Saudi Pharmaceutical Journal (2017) **25**, 32–43

King Saud University

Saudi Pharmaceutical Journal

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Polymeric films as a promising carrier for bioadhesive drug delivery: Development, characterization and optimization

Pallavi Bassi, Gurpreet Kaur *

Department of Pharmaceutical Sciences & Drug Research, Punjabi University, Patiala, Punjab, India

Received 30 March 2015; accepted 8 June 2015
Available online 25 June 2015

KEYWORDS

Polymeric films;
Response surface methodology;
Candidiasis;
Vaginal delivery

Abstract Bioadhesive films using tamarind seed polysaccharide were prepared for the treatment of candida vaginitis using nystatin as the model drug. Films were prepared by solvent casting method. A 3^2 factorial design was employed to study the effect of independent variables (polymer and plasticizer concentration) on a range of dependent variables namely mechanical, swelling, interfacial, and bioadhesive properties through response surface methodological approach, using Design Expert® software. Formulation composition that provided the most desired and optimized results was selected using desirability approach. Nystatin was solubilized using Tween 60 and was incorporated into the selected film. Drug solubilization and dispersion were confirmed by scanning electron microscopy and differential scanning calorimetry. The optimized film released 73.92 ± 2.54% of nystatin at the end of 8 h in simulated vaginal fluid and the release data showed best fit to Korsmeyer–Peppas model with R^2 of 0.9990 and the release mechanism to be super case-II. The optimized film also showed appropriate anti candida activity through appearance of zone of inhibition during antifungal activity testing study.

1. Introduction

Polymers derived from natural sources have been reported to possess versatile applications in biomedical and pharmaceuticals. Their availability in abundance, renewability, safety and biocompatible nature has encouraged the formulation scientist to substitute them for synthetic additives. Further, the presence of large number of reactive functional groups on the polymeric backbone of polysaccharides endows them with inherent bioadhesive potential. Natural polysaccharidic bioadhesive films as dosage forms are receiving considerable attention in the pharmaceutical industry as novel, patient compliant and convenient products due to their small size and thickness (Hariharan and Bogue, 2009; Lee and Chien, 1995; Li et al., 1998; Peh and Wong, 1999). Moreover, ease of manufacturing, cost effective method of preparation and

* Corresponding author. Tel.: +91 9814724622.
E-mail address: kaurgpt@gmail.com (G. Kaur).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2015.06.003
1319-0164

biocompatible nature of these films have promoted their applicability for both local and systemic delivery of therapeutic agents.

Tamarind Seed Polysaccharide (TSP) is derived from seed kernels of Tamarind (*Tamarindus indica* L.), belonging to family Leguminosae, a plant indigenous to India, Bangladesh, Myanmar, Sri Lanka, Malaysia, and Thailand (El-Siddig et al., 2006). The TSP structure comprises of β (1→4)-D-glucan backbone, substituted at position 6 of the glucopyranosyl units mainly by single α-D-xylopyranosyl residues as well as by disaccharide side chains composed of β-D-galactopyranosyl-(1→2)-α-D-xylopyranosyl residues (Patel et al., 2008). TSP is a high molecular weight polysaccharide (720–880 kDa), containing glucose, xylose and galactose units, in a molecular ratio of ~3:2:1 (Freitas et al., 2005). TSP has been reported to possess mucoadhesive (Sahoo et al., 2010) and control release properties (Sumathi and Alok, 2002). It has been employed in the textile printing as a thickener (Abo-Shosha et al., 2008) and in food industry as a thickening, stabilizing and gelling agent (Nishinari et al., 2000).

Candida vaginitis is one of the most commonly occurring infection affecting the majority of women during their lifetime. The vast incidence of this infection has stimulated the need for the development of therapeutic strategies that ensure successful eradication of the infection while maintaining the safety and therapeutic efficacy of the formulation and avoid problems like first pass effect associated with systemic delivery. In this scenario, local treatment of *C. vaginitis* represents a rational choice for its management.

Nystatin is a broad spectrum polyene antibiotic, produced by *Streptomyces noursei* strains (Kaur and Kakkar, 2010). It exerts its antifungal action by binding to sterols, chiefly ergosterol of the fungal cell membrane, and the formation of barrel-like membrane-spanning channels (Coutinho and Prieto, 2003). Nystatin has both an antifungal and fungistatic activities (Recamier et al., 2010) and has been found to possess broader spectrum of activity as compared to azole antifungals (Das-Neves et al., 2008). Commercially, very few vaginal nystatin formulations are available (Mycostatin®, Nilstat®, Nadostine®). These are cream formulations that suffer from the drawbacks of being leaky and messy in nature and also require a frequent dosing regimen owing to the self-cleansing action of the vagina, namely the secretion of mucus and humid site of administration (Valenta, 2005). In order to overcome these problems researchers started working up on designing of bioadhesive vaginal formulations, which would provide an intimate contact of the formulation at target site, improve residence time and thereby provide appropriate drug release characteristics. Nystatin gels (Hombach et al., 2009) and microparticulate (Martín-Villena et al., 2013) bioadhesive formulations have been designed for vaginal delivery of nystatin, however the release of nystatin from these formulations is either too little (30% nystatin release from polyacrylic acid cysteamine conjugate gels in 7 days) (Hombach et al., 2009) or a burst release has been observed (Martín-Villena et al., 2013), indicating a need towards the development of a mucoadhesive formulation that would provide controlled drug release and vaginal residence characteristics.

Response Surface Methodology (RSM) is widely used as a tool for designing of experiments in the development and optimization of drug delivery systems (Aberturas et al., 2002; Singh et al., 2005a,b) including preformulation studies to facilitate screening of excipients and to study the effects of different formulations and/or process variables on the drug release or dissolution characteristics (Chopra et al., 2007; Hooda et al., 2012; Mennini et al., 2008).

In the present study, Tamarind seed polysaccharide (TSP) bioadhesive films were prepared employing 3^2 randomized full factorial design and optimized in terms of different properties using RSM approach. The simultaneous evaluation of the effects of formulation variables (polymer and plasticizer concentration) on mechanical, swelling and bioadhesive properties of the film was carried out to determine the optimum formulation composition using RSM approach. TSP films were tested as drug carrier systems for vaginal delivery of nystatin. In vitro drug release studies and residence time studies were carried out to ensure appropriate drug release characteristics and vaginal retention. The antifungal activity of vaginal films was also determined by observing the zone of inhibition produced in vitro.

2. Material and method

2.1. Materials

Tamarind seed polysaccharide (TSP) was received as a gift sample from Encore Natural Polymer Pvt. Ltd (Naroda, Ahmadabad, India). Propylene glycol (PG) was procured from SD Fine chemicals ltd, India. Nystatin was received as a gift sample from DSM Sinochem Pharmaceuticals, India. *Candida albicans* ATCC 10231 was purchased from Institute of Microbial Technology (IMTECH), Chandigarh, India. All reagents and chemicals were of analytical grade and used as received.

Simulated vaginal fluid (SVF) was prepared according to the previous literature report with the following composition (g L^{-1}): NaCl, 3.51; KOH, 1.40; $Ca(OH)_2$, 0.222; bovine serum albumin, 0.018; lactic acid, 2.00; acetic acid, 1.00; glycerol, 0.160; urea, 0.400 and glucose, 5.00. The mixed solution was adjusted to a pH of 4.2 (Owen and Katz, 1999).

2.2. Preparation of TSP films

TSP films were prepared by the solvent casting method (Salamat-Miller et al., 2005). Briefly TSP (1–2% w/v) was dissolved in distilled water on a magnetic stirrer (Remi equipments, Mumbai India), this was followed by the addition of plasticizer (PG; 15–20%v/v). The resulting viscous solution (50 mL) was poured into polypropylene petri plates (553.86 cm^2). The petri plates were stored at 4 °C for 24 h to remove all the entrapped air bubbles (Mura et al., 2010) and then dried in an oven (Narang Scientific Works Pvt. Ltd., New Delhi) at 50 °C for 72 h. The dried films were carefully removed and checked for any imperfections or air bubbles and stored in desiccator till use.

2.3. Experimental design for optimization

A 3^2 randomized full factorial design with replicated centre point, consisting of 13 runs (Table 1), was used for optimization of films. Response surface methodology (RSM) was used to investigate the effect of independent variables (TSP concentration; X_1 and PG (plasticizer) concentration; X_2) on a range of dependent variables. The independent variables were