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Research Article

HPMC-based fast-dissolving oral films with galantamine-loaded chitosan nanoparticles

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Abstract

Alzheimer's disease is a brain disorder characterized by a gradual decline in memory, thinking, behavior, and social skills. Galantamine hydrobromide is a reversible competitive cholinesterase inhibitor used for managing Alzheimer's disease. Its oral administration, however, is accompanied by unwanted side effects, such as gastrointestinal disturbances, nausea, and vomiting. These side effects could be avoided by the incorporation of galantamine into nanoparticles. The present study describes the preparation and characterization of HPMC-based fast-dissolving oral films with galantamine-loaded chitosan nanoparticles. Galantamine-loaded chitosan nanoparticles were prepared using the ionotropic gelation method. High values for loading efficiency were established. DLS was used to evaluate the particle size and the Z-potential. The polymer used in this study for the preparation of the fast-dissolving oral films was HPMC, and PEG 400 was used as a plasticizer. The quality of the prepared films was evaluated based on the following criteria: flexibility, spreading ability, adhesiveness, non-sticky and easily peeled, and appearance. The thickness, folding endurance, and disintegration times of the prepared films were determined. In vitro dissolution studies were conducted in order to establish the drug release rate from the films.

Keywords

galantamine hydrobromide, hydroxypropyl methylcellulose, fast-dissolving oral films, chitosan nanoparticles, Alzheimer`s disease

Introduction

Alzheimer's disease (AD) is a brain disorder characterized by a gradual decline in memory, thinking, behavior, and social skills. AD patients' number is expected to reach 152 million by 2050 (Breijyeh and Karaman 2020). Presently, there is no remedy for Alzheimer's disease, but only therapies that improve the symptoms (Livingston et al. 2020; Yiannopoulou and Papageorgiou 2020). The drugs that are used to reduce the symptoms and improve the quality of life of the patients are called cholinesterase inhibitors.

Galantamine hydrobromide (Gal) is a reversible competitive cholinesterase inhibitor used for managing AD. It has been found that it increases receptor sensitivity towards acetylcholine and slows down plaque formation and behavioral decline (Bhattacharya et al. 2014; Dineley et al. 2015). The oral administration of Gal, however, is accompanied by unwanted side effects, such as gastrointestinal disturbances, nausea, and vomiting (Inglis 2002). These side effects could be avoided by the incorporation of Gal into nanoparticles.

Chitosan is one of the frequently studied polymers for the preparation of nanoparticles used for the delivery of various medicinal substances (Liu et al. 2018; Jin et al. 2021). The growing interest in biomedical applications of chitosan is due to its properties, namely biocompatibility,

low toxicity, low immunogenicity, and antibacterial activity. Chitosan-based nanoparticles are biodegradable yet stable carriers for drug delivery to the central nervous system. Furthermore, chitosan nanoparticles can be easily prepared by the ionic gelation method. Except for the preparation of nanoparticles, chitosan is one of the polymers used for the fabrication of fast-dissolving oral films. It is preferred for its mucoadhesive property due to the electrostatic interactions between positively charged chitosan and negatively charged mucous membrane. Besides, chitosan increases the permeability of drugs through the oral mucosa. These characteristics of chitosan are advantageous for increasing the bioavailability of the drugs (Qin et al. 2019).

Fast-dissolving oral films are an innovative drug delivery system designed to disintegrate and absorb rapidly on contact with the oral mucosa. Unlike traditional tablets or capsules, fast-dissolving oral films do not require chewing or the presence of water for administration, making them more convenient for patients (Bala et al. 2013). They provide rapid absorption and immediate bioavailability of drugs due to the intense blood flow and permeability of the oral cavity mucosa, which is greater than that of the skin (Siddiqui et al. 2011). Fast-dissolving oral films are useful in geriatric and pediatric patients with conditions associated with vomiting and diarrhea as a local anesthetic for oral ulcers or toothaches. Fast-dissolving oral films overcome the main disadvantages of rapidly disintegrating tablets, related to their fragility and fear of choking, and can also be used by patients with schizophrenia and dysphasia (Nikunj et al. 2011). Fast-dissolving oral films typically consist of various components, including hydrophilic polymers, plasticizers, sweeteners, and colorants. Polymers play an important role in the preparation of fast-dissolving oral films. Hydrophilic polymers are mainly used so that the film can quickly and easily dissolve in the oral cavity in order for the drug to be delivered into the systemic circulation when it comes into contact with the saliva in the oral cavity. Film-forming polymers can be used alone or in combination to achieve desired film properties. The mechanical properties of the films depend on the amount and type of polymer in the composition. Both synthetic and natural polymers are used to prepare fast-dissolving oral films.

In recent years, intensively studied are chitosan, sodium alginate, cellulose derivatives, polyethylene oxide, and polyacrylic acid (Doseva et al. 2002; Dimitrov et al. 2004). Different methods are applied for the preparation of fast-dissolving oral films, such as the solvent casting method, semisolid casting method, hot melt extrusion, solid dispersion extrusion, rolling method, and lately, new fabrication methods such as 3D printing technology (Ilieva et al. 2023; Dimitrov et al. 2023), electrospinning method (Qin et al. 2019), etc.

The aim of the present study was to prepare and characterize HPMC-based fast-dissolving oral films with galantamine-loaded chitosan nanoparticles.

Materials and methods

Materials

Hydroxypropyl methylcellulose (HPMC), maltodextrin, and PEG 400 were purchased from Labimex Ltd. (Sofia, Bulgaria). Galantamine hydrobromide (Gal) was supplied from Sopharma AD (Sofia, Bulgaria). Chitosan and tripolyphosphate pentasodium (TPP) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Glacial acetic acid was supplied by Labimex Ltd. (Sofia, Bulgaria).

Preparation of galantamine-loaded chitosan nanoparticles

Galantamine-loaded chitosan nanoparticles were prepared according to a previously optimized procedure (Georgieva et al. 2023): chitosan (1.25 mg/mL) and gal (0.35 mg/mL) were dissolved in a 1% (v/v) acetic acid solution under vigorous stirring for a period of 24 h. Afterwards, a solution of TPP (0.75 mg/mL) was added dropwise with stirring for 30 min. The resulting solution was left overnight at room temperature until the formation of the particles, then stored in a refrigerator.

Loading efficiency (%)

The loading efficiency (LE%) was determined by centrifugation. The Gal-loaded nanoparticles were separated from the solution by ultracentrifugation (Beckman OptimaTM LE-80 K Ultracentrifuge, GMI, Ramsey, MN, USA) at 14 000 rpm for 40 min. The amount of non-incorporated Gal in the supernatant was determined at 288 nm using a Hewlett-Packard 8452 A Diode Array spectrophotometer (Walldorf, Germany). The LE (%) was calculated using the following equation:

$$\text{LE}\,(\%) = \frac{\text{total amount of Gal}\,(\text{g}) - \text{non incorporated Gal}\,(\text{g})}{\text{total amount of Gal}\,(\text{g})} \times 100$$

Characterization of galantamine-loaded chitosan nanoparticles

The nanoparticles were characterized by dynamic light scattering (DLS) in order to study their size and by measuring the Z-potential to investigate their stability. The nanoparticle solution was subjected to DLS analysis with a Zetasizer Nano ZS apparatus (Malvern Instruments, Worcestershire, UK). The device consists of a 632-nm HeNe gas laser and an optical detector. Three measurements were made at a temperature of 25 °C.

Preparation of HPMC-based fast-dissolving oral films with galantamine-loaded chitosan nanoparticles

The films consisted of a film-forming polymer (HPMC), a film modifier (maltodextrin), and a plasticizer (PEG 400),

and were prepared by the solvent casting method (Bala et al. 2013). HPMC was dispersed in hot, distilled water in a beaker and allowed to swell. Maltodextrin and PEG 400 were then added to the swollen polymer, and the solution was left in the refrigerator until the HPMC was completely dissolved (for a period of 12 h to 24 h), with the system being stirred at given time intervals to accelerate the dissolution. Four solutions were prepared with different concentrations of the compounds. Then, each of these four solutions was mixed with the solution containing the nanoparticles. The resulting polymer solutions (F1, F2, F3, and F4) were poured into clean and dry silicone molds with an area of 10 cm2. The films were dried in a dryer (Aeromatic, Germany) at 40 °C for 24 h. After drying, the films were carefully removed from the molds and stored in a desiccator at room temperature. The composition of the different formulations is presented in Table 1.

Table 1. Composition of the prepared formulations.

Formulation	F1	F2	F3	F4
Components				
Gal (%)	0.05	0.05	0.05	0.05
Chitosan (%)	0.18	0.18	0.18	0.18
TPP (%)	0.04	0.04	0.04	0.04
HPMC (%)	3	9	15	21
Maltodextrin (%)	2	7	12	17
PEG 400 (%)	0.34	1	1.7	2.4

Study of the quality of the prepared films

The quality of the prepared films was evaluated based on the following criteria: flexibility, spreading ability, adhesiveness, non-sticky and easily peeled, and appearance. The appearance of the films was checked by visual inspection, determining the homogeneity and texture by touching.

Thickness

Thickness was measured at five different locations on each film using a micrometer. The test was performed in triplicate (Bhyan et al. 2011).

Folding endurance

To determine the folding endurance, a strip is cut from the film and is repeatedly folded in the same place until it breaks. The number of times the film is folded in the same place without breaking represents the folding endurance value.

Disintegration time

Disintegration time is the time (in seconds) required for the film to break on contact with water or saliva. The determination is carried out by placing the film in a Petri dish and dropping 2 mL of distilled water onto it. The time when the film breaks or disintegrates into small fragments is noted.

In vitro dissolution studies

The study was conducted using a shaking water bath (IKASH-B20, Staufen, Germany). The tests were carried out at a shaking speed of 50 rpm and a temperature maintained at 37 ± 0.5 °C in 100 mL of distilled water. At certain time intervals, 2 mL of samples were taken for analysis. After each sampling, the volume was restored with 2 mL of distilled water. The amount of released galantamine was determined by UV spectroscopy (absorbance at 288 nm) using a Hewlett-Packard 8452 A Diode Array spectrophotometer. The percentage of galantamine released was calculated using the data obtained from the study.

Results and discussion

Preparation of galantamine-loaded chitosan nanoparticles

Gal-loaded chitosan NPs were prepared using the ionotropic gelation method. TPP was used as a cross-linking agent. Chitosan interacts with the oppositely charged TPP, thus leading to the formation of the particles. An advantage of the method is that it does not use any harmful organic solvents and is carried out at room temperature, which helps effectively preserve the bioactivity of the drug during incorporation into the particles.

Loading efficiency (%)

The results obtained from the study showed high values for the LE (%), namely 69%. This indicates that the method used is suitable for incorporating water-soluble drugs into chitosan particles.

Characterization of galantamine-loaded chitosan nanoparticles

DLS was used to evaluate the particle size and the Z-potential. It was found that the average size of the obtained particles was 260 nm, and the Z-potential values were 58 mV. These results showed that the particles obtained were nanosized and stable.

Preparation of HPMC-based fast-dissolving oral films with galantamine-loaded chitosan nanoparticles

Since the use of orally dispersible films relies on their disintegration in the saliva in order to achieve the desired effect, the final film must necessarily be water-soluble. This requires the use of a water-soluble polymer with a low molecular weight and excellent film-forming capacity (Kulkarni et al. 2010). The polymer used in this study was HPMC, and PEG 400 was used as a plasticizer. Maltodextrin was included in the composition in order to improve the flexibility and reduce the cracking of the films (Chapdelaine et al. 2002).

Study of the quality of the prepared films

The quality of the prepared films was evaluated based on the following criteria: flexibility, spreading ability, adhesiveness, non-sticky and easily peeled, and appearance. The visual inspection confirmed successfully obtaining good-quality films. They were elastic, did not stick to the molds, and were easily peeled without cracking. The films were characterized by different homogeneity, as can be seen from Fig. 1. It was established that increasing the concentration of HPMC led to a decrease in the homogeneity of the prepared films.

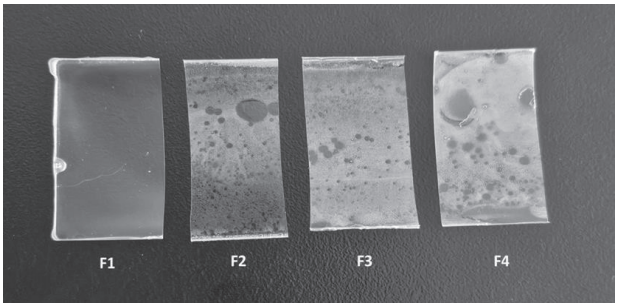

Figure 1. Image of the different films.

Thickness

From the data presented in Fig. 2, it is evident that increasing the concentration of HPMC led to an increase in the film thickness, which varied from 0.30 to 0.47 mm.

Folding endurance

The folding endurance value takes into account the film's ability to withstand tearing; the higher the folding endurance value, the less likely the film is to crack easily. The folding endurance of the films was determined by repeatedly folding a small strip of each film in the same place until it broke. The folding endurance of films ranged from 22 ± 0.24 to 50 ± 1.21, as given in Fig. 3. As can be seen from the results presented, formulation F1 was characterized by the highest value of folding endurance, although it had the lowest concentration of HPMC and the lowest thickness. This was probably due to the fact that this formulation had the highest ratio of chitosan to HPMC, which granted flexibility to the film, which in turn led to an increase in folding endurance. This fact has also been established by other scientific groups that used chitosan as a component in the composition of orally dispersible films, which led to an increase in flexibility and tensile strength (Cardelle-Cobas et al. 2015; AnjiReddy and Karpagam 2017). Formulations F2, F3, and F4 showed a lowering of the folding endurance from 40 to 22.

This was due to two factors, namely: a decrease in the ratio chitosan/HPMC, which led to a decrease in the flexibility of the films; and, on the other hand, an increase in the concentration of HPMC led to an increase in the thickness of the films, which negatively affected their flexibility.

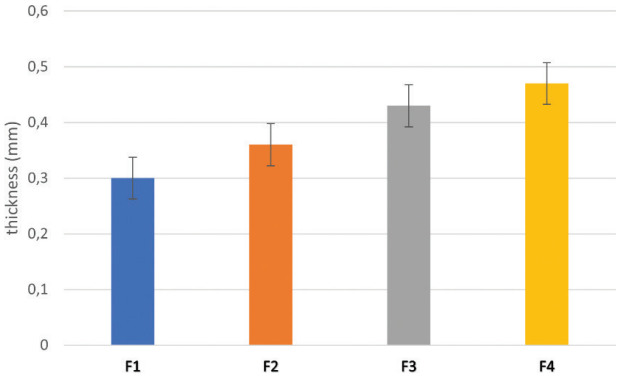

Figure 2. Thickness of the different formulations.

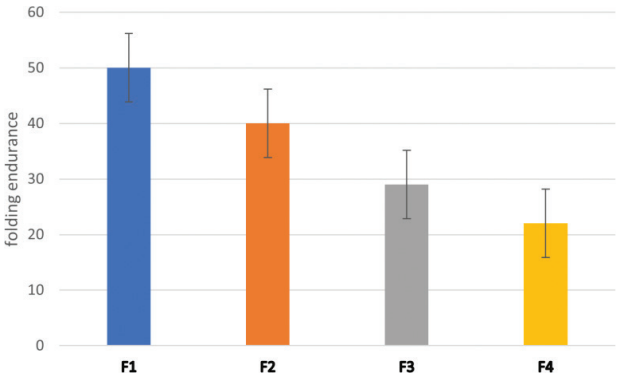

Figure 3. Folding endurance of the prepared films.

Disintegration time

Disintegration time is a critical parameter that plays an important role in the release and subsequent absorption of the drug across biological membranes. The rapid disintegration of orally dispersible films is important to ensure the rapid obtaining of smaller fragments, resulting in the largest possible surface area (Elkordy et al. 2013). The prepared formulations showed variation in disintegration times; the results are presented in Fig. 4. It is evident from the data that all the formulations showed fast disintegration times ranging from 15 to 60 sec. The research conducted showed that the concentration of HPMC had a major effect on the disintegration time. Increasing the polymer concentration resulted in a significant increase in the disintegration time.

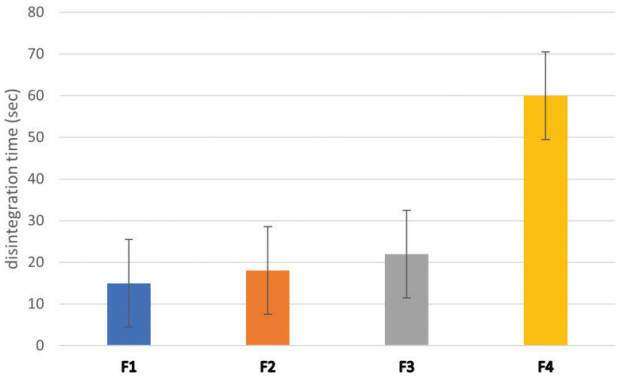

Figure 4. Disintegration time of the different formulations.

In vitro dissolution studies

The results obtained from the in vitro dissolution studies are presented in Fig. 5. From the data obtained from the study, it can be seen that the different films released a different amount of the incorporated galantamine within 9 minutes. When comparing the different formulations, it is evident that the fastest release of the loaded galantamine was observed from the film with the lowest concentration of HPMC (F1), and the drug release rate decreased as the concentration of HPMC increased. These results are expected given the disintegration times of the different films.

Based on the research conducted, it can be concluded that F1 has potential as a drug delivery system in cases where a rapid effect is desired.

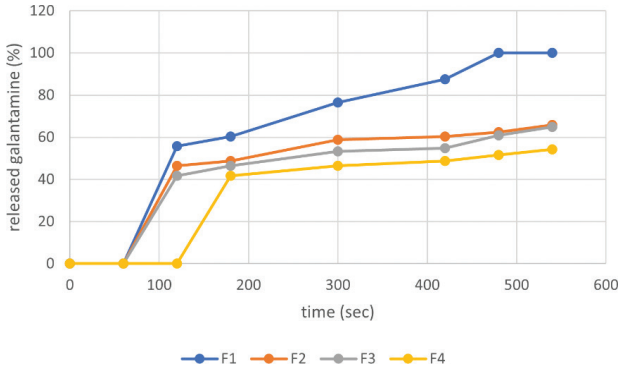

Figure 5. In vitro galantamine release from the different films in distilled water at 37 °C.

Conclusions

The present study describes the preparation and characterization of HPMC-based fast-dissolving oral films with galantamine-loaded chitosan nanoparticles. Galantamine-loaded chitosan nanoparticles were prepared using the ionotropic gelation method. High values for the loading efficiency were established, namely 69%. DLS was used to evaluate the particle size and the Z-potential. It was found that the average size of the obtained particles was 260 nm, and the Z-potential values were 58 mV. The films were prepared by the solvent casting method, and the polymer used in this study was HPMC, and PEG 400 was used as a plasticizer. The visual inspection confirmed successfully obtaining good-quality films. The films were characterized by different homogeneities, as it was established that increasing the concentration of HPMC led to a decrease in the homogeneity of the prepared films. The thickness, folding endurance, and disintegration times of the prepared films were also determined. It was established that increasing the concentration of HPMC led to an increase in the film thickness. The values of the folding endurance varied, as formulation F1 showed the highest folding endurance, while formulation F4 was characterized by the lowest folding endurance. This was due to the fact that the decrease in the ratio of chitosan to HPMC led to a decrease in the flexibility of the films, and the increase in the concentration of HPMC led to an increase in the thickness of the films, which negatively affected their flexibility. All the formulations showed fast disintegration times ranging from 15 to 60 sec. The research conducted showed that the concentration of HPMC had a major effect on the disintegration time. Increasing the polymer concentration resulted in a significant increase in the disintegration time. The in vitro dissolution studies confirmed that the different films released a different amount of the incorporated galantamine within 9 minutes. The fastest release of the loaded galantamine was observed from the film with the lowest concentration of HPMC (F1), and the drug release rate decreased as the concentration of HPMC increased. Based on the research conducted, it can be concluded that F1 has potential as a drug delivery system in cases where a rapid effect is desired.

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