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Research Article

DEVELOPMENT OF pH SENSITIVE HYDROGEL FOR INTESTINAL DELIVERY OF METHYL PREDNISOLONE USING NOVEL CHITOSAN DERIVATIVE

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ABSTRACT

Hydrogels can be formulated sensitive to several stimuli, of which the pH sensitive drug delivery system is gaining importance for oral route of administration, considering the variation in pH along the GIT. In the present study, Carboxymethylchitosan was prepared and was characterized by FT-IR and NMR. Eight different formulations were prepared by varying the concentration of the carboxymethylchitosan and carbopol 934. pH sensitive hydrogels of Methylprednisolone Hemisuccinate were formulated using Carboxymethylchitosan and carbopol 934 as monomers where the polymer carbopol 934, act as a crosslinking agent. The prepared hydrogel were characterized by FT-IR, SEM and DSC studies. They were evaluated for swelling, drug content and *in vitro* drug release studies.

FT-IR and DSC studies showed no chemical interaction between drug and the polymers used. The surface morphology study by SEM has shown that the prepared hydrogel was porous in nature. The swelling studies have shown little swelling in acidic pH around 220% at the end of two hour and in basic pH around 4200% at the end of 12 hours which could be attributed to the dissociation of –COOH group, thereby increasing the osmotic pressure inside the hydrogels which result in increased swelling. The release profile in the formulation F-1 containing carboxymethylchitosan and carbopol in 1:1 ratio showed sustained release. The drug release was found low in acidic pH and increased when pH was changed to basic. The prepared hydrogels are suitable for the delivery of methyl prednisolone as the drug is not stable in the stomach thus can be delivered efficiently to the intestine when the pH is favourable.

Keyword: Corboxymethyl Chitosan, Hydrogels, Intestinal drug delivery.

INTRODUCTION

Chitin, a polysaccharide usually isolated from the carapaces of marines animals such as crabs and shrimps, is a homopolymer composed of 2-acetamide-2-deoxy-Dglucopyranose units linked by β(1→4) bonds. Chitosan is a copolymer of 2-amino-2-deoxy-D-glucopyranose and 2-acetamide-2-deoxy-D-glucopyranose also linked by β(1→4) bonds which is commercially available from the deacetylation of chitin.

The oral delivery of drug is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. For many decades, pharmaceutical dosage form like tablets, capsules, creams, liquids, and injectable as drug carriers have mostly accomplished treatment of acute disease[1].

Hydrogels are three dimensional, crosslinked polymeric networks that are not soluble, but can absorb large quantity of water or biological fluids. The networks consist of hydrophilic homo polymers or co polymers crosslinked physically or chemically. The physical crosslinks can be entanglements, crystallites or weak association like Vander waal forces or hydrogen bonds. The crosslinks provide the network structure and physical integrity. pH dependent Hydrogels exhibit swelling behaviour as they contain ionizable side or pendant groups like carboxylic acid (acidic) and amine (basic). In a medium of optimum pH and ionic strength, the pendant groups ionize and develop fixed charges on the gel and also swelling force in the gel. This swelling force increases in the gel due to localization of fixed charges on the pendant group and as a result, the mesh size of the network changes with small change in pH[2]. The drug used in the study was methyl prednisolone. The drug is unstable at the acidic pH in the stomach thus there is need to protect the drug and release in the later part of gastrointestinal tract. For this purpose the pH sensitive hydrogels of carboxymethyl chitosan were prepared and evaluated.

MATERIALS

Methylprednisolone hemisuccinate is taken as a gift sample from Strides Arco lab Limited, Bangalore. Chitosan and Carbopol- 934 were purchased from Marine chemicals, Cochin, Kerala, and LOBA Chemicals, Mumbai respectively. All other reagents used were of analytical grade.

METHODS

Preparation of Carboxymethylchitosan

N-acetyl chitosan synthesis[3]: A solution of chitosan (20g) in aqueous 10 %(w/w) acetic acid (400ml) was diluted with methanol (1600ml), acetic anhydride was added with stirring at room temperature. The reaction mixture was stored overnight at room temperature to give rigid gel. The gel was stirred with 0.5 M NaOH in ethanol at room temperature overnight. The solution was precipitated by addition of concentrated NH_4OH solution and filtered off. The product was then washed with 75% ethanol, and vacuum dried to give N-acetyl chitosan.

Carboxymethylation of chitosan [4-5]: N-acetyl chitosan (10g) suspended in 50 % (w/w) NaOH was kept at -20ºC overnight. The frozen alkali chitosan was transferred to 2-propanol (100ml), and chloroacetic acid was added in portions under stirring at room temperature and further at 60 ºC for another 2 h. After dialyzing against deionized water for 3 days, the product was vacuum dried at room temperature.

Preparation of hydrogels[6]

Carboxymethylchitosan solution was prepared in 0.1N Acetic acid under stirring at 5000 rpm for 30 min. Then specified amount of drug was added to Carboxymethylchitosan solution. The above solution was stirred for 15 min. Carbopol 934 (poly acrylic acid) solution was prepared in 1.75 M acetic acid. After that Carboxymethylchitosan solution was gradually added to carbopol solution and mixed. The solution obtained was then poured in petridish and kept overnight for cross linking at room temperature. The hydrogel obtained was cut into 1 cm × 1 cm pieces and dried for 24 hour under vacuum. The dried hydrogel was crushed and passed through sieve # 60/85. The hydrogel particles retained on sieve #85 were taken for further studies.

Table 1: Formulation chart of Methylprednisolone hemisuccinate hydrogels

Sl. No	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
1	Methylprednisolone hemisuccinate (mg)	250	250	250	250	250	250	250	250
2	Carboxymethylchitosan (mg)	1000	1250	1500	1750	1000	250	1500	125
3	Carbopol 934 (mg)	1000	1000	1000	1000	500	500	500	500
4	0.1 N Acetic acid (ml)	25	25	25	25	25	25	25	25
5	1.75 M Acetic acid (ml)	25	25	25	25	25	25	25	25

Swelling studies[7-10]

The pH dependent swelling property of the hydrogels was studied in both 1.2 pH HCl buffer and 7.4 pH Phosphate buffer. 300mg of hydrogels were placed in 20ml of 1.2 pH HCl buffer for the first 2 hours, and then the hydrogels were transferred to 7.4 phosphate buffer solution. At every hour interval, the hydrogels were removed and excess surface liquid was removed by blotting and their weights were recorded. The swelling studies were carried for a 910 hours.

The percentage swelling (S) was determined by the following equation,

$$S = \frac{(\text{weight of swollen hydrogel} - \text{weight of dry hydrogel}) \times 100}{\text{weight of swollen hydrogel}}$$

Drug content[11-13]

The prepared hydrogel were passed through sieve # 60/85. The hydrogel particles retained on #85 were taken for drug content studies. A 25 mg of hydrogel was taken in 25 ml standard volumetric flask. To this 20 ml of 7.4 pH phosphate buffer was added and kept overnight. The volume was made up with 7.4 pH phosphate buffer. The final solution was filtered using Whatman filter paper. From this 10ml was pipetted out into a 25ml standard volumetric flask and made up to volume with pH 7.4 phosphate buffer and estimated for drug content.

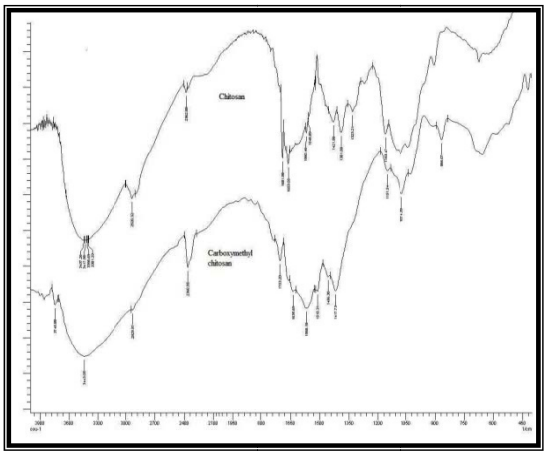


Fig. 1: FT-IR spectra of chitosan and carboxymethylchitosan Chitosan

***In vitro* drug release studies[14--15]**

In vitro drug release from the hydrogels was carried out in triplicate at 37°C±0.5°C in TDT-08L dissolution tester at a rotation speed of 50 rpm. Drug release from hydrogels was studied in 900 ml of 1.2 pH HCl buffer for the first two hours and at pH 7.4 phosphate buffer for next 10 hours. Every one hour, samples were withdrawn and analyzed for the drug using UV visible spectrophotometer. The release data obtained were fitted into various mathematical models to know which mathematical model is best fitting the obtained release profile.

RESULTS AND DISCUSSIONS

FT-IR analysis

FT-IR studies were carried out for carboxymethylchitosan and chitosan. Spectra showed signals of non-modified chitosan at 1,653 and 1,560 cm^{-1} for the C–O stretching (amide) and N–H bending (amine), respectively. The spectra of Carboxymethyl chitosan is similar to that of the original chitosan with a new peak appearing at 1,703 cm^{-1} which is assigned to the carbonyl groups. This confirmed the conversion of chitosan to Carboxymethylchitosan (Fig.1).

Methylprednisolone hemisuccinate (pure drug) and hydrogel formulations F1, F3 and F5 were also subjected for FT-IR spectroscopic analysis and it was concluded that the drug is in free state and there is no interaction between drug and polymer used (Fig.2).

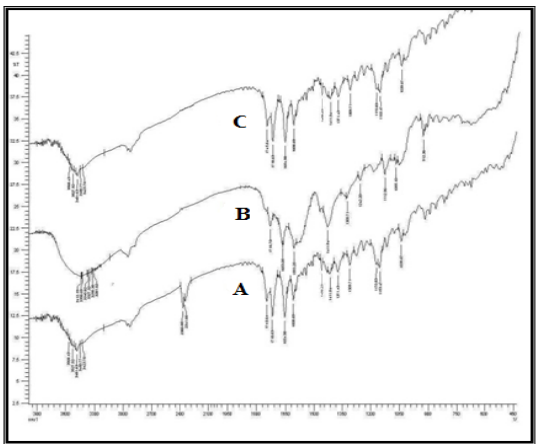


Fig. 2: FT-IR spectra of different formulation F1, F3, F5 (A, B, C) respectively of hydrogel with drug Methylprednisolone hemisuccinate

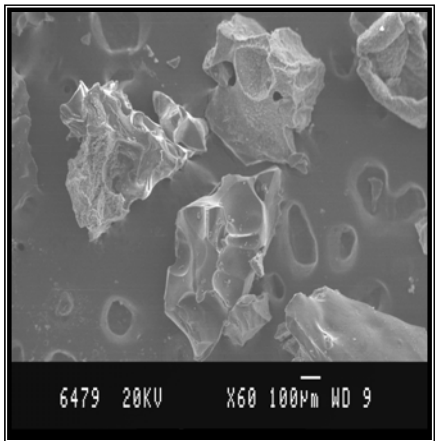
Scanning electron microscopy of hydrogel

Scanning Electron microscopy was carried out in order to study surface morphology, texture and porosity of hydrogels. The SEM photograph of hydrogel and formulation F1 clearly showed the porous nature of hydrogels (Fig. 3 and Fig. 4).

Differential scanning calorimetry

DSC studies of pure drug and F1 formulation hydrogel were studied to determine the possible interaction between the drug and the hydrogel. Thermogram of Methylprednisolone hemisuccinate has shown a sharp endothermic peak at 240.41°C, which corresponds to its melting point. Formulation hydrogel also showed endothermic

peaks at 242.09°C respectively due to the presence of Methylprednisolone hemisuccinate. The evaluation of thermograms obtained from DSC revealed no interaction between the drug and polymers used. The obtained results are shown in Fig.5 and Fig.6).



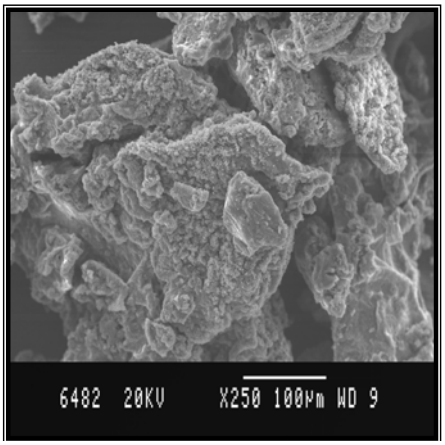


Fig. 3: SEM photograph of plain hydrogel in 60X. Fig 4: SEM photograph of hydrogel with drug in 250X

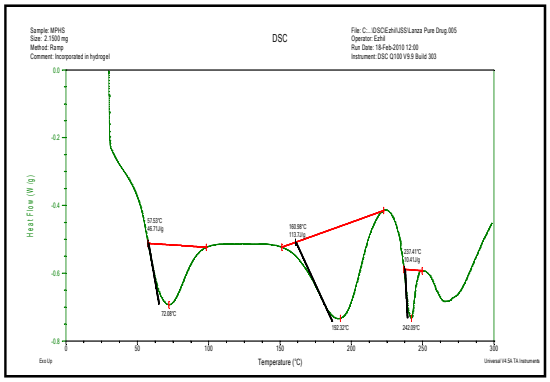


Fig. 5: DSC of Methylprednisolone hemisuccinate pure drug

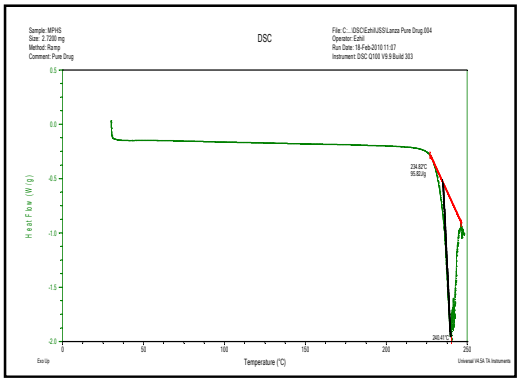


Fig. 6: DSC of F1 formulation including Methylprednisolone hemisuccinate

Table 2: DSC data of pure drug and F1 Formulation

Sl. No.	Drug & with hydrogel	T_0 (°C)	T_m (°C)	T_c (°C)	Melting Range (°C)
1	Drug	234.82	240.41	246.19	3.43
2	F1 formulation	237.41	242.09	249.66	5.24

Table 3: Drug content data of Methylprednisolone hemisuccinate loaded hydrogels

SL.No	Formulation of Methylprednisolone hemisuccinate	Trial 1	Trial 2	Trial 3	Average Mean (mg) ± S.D.*
1	F1	10.06	10.19	9.91	10.05±0.32
2	F2	10.04	10.03	10.04	10.36±0.08
3	F3	13.81	11.89	12.84	12.84±0.30
4	F4	11.21	10.08	11.19	10.82±0.32
5	F5	7.97	8.41	7.99	8.13±0.30

***** Standard deviation n=3

Drug content for hydrogels containing Methylprednisolone hemisuccinate

From the results of drug content it is observed that the % entrapment of drug was found to be 42 % (Table 3).

Swelling studies

The results indicate that with an increase in pH from 1.2 to 7.4, a considerable increase in swelling was observed for all the hydrogel formulations, which may be due to the dissociation of the -COOH

groups of acrylic acid, thereby increasing the osmotic pressure inside the hydrogels resulting in increased swelling (Fig. 7).

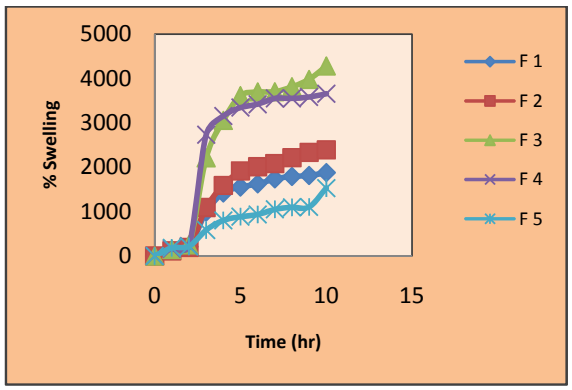


Fig. 7: Graph showing the percentage swelling of hydrogels

***In vitro* drug release study**

The *in vitro* drug release data for the hydrogels of Methylprednisolone hemisuccinate is represented in figure 8. For the initial 2 hours i.e. in the pH 1.2 HCl buffer, the percentage drug release was found to be low in all the cases; this can be attributed to the fact that the hydrogel swells less in the acidic medium. When the dissolution medium was changed to pH 7.4 pH phosphate buffer the release was found to increase with time.

It was observed that the formulation F1 shows sustained release. All formulations present an initial burst effect it may be attributed to diffusion of the drug caused by rapid gel swelling and also the release of drug adsorbed towards the surface of the gel matrix (Fig 8).

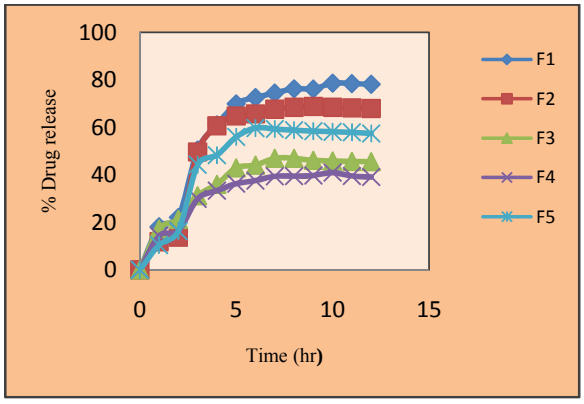


Fig 8: Graph showing the *in vitro* drug release of hydrogel

Stability Studies of optimized Formulation

Stability studies of optimized formulations F1 of hydrogels were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation under accelerated temperature. Stability studies shown that after 60 days, there was no significant change in the drug content and *in vitro* drug release.

CONCLUSION

From the results obtained it may be concluded that the prepared hydrogels were pH sensitive and the degree of swelling of hydrogel depends on the concentration of cross linking agent as well as on the pH of the environment. The swelling is in turn related to the amount of drug release and the drug release is found to be minimal in acidic pH and maximum and constant at basic pH. The amount of methyl prednisolone entrapment inside hydrogels was satisfactory to the extent of 42%. The hydrogel release minimum amount in the acidic pH but the drug release is high and sustained in the basic pH of intestine. Thus the hydrogel prepared using carboxymethyl chitosan can be used to deliver methyl prednisolone in sustained manner in the intestine and thus other drugs which are not stable in the acidic pH of the stomach can be delivered efficiently to the intestine with the help of pH sensitive hydrogels prepared using carboxymethyl chitosan.

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