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SCIENTIFIC ARTICLE

Mucoadhesive buccal films of tramadol for effective pain management

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Abstract
Background and objectives: Tramadol hydrochloride is a centrally-acting synthetic opioid analgesic binding to specific opioid receptors. It is used in the management of chronic pain and is recommended as first line drug in the treatment of postoperative or orthopedic injury induced acute pain. The present work is designed to prepare and evaluate mucoadhesive buccal film of tramadol hydrochloride as a novel form of prolonged analgesia for patients with orthopedic injuries.
Methods: Buccal films of tramadol hydrochloride were prepared by solvent casting method. The prepared films were evaluated for the various evaluation parameters like thickness, surface pH, weight uniformity, content uniformity, folding endurance, swelling index, in vitro drug release study, in vitro test for mucoadhesion and in vivo studies (primary mucosal irritancy test and analgesic activity).
Results: All the formulations exhibited good results for physicochemical characterizations. In in vitro drug release study the films exhibited controlled release more than 12 hours. The formulation BFT2 (containing chitosan and PVP K-90) showed no irritant effect on buccal mucosa and elicit the significant in vivo analgesic activity with 57.14% analgesia against that of standard (61.04%). It was concluded that the mucoadhesive films of tramadol hydrochloride can be effectively used to alleviate the severe pain of orthopedic injuries with prompt onset and prolonged action.

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PALAVRAS-CHAVE
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Lesão ortopédica

Filmes bucais mucoadesivos de tramadol para o controle eficaz da dor

Resumo
Justificativa e objetivos: O cloridrato de tramadol é um analgésico opioide de ação central que se liga a receptores opioides específicos. É usado no tratamento de dor crônica e recomendado como fármaco de primeira linha para o tratamento no pós-operatório ou em dor aguda induzida por lesão ortopédica. O presente estudo visa preparar e avaliar o filme bucal mucoadesivo de cloridrato de tramadol como uma nova forma de analgesia prolongada para pacientes com lesões ortopédicas.
Método: Filmes bucais de cloridrato de tramadol foram preparados pelo método de evaporação de solvente. Os filmes preparados foram avaliados para os vários parâmetros de avaliação como espessura, pH da superfície, uniformidade do peso, uniformidade do conteúdo, resistência a dobras, índice de intumescimento, estudo de liberação da droga in vitro, teste in vitro para mucoadesão e estudos in vivo (teste de irritação da mucosa primária e atividade analgésica).
Resultados: Todas as formulações apresentaram bons resultados para caracterizações físico-químicas. Em estudo de libertação de droga in vitro, os filmes exibiram liberação controlada mais de 12 horas. A formulação de BFT2 (contendo quitosana e PVP K-90) não mostrou efeito irritante sobre a mucosa bucal e provocou uma atividade analgésica significativa in vivo com 57,14% de analgesia versus a do padrão (61,04%). Concluiu-se que os filmes mucoadesivos de cloridrato de tramadol podem ser usados eficazmente para aliviar a dor intensa de lesões ortopédicas com início rápido e ação prolongada.

Introduction

Buccal drug administration is very widely accepted route of administration for potent medicines for the clinical conditions which is associated with severe pain and discomfort.[1] Generally orthopedic patients suffering from disorders of the skeletal system and associated muscles, joints, and ligaments needs constant and prolonged drug delivery for effective management of therapeutic condition.[2] Buccoadhesive drug delivery avoids the destruction by gastrointestinal contents or hepatic first-pass inactivation of drug and ensures intimate contact of drug to the biological system for better drug absorption.[3,4]

Generally post-operative pain is effectively managed by opioid analgesic, semisynthetic opioids, neuroleptic analgesic and potent NSAIDS. But immediate after surgery many a time's even very strong analgesics cannot effectively manage the pain. When the effect of general anesthesia subsides (generally after 6–12 h after surgery) patients feels a great pain which might not be managed by any means and many times are intolerable. Therefore, the present study was conducted to explore the feasibility and effectiveness of buccal mucoadhesive drug delivery of tramadol as an effective alternative of NSAIDs in relieving pain after surgery or orthopedic injury. In an attempt to reduce the relatively high incidence of serious adverse effects associated with the systemic use of NSAIDs, a growing number of topical formulations of these drugs have become commercially available.[5] The present work is designed to prepare and evaluate mucoadhesive buccal film of tramadol hydrochloride as a novel form of prolonged analgesia for patients with orthopedic injuries.

Tramadol hydrochloride is a centrally-acting synthetic opioid analgesic binding to specific opioid receptors. It is a non-selective, pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu receptor.[2,6] Tramadol HCl is freely soluble in water, and readily absorbed following oral administration. The systemic bioavailability of tramadol hydrochloride is approximately 68% after oral administration. Tramadol HCl is a centrally acting analgesic used in management of chronic pain and is recommended as first line drug treatment of orthopedic injury to produce adequate pain relief. The half-life of a drug is about 5.5 h and the usual oral dosage regimen is 50–100 mg every 4–6 h with a maximum dosage of 400 mg·day^{-1}.[7]

Methods

Chitosan, PVP K-90 and PVP K-70 were purchased from Sigma–Aldrich. All other chemicals used were of analytical grades.

Preparations of buccal film of tramadol

Buccal film of tramadol hydrochloride were prepared by solvent casting methods using two different grades of PVP K-90 and PVP K-70 and chitosan as mucoadhesive polymers. Polymeric solution of chitosan was prepared by dissolving chitosan in acetic acid in distilled water with constant stirring. PVP was added to the solution of chitosan with stirring. Propylene glycol (5%, V/V) was added as plasticizer. This solution was kept overnight to ensure clear bubble free solution. The weighed quantity of tramadol HCl was added to

polymeric solution and the solution was poured into a glass Petri dish having 9.5 cm diameter. The Petri dishes were kept on flat surface and covered by inverted funnel to allow controlled evaporation of solvent at 40 °C till a flexible film was formed. Dried films were carefully removed, checked for any imperfections or air bubbles and cut into films of 10 mm in diameter.[8,9]

Thickness and weight uniformity

A standard screw gauge was used to measure the thickness of three randomly selected buccal films from each batch. Weight uniformity of film was tested by taking weight of five films of sizes 10 mm diameter from each batch and weigh individually on electronic balance and the average weight was calculated.[10]

Content uniformity

Drug content uniformity was determined by dissolving the buccal film (10 mm in diameter) from each batch by homogenization in 100 mL of an isotonic phosphate buffer (pH 6.8) for 6 h under occasional shaking. The drug content was then determined after proper dilution and measured the absorbance at 271 nm using a UV–visible spectrophotometer.[11]

Folding endurance

Randomly selected three films from each batch were taken to measure the folding endurance. The films were repeatedly folded at the same place till it broke. The films folded up to 300 times manually was considered satisfactory value.[12] The number of times of film could be folded at the same place without breaking gave the value of the folding endurance.

Surface pH

Buccal films were left to swell for 1 h on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 6.8 under stirring and then poured the solution into the petridish allowed to stand till gelling at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen film.[13,14]

Swelling index

The water uptake was determined gravimetrically. The dried films fixed to stainless steel support were immersed in a beaker containing 25 mL distilled water at room temperature. At specific intervals up to 3 h, the swollen sample with the pre-weighed mesh were weighed after removal of excess surface water by light blotting with a filter paper. The experiment was discontinued when the films begin to disintegrate or dissolve.[15] To quantify the swelling process, the swelling index percentage was calculated as follows:

$$\text{Swelling index}\,\% = \left(\frac{W_s - W_d}{W_d}\right) \times 100$$

where W_d is the weight of the dried polymer film and W_s is the weight after swelling.

In vitro release study

In vitro drug release study was carried out by using modified dissolution test apparatus type 1 (eight-station dissolution apparatus). The dissolution medium, 50 mL IPB, pH 6.8, were maintained at 37 ± 0.50 °C and it was kept in a glass beaker placed inside the dissolution flask. The film was attached to end of the shaft (without basket) with the help of cyanoacrylate adhesive, which was rotated at 50 rpm.[16] Aliquots of samples (2 mL) were withdrawn at the intervals of 1, 2, 3, 4, 5, 6 and 7 h and filtered using Whatman filter paper No. 1. The withdrawals were compensated using equal volumes of IPB kept at the same temperature. The concentration of drug released in the medium was measured spectrophotometrically at 271 nm after suitable dilution with the dissolution medium.

In vitro mucoadhesion test

The in vitro mucoadhesion time was determined by using a modified USP disintegration apparatus. 800 mL of phosphate buffer of pH 6.8 (IPB) maintained at 37 ± 0.50 °C were used as disintegration medium. A piece of porcine buccal mucosa, 3 cm length was taken for the study. The buccal mucosa was attached to a rectangular glass piece using cyanoacrylate adhesive from non-mucosal surface. The mucoadhesive film was hydrated from one surface using pH 6.8 IPB and then the hydrated surface was brought in contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the film was completely immersed in the buffer solution at the lowest point and was out at the highest point.[17] The time necessary for complete detachment of the film from the mucosal surface was observed and recorded ($n = 3$).

In vivo study

The healthy male Wistar rats (200–250 g) were used for the study. The rats were kept in cages in standard environmental conditions of light and temperature. The rats were allowed free access to drinking water and standard diet. The protocols of the animal study were approved by the Institutional Animal Care and Use Committee of Zhejiang University, Hangzhou (approval ref no. 109. 10/08/2014); and was carried out in compliance with the Directive.

Primary mucosal irritancy studies

The irritant effect or any chance of edema with the use of buccal films was assessed by primary mucosal irritancy test. The healthy male rats (200–250 g) were divided into three groups of three rats each. The non-medicated film

Table 1 Formulations of buccal films of tramadol hydrochloride.

Formulation code	Chitosan % (w/w)	PVP K-90 (mg)	PVP K-70 (mg)	Propylene glycol (%)	Tramadol (mg)
BFT1	1	50	–	5	500
BFT2	1	100	–	5	500
BFT3	1.5	50	–	5	500
BFT4	1.5	100	–	5	500
BFT5	1	–	50	5	500
BFT6	1.5	–	100	5	500

was applied to oral mucosa (of urethane anesthetized rats) to the group I (control) using an adhesive tape USP. To the group II (test) transmucosal patch formulation BFT2 (containing chitosan and PVP K-90) was applied. To the group III (standard) 0.8% v/v aqueous solution of formaldehyde (irritant) was applied. The application sites were observed for any erythema and edema on the mucosal surface for 2 days after application and the scoring was done (Table 1).

In vivo analgesic activity

Mal albino rats were divided in three groups of six rats each. The first group served as control and it received non-medicated buccal films. The test group II received buccal films (BFT2, 50 $\mu g \cdot kg^{-1}$ body mass). The third group received standard (transmucosal gel of fentanyl citrate, 10 $\mu g \cdot kg^{-1}$ body mass). Three hours after treatment, 0.6% (V/V) acetic acid solution (10 $mL \cdot kg^{-1}$) was injected to rats intraperitoneally. Total number of writhes, which was a parameter of chemically induced pain (i.e., constriction of abdomen, turning of trunk and extension of hind legs), was counted for 20 min The analgesic effect was expressed as percent reduction of writhes in comparison with the control.

Statistical analysis

Results were expressed as mean values ± standard deviations. Statistical analysis was carried out using the analysis of variance (ANOVA). A probability value less than 0.05 ($p < 0.05$) was considered to be a significant value.

Results

Buccal films of tramadol hydrochloride were prepared by solvent casting method by using Chitosan PVP K-70 and PVP K-90 as mucoadhesive polymers. The prepared films were evaluated for the various physicochemical evaluation parameters like thickness, surface pH, weight uniformity, content uniformity, folding endurance and swelling index (Table 2). Thickness of all six formulations was found to be in the range of 0.24 ± 0.04 to 0.54 ± 0.02 mm The all prepared formulation of tramadol hydrochloride buccal film showed the pH range within the range of salivary pH i.e. 6.32–6.82. The observed surface pH of the formulation BFT1, BFT2, BFT3, BFT4, BFT5 and BFT6 are 6.82 ± 0.28, 6.40 ± 0.16, 6.44 ± 0.09, 6.59 ± 0.12, 6.52 ± 0.44, 6.53 ± 0.23 respectively. The result of film thickness showed that there was no significant difference of surface pH in all the formulation. The folding endurance was measured manually, by folding the film repeatedly at a point till it broke. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. Hence the breaking time was taken as the end point. The folding endurance was found to be highest for formulation BFT6 (298 ± 5.211) and the lowest for formulation BFT1 (238 ± 4.211). It was found that the folding endurance was increased with the addition of PVP with increased concentration of chitosan.[18,19] Percent swelling of buccal films were found to be in the range of 17.40 ± 0.28 to 24.66 ± 1.50. It was concluded that more hydrophilic nature of polymer in BFT2 resulted in maximum swelling as compared to the other formulations.

In vitro drug release study was carried out by using modified dissolution test apparatus (Fig. 1). The study revealed that the drug release was dependent on the concentration and different grades of polymers used. Among all the formulations of buccal films formulation BFT2 showed maximum drug release at the end of 12 h. In vitro mucoadhesion test was performed by using modified disintegrating apparatus. Results of in vitro mucoadhesion test showed that

Table 2 Physicochemical characteristics of prepared buccal films of tramadol HCl.

Buccal film code	Thickness (mm)	Surface pH	Weight uniformity (mg)	Folding endurance	Drug content (%)	Swelling % after 6 h
BFT1	0.24 ± 0.04	6.82 ± 0.28	36.6 ± 1.53	238 ± 4.211	96.66 ± 1.2	17.40 ± 0.28
BFT2	0.26 ± 0.03	6.40 ± 0.16	35.6 ± 1.52	244 ± 5.311	92.14 ± 1.1	24.66 ± 1.50
BFT3	0.31 ± 0.03	6.44 ± 0.09	31.1 ± 1.64	253 ± 6.211	95.51 ± 3.4	22.11 ± 1.08
BFT4	0.32 ± 0.02	6.59 ± 0.12	39.7 ± 1.60	254 ± 2.241	93.81 ± 1.0	23.66 ± 1.12
BFT5	0.49 ± 0.06	6.52 ± 0.44	46.2 ± 1.38	279 ± 8.111	91.56 ± 2.5	17.66 ± 1.52
BFT6	0.54 ± 0.02	6.53 ± 0.23	50.1 ± 1.32	298 ± 5.211	95.87 ± 2.1	18.33 ± 1.61

Table 3 Primary mucosal irritation test of transmucosal mucoadhesive buccal films of tramadol.

Rat no.	Control group I		Test (BFT2) group II		Standard irritant group III	
	Erythema[a]	Edema[b]	Erythema[a]	Edema[b]	Erythema[a]	Edema[b]
1	1	0	1	1	3	2
2	0	1	0	1	3	2
3	0	1	0	0	3	1
Average ± S.D	0.34 ± 0.58[c]	0.67 ± 0.58[c]	0.34 ± 0.58[c]	0.67 ± 0.58[c]	3 ± 0	1.67 ± 0.50

[a] Erythema scale: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, scar formation.
[b] Edema scale: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, severe; $n = 3$.
[c] $p < 0.05$, significant compared with formalin.

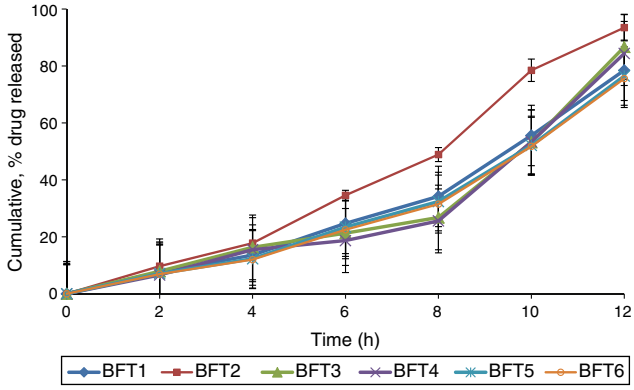

Figure 1 In vitro drug release study of buccal films of tramadol hydrochloride in phosphate buffer of pH 6.8.

formulation BFT6 with higher concentration of chitosan showed the maximum mucoadhesion property as compared to others.[20,21] Whereas BFT2 had the least mucoadhesion property, which might be due to hydrophilic nature of PVP K-90 which loosen the bond strength from the mucosal area.

Formulation BFT2 was subjected to in vivo studies for primary mucosal irritancy test and analgesic activity. The BFT2 films were found to be non-irritant in the primary mucosal irritation test (Table 3). The formulation BFT2 showed significantly good in vivo analgesic activity with 57.14% analgesia against that of standard which showed 61.04% analgesia (Table 4).

Discussion

Mucoadhesion is one of the most widely investigated approaches in delivering the drugs for quick onset of action and improved bioavailability. The buccal mucosa being rich in vasculature provides a very good platform for delivering the drug directly to the systemic circulation. The dosage requirement is very less as compared to that of oral drug delivery. In orthopedic patients the acute pain is many a times is to be dealt immediately with high efficacy. And for the same buccal mucoadhesive patches are considered to be the best approach.[21–24] The mucoadhesive buccal patches of analgesics have been investigated inclusive of tramadol.[25–27] Oral Transmucosal Fentanyl Citrate (OTFC) provides the rapid-onset opioids and a short duration of analgesia. Extensive researches have been done on the transmucosal drug delivery system of fentanyl for buccal, sublingual and nasal mucosal delivery.[28–31]

The various alternative dosage forms of tramadol have been investigated for improving the efficacy of the treatment.[32–34] In some previous studies also the mucoadhesive dosage forms have been developed for tramadol.[27,34]

In the present study, as compared to other formulations BFT2 (containing chitosan and PVP K-90) showed increased surface wetting and water penetration which resulted in good dissolution profile. On the other hand, formulation BFT6 (containing chitosan and PVP K-70) showed minimum drug release; might be due to more concentration of chitosan which being less water soluble retarded the drug release. Results of in vitro release study indicated that varying concentration of chitosan did not affect the drug release significantly.

Table 4 In vivo analgesic activity of transmucosal mucoadhesive buccal films of films of tramadol.

Drug	Oral dose[a] ($\mu g \cdot kg^{-1}$)	Analgesic activity	
		N° of writhes[b]	Analgesia%
Control (blank films)	–	77 ± 4	–
Fentanyl citrate (standard)	10	30 ± 1[c]	61.04
BFT2	20	33 ± 2[c]	57.14

[a] Dose equimolar to the parent drug calculated on the basis of drug contents.
[b] Mean ± SEM, $n = 6$.
[c] $p < 0.05$ vs. control.

BFT2 showed excellent analgesic activity with no irritation on the mucosa. The analgesic activity was very much comparable to the standard oral mucoadhesive formulation of fentanyl citrate which is a very well known analgesic opioid with rapid-onset and a short duration of analgesia. So not only the rapid onset of action but also the prolonged release (as indicated by in vitro release data) (Fig. 1) can be achieved with the present formulation of tramadol.

Summary

The results of the study show that therapeutic levels of tramadol can be delivered through buccal route. The present study concludes that these erodible mucoadhesive buccal films containing tramadol can be very promising for effective doses to systemic circulation in patients of orthopedic injuries. Films exhibited controlled release over more than 10 h with no irritation on mucosa. The films showed comparable analgesic effect in vivo studies. Thus these films can be selected for the development of buccal film for effective therapeutic uses.

Conflicts of interest

The authors declare no conflicts of interest.

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