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GUARGUM-GRAFTED-POLY ACRYL AMIDE AND SUCCINYL CHITOSAN MICROSPHERES AS SYNTHESIS AND CHARACTERIZATION OF CONTROLLED RELEASE OF THE CHLORPHENIRAMINE MALEATE

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ABSTRACT

Guar gum-g-poly (acrylamide) and Succinyl chitosan microspheres were made by water-in-oil (W/O) emulsion method. These microspheres were loaded with Chlorpheniramine maleate (CPM) and stabilized by cross-linking with glutaraldehyde (GA). The modified microspheres have been characterized by using several techniques. Differential Scanning Calorimetry (DSC) showed that CPM was uniformly dispersed at the molecular level within the polymer matrix. Scanning Electron Microscopy (SEM) revealed that the microspheres were spherical and well-formed, while laser diffraction analysis confirmed their particle size and distribution, ensuring consistency for drug delivery use. Swelling studies provided valuable insights into how the drug diffuses through the polymer network. The in vitro release profile of CPM, studied in phosphate buffer (pH 7.4), demonstrated a sustained release over 12 hours. The release

data were further analyzed with a mathematical model to better understand the mechanism of drug transport. Overall, the results highlight that the developed AAm-g-GG/SCS microspheres have strong potential as a controlled drug delivery system, offering stable and predictable release of CPM.

KEYWORDS: Guargum (GG), Polyacrylamide (PAAm), Succinyl chitosan (SCS), Groft polymer, Chlorpheniramine maleate (CPM) controlled release etc.

INTRODUCTION

For biomedical and pharmaceutical applications, polymer microspheres are of great potential.[1] functioning as continuous and confined modulators for transdermally administered medications. The spatial and temporal modulation of drug release improves the treatment outcome. In controlled release systems, natural polymers as compared to synthetic polymers have better biocompatibility, biodegradability, availability, and low cost. They also have drawbacks like low mechanical strength and high microbial attack. To overcome these weaknesses, researchers have created composite structures consisting of natural and synthetic polymers. Out of the different strategies, modification by graft copolymerization is among the most versatile and simplest approaches to change natural polymers for biomaterial modifications.[2-5]

Polysaccharides are natural polymers that are used extensively in many industries especially in the food industry as a gelling agent and in drugs and pharmaceutical industries as a slow delivery method to enclose live cells and drugs into small capsules. Of these, guar gum (GG) has received a lot of interest in the past few years. It is a highly molecular-weight, hydro colloidal hetero-polysaccharide consisted of galactose and mannose units. Guar gum has been modified by derivatization, grafting, and forming a network to improve its properties to various applications.[6-8] Different grafting methods have been used, such as the attachment of monomers such as methacrylamide, acrylonitrile and acrylic acid and more acrylamide to guar gum with the help of various initiators. Also, acryl amide grafting on guar gum has been realized by means of microwave exposure and high energy radiation like the cobalt-60 gamma ray.[9-10]

Polyacrylamide is a water soluble, synthetic polymer, whose main chain is hydrophobic with hydrophilic side groups. Polyacrylamide in a crosslinked state forms a hydrogel that is characterized by swelling capacity, relatively independent of pH changes or the presence of

electrolytes. The advantage with the inclusion of amide groups is that it allows introduction of ionic functionality to the gel thus conferring pH-sensitive properties. Hydrogels derived by reacting natural polymers with polyacrylmide have wide applications such as drug delivery systems and other medical applications. The water transport characteristics and drug release mechanisms of the cross-linked polyacrylamide grafted guar gum hydrogel microspheres that have been especially developed to find use in controlled release are also studied.[11-14]

Chlorpheniramine maleate (CPM) is an inverse H1 antihistamine which is usually used in the treatment of asthma and other allergens affecting the respiratory tract. It is often combined in formulations meant to relieve coughs and colds in a symptomatic manner. The gastrointestinal uptake of the drug is relatively slow and plasma concentrations of up to 5.9 to 11 micrograms per milliliters are attained at straddling 2.5 to 6 hours post oral consumption. After a single dose, CPM has a terminal half-life in human beings of 21 to 27 hours. Its oral bioavailability is not high, but it range between 25% and 50%. This means that in order to achieve good therapeutic concentrations, the dosage is commonly performed more than once per day typically 4 milligrams every four to six hours. Another issue with CPM is that it has a bitter taste and this may influence patient compliance. To defeat this, development of a controlled-release drug delivery system has been suggested. This kind of system would enable one dose to release the drug over some time such that it does not require frequent dosing, the total dosage may be less so as to produce the desired effects, and the same may reduce the side effects. The occurrence of sudden increases in the levels of drugs in the GI tract following the conventional unit-dose application is problematic and continues to pose a risk of gastrointestinal irritation. Micro-particulate drug delivery systems offer one of the promising solutions to this because they distribute the medication more evenly across the gastrointestinal tract. The given method may contribute to the reduction of concentration-related problems and enhance safety and efficacy. Micro-particulate delivery of CPM may produce more efficient and risk-free treatment of asthma, as well as its aversion of bitter taste. Moreover, these systems might promote the oral bioavailability which eventually would lead to patient adherence and therapeutic merit.[15-17]

In the present study to improve mechanical properties and chemical stability guar gum grafted poly acrylamide can be added to Succinyl chitosan. CPM was successfully loaded into semi IPN microspheres composed GG-g-AAm/ Succinyl chitosan. The resulting microspheres are capable of being to control the release of CPM more than 12 hours.

EXPERIMENTAL

Materials and methods

Guar gum(G.G), Acryl amide (AAm), Potassium persulphate, Glutaraldehyde (GA) solution 25% (V/V), Hydrochloric acid (HCl), n-hexane, Liquid paraffin oil (light) and Succinyl chitosan (SCS) were purchased from S. D. Fine Chemicals Ltd., Mumbai, India. Tween-80 was purchased from Aldrich., USA. Chlorpheniramine maleate (CPM) drug was purchased from WaksmanSaleman Pvt. Ltd. Anantapur, India. Double-distilled water collected in the laboratory was used throughout this research work. All the chemicals were used as received without further purification.

Preparation of AAm-g-Guar gum /Succinyl chitosan CPM loaded IPN microspheres

Interpenetrating network (IPN), microspheres of acrylamide grafted on G.G and blended with Succinyl chitosan have been prepared by emulsion cross linking method. In brief, known amount of G.G was dissolved in double-distilled water by continuous stirring until a homogeneous solution was obtained. To this solution different amount of acryl amide and potassium per sulphate were added and stirred well to make a homogeneous solution. This reaction mixture is polymerized under nitrogen atmosphere for 6 h at 70^{o}C. This polymerized AAm-g-G.G polymer product is cooled and precipitated in acetone and the precipitate was dried under vacuum for 24 h. A different weight ratio of Succinyl chitosan and AAm-g-G.G was dissolved in double-distilled water and stirred overnight until a homogeneous solution was obtained. A known amount of the Chlorpheniramine maleate (CPM) was dissolved in 1 mL of double-distilled water and is added into the blend polymer solution. The above drug loaded polymer solution was added slowly to a mixture of petroleum ether and light liquid paraffin (40:60, w/w) containing 1% (w/w) tween-80 under constant stirring at 300 rpm speed for 10 min. To this emulsion, 1 mL of 0.1 M HCl and GA was added slowly and further stirred for 30 min. This emulsion solution was filtered using Vacuum pump (High vacuum pump, Bangalore) and washed repeatedly with n hexane and distilled water to remove the oil and excess amount of unreacted GA.

Microspheres thus formed were dried under vacuum at 40^{0}C for 24 h and stored in desiccator for further analysis and characterization. Repeating the above procedure various formulations were prepared by varying Succinyl chitosan, G.G, GA and CPM compositions and these are designated as SCS-1 to SCS-9 in **Table.1.**

Formulation Codes	% NSCS in microspheres	% GG-g-AAm in microspheres	Amount of GA added (mL)	% 5-CPM added	Encapsulation efficiency ±SD (%)	% Equilibrium swelling
SCS-1	0	100	5	5	76 ± 0.9	332
SCS-2	25	75	5	5	70 ± 1.1	362
SCS-3	50	50	5	5	68 ± 0.9	424
SCS-4	50	50	2.5	5	62 ± 1.1	498
SCS-5	50	50	5	5	52 ± 0.8	424
SCS-6	50	50	7.5	5	47 ± 1.1	375
SCS-7	50	50	5	5	68 ± 0.9	342
SCS-8	50	50	5	10	72± 0.6	455
SCS-9	50	50	5	15	78 ± 0.6	495

***In-vitro* Release study**

In-vitro release studies have been carried out by performing the dissolution experiments using a tablet dissolution tester (Lab India, Mumbai, India). Dissolution rates were measured at 37 ± 0.5^0C at constant speed of 100 rpm. Drug release from the microspheres was studied in 0.1 M HCl and in 7.4 pH Phosphate buffer solutions. At regular intervals of time, sample aliquots were withdrawn and analyzed by UV spectrophotometer (Lab India, Mumbai, India) at the fixed λmax value of 264 nm. After each collection, the same amount of fresh medium at the same temperature was added to the release medium to maintain the sink condition.

Estimation of Drug Loading and Encapsulation Efficiency

The exact amount of dry microspheres was actively stirred in a beaker with 10 mL of dichloromethane to ease in the extraction of Chlorpheniramine maleate (CPM) in the IPN microspheres. Then 10 mL of phosphate buffer solution pH 7.4 with 0.02% Tween-80 were introduced into the mixture. This was then heated gently and stirred continuous to facilitate evaporation of the extracted Chlorpheniramine maleate (CPM).

The aqueous solution was filtered and assayed by UV max valueλspectrophotometer (Lab India, Mumbai, India) at fixed of 264 nm. The encapsulation efficiency is given with two digits with SD, which was measured by diffusion method i.e. the microspheres were dispersed in a buffer solution and made to swell. The release of drug into the buffer solution was measured spectrophotometrically. The results of % drug loading and encapsulation efficiency were calculated using **Eqs: 1** and **2** respectively.

$$\% \text{ CPM loading} = \frac{Weight\ of\ CPM\ in\ microspheres}{Weight\ of\ microspheres} \text{ X } 100 \quad \text{----- (1)}$$

$$\% \text{ Encapsulation efficiency} = \frac{Actuval\ CPM\ loading}{Theoritical\ CPM loading} \text{ X } 100 \text{ ----- (2)}$$

Swelling studies

The dynamic swelling behavior of GG-g-AAm blended Succinyl chitosan microspheres was investigated by preparing samples with three different concentrations of cross-linker and three varying drug loadings. The swelling process was studied in water by measuring the amount of water absorbed over time. All swelling experiments were conducted in a phosphate buffer solution at pH 7.4. To carry out these experiments, the microspheres were immersed in the buffer solution. At specific time intervals, a number of microspheres were carefully removed from the solution and gently blotted with tissue paper to eliminate any surface-adherent liquid without applying excessive pressure. The initial wet weight of each microsphere was then recorded using an electronic microbalance (model ADAM AFP-120 L, precision ±0.0001 g). Subsequently, the microspheres were dried in a controlled oven maintained at 40°C for five hours until reaching a constant weight. All swelling measurements were repeated three times for each sample to ensure accuracy, and the average values were considered for analysis. The standard deviation in all measurements was < 5%. The percentage of water uptake by the microspheres was calculated using **Eqn: 3**

$$\% \text{ Equilibrium swelling} = \frac{Wt.of\ Ms - Wt.of\ Md}{Wt.of\ Md} \text{ X } 100 \quad \ldots\ldots (3)$$

RESULTS AND DISCUSSIONS

Fig. 1 displays FT-IR spectra of native GG and AM monomer. The characteristic vibrational bands at the characteristic wave numbers were labeled.

The vibrational spectral bands in the FTIR have been allocated on the basis of their wave numbers (cm^{-1}). In the case of native guar gum (GG), the following main characteristics can be identified. A broad band at 3408 cm^{-1} O-H stretching vibrations, a band at 2932 $^{cm-1}$ C-H stretching vibrations in CH_2 groups, a peak at 1654 cm^{-1} ring vibrations and water molecules, a band at 1432 cm^{-1} symmetrical CH_2 deformations, and bands at 1152 and 1092 cm^{-1} due to C-OH and primary alcohol Peaks at 3351 and 3195 cm^{-1}, which are NH_2 stretching vibrations of the amide group, a C-H stretch at 2813 cm^{-1}, a C=O stretching vibration at 1674 cm^{-1}, a C=C stretch at 1609 cm^{-1}, and a C-N vibration at 1430 cm^{-1} are characteristic of the native acrylamide monomer. In the case of the GG-g-PAM hydrogel, a broad peak of 3439 cm^{-1} in the FTIR spectrum is obtained as a result of overlapping O-H and N-H stretching vibrations. Other salient bands are 2943 cm^{-1} and C-H stretches at the 1658 cm^{-1} and 1447 cm^{-1} which are C=O stretching and C-N stretching vibrations respectively. The characteristic amide band at 1658 cm^{-1} indicates that a successful grafting of acryl amide on the guar gum backbone has

taken place, and the loss of C=C stretching band at 1609 cm^{-1} also support the grafting process.

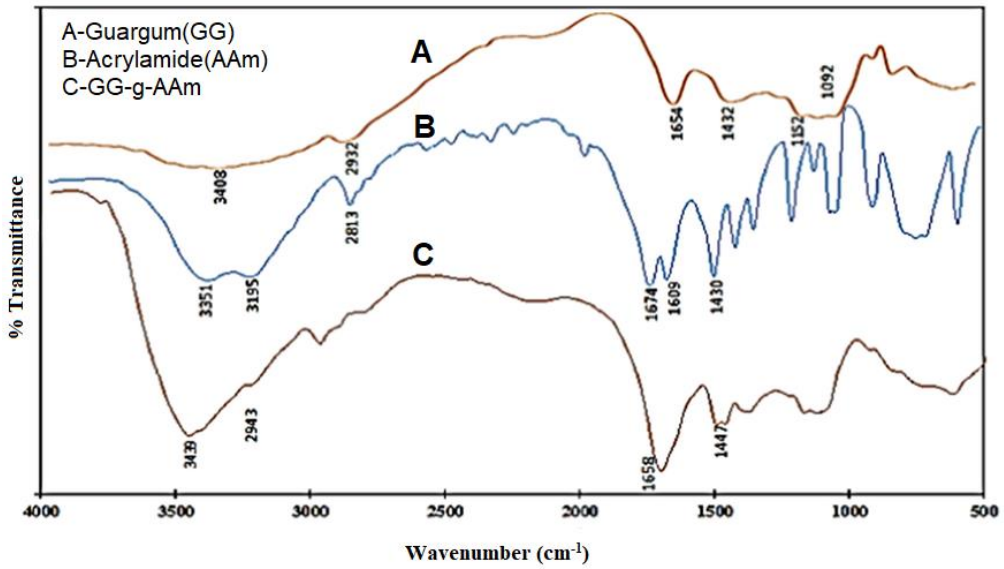

Fig. 1: FTIR spectra of Guargum (GG), Acrylamide (AAm) and GG-g-AAM.

Scanning Electron Microscopic (SEM) studies

The CPM loaded GG-g-AAm/ Succinyl chitosan microspheres are spherical in shape and are agglomerated as indicated by the SEM photograph shown in **Fig 2**. The microspheres have a mean diameter ranging from 50 to 100µm. The surface appears to be highly porous.

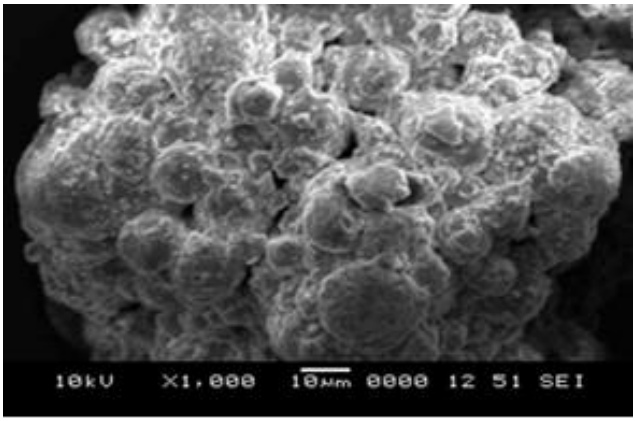

Fig. 2: SEM micrographs of CPM loaded GG-g-AAm/ SCS chitosan microspheres.

Differential scanning calorimetry (DSC)

Differential scanning calorimetric (DSC) curves for CPM loaded microspheres and pure CPM drug are shown in **Fig 3.** The drug CPM, exhibit sharp peak at 135°C due to polymorphism and melting. However, this peak is not appeared in the curve of CPM loaded

microspheres, suggesting that most of the drug was uniformly dispersed in polymer matrices at molecular level.

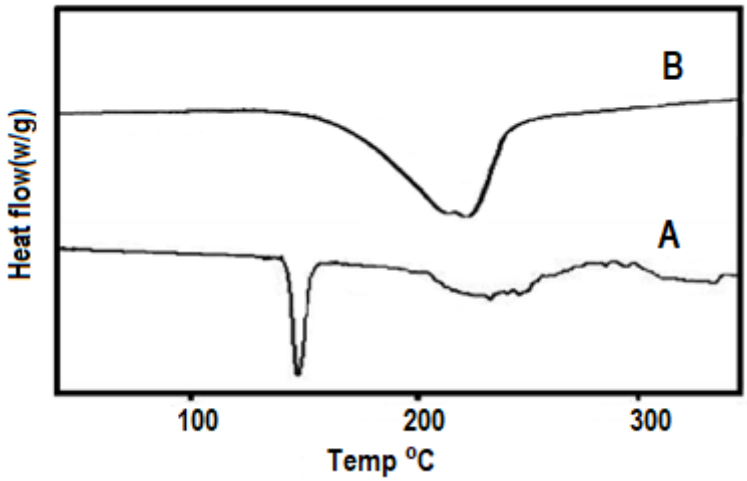

Fig. 3: DSC thermograms of (A) CPM and (B) CPM-loaded blend microspheres.

In-vitro release studies

To understand the mechanism of drug release, *in vitro* release data have been analyzed using the empirical kinetic equation as given below (Ritger and Peppas, 1987).[18].

$$(M_t / M_\infty) = kt^n \text{ --- (4)}$$

Here, M_t / M_∞ represents the fractional drug release at time t; k is a constant characteristic of the drug-polymer system and 'n' is an empirical parameter characterizing the release mechanism. Using the least square procedure, the estimated values of 'n' and k for all the formulation are given in **Table: 2.** If n = 0.5, then drug diffuses and releases from the polymer matrix following a Fickian diffusion. For n > 0.5, anomalous or non-fickian type drug diffusion occurs. If n = 1, a completely nonFickian of case II release kinetics is operative. The intermediary values ranging between 0.5 to 1 are attributed to the anomalous type of transport. In this study k and n values dependence on extent of crossliking, % drug loading of the formulation. n values of microspheres prepared by varying the amount of SCS (25, 50, and 75 %) by keeping 5-FU (5%) and GA (5 mL GA) constant, ranged from 0.84 to 0.90, indicate the shift of transport from Fickian to anomalous type. The 5-FU-loaded particles have shown the n values ranging from 0.52 to 0.92 (**Table -II**), indicating the shift from erosion type release to a swelling controlled, non- Fickian mechanism. This may be due to a reduction in the regions of low microviscosity and closure of microcavities in the swollen state. The values of exponent 'n' ranges between 0.52 and 0.92 as calculated from empirical, which indicated that drug release followed by an anomalous no transport occurs.

Table 2: Release Kinetics Parameters of Different Formulations.

Formulation code	*k*	*n*	Correlation coefficient, *r*
SCS-1	0.980	0.92	0.993
SCS-2	0.992	0.82	0.982
SCS-3	0.994	0.85	0.966
SCS-4	0.946	0.90	0.945
SCS-5	0.942	0.52	0.965
SCS-6	0.962	0.66	0.958
SCS-7	0.984	0.72	0.967
SCS-8	0.980	0.84	0.992
SCS-9	0.960	0.90	0.995

Effect of Succinyl chitosan content

The influence of different SCS concentration was studied with constant drug loading. **Fig 4.** shows the release profiles of AAm-g-GG/SCS microspheres prepared with varying amount of SCS. These microspheres had a consistent swelling behavior during the dissolution process, but the swelling behavior decreased with decreased SCS content. The tendency can probably be attributed to the development of loosely crosslinked SCS networks.

The higher the amount of SCS, the lower the cumulative release of the drug was, mainly due to the reduction of the swelling rate of the chains of SCS in comparison to GG. This is explained by the fact that the increase in the concentration of SCS in the semi-interpenetrating polymer network (semi-IPN) contributes to the overall hydrophobic nature of the matrix and the rate of drug release is delayed. Moreover, the polymer chains can also experience a relaxation response to the stresses caused by the solvent around it when it is in solution. This stress has the potential to make the chain reduce in size, e.g. the radius of gyration, resulting in the shrinkage of the hydrated polymer. Consequently, the SCS component swelling is reduced, thus reducing the amount of free volume in the matrix. The resultant effect of this sequence of events is a slower process of release of the drug since there is a restriction of the available space in the polymer network to the diffusion process.

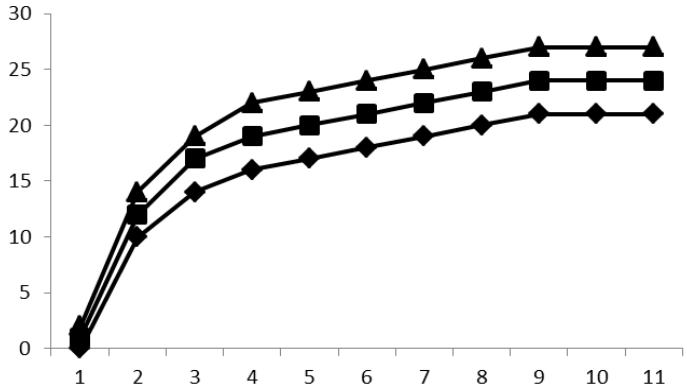

Fig. 4: % Cumulative release of CPM through AAm–g-GG /SCS microspheres containing different amount of SCS. Symbols: (◊) 0 wt. %. % (■) 25 wt. %(Δ) 50 wt.

Effect of Cross linker

Fig 5. represents the plot that depicts the percentage of cumulative drug release with time of various amounts of glutaraldehyde (GA) namely 2.5 mL, 5.0 mL, and 7.5 mL but with a constant drug content of 20%. It was noted that the cumulative rate of release is much faster and higher under lower GA concentration of 2.5 mL. On the other hand, the rate of the release decreases significantly when there is an increase in the quantity of GA to 7.5 mL. The total proportion of drug released is comparatively decreased at the low levels of GA probably because the higher the concentrations of GA at that time the more the rigidity of the polymer network. This is due to the fact that contraction of micro voids in the matrix occurs which limits diffusion of 5-fluorouracil (CPM) through the polymeric structure. As expected, an increase in the levels of GA in the body would lead to the decrease in the rate of drug release, but the decrease in the levels of GA would lead to increased drug release profile.

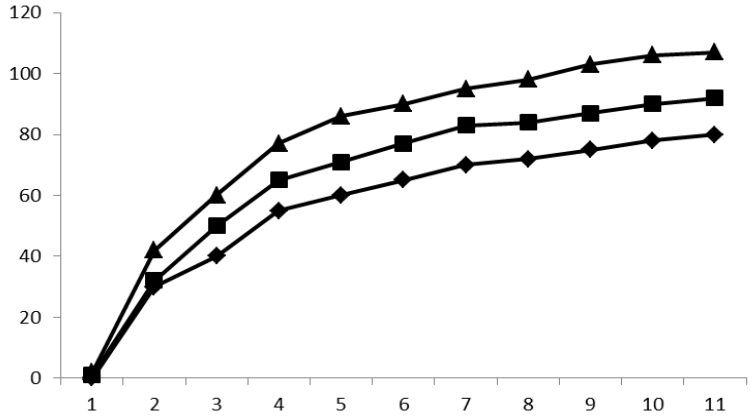

Fig. 5: % Cumulative release of CPM through AAm–g-GG /SCS microspheres containing different amount of crosslinker. Symbols: (◊) 2.5mL (■) 5mL. (Δ) 7.5Ml.

Effect of Drug

Fig 6. shows the release pattern of 5-fluorouracil (CPM) loaded microspheres using different drug loadings. The data of release indicate that the formulations with the maximum level of drug concentration had rapid and significantly greater release than the ones with lower drug content. On the other hand, the microspheres containing lower concentrations of CPM exhibited a longer, slower release profile. Essentially, the lower the drug loading in the microspheres, the slower is the rate of release. This is due to the slower diffusion of the drug molecules as evidenced by an increase in the free areas in the matrix and, accordingly, reduces the number of molecules of the drug that is available to be diffused, thus regulating the overall rate of release.

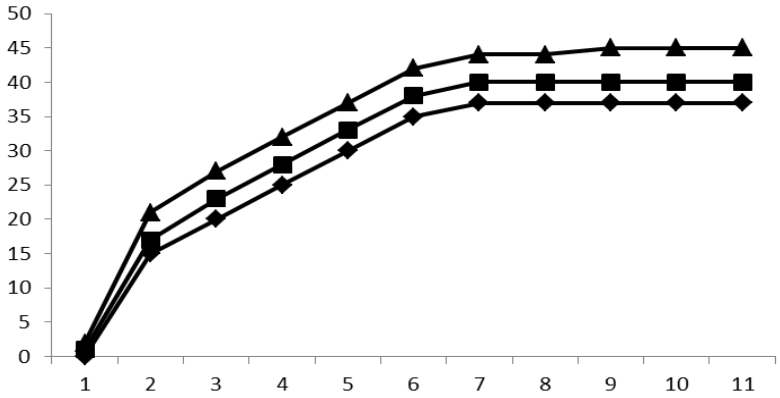

Fig. 6: % Cumulative release of CPM through AAm–g-GG /SCS microspheres containing different amount of CPM. Symbols: (◊) 5 wt. %. % (■) 10 wt. %(Δ) 15 wt.

CONCLUSIONS

Polymeric microspheres based on carbohydrates grafted with AAm-g-GG and added to Succinyl chitosan were prepared and fully studied with the help of such methods as differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). DSC analysis established that the distribution of the drug molecules in the microspheres is homogenous. SEM images depicted that the microspheres were of a spherical shape. The release of the drug was in a controlled and constant way with time. Experiments on swelling demonstrated that as the composition of the AAm-g-GG in the microspheres was increased the water absorption rate increased. This swelling trend had a direct effect on the drug release rates of microspheres having different AAm-g-GG content. Moreover, such microspheres had low densities, which enabled them to stay in the gastric environment more than 10 hours. This prolonged retention may probably increase the bioavailability of CPM.

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