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Characterization of natural polymers from jackfruit pulp, calendula flowers and tara seeds as mucoadhesive and controlled release components in buccal tablets

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ABSTRACT

Identification and physiochemical parameters such as solubility, loss on drying, viscosity, pH, swelling index, starch and gum constituents were determined in natural polymers and showed satisfactory results. Spectral studies established the compatibility of natural polymers. The drug release kinetics in preliminary trial batches showed that tablets containing natural mucilages and gum showed a prolonged drug release comparable to Carbopol 974P and Methocel K4M. Also, all tablets showed a satisfactory drug permeability flux. Acute toxicity studies confirmed the safety of natural polymers. Using response surface method supported by 2^3 factorial design, the optimized buccoadhesive tablets (C1) with drug release at 8 h (R8h, %) of $53.48 \pm 0.048\%$ showed controlled release over ≥8 h and followed the Korsmeyer-Peppas model with anomalous (non-Fickian) diffusion mechanism. Mucoadhesive strength was found to be 42.71 ± 0.49 g. Comparative dissolution study between prepared and marketed formulation showed that there was no significant difference in drug release profile having similarity factor 82.97. *In vivo* study for optimized formulation of the buccoadhesive tablets showed the better absolute bioavailability (71.26%) against the oral solution (51.22%). Histological study confirmed non-irritant nature and stability study indicated stability of the formulation.

1. Introduction

In comparison to conventional drug delivery systems, buccoadhesive drug delivery systems propose many advantages like ease of administration, rapid execution of therapy and administration to unconscious patients. This route is useful for the drugs which are spoiled by the enzymatic or alkaline intestinal environment and which are unstable in the acidic stomach environment [1].

Controlled release systems provide continuous drug release at a predetermined rate and for a predetermined time. These systems facilitate better control of drug release over the time, assist drug in crossing physiological barriers, protect drug from premature elimination, and push the drug to the desired site of action while minimizing drug exposure elsewhere in the body. Controlled release systems may also reduce frequency of dosing and increase patient compliance. By extending patent protection these systems may add commercial value to the marketed drugs and may also reduce performance of drug products variability [2].

Buccal tablets have a great potential as a mucosal drug delivery system owing to their simplicity, reduced risk of systemic toxicity and minimal chances of dose dumping. Complicated production methods like coating and pelletization during preparation of buccal tablets are avoided and controlled drug release rate from the formulation is reliant on the type and amount of polymer used in the formulations [3].

The natural polymers are remarkably used for pharmaceutical purpose owing to certain advantages such as economy, ready availability, nontoxicity and capability of chemical alteration, potential biodegradability and sometimes biocompatibility with few exceptions [4]. In various pharmaceutical dosage forms such as matrix systems, film coaters, films for buccal drug delivery, microspheres, nanoparticles, viscous ophthalmic solutions, suspensions and implants, the application of natural polymers derived from plant sources have been investigated with proven efficacy.

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These natural polymers are also used as viscosity builders, stabilizing agents, disintegrating agents, solubilizing agents, emulsifying agents, suspending agents, gel formers, bio/mucoadhesives and binding agents in various formulations [5–8].

Physiological products of the plants are mucilages whereas pathological products are gums [9]. Both, mucilages and gums are plant hydrocolloids and monosaccharide or mixed monosaccharides polymers. Many of the mucilages and gums are amorphous translucent substances united with uronic acids. Both mucilages and gums possess alike components and on hydrolysis they yield a mixture of sugars and uronic acids. Hydrophilic molecules in mucilages and gums can form viscous solutions or gels with water [10–13].

Jackfruit pulp mucilage (JM), Calendula flowers mucilage (CM) and Tara gum (TG) are obtained from natural sources such as *Artocarpus heterophyllus* Lam. (Moraceae), *Calendula officinalis* L. (Asteraceae/Compositae) and seed of *Caesalpinia spinosa*, belonging to the family Leguminosae or Fabaceae. The controlled release and mucoadhesive potential of these polymers have not been reported in the literature. Therefore, the present investigation attempted to explore the controlled release and mucoadhesive characteristics of Jackfruit pulp mucilage, Calendula flowers mucilage and Tara gum.

The purpose of the current study was to formulate buccoadhesive tablets [14] for controlled release containing a blend of Jackfruit pulp mucilage, Calendula mucilage and Tara gum by direct compression method using response surface methodology [15] with an objective to circumvent pre-systemic metabolism and also to enhance buccal retention time of the drug.

In geriatric and unconscious patients, oral route of drug administration is not feasible and mucoadhesive formulation with controlled release is need of an hour. Hence, formulating mucoadhesive formulation for 8 h may be important for the treatment of both topical and systemic diseases. Chlorpheniramine maleate (CPM), [16] an antihistaminic drug used for symptomatic relief of the common cold and allergy was employed as a model drug to assess the controlled-release potential of the mucilages and gum.

Optimization technique using 2^3 (three-factor and two-level) factorial design was employed to study the effect of the amounts of natural polymers viz., Jackfruit pulp mucilage, Calendula mucilage and Tara gum on the properties of buccoadhesive tablets like Percentage Cumulative Drug Release (% CDR) and mucoadhesive strength.

Thus, to overcome the drawbacks associated with conventional tablets as well as with synthetic polymers, the present investigation was undertaken with an objective to control the drug release with the use of natural polymers in buccoadhesive tablets.

2. Materials and methods

2.1. Materials

CPM was obtained as gift sample from Alembic Ltd. Vadodara, Gujarat. Jackfruit, Tara Gum, and Calendula flowers were procured from local market and nursery of Vadodara town. Methocel K4M, Carbopol 974P were procured form Loba Chem (Mumbai, India) and used as received. All other reagents used were of analytical grade.

2.2. Characterization of mucilages and gum

Mucilages and gum were characterized for identification and various physiochemical parameters such as colour, solubility, loss on drying [17], viscosity, pH, swelling index, starch and gum constituents [18].

2.3. Compatibility study

Mixtures consisting of different ratios of CPM/JM, CPM/CM, CPM/TG and either CPM or mucilages/gum alone were subjected to FTIR analysis using a model BRUKER ALPHA T FTIR spectrophotometer (Bruker Optik GmbH, Germany).

2.4. Comparative mucoadhesive characterization of mucilages and gum with methocel K4M and carbopol 974P as standard polymers; shear stress measurement

The mucoadhesive agent solution (3% w/v) using Carbopol 974P, Methocel K4M and a natural mucilages and gum was prepared. Shear stress was calculated by self fabricated apparatus made of wooden board with scale and two glass slides having two pans on the both sides mounted on a pulley [19].

2.5. Acute toxicity studies

Acute oral toxicity study was performed as per Organization for Economic Cooperation and Development-425 [OECD-425] guidelines (acute toxic class method) [20].

2.6. Formulation and evaluation of buccal tablets containing carbopol 974P, methocel K4M, JM, CM and TG

Three batches of tablets (each containing CPM as model drug 8 mg) were prepared (preliminary trial batches) using varying concentration of the mucoadhesive agent (25 mg, 50 mg and 75 mg) by direct compression method using flat faced 6 mm punch (Rimek Mini Press-I machine), resulting in 27 different formulations (CF1, CF2, CF3 for Carbopol 974P; HF1, HF2, HF3 for Methocel K4M; JMF1, JMF2, JMF3; CMF1, CMF2, CMF3;TGF1, TGF2, TGF3 for mucilages and gum). The tablet weight was adjusted to 150 mg. The prepared tablets were evaluated for average thickness, hardness, friability test, weight variation test and mucoadhesive strength measurement [21,22].

2.7. Dissolution testing

Dissolution studies were performed using a USP dissolution apparatus 2 (paddle method) at 50 rpm. The values of n and K were calculated by regression analysis and the statistical parameter R^2 was established to evaluate the fitting of the semi-empirical equation $Mt/M\infty = Ktn$ (where $Mt/M\infty$ is the fractional amount of the drug at the time t, K is a kinetic constant of the system which indicates rate of the release and the n is the release exponent, indicative of the mechanism of release.) to the release kinetics [23].

2.8. Mucoadhesion studies

The force of detachment (mucoadhesive strength) of CPM buccal tablets applied to freshly excised goat buccal mucosa as a model membrane was measured in grams by using self fabricated apparatus (modified physical balance) as per the reference given in the literature with little modifications [24].

2.9. In vitro *drug permeation*

The *in vitro* buccal drug permeation studies of CPM through the goat buccal mucosa were done by using modified Franz diffusion cell at $37\,^{\circ}C \pm 0.5\,^{\circ}C$ (Diameter of 1.5 cm with a diffusional area of 1.76 cm^2).

A test on the reference solution was carried out by placing 2 ml of the solution in the donor compartment. The solution was obtained adding an excess of drug in purified water at room temperature.