RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Polyacrylamide grafted guar gum based glimepiride loaded pH sensitive pellets for colon specific drug delivery: Fabrication and characterization

Gowrav M.P., Umme Hani*, Hosakote G. Shivakumar, Riyaz Ali M. Osmani and Atul Srivastava

Dept. of Pharmaceutics, JSS College of Pharmacy, JSS University,

Sri Shivarathreeshwara Nagar, Mysore-570 015, Karnataka, India.

*Address correspondence to this author at the Dept. of Pharmaceutics, JSS College of Pharmacy, JSS University, Sri Shivarathreeshwara Nagar, Mysore-570 015, Karnataka, India.

E-mail: ummehaniahmed@gmail.com

Abstract

Purpose: The purpose of this study was to prepare pH-sensitive pellets using extrusion-spheronization pelletization (ESP) technique.

Method: Polyacrylamide-grafted-guar gum (pAAm-g-GG) was prepared by taking three different ratios of guar gum to acrylamide (1:2, 1:3.5 and 1:5). Amide groups of these grafted copolymers were converted into carboxylic functional groups. Fourier Transform Infrared (FT-IR) Spectroscopy, Differential Scanning Calorimetry (DSC) and ^{1}H-NMR Spectroscopy were used to characterize grafted copolymers. Pellets were prepared by pAAm-g-GG (1.0-4.5%) and microcrystalline cellulose incorporating an anti-diabetic drug viz., glimepiride. Here, variables were studied and pellets were characterized for average size, surface morphology, friability, bulk density and flow properties. *In vitro* drug release was carried out in simulated gastric and intestinal conditions.

Result: *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.

Conclusion: It has been concluded that prepared pellets demonstrates the potential use of MCC and pAAm-g-GG for the development of pH sensitive colon specific controlled drug delivery systems of glimepiride for diabetic therapy.

Keywords: Controlled release, Extrusion-spheronization technique, Grafting, Glimepiride, Pellets.

1. Introduction

pH sensitive drug delivery systems are gaining importance as these systems offers high therapeutic efficacy and patient compliance. Diseases wherein pH sensitive drug delivery systems are promising include asthma, peptic ulcer, diabetes, cardiovascular diseases (CVDs), 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 the 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 while developing drug delivery systems intended for the treatment of disease with adequate dose.[1]

The process of extrusion or spheronization is a most widely accepted method of producing pellets. This process basically consists of five unit operations, i.e., blending, wet massing, extrusion, spheronization and drying; resulting in the formation of spherical pellets showing a homogeneous surface. Pellets are agglomerates of bulk drugs and excipients. They consist of small, free-flowing, spherical solid units, typically varies from 0.5 to 1.5 mm and are intended for oral administration.[2,3] Thus, these multiparticulate dosage forms are pharmaceutical formulations in which the active ingredient is present as small independent subunits. The pellets have certain specific advantages over conventional solid dosage forms like free flow and ease of packing; resulting in reproducible and uniform fill weight of capsules. It has been found that spheroidal particles smaller than 2.4 mm diameter are free from digestive function of the stomach and the closing system of pyloric sphincter of stomach.[4,5] Also, implants of small cylinders formed by compression from medicated masses are also defined as pellets.[6,7] Several

methods have been reported for the preparation of pellets: melt spheronization, compaction, globulation drug layering, balling, compression, and extrusion-spheronization. Among all these, extrusion-spheronization pelletization (ESP) is the most widely used method.[8]

Guar gum (GG) is a natural branched polygalactomannan isolated from the seeds of leguminous herbs.[9] It is a linear h (1→4) mannose to which (1→6) galactopyranoside single subunits are attached as the side chains.[10] GG is most commonly used as a thickening agent in food industries. It is also used as a binder and as a disintegrating agent in solid dosage forms, as well as thickening and stabilizing agent in liquid products. Almost a decade ago GG was explored for sustained release applications. Later, it was found to be a release retardant in phenylpropanolamine, theophylline, diltiazem hydrochloride and ionized sustained release tablets.[11] Its use in three-layer matrix tablet was also reported for the controlled release of trimetazidine dihydrochloride.[12] It has been also used as a carrier for colon targeted drug delivery in pure as well as modified forms.[13-15]

The present study explains modifications of GG by grafting it with polyacrylamide (pAAm) in diverse ratios. Amide groups of the derived copolymers were converted to carboxylic acid groups by free radical polymerization reaction. The grafted polymers were extruded and spheronized into pellet after incorporation of glimepiride. The *in vitro* release profiles have been evaluated in gastric and intestinal conditions to study the drug release characteristics and to assess the potential of pAAm-g-GG for pH sensitive colon specific delivery.

2. Materials and methods

2.1. Materials

Glimepiride was a gift sample from Micro Labs, Bangalore, India. Acrylamide (AAm), guar gum (GG), microcrystalline cellulose (MCC), isopropyl alcohol and ammonium per sulphate (APS)

were purchased from Loba Chemie, Mumbai, India. All other solvents, reagents and chemicals used were of analytical grade.

2.2. Methods

2.2.1. Synthesis of pAAm-g-GG copolymer

Various ratios of GG: acrylamide were used for the synthesis of pAAm-g-GG copolymer by free radical polymerization reaction (Table 1). 2 gm of GG was dissolved in 100 ml double distilled water. The flask was heated at 80°C; required amount of acrylamide and 0.139 gm of ammonium peroxodisulphate were added to GG solution. Polymerization was carried out for 60 min. The resulting solution was then allowed to cool at ambient temperature; the product was poured into excess of methanol and kept for 24 h. The copolymer obtained was then filtered, washed repeatedly with methanol, dried at 50 °C over night and stored in desiccator.[16, 17]

2.2.2. Alkaline hydrolysis of pAAm-g-GG copolymer

Required amount of pAAm-g-GG copolymer was dissolved in 100 ml of 0.9M NaOH solution and stirred at 75°C for 60 min in a thermostatic water bath. At the end of reaction, the solution was cooled and poured in excess of methanol. The hydrolysed copolymer was separated by filtration and washed repeatedly with methanol and dried overnight at 50 °C.

2.2.3. Preparation of pellets

For preparation of pellets, initially different concentration of pAAm-g-GG and MCC as pelletization aid along with the drug (glimepiride) were mixed together for 10 min (Table 2). 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 then passed through a rotating roller extruder (EXT-65/037, R.R. Enterprises, Thane, India) and spheronizer (SPH-150/010,

R.R. Enterprises, Thane, India) at 1600 rpm. The obtained pellets were dried at 40 °C for 10 h in a conventional hot air oven and stored.

2.2.4. Characterization of pellets

2.2.4.1. Particle size analysis

The particle size of the formulated pellets was measured using a Malvern Mastersizer 2000 version 5.1 (Malvern, UK). The glimepiride loaded pellets were separately dispersed in ratio 1:20 with methanol and measured at 37°C temperature.

2.2.4.2. Micromeritic properties

Tap densities of the prepared pellets were determined using tap density tester and percentage Carr's index was calculated.

2.2.4.2.1. Angle of repose

Angle of repose was assessed to know the flowability of pellets, by fixed funnel method. A funnel with the end of the stem cut perpendicular to its axis of symmetry was securely arranged to a specific height above the graph paper which was placed on a flat horizontal surface. Glimepiride pellets were carefully poured through the funnel until the apex of the conical pile just reaches the tip of the funnel. The radius (r) and height of the pile (h) were then determined. The angle of repose (θ) for samples was calculated using the formula in Eq. 1.

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

2.2.4.2.2. Compressibility

Carr's index is a dimensionless quantity, which proved to be useful in predicting the flow behavior. Apparent bulk density was determined by pouring the bulk samples into a graduated cylinder. Tapped density was determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapper apparatus (Electro Lab tap density tester). Samples were

tapped until no further reduction in volume of the sample was observed. Carr's index was calculated using the formula mentioned below. The mean of three determinations was used to calculate the compressibility index from each of the formulation using the Eq. 2.[18]

$$\text{Carr's index} = \frac{(Tapped\ density - Bulk\ density)}{Tapped\ density} \quad (2)$$

2.2.4.3. Scanning electron microscopy (SEM)

SEM photographs were taken with a scanning electron microscope (Model Joel-LV-5600, USA) at the required magnification at room temperature. The photographs were observed for morphological characteristics and to confirm the spherical nature of prepared pellets.

2.2.4.4. Spheroid size

Spheroid size was determined using an image analysis system. Photomicrographs were taken with a digital camera (Cybershot, DSC-HX20V/B, Sony, Japan). The obtained images were processed by image analysis software (AnalySIS®; Soft Imaging System, Munster, Germany) to characterize each individual spheroid by mean Feret diameter (FD) (average of 180 calliper measurements with an angle of rotation of 1◦), aspect ratio (AR) (ratio of longest Feret diameter and its longest perpendicular diameter) and two-dimensional shape factor (eR) as in Eq. 3.

$$-e_{R=\frac{2\pi r}{P_m}-\sqrt{1-(b|l)2}} \quad (3)$$

Where r is the radius, Pm is the perimeter, l is the length (longest Feret diameter) and b is the width (longest perpendicular diameter to the longest Feret diameter) of the spheroid.[19]

2.2.4.5. Physicochemical interaction studies: DSC

The compatibility of glimepiride-excipient, as well as excipient–excipient compatibility after formulating to a pellet and the effect of compression force on thermal profiles of all the components was assessed using Differential Scanning Calorimetry (DSC). DSC scans of the pure

glimepiride and F-5 were carried out using a DSC TA 60 (Shimadzu, Japan). The calorimetric measurements were made with an empty cell (high purity alpha alumina discs from Shimadzu) as the reference. The scans were taken under nitrogen atmosphere over a temperature range of 25 to 330 °C and at a scan rate of 10.0 °C/min.

2.2.4.6. Physicochemical interaction studies: FT-IR

The grafting reaction was confirmed by FT-IR spectroscopy (FT-IR, Shimadzu 8400 S, Japan). Samples were prepared in KBr discs using KBr press (Technosearch, Mumbai, India). The scanning wave number range was 400-4000 cm^{-1}.

2.2.4.7. ^{1}H-NMR analysis

In order to show that the grafting had taken place, proton nuclear magnetic resonance (^{1}H-NMR) spectroscopic analysis of native GG and pAAm-g-GG were performed with JEOL AL300 FTNMR spectrometer (Fig. 3). The spectra were recorded in chemical shift (δ) range of 0-7 ppm and the solvent used was deuterium oxide (D_2O).

2.2.5. Evaluation of pellets

2.2.5.1. Friability

Friability testing was conducted using a friability tester (Roche friabilator). A 10 gm pellet sample was placed into the drum together with 10 gm glass spheres of 5 mm diameter, and rotated for 10 min at 25 rpm. Pellets were then weighed and friability was calculated according to Eq. 4.

$$\%F = 100\,(\,m_b - m_a/\,m_b) \quad (4)$$

Where m_b and m_a are the masses of pellets before and after testing, and the result was the mean of three runs.[20]

2.2.5.2. Percentage yield

The yield was determined by weighing the glimepiride pellets separately and then finding out the percentage yield with respect to the weight of the input materials, i.e., the weight of drug and polymers used. The formula for calculation of % yield used was mentioned in Eq. 5.

$$\% \text{ yield} = \frac{\text{Wt.of pellets} \times 100}{\text{Wt.of drug} + \text{Wt.of polymers}} \quad (5)$$

2.2.5.3. Drug loading and entrapment efficiency

Drug loading is important with regard to release characteristics. Generally, increased drug loading leads to an acceleration of the drug release. Drug entrapment efficiency represents the proportion of the initial amount of drug, which has been incorporated into the pellets. To assess the entrapment efficiency, specific amount of crushed pellets were suspended in 100 ml of phosphate buffer solution (PBS, pH 7.2) with constant agitation at room temperature for 24 h. Later, the solution was filtered through Whatman filter paper, and drug content was determined spectrophotometrically at the wavelength of 229 nm, using PBS (pH 7.2) as blank. The entrapment efficiency and percent drug loading were calculated using formulae mentioned in the Eq. 6 and 7 respectively.

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug content}}{\text{Theoritical drug content}} \text{X } 100 \quad (6)$$

$$\% \text{ Drug loading} = \frac{\text{Amount of drug in the sampled pellets}}{\text{Weight of pellets}} \text{X } 100 \quad (7)$$

2.2.6. *In vitro* drug release studies

To study the *in vitro* dissolution profile, pellets equivalent to 3 mg of glimepiride were filled in hard gelatin capsules. Dissolution studies were carried out initially at gastric pH (pH 1.2) for 2 hr followed by pH 7.2 for rest of the study, using dissolution apparatus USP-XXIII attached with paddle (Electrolab, Mumbai, India). Freshly prepared buffers were used as dissolution media

with 50 rpm paddle rotation at 37±1 ^{o}C. 5 ml of samples were withdrawn on definite time intervals and immediately replaced with an equal volume of fresh buffer. The amount of drug released was quantified using the high performance liquid chromatography (HPLC) method by directly injecting samples to the HPLC system. The HPLC system comprises of SHIMADZU LC-2010 AHT with auto sampler and UV-visible detector. Chromatographic separation was achieved using a Phenomenex C 18 column (250 mm × 4.6 mm i.d., 5 µm particle sizes). The glimepiride in samples was analyzed at 229 nm.

2.2.7. Stability studies

The ideal batches of the formulated pellets containing 3 mg equivalent glimepiride were filled in capsules; blister packed and then kept in the stability chamber at 25 ^{o}C/60% RH, 40^{o}C/75% RH and room temperature. Samples were withdrawn at 15, 30 and 60 days and evaluated for their physical appearance, friability and drug content.

3. Results and discussion

3.1. Synthesis of poly (acrylamide)-grafted-guar gum (pAAm-g-GG)

The grafting of AAm on the backbone of GG was carried out by free radical polymerization reaction using ammonium per sulphate (APS) as reaction initiator under nitrogen atmosphere. The reaction temperature was maintained at 80 $^{\circ}$C at which the APS undergoes decomposition to produce sulfate anion free radical; which abstracts the hydrogen from hydroxyl group of GG to form alkoxy radical on the substrate. Then the resulting macro radical initiates the graft copolymerization of AAm on to the backbone of GG. Fig. 1 gives the copolymerization of AAm on to the backbone of GG.

Diverse successful trials were performed between GG1-GG6 (1:0.5 to 1:8). The percentage grafting and efficiency was found to be increased with increase in acrylamide concentration up to GG4 (1:5) because of the formation of more free radicals due to the availability of more monomer molecules; which in turn generate more grafting sites on the GG by abstraction of H atoms. Further increase in acrylamide concentration in GG5 and GG6 (1:6.5 and 1:8 respectively) resulted in decreased percentage grafting and efficiency; which may be due to the gel effect. Moreover, at higher concentrations, separation of homopolymer from grafted GG was found to be difficult as reported previously by Bajpai *et al.*[21] During the alkaline hydrolysis, $-CONH_2$ groups of pAAm present on the back bone of GG were converted to –COOH functional groups resulting in pH sensitive polymer.

3.2. Characterization of pAAm-g-GG

3.2.1. FT-IR spectroscopy

Characterization of pAAm-g-GG was done by FT-IR spectroscopy. FT-IR spectra of GG, pAAm-g-GG and hydrolyzed pAAm-g-GG were traced (Fig. 2) as per the method described in section 2.2.4.6. The pure GG showed a broad peak at 3423 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 3348 cm^{-1}, 3174 cm^{-1}, 1641 cm^{-1}, 1415 cm^{-1} and 1124 cm^{-1}. The peaks at 3348 cm^{-1} and 3174 cm^{-1} were assigned to overlap of N-H stretching band of amide group and O-H stretching band of hydroxyl groups of GG. The peaks at 1641 cm^{-1} and 1415 cm^{-1} were because of the primary amide on the backbone of GG. The peak at 1124 cm^{-1} was 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 3174 cm^{-1} was absent, indicating the

absence of N-H band. The peaks at 1641 cm^{-1} and 1415 cm^{-1} were due to COO^- groups. All these results confirm the hydrolysis reaction.

3.2.2. ^{1}H-NMR spectroscopy

Moreover, to confirm pAAm grafting on the GG backbone, comparative studies were carried out using ^{1}H-NMR of the grafted copolymer and purified GG (Fig. 3). The signals traced in the purified GG spectrum (Fig. 3A) were verified with published data and were found to be consistent with the literature. The signals of GG were experiential in case of pAAm-g-GG spectrum (Fig. 3B) with additional resonances at 2.1 and 1.5 ppm; which was attributed to the protons of –CH and CH_2 groups respectively, of amide in the pAAm molecule. Also, the ethylenic protons peaks were absent reflecting the removal of monomer in the graft copolymer, whereas pAAm was traced in the product. Thus, ^{1}H-NMR spectroscopy results confirmed pAAm grafting on the GG.

3.3. Preparation and characterization of pH sensitive pellets

In the present study, spheronization has been carried out by the mechanism described by Rowe *et al*. [22] It was found that extrudates broke into small cylindrical particles, may be because of the friction of spheronizer plate, further which went through several shape changing process, i.e., cylinders with rounded ends, dumbbells, ellipsoids and finally spheroidal.[23]

One of the key factors affecting the extrusion process was the wet massing liquid content. The right amount of water and isopropyl alcohol levels need 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 into a large yield of fines. This may be assigned to lack of plastic properties in the wet mass, because of lower water content.

Conversely, increasing the water level 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 was found that, the surface of pellets gets smoother with the increasing amount of wet massing liquid.[24] Formation of suitably shaped pellets required the extrudates with sufficient plastic properties, which were 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.[25, 26] 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 GG; where the extrudates resist to convert into pellets. Further increasing the spheronization speed upto 1600 rpm, more energy was imparted to the particles which resulted in more force during collision as shown in Table 3 and 4. The optimum speed depends on the characteristics of the product being used and the particle size required. In general, smaller particles require higher speed while bigger particles (with higher mass which result in more force during a collision) require lower speed. However, when the spheronization speed was increased, the yield was reduced due to high centrifugal forces on the extrudates which resulted in excessive breaking and conversion into powder form.[27]

The micromeritic properties of different batches of spheroid are shown in Table 5. The average size, angle of repose, tapped density, granule density, carr's index and friability revealed no significant difference among the diverse batches. Thus, from micromeritic data it was evident that blends of different formulation batches prepared with MCC and pAAm-g-GG possessed

comparable flow properties and Carr's index. During size distribution analysis, it was found that pellets were within size range of 1048-1345 µm with normal size distribution and with an average particle size of 1188 µm.

The bulk density of the pellets was found in the range of 1.03-1.07 gm/cm^3; which indicates close packing arrangement because of narrow particle size distribution. The friability values for all the batches were found to be within the limits. Furthermore, angle of repose for all the batches were in the range between 19.45-26.48 °; indicating good flow properties of pellets which can be attributed to spherical shape and smooth surface of pellets (Table 5).

SEM photomicrographs of the optimized pellets (Fig. 4) clearly depicted the spherical shape with smooth and non-porous surface. DSC thermogram of pure glimepiride exhibited an endothermic peak at 217.62 °C corresponding to its melting point. In case of the optimized formulation the drug melting peak was traced at 219.12 °C (Fig. 5). This indicated that no change in drug crystallinity was occurred; confirming drug-polymer compatibility with no harsh effect on formulation stability.

3.4. Drug loading and entrapment efficiency

Drug loading and encapsulation efficiency of the pellets were as quoted in Table 6. Drug loading for all the formulations were in the range of 19.23 ± 0.63% to 23.84 ± 0.32%. The drug loading (23.84±0.32%) and entrapment efficiency (95.91 ± 0.57%) of formulation F-7 was found to be highest with respect to all other formulations.

3.5. *In vitro* drug release studies

The pellets were filled in hard gelatin capsules and evaluated for *in vitro* drug release. The drug dissolution profiles of matrix pellets formulated using pAAm-g-GG are depicted in Fig. 6. It has been noted that increasing the polymer concentration level from 1-4.5% caused

significant reduction in the drug release. A controlled release of drug from the pAAm-g-GG pellets was observed; which can be attributed to the hydrophobic barrier limiting access of water and dissolution of drug. As reported earlier by Kiortsis *et al.*[28], the drug release from dosage form comprising of cellulosic and hydrophobic matrix follows three steps. The first step is the penetration of the dissolution medium into the dosage form (hydration). The second step is erosion of the matrix and the third step is transport of the dissolved drug either through the hydrated matrix or from the parts of eroded area of dosage form, to the surrounding dissolution medium.

From the *in vitro* release data, it was found that all the formulations do not release the drug in the acidic pH. This could be attributed to the fact that the pellets carry –COOH functional groups, thus remain unionized at gastric pH leading to negligible swelling and drug release, but undergoes ionization at higher pH which led to maximum swelling and drug release in the intestine, as anticipated. In the alkaline medium formulations F-1, F-2, F-3, F-4, F-5 and F-6 containing pAAm-g-GG in concentration 1 %, 1.5%, 2.0%, 2.5%, 3% and 3.5% (w/w) respectively, released 96.1 ± 1.7%, 92.32 ± 1.4%, 87.91 ± 1.2%, 82.40 ± 1.4%, 77 ± 2.2% and 73± 1.6% of drug at the end of 12 h study; indicating that the polymer in each formulation was insufficient to control the drug release. The drug release from F-7 batch prepared with 4 % (w/w) pAAm-g-GG concentration was extremely significant in comparison to other batches. For F-7, the amount of drug released at the end of 12 h was found to be 62.53 ± 0.9%. This might be due to higher concentration of the guar gum, which consequently led to slower penetration of dissolution medium in the matrices. The formulations F-8 consisting of 4.5% (w/w) pAAm-g-GG depicted insufficient release at the end of 12 h because of elevated polymer concentrations.

From Fig. 6 it was observed that for all the formulations, drug release was inversely proportional to the concentration of rate retarding matrix former (polymer) present in the matrix system, i.e., the rate and extent of drug release decreased with an increase in concentration of polymer. The difference in mean % drug release between batch series was significant ($p<0.05$). From the all observations the drug release retardation from the formulations were found in order F-1 < F-2 < F-3 < F-4 < F-5 < F-6 < F-7 < F-8. A formulation prepared with 4.0% (w/w) pAAm-g-GG, i.e., F-7 was identified as an ideal batch based on its physicochemical and release characteristics. The drug release data of optimized formulation (F-7) was subjected to diverse release kinetic models, which indicated that batch F-7 followed zero-order release kinetic ($r^2 = 0.993$).

It was disclosed through investigations [29, 30] that acrylamide was not released from polyacrylamide through the process of degradation, even though acrylamide was earlier reported to be a deadly neurotoxin that was used to induce cancer in the laboratory animals. In reality, unambiguous difference of opinion over the disintegration of polyacrylamide degradation is noted. Furthermore, the total gastrointestinal transit time for an oral formulation won't exceed 24 h, while the PAM chains disintegrate very slowly (less than 10% in 28 days).[31] Therefore, the method studied here is projected to get disposed alongside other waste materials from the body without producing toxic effect.

3.6. Stability studies

Stability studies of formulated pAAm-g-GG based pH sensitive glimepiride pellets (F-7) were carried out at 25 °C/60% RH and 40 °C/75% RH. The optimized formulation was subjected to various evaluation parameters and the results obtained were within the range. There was no significant change in physicochemical properties of the pellets. The loss in total weight in friability test was in the range of 0.57 ± 0.82 to 0.61 ± 0.20%. The percent drug content for

different formulation varied from 97.19 ± 0.22 to 98.21 ± 0.23%. Based on the results it has been concluded that the formulated pH sensitive glimepiride pellets were stable over a period of 60 days.

4. Conclusions

Modification of guar gum (GG) was achieved by a grafting reaction using different ratios of acrylamide (AAm). Hydrolyzing the amide groups into carboxylic groups modified the matrices. Modified polymers were formulated into pellets by extrusion spheronization pelletization (ESP) technique; which was simple, rapid and economical. The results of micromeritic properties, compressibility and friability were within the limit; indicating good flow potential of the prepared pellets. The drug loaded pellets were found to be spherical in shape as reflected by SEM photomicrographs. From the DSC studies, it was evident that there were no chemical interactions between the drug and polymers used; reflecting drug compatibility and stability in the formulation. The pellets fabricated using 4 % (w/w) pAAm-g-GG was found to control the drug release over a period of 12 h. Thus, it has been concluded that the rate of drug release can be modulated by varying the concentration of polymer included in the formulation. From the present work, it was concluded that the prepared pellets demonstrate the potential use of pAAm-g-GG for the development of controlled drug delivery systems for many water insoluble drugs.

ACKNOWLEDGEMENT

Authors are very much grateful to UGC for providing fellowship and JSS University to carryout research.

References

[1] V. Balamuralidhara, T.M. Pramodkumar, N. Srujana, M.P Venkatesh, G. Vishal, K.L. Krishna and H.V. Gangadharappa, *Am J Drug Dis Dev.* 2011, **1**, 24-48.

[2] B. Gajdos, *Drugs Made Ger.* 1984, **27**, 30-36.

[3] I. Ghebre-Sellassie. Pharmaceutical Pelletization Technology. Marcel Dekker, New York (Chapter 1). 1989

[4] S.S. Davies, C.G. Wilson and N. Washington, *Int J Pharm*. 1987, **35**, 253-8.

[5] L.C. Feely, R. Khosla and S.S. Davis, *J Pharm Pharmacol.* 1987, **39**, 31.

[6] P.H. Cox and F. Spanjers, *Pharm. Weekblad.* 1970, **105**, 681-684.

[7] M. Niskanen . Ph.D. Thesis, University of Helsinki. 1992

[8] E.S. Ghali, A.M. Contractor, A.D. Mankad, O. Connor and R.E Schwartz, *Pharm. Technol*. 1990, 60-66.

[9] G.J.S. Raid, P.M. Day, R.A. Dixon (Eds.) Biochemistry of Storage Carbohydrates, Academic Press, London. 1985; 265-285.

[10] B.V. McCleary, A.H. Clark, I.C.M. Dea, and D.A. Rees, *Carbohydr Res.* 1981, **2**, 269-285.

[11] S.K. Baveja, K.V. Ranga Rao, J. Arora, N.K. Mathur and V.K. Vinayak, *Indian J. Chem* 1991, **30**, 133-137.

[12] YSR Krishnaiah, R.S. Karthikeyan, V. Gouri Sankar and V. Satyanarayana, *J. Control. Release.* 2002, **81**, 45-46.

[13] Y.V. Rama Prasad, Y.S.R. Krishnaiah and S. Satyanarayana, *J. Control. Release.* 1998; 51: 281-7.

[14] Y.S.R. Krishnaiah, S. Satyanarayana and Y.V. Rama Prasad, *Drug Dev Ind Pharm,* 1999, **25**, 651-7.

[15] B. Gliko-Kabir. A. Yagen, Penhasi and A. Rubinstein, *J Contr Rel,* 2000, **63**, 121-7.

[16] U.S. Toti, M.Y. Kariduraganavar, K.S. Soppimath and T.M. Aminabhavi, *J Appl Polym Sci.* 2002, **83**, 259-72.

[17] K.S. Soppimath, A.R. Kulkarni and T.M. Aminabhavi, *Eur J Pharm Biopharm*. 2002, **53**, 87-98.

[18] T.W. Wong, L.W. Chan, H.Y. Lee and P.W. Heng, *J Microencapsulation.* 2002, **19**, 511-22.

[19] A. Cosijins, D. Nizet and I. Nikolokakis, *Drug Dev Ind Pharm.* 2009, **35**, 655-62.

[20] M.P. Chaudhari and D.P. Chaudhari, *J Pharm Bioallied Sci*. 2012, **4**, 71-73.

[21] U. D. N. Bajpai and A. Jain. *Polym Int.* 1993, **31**, 1-7.

[22] Rowe RC. Spheronization: a novel pill-making process. Pharm. Int. 1985; 6, 119-123.

[23] R. Chatlapalli, B.D. Rohera, *Int J Pharm*. 1985, **161**, 179-193.

[24] T. Iosio, D. Voinovich, M. Grassi, J.F. Pinto, B. Perissutti, M. Zacchigna, U. Quintavalle and F. Serdoz, *Eur J Pharm Biopharm*. 2008, **69**, 686- 97.

[25] D.S. Hicks and H.L. Freese, Extrusion and spheronizing equipment. In: Pharmaceutical Pelletisation Technology. Marcel Dekker Inc., New York/Basel, pp. 1989; 71-100.

[26] C. Vervaet, L. Baert and J.P. Remon, *Int J Pharm.* 1995, **116**, 131-146.

[27] K. Umprayn, P. Chitropas and S. Amarekajorn, *Drug Dev Ind Pharm.* 1999, **21** (1), 45-61.

[28] S. Kiortsis, K. Kachrimanis, T. Broussali and S. Malamataris, *Eur J Pharm Biopharm*. 2005, **59**, 73-83.

[29] M. Caufield, G. Qiao and D. Soloman. *Chem Rev.* 2002, **102**, 3067-3084.

[30] L.M. Vers. *J Chromatogr Sci.* 1999, **37**, 486-494.

[31] S. Ghosh and S. Pal. *Int J Biol Macromol.* 2013, **58**, 296-300.

List of Tables:

Table 1: Synthetic details of Polyacrylamide Grafted GG.

Formulation code	Mass of GG (gm)	Mass of AAm (gm)	Mass of initiator (w/w of polymer)	Grafting efficiency	% Conversion of AAm
GG1	2	1	0.145	60.1	68.58
GG2	2	4	0.145	73.3	83.65
GG3	2	7	0.145	80.6	91.99
GG4	2	10	0.145	84.3	96.22
GG5	2	13	0.145	79.4	90.62
GG6	2	16	0.145	74.2	84.68

Table 2: Formulation chart of pH sensitive glimepiride pellets.

Formulation code	Glimepiride (mg)	MCC % (w/w)	pAAm-g-GG % (w/w)	Wetting agent volume (Water : IPA) (5:2) (ml/gm)
F-1	2.5	96.5	1.0	0.8
F-2	2.5	96.0	1.5	0.77
F-3	2.5	95.5	2.0	0.77
F-4	2.5	95.0	2.5	0.7
F-5	2.5	94.5	3.0	0.77
F-6	2.5	94.0	3.5	0.84
F-7	2.5	93.5	4.0	0.84
F-8	2.5	93.0	4.5	0.8

Table 3: Optimization of spheronization speed for pH sensitive glimepiride pellets.

Spheronization speed (rpm)	Spheroid description
400	Dumbbell shape
800	Dumbbell shape
1400	Dumbbell shape
1600	Spheroids with narrow size range

Table 4: Optimization of spheronization time for pH sensitive glimepiride pellets

Formulation code	Spheronization speed (rpm)	Spheronization time (min)	Spheroid description
F1 to F8	1600	5	Spheroids not formed
		10	Spheroids formed
		15	Spheroids formed

Table 5: Characteristics of pH sensitive glimepiride spheroids.

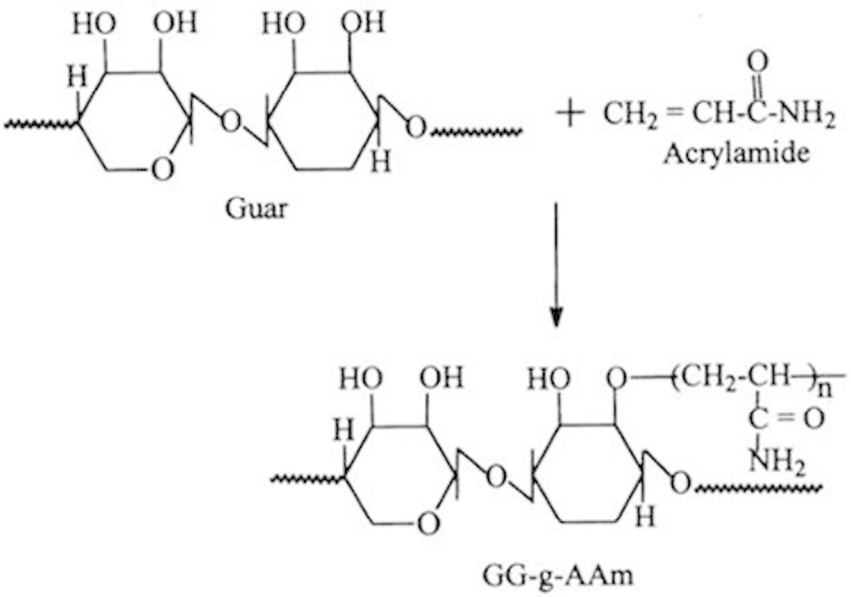
Formulation code	Average size (μm) ± S.D.*	Angle of repose θ^0 ± S.D.*	Tapped density (gm/cm^3) ± S.D.*	Carr's index (%) ± S.D.*	Friability (%) ± S.D.*	Granule density gm/cm^3 ± S.D.*
F-1	1048±0.51	24.32±0.22	0.85±0.42	9.12±0.23	0.55±0.54	1.04±0.83
F-2	1147±0.57	22.17±0.11	0.83±0.58	8.56±0.66	0.58±0.33	1.03±0.82
F-3	1129 ±0.34	20.34±0.27	0.86± 0.24	8.99±0.85	0.55±0.83	1.02±1.84
F-4	1284±0.45	22.36±0.39	0.87±0.36	8.63±0.56	0.49±0.45	1.04±0.65
F-5	1232±0.24	24.35±0.36	0.84±0.29	8.56±2.31	0.55±0.47	1.06±0.26
F-6	1241±0.28	25.27±0.47	0.88±0.36	8.29±2.14	0.62±0.43	1.07±0.61
F-7	1335±0.62	24.33±0.34	0.86±0.12	8.75±0.45	0.47±0.61	1.04±0.48
F-8	1142±0.43	24.61±0.39	0.89±0.23	9.12±0.27	0.55±0.22	1.08±0.44

mean ± S.D., n = 3

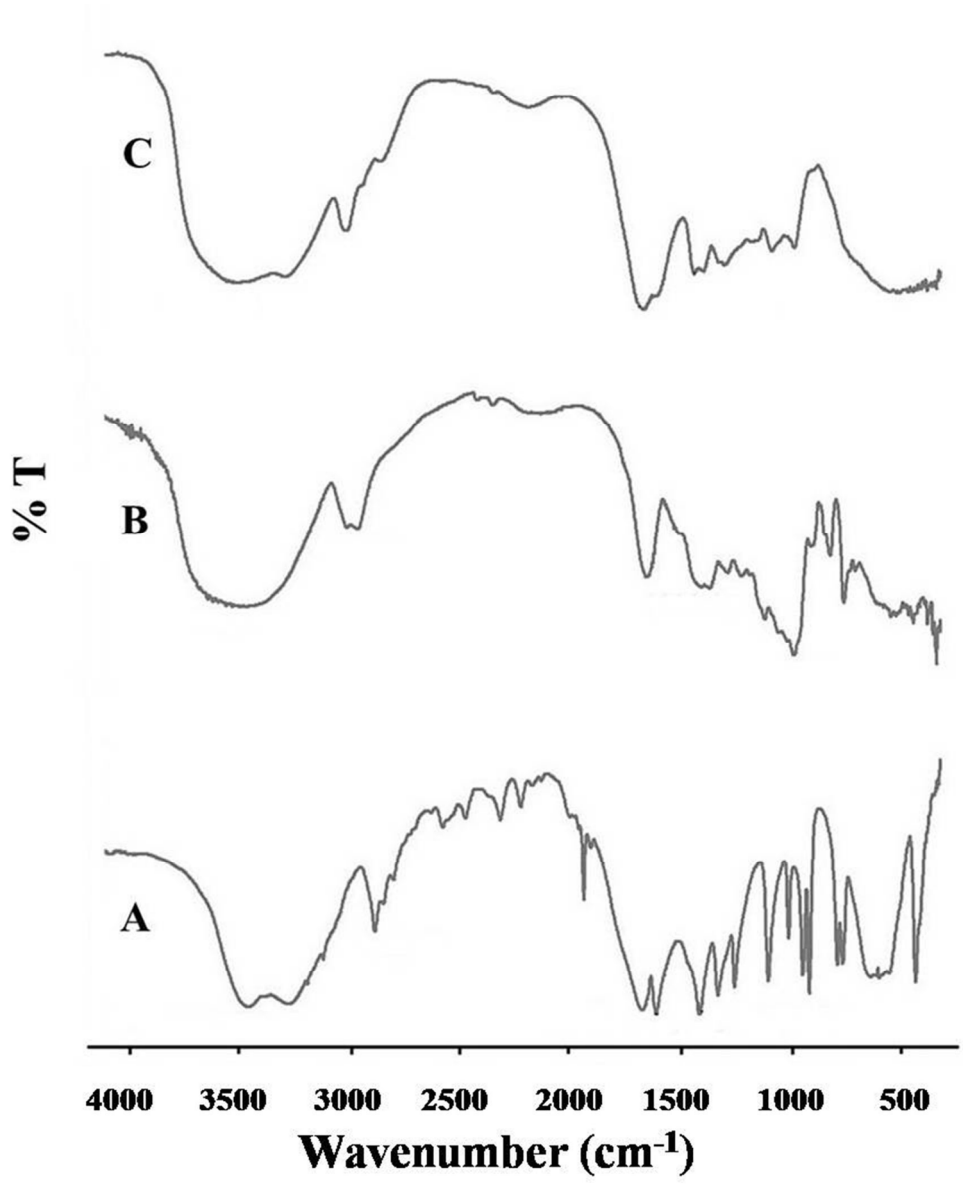
Table 6: Drug loading and entrapment efficiency of pH sensitive glimepiride pellet formulations.

Formulation	Drug loading (%) ± S.D.*	Entrapment efficiency (%) ± S.D.*
F-1	23.32±0.45	90.88±1.01
F-2	19.23±0.63	91.12±0.71
F-3	21.32±0.43	93.24±0.34
F-4	19.34±0.92	94.12±0.21
F-5	20.56±0.41	92.22±0.56
F-6	21.45±0.87	90.87±0.87
F-7	23.84±0.32	95.91±0.57
F-8	21.22±0.81	93.78±0.36

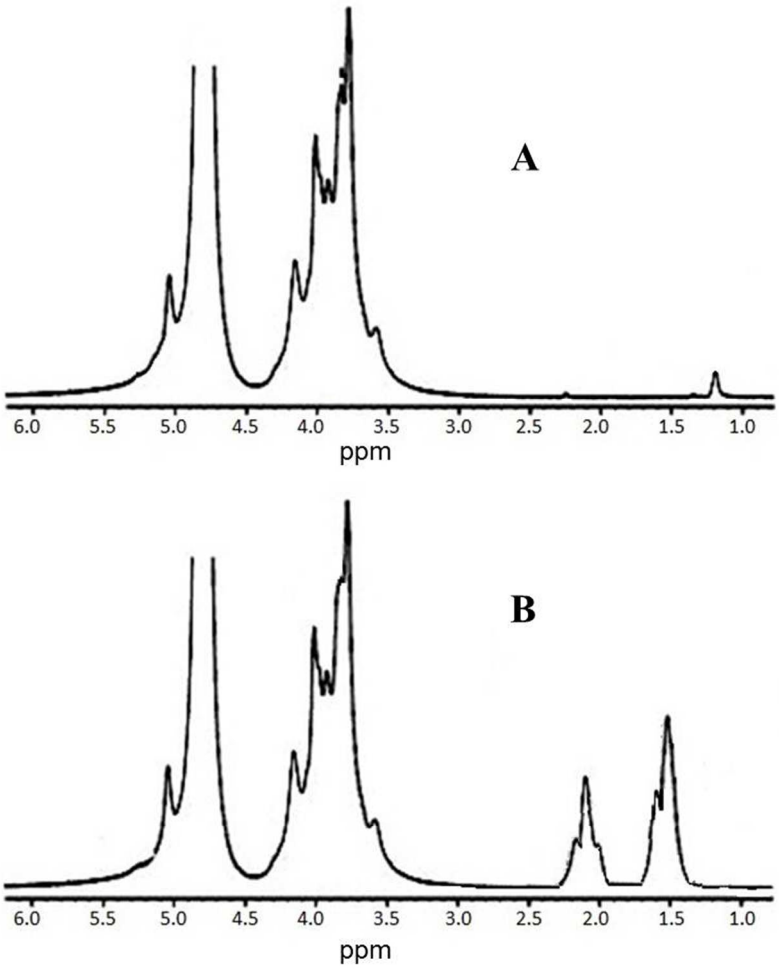
*mean ± S.D., n = 3



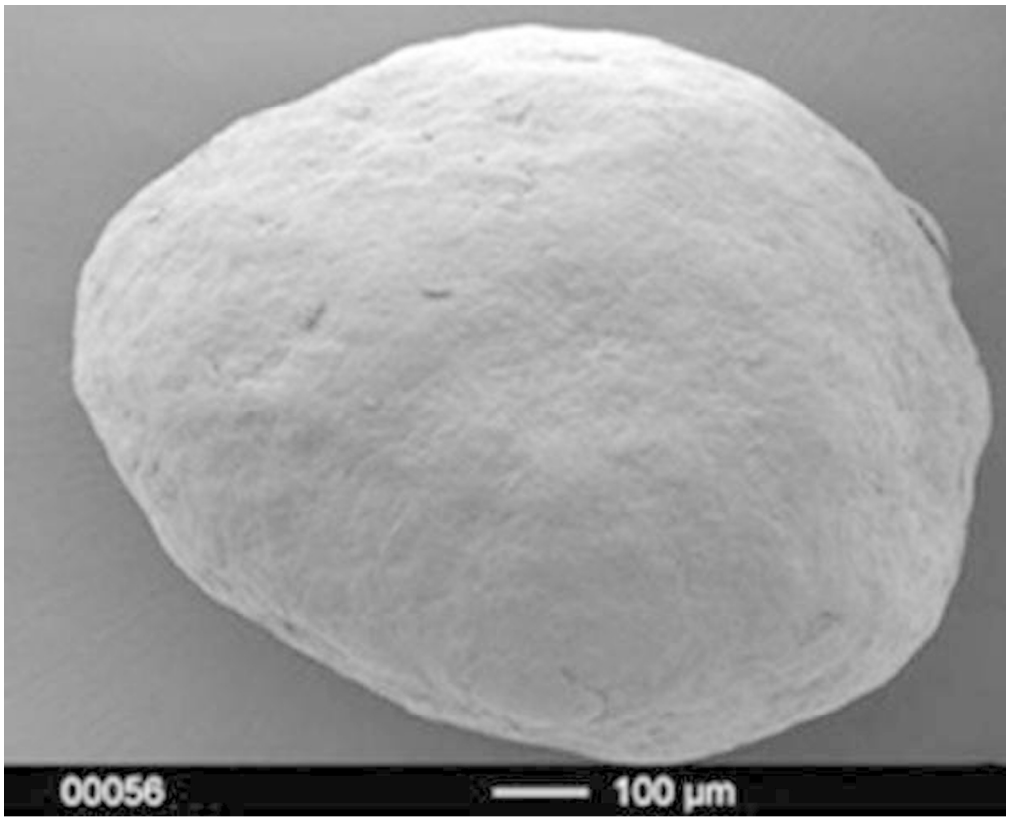
Copolymerization of AAm on to the backbone of GG
129x83mm (300 x 300 DPI)



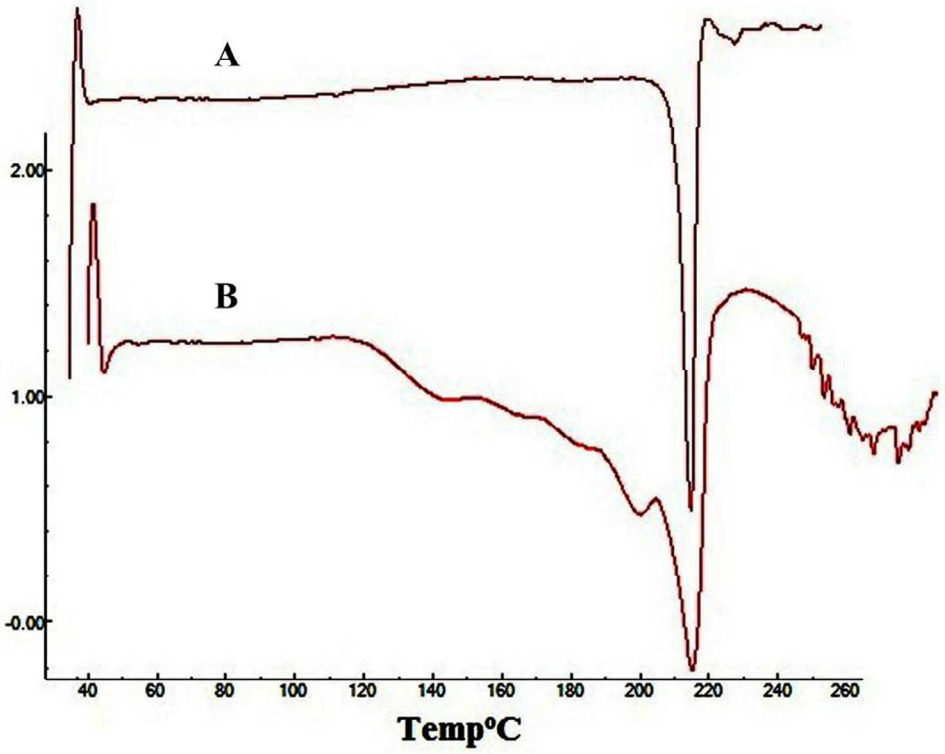
Copolymerization of AAm on to the backbone of GG
148x180mm (300 x 300 DPI)



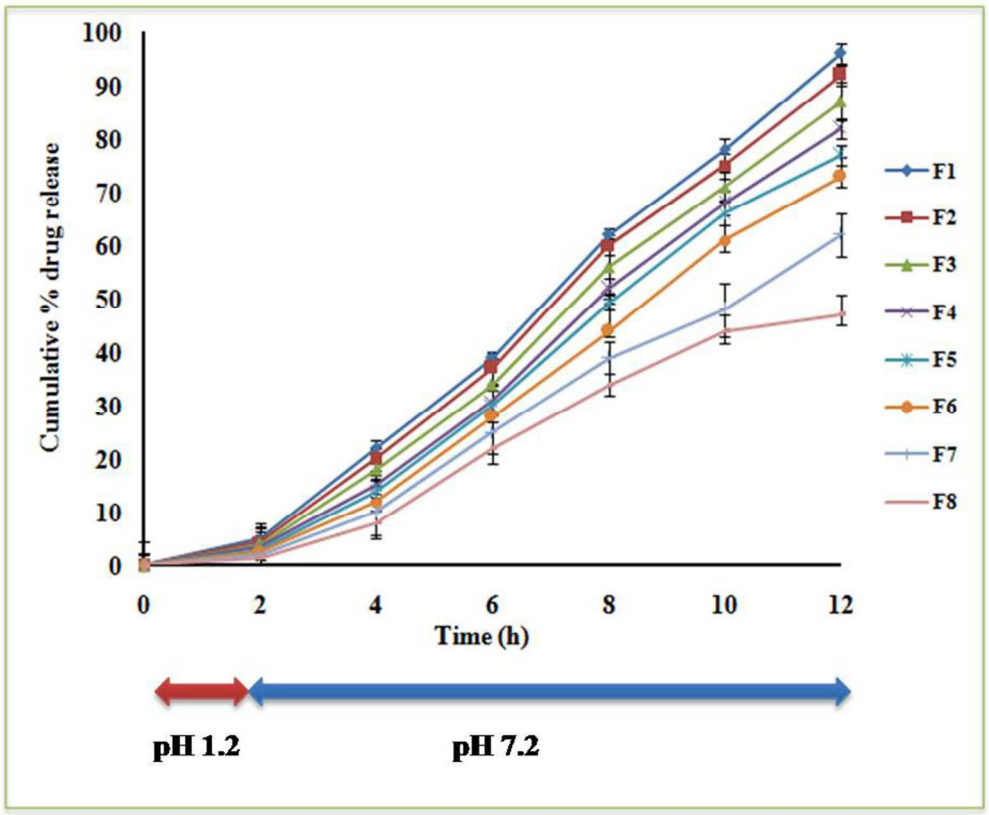
1H-NMR spectra of GG (A) and pAAm-g-GG (B)
161x171mm (300 x 300 DPI)



SEM photomicrograph of the formulated spheroid (magnification 25×)
160x130mm (300 x 300 DPI)



DSC thermogram of Glimepiride Pure Drug (A) and Formulation-5(B)
174x144mm (300 x 300 DPI)



In vitro dissolution profile of pH sensitive glimepiride pellet formulations (F1-F8) in pH 1.2 and pH 7.2
158x130mm (300 x 300 DPI)