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Indian
Journal of Advances in
Chemical Science

Indian Journal of Advances in Chemical Science 2 (2014) 46-49

Formulation and Evaluation of pH Sensitive Pellets for the Treatment of Type II Diabetes Mellitus

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Received 6th April 2014; Accepted 21st April 2014.
Editor in Chief: Dr. K.S.V. Krishna Rao; Guest Editors: Dr. Siddaramaiah, Dr. G. M. Shashidhara.
Presented at the POLYCON-2014, 6th National Conferences on Advances in Polymeric Materials [Energy, Environment & Health] (NCAPM), Mysore, India, 25-26 April 2014.

ABSTRACT
The aim of this study was to investigate extrusion-spheronization pelletization for preparing pH-sensitive pellets for colon-specific drug delivery. Polyacrylamide-grafted-guar gum (pAAm-g-GG) was prepared by taking three different ratios of guar gum to acrylamide. Amide groups of these grafted copolymers were converted into carboxylic functional groups. Fourier transform infrared (FTIR) spectroscopy and differential scanning calorimetry were used to characterize copolymers. Pellets were prepared by incorporating an antidiabetic drug viz., Glimepiride. In-vitro drug release was carried out in simulated gastric and intestinal conditions. The effects of three independent variables (Microcrystalline cellulose, Polyacrylamide-grafted-guar gum (pAAm-g-GG) and Wetting agent) on pellet size, friability, and drug release were studied with 2^3 factorial design. In vitro drug release profile indicated an increase in drug release retardation with increasing pAAm-g-GG concentration. The formulated pellets were stable with respect to their physicochemical characters and drug content over a period of 60 days at different temperatures and relative humidity.

Keywords: *Extrusion-spheronization, Graft copolymer, Glimepiride, Controlled release.*

1. INTRODUCTION

pH sensitive drug delivery systems are gaining importance as these systems deliver patient therapeutic efficacy and compliance. Diseases wherein pH sensitive drug delivery systems are promising include asthma, peptic ulcer, diabetes, cardiovascular diseases, cancer and hypertension. The specific time that patients take their medication is very important as it has significant impact on treatment success. Optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. If symptoms of a disease display circadian variation, drug release should also vary over time. Drug pharmacokinetics can also be pH-sensitive: therefore, variations both in a disease state and in drug plasma concentration need to be taken into consideration in developing drug delivery systems intended for the treatment of disease with adequate dose.(1)

2. MATERIALS AND METHODS

2.1. Materials

Glimepiride was a gift sample from micro labs, Bangalore, Microcrystalline cellulose (MCC) was purchase from Loba Chemie, Mumbai, India, Polyacrylamide and Guar Gum (GG) from Loba Chemie, Mumbai, India, were used as the pH sensitive polymers for pellet preparation. Isopropyl alcohol (Loba Chemie, Mumbai, India).

1.2 Experimental design

A 2^3 full factorial design was used for the preparation of pellets. The independent variables studied were microcrystalline cellulose, polyacrylamide grafted guargum and wetting agent. The chosen dependent variables or responses were pellet size, friability and in vitro drug release of pellets, respectively.

2.3. Preparation of pellets

The solid components of each formulation (50 g) were mixed together for 10 min. Micro crystalline cellulose was used as a pelletization aid in all formulations. The required amount of mixture of water and isopropyl alcohol was slowly added to the dry blend to make a wet mass with a suitable consistency. The wet mass was passed through a rotating roller extruder (EXT-65/037, R.R.

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Enterprises, Thane, India) & Spheronizer (SPH-150/010, R.R. Enterprises) at 1600 rpm. The obtained pellets were dried at 40 ^{o}C for 10 h in a conventional hot air oven.

3. RESULTS AND DISCUSSION

3.1. Characterization of pAAm-g-GG.

Characterization of pAAm-g-GG FT-IR spectroscopy was conducted. FT-IR spectra of GG, PAAm-g-GG and physical hydrolyzed pAAm-g-GG was carried out.

The pure GG showed a broad peak at 3415 cm^{-1} due to the presence of hydrogen bonded OH groups. In the spectrum of pAAm-g-GG, apart from these peaks, additional peaks were observed at 3438, 3144, 1637, 1400 and 1105 cm^{-1}. The peaks at 3438 and 3144 cm^{-1} are assigned to overlap of N-H stretching band of amide group and O-H stretching band of hydroxyl groups of GG. The peaks at 1637 and 1,400 cm^{-1} are because of the primary amide on the backbone of GG. The peak at 1,105 cm^{-1} is due to the presence of the ether linkage formed by the reaction between OH groups of GG and acrylamide. In case of alkaline hydrolyzed pAAm-g-GG, the peak appearing at 3144 cm^{-1} was absent, indicating the absence of N-H band. The peaks at 1617 and 1400 cm^{-1} are due to COO^{-} groups. This confirms the hydrolysis reaction. The obtained FTIR spectra are shown in Figure 1.

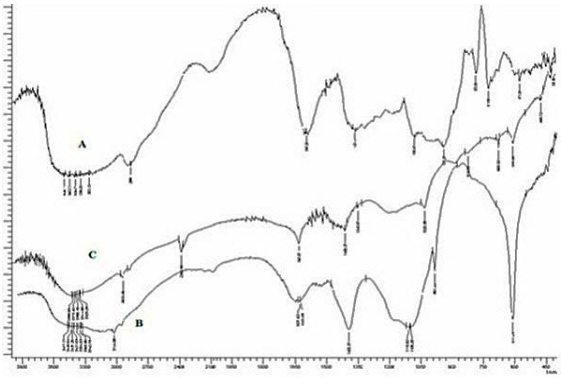

Figure 1: FT-IR spectra of GG (A), PAAm-g-GG (B) and hydrolyzed pAAm-g-GG (C).

In the present study, spheronization have been occurred by the mechanism described by (2). It was found that extrudate broke into small cyclindrical particles, may be because of the friction of spheronization plate, further which went through several shape changes process, i.e., cylinders with rounded ends, dumbbells, ellipsoids and finally spheroidal. (3).

One of the key factor affecting the extrusion process is the wet massing liquid content. The right amount of water and isopropyl alcohol levels needs to be optimized for extrusion mass. It was observed that if the moisture content of the extrusion mass was less than the lower limit, the mixtures do not flow satisfactorily through the extruder barrel. During the process of spheronization, a lot of dust was generated resulting in a large yield of fines. This may be explained due to lack of plastic properties in the wet mass, because of lower water content. Conversely, increasing the water levels facilitates easy extrusion of mass by reducing viscosity, as wetter mass becomes softer and less force is required for extrusion. However, above the upper limit of moisture content, the mass gets extruded satisfactorily, but it resulted in large agglomerates on spheronization. It has been found that, the surface of pellets gets smoother with increasing the amount of wet massing liquid (4). The formation of suitably shaped pellets, require the extrudates with sufficient plastic properties, that are spheronized by the forces that occurred from the movement of the friction plate of spheronizer. When the polymer concentration was increased, the longer rod shaped pellets were obtained at low speed and pellets with decreased sphericity with larger size were obtained at higher speed (5)(6). In the process of spheronization speed optimization, it was found that at lower speed, more number of rod and dumbbell shaped particles were obtained due to the rheological properties of chemically modified guar gum, where the extrudates resist to convert into pellets. Further increasing the spheronization speed to 1600 rpm, the more energy is imparted to the particles which results in more force during collision. The optimum speed depends on the characteristics of the product being used and particle size required.

The micromeritic properties of different batches as shown in Table 2, like average size, angle of repose, tapped density, granule density, Carr's index and friability revealed no significant difference among the different batches. Thus, from the above micromeritic data it is evident that blends of different formulation batches prepared with MCC and PAAm-g-GG possess comparable flow properties and carr's index. In size distribution analysis, it was found that pellets were within size range of 1028-1305 µm with normal size distribution with average particle size of pellets 1188 µm.

The bulk densities of pellets were found to be in between 1.02 and 1.06 g/cm3, which indicates close packing arrangement because of narrow particle size distribution. The friability values for all batches were found to be within the limits. Angle of repose for all batches was ranged between 18.35◦ and 26.18◦ indicating good flow properties

of pellets which can be attributed to spherical shape and smooth surface of pellets.

Table 1: Optimization of pH sensitive Glimepiride pellets on spheronization speed.

Spheronization speed (rpm)	Spheroid description
400	Dumbbell shape
800	Dumbbell shape
1200	Dumbbell shape
1600	Pellets with narrow size range

2.2 Experimental design

By regression of these results against MCC, pAAm-g-GG and Wetting agent .we can obtain following models for Particle size, friability and invitro drug release: R^2 = 0.9821(Particle size), R^2=0.9485(friability), R^2 = 0.9477 (invitro drug release), The amount of drug released at the end of 12 h was found to be 92.30 ± 1.6%. This might be due to higher concentration of the pAAm-g-GG, which may be attributed to slower penetration of dissolution medium in the matrices. The rate and extent of drug release decreases with increase in total concentration of polymer. Here all the parameters were run for 6 times (n = 6). The difference in mean of % drug release between batch series was significant ($p < 0.05$). A formulation prepared with 3% (w/w) pAAm-g-GG, i.e., F-3 was identified as an ideal batch based on its physicochemical and release characteristics.

Table 2: The micromeritic properties of different batches.

Formulation code	Average size (μm)	Angle of repose θ^0	Tapped density (g/cm^3)	Carr's index (%)	Friability (%)	Granule density g/cm^3
F-1	1028±0.50	23.14±0.12	0.84±0.64	9.10±0.32	0.56±0.78	1.05±0.79
F-2	1100±0.23	21.22±0.18	0.86 ±0.92	8.89±0.90	0.63±0.45	1.06±0.17
F-3	1126±0.22	18.35±0.26	0.90±1.40	9.49±0.53	0.57±0.82	1.05±1.35
F-4	1277±0.35	23.10±0.35	0.89±1.01	8.83±0.98	0.48±0.36	1.06±0.92
F-5	1218±0.10	23.21±0.30	0.83±0.55	8.76±1.76	0.50±0.78	1.04±0.69
F-6	1244±0.32	26.18±0.44	0.83±0.82	8.59±2.01	0.60±0.22	1.06±0.81
F-7	1305±0.16	24.16±0.15	0.84±0.62	8.75±1.11	0.43±0.91	1.02±0.78
F-8	1135±0.21	23.45±0.88	0.90±1.43	9.49±0.53	0.58±0.82	1.05±0.47

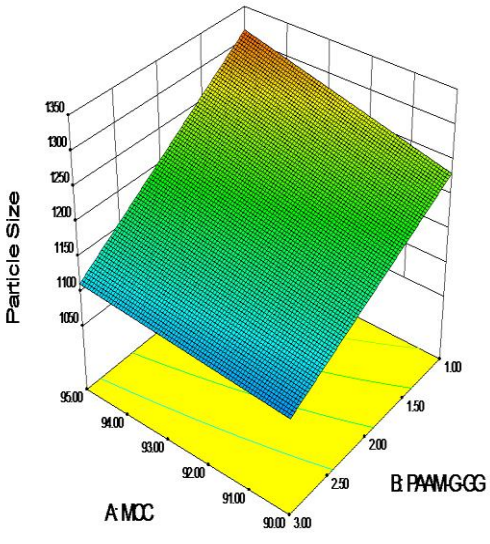

Figure 2: Influence of MCC and pAAm-g-GG on Particle size of pellets.

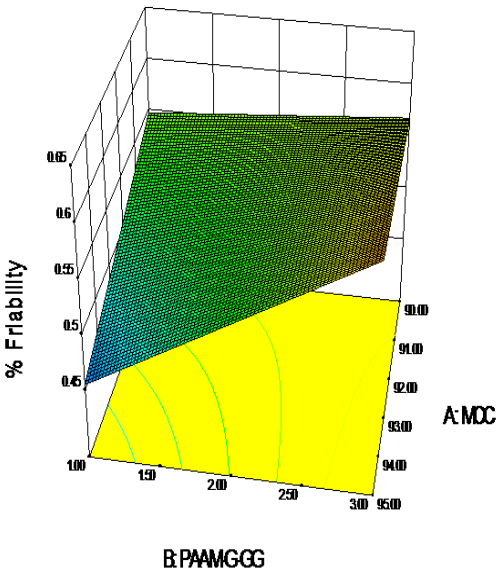

Figure 3: Influence of MCC and pAAm-g-GG on Friability of pellets.

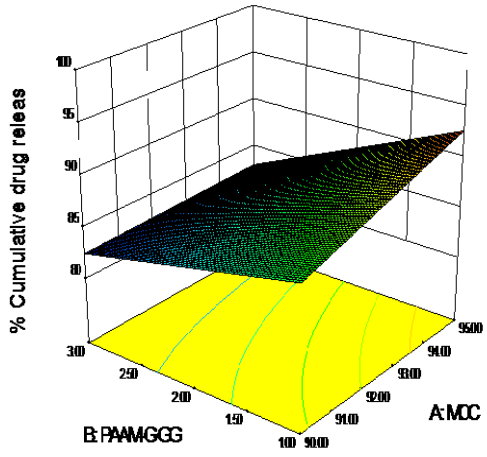

Figure 4: Influence of MCC and pAAm-g-GG on invitro drug release of pellets.

4. CONCLUSION

Modification of guar gum was achieved by a grafting reaction using different ratios of acrylamide. Hydrolyzing the amide groups into carboxylic groups modified the matrices. Modified polymers were formulated into pellets by extrusion/spheronization. The method which was employed is simple, rapid and economical. The results of micromeritic properties, Hausner's ratio and friability, were within the limit, indicating good flow potential of the prepared pellets. The pAAm-g-GG pellets of glimepiride, the release continued up to 12 h. The conclusion of the study is that the rate of drug release can be modulated by varying the concentration of polymer included in the formulation. From the present work, it can be concluded that the prepared spheroid demonstrates the potential use of MCC and pAAm-g-GG for the development of controlled drug delivery systems for many water insoluble drugs.

Acknowledgments: The author thank JSS college of pharmacy, JSS University and UGC, New Delhi for providing the facilities to carry out the research work.

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