Preparation and Evaluation of Gastroretentive Floating Tablets of Silymarin

Rajeev Garg* and Ghanshyam Das Gupta

Department of Pharmaceutics, ASBASJSM College of Pharmacy; Bela, Ropar–140111, India.
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The present study performed by preparation and evaluation of floating tablets of Silymarin 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 microcrystalline cellulose and gas generating agent like sodium bicarbonate and citric acid and evaluated for floating properties, swelling characteristics and *in vitro* drug release studies. Floating noneffervescent 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 Korsemeyer and Peppas equation. The drug release mechanism was found fickian type in most of the formulations. The developed floating tablets of Silymarin may be used in clinic for prolonged drug release for at least 24 h, thereby improving the bioavailability and patient compliance.

Key words Silymarin; floating; gastroretentive; crospovidone; microcrystalline cellulose; polypropylene foam powder

A new strategy is proposed for the development of floating drug delivery system of Silymarin preferable once daily. Oral sustained drug delivery system is complicated by limited gastric residence time. Rapid gastrointestinal transit can prevent complete drug release in the absorption zone and reduce the efficacy of administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine.[1] Dosage forms that can be retained in the stomach are called gastroretentive drug delivery systems (GRDDS).[2] GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability.[3]

The controlled gastric retention of solid dosage forms may be achieved by Mucoadhesion,[4] Floatation,[5] Sedimentation,[6] Expansion,[7] Modified shape system[8] and Simultaneous administration of pharmacological agents.[9,10] 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 C_{max} and prolonged drug levels above the minimum effective concentration, and improved safety profile for drugs with side-effects associated with high C_{max}.[11]

The aim of the present investigation was to design and evaluate gastroretentive floating effervescent and noneffervescent tablets of Silymarin to increase the efficacy and stability of the drug in the stomach. Silymarin is a standardized seed extract rich in a type of flavonoid compounds known as flavonolignans.[12] The main flavonolignans in Silymarin are the isomers silybin (also known as silibinin), silydianin, and silychristin. Silymarin acts as antioxidants, scavengers and regulators of the intracellular content of glutathione, as cell membrane stabilizers and permeability regulators that prevent hepatotoxic agents from entering hepatocytes, as promoters of ribosomal RNA synthesis,[13] stimulating liver regeneration and as inhibitors of the transformation of stellate hepatocytes into myofibroblasts, the process responsible for the deposition of collagen fibres leading to cirrhosis. It is usually given by mouth since silymarin is poorly water-soluble and therefore unsuitable for intravenous use. A usual dose of up to 140 mg two or three times daily by mouth has been suggested for hepatic disorders.[14] The low bioavailability is owing to the rapid biotransformation in the liver with a biological half life of 6 h. The short half life, poor bioavailability and faster solubility in acidic medium[15] makes it a suitable candidate for gastroretentive drug delivery system.

Experimental

Materials Silymarin was received as a gift sample from Micro Lab. Ltd., India, hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M), crospovidone (Kollidon), microcrystalline cellulose (Avicel PH 101) and β-cyclodextrin were obtained as a gift samples from Signet Chemicals, Mumbai, India. Polypropylene foam powder (Accurel) from Membrana, Obernburg, Germany. HPMC E5, HPMC E50, 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.

Methods. Preparation of Silymarin Floating Tablets 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 in sufficient isopropyl alcohol. 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 compressed into tablets using single station tablet punch machine.

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 simulated gastric fluid at pH 1.2. The measurements were carried out for each formulation of tablets (n=6). The time of duration of floatation was observed visually.[16]

Water Uptake Study It is important parameter for determining the swelling of the polymers by their ability to absorb water. The water uptake

* To whom correspondence should be addressed. e-mail: indianpharmacist@sify.com

Table 1. Formulation Composition to Study the Effect of Various Polymers on Swelling and *in Vitro* Release of Silymarin in Effervescent System

Composition (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	420	420	420	420	420	420	420	420	420	420
HPMC K4M	100	100	100	100	100	—	100	100	150	200
HPMC K15M	—	—	—	—	—	100	—	—	—	—
Psyllium Husk	50	50	50	50	50	50	50	50	50	50
Crospovidone	—	20	40	—	—	—	—	—	40	40
β-Cyclodextrin	40	40	40	—	20	40	40	40	40	40
Microcrystalline cellulose	—	—	—	—	—	—	20	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

Table 2. Formulation Composition to Study the Effect of Various Types of Matrix Forming Polymers on *in Vitro* Release of Silymarin in Noneffervescent System

Composition (mg/tablet)	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21
Drug	420	420	420	420	420	420	420	420	420	420	420
HPMC K4M	300	250	200	—	—	—	150	75	75	75	75
HPMC E50	—	—	—	200	—	—	—	—	—	—	—
HPMC E5	—	—	—	—	200	—	—	—	—	—	—
Carbopol 934P	—	—	—	—	—	200	—	—	—	—	75
Xanthan gum	—	—	—	—	—	—	—	75	—	—	—
Guar gum	—	—	—	—	—	—	—	—	75	—	—
Sodium alginate	—	—	—	—	—	—	—	—	—	75	—
Lactose	—	—	—	—	—	—	50	50	50	50	50
Polypropylene foam powder	—	50	100	100	100	100	100	100	100	100	100

(WU) study of the tablets was done using USP 24 dissolution apparatus II. The medium used was 0.1 N 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.[17] Swelling characteristics of the tablets were expressed in terms of water uptake (Eq. 1).

$$WU\% = (\text{weight of the swollen tablet} - \text{initial weight of tablet}) / \text{initial weight of the tablet} \quad (1)$$

***In Vitro* Drug Release Study** The *in vitro* dissolution study of Silymarin tablets was determined spectrophotometrically[18] using USP 24 paddle dissolution apparatus in 900 ml of 0.1 N HCl at 37±0.5 °C.[19] The paddle rotation speed was kept at 75 rpm and temperature of 37±0.5 °C was maintained. At predetermined time interval of 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16 and 24 h, 10 ml sample was withdrawn, filtered, suitably diluted and assayed at 288 nm by UV spectrophotometer (Shimadzu 1700).

Results and Discussion

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 24 h without disintegration. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in the presence of dissolution medium (0.1 N hydrochloric acid). 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 tablet swelled radially and axially during *in vitro* buoyancy studies.

All the batches of tablets were found to exhibit short floating lag times due to the presence of sodium bicarbonate and citric acid. The pH of the stomach is elevated under fed condition (*ca.* 3.5); therefore citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate. The tablets with low-viscosity grade methocel K15 exhibited short floating lag time (25 s) as compared with formulations containing high viscosity grade methocel K4M (42 s). This indicated that the molecular weight distribution or viscosity of the gel-forming polymer methocel influenced the *in vitro* buoyancy.[20]

The swelling of the polymers used (crospovidone, microcrystalline cellulose, HPMC K4M) were determined by water uptake of the tablet and illustrated in Fig. 1. Comparing different formulation containing the same amount of HPMC and varying amount of superdisintegrants maximum swelling (>150%) was observed in formulation containing 40 mg crospovidone (F3). Formulation containing 0 mg crospovidone (F1) and 20 mg crospovidone (F2) swelling was found to be 64.42±4.38% and 110.95±3.52%. Avicel showed less swelling as comparison with crospovidone. Formulation containing 20 mg microcrystalline cellulose (F7) and 40 mg microcrystalline cellulose (F8) was found to be 90±2.59% and 125±3.79% swelling.

All floating effervescent formulations (F1—F10) tested showed a sustained release pattern of Silymarin over 24 h with varying cumulative percentage released. Effects of various ingredients and their concentration on drug release were studied. It was found that increasing the concentration of crospovidone and microcrystalline cellulose increases drug release (Figs. 2A, B). Crospovidone and microcrystalline cellulose act as swelling agent which is capable of swelling when coming into contact with aqueous fluid such as simulated gastric fluid.[21,22] As the concentration of crospovidone and microcrystalline cellulose increased, water uptake capacity of the formulation increased. This increased the porosity of the matrix which results in increased drug release from the matrix system. Three different concentration of each were formulated. As the concentration of microcrystalline cellulose increases as 0 mg (F1), 20 mg (F7), 40 mg (F8) the drug release after 24 h was found to be 65.23±2.68%, 78.67±3.19%, 83.41±2.49% respectively. Formulation containing 20 mg (F2) and 40 mg (F3) crospovidone cumulative

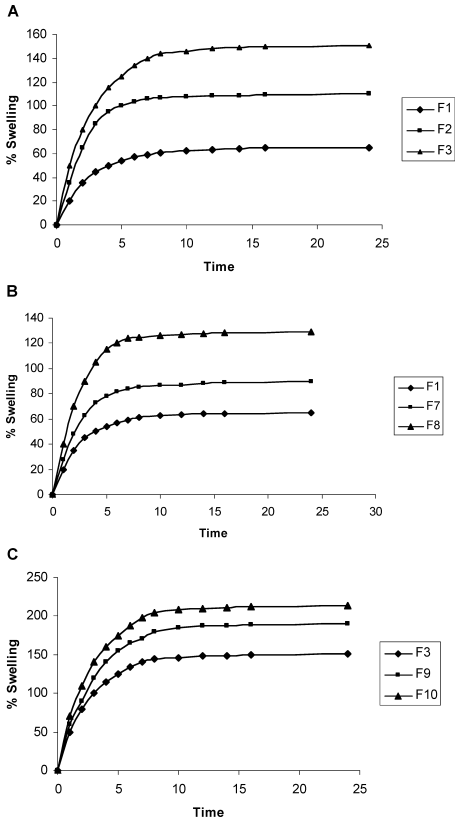

Fig. 1. Effect of Different Concentration of Crospovidone (A), Microcrystalline Cellulose (B) and HPMC K 4M (C) on Swelling Behavior

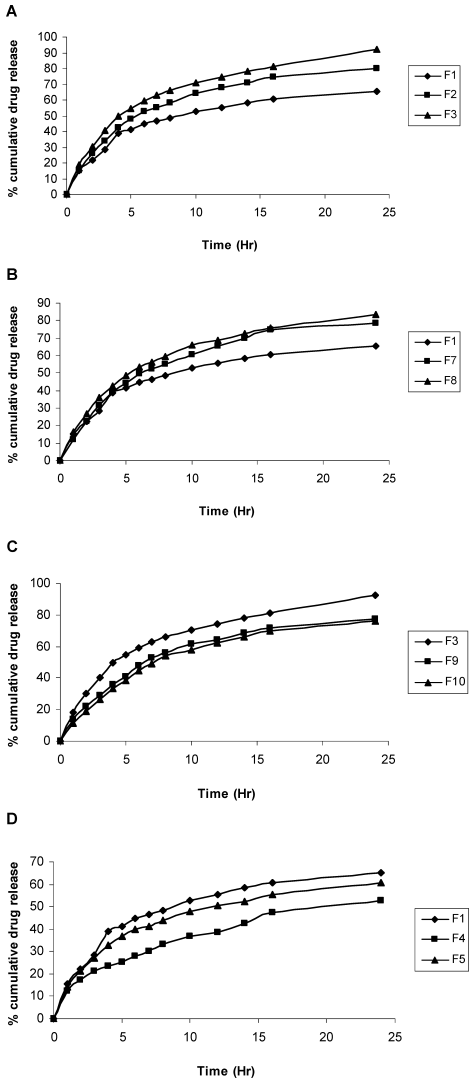

Fig. 2. Effect of Different Concentration of Crospovidone (A), Microcrystalline Cellulose (B), HPMC K 4M (C) and β-Cyclodextrin (D) on *in Vitro* Release of Silymarin

percent drug release after 24 h was found to be 80.17±1.79% and 92.38±2.83% respectively.

HPMC K15 M (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 h 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 (150 mg) and F10 (200 mg) were prepared. From the dissolution profile it was observed that increasing the concentration of HPMC K 4M, the burst drug release and on 24 h release rate of drug was decreased.[23] The cumulative drug release after 24 h was found 76.53±3.11% and 74.23±1.85% respectively. While the formulation containing 100 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.

A direct correlation between the swelling and drug release was found. As described by researchers diffusion of drug significantly depends on the water content of the system.[24] About 60% of the drug was found to be released at the end of 8 h. The tablet was swollen almost to its maximum and erosion process might have initiated attributing gradual decrease in percent swelling after 8 h. This may be because the mobility of the polymer chains strongly depends on the water content of the system. At high water content, polymer chain relaxation takes place with volume expansion giving high swelling of the system. Also from the Fig. 1 and Fig. 2 it can be seen that the swelling of the tablet was much faster than drug release from the tablet. Swelling predicts the higher penetration of the gastric fluid into the tablet leading to faster carbon dioxide gas generation and thus reducing the floating lag time. Faster and higher swelling of the tablet led to increase in dimension of the tablets leading to increasing in diffusion pathway and further decreasing diffusion rates. So the drug release was found to be high initially and then gradually decreased.

Effect of β-cyclodextrin on drug release was also studied. β-Cyclodextrin founds to improve the drug release of the formulations. As the concentration of β-cyclodextrin increases drug release was found to be increased (Fig. 2D). In case of formulation containing 0 mg (F4), 20 mg (F5) and 40 mg (F1) cumulative drug release after 24 h was found to be

52.83±2.45%, 60.76±1.32%, 65.23±2.68% respectively. β-Cyclodextrin dissolves rapidly from the tablet matrix into the medium and it creates the porosity to the matrix which results in increase in drug release from the tablet matrix.[25]

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 100 mg and reducing the amount of HPMC K 4M from 300 to 200 mg. This can be due to the different properties of the polymer networks through which the drug must diffuse. Accurel MP is the microporous polymer products made from resins. Microporous structures act like tiny sponges with the ability to absorb several times their own weight. When liquids or meltable solids are mixed with the porous polymer, the micron-size voids in the polymer are filled by capillary absorption.[26]

Polypropylene can be regarded as impermeable for the drug so drug diffusion is restricted to water filled pores within the foam powder particles and to the swollen HPMC Hydrogel. With decreasing amounts of HPMC the density of the swollen hydrogel network decreases, presenting less hindrance for drug diffusion and result in increased drug release rate.

The effect of adding water soluble lactose on drug release was studied. The release rate was found to be increased when adding the filler. The slight increase in drug release can probably be explained by the decreasing relative HPMC amount and thus less tight hydrogel structure upon swelling.[27] 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.[28] The different polymer behavior could be observed visually

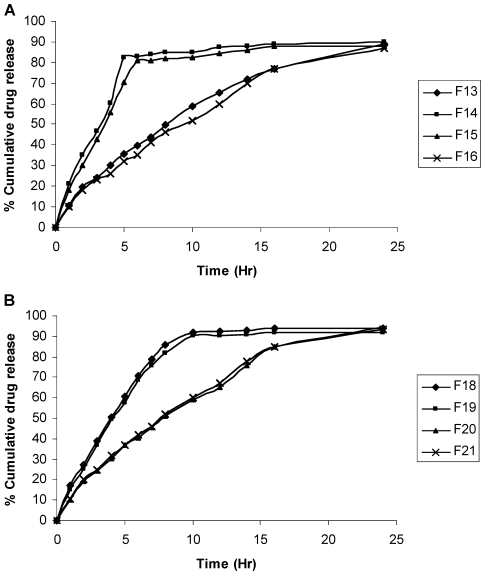

Fig. 3. Effect of Different Type of Matrix Polymer (A), Effect of Use of Blends of Matrix Forming Polymer with HPMC K 4M (B) on *in Vitro* Release of Silymarin in Noneffervescent Formulations

by the release of the low density polypropylene foam powder. Polypropylene foam powder release from tablet containing HPMC E5 and E50 grade was comparatively more than HPMC K 4M and Carbopol 934P based system during the observation period. This can be explained by the different chemical structures of the polymers.

Instead of using only a single polymer blends of different macromolecules can also serve as matrix formers. 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.[29]

Analysis of Drug Release Data The dissolution data obtained were plotted as cumulative percentage drug released *vs.* time as zero order,[30] Log cumulative percentage drug retained *vs.* time as First order release kinetics,[31] Cumulative percentage drug released *vs.* square root of time as Higuchi equation[32] and Log of fraction of drug released *vs.* Log time as per Korsmeyer and Peppas equation.[33]

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

Table 3. Kinetics of *in Vitro* Release from Floating Tablets of Silymarin

Formulations	Zero order R^2	First order R^2	Higuchi kinetics R^2	Peppas equation n	Peppas equation R^2
F1	0.7459	0.8577	0.913	0.4911	0.9284
F2	0.7773	0.9293	0.9405	0.5201	0.9536
F3	0.7791	0.9800	0.9476	0.4907	0.9533
F4	0.8778	0.9417	0.9929	0.4621	0.9962
F5	0.7789	0.8796	0.9548	0.4603	0.9702
F6	0.8351	0.9305	0.9622	0.630	0.9457
F7	0.8041	0.9362	0.9483	0.5867	0.9482
F8	0.7905	0.9528	0.9523	0.5083	0.9626
F9	0.8024	0.9236	0.9444	0.5669	0.9654
F10	0.8155	0.9249	0.9473	0.6217	0.9609
F11	0.9061	0.9741	0.9804	0.8955	0.9620
F12	0.8990	0.9765	0.9796	0.7596	0.9766
F13	0.9262	0.9976	0.9924	0.6891	0.9916
F14	0.5286	0.6758	0.6828	0.4583	0.8138
F15	0.5780	0.7328	0.7356	0.5101	0.8425
F16	0.9416	0.9880	0.9854	0.6858	0.9944
F17	0.9098	0.9904	0.9830	0.6821	0.9901
F18	0.6736	0.8259	0.8256	0.5830	0.9062
F19	0.6829	0.8287	0.8317	0.6152	0.9050
F20	0.9351	0.9751	0.9884	0.7093	0.9927
F21	0.9218	0.9836	0.9856	0.6945	0.9909

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.[34] 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.

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 Silymarin 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 drug release pattern can effectively be adjusted by varying formulation parameters such as concentration of swelling agent and β-cyclodextrin, type of matrix forming polymers and blend of matrix forming polymers. The formulations followed Higuchi kinetics while the drug release was found to be diffusion controlled. The developed floating tablets of Silymarin may be used for prolonged drug release, thereby improving the bioavailability and patient compliance.

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