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# Radiation Cross-Linked Carboxymethyl Sago Pulp Discs for Sustained Drug Delivery: Ciprofloxacin Uptake and Physicochemical Characterization

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**ABSTRACT**

Radiation cross-linked carboxymethyl sago pulp (CMSP) hydrogel discs with a gel fraction of 9.21% w/w were prepared at the radiation doses of 25 kGy. CMSP disc was loaded with ciprofloxacin hydrochloride by immersing in drug solution and evaluated for loading efficiency. The drug was loaded into the pre-cross-linked hydrogel to avoid radiation-induced degradation of the loaded drug. Drug loading of each disc (2 ± 0.2 mm thickness and of 4 ± 0.4 mm diameter) was found to be 2.96 ± 0.36 mg. Infrared and thermal analysis revealed no polymer-drug interaction and transformation of ciprofloxacin hydrochloride into ciprofloxacin base during the loading process. Thermal analysis and scanning electron microscopy revealed the crystalline nature of the loaded drug. The hydrogels sustained the drug release over 24 h and could be developed as sterile inserts for ophthalmic application to treat eye infections. The drug release from the hydrogel found to follow the first order and anomalous transport mechanism.

## INTRODUCTION

As an approach to implementing environmentally friendly industries, the conversion of plant waste into a useful product is one of the most important innovations in the recent years. In Sarawak, Malaysia, sago palm (*Metroxylan sago*) is an essential resource of polysaccharides, mainly, its starch. Production of the sago starch, however, produced sago waste as its by-product. The sago waste can be used to produce polymeric materials of industrial and medicinal importance (Veeramachineni *et al.*, 2016). Ciprofloxacin hydrochloride, a fluorinated quinolone was used as the model drug in this study. It is a common antibacterial for various systemic infections as well as eye infection (Yi Lyn *et al.*, 2015). Hydrogels loaded with ciprofloxacin, particularly ocuserts could be used in treating eye infections.

Synthesis and characterization of ciprofloxacin-loaded radiation cross-linked carboxymethyl sago pulp (CMSP) discs were recently reported by us (Yi Lyn *et al.*, 2015) for ophthalmic drug delivery. One of the critical issues for this type of dosage form is the exposure radiation on the active pharmaceutical ingredient which might result in radiation-induced degradation. In the present work, we have attempted to load the drug in pre cross-liked CMSP hydrogels, which could be useful for radiation sensitive drugs. The radiation applied during the synthesis of CMSP disc also assures the sterility of the eye formulation. These pre-sterilized hydrogel discs can load any drugs by simple immersion technique at the time of application. However, many preformulation parameters, notably absence of drug-polymer interaction should be done before proceeding to the actual formulation. In the present work, ciprofloxacin uptake by the CMSP discs was evaluated. Further, the drug-loaded discs were characterized by Fourier-Infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and *in vitro* release studies.

## MATERIAL AND METHODS

### Materials

Ciprofloxacin hydrochloride was kindly donated by Goodman Pharmaceuticals, Pondicherry, India. Distilled water

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was used for all aqueous solution preparations. All other chemicals used were of analytical grade. CMSP was synthesized from sago biomass by classical Williamson etherification as reported by (Pushpamalar *et al.*, 2013). The degree of substitution, viscosity and molecular weight of synthesized CMSP were 0.4, 184.33 dl/g and 75974 g/mol, respectively.

**Preparation of radiation cross-linked discs**

Radiation cross-linked CMSP hydrogel discs were prepared as described in our previous publication (Yi Lyn *et al.*, 2015). Briefly, 100 ml of 20% w/v CMSP solutions were prepared and spread onto a separate thin mould and sealed in a plastic bag. The CMSP mixture was cross-linked by two MeV electron beam accelerator (model EPS-3000, current was 10 mA) by applying 25 kGy irradiation dose. After irradiation, the hydrogel was soaked in water for six h at room temperature and then cut into discs of six mm diameter using a single paper punch. The diameter and thickness of the discs were again measured after complete drying (overnight at 70˚C) using a Vernier caliper. Discs with a thickness of 2 ± 0.2 mm and diameter of 4 ± 0.4 mm was selected for drug loading.

**Loading ciprofloxacin in discs**

The drug solution was prepared by dissolving 0.3 g of ciprofloxacin hydrochloride in 10 ml water. The loading was carried out at room temperature by immersing the discs ($n$ = 3) in the drug solution for 24 h. Then the discs were washed once with water and were dried in an oven overnight at 70˚C. The amount of drugs loaded was measured by macerating the discs in the phosphate buffer pH 7.4 at 37˚C for 48 h. Subsequently, the drug content in the buffer was determined at 271 nm (Yi Lyn *et al.*, 2015) using a UV-Vis Spectrophotometer (Shimadzu 1240).

**Characterization of ciprofloxacin loaded disc**

The infrared spectrums of samples were recorded with Perkin Elmer FTIR spectrophotometer using KBr pellet method. DSC profiles of CMSP disc and ciprofloxacin hydrochloride were recorded using Mettler Toledo DSC 822e. About 5-10 mg of the hydrogel sample was sealed in an aluminium pan and heated from 50˚C to 350˚C at a heating rate of 10˚C/min. The flow rate of nitrogen was maintained at 50 ml/min. Scanning Electron Microscope (SEM) model Quanta 400 ESEM was used to study the surface morphology of the discs. The samples were coated with a thin layer of gold by evaporation and were observed at an accelerating voltage of 5-10 kV.

***In vitro* release**

The *in vitro* release studies were carried out in an EDC-07 Franz's diffusion cell (Electrolab, India) using five ml of phosphate buffer (pH 7.4) as the release medium (Yi Lyn *et al.*, 2015) in the receptor compartment. Drug-loaded discs were placed in donor compartment over a dialysing membrane and wetted using 0.5 ml of the release medium. The dissolution rates were measured at 37.0 ± 0.5˚C while stirring the release medium at 50 rpm. One ml of samples were withdrawn using sample port, and the same volume of the release medium was replaced. The amount of drug present in the sample was estimated at 271 nm using UV–vis spectrophotometer.

**RESULTS AND DISCUSSION**

Based on our previous studies, 20% w/w CMSP was selected and irradiated at 25 kGy to yield a hydrogel with a gel fraction of 8.45% w/w. As irradiation dose increases, scission predominates over crosslinking and resulting in lower gel fraction (Yi Lyn *et al.*, 2015). In radiation sterilization processes, a radiation absorbed dose of 25 kGy is required to achieve a required sterility level. Sterility is one of the formulation criteria for eye formulation. Radiation doses higher than 25 kGy has produced weaker gels with physically unstable discs. Hence, gels crosslinked at 25 kGy was used in the present study. The thickness and the diameter of each disc were standardized as both parameters can affect the loading and release of drugs through the polymer matrix. The discs were impregnated with the drug solution to load the drug. Loading by immersion is selected to mimic practicing pharmacist at the hospital, i.e., the hydrogels irradiated at the sterilization doses impregnated with sterile drug solution aseptically. Impregnation of the hydrogel in drug solution would be useful to establish required swelling equilibrium with water to ease its

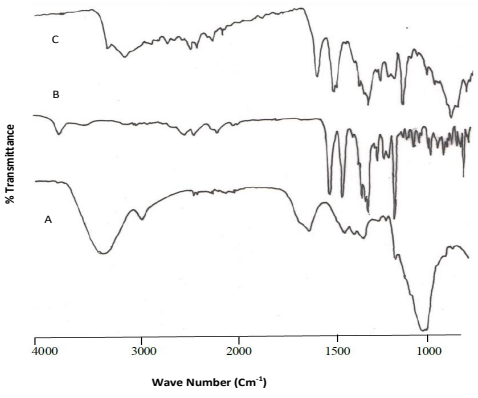


**Fig. 1**: FT-IR spectrum of CMSP hydrogel disk (A), ciprofloxacin hydrochloride (B) and CMSP hydrogel disk loaded with ciprofloxacin hydrochloride (C).

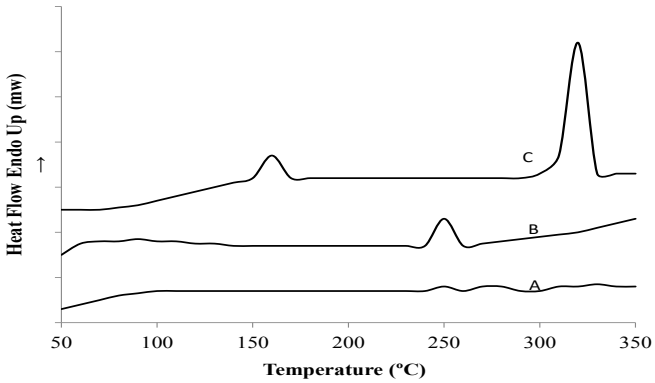


**Fig. 2**: DSC thermogram of CMSP hydrogel disc (A), CMSP hydrogel disc loaded with ciprofloxacin (B) and ciprofloxacin hydrochloride (C).

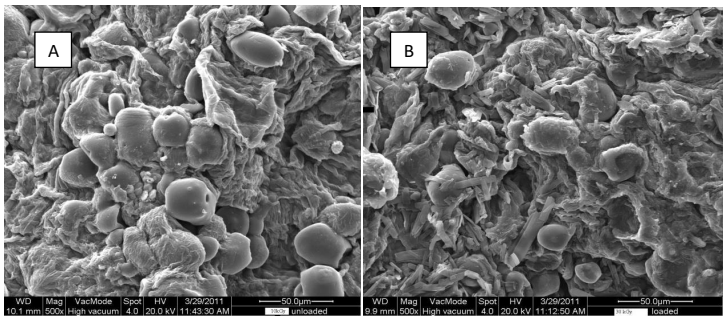


**Fig. 3**: SEM Photographs shows surface of cross-linked unloaded (A) and drug loaded (B) CMSP hydrogel discs. The drug crystals are seen on the surface of drug loaded discs.

application than the dry one. The CMSP hydrogel disc has shown a drug loading of 2.96 ± 0.36 mg of ciprofloxacin per disc.

The IR spectrum of CMSP showed a broad peak at 3326 $cm^{-1}$ due to stretching vibration of –OH group (Fig. 1 A). The peak at 2897 $cm^{-1}$ is due to C-H stretching vibration. The presence of a strong absorption band at 1596 $cm^{-1}$ confirms the presence of $–COO^-$ group and act as evidence of carboxylation of sago pulp. The bands at 1417 and 1319 $cm^{-1}$ are for $CH_2$ scissors and OH bending vibration, respectively. The broad bands from 1000 to 1200 $cm^{-1}$ were due to sugar ring absorption (Barbucci *et al.*, 2000; Charpentier-Valenza *et al.*, 2005). In the spectrum of ciprofloxacin hydrochloride (Fig. 1 B), the peaks at 1300-1250 and 3550-3450 $cm^{-1}$ are due to stretching vibration of the hydroxyl group. The characteristic absorption bands at 1271 and 1623 $cm^{-1}$ of ciprofloxacin hydrochloride were due to stretching vibration of the C-F bond, and the vibration of the phenyl framework conjugated to –COOH, respectively (Wang *et al.*, 2007). The stretching vibration at 1705 $cm^{-1}$ was due to CO group of acid. Peaks at 3085 and 2926 $cm^{-1}$ were observed for vibration of C-H from the phenyl framework. These drug peaks also appeared in the spectrum of drug loaded discs (Fig. 1 C). The bands observed in CMSP hydrogels were also appeared in the drug-loaded CMSPC disc suggesting no interaction. All these observations were similar as reported in our previous publication (Yi Lyn *et al.*, 2015).

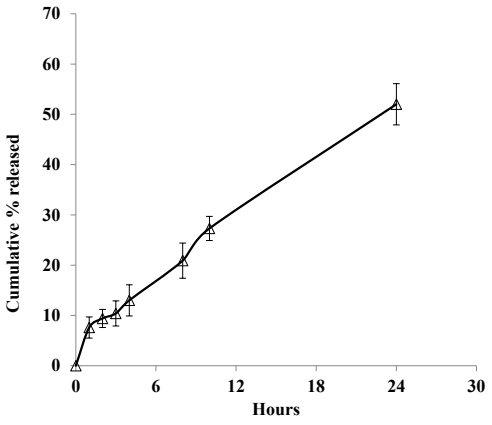


**Fig. 4**: *In vitro* release profile of ciprofloxacin from CMSP disc ($n = 3 \pm$ s.d.).

The DSC thermograms of CMSP hydrogels unloaded, loaded and ciprofloxacin hydrochloride is given in Fig. 2 A, B and C, respectively. The CMSP hydrogels showed no prominent peaks and indicated amorphous nature of the cross-linked polymer. The drug-loaded hydrogels showed a peak at 246˚C. The ciprofloxacin hydrochloride showed a peak at 160˚C for the presence of the water molecule and also a peak observed at it melting point of 323˚C (Prabhu *et al.*, 2008). The peak at 323˚C shifted to 246˚C in drug-loaded hydrogels, which is at the melting point of ciprofloxacin base (Francis *et al.*, 1991). This observation suggests conversion of ciprofloxacin hydrochloride to ciprofloxacin during the loading process. The conversion could be due to alkaline nature of CMSP, and when ciprofloxacin hydrochloride comes in contact with hydrogels, converted into the base. In support of IR data, it can be concluded that the drug loaded in hydrogel as a free base form of ciprofloxacin. These observations were in contrast to our previous report. The addition of ciprofloxacin hydrochloride before irradiation resulted in amorphous but as hydrochloride salt of the drug in the CMSP disc (Yi Lyn *et al.*, 2015). Ciprofloxacin is a zwitterion, and its presence in base form (neutral or unionized form) could be useful in the best antibacterial effect due to more lipophilicity. Neutral ions possess better membrane permeability than the charged ions. Thus, the ciprofloxacin disc prepared by the present method might produce a best anti-bacterial effect.

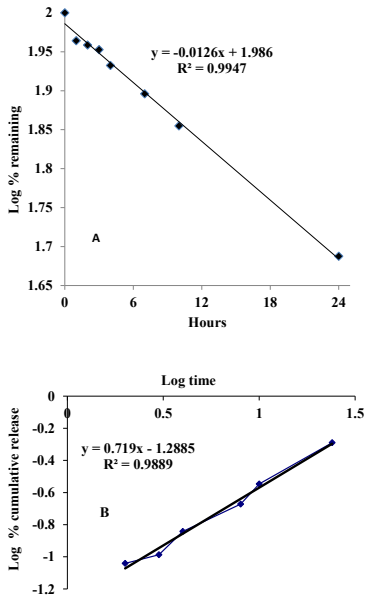


**Fig. 5**: First order (A) and Korsmeyer-Peppas (B) plot of release profile.

As shown in Fig. 3, when compared with drug-loaded hydrogels, the surfaces of unloaded hydrogels were smooth. The surfaces of the drug-loaded hydrogels were rough due to the presence of drug crystals. Drug crystals were visible on the hydrogel surface. This observation supports the appearance of crystalline drug peaks in DSC studies. The CMSP hydrogel can be able to sustain the drug release more than 24 h. An initial burst effect was observed, and later it was sustained (Fig. 4) and released in almost zero-order fashion. The first burst release could be due to the surface (as seen in SEM picture) drug or poorly bound drug on the surface of the polymer matrix. Data obtained from *in vitro* release studies were fitted to various kinetic equations (Costa and Lobo, 2001) to find out the mechanism of release. Higher correlations were obtained in first ($r^2$ = 0.9947) order (Fig. 5) rather than zero ($r^2$ = 0.9838) and Higuchi ($r^2$ = 0.9735) equations. Whereas Korsmeyer-Peppas showed a better correlation ($r^2$ = 0.9889). The release exponent *n* value of 0.72 suggests non-Fickian or anomalous transport mechanism (Fig. 5). However, little low n value (0.72) achieved by the disc immersed in drug solution than the disc reported (0.82) in our previous study (Yi Lyn *et al.*, 2015). Also, drug release is relatively faster in the disc prepared by immersion than the earlier one which extended the release beyond 36 h.

## CONCLUSION

The CMSP hydrogels successfully loaded with ciprofloxacin by simple immersion and could sustain the drug release more than 24 h. However, further studies are required with modifications in the size of the hydrogel and method of drug loading to optimize the release kinetics of the drug. As the hydrogel sterilized during radiation cross-linking, with suitable size and ciprofloxacin loading, it could also be used as wound dressing. Moreover, the pre-sterilized hydrogel can be used to load any other drug by immersing in sterile drug solution to get a desired therapeutic effect.

## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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