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Development of locust bean gum and xanthan gum based biodegradable microparticles of celecoxib using a central composite design and its evaluation

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ABSTRACT

Biopolymers are naturally occurring polymeric biomolecules. They are easily accessible, relatively cheap, can be synthetically altered and biodegradable. Locust bean gum and Xanthan gum is widely used ingredient in drug formulations due to their non interacting behavior with the drug and less toxicity. Microparticle formulations of celecoxib, a COX-2 inhibitor were formulated using Locust bean gum and Xanthan gum. Quality by design approach was used and two-factor five level central composite designs were used to perform the experiment. A quadratic polynomial model was produced to anticipate the independent variables with respect to the dependent variable. Studies on formulation variables were done and microparticles were characterized for their size, micrometric properties and surface morphology. *In vitro* experiments on drug release profile studies have indicated an increase in the drug release retardation with increasing Locust bean gum and Xanthan gum concentration. The microparticles that were formulated were found to be stable with respect to their drug content and physicochemical characters for over a period of 6 months at different temperatures as per the ICH Q1A guidelines.

1. Introduction

The selection, modification and elaboration of new materials for various applications are important criteria in the development of innovative products. Micro particulate systems is emerging as a favored system for drug carriers in pharmaceutical field (Chen et al., 1987; Gupta and Hung, 1989; Sharma et al., 2013a,b) to make solid entities from oils, to control taste or odor, to protect drugs from getting oxidized, to change solubility, to defer volatilization, and to avoid incompatibilities (Luzzi and Palmieri, 1985; Movva et al., 2013). Studies on natural polysaccharides based microparticles are being extensively done as carriers for immobilization of cells, proteins and enzymes and for controlled release of drugs (Chan et al., 2002a,b; Tonnesen and Karlsen, 2002) due to their distinctive characteristics, including biocompatibility, natural origin and comparatively lower costs. The application of microparticle in the controlled drug delivery has been an object of study in the last years (Soppimath et al., 2001; Beneke et al., 2009; Sharma et al., 2015).

In the last few decades, polysaccharides extracted or isolated from plant seed sources have emerged as a very interesting material for its function in biomedical applications and in biopharmaceutical field (Marita and Ana, 2012). In these study biodegradable and biocompatible materials such as Locust bean gum (LBG) and Xanthan gum (XG) have been investigated for microparticulation properties (Vipul Prajapati et al., 2013; Lungan et al., 2014).

LBG is a non starch polysaccharides obtained from seeds of the Ceratoniasiliqua (Family: Fabaceae), consisting of galactose and mannose in the ratio of 1:4 (Parvathy et al., 2005). LBG is a popular natural polymer, frequently used in pharmaceutical and food industries (Prajapati et al., 2013). Due to the thickening and gelling property of this natural polymer, it is conventionally used as excipients in manufacturing of different pharmaceutical formulations (Paramita et al., 2011; Üner and Altınkurt, 2004).

XG polysaccharide is obtained from secretions of Xanthomonas campestris bacterium, which is widely used in pharmaceutical formulations for their functional properties such as emulsifying, thickening, gelling abilities and in addition to that it has also been reported to utilize as matrix retardant in solid dosage forms.

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Moreover, they are often conjointly used to take advantage of their corresponding properties. In some cases, mixture of two polysaccharides initiates a synergy of the properties due to specific interactions between gums. For example, mixture of xanthan gum and galactomannan have strong rheological enhancement. (Dea et al., 1977; Tako and Nakamura, 1985). The application of LBG and XG in microparticle dosage forms with systemic effect is mainly based on LBG polysaccharide from which the release of incorporated drug is controlled by the mechanism of diffusion. Whereas the LBG micro particles show excellent bioadhesive properties and strong affinity for gastric mucosa specifically in presence of XG.

Celecoxib (CXB), 4-[5-(4-methylphenyl)-3-trifluoromethyl-1H-pyrazol-1-yl] benzenesulfonamide [specific inhibitor ofcycloxygenase-2 (COX-2)] is extensively used as analgesic in the treatment of rheumatoid arthritis and osteoarthritis, primary dysmenorrhea and familial adenomatous polyposis (Tindall, 1999; Steinbach et al., 2000). A chemo preventive activity against colon carcinogenesis is also shown (Kawamori et al., 1998). On the other hand, according to the biopharmaceutical classification system, CXB is a class II drug, which is poorly water-soluble and therefore gives rise not only to low and highly variable bioavailability but also to formulation problems (Paulson et al., 2001).

Response surface methodology (RSM), backed by statistical software, is a well- proven approach for pharmaceutical formulation development and optimization, allowing extraction of maximal information out of few well-designed experiments (Sharma et al., 2013a,b). Central composite factor design (CCD) (one of the techniques in RSM) is suitable for selection of the optimal composition for achieving the desired object and pharmaceutical blending problems along with the least number of experiment (El-Malah et al., 2006). Microparticles have been optimized with the extensive use of CCD (Billona et al., 2000).

The aim of the present study was to explore the potential of binary combination of LBG and XG in formulation of the CXB microparticles. Then the synthesized microparticles were characterized for the micrometric properties, particle size, angle of repose, compressibility, sphericity, differential scanning calorimetry and scanning electron microscopy studies (Mofidi et al., 2000). Further the evaluation of microparticles has been done for the percentage yield, drug loading and encapsulation efficiency, *in vitro* drug release behavior along with the stability studies.

2. Materials and methods

2.1. Materials

Celecoxib and Celedol® 200 mg Tablet was a kind gift from the IPCA Laboratories (Mumbai, India). LBG, XG, Liquid Paraffin, glutaraldehyde, isopropyl alcohol and polyoxyethylene sorbitan monooleate (Tween®80) of commercial grade were obtained from Sigma–Aldrich (Germany). Water used in all experiments was obtained from a Synergy 185 Milli-Q® water purification system (Millipore, Saint-Quentin-en-Yvelines, France). All other chemicals used as received without further purification.

2.2. Characterization of gum

The viscosity of 1% solution of the XG and LBG were determined in distilled water with pH 7.2 and pH 1.2 phosphate buffers respectively, using a Brookfield RVDV II+ viscometer (Brookfield Engineering, USA), spindle # S28, at 50 rpm. A digital pH meter (Oakton Benchtop pH 700 Meter) was used to determine the pH of the LBG and XG solution (1%, w/v in distilled water). The scanning electron micrograph (Joel-LV-5600) is used to study the surface characteristics of polysaccharide powder. Powder was sputtered with gold to make the samples electrically coupled which further help in the imaging of the microparticles.

2.3. Preparation of drug-loaded microparticles

Drug-loaded LBG and XG microparticles were prepared by the emulsification method. An aqueous dispersion of the blend of LBG and XG 40 g (1:1) 3% w/v was dispersed in a specified volume of cold water containing the CXB (200 mg) and allowed to swell for 2 h. It was dispersed in 100 ml of liquid paraffin containing 3 ml of Tween 80 using a mechanical stirrer at 700 rpm. After complete mixing, 5 ml of glutaraldehyde was added to the dispersion, followed by stirring at a constant speed for 5 h at 45 °C. The microparticles formed were collected by sedimentation followed by decantation of oil, then washed with several fractions of isopropyl alcohol. Prepared microparticles were spherical in shape and free-flowing.

2.4. Central composite factorial design

The rotatability in the design was fulfilled by the value for alpha (1.414). The dependent variables selected were the Physicochemical properties of the produced micro particles, i.e., encapsulation efficiency (Y1), drug loading (Y2) and percentage yield (% yield) (Y3). The actual and coded values of the variables are given in Table 1. A total of 13 experiments, including four factorial points, four axial points and five replicated center points for statistical assessment the pure error sum of squares, were constructed by Design-Expert software which works according to the CCD matrix generated (Trial Version 7.1.6, Stat-Ease Inc., MN), (Gonzalez-Mira et al., 2011). For the best suitable formulation two-factor (2F) interaction model, quadratic model and linear model were assessed. Due to the analysis of variance p-value and to emphasis on model maximizing multiple correlation coefficient r^2, predicted r^2 and adjusted r^2 as quality indicators in the model summary statistic list. The p-value less than 0.05 were considered to be statistically significant. Optimization in the software was done by using above mentioned function and constraints such as encapsulation efficiency, drug loading and% yield respectively.

2.5. Characterization of microparticles

2.5.1. Particle size analysis

The measurement of particle size was done using a Malvern mastersizer 2000 version 5.1 (Malvern, U.K) Samples of XG and LBG based microparticles were dispersed in 20:1 with methanol and measured at temperature of 37 °C.

2.5.2. Micromeritic properties

A tap density tester (Electrolab, ETD 1020) was used to determine tap densities of the prepared microparticlesand percentage Carr's index was calculated.

2.5.2.1. Angle of repose. The angle of repose was determined by using the fixed funnel method. The graph paper was laid on a flat horizontal surface and a funnel with the end of the stem cut perpendicular to its axis of symmetry was securely arranged above it. Microparticles were prudently poured through the funnel until the apex of the conical pile just reaches the tip of the funnel. The height and radius of the pile were then determined. The angle of repose (θ) for samples was calculated using the Eq. (1):

$$\text{Angle of repose } (\theta) = \tan^{-1}\left(\frac{h}{r}\right) \quad (1)$$

Where 'h' is height of heap and 'r' is radius of the heap.