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ORIGINAL ARTICLE

Formulation and Evaluation of Xanthan Gum Microspheres for the Sustained Release of Metformine Hydrochloride

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Abstract

Purpose The aim of this work was to formulate xanthan gum microspheres for the encapsulation of Metformin hydrochloride according to the process of ionotropic gelation.
Methods The obtained microparticles based on various fractions of xanthan gum (0.5-1.25) were subjected to different physic-chemical tests and a drug release study.
Results Microspheres with an average size of 206.55µm were obtained. Encapsulation efficiency has reached 93.11% at 1.25% biopolymer concentration. The swelling study showed a swelling rate reaching 29.8% in gastric medium (pH1.2) and 360% in intestinal medium (pH 6.8). The drug release studies showed a complete Metformin hydrochloride release from the beads, especially those prepared from Xanthan Gum at the concentration of 1.25%, in intestinal medium 90.00% after 8 hours. However, limited and insignificant drug release was observed within the gastric medium (32.50%).The dissolution profiles show sustained release kinetics.

Keywords Xanthan Gum. Metformin chloride. Encapsulation. Gelling. Extended-Release.

Introduction

Microencapsulation is a process by which it is possible to produce individualized microparticles using a polymeric material intended to contain an active substance in an amount of 5 to 90%. This technic is applied to several fields such as food, pharmacy, cosmetics, or other fields like catalysis. In the pharmaceutical field, encapsulation is used for different purposes, namely: the immobilisation and the protection of the active ingredient, masking some of its undesirable organoleptic proprieties like odor, or even making it possible to control and trigger the release of drugs [1], [2].

Polysaccharides represent the largest category of materials used as encapsulating agents, due to their multiple advantages, particularly: their biocompatibility and biodegradability additionally to their low toxicity and gelling capacity.

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Among these biopolymers, alginate, pectin or chitosan and xanthan gum were largely used for the encapsulation of active substances like drugs, essential oils as well as viable cells [3]-[5].

Metformine hydrochloride is an anti-diabetic active ingredient belonging to the biguanide family [6],[7], administered for the treatment of type II diabetes as a regulator of blood sugar levels, requiring several administrations per day, hence negatively influencing the good compliance with the treatment and therefore its effectiveness. These major drawbacks make metformin a good candidate for sustained release by using a suitable dosage form. As metformin hydrochloride is administered orally, it undergoes alteration as it passes through the digestive tract where the pH is very acid in addition to the presence of enzymes. Added to this, it is characterized by a short half-life of around 1.5 to 3 hours [8].

The main objective of this work was therefore to formulate an encapsulation system for metformin hydrochloride, based on xanthan gum, in order to control and modulate its release. The method used to develop this system is ionotropic gelation in the presence of aluminum chloride as a crosslinking agent. The microparticles obtained will then be subjected to several physicochemical characterizations such as the particle size measurement, the swelling rate and the release kinetics.

Materials and Methods

Materials

Metformine hydrochloride (MTH) was generously obtained as a gift from Saidal Medea (Algeria), Xanthan gum (XG) and Aluminium trichloride, Sodium hydroxide and Hydrochloric acid were purchased from sigma Aldrich (Germany). All other chemicals used were of analytical grade.

Fourier transform infrared (FTIR) analysis

The compatibility study between MTH and XG was assessed by FTIR spectroscopy with a Fourier transform infrared spectrophotometer (Shimadzu, Japan). The spectra with resolution of 4 cm^{-1}, using 10 scans were then recorded in the range of 4000–500 cm^{-1}.

Formulation and characterization of MTH microparticles

Different solutions of xanthan gum (XG), were first prepared by the dispersion of a defined mass (0.5, 0.75, 1 and 1.25%) of this polymer in an aqueous solution of NaCl (0.1M) under vigorous magnetic stirring. The obtained solutions were left to rest overnight. Subsequently, the MTH is introduced into each xanthan gum solution and the mixture thus obtained is extruded dropwise using a 10ml syringe into a 5% $AlCl_3$ solution at a rate of 0.5ml / min. The capsules formed are left in the $AlCl_3$ solution with magnetic stirring at 100 rpm for 1h.

Particles size measurement

The particles size of the obtained is measured by a digital caliper having an accuracy of 0.001mm. A random choice of three (03) series of 20 microparticles for each analysis is made. A statistical analysis of the mean and the variation coefficient are carried out on each series of analysis.

Swelling study of MTH microparticles

The swelling study was carried out in two dissolution media at pH 1.2 and pH 6.8. About 50 mg of dry microparticles are carefully introduced into 25 ml of the dissolution medium. At regular time intervals, the particles are removed from the dissolution medium and stripped of excess liquid; before being weighed using a precision analytical balance. The swelling rates (SR) are calculated by the following equation [9]:

$$SR\ (\%) = \frac{Wg - Wi}{Wi} * 100 \qquad (1)$$

Wi, wg the mass of the capsules in the initial state (at time t0) and in the swollen state (at time t), respectively.

Encapsulation efficiency

The encapsulation efficiency (EE) are calculated by indirect assay of the amount of unencapsulated Metformin hydrochloride present in the filtrate recovered after filtration of the formulation of the capsules, at a wavelength of 234 nm. They are calculated by the following formula [9]:

$$EE\ (\%) = \frac{C_n - C_0}{C_0} 100 \qquad (2)$$

C_0 Concentration of initial MTH
C_n Concentration of unencapsulated MTH.

In-vitro Release study

The in vitro dissolution study was carried out in two different simulated media pH 1.2 and pH 6.8 using a USP dissolution apparatus II, at the temperature of 37 ± 0.5 ° C and the stirring speed of 100 rpm. An accurately weighted sample of microcapsules (100 mg) was introduced into the basket and placed in the dissolution medium. At defined time intervals [10], a 10 ml sample was withdrawn and filtered with a syringe filter (0.45 µm), then replaced by the same volume with the dissolution medium. The samples obtained are then analyzed by UV-VIS (PerkinElmer Lambda 25) at the wavelength of 234nm, after suitable dilution.

Results and Discussion

Fourier transform infrared (FTIR) analysis

The FTIR analysis of XG, MTH and their mixture confirmed the compatibility of MTH with XG. The appearance of the main characteristic peaks of MTH and XG on the spectrum of the mixture (MTH/XG) was clearly noticed (Table 1), with the observation of the N-H stretching of primary amine group of metformin in the range of 3400 to 3100 cm^{-1}, along with the presence of two bands at 1038 cm^{-1} et 1166 cm^{-1} ascribed to C-N stretching as well as the N-H deformation at 1602.34 cm^{-1} [6], [8]. Characteristic absorption bands of XG were also observed at 1015.55 cm^{-1}, 1407.66 cm^{-1}, and 1732.13 cm^{-1} corresponding respectively to the elongation of the ether COC function, the CH bonds of the methyl groups, and the asymmetric vibrations of COO^- as well as the elongation of the acetyl group [11],[12].

Table 1 Major FTIR assignments of Metformin hydrochloride (MTH)

Energy (cm^{-1})	Assignements
936,79	CH_3 rock
1166,13	C-N stretch
1548,51	Asymmetric N-C-N stretch
1621,84	NH deformation
1413, 1448 and 1472	CH3 symmetric and asymmetric deformations

Particles size measurement

The capsules obtained (Figure 1) all have a homogeneous spherical shape both in the wet or dry state.

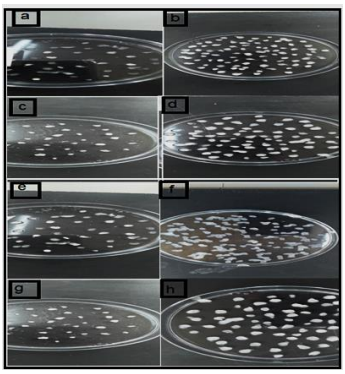

Fig.1 Shapes and appearance of the dry capsules (left) and wet (right) : (a ,b): at 0,5 % (w /v) (c, d): at 0,75 % (w /v) , (e ,f): at 1 % (w /v), (g ,h): at 1,25 % (w /v)

The Figure2 illustrates the results of particle size measurements. These results show that the size of the capsules varies from one formula to another depending on the concentration of xanthan gum. Indeed, the average diameter of the capsules for formula F1 is (1.1045 ± 0.026) mm and increases with increasing concentration of xanthan gum to finally reach a value of (2.0655 ± 0.039) mm for formula F4 composed of 1.25% xanthan gum. This can be explained by the fact that the viscosity of the initial solution increases with the increase in the concentration of biopolymer, this leads to the formation of much larger capsules during extrusion through the syringe.

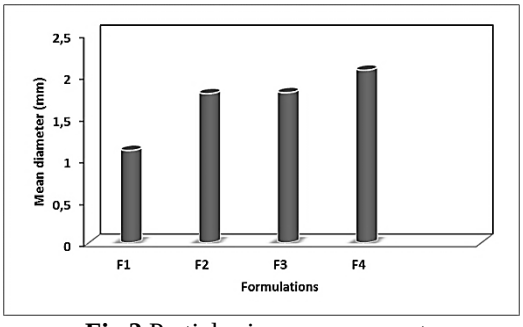

Fig.2 Particle size measurements

Swelling study

The swelling study based on gravimetry, allows establishing the kinetics of penetration of the dissolution medium in the capsules. This study establishes its absorption rate and its increase in volume over time.

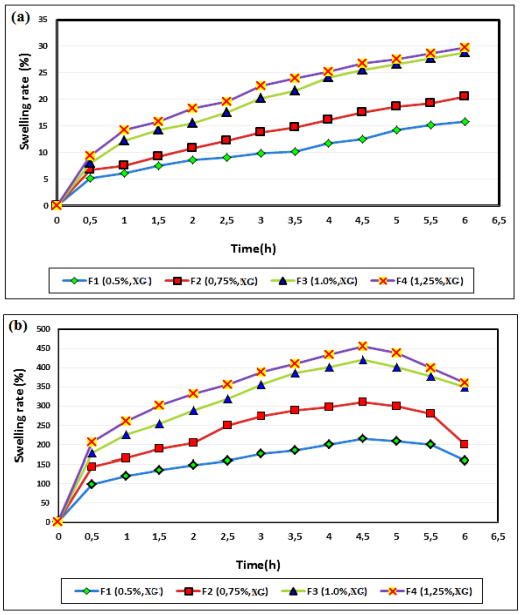

Fig.3 Swelling kinetics of MTH microparticles at ph1.2 (a) and ph 6.8 (b)

At a pH slightly below 3.5, the neutralization of the charges leads to a bringing together of the chains which insolubilize and precipitate. Below pH 3 a risk of chain hydrolysis is very likely; which explains the low swelling rates in the pH1.2 medium [13]. For pH values between 3.5 and 10, strong electrostatic repulsions between carboxylate groups tend to separate the chains from each other, producing viscous and stable solutions [13]. These data are in agreement with the high swelling rates obtained in pH 6.8 media and distilled water.

Entrapment Efficiency

Figure 4 illustrates the results of metformin entrapment efficiency (EE) as a function of XG concentration where, it is clearly shown that the rates of encapsulation of MTH vary between 76.75% and 93.11%, depending on the different formulas studied. It is also noted that the rate of encapsulation increases with the increase in the concentration of XG. Indeed, when the xanthan concentration is 0.5% (F1), the encapsulation rate is 76.75%, this rate reaches 82.27% when the xanthan gum concentration is 0.75% (F2), and passes to 86.94% in the formula F3 (1.0% XG) to and finally reaches a maximum of 93.11% at XG concentrations of 1.25% (F4).

This may be explained by the fact that the increase in the concentration of the biopolymer leads to greater

crosslinking of the latter by the Al^{+3} ions contained in the crosslinking solution. This causes the capsules to harden more quickly, preventing the active ingredient from emerging and being expelled to the outside environment. The low concentrations of xanthan gum lead to the formation of capsules whose membrane is much thinner and therefore the presence of pores on the surface allow the early release of MTH and therefore a lower rate of encapsulation.

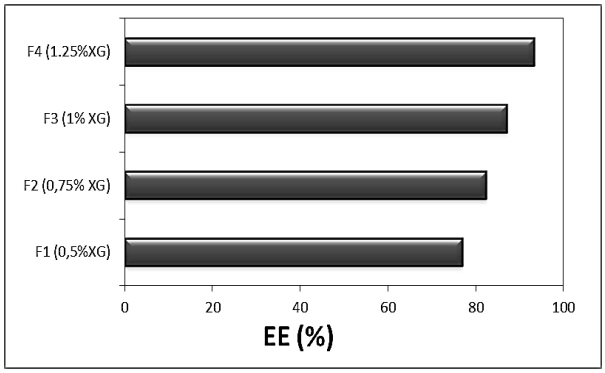

Fig.4 Entrapment efficiency of MTH microparticles

In-vitro release study

The dissolution profiles show (Figure 5) an increase in the levels of MTH released as a function of time according to a non-linear relationship.

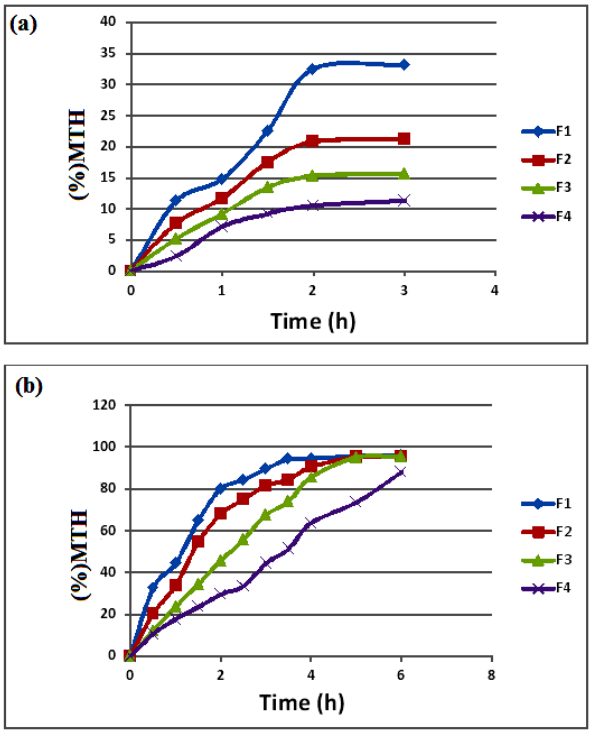

Fig. 5 In vitro drug release of MTH from xg microparticles at pH 1,2 (a) and pH 6.8 (b)

It is observed that the maximum release rates of MTH are greater in the F1 formulas (0.5 of XG %) with a value of 32.5% in 2.0 hours while this rate decreases by increasing the concentration of xanthan gum. Indeed, the release rates of Metformin hydrochloride are respectively 20.8%, 15.3%, and 10.5%, for F2 (0.75% of XG), F3 (1.0% of XG) and F4 (1.25% XG). These results indicate that with the increase in the biopolymer concentration, the hydrophilic matrix forming the capsules is more resistant to the release of Metformin hydrochloride because of the entanglement of the polysaccharide chains that becomes more and more important, hence reducing the porosity of the XG core.

The results of the in-vitro release study of Metformin as a function of time from the microcapsules of xanthan gum in the intestinal medium at pH 6.8 are shown in Figure 5. b. These dissolution profiles show a gradual and continuous release of Metformin over time. Formula F1 containing 0.5% XG releases 90.2% of MTH in 3.0 hours, while this rate decreases by increasing the concentration of xanthan gum where the release rates of MTH are 90.4% after 4 hours in formula F2 (0.75 GX%), 99.65% after 5 hours in formula F3 (1.0% GX), 95.9%, and finally a rate of 90.6% after 8.0 hours in formula F4 (1.25% GX). At pH 6.8 the gel of the membrane is in a more hydrated state, increasing the permeability and the rate of MTH released. The xanthan gum being very hydrophilic, its network will swell and the calcium ions will gradually diffuse in the external medium, which has the consequence of increasing the dimension of the meshes of the network, and consequently the diffusion of MTH, until to degrade completely, because the polymer chains become too far from each other and the hydrogel layer disintegrates [14],[15].

Conclusion

The encapsulation of Metformin hydrochloride in xanthan gum capsules has been successfully carried out using the gelation method where, micrometric particles were obtained. The encapsulation rates of MTH vary between 76.75% and 93.0%, depending on the XG concentration, reaching a maximum in formula F4 that contains 1.25% of XG (F4). Low concentrations of xanthan gum lead to the formation of capsules with a much thinner membrane and therefore allow the early release of MTH and a lower encapsulation rate. Additionally, this study showed that the swelling rate at pH 1.2 reached a maximum of 29.8%, and 360% at pH 6.8 at xanthan gum concentrations of 1.25% (F4).

The release kinetic is also influenced by increasing the biopolymer concentration. The kinetics of release of MTH is very low in the pH1.2 medium, with higher rates for formula F1 (0.5% of XG) while this rate decreases by increasing the concentration of xanthan gum.

At pH 6.8, the kinetics of release is more prolonged in time with maximum release rates of 90.0% after 8.0 hours found in formula F4 (1.25% GX).
These results indicate that with increasing biopolymer concentration, the hydrophilic matrix forming the xanthan gum capsules is more resistant to the release of Metformin hydrochloride.

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