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Alginate Metal Complexes and Their Application

Ghaidaa Alkhayer

Abstract

Alginate is a natural polymer that can form complexes in the presence of multi-valent metal. In this chapter, we summarized the newest alginate metal complexes application in many fields; organic synthesis, environmental and medical application. The main idea was about alginate complexes' role in the drug delivery system as a chiral excipient to reach the enantioselective release in the case of chiral drugs. We also present a case study about the ketoprofen enantioselective release investigation from alginate mixed beads with two ion metal types.

Keywords: Alginate-metal complex, ionotropic method, chiral excipient, enantioselective release, enantiomers, chiral HPLC

1. Introduction

Many publications in the last decade dealt with different applications of alginate in several fields. Alginates application is depending on its source, extraction methods, its physiological characteristics, functions, and properties [1]. Developing alginate and its derivatives were designed in various formulations for biomedical applications; such as wound dressing, tissue engineering, drug delivery, and dental application. Numerous natural polymers have been investigated for the development of different drug delivery systems [2–4]. For this use, alginate was developed and applied in drug delivery systems in form of capsules, hydrogels, tablets, nanoparticles, beads, microspheres, films, membranes, and others [4–7].

In the process, the chapter focus on the alginate metal complex preparation, application of the prepared complexes, a comparison of the release behavior between different alginate metal complex loaded with two chiral drugs (Profens). This includes the effect of bead kind on the enantioselective release (ESR) and the release mechanism due to the chiral interaction between alginate complexes and chiral drugs. Finally, the case study section discusses ketoprofen-loaded beads preparation in the presence of two ion metal types and an In-vitro ESR study for the prepared beads during the experiment time. Therefore, this chapter summarizes our current thought about alginate metal complex application as an ESR agent in addition to its role in many other fields.

2. General properties of alginate

Sodium alginate is the most common salt of alginic acid, it is a water-soluble and natural nontoxic polysaccharide extracted from marine brown algae. It contains 2

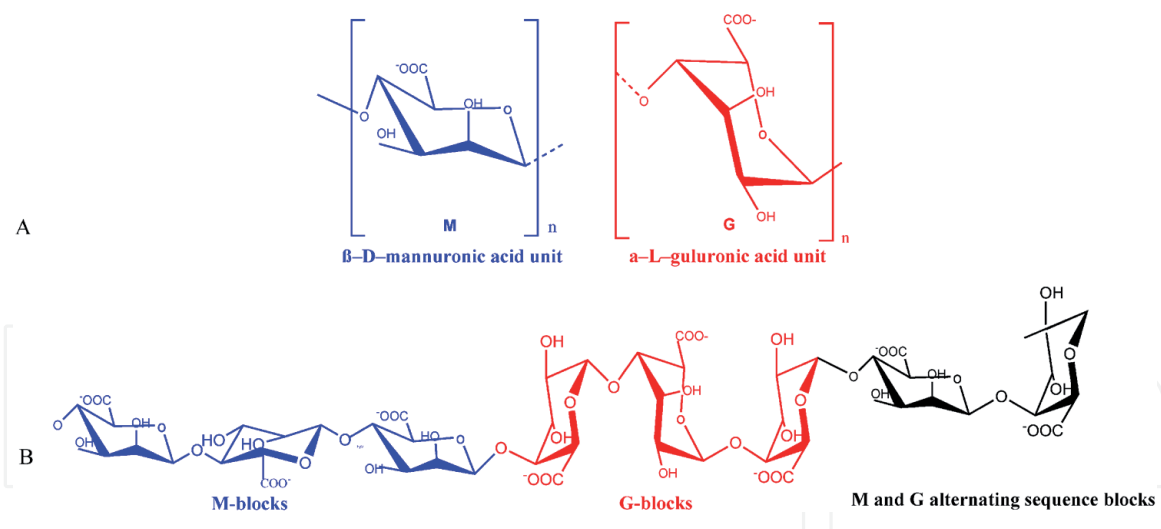


Figure 1. Chemical structure of alginate, A: alginate monomers, B: structures of G-block, M-block, and alternating block in alginate.

uronic acids, β-D-mannuronic acid (M) and α-L-guluronic acid (G) [8], and it is composed of homopolymeric blocks MM or GG, and blocks with an alternating sequence (MG blocks) [9, 10], **Figure 1**. The alginate's rigidity decreases along with the series GG > MM > MG due to its different contents of M and G; which depends on alginates' different sources. On the other hand, the divalent metal ions affinities to alginate are dependent on the M: G units' ratio.

The alginate's affinity for divalent ions increases in the order [9]:

a. Alginate from *Laminaria digitata* rich with M units:



b. Alginate from *Laminaria Hyperborea* rich with G units:



The divalent cations concentration for complex formation from the two types of seaweeds is the same and follow the order:



3. Alginate metal complexes preparation by Ionic crosslinking

The ease of beads preparation and the mild conditions of alginate metal complexes preparation make it very unique compared to other polysaccharides. The ability to ion binding is selectively linked to the guluronate units (G). The M/G ratio, G-block length, and sequence of M and G blocks are the most important factors affecting the resulted alginate complexes.

Alginate forms hydrophilic gels by interaction with multivalent metal ions [9]. Since alginate gel can easily be formed by this ionic interaction in an aqueous medium; gel beads are commonly obtained by dropping solutions of sodium alginate into solutions of ion metal chloride [11–21], **Figure 2**. Generally, calcium chloride is one of the most commonly used as an ionically cross-linked agent

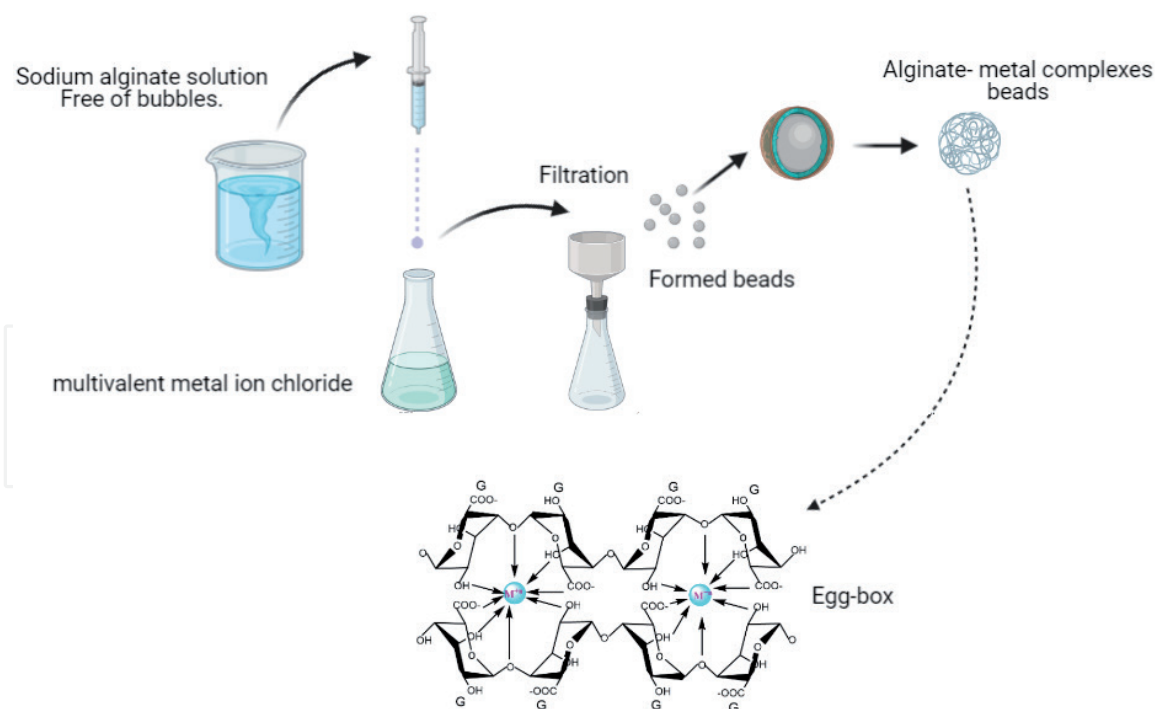


Figure 2.
Alginate gelation by ionic interaction between alginate and a multivalent cation.

to alginate. On the other hand, the gelation rate is depending on many factors, such as congealing time, temperature, and congealing sequence in the case of mixed beads (have two ion types). The formed egg-box has cavities between the G blockchains and the multivalent cation. In which the cavity fits the used cation [9].

4. Applications of alginate metal complexes

4.1 Organic synthesis field

Click chemistry is a new approach for drug industries based on the chemical reactions with high yields, and stereo-selectivity results with low reaction time. Bahsis et al [22] studied the synthesis of hydrogel catalyst; consist of sodium alginate with copper (II) for the azide-alkyne cycloaddition in the form of spherical beads. The prepared beads showed high catalytic activity for the required interaction.

Pua et al. [23] studied the synthesis of three alginate catalysts for the esterification of oleic acid. Ferric-alginate, Copper-alginate, and Nickel alginate beads were used to esterify the free fatty acid, and Fe- beads were the most successful ones.

In the work of Souza et al. [24], Alg-Cu⁺² microspheres were prepared via an ion exchange process, and it was examined as a catalyst for the synthesis of some substituted pyrazoles. The resulted product was in excellent yield, and the catalyst activity still good even after five reactions.

Qiao et al. [25] introduced a new hybrid material of Ni-alginate beads. They distinguished with their remarkable activity and stability as styrene hydrogenation catalyst with recycling ability for 20 times. On the other hand, the ease of this hybrid material preparation allows examining its hydrogenation activity of unsaturated substrates.

4.2 Environmental field

In the past decades, many researchers have been aware of the heavy metals that affected the environment, due to Pollution caused by mining and different manufacturing. The industrial wastewaters clean-up of toxic metals such as Pb, Hg, Ni, Cr, Cd, As is challenging for many research centers [26–28].

Membrane filtration, electrodeposition, ion exchange, and chemical precipitation were the most techniques involved in removing metal from aqueous contaminated solutions. However, there were disadvantages to some of these methods compared to the treatment of complex [29]. Sodium alginate is one of the rawest materials using in synthesis methods as adsorbents to remove heavy metal ions from aqueous solutions.

Gao et al. [30] reviewed the Possibility of developing the sodium alginate as adsorbents, the involved mechanisms in the adsorption process were; electrostatic interaction, ion exchange, reduction, and photocatalytic reduction. In another study, they provide a synthesized sodium alginate adsorbent which showed notable selectivity towards Pd (II). Therefore, they provide selective industrial applications to reduce the Pd (II) from effluents.

Clinoptilolite/Nickel Ferrite/Sodium Alginate Nanocomposite beads were prepared by Bayat et al. [31] via many stages to remove methylene blue dye from water. Pseudo-second-order was the best fit model for adsorption kinetic, and the optimal pH was 5 for methylene blue adsorption.

4.3 Pharmaceutical field

The development of a drug delivery system is one of the most researcher's concerns. Particularly, in the case of chiral excipients [7, 32–34], which leads to possible steric interactions between chiral excipient and the chiral drug due to enantioselective release. Thus, it could affect the pharmacological and bioavailability studies of chiral drugs. Many chiral excipients were used in several pharmaceutical formulations, and numerous researchers have studied the effect of chirality on the drug release [35] such as ketoprofen [36, 37], propranolol [38, 39], metoprolol [40], tiaprofenic acid [41], ibuprofen [42], salbutamol [43, 44] and verapamil [45] from its formulations.

Sodium alginate can interact with multivalent metal ions leading to the proposed egg-box model [14]. Thus, drug-loaded beads could be prepared by the ionotropic gelation method, this allows the study of drug release behavior.

Alginate's common role in pharmaceutical industries includes gel-forming, stabilizing, and thickening agents. Nowadays, it can play an important role in drug-controlled release [8, 10]. The most frequent use of alginate and/or its derivatives is in oral dosage forms, but the use of alginate metal complex is still under investigation in many cases, especially in the case of studying the drug release behavior. Here, we briefly describe the use of the alginate metal complex in sustained and enantioselective release for some chiral drugs.

4.3.1 Sustained release applications

Alginates were classified among the most varied biopolymers, due to their flexibility for modification. Thus, it was widely used in food, drugs, and cosmetics. This kind of polymers could be useful as an excipient for sustained and controlled drug delivery. Therefore, many researchers introduced the use of alginate in the pharmaceutical field and biomedical applications. **Table 1** summarizes some examples of the alginate metal complex's application as sustained or prolonged drug release agents.

Type of complex	Dosage form	Drug	Remarks	Ref.
Calcium alginate with acrycoat E30D	Microparticles	Ketoprofen	The ketoprofen release from the prepared microparticles was significantly prolonged	[46]
Chitosan- calcium alginate with PNI-PAAM [†]	Beeds	Indomethacin	The prepared beads were used as a pH/temperature-sensitive drug delivery system, and they could be useful for the controlled release of bioactive agents.	[47]
Calcium alginate with PNI-PAM	Semi-IPN Beads	Indomethacin	The prepared beads have the potential to be used as a pH/temperature-sensitive drug delivery system.	[48]
Calcium alginate	Beeds	Trimetazidine	Generally, beads were prepared in two methods; the drug content was higher in the sequential and simultaneous methods with increased CaCl ₂ and polymer concentration, but lower with increased drug concentration in the sequential method.	[49]
Calcium alginate with HPMC	Microbeads	Flurbiprofen	Flurbiprofen was successfully loaded with high efficiency and prolonged release from the prepared beads.	[50]
Calcium alginate	Microspheres	Ketoprofen	The prepared microspheres could be used for sustaining drug release, and the increasing of polymer concentration leads to slower drug release.	[51]
Calcium alginate	Beeds	Propranolol	The drug content increased with decreasing Ca ²⁺ concentration in the prepared beads.	[52]
Calcium alginate with chitosan-	Beeds	protein drugs	The formed beads could preserve the bioactivity of the studied drugs due to drug loading in an aqueous medium.	[53]
Calcium alginate	Beeds	5-fluorouracil	The prepared beads were designed to release the maximum drug release in the colon.	[54]
Calcium alginate	Beeds	Ketoprofen	The prepared beads showed interesting results for fast delivery to the upper gastrointestinal tract.	[55]
Carboxymethyl Chitosan with Calcium alginate	Beeds	Insulin	The pH-sensitive prepared beads were loaded with insulin at different weight ratios, and the released insulin was stable and biologically active. The beads could be useful for insulin as an oral dosage form.	[56]

Type of complex	Dosage form	Drug	Remarks	Ref.
Zink alginate	Beeds	Ketoprofen	Zn-alginate beads were prepared and loaded with ketoprofen. In vitro and in vivo release were studied, and the result showed the beads could be suitable for a delayed release of anti-inflammatory drugs.	[57]
Calcium alginate	Microspheres	Risperidone	The microspheres showed sustained drug release, and they were feasible to serve the delivery system of therapeutic agents.	[58]
Calcium alginate with carbopol	Microbeads	Clarithromycin	The release of clarithromycin from microbeads showed promising results in vitro for the eradication of <i>H. pylori</i> infection.	[59]
Calcium alginate with chitosan	Beeds	Ketoprofen	The chitosan-alginate beads showed a sufficient sustained release of ketoprofen and low gastrointestinal irritation.	[60]

*PNI-PAAM: poly(*N*-isopropylacrylamide), Semi-IPN: semi-interpenetrating, HPMC: Hydroxyl propyl methyl cellulose.

Table 1.
Some examples of alginate metal complex application as sustained release agent.

4.3.2 Enantioselective release applications

Academic researchers recognized the importance of developing chiral drugs and their pharmaceutical industry. Investigation of enantioselective release (ESR) was discussed with two main strategies: 1- chiral interactions between a chiral drug and chiral matrices, 2- key-to-lock strategy with molecular-imprinting polymers [35, 61]. Several publications discussed the ESR, but few of them dealt with the alginate metal complex as a chiral excipient. This review focuses on the alginate complexes and their role in some profens ESR.

As mentioned above, alginate metal complexes have been extensively used in the pharmaceutical field. However, the enantioselective release of chiral drugs from alginate complexes is very rare.

Our previous studies were among the first publications in this field [62–64]. Alginate metal complexes in form of beads were prepared by the ionotropic gelation method. Ketoprofen (KTP) was loaded in the first group of beads [62], and tiaprofenic acid (Tia) was loaded in the second one [63]. In all cases, the resulted beads were characterized; bead size, metal content, shrinkage ratio, drug loading, and loading efficiency were calculated. The in-vitro release was carried out in an aqueous phosphate buffer that resembles gastric medium (6.8–7.4), and the enantioselective release (ESR) was observed in many complexes [62–64].

Beads in the two groups tend to have a metal content higher than the calculated ones. These results may due to the retention of free ions in the resulted network. On the other hand, in both cases, the divalent ion metal beads show a smaller size than the beads with trivalent ones. **Figure 3** shows the drug-loaded beads (KTP and Tia) metal contents compared to blank beads.

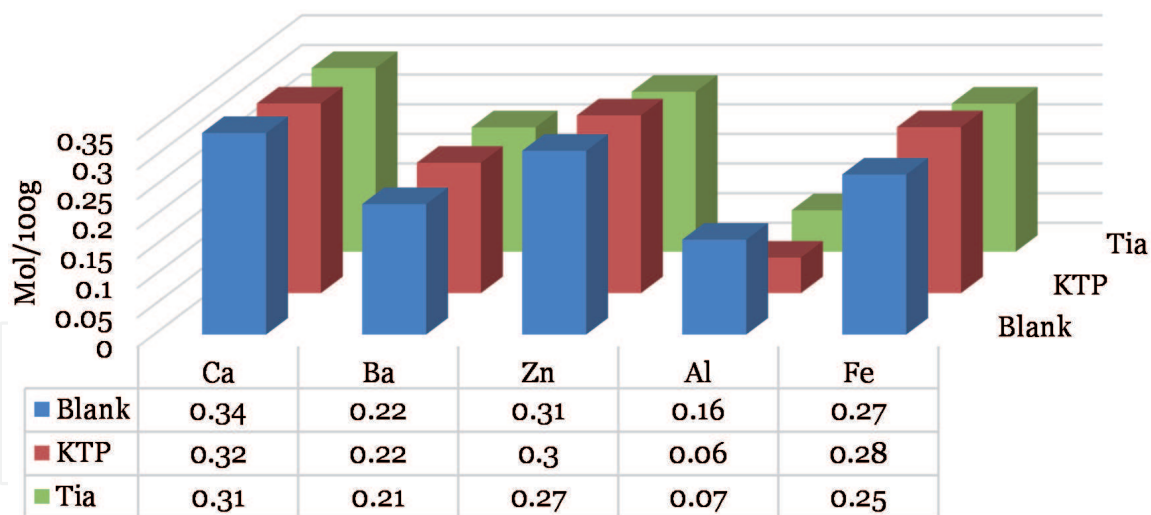


Figure 3. Comparison of metal content (mol/100 g) for blank beads (blue column), KTP loaded beads (red column), and Tia loaded beads (green column).

In order to explore the ESR result, the IR spectrum for all prepared beads types was determined at a range of 4000–400 cm^{-1} [62, 63]. There was an obvious hydrogen bonding between hydroxyl and carboxyl groups of alginates with the Tia and KTP ketone and carboxylic hydroxyl. The OH signals of KTP and Tia and the alginates' OH combines together in one signal due to hydrogen bonding interaction which could explain the ESR results. More discussion was described in detail in references [62, 63].

ESR comparison between KTP and Tia loaded beads shows a similar ESR behavior for AZnK and AZnT beads as shown in **Figure 4**. In both cases, the ESR > 1 indicating to a stronger interaction with S- enantiomer meaning more

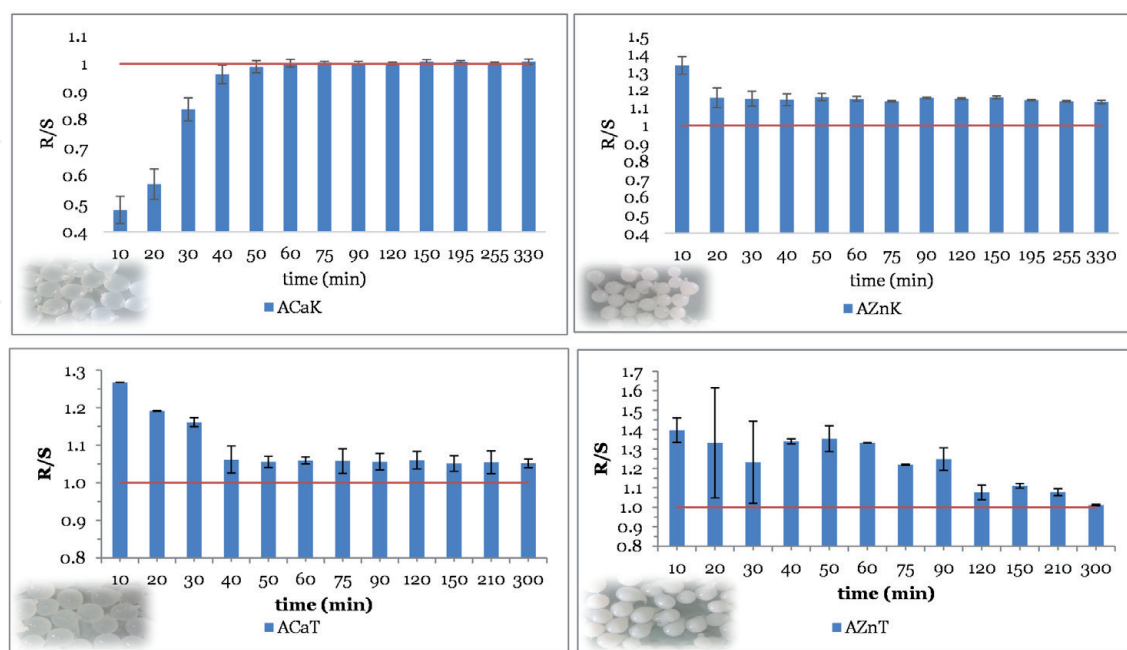


Figure 4. ESR for KTP and Tia from divalent alginate-metal complexes beads as R/S ratio (blue column), racemic release R/S = 1 (red line).

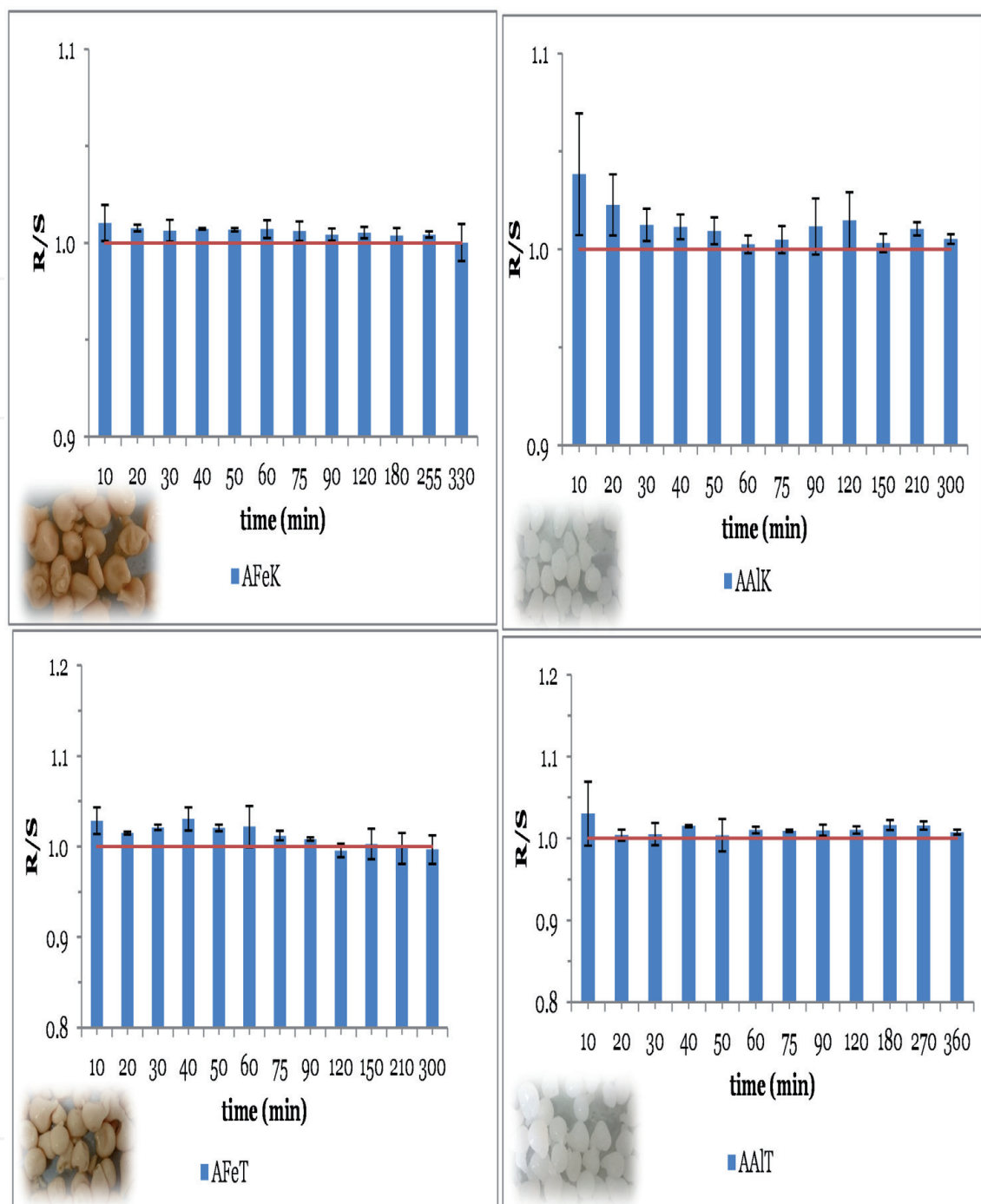
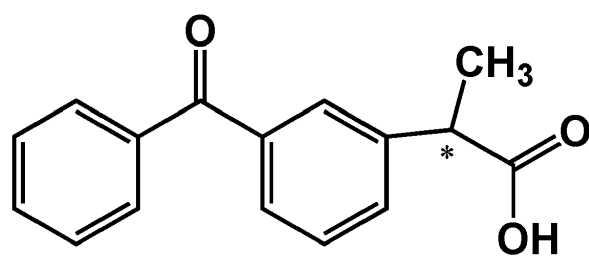


Figure 5. ESR for KTP and Tia from trivalent alginate-metal complexes beads as R/S ratio (blue column), racemic release R/S = 1 (red line).

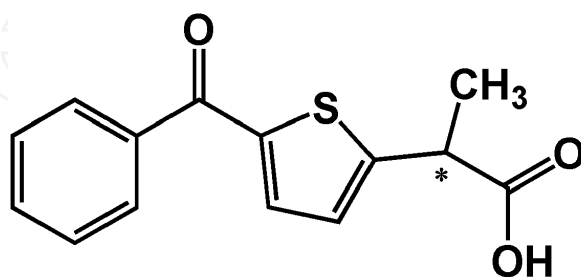
retention of S-enantiomer in contrast to R-enantiomer. **Figure 5** shows that there were not any significant differences between the trivalent loaded beads. In both cases, The ESR was almost =1 with the racemic release. However, ACa beads show an obvious ESR for both KTP and Tia but in a contrasting way. The ESR < 1 in ACaK indicating to strong chiral interaction with R- enantiomer. While ESR > 1 in ACaT indicating to strong chiral interaction with S- enantiomer. These different results in many cases due to the difference in KTP and Tia structures

Figure 6.

On the other hand, the kinetic simulation of studied beads [63, 64] shows that the best fit models for each enantiomer and the racemic mixture were the same. However, the obtained models differ depending on the type of complexation due to the resulting “egg-box” structure.



KTP



Tia

Figure 6.
Tiaprofenic acid (Tia) and ketoprofen (KTP) chemical structure, asymmetric carbon labeled with.*

5. Case study

Case study 1: Enantioselective release of ketoprofen enantiomers from alginate complexes with two ion metal type.

5.1 Drug loading and beads preparation

An ionotropic method was used to prepare alginate metal complex beads. Racemic ketoprofen was dissolved with sodium alginate in phosphate buffer solution (PBS, pH = 7.4). The final ratio was 1 to 3.75 (w/w) [62–64]. The congealing solution contained a metal chloride (3% w/v) at room temperature. Beads were commonly formed by dropping the alginate solution into the metal chloride. In this case, beads congealed with barium chloride for 3 hours. After that, the congealing continued with the other metal chloride (Ca, Zn, Al, Fe), and the total congealing time 24 hours. Beads were separated and dried at 40°C for 48 h, the method was described in detail in Refs. [62–64]. However, beads were released in PBS with pH = 7.4. 0.2 ml of aliquot was taken at different time intervals, and replenished to the release medium with fresh PBS to maintain the volume to 5 ml. the aliquot was extracted and analyzed by chiral HPLC.

Drug loading (KTP%) and loading efficiency (L%) were determined by the following equations:

$$\text{Drug loading (KTP\%)} = (W_l / W_{db}) * 100 \quad (1)$$

$$\text{Loading efficiency (L\%)} = (W_l / W_t) * 100 \quad (2)$$

Where W_l : loaded KTP weight, W_t : Initial KTP weight, and W_{db} : total dried beads weight. The shrinkage ratio was calculated using the formula:

Beads name	Initial weight		Formed beads			Dried beads		S%	
	W_{Alg} (mg)	KTP W_t (mg)	Wet beads (g)	KTP W_{res} (mg)	KTP W_l (mg)	KTP L%	W_{db} (mg)		KTP %
ABaCaK	316	83	8.490	11.21	71.8	86.5	469	15.3	57.8
ABaZnK	315	81	8.286	7.86	73.1	90.2	495	14.8	60.9
ABaAlK	312	80	10.544	3.75	76.3	95.4	558	13.7	64.7
ABaFeK	317	81	10.282	1.63	79.4	80.0	532	14.9	62.2

W_{Alg} : Initial alginate weight, W_{res} : residual KTP in congealing bath.

Table 2. Drug loading and loading efficiency results for of the prepared beads.

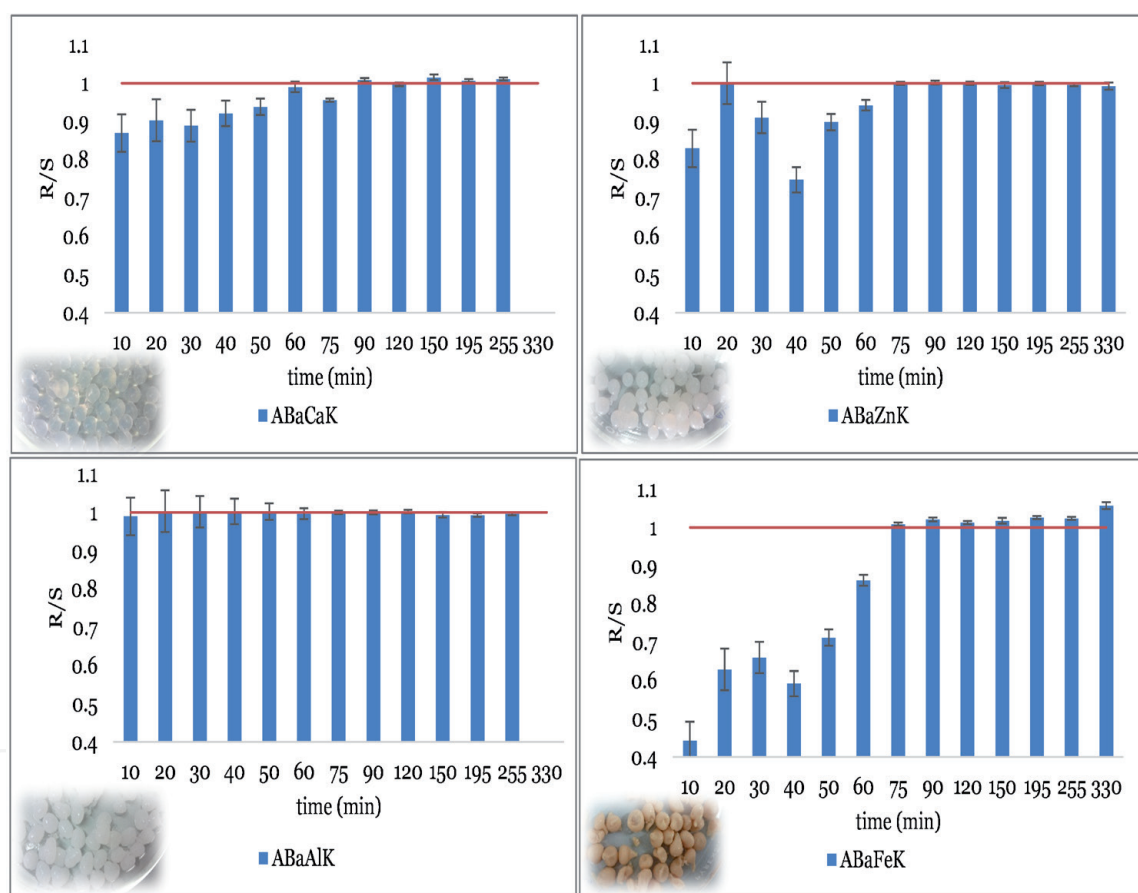


Figure 7. ESR for KTP from mixed alginate-metal complexes beads as R/S ratio (blue column), racemic release R/S = 1 (red line).

$$\text{Shrinkage ratio (S\%)} = \left(\frac{D_b - D_a}{D_b} \right) * 100 \quad (3)$$

Where, D_b and D_a are the diameters of the beads before and after drying respectively.

Table 2 shows that KTP% values varied from 13.7 for ABaAlK to 15.3 for ABaCaK, while ABaAlK and ABaFeK have the highest shrinkage ratio due to the trivalent ion metal in the formed complex.

5.2 Enantioselective release study

Chiral HPLC was used to monitor the ESR and expressed as the R/S enantiomers ratio of chromatographic area. The mobile phase consists of hexane: isopropanol: TFA (90:10:0.1 v/v%), with a 1 ml min⁻¹ flow rate. The column, Kromasil®-5-amy- coat (250 X 4.6 mm i.d) 5 mm, was equilibrated for at least 30 min, at temperature (30 C°). ESR values in **Figure 7** shows that ESR <1 for ABaCaK, ABaZnK, and ABaFeK beads within the first 60 min due to a strong interaction with R- enantiomer; which retains in the beads for more time compared to S- enantiomer. However, ESR had opposite behaviors; ESR < 1 for ABaZnK compared with AZnK result in **Figure 4**, while ABaFeK shows an obvious ESR comparing to AFeK in **Figure 5** indicating the role of the mixed congealing with Ba to alter the KTP release behavior. In fact, no significant ESR was obtained for ABaAlK and the release was practically racemic all over the experiment time. These results suggest differences in egg-box stereochemistry due to different binding strengths depending on the congealing method, ion metal type, and the complexation kind (with one or mixed metals).

6. Conclusions

Natural and biodegradable polymers were used increasingly in pharmaceutical formulations, food, and some industrial applications. This chapter has introduced various aspects of alginate metal complexes preparation and its application in organic synthesis, environmental and pharmaceutical fields as a chiral excipient. The latest case involved alginate's ability to build complexes in the presence of multivalent metal. The prepared beads were loaded with racemic profens by an ionotropic method, and the chiral interactions are assumed to affect the drug release due to alginates and profen's chirality, by an in-vitro release in the aqueous solution resembles an intestine medium (6.8–7.4), and the enantioselective release (ESR) was observed in many complexes and differ depending on the alginate-metal complexes type.

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Abbreviations

ESR	enantioselective release
KTP	Ketoprofen
Tia	Tiaprofenic acid
Alg	alginate
ACaK	alginate calcium beads loaded with KTP
ACaT	alginate calcium beads loaded with Tia
AZnK	alginate zink beads loaded with KTP
AZnT	alginate zink beads loaded with Tia

AFeK	alginate iron (III) beads loaded with KTP
AFeT	alginate iron (III) beads loaded with Tia
AAIK	alginate aluminum beads loaded with KTP
AAIT	alginate aluminum beads loaded with Tia
PBS	phosphate buffer solution

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References

- [1] Puscaselu RG, Lobiuc A, Dimian M, et al. Alginate: From food industry to biomedical applications and management of metabolic disorders. *Polymers (Basel)* 2020; 12: 1-30.
- [2] Shin DY, Park JU, Choi MH, et al. Polydeoxyribonucleotide-delivering therapeutic hydrogel for diabetic wound healing. *Sci Rep* 2020; 10: 1-15.
- [3] Kamaly N, Yameen B, Wu J, et al. Degradable controlled-release polymers and polymeric nanoparticles: Mechanisms of controlling drug release. *Chem Rev* 2016; 116: 2602-2663.
- [4] Mantha S, Pillai S, Khayambashi P, et al. Smart Hydrogels in Tissue Engineering and. *Materials (Basel)* 2019; 12: 33.
- [5] Mørch YA. *Novel alginate microcapsules for cell therapy*. 2008.
- [6] Hasnain MS, Nayak AK. *Alginate-inorganic composite particles as sustained drug delivery matrices*. Elsevier Inc. Epub ahead of print 2018. DOI: 10.1016/B978-0-12-813741-3.00003-0.
- [7] Abasalizadeh F, Moghaddam SV, Alizadeh E, et al. Alginate-based hydrogels as drug delivery vehicles in cancer treatment and their applications in wound dressing and 3D bioprinting. *J Biol Eng* 2020; 14: 1-22.
- [8] Ahmad Raus R, Wan Nawawi WMF, Nasaruddin RR. Alginate and alginate composites for biomedical applications. *Asian J Pharm Sci* 2021; 1-27.
- [9] Hasnain MS, Nayak AK. *Alginates Versatile, Versatile Polymers in Biomedical Applications and Therapeutics*. 2019. Epub ahead of print 2019. DOI: 10.1017/CBO9781107415324.004.
- [10] Lee KY, Mooney DJ. Alginate: Properties and biomedical applications. *Prog Polym Sci* 2012; 37: 106-126.
- [11] Vicini S, Mauri M, Wichert J, et al. Alginate Gelling Process: Use of Bivalent Ions Rich Microspheres. *Polym Eng Sci* 2017; 1-6.
- [12] Sun D, Liu Y, Wu H, et al. *Effects of gelling bath on the physical properties of alginate gel beads and the biological characteristics of entrapped HepG2 cells*. 2018. Epub ahead of print 2018. DOI: 10.1002/bab.1585.
- [13] Cheryl-low YL, Theam KL, Lee H V. Alginate-derived solid acid catalyst for esterification of low-cost palm fatty acid distillate. *ENERGY Convers Manag* 2015; 106: 932-940.
- [14] Mørch AA, Donati I, Strand BL, et al. Effect of Ca²⁺, Ba²⁺, and Sr²⁺ on Alginate Microbeads. *Society* 2006; 1471-1480.
- [15] Mørch YA, Qi M, Gundersen POM, et al. Binding and leakage of barium in alginate microbeads. *J Biomed Mater Res - Part A* 2012; 100 A: 2939-2947.
- [16] Yildiz A, Sensoy D, Baytokova A, et al. Preparation of sustained-release Tiaprofenic acid beads. *J Fac Plzarnz Istanblll* 2001; 34: 27-33.
- [17] Kragovi, Milan, Snežana Pašalić, Marija Marković, Marija Petrović, Blagoje Nedeljković MM and MS. Natural and Modified Zeolite—Alginate Composites. Application for Removal of Heavy Metal Cations from Contaminated Water Solutions. *Minerals* 2018; 8: 1-16.
- [18] Wang N, Liu Q, Li Y, et al. Self-crosslink assisted synthesis of 3D porous branch-like Fe₃O₄/C hybrids for high-performance lithium/sodium-ion batteries. *RSC Adv* 2017; 7: 50307-50316.
- [19] Horniblow RD, Latunde-dada GO, Harding SE, et al. The chelation of colonic luminal iron by a unique sodium

alginate for the improvement of gastrointestinal health. *Mol Nutr Food Res* 2016; 1-11.

[20] Konwar A, Chowdhury D. Property relationship of alginate and alginate-carbon dot nanocomposites with bivalent and trivalent cross-linker ions. *RSC Adv* 2015; 5: 62864-62870.

[21] Wan J, Tao T, Zhang Y, et al. Phosphate adsorption on novel hydrogel beads with interpenetrating network (IPN) structure in aqueous solutions: Kinetics, isotherms and regeneration. *RSC Adv* 2016; 6: 23233-23241.

[22] Bahsis L, Ablouh EH, Anane H, et al. Cu(ii)-alginate-based superporous hydrogel catalyst for click chemistry azide-alkyne cycloaddition type reactions in water. *RSC Adv* 2020; 10: 32821-32832.

[23] Pua FL, Looi KT, Shamala Gowri K, et al. Synthesis and characterization of different transition metal-alginate based heterogeneous catalyst for esterification reaction. *Key Eng Mater* 2016; 709: 57-60.

[24] Souza JF, De Aquino TFB, Nascimento JER. Alginate-copper microspheres as efficient and reusable heterogeneous catalysts for the one-pot synthesis of 4-organylselanyl-1: H-pyrazoles. *Catal Sci Technol* 2020; 10: 3918-3930.

[25] Qiao X, Niu L, Zhang H, et al. Controllable fabrication of a novel porous Ni-alginate hybrid material for hydrogenation. *Appl Catal B Environ* 2017; 218: 721-730.

[26] Muedi VM and KL. Environmental Contamination by Heavy Metals. In: *Intech*, pp. 115-133.

[27] Motlochová M, Slovák V, Plížingrová E, et al. Highly-efficient removal of Pb(II), Cu(II) and Cd(II) from water by novel lithium, sodium

and potassium titanate reusable microrods. *RSC Adv* 2020; 10: 3694-3704.

[28] de Oliveira Sousa Neto V, Saraiva GD, Carvalho TV, et al. *Heavy metal removal from industrial effluents using biopolymer membranes*. Elsevier Inc. Epub ahead of print 2020. DOI: 10.1016/b978-0-12-818134-8.00014-6.

[29] Gao X, Guo C, Hao J, et al. International Journal of Biological Macromolecules Adsorption of heavy metal ions by sodium alginate based adsorbent-a review and new perspectives. *Int J Biol Macromol* 2020; 164: 4423-4434.

[30] Gao X, Guo C, Hao J, et al. Selective adsorption of Pd (II) by ion-imprinted porous alginate beads: Experimental and density functional theory study. *Int J Biol Macromol* 2020; 157: 401-413.

[31] Bayat M, Javanbakht V, Esmaili J. Synthesis of zeolite/nickel ferrite/ sodium alginate bionanocomposite via a co-precipitation technique for efficient removal of water-soluble methylene blue dye. *Int J Biol Macromol* 2018; 116: 607-619.

[32] Rowe RC, Sheskey PJ, Quinn ME. *Handbook of Pharmaceutical Excipients*. Sixth edit. USA: Pharmaceutical Press and American Pharmacists Association, 2009.

[33] Christianah Adeyeye M. Use of Chiral Excipients in Formulations Containing Chiral Drugs. In: *Chirality in Drug Design and Development*. 2004. Epub ahead of print 2004. DOI: 10.1201/9780203021811.ch2.

[34] REDDY IK, MEHVA R. *Chirality in Drug Design and Development*. USA, 2004.

[35] Yu H, Yong X, Liang J, et al. Materials Established for Enantioselective Release of Chiral

Compounds. *Ind Eng Chem Res* 2016; 55: 6037-6048.

[36] Solinís MA, De La Cruz Y, Hernández RM, et al. Release of ketoprofen enantiomers from HPMC K100M matrices - Diffusion studies. *Int J Pharm* 2002; 239: 61-68.

[37] Álvarez C, Torrado JJ, Cadórniga R. Stereoselective drug release from ketoprofen and ricobendazole matrix tablets. *Chirality* 1999; 11: 611-615.

[38] Bodhibukkana C, Srichana T, Kaewnopparat S, et al. Composite membrane of bacterially-derived cellulose and molecularly imprinted polymer for use as a transdermal enantioselective controlled-release system of racemic propranolol. *J Control Release* 2006; 113: 43-56.

[39] Jantarat C, Tangthong N, Songkro S, et al. S-Propranolol imprinted polymer nanoparticle-on-microsphere composite porous cellulose membrane for the enantioselectively controlled delivery of racemic propranolol. *Int J Pharm* 2008; 349: 212-225.

[40] Guo Z, Du Y, Liu X, et al. Enantioselectively controlled release of chiral drug (metoprolol) using chiral mesoporous silica materials. *Nanotechnology*; 21. Epub ahead of print 2010. DOI: 10.1088/0957-4484/21/16/165103.

[41] Vakily M, Jama F. Human pharmacokinetics of Tiaprofenic Acid after Regular and Sustained Release Formulations: Lack of Chiral Inversion and Stereoselective Release. *J Pharm Sci* 1994; 83: 495-498.

[42] Cheng R, Liu J, Xie P, et al. Chiral, pH-sensitive polyacrylamide hydrogels: Preparation and enantio-differentiating release ability. *Polymer (Guildf)* 2015; 68: 246-252.

[43] Solinís MA, Lugará S, Calvo B, et al. Release of salbutamol sulfate

enantiomers from hydroxypropyl methylcellulose matrices. *Int J Pharm* 1998; 161: 37-43.

[44] Srichana T, Suedee R. Evaluation of stereoselective dissolution of racemic salbutamol matrices prepared with commonly used excipients and ¹H-NMR study. *Drug Dev Ind Pharm* 2001; 27: 457-464.

[45] Aubry A -F, Wainer IW. An in vitro study of the stereoselective dissolution of (rac)-verapamil from two sustained release formulations. *Chirality* 1993; 5: 84-90.

[46] Rajesh KS, Khanrah A, Biswanath S. Release of Ketoprofen from alginate microparticles containing film forming polymers. *J Sci Ind Res (India)* 2003; 62: 985-989.

[47] Shi J, Alves NM, Mano JF. Chitosan coated alginate beads containing poly(N-isopropylacrylamide) for dual-stimuli-responsive drug release. *J Biomed Mater Res - Part B Appl Biomater* 2008; 84: 595-603.

[48] Shi J, Alves NM, Mano JF. Drug release of pH/temperature-responsive calcium alginate/poly(N-isopropylacrylamide) semi-IPN beads. *Macromol Biosci* 2006; 6: 358-363.

[49] Mandal S, Senthil Kumar S, Krishnamoorthy B, et al. Development and evaluation of calcium alginate beads prepared by sequential and simultaneous methods. *Brazilian J Pharm Sci* 2010; 46: 785-793.

[50] Badarinath A V., Ravi Kumar Reddy J, Mallikarjuna Rao K, et al. Formulation and characterization of alginate microbeads of flurbiprofen by ionotropic gelation technique. *Int J ChemTech Res* 2010; 2: 361-367.

[51] Al-tahami K. Preparation, characterization, and in vitro release of ketoprofen loaded alginate

- microspheres. *Int J Appl Pharm ISSN-2014*; 6: 9-12.
- [52] Lim LY, Wan LSC. Propranolol hydrochloride binding in calcium alginate beads. *Drug Dev Ind Pharm* 1997; 23: 973-980.
- [53] Lin YH, Liang HF, Chung CK, et al. Physically crosslinked alginate/N,O-carboxymethyl chitosan hydrogels with calcium for oral delivery of protein drugs. *Biomaterials* 2005; 26: 2105-2113.
- [54] Patel H, Nagle A, Murthy R. Characterization of calcium alginate beads of 5-fluorouracil for colon delivery. *Asian J Pharm* 2008; 2: 241.
- [55] Psimadas D, Georgoulis P, Valotassiou V, et al. Design of Alginate-Based Aerogel for Nonsteroidal Anti-Inflammatory Drugs Controlled Delivery Systems Using Prilling and Supercritical-Assisted Drying. *J Pharm Sci* 2012; 102: 185-194.
- [56] Mukhopadhyay P, Sarkar K, Soam S, et al. Formulation of pH-responsive carboxymethyl chitosan and alginate beads for the oral delivery of insulin. *J Appl Polym Sci* 2013; 129: 835-845.
- [57] Cerciello A, Auriemma G, Morello S, et al. Design and in Vivo Anti-Inflammatory Effect of Ketoprofen Delayed Delivery Systems. *J Pharm Sci* 2015; 104: 3451-3458.
- [58] Al-Tahami K. Preparation of Alginate Microspheres for the Delivery of Risperidone. *Yemeni J Med Sci* 2014; 8: 5-5.
- [59] Pal R, Bhadoria APS, Ramteke S. Preparation and characterization of sodium alginate-carbopol-934P based mucoadhesive microbeads. *Der Pharm Lett* 2011; 3: 1-11.
- [60] Cheng B, Li D, Huo Q, et al. Two kinds of ketoprofen enteric gel beads (CA and CS-SA) using biopolymer alginate. *Asian J Pharm Sci* 2018; 13: 120-130.
- [61] Song L, Pan M, Zhao R, et al. Recent advances, challenges and perspectives in enantioselective release. *J Control Release* 2020; 324: 156-171.
- [62] Alkhayer G, Khudr H, Koudsi Y. Enantioselective Release Behavior of Ketoprofen Enantiomers from Alginate-metal Complexes, Monitored by Chiral HPLC. *Anal Bioanal Chem reserch* 2020; 7: 61-76.
- [63] Alkhayer G, Khudr H, Koudsi Y. Spectroscopic and chromatographic investigation of chiral interactions between tiaprofenic acid and alginate-metal-complexes. *RSC Adv* 2020; 10: 35121-35130.
- [64] Alkhayer G, Khudr H, Koudsi Y. In vitro kinetic release study of ketoprofen enantiomers from alginate metal complexes. *Futur J Pharm Sci* 2021; 7: 1-11.