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Microwave assisted synthesis and optimization of *Aegle marmelos*-g-poly(acrylamide): Release kinetics studies

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ABSTRACT

Microwave assisted grafting of poly(acrylamide) on to *Aegle marmelos* gum was carried out employing 3-factor 3-level full factorial design. Microwave power, microwave exposure time and concentration of gum were selected as independent variable and grafting efficiency was taken as dependent variable. *A. marmelos*-g-poly(acrylamide) was characterized by FTIR, DSC, X-ray diffraction and scanning electron microscopy.

Microwave power, microwave exposure time had synergistic effect on grafting efficiency where as concentration of the gum did not contributed much to grafting efficiency. Batch having microwave power – 80%, microwave exposure time –120 s and concentration of *A. marmelos* gum – 2% was selected as the optimized formulation. Comparative release behaviour of diclofenac sodium from the matrix tablets of *A. marmelos* gum and *A. marmelos*-g-polyacrylamide was evaluated. The results of kinetic studies revealed that the graft copolymer matrix, marketed tablets and polymer matrix tablets of *A. marmelos* gum released the drug by zero order kinetics and with *n* value greater than 1, indicating that the mechanism for release as super case II transport i.e. dominated by the erosion and swelling of the polymer.

1. Introduction

Natural polysaccharides and their derivatives are widely used as excipients in conventional and controlled drug delivery systems. Various advantages of controlled drug delivery systems are the achievement of an optimum concentration, usually for prolonged time, the enhancement of the activity of labile drugs, due to their protection against hostile environments, and the diminishing of side effects due to the reduction of high initial blood concentrations [1]. The natural polysaccharides do hold advantages over the synthetic polymers, generally because they are less expensive, nontoxic, biodegradable, and easily available, compared to their synthetic counterparts. Further, in past few years, modifications have been used to impart desirable chemical, physical, and biological properties to the natural polymers. Natural gums can also be modified to have tailor-made materials for drug delivery systems [2].

Modification of natural polymers is often carried out through variety of approaches such as etherification, derivatization of functional groups [3,4], grafting of polymeric chains [5,6] and by oxidative [7] or hydrolytic [8] degradation. In grafting method, monomers are covalently bonded (modified) onto the polymer chain backbone. Thus, it can be described as, copolymer, where the main polymer backbone, commonly referred to as the trunk polymer, having branches of another polymeric chain [9]. Grafting method offers one of the best ways to use natural polysaccharides for controlled drug delivery systems. Grafting of gums with synthetic polymers can be used to design new materials with desirable release characteristics.

Various techniques of graft copolymerization such as radiation and chemical initiation, were reported in the literature [10]. The properties of natural polymers have earlier been modified by grafting with a variety of vinyl monomers such as acrylic acid [11], methyl acrylate [12], acrylonitrile [13] and acrylamide [14].

Conventionally graft copolymerization reactions are carried out using redox-initiator induced reactions, which require a long time and give graft copolymer with lower grafting. Microwave emerged as an efficient method, which results in rapid transfer of energy in the bulk of the reaction mixture. Microwave assisted free radical polymerization is also emerging as a novel technique in the field of polymer science to get grafted biomaterial with or without catalyst [15,16].

Earlier studies reported microwave-assisted synthesis of chitosan-g-styrene [17], guar gum-g-poly(caprolactone) [18], xanthan-g-poly(acrylamide) [19] and graft copolymer of Mimosa

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mucilage and acrylamide [20] with higher grafting percentage in a short reaction time.

Gum obtained from fruits of *Aegle marmelos* (Rutaceae) is indigenous to India. The ripen fruit pulp is red in colour with mucilaginous and astringent taste. The pulp contains carbohydrates, proteins, vitamin C, vitamin A, angelenine, marmeline, dictamine, O-methyl fordinol and isopentyl halfordinol [21]. The different parts of *A. marmelos* are used for various therapeutic purposes, such as for treatment of asthma, anaemia, fractures, healing of wounds, swollen joints, high blood pressure, jaundice, diarrhoea healthy mind and brain typhoid troubles during pregnancy [22].

The purpose of the present investigation was synthesis and optimization of the graft copolymer of acrylamide and *A. marmelos*, and to evaluate its drug release behaviour. The microwave-assisted graft-copolymerization of acrylamide on *A. marmelos* was optimized using 3-level, 3-factor full factorial experimental design.

2. Materials

Bael fruit was purchased from local market. Acrylamide and ammonium persulfate GR (purity 99%) was procured from Rankem, India. Diclofenac sodium was obtained as gift sample from Ranbaxy Laboratories, Gurgaon, India. All other chemicals used were of reagent grade and were used as such.

3. Methods

3.1. Extraction of A. marmelos gum (AMG)

AMG was extracted by earlier reported method [23]. Partially riped fruits of bael were purchased from the local market. The spherical and woody fruits were broken down into two equal parts. The amber coloured viscous, gummy substance along with the pulp and seeds was separated from the fruit outer wall. The pulp and seeds thus obtained were collected in a beaker containing 2% (v/v) glacial acetic acid solution. The slurry was boiled on water bath for 45 min with continuous stirring and stored overnight. The slurry was filtered through muslin cloth to remove debris. The gum was precipitated from the filtered slurry by adding acetone. The precipitates were dried in a vacuum oven at 50 °C and grounded to obtain light brown fine powder. The gum was further purified by dialysis against deionized water at 25 °C, using 3500 Da molecular weight cut off membrane (Himedia-60 LA390-5MT) followed by freeze drying (Freeze dryer; Alpha 2-4 LD Plus CHRIST) at −90 °C and a vacuum of 0.0010 mbar for 24 h then hand ground in an agate mortar and pestle.

3.2. Preparation of A. marmelos-g-poly(acrylamide)

Microwave-assisted grafting of acrylamide on *A. marmelos* was done using microwave assisted method [24] shown in Fig. 1. Powdered gum *A. marmelos* (2–4%, w/v) was dissolved in 25 ml distilled water by stirring overnight. An aqueous solution of acrylamide (10 mmol) followed by addition of ammonium persulfate (10 mmol), a redox initiator was added with continuous stirring in a reaction vessel (500 ml borosil beaker). The resultant solution was irradiated by domestic microwave oven (2300 ET-B, Power 1000 W, Bajaj Electricals Ltd., Mumbai, India) for different times and different power to prepare various batches of grafted gum (Table 1). The temperature of the reaction mixture was found to be <100 °C as measured by inserting the thermometer in the reaction vessel just after the exposure. After the microwave irradiation, the grafted gum thus prepared was treated with acetone and finally washed with mixture of methanol:water (80:20) to remove the unreacted monomer and reagent. The resultant grafted polymer was collected

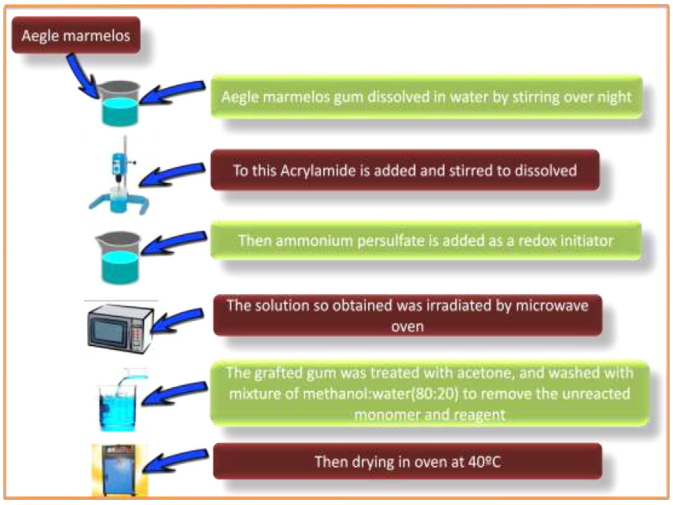

Fig. 1. Preparation of *Aegle marmelos*-g-poly(acrylamide).

and dried in hot air oven at 40 °C for 12 h. Subsequently, it was pulverized and sieved. The grafting efficiency (%) was calculated using the following equation:

$$\text{Grafting efficiency}\,(\%) = \frac{W_1 - W_0}{W_2} \times 100$$

where W_0 is the weight of gum, W_1 is the weight of grafted copolymer and W_2 is the weight of acrylamide.

3.3. Experimental design

Response surface methodology (RSM) is a collection of statistical and mathematical techniques for empirical model building. By careful design of experiments, the objective is to optimize a response (dependent variable) which is influenced by various independent variables. Factorial designs are very frequently used response surface experimental designs in which all levels of a given factor are combined with all levels of every other factor in the experiment. In the present study, three-factor, three-level, full factorial design (3^3 designs) was employed for optimization of grafting of acrylamide on *A. marmelos*. The concentrations of *A. marmelos*, microwave power and exposure time were selected as the independent variables and grafting efficiency (% GE) was selected as the dependent variable. Each independent variable was investigated at three levels. The general equation showing mathematical relationship for the FDs involving main effects and the interaction terms is as follows:

$$Y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3 + b_{11}x_1^2 + b_{22}x_2^2 + b_{33}x_3^2$$

The graft co-polymer of acrylamide and *A. marmelos* was characterized by FTIR spectroscopy, differential scanning calorimetry, X-ray diffractometry, and scanning electron microscopy.

3.4. FTIR spectroscopy

The samples were subjected to FTIR spectroscopy in a Fourier transform infrared spectrophotometer (Nicolet-380, thermo scientific, USA) in range of 4000–500 cm^{-1} as KBr pellet.

3.5. Differential scanning calorimetry

Differential scanning calorimetric thermogram of *A. marmelos*, acrylamide, and *A. marmelos*-g-poly(acrylamide) was recorded