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Preparation and Evaluation of Microsphere Loaded Transdermal Drug Delivery System for Anti-Hypertensive Drug.

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ABSTRACT: The objective of present study was to develop chitosan-based sustained release Losartan Potassium microspheres Loaded TDDS to reduce the dosing frequency. Materials and Methods: The Losartan Potassium -loaded chitosan microspheres were formulated by emulsion crosslinking method. A 3^2 factorial design was employed to study the influence of drug:Polymer ratio and volume of glutaraldehyde (GA) on percentage entrapment Efficiency, particle size, and % Yield. Later % Drug release from transdermal patch was monitored at 168hours.Results:The entrapment efficiency was found to be 71.70%and particle size 100µm. The batch 4 showed 58±0.85and 95.8±0.98drug release at 24 and 168 h, respectively. Conclusions: Drug: Polymer ratio and volume of GA had significant effect on % entrapment efficiency, particle size, and % drug release. From the scanning electron microscopy (SEM) study observed that microspheres were spherical and fairly smooth surface.

KEYWORDS: Chitosan, emulsion crosslinking method, glutaraldehyde, microspheres, Transdermal Patch, Glycerine, propylene glycol, Solvent Casting Method

I. INTRODUCTION

Losartan comes under BCS class III which has high solubility and low permeability. In order to increase its permeability, the microspheres were formulated.It has 2 hours of half-life so to provide better permeation and increase half-life microspheres were formulated. A transdermal drug delivery system (TDDS) may prevent pre-systemic metabolism and gastrointestinal degradation of these drug and improve patient compliance, thereby solving the problem associated with traditional medical system.

The aim of this study was to prepare chitosanmicrospheres containing Losartan Potassium by emulsion chemical crosslinking method and then Losartan Potassium Microsphere loaded patch to achieve a controlled drug release profileand to study the effect of different formulation variables such as drug:polymer ratio and GA on particle size, encapsulation efficiency, and its in vitro release behaviour

II. MATERIALS AND METHODS

Losartan Potassium was obtained as a gift samplefrom Brilliant life science Pvt.Ltd. Chitosan was procured from Yarrow Chemicals Limited. Liquid paraffin was purchased from Oryn Healthcare pvt ltd. acetic acid,Span 80 and GA were purchased from Estron Chemical.

Drug and excipient compatibility study by FTIR

The FTIR study was carried out using IR Spirit Shimadzu (Shimadzu Corporation, Japan). The instrument comprises of calorimeter, The samples were Scanned between 400 – 1500 nm. Interpretation of functional group was determined for the sample.

Preparation of microspheres

Weigh amount chitosan and 50 mg of drug was dissolved in 100 ml 4% acetic acid. The drug-polymer dispersion wasadded in a 100 ml liquid paraffin (50 ml light liquid paraffin + 50 ml heavy liquid paraffin) containing 1.5 ml span 80 and it was stirred with the help of mechanical stirrer at 1000 revolutions per minute (rpm). After 30 min, GA (25% aqueous solution) was added and stirred continuously till 3 h. Suspension of chitosan microspheres in paraffin oil, thus obtained was allowed to stand for 15 min to let the microspheres settle down under gravity. Supernatant was decanted and filtered. Microspheres obtained as residue were washed four times with solvent n-hexane to remove traces of the oil. They were finally washed with

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water to remove excess GA. The microspheres were dried at 45°C for 24 h. A total of nine batches, each in triplicate, were prepared as per the factorial design (3^2).
The amount of crosslinking agent and drug: polymer ratio was varied in batch no1 to 9.

Experimental design

In this design, two factors were evaluated each at three levels and experimental trials were performed using all possible nine combination. In this present study, drug: polymer ratio (X1) and volume of GA (X2) were selected as independent variables. The % entrapment efficiency, particle size, and % yield was selected as dependent variables. A statistical model, incorporating interactive and polynomial terms was used to evaluate the response.

Table 1: Variables in 3^2 factorial design

	Factors	Coded levels		
	Independent variables	Low level (-1)	Medium level (0)	High level (+1)
X1	% Chitosan	2	4	6
X2	% Glutaraldehyde	1	2	3

III. EVALUATION OF MICROSPHERES

% Entrapment Efficiency (%EE): -

The drug content of drug loaded microsphere was determined by dispersing 10 mg of microspheres in 10 ml ethanol followed by agitation with of magnetic stirrer for about 30 min to extract the drug and dissolved completely. After filtration though paper the 1 ml of filtrate is pipette out and diluted up to 10 ml volumetric flask. Drug concentration in ethanol phase was recorded by taking absorbance of this solution. The drug concentration was calculated. Thus, the total drug entrapped in total yield of microspheres from the procedure was calculated.
%EE= Total drug- Free drug/Total drug*100

Particle size: -

A small number of dry microspheres was suspended in purified water (10 ml). The suspension was ultrasonicated for 5 seconds. A small drop of suspension thus obtained was placed on a clean glass slide. The slide containing chitosan microspheres was mounted on the stage of the microscope and Ferret's diameter of at least 100 particles was measured using a calibrated ocular micrometre.The process was repeated for each batch prepared. 100 particle size was measured, and Uniformity Index was found using the below equation:
UniformityIndex= Standarddeviation*2/Average microspheres

% Yield: -

The % Yield of the Formulated Batches of Microspheres from Batch F1 to F9. The percent yield for the microsphere formulations wasdetermined using the following equation.wherein the theoretical weight of microspheres constitutes the total polymer weight plus the drug used.
Percent yield = Actual weight of microsphere/ Theoretical weight of microspheres ×100

IV. FORMULATION OF TRANSDERMAL PATCH

Transdermal patch containing Losartan Potassium microsphere were prepared by solvent casting technique. 10 formulations were formulated using different ratios of polymers and plasticizer(glycerine and propylene glycol).Permeation Enhancers were also used to improve skin permeability.

In vitro drug release

Transdermal patch of Losartan Potassium was kept in dissolution apparatus. Dissolution tests wereperformed in a USP Dissolution Test Apparatus type-V (Paddle over disk)at 32 ± 0.5^0 C. The baskets were rotated at a speed of 50 rpm. The dissolution medium consisted of Phosphate buffer pH 6.8(900 ml). Aliquots of 5 ml were withdrawn at different time intervals, filtered through Whatman filter paper and the content of Losartan Potassiumwasdetermined spectrophotometrically at a wavelength of 254 nm using ultraviolet (UV) spectrophotometer.

V. RESULT AND DISCUSSION

Drug-excipient compatibility study by FTIR
FTIR of the Losartan Potassium and Losartan

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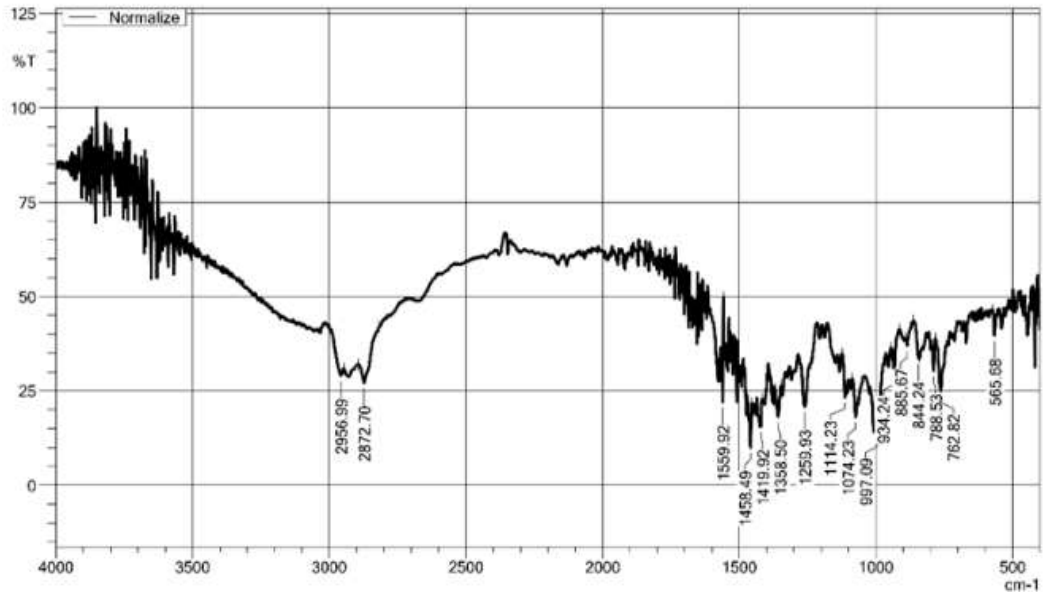
Potassium: chitosan mixtures show no interaction of the drug and drug: chitosan mixture. So, it was concluded that drug and chitosan was compatible with the each other [Figures 1]



Result of batches of Losartan Potassium microspheres

Batch	Response 1 Particle Size µm	Response 2 Entrapment Efficiency %	Response 3 % Yield
F1	165	63.30%	52.4
F2	175	61.20%	67.8
F3	153	66.60%	69.9
F4	100	71.70%	78.7
F5	155	60.10%	55.9
F6	163	64.90%	66.8
F7	181	59.20%	72.3
F8	183	56.80%	43.4
F9	179	55.50%	41.3

Table 2: Composition of batches nicorandil microspheres

Percentage entrapment efficiency

The entrapment efficiency in chitosan microspheres was found 71.70%. Here drug: polymer ratio and volume of GA had significant effect on entrapment efficiency.

Particle size analysis

An increase in the volume GA can increase the efficiency of the stirrer due to decreased viscosity of the oil phase that may result in decreasing the particle size. Chitosan microspheres formulated with a higher GA concentration develop a greater number of covalent bonds, thus the polymeric matrix becomes stiffer, which is responsible for low microsphere size.

In vitro drug release of Transdermal Patch

The drug release was found 58±0.85% at 24 hour and later it was found 95.8±0.98% at 168 hour. Theoretically, the rate of drug release from microspheres decreases with an increase in polymer concentration due to the prolongation of the

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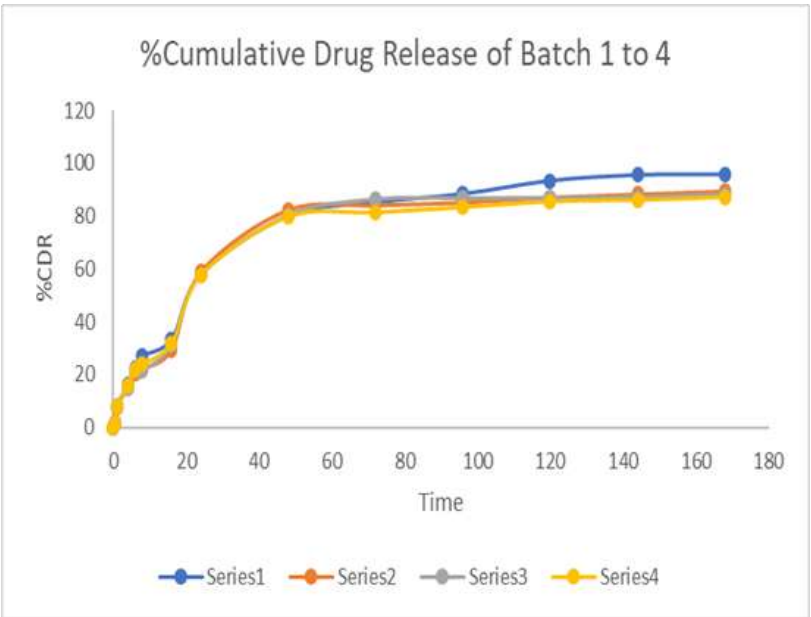
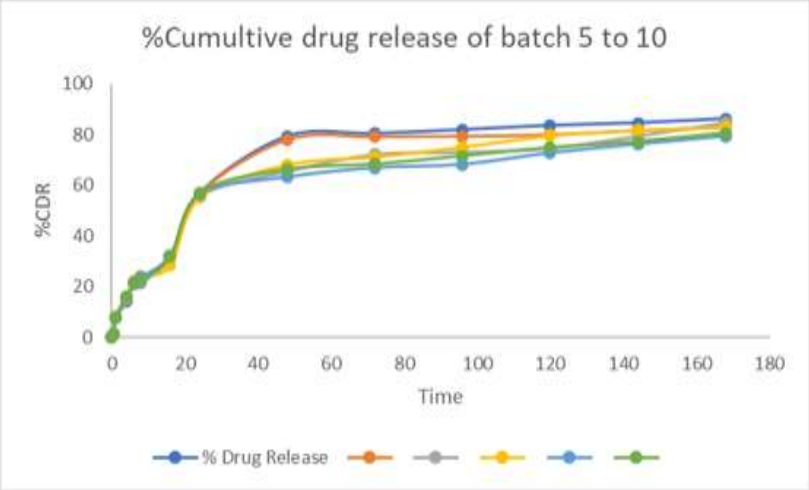
diffusion.





CONCLUSION

Losartan Potassium microspheres were preparedsuccessfully by emulsioncrosslinking method. And later microspheres were formulated in to the Transdermal patch by solvent casting metho. Drug: polymer ratio and volume of GA had significant effect on various parameters like percentage entrapment efficiency, particle size, and % in vitro drug release. The batch 01 showed the drug release 95% after 168hours.

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