Original Article

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Preparation and Evaluation of Carbamazepine Particles Loaded in Mucoadhesive Film for Treatment of Trigeminal Neuralgia

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Abstract

The trigeminal nerve is the largest craniofacial nerve, responsible for detecting sensory stimuli originating from the cranial and facial areas. Trigeminal neuralgia is a common form of craniofacial neuropathic pain that causes one of the most severe pain episodes a person can endure. The pain attacks would impact quality of life and mental health of patients. Carbamazepine and oxcarbazepine are recommended as first-line treatments to control pain in patients with trigeminal neuralgia. Oral administration of the mentioned drugs requires higher doses and as a result, higher risk of side effects due to the metabolic processes. Local mucosal drug delivery might be a proper alternative for oral systemic therapy in order to localize the treatment and reduce the side effects. The goal of this study was to develop an oral film containing particles of carbamazepine for treatment of trigeminal neuralgia. Particles were prepared by solvent evaporation method using chloroform and dichloromethane as organic solvents and ethyl cellulose and hydroxypropyl methylcellulose as coating polymers. The optimized particle contained equal weight ratios of polymers and was prepared using chloroform. The particles released about 70% of carbamazepine content within an hour. Optimized particles were loaded in an oral film containing 5% acacia, 10% gelatin as the film-forming polymers, and 1% glycerol and 10% PEG 400 as plasticizers. Satisfactory results were obtained from evaluation of physical characteristics of carbamazepine loaded film including: peak load was equal to 1506 mN, average thickness was 0.49 ± 0.003 mm and average weight was 1.53 ± 0.005 g. Film was completely dissolved in water. Also, release of the pure and coated drug from the optimized film was about 55% and 30%, respectively within 1 hour and about 42% and 80%, respectively after 2 hours. These preliminary results indicate that polymeric film containing particles can be a potentially successful system for delivery of carbamazepine to the oral mucosa.

Keywords: Microparticle, Carbamazepine, Trigeminal Neuralgia, Oral Film.

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1. Introduction

The trigeminal nerve, originates from the craniofacial regions, is the fifth and largest cranial nerve. It divides to three divisions: ophthalmic, maxillary, and mandibular branch. The ophthalmic branch supplies the upper part of the head, the nose, and the cornea. The maxillary branch innervates the upper lip, upper jaw teeth, and mucous membranes, and the mandibular branch supplies the lower jaw, lower lip, mucous membranes, and lower jaw teeth. All sensory information collected through the trigeminal nerve is transmitted to the thalamus and other brain regions to interpret sensory information (1-3).

Trigeminal neuralgia as a craniofacial

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neuropathic pain is confined to any part innervated by the trigeminal nerve. The pain is typically described as a sudden, paroxysmal, electric shock-like or burning pain (3). Common triggers such as gentle facial touch, brushing teeth, speaking and eating can provoke pain attacks that last from a few seconds to several minutes. In recurrent pain episodes, patients might be unable to do daily activities and even avoid eating meals or speaking due to the concern of triggering a pain outbreak (1, 3-5).

The treatment of trigeminal neuralgia includes mono or combination medication therapy. Anticonvulsant medications especially carbamazepine and oxcarbazepine are recommended as the first-line treatments for pain control in patients. However, other drugs such as pregabalin, gabapentin, topiramate, or baclofen can be replaced or combined with.

It is found that carbamazepine is effective in reducing pain in 70% of cases. Carbamazepine blocks sodium channels that lead to reduced synaptic transmission, and stabilization of membrane potential in hyper excitable neurons (1, 6, 7).

Systemic administration of carbamazepine can cause different side effects such as nausea, vomiting, drowsiness, ataxia, and so on. Therefore, local delivery to the oral cavity, due to immediacy to the trigeminal nerve, can result in higher concentration of the drug at the site of action, reducing the dosage and thus minimizing side effects. Furthermore, oral mucosa is highly accessible and preserves drugs from first-pass hepatic metabolism, that results in increased drug bioavailability (8).

Various drug formulations are used in oral mucosa drug delivery, but oral films are more common because of simplicity in production, efficient drug loading, and proper physicochemical characteristics (9, 10). The only drawback of oral films is their fast drug release that could be modulated by some strategies. One of these strategies is loading drug particles into the film instead of free drug.

Drug loaded particles can be prepared by different methods and are widely used to control drug release in different formulations. One of the most common methods of particle preparation is solvent evaporation (11). Typically, polymer and the drug are dissolved in a water immiscible organic solvent. The resulting solution is then mixed with an aqueous phase containing additives such as a surfactant or a stabilizer, to form an emulsion. After that, the organic solvent is removed by either increasing the temperature or continuous stirring, resulting in the formation of drug particles.

The objective of this study was to develop controlled-release particles containing carbamazepine and load the particles in a mucoadhesive film that possesses suitable film-forming properties which effectively remains in the oral mucosa, and increase the duration of action.

Therefore, based on previous studies, different ratios of ethyl cellulose and hydroxypropyl methylcellulose (12, 13), as well as various organic solvents, including dichloromethane, and chloroform (13, 14), were examined for producing particles. The optimized particles were then loaded into the film and the physicochemical and pharmaceutical characteristics were evaluated accordingly.

2. Material and methods

2.1. Materials

Carbamazepine was purchased from Amin pharmaceutical company, Iran. Hydroxypropyl methyl cellulose (HPMC-K100m), acacia, gelatine, polyvinyl alcohol (PVA), ethyl cellulose (EC), polyethylene glycol 400 (PEG400), glycerol, sodium hydrogen phosphate, sodium dihydrogen phosphate, dichloromethane and chloroform were obtained from Merck, Germany. All other chemicals and reagents were of analytical grade.

2.2. Carbamazepine analysis validation

UV-vis spectrophotometer (T80, Germany) was applied at a maximum absorbance wavelength of 285 nm for carbamazepine quantification. Two calibration curves were constructed in water: ethanol (50:50) and phosphate buffer solution pH 6.8 as the analysis media. All carbamazepine concentrations (20, 15, 10, 5, and 2.5 µg/mL) were prepared in three different days, and each concentration was tested three times a day. The method was validated for linearity, inter-day and intra-day precision, and accuracy.

2.3. Preparation and optimization of particles

2.3.1. Preparation of particles

To prepare carbamazepine particles, solvent evaporation method was employed as fol-

lows:

Initially, aqueous and organic phases were separately prepared for each formulation. HPMC was dissolved in deionized water containing a specific amount of PVA or Tween 80. The polymer solution was stirred on a magnetic stirrer until complete dissolution. To expedite HPMC dissolution, an ice bath was used.

To prepare the organic phase, EC and carbamazepine were fully dissolved in two different solvents, including dichloromethane, and chloroform, at various ratios depending on the formulation. The organic phase was then added dropwise to the beaker containing the aqueous phase, which was being stirred at room temperature and a speed of 1000 rpm. The mixture was then stirred until complete evaporation of the organic phase.

The resulting formulations were centrifuged at 10,000 rpm for 10 minutes, and the sediment, which contained drug particles, was collected. The ratios of polymers and phases were selected based on the previous studies (13).

Compositions of different formulations at different ratios are shown in Table 1.

2.3.2. Optimization of particle formulations

To select the optimum formulations, drug release from the particles and drug content were studied.

To determine drug content amount, defined weight of particles was completely dissolved in a mixture of water and methanol. Subsequently, the absorbance of this solution was recorded using UV spectrophotometer at 285 nm.

In order to evaluate the drug release from the particles, defined amounts of the prepared particles were dispersed in phosphate buffer solution pH 6.8±0.1. The dispersion was placed on a stirrer at the room temperature with a constant stirring speed of 1000 rpm. At predetermined time intervals (5, 15, 30, 45, 60, 90, and 150 min), samples were taken from the containers' content and the percentage of released drug was calculated using UV calibration at 285 nm wavelength.

2.4. Film Preparation and carbamazepine loading

2.4.1. Film preparation

Based on the previous study (15), oral film was prepared by casting-solvent evaporation technique. Briefly, 0.25% w/v carbamazepine containing particles, 5% w/v acacia, 10% w/v gelatin as the film-forming polymers, and 1% v/v glycerol and 10% v/v PEG 400 as plasticizers were dissolved in 20 mL deionized water and mixed under constant magnetic stirring at room temperature. Resulting solution was left to allow the entrapped air bubbles being removed, then poured on a Teflon plate and completely dried at room temperature for 48 hours. For better comparison, a film containing the equal amount of pure carbamazepine was also prepared by the same method and further studies were performed.

2.5. Evaluation of film

2.5.1. Measurement of film tensile strength

The mechanical properties of film were evaluated using a texture analyzer (model CT3, Brookfield, USA) with a 1-kg load cell. Film strips

Table 1. Composition of formulations prepared with different organic solvents.

Organic solvent	Formulations	Water: organic phase	Polymer: drug (weight)	HPMC: EC (weight)	Stabilizer/ Surfactant
Dichloromethane	F1	5:4	1: 2	1:1	Tween80 0.5%
	F2	5:4	1:1	1:1	
	F3	5:4	1:1	1:3	
	F4	5:4	1:1	3:1	
	F5	5:4	2:1	1:1	
Chloroform	F6	4:1	1:1	1:1	PVA 0.1%
	F7	4:1	1:1	3:1	
	F8	4:1	1:1	1:3	
	F9	4:1	2:1	1:1	
	F10	4:1	1:2	1:1	

HPMC: Hydroxypropyl methyl cellulose; EC: Ethyl cellulose.

in the constant dimension (10 cm x 2 cm) and thickness of 0.48 mm, free from any physical imperfection were held between two clamps positioned at a distance of 8 cm. The film strips were pulled by the upper clamp at a rate of 0.2 mm/s. The force and elongation were measured during measurement. Measurements were run in triplicate for optimized formulation. Elongation at Break (cm) (increase in length at break to the original length), Peak Load (mN) (maximum load the specimen sustains during the test) and Work (mJ) were reported for the evaluation of the films.

2.5.2. Determination of thickness and weight

The thickness of the optimized film was measured using the manual Vernier caliper. Measurement was done at 10 different positions, and the average thickness was calculated for each film.

To measure the average weight, 4 cm2 pieces of 10 films were evaluated by a digital balance (Scaltec, Germany).

2.5.3. Water solubility of the film

Film portions with 2-cm diameter and definite weight were placed in breakers with 10 mL deionized water, and let stand at room temperature. After 3 hours, the solution was filtered through Whatman no. 1 filter paper and dried at room temperature for 24 h.

Film solubility was calculated by the equation:

$$FS\ (\%) = ((Wo - Wf)/Wo) \times 100$$

Where Wo was the initial weight of the film and Wf was the weight of the undissolved dried film residue. All tests were carried out in triplicate.

2.5.4. In vitro release study

In vitro release test of carbamazepine films was carried out using Franz cells.

The dissolution medium was USP phosphate buffer pH 6.8, 35 mL (sink condition) at 35±1°C, and at a stirring rate of 100 rpm. Film portions (2 cm diameter) containing 0.7 mg pure carbamazepine and carbamazepine-loaded particles (with equivalent amount of carbamazepine) were mounted on Franz cell.

At appropriate time intervals (15, 30, 60, 90, 120, 150, 180, 240, and 300 min) 1 mL samples were withdrawn and then replaced with the same volume of buffer. The experiment was repeated 3 times for each sample and drug concentration was determined by a spectrophotometer at the wavelength of 285 nm.

To ensure there was no interference from excipients in the process, another Franz cell, with a piece of the base film on it was used in the similar condition.

3. Results and discussion

3.1. Carbamazepine analysis validation

Carbamazepine analysis in water: ethanol (50:50) and phosphate buffer solution pH 6.8 was performed at λmax 285 nm. Data of the regression equation, the correlation coefficient (r2) of the standard curve, and the results of validation of the precision and accuracy of the analytical method are presented in Table 2.

All the results implied acceptable precision, and accuracy which approved the application of carbamazepine analysis method in the rest of the study is valid.

3.2. Optimization of particles

One of the main factors to choose the optimized particle was the drug content. Particles prepared by chloroform as the organic phase showed higher drug loading content (Table 3). Among

Table 2. Validation parameters of different analytical curves of carbamazepine (n=9).

Solvent	Equation	r^2	Precision% (Intraday)	Precision% (Interday)	Accuracy%
Water: Ethanol (50:50)	y = 0.0514x + 0.0316	0.999	97.6±0.7	97.9±1.2	100.4±2.9
Phosphate buffer pH 6.8	y = 0.0513x + 0.0312	0.999	97.9±1.2	98.1±1.4	99.8±2.8

Table 3. Carbamazepine content in different formulations.

Organic solvent	Formulation	Content %
Dichloromethane	F1	57.3 ±3.1
	F2	58.2±1.2
	F3	52.0±5.6
	F4	49.3±1.1
	F5	60.3±2.1
Chloroform	F6	71.2±3.3
	F7	68.9±2.2
	F8	60.8±2.2
	F9	72.4±1.7
	F10	68.5±5.0

the essential factors for optimal drug loading into particles are the low solubility or insolubility of the organic solvent in the aqueous phase, the low solubility of the drug in the aqueous phase, and the high solubility and concentration of the polymer in the organic phase (16). Chloroform has lower solubility in water compared to dichloromethane, and both ethyl cellulose and carbamazepine are readily dissolved in chloroform in a greater extent (17). As a result, formulations prepared by chloroform were selected for further evaluations.

Another variable examined in selected formulations (F6 to F10) was the polymer: drug ratio. Ratios of 1:1, 1:2, and 2:1 of polymer to drug were prepared and evaluated. In the 1:2 polymer: drug ratio, the drug content was approximately 68%, while for the 1:1 and 2:1 ratio, these amounts were 71% and 72%, respectively. As expected, with an increase in the polymer: drug ratio, the drug loading increased. However, the increase was not significant. Therefore, since further increasing of the polymer ratio did not provide a significant advantage and the drug loading percentage remained almost unchanged, the 1:1 ratio of polymer: drug was chosen as the optimal ratio (F6 to F8, Table 3) (18).

Formulation selection was approved in release study. Particles were dispersed in buffer, and their dissolution was measured at various time points by sampling from the container's contents and reported as the percentage of released drug. Particles prepared using dichloromethane, released high percentage of the drug in less than 10 minutes, which was inconsistent with the goal of study. On the other hand, particles prepared with chloroform slowed down the drug release, significantly (Figure 1).

Another factor examined, was the different ratios of HPMC to EC, including ratios of 1:3, 1:1, and 3:1 in chloroform. It was expected that increasing in EC amount would slow down the drug release, but the 1:1 ratio exhibited a slower drug

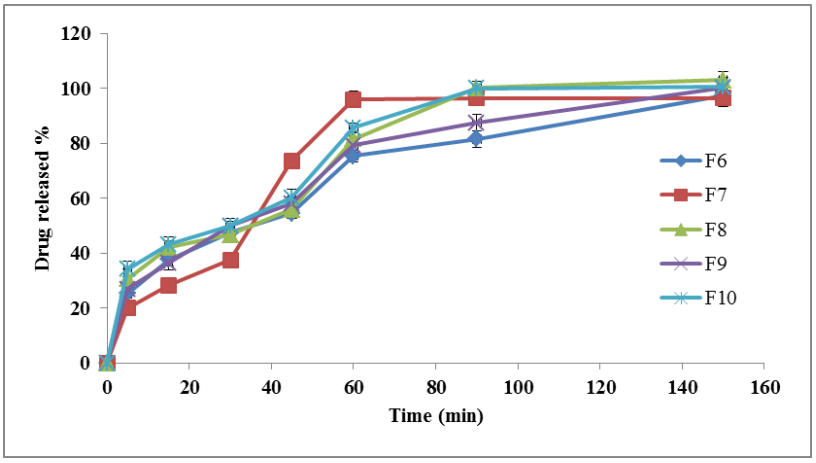

Figure 1. The drug release profile of particles prepared by chloroform as the organic phase.

Table 4. Results of physicochemical properties of the film.

Test	Results
Thickness (mm)	0.49 ± 0.03
Film Dissolution Time (hour)	2 ± 0.2
Wight (mg)	1.53 ± 0.05

release than the 1:3 ratio, with approximately 10% less drug loading in the 1:3 ratio. One possible reason for this difference could be the increased amount of EC and its decreased solubility in the organic solvent. In the case of 3:1 ratio, drug release was faster, occurring in a shorter period of time, which can be attributed to the higher content of HPMC and its solubility in water. Considering these factors, the 1:1 ratio of HPMC to EC was chosen as the optimal ratio (F6) (12).

3.3. Film characteristics

3.3.1. Film physical properties

Since the goal of this study was to produce an oral mucoadhesive film, optimized film formulation was prepared based on previous research(15), which included 5% acacia, 10% gelatin, 1% glycerol and 10% PEG400.

The tensile strength of the optimal film was measured, and the film strength was entirely acceptable. Film elongation at break was 0.32 mm, peak load was 1506 mN and work at fracture was 0.41 mJ.

Therefore, the likelihood of film rupture is very low before any therapeutic effect is achieved.

The thickness and average weight of the film fell within an acceptable range (Table 4) compared to other films produced in various studies (18و 19). Consequently, the film's thickness is suitable for placement in the oral cavity, and since there is not much difference in thickness and weight between the measured films, it can be concluded that the film has good uniformity.

The dissolution of the film in deionized water was measured (Table 4), and similar to previous studies(15), the film was dissolved completely. So, the film is entirely soluble in saliva, and our goal of creating a mouth-dissolving film has been achieved.

3.3.2. In vitro release study

To evaluate and compare drug release behavior of the film, pure carbamazepine and carbamazepine particles were separately loaded into the base film.

Comparing the drug release profiles of the films confirmed the slower release of the coated drug compared to the pure drug (Figure 2). It was in accordance with other studies (20), that drug release was well-controlled.

4. Conclusion

Carbamazepine is a standard agent for medical treatment of trigeminal neuralgia. Oral administration of carbamazepine has many side effects with different severity and frequency. Common side effects are dizziness, somnolence and ataxia. Due to the systemic side effects, alternative routes of administration might be used. Local administration of the drug to the oral cavity, due to lack of first-pass metabolism and proximity to the trigeminal nerve, can achieve a higher concentration of the drug at the site of action and reduce the side effects. The aim of this study was to prepare carbamazepine loaded particles in buccal film

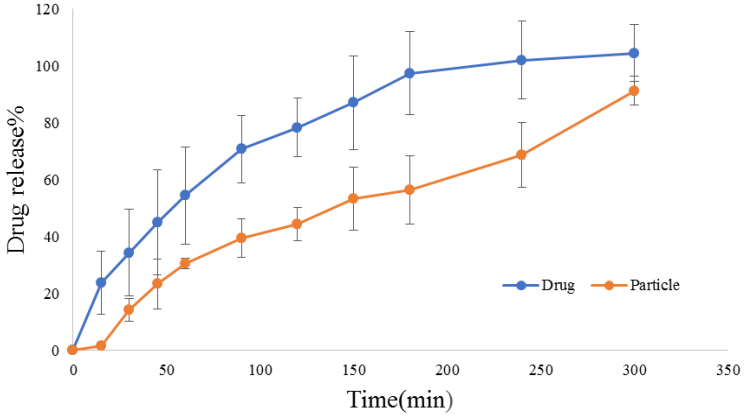

Figure 2. Release of pure carbamazepine and carbamazepine loaded in the particles from the film.

formulation. Particles were able to load proper amount of carbamazepine as well as release it in a slower rate. Some physicochemical properties of the film, drug content, and drug release from the film containing pure drug and the film loaded with carbamazepine particles were evaluated. The results indicated that the film was acceptable in terms of physicochemical properties, and drug release from the film containing carbamazepine particles was significantly controlled compared to the film containing pure carbamazepine. Taking these factors into consideration, the film loaded with optimized particles can be considered as a suitable alternative for high-dose oral administration of this drug.

Conflict of Interest

The authors declare no conflict of interest.

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