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Research paper

Combined dosage form of pioglitazone and felodipine as mucoadhesive pellets via hot melt extrusion for improved buccal delivery with application of quality by design approach

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ABSTRACT

The content of investigation was to develop and optimize buccal hot melt extruded (HME) pellets for Pioglitazone (PIO) and Felodipine (FDP) in combined dosage form for the management of diabetes and hypertension using Box–Behnken design. In this study, three factors evaluated at three levels. Amount of PEON80 (A_1), amount of HPMCK$_4$M (A_2) and amount of plasticizer (A_3) as independent variables and bioadhesion strength (BS) (B_1), erosion (B_2) and percent drug release in 1 h Q_1 (B_3) as responses. Pellets were prepared by hot melt extrusion technique. HME pellets were evaluated for compatibility, physicochemical properties, *ex vivo* permeation, *in vivo* bioavailability in pigs and stability studies. Pellets demonstrated no drug excipient interaction and excellent content uniformity. Statistically optimized HME pellet showed BS of 2.92 ± 0.04 N, erosion of 10.5 ± 2.05% and percent drug release of 31.9 ± 2.1% and 29.2 ± 1.9% for PIO and FDP respectively. Statistically optimized pellet prolonged *in vitro* drug release of 96.6% PIO and 94.5% FDP release in 6 h and permeated 68.6 and 66.4% with flux of 0.372 and 0.361 mg h^{-1} cm^{-2} of PIO and FDP respectively through porcine buccal membrane. Statistically significant ($p < 0.01$) improvement in bioavailability was observed for PIO (1.9-folds) and FDP (2.1-folds). No significant changes were observed in 6 months during stability studies.

1. Back ground

Hot melt extrusion technology is a processing technique widely applied in the plastics industry [1,2]. Hot-melt extrusion is used not only in the production of plastic goods, but also in polymer production and compounding. However, over the past couple of decades, its focus has been on myriad applications in the growing pharmaceutical field, which is evident from the published scientific literature [2] and will yield only few articles with this technology applied to pharmaceutical systems. A few researchers have recently demonstrated that the HME technique is a viable method to prepare pellets [3], sustained release tablets [4] and novel delivery systems via extruded films [5,6]. Transmucosal delivery systems are primarily produced by films cast from organic or aqueous solvents and the disadvantages accompanying with these techniques are long processing times, environmental concerns (organic solvent disposal), and excessive costs [6]. Hot melt extrusion technology offers many advantages over these traditional processing techniques including the fact that no solvents are utilized, fewer processing steps in only single equipment, providing a more environmental friendly technology, good drug content uniformity due to intense mixing and agitation, improved bioavailability through drug solubilization or dispersion at the molecular level [2]. In addition, HME entails a potential continuous process which can translate into decreased production costs. Thus, an efficient, economical drug delivery system, such as the transmucosal delivery, is a very likely outcome utilizing HME.

The buccal administration of drugs is drawing considerable attention since it has an excellent accessibility, an expanse of smooth muscle, robustness of the epithelium, relatively immobile mucosa and comparatively less susceptibility to enzymatic activity,

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hence suitable for administration of retentive dosage forms [7]. Direct access to systemic circulation through the internal jugular vein bypasses drugs from the hepatic first-pass metabolism leading to high bioavailability [8].

Buccal bioadhesive drug devices designed to remain in contact with buccal mucosa and release the drug over a longer period of time in a controlled fashion, overcomes drug degradation in the GI tract, active drug loss due to first pass metabolism, and inconvenience of parenteral administration [9]. Buccal delivery is high patient acceptability compared to other non-oral routes of drug administration and controls plasma concentrations of potent drugs and can interrupt drug input quickly in case of toxicity [10].

Response surface methodology (RSM), is a collection of mathematical and statistical techniques that are useful for modeling and analysis in applications where a response of interest is influenced by several variables and the objective is to optimize the response [11]. Box–Behnken Design (BBD) is a popular form of RSM and is a very useful tool in understanding the interactions among the parameters that have been optimized. This method is suitable for fitting a quadratic surface and the minimum number of levels required for a factor to quantify that behavior is three. One might logically assume that adding center points to a two-level design would satisfy that requirement, but the arrangement of the treatments in such a matrix confounds all quadratic effects with each other [12].

Pioglitazone (PIO) is a thiazolidinedione compound used in the treatment of type 2 diabetes. It is an insulin sensitizer that acts as agonist of the peroxisome proliferators activated receptor subtype gamma (PPAR-γ) [13]. Pioglitazone is rapidly absorbed, its oral bioavailability 80%, and it is extensively metabolized by hydroxylation and oxidation to active and inactive metabolites in the liver [14]. Felodipine (FDP), a calcium channel blocker belonging to dihydropyridines is used as a potent peripheral vasodilator, which effectively reduces blood pressure when given at doses of 5–20 mg per day. After a single, 20 mg oral dose of FDP, peak plasma concentrations are achieved within 2.5–5 h [15]. It was reported to be well absorbed following oral administration, but undergoes extensive first pass metabolism; leading to poor bioavailability [16]. Patients with hyperglycemia also suffered from hypertension therefore combination of two drugs is prescribed to patients. Currently there is no combined dosage form available and is available as individual tablets FDP (Plendil) and PIO (Actos). Therefore, PIO for diabetes and FDP for hypertension selected as a model drug for combined delivery and an alternative mode of delivery system like buccal delivery system is desired.

The aim of the present investigation is to study the feasibility of producing stable controlled release hot melt extruded (HME) pellets containing PIO and FDP in combined dosage form using Box–Behnken design for the management of diabetes and hypertension for buccal delivery. These extruded pellets were subjected to wide-ranging *in vitro* characterization tests such as bioadhesion, *in vitro* release, *ex vivo* permeation, *in vivo* bioavailability in pigs and stability.

2. Materials and methods

2.1. Materials

Felodipine was gifted by Sun pharmaceuticals (Baroda, India). Pioglitazone, Nitrendipine and HPMC K_4M were gifted by Dr. Reddys Laboratories (Hyderabad, India). PEO (PolyOx WSR N-80 [PEO N-80], MW 200,000 Da) was kindly donated by Dow Chemical Co (Midland, MI, USA). Polyester backing membrane was gifted by 3 M (St. Paul, MI, USA). Mucin (Crude Type II) was procured from Sigma–Aldrich, (Germany) and was used without further purification. All reagents used were of analytical grade.

2.2. Methods

2.2.1. Ex vivo drug permeation

Porcine buccal mucosa was used for drug permeation study as it resembles the human buccal mucosa regarding permeability, barrier lipid composition, thickness and histology [17]. Buccal tissue from pigs was obtained from local slaughterhouse and used within 2 h of slaughter. The tissue was stored in Krebs buffer at 4 °C after collection and separated from the underlying connective tissue with surgical technique. Franz diffusion cell was used for this study. The buccal epithelium was carefully mounted between donor and receptor compartment. Phosphate buffer saline (PBS) pH 7.4 containing polyethylene glycol (PEG 400) and 5% v/v alcohol was placed in receptor compartment. PBS pH 7.4 containing 15 mg of PIO, 5 mg of FDP and a marker compound, phenol red (20 μg ml^{-1}) was placed in donor compartment. The entire set up was placed over magnetic stirrer and temperature was maintained at 37 °C [18,19]. Samples of 1 ml were collected at predetermined time points from receptor compartment and replaced with an equal volume of fresh solution and analyzed utilizing high performance liquid chromatography (HPLC).

2.2.2. Determination of drug content in the samples by HPLC

The HPLC system (Shimadzu, Kyoto, Japan) consisting of a LC-10AT solvent module, SPD10A UV–visible detector with LC10 software. The analytical column used was C_{18} (Inertsil, 150 × 4.6 mm i.d., particle size 5 μm) at an ambient temperature. The mobile phase used was acetonitrile and 50 mM ammonium acetate buffer (pH 5.0, adjusted with glacial acetic acid) (67:33%, v/v) at a flow rate of 1.0 ml min^{-1}. The linearity range of proposed method was 1–5000 ng/ml for each analyte with regression coefficient greater than 0.999. The retention times for PIO, FDP and Nitrendipine (NTDP) were found to be 5.32, 10.68 and 7.26 min respectively. The required studies were carried out to estimate the precision and accuracy of the HPLC method [20].

2.2.3. Box–Behnken design

In this study, a BBD was used to optimize the formulation variables of HME buccal pellets containing 3 factors and evaluated at 3 levels. Amount of PEO N80 (A_1), amount of HPMCK_4M (A_2) and amount of plasticizer (Vitamin E Succinate) (A_3) as independent variables and bioadhesion strength (BS) (B_1), erosion (B_2) and percent drug release at 1 h (Q_1, B_3) as responses. The independent factors and their range levels used in the study are presented in Table 1. The experiments were designed by using DOE software (Version 9.0.0.1, Stat-Ease Inc., Minneapolis, MN, USA) and the layout of the design is shown in Table 2. A total of 17 formulations were designed by the software with 5 center points.

The DOE software was used to give information not only on the critical values required to achieve the desired response but also the possible interactions of the selected independent variables on the dependent variables [21]. The response surface method normally

Table 1
Independent variables and their selected range used in Box–Behnken design for hot melt extruded buccal pellets of pioglitazone and felodipine.

Independent variables	Levels used, actual (coded)		
	Low (−1)	Medium (0)	High (+1)
A_1:amount of PEO N80 (mg)	50	60	70
A_2: amount of HPMC K_4M (mg)	5	12.5	20
A_3: amount of plasticizer (mg)	6	8	10