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ORIGINAL ARTICLE

Effect of Sodium Alginate-Gelatin System on the Dissolution Behavior of Diclofenac Sodium Microparticles

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Abstract

Purpose to acheive sustained delivery of diclofenac sodium (DFS) from biopolymeric system (sodium alginate – gelatin).
Methods DFS microparticles were prepared by complex coacervation technique. DFS microparticles were formulated by using different drug and polymers ratios (drug/polymers = 1:1; 1:2 and 1:5 and alginate/gelatin = 1:2; 1:3 and 1:4). Nine (09) essays F1, F2, F3, F4, F5, F6, F7, F8 & F9 of varying concentrations of drug, sodium alginate and gelatin were prepared. DFS microparticles were examined for *in-vitro* dissolution at pH 6.8 and pH 1.2 to make out the effect of biopolymeric system on the *in-vitro* drug release. Further, DFS microparticles were characterized by Fourrier Transform Infrared spectroscopy (FTIR). The surface morphology was done by microscopic observation. For each formulation, the production yield was calculated.
Results the *in-vitro* release study indicates that microparticles formulated with 1:2 drug/polymers ratio and 1:3 alginate/gelatin ratio (F5) has shown prolonged drug release in phosphate buffered medium (pH6,8).
Conclusion: microparticles loaded with DFS prepared by complex coacervation with sodium alginate-gelatin system could be used for sustained delivery of DFS.

Keywords Diclofenac sodium. Sodium alginate. Gelatin. Microparticles. in-vitro dissolution.

Introduction

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired concentration. That is drug delivery system should deliver the drug at a rate dictated by needs of the body aver a specific period of treatment [**1]**.
The design of effective drug delivery systems has recently become an integral part of the development of new medicines. Hence, research continuously keeps on searching for ways to deliver drugs over an extended period, with a well-controlled release profile [**2**].For many decades treatments of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various.
conventional pharmaceutical dosages like tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectable as drug carriers. This type of drug delivery system is known to provide a prompt release of drug. So to achieve and maintain the drug concentration within therapeutically effective range needed for treatment, it is often essential to take this type drug delivery system several times a day which results in a significant fluctuation in drug levels. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with acceptable level of safety to the patient [**3**].
Alleviation of the problems faced in the conventional dosage forms and conventional therapy is achieved by designing as well structured controlled drug delivery system and enhances the therapeutic efficacy of the drug of choice. Maximum therapeutic efficacy can be accomplished when the drug delivered by the carrier to the target tissue in right amount in right period, in such a way that it could minimize toxicity and adverse effects [**4, 5**].

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Microencapsulation technology as a prominent multidisciplinary area has its wide impact in many fields including pharmaceutical, biotechnology, cosmetic, agriculture, food and flavor industry [**6**]. This technology has been extensively adopted for the practical applications for encapsulation of drugs [**7**, **8**, 9]. The use of microparticles for either in the form of microspheres or microcapsules for controlled release of drugs is a prospective field of interest in pharmaceutical.

Microencapsulation is a technology that applies thin polymeric coating on solids, liquid droplets, or gaseous materials in order to form these particles which can release their content under specific conditions at a specific speed [**10**].

Complex coacervation is a process used to produce microcapsules. It forms a coating capable of protecting the encapsulated active compounds [**11**, **12**]. This process consists of a spontaneous phase separation, which leads to the formation of an insoluble polymer complex (coacervate – the polymer-rich phase), and of another phase, which is poor in polymer [**13**].

Complex coacervation involves at least two substances, typically biopolymers of opposite ionic charges, in an aqueous system. The basic principle for the formation of ionic charges on biopolymers, usually a protein and a polysaccharide, is the pH change [**14**].

Proteins are positively charged below their isoelectric point and negatively charged above it. Polysaccharides with anionic carboxyl groups, in their turn, act as polyanions and, in contact with proteins, produce electrostatic complexes at pH values ranging generally from 2 to 5, depending on the type of protein [**15**, **16**]. Due to these characteristics, gelatin and sodium alginate are appropriate coating materials for microencapsulation processes [**17**].

Diclofenc sodium is a non-steroidal anti-inflammatory drug (NSAID), commonly used in the long-term therapy for rheumatoid arthritis. The biological half-life of diclofenac sodium is about 1-2 hours; therefore multiple dosing is required to maintain therapeutic drug blood level. The most frequently reported side effects of diclofenac sodium on long-term administration are gastrointestinal disturbances, peptic ulceration and gastrointestinal bleeding. Diclofenac sodium is poorly soluble in water and has acidic pH (1-3) but is rapidly soluble in alkaline pH (5-8). Hence, attempt was made to formulate a sustained release formulation with increased patient compliance and decreased signs of adverse effects [**18**].

Alginate, a natural polysaccharide found in brown algae, is a linear 1,4 linked copolymer of β-D-mannuronic acid (M) and α-L-guluronic acid (G) and has the benefit of being non-toxic [**19**]. It is used as matrix material in various formulations due to its hydrogel-forming properties [**20**].

Gelatin is a protein derived from denatured collogen that contains high levels of hydroxyproline, proline and glycine. It is useful as a thermally reversible gelling agent for encapsulation. Gelatin was selected here because of its excellent membrane-forming ability, biocompatibility, and non-toxicity. The applicability of gelatin as a hydrogel matrix is limited because of its low network rigidity. However, its physical properties can be improved through the addition of crosslinking agents. Because of its amphoteric nature, it is also an excellent candidate for cooperation with anionic polysaccharides such as alginate [**19**].

By taking the view of advantages microparticles and the drug profile of diclofenac sodium into consideration, we have decided to carry out our work on diclofenac sodium microparticles by complex coacervation method using sodium alginate and gelatin.

Materials and Methods

Materials

Diclofenac sodium (DFS) was procured as a gift sample from Pharmaceutical Industry (Algiers, Algeria). Sodium alginate and gelatin were purchased from Sigma (St. Louis, MO. USA). All others reagents (acetic acid, hydrochloric acid, potassium phosphate hydrogenate, sodium hydroxide) were of analytical grade.

Methods

Preparation of microparticles

Sodium alginate –gelatin mixture containing DFS microparticles were prepared by complex coacervation technique utilizing pH change.

Aqueous sodium alginate solution was mixed under magnetic stirring with aqueous gelatin solution prepared according to the different drug and biopolymers ratios (alginate/gelatin= 1:2; 1:3 and 1:4, drug/polymers= 1:1; 1:2 and 1:5). To this mixture, DFS was added and stirred approximately at 300 rpm to get a stable dispersion. To induce coacervation, the pH medium was adjusted to 3.5 by adding diluted acetic acid under constant magnetic stirring. The obtained samples were stored at 5°C ± 1°C overnight to promote decantation. Finally, the precipitate was dried in an oven. Nine different formulations were prepared and coded as F1, F2, F3, F4, F5, F6, F7, F8 & F9.

Production yield (PY)

The production yield of the microparticles was determined using the weight of final product after drying with respect to the initial total weight of the drug and polymers used for preparation of

microparticles. The percent production yields were calculated by the following equation to determine the efficiency of the process.

$$\text{Product yield (\%)} = \frac{Mp}{Mt} * 100 \quad (1)$$

M_p Practical mass (microparticles)
M_tTheoretical mass (drug + polymers)

Microscopic observation

The morphology of all the microparticles formulated by complex coacervation was analyzed with optical microscope (Olympus).

In vitro dissolution studies

In vitro dissolution studies of DFS alone and different formulations prepared were evaluated using USP XXIII apparatus (Vankel VK 7000). The rotation speed was 50 rpm, and the temperature was adjusted at 37°C±0.5°C. Microparticles containing DFS equivalent to 100 mg were taken in 900 ml of dissolution medium (phosphate buffer pH 6.8 or 0.1 M HCl pH 1.2). Samples were filtered through 0.45µm. An equal volume of drug free medium (5ml) were added into the in of each dissolution vessel, to maintain a constant volume of medium during the dissolution test. The percentage drug released at each time point was quantified by using UltraViolet spectrophotometer (Shimadsu) at 276 nm wavelength.

Fourier transform infrared spectroscopy (FTIR)

Attenuated Total Reflection (ATR) - FT-IR measurements were performed on the powders. The samples were placed on a wedged (Ge-ATR crystal), pressed with a force of 80 N and spectra were then recorded using a Spectrum One (Perkin-Elmer, USA). Each analysis has been conducted in frequency range between 4000 cm^{-1} and 600 cm^{-1}, at a resolution of 8cm^{-1} and with 20 scans. All measurements were performed in triplicate.

Results and Discussion

Production yield

The results showed that the production yield of the prepared DFS microparticles was found to be between 39.8 % and 98.3% so it indicates that drug : polymers ratio and alginate : gelatin ratio were significant effect on %yield (**table 1**).
Higher %yield obtained was for F9. Here it was clear that when increase the drug polymer ratio, increase the %yield. Also the %yield of microparticles was increased by increasing alginate: gelatin ratio.

Microscopic observation

The DFS microparticles prepared by complex coacervation appeared spherical and distinct from each other with different size (**Fig.1**).

Table 1 Production yield of DFS microparticles

Code	Alginate : Gelatin Ratio	DFS : Polymers ratio	%Yield
F1	1 : 2	1 : 1	39.8
F2		1 : 2	91.7
F3		1 : 5	93.9
F4	1 : 3	1 : 1	50.8
F5		1 : 2	93.4
F6		1 : 5	96.7
F7	1 : 4	1 : 1	80.2
F8		1 : 2	95.5
F9		1 : 5	98.3

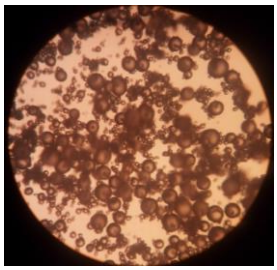


Fig.1 Micrograph of DFS microparticles (F5)

In vitro dissolution studies

The release profiles of DFS from alginate-gelatin microparticles in phosphate buffer solution pH 6.8 and in 0.1 M HCl at 37°C were determined. The cumulative percentage drug releases from the different formulations were plotted (**Fig.2**). The in-vitro dissolution profile of alginate-gelatin containing DFS microparticles in phosphate buffer showed that microparticles with higher amount of gelatin (F4, F5, F6, F7, F8 and F9) released 81 - 84% of DFS after 5 hours while microparticles prepared with low amount of gelatin (F1, F2 and F3) released only 28 - 41% of DFS.

For alginate : gelatin ratio (1 : 2), when increase the drug polymer ratio (1:1; 1:2 ; 1 :5), decrease the dissolution rate of DFS (F1, F2 and F3). Their rate dissolution was slow; it didn't exceed 28-41% over 05 hours. In contrast, the others formulations (F4, F5, F6, F7, F8 and F9) showed higher dissolution rate with a maximum about 84%. Excepted F5, these formulations reached their plateau in 3 - 4 hours. F5 showed relatively a sustained release pattern up to 5 hours with a maximum of 81% release. This formulation

correspond to alginate: gelatin ratio= 1: 3 and drug: polymers ratio = 1:2.

The results of research works of B. Umamahesh et al. (2011) [**20**] carried out on the encapsulation of diclofenac sodium by complex coacervation technique using two polymers; gelatin and HPMC, showed a prolonged release of the drug in a phosphate buffer (pH 7.4). Gelatin microspheres with gelatin / Pa mass ratio = 1: 1, showed higher drug release (89%) than those with gelatin / Pa mass ratio = 1: 3; their dissolution rate was only 67.9%. after 8 hours.

The gelatin-HPMC microspheres with gelatin-HPMC mass ratio = 1: 3 and polymer /Pa ratio = 1: 1, showed a low dissolution rate (71.4%) than those with gelatin HPMC mass ratio = 3: 1 (87.7%) [**20**].

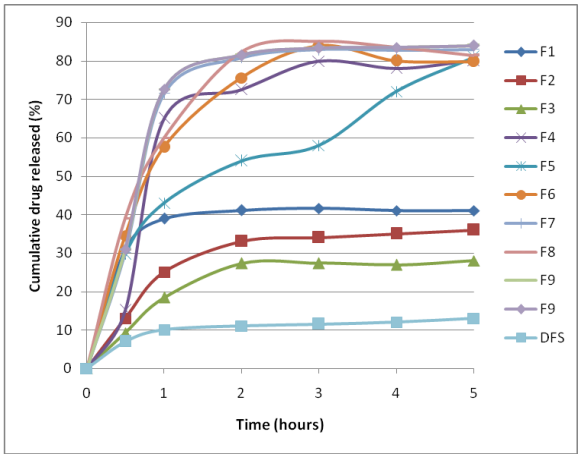


Fig.2 In vitro: drug release profile of the prepared formulations in phosphate buffer pH=6.8

The in-vitro dissolution profile of alginate-gelatin containing DFS microparticles in acidic medium showed that for alginate : gelatin ratio (1:2; 1 :3 and 1 : 4) and for all drug : polymers ratio (1:1; 1:2 ; 1 :5), the rate dissolution was very slow, it didn't exceed 13,5% of DFS over two (02) hours.

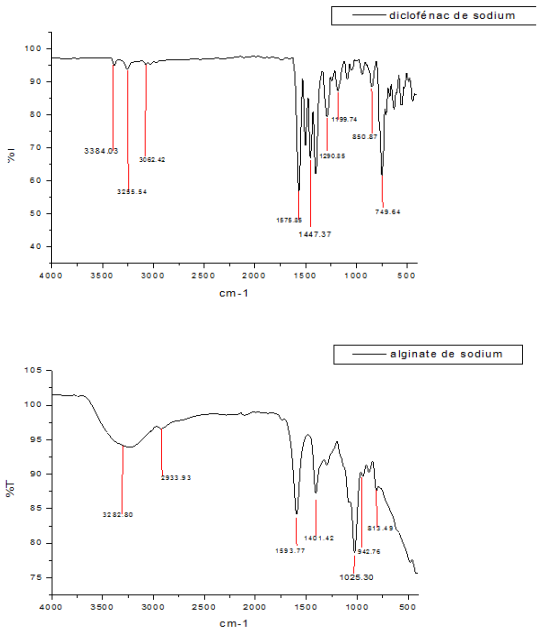
The research works of P. S. Goudanavar et al. (2010) [**21**] and Mahmoud M. Ahmed et al. (2013) [**22**] carried out on the encapsulation of diclofenac sodium by the ionotropic gelation technique with sodium alginate or/and HPMC, chitosan, showed a very slow release of DFS in an acidic dissolution medium (pH 1.2) over two (02) hours. All microparticles are almost kept intact without any swelling. The maximum dissolution rate of DFS did not exceed 5% and 16% for the studies of Goudanavar et al. (2010) and Mahmoud. M Ahmed et al. (2013) respectively. Note that during our dissolution tests, we also observed the swelling of the microparticles in the basic medium (pH 6.8), however in the acid medium (pH 1.2), this phenomenon was not observed. Indeed, the low solubility of diclofenac sodium in an acid medium plays an important role on the delayed effect of the release of DFS from microparticles [**22**]. In addition, the calcium ions in the alginate beads are completely discharged in an acidic environment and the carboxyl groups are moved to a unionized form [**21**].

Mohamed Fertah et al. 2015 [**23**] carried out a dissolution study of sodium diclofenac with calcium alginate at acid pH 2.5 and at basic pH 6.8. The release of diclofenac in the basic medium is much faster than in the acid medium because calcium alginate is more soluble in the basic medium. At alcaline pH, the dissolution rate reaches 60% after 40 min and 80% after 02 hours. However, at acid pH, the release of DFS is very slow over time; so that it only reaches 20% after 04 days [**23**]. The increase in the rate of dissolution in an alkaline medium probably results from the swelling of the microparticles and / or from the increase in the solubility of DFS.

Fourier Transform Infrared (FTIR) Spectroscopy

Compatibility study of drug and polymers were conducted by employing IR spectral studies. The IR spectrum of DFS, alginate, gelatin and its formulation is shown in **Fig.3**.

The disappearance of the peaks corresponding to the NH group (3384.03 cm^{-1} and 3255.54 cm^{-1}) of DFS and the shift of peaks observed on the IR spectrum of the different formulations: -CH of sodium alginate, NH of gelatin and = CH of DFS assume the presence of electrostatic interactions between sodium alginate, gelatin and DFS.



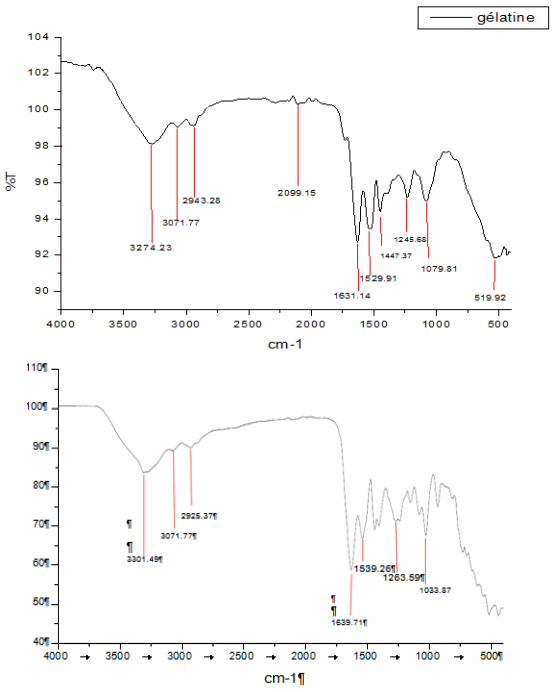


Fig.3 IR spectra of drug diclofenac sodium, sodium alginate, gelatin and DFS microparticles (F5)

Conclusion

From the experimental results, it can be concluded that the microparticles of Diclofenac Sodium formulated by complex coacervation with alginate sodium and gelatin, could be promoted for sustained delivery of DFS since the formulation (F5) with alginate : gelatin ratio = 1 : 3 and drug : polymers ratio = 1 :2 presented a controlled drug release polymers up to 5 hours.

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