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Microparticles of Diethylcarbamazine Citrate for the Treatment of Lymphatic Filariasis†

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The aim of the study is to study the fabrication of microparticles for antifilarial drug diethylcarbamazine citrate with increased efficacy, decrease dose and minimise its side effects. Lymphatic filariasis is one of the major causes of chronic disability in the developing countries and, as such, produces a considerable economic burden. The microparticles were prepared by two steps, using alginates by spray-drying step and crosslinking step. Entrapment efficiency, *in vitro* drug release study was performed of the developed formulations. FT-IR and mass spectrophotometry were performed of the formulations. Diethylcarbamazine citrate is drug used in the management of lymphatic filariasis in both early and advanced stages. In the development of alginate/chitosan microparticles for the diethylcarbamazine citrate delivery to lymphatic system, the preformulations studies were performed. Microparticles polymer network and, consequently, drug loading level and release, were affected by the alginate and crosslinking agent concentrations. Results were favourable for our novel drug delivery system developed for neglected tropical disease such as filariasis.

Key Words: Diethlcarbamazine citrate, Microparicles, Lymphatic filariasis.

INTRODUCTION

Lymphatic filariasis remains a significant health problem in India. Approximately 45 % of India's one billion populations live in known endemic areas and 48 million are infected, accounting for 40 % of the global lymphatic filariasis burden. Although the disease severely undermines the socioeconomic progress of the affected communities. Lymphatic filariasis caused by infection with *Wuchereria bancrofti, Brugia malayi* or *Brugia timori*[1].

Diethylcarbamazine citrate (DEC) (Fig. 1) is a drug choice for lymphatic filariasis. Diethylcarbamazine citrate, (1-diethylcarbamyl-4-methylpiperazine) is an antiparasitic piperazine derivative used in the treatment of lymphatic filariasis. Despite new chemotherapy protocols, filariasis is still considered a serious debilitating disease in the tropical and sub tropical regions of the world[2]. In fact, lymphatic filariasis has been recognized as one of the leading cause of the disability, resulting into huge loss of man-days[3]. Several lines of evidences suggest that filarial parasite establishes itself by interacting with the host's immune system,leading to the wide spread immunosuppression[4]. Interestingly, some of the widely used drugs, such as diethylcarbamazine citrate, have been reported to inhibit mainly the microfilarial stage of the parasite. Microparticles delivery system is to encapsulate an active material in pharmaceutical delivery are for protection and to control release. Encapsulation will, increase drug delivery efficiency, which will consequently decrease the amount of drug needed compared to non-encapsulated drugs.

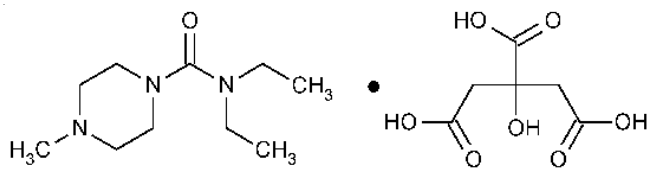

Fig. 1. Structure of diethlcarbamazine citrate

EXPERIMENTAL

Diethylcarbamazine citrate gift sample from Fourrts (India) Ltd., Chennai, sodium alginate (S.D. Fine-Chem. Ltd.), Chitosan and $CaCl_2$ Sigma Chemical Co. U.S.A., KH_2PO_4 S.D. Fine-Chem. Ltd., India,

Preparation of microparticles: Microparticles were prepared by two steps[5-7].

Spray drying step: 500 mg diethylcarbamazine citrate was dispersed into 500 mL aqueous solution of sodium alginate (0.5 %, 1 %, 1.5 % w/v; prepared by dissolving sodium alginate in boiled triple distilled water under stirring), alginate/diethyl-carbamazine citrate mixture was spray dried to obtain uncross

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linked microparticles under following operating conditions (Table-1)[6].

TABLE-1
OPERATING CONDITIONS FOR SPRAY DRYING

Liquid feed rate	5 mL/min
Inlet temperature of drying air	125 ºC
Outlet temperature	70 ºC
Spray flow	600 Nlh^{-1}
Aspirator setting	15

Cross linking step: Un-crosslinked micropraticles were suspended in $CaCl_2$ aqueous solution, under mechanical stirring using ultra turrax at 15000 rpm for 10 min. Subsequently, an equal volume of 1 % (w/v) chitosan (CHT), solubilized in pH 5.5 acetic acid solution, was added to the microparticles suspension under mechanical stirring and maintained for 10 min. The crosslinked microparticles were then recovered by centrifugation, rinsed with water and freeze dried.

RESULTS AND DISCUSSION

Particle size distribution: The particle size and size distributions of the formulations have been measured by master sizer (Malvern corp.). It indicates that 50 % particles are below 6.8 µm and 90 % particles are below 10 µm. Fig. 2. Indicates cross-linked chitosan coated MPs in which 50% particles are below 6.7 µm and 90% are below 9.8 µm.[7]

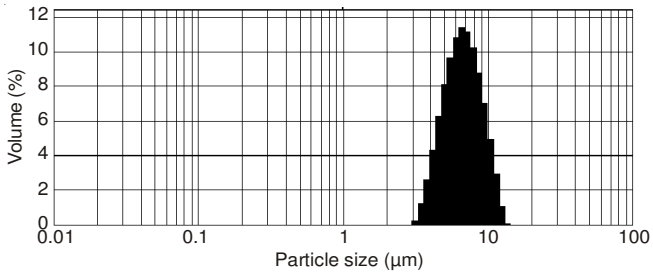

Fig. 2. Particle size of DEC loaded microparticles (D2CA-2)

SEM Characterization: The morphology of the particles was determined under a scanning electron microscope. There are smaller smooth spheres and dimpled particles present. Maa *et al.*[7] proposed a mechanism, which could occur during the drying process, to explain the dimples present on some spray dried particles. The formation of a polymer film at the external surface of the droplet during the early stages of drying caused by rapid evaporation of solvent at the surface. The subsequent increase in the concentration of the polymer at the surface could impede the diffusion of water to the periphery of the droplet and cause a buildup of water vapour pressure inside the particle. At a certain point, the film would burst resulting in particles that have dimples or holes examined under SEM (Fig. 3)[8,9].

Drug loading and Entrapment efficiency: Drug loading efficiency and entrapment efficiency of different formulations has been shown in Table. Loading efficiency and entrapment efficiency were increased with increasing $CaCl_2$ concentration as crosslinkink agent has been reported in Table-2. Drug loading was calculated with regards to microparticles yield

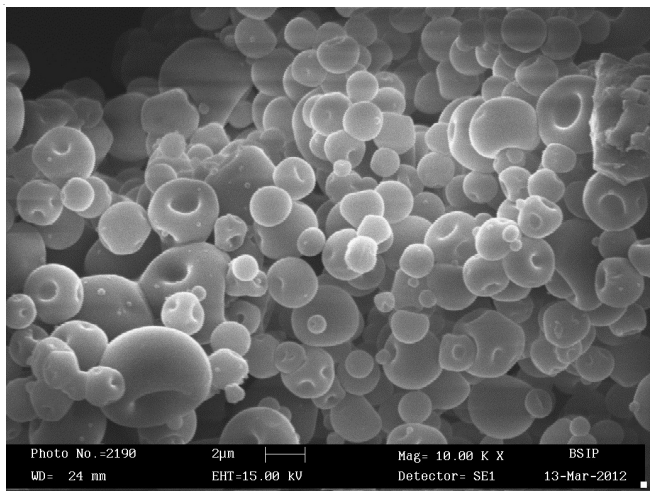

Fig. 3. Scanning electron microscope microparticles were smooth, spherical and having dimpled particles

obtained after spray drying because microparticles yield obtained was less in comparision to amount initially fed into the spray dryer.

TABLE-2
EFFECT OF DIFFERENT CONC. OF CROSS-LINKING AGENT ON SIZE, ENTRAPMENT EFFICIENCY AND LOADING EFFICIENCY

Formulation	$CaCl_2$ (%w/v)	Size (µm)	Drug loading (%)	Entrapment efficiency (%)
D2CA1	5	6.98 ± 0.58	10.47 ± 0.42	28.14 ± 0.47
D2CA2	7.5	6.68 ± 0.72	12.26 ± 0.23	33.34 ± 0.32
D2CA3	10	13.3 ± 0.85	12.43 ± 0.52	36.48 ± 0.31

***In vitro* release studies: diethylcarbamazine citrate loaded crosslinked chitosan alginate microparticles:** The release pattern of diethylcarbamazine citrate from chitosan cross-linked alginate microparticles was shown in Fig. 4. After 10 h, release was found D2CA-1(71.7 %), D2CA-2(64.7 %) and D2CA-3(57.9 %) followed by sustained release as shown in Fig. 4. After 2 h, in SGF the release was almost same however at pH 6.8 the release was slightly rapid. This could be due to the higher water solubility of diethylcarbamazine citrate.

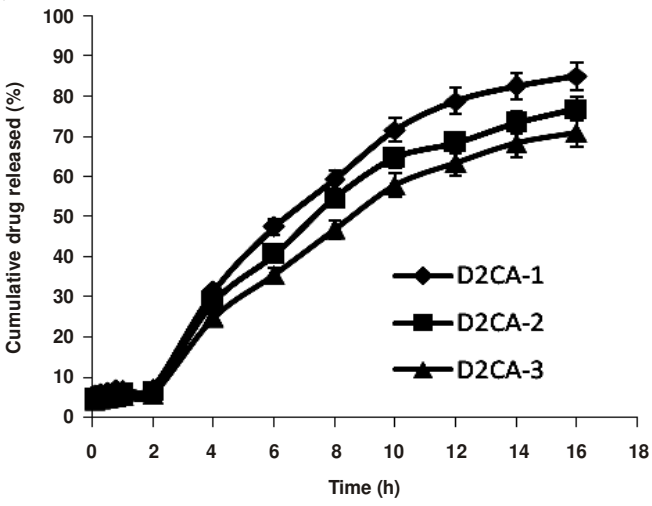

Fig. 4. *In vitro* release profile of DEC from D2CA-1,D2CA-2 and D2CA-3

Conclusion

In the present work, a novel formulations of diethylcarbamazine citrate microparticles were successfully evaluated *in vitro*. It was found that alginate feed and cross linking agents concentration affects microparticle size, entrapment efficiency and loading efficiency. Microparticle size obtained were optimized and found appropriate for the lymphatic delivery because the size obtained was less than 10 micron which is requirement for the uptake by the peyer's patches. Varying the concentration of cross-linking agent ($CaCl_2$) affects the release behaviour of the microparticle formulations[10,11]. Higher concentration of cross-linking agent would release the drug slowly for longer times. *In vitro* release studies indicate that the sustained release pattern for diethylcarbamazine citrate micropartcles. The developed formulations of diethylcarbamazine citrate hopefully will show higher efficacy in lymphatic filariasis as it sustaining the release of drug. Further studies need to be done for diethylcarbamazine citrate microparticles seeing activity on Animal Model such as Mastomys/Gerbils for lymphatic filariasis.

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