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Research Article

# Biomaterials Based Micro-Composite for Controlled Release of Antihypertensive Drug

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## Abstract

The polymeric matrix is emerging as a promising technique for controlled drug delivery systems (CDDS). Natural Polymer based microcomposites have been attention due to their stability and ease of surface modification, and site-specific drug targeting. Natural polymers are biodegradable, biocompatible and nontoxic and bio adhesive in nature. In these work natural biomaterials based composites containing antihypertensive drug was prepared through ionic interaction method. Losartan potassium is a potent, highly specific angiotensin-II receptor type 1(AT 1) antagonist. It belongs to BCS class III. Losartan potassium is having narrow therapeutic index, poor bio availability (25 to 35%) and short biological half life It is the first of a new class of drug to be introduced for clinical use in hypertension due to selectively blockade of AT-1 receptors and consequent reduced pressure effect of angiotensin II. The formulated micro-composite was characterized by drug entrapment efficiency, surface morphology (SEM) analysis. In-vitro release study was performed in phosphate buffer medium up to 7 h. The release kinetic data was evaluated by the mathematical model. So in these results revealed that natural biopolymer based micro composite may be used as a carrier matrix for drug delivery application.

**Keywords:** Biopolymer, biodegradable, drug delivery, composite, losartan

### Introduction

The drug has to be delivered for a prolonged period of time for the chronic patients. There are many drug delivery systems are present for controlled release drug delivery now a days. One such in micro composites as carriers of drug become an approach of controlled release dosage form in novel drug delivery system.

Controlled drug delivery system is the one deliver drug at predetermined rate, locally or systemically, for a specified period of time to achieve and maintain the concentration of a administered drug within therapeutically effective range, it is often necessary to take drug dosage several times and this results in a fluctuating drug levels in plasma. Controlled drug delivery system has been introduced for following reasons, reduced dose frequency, and as a result, this can lead to improve patient compliance; they have a reduced side-effect profile, they have been introduced to overcome the drawback of fluctuating drug levels associated with conventional dosage form; It reduced local irritation and a steady state rise in serum levels due to a slow release or targeted nature of delivery; they improved drug tolerance; it also provides increased duration of drug therapeutic effect[1].

Composites can be defined as materials that consist of two or more chemically and physically different phases separated by a distinct interface [2].

The average particle size of microcomposite polymer-based matrix systems is with a 1–1000 μm. Microcomposite carrier systems for drug delivery applications offer advantages such as limited fluctuation of drug–plasma profile within a therapeutic range, reduction in side effects, decreased dosing frequency and improved patient compliance [3].

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium , results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. However they provide wide range of application in microsphere based treatment.

Biopolymer particles can be prepared using many types of generally recognized as safe (GRAS) proteins and polysaccharides [4].

Alginate is found in marine organisms cell walls. Alginate is a water soluble linear polysaccharide extracted from brown seaweed and is composed of alternating blocks of 1–4 linked α-L-guluronic and β-D-mannuronic acid residues.

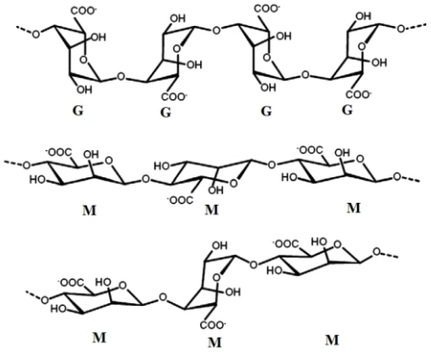


**Figure 1:** Chemical structures of alginate

Figure 1 shows the structures of mannuronic and guluronic acid residues and the binding between these residues in alginate. Because of the particular shapes of the monomers and their modes of linkage in the polymer, the geometries of the G-block regions, M-block regions, and alternating regions are substantially different. Specifically, the G-blocks are buckled, while the M-blocks have a shape referred to as an extended ribbon. If two G-block regions are aligned side by side, a diamond shaped hole is being formed. This hole has dimensions that are ideal for the cooperative binding of calcium ions. The homopolymeric regions of β-D-mannuronic acid blocks and β -L-guluronic acid blocks are inter dispersed with regions of alternating structure (β–D-mannuronic acid– β -L-guluronic acid blocks) [3, 5-6].

Alginates have been used as matrix material in the formulation of various drug delivery systems to achieve sustained drug release over a prolonged period due to its hydrogel forming properties [7-8]. Sodium alginate have ability to undergo ionotropic gelation in aqueous solution in presence of multivalent cations like $Ca^{2+}$, $Zn^{2+}$, $Pb^{2+}$, $Cd^{2+}$, $Al^{3+}$, etc.[3, 8].

Guar gum (Figure 2) is a polysaccharide derived from the seeds of Cyamopsis tetragonolobus, of the Leguminosae family. Chemically guar gum is a galactomannan, which occurs as a storage polysaccharide in the seed endosperm of plants in the Fabaceae family.

Galactomannans are linear polysaccharides consisting of (1→ 4)-diequatorially linked β-D-mannose monomers, some of which are linked to single sugar side-chains of α-D-galactose. In pharmaceutical formulations, guar gum is used as a binder, disintegrant, suspending agent, thickening agent and stabilising agent. GG contains about 80% galactomannan, 12% water, 5% protein, 2% acidic insoluble ash, 0.7% ash and 0.7% fat [9-12].

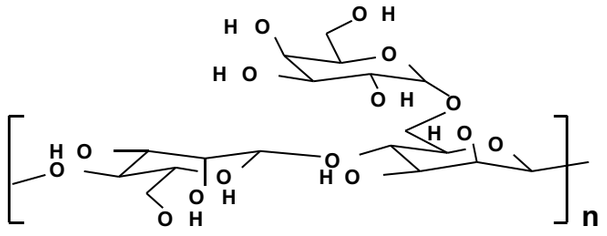

**Figure 2:** Guar gum structure

The guar gum gelling as drug carrier property and enzymatic degradation in the colon has been reported [13-14]. Guar gum was found to be a colon-specific drug carrier in the form of a matrix and compression coated tablets [15-16].

Losartan potassium is a potent, highly specific angiotensin-II receptor type 1(AT 1) antagonist. It belongs to class III, is soluble in acidic pH. Losartan potassium is having narrow therapeutic index, poor bio availability (25 to 35%) and short biological half life. It is the first of a new class of drug to be introduced for clinical use in "hypertension" due to selectively blockade of AT-1 receptors and consequent reduced pressure effect of angiotensin II. Conventional tablets should be administered 3-4 times per day [17-19].

## Materials and Methods

### Materials

Losartan was received as gift sample from Cipla Pvt. Ltd., Sikkim, sodium alginate was purchased from LobaChemie, Mumbai, guar gum was gifted from Hindustan Gums, calcium chloride dihydrate was purchased from Merck Specialized Private Limited, Mumbai, glutaraldehyde was purchased from Merck Specialized Private Limited, Mumbai, potassium dihydrogen phosphate was purchased from Fisher Scientific, Mumbai.

### Preparation of standard curve of losartan

### Preparation of phosphate buffer pH 6.8

6.8 gm. of potassium dihydrogen phosphate ($KH_2PO_4$) was weighed accurately and dissolved in distilled water to make 250 ml solution. In another beaker 0.896 gm sodium hydroxide (NaOH) was taken and dissolved in 112 ml distilled water to make a solution. Then both solutions were mixed together in a measuring cylinder and the volume was made up to 1000 ml with distilled water, pH was checked by using digital pH meter.

Preparation of standard curve of losartan in pH 6.8 phosphate buffer solution

Accurately weighed 10 mg of losartan and placed it in 100 ml volumetric flask, after that 10 ml of phosphate buffer (pH6.8) was added to it and shaken vigorously, there after volume was made up to 100 ml by the same. From this stock solution 0.2, 0.4, 0.6, 0.8, 1.0, 1.4, 1.6 ml sample was withdrawn and diluted to 10 ml with fresh buffer to have a series of concentration 2, 4, 6, 8, 10, 14, 16, $\mu$g/ml to prepare the standard curve of losartan (Figure 3), where concentration and absorbance are given in the Table 1.

**Table1:** Table for concentration and absorbance for determination of standard curve

| Concentration ($\mu$g/ml) | Absorbance (at λmax228 nm) |
|---|---|
| 0 | 0 |
| 2 | 0.102 |
| 4 | 0.182 |
| 6 | 0.281 |
| 8 | 0.353 |
| 10 | 0.472 |
| 12 | 0.563 |
| 16 | 0.759 |

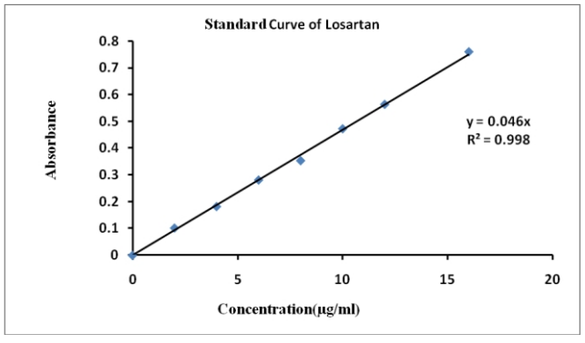


**Figure 3:** Standard curve of losartan

### Preparation of drug loaded microcomposite

The losartan-loaded microspheres made of alginate/guargum were prepared through dual crosslinking. Briefly, required amounts of sodium alginate and guargum were dissolved in deionized water (100 ml) using magnetic stirring of 300 rpm for 30 min at 75 °C, separately. Both the polymer solution was mixed with continuous magnetic stirring of 300 rpm for 30 min again. Afterwards, losartan was added to the mixture gels of sodium alginate and guargum. Losartan containing polymeric gels were stirred using magnetic stirring of 300 rpm until they became bubble free. The prepared homogeneous bubble-free drug-polymeric solutions were separately extruded drop wise into different counter ion solutions using a 25 ml hypodermic syringe (1 mm diameter) with constant stirring. The different counter-ion solutions contain different combination of cross-linking agents such as calcium chloride, glutaraldehyde. Added droplets were retained in the counter-ion solutions for 5 min to complete the curing reaction and to produce rigid microspheres. The wet microspheres were collected by decantation, and washed two times with distilled water and dried in room temperature for overnight. The dried microcomposites containing losartan were stored in desiccators until used. Different microsphere formulations along with percentage of polymers, drug (losartan) and cross-linkers are enlisted in Table 2.

**Table 2:** Formulation table of polymer, drug and crosslinker

| Sl. No. | Formulation Code | Alginate (mg) | Guar gum (mg) | Drug (Losartan) (mg) | Calcium Chloride ($CaCl_2$) (%W/V) | Glutaraldehyde (GA) (%V/V) |
|---|---|---|---|---|---|---|
| 1 | C1 | 300 | 100 | 100 | 3 | 1 |
| 2 | C2 | 400 | — | 100 | 3 | 1 |
| 3 | C3 | 200 | 200 | 100 | 3 | 1 |
| 4 | C4 | 100 | 300 | 100 | 3 | 1 |
| 5 | C5 | 300 | 100 | 100 | 3 | — |

**Characterization of microspheres**

**Percentage yield**

The dried microcomposite was collected and weighed by electronic balance and calculated the yield (Table 3).

**Table 3:** Percentage yield of various formulations

| Formulation Code | Percentage yield (%) |
|---|---|
| C1 | 89.26 |
| C2 | 85.64 |
| C3 | 96.04 |
| C4 | 95.32 |
| C5 | 92.34 |

**Entrapment efficiency**

Microcomposite containing of drug (5 mg) were crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 h, and was filtered then assayed by UV-VIS spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content.

Entrapment efficiency = (actual drug loading / theoretical drug loading) X 100 %

***In vitro* dissolution study**

*In vitro* release of losartan from drug loaded alginate-guar gum microspheres was studied as follows. The microspheres equivalent to100 mg losartan were placed in vessel of USP type II dissolution apparatus (Veego VDA-6D, Veego Instruments Co-operation, India) containing 900 ml of phosphate buffer (pH 6.8) solution. The system was maintained at 37 ± 1°C with a paddle speed of 50 rpm. An aliquot (5 ml) was collected at regular time intervals, and the same volume of fresh medium was added into dissolution vessel to maintain the sink condition throughout the experiment. The aliquots were then filtered, suitably diluted and analyzed using a UV-Vis spectrophotometer (Thermo Scientific, UK) at 228 nm. The drug release also continued in pH 6.8 for 7 h under similar experimental conditions.

**Kinetic model design**

In order to predict and correlate the in vitro drug release behavior from formulated microsphere containing losartan, it is necessary to fit into a suitable mathematical model. The in vitro drug release data were evaluated kinetically using various important mathematical models like zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models.

Zero-order model: Q = kt + Q0; where Q represents the drug release amount in time t, and Q0 is the start value of Q; k is the rate constant. Plotting time vs percent amount drug release.

First-order model: logC = (logC0- k1t/2.303) where Q represents the drug released amount in time t, and Q0 is the start value of Q; k is the rate constant. Plotting time vs log percent amount drug remaining to be release.

Higuchi model: Q = kH√ t; where Q represents the drug released amount in time t, and k is the rate constant. Plotting square root of time vs percent amount drug release.

Hixson-Crowell model:Q1/3 = kt + Q01/3; where Q represents the drug released amount in time t, and Q0 is the start value of Q; k is the rate constant.

Korsmeyer-Peppasmodel:Q = ktn; where Q represents the drug released amount in time t, k is the rate constant and n is the diffusional exponent, indicative of drug release mechanism.

Again, the Korsmeyer-Peppas model was employed in the in vitro drug release behavior analysis of these formulations to distinguish between competing release mechanisms: Fickian release (diffusion-controlled release), non-Fickian release (anomalous transport), and case-II transport (relaxation-controlled release). When n is ≤0.43, it is Fickian release. The n value between 0.43 and 0.85 is defined as non-Fickian release. When, n ≥0.85, it is case-II transport [3, 8].

**Field emission-scanning electron microscopy (FE-SEM)**

The dried microcomposites were spread onto metallic stubs and platinum coating applied by using an ion-sputtering device. The coated particles were then examined under FE-SEM (ZEISS, Japan).

**Analysis of variance**

All data are calculated by using ANOVA analysis in Graphpad Prism software (Trial version).

**Results and Discussion**

**Yield and drug entrapment efficiency**

Entrapment efficiency was expressed as the percentage of losartan entrapped in these prepared alginate-guar gum particles compared to the initial amount of losartan included in the formulation. The drug entrapment efficiency of these particles was achieved 74.50-94.20 % (Table 4). Highest drug entrapment efficiency was found in case of formulation C3, prepared using 200 mg sodium alginate, 200 mg guar gum, 3 % w/v calcium chloride, 1% v/v glutaraldehyde and 100 mg Losartan. Increasing drug entrapment was observed with the polymer and drug ratio (1:1:1), dual crosslinking (calcium chloride and glutaraldehyde).

**Table 4:** Drug entrapment efficiency

| Sl. no. | Formulation Code | Drug Entrapment Efficiency (% DEE) |
|---|---|---|
| 1 | C1 | 80.97 |
| 2 | C2 | 86.42 |
| 3 | C3 | 94.20 |
| 4 | C4 | 74.50 |
| 5 | C5 | 78.73 |

### *In vitro* drug release studies

*In vitro* drug release from these prepared microspheres was evaluated in phosphate buffer, pH 6.8. The modifications with guar gum protect the burst release of drug from alginate beads. The microsphere were prepared by different polymer drug ratio such as, C3 (polymers and drug ratio 1:1:1; both crosslinking) showed good results in in-vitro drug release in comparisons of C2 (polymers and drug ratio 4:0:1; both crosslinking), C4 (polymers and drug ratio 1:3:1; both crosslinking), C5 (polymers and drug ratio 3:1:1; single crosslinking). The cumulative percentage of release of losartan release from drug loaded microsphere was found sustained over a period of 7 hours (Figure 4). The percentage drug released from losartan-loaded alginate-guar gum microsphere in 6 hours was within the range of 86.12 (C1) to 85.31 (C2), 72.15(C3), 79.02(C4), 89.05(C5). Decreasing cumulative percent drug release from these newly prepared losartan loaded alginate-guar gum microsphere (C3) was found with the both glutaraldehyde and calcium chloride used as cross-linker in their preparation and the 1: 1 ratio of polymer bend to form uniform interaction and rigid structure. In the other hand change the polymers ratio in formulation causes the first release of drug.

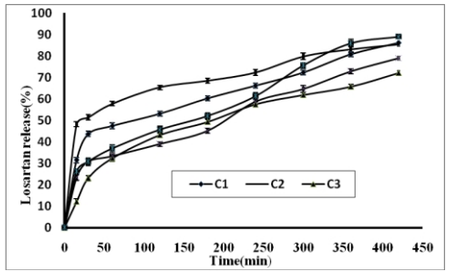


**Figure 4:** *In-vitro* losartan release from different formulation

### Drug release kinetics study

The *in vitro* drug release data from various losartan-loaded alginate-guar gum microsphere were evaluated kinetically using various important mathematical models like zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models. The $R^2$ values of these models were determined for evaluation of accuracy. The result of the curve fitting into various mathematical models is given in Table 5. When the respective $R^2$ of these losartan-loaded alginate-guargum microsphere were compared, it was found to follow the Korsmeyer-Peppas model ($R^2$=0.913-0.994). The value of release exponent (n) determined from *in vitro* losartan release data of various losartan-loaded alginate-guar gum microsphere ranged from 0.52 to 0.75, indicating anomalous (non-Fickian) diffusion mechanism for drug release. The anomalous diffusion mechanism of drug release demonstrates both diffusion controlled, and swelling controlled drug release.

### Morphological analysis

The surface morphological analysis of losartan-loaded microspheres made of alginate/ guargum was analyzed by FESEM and is presented in Figure 5. They were found almost spherical in shape and dense with thick polymer coat. Elongated tails in the microspheres was observed when the concentration of the polymer was increased. The surface topography of these microspheres observed rough surfaces with wrinkles, which might be caused by partly collapsing the polymeric gel network during drying. The microspheres, which were prepared dual cross linking, were found more rigid in nature than the microspheres prepared by the cross-linking with $CaCl_2$ and GA. This phenomenon could be attributed by the possibility of increased bond strength due to dual cross linking.

**Table 5:** Release kinetics of losartan from various micro-composite formulations

| Formulation Code | Correlation coefficient ($R^2$) | | | | Release exponent | |
|---|---|---|---|---|---|---|
| | Zero order model | 1st order model | Higuchi model | Hixson–Crowell model | Korsmeyer–Peppas model | |
| | | | | | $R^2$ | n |
| C1 | 0.919 | 0.974 | 0.978 | 0.981 | 0.959 | 0.69 |
| C2 | 0.904 | 0.897 | 0.938 | 0.923 | 0.913 | 0.56 |
| C3 | 0.918 | 0.967 | 0.858 | 0.893 | 0.994 | 0.63 |
| C4 | 0.926 | 0.987 | 0.988 | 0.973 | 0.981 | 0.75 |
| C5 | 0.935 | 0.996 | 0.850 | 0.878 | 0.987 | 0.52 |

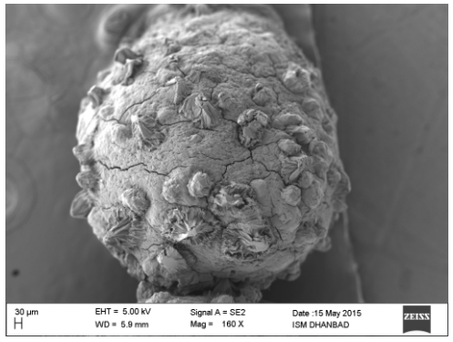


**Figure 5:** FE-SEM photographs of losartan loaded (C3) alginate- guargum microcomposite

### Conclusion

Alginate-guargum microcomposite crosslinked with calcium Chloride and glutaraldehyde crosslinked microcomposite could control the release of losartan. The composites improved the drug entrapment efficiency to a considerable extent. The drug release could be extended for a prolonged period. The drug was found compatible in the composites. Therefore alginate- guargum microcomposite showed the potential to act as an oral delivery vehicles for losartan.

### Acknowledgement

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### Conflict of interest

The authors declare no conflicts of interest.

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