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Pullulan based oral thin film formulation of zolmitriptan: Development and optimization using factorial design

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ABSTRACT

The goal of study was to formulate and characterize pullulan based oral thin film (OTF) of zolmitriptan by solvent casting method. Based on preliminary trials, glass, PEG 400 and sucralose were selected as casting surface, water-miscible plasticizer and sweetener for OTF, respectively. A 3^2 factorial design was used to study the effect of amount of PEG 400 (X_1) and sucralose (X_2) as independent variables on tensile strength (Y_1), elasticity (Y_2), % *in-vitro* drug release in phosphate buffer of pH 6.8 at 5 min (Q_{5min}, Y_3) and overall taste of OTF (Y_4) as responses. OTF of batch F4 (PEG 400, 200 mg; sucralose, 12 mg) was identified as an optimized batch showing *in-vitro*, *in-vivo* disintegration time 20.70 and 21.58 s, respectively; 95.53% Q_{5min}; satisfactory thickness, strength, % elongation, ease of handling, smooth mouthfeel, excellent overall taste; even distribution of all ingredients in pullulan OTF (SEM study); and stable film at specified conditions concluding that pullulan, PEG 400 and sucralose are used in combination to make palatable, stable OTF of zolmitriptan.

1. Introduction

Research work on oral drug delivery has led to progress of solid oral dosage forms from simple to modified release tablets, oral disintegrating tablets (ODT) to oral thin films (OTF). OTF is as a thin film of stamp size containing a drug molecule and other excipients, prepared either by solvent casting or extrusion method that rapidly dissolves on patient's tongue when used without water [1]. It is highly preferred formulation by patients due to ease of preparation, handling, transportation, palatability, and dose uniformity [2]. OTF acts as mouth refreshing formulation and a carrier for bioactive components such as caffeine and other medicaments that are significantly tolerated by the U.S. Population [3].

OTF becomes more popular for various potent medicaments in contrast to immediate release ODT. With ODT, the health care professionals' are facing non-compliance in treatment of paediatric and geriatric patients. But the OTF has the superiorities of large surface area for rapid disintegration/dissolution and hence consumer-friendly [4]. Although ODT was designed for fast disintegration in mouth, but the panic of taking them and their risk of choking for certain patients can still exist, while OTF formulation can resolve the problem of swallowing and improves patient-compliance [5].

Various hydrophilic polymers are used as film formers for OTF such as pullulan [6,7], hydroxypropyl methyl cellulose [8], polyvinyl alcohol [9], maltodextrin [10], and Kollicoat® IR [11,12]. They have been widely accepted for OTF products. All these polymers are providing acceptable mechanical properties to OTF formulation, rapid dissolution in saliva and excellent mouth feel quality [13].

Pullulan, a natural biodegradable-biocompatible non-ionic water soluble extracellular film forming polysaccharide, is obtained from the fermentation medium of the black yeast such as *Aureobasidium pullulan* [14,15]. Due to its excellent film forming properties, it has been widely used as an edible film for various drugs [7], herb extracts, spices and flavours. Pullulan films are non-toxic, non-immunogenic, non-mutagenic, non-carcinogenic, non-reducing, blood compatible, hydrophilic, biodegradable, tasteless, colourless, resistant to oil, heat-stable, and impermeable to oxygen characteristics [16,17]. Based on these properties and advantages, pullulan was used as a film former in present investigation.

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Geriatric patients usually take more than one medication per day. Therefore, ease of administration of dosage forms is of paramount importance, especially among patients suffering from Alzheimer, Bipolar disorder, Migraine, Parkinson and Schizophrenia [18]. Among all types of dosage form, OTF is highly accepted due to its own advantages along with ease of oral delivery of various drugs (e.g., analgesics, anti-histamines, anti-asthmatics, cardiovascular drugs, neuroleptics, and drugs for erectile dysfunction) [19].

According to world federation of neurology, migraine is a familiar disorder characterized by recurrent attacks of headache, widely variable in intensity, frequency and duration. The WHO ranks migraine as the most disabling medical illness [20]. Zolmitriptan (ZMT), a 5-HT receptor agonist of BCS class III, has been widely prescribed for patients with migraine attacks, with or without an aura, and cluster headaches. It is vastly effective in reducing migraine symptoms, including pain, nausea and photo/phonophobia. It is available as conventional oral tablets (2.5, 5 mg), mouth dissolving tablets (2.5 mg), and nasal sprays (5 mg) in the market [21]. But nasal route has its own limitations such as rapid mucociliary clearance and low permeability of drugs through nasal mucosa [22]. This justifies the need of development of other effective alternatives such as OTF formulation.

Hence, based on rationale and background of pullulan and zolmitriptan, the aim of present investigation was to develop and formulate palatable pullulan based OTF of ZMT using desired evaluations following optimization of process factors. The proposed formulation has potential to improve compliance and quick onset of action in migraine patients than the available tablets of ZMT. This ZMT loaded pullulan based OTF presents multiple competitive advantages over its marketed oral dosage forms such as ease of swallowing without water, vary easy to formulate, simplicity to handle, store and carry away.

2. Materials and methods

2.1. Materials

Zolmitriptan (99.98% purity identified by HPLC method) and pullulan were received as gift samples from Alembic Pharmaceuticals Pvt. Ltd., Vadodara, India and from Gangwal Chemicals Pvt. Ltd. Mumbai, India (received through Hayashibara Biochemical Laboratories Inc. Okayama, Japan), respectively. PEG 400 and sucralose were purchased from Chemdyes Corporation Pvt. Ltd., Rajkot, India. Citric acid was purchased from S.D. Fine-Chem. Ltd., Mumbai, India. Freshly prepared distilled water was used whenever required.

2.2. Preliminary batches of pullulan based oral thin film

Preliminary batches of pullulan based OTF formulation using the ingredients as shown in Table 1 were prepared by solvent casting method as described below to identify the best compatible plasticizers (batch A–F) and sweeteners (batch G–L) as additives with their proportions and smooth uniform loading of ZMT (batch Z_1–Z_4) in final OTF.

2.3. Selection of plasticizers

Selection of best compatible plasticizer is essential for pullulan based OTF. Based on literature work it was identified that from the varieties of plasticizers [6,7], three plasticizers namely glycerine, propylene glycol and polyethylene glycol (PEG 400) are commonly preferred to make stable, flexible with desired mechanical strength thin film of natural polymers. Hence, at preliminary trial batches, plasticizers namely glycerine, propylene glycol and polyethylene glycol (PEG 400) were used to identify the best one for making flexible with required mechanical strength, stable, compatible OTF of pullulan (batch A–F, Table 1).

2.4. Selection of sweeteners

To identify compatibility and influence of sweeteners (aspartame, sucralose and sodium saccharine) on palatability of pullulan based OTF, batch G–L (Table 1) were prepared. ZMT is bitter in taste [23] and essential to make its palatable OTF. To enhance palatability of ZMT in pullulan based OTF, sucralose was used as a semi-synthetic sweetener due to its advantages in comparison to other selected sweeteners. It is non-toxic, non-carcinogenic, non-irritant, non-nutritional, highly stable, having high sweetening power and universally accepted as a sweetener for varieties of food and pharmaceutical products [24]. Required amount of citric acid (acts as salivary stimulant) was incorporated in pullulan based OTF of zolmitriptan in order to minimize recrystallization of ZMT in resultant OTF (batch Z_1–Z_4, Table 1**)**.

2.5. Preparation of pullulan based oral thin films (OTF)

Solvent casting method was used. Accurate weigh of pullulan was dissolved in beaker (50 ml capacity) containing 10 ml of distilled water. Needful quantity of glycerine, propylene glycol, and PEG 400 were added in respective batch of pullulan aqueous solution under stirring to get clean homogeneous solution. At the end, required quantities of sweeteners were added with stirring until the preparation became homogeneous without any air-entrapment. The obtained solution of each batch was allowed to stand for half-an-hour to remove air-bubble, if any. The smooth homogeneous solution of each batch was poured gently in transparent glass petri-plates of uniform size ($10 \times 10 \times 0.5\,cm^3$) and allowed to dry at ambient temperature ($28 \pm 1\,^{\circ}C$) until the preparation became a dry film. The developed each dry film was then carefully removed from plates using spatula, segmented into pieces ($2 \times 2\,cm^2$) and stored in aluminium sachets at 2–8 °C until further studies.

2.6. Preparation of zolmitriptan loaded pullulan based oral thin films (OTF)

Pullulan based OTF of ZMT (batch Z_1–Z_4, Table 1) was prepared using same method as described in Section 2.5 with minor changes. Needful quantity of citric acid (saliva stimulator) was added in aqueous pullulan solution to minimize recrystallization of ZMT. It was allowed to stir for few minutes using magnetic stirrer (MS-500, REMI, India) until it dissolved. On its dissolution, accurately 62.5 mg of ZMT was added with stirring. When the solution found clear smooth homogeneous, accurately 200 mg of PEG 400, requisite quantities of sucralose and mint flavour (5 mg) were added in the preparation under stirring to get clear homogeneous preparation. The solutions were allowed to stand for half-an-hour to remove air-bubble, if any. The remaining procedure was same as described Section 2.5. The resulting dried piece ($2 \times 2\,cm^2$) of pullulan based OTF of ZMT was stored in aluminium sachet at refrigerated temperature (2–8 °C) until further studies. Fig. 1 illustrates schematic representation of laboratory scale preparation of pullulan based OTF with/without ZMT.

2.7. Preparation of pullulan based oral thin film of zolmitriptan using factorial design

To get an optimized ZMT loaded pullulan based OTF, a 3^2 (two-factor and three-level) factorial design was applied. Amount of PEG 400 (X_1, mg) and sucralose (X_2, mg) were selected as independent variables (Table 2). Tensile strength (Y_1), percentage elongation