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Research paper

# Hollow chitosan nanocomposite as drug carrier system for controlled delivery of ramipril

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ABSTRACT

Hollow biodegradable polymer nanoparticles as drug carrier possess effective low density and higher surface area. Chitosan hollow nanospheres were prepared using poly-D,L-lactide-co-glycolide as template by single emulsion method. The DLS studies showed increase in size from 125 nm to 186 nm for the formation of core@shell structure. The BET surface area increased from 62 $m^2 g^{-1}$ for chitosan@poly-D,L-lactide-co-glycolide to 111 $m^2 g^{-1}$ for hollow chitosan nanospheres. TEM analyses indicated core@shell, chitosan@poly-D,L-lactide-co-glycolide and the hollow morphology of the chitosan nanospheres. Ramipril in acetone (1.5 mg/mL, 3 mg/mL and 5 mg/mL) was physically adsorbed onto hollow chitosan nanospheres and the amount of adsorbed ramipril was determined by HPLC. Higher entrapment efficiency (91%) with 96% of the drug content was observed for the sample with 5 mg/mL of the drug. The *in-vitro* release of ramipril of 86% and 73% was achieved in acetate (pH-3.3) and phosphate (pH-6.3) buffers respectively while only 48% of ramipril in Tris buffer (pH-8.0) medium. Korsemeyer-Peppas model of drug release indicated the release of ramipril being swelling controlled.



## 1. Introduction

Biodegradable polymers have gained immense importance in the field of controlled drug delivery due to their various properties like small size and simplistic fabrication techniques. The main advantage of these biodegradable drug loaded polymers is their enhanced therapeutic effect of drug, subsequent lower dose requirement and reduction in toxic side effects [1]. Poly-D,L-lactide-co-glycolide (PLGA) and chitosan (Cs) are two widely used biodegradable polymers. PLGA is biocompatible, non-toxic biopolymer [2] that degrades into lactic and glycolic acid in the body that are utilized into the natural metabolic pathway kreb's cycle also called as the TCA cycle inside the body and finally eliminates out as $H_2O$ & $CO_2$. Similarly, Cs, a biopolymer of chitin is an exceptional flocculent, adhering to negatively charged surfaces is non-toxic, biocompatible, biodegradable and also have fungicidal activities [3–7], besides having a unique chemical structure as a linear polyelectrolyte with a high charge density and reactive hydroxyl and amino groups [8]. Chitosan and its derivatives are widely used as drug delivery vehicles [9] like; chitosan modified with PLGA nanoparticles for improved drug delivery was reported by Wang and co-workers [10]. Also, Campos and co-workers [11] reported the use of chitosan as solid lipid nanoparticle (SLN) for effective delivery of paclitaxel. Chitosan microspheres have also been used in gastric drug delivery [12]. To increase insulin's intestinal absorption and enhance its pharmacological bioavailability insulin loaded chitosan nanospheres have been used [13]. Chitosan also exhibits various fascinating biological activities which include induced disease resistance in plants, antimicrobial activity, etc. [14,15]. All these properties of chitosan makes it useful in many different fields that includes food and chemical engineering, pharmaceuticals, nutrition, etc. [16].

In recent years, hollow nanospheres have attracted great potential as drug delivery carriers due to high surface area and low effective density [17]. Several methods for preparation of hollow nanospheres are available [18] like emulsion polymerization [19,20], self-assembly of block copolymers [21–23], template polymerization [24,25], etc. Although, there are many methods to prepare hollow nanospheres still the template method is the most frequently used method, as it can control the core size and hollow structure can easily be obtained after removal of the template by evaporation or thermolysis. Drug loading in the polymer nanoparticles takes place by two ways firstly, addition of drug during the preparation of particles itself and secondly, after the formation of the particles. In case of hollow nanospheres, the second method is applied i.e. the drug is loaded afterwards and hence, the aqueous/organic interface produced by water-in-oil micro emulsion

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and the acute shearing strength brought by a high-speed homogenizer causing drug like bio macromolecules denaturation and aggregation could be avoided, which is advantageous compared to non-hollow nanoparticles [26].

Ramipril, a prodrug, belonging to the angiotensin-converting enzyme (ACE) inhibitor class of medications is metabolized to its active metabolite ramiprilat in the liver. Ramiprilat is a potent, competitive inhibitor of ACE, the enzyme responsible for the conversion of angiotensin I (AT I) to angiotensin II (AT II). AT II regulates blood pressure and is a key component of the rennin-angiotensin-aldosterone system (RAAS). Ramipril is used in the treatment of hypertension, congestive heart failure, nephropathy, and to reduce the rate of death, myocardial infarction and stroke in individuals at high risk of cardiovascular events.

In the present study, template method was employed to prepare hollow Cs nanospheres. Presence of positive charge over the surface of Cs allows it to readily bind to negatively charged surfaces. For superior binding of the chitosan shell to the PLGA template core, the negative charge on the surface of PLGA template was enhanced by treating it with sodium dodecyl sulfate (SDS). The adsorption of chitosan over PLGA template occurred mainly due to the electrostatic interactions between sulfuric acid groups of SDS present on the PLGA template and amino groups of chitosan. The adsorbed Cs layer was further crosslinked to the PLGA template with a non-toxic crosslinker D, L-.glyceraldehyde to further solidify the chitosan layer over the PLGA template. The hollow chitosan nanospheres (CsNs) were then obtained by subsequent removal of PLGA template in acetone as shown in Scheme 1.

## 2. Materials and methods

### 2.1. Materials

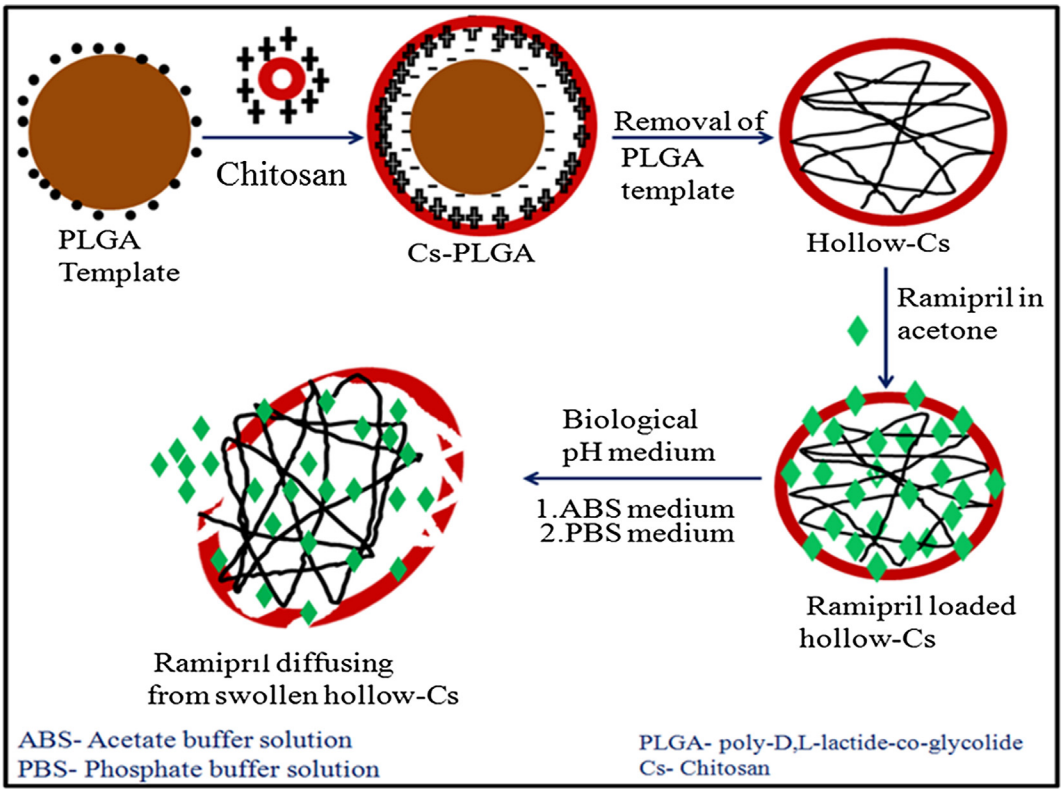
Poly-D, L-lactide-co-glycolide (50:50), Chitosan, PEG 6000, and Tween 80 were purchased from Sigma-Aldrich. Ramipril was received as a gift sample from Mefro Pharmaceuticals (Mohali, Punjab, India). All other reagents were obtained from Loba Chemie, India and used as received without further purification. De-ionized water was obtained using an ultra filtration system (Milli-Q, Millipore).

### 2.2. Preparation of PLGA nanoparticle template

The PLGA template was prepared by single emulsion (o/w) method based on solvent evaporation as reported previously [27,28]. PLGA (0.2 mg) was dissolved in 5 ml of acetone and mixed with Tween 80 (600 μL). This formed the stable organic layer. The contents were then added drop wise into a continuously stirring 1% PEG aqueous solution (50 ml). The solution was then stirred for 2 h. Acetone was removed from the solution under reduced pressure using rota evaporator, and after the complete evaporation of solvent the nanoparticles were centrifuged for 15 min at 10,000 rpm. Slurry was then dispersed in 10 ml of 1% SDS solution and again stirred gently for 4 h. This suspension of nanoparticles was centrifuged again to remove any additional SDS, and then lyophilized overnight to obtain the PLGA template NP.

### 2.3. Preparation of core@ shell Cs@PLGA nanospheres

0.4 mg chitosan was dissolved in10 ml (0.1 mol/L) acetic acid solution and the solution was made up to 50 ml with distilled water. Further, 0.2 mg of prepared SDS coated PLGA template was redispersed in 10 ml of Cs aqueous solution and subsequently stirred continuously for about 14 h. The resulting nanosphere containing solution was then centrifuged to remove redundant chitosan. The chitosan adsorbed PLGA template particles were then redispersed in 10 ml (2%) D,L-glyceraldehyde aqueous solution as cross-linker [29] for about 40 min under gentle stirring for further solidification of chitosan layer over the PLGA template. Subsequent washing was given to the resultant nanospheres with distilled




**Scheme 1.** Schematic representation of preparation of hollow chitosan nanospheres and diffusion of drug through hollow chitosan matrix in different biological pH mediums.