ORIGINAL ARTICLE

Effect of bioadhesion on initial *in vitro* buoyancy of effervescent floating matrix tablets of ciprofloxacin HCL

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ABSTRACT

The purpose of this study was to investigate effect of bioadhesion on the initial *in vitro* buoyancy behaviour of effervescent matrix tablets of ciprofloxacin HCl (CIPRO). Tablets were prepared by direct compression using HPMC K4M and Carbopol 971P as hydrophilic-controlled release polymers, sodium bicarbonate ($NaHCO_3$) as gas-generating agent, polyplasdone XL, Explotab and Ac-Di-Sol as swelling agents. Tablets were evaluated for normal and modified initial *in vitro* floating behavior, floating duration, swelling behavior and *in vitro* drug release studies. A modified buoyancy lag time for tablets was determined in order to include the effect of bioadhesion on initial buoyancy. The initial buoyancy was found depended on bioadhesion ability of tablets. The lowest modified buoyancy lag time of 20 seconds was obtained for Formulation F7 having both $NaHCO_3$ and polyplasdone XL. The floating duration was also found dependent on concentration of $NaHCO_3$ and swelling agents. The drug release of F7 was also sustained up to 12-hr duration with anomalous drug transport mechanism.

Key words: Bioadhesion, effervescent matrix tablets, gastroretention, modified buoyancy lag time, swelling agents

INTRODUCTION

The drug delivery inside gastric region is a suitable approach for drugs, preferentially absorbed through upper part of gastric region. Sustained drug release for longer duration can also be achieved within gastric region.[1-3] Several approaches have been successfully utilized for sustained drug delivery inside gastric environment. Floating tablets,[4] multiunit systems,[5] void assemblage system,[6] bioadhesive tablets,[7] swellable systems,[8] etc. are some example of dosage forms developed for drug release within gastric region. The floating matrix tablets may be effervescent[9] or non-effervescent in nature. Non-effervescent floating matrix tablets contain low density excipients like propylene foam powder and aerosil.[10] The presence of sodium bicarbonates ($NaHCO_3$) in effervescent tablets leads to carbon dioxide bubbles formation which provides buoyancy to matrix tablets. The floating behavior of tablets can be determined by both *in vitro* and *in vivo* methods. Both initial buoyancy and long-term buoyancy were important in case of sustained release floating systems. Generally authors utilized buoyancy lag time as an indicator for initial *in vitro* buoyancy behavior and floating duration (FD) for long-term *in vitro* buoyancy behavior. In addition to floating behavior the bioadhesion of hydrophilic polymer was also found responsible for gastro retention. Earlier, researcher separately determined buoyancy lag time value and bioadhesion nature of tablets.[11] In this work, we modified the buoyancy lag time determination experiment in order to study the impact of bioadhesion on initial buoyancy of dosage form. The ciprofloxacin HCL (CIPRO) was selected as model drug. CIPRO is well absorbed from proximal part of gastrointestinal tract and due to its short half life (4 hr) it is suitable for once daily administration.[11]

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MATERIALS AND METHODS

Ciprofloxacin HCl and HPMC K4M were obtained as gift sample from Sanjivani Parenteral Ltd. Selaquai, Dehradun.

Polyplasdone XL (crospovidone), explotab (sodium starch glycolate), Ac-Di-Sol (croscarmellose sodium) were obtained as gift sample from GlaxoSmithKline Pharmaceuticals Ltd., Nasik, India. Carbopol 971P, PVP K30, Talc and $NaHCO_3$ were purchased from Central drug house (CDH Ltd.), India.

Preparation of Matrix Tablets

CIPRO and other excipients [Tables 1 and 2] were mixed in a double cone mixer for 5 min. Magnesium stearate (0.5%) was added into previous mixture as lubricant and blended for another 2 min. Tablets were prepared by direct compression using 12-mm flat-faced punch on a sixteen station single rotary compression machine (Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, India). The hardness of different tablets was kept constant at 5 kg/cm^2 using thickness adjustment and measured by a Monsanto hardness tester (Rimek, Mumbai, India).

Initial *In vitro* Floating Behavior

Normal buoyancy lag time

In vitro floating behavior of floating matrix tablets was performed in a 1000-ml beaker having 900 ml of 0.1 N HCl. Normal buoyancy lag time (NBLT) was the time taken by tablets to reach the surface of release medium.

Modified buoyancy lag time

Concentrated slurry of agar (20% w/w) in 0.1 N HCl was prepared. The appropriate quantity of slurry was poured in petri dish. The agar petri dish was further dried in hot air oven to allow agar to adhere with glass petri dish. Experiment was performed in 1000 ml. Beaker having 900 ml of 0.1 N HCl. Agar dish was placed at the bottom of beaker. When tablet placed in beaker, it dipped initially toward the bottom and interacts with agar dish. Tablets were tried to detach from agar dish and headed toward surface of release medium [Figure 1]. In this whole process the time taken by tablet to reach at the surface was recorded as the Modified buoyancy lag time (MBLT).

Floating Duration

Tablet was placed into a 1000 ml beaker filled with 900-ml 0.1 N HCl. The duration for which tablet constantly remained buoyant was recorded as floating duration.

Swelling Ability

The swelling behavior of tablets was determined in USP XXVI dissolution apparatus II (Lab India Disso 2000) filled with 900 ml 0.1 N HCl at 37± 0.5°C and 50 rpm. The tablets were removed at regular time interval and excess liquid was removed with help of filter paper. Then weight of swollen tablet was recorded and swelling index was calculated using given formula;[8,11]

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

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

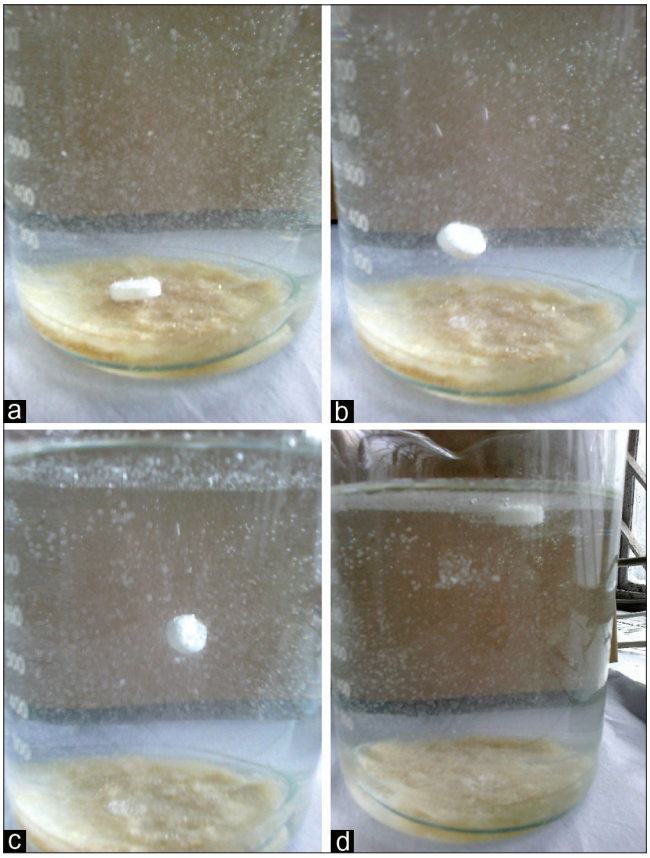

Figure 1: Photographs of formulation F3 showing MBLT in 0.1 N HCL at different time intervals (a) 30 sec (b) 35 sec (c) 40 sec (d) 45 sec

Table 1: Composition of various matrix tablets

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
CIPRO (mg)	291	291	291	291	291	291	291	291	291	291	291	291	291	291
HPMC K4M (mg)	280	280	280	280	280	280	280	280	280	240	200			
Sodium bicarbonate (mg)		35	47	60	35	35	35	35	35	35	35	35	35	35
Polyplasdone XL (mg)					20	40	60			40	40			
Explotab (mg)								40						
Ac-Di-Sol (mg)									40				40	40
Carbopol (mg)												280	280	240
Talc (mg)	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Table 2: Floating behaviour of different formulations

	NBLT (min)	MBLT (min)	FD (hr)
F1	120 ± 8	210 ± 10	-
F2	<0.25	2 ± 0.16	7
F3	<0.25	0.75 ± 0.05	9.5
F4	<0.25	0.42 ± 0.05	>12
F5	<0.25	1 ± 0.10	8.3
F6	<0.25	0.66 ± 0.04	11
F7	<0.25	0.33 ± 0.05	>12
F8	<0.25	1.66 ± 0.12	9.5
F9	<0.25	1.33 ± 0.08	8.5
F10	<0.25	1.5 ± 0.05	7.2
F11	<0.25	1.16 ± 0.05	4
F12	<0.25	4 ± 0.11	6.9
F13	<0.25	2 ± 0.05	10
F14	<0.25	1.5 ± 0.05	8

NBLT: Normal buoyancy lag time; MBLT: Modified buoyancy lag time

In vitro Drug Release

In vitro drug release studies of the prepared matrix floating tablets were conducted in a USP XXVI dissolution apparatus II (Lab India Disso 2000) filled with 900 ml 0.1 N HCl at 37 ± 0.5°C and 100 rpm. Aliquot of 5 ml were withdrawn from dissolution medium at predetermined time intervals of 1, 2, 4, 6, 8 and 12 hr and 5 ml of fresh medium were replaced with every withdrawal. The samples were analyzed by a UV spectrophotometer (Shimadzu UV-250 1PC double beam) at 278 nm, after filtration and appropriate dilution ($y = 0.12x + 0.001$; $r^2 = 0.999$).

Drug Release Kinetics

All the drug release data were fitted for zero-order, first-order, Higuchi model and Koresmeyer-Peppas model with help of PCP-Disso V3.0 software. The Koresmeyer-Peppas equation was utilized for determination of drug release mechanism;[12]

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

Where, M_t/M_∞ is 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 drug release mechanism was determined by calculating value of n for the portion of drug release curve where value of fraction of drug release (M_t/M_∞) was equal or less than 0.6.[13]

RESULTS AND DISCUSSION

In vitro Floating Behavior

In present study we modified initial *in vitro* buoyancy determination experiment in order to include the effect of bioadhesion on initial buoyancy of tablets. The modified BLT value reflected initial buoyancy behavior of tablets with considering their bioadhesion ability.

Initially we compared both NBLT and MBLT values for F1 having only drug and HPMC. The NBLT value for F1 was found 2 hr. In hydrophilic polymer matrix tablets, the release medium penetrates the matrix which is followed by the swelling and gel formation of hydrophilic polymeric chains.[14] Thus higher value of NBLT was due to the time required for appropriate expansion of matrix tablets. Further the wetting of polymeric chains can also leads to the bioadhesion of dosage form.[8] The MBLT value for F1 was found 3.5 hr Table 2. Difference in NBLT and MBLT values for F1 suggested that the bioadhesion of polymeric chains might be responsible for higher MBLT value of F1.

Effect of $NaHCO_3$ on *In vitro* Floating Behavior

The *in vitro* floating behaviors of F1 and F2 were compared in order to examine the effect of SB. The presence of SB in HPMC matrix tablets was resulted in the lower NBLT values. In matrix tablets SB particles were distributed evenly. When tablets came in contact with acidic release medium, the SB particles present at outer surface were form bubbles and propel the tablet toward release medium surface. The bubble formation at the surface of matrix tablet was responsible for initial buoyancy of tablets. Again, NBLT and MBLT values were found different for SB-containing formulations F2, F3 and F4. The wetted polymeric chains of hydrophilic polymer were adhering with agar plate and tried to retain tablet at the bottom. But the bubble formation at the surface of tablets tried to propel them upwardly. Thus the MBLT value of SB-containing formulation indicates the time required to overcome the bioadhesion with help of CO_2 bubble formation.

The MBLT value decreased with an increase in SB concentration in tablets. At 35, 47, 60 mg of SB the MBLT values were found 2 min, 45 sec and 25 sec [Figure 2]. At lower concentration of SB the more time was required to detach the tablet from agar plate. But with increase in SB concentration the tablets were detached early and became buoyant.

Further the entrapment of CO_2 bubbles within the gel matrix was resulted in longer FD of matrix tablets. As the concentration of SB increased, the FD values were also increased for matrix tablets Table 2.

Effect of Swelling Agent on *In vitro* Floating Behavior

In presence of swelling agent, expansion of tablet was resulted in density reduction of dosage form and provided appropriate buoyancy.[7] Three different types of swelling agents were utilized in formulations. The lowest BLT values were achieved for polyplasdone XL-containing tablets. The NBLT and MBLT values for F5 were 10 sec and 1 min. The MBLT value of F5 was lower than that for F2. This difference might be due to the presence of polyplasdone XL. In addition to bubble formation by SB particles, the presence of swelling agent further reduced the MBLT value of matrix tablets.

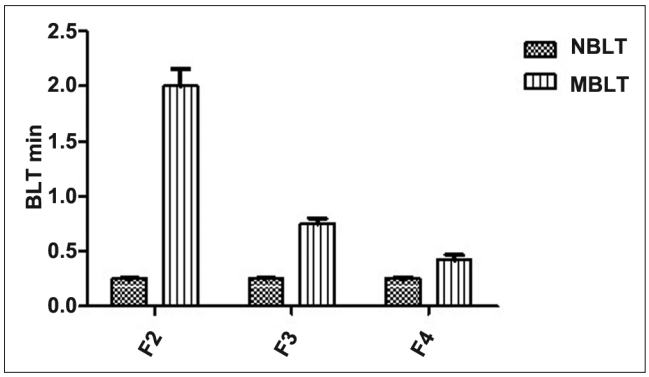

Figure 2: Effect of SB on NBLT and MBLT of matrix tablets (mean ± SD, $n = 3$)

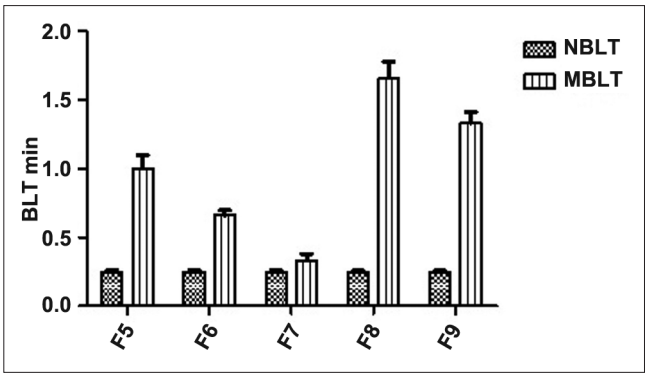

Figure 3: Effect of swelling agents on NBLT and MBLT of matrix tablets (mean ± SD, $n = 3$)

The MBLT values for explotab and Ac-Di-sol (F8 and F9) were higher in comparison to polyplasdone XL-containing tablets [Figure 3]. This difference might be due to different swelling mechanism of swelling agents.[15] Polyplsdone XL is having rapid expansion ability due to wicking mechanism whereas Explotab and Ac-Di-sol were having slow expansion due to swelling mechanism.[16] Further the concentration of polyplasdone XL was varied from 20 to 60 mg (F5-F7). As the concentration of polyplasdone XL was increased, the MBLT values were also reduced. Early detachment of matrix tablet from agar plate was obtained at higher proportion of polyplasdone XL.

Again polyplasdone XL containing tablets were remained afloat for longer duration in comparison to other swelling agents. The FD of matrix tablets increased with increase in proportion of swelling agents.

Effect of Hydrophilic Polymer on *In vitro* Floating Behavior

Two different hydrophilic polymers were utilized to develop floating matrix tablets. The hydrophilic polymer chains swelled on contact with release medium and form swollen gel matrix.[17] The CO_2 bubbles and swollen particles of swelling agents were get entrapped inside gel matrix of hydrophilic polymer and as a result the density reduction of matrix tablets provided buoyancy to matrix tablets.

Tablets containing HPMC K4M achieved lower MBLT values in comparison to carbopol-containing tablets. Although very little difference was observed between NBLT values of HPMC K4M and carbopol formulation but difference between MBLT values was more. This certainly was due to higher bioadhesion efficiency of carbopol in comparison to HPMC K4M.[18] Thus more time was required to detach the carbopol containing tablets from agar plates.

Further reduction in proportion of hydrophilic polymer (F6, F10 and F11) resulted in lower MBLT value but tablets integrity was also affected. The FD was also reduced with reduction in proportion of hydrophilic polymer. At low concentration (F11) of hydrophilic polymer the resulted swollen gel might not able to hold CO_2 bubbles and swelling agent particles and tablets lost integrity within 4 hrs.

Swelling Behavior

The maximum swelling index for F1 was achieved after 5 hrs. Viridéna *et al.*[19] suggested that the diffusion of water into glassy HPMC chains reduces its glass transition temperature, T_g. Due to reduction in T_g, the glassy polymer converted into rubbery form. Further diffusion of water resulted in expansion of rubbery HPMC matrix and swelling occurs. After reaching a specific maximum swelling the erosion of hydrophilic chains occurs due to polymer chain relaxation.[20]

Increase in swelling indices were observed with the formulations (F2, F3 and F4) containing SB [Figure 4]. The maximum swelling indices for these formulations were obtained in 4 hrs.

The rapid bubble formation was responsible for rapid volume expansion of SB containing formulations. The erosion tendency of SB containing formulations was also higher in comparison to F1.

Further, more increase in swelling was observed with matrix formulation having swelling agents [Figure 5]. For swelling agents containing tablets, maximum swelling indices were observed within 3 hrs. Out of three different swelling agents, highest swelling indices were obtained for polyplasdone XL-containing matrix tablets. Both wicking and swelling of polyplasdone XL particles might be responsible for higher swelling indices of tablets. Again maximum swelling was followed by erosion of matrix due to polymeric chain relaxations as swelling agent particles detached from matrix.

In comparison to HPMC K4M formulations, the maximum swelling index for carbopol containing tablets (F13, F14) were achieved after 4 hr. [Figure 6]. Rapid hydration of carbopol might be responsible for this behavior.

In vitro Drug Release Studies

The high viscosity of hydrophilic polymeric chains is responsible for high viscosity gel formation and subsequently drug release retardation.[21,22] At 200 mg concentration of HPMC (F11), the complete drug release was achieved within 8 hrs. With 280 mg concentration (F9) of HPMC, the drug release was further sustained up to 12 hrs [Figure 7a]. Similar pattern of drug release reduction was observed with increase in carbopol concentration [Figure 7d].

The presence of gas-generating agent was further increased the drug release rate from matrix tablets of HPMC K4M. The effect of the SB on the release of the drug from the tablets in 0.1N HCl (pH 1.2) is shown in [Figure 7b]. Increase in concentration of SB was also resulted in increase in drug release rate from matrix tablets. At high concentration of SB (F4), the formation of more effervescence would leads to the faster hydration of matrix and consequently rapid drug release rate.

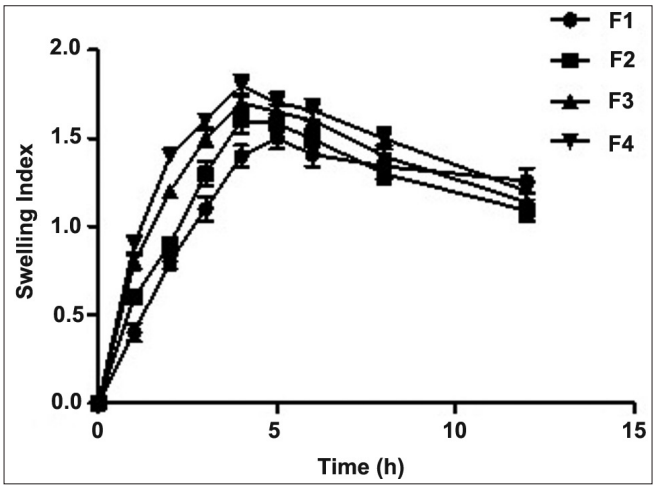

Figure 4: Swelling patterns of matrix tablets with change in SB concentration (mean ± SD, $n = 3$)

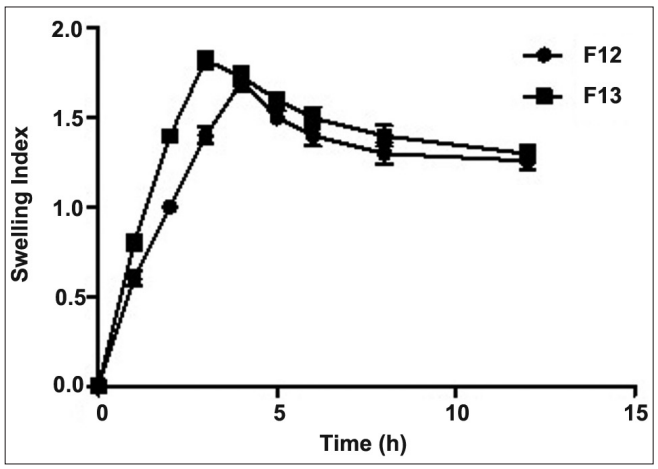

Figure 6: Swelling behavior of carbopol containing tablets (mean ± SD, $n = 3$)

High initial burst effect was observed with formulations having swelling agents in comparison to other formulations [Figure 7]. The swelling tendency of super-disintegrants might be responsible for this high initial burst drug release. Later, slow drug release was observed due to formation of swollen gel matrix. As the time progress the hydration of polymeric chains leads to gel formation and subsequently entrapped the swollen particles of swelling agents. Also, the drug release rate from matrix tablets was increased with the increase in concentration of polyplasdone XL.

The drug release data was further subjected to the various models to get the information about the drug release kinetics. The release data was treated with zero order, first order, Higuchi model and Koresmeyer-Peppas (KP) model. The best model was selected according to highest

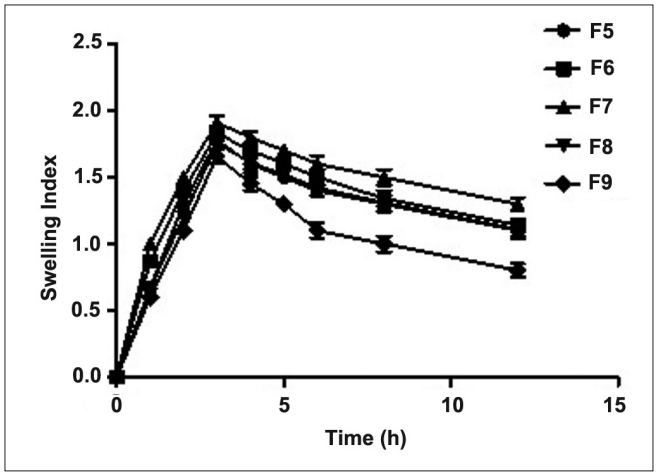

Figure 5: Swelling patterns of matrix tablets with change in swelling agent concentration (mean ± SD, $n = 3$)

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 Model R^2	Koresmeyer-Peppas R^2	n
F1	0.996	0.903	0.991	0.997	0.782
F2	0.997	0.915	0.956	0.999	0.874
F3	0.994	0.883	0.963	0.998	0.78
F4	0.995	0.745	0.976	0.999	0.73
F5	0.991	0.892	0.983	0.995	0.589
F6	0.993	0.912	0.979	0.997	0.592
F7	0.986	0.861	0.983	0.992	0.564
F8	0.984	0.932	0.963	0.998	0.598
F9	0.979	0.919	0.959	0.989	0.586
F10	0.97	0.909	0.987	0.993	0.567
F11	0.802	0.957	0.931	0.95	0.604
F12	0.992	0.953	0.956	0.997	0.632
F13	0.989	0.889	0.982	0.994	0.596
F14	0.96	0.923	0.984	0.992	0.513

R^2: Regression coefficient; n: Diffusion exponent

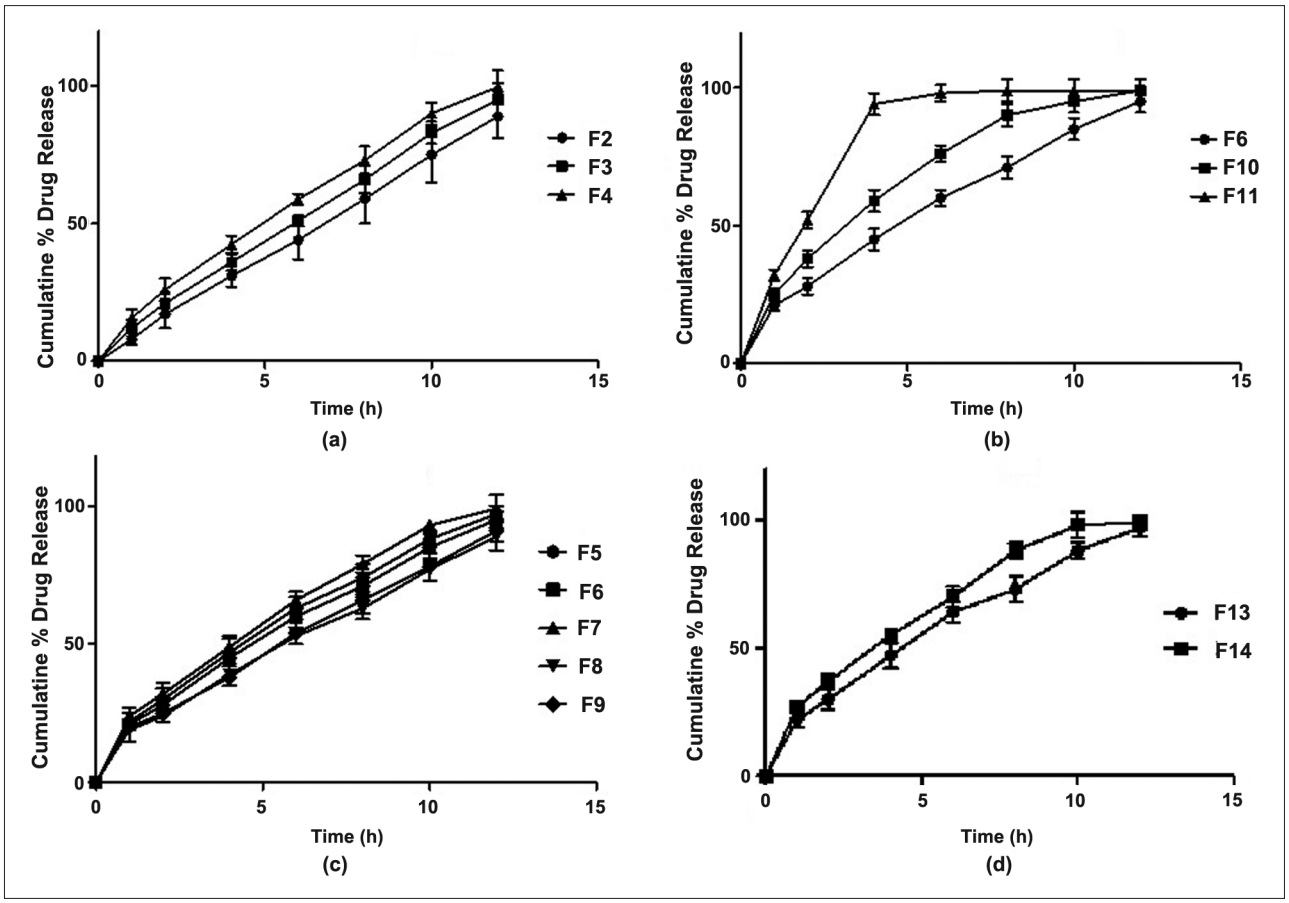

Figure 7: Drug release profiles (mean ± SD, $n = 3$) (a) Effect of SB concentration on drug release. (b) Effect of HPMC K4M concentration on drug release. (c) Effect of swelling agents on drug release. (d) Effect of carbopol concentration on drug release

value of regression coefficient ($R^{[2]}$). The release data was best fitted with KP model Table 3. Further the mechanism of drug release was determined by using Ritger-Peppas model (considering $Mt/M\infty \leq 0.6$). The value of diffusion constant (n) is shown in table. Because the value of n was found between 0.45-0.89 (anomalous drug transport) thus both diffusion and polymeric chain relaxation were found responsible for drug release.[23,24]

CONCLUSIONS

Controlled release effervescent floating matrix tablets of CIPRO were successfully prepared. The initial buoyancy behavior was affected by the bioadhesion nature of matrix tablets. Also, better *in vitro* MBLT and FD were depends on the proportion of SB and polyplasdone XL in matrix tablets. The drug release was successfully sustained for 12 hr and mechanism of drug release was associated with both swelling and erosion of polymeric chains.

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