ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

NOVEL INTERPENETRATING POLYMER NETWORK MICROSPHERES FOR CONTROLLED RELEASE OF ANTIVIRAL DRUG

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ABSTRACT

Objective: Ganciclovir (GCV), a 2'-deoxyguanosine analog, is the most widely used antiviral drug against human cytomegalovirus (HCMV) infections. It has an extremely short half life (2-4 h) and low bioavailability (5-7%) due to first-pass metabolism which favors the development of IPN based drug delivery system.

Methods: Novel interpenetrating polymer network (IPN) of xanthan gum (XG) and poly vinyl alcohol (PVA) was prepared by emulsion cross-linking method to deliver model anti-viral drug, ganciclovir, cross-linked with glutaraldehyde (GA) to form microspheres. Various formulations were prepared by changing the ratio of XG: PVA, extent of cross-linking in order to optimize the formulation variables on drug encapsulation efficiency and release rate. FTIR spectroscopy was done to confirm the formation of IPN matrix and the chemical stability of ganciclovir after penetration of microspheres.

Results: Microspheres formed were spherical with smooth surfaces as revealed by SEM. IPN formulation F9 composed of XG: PVA (1:4) and glutaraldehyde (5.5 ml) gave the most advantageous entrapment (83.66±2.57%) and release results after 8 hrs (Q8h=54.00±0.61%) in 0.1N HCl, pH 1.2 as compared to other compositions. These results suggest that the IPN microspheres are promising carriers for the controlled delivery of ganciclovir.

Keywords: Ganciclovir, Interpenetrating Polymer Network (IPN), Xanthan gum, Poly vinyl alcohol, Microspheres.

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INTRODUCTION

Ganciclovir (GCV), a 2'-deoxyguanosine analog, is the most widely used antiviral drug against human cytomegalovirus (HCMV) infections. As a result of its hydrophilic nature and poor membrane permeability, its oral bioavailability is very low (5-7%). In addition, its short biological half-life (2-4 hours) necessitates an increased frequency of GCV dosing, causing tremendous discomfort to the patient [1]. These problems can be minimized by the use of interpenetrating polymer network (IPN) based microsphere systems. These systems as drug delivery vehicles has certain advantages, such as enhanced effectiveness and reduced toxicity of the incorporated agents to non-targeted cells and tissues. Biodegradable microspheres can be utilized to direct drugs to organs by lodging them into the environment of the end organ [2].

Microsphere carrier systems made from the combination of natural and synthetic polymers have attracted considerable attention for several years in sustained drug delivery [3]. Among these methods, IPN structures have received greater attention as they increase the phase stability and enhance the mechanical properties of the final product. Better mechanical properties of IPN make it suitable for microspheres preparation for the controlled delivery of drugs [4]. An IPN is a composite of two polymers, which is obtained when at least one polymer network is synthesized or cross-linked independently in the immediate presence of the other [5-8].

Xanthan gum is a high molecular weight exopolysaccharide produced by xanthomonas campestris. XG has been widely used in oral topical formulations as a suspending and stabilizing agent, and a release sustaining agent in hydrophilic matrix tablets, and pellets [9]. PVA is a widely used hydrophilic synthetic polymer because of its process ability, strength, and pH as well as its temperature stability. Because it is biocompatible and non-toxic, it has a wide variety of pharmaceutical applications [10]. Therefore, the present study presents the development of novel IPN of xanthan gum (XG) and poly vinyl alcohol (PVA), cross-linked with glutaraldehyde (GA) to form microspheres by emulsion cross-linking method to deliver model anti-viral drug, ganciclovir.

MATERIALS AND METHODS

The ganciclovir was kindly received as a gift sample by Joshi Agrochem Pharma Pvt Ltd., Mumbai, India. Polymers were procured from Loba Chemie Pvt. Ltd. (Mumbai, India). Double distilled water was used throughout the study.

Preparation of IPN microspheres

Xanthan gum and poly vinyl alcohol (XG-PVA) IPN microspheres containing ganciclovir were prepared by the emulsion cross-linking method. PVA was first dissolved in hot water at 80°C, then, XG was added (total polymer concentration was 5% w/v) and stirred overnight to get homogenous solution. Ganciclovir (1% w/v) was dissolved in ethanol and then added to the mixture of XG and PVA and the solution was stirred for 30 min to get a uniform suspension. This suspension was added to the mixture of soyabean oil (100 ml) and 1% w/w span 80 with stirring at 900 rpm for 40 min. Then glutaraldehyde and 1 ml 1N hydrochloric acid was added slowly and stirred for 4 h at 2100 rpm. After 4 h hardened microspheres were formed and they

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

were separated by filtration and washed with acetone and distilled water to remove the oil as surfactant. Finally the microspheres were washed with 0.1M glycine solution to mask the untreated glutaraldehyde and distilled water to remove the unreacted glutaraldehyde [11]. Then the prepared microspheres were dried at 36°C for 24 h (Table 1).

Table 1: Composition for the preparation of IPN microspheres

Formulation Batches	XG: PVA ratio	Quantity of Polymer Used (mg)		Quantity of Ganciclovir (mg)	Glutaraldehyde (ml)
		XG	PVA		
F1	1:2	100	200	100	3.5
F2	1:3	100	300	100	3.5
F3	1:4	100	400	100	3.5
F4	1:2	100	200	100	4.5
F5	1:3	100	300	100	4.5
F6	1:4	100	400	100	4.5
F7	1:2	100	200	100	5.5
F8	1:3	100	300	100	5.5
F9	1:4	100	400	100	5.5

Evaluation of IPN microspheres

Fourier transform infrared (FTIR) spectral studies

FTIR spectral measurements were performed using FTIR-8400S spectrophotometer, Shimadzu (Japan) to confirm the formation of IPN structure, presence of cross-linking agent in XG and PVA and also to find the chemical stability of the drug in the microspheres. FTIR spectra of drug-loaded microspheres were obtained. Samples were crushed with KBr to get pellets at 600 kg/cm^2 pressure [12]. Spectral scanning was done in the range between 4000–400 cm^{-1}.

Estimation of drug entrapment efficiency (% EE)

The actual amount of ganciclovir present in the different formulations of IPN microspheres were estimated by crushing the swollen microspheres (10 mg) in 100 ml of 0.1N HCl, pH 1.2 at 50°C temperature to extract the drug from the microspheres in a water bath. The whole system was kept for 24 hours. Then, the whole solution was centrifuged (Remi Equipments Private Limited, Mumbai, India) to remove the suspended polymeric debris and the clear supernatant liquid was taken for the determination of drug content spectrophotometrically by using UV spectrophotometer at a wavelength of 254 nm against appropriate blank [13]. Study was done in triplicate and % EE can be calculated by using following formula:

Entrapment efficiency (%) = (actual drug content/theoretical drug content) × 100

Particle size measurements

Vesicle size of different IPN based formulations was observed under an optical microscope (Olympus Model BX 41, Japan) at suitable magnification and volume mean diameter (V_d) was recorded [13].

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In-vitro drug release study

In-vitro release of ganciclovir loaded IPN microspheres were monitored in 0.1N HCl, pH 1.2 at 37°C using programmable dissolution tester (Paddle type, Electrolab, model TDT-08L, USP, Mumbai, India). Microspheres (100 mg) were immersed in 900 ml of the respective medium and stirred at 100 rpm. Aliquots were removed at pre-determined times and were replenished immediately with the same volume of fresh media and were assayed spectrophotometrically at 254 nm [13].

RESULTS AND DISCUSSION

Evaluation of IPN microspheres

The prepared formulations were evaluated for different parameters. It was confirmed by FTIR that the entire principal peaks of ganciclovir are present in IPN microparticles, which confirm the stability of ganciclovir in IPN microparticles (Figure 1). It was indicated that % drug entrapment efficiency (% EE) of the microparticles was in the range between 64.43±2.56% to 83.66±2.57% as shown in Table 4 and it depends on the glutaraldehyde concentration. The IPN microspheres obtained fell in the size range of 9.83±0.74 μm to 19.85±0.65 μm (Table 4). An increase in size of microspheres was observed with the increase in ratio of polymer (XG: PVA) in the microspheres.

The cumulative percentage of drug released after 8 hr from the prepared ganciclovir loaded IPN microspheres at 0.1N HCl (pH 1.2) varied from 54.00±0.61% to 67.82±0.89% as shown in Figure 2 and the data was presented in Table 4. This indicates that the release was slower for those formulations in which a higher amount of glutaraldehyde was used compared to those where lower glutaraldehyde was used. This confirms the formation of a denser network structure, which reduces the rate of swelling as well as the rate of drug release from the matrix. It was also found that with increase in the ratio of XG: PVA, the swelling of the matrix decreases which leads to the slower release of drug from the matrix.

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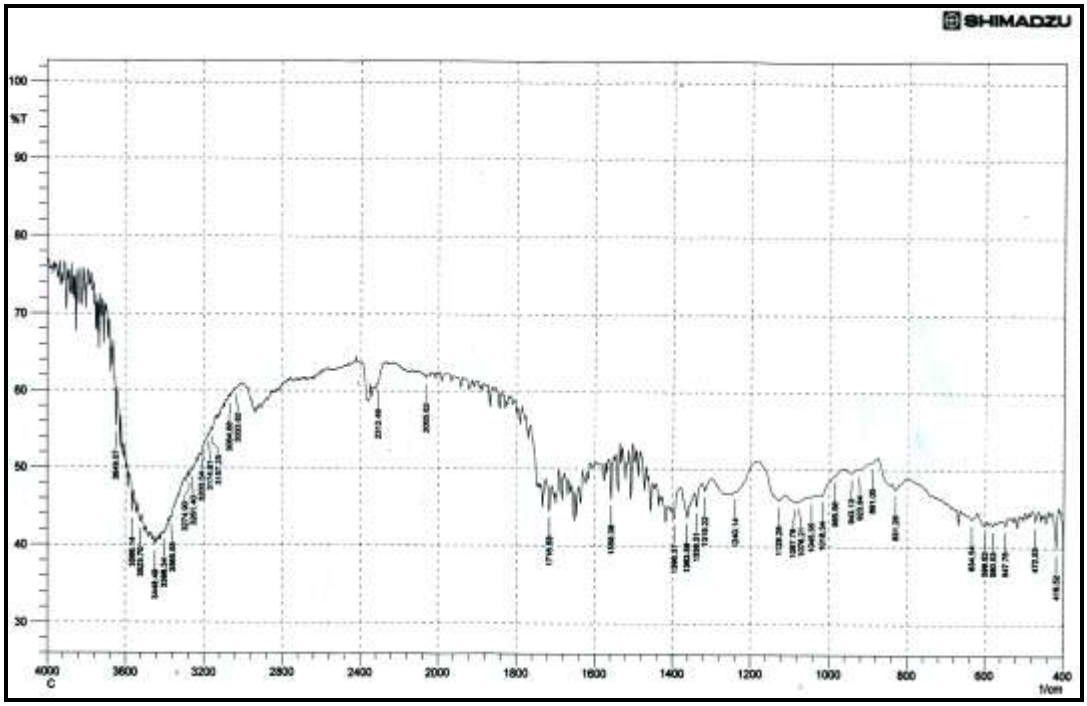

Figure 1: FTIR spectra of drug loaded microsphere

Table 4: Evaluation of ganciclovir loaded IPN microspheres

Formulation code	% EE (± SD, n=3)	Volume mean diameter (µm) (± SD, n=3)	*In-vitro* release (8 h) (± SD, n=3)
F1	64.43±2.56	9.83±0.74	67.32±0.47
F2	66.80±1.97	10.81±0.64	63.13±0.48
F3	72.01±1.86	11.90±0.76	61.48±0.37
F4	75.16±2.55	12.88±0.32	67.82±0.89
F5	77.28±3.51	13.96±0.56	60.90±0.80
F6	79.86±2.97	14.75±0.64	58.14±1.30
F7	81.30±1.27	18.85±0.75	59.76±0.69
F8	82.12±3.66	19.13±0.73	56.36±0.45
F9	83.66±2.57	19.85±0.65	54.00±0.61

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 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

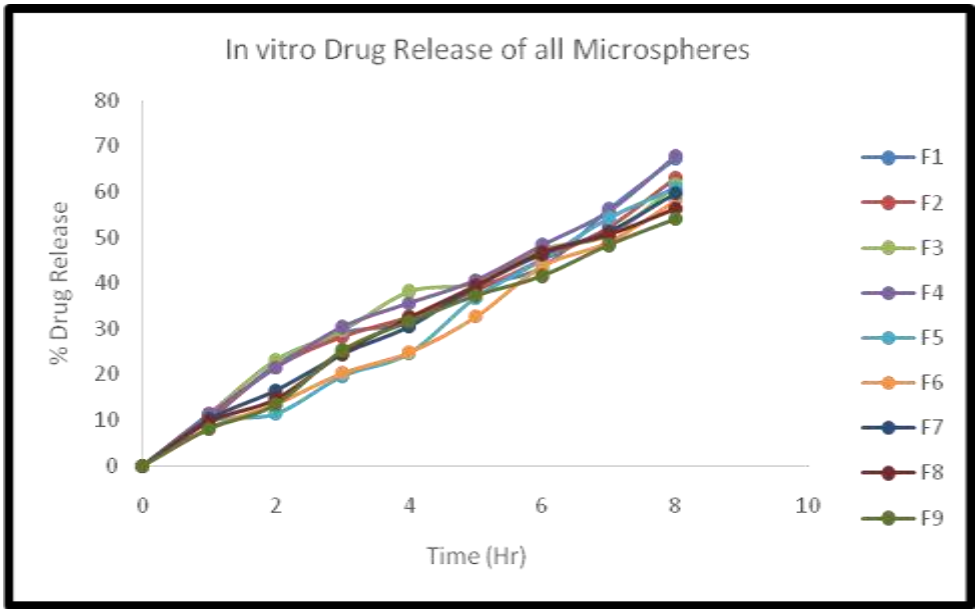

Figure 2: *In-vitro* release profile of different IPN formulations.

CONCLUSION

IPN formulation F9 composed of XG: PVA (1:4) and glutaraldehyde (5.5 ml) gave the most advantageous entrapment (83.66±2.57%) and release results after 8 hrs (Q8h=54.00±0.61%) in 0.1N HCl, pH 1.2 as compared to other compositions. These results suggest that the IPN microspheres are promising carriers for the controlled delivery of ganciclovir.

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