Mucoadhesive Films Containing Chitosan-Coated Nanoparticles: A New Strategy for Buccal Curcumin Release

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ABSTRACT: Mucoadhesive films containing curcumin-loaded nanoparticles were developed, aiming to prolong the residence time of the dosage form in the oral cavity and to increase drug absorption through the buccal mucosa. Films were prepared by the casting method after incorporation of curcumin-loaded chitosan-coated polycaprolactone nanoparticles into plasticized chitosan solutions. Different molar masses of mucoadhesive polysaccharide chitosan and concentrations of plasticizer glycerol were used to optimize the preparation conditions. Films obtained using medium and high molar mass chitosan were found to be homogeneous and flexible. Curcumin-loaded nanoparticles were uniformly distributed on the film surface, as evidenced by atomic force microscopy and high-resolution field-emission gun scanning electron microscopy (FEG-SEM) images. Analyses of film cross sections using FEG-SEM demonstrate the presence of nanoparticles inside the films. In addition, films proved to have a good rate of hydration in simulated saliva solution, displaying a maximum swelling of around 80% and *in vitro* prolonged-controlled delivery of curcumin. These results indicate that the mucoadhesive films containing nanoparticles offer a promising approach for buccal delivery of curcumin, which may be particularly useful in the treatment of periodontal diseases that require a sustained drug delivery. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:3764–3771, 2014

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INTRODUCTION

The buccal cavity constitutes an attractive route for administration of drugs. Among the various mucosal membranes available, buccal mucosa is the most convenient and easily accessible for the delivery of therapeutic agents for either local or systemic effects. Besides, this region is highly vascularized and permits the direct access to the systemic circulation through the internal jugular vein bypassing the first pass metabolism, improving the systemic bioavailability of drugs.[1] The buccal route has a high patient acceptability when compared with other nonoral routes of drug administration.[2] However, the short residence time at the site of application displayed by conventional formulations because of the washing effect of saliva limits the absorption of drugs through the buccal mucosa.[3]

Mucoadhesive systems including tablets, gels, ointments, and films have shown to improve the drug delivery by prolonging the residence time at the site of application and providing an intimate contact with the absorbing membranes. Among the mucoadhesive dosage forms designed for buccal administration, films are preferable in terms of flexibility and comfort over buccal tablets and circumvent the relatively short residence time of gels and ointments on the mucosa. Moreover, buccal films also provide physical protection to the wound surfaces by reducing the pain and increasing the treatment effectiveness.[4,5] Some studies have demonstrated the promising use of films for drug delivery into the periodontal pocket. Films have proved to be suitable to incorporate and promote a sustained release of several therapeutic agents. Chitosan/poly(D,L-lactide-co-glycolide) films prolong the ipriflavone release, a synthetic flavonoid derivative, for 20 days. Additionally, these systems showed good morphological characteristics, such as thickness and flexibility, desirable for application in the oral cavity.[6] Recently, the development of films consisting of ethyl cellulose for delivery of antibacterial agent ornidazole in the treatment of periodontitis has also been reported. The polymeric films showed a sustained release of ornidazole over a period of 9 days and *in vitro* antibacterial activity against oral bacteria *Streptococcus mutans*.[7]

More recently, the use of mucoadhesive carriers, such as microparticles and nanoparticles, has emerged as another potential strategy for drug delivery through the mucosa. The additional advantages related to the use of colloidal carriers include the possibility to modify the release and absorption characteristics of drugs, drug protection against biological degradation, improved drug bioavailability, and possibility of hydrophobic drug administration as an aqueous dispersion.[8–10] Nanoparticles coated with the polysaccharide chitosan have attracted a special interest for mucoadhesive applications, mainly because of its ability to interact with the negatively charged mucosal surface and increase the absorption of drugs by reorganizing the tight junctions between mucosal cells.[11]

On the basis of above-mentioned considerations, the possibility of combining the advantages of mucoadhesive films with

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those of the nanoparticles, as the ability to provide a high dispersion of the drug throughout the dosage form, to protect drug from degradation, and to control the drug release, in one single system seems to be an interesting strategy for buccal administration of drugs. In the last years, few studies on the films containing nanoparticles have been described in the literature.[12,13] Herein, we report the development of nanostructured films aiming the buccal delivery of curcumin.

Curcumin, a natural polyphenol compound derived from turmeric, has been shown to exhibit several pharmacological activities (e.g., antioxidant, anti-inflammatory, antiviral, antimicrobial, and anticancer) and thus presents a potential therapeutic role in different diseases.[14] However, the clinical application of curcumin has been hindered by its poor aqueous solubility, fast hydrolytic degradation at physiological pH, presystemic metabolism by action of colonic enzymes, and, hence, by its low bioavailability when orally administered.[15] In this sense, the buccal route may be considered as an alternative to deliver curcumin for the local treatment of many disorders that affect the oral cavity, including gingivitis, periodontal diseases, bacterial and fungal infections, aphthous ulcers, inflammations, and oral cancers. In this study, nanostructured films composed of a mucoadhesive matrix of chitosan containing curcumin-loaded chitosan-coated nanoparticles were prepared. Different concentrations of the mucoadhesive polysaccharide chitosan and a plasticizer agent were tested to obtain homogenous and flexible films. The nanostructured films were evaluated in terms of weight, thickness, morphology, swelling, and *in vitro* curcumin release properties.

MATERIALS AND METHODS

Materials

Curcumin (≥94% curcuminoid content), polycaprolactone [PCL, molecular weight (MW) 60,000 Da], and glycerol (ReagentPlus®, ≥99%) were purchased from Sigma–Aldrich (St. Louis, Missouri). Poloxamer 188 (Lutrol F68®) was kindly donated by BASF Chemical Company (Ludwigshafen, Germany). Three different molar mass chitosan—low (CSL 50,000–190,000 Da), medium (CSM 190,000–310,000 Da), and high molar mass (CSH 310,000 to >375,000 Da)—were purchased from Sigma–Aldrich. The degree of deacetylation is between 75% and 85% for CSL and CSM, respectively, and higher than 75% for CSH.

Preparation of Chitosan-Coated PCL Nanoparticles

Chitosan-coated PCL nanoparticles loaded with curcumin (CurNP) were prepared using the nanoprecipitation method as previously described by Mazzarino et al.[16] Briefly, 60 mg of PCL and 5 mg of curcumin were dissolved in 12 mL of acetone. This organic phase was poured into 24 mL of an aqueous phase (pH 5) containing 1% acetic acid; 0.25% (w/v) poloxamer 188; and 0.1% low, medium, or high molar mass chitosan (CSL, CSM, or CSH, respectively) under magnetic stirring. The acetone was then eliminated by evaporation under reduced pressure, and the colloidal suspension was concentrated to 10 mL. Finally, the polymeric nanoparticle suspensions were filtered through 1.2-μm pore size filter paper.

Preparation of Chitosan Films Containing Nanoparticles

Films were prepared by casting/solvent evaporation method. Initially, 1% (w/v) low, medium, or high molar mass chitosan solutions were prepared in 1% acetic acid and filtered through nonwoven gauzes to remove any suspended impurities. Glycerol 5% or 10% (w/w) was added to the chitosan solutions as a plasticizer agent. Films containing chitosan-coated nanoparticles loaded with curcumin were prepared according to the same procedure by adding 1 mL of the nanoparticle suspensions to 2 mL of the plasticized chitosan solution, followed by magnetic stirring during 15 min. The obtained mixtures were cast onto polystyrene dishes (9.62 cm^2) overnight under room temperature. Finally, films were cut into 0.785 cm^2 circles.

Characterization of Chitosan-Coated PCL Nanoparticles

Particle Size

The size distribution, mean particle size, and polydispersity index (PdI) of the nanoparticle suspensions were determined using dynamic light scattering (DLS) using an ALV 5000 (ALV, Langen, Germany) equipped with a red helium–neon laser at a wavelength of 632.8 nm and a power of 35 mW. After appropriate dilution in ultrapure Milli-Q® water, samples were placed in cylindrical measurement cells and immersed in a toluene bath with temperature regulated at 25°C. Each analysis was performed during 300 s, and the scattered light was measured at different angles ranging from 20° to 150°. The hydrodynamic radius (R_h) was determined using Stokes–Einstein equation, $R_h = \kappa_B T/6\pi\eta D$, where κ_B is Boltzmann constant (in J/K), T is the temperature (in K), D is the diffusion coefficient, and $\eta$is the viscosity of the medium—pure water in this case ($\eta = 0.89$ cP at 25°C).

Zeta Potential Measurements

Zeta potential was determined using laser Doppler anemometry using a Zetasizer Nano Series (Malvern Instruments, Worcestershire, UK). Nanoparticle samples were diluted in ultrapure Milli-Q® water and placed in the electrophoretic cell where a potential of ±150 mV was established. The zeta potential values were calculated as mean electrophoretic mobility values using Smoluchowski's equation.

Nanoparticles Drug Content

Curcumin content in the nanoparticle suspensions was determined using a PerkinElmer Lambda 10 UV/VIS spectrophotometer at 420 nm. The calibration graph for curcumin in acetonitrile was linear over the range of 1.0–6.0 μg/mL with a correlation coefficient of 0.997. For determination of the entrapment efficiency, each sample was placed in Amicon centrifugal filter device with Ultracel-100 membrane (100 kDa, Millipore Corporation, Billerica, MA) and centrifuged at 6,200 g for 15 min to separate the free drug in the supernatant from the curcumin incorporated in the nanoparticles. The amount of drug incorporated in nanoparticles was calculated from the difference between the total concentration of curcumin found in the nanoparticle suspensions after their complete dissolution in acetonitrile and the concentration of drug in the supernatant. Drug recovery was calculated from the difference between the total concentration of drug found in the colloidal suspensions and the initial concentration added to the formulations.