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Development and characterization of autolymphotropic carrier system for oral bioavailability enhancement of anitcancer drug

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INTRODUCTION AND OBJECTIVES

Intestinal lymphatic system has gain-renewed interest for delivery of hydrophobic drugs, macromolecules like peptides, proteins and vaccines. It offer several advantages including avoidance of first pass metabolism, selective treatment of diseases and infections of the mesenteric lymphatics, enhancement of the absorption of the large molecules such as peptides/particulates and inhibition of cancer cell metastasis (Paliwal 2009). A major function of the intestinal lymphatics is to facilitate the absorption of long chain fatty acids via re-esterification and reassembling them into chylomicrons within the enterocytes. Exogenous compounds absorbed via the intestinal lymph are generally transported in association with the lipid core of intestinal lipoproteins thereby requiring co-administered lipid to stimulate lipoprotein formation and to deliver the content in the systemic circulation through well known transcellular mechanism of lipid transport (O'Driscoll 2002). This study was aimed to develop, compritol cored methotrexate (MTX) loaded emulsome which could solubilize and retain MTX within multiple bilayers of lecithin purposely specific for treatment of intestinal lymphosarcoma.

MATERIALS AND METHODS

MTX loaded EML was prepared by cast film method. Briefly, CA and PC in different molar ratio were taken in a round-bottom flask and dissolved in minimum amount of chloroform. The chloroform was then evaporated until complete dryness under reduced pressure using rotary flash evaporator to form a thin lipid film on walls of the round-bottom flask. The dried film was hydrated with 10 mL phosphate buffered saline (PBS pH 7.4) containing 10 mg MTX and homogenized by ultasonication (Soniweld, India) for 10 min at 40% frequency to obtain nanosized EML. The free unentrapped drug was removed by passing the dispersion through a sephadex G-50 column. The so obtained EML dispersion was lyophilized using 100 mg sucrose as cryoprotectant in 1 mL dispersion stored at -50°C for 5 h and then kept under vaccum for 36 h. The lyophilized formulations were stored at refrigerated temperature till further use.

The MTX-loaded EML were optimized and studied for their particle size and shape to correlate structural resemblance with chylomicrons, drug entrapment efficiency, *in vitro* release in simulated pH conditions of gastrointestinal tract to assess its potential as oral formulation and storage stability at various temperatures. The thermal analysis was performed to observe modifications in crystalline behavior of lipid. The *in vivo* study protocol was designed for estimating both blood plasma profile and lymphatic concentration of the MTX after intraduodonal administration.

RESULTS AND DISCUSSION

The optimized emulsome (1:1.2 mole ratio of CA: PC) showed mean particle size of 160.3±10.2 nm and with 72.8±6.5 % drug entrapment efficiency. It was clear from the TEM photograph of EML that particle were surrounded by multiple bilayers of phospholipids.

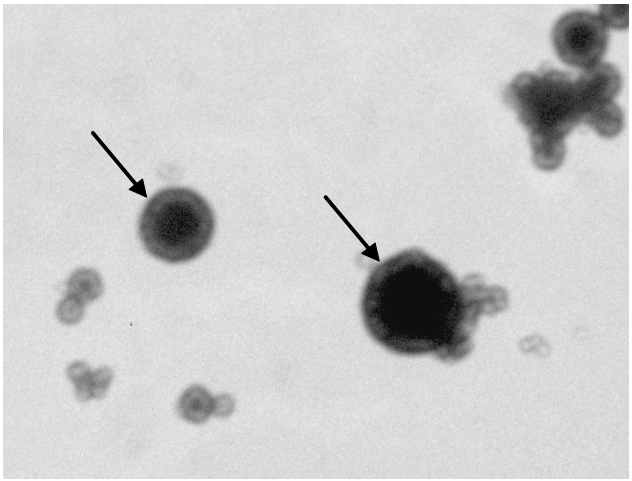

Fig.1. TEM of Emulsome

The differential scanning calorimetric studies revealed a depression in endothermic onset for MTX loaded emulsome. The rapid burst release of the drug was observed in simulated gastric fluid (SGF pH 1.2) with significant increase in particle size of emulsome. However in simulated intestinal fluid (SIF, pH 7.4) a slow and consistent release of the drug was obtained over period of 24 h.

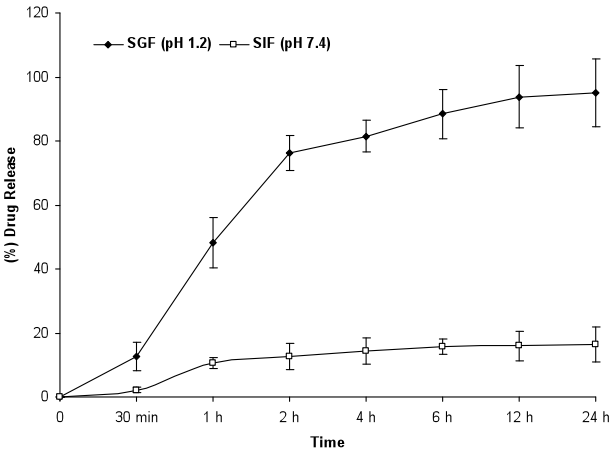

Fig. 2 *In Vitro* Drug Release

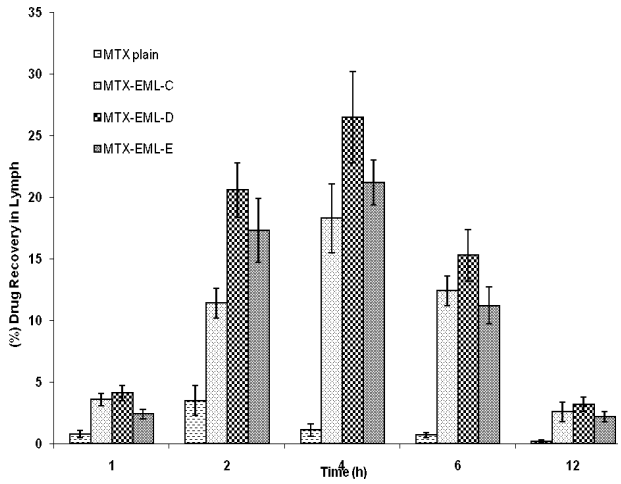

Fig. 4 Lymphatic Drug Uptake Profile

Storage stability studies were performed at different temperatures (4±1˚C, 25±1˚C) for 3 months which suggested that EML remain more stable when stored at refrigerated condition. The *in-vivo* studies were carried out on albino rats and response was estimated collecting blood and lymph both. The pharmacokinetic parameters C_{max}, t_{max} and $AUC_{0\rightarrow12h}$ after duodenal administration of optimized emulsomal formulation and plain MTX solution were 7.1 and 2.4 µg/mL, 4 and 1 h, 40.45 and 7.2 h.µg/mL respectively. The relative bioavailability of MTX was enhanced nearly 5.7 times with optimized EML formulation when compared to plain MTX solution with higher uptake and longer residence time of MTX molecules in lymphatics. Thus, emulsome could be used as lymphotropic carrier for delivery of bioactive(s) and hence for bioavailability enhancement.

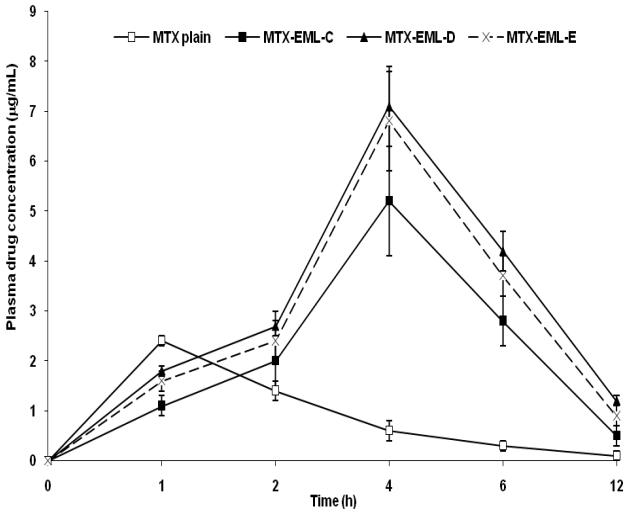

Fig. 3 Plasma Drug Concentration Profile

CONCLUSIONS

Lymphatic delivery through intestinal milieu could be achieved through successful engineering of drug carriers. Nanosized chylomicron mimicking cargos such as EML showed promising potential for delivery of MTX. EML mediated delivery supported synergistic effect of both the route and/ or mechanism that is paracellular and transcellular as the higher concentration of MTX was observed in comparison to plain drug solution. The instability of formulations in acidic medium suggested that formulations should also be protected from harnessing gastric environment of stomach before oral administration. A much higher bioavailability of MTX may be achieved successfully with lipid based carrier system like EML. This mechanism could be further utilized in order to improve oral controlled delivery of drug, vaccine and bioamcromolecules.

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