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Glutaraldehyde cross-linked ciprofloxacin PVA microspheres and their *in vitro* evaluation

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ABSTRACT

Drug containing biocompatible polyvinyl (PVA) micro spheres were prepared by using emulsification and polymerization techniques. The drug delivery system should be capable of drug release over an extended period of time. An aqueous solution of PVA containing various concentration of drug-Ciprofloxacin was dispersed as droplets in liquid paraffin using suitable stabilizing agent. Cross-linking of PVA droplets with glutaraldehyde was introduced by an acid catalyst, which was produced by the addition of small quantities of benzoyl chloride in to the dispersion medium. The drug release studies were carried out in the simulated gastric and intestinal fluids without the digestive enzymes at 37^{0}C. This study indicates that the cross-linked PVA could be used as a polymer for controlled release dosage form of ciprofloxacin hydrochloride .The microspheres were characterized for their particle size analysis.

KEYWORDS

Polyvinyl alcohol;
Ciprofloxacin;
Glutaraldehyde;
Microspheres.

INTRODUCTION

A wide variety of micro encapsulation technique exists for the formation of polymeric micro particulate drug delivery system[1]. Most of the micro encapsulation techniques used to prepare biodegradable microcapsules (or) micro spheres allow either the encapsulation of water-soluble or water insoluble drugs with either hydrophilic or hydrophobic polymers. The choice of one particular method is governed to a great extent by the solubility characteristics of the active compound and the coating polymer. PVA and its copolymers have found applications in the controlled release of pharmaceuticals[2,3,4]. PVA based systems have also been investigated for the controlled release of macromolecules such as polypeptides. PVA based matrices[5] having a thin layer of PVA cross linked by UV radiation on the surface were also formulated for sustained drug delivery .PVA and its combination with other excipients and the drug have been used to prepare compressed tablets as well as swelling controlled release system[6]. PVA in the form of cross linked films have been investigated for the controlled release of oral drugs such as theophylline. A new method[8] for the preparation of microspheres as an alternative to the conventional microencapsulation technique has been carried in this research work. This paper reports on the preparation of cross-linked PVA microspheres containing ciprofloxacin

and release of the drug in to the simulated gastric and intestinal fluids *in vitro*.

EXPERIMENTAL

Ciprofloxacin hydrochloride- gift sample received from Arvind Remedies Ltd.Chennai, India.Hot water soluble PVA (average Mol.weight), Glutaraldehyde, span 80, benzoyl chloride, liquid paraffin (SD fine chemicals.) All other chemicals were of analytical grade.

Preparation of microspheres

A 20% PVA solution was prepared in sterile hot distilled water. The required amount of the drug and glutaraldehyde solution was mixed with 6.5g of the PVA solution[7]. The drug polymer pasty mass was then dispersed in 50ml dispersion medium which containing 0.1 % w/v of span 80 in 100ml round bottomed flask. The system was kept stirred at 8000±100rpm with motor driven stainless steel stirrer at 32^{0}C.After dispersing for 120 minutes, 0.5ml benzoyl chloride was added slowly in drop wise over a period of 120 minutes and the stirring was continued at the same rpm for 30 minutes maintaining the same temperature. The formation of spheres could be observed and the hardened spheres were filtered off from the solution using whatman filter and the resides were washed several times using petroleum ether until the washing solution gives no positive results for the presence of trace amounts of ciprofloxacin. Then the petroleum ether is dried off from the microspheres by storing under a vacuum. The beads were washed twice with 15% solution w/v of sodium bisulphate and thrice with the limited quantity of cold distilled water to remove unreacted glutaraldehyde. The beads were air dried and desiccated for release studies.

Particle size analysis

The microsperes were dispersed in acetone/water mixture .A smear was made on a glass slide and the particle size analysis was carried out by using optical microscopy after calibrating the eye piece with standardized stage micrometer.

Loading and encapsulation efficiency

The drug loading efficiency of the microspheres was determined using spectroscopic methods by estimating quantitatively at the λ_{max} 432nm using the formulation of 50mg microspheres and extracting the same using 200ml of methanol.

In vitro release studies

In vitro release studies of the drug from the microspheres were carried out at 37^{0}C in simulated gastric and intestinal fluids without enzymes according to the US pharmacopoeia. An 100mg drug equivalent microspheres was added to 500ml of the dissolution fluid in an IL Erlenmeyer flask. The flask was shaken in a bath incubator shaker at 37^{0}C 75 cycles/min. Aliquots of 1ml were withdrawn at specified time intervals and analyzed specrtometrically at λ_{max} 432nm(Shimadzu UC-1601).

RESULTS AND DISCUSSION

Acid catalyzed cross-linking of PVA with glutaraldehyde is an instantaneous reaction leading to the gelling of polymer. Drug incorporation before cross linking leads to the drug loaded matrix which has been prepared in the form of sheets and other molded forms[7]. The method reported in this study appears to be eminently suitable for the preparation of PVA micro spheres containing various drugs in a simple and efficient manner. The cross linking was attempted using benzoyl chloride as the catalyst. We tried different types of emulsifying agent such as span 80, span 20 in order to take a stable dispersion of globules containing ciprofloxacin and PVA in water. A solution of 0.1% w/v span 80 was found to be effective emulsifying system than otters.

Loading and encapsulation efficiency

The drug loading and encapsulation efficiency of PVA microspheres are shown in TABLE 1. As the amount of ciprofloxacin added for encapsulation, the percentage of loading also increased .The same was

TABLE 1 : Percentage of loading, entrapment and encapsulation efficiency of PVA micro spheres

Drug : polymer ratio	Ciprofloxacin (gms)	PVA* (gms)	Drug content %w/w		% of entrapment	Percentage of encapsulation efficiency
			Theoretical	Actual		
1:1	1	1	50	45	90	72
1:2	1	2	33.5	26	78	68
2:1	2	1	66.6	48	72	67
0:1	0	1	-	-	-	-

***Actual PVA content is 6.5gms of 20% solution**

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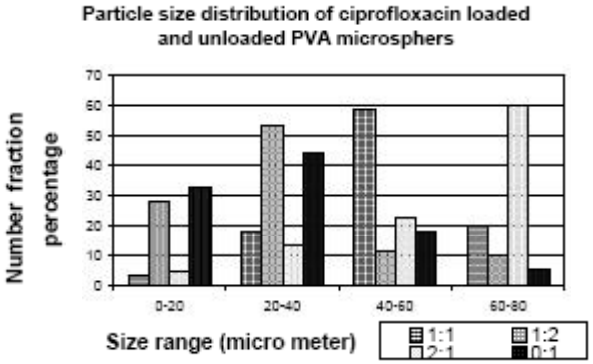
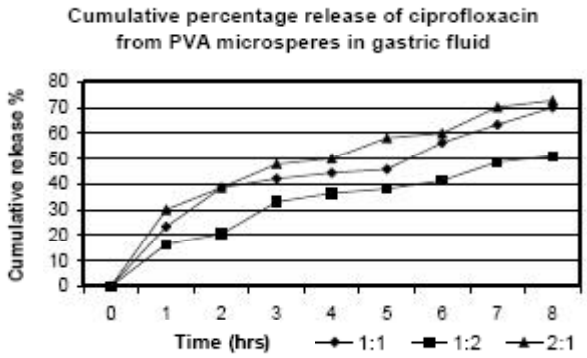
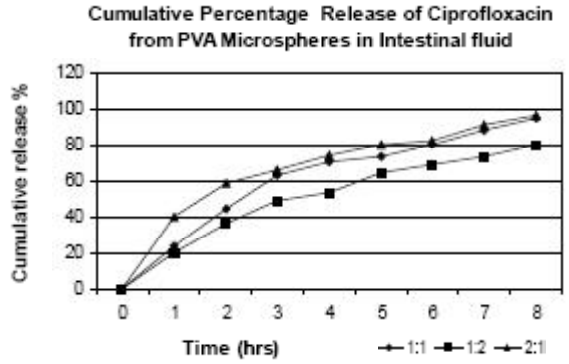


Graph 1



Graph 2



Graph 3

observed in case of percentage entrapment and percentage of encapsulation. The percentage of entrapment was found to be high in case of 1:1 ratio than compared with the other ratios.

Particle size analysis

The particle size of both the loaded and unloaded micro spheres containing ciprofloxacin were determined. All the batches of microspheres showed uniform size distribution.

The drug loaded beads were larger of 40-60μm size range for 1:1 ratio formulation than the unloaded microspheres .The average particle size of unloaded micro spheres was found to be about 25μm with very low number fraction for 60-80μm size range .The ciprofloxacin loaded microspheres (1:1)exhibited average diameter of about 50μm .The particle size distribution of 1:1,1:2,2:1 micro spheres and 0:1 unloaded PVA microspheres respectively are shown in graph 1.

Invitro release

The release of ciprofloxacin from PVA was carried out as explained in the experimental procedure. The cumulative percentage release of the drug in simulated gastric and intestinal fluid s are shown in graph 2 and graph 3.

The release profile showed that the 1:1(drug: polymer) sustained the release of ciprofloxacin for 8hrs with 95.8% release in the intestinal fluid medium and 70.2% release at 8 hrs in gastric medium. This ratio of 1:1 also showed better loading and encapsulation when compared to the other ratios. Thus from the results it appeared that the PVA microspheres cross-linked with glutaraldehyde can be used for the controlled release of oral drugs like ciprofloxacin.

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