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Development of cellulosic polymer based gel of novel ternary mixture of miconazole nitrate for buccal delivery

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ABSTRACT

Aim of the present investigation was to develop cellulosic polymer based mucoadhesive antifungal gel comprising novel ternary mixture of miconazole nitrate (MN) for buccal delivery. Crosslinking of gel was made by adjusting pH with triethanolamine (TEA) and gel formulation was optimized on the basis of flux of MN (0.562–1.751 mg/cm^2/h) calculated from *ex vivo* permeation study. Based on statistically validated polynomial equation and plotted response surfaces, B17 was found to be the optimum batch. Texture profile in terms of adhesiveness (3.24 ± 0.012 g), firmness (10.83 ± 0.067 g), spreadability (3.63 ± 0.033 mJ) and extrudability (35.6 ± 0.1 mJ) of B17 was evaluated using a novel instrumental approach. The texture parameters were found to be consistent over 90 days. Ternary mixture containing gel showed broader zone of growth inhibition (32.67–47.33 mm) in comparison to marketed formulation containing pure MN (17.50–40.33 mm) against selected strains of fungi. In conclusion, consistent and effective mucoadhesive antifungal gel of MN with extended residence time in oral mucosa was developed.

1. Introduction

Drug delivery *via* buccal mucosa is a very challenging task, especially when the drug is very slightly soluble in water and has no/very low systemic availability when administered orally. Permeability of the drug through biological membrane is the second point of consideration, in order to get the desired systemic availability. A BCS class II drug could possibly be a good choice for buccal delivery. One of the well-known member of BCS class II drugs is imidazole derivative miconazole nitrate (MN) which is a potent antifungal drug used in various ailments like foot lesions (Sharma et al., 2011), cutaneous mycosis (Ghaninejad et al., 2009), diaper dermatitis (Eichenfield & Bogen, 2007), angular cheilitis (Cross & Short, 2008; MacFarlane, Ferguson, & MacKenzie, 1978) and oropharyngeal candidiasis (Lalla & Bensadoun, 2011). Variety of topical formulations comprising MN is available in the market however its oral/oropharyngeal delivery is not attempted yet which is of utmost importance (Kimbleton, Liu, Sun, & Wang, 1999). The possible reason could be its very less aqueous solubility; however it has very high permeability (Nafee, Ismail, Boraie, & Mortada, 2003). Recently, a novel ternary mixture (SolD-IC4) of MN, β-CD and lactose with enhanced aqueous solubility of MN was reported by us. Owing to the presence of β-CD and lactose, this ternary mixture enhanced the aqueous solubility of MN *i.e.* from 110.4 to 57,640.0 μg/ml (316 times higher). The remarkable upsurge in solubility of MN by ternary mixture was possibly due to blending of water soluble polymers, *i.e.* lactose with β-CD which enhanced the solubilizing nature of β-CD (Rai, Dwivedi, Yadav, Chanotiya, & Saraf, 2013). Therefore, ternary mixture (SolD-IC4) of MN was used to develop the buccoadhesive antifungal gel formulation.

Cellulosic mucoadhesive polymers are recognized as a smart strategy to extend the residence time and to enhance explicit localization of drug on several membranes (Khan, Gajbhiye, Singhavi, & Yeole, 2012; Pathak, Chhabra, & Pathak, 2013). Study of mucoadhesive properties of various polymers revealed that the bioadhesive potential in hydrophilic macromolecules is due to abundant hydrogen bond forming groups that help macromolecules to hydrate and swell in aqueous solutions (Lefnaoui & Moulai-Mostefa, 2011) under some specific stimuli like change in pH, temperature, light, electric field and osmotic pressure

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(Marcombe et al., 2010). Cellulosic polymers such as hydroxyl ethyl cellulose (HEC), hydroxypropyl methyl cellulose (HPMC) and sodium carboxymethylcellulose (SCMC) (Schmaljohann, 2006) are some of the well-known mucoadhesive polymers which have been used in the development of oral, nasal, anal and vaginal dosage forms (Bansal et al., 2009; Gonjari et al., 2009). These polymers are biodegradable and have a high degree of mucoadhesive properties with swelling in aqueous solvents (Gross & Kalra, 2002). A combination of HEC and carbopol was used to get escalated residence time of the drug and optimum mucoadhesiveness of gel in oral mucosa (Lefnaoui & Moulai-Mostefa, 2011). Therefore, the aim of the present investigation was to develop cellulosic polymer based mucoadhesive antifungal gel incorporating novel ternary mixture (SolD-IC4) in miconazole nitrate for buccal delivery.

2. Materials and methods

2.1. Materials

A novel ternary mixture of miconazole nitrate (SolD-IC4) was formulated using the methodology reported by Rai et al. (2013). The above ternary mixture was used to develop the mucoadhesive antifungal gel. Hydroxypropyl methyl cellulose (HPMC), carbopol 940, methyl paraben (MP) and propyl paraben (PP) were purchased from HiMedia Pvt. Ltd. (Mumbai, India). Glycerol was purchased from Qualigens Fine Chemicals (Mumbai, India). Polyethylene glycol 400 (PEG 400), propylene glycol (PG), hydroxyethyl cellulose (HEC) and sodium carboxy-methyl cellulose (SCMC) were purchased from CDH Ltd. (New Delhi, India). Tween 20 and Tween 80 were purchased from Thomas Baker Pvt. Ltd. (Mumbai, India). Triethanolamine was purchased from Fisher Scientific (Mumbai, India). Cultures of fungus *viz. Candida albicans* (CA) and *Sporothrix schenckii* (SS) were obtained from CSIR-Institute of Microbial Technology, India and *Cryptococcus neoformans* (CN) was received from All India Institute of Medical Sciences, New Delhi. All the chemicals used in the study were of analytical grade and double distilled water was used throughout the study.

2.2. Methods

2.2.1. Selection of polymer

Polymers were selected on the basis of their adhesiveness and gelling behavior. Pilot batches of gel were prepared using different grades of polymers such as HPMC, SCMC, HEC in various permutations and combinations for instance HEC and HPMC, HEC and SCMC, HPMC and SCMC, carbopol and HEC, carbopol and HPMC. A combination of carbopol and HEC was selected on the basis of its optimum adhesiveness and good consistency. At different concentrations of carbopol and HEC various prototype were prepared. Finally 1:1 (w/w) ratio of these polymers was found to be best which was selected as a final polymer combination to develop the desired gel.

2.2.2. Preparation of gel

Propyl paraben (0.05%, w/v) and methyl paraben (0.1%, w/v) were taken as a preservative in a beaker containing propylene glycol (1.0%, v/v as penetration enhancer). These were mixed properly by gentle stirring (100 rpm) and heating (50 °C) on a hot magnetic plate (Magnetic Stirrer IKA RCT basic). A sufficient quantity of water was added in a beaker. Carbopol 940 (0.75%, w/v; polymer) was dispersed slowly into the solution and allowed to soak for 24 h. After hydration, HEC (0.75%, w/v; polymer) was dispersed into soaked carbopol 940 mixture and stirred for about 30 min at 600 rpm followed by the addition of glycerin (10%, v/v; humectant) and polyethylene glycol 400 (5%, v/v; humectant). Ternary mixture equivalent to 1% (w/v) of miconazole nitrate (SolD-IC4; antifungal agent), Tween 20 (4%, w/v; surfactant), Tween 80 (1%, w/v; surfactant) and ethanol (4%, v/v) were taken in a 15 ml centrifuge tube which was vortexed (Tarsons Spinix 2883) for 15 min. The SolD-IC4 solution was mixed in previously prepared polymer solution by vigorous stirring at 1200 rpm for 15 min with the help of a mechanical stirrer (IKA® Eurostar, IKA India Pvt. Ltd., India). Triethanolamine (pH adjuster) was added drop by drop to the final mixture and stirred thoroughly until clear viscous homogeneous gel was obtained. The pH of the prepared buccoadhesive antifungal gel was kept in the range of 6.0–8.0.

Table 1
Coded levels of the independent variables used in the experimental design for the formulation of buccoadhesive antifungal gel of ternary mixture of MN.

Variables	Coded X_i	Coded level					ΔX
		$-\alpha$	−1	0	+1	$+\alpha$	
Concentration of polymer blend	X_1	0.66	1.00	1.50	2.00	2.34	0.50
Concentration of TEA	X_2	0.17	0.20	0.25	0.30	0.33	0.05
Concentration of Tween 20	X_3	0.64	2.00	4.00	6.00	7.36	2.00

ΔX is the increment of each experiment factor value corresponding to one unit of the coded variables.

2.2.3. Experimental design

Based on the flux of MN, a response surface methodology using a three-factor-three-level central composite design was employed, in order to optimize the formulation parameters of buccoadhesive antifungal gel. Quadratic equation was demonstrated by Design Expert® (trial version 8.0.7.1 Stat Ease Inc. USA). The concentration of 1:1 (w/w) ratio of HEC and carbopol 940 (X_1; weight %), TEA concentration (X_2; weight %) and Tween 20 concentration (X_3; weight %) were selected as the independent variables and analyzed at three coded levels *i.e.* low, medium and high (−1, 0 and +1 respectively). The dependent variable investigated was the flux of MN (Y, μg/cm^2/h). The selected factor combinations indicating the actual and coded levels as per the design are represented in Tables 1 and 2. The experimentally determined data was fitted to the least square regression model to get the optimum value of the independent variables (Chaudhary, Rohilla, Rathee, & Kumar, 2013; Solomon, Sahle, Gebre-Mariam, Asres, & Neubert, 2012). The regression model equation for Y (flux of MN) was evaluated using quadratic models (Eq. (1)) generated for each response parameter.

$$Y = \beta_0 + \sum_{i=1}^{3}\beta_i X_i + \sum_{j=1}^{3}\beta_{ii} X_i^2 + \sum_{i=1}^{3}\sum_{j-i=1}^{2}\beta_{ij} X_i X_j \quad (1)$$

where Y is the level of the measured response; β_0, β_i, β_{ii} and β_{ij} are regression coefficients for intercept, linear, quadratic and interaction coefficients, respectively; X_i and X_j stand for coded independent variables, the main effects and X_{ij} is the interaction between the main effects.

2.2.4. Characterization and evaluation of gel

2.2.4.1. Drug content. Gel equivalent to 10 mg of MN was dissolved in 100 ml distilled water and measured spectrophotometrically using UV–visible spectrophotometer (Shimadzu 1800) at 220.8 nm. Experiments were performed in triplicate.

2.2.4.2. pH evaluation. About 10% (w/v) solution of buccoadhesive antifungal gel in distilled water was used to measure the pH using a digital pH meter (Mettler Toledo LE-438) for all the experimental formulations (B1–B20). Experiments were performed in triplicate.