

Formulation and Evaluation of Floating Alginate Beads of Diclofenac Sodium

Mohammad Abu Taher Rasel and Moynul Hasan

Department of Pharmacy, Dhaka International University, Banani, Dhaka-1213, Bangladesh

ABSTRACT: The objective of this present investigation is to develop gastroretentive sustained release alginate beads of Diclofenac sodium by the ionotropic gelation method. The floating beads were prepared by dispersing Diclofenac sodium together with CaCO_3 (as gas forming agent) into a solution of sodium alginate. The resulting solution was then extruded through a 22 gauge syringe needle into 100 ml cross-linking solution containing calcium chloride (1% w/v) plus acetic acid (10% v/v). Prepared beads were evaluated for their encapsulation efficiency, buoyancy test, FT-IR spectroscopy, scanning electron microscopy (SEM) and release behaviour. *In vivo* floating behaviour was studied by sonography. The drug entrapment efficiency was increased with the increment of polymer ratio. All of the formulations (F1 to F5) floated immediately or with a very short lag time and remained floating upto 24 hours. Rough and porous surface was observed in case of surface SEM and many large hollow pores or multiple small hollow pockets were observed in case of cross-sectional SEM of beads. *In vivo* floating behaviour of the beads was confirmed by ultrasonographic examination of a healthy male volunteer after ingestion of capsule containing floating beads. *In vitro* dissolution studies were performed for eleven hours into 900 ml 0.1N HCl (pH 1.2) using USP Apparatus II (paddle type) maintained at a temperature of 37°C and stirred at a speed of 50 rpm. The dissolution study revealed that, after eleven hours the percent of drug release for five formulations were 76.7% (F1), 73.5 % (F2), 72.2 % (F3), 70.56% (F4), and 69.1 % (F5) and all of the formulations followed zero order and Higuchi model.

Key words: Floating-alginate beads, Diclofenac sodium, Ultrasonographic examination, Scanning electron microscopy (SEM)

INTRODUCTION

The drug bioavailability of pharmaceutical dosage forms is influenced by various factors. One of which is gastric residence time (GRT).¹ The gastric emptying process from the stomach to small intestine generally lasts from a few minutes to 12 h. This variability leads to an unpredictable bioavailability of an orally administered dosage form.² Furthermore, the relatively short gastric emptying time can result in an incomplete release of drug from dosage form. Floating drug delivery system (FDDS) is one of gastroretentive dosage forms that could prolong GRT to obtain sufficient drug bioavailability.³⁻⁶ FDDS have a lower density than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.⁴

In our work, the floating drug delivery system employed calcium carbonate (CaCO_3) as a gas-forming agent dispersed in an alginate matrix. Alginate is a polysaccharide which contains varying amounts of 1,4'-linked β -D-mannuronic acid, α -L-guluronic acid residues.⁷ As biocompatible and biodegradable biopolymer, it forms a bio-adhesive and stable gel with divalent cations such as Ca^{2+} , Sr^{2+} , and Ba^{2+} .⁸ These properties have enabled wide spread use of sustained release of drugs.⁹ Alginate beads are stable in acidic media and easily depredated in alkaline media. During formation of the floating drug beads, carbonate react with acetic acid to produce carbon dioxide. The evolving gas permeates through the alginate leaving gas bubbles or pores.⁷

In our study diclofenac sodium, an acid-insoluble NSAID, was used as model drug. This drug requires multiple dosing due to its short biological

Correspondence to: Moynul Hasan
E-mail: moynul_47@yahoo.com

half life and it may lead to fluctuation in the plasma drug concentration and may also fail to release the drug at the desired amount which often results in poor patient compliance and inefficient therapy.^{10,11} Thus, in this study, an attempt has been made to prepare controlled release sodium alginate beads containing diclofenac sodium using calcium carbonate (CaCO_3) as gas forming agent. The obtained beads were evaluated for encapsulation efficiency, infrared spectroscopy, scanning electron microscopy (SEM), *in vitro* and *in vivo* floating properties and *in vitro* release behaviour.

MATERIALS AND METHODS

Materials

Diclofenac sodium and sodium alginate were obtained as gift samples from Medicon Laboratories Ltd. Calcium chloride and calcium carbonate were purchased from local market of Bangladesh. All other reagents used were analytical grade.

Table 1. Formulation design of floating alginate beads.

Formulation code	Sodium alginate (gm)	Drug (gm)	CaCO_3 (gm)	CaCl_2 solution (%)
F1	2.0	1	1.5	1
F2	2.5	1	1.5	1
F3	3.0	1	1.5	1
F4	3.5	1	1.5	1
F5	4.0	1	1.5	1

Determination of drug encapsulation efficiency. 50 mg of beads from each formulation were weighed and crushed in a mortar and pestle and the crushed material was dissolved in 100 ml of phosphate buffer at pH 7.4. This solution was mechanically agitated on shaker at 200 rpm for 2 hours. The resultant dispersions were filtered and analyzed at 276 nm using UV spectrophotometer (JASCO-V500, Kyoto, Japan). The encapsulation efficiency was determined by the following formula.¹¹

Methods

Preparations of floating alginate beads.

Sodium alginate solutions of different concentrations were prepared by dissolving required amount of alginate (Table 1) in 100 ml of deionized water under gentle agitation. Diclofenac sodium and calcium carbonate (as gas forming agent) were dispersed in alginate solution under constant stirring for uniform mixing. The dispersion was sonicated for 30 minutes to remove any air bubbles. The resultant dispersion was dropped through a 22 gauge syringe needle into 100 ml of 1% (w/v) calcium chloride solution containing 10% (v/v) acetic acid at room temperature. Then the beads formed were allowed to remain in the stirred solution for 10 min. The beads were filtered and subsequently oven-dried at 50°C for 4 hours.

Encapsulation efficiency = $(\text{AQ}/\text{TQ}) \times 100$

where AQ is the actual drug content of beads and TQ is the theoretical quantity of drug present in beads.

Buoyancy test. The obtained beads were studied for buoyancy¹² and floating time using USP Apparatus II (paddle type). One hundred beads of each batch were placed in 900 ml of 0.1 N HCl (pH 1.2) containing 0.02% w/v Tween 80 and agitated at 50 rpm, temperature was maintained at 37°C.

FT-IR study. Drug polymer interactions were studied by FT-IR spectroscopy. The infrared spectra of sodium alginate, diclofenac sodium and drug loaded beads were recorded on FT-IR (Shimadzu-

FTIR 8400S). The samples were prepared on KBr press and the spectra were recorded over the wave number range of 4,000 to 400 cm^{-1} .

Scanning electron microscopy (SEM). The surfaces and cross-section morphologies of the beads were observed using a scanning electron microscope (SEM) (JSM-6490 LA, JEOL, Tokyo, Japan) operated at an acceleration voltage of 25 kV. The beads were made conductive by sputtering thin coat of platinum under vacuum using Jeol JFC-1600 autofine coater and then the images were recorded at different magnifications.

In vitro dissolution studies. *In vitro* dissolution studies were performed for all the formulations using USP apparatus II (paddle type). An accurately weighed floating alginate beads were taken into 900 ml 0.1N HCL buffer (pH 1.2). The temperature was maintained at 37°C and stirred at a speed of 50 rpm. At 30 minutes time intervals, a 10-ml aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of plain dissolution medium kept at 37°C. The collected samples were filtered and analyzed at 276 nm using UV- visible spectrophotometer against 0.1N HCL buffer (pH 1.2) taken as blank. The release mechanism was explained with zero order and Higuchi model.

In vivo evaluation of gastric retention by ultrasonography. The *in vivo* gastric residence of the beads was studied by ultrasonographic examination. 50 mg of beads was taken in a hard gelatin capsule (o size) and this capsule was orally administered to a healthy male volunteer (height: 1.70 metre, weight: 50 kg). By maintaining the required conditions of ultrasonography, the whole abdomen was observed. The ultrasonography images were collected at 30 minutes and 3 hours after ingestion of capsule.

RESULTS AND DISCUSSION

Determination of drug encapsulation efficiency. The drug encapsulation efficiency was increased with the increment of drug to polymer ratio. In case of Formulation-1, the % of

encapsulation was 75%, where the drug to alginate ratio was 1:2. But, this was increased in F-2 to F-5 where entrapment efficiency was 80.8% to 88.9%.

Buoyancy test. Floating properties of beads were studied by determining buoyancy and time required for sinking all the beads under study. The surfactant was used in medium to simulate surface tension of human gastric juice. Beads of all Formulations floated immediately (very short lag time) and remained floating up to 24 hours.

FT-IR study. FT-IR spectra of sodium alginate (Figure 1) showed the bands around 3443, 1632, 1415 and 1039 cm^{-1} , indicating the stretching of O-H, COO^- (asymmetric), COO^- (symmetric) and C-O-C, respectively. FT-IR spectra of Formulation 3 showed (Figure 3) the characteristic absorption band of diclofenac sodium at 1505 cm^{-1} which indicated that diclofenac sodium (Figure 2) was successfully entrapped into the sodium alginate matrices and a remarkable shift to lower wave number of COO^- (asymmetric) and C-O-C stretching peaks of sodium alginate with a decrease in intensity of COO^- (asymmetric) stretching peaks. It can be described that amino groups of diclofenac could protonate in sodium alginate dispersion and then interacted with carboxyl and ether groups of alginate before cross-linking process and after crosslinking calcium ion form ionic bond and a partial covalent bond with carboxyl groups and ether groups of alginate respectively.^{11,13}

Scanning electron microscopy (SEM). Figure 4 shows the surface and cross-sectional SEM pictures of the beads. The surface of the dried beads of Formulation 3 were rough and porous (Fig. 4A and 4B). The cross-sectional morphologies of floating beads were also examined with SEM (Fig. 4C-4F). Many large hollow pores or multiple small hollow pockets were observed in the alginate matrix. The number of observed pores appears to be directly related to the amount of incorporated gas-forming agent. The precipitated drug crystals can be seen embedded in the matrix.

In vitro release kinetics. After eleven hours the percent of drug release (Figure 5) for five formulations were 76.7% (F1), 73.5 % (F2), 72.2 %

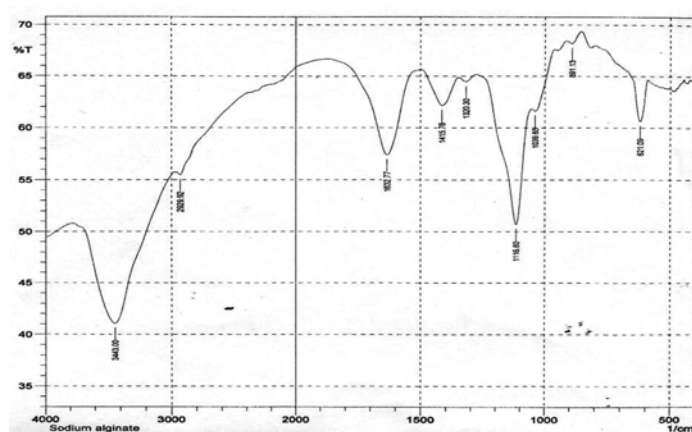


Figure 1. The FT-IR spectra of Sodium alginate.

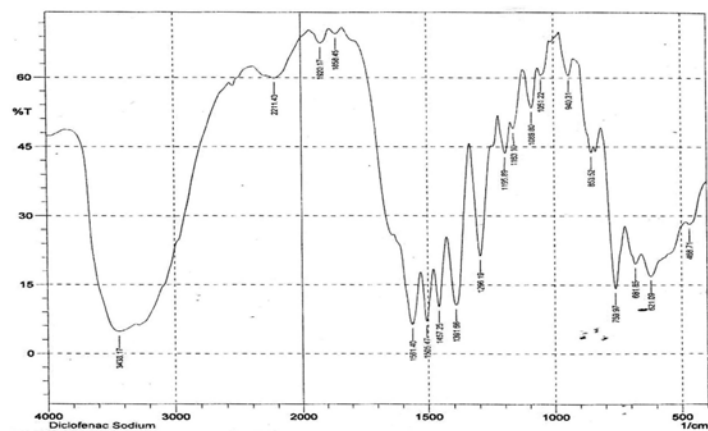


Figure 2. The FT-IR spectra of Diclofenac sodium.

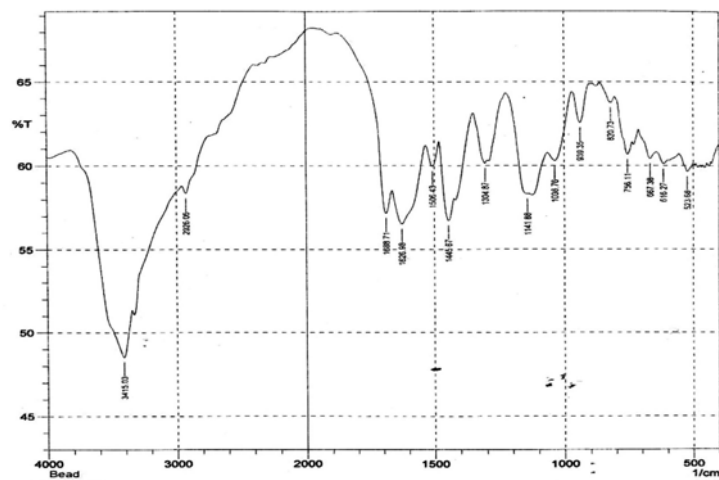


Figure 3. The FT-IR spectra of Formulation (F3).

Table 2. Correlation coefficient and release rate of Diclofenac sodium containing alginate beads.

Formulation code	Alginate : Drug	Correlation coefficient(r^2)		% of drug release after 11 hours
		Zero order	First order	
F1	2:1	0.9868	0.9806	76.7
F2	2.5:1	0.9925	0.9852	73.5
F3	3:1	0.9925	0.9852	72.7
F4	3.5:1	0.9959	0.9895	70.56
F5	4:1	0.9973	0.9914	69.1

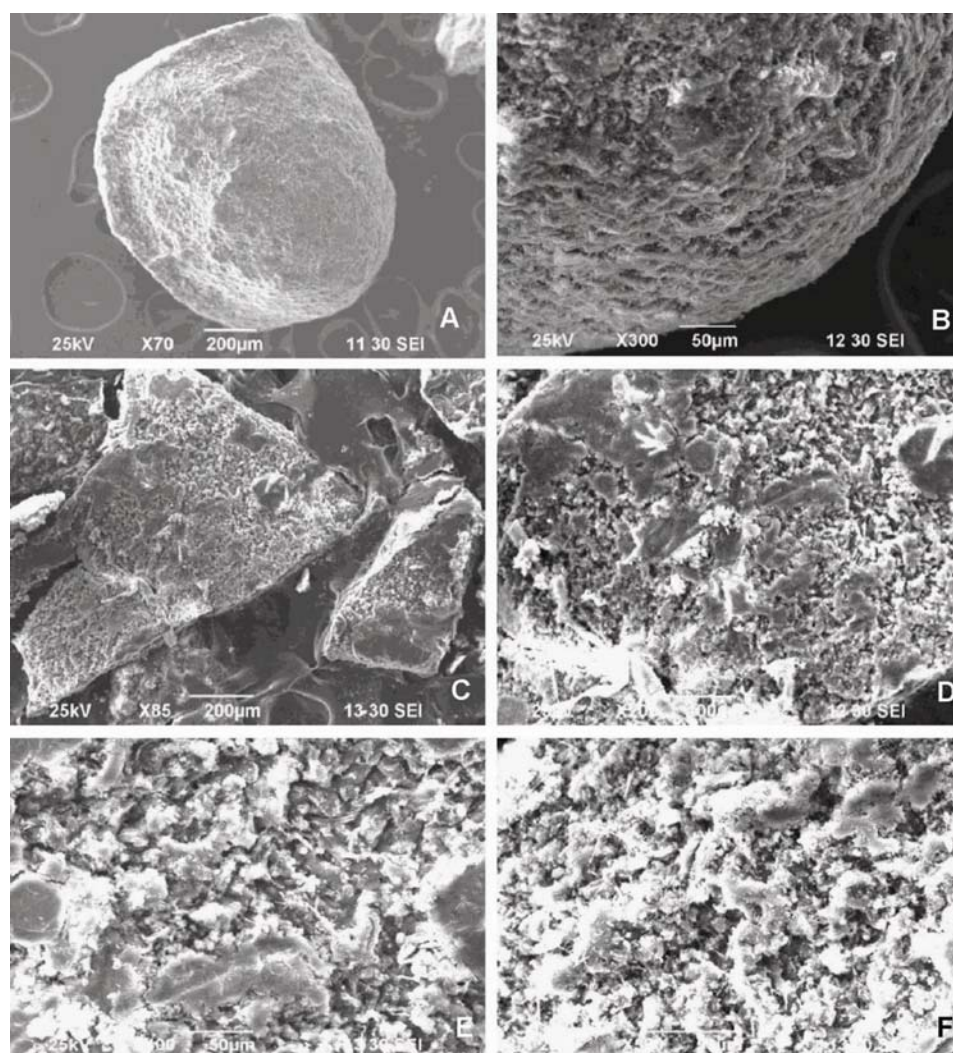


Figure 4. SEM photographs of Formulation F3, Surface morphologies (A, B) and cross-sectional morphologies (C-F).

(F3), 70.56% (F4) and 69.1 % (F5). The decrease in drug release was due to simultaneous increase in alginate amount. Because the more the amount of alginate, more would be the cross-linking between sodium alginate and calcium chloride; thus more drug

would remain entrapped and decrease the release. In the absence of gas-forming agent the release rate was very slow. CaCO_3 is present as an insoluble dispersion in neutral pH aqueous alginate solution. However in acidic media, the CaCO_3 becomes water

soluble. After studying the drug release kinetics, it was observed that all the formulation follow both zero order and Higuchi release kinetics (Table 2).

In vivo evaluation of gastric retention by ultrasonography. The prepared beads (F3) were selected for evaluation of gastric retention by ultrasonographic examination. After 30 minutes the capsule was identified and some beads seen floating in the stomach (Figure 6) and after 3 hours numerous beads were seen floating in different location of stomach (Figure 7). These images confirmed the floating and non mucoadhesion behaviour of the beads.

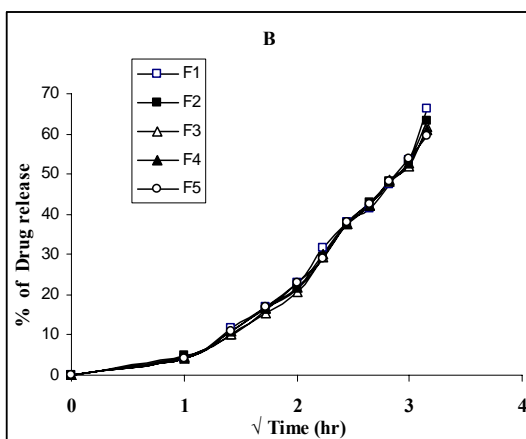
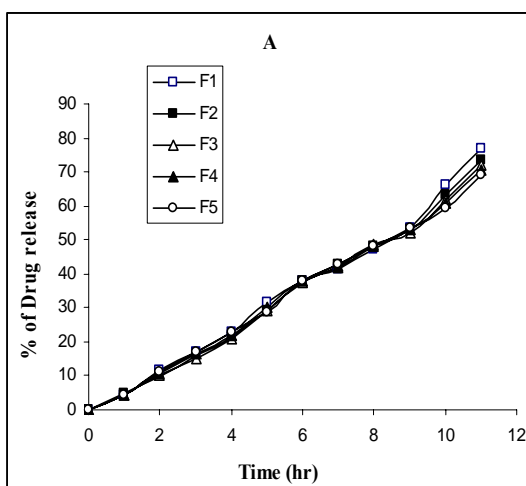


Figure 5. Zero order (A) and Higuchi release (B) of floating alginate beads Diclofenac sodium.

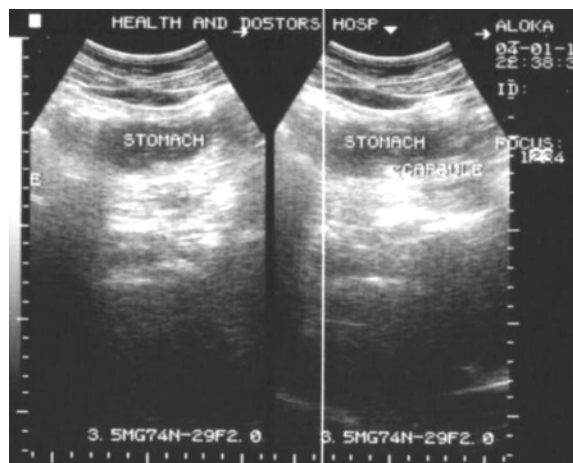


Figure 6. Ultrasonogram images of Formulation F3 at 15 minutes.

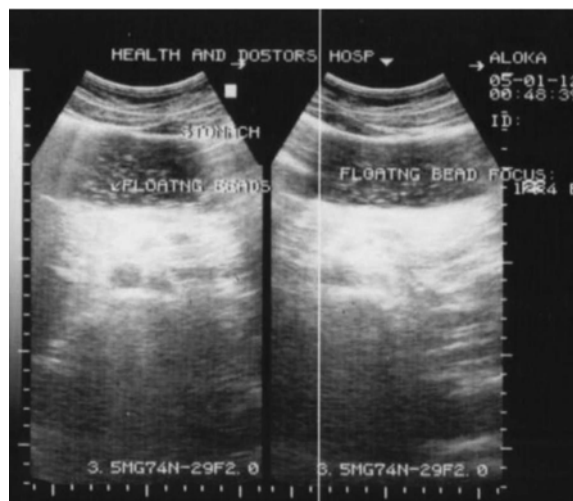


Figure 7. Ultrasonogram images of Formulation F3 at 3 hours.

ACKNOWLEDGEMENTS

The authors are thankful to the authority of Centre of Advanced Research in Sciences (CARS), University of Dhaka, for providing the facility for FT-IR study and SEM.

REFERENCES

- Desai, S. and Bolton, S. 1993. A floating controlled-release drug delivery systems: in vitro–in vivo evaluation. *Pharm. Res.* **10**, 1321-1325.
- Chueh, H.R., Zia, H. and Rhodes, C.T. 1995. Optimization of sotalol floating and bioadhesive extended release tablet formulations. *Drug Dev. Ind. Pharm.* **21**, 1725-1747.

3. Whitehead, L., Fell, J.T., Collett, J.H., Sharma, H.L. and Smith, A.M. 1998. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. *J. Control. Release.* **55**, 3-12.
4. Singh, B.N. and Kim, K.H. 2000. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, *J. Control. Release.* **63**, 235-259.
5. Arora, S., Ali, J., Ahuja, A., Khar, R.K. and S. Baboota. 2005. Floating drug delivery systems: a review. *AAPS Pharm. Sci. Technol.* **6**, E372 -E390.
6. Bardonnnet, P.L., Faivre, V., Pugh, W.J., Piffaretti J.C. and F. Falson. 2006. Gastroretentive dosage forms: overview and special case of *Helicobacter pylori*, *J. Control. Release.* **111**, 1-18.
7. Polymer Macro- and Micro-Gel Beads: Fundamentals and Applications. Amos Nussinovitch. Springer New York Dordrecht, Heidelberg, London.
8. Grant, G.T., Morris, E.R., Rees, D.A., Smith, P.J.C. and Thom, D. 1973. Biological interactions between polysaccharides and divalent cations: the egg-box model. *FEBS Lett.* **2**, 195-198.
9. Badwan, A.A., Abumaloooh, A., Sallam, E., Abukalaf, A. and Jawan, O. 1985. A sustained release drug delivery system using calcium alginate beads. *Drug Dev. Ind. Pharm.* **11**, 239-256.
10. Zhang, J.P., Wang, Q., Xie, X.L., Li, X. and Wang, A.Q. 2010. Preparation and swelling properties of pH-sensitive sodium alginate/layered double hydroxides hybrid beads for controlled release of diclofenac sodium. *J. Biomed. Mater. Res. Part B Appl Biomater.* **92**, 205-214.
11. Hua, S., Huixia Yang, H., Li, Q., Zhang, J. and Wang, A. 2012. pH-sensitive sodium alginate/calced hydrotalcite hybrid beads for controlled release of diclofenac sodium. *Drug Dev. Ind. Pharm.* **38**, 728-734
12. El-Gibaly, I. 2002. Development and in vitro evaluation of novel floating chitosan microcapsules for oral use: comparison with non floating chitosan microspheres, *Int. J. Pharm.* **249**, 7-21.
13. Pongjanyakul, T. and Puttipipatkachorn, S. 2007. Xanthan alginate composite gel beads: molecular interaction and *in vitro* characterization. *Int. J. Pharm.* **331**, 61-71.