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Formulation and evaluation of gastroretentive floating tablet of aceclofenac

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ABSTRACT

Tablet can be Utilized for precise delivery of drugs and reduce the drug concentrations at sites other than the target organ. The present study performed by preparation and evaluation of floating tablets of Aceclofenac as model drug. For prolongation of gastric residence time. Floating effervescent tablets were formulated by various materials like. hydroxypropyl methylcellulose (HPMC) K 4M, K 15M, psyllium husk, swelling agent as crospovidone and micro crystalline cellulose and gas generating agent like sodium bicarbonate and citric acid and evaluated for floating properties, swelling characteristics and drug release studies. Floating non effervescent tablets were prepared by polypropylene foam powder and different matrix forming polymers like HPMC K 4M, Carbopol 934P xanthan gum and sodium alginate. In vitro drug release studies were performed and drug release kinetics evaluated using the linear regression method was found to follow both the Higuchi and the Korsmeyer and Peppas equation. The drug release mechanism was found fickian type in most of the formulations. The developed floating tablets of Aceclofenac may be used in clinic for prolonged drug release for at least 24 h, thereby improving the bioavailability and patient compliance.

KEY WORDS: Aceclofenac, HPMC, crospovidone; microcrystalline cellulose; Polypropylene foam powder.

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INTRODUCTION

The aim of the present investigation was to design and evaluate gastro retentive floating effervescent and non effervescent tablets of Aceclofenac to increase the efficacy and stability of the drug in the stomach. Aceclofenac is a newer derivative of the Diclofenac group of non-steroidal anti inflammatory drug (NSAID) that exhibits analgesic and anti-inflammatory activities. It directly blocks the prostaglandin E2 secretion at the site of inflammation by inhibiting IL-Beta and Tumour necrosis factor in the inflammatory cells. Recommended dose of Aceclofenac is 100 mg twice daily, due to short biological half life of the drug (3-4h) makes it suitable candidate for the modified release dosage forms. It has less gastro intestinal complications.^{1,2} Aceclofenac is having, rapid absorption, and shorter half-life, and hence necessitate for modified release formulation³

It is considered to be the first-line drug in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.⁴ The aim of this work was to prepare and evaluate the Aceclofenac once daily sustained release tablets and to compare them with marketed products. Wet granulation method was adopted for the preparation of tablets using different retardant polymer excipients namely; hydroxypropyl methyl cellulose K4M/K15M/K100M and 15CPS, Guar gum, ethyl cellulose, directly compressible microcrystalline cellulose (pH 102), lactose, fumaric acid, povidone (PVPK-30), sodium propyl paraben, magnesium stearate and talcum.

The Controlled gastric retention of solid dosage forms may be achieved by Mucoadhesion,⁶ Flootation, Sedimentation, and simultaneous administration of pharmacological agents. Gastroretentive floating drug delivery system (GRFDDS) has bulk density lower than gastric fluids and thus remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric content, the drug is released slowly at a desired rate from the system. Floating drug delivery systems offer important advantages: as they are less prone to gastric emptying resulting in reduced intra and intersubject variability in plasma drug levels, effective for delivery of drugs with narrow Absorption windows, reduced dosing and increased patient compliance, reduced Cmax and prolonged drug levels above the minimum effective concentration, and improved safety profile for drugs with side-effects associated with high Cmax⁵.

MATERIALS AND METHODS

Aceclofenac was received as a gift sample from Mepro Pharmaceuticals Pvt. Ltd. Surendranagar, Gujarat, hydroxypropyl methylcellulose (HPMC K4M, K15M,), crospovidone (kollidon), microcrystalline cellulose (Avicel PH 101) were obtained as a gift samples from Signet Chemicals, Mumbai, India. Sodium bicarbonate, PVP K30, citric acid, Carbopol 934P, xanthan gum, guar gum, sodium alginate, hydrochloric

acid, magnesium stearate, talc and all other chemicals used were of analytical grade.

Tablets were prepared by conventional wet granulation method. The various excipients used were listed in Table 1 (Effervescent System) and Table 2 (Noneffervescent System). Ingredients except glidants and lubricant were thoroughly mixed and passed through sieve no. 60. Granulation was done with a solution of calculated quantity of PVP K30(binding agent) in sufficient isopropyl alcohol.(granulating agent) The wet mass was passed through sieve no. 12 and dried at 50 °C for 2 h. The dried granules were lubricated with magnesium stearate and talc and com- pressed into tablets using single station tablet punch machine with 11 mm Flat-faced punches. (CIP Machineries, India).

FLOATING PROPERTIES

The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) and duration of time the dosage form to constantly remain on surface of medium is called the total floating time (TFT). The buoyancy of the tablets was studied in USP 24 type II

Dissolution apparatus at 37± 0.5 °C in 900 ml of 0.1N HCL (pH 1.2) the measurements were carried out for each formulation of tablets. The time of duration of floatation was observed visually⁷.

WATER UPTAKE STUDY

It is important parameter for determining the swelling of the polymers by their ability to absorb water. The water uptake (WU) study of the tablets was done using USP 24 dissolution apparatus II. The medium used was 0.1 HCl, 900 ml at 37± 0.5 °C rotated at 50 rpm. After a predetermined intervals the tablets were withdrawn blotted to remove excess water and weighed.⁸ Swelling characteristics of the tablets were expressed in terms of water uptake .

$WU\% = (\text{weight of the swollen tablet} - \text{initial weight of tablet}) / \text{initial weight of the tablet}$.

INVITRO DRUG RELEASE STUDY

The Drug Release Studies of Aceclofenac was determined spectrophotometrically⁹ using USP 24 paddle dissolution apparatus in 900 ml of 0.1 N HCL at 37± 0.5 °C rotated at 50 rpm The Samples Were withdrawn at predetermined time intervals each time fresh media was replaced in same amount. Sample absorbance was measured spectrophotometrically at a Wavelength of 275nm.

RESULT AND DISCUSSION

Preformulation study and drug excipients compatibility study was done initially and results directed the further course of formulation. IR Spectra studies revealed that the drug and the polymers used were

compatible.

Table-1: Effect of various polymers on swelling and invitro release of aceclofenac in effervescent system

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	100	100	100	100	100	100	100	100	100	100
HPMC K4M	50	50	50	50	50		50	50	60	80
HPMC K15M	-	-	-	-	-	50	-	-	-	-
Psyllium Husk	20	20	20		20	20	-	20	20	20
Crosspovidone	-	20	40	-	-	-	-	-	40	40
Microcrystalline Cellulose	-	-	-	20	20	-	30	40	-	-
Sodium Bicarbonate	30	30	30	30	30	30	30	30	30	30
Citric acid	10	10	10	10	10	10	10	10	10	10
Mg Stearate	8	8	8	8	8	8	8	8	8	8
Talc	7	7	7	7	7	7	7	7	7	7
Lactose	100	80	60	100	80	100	90	60	50	30
Total	325	325	325	325	325	325	325	325	325	325

Table-2: Effect of various polymers on swelling and invitro release of aceclofenac in non-effervescent system

Ingredients (mg/tablet)	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21
Drug	100	100	100	100	100	100	100	100	100	100	100
HPMC K4M	75	60	50	-	-	-	40	25	25	25	25
HPMC E50	-	-	-	50	-	-	-	-	-	-	-
HPMC E5	-	-	-	-	50	-	-	-	-	-	-
Carbopol 934p	-	-	-	-	-	50	-	-	-	-	25
Xanthan gum	-	-	-	-	-	-	-	25	-	-	-
Guar gum	-	-	-	-	-	-	-	-	25	-	-
Sodium alginate	-	-	-	-	-	-	-	-	-	25	-
Polypropylene foam powder	-	25	50	50	50	50	50	50	50	50	50
Mg Stearate	8	8	8	8	8	8	8	8	8	8	8
Talc	7	7	7	7	7	7	7	7	7	7	7
Lactose	135	125	110	110	110	110	120	110	110	110	110
Total	325	325	325	325	325	325	325	325	325	325	325

EFFERVESCENT SYSTEM

On Immersion in 0.1 N HCL, pH 1.2 solution at 37 ± 0.5 °C all floating effervescent tablets float immediately and remain buoyant up to 24h without disintegration. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in the presence of

dissolution medium (0.1N HCL). It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (methocel), thus decreasing the density of the tablet below 1 and tablet becomes buoyant.

The tablets with low-viscosity grade methocel K4M exhibited short floating lag time (25 s) as compared with formulations containing high viscosity grade methocel K15M (42s). This indicated that the molecular weight distribution or viscosity of the gel-forming polymer methocel influenced the *in vitro* buoyancy¹⁰. Avicel showed less swelling as comparison with crospovidone. It was found that increasing the concentration of crospovidone and Avicel increase drug release (FIG 2A,B) crospovidone and microcrystalline cellulose act as a swelling agent which is capable of swelling when coming into contact with simulated gastric fluid.^{11,12} Three different concentration of each were formulated as the concentration of microcrystalline cellulose increase as 0 mg (F1) , 20 mg (F7), 40 mg (F8) the drug release after 24 hr found to be 65.23±2.68%, 78.67±3.19%,83.41±2.49 respectively. Formulation containing 20 mg and 40 mg crospovidone cumulative percent drug release after 24 hr was found to be 80.17±1.79%and 92.38±2.83% respectively.

HPMC K15M (F6) gave comparatively good dissolution profile 8.16±1.12% as compared to HPMC K 4M (F1) that was 15.32±1.54 % after 1 hr despite presence of high viscosity grade which sustained the drug release. There is significant difference between in burst effect from formulation fabricated from polymers with different viscosity grade but not significant difference observed for second phase of drug release which might suggest that the initial burst effect is followed by completion of a stable gel layer which in turns controls the drug release from drug delivery system. To determine effect of various concentration of HPMC K 4M on drug release, formulation F9 (60 mg) and F10 (80 mg) were prepared. From the dissolution profile it was observed that increasing the concentration of HPMC K4M, the burst drug release and on 24 h release rate of drug was decreased. The cumulative drug release after 24 h was found 76.53±3.11% and 74.23±1.85% respectively. While the formulation containing 50 mg of HPMC (F3) the drug release was 92.38±2.83% (Fig. 2C). High HPMC K 4M contents result in a greater amount of gel being formed. This gel increases diffusion path length of the drug. Its viscous nature also affects the diffusion coefficient of the drug. As a result reduction in drug release is obtained.

NON EFFERVESCENT SYSTEM

As expected tablet without polypropylene foam powder first sank before floating, showing floating lag time of 20 to 25 min. Other formulations of non effervescent system found to achieve proper *in vitro* floating behavior. The tablets were found to be floated immediately upon contact with the release medium showing no lag times in floating behavior because the low density is provided from the beginning. Extended floating times are achieved due to the air entrapped within the foam powder

particles which is only slowly removed from the system upon contact with the release medium. The drug release studies of non effervescent floating formulations (F11—F21) were studied. The drug release increased when increasing the amount of foam powder from 0 to 50 mg and reducing the amount of HPMC K 4M from 75 to 50 mg. This can be due to the different properties of the polymer networks through which the drug must diffuse.

There was not more effect of filler was seen on drug release mechanism. Thus HPMC is clearly the dominating compound controlling the release rate of the drug in the prepared tablets. The effect of type of matrix polymer HPMC E5, HPMC E50, HPMC K 4M and Carbopol 934P used for the preparation of floating, low density tablets on the resulting drug kinetics are shown in Fig. 3A. The three HPMC types/grades differ in the type of substitution and/or molecular weight which can be correlated with the polymer viscosity. HPMC E and K contain 28—30 and 19—24% methoxy group and the viscosities of 2% aqueous solutions of HPMC E5, HPMC E50, HPMC K 4M at 20 °C are 5, 50 and 4000 cps respectively. The drug release rate decreased in the rank order HPMC E grade (F15 and F14)>HPMC K 4M (F13)>Carbopol 934P (F16). This can probably be attributed to the different diffusion and swelling behavior of these polymers. With increasing macromolecular weight the degree of entanglement of the polymer chains increases. So the mobility of the macromolecules in the fully swollen system decreases. This leads to decreased drug diffusion coefficients and decreased drug release rate with increasing molecular weight.¹³

The effect of varying the blend ratio on drug release for hydrogel combination was studied and illustrated in Fig. 3B. Xanthan gum (F18), guar gum (F19), sodium alginate (F20) and Carbopol 934P (F21) used as second Hydrogel former led to a rather rapid drug release. Xanthan gum and guar gum systems showed rapid drug release in first 6 h, so these systems cannot provide extended drug delivery over prolonged period of time, probably due to rapid partial tablet disintegration and slower swelling of these polymers resulting in a lack of contribution to hydrogel formation. However with sodium alginate and carbopol, sustained drug release was achieved similar to systems based on only HPMC.¹⁴

ANALYSIS OF DRUG RELEASE DATA

The dissolution data obtained were plotted as cumulative percentage drug release *vs.* time as zero order,¹⁵ Log cumulative percentage drug retained *vs.* time as First order release kinetics,¹⁶ Cumulative percentage drug released *vs.* square root of time as Higuchi equation¹⁷ and Log of fraction of drug released *vs.* Log time as per Korsmeyer and Peppas equation.¹⁸

The drug release data were explored for the type of release mechanism followed. The best fit with the highest determination *R*² coefficients was shown by both the Higuchi and first order models followed by zero order which indicate the drug release *via* diffusion mechanism.

In controlled or sustained release formulations diffusion, swelling and erosion are the three most important rate controlling mechanism followed. The drug release from the polymeric system is mostly by diffusion and best described by fickian diffusion. But in case of formulations containing swelling polymers, other processes include relaxation of polymers chain, imbition of water causing polymers to swell and changing them from initial glassy to rubbery state. Due to swelling considerable volume expansion takes place leading to moving diffusion boundaries complicating the solution of Fick's second law of diffusion.¹⁹ So to explore the release pattern, results of the *in vitro* release data were fitted to Korsmeyer and Peppas equation ($M_t/M_\infty=kt^n$, where M_t/M_∞ is the fraction of drug released after time t in respect to amount of drug released at infinite time, k is the rate constant and n is the diffusion exponent) which characterize the transport mechanism.

Table 3: Kinetic of invitro release from floating tablet of aceclofenac

Code	Zero order (R ²)	First order (R ²)	Higuchi' plot (R ²)	Koresmeyer plot	
				n	(R ²)
F1	0.9591	0.9887	0.9591	0.7811	0.5985
F2	0.9692	0.9767	0.9692	0.5201	0.6149
F3	0.9861	0.7909	0.9861	0.5906	0.6509
F4	0.9751	0.9871	0.9751	0.8621	0.6429
F5	0.9774	0.9718	0.9774	0.6603	0.6378
F6	0.9673	0.9865	0.9673	0.7301	0.6741
F7	0.9391	0.9876	0.9391	0.5865	0.6592
F8	0.9927	0.8968	0.9927	0.5083	0.6607
F9	0.9791	0.9777	0.9791	0.5667	0.6469
F10	0.9769	0.9867	0.9769	0.6217	0.6638
F11	0.9662	0.9809	0.9662	0.8955	0.6888
F12	0.9868	0.9859	0.9868	0.7595	0.687
F13	0.9952	0.9295	0.9952	0.6891	0.686
F14	0.9521	0.9825	0.9521	0.5583	0.5836
F15	0.9506	0.9863	0.9506	0.5101	0.6097
F16	0.9908	0.9417	0.9908	0.6857	0.7756
F17	0.9896	0.9795	0.9896	0.6821	0.6805
F18	0.8992	0.9827	0.8992	0.5830	0.5784
F19	0.8993	0.9849	0.8993	0.6152	0.6315
F20	0.9156	0.9891	0.9156	0.7093	0.6116
F21	0.9224	0.9896	0.9224	0.6845	0.6214

This equation is a generalization of the observation that superposes two apparently independent mechanism of drug transport, fickian diffusion and a case II transport describes drug release from a swelling polymer. The value of n gives an indication of the release mechanism; When $n=1$, the release rate is independent of time (Zero order) (case II transport), $n=0.5$ for fickian diffusion and when between 0.5 and 1.0, diffusion and non-fickian transport are implicated. Lastly when n is more than 1.0 supercase

II transport is apparent. 'n' is the slope value of $\log M_t/M_\infty$ vs. log time curve. The value of n with regression coefficient for all the formulations is shown in Table 3.

The values of n were in the range of 0.45 to 0.89, indicating fickian release governed by the drug diffusion. However as indicated by the values of R^2 both of the models (Higuchi and Peppas) were found to be efficient in describing the release of Aceclofenac from the floating tablets.

CONCLUSION

We concluded that HPMC in combination with crospovidone and microcrystalline cellulose can be promising polymers for effervescent gastroretentive drug delivery system. Swelling studies indicate significant water uptake and contributed to drug release and could be significant in gastric retention. On the other case noneffervescent floating formulations based on polypropylene foam powder studied for their ability to control drug release over prolonged period of time. The formulations followed Higuchi kinetics while the drug release was found to be diffusion controlled. The developed floating tablets of Aceclofenac may be used for prolonged drug release, thereby improving the bioavailability and patient compliance.

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