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Core-shell alginate-ghatti gum modified montmorillonite composite matrices for stomach-specific flurbiprofen delivery

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ABSTRACT

Novel alginate-arabic gum (AG) gel membrane coated alginate-ghatti gum (GG) modified montmorillonite (MMT) composite matrices were developed for intragastric flurbiprofen (FLU) delivery by combining floating and mucoadhesion mechanisms. The clay-biopolymer composite matrices containing FLU as core were accomplished by ionic-gelation technique. Effects of polymer-blend (alginate:GG) ratios and crosslinker ($CaCl_2$) concentrations on drug entrapment efficiency (DEE, %) and cumulative drug release after 8 h (Q_{8h}, %) were studied to optimize the core matrices by a 3^2 factorial design. The optimized matrices (F-O) demonstrated DEE of 91.69 ± 1.43% and Q_{8h} of 74.96 ± 1.56% with minimum errors in prediction. The alginate-AG gel membrane enveloped optimized matrices (F-O, coated) exhibited superior buoyancy, better *ex vivo* mucoadhesion and slower drug release rate. The drug release profile of FLU-loaded uncoated and coated optimized matrices was best fitted in Korsmeyer-Peppas model with anomalous diffusion and case-II transport driven mechanism, respectively. The uncoated and coated matrices containing FLU were also characterized for drug-excipients compatibility, drug crystallinity, thermal behaviour and surface morphology. Thus, the newly developed alginate-AG gel membrane coated alginate-GG modified MMT composite matrices are appropriate for intragastric delivery of FLU over an extended period of time with improved therapeutic benefits.

1. Introduction

During the past few decades, stomach-specific drug delivery systems encompassing an array of devices such as floating, mucoadhesive, high density, swelling or size-expanding systems have been extensively investigated [1]. The combined floatation-mucoadhesion approaches for stomach targeted drug delivery are presently receiving overwhelming attention as these systems demonstrate a superior gastroretention by virtue of their floating and bio-adhesive capabilities [2]. In recent years, the stomach-specific deliveries of bioactive molecules intercalated into the interlayer space of montmorillonite (MMT) have been reported [3–4]. MMT, a smectite clay mineral, is characterized by the properties of large specific surface area, excellent adsorption and cation exchange capacity with gastroprotective antacid activity. It also exhibits standout bioadhesive property due to its various interactions with the mucus glycoproteins [3]. The 2:1 layered structure of MMT is comprised of two fused silica tetrahedral sheets sandwiching an edge-shared octahedral sheet of aluminium. Various poorly soluble drug molecules, typically anchored by electrostatic interactions and hydrogen bonding contacts between the inorganic layers, display enhanced solubility with controlled drug release profile in physiological environment [5–6]. At present, the development of various biopolymer-smectite clay based composite matrices, particularly sodium alginate-MMT hybrid composites has gained explicit emphasis due to their distinct ability to improve drug delivery characteristics [7–10].

Sodium alginate is an anionic heteropolysaccharide comprising β-1,4-linked D-mannuronic acid and α-1,4-linked L-glucuronic acid residues, which randomly arrange along the chains [11]. It has distinctive feature of being instantaneously gelled when contacted with multivalent metal cations (*e.g.*, Ca^{+2} and Zn^{+2}), which has long been employed as a facile method to formulate alginate-based floating drug delivery carriers [12]. Unfortunately, many advantages offered by MMT-blended alginate floating matrices are complemented by their shortfalls like poor drug encapsulation endowed with accelerated drug release rate [13]. This could be attributed to the inability of alginate molecules to enter the silicate layers of MMT due to the repulsive forces between negatively charged clay surfaces and carboxylic groups of polymer. Thus, MMT is often organically modified by blending with various types of surfactants in order to achieve sufficient exfoliation or enlargement of the interlayer gallery space. It ensures excellent intercalation of

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alginate molecules into the silicate layers of MMT with improved compatibility and drug delivery characteristics [14]. Ghatti gum (GG) is a plant-derived amphiphilic glycoprotein obtained from *Anogeissus latifolia* [15]. It displays outstanding emulsifying property, which encouraged us to use GG as an intercalating agent to enlarge interlayer space of MMT. GG consists mainly of alternating 4-O-subsituted and 2-O-subsituted α-D-mannopyranose residues and chains of β-1,6-linked D-galactopyranose backbone with a single L-arabinofuranose unit as side chain. The carbohydrate part of GG is covalently linked with highly hydrophobic protein moieties [16–17].

Recently, a flurry of scientific investigations has employed bio-adhesive biopolymer-blended alginate based gel coating on floating devices [1,12,18] to improve the bio-performance of the drug delivery carriers. Arabic gum (AG), a naturally occurring polysaccharide with gastric ulcer protective activity, is isolated from *Acacia sengegal* and *Acacia seyal*. It is built from β-1,3 and 1,6-linked D-galactopyranosyl units along with β-1,6-linked D-glucopyranosyluronic acid residues. The side branch contains α-L-rhamnopyranose, β-D-glucuronic acid, β-D-galactopyranose and α-L-arabinofuranosyl units with (1 → 3), (1 → 4) and (1 → 6) glycosidic linkages, respectively. AG demonstrates excellent mucoadhesive property, which boosted pioneering research groups to develop crosslinked AG-blended alginate mucoadhesive matrices [19].

The current work illustrates an experimental demonstration of the credibility of novel floating-mucoadhesive alginate-AG gel coated Ca-alginate-GG modified MMT (Ca-alginate-GG-MMT) composite matrices for flurbiprofen (FLU) delivery. FLU, a poorly water soluble non-steroidal anti-inflammatory agent of 2-arylpropionic acid class (Fig. 1), is often clinically recommended for inflammation and arthritis management [20]. It produces ulcerogenic adverse effect with abdominal discomfort [21]. The shorter half life of the drug (4.9 h) has triggered an increased interest for developing the sustained release drug delivery systems [1,22–23]. Herein, a 3^2 factorial design based FLU-loaded Ca-alginate-GG-MMT composite core matrices were formulated by ionotropic emulsion gelation technique and systematically optimized. The optimized matrices were further coated by Ca^{+2} harden alginate-AG hybrid gel membrane. The presence of AG in coating membrane was speculated to minimize the gastric ulcerogenicity of FLU. The uncoated and coated matrices were subjected to various *in vitro* investigations.

2. Materials and methods

2.1. Materials

FLU (Sun Pharmaceuticals, India), sodium alginate (Mw: 7.72 × 10^4 g/mol, degree of polymerization: 476 and M/G ratio: 1.08, S.D. Fine Chemicals Ltd., India), GG (Mw of soluble portion: 12,000 g/mol, protein content: 3.4%, Nutriroma, India), AG (Mw: 250,000 g/mol, S.D. Fine Chemicals Ltd., India), MMT (Qualigens Fine Chemicals, India) and calcium chloride ($CaCl_2$, Merck Ltd., India) were used. All the chemicals and reagents were of analytical grade.

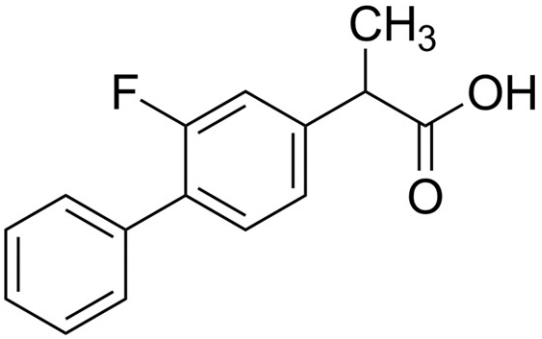

Fig. 1. Chemical structure of FLU.

2.2. Preparation of Ca-alginate-GG-MMT composite matrices containing FLU

MMT (0.6% w/v) was suspended in distilled water containing GG at variable concentrations and stirred for 30 min by a magnetic stirrer. FLU (0.6% w/v) and the required quantity of sodium alginate were introduced to MMT-GG suspension to produce variable alginate to GG ratios (*i.e.*, 5:1, 3:1 and 1:1) and the mixture was agitated for another 30 min. Finally, it was homogenized with a homogenizer operating at 5000 rpm for 20 min. The drug to MMT ratio of 1:1 was selected based on published literature [24]. The drug to biopolymer (including alginate and GG) ratio of 1:3 was maintained for all the formulations (Tables 1 and 2). The resulting dispersion was then extruded through 21G needles into gently stirred $CaCl_2$ solution (5–10% w/v) at room temperature. The resulting bead-shaped matrices were allowed to stand in $CaCl_2$ solution for 20 min, collected by filtration and washed three times with distilled water. The beads were dried at ambient temperature to constant weight and stored in a desiccator [18].

2.3. Experimental design

A 3^2 factorial design was adopted to assess the influences of two independent variables *viz.*, sodium alginate to GG ratios (X_1) and $CaCl_2$ concentrations (X_2) on the response variables *i.e.*, drug entrapment efficiency (DEE, %) and cumulative drug release after 8 h (Q_{8h}, %) in 0.1 N HCl (pH 1.2) [12]. Both independent factors (X_1 and X_2) were varied at three levels (high, medium and low). The experimental trials consisted of all the nine possible combinations were conducted. All other parameters were kept constant (Tables 1 and 2). The software derived quadratic equations including interactive and polynomial terms for each response can be expressed as [2]:

$Y = b_o + b_1 X_1 + b_2 X_2 + b_3 X_1 X_2 + b_4 X_1^2 + b_5 X_2^2$, where, Y denotes the response variable, b_o represents the arithmetic mean response of nine runs and b_i refers to the estimated coefficient for the independent variables X_i. X_1 and X_2 depict the individual effects, X_1X_2 describes interaction effects and polynomial terms (X_1^2 and X_2^2) signify the nonlinearity of the model. One-way ANOVA analysis was utilized to estimate the significance of the models as well as individual independent variables ($p < 0.05$).

2.4. Alginate-AG gel coating onto Ca-alginate-GG-MMT composite matrices

The optimized *Ca-alginate-GG-MMT* hybrid matrices containing FLU were placed in a 1.0% (w/w) aqueous dispersion of sodium alginate and AG (1:1). After 5 min, the beads were transferred into $CaCl_2$ solution (5% w/v) and allowed to harden for 10 min. The coated matrices were subsequently filtered, washed with distilled water and dried at ambient temperature until the beads weight remained constant for two successive measurements [18].

2.5. P-XRD studies

The structural changes in MMT lattice and the alteration of drug crystallinity in composite matrices were examined by powder X-ray diffraction (*P*-XRD) (Bruker-AXS D8) with a CuKα radiation detector, operating at 40 kV voltage and 30 mA input current [25].

Table 1
Independent variables and their levels adopted to accomplish uncoated Ca-alginate-GG-MMT composite matrices containing FLU.

Independent variable	Level		
	(+1)	(0)	(−1)
Alginate to GG ratio (by weight)—X_1	5:1	3:1	1:1
$CaCl_2$ solution (% w/v)—X_2	10	7.5	5