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ORIGINAL ARTICLE

Formulations of zero-order, pH-dependent, sustained release matrix systems by ionotropic gelation of alginate-containing mixtures

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Abstract

Background: Matrix type, monolithic, dosage forms suitable for controlled release that exhibit pH-dependent behavior are considerably less common than similarly behaving multiparticulated, enterically coated dosage forms, although simpler and less expensive to make. *Aim*: Evaluate the properties of alginates and alginate-containing systems to produce pH-sensitive, monolithic, controlled release dosage forms that perform acceptably and determine their limits of application in regard with stability, pH and Ca^{++} sensitivity, and appropriated rate of release. *Method*: Mixtures of the ionic gum sodium alginate (Na Alg.) with other gel-forming gums such as propylene glycol alginate (PGA), xanthan, or hydroxypropyl methylcellulose have been evaluated for applicability in the manufacture of controlled release dosage forms with three drugs of different solubility and ionic character. Mixture have been compressed into tablets and tested under a variety of pHs to simulate transit through the GI tract, in the presence of Ca^{++}, and for stability. *Results*: These mixtures have been able to sustain drug release for up to 12 hours with acceptable performance going from acidic to alkaline pHs to simulate travel through the GI tract and in the presence of Ca^{++}. Release rate has been adjusted by selecting a suitable Na Alg./other gum combination at an appropriated ratio. *Conclusions*: Mixtures of Na Alg. with a number of other gums have been demonstrated suitable to manufacture pH-sensitive, matrix-type solid dosage forms with release-controlling properties for up to 12 hours.

Keywords: Algin, hydroxypropyl methyl cellulose, pH dependent, propylene glycol alginate, sodium alginate, solid dosage forms, sustained release, xanthan gum

Introduction

Sodium alginate (Na Alg.)[1] is a naturally derived gel-forming, polymer-containing sequence of mannuronic and guluronic acid[2,3] with a highly pH-dependent behavior and sensitivity to multivalent ions in solution[4]. Na Alg. molecules are known to complex with a number of macromolecules, proteins, metal ions, and polyions[5–9]. For these reasons, Na Alg. has frequently been used in drug delivery systems, either alone or in combination with other excipients[10–12]. On the other hand, gums such as propylene glycol alginate (PGA), xanthan, gellan, and hydoxypropyl cellulose do not exhibit a similar dependence on low pH or high polyvalent ion concentration because of inaccessible ester functionalities, or a lack of carboxyl groups[13,14]. Because of its high pH sensitivity, Na Alg. is not usually used as the sole rate-controlling component in sustained release systems, although it has been used to fine-tune their performances[15,16]. Addition of Na Alg. has been reported, for example, to prevent a burst of release from dosage forms containing drugs with high solubility in the acidic gastric environment[17,18]. Consequently, a system containing Na Alg. in combination with other gel-forming, but pH-independent, excipients may allow the realization of a dosage form with limited or no drug release in the stomach, and sustained release in either the small or the large intestine, preferably for up to 12 hours[19–22]. Such a system can be advantageous when used to protect acid-sensitive drugs from release

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in the stomach while allowing sustained release in the intestine or to avoid a burst of release in the stomach by highly soluble drugs or weakly basic drugs[23,24]. Combinations of various grades of Na Alg. with PGA, xanthan gum, and hydoxypropyl methyl cellulose have, therefore, been evaluated for their ability to meet the above-described goals.

Experimental design and formulations

The release-sustaining performances of Na Alg./PGA systems were tested with a weakly basic, soluble (propranolol HCl), a weakly acidic (Na diclofenac), and a neutral (theophylline) drug, both sparingly soluble.

In the first phase, a fractional factorial design (Table 1) was conducted with propranolol HCl, to screen the effect of three factors:

- Na Alg. type: High viscosity (Keltone HVCR 400 cps @ 1%) versus low viscosity (Manugel LBA 500 cps @ 10%)
- PGA type: LVF (Kelcoloid LVF/426 low viscosity, 120 cps @ 1%, and high degree of esterification) versus HVF (Kelcoloid HVF, high viscosity, 400 cps @ 1%, medium degree of esterification)
- Na Alg./PGA ratio in the formulation (high: 5 and low: 1.25)

In a second phase (Table 2) a mixture design was conducted with propranolol HCl, sodium diclofenac, and theophylline to find the optimal ranges of drug and excipients.

- Na Alg. HV level (25% or 40%)
- PGA LVF level (4% or 12%)
- drug level (68%, 53%, 60%, 45%)

Table 1. Phase I Propranolol HCl formulations.

Formulation component	1a (%)	1b (%)	1c (%)	1d (%)
Propranolol HCl	50	50	50	50
Na Alg. HV	30	–	20	–
Na Alg. LBA	–	20	–	30
PGA LVF	6	16	–	–
PGA HVF	–	–	16	6
MCC 101	7	7	7	7
Povidone K-90	2	2	2	2
Lactose (monohydr.)	4	4	4	4
Magnesium stearate	1	1	1	1

Table 2. Phase II formulations.

Formulation component	2a (%)	2b (%)	2c (%)	2d (%)
Drug[a]	68	53	60	45
NA Alg. HV	25	40	25	40
PGA LVF	4	4	12	12
Povidone K-90	2	2	2	2
Magnesium stearate	1	1	1	1

[a]propranolol, Na diclofenac, or theophylline.

Table 3. Formulations.

Formulation component	3a (%)	3b (%)	3c (%)	3d (%)
Drug[a]	75	45	69	39
Na Alg. HV	20	50	20	50
Co-carrier[b]	2	2	8	8
Povidone K-90	2	2	2	2
Magnesium stearate	1	1	1	1

[a]propranolol, Na diclofenac, or theophylline. [b]PGA ('k' form.), Xanthan ('x' form.), or HPMC ('m' form.)

Finally, in a third phase (Table 3), the performance of Na Alg. was tested in combination with either PGA LVF, xanthan gum (Xantural 75) or hydroxypropyl methyl cellulose (Methocel K4M) in an extended range with the same drugs. Again, a mixture design was conducted to find the optimal ranges of drug and excipients:

- Na Alg. HV level (20% or 50%)
- PGA, xanthan, or hydroxypropyl methylcellulose (HPMC) level (2% or 8%)
- Drug level (75%, 45%, 69%, and 39%)

With propranolol HCl and Na diclofenac, granulations were performed in a Uni-Glatt fluid bed granulator. Table 4 reports a typical run set up.

With theophylline, tablets were developed by powder mixing followed by direct compression.

Tableting was performed using a Stokes B2 tablet press equipped with round, flat-faced punches 9.5 mm in diameter to obtain tablet hardness of 8–10 Kp. Dissolution studies were conducted in acid (0.1 N HCl, pH 1.2) for 2 hours and alkaline (potassium phosphate buffer, pH 7.2) media at 37°C. Performances were evaluated as following:

- <40% dissolution in an acid medium in 2 hours
- and at least 10 hours for the dissolution of remaining drug

Formulations were also evaluated for Ca^{++} sensitivity and stability after 3 month's treatment either at room temperature or under accelerated conditions (40°C, 75% RH).

Table 4. Fluid bed process conditions.

Conditions	Settings
Spay rate (g/min)	12
Inlet temperature (°C)	60
Atomization air (bar)	1.5
Shake interval (sec)	30
Shake duration (sec)	4
Flap (%)	10
Port Size (mm)	1

Materials

Na Alg. and propylene glycol alginates were obtained from FMC Alginates, Philadelphia, PA, USA (Na Alg.: Keltone HVCR is NF; Manucol LBA is both NF and EP; PGA: Kelcoloid LVF properties are equivalent to Kelcoloid 426, propylene glycol alginate NF);

Povidone (Plasdone® K-90) was obtained from ISP, Wayne, NJ, USA; Xanthan gum was obtained from CP Kelco, Wilmington, DE, USA; HPMC was obtained from Dow Chemical, Midland, MI, USA. All drugs and the remaining excipients were purchased from the Sigma Aldrich Catalog, Sigma Aldrich Co, St. Louis, MO, USA.

Results and discussion

Phase I

Dissolution profiles of propranolol HCl are shown in Figure 1. Na Alg. HV-based formulations (1a and 1c) successfully fit the criteria set, with the first one performing the best. The other two, Na Alg. LBA-based formulations (1b and 1d) did not fit the criteria and are considered less desirable because of a sudden change in release rate, as evidenced by the 'break' in the dissolution curves.

Main effects plots shown in Figure 2 using these data indicate that Na Alg. HV is a more effective release-slowing agent than LBA, that PGA LVF is a more effective release-slowing agent than HVF, an indication that its higher esterification level has more effect than molecular weight on its release-slowing performances and, finally, that the Na Alg./PGA ratio did not make much difference.

In all cases, the presence of alginates prevents excessive release of propranolol HCl at low pH, where this drug is highly soluble.

Phase II

The set of mixture design experiments from Phase II gave the following results. With propranolol HCl, only one of the formulations (2d), prepared using Na Alg. HV (40%)/PGA LVF (12%) successfully fit the criteria set. The other three formulations, 2a, 2b, and 2c did not fit the criteria and are considered undesirables because of dose dumping, as made evident by the 'break' in the dissolution curves. As shown in Figure 3, the drug release profiles for all the formulations tested were somewhat linear in alkaline pH. Therefore the slope of linear fit was estimated as the rate of dissolution for each formulation from 2 hours to 80% drug release.

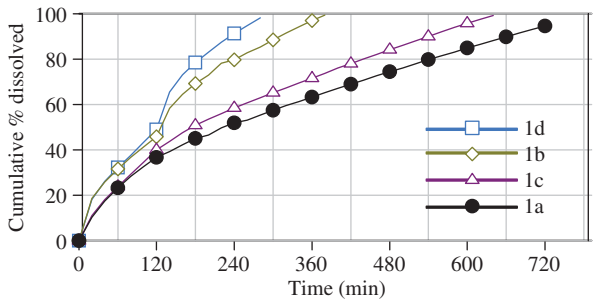

Figure 1. Dissolution profiles of Phase I propranolol HCl tablets containing sodium alginate and PGA.

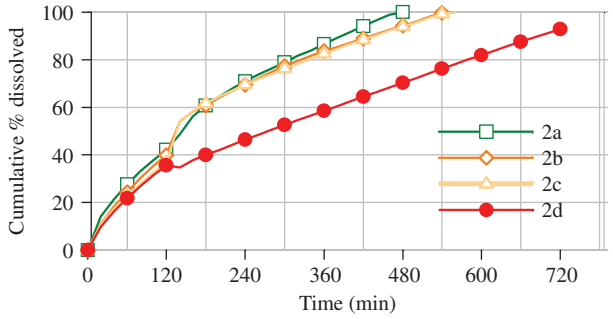

Figure 3. Cumulative % dissolved profiles of Phase II propranolol HCl formulations.

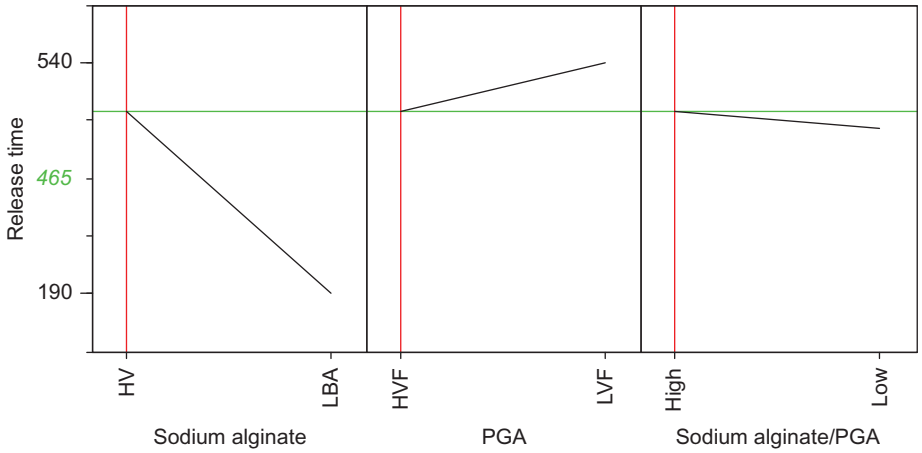

Figure 2. Main effects plots of time to reach 80% dissolved propranolol HCl.

The release in alkaline conditions ranged from 8 hours for formulation 2a (Na Alg. HV 25%/PGA LVF 4%), to 9 hours for formulation 2b (Na Alg. HV 40%/PGA LVF 4%) and formulation 2c (Na Alg. HV 25%/PGA LVF 12%) to 12 hours for formulation 2d (Na Alg. HV 40%/PGA LVF 12%). In this and subsequent plots, curve colors relate to the colored areas of Figures 4, 6, and 8.

The estimated slopes do not take into consideration the curve shifts that occur for LBA containing formulations as the pH changes. The linear dissolution profiles also suggest a release not controlled by diffusion, but rather by swelling/erosion. The ternary plot shown in Figure 4 can be used to estimate the rate of dissolution (slope) of propranolol HCl as a function of the conditions of each axis (amount of components). The red area at the top corner represents the conditions necessary to produce a rate of dissolution lower than 0.10% dissolved/min, corresponding to a 12 hours' release. The orange center area represents a dissolution rate lower than 0.11% dissolved/min, but greater than 0.10% dissolved/min (somewhat too fast) while the yellow and green lower corner areas represent dissolution rates respectively greater than 0.11% and 0.12% dissolved/min (too fast). Using this plot, a formulator can estimate the relative amounts of each component that are necessary to give the desired dissolution rate, within the area of the experimental constraints.

Dissolution profiles of diclofenac Na tablets are shown in Figure 5. Release profiles for all the formulations were quite linear, suggesting a release not controlled by diffusion, but rather by swelling/erosion. Therefore the slope of linear fit (2 hours – 80% release) was estimated as the rate of dissolution for each formulation.

One of the formulations prepared, 2b, successfully met the criteria set. On the other hand, formulation 2a and 2d were too fast and 2c was too slow.

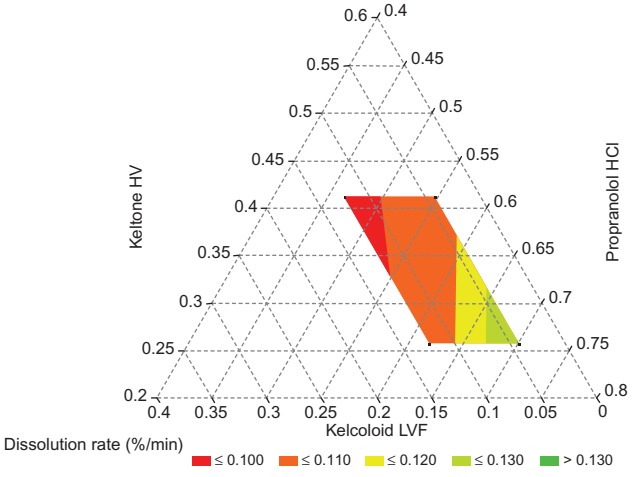

Figure 4. Estimated dissolution rate as a function of formulation components level for propranolol HCl Phase II formulations (estimated from the slope of linear fit from 2 hours to 80% release in Figure 3).

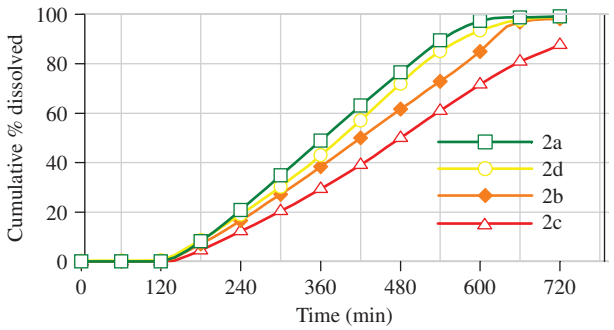

Figure 5. Dissolution profiles of diclofenac Na tablets containing sodium alginate and PGA.

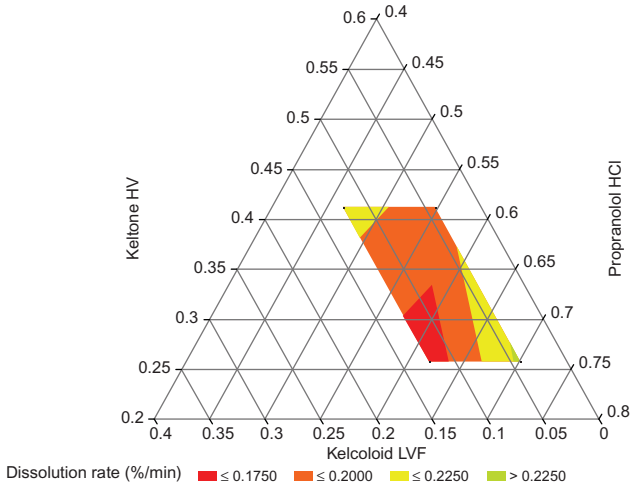

Figure 6. Estimated dissolution rate as a function of formulation components level for sodium diclofenac Phase II formulations (estimated from the slope of linear fit from 2 hours to 80% release in Figure 5).

The ternary plot shown in Figure 6 can be used to estimate the rate of dissolution (slope) of diclofenac Na as a function of the amount of the various components. The area at the center represents the conditions necessary to produce a rate of dissolution (0.1750 < rate < 0.2% dissolved/min), corresponding to 11–12 hours' release. The corner areas represent a dissolution rate greater than 0.2% (too fast) while the leftmost lower corner area represents dissolution rate lower than 0.1750% (too slow).

Dissolution profiles of theophylline formulations are shown in Figure 7. Three of the formulations prepared, 2a, 2b, and 2c did not meet the criteria set as they released 100% of the drug in 8 hours or less. On the other hand formulation 2d showed 100% drug release in 10 hours. Drug release profiles for all the formulations were quite linear; therefore the slope of the linear fit was estimated as the rate of dissolution for each formulation. The ternary plot shown in Figure 8 can be used to estimate the rate of dissolution (slope) of theophylline

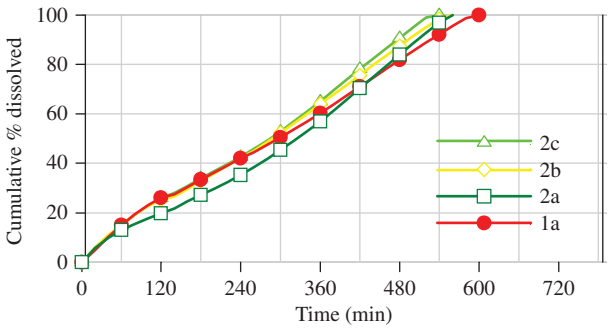

Figure 7. Dissolution profiles of theophylline tablets containing various amounts of sodium alginate and propylene glycol alginate.

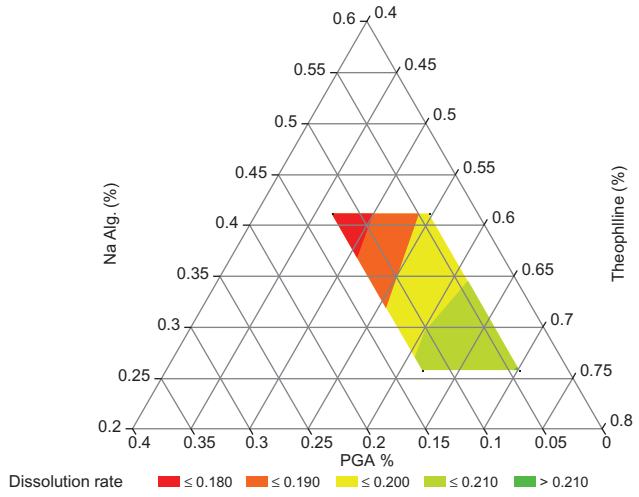

Figure 8. Estimated dissolution rate as a function of formulation component level for Theophylline (estimated from the slope of linear fit in the interval 2 hours to 80% released in Figure 7).

as a function of the conditions of each axis (amount of components). The green corner area (formulation 2c) represents a dissolution rate greater than 0.21% corresponding to a 9 hours' drug release (too fast). The yellow (formulation 2a) and orange (formulation 2b) areas toward the center represents the conditions necessary to produce a rate of dissolution lower than 0.2% and 0.19% dissolved/min., respectively, corresponding to a 9.5 hours' drug release (borderline fast), while the red corner area (formulation 2d) represents a dissolution rate lower than 0.18% dissolved/min. corresponding to a 10 hours' drug release, which is approximately the optimal rate. Dissolution rates of Phase II formulations are reported in Table 5.

Phase III

In this phase, the release modulating effect of Na Alg. HV was modified by the presence of an additional gum, such as PGA LVF ('k' systems), xathan 75 ('x' systems), and HPMC K4m ('m' systems). Dissolution profiles of propranolol HCl formulations are shown in Figure 9.

Table 5. Release rate (min^{-1}) for phase II formulations.

Formulation	Propranolol HCl	Na diclofenac	Theophylline
2a	0.131	0.232	0.209
2b	0.103	0.190	0.194
2c	0.101	0.167	0.202
2d	0.098	0.225	0.169

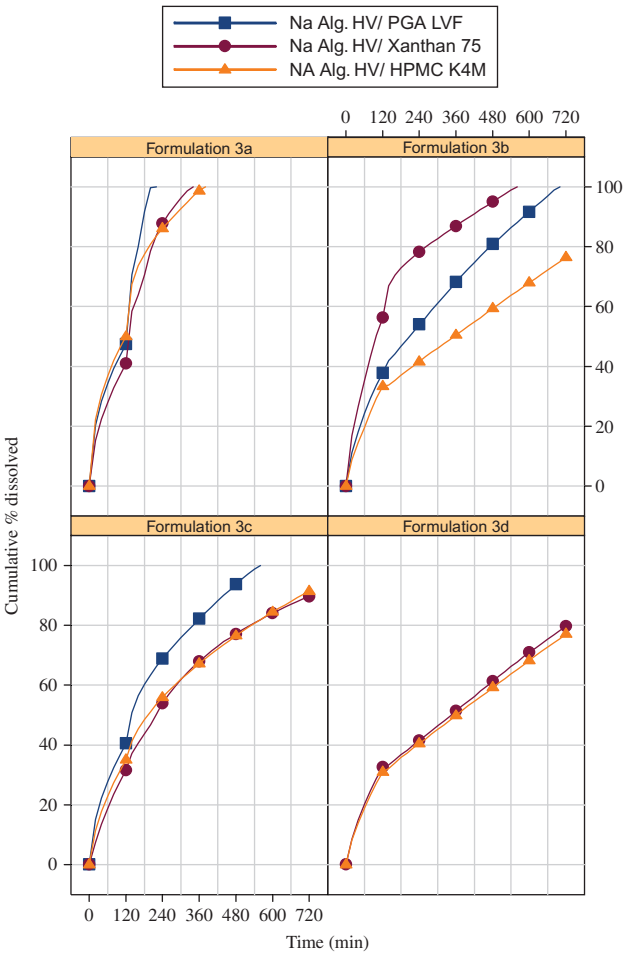

Figure 9. Dissolution profiles of Phase III propranolol HCl tablets containing sodium alginate and another gum.

Formulation set '3a' releases drug faster than desired in both cases (less than 7 hours). On the other hand, formulations sets '3b' and '3d' release drug slower than desired and also show a substantial change in release rate going from acidic to basic pH. Formulation set '3c' releases drug in about 12 hours as desired and appears to be the closest mach to the objective set. In all cases, the release burst in acidic pH, where propranolol HCl is highly soluble, appears to have been controlled. Estimated release rates for various combinations of Na Alg. HV with either xanthan 75 or HPMC K4M are shown in Figures 10 and 11, respectively.

Dissolution profiles of Na diclofenac are shown in Figure 12. With this drug, no release is observed in acidic pH, where both drug and Na Alg. are insoluble. Release

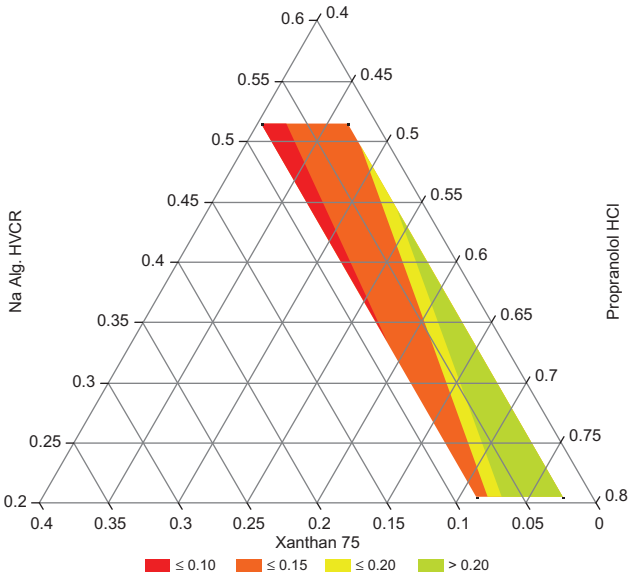

Figure 10. Estimated dissolution rate as a function of Phase III formulation component level for propranolol HCl/Na alginate HV/xanthan 75.

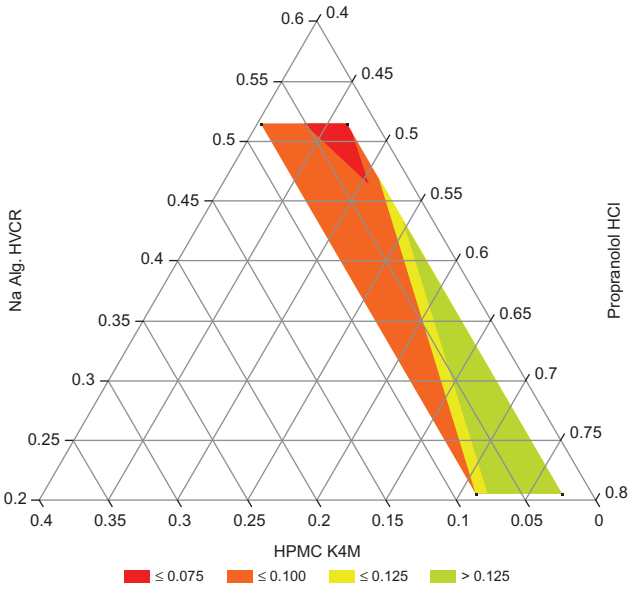

Figure 11. Estimated dissolution rate as a function of Phase III formulation component level for propranolol HCl/Na alginate HV/HPMC K4M.

in alkaline pH varies from a minimum of 8–9 hours to about 12 hours with either co-carrier. In all cases a linear release profile with an overall duration of 10–12 hours was obtained. Estimated release rates for various combinations of Na Alg. HV with either xanthan 75 or HPMC K4M are shown in Figures 13 and 14, respectively. Formulations 3d with Na Alg. and PGA mixtures for both propranolol HCl and Na diclofenac system were not prepared as such mixtures were impossible to fluidize because their low bulk density caused the materials to float at the top of the

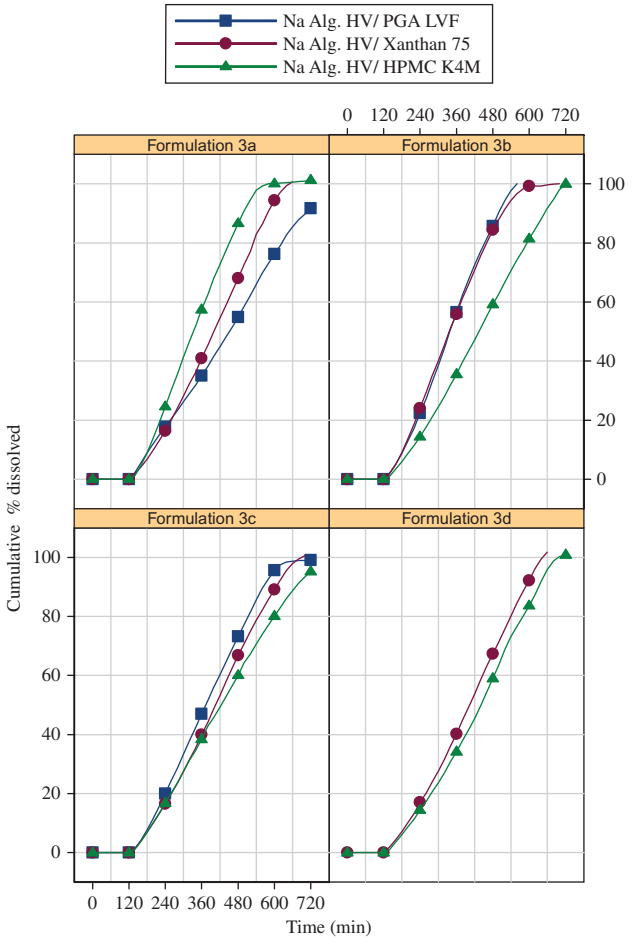

Figure 12. Dissolution profiles of Phase III diclofenac Na tablets containing sodium alginate and another gum.

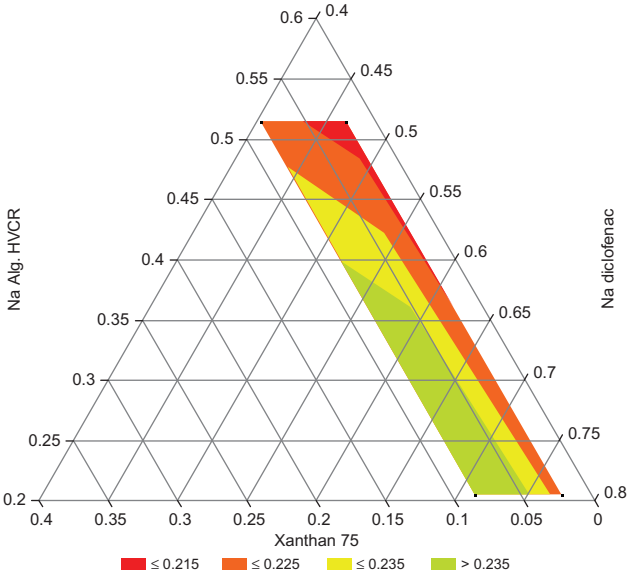

Figure 13. Estimated dissolution rate as a function of Phase III formulation component level for Na diclofenac/Na alginate HV/xanthan 75.

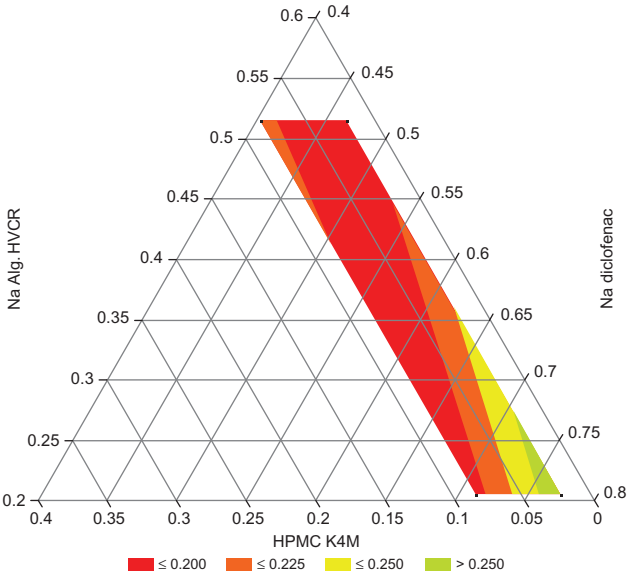

Figure 14. Estimated dissolution rate as a function of Phase III formulation component level for Na diclofenac/Na alginate HV/ HPMC K4M.

chamber at any practical air flow rate. Therefore, estimated release rate plots are not shown.

Theophylline formulations, shown in Figure 15, deliver acceptable, linear release profiles in a range of durations using alginate-containing systems. Overall drug release duration for Na Alg. containing formulations went from a minimum of about 8 hours for formulation 3ak (Keltone HV 20%/ Kelcoloid LVF 2%), to 10 hours for 3ck (Keltone HV 20%/ Kelcoloid LVF 8%) and 3bk (Keltone HV 50%/ Kelcoloid LVF 2%), to about 12 hours for formulation 3ax (Keltone HV 20 Xanthural 75 2%), 3dm (Keltone HV 50%/ Methocel K4M 8%), 3dx (Keltone HV 50%/ Xanthural 75 8%) and, finally, to over 12 hours for formulation 3dk (Keltone HV 50%/ Kelcoloid LVF 8%) and 3bx (Keltone HV 50%, Xanthural 75 2%). Estimated release rates for various combinations of Na Alg. HV with either xanthan 75 or HPMC K4M are shown in Figures 16 and 17, respectively.

As shown in Table 6, the three insoluble drug/Na Alg./co-carrier formulations behave differently as the components relative ratios change. In fact, release rate appears to be controlled by several interacting factors, such as amount and type of release slowing carriers and amount of poorly soluble drug. For example, in the case of Na Alg./ PGA release rates, as expected, the release rate increases as carrier amount decreases while the Na Alg./xanthan system shows release rate oscillations up and down as the component ratio changes, a sign of the competing release slowing effects of both carrier and poorly soluble drug. Similarly, the Na Alg./HPMC system shows a maximum release rate at the 69/20/8 formulation. The release rate decreases quickly as the amount of carrier is increased, and decreases more slowly as the amount of carrier is decreased.

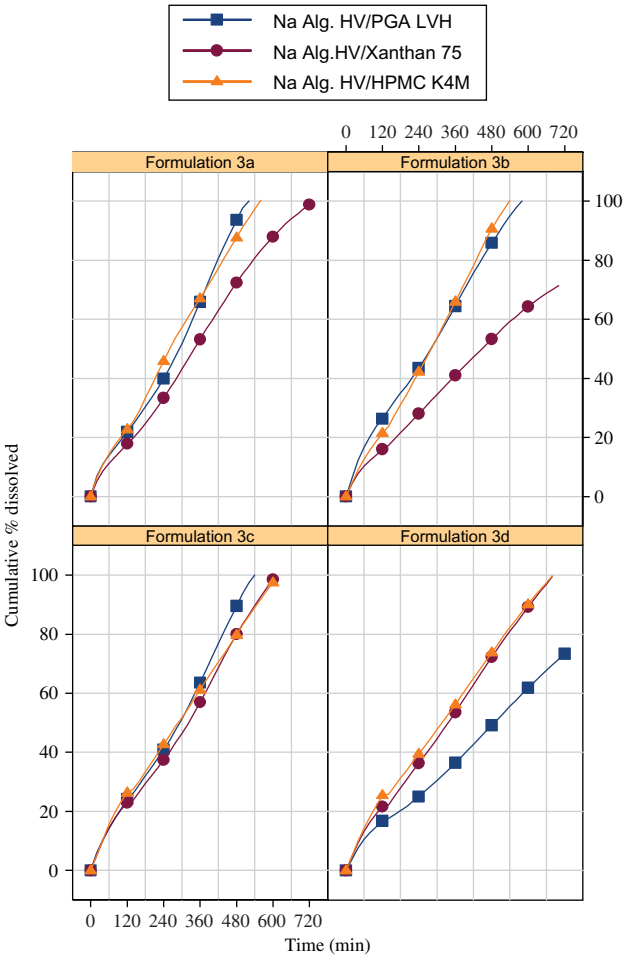

Figure 15. Dissolution profiles of Phase III theophylline tablets containing sodium alginate and another gum.

However, with all of these systems it is possible to obtain the targeted 12-hour's release, although at different relative amounts of carriers and drug levels. With the Na Alg./PGA system the desired 12 hours' release duration has been bracketed by the 45/50/2 and 39/50/8 systems, thus it is conceivable that an intermediate formulation will give the desired release duration.

Release profiles in alkaline media for all formulations were relatively linear, suggesting a release controlled by swelling/erosion, rather than diffusion. Therefore, the slope of linear fit (2 hours to 80% drug released) was estimated as the rate of dissolution for each formulation.

The unique behavior of these systems may thus allow the clever formulator to take advantage of each system's different performance to select the one that will more closely provide the desired release rate at the drug dose and total tablet weight selected.

Effect of calcium ions

Na Alg. solution properties have been shown to be affected by the presence of soluble calcium ions that can influence its hydration state and rheological properties, and thus gel layer integrity. PGA is unaffected by the

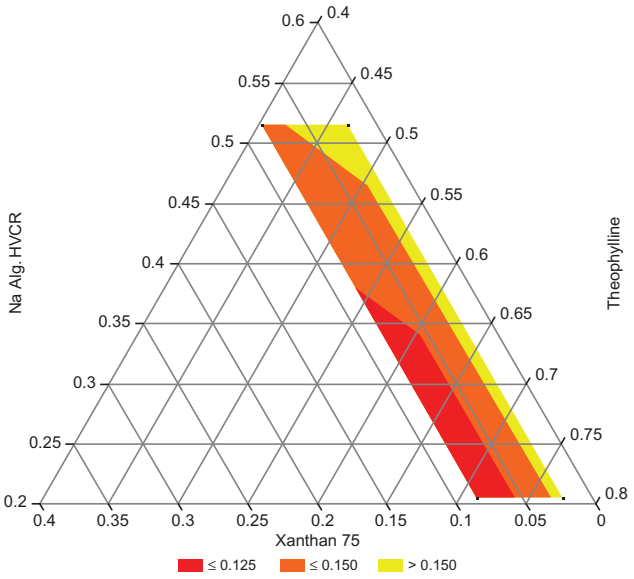

Figure 16. Estimated dissolution rate as a function of Phase III formulation component level for theophylline/Na alginate HV/xanthan 75.

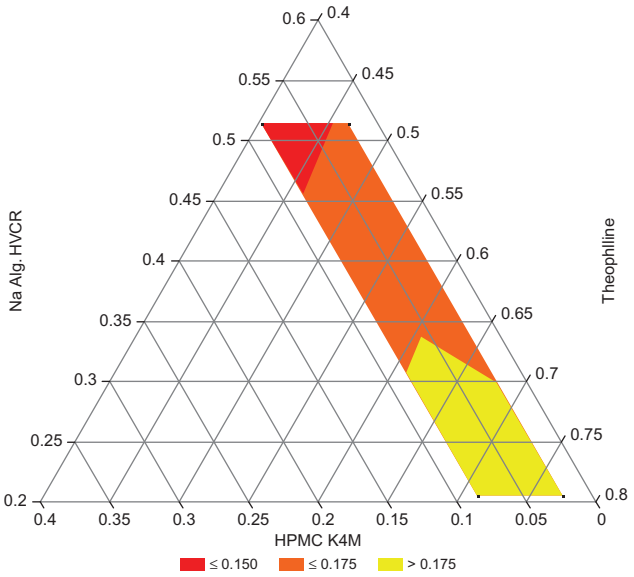

Figure 17. Estimated dissolution rate as a function of Phase III formulation component level for theophylline/Na alginate HV/HPMC K4M.

presence of calcium. Formulations containing highly water soluble ionic drugs, such as propranolol HCl, are particularly susceptible to this effect. Therefore, the propranolol HCl formulations developed have been tested, as a worst case, in the presence of Ca^{++} to ascertain how its presence affects the tablet release performances.

As shown in Figure 18, although the presence of Ca^{++} makes propranolol HCl release faster at alkaline pH's, no dose dumping occurs at concentrations lower than 0.5M, or in acidic solutions. It is very unlikely that Ca^{++} concentrations higher than 0.5M are encountered in any segment of the GI tract even after the ingestion of milk ([Ca^{++}].07M) or calcium supplements.

Stability

Alginate based formulations showed acceptable stability after storage at both room temperature and accelerated conditions (40°C, 75% RH).

In the case of Na diclofenac formulations, Figure 19, only slight changes in release profile were observed after 3 month's storage at room temperature. Formulations showed a significant but still acceptable increase in the dissolution rate following storage at accelerated conditions.

Conclusions

With appropriate combinations of Na Alg., and either PGA, xanthan gum, or hydroxypropyl methylcellulose, tablets can be made that sustain the release of three different types of drugs for up to 12 hours in alkaline pH without early drug solubilization in acidic conditions. The following conclusions can also be drawn:

- Na Alg.: Na Alg. HV is a more effective release-slowing agent than LBA.
- PGA type: LVF is a more effective release-slowing agent than HVF.
- % of PGA had a stronger effect on release duration than % of Na Alg.
- Ca^{++} concentrations likely to be encountered in the GI tract do not significantly affect the system performance.
- Alginate based formulations show acceptable stability.

As discussed previously, a 12-hour release can be obtained at different drug levels by choosing the appropriate co-carrier; this allows one to take advantage of each system's particular behavior in order to obtain the desired release duration at the drug load and desired total tablet weight.

Table 6. Release rate constants (min^{-1}) for Na alginate/ other carrier formulations (2 hours to 80% released).

	Propranolol HCl			Na Diclofenac			Theophylline		
Formulation	PGA LVF 'k'	Xanthan 75 'x'	HPMC 4KM 'm'	PGA LVF 'k'	Xanthan 75 'x'	HPMC 4KM 'm'	PGA LVF 'k'	Xanthan 75 'x'	HPMC 4KM 'm'
3a	0.78	0.40	0.30	0.17	0.22	0.27	0.23	0.158	0.185
3b	0.11	0.13	0.07	0.29	0.21	0.18	0.18	0.16	0.152
3c	0.10	0.11	0.10	0.22	0.26	0.19	0.22	0.098	0.192
3d	N/A	0.88	0.08	N/A	0.22	0.20	0.11	0.146	0.14

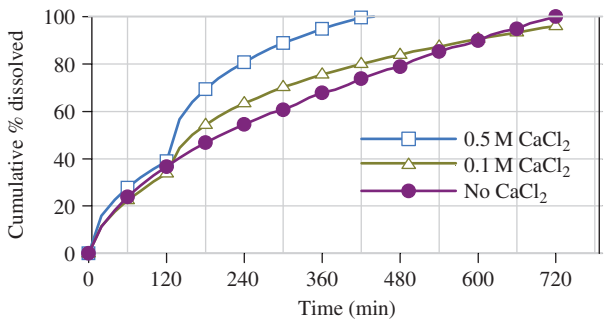

Figure 18. Release profiles of propranolol HCl in 0.1N HCl for 2 hours followed by pH 7.2 phosphate buffer in the presence of various concentrations of Ca^{++}.

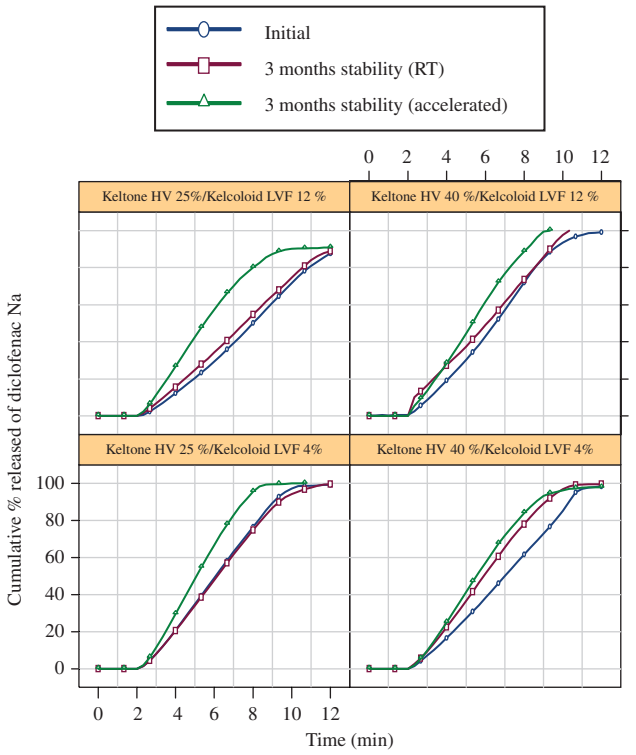

Figure 19. Release profile of Na diclofenac alginates formulations after 3 month's treatment at room temperature and accelerated conditions.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1. FMC product brochure 'Alginates for Pharmaceutical Applications' (2010) for basic information including regulatory status on alginates.
2. Murillo-Alvarez JI, Hernandez-Carmona G. (2007). Monomer composition and sequence of sodium alginate extracted at pilot plant scale from three commercially important seaweeds from Mexico. J Appl Phycol, 19:545–8.
3. Chhatbar M, Meena R, Prasad K, Siddhanta AK. (2009). Microwave assisted rapid method for hydrolysis of sodium alginate for M/G ratio determination. Carb Polym, 76:650–6.
4. McDowell RH. (1986). Properties of alginates. 5th ed. London: Kelco International.
5. Hebrard G, Hoffart V, Cardot JM, Subirade M, Alric M, Beyssac E. (2009). Investigation of coated whey protein/alginate beads as sustained release dosage form in simulated gastrointestinal environment. Drug Dev Ind Pharm, 35(9):1103–12.
6. Braccini I, Perez, S. (2001). Molecular basis of Ca2+ Induced gelation in alginates and pectins: The egg-box model revisited. Biomacromolecules, 2:1089–96.
7. McClement DJ. (2006). Non-covalent interactions between proteins and polysaccharides. Biotechnol Adv, 24:621–5.
8. Takahashi T, Takayaa K, Machida Y, Nagai T. (1990). Characterization of polyion complexes of chitosan with sodium alginate and sodium polyacrylate. Int J Pharm, 61:35–41.
9. Moustafine RI, Salachove AI, Frolova ES, Kemenova VA, Van den Mooter G. (2009). Interpolyelectrolyte complex of Eudragit® EPO with sodium alginate as potential carrier for colonic drug delivery: Monitoring of structural transformation and composition charges during swellability and release evaluating. Drug Dev Ind Pharm, 35(12):1439–51.
10. Tonnesen HH, Karlsen J. (2002). Alginate in drug delivery systems. Drug Dev Ind Pharm, 28:621–30.
11. Hodson AC, Mitchell JR, Davies MC, Melia CD. (1995). Structure and behavior in hydrophilic matrix sustained release dosage forms: 3. The influence of pH on the sustained release performances and internal gel structure of sodium alginate matrices. J Control Rel, 33:143–52.
12. Liew CV, Chan LW, Ching AL, Heng PWS. (2006). Evaluation of sodium alginate as drug release modifier in matrix tablets. Int J Pharm, 309:25–37.
13. Kubo W, Miyazaki S, Atwood D. (2003). Oral sustained delivery of paracetamol from in-situ gelling gellan and sodium alginate formulations. Int J Pharm, 258:55–64.
14. Miyazaki S, Kubo W, Attwood D. (2000). Oral sustained delivery of theophylline using in-situ gelation of sodium alginate. J Control Release, 67:275–80
15. Itoh K, Tsuruya R, Shimoyama T, Watanabe H, Miyazaki S, D'Emanuele A, et al. (2010). In-situ gelling xyloglucan/alginate liquid formulation for oral sustained drug delivery to dysphagic patients. Drug Dev Ind. Pharm, 36(4):449–55.
16. Stockwell AF, Davis SS. (1986). In-vitro evaluation of alginate gel systems. J Contr Rel, 3:167–75.
17. Gutsche S, Krause M, Kranz H. (2008). Strategies to overcome pH-dependent solubility of weakly basic drugs by using different types of alginates. Drug Dev Ind Pharm, 34:1277–84.
18. Timmins P, Delargy A.M., Howard JR, Rowlands EA. (1991). Evaluation of the granulation of a hydrophylic matrix sustained release tablet. Drug Dev Ind Pharm, 17:531–50.
19. Cekc ND, Milic JM, Savic SD, Savic MM, Jovic Z, Daniels R. (2009). Influence of the preparation procedure and chitosan type on physicochemical properties and release behavior of alginate-chitosan microparticles. Drug Dev Ind Pharm, 35(9):1092–1102.
20. DrefkoW, Moroni A. (2001). Applications of alginate mixtures as pH dependent sustained release systems. Proceedings of the 28th Symposium Control Release Bioact Mater, Abstract #6074, San Diego, CA, June 23–27.
21. Moroni A, Drefko W. (2002). Applications of alginate mixtures as pH dependent sustained release systems II. Proceedings of the 29th Symposium Control Release Bioact Mater, Abstract #577, Seoul, Korea, July 21–25.
22. Moroni A, Drefko W. (2002). pH-dependent sustained release, drug delivery compositions. US patent application 6,465,014 B1.
23. Kranz H, Guthmann C, Wagner T, Lipp R, Reinhard J. (2005). Development of a single unit extended release formulation for ZK 811 752, a weakly basic drug. Eur J Pharm Sci, 26:47–53.
24. Zhang SQ, Rahman Z, Thumma S, Repka MA, Chen GH, Li SM. (2009). Development and evaluation of a pH-dependent sustained release tablet for irritable bowel syndrome. Drug Dev Ind Pharm, 35:57–64.