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RESEARCH PAPER

Influence of Physiological Variables on the In Vitro Drug-Release Behavior of a Polysaccharide Matrix Controlled-Release System

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Key Words: Xanthan gum; Locust bean gum; Polysaccharide; Matrix; Type III dissolution.

INTRODUCTION

Hydrophilic matrix systems are popular and versatile controlled release systems. Amongst polysaccharide derivatives used to produce such systems, there are a range of cellulose ethers, e.g., hydroxypropylmethylcellulose (HPMC) and a diverse range of other materials, including sodium alginate, carrageenan, chitosan, and xanthan gum.[1,2]

The hydrophilic matrix systems being investigated in this study consist of two heteropolysaccharides—xanthan gum (XG) and locust bean gum (LBG)—and the principle of this formulation is that it utilizes the synergistic interaction of two biopolymers to produce a strong and elastic gel in the presence of a ternary component to control the drug-release process.[3]

Hydrophilic matrix tablets generally control and prolong drug release by rapidly forming a protective viscous gel layer while releasing exposed drug around the tablet surface when exposed to gastrointestinal fluid.[1] It is generally believed that drug release from a swollen gel layer may be governed by drug diffusion through and/or erosion of the gel layer depending on the solubility of a drug.[4–7] Therefore, many factors influencing the properties of the gel may significantly modify the drug-release behavior of the system. These factors may include physicochemical properties of the drug and polymers,[8–10] formulation composition,[11–13] processing conditions,[14] and environmental variables such as the characteristics of gastrointestinal fluids.[15–17]

The ideal oral controlled-release system should not be or be minimally influenced by the in vivo environment of the gastrointestinal tract (GIT), as any significant changes of the system may potentially lead to a failure of the product or serious therapeutic toxicity.[18,19] Certain hydrophilic matrix formulations have been shown to erode in the GIT much faster postprandially than under fasting conditions,

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which differ significantly from those pertaining under fed conditions.[20–23] However, there are few reports giving a clear explanation for what caused the modification of drug release and absorption from such hydrophilic matrix systems.

Xanthan gum is a soluble, anionic-bacterial heteropolysaccharide, while LBG is a neutral plant galactomannan. Both materials have been extensively studied[24–26] in a range of environments, with some sensitivity to pH and ionic strength demonstrated. The synergistic gelation of XG and LBG has also been reported to decrease dramatically below pH 5, although it is independent of pH within the range of 5–10.[26]

pH and ionic strength are known to be two major properties of GI fluids due to GI secretions, and both are extremely variable along different parts of GIT and from fasted to fed state, particularly the pH in the stomach.[20,27] Given these features of GI fluids and the potential influence of pH and ionic strength on the gel properties of XG/LBG systems as analyzed above, it is important to examine the effects of pH and ionic strength on drug-release behavior of this heterodisperse polysaccharide-based controlled release system (HPCRS). As a result, this may somehow help predict a possible in vivo performance of the HPCRS in a changing environment of GIT under both fasting and fed conditions. Most importantly, it will direct strategic formulation development and guide clinical therapy.

In this study, attempts have been made to establish in vitro testing conditions reflecting the range of physiological characteristics of both the pH and ionic strength of GI fluids from different parts of the GIT, in fasted and fed states. USP type III Bio-Dis dissolution apparatus was used to conduct the studies with respect to the influences of these physiological factors on the performance of the HPCRS. Propranolol HCL (PLHCL) was used as a model drug.

EXPERIMENTAL

Materials

Xanthan gum (Lot No. P5086), locust bean gum (Lot No. B21577), and dextrose (Lot No. CD 4R02005) were supplied by Penwest Pharmaceuticals (Patterson, NY, USA). The gums are utilized as matrix-forming agents. Dextrose is added to the system to aid in wetting and to add integrity to the matrix during tableting. Propranolol hydrochloride (Lot No. 12896034, USP23/BP grade) was obtained from Chemo Italia. Sodium stearyl fumarate (Lot No. 212-01X), a tablet lubricant, was supplied by Penwest Pharmaceuticals. Hydrochloric acid and potassium dihydrogen phosphate were purchased from Fisons Scientific Equipment (Loughborough, UK), sodium hydroxide from Fisher Chemicals (Loughborough, UK), and sodium chloride from Aldrich Chemical Co. Ltd. (Dorset, England). The general chemicals were all of analytical grades. In all preparations of solutions and buffers, distilled water produced from Millipore Elix S system was used at all times.

Tablet Preparation

A batch size of 300 g was prepared for both extragranular and intragranular formulations. In extragranular formulations, xanthan gum, locust bean gum, and dextrose (1:1:2) were blended in a high-speed mixer (Cuisine Systemee Magimix 5000, Magimix, Vincennes Cedex, France) for 5 min and then 25% (w/w) distilled water, previously determined by initial studies, was added gradually. The mixture was mixed for another 5 min. Thereafter, the wet granules obtained were dried at 60°C in an oven (Gallenkamp, 1H-150, Sanyo-Gallenkamp PLC, Loughborough, UK) for 24 hr. Finally, the granules were comminuted through an oscillating granulator (Frewitt MGL4A, Frewitt Ltd., Fribourg, Switzerland) so that the discrete granules sized below 320 μm were produced. In the intragranular formulation, 10% (w/w) PLHCL was mixed with the matrix components (the ratio of the components kept unchanged) under the conditions as above. The subsequent granulation steps were as above.

Next, 10% (w/w) PLHCL was added to an extragranular formulation and the mixture was mixed at 90 rpm for 20 min in a Turbula mixer (Glen Creston, Stanmore, England). Then, 1% (w/w) sodium stearyl fumarate (PRUV) was added and the formulation was further blended at 50 rpm for 1 min.

An intragranular formulation was mixed with 1% (w/w) PRUV under the same conditions as above.

The tablets were produced by compressing the formulation on a single-punch tabletting press (Manesty type F3, Manesty, Knowsley, UK) with round 10-mm flat-faced punches and die. The compression forces used during compression were kept constant. The weight of each tablet was controlled to about 500 mg.

Moisture Content of the Granules

The moisture content of the granules was determined thermogravimetrically by heating the granules at 75°C for 20 min in a Mettler LP 16 Infrared dryer coupled with a LJ 16 Moisture Analyzer (Mettler-Toledo AG, Im Langacher, Greifensee, Switzerland), and the values of loss-on-drying (LOD) were obtained.

Bulk and Tap Densities of the Granules

The bulk density of the granules was determined by measuring the volume of the weighed granules using a 100 mL cylinder. Tapped density of the granules was determined by a jolting volumeter (Stampfvolumeter STAV 2003 JEL, J. Engelsmann AG, Ludwigshafen am Rhein, Germany). The sample was tapped 500 times and further tapping resulted in no change in volume. All measurements were made in triplicate. Carr's compressibility index and Hausner ratio were calculated.[28]

Tablet Hardness

The hardness of the tablets was determined by use of a Schleuniger-2-E laboratory hardness tester (Schleuniger GmbH, Neuhausen, Germany).

Tablet Porosity

The true density of the powder (ρ_{powder}) for the tablets was determined by Micromeritics AccuPyc 1330 pycnometer (Norcross, USA). The mean value of ten readings was taken. Tablet porosity (P) was calculated using Eq. (1)[6]:

$$P = \left(1 - \frac{W_{\text{tab}}/V_{\text{tab}}}{\rho_{\text{powder}}}\right) \times 100 \quad (1)$$

where W_{tab} is the tablet weight (mean value, $n = 20$), V_{tab} represents the volume of the tablet ($n = 10$), and ρ_{powder} is the true density of the powder.

Content Uniformity of the Tablets

One tablet was ground into the powder in a mortar and 70 mL of methanol was added. The slurry was then transferred into a volumetric flask of 100 mL and swirled. The mixture was further sonicated for 1 min and diluted to the volume with methanol. A portion of the resulting dispersion was centrifuged (30–35 mL, 10 min, 6000 rpm, in JA-14, Beckman J2-MC centrifuge, Beckman Coulter, Inc., Fullerton, CA, USA) and 4 mL of the clear solution was diluted with methanol to provide a solution containing PLHCL of about 40 μg/mL. The UV absorbance of the sample solution and a solution of PLHCL of USP RS with known concentration of 40 μg/mL were both measured at $\lambda_{\max}$ 288, using methanol as a blank. The quantity of PLHCL was then calculated, in mg, in per tablet.[29] The uniformity of content of tablet was obtained from the determination of 10 tablets chosen from the bulk of tablets.

Dissolution Studies

Dissolution tests were carried out using an automated USP type III Bio-Dis 3 release-rate tester (Caleva Instruments, Sturminster Newton, UK) with dipping speed set at 20 dpm, in 250 mL dissolution medium, at 37 ± 0.2°C. The glass tube holder with top screen mesh of 820 μm and bottom screen mesh of 380 μm was used. Once a test run was finished, the sample solutions were taken out from the dissolution vessels, filtered through 1.0 μm cellulose-nitrate membrane filters (Whatman international Ltd, Maidstone, Kent, UK), and analyzed for UV absorption at $\lambda_{\max}$ 288 nm. The cumulative percentage of drug released was calculated according to a PLHCL calibration curve of $Y = 0.01103 + 0.01953\ X$ ($n = 15$, $r = 0.9999$, Y—absorbance, X—concentration) which covers a pH range of 1.2–7.5 for PLHCL buffer solutions.

Effect of pH

The effect of pH of the dissolution medium on the drug-release behavior of both intragranular and extragranular tablets was investigated to identify the sensitivity of HPCRS to the change of physiological pH. Only the range of pH occurring in a normal physiological environment of the GIT under both fasted and fed conditions was covered in the investigation. Therefore, a series of buffer solutions having pH values of 1.2, 2.5, 4.5, 6.8, and 7.5, respectively, were chosen as the dissolution media to mimic in vivo pH environment mainly in the stomach and intestine in fasted and fed state.

The buffer solutions as dissolution media were produced from the simulated gastric fluid without pepsin (pH 1.2) and buffers of HCL/KCL (pH 2.5), KH_2PO_4 (pH 4.5), and KH_2PO_4/NaOH (pH 6.8, 7.5). The length of dissolution test at each pH level was unified to 24 hr only for the purpose of comparison.

Influence of Ionic Strength on Drug Release

The influence of the ionic strength of the dissolution medium on the drug-release performance of HPCRS tablets was studied within a range of ionic strength of 0–0.4, which covered a physiologically varying range of ionic strength of GIT for both fasted and fed state in man, under various physiological pH conditions.[16] The ionic strength of buffer solutions used was regulated by sodium chloride (NaCl). NaCl was chosen as an ionic regulating agent because it falls in the midrange of lyotropic series for its ability to salt out polymer and it is the electrolyte with the highest concentration in GI fluids.[16]

Data Treatment

To characterize the drug-release profile, the experimental results were fitted into an exponential Eq. (2):

$$M_t/M_\infty = Kt^n \tag{2}$$

where M_t/M_∞ is the fraction of drug released up to time t, K is a kinetic constant that measures the velocity of drug release and n is the release exponent indicative of the release mechanism.[30] Since K has the dimension time^{-n}, the release constants of different kinetics cannot be compared directly. Thus, to analyze and compare the drug release rate, the mean dissolution time (MDT) was applied. MDT is the sum of different periods of time during which drug molecules or fractions of dose stay in the dosage form before release divided by the total number of molecules or the total dose, respectively.[31] The MDT is calculated according to Eq. (3)[31]:

$$MT = \frac{n}{n+1} K^{-1/n} \tag{3}$$

To compare the means at different experimental conditions and to assess the statistical significance, one-way analysis of variance (ANOVA) was carried out at the level of 5%, except where two samples were compared, under which circumstance a two-sample t-test was used to analyze the results. Post-ANOVA analysis was carried out using Fisher pairwise comparisons (on Minitab Software).

RESULTS AND DISCUSSION

The data from Tables 1 and 2 showed that both the granules and tablets made from either an intragranular or extragranular formulation presented similar physical properties. Both granules have good flow properties, resulting in tablets with satisfactory weight and content uniformity. Both batches of tablets have similar and acceptable tablet strength. Their initial figures of the porosity of the tablets are close to each other.

Influence of pH on Release

The results (Table 3) reveal that pH has an influence on the drug-release rate from both extragranular and intragranular HPCRS tablets. Drug release

Table 1. Characterization of HPCRS granules.

Formulation	Extragranular	Intragranular
Moisture content (H_2O%)	1.4	1.9
Bulk density (gcm^{-3})	0.531 ± 0.018	0.451 ± 0.003
Tapped density (gcm^{-3})	0.600 ± 0.009	0.551 ± 0.008
Hausner ratio	1.13	1.15
Carr's index	11.50	13.10

Table 2. Characterization of HPCRS tablets.

Formulation	Extragranular	Intragranular
Hardness (Kp)	6.873 ± 0.36	8.100 ± 1.20
Thickness (mm)	4.9 ± 0.08	5.1 ± 0.162
Weight uniformity (mg)	508.1 ± 0.011	522.8 ± 0.027
Content uniformity (mg)	45.58 ± 2.61	49.50 ± 1.05
True density (gcm^{-3})	1.4920 ± 0.0002	1.4869 ± 0.0002
Volume of tablet (cm^3)	0.3815	0.4036
Porosity (%)	10.8	12.9

Table 3. Influence of pH on drug-release rate (mean dissolution time, MDT) and release mechanism of extragranular (E) and intragranular (I) tablets ($n = 3$).

	Properties of dissolution medium		Drug-release characteristics				
Formulation	pH	μ	MDT (h)	±SD	n	±SD	r
E	1.2	0.114	3.319	0.170	0.622	0.010	0.9999
I	1.2	0.114	3.426	0.275	0.655	0.003	0.9999
E	2.5	0.054	4.006	0.226	0.670	0.010	0.9998
I	2.5	0.054	4.478	0.426	0.683	0.008	0.9999
E	4.5	0.05	5.086	0.237	0.709	0.009	0.9994
I	4.5	0.05	5.005	0.317	0.741	0.042	0.9998
E	6.8	0.07	5.376	0.171	0.710	0.019	0.9994
I	6.8	0.07	4.909	0.135	0.748	0.022	0.9997
E	7.5	0.09	5.209	0.049	0.695	0.009	0.9996
I	7.5	0.09	5.089	0.357	0.735	0.023	0.9997

appeared faster in an acidic pH range of 1.2–2.5. The statistical analysis of MDT from drug-release profiles of extragranular system at all pH levels selected indicated that the release rates of PLHCL at pH of both 1.2 and 2.5 were significantly higher than those at pH of 4.5, 6.8, and 7.5 ($p < 0.05$). There was no significant difference observed in drug-release rate among pH of 4.5, 6.8, and 7.5 ($p > 0.05$). When comparing the values of MDT from intragranular systems at various pH levels, it was found that MDT at pH of 1.2 is significantly less than those from other pH levels ($p < 0.05$). Again, no statistical difference was found among MDT values at pH levels of 4.5, 6.8, and 7.5 ($p > 0.05$). However, drug release at pH of 2.5 was only different from those at a pH of 1.2 and 7.5 ($p < 0.05$), but not from those at pH 4.5 and 6.8 ($p > 0.05$).

As the original buffers used in the investigation of pH effect have slightly different levels of ionic strength ranging within 0.05–0.1145, NaCl was added to adjust the ion concentrations in dissolution media to the same level, i.e., $\mu \approx 0.1$, and then determined the drug release rate again from extragranular system in dissolution media of different pH. The results are shown in Table 4. Again, the drug release from acidic and weakly acidic media (pH of 1.2, 2.5, and 4.5) was significantly faster than in neutral media (pH of 6.8 and 7.5) ($p < 0.05$). There were also significant differences among the values of MDT obtained from drug-release data in the media of pH of 1.2, 2.5, and 4.5 ($p < 0.05$), which followed an order of release in medium of pH of $1.2 > 2.5 > 4.5$. The interference of the effect of ionic strength can thus be reasonably excluded and the results confirmed further the fact that pH influenced the drug-release behavior of the HPCRS system.

Table 4. Influence of pH on the drug-release rate (mean dissolution time, MDT) from extragranular tablets ($\mu \approx 0.1$, $n = 3$).

Dissolution medium		Release rate of PLHCL		
pH	μ	MDT (h)	±SD	r
1.2	0.1145	3.319	0.170	0.9999
2.5	0.1040	4.030	0.095	0.9998
4.5	0.1000	4.716	0.067	0.9997
6.8	0.1020	5.219	0.170	0.9996
7.5	0.0900	5.209	0.049	0.9996

The pH-dependence of drug release for a drug product is normally attributed to either the drug carrier system or the varying solubility of drug itself in dissolution media of different pH. It is known that the solubility of PLHCL is pH-dependent. PLHCL has a pK_a value of 9.45, and at 37°C, its solubility measured in the media of pH 1.0 (0.1 N HCL) and 7.4 (0.1 M phosphate buffer) is 249 and 301 mg/mL,[32] respectively, i.e., PLHCL has a higher solubility in near-neutral medium than in an acidic medium; however, there is not a large difference. Drug release should therefore be faster in the media of higher values of pH, e.g., pH of 6.8 and 7.5. However, the opposite trend of drug-release profiles of HPCRS obtained at a range of chosen pH's excluded the solubility of PLHCL as the main contributing factor leading to a pH-dependent drug release from the HPCRS.

When analyzing the composition of HPCRS, it can be seen that that XG is the major component most susceptible to pH as it is an anionic polyelectrolyte and has a pK_a of 3.1. Both conformations of XG in solution and weak-gel behavior of aqueous dispersions of XG are reported to be sensitive to pH in certain range. Talukdar et al.[6,33] noticed that the swelling and drug-release behavior of XG controlled-release matrix tablets appeared different in a medium of pH 1.2 from those in neutral or near-neutral media. Apparently, at lower pH, more acidic groups in XG molecules will be unionized and, therefore, the polymer will become less soluble. In turn, this can affect the hydration of XG in an aqueous medium, and therefore, the swelling behavior of XG matrix. Moreover, the undissociated form of the carboxylic groups of XG in acidic medium may influence intra- and inter-molecular association of XG molecules, and consequently, the conformational change of XG and its rheological properties. Tako[26] found that the gel strength of XG/LBG mixtures is almost independent of pH within pH values of 5–10, but reduced dramatically below pH of 5. Poor solubilization of XG in an aqueous environment of low value of pH will result in a reduction in both the rate and extent of hydration of the matrix system. It has been observed that the degree of swelling of HPCRS tablets during dissolution process at acidic media of pH 1.2 and 2.5 is much lower than in neutral media and water. Secondly, the carboxylic functions in XG molecules may possibly be involved in the synergistic interaction between XG and LBG; thus, the change of ionisation of these groups due to a change in pH may partly break the intermolecular heterotypic binding.[26] Both decreased hydration of the polymer and possibly weakened synergistic interaction of XG/LBG may be responsible for the faster drug-release behavior of HPCRS in extreme acidic media.

The release exponent n was calculated according to Eq. (2) from the data of $M_t/M_\infty < 0.8$ for all release profiles obtained under various pH conditions. The exponent n gives information of drug-release kinetics and release mechanisms. It was found that an anomalous transport dominates the drug release at lower range of pH (1.2 and 2.5) of dissolution media. However, in higher or neutral pH media, the release mechanism showed a trend approaching toward case II transport. This means that pH is capable of modifying the controlled-release mechanism of HPCRS. Based on experimental observation and literature reports, the difference in release mechanism between lower and higher pH values may be explained as follows. In a highly acidic medium, the HPCRS does not swell fully due to the decreased solubility of XG; therefore, the system may contain larger areas of poorly hydrated and ungelled glassy core throughout the matrix. As a consequence, the gel layer may contain many holes or water-filled pores that exhibit characteristics of low microviscosity and increase the total porosity of the gel. These pores and channels within the matrix allow the drug to diffuse through the matrix more quickly, i.e., an inferior barrier resulting in a faster drug-release profile in acidic medium. Thus, this explains the mechanism of drug release in lower pH media being more diffusion-driven coupled with swelling control. In contrast, in higher pH media, the hydration of HPCRS is quicker, fuller, and more homogeneous, i.e., there are fewer pores or smaller areas of low microviscosity inside the gel layer. Therefore, the formation of an efficient and continuous retarding gel layer leads to a slower drug release and reduces the impact of diffusion to drug release, altering the release mechanism to a more swelling-controlled behavior, i.e., case II transport mechanism. This has previously been demonstrated for related systems.[15]

Finally, it was found that in vitro drug-release behavior of both extragranular and intragranular HPCRS tablets was more or less the same at every pH level except at pH 6.8 ($p < 0.05$). The release exponent n appeared also to be consistent within these two different processing systems at each pH level; however, n values of intragranular formulation at pH of 4.5, 6.8, and 7.5 generally are slightly higher than those of the extragranular system. The data obtained demonstrate that under employed processing conditions, there was little difference in release rates. This may indicate that, under those circumstances, drug binding to the formulation components, previously demonstrated for related systems[34] during manufacture, does not influence the drug release.

Influence of Ionic Strength on Release

The results revealed that ionic strength also had an effect on drug release from the HPCRS. Drug release in distilled water, i.e., $\mu = 0$, exhibits the slowest rate when compared with all other drug-release profiles in either water solutions or dissolution media with different values of pH within ionic

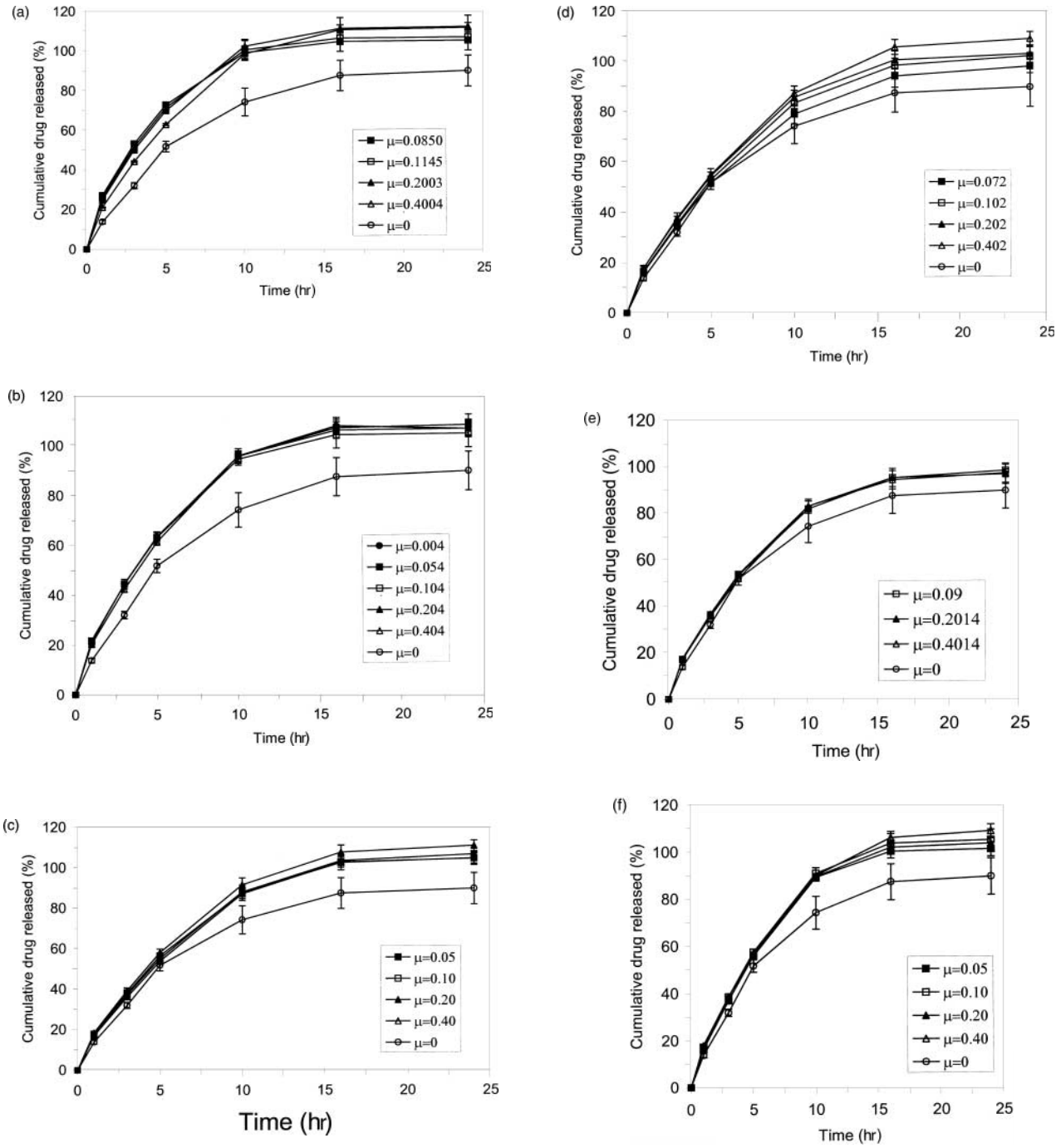

Figure 1. Influence of ionic strength on drug release from matrices. (a) pH 1.2; (b) pH 2.5; (c) pH 4.5; (d) pH 6.8; (e) pH 7.5 and (f) NaCl in distilled water.

strength range of $0 > \mu < 0.4$ (Fig. 1). In neutral aqueous media, when ionic strength was increased up to a value of 0.05, drug release appeared significantly faster than that in pure water ($p < 0.05$). However, further increases in ionic strength resulted in no significant change in drug release rate ($p > 0.05$). This implied that there must be a critical value of μ beyond which the ionic strength exerts no further

effect on drug release of HPCRS. There are differences among the release curves of different levels of ionic strength at pH of 1.2 and 4.5 when comparing their MDT values ($p < 0.05$). Under these circumstances, however, no special relationship between ionic strength and the corresponding MDT can be found, meaning that experimental error may have been the biggest contributor to these small, but significant, differences. Nevertheless, from the biopharmaceutical point of view, we may conclude that changes of ionic strength within physiological range of GIT will not profoundly affect the in vivo performance of HPCRS. Therefore, ionic strength may not be considered as a contributing factor to any indirect food effects and HPCRS can be basically regarded as a system independent of ionic strength under normal physiological conditions.

It is worth noticing, however, that the displacement of the release profiles with different levels of ionic strength at each chosen pH, relative to the release curve in pure water ($\mu = 0$), should not be exclusively attributed to the effect of ions, but on the contrary, the contribution of pH effect should be considered, especially in lower range of pH, e.g., pH of 1.2 and 2.5. For example, in pH 2.5, when the ionic strength of the dissolution medium is 0.004, which is mainly due to the existence of ions from hydrochloric acid, the release curve shows a distinct deviation from that in water. In this case, the influence on drug release may predominantly derive from pH, rather than the effect of ions. Furthermore, we found that the average values of MDT of different levels of ionic strength at acidic pH of 1.2 and 2.5 are generally smaller than that in water solutions of NaCl (Table 5). On one hand, these findings further confirmed pH effects on the HPCRS, but on the other hand, it may imply that the impact of pH on the system was more important than ionic strength.

Table 5. Influence of ionic strength (μ) of the dissolution medium on the release rate (mean dissolution time, MDT) and release mechanism of PLHCL from extragranular tablets ($n = 3$).

Properties of dissolution medium		Drug-release behavior				
pH	μ	MDT (h)	±SD	n	±SD	r
1.2	0.0805	3.187	0.111	0.614	0.010	0.9999
	0.1145	3.319	0.170	0.622	0.010	0.9999
	0.2003	3.421	0.045	0.643	0.011	0.9999
	0.4004	4.025	0.059	0.676	0.012	0.9999
2.5	0.004	3.969	0.157	0.680	0.010	0.9999
	0.054	4.006	0.226	0.670	0.010	0.9998
	0.104	4.030	0.095	0.658	0.010	0.9998
	0.204	4.013	0.041	0.668	0.009	0.9999
	0.404	4.210	0.113	0.683	0.008	0.9997
4.5	0.05	5.086	0.237	0.709	0.009	0.9994
	0.10	4.716	0.067	0.717	0.047	0.9996
	0.20	4.557	0.186	0.707	0.014	0.9996
	0.40	4.924	0.150	0.701	0.011	0.9996
6.8	0.07	5.376	0.171	0.710	0.019	0.9993
	0.102	5.219	0.170	0.710	0.016	0.9996
	0.202	5.030	0.194	0.685	0.007	0.9995
	0.402	4.932	0.307	0.694	0.012	0.9998
7.5	0.09	5.209	0.049	0.695	0.009	0.9996
	0.2014	5.101	0.199	0.695	0.011	0.9997
	0.4045	5.375	0.159	0.687	0.004	0.9997
H_2O	0.00	5.214	0.341	0.809	0.051	0.9998
	0.05	4.706	0.071	0.756	0.011	0.9996
	0.10	4.535	0.119	0.740	0.008	0.9998
	0.20	4.606	0.017	0.720	0.007	0.9997
	0.40	4.669	0.075	0.709	0.015	0.9997

The release exponent n at different levels of ionic strength under each pH condition was almost unchanged, which clarified that the ionic strength does not significantly modify the release mechanism of HPCRS as pH does. However, the exponent n in pure water ($\mu = 0$) is higher, which indicates a swelling-controlled mechanism prevails under the condition where the system can gain a maximum degree of swelling.

The effect of ionic strength on synergistic interaction of XG/LBG has been discussed previously,[26,35–37] as has the effect of salts on XG matrices.[33] However, there are also reports presented showing no distinct effect of salts on gel properties of the XG/LBG system.[38]

In summary, we can conclude that ions do interfere with the synergistic interaction of XG/LBG system, therefore influencing the hydration, swelling, and drug-release behavior of XG/LBG matrix system. However, the threshold value for influence is below that for the physiological range, suggesting that in vivo results will not be much influenced by this phenomenon.

CONCLUSIONS

The HPCRS is a pH-dependent system, releasing drug at a slightly higher rate in acidic medium than in neutral medium. This may have a small potential impact on the in vivo performance variation of HPCRS between fasted and fed state as it may be one of the contributing factors for any possibly occurring food effects. Ionic strength, within the physiological range, has a more limited effect.

More substantial influences on the release properties of such a matrix may be provided by other food components, and these effects will be examined in a subsequent study.

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