A Floating dosage form is useful for those drugs that act locally in the proximal gastrointestinal tract (GIT), or unstable in lower parts of GIT, or are poorly absorbed in intestine[4-5]. While the system floats over the gastric contents, the drug is released slowly at the desired rate, while results in increased gastric retentive time and reduces fluctuation in plasma drug concentration[6-7].

Diclofenac sodium is a traditional non-steroidal anti inflammatory drug (NSAID). It is non selective cyclooxygenase inhibitor. It inhibits the prostaglandin synthesis. Sodium Salt increases stability and reduces side effects. It is used as analgesic, anti-inflammatory and antipyretic. It is well absorbed orally, 99% protein bound, metabolized and excreted both in urine and bile secretion. The plasma t1/2 is 2 hours. However it has good tissue penetrability and concentration in synovial fluid is maintained for 3 times longer period then in plasma, extended therapeutic effect within joints. Diclofenac sodium is among the most extensively used NSAIDs; employed in rheumatoid arthritis and osteoarthritis, bursitis, ankylosing spondylitis, toothache, dysmenorrhoea, post-traumatic and postoperative inflammatory conditions, affords quick relief of pain and wound edema[8-9]. The objective of this study was to prepare Floating matrix tablets of Diclofenac sodium using hydrophobic wax materials, bees wax in the combination with Hydroxyl propyl methyl cellulose (HPMC) K4M; Citric acid and Sodium bicarbonate as gas generating agents and also to evaluate the *in vitro* release characteristics and therefore to predict and correlate the release behaviour of Diclofenac sodium from the prepared matrix.

MATERIALS AND METHODS

Diclofenac Sodium, Hydroxyl propyl methyl cellulose (HPMC) K4M, Magnesium , Sodium bicarbonate and Isopropyl alcohol were purchased from seva fines, Ahmedabad. Bees wax, Citric acid and Sudan red were purchased from chemdyes corporation, Ahmedabad. Dicalcium phosphate was purchased from Central drug store (p) Ltd, New Delhi. Polyvinyl pyrollidone (PVP) K30 was purchased from Loba chemicals Pvt Ltd.

Preparation of Diclofenac Sodium floating tablets: Bees wax was melted in a porcelain dish using a hot plate. Diclofenac sodium was added to the molten mass. Previously prepared geometric mixture of HPMC K4M, Sodium bicarbonate, Dicalcium phosphate and Citric acid were added to the molten Diclofenac sodium-bees wax mixture and stirred well to mix. The coherent mass was removed from the hot plate and subjected to scrapping until it attained room temperature. PVP K30 and Sudan red were dissolved in Isopropyl alcohol and above mass was granulated using it. The coherent mass was passed through 20 # sieve. The granules were collected, dried using a tray dryer. The dried granules were passed through 20 # sieve and mixed with Talc and Magnesium stearate which were previously passed through 40 # sieve. This lubricated blend was compressed into tablets using tablet punching machine. Compression force was adjusted to obtain tablets with hardness in range of about 4-5 kg/cm^2.[10]

Table 1: Precompression properties of Diclofenac granules.

Formulation Code	Angle of Repose(θ)	Bulk Density	Tapped Density	Carr's index (%)	Hausner ratio
F1	25.1	0.56	0.74	24.32	1.32
F2	24.3	0.57	0.70	18.57	1.22
F3	27.3	0.54	0.74	27.02	1.37
F4	27.9	0.52	0.77	32.46	1.48
F5	28.2	0.55	0.75	26.66	1.36

F6	32.7	0.54	0.79	31.64	1.46
F7	26.8	0.56	0.73	23.28	1.30
F8	24.3	0.57	0.78	26.92	1.30
F9	27.3	0.58	0.76	23.68	1.31
F10	25.1	0.56	0.74	24.32	1.32

Table 2: Formulation Design of Diclofenac sodium Floating tablets

Formulation Code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Name of Ingredients	**Quantity (mg/tablet)**									
Diclofenac sodium	50	50	50	50	50	50	50	50	50	50
Dicalcium phosphate	126	120	113	94	87.6	81.2	43.2	35.8	30	23.6
Bees wax	32	32	32	48	48	48	80	80	80	80
HPMC K4M	57.6	64	70.4	57.6	64	70.4	76.4	83.8	89.6	96
Sodium bicarbonate	25.6	25.6	25.6	38.4	38.4	38.4	38.4	38.4	38.4	38.4
Citric acid	9.6	9.6	9.6	12.8	12.8	12.8	12.8	12.8	12.8	12.8
PVP K30	12.8	12.8	12.8	12.8	12.8	12.8	12.8	12.8	12.8	12.8
Sudan red	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talc	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2
Magnesium stearate	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Total	**320**	**320**	**320**	**320**	**320**	**320**	**320**	**320**	**320**	**320**

Table 3: Evaluation parameters of Diclofenac sodium floating tablets

Tests	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Weight Variation (mg)	320	298	322	320	297	321	322	321	322	320
Hardness (kg/cm^2)	4.5	5	4.5	5	5.5	5	4.5	5	4.5	5
Friabilty (%)	0.2	0.35	0.4	0.5	0.35	0.21	0.4	0.25	0.55	0.2
Thickness (mm)	3	2.9	2.8	3	2.9	2.7	3	3.1	3.2	3
Floating lag time (sec)	95	260	> 300	125	150	165	130	135	132	150
Total Floating time (hrs) without rupture of tablets	~ 4	~ 4	~ 4	~ 10	~ 10	~ 10	> 12	> 12	> 12	> 12

Weight Variation

Twenty tablets were taken at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with a average weight[11.]

Friability

Friability of tablets was checked by using Roche Friabilator. The device subjects a number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets at distance of 6 inches with

each revolution. Pre weighed sample of tablets was placed in the Friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed, then % friability (% w/w) was calculated using following formula. Tablet requires certain amount of hardness to withstand mechanical shock.

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

Hardness

Tablet hardness has been defined as "the force required to break a tablet in a diametric compression test." The Pfizer tester was used to measure tablet hardness[11]. Five tablets were evaluated and the mean value was calculated. During compression process, care was taken so that the hardness of tablets was adjusted at about 4-5 kg/cm^2.

Thickness

Thickness of the tablets was measured by sliding calliper scale (Vanier callipers). Five tablets were evaluated and the mean value was calculated. Tablet thickness should be controlled within 5% variation of standard value[12].

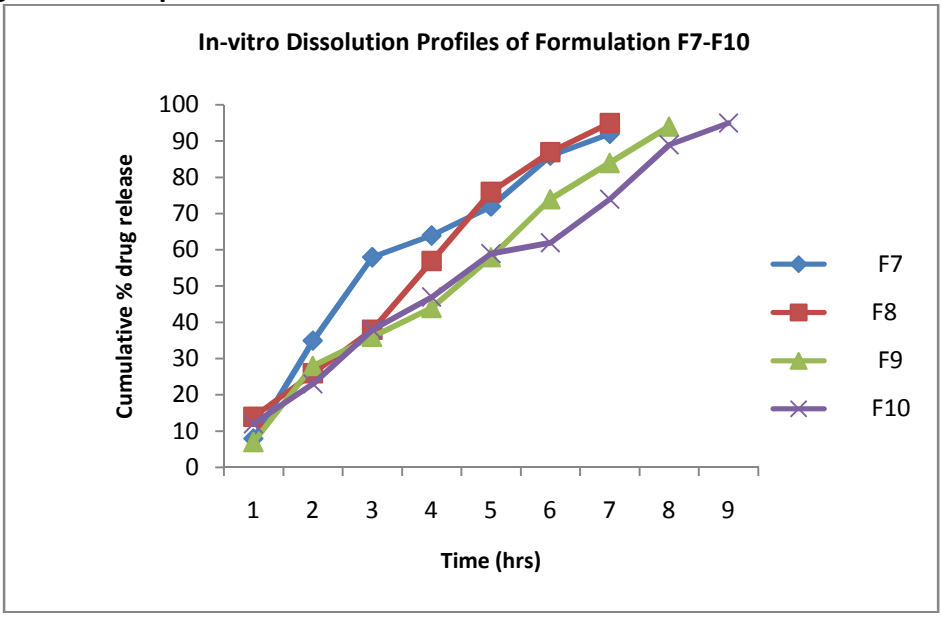
In-vitro buoyancy study

In vitro buoyancy studies were performed for all the ten formulations as per the method described by Rosa *et al*[13]. The randomly selected tablets from each formulation were kept in 100 ml 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 floating lag time (FLT). The duration of time of the dosage foam constantly remained on the surface of medium was determined as the total floating time (TFT).

In-vitro dissolution study

Dissolution rate was studied by using USP type II apparatus, rotated at 50 rpm; 900 ml of 0.1N HCl solution was used as dissolution medium. Temperature of dissolution medium was maintained at 37± 0.5^{o}C. Aliquot of dissolution medium was withdrawn at specific time interval and it was filtered. Absorption of filtered solution was checked by UV spectroscopy at 283 nm and drug content was determined from standard calibration curve. Dissolution rate was studied for selected formulations[14].

Figure 1: Comparison of in-vitro Dissolution Profiles of Formulation F7-F10.



RESULT AND DISCUSSION

Diclofenac sodium has poor inherent compressibility coupled with associated side effect posses' significant challenges for developing floating tablets. For developing floating tablets with desirable drug release profile combination of

HPMC K4M, bees wax, dicalcium phosphate as release controlling polymers. Sodium bicarbonate was added as a gas generating agent. Formulation of proper granule blends of different formulations (F1-F10) were evaluated for Angle of repose, tapped density, Bulk density, Carr's index and Hausner ratio.

The compositions of the formulations are shown in the Table 1. The evaluation parameters like Weight Variation, Hardness, Thickness, Friability, Floating lag time, Total Floating time were satisfactory for all the prepared formulations. In first three formulations (F1-F3), the floating lag time was higher and tablets were dispersed within 4 hrs during buoyancy test. It may be happened due to the insufficient amount of Bees wax (10 %), because Bees wax is used as a material which keep the tablets intact. Therefore, it was decided to increase the concentration of bees wax in further formulations, F4-F6 (15%) and F7-F8 (25%). Hence, the concentrations of bees wax was decided to optimize 15% to 25%. HPMC K4M was selected as a matrixing agent considering its widespread applicability and excellent gelling activity in sustained release formulations. Here we used HPMC K4M in first three (F1-F3) formulations in the concentration of 20-22% respectively. But in that much concentration the tablets were dispersed within 4 hrs and Floating lag time was >5mins. So we increased amount of gas forming agent. In formulations (F4-F6) the tablet were dispersed within 10 hrs so we used 25% to 35% of HPMC K4M, for better floating time in the stomach and for better matrixing property. Sodium bicarbonate & citric acid generates CO2 in the presence of hydrochloric acid present in the dissolution medium. In formulations (F1-F3) the amount of sodium bicarbonate was 5-10%. In that amount the floating lag time of tablet was increase. Hence in further formulations we increased the amount of sodium bicarbonate for reducing the floating lag time. In formulations (F7-F10) tablet has a proper floating lag time as required. So the amount of sodium bicarbonate was keep 25-30%. Dissolution profile of formulations (F7-F10) is sawn in Figure no 1. It was give satisfactory dissolution profile.

CONCLUSION

The present study was aimed at developing a floating system for Diclofenac with the use of wax material and gas generating agents which proved to be an ideal formulation, as it releases the drug in a controlled manner for extended period of time by maintaining the buoyancy. The optimized formulation gives the best result in terms of floating lag time (5 minutes) and floating duration of 12 hours and drug release (90%) at the end of 12 hours.

ACKNOWLEDGEMENTS

Authors thank C.U.Shah College of Pharmacy and Research, Wadhwan for providing support during our experimental work.

REFERENCES

1) Colombo P, Bettini R, Santi P, Pappas NA. Swellable matrices for controlled drug delivery, Gel layer behaviour, mechanism and optimal performance. Pharma Sci Techno Today 2000, 3, 1-8.
2) Swamy PV, Bhosale UV, Hire math SN, Shirsand SB, Raju SA. Formulation and optimization of Gastric Floating Drug Delivery System of Atenolol Using 3^2 Full Factorial Design, Indian Drugs 2008, 45,293-300.
3) Atyab F, Sharma HL, Mohammad HAH, Fell JT: In Vivo evaluation of novel gastric retentive formulation based on ion exchange resins. J control Release, 1996, 42,105-108.
4) Srivastava AK, wadhwa S, Ridhurker D, Mishra B. "Oral Sustained delivery of atenolol from floating matrix tablets- Formulation on in vitro evaluation." Drug Dev Ind Pharm, 2005, 31,367-374.
5) Dave BS, Amin AF, Patel MM, 2004. "Gastro retentive drug delivery systems of ranitidine hydrochloride: formulation and in vitro evaluation", AAPS Pharm Sci Tech., Article 34.

6) Khatri S, girdhari D, pahwa R. Recent advances in floating drug delivery system. The Indian Pharmacist.2007, 17-20.
7) Arora S, et al. floating drug delivery systems: A Review. AAPS Pharma Sci Tech.2005, 06,372-390.
8) Tripathi KD, Essential of medical publishers 6th edition, Jaypee Brothers Medical Publishers(P) LTD, New Delhi,2008,184-206.
9) Rang HP, Dale MM, Ritter JM, Flower RJ, Rang and Dale's pharmacology, 6th edition, Churchill Livingstone Elsevier, 2007, 227-233.
10) D.M.Patel, N.M.Patel,N.N.Pandya and P.D.Jogani,Indian Journal of Pharmaceutical Sciences, Formulation evaluation of carbamazepine Floating Tablets, volume 69, Nov-Dec 2007,763-767.
11) Banker GS and Anderson GR, Lachman L, Lieberman HA, Kanig JL, The Theory and Practice of Industrial Pharmacy, 3rd Edition, Varghese Publishing House, Mumbai, 1987,293.
12) Yunxia B, Sunada H, Yonezawa Y and danjo K, Evaluation of Rapid Disintegrating Tablets prepared by direct compression method, Drug Dev, Ind.pharm.,2595),1999,571.
13) Cedillo-Ramirez E, Villafuerte-Robles L, Hernandez-Leon A. 'Effect of added pharmatose DCL11 on the sustained-release of metronidazole from methocel K4M and carbopol 971 NF floating matrices", Drug Dev Ind Pharm,2006,32,955-965.
14) The United States Pharmacopoeia-24/ National formulary-19, Asian Edition, U.S.pharmacopoeial Convention, Inc., Rockville MD, 2000, 1942.

*****