RESEARCH ARTICLE

Development of non-effervescent floating matrix tablets based on *Euryale ferox* seeds

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Euryale ferox (family Nymphaeaceae), a plant belonging to the water lily family, grows in water ponds and remains buoyant on water surface. Similarly, its edible seeds also remain afloat in a wide variety of liquid mediums. Thus, the purpose of this study was to develop non-effervescent floating matrix tablets using *E. ferox* seeds powder (EFSP). Different matrix tablets were prepared using hydroxy propyl methyl cellulose (HPMC) K4M, ciprofloxacin HCl and EFSP. The effects of various formulation variables were investigated on *in vitro* drug release and *in vitro* floating behavior of the matrix tablets. With increase in EFSP proportion in the matrix tablets, improvement in buoyancy was observed. The floating behavior of tablets was also found to be dependent on particle size of EFSP. Further, surface morphology of different particle sizes of EFSP was studied with Scanning Electron Microscope images. Drug release from matrix tablets was reduced in the presence of EFSP particles. Most of the formulations were best fitted with Korsmeyer–Peppas and zero-order release kinetics. The value of *n* was found to be between 0.45 and 0.89, which indicates non-fickian drug transport. Thus, non-effervescent floating behavior can be successfully achieved by using EFSP in HPMC K4M based matrix tablets.

Key words: *Euryale ferox, gastroretention, makhana, matrix tablets, non-effervescent floating*

INTRODUCTION

Development of floating drug delivery system is a widely acceptable approach for gastric retention.[1-3] Floating drug delivery system of narrow absorption window drug can specifically release the drug at upper part of gastric region, with the additional advantage of controlled release for a longer duration.[4] But in order to remain afloat in the gastric region, this system must achieve a density lower than that of gastric content. Several types of floating drug delivery systems have been developed such as floating bilayer or matrix tablets,[5-7] multiunits systems,[8,9] *in situ* gelling system[10,11] and void assembled modules.[12] The most common approach for floating matrix tablets is to use a mixture of hydrophilic polymer and gas generating agent like sodium bicarbonate in the formulation.[13] CO_2 gas is generated when sodium bicarbonate reacts with acidic medium and it provides buoyancy to the dosage form by its entrapment within hydrophilic polymer network. However, the effectiveness of this type of system can be reduced by fluctuation in gastric pH due to factors like disease condition and presence of food.[14] Other non-effervescent approaches for improvement in floating pattern of matrix tablets are porosity enhancement, entrapment of swollen particles of superdisintegrant in gel matrix,[15] and addition of low-density excipients in formulation, such as polypropylene foam powder and aerosol. Sauzet *et al.*[16] improved the buoyancy first by using a high content of hydrophobic compounds and secondly by increasing the porosity of granules by incorporation of air during wet granulation process. Streubel *et al.*[17] prepared floating matrix tablets consisting of a low-density polypropylene foam powder. These systems achieved immediate buoyancy because the low density is provided from the beginning ($t=0$). A wide variety of plants have been increasingly popular for their medicinal value in the South Asia region since a long

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time. In addition, plants can also be very good source of excipients for different formulation strategies. *Euryale ferox* plant (also known as fox nut, gorgon nut or makhana) is a giant water lily and belongs to family Nymphaeaceae.[18] It grows in water and the plant floats on the water surface. *E. ferox* is widely cultivated in India, Japan and China for its seeds. The seeds [Figure 1] of *E. ferox* are white in color and have been utilized as food for several thousand years. Apart from carbohydrate (76.9%), the edible part of *E. ferox* seed also contains protein, fat, iron and mineral matters.[19] Some authors have also studied the antioxidant potential of *E. ferox* seeds.[20,21] The seeds of *E. ferox* also remain buoyant in water and this behavior is the basis of this study. This work was designed to study the potential of *E. ferox* seeds in the development of gastroretentive dosage form. Ciprofloxacin hydrochloride (CIPRO) was selected as the model drug for this study because it is mainly absorbed in the proximal areas of gastrointestinal tract.[22] It is a broad-spectrum antibiotic and its elimination half-life is about 4 hours, so it is a suitable candidate for sustained-release floating matrix tablets.

Figure 1: Photograph showing white seeds of *Euryale ferox*

MATERIALS AND METHODS

Hydroxy propyl methyl cellulose (HPMC) K4M and ciprofloxacin HCl were obtained as gift samples from Sanjivani Parenterals Ltd. (Dehradun, India). Polyvinylpyrrolidone (PVP) K30 was purchased from Hi-media chemicals (Mumbai, India). *E. ferox* seeds were purchased from a local vendor.

Size reduction of *Euryale ferox* seeds

E. ferox seeds were subjected to size reduction using mixer grinder (Bajaj Ltd., India). Size separation of EFSP was done by sieving method. Sieves were arranged in a nest with the coarsest at the top. The sieves were shaken for a predetermined period of time with the help of a sieve shaker (Hicon Ltd., New Delhi, India). Three different particle size ranges (geometric mean weight diameters) of EFSP were separated for further studies.

Preparation of matrix tablets

CIPRO and other excipients (as listed in Tables 1 and 2) were blended in a double cone mixer for 10 min. Constant amount of magnesium stearate (0.5%) was added as lubricant and blended for another 2 min. Tablets were prepared by direct compression using 12-mm flat-faced punch on a 16-station single rotary compression machine (Cadmach Machinery Co.

Table 1: BLT and apparent density of matrix tablets with respect to variation in drug concentration (*n*=3)

Formulation code	CIPRO (mg)	HPMC K4M (mg)	EFSP (mg)	BLT (min)	Apparent density (g/cm^3)
F1	0	600	0	0±0.01	0.884
F2	90	510	0	20±0.5	0.931
F3	180	420	0	52±02	0.983
F4	291	309	0	120±03	1.041
F5	291	209	100	65±02	1.041
F6	291	159	150	0±0.03	1.041

Table 2: Composition in milligram of various matrix tablets with their floating behavior (*n*=3)

Formulation code	CIPRO (mg)	HPMC K4M (mg)	EFSP (mg)	PVP K30	Hardness (kg/cm^2)	Thickness (cm)	Apparent density (g/cm^3)	BLT (min)	FD (hours)
F7	291	180	0	29	5±0.2	0.42±0.01	0.921	Sink	0
F8	291	180	50	29	4.9±0.1	0.5±0.15	0.972	100±03	8.5±0.16
F9	291	180	100	29	5±0.3	0.55±0.04	0.964	75±02	9.5±0.06
F10	291	180	150	29	5.1±0.2	0.59±0.02	0.974	0±0.08	>12
F11	291	150	150	29	5±0.1	0.56±0.10	0.979	0±0.08	10±0.1
F12	291	130	150	29	4.9±0.1	0.52±0.10	1.010	80±03	8±0.12
F13	291	180	100	59	5±0.2	0.58±0.04	0.960	180±05	6±0.11
F14	291	180	100	89	5±0.2	0.61±0.01	0.956	Sink	0
F15	291	150	150	29	4.9±0.1	0.55±0.01	0.996	0±0.03	9±0.07
F16	291	150	150	29	5±0.2	0.52±0.12	1.054	100±04	8±0.08

FD=floating duration

Pvt. Ltd., Ahmedabad, India). The hardness of all tablets was kept constant around 5 kg/cm^2 using thickness regulating cam in order to avoid the impact of hardness on drug floating behavior and measured by a Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India).

In vitro floating behavior

In vitro floating behavior of floating matrix tablets was determined in 900 ml of 0.1 N HCl using the USP XVI apparatus II at 100 rpm and 37±0.5°C [6]. Buoyancy lag time (BLT), time taken by the tablets to achieve buoyancy, and floating duration were recorded by visual observation. For better floating behavior, small BLT and long floating duration (>10 hours) were required.

Swelling ability

The swelling behavior of tablets was determined in USP XXVI dissolution apparatus II (Lab India Disso 2000, India) at 37±0.5°C and 100 rpm using 0.1 N HCl. The tablets were removed at regular time intervals and excess fluid was removed with the help of a filter paper.[22,23] Then, the weight of swollen tablet was recorded and swelling index was calculated using the following formula:

$$\text{Swelling index} = W_2 - W_1/W_1 \quad (1)$$

W_1 – initial weight; W_2 – weight after a given time interval.

In vitro drug release

In vitro drug release studies of the prepared matrix floating tablets were conducted in a USP XXVI dissolution apparatus I (Lab India Disso 2000, Mumbai, India) at 37±0.5°C and 100 rpm. Filled in dissolution flask, the dissolution medium was 0.1 N HCl (900 ml). Aliquots of 5 ml were withdrawn from the dissolution medium at predetermined time intervals of 1, 2, 4, 6, 8, 12 hours and 5 ml of fresh medium was replaced with every withdrawal. After filtration and appropriate dilution, the samples were analyzed by a UV spectrophotometer (Shimadzu UV-250 1PC double beam spectrometer, Mumbai, India) at 278 nm (y=0.1208 + 0.0002, r^2=0.9992).

Drug release kinetics

All the drug release data were fitted for zero-order, first-order, Higuchi and Korsmeyer–Peppas (KP) kinetics with the help of PCP-Disso V3.0 software (Pune College of Pharmacy, Pune, India). Further, drug release mechanism was determined by using Ritger–Peppas equation:[24,25]

$$M_t/M_\infty = kt^n \quad (2)$$

where M_t/M_∞ is the fraction of drug release, t is time, k is the constant incorporating structural and geometrical characteristics of dosage form and n is release exponent. The value of n was calculated only for the portion of drug release curve where M_t/M_∞ was ≤0.6.

Density measurement of matrix tablets

The volumes and masses of matrix tablets were recorded in order to calculate their apparent densities. For the calculation of volume of the cylindrical tablet ($v=\pi r^2 h$), the height (h) and the diameter of the tablets were measured with a micrometer gauge.

Scanning electron microscopy

The particles of EFSP powder were mounted on double side carbon tape and coated with a thin gold layer. The surface topography was analyzed with a scanning electron microscope (SEM; ZEISS EVO® - 40 EP series, Carl Zeiss, Cambridge, England) operated at an acceleration voltage of 20 kV.

RESULTS AND DISCUSSION

In vitro floating behavior

The floatation characteristics of matrix tablets containing HPMC, EFSP and drug are summarized in Table 1. The floating pattern of matrix tablets was studied with variation in drug proportion. Tablets containing only HPMC (0% drug) remained afloat as soon as they came in contact with the medium (t=0). However, the BLT was increased as the proportion of drug increased in formulations. This behavior can be explained in terms of apparent density of tablets, which increased with increase in drug proportion [Table 1]. Similar pattern of density enhancement with increment in drug content was also reported by Strubing *et al*.[26] for propranolol and Sauzet *et al*.[16] for theophylline. Further, tablets containing once daily dose of CIPRO (F4) sank immediately and became buoyant after 2 hours. This higher BLT value might be due to volume expansion (swelling of matrix) after hydration of polymeric chains. Thus, BLT of matrix tablets was found to be dependent upon the proportion of CIPRO within HPMC matrix. In order to improve the buoyancy of matrix tablets, specified amount of HPMC K4M was replaced with EFSP. This replacement resulted in improvement in BLT of matrix tablets. Due to the low bulk density profile, the volume occupied by EFSP was higher than that of HPMC for a given weight. In addition to having low bulk density (0.0961 g/cm^3), the EFSP was also insoluble in water. In a previous work, the high content of hydrophobic compound was found suitable for buoyancy of matrix tablets.[16] Initially, 100 and 150 mg HPMC was replaced with EFSP (F5, F6). The EFSP containing formulations (F5 and F6) showed lower BLT (0–65 mins) in comparison to F4 (120 mins) and remained buoyant for more than 10 hours. However, interestingly, no improvement in apparent density was observed on replacement with EFSP. This indicates that apparent density could not be the mechanism of buoyancy improvement due to EFSP replacement. The presence of porous network was observed in SEM images of EFSP particles [Figure 2]. The presence of air associated with the EFSP particle internal voids was responsible for improved buoyancy behavior of matrix tablets. The low bulk density nature of EFSP due to natural porous networking might be

responsible for buoyancy improvement of matrix tablets. Thus, replacement of 10–20% HPMC with EFSP resulted in improvement of buoyancy.

Effect of EFSP concentration

The amount of HPMC was kept constant (180 mg) for studying the effect of EFSP concentration on floating behavior. Also, 29 mg PVP K30 was included and kept constant in the formulation to improve cohesion among hydrophobic EFSP particles. All the formulations are listed in Table 2 with results. First formulation (F7) was prepared without EFSP and contains only CIPRO, HPMC K4M and PVP K30. F7 sank initially and remained at the bottom for 10 hours without any sign of buoyancy at all. Further, EFSP (50–150 mg) was added gradually (F8–F10) and reduction in BLT was observed with increment of EFSP proportion [Table 2]. At low EFSP proportion, hydration of polymeric chains resulted in the formation of swollen gel layer of HPMC, and entrapment of insoluble low-density EFSP particles in gel layer further improved the density of matrix and provided buoyancy. Thus, at low concentration of EFSP, both hydration of polymer chains and low density of EFSP were responsible for improvement in BLT. *E. ferox* seed can float on the surface of release medium for a longer duration. Similarly, with 150 mg EFSP (F10), tablets remained buoyant immediately upon contact with the release medium and floated for more than 12 hours [Figure 3]. This indicates the fact that at higher proportion of EFSP, immediate buoyancy was not associated with hydration of polymeric chain and only low-density profile (due to porous network) of EFSP was responsible for this. Similar observations were discussed by Streubel *et al*.[17] who concluded that presence of highly porous foam powder resulted in low density from the beginning ($t=0$). Thus, at higher concentration of EFSP, only low density of EFSP was responsible for low BLT value ($t=0$). The tablets containing lower concentration of EFSP had lower value of floating duration. Similarly, tablets containing higher concentration of EFSP remained buoyant for more than 12 hours. Thus, floating duration of tablets was also found to depend upon the proportion of EFSP. The EFSP particles were detached continuously from swollen matrix of HPMC K4M. At lower concentration, EFSP particles were detached early from the matrix and resulted in lower floating duration. Thus, with higher EFSP concentration, tablets remained buoyant for a longer duration.

Effect of HPMC K4M and PVP concentration

HPMC has been extensively utilized in matrix tablets for controlling drug release by rapid formation of gel layer.[27] In this work, the effect of HPMC on floating behavior was also studied. For this investigation, the concentration of HPMC was changed from 180 to 130 mg with constant amount of drug, EFSP and PVPK30. When HPMC concentration was reduced from 180 to 150 mg, no change in floating behavior was observed. This concludes that HPMC was not having significant effect on BLT and only EFSP was responsible for immediate buoyancy. However, at 130 mg concentration,

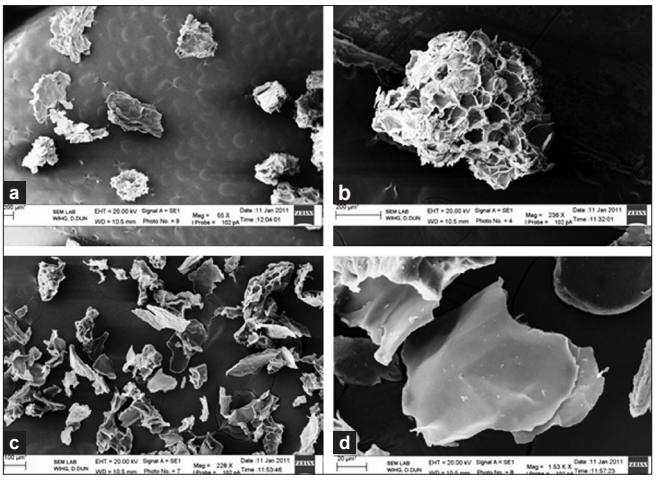

Figure 2: SEM images of different EFSP particle sizes at different magnifications. Particle size 605 µm at 55× (a) and 236× (b); particle size 125 µm at 228× (c) and 1.3 K× (d)

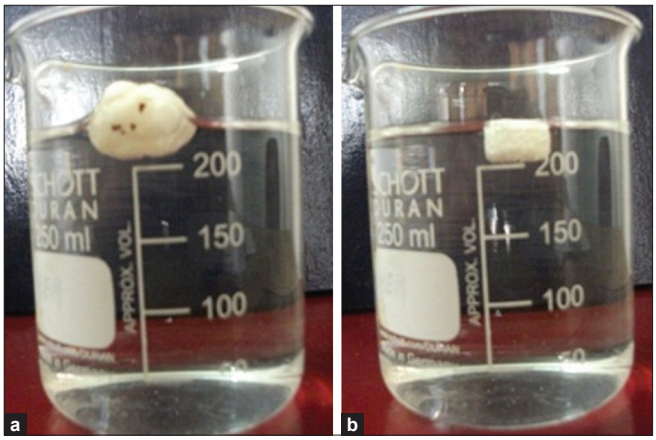

Figure 3: Photographs showing BLT ($t=0$) in 0.1 N HCl of (a) *Euryale ferox* seed and (b) formulation F10 having EFSP

BLT value was increased. This indicates the fact that HPMC concentration should not reduce below a certain level. Further, increase in PVP concentration resulted in higher BLT values. Thus, lower amount of PVP was found suitable for floating matrix tablets.

Effect of particle size of EFSP powder

The different BLT values for different particle sizes of EFSP powder is shown in Table 2. Three different particle size ranges were included in formulations F11, F15 and F16, while other ingredients were kept constant. The particle size of EFSP was kept constant (302 μm) for all formulations except in formulations F15 (605 μm) and F16 (125 μm). At 605-μm and 302-μm particle size, tablets remained buoyant, but at 125-μm particle size, tablets' BLT value increased. These results show that higher particle size ranges are favorable for good buoyancy. Further, SEM images of larger (605 μm) and smaller particles (125 μm) of EFSP proved the reduction in porous network with reduction in particle size [Figure 2]. Thus, higher inherent porosity of larger particles was responsible for lower BLT value.

With 605-μm and 125-μm particle size, the floating duration was less than 9 hours, whereas with 302-μm particle size, more than 12 hours of floating duration was obtained. This behavior might be due to the faster erosion rate with 605-μm and 125-μm particle size.

Swelling pattern

The hydration ability of polymer matrix can affect both buoyancy behavior and drug release pattern. The hydration of hydrophilic groups of polymer results in entry of release medium into polymer matrix and expansion of polymeric chains occurs. As the release medium continues to penetrate the matrix, the concentrated gel formation and the volume of tablet increases.[28] After maximum swelling, the polymeric chains detach from the swollen gel matrix. Due to this erosion tendency, the volume reduction of tablet matrix occurs. Peppas and Khare suggested that the maximum swelling index value depends on the osmotic forces of hydrated hydrophilic groups and the restrictive forces due to ordering of polymeric chains.[29]

Figure 4 shows the change in volume with time for HPMC K4M matrices having different proportions of EFSP. Formulations F8 and F9 achieved maximum swelling indices (1.927±0.12, 1.85±0.07) in 5.5 hours, followed by volume reduction due to matrix erosion. With higher concentration of EFSP (F10), the maximum swelling index (1.508±0.08) was lower than that achieved by F8 and F9. This indicates that with increase in EFSP proportion, the swelling extent of matrix was reduced. This behavior could be attributed to initial detachment of water-insoluble EFSP particles from the matrix. However, once the HPMC K4M forms a viscous gel, the EFSP particles' rate of erosion was reduced. The effect of particle size of EFSP on swelling behavior is shown in Figure 5. The maximum swelling indices of matrix tablets (F15, F11) having 605-μm and 302-μm particle sizes of EFSP (1.870±0.1, 1.774±0.15) were achieved after 5.5 hours. With 125-μm particle size (F16), the maximum swelling index was achieved after 3.5 hours. However, faster erosion was observed with 605-μm and 125-μm EFSP formulations. This lower erosion tendency of 302-μm particles of EFSP resulted in better entrapment of EFSP particles in swollen HPMC K4M matrix, which leads to better *in vitro* buoyancy behavior of matrix tablets.

In vitro drug release studies

Drug release profiles of matrix tablets were studied for 12 hours. The effects of HPMC, EFSP and particle size of EFSP on drug release behavior were studied.

Effect of EFSP on drug release

HPMC can control the drug release for a longer duration. The effect of various combinations of HPMC with other polymers on drug release also has been investigated earlier.[30,31] This study was also designed to find out the effect of EFSP inclusion on drug release from HPMC matrix tablets. In the presence of EFSP, the drug release from matrix tablets was relatively lower than that from matrix tablets not having EFSP. This indicates that the drug release was reduced in the presence of EFSP. The drug particles tried to diffuse through viscous gel layer of swollen matrix of HPMC K4M.[32] Tajiri *et al*. also observed that the cumulative drug release can be reduced with increase in gel layer thickness and drug diffusion length.[33] EFSP particles are water insoluble, so they might remain entrapped within HPMC gel layer. However, their presence might further increase the tortuosity or channels within HPMC gel, so the path for drug diffusion will be increased which is ultimately responsible for drug release retardation. Further, the EFSP concentration was varied from 50 to 150 mg (F8–F10). The influence of EFSP concentration on drug release is shown in Figure 6a. Again, reduction in drug release rate was observed with increase in EFSP concentration (60% after 12 hours for F10). Thus, with increment in EFSP proportion, the diffusion path length for drug release might further increase.

Effect of HPMC on drug release

Drug release from the matrix of hydrophilic polymer like HPMC depends on the viscosity of swollen polymeric chain.[34] The HPMC concentration was reduced from 180 to 130 mg (F10–F12). Expectedly, decrease in concentration of polymer resulted in higher drug release [Figure 6b]. When HPMC concentration

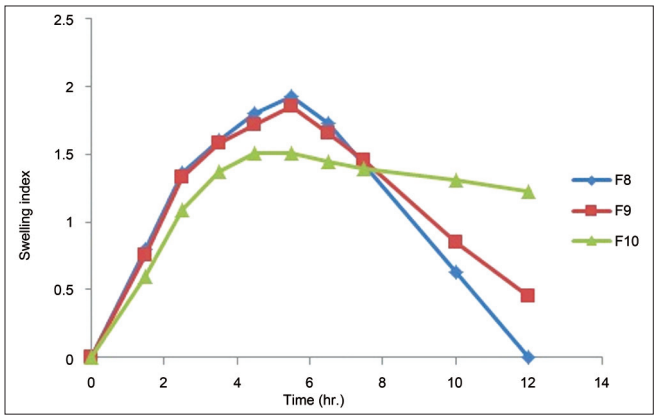

Figure 4: Effect of EFSP concentration on the swelling behavior of matrix tablets (*n*=3)

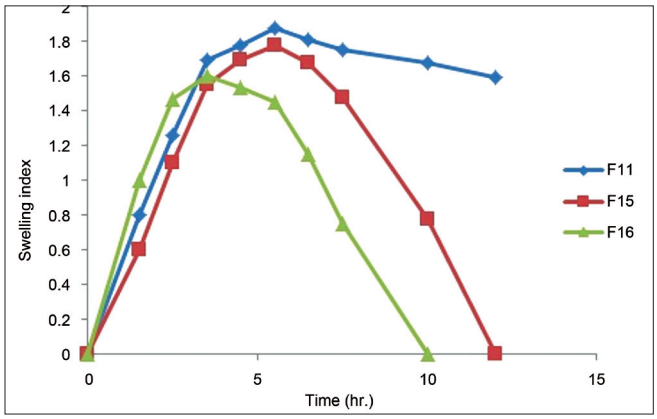

Figure 5: Effect of different EFSP particle sizes on the swelling behavior of matrix tablets (*n*=3)

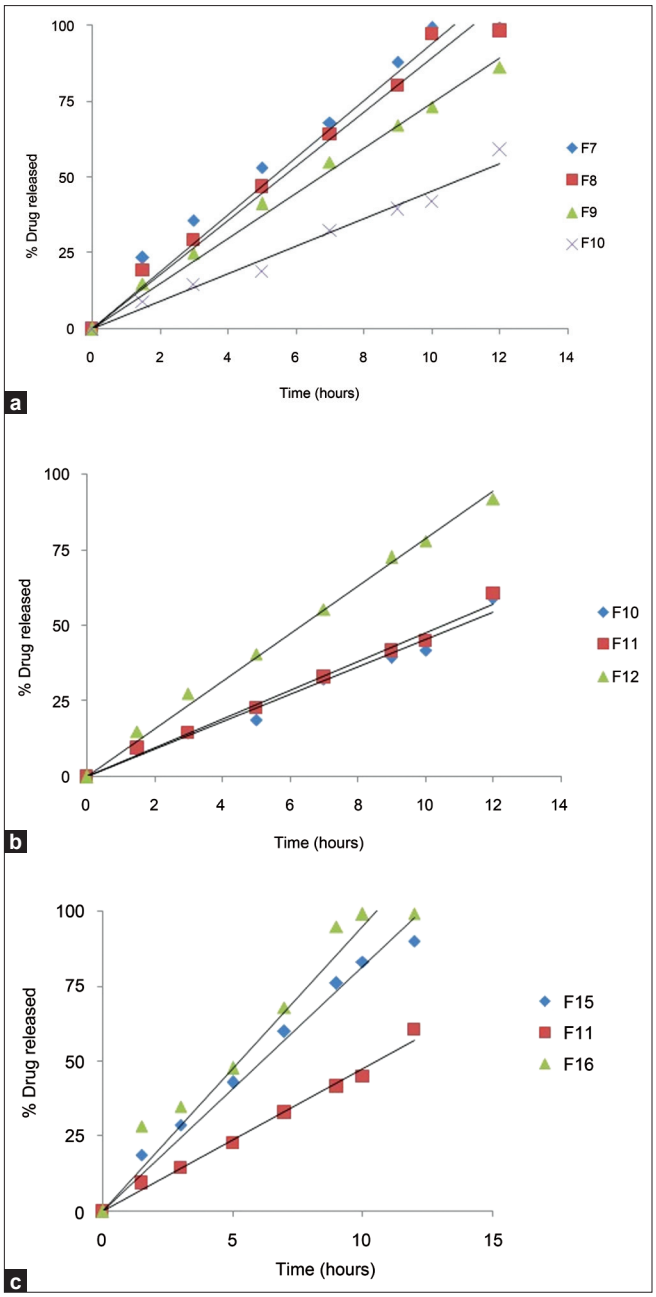

Figure 6: Drug release profiles (n=3). (a) Effect of EFSP concentration on drug release. (b) Effect of HPMC K4M concentration on drug release. (c) Effect on particle size of EFSP on drug release

was reduced from 180 to 150 mg, only slight increase (not more than 5%) in drug release was observed, whereas reduction from 150 to 130 mg resulted in drastic increase in drug release (30% increase). This behavior might be attributed to the rapid matrix erosion at lower HPMC concentration. Thus, a minimum concentration of HPMC was found necessary for maintaining the integrity of matrix by proper entrapment of EFSP.

Effect of EFSP particle size

Three different average particle sizes of EFSP were selected in order to study the effect of particle size on drug release (larger size 605 μm in F15, medium size 302 μm in F11 and fine size 125 μm in F16). With medium particle size (302 μm), the drug release was found to be 60% after 12 hours. However, higher drug release was obtained with both extreme particle size ranges (605 μm and 125 μm) [Figure 6c]. This behavior might be attributed to the high erosion tendency of both larger and fine EFSP particles; however, the reason could be different. Reduction in the particle size of a solid results in higher surface area. The viscous gel of matrix tablets, having a constant HPMC K4M concentration, might not be enough to entrap the large surface area of 125-μm particles of EFSP in comparison to 302-μm size range. Thus, high surface area of fine particles could be the reason for high erosion tendency and drug release from formulation F16. Moreover, with 125-μm size range, the tablets were able to sustain the drug release only for 10 hours instead of 12 hours. Thus, either an increase in HPMC K4M concentration or replacement with higher viscosity grade of polymer may entrap 125-μm particles effectively and sustain the drug release for a longer duration. Further, the reason for high erosion tendency of 603-μm size could be the high air content. The high air content in larger particles was due to the high porous network as shown in Figure 3. Therefore, increased tendency of detachment from gel layer due to the high air content might be the reason for higher erosion tendency and drug release from F15.

Drug release kinetics

The values of regression coefficient for various release kinetics models are shown in Table 3. The drug release from HPMC matrix tablets depends upon the water penetration rate, swelling of polymeric chain, diffusion of drug and matrix

Table 3: R^2 for different release kinetics models with n for various matrix tablets

Formulation code	Zero-order R^2	First-order R^2	Higuchi R^2	Korsmeyer–Peppas		Best model
				R^2	n	
F7	0.9781	0.8790	0.9716	0.9955	0.6960	Peppas
F8	0.9898	0.8885	0.9540	0.9940	0.7790	Peppas
F9	0.9955	0.9680	0.9604	0.9992	0.8510	Peppas
F10	0.9900	0.9631	0.9187	0.9853	0.8860	Zero order
F11	0.9953	0.9723	0.9312	0.9921	0.8827	Zero order
F12	0.9975	0.9380	0.9539	0.9994	0.8410	Peppas
F15	0.9901	0.9698	0.9651	0.9961	0.7380	Peppas
F16	0.9703	0.9002	0.9628	0.9728	0.6814	Peppas

R^2=regression coefficient; n=diffusion exponent

erosion.[35] Both expansion of matrix due to swelling and drug diffusion were included in the model explained by Peppas *et al*.[36,37] The drug release data for formulation containing only HPMC matrix (F7) was best fitted with KP model (highest R^2). Drug release from HPMC containing matrix tablets might be modified with inclusion of soluble or inert fillers.[30,31] Similarly, with the increase in concentration of EFSP powder, drug release kinetics was also found different. At lower EFSP concentration, the matrix best fitted with KP model. However, zero-order release kinetics was found best at 150 mg concentration of EFSP. This indicates the shifting of KP kinetics toward zero-order release kinetics with higher concentration of EFSP powder. Similarly, constant drug release was reported by other authors.[38-40] This constant drug release might be due to synchronization of both swelling front and erosion front.[41,42] Further, with larger (605 μm) and smaller (125 μm) particle sizes, the KP release kinetics was found best, whereas with medium size (302 μm), zero-order release kinetics was found suitable. This indicates that uneven movement of swelling and erosion front might occur with extreme particle size ranges of EFSP particle. Further, mechanism of drug release was checked by measuring diffusion exponent, n, with Ritger–Peppas model (considering $M_t/M_\infty \leq 0.6$). The value of n for different formulations is shown in Table 3. The value of n was found to be between 0.49 and 0.89 which indicates the anomalous drug transport. Thus, both diffusion and relaxation mechanisms were responsible for the drug release from matrix tablets of HPMC having EFSP powder.

CONCLUSION

The EFSP has been incorporated into HPMC K4M based formulations in order to develop non-effervescent floating matrix tablets of CIPRO. Immediate buoyancy ($t=0$) can be achieved with EFSP containing formulations. The buoyancy is provided by high air content due to natural porous network of EFSP. On the other hand, the drug release is reduced in the presence of insoluble EFSP particles. This reduction in drug release is due to increase in drug diffusion length in viscous gel layer. Hence, the EFSP can be utilized for the gastroretentive prolonged delivery of narrow absorption window drugs which are preferentially absorbed through upper gastric region.

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