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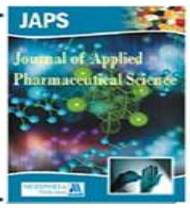

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Formulation and Evaluation of Chitosan Beads of Levocetirizine Dihydrochloride

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ABSTRACT

Our study aims to design a controlled drug delivery system for Levocetirizine dihydrochloride by using chitosan beads. The beads were prepared by ionotropic gelation process, with Sodium tri poly phosphate (TPP) as an ionic agent**.** The formed beads were then further crosslinked using glutaraldehyde and the excess glutaraldehyde were then washed. The physical properties of the prepared beads such as beads sizes, shapes, encapsulation efficiencies, invitro release and degree of swelling were determined. The produced beads from all batches showed a very good spherical geometry with the bead size found to be less than 2mm. The drug loading efficiency was around 77.5% for all batches. The degree of swelling was found to be 1.4. FTIR, DSC and XRD studies shows the absence of the interaction between chitosan and the drug. This methodology of preparation of chitosan beads seems to be highly simple, commercially viable and a promising technique for controlling the release of drugs.

Keywords: Levocetirizine, swelling, chitosan, controlled-release,TPP

INTRODUCTION

Levocetirizine dihydrochloride is a third generation non-sedative antihistamine, developed from the second-generation antihistamine, cetirizine. Levocetirizine works by blocking histamine receptors. It does not prevent the actual release of histamine from mast cells, but prevents it binding to receptors (Grant *et al.,* 1995). In addition, it is an important drug in the treatment of allergies and idiopathic urticaria (Sharma *et al.,* 2012). Levocetirizine is called a non-sedating antihistamine as it does not enter the brain in significant amounts, and is therefore unlikely to cause drowsiness. Levocetirizine has several pharmacokinetic properties that are desirable for an antihistamine providing a combination of both potency and safety. Its clinical advantages are derived from its rapid and extensive absorption, limited distribution and its very low degree of metabolism (Ferrer *et al.,* 2011). The incorporation of Levocetirizine in an extended-release of oral dosage form would have many disadvantages such as aiding in enhancement of bioavailability. Hydrogels are one of the upcoming classes of polymer-based controlled-release drug delivery systems. Besides exhibiting swelling-controlled drug release, hydrogels also show stimuli-responsive changes in their structural network and hence, the drug release (Gupta *et al.,* 2002).

Among all the hydrogels, chitosan is found to be highly significant in the pharmaceutical field because of its favorable biological properties such as biodegradability (Struszczyk et al., 1991) and biocompatibility (Chandy et al., 1990; Hiran et al., 1990) Chitosan, a deacetylated derivative of chitin, is a naturally occurring polysaccharide found abundantly in marine crustaceans, insects and fungi. The drug release studies show that chitosan has been proved to be a very good agent for controlled drug release. There are many processes that can be used to encapsulate drugs within chitosan matrixes such as ionotropic gelation, Prilling Method, Extrusion Method, spray drying, emulsification- solvent evaporation and coacervation. Combinations of these processes are also used in order to obtain microparticles with specific properties and performances (Singh et al., 2011). Biodegradable polymers are recently used for research as they have got superior functional qualities such as their ability to be safely administered within the body, negating the need for surgery, triggers drug release at local sites preventing systemic toxicity, and degrade in a controlled manner for effective, long-term drug release. Therefore, as a growing need of environmental simulation there are various researches done on biodegradable polymers (Xi Zhu et al., 2012). Chitosan being a biodegradable polymer has been a part of smart delivery systems as they possess characteristics like biocompatibility, biodegradability, mucoadhesive, antimicrobial, biocompatibility and bioadhesion (Sharma et al., 2012). Chitosan beads have high potential for developing a successful gastroretentive drug delivery system since they combine both bioadhesion and floating capabilities, especially for drugs that are poorly soluble in intestinal medium and readily soluble acidic medium. The chitosan beads will serve as depot reservoir that will allow the continuous gradual release of small amounts of drug in solution form to the upper part of the small intestine (the main site of absorption) leading to higher and more uniform blood levels of the drug. Thus, reduced adverse effects are highly expected. The qualities of using chitosan as a drug delivery system involves controlled release, decreased particle size leads to increases surface area and hence increased therapeutic action, increased efficacy, decreased toxicity and Increased patient compliance and convenience (Mirkka et al., 2012).In our study, Levocetirizine dihydrochloride was incorporated in a system consisting of hydrogel beads formed by chitosan and were investigated for their in vitro drug release and interactive effects of polymer and drug.

MATERIALS AND METHODS

Materials

Levocetirizine was obtained as a gift sample from Praveen Laboratories Pvt Ltd, Gujarat and Chitosan was purchased from Indian Sea Foods, Kerala. Sodium Tri Poly Phosphate (TPP) was purchased from Himedia laboratories pvt.ltd, Mumbai.

Experimental Methods

Preparation of Levocetirizine dihydrochloride loaded beads

The chitosan beads were prepared by ionotropic gelation process, with Sodium tri poly phosphate (TPP) as an ionic agent**.** The end quality of particles are formed by employing optimized parameters for bead formation i.e. fixed concentration of chitosan, acetic acid concentration and TPP solution being 5%, 1% and 10% respectively. The beads were formed using a disposable plastic syringe with a 22 gauge needle under constant pressure applied on the syringe to get stable beads. The formed beads were cross-linked with 3.15% W/V of glutaraldehyde and then washed with water to remove the excess glutaraldehyde and finally dried at ambient temperature. This method was adopted to prepare placebo and Levocetirizine dihydrochloride loaded beads.

Morphological analysis by Scanning Electron Microscopy (SEM)

The bead morphology of chitosan was examined using Scanning electron microscope (HITACHI-S3400N). Beads are sprinkled on adhesive aluminium stub and then surface coated with gold to a thickness of ~300°A using a sputter coater (SPI Sputter™ Coating Unit, SPI Supplies, Division of Structure Probe, Inc., PA USA).

Fourier Transform Infra Red Spectroscopic Analysis (FTIR)

Interaction between polymers and their functional groups in the polymeric structures were studied using FTIR (Model: AVATAR 330, Spectral Range: 7800-375 cm^{-1}). Spectra of the polymer were taken in the wavelength region 500-4000 cm^{-1}. Polymeric beads were placed on a KBr holder in an enclosed sample chamber for FTIR spectroscopic study

Thermal Analysis

Differential scanning calorimetric (DSC) analysis of the samples (placebo and loaded chitosan beads) were carried out by using differential scanning calorimeter (NETZSCH DSC 204) Samples (10 mg) were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 20°C/min in the temperature range of 50-200 ºC.

X-Ray Diffraction Studies

The X-ray diffractograms of the beads and the Levocetirizine dihydrochloride loaded beads were obtained in a D8 Advance Model X-Ray Diffractometer (Bruker, Germany) using Ni filtered radiation (l = 15.4 nm, 40 kV and 30 mA). The measurements were carried out using PMMA sample holder and lynx eye detector.

Entrapment Efficiency

Entrapment efficiency was calculated by weighing 10 mg of the loaded beads and dispersing them in 50ml of phosphate buffer saline (PBS), pH 7.4. The solution was stirred by magnetic stirrer and left to equilibrate for 12 hours at room temperature. The beads were filtered from the PBS solution and analyzed in the UV spectrophotometer at 230nm.

$$\text{Entrapment efficiency } (\%) = \frac{\text{Actual Weight (Wa)}}{\text{Theoretical Weight (Wt)}} \text{ X } 100$$

In-vitro release

Levocetirizine dihydrochloride loaded chitosan beads were subjected to *in vitro* release in Simulated Intestinal Fluid (SIF, pH 7.4) and Simulated Gastric Fluid (SGF, pH 1.2). Levocetirizine dihydrochloride loaded beads (50 mg) was dialyzed (6 kDa MWCO) against 0.5 M PBS (pH 7.4). The system was incubated at 37ºC. Aliquots of 0.5 ml were taken at predetermined time points (0, 0.5, 1, 2, 3, 4, 5, 6, 8 hr) and equal amount of dialysis buffer was replaced to maintain constant volume. The amount of Levocetirizine dihydrochloride released was quantified as mentioned earlier. The values reported are the average of three independent measurements.

Equilibrium Swelling studies of chitosan beads

A pre weighed amount (100mg) of beads was placed in 0.5 M phosphate buffer saline (PBS), pH 7.4 and allowed to swell to a constant weight. The beads were removed and blotted with filter paper, and their changes in weight were measured. The degree of swelling (α) was then calculated from the following formula.

$$\alpha = \frac{Wg - Wo}{Wo}$$

Where Wo is the initial weight of the beads and Wg is the weight of the beads at equilibrium swelling in the medium.

RESULTS AND DISCUSSION

This method of preparation resultantly produces beads smaller than 2 mm significantly. The beads were further evaluated by SEM to know their morphology. **Figure 1** reveals that the beads were found to be spherical in shape and Levocetirizine dihydrochloride was successfully entrapped into them. The encapsulation efficiency of beads prepared in our study varied between 77.50 %. Polymer, drug as well as the formulations were characterized by FTIR spectroscopy to know any possible interaction between drug, polymer and the crosslinking agent The FTIR spectrum of chitosan in **figure 2** showed peaks corresponding to O-H stretching at 3431 cm- 1 and amine group (NH2) stretching at 2925 cm-1 respectively. The spectrum of drug loaded beads denotes that the drug was intact in the formulation and the absence of drug-polymer interaction. **Figure 3** depicts the thermogram of Levocetirizine dihydrochloride loaded chitosan which is characterized by a sharp exothermic peak at 142.7 ºC. Drug loaded beads showed almost similar thermo grams of placebo beads in which no other peaks were observed indicating the amorphous dispersion of drug into the beads. The bands observed in the Levocetirizine dihydrochloride loaded chitosan beads spectrum (**Figure 4**) did not show any significant shift, suggesting that no new chemical bond was formed after preparing the formulation and the results confirmed that the drug is physically encapsulated inside the polymer matrix. This indicates that the drug is molecular dispersed in the matrix and there could be less or no free drug (in crystalline form) on surface of the beads. This confirmed the amorphous nature of the drug which is encapsulated in the beads. In order to evaluate its potential as a controlled drug delivery system it must be released from the beads. Therefore the release profile of Levocetirizine dihydrochloride from chitosan beads was evaluated. The release profile of Levocetirizine dihydrochloride was illustrated in **figure 5** is characterized by an important initial burst effect followed by a continuous and fast release of drug from the beads. It should be pointed out that the release of the drug follows a biphasic pattern as reported with other delivery systems. However, the Levocetirizine dihydrochloride loaded have a burst phase, with close to 50% of the drug being released within 4 hrs. This indicates that this formulation was capable of slow and sustained release of the drug over a longer period of time.

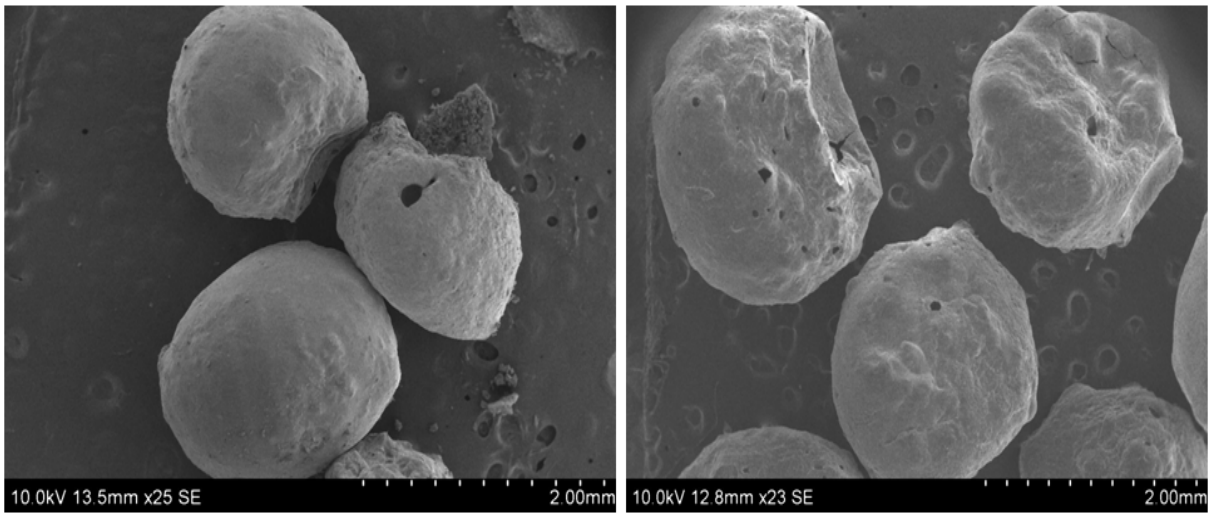

Fig. 1: Scanning Electron Micrograph of Chitosan beads

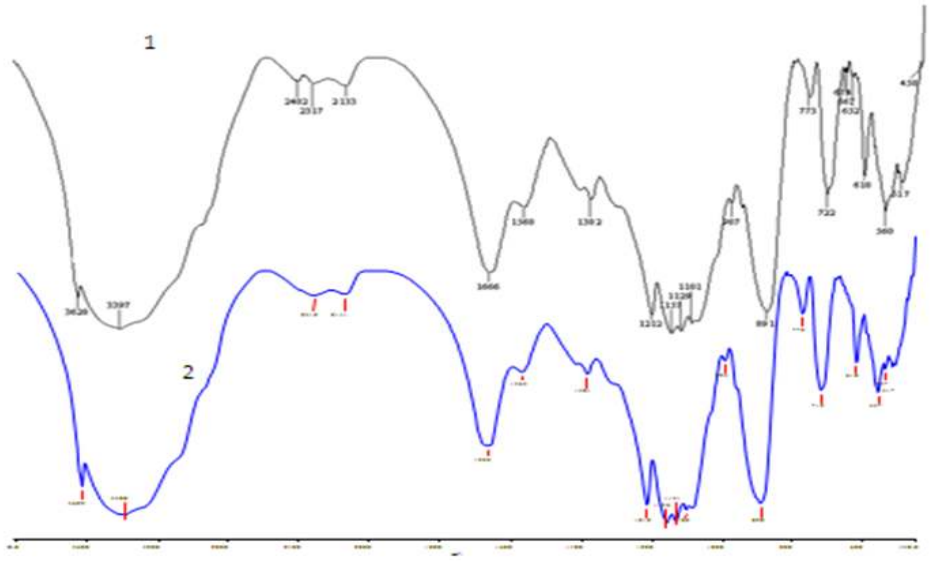

Fig. 2: IR Spectra of (1) Placebo chitosan beads (2) Levocetirizine loaded chitosan beads

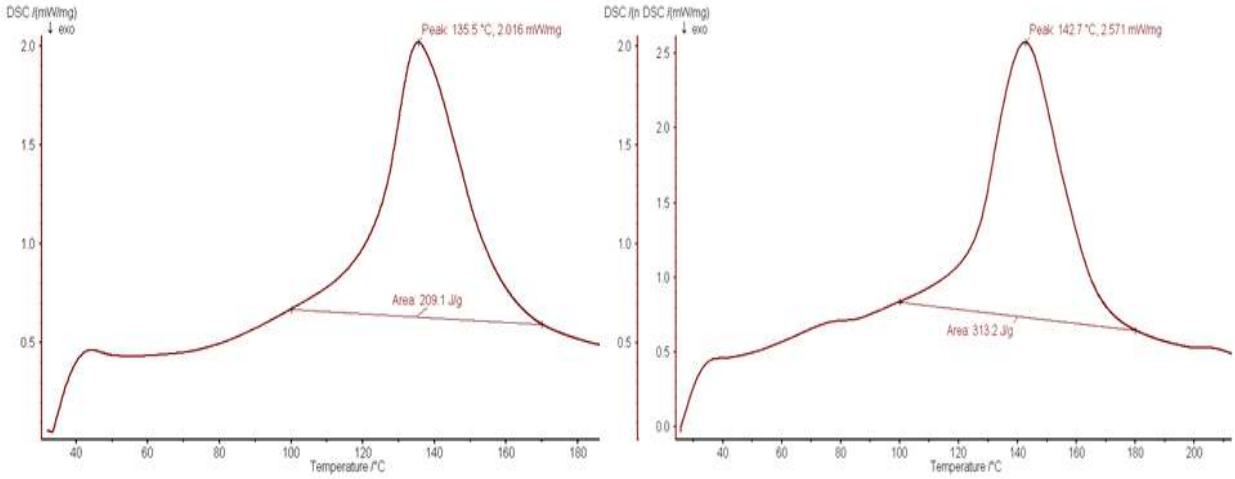

Fig. 3: DSC Thermogram of (1) Placebo chitosan beads (2) Levocetirizine loaded chitosan beads

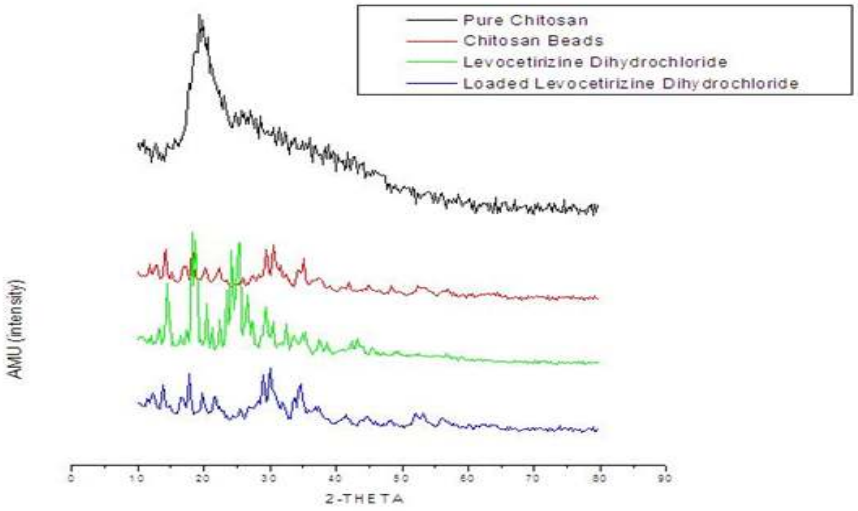

Fig. 4: XRD Pattern with constant X- axis

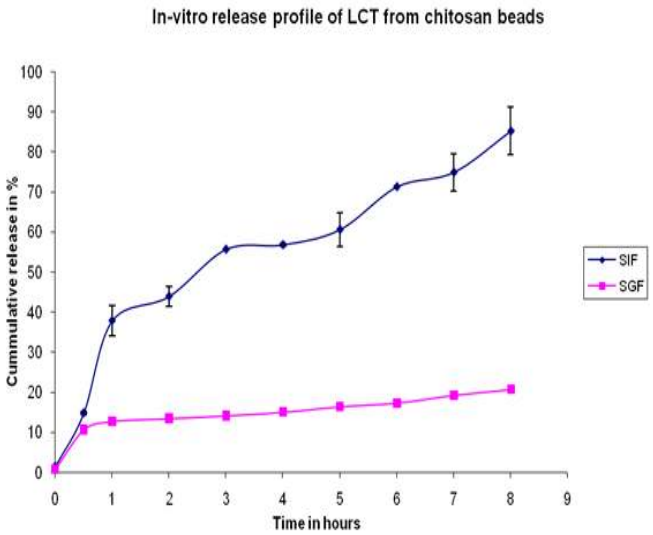

Fig. 5: Dissolution profile in SIF and SGF

CONCLUSION

The main theme of this research is focused on the synthesis of chitosan beads which can be loaded with a range of drugs and the effects of processing conditions on particle size, drug loading and release. Chitosan beads were prepared by ionotropic gelation. The process variables such as concentration of chitosan solution, TPP concentration, stirring rate, volume of chitosan solution and TPP concentration were optimized. Round spherical beads were obtained at 5% chitosan solution and 10% TPP solution. The chitosan beads size was characterized by SEM. The unique XRD and FTIR data denotes the dispersion of drug within the polymers itself. The release of the drug Levocetirizine dihydrochloride was found to be steadily increasing till 8 hours. This may represent that drug can be released within the therapeutic level. The Levocetirizine dihydrochloride loaded chitosan beads found to be stable in Simulated Gastric fluid (SGF) and released a minimum amount of drug. Hence, these particles used to target intestinal tract. From these data it is evident that chitosan beads can be prepared potential biodegradable matrix for the delivery of drugs.

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