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Modified drug release of poloxamer matrix by including water-soluble and water-insoluble polymer

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Abstract

Background: The ability of poloxamer 407 to control drug release was investigated along with the effect of incorporation of a second polymer with poloxamer on dissolution behavior. *Methods*: Tablets made of 30% w/w/ theophylline and 15%, 25%, 50%, or 69% poloxamer were prepared. Additionally, tablets containing mixture of poloxamer with carbomer or hypromellose in a 1:1 ratio and at different total levels (15%, 30%, and 50%) were also tested. *Results*: Data show that as the level of poloxamer increased, drug release decreased. Formulations containing poloxamer: hypromellose 1:1 at 50% level and formulations containing poloxamer: carbomer 1:1 at 30% level produced controlled release matrices over 24 hours of testing dissolution. The mechanism of drug release follows anomalous relaxation non-Fickian diffusion model. *Conclusions*: These results suggest that the combination of poloxamer 407 with hypromellose or carbomer is feasible and has potential to offer the formulator control over drug release.

Key words: *Poloxamer 407; theophylline swellable matrix; carbopol; hydroxypropyl methylcellulose; sustained release*

Introduction

Controlled release dosage forms are designed to deliver the drug at a rate required to achieve and maintain constant drug level in the blood. There are several advantages to the use of controlled release dosage forms such as prolonged activity, fewer doses, fewer side effects, reduced toxicity, and better patient compliance among others[1].

The basic controlled release formulation consists of a drug and a carrier that may be a single polymer or a combination of polymers and other excipients arranged so as to allow the drug to be released over a period of time at a controlled rate[2]. There are many new materials being investigated for use as directly compressible vehicles. Several investigators have studied the ability of hydrophobic and hydrophilic materials to produce controlled release dosage forms[3,4]. Also mixtures of polymers have been investigated to produce controlled release dosage forms[5].

Lutrol F grades are block copolymers better known as poloxamers. Poloxamers consist of polyoxyethylene, which compose the hydrophilic part, and polyoxypropylene, which compose the hydrophobic part. Poloxamers have been used for several pharmaceutical applications such as solubilizers and stabilizers[6]. Poloxamer high-molecular weight variant such as poloxamer 407 can form thermoreversible gels. Reversible gels refer to those that have the capacity to make, break, and modify the bonds responsible for holding the network together. Poloxamer is a thermoreversible gel; this property has been studied in the delivery of topical, intraocular, intranasal, and implantable dosage forms[7–11]. In ocular drug delivery, the increase in viscosity of poloxamer 407 at body temperature increases the residence time of the drug in the eyes[12]. Drug release is dependent on the dissolution of the gel, which is a zero-order release process[12]. Because of these characteristics, poloxamer 407 has been used as a potential candidate in several controlled release systems[13–15]. Recently, a procedure was developed to reduce the particle size of poloxamer to 50 μm. With the reduced particle size, poloxamer 407 becomes more suitable for direct compression method and can be a potential candidate for use in controlled release tablets.

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In this research, poloxamer 407 small particle size was used alone or in combination with other polymers to design formulations for theophylline matrices. The hypothesis is that the alteration of poloxamer 407 content by adding other polymers can change the rate at which a drug is released. The purpose of this study is to investigate the effect of poloxamer 407 (15%, 25%, 50%, and 69%, w/w) and 1:1 poloxamer/hydroxypropyl methylcellulose (HPMC) or poloxamer/carbomer (15%, 30%, and 50%, w/w) on the rate and mechanism of drug release. We will also examine the effect of pH of dissolution media on the drug release profile.

Materials and methods

Materials

Poloxamer 407 (Lutrol micro 127, lot no. 9205-1395, supplied by BASF, Mt. Olive, NJ, USA), hypromellose K 4M (HPMC, lot no. 8004038, supplied by Dow Chemical, Charleston, WV, USA), carbomer NF (Carbopol 71G, lot no. TW45GAK037, supplied by Noveon, Painesville, OH, USA), theophylline anhydrous (lot no. 056K0686, supplied by Sigma, St. Louis, MO, USA), spray-dried lactose monohydrate (Lactose fast Flo 316, lot no. 64044-51-5, supplied by Foremost Farm, Baraboo, WI, USA), and magnesium stearate (lot no. 225E19, supplied by Mallinckrodt, St. Louis, MO, USA).

Methods

In the first stage of this research, four formulations of poloxamer 407 micro (15%, 25%, 50%, and 69%, w/w) were prepared. In the second stage, two factors were investigated at three levels; the two factors are poloxamer:hypromellose and poloxamer:carbomer at 1:1 ratio. The three levels are 15%, 25%, and 50%. Additionally, three control formulations were also prepared.

The best combined polymer level was selected and tested for dissolution in different dissolution media and at different rotational speeds. The mechanism of drug release was determined using Peppas model. The composition of all formulations is listed in Table 1.

Manufacturing process

All formulations described in Table 1 were prepared by direct compression. The blends were directly compressed into tablets using Manesty B-3B compression machine equipped with 12/32 in. flat-faced punches. The target tablet weight was 400 mg ± 5% and the target hardness was 7–9 kp.

Drug content

Four tablets from each batch were grinded to fine powder using mortar and pestle. Three samples each of 0.4 g were transferred to a 1000-ml volumetric flask and completed to volume with distilled water. The mixture in each flask was stirred for 6 hours. A portion of each mixture was filtered through Millipore filter of 0.22 μm, and the absorbance was measured using UV spectrophotometer (model DU 520; Beckman Instruments, Fullerton, CA, USA). Number of replicate was $n = 3$.

Physical properties

Ten tablets from each batch were tested for weight (analytical balance, M 220, serial no. P9107464; Denver Instrument Company, Denver, CO, USA), thickness (portable hand gauge, serial no. 1015MA-481; MA, USA), and hardness (model 2F/106, serial no. 7410; Dr. Schleninger and Co., Zurich, Switzerland).

Disintegration time

Tablets from each batch were introduced in the basket tube of the disintegration apparatus (model ZT B-2, serial no. 53354; Erweka, Heusenstamin, Germany) and were tested for disintegration in 900 ml distilled water at 37 ± 2°C.

Table 1. Formulation of 30% theophylline, mixture of poloxamer with polymer, and spray-dried lactose.

Only one polymer (%)	1:1 poloxamer : hypromellose	1:1 poloxamer : carbomer
Poloxamer: 0, 15, 2550, 69	—	—
Hypromellose: 25	—	—
Carbomer: 15	—	—
—	50% (25% poloxamer and 25% hypromellose), 30% (15% poloxamer and 15% hypromellose), 15% (7.5% poloxamer and 7.5% hypromellose).	—
—	—	50% (25% poloxamer and 25% carbomer), 30% (15% poloxamer and 15% carbomer), 15% (7.5% poloxamer and 7.5% carbomer).

Dissolution testing

All batches were tested for dissolution using USP Apparatus 1 (baskets) at 50, 100, and 150 rpm using 900 ml distilled water at 37 ± 0.5°C (model R2, serial no. 21-78-29; Hansen Research, Chatsworth, CA, USA). Sample volume was 10 ml, replaced by 10 ml dissolution medium [distilled water, 0.1 N HCl, and phosphate buffer (pH 7.4)] at room temperature. Drug concentration was determined by measuring absorbance at a wavelength of 272 nm UV spectrophotometer (model DU 520, Beckman Instruments) using slope and intercept obtained from the standard curve. The number of samples tested was $n = 3$.

Peppas model for analysis of drug release kinetics

Ritinger and Pepas[16] established that the prevailing molecular mechanism involved in swelling control systems is a coupling of diffusion and macromolecular relaxation as a result of which the drug diffuses outward with a kinetic behavior that is dependent on the relative ratio of diffusion and relaxation. The equation describes the relation of the fraction of drug release with time as follows:

$$\frac{M_t}{M_\infty} = Kt^n$$

where M_t/M_∞ is the fraction of drug released, t is the release time, K is the constant incorporating structural and geometrical characteristics of the tablets, and n is the release exponent. By taking the logarithm of both sides of the equation, it is possible to obtain K and n values: Log M_t/M_∞ = log K + n log t. The exponent n has values that range from 0.43 to 1.0. For a cylinder, an n value of 0.45 indicates a Fickian diffusion in which the relative relaxation time of the polymer is shorter than the diffusion time for water transport. In the case n, which is the relaxation of the polymer and is the rate-limiting step for water transport, case II is observed and the n value equals 0.89. When the n value is within 0.45–0.89, anomalous transport is present, which is an intermediate behavior between Fickian diffusion and case II.

Statistical analysis

The analysis of variance (ANOVA) was used to determine whether there was a significant difference between the samples compared. Tukey test was used with ANOVA for pair comparison, Tukey t-test is essential for ANOVA especially when there are multiple comparisons[17]. t-Test was used for comparison between two samples. The t-test depends on both mean and SD of the samples compared[18].

Results and discussions

Matrices of theophylline–poloxamer alone and theophylline—combined mixture of poloxamer:hypromellose or poloxamer:carbomer at 1:1 ratio—were prepared successfully. Drug content in all formulations was 200 mg ± 5%. All tablet physical properties were within specifications.

The effect of poloxamer 407 alone on the rate of drug release is shown in Figure 1. As the amount of poloxamer was increased, the gel formation and the viscosity of the gel around the tablet were increased and the drug release was decreased. Formulation containing 15% poloxamer 407 released the entire drug at 3 hours whereas formulation containing 69% poloxamer released only 78% of drug. The control batch without poloxamer released 99% at 45 minutes.

ANOVA showed significant differences between formulations containing poloxamer at different levels (15%, 25%, 50%, and 69%, w/w) at all time intervals of testing dissolution as shown in Table 2. The Tukey pair comparison tests also showed significant difference between comparison of all pairs. The effect of addition of hypromellose to poloxamer on drug release is shown in Figure 2. Formulations containing 50% poloxamer alone released 97% of drug at 6 hours of testing dissolution whereas formulations containing poloxamer: hypromellose 1:1 at 50% combined polymers level (25% poloxamer and 25% hypromellose) released only 48% of drug. The alteration of poloxamer 407 content by the incorporation of hypromellose decreased drug release. The formulation containing only 25% hypromellose gave 84% drug release whereas formulations containing poloxamer:hypromellose 1:1 at 30% combined polymers level (15% poloxamer and 15% hypromellose) gave only 70% drug release at 6 hours of testing dissolution. It is theoretically possible that these data indicate that the hydrogen bonding between poloxamer and hypromellose plays a role in reducing the swelling ratio and in turn the dissolution rate of the

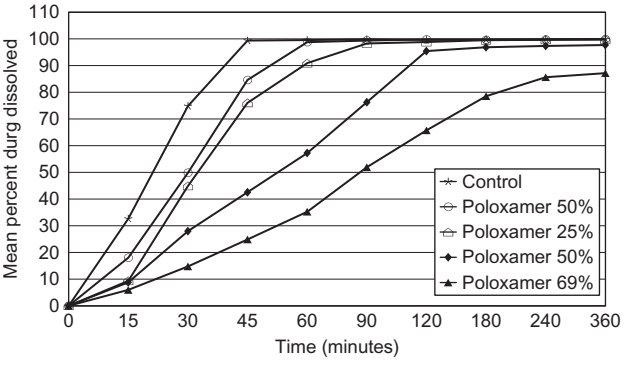

Figure 1. Effect of poloxamer level on theophylline release rate.

Table 2. ANOVA and Tukey pair comparison test for formulations containing different levels of poloxamer 407 (control, 15%, 25%, 50%, and 69%, w/w).

Time (minutes)	*f*-Value	*p*-Value	Tukey pair comparison
15	103.40	0.000	Control versus all; P15 versus all; P25 versus P69
30	777.46	0.000	Control versus all; P15 versus all; P25 versus P50; P25 versus P69; P50 versus P69
45	78.72	0.000	Control versus P25; Control versus P50; Control versus P69; P15 versus P50; P15 versus P69; P25 versus P50; P25 versus P69; P50 versus P69
60	83.32	0.000	Control versus P50; Control versus P69; P15 versus P50; P15 versus P69; P25 versus P50; P25 versus P69; P50 versus P69
90	121.38	0.000	Control versus P50; Control versus P69; P15 versus P50; P15 versus P69; P26 versus P50; P25 versus P69; P50 versus P69
120	41.63	0.000	Control versus P69; P15 versus P69; P25 versus P69; P50 versus P69
180	44.88	0.000	Control versus P69; P15 versus P69; P25 versus P69; P50 versus P69
240	18.30	0.000	Control versus P69; P15 versus P69; P25 versus P69; P50 versus P69
360	18.64	0.000	Control versus P69; P15 versus P69; P25 versus P69; P50 versus P69

P15 = 15% poloxamer; P25 = 25% poloxamer; P50 = 50% poloxamer; P69 = 69% poloxamer.

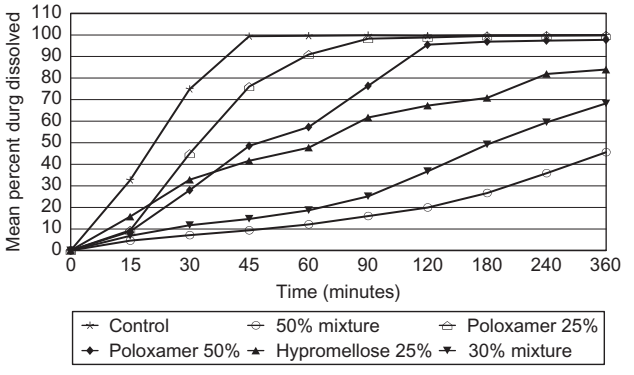

Figure 2. Theophylline release from formulations containing poloxamer:hypromellose 1:1 (30%, 50%).

drug. Poloxamer may reduce the glass transition temperature of hypromellose and increase the flexibility of hypromellose, which in turn will decrease drug release[19].

Table 3. ANOVA and Tukey pair comparison for theophylline tablets containing 1:1 poloxamer:hypromellose (15%, 25%, and 50%, w/w).

Time (minutes)	*f*-Value	*p*-Value	Tukey pair comparison
15	391.66	0.000	Control versus all; H25 versus HP15; H25 versus HP30; H25 versus HP50; HP15 versus HP30; HP15 versus HP50
30	25397.58	0.000	Control versus all; H25 versus HP15; H25 versus HP30; H25 versus HP50; HP15 versus P30; HP15 versus HP50; HP30 versus HP50
45	76355.26	0.000	Control versus all; H25 versus HP15; H25 versus HP30; H25 versus HP50; HP15 versus HP30; HP15 versus HP50; HP30 versus HP50
60	26759.63	0.000	Control versus all; H25 versus HP15; H25 versus HP30; H25 versus HP50; H15 versus P30; HP15 versus HP50; HP30 versus HP50
90	16935.45	0.000	Control versus all; H25 versus HP15; H25 versus HP30; H25 versus HP50; H15 versus P30; HP15 versus HP50; HP30 versus HP50
120	5996.34	0.000	Control versus all; H25 versus HP15; H25 versus HP30; H25 versus HP50; H15 versus P30; HP15 versus HP50; HP30 versus HP50
180	6512..21	0.000	Control versus all; H25 versus HP15; H25 versus HP30; H25 versus HP50; H15 versus HP30; HP15 versus HP50; HP30 versus HP5
240	2646.83	0.000	Control versus all; H25 versus HP15; H25 versus HP30; H25 versus HP50; H15 versus HP30; HP15 versus HP50; HP30 versus HP5
360	445.70	0.000	Control versus all; H25 versus HP15; H25 versus HP30; H25 versus HP50; H15 versus HP30; HP15 versus HP50; HP30 versus HP5

H25 = 25% hypromellose; HP15 = 1:1 hypromellose:poloxamer at 15%; HPHP30 = 1:1 hypromellose:poloxamer at 30%; HP50 = 1:1 hypromellose:poloxamer at 50%.

ANOVA showed significant difference between all formulations at different time intervals of dissolution testing (Table 3). The Tukey pair comparison tests also showed significant difference between comparison of all pairs. The effect of alteration of poloxamer with the addition of carbomer is shown in Figure 3. Formulation containing 15% poloxamer released the entire drug at 90 minutes, and formulation containing only 15%

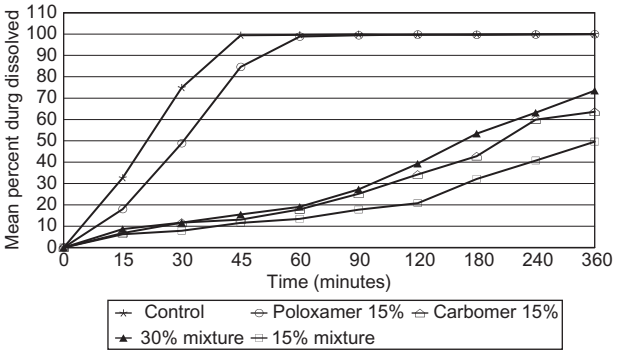

Figure 3. Theophylline release from formulations containing poloxamer:carbomer 1:1 (30%, 50%).

carbomer released 64% drug at 6 hours whereas formulation containing 15% combined mixture of the two polymers (7.5% carbomer and 7.5% poloxamer) released 74% drug at 6 hours of dissolution testing. These data indicate that an alteration of drug release rate and performance of each polymer occurred when the two polymers were combined together. The formulation containing a mixture of carbomer:poloxamer 1:1 at 30% level (15% carbomer and 15% poloxamer) released only 50% of drug at 6 hours.

Incorporation of carbomer with poloxamer decreased the drug release proportional to the level used. It is theoretically possible that these data indicate that hydrogen bonding between poloxamer and carbomer may lead to the reduction of both swelling ratio and dissolution rate. Control batches without polymer released 99% of drug at 45 minutes. The use of poloxamer decreased drug release proportional to the level used, whereas alteration of the poloxamer content by adding carbomer decreased drug release further.

ANOVA showed significant difference between formulations at the different time intervals of testing dissolution, and the Tukey test was used for pair comparison (Table 4). Formulations containing 50% total polymer (25% poloxamer and 25% hypromellose) and formulations containing 30% total polymer (15% poloxamer and 15% carbomer) were selected as the best formulations in terms of drug release and were tested for dissolution up to 24 hours. They were also tested in different dissolution media and at different basket rotational speed. Sustained release profiles were obtained and the drug release from the formulation containing 25% poloxamer and 25% hypromellose was 98% at 24 hours whereas the drug release from the formulation containing 15% poloxamer and 15% carbomer was 92% (Figure 4). These data may be because the swelling ratio and the erosion rate of matrix-containing hypromellose are higher than that of the matrix-containing carbomer and also may be due to the differences in the solubility of the two polymers in water, although both form hydrogels upon contact with water. The *t*-test for pair comparison[18] showed no significant difference between the two formulations up to 120 minutes. However, after 120 minutes, there was significant difference in drug release between the two formulations (Table 5).

Dissolution testing was performed for the selected formulations at different basket rotational speeds. Both formulations showed an increase in drug release as the basket rotational speed increased (Figures 5 and 6).

Table 4. ANOVA and Tukey pair comparison for theophylline tablets containing 1:1 poloxamer:carbomer (15%, 30%, and 50%, w/w).

Time (minutes)	*f*-Value	*p*-Value	Tukey pair comparison
15	425.01	0.00	Control versus all; C15 versus CP30; C15 versus CP50; ZP15 versus CP50; CP30 versus CP50
30	43485.43	0.000	Control versus all; C15 versus CP15; C15 versus CP30; 15 versus CP50; CP15 versus CP30; CP15 versus CP50; CP30 versus CP50
45	46454.38	0.00	Control versus all; C15 versus CP15; C15 versus CP30; C15 versus CP50; CP15 versus CP30; CP15 versus CP50; CP30 versus CP50
60	43863.79	0.00	Control versus all; C15 versus CP15; C15 versus CP30; C15 versus CP50; CP15 versus CP30; CP15 versus CP50; CP30 versus CP50
90	11571.89	0.00	Control versus all; C15 versus CP15; C15 versus CP30; C15 versus CP50; CP15 versus CP30; CP15 versus CP50; CP30 versus CP50
120	20895.99	0.00	Control versus all; C15 versus CP15; C15 versus CP30; C15 versus CP50; CP15 versus CP30; CP15 versus CP50; CP30 versus CP50
180	20895.99	0.00	Control versus all; C15 versus CP15; C15 versus CP30; C15 versus CP50; CP15 versus CP30; CP15 versus CP50; CP30 versus CP50
240	6016.64	0.00	Control versus all; C15 versus CP15; C15 versus CP30; C15 versus CP50; CP15 versus CP30; CP15 versus CP50; CP30 versus CP50
369	2508.67	0.00	Control versus all; C15 versus CP15; C15 versus CP30; C15 versus CP50; CP15 versus CP30; CP15 versus CP50; CP30 versus CP50

C15 = 15% carbomer; CP15 = 1:1 carbomer:poloxamer at 15%; CP30 = 1:1 carbomer:poloxamer at 30%; CP50 = 1:1 carbomer: poloxamer at 50%.

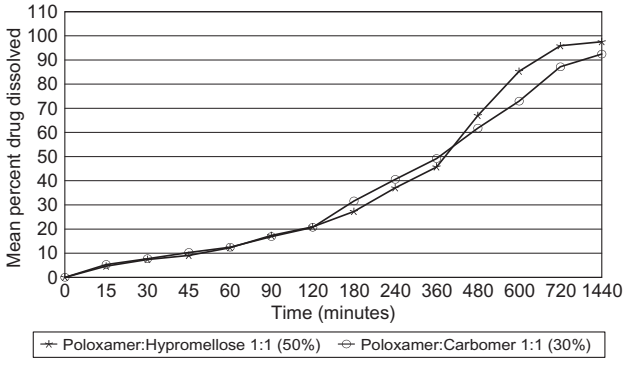

Figure 4. Dissolution profiles for poloxamer:hypromellose 1:1 (50%) and poloxamer:carbomer 1:1 (30%).

Table 5. *t*-Test pair comparison for selected formulations, of 1:1 poloxamer:hypromellose at 50% and 1:1 poloxamer:carbomer at 30%.

Time (minutes)	*t*-Value	*p*-Value	Results
15	−3.39	0.077	NS
30	−2.39	0.097	NS
45	−2.03	0.136	NS
60	−0.91	0.428	NS
90	0.65	0.564	NS
120	0.75	0.530	NS
180	−28.96	0.000	S
240	−20.53	0.000	S
360	−14.47	0.001	S
480	29.16	0.000	S
600	37.22	0.001	S
720	28.08	0.000	S
1440	36.34	0.000	S

S, significant difference; NS, no significant difference.

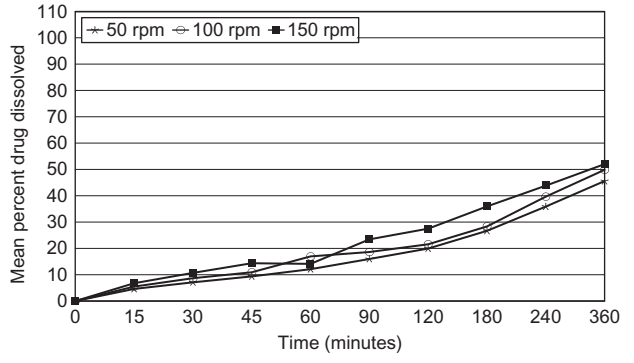

Figure 5. Effect of basket rotational speed on drug release from formulation containing poloxamer:hypromellose 1:1 (50%).

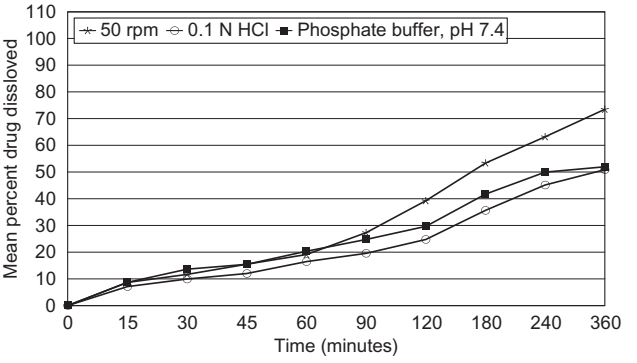

Figure 6. Effect of basket rotational speed on drug release from formulation containing poloxamer:carbomer 1:1 (30%).

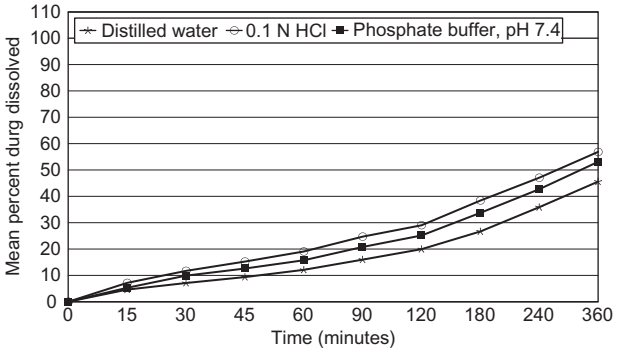

Figure 7. Effect of dissolution medium on drug release from formulation containing poloxamer:hypromellose 1:1 (50%).

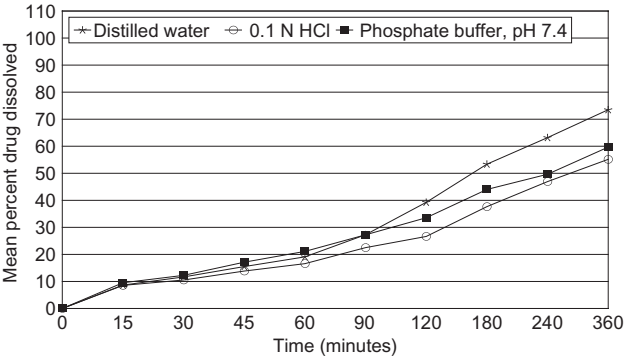

Figure 8. Effect of dissolution medium on drug release from formulation containing poloxamer:carbomer 1:1 (30%).

These data may be due to the possibility of high erosion rate as the agitation was increased. ANOVA showed a significant difference in drug release at different basket rotational speeds. Figures 7 and 8 depict the drug release from the two selected formulations in different dissolution media at 50 rpm. The drug release from the formulation containing 25% poloxamer and 25% hypromellose released approximately 45% of drug in distilled water, 57% in 0.1 N HCl, and 53% in phosphate buffer whereas the formulation containing 15% poloxamer and 15% carbomer released 50% in distilled water, 56% in 0.1 N HCl, and 51% in phosphate buffer.

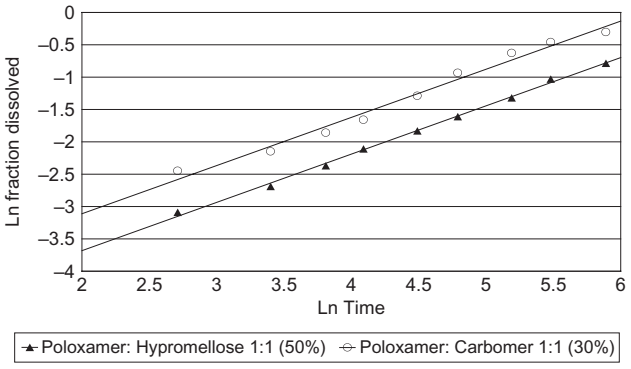

Figure 9. Mechanism of drug release from formulations containing poloxamer:hypromellose 1:1 (50%) and poloxamer:carbomer 1:1 (30%).

Table 6. Mechanism of drug release from the selected formulations.

Formulations	N = slope mechanism of drug release	K indicates	Regression coefficient
1:1 Poloxamer: hypromellose at 50%	0.761 (anomalous transport)	5.174	0.999
1:1 Poloxamer: carbomer at 30%	0.745 (anomalous transport)	4.606	0.992

K is a constant that incorporates both structural and geometric characteristics of the release device.

ANOVA showed little difference in drug release between different formulations tested in different dissolution media, which can be considered as not significant. These findings may be because no erosion was observed during dissolution testing. It was expected that different pH dissolution media will not show difference in drug release because the polymers used for preparing the matrices were nonionic.

The data depicted in Figure 9 represent a release rate that follows anomalous transport[16] where n is more than 0.45 and less than 1. The n values indicate that both diffusion and erosion contribute to drug release from the matrix. Table 6 shows the n values for the two selected formulations are 0.746 and 0.745 and the K values (constant incorporated both structural and geometric characteristics of the release device).

Conclusion

The combination of poloxamer 407 with hypromellose and/or carbomer offers control of drug release. Diffusion of theophylline from poloxamer and poloxamer combined with hypromellose or carbomer was found to be dependent on the concentration, swelling ratio, and erosion rate. The drug release from the matrix decreased significantly as hypromellose or carbomer is combined with poloxamer. Combination of poloxamer with hypromellose or carbomer resulted in formation of hydrogen bonding that played an important role in reducing both swelling ratio and dissolution rate. Varying the pH of the dissolution media did not affect the dissolution rate or the swelling ratio. However, the increase in rotational speed did increase the erosion rate and consequently increased drug release. The mechanism of drug release follows the anomalous relaxation non-Fickian diffusion model.

Declaration of interest

The authors report no conflicts of interest.

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