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Preparation and Characterization of Chitosan coated alginate and carrageenan beads Loaded with Venlafaxine HCl: A Comprehensive Study

Krishnamoorthy B*[1], Chanchal Navin Raj[2]

[1]Department of Pharmaceutics, Sanjivani College of Pharmaceutical Sciences, Rajota, Khetri (Raj), Jhunjhunu, Rajasthan, India
[2]Sun Rise University,Bagd Rajput, Ramgarh, Alwar (Raj), Ramgarh, Rajasthan, India

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ABSTRACT

This study focuses on the development of microsphere systems for the sustained release of Venlafaxine Hydrochloride (HCl) using the ionotropic gelation method with sodium alginate, chitosan, carrageenan and calcium chloride as key components. The microspheres were characterized for their size, shape, and surface morphology using scanning electron microscopy (SEM). X-ray powder diffraction analysis (X-RD) was employed to determine the physical state of the drug within the formulations, while Fourier-transform infrared spectroscopy (FTIR) was used to investigate the drug-polymer interactions. Additionally, entrapment efficiency, in vitro release, and release kinetics were evaluated.The results of FTIR analysis indicated no significant interactions between the drug and polymers, ensuring the stability of the formulated microspheres. X-RD analysis confirmed the presence of the drug in an amorphous state within the beads, facilitating its sustained release. Furthermore, the absence of significant drug-polymer interactions, as indicated by FTIR analysis, supports the stability and integrity of the formulated beads. In conclusion, the developed microsphere systems demonstrate promising potential for the sustained release of Venlafaxine HCl. Their high entrapment efficiency, controlled release rate, and stability make them viable option for improving the therapeutic efficacy and patient compliance associated with Venlafaxine HCl administration. Further studies are warranted to evaluate their pharmacokinetic and pharmacodynamic profiles, as well as their long-term stability, to ensure their suitability for clinical applications.

*Corresponding Author

Name: Krishnamoorthy B
Phone: +919666499784
Email: bkrishmoorthy2004@gmail.com

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INTRODUCTION

In the field of drug delivery systems, the development of efficient and controlled-release formulations has garnered significant attention [1]. Venlafaxine HCl, an antidepressant widely used for the treatment of depression and anxiety disorders, requires controlled release to optimize therapeutic outcomes. In this comprehensive study, we present the preparation and characterization of chitosan-coated alginate and carrageenan beads loaded with Venlafaxine HCl, aiming to enhance drug stability and achieve sustained release [2]. The synergistic

combination of alginate and carrageenan as polymeric matrices offers unique advantages, while the chitosan coating provides additional protection and controlled drug release. The objective of this study was to investigate the physicochemical properties, drug loading efficiency, release kinetics, and stability of the developed beads [3]. The findings from this research contribute to the advancement of drug delivery systems and hold promise for improved therapeutic efficacy in the treatment of depression and anxiety disorders.

MATERIALS AND METHODS

Sodium alginate was dissolved in distilled water at concentrations ranging from 1% to 4% (w/v), while carrageenan was dissolved separately in various ratios (1:1, 2:1, 3:1, 3:2) as indicated in Table 1. Venlafaxine Hydrochloride was dissolved in distilled water and gradually added to the sodium alginate and carrageenan solution with continuous stirring. The mixture was sonicated for 30 minutes to eliminate any air bubbles that may have formed during mixing. The gelation medium was prepared by combining equal amounts of $CaCl_2$ solution (0.5-2% w/v) with different concentrations of chitosan solution (0.5-2%) previously prepared with 2.4% lactic acid, and the pH was adjusted to 4.5 $\pm$ 0.1. The medium was mixed for 2 hours before use. The homogeneous mixture of sodium alginate, carrageenan, and the drug was added dropwise into the gelation medium using a 5 ml hypodermic syringe through a #21 needle while stirring continuously at room temperature. The resulting beads were cured in the gelation medium for 4 hours, followed by washing with distilled water and drying at room temperature (25ºC) in a dust-free chamber until a constant weight was achieved. The prepared beads were then stored in an airtight container at room temperature.

Determination of particle size and shape

In this study, particle size analysis was conducted on the beads using optical microscopy. The instrument was calibrated, and the size of approximately 50 beads per sample was determined.

$\bar{X}=\frac{\sum_{x_i}}{N}$

$\bar{X}$=Estimation of average diameter of the beads

Xi= Individual diameter of the beads

N= Number of beads

The standard deviation (σ) was calculated by using the formula,

$\sigma = \frac{\sqrt{\sum_{(xi-X\ bar)^2}}}{N-1}$

The results are summarized in Table 2. Furthermore, the shape and surface morphology of the drug-loaded beads were investigated using scanning electron microscopy (SEM) with Vega © Tescan, USA.

Drug loading and entrapment efficacy study

For the determination of drug loading and entrapment efficiency, 50 mg of venlafaxine hydrochloride-loaded chitosan-coated alginate/carrageenan beads from each batch were immersed in 100 ml of distilled water for 24 hours with intermittent shaking. The filtered solution was subjected to spectrophotometric analysis (UV-Visible spectrophotometer, Shimadzu 1800, Japan) at 274 nm after suitable dilution. The drug loading was calculated[4]using below equation,

Drug Loading in % = W/W_t x 100

where W represents the drug content of the beads and Wt is the weight of the beads.

Theoretical drug loading was estimated assuming complete entrapment of the drug in the polymer solution without any loss during bead preparation.

Entrapment efficiency [4] was determined using below Equation, comparing the experimental drug content with the theoretical drug content.

$$Entrapment\ Efficiency = (Experiental\ Drug\ Content/ Theoritical\ Drug\ Content) \times 100$$

All experiments were conducted in triplicate. The results are presented in the Table 2.

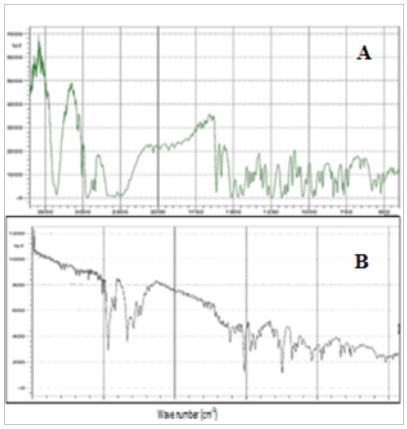

Figure 1: Shows FTIR spectra of A) pure of venlafaxine hydrochloride and B) optimized formulation

FT-IR spectroscopy, Thermograms and X-Ray Powder Diffractometry [X-RD] Analysis

The interaction between the drug and polymer was studied using FT-IR spectroscopy (Shimadzu,

Table 1: Exhibits the composition of venlafaxine hydrochloride-loaded chitosan-coated alginate/carrageenan beads

Formulation code	VAC1	VAC2	VAC3	VAC4	VAC5	VAC6	VAC7	VAC8	VAC9	VAC10	VAC11
Sodium alginate (% w/v)	3	3	3	3	3	2	3	3	3	1	3
Sodium alginate carrageenan ratio	3:01	3:01	3:01	3:01	3:01	2:01	3:01	3:01	3:02	1:01	3:01
Calcium Chloride (% w/v)	2	2	2	2	2	2	1	2	2	2	-
Chitosan (% w/v)	0.5	1	1	1	1	1	1	2	2	2	2
Drug : Alginate ratio	1:04	1:04	1:03	1:02	1:04	1:04	1:04	1:04	1:04	1:04	1:04
Gelation time (h)	4	4	4	4	2	4	4	8	4	4	4

Table 2: Exhibits the results of drug loading, entrapment efficiency and average particle size of formulated beads

Formula code	VAC1	VAC2	VAC3	VAC4	VAC5	VAC6	VAC7	VAC8	VAC9	VAC10	VAC11
Particle size (μm)	665.72 ± 3.96	747.70 ± 2.75	714.40 ± 5.77	748.12 ± 2.72	722.56 ± 2.50	765.8 ± 4.01	706.55 ± 1.00	712.33 ± 1.52	804.35 ± 1.37	814.75 ± 1.10	716.67 ± 1.51
Drug loading (%)	13.47 ± 1.52	19.73 ± 1.70	24.00 ± 1.20	22.36 ± 1.71	19.18 ± 2.84	20.78 ± 0.98	19.36 ± 0.06	19.68 ± 1.52	20.27 ± 0.24	14.07 ± 0.14	15.48 ± 0.72
Entrapment Efficiency (%)	74.01 ± 1.01	96.57 ± 1.50	99.53 ± 0.63	89.32 ± 1.87	89.89 ± 3.40	98.41 ± 1.58	91.41 ± 1.19	95.08 ± 3.11	87.79 ± 1.43	84.97 ± 0.25	64.87 ± 0.66

Japan). Samples of pure drug, polymers, physical mixtures, blank beads, and drug-loaded beads were mixed with potassium bromide, compressed into pellets, and analyzed. The FT-IR spectra of venlafaxine hydrochloride are presented in Figure 1. Differential scanning calorimetry (DSC) was performed using a Pyris Diamond TG/DTA instrument (PerkinElmer, Singapore) in a nitrogen atmosphere. The thermal behaviors of pure drug, polymers, physical mixtures, and drug-loaded beads were investigated. DSC thermograms for venlafaxine hydrochloride-loaded beads are shown in Figure 2. X-ray diffraction (XRD) patterns were recorded using a Miniflex goniometer to examine the physical state of the drugs in the formulations. The instrument operated at a scanning speed of 1º/ min over a 2θ angle range of 10-70. The diffractograms for venlafaxine hydrochloride are presented in Figures 3, 4 and 5.

Invitro release and its release behavior studies

To assess drug release, in vitro dissolution studies were performed on samples consisting of 100 mg of drug-loaded beads. The studies were conducted in a USP XXI dissolution rate test apparatus, using 350 ml of double-distilled water at 37 ± 0.5ºC and a stirring speed of 50 rpm for 6 hours. At predetermined time intervals, 3 ml of the dissolution medium was collected, filtered through Whatman No. 1 qualitative filter paper, and analyzed for drug content

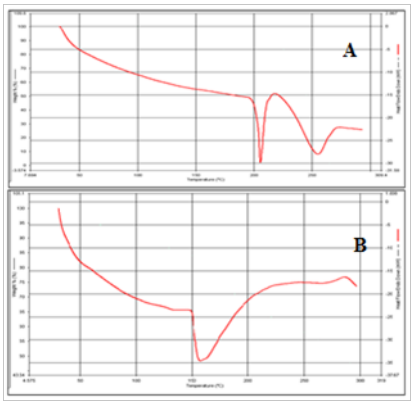

Figure 2: Depicts thermograms for A) venlafaxine hydrochloride, B) venlafaxine hydrochloride-loaded beads

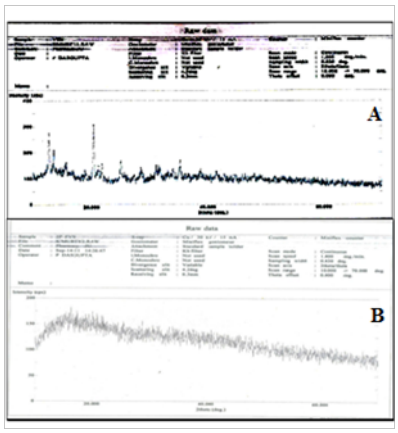

Figure 3: Displays the x-ray diffraction patterns of A) pure form of venlafaxine hydrochloride, B) venlafaxine hydrochloride-loaded beads

at 274 nm using a Shimadzu 1800 UV spectrophotometer (Japan). The experiments were conducted in triplicate. The release data were fitted into various kinetic models, including zero-order, first-order, and Higuchi's model. The obtained data were used to calculate correlation coefficients for each kinetic equation.

Stability studies

The prepared beads were subjected to stability studies for three months according to the ICH guidelines, stored in aluminum foil at 25ºC and 65% RH, and 40ºC and 75% RH. The humidity was maintained using a saturated solution of sodium chloride [5].

RESULTS AND DISCUSSION

Particle size analysis showed that the mean particle size ranged from 665.72 μm to 844.75 μm, and SEM photographs confirmed the spherical shape of the prepared beads. The drug loading studies and entrapment efficiency determination aimed to assess the ability of the polymer and manufacturing process to encapsulate the drug. Venlafaxine hydrochloride loaded chitosan-coated alginate and carrageenan beads were examined. The highest drug loading was observed in batch VAC3 (24.00%),

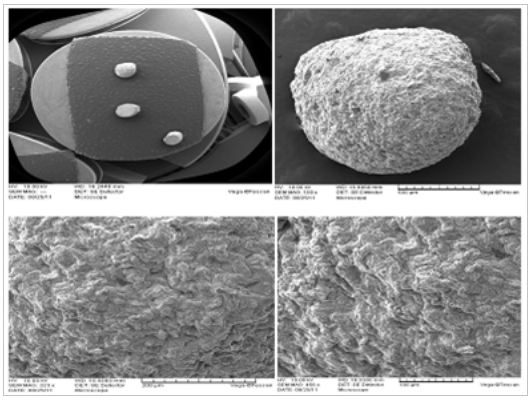

Figure 4: Reveals the SEM photographs of surface morphology of the drug-loaded beads

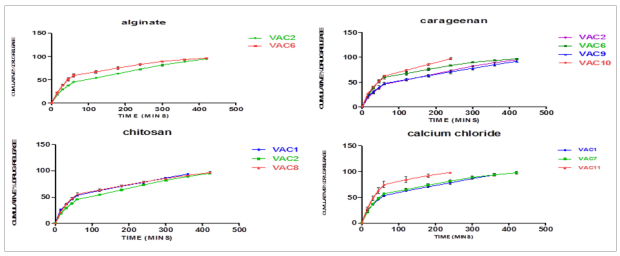

Figure 5: Shows effects of formulation variables in vitro drug release

while the lowest was in VAC1. There were no significant differences in drug loading with varying concentrations of sodium alginate (VAC6, VAC2) and calcium chloride (VAC11, VAC7, VAC2). Increasing the chitosan concentration up to 1% w/v led to higher drug loading (VAC1, VAC2). Decreasing the drug-to-polymer ratio increased drug loading (VAC2, VAC3). Gelation time did not affect drug loading (VAC5, VAC2). The drug loading was higher with a sodium alginate to carrageenan ratio of 2:1 (VAC6), but further increases resulted in a slight decrease. Entrapment efficiency ranged from 64.87% to 99.53%. FTIR analysis indicated the absence of chemical interactions between the drug and polymers or cross-linking agents [6]. DSC tracing showed uniform dispersion of the drug in the polymer matrix [7]. X-ray diffraction patterns revealed that the drug loaded in the beads was not in a crystalline state [8]. The release of venlafaxine hydrochloride from the beads depended on the penetration of the dissolution medium, swelling, and leeching of the drug through the swollen matrix. Increasing the concentration of sodium alginate prolonged drug release, while increasing calcium chloride concentration delayed it [9]. Higher chi-

tosan concentration retarded drug release due to the formation of a polyelectrolyte complex with alginate [10]. Gelation time influenced the rate of drug release, with longer times resulting in delayed release due to increased interaction between alginate and chitosan, leading to lower bead porosity. Altering the alginate-to-drug ratio did not significantly affect the drug release profile [11]. Additional coating with sodium alginate decreased drug loading and did not sustain drug release further. The first-order kinetics model described the release of venlafaxine hydrochloride-loaded beads, showing a linear relationship between the logarithm of the remaining drug and time. Short-term stability studies confirmed the stability of the optimized batches with no significant changes in drug loading and release profiles.

CONCLUSION

In conclusion, the drug loading and entrapment efficiency studies demonstrated the effectiveness of the polymer and manufacturing process in encapsulating venlafaxine hydrochloride. Different parameters such as chitosan concentration, drug-to-polymer ratio, and sodium alginate to carrageenan ratio influenced drug loading. The beads exhibited high entrapment efficiency and a controlled release rate.Sodium alginate concentration prolonged drug release, while calcium chloride delayed it. Gelation time and alginate-to-drug ratio had minor effects. Additional coating with sodium alginate reduced drug loading without sustaining release.These findings highlight the potential of these beads in improving the therapeutic efficacy and patient compliance of venlafaxine hydrochloride administration. Further research is needed to evaluate their pharmacokinetic and pharmacodynamic profiles, as well as long-term stability for clinical applications.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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