INTERNATIONAL JOURNAL OF PLANT, ANIMAL AND ENVIRONMENTAL SCIENCES
IJPAES

Volume-3, Issue-3, July-Sept-2013
ISSN 2231-4490
www.ijpaes.com

Received: 1st Mar-2013 *Revised: 28th Mar-2013* *Accepted: 9th June-2013*

Research article

CARBOXYMETHYLCELLULOSE-G-ACRYLAMIDE BLEND CHITOSAN MICROSPHERES FOR CONTROL RELEASE OF CHLORO PHENIRAMINE MALIATE

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ABSTRACT: Semi-interpenetrating polymer network [IPN] microspheres of carboxymethylcellulose-grafted acryl amide/Chitosan microspheres were prepared by water-in-oil (W/O) emulsion method. These microspheres were loaded with, Chloro pheniramine maliate and Cross-linked with glutarldehyde; these microspheres were characterized by differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and laser particle size analyzer. DSC thermograms of Chloro pheniramine maliate.-loaded AAm-CMC/ Chitosan microspheres confirmed the molecular level distribution of Chloro pheniramine maliate in the polymer matrix. SEM of the microspheres suggested the formation of spherical particles. Swelling experiments on the microspheres provided important information on drug diffusion properties. Release data have been analyzed using an empirical equation to understand the nature of transport of drug containing solution through the polymeric matrices. The controlled release characteristic of the matrices for Chloro pheniramine maliate was investigated in pH 7.4 media. Particle size and size distribution of the microspheres was studied by laser light diffraction particle size analyzer. Drug was released in a controlled manner up to 12 h.
Key words: Carbohydrate polymers, Semi-interpenetrating polymer network [IPN], crosslinking, controlled release etc.

INTRODUCTION

Polysaccharides, a class of naturally available carbohydrate polymers, have been used extensively in food industry as gelling agents and for encapsulation of living cells, drugs [1-3] among the systems for controlled release, prime attention has been paid in recent years to polymeric carriers [4] systems which may be natural [5] or synthetic [6] or combination of both the polymers [7]. Natural polymers are biocompatible and biodegradable and some of the synthetic polymers are biocompatible. Combination of these two types of polymers will enhance the properties of the matrix. One of the ways to increase the properties of natural [8-10] and synthetic [11-12] polymers and to give them new properties is by graft copolymerization**.** The grafting of vinyl monomers on the natural polymers such as cellulose and its derivatives is been camed out. Carboxymethylcellulose, (CMC) is a carbohydrate polymer it is a cellulose derivative with carboxymethyl groups (-CH_2-COOH) bound to some of the hydroxyl groups of the glucopyranose monomers that make up the cellulose backbone, is soluble in water. CMC forms aqueous solutions, and it demonstrates the unique property of forming reversible physical gels due to hydrophobic interactions when heated above a particular temperature. CMC is used in food science as a viscosity modifier or thickener and to stabilize emulsion for instance in ice cream. It has E number E466. It is also a constituent of many non-food products [13], such as K-Y Jelly, toothpaste, laxatives, diet pills, water-based paints, detergents, and various paper products. They have high viscosity, are not toxic, and are generally non-allergenic. CMC is used as a lubricant in non-volatile eye drops (artificial tears). Cellulose, the raw material of CMC, is hydrophilic, but cellulose fibers contain the crystalline ordered regions formed by the intra and intermolecular hydrogen bonds; consequently, cellulose does not dissolve in water. However, the crystalline fraction depends on the source of cellulose, but when carboxyl groups are substituted by certain number of hydroxyl groups, some hydrogen bonds are broken and CMC becomes water-soluble. Commercial CMC synthesized by the alkali-catalyzed chemical reaction of cellulose with chloroacetic acid. The polar (organic acid) carboxyl groups render the cellulose soluble and chemically reactive.

Poly (acryl amide) has limited applicability because of its poor mechanical properties due to its high degree of hydration. The copolymers of acryl amide as hydro gels are important in biomedical applications [14-15].

Chitosan, obtained from deacetylation of chitin, is one of the most facile chemicals for allowing alteration that gives useful hydrogel and microparticals (16-17). Chitosan appears to be more useful in biomedical applications and for the degradation of aqueous solutions than chitin, as it has both hydroxyl and amino groups that can be easily modified (18-19).

The key properties of chitosan in this respect are its biocompatibility, nonantigenicity, and nontoxicity (its degradation products are known natural metabolites), the ability to improve wound healing, sustained release and blood clotting, the ability to absorb liquids and form protective films and coatings, and selective binding of liquids, which have been used to lower serum cholesterol levels. Chitosan is a copolymer of D-glucosamine and N-acetyl glucosamine derived from chitin. For drug delivery applications, chitosan needs to be crosslinked due to its hydrophilic property. Various crosslinking agents such as formaldehyde and glutaraldehyde have been used to crosslink chitosan. The crosslinked chitosan as a pH- sensitive material swells under acidic conditions due to protonation of their free amino groups. Therefore Chitosan material has been widely used for sustained drug delivery in the stomach via the oral route.

MATERIALS AND METHODS

Carboxymethylcellulose (CMC), Acrylamide (AAm), Chitosan (CS), light paraffin oil, glutarldehyde (25 % aqueous solution) (GA) were purchased from s.d. Fine Chemicals, Mumbai, India. Tween-80 was purchased from Sigma Chemicals Chloro pheniramine maliate (CPM) was given as gift sample from Waksman Saleman pharmaceuticals, Anantapur, India.

Preparation of CMC-grafted-Acrylamide/chitosan microspheres

Varying amount of Carboxy Methyl Cellulose was weighed and dissolved in water by overnight stirring. To this solution different amount of acryl amide and potassium persulphate were added and stirred well. This reaction mixture is polymerized under nitrogen atmosphere for 6 h at 70^{o}C. This polymerized is cooled and polymer was extracted by precipitating the polymer in acetone and precipitated polymer was dried under vacuum for 24 h.

A different weight ratio of chitosan and carboxy methyl cellulose-g-acryl amide was dissolved in the water of certain concentration overnight. The two polymer solutions were mixed and stirred well for proper mixing which lead to miscible polymer solution. A known amount of the Chloro pheniramine maliate was dissolved in 1 mL of DM Water and is added into the blend polymer solution. The drug loaded blend polymer solution was emulsified into liquid paraffin to form a water-in-oil (w/o) emulsion at 400 rpm using Eurostar (IKA Labortechnik, Germany) high-speed stirrer for 30 min in a separate 500 mL beaker containing 100 mL of light liquid paraffin oil, 2 % (w/v) of Tween-80, 1 mL of 0.1 M HCl and the required amount of GA is added. The microspheres formed were filtered, washed repeatedly with hexane and water to remove the oil as well as excess amount of surfactant and the unreacted GA. These microspheres were dried under vacuum at 40^{0}C and stored in desiccators before further analysis.

RESULTS AND DISCUSSIONS

Differential scanning calorimetry (DSC) studies

DSC thermograms of plain Chloro pheniramine maliate, AAm-g-CMC/ Chitosan microspheres and Chloro pheniramine maliate-loaded CMC-AAm/Chitosan microspheres were recorded using Rheometric Scientific differential scanning calorimeter (Model-DSC SP, UK). The analysis was performed by heating the samples at the rate of 10^{0}C/min under inert atmosphere. Figures suggests that Chloro pheniramine maliate molecularly disperses in the IPN matrix.

Fourier transform infrared spectroscopy (FTIR)

IR Spectra of unloaded and graft polymers are depicted in fig.2. The spectra clearly marks the presence of amide group at 3420cm^{-1}(N-H stretching) and 1680 and 1660cm^{-1} (NH_2 bending), carboxymethylcellulose unit bearing carboxylate ion at 1600 cm^{-1} (strong asymmetrical stretching band) and 1450 cm^{-1}(O-H bending of carboxylate ion), the entrapment of KNO_3 is evident from vibrational frequency of nitrate ion at 1380 cm^{-1} the broad bands from 1200 to 1000 cm^{-1}were due to sugar ring absorption.

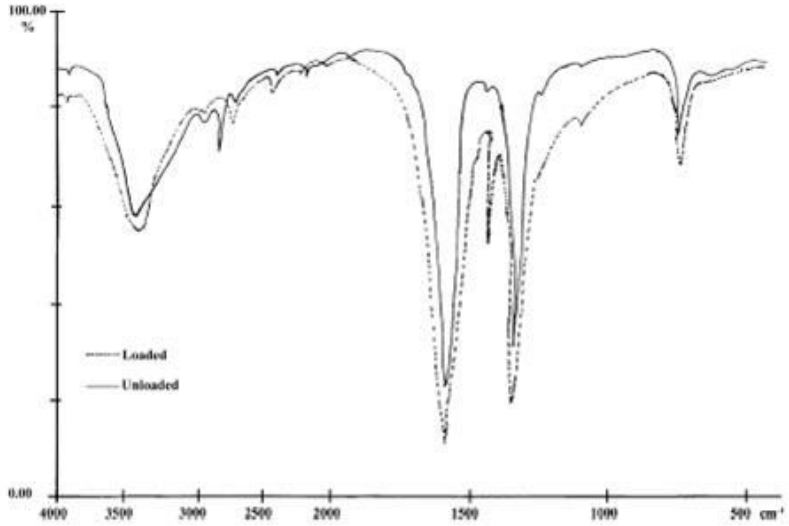


Fig-1: IR spectra of loaded and unloaded gel

Scanning electron microscopic (SEM) studies

SEM images of the microspheres were recorded using a Hitachi S520 scanning electron microscope (Japan) at the required magnification. Working distance of 33.5 mm was maintained and the acceleration voltage used was 10 kV with the secondary electron image (SEI) as a detector. Fig.3.shows the cross-sectional SEM micrograph of Chloro pheniramine maliate loaded CMC-g-AAm/Chitosan microspheres. Cross-section of the CMC-g-AAm/Chitosan microspheres show corrugated structures that are common with the graft copolymers.

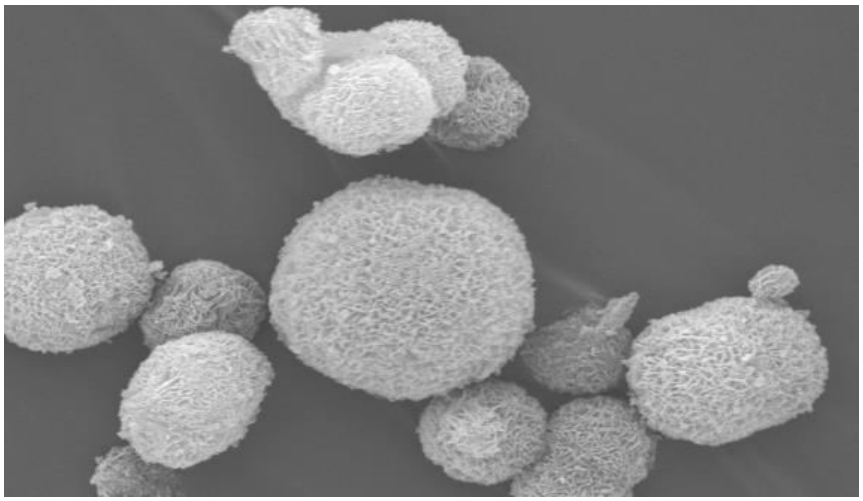


Fig.2. Scanning electron micrograph of AAm-g-CMC/NaAlg Microspheres.

Particle size analysis

Particle size and size distributions have been analyzed by using a particle size analyzer (Mastersizer 2000, Malvern Instruments, UK). Results of volume mean diameter of the microspheres produced by taking three different amounts of crosslinking agent are include in table.1. These results suggest that as the extent of crosslinking increases, the volume mean diameter decreased. On a population basis, particle size distribution is unimodel. Microspheres used in preparing the drug-loaded formulations were selected from a uniform size distribution range as displayed in fig.4. A narrow size distribution of microspheres was observed with particle size 90-450 µm, but majority of particles is in the size range between 150-220 µm.

Estimation of drug loading and encapsulation efficiency

Specific amount of dry microspheres were vigorously stirred in a beaker containing 10 mL of dichloromethane to extract the drug from the microspheres. A 10 mL of 7.4-pH phosphate buffer containing 0.02 % Tween-80 was added to the above solution to make the drug soluble and dichloromethane was evaporated with a gentle heating and continuous shaking.

The aqueous solution was then filtered and assayed by a UV spectrophotometer (model Anthelie, Secomam, Dumont, France) at the fixed λ_{max} value of 262nm. The results of % Chloro pheniramine maliate loading and encapsulation efficiency were calculated using Esq. (1) and (2). These results are compiled in Table.1.

$$\%\ \text{Drug loading} = \left(\frac{\text{Amount of drug in beads}}{\text{Amount of beads}}\right) \text{x}\, 100 \qquad (1)$$

$$\%\ \text{Encapsulation efficiency} = \left(\frac{\text{Actual loading}}{\text{Theoretical loading}}\right) \text{x}\, 100 \qquad (2)$$

Swelling studies

Dynamic swelling of the CMC-AAm/Chitosan microspheres were prepared by using three different concentration of crosslinker as well as three different drug loadings was studied in water by mass uptake measurements with time. Swelling experiments performed in 7.4 pH buffer solutions produced no significant changes and hence, we studied the swelling of microspheres in water. To perform swelling experiments, microspheres were soaked in water; several of them were removed from the swelling bottles at different time intervals and blotted carefully (without pressing hard) to remove the surface-adhered water. The microspheres were then weighed (w_1) on an electronic microbalance (Mettler, AT 120, Switzerland) accurate to ± 0.0001 g. The microspheres were then dried to a constant weight (w_2) in an oven maintained at 60^0C for 5 h. Swelling experiments were repeated thrice for each sample and average values were used in data analysis. The standard deviations (S.D.) in all cases were < 5 %. The weight % water uptake was calculated as:

$$\%\,\text{Water uptake} = \left(\frac{\text{Weight of swollen } MGs\ (w_1) - \text{Weight of dry } MGs\ (w_2)}{\text{Weight of dry } MGs\,(w_2)}\right) \times 100 \qquad (3)$$

Effect of Acrylamide

Fig. 5a shows the *in vitro* release data of Chloro pheniramine maliate from the microspheres particles performed with different ratio of AAm in the polymeric particles. The data shows that higher amount of AAm containing particles have more encapsulation efficiency and also the release studies shown that higher amount of AAm containing particles have shown prolonged release characteristics than the microspheres containing lower amount of AAm. Generally, the drug release pattern depends on many factors like particle size, crystallanity, surface character, molecular weight, polymer composition, swelling ratio, degradation rate, drug binding affinity and the rate of hydration of the polymeric materials, etc. In the release behavior of polymeric system we can consider the binding affinity of drug and polymer swelling property of AAm. A rapid release of more than 98% of drug was observed within 12 h from the microspheres containing lower amount of AAm indicating that interaction between the two polymers.

Effect of crosslinking agent

The % cumulative release data vs. time plots for varying amounts of GA i.e., 2.5, 5.0 and 7.5 mL at the fixed amount of the drug (5 %) are displayed in Fig.5.The % cumulative release is quite fast and large at the lower amount of GA (i.e., 2.5 mL), whereas the release is quite slower at higher amount of GA (i.e., 7.5 mL). The cumulative release is somewhat smaller when lower amount of GA was used probably because at higher concentration of GA, polymeric chains become rigid due to the contraction of microvoids, thus decreasing % cumulative release of Chloro pheniramine maliate through the polymeric matrices. As expected, the release becomes slower at higher amount of GA, but becomes faster at lower amount of GA. As shown in Fig.2a-d

Effect of percent drug loading

Fig.5c shows the release profiles of Chloro pheniramine maliate-loaded NaAlg-CMC microspheres at different amount of drug loadings. Release data showed that formulations containing the highest amount of drug (15 %) displayed fast and higher release rates than those formulations containing a small amount of Chloro pheniramine maliate. A prolonged release was observed for the formulation containing lower amount of Chloro pheniramine maliate. In other words, with a decreasing amount of drug in the matrix, it is noticed that the release rate becomes quite slower at the lower amount of drug in the matrix, and this is due to the availability of more free void spaces through which lesser number of drug molecules will transport. For all the Chloro pheniramine maliate-loaded formulations, the complete release of Chloro pheniramine maliate was not observed even after 600 min, but the release rates were around 700 min.

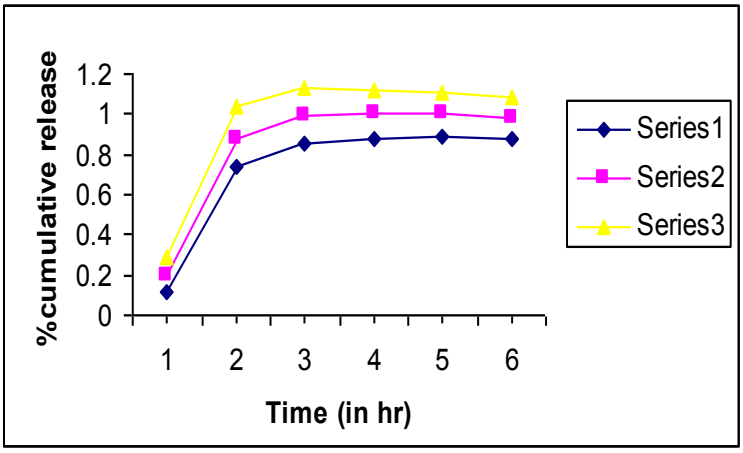
IN-VITRO RELEASE

In-vitro release studies have been carried out by performing the dissolution experiments using a tablet dissolution tester (Lab India, Mumbai, India) equipped with eight baskets. Dissolution rates were measured at 37^0C under 100 rpm speed. Drug release from the microspheres was studied in an intestinal (7.4 pH phosphate buffer) fluid. At regular intervals of time, sample aliquots were withdrawn and analyzed by UV spectrophotometer (Model Anthelie, Secomam, Dumont, France) at the fixed λ_{max} value of 262 nm.

Table 1. Results % of encapsulation efficiency, mean size and water uptake of different formulations.

Formulation codes	% of CS: in CMC microspheres	Amount of AAm Added	%CPM loaded	Amount of GA added (mL)	% Encapsulation efficiency ± S.D.	Mean particle size (μm) ± S.D.	% Water uptake
AAm-g-CMC/CS	10:90	10	5	2.5	68.2 ± 0.8	168 ± 5	495
AAm-g-CMC/CS	10:90	10	5	5	66.4 ± 1.1	156 ± 6	458
AAm-g-CMC/CS	10:90	10	5	7.5	61.5 ± 0.9	112 ± 8	343
AAm-g-CMC/CS	20:80	10	5	5	72.6 ± 0.8	160 ± 7	395
AAm-g-CMC/CS	30:70	10	5	5	79.8 ± 1.2	145 ± 9	420
AAm-g-CMC/CS	10:90	10	10	5	68.5 ± 1.1	198 ± 5	464
AAm-g-CMC/CS	10:90	10	15	5	70.9 ± 1.5	205 ± 6	486
AAm-g-CMC/CS	00:100	10	5	5	61.8 ± 0.6	118 ± 5	518
AAm-g-CMC/CS	10:90	20	5	5	58.2 ± 0.4	135 ± 4	495
AAm-g-CMC/CS	10:90	30	5	5	49.5 ± 0.6	158 ± 9	451

S.D.: standard deviation



Fg.2a.Cumulative % release of THCM through C.M.C–g-AAm/Chitosan microspheres containing different amount of drug Symbols: (◊) 10 wt. % drug (■) 20 wt. % drug (Δ) 30 wt. % drugs

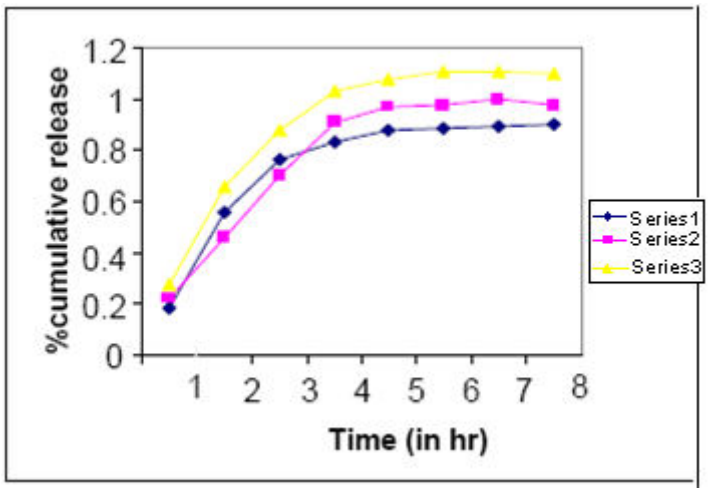


Figure.2b.Cumulative % release of THCM through CMC–g-AAm/Chitosan microspheres containing different amount of AAm Symbols: (Δ) 10 wt. % AAm, (■) 20 wt. % AAm, (◊) 30 wt. % AAm

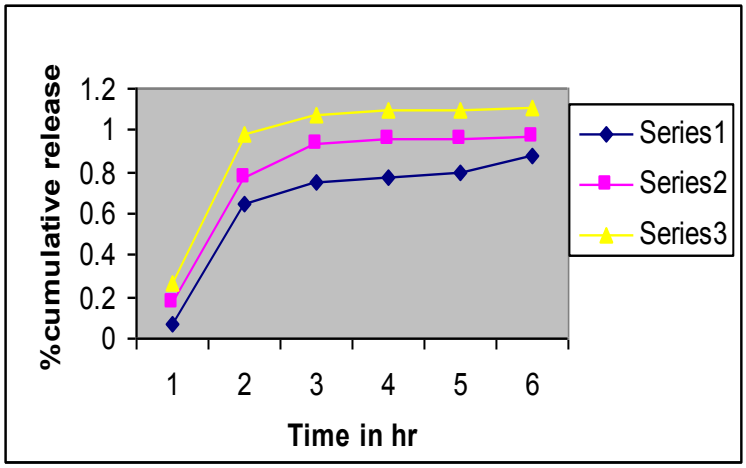


Fig.2c Cumulative % release of THCM through CMC–g- AAm/Chitosan Microspheres containing different amount of CS Symbols :(◊) 10 wt. % CS (■) 20 wt. % CS, (Δ) 30 wt. % CS

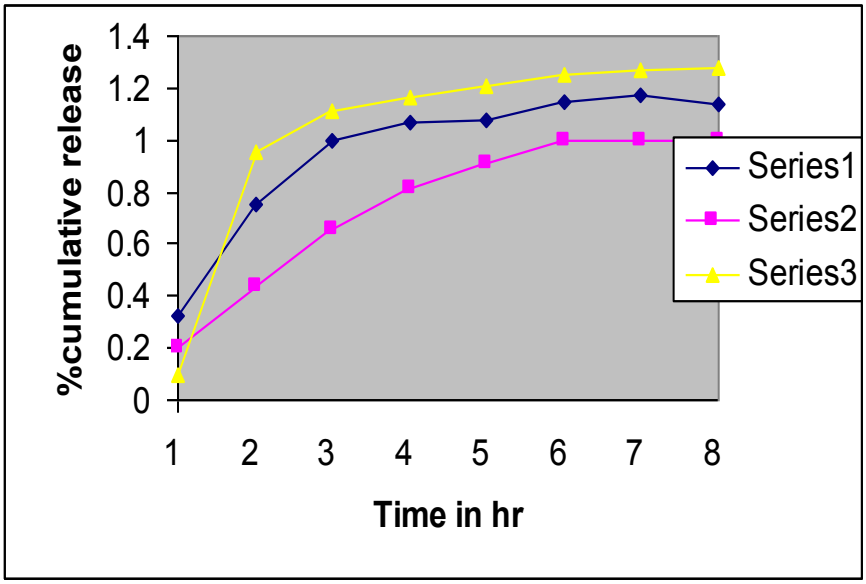


Fig.2d.Cumulative % release of THCM through CMC–g- AAm/Chitosan Microspheres containing different amount of Cross linking agent Symbols :(◊) 5mL (Δ) 2.5mL (■) 7.5mL

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