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INVITRO EVALUATION OF NOVEL INTERPENETRATING POLYMER NETWORK MICROSPHERES FOR THE CONTROLLED RELEASE OF HYPOLIPIDEMIC DRUG

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ABSTRACT

Novel interpenetrating polymer network (IPN) of *Lepidium sativum* (Ls) and poly vinyl alcohol (PVA) were prepared and cross-linked with glutaraldehyde (GA) to form microspheres by emulsion cross-linking method to deliver model drug, simvastatin. In the present study, the seeds of *Lepidium sativum* were selected for the isolation of mucilage. The work also emphasizes to study the physicochemical characteristics of mucilage from *Lepidium sativum* seeds. Various formulations were prepared by changing the ratio of Ls:PVA, extent of cross-linking in order to optimize the formulation variables on drug encapsulation efficiency and release rate. Fourier transform infrared (FTIR) spectroscopy was done to confirm the formation of interpenetrating network and the chemical stability of simvastatin after penetration of microspheres. Microspheres formed were spherical with smooth surfaces as revealed by scanning electron microscopy (SEM), and mean particle size as measured by optical microscopy ranged between 20.14±1.11 to 39.73±0.53 µm. Drug encapsulation of up to 86.65% was achieved as measured by UV method. Both equilibrium swelling studies and *in-vitro* release studies were performed in pH 7.4 media. Release data indicated that a drug release which depends on the extent of cross-linking and the ratio of Ls:PVA present in the microsphere. Based on the results of *in-vitro* studies it was concluded that these IPN microspheres provided oral controlled release of simvastatin.

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Keywords: Interpenetrating polymer network, *Lepidium sativum*, Poly vinyl alcohol, Microspheres, Simvastatin

INTRODUCTION

Oral ingestion is the most convenient and commonly employed route of drug delivery[1]. Though, the low bioavailability and short biological half-life of drug for the oral administration favors the development of a controlled release formulation[2]. Controlled drug delivery systems offer numerous advantages compared to conventional dosage forms such as improved efficiency, reduced toxicity and improved patient compliance and convenience[3]. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems[4,5]. In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance[6]. These polymeric systems have been the potential candidates to deliver bioactive molecules, particularly in controlled release applications[7,8]. Such naturally abundant carbohydrate polymer though exhibiting some limitations in their reactivity and processibility but have still been used after being modified by blending, crosslinking etc. The chemical and physical combination methods and properties of multipolymers have been of great practical and academic interest for the controlled release of drugs because they provide a convenient route for the modification of properties to meet specific needs[9]. Among these methods, interpenetrating polymer network (IPN) has received greater attention as they increase the phase stability and enhance the mechanical properties of the final product[10]. Enhanced mechanical properties of IPN make it appropriate for microspheres preparation for the controlled delivery of drugs[11]. 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[12,13]. Moreover, oral controlled release multiple unit dosage forms are becoming more popular than single unit dosage forms as they spread uniformly throughout the gastrointestinal tract, avoiding the vagaries of gastric emptying and different transit rates, resulting in more uniform drug absorption and reduced local irritation as compared to single unit dosage forms[14].

This study presents the development of novel interpenetrating network microspheres of *Lepidium sativum* and PVA for the controlled release of simvastatin. In the present study, the seeds of *Lepidium sativum* were selected for the isolation of mucilage. *Lepidium sativum* are commonly known as pepper grass, pepper wort and garden cress belonging to family brassicaceae, which contain a high proportion of mucilage and it also being used for different therapeutic purposes[15]. Mucilages are polysaccharide complexes which on hydrolysis yields arabinose, galactose, glucose, mannose, xylose and various uronic acids. The work also emphasizes to study the physicochemical characteristics of mucilage from *Lepidium sativum* seeds. Poly vinyl alcohol

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(PVA) is a widely used hydrophilic polymer because of its processability, strength, and pH as well as its temperature stability. Because it is biocompatible and non-toxic, it has a wide variety of pharmaceutical applications[16]. Simvastatin is a hypolipidemic drug used to control elevated cholesterol or hypercholesterolemia, has been used as a model drug. It basically acts by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of the HMG-CoA reductase pathway which is responsible for the endogenous production of cholesterol. It has short biological half-life (2 h) and low bioavailability (5%) that leads to the development of controlled release formulation[17].

MATERIALS AND METHODS

Materials

The simvastatin was kindly received as a gift sample by M/s Zydus Cadila Health Care Ltd. (Ahmedabad, India). Poly vinyl alcohol was a gift sample procured from Loba Chemie Pvt. Ltd. (Mumbai, India). Analytical reagent grade samples of glutaraldehyde (25% v/v), soyabean oil, span 80 and acetone were purchased from S.D Fine chemicals (Mumbai, India). Double distilled water was used throughout the work.

Isolation of mucilage

The mucilage of *Lepidium sativum* was collected from seeds. *Lepidium sativum* was procured form local market in the form of very small brown seeds. Mucilage was extracted by soaking the seeds of *Lepidium sativum* with 10 times its weight of distilled water and kept for 24 hrs. The obtained viscous solution was passed through the muslin cloth. The mucilage was precipitated out by addition of 95% ethanol in the ratio of 1:2 by continuous stirring. The pH of mucilage was adjusted to neutrality. Then, the obtained coagulated mass was dried in oven at 35-40^{0}C and powdered by passing through sieve and stored in airtight container[15].

Physicochemical characterization of mucilage

The evaluation of separated mucilage was done for its physicochemical characteristics such as its morphological characteristics, solubility, pH, loss on drying, swelling index, identification by chemical tests, ash values, and flow properties etc[18]. The evaluation was carried out as per procedures describe in official books[19].

Preparation of IPN microspheres

Lepidium sativum and poly vinyl alcohol (Ls-PVA) IPN microspheres containing simvastatin were prepared by the emulsion cross-linking method. PVA was first dissolved in hot water at 80°C, then, Ls was added (total polymer concentration was 5% w/v) and stirred overnight to get homogenous solution. Simvastatin (1% w/v) was dissolved in ethanol and then added to the mixture of Ls 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 800 rpm for 30 min. Then glutaraldehyde and 1 ml 1N H_2SO_4 was added slowly and stirred for 4 h at 2100 rpm. After 4 h hardened microspheres were formed and they were separated by

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filtration and washed with acetone and distilled water to remove the oil as surfactant. Finally the microspheres were washed with 0.1 M glycine solution to mask the untreated glutaraldehyde and distilled water to remove the unreacted glutaraldehyde[20]. Then the prepared microspheres were dried at 37°C for 24 h. In total, nine formulations were prepared to study the effect of different formulation variables on the characteristics of IPN microspheres (Table 1).

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 Ls and PVA and also to find the chemical stability of the drug in the microspheres. FTIR spectra of the placebo microspheres, drug-loaded microspheres and simvastatin were obtained. Samples were crushed with KBr to get pellets. Spectral scanning was done in the range between 4000–400 cm^{-1}.

Scanning electron microscopy (SEM)

SEM photographs of the IPN microspheres were taken at the required magnification. Microspheres were mounted onto stubs using double sided adhesive tape and vacuum coated with gold film using a sputter coater. The coated surface was observed under SEM (LEO 435VP model, Cambridge, UK) for surface appearance. The working distance of 26 mm was maintained and acceleration voltage used was 15 kV with the secondary electron image (SEI) as a detector.

Estimation of percentage yield

The percentage yield of the microspheres was calculated using the formula[21]:

Percentage yield = (amount of microspheres/amount of drug + amount of polymer) × 100

Estimation of drug entrapment efficiency

The actual amount of simvastatin present in the different formulations of *Lepidium sativum* and poly vinyl alcohol interpenetrating polymer network microspheres was estimated by crushing the swollen microspheres (10 mg) in 100 ml of phosphate buffer saline pH (7.4) 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 simvastatin content spectrophotometrically by using UV spectrophotometer at a wavelength of 238 nm against appropriate blank. In order to maintain the accuracy, experiments were carried out in triplicate for all the formulations to check its reproducibility. The average drug entrapment efficiency values were considered for data treatment and calculations along with standard deviation values. These data are presented in Table 4.

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

Particle size determination

Particle size of IPN based formulations were measured using an optical microscope. A standard stage micrometer was used to calibrate the eye-piece micrometer. Dried IPN microspheres were placed in a glass slide and the number of divisions of the calibrated eye piece was counted. A

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hundred particles were randomly selected from each formulation and the individual particle diameter was calculated based on this formula: 1 eyepiece division = [(no of stage micrometer divisions/no of eyepiece micrometer division) × 10 μm]. For measurement of particle size of different formulations, volume mean diameter (V_d) was recorded[22]. These data are presented in Table 4.

% Equilibrium liquid uptake studies

The pH-dependent equilibrium swelling of the drug loaded cross-linked microspheres were studied in phosphate buffer saline (pH 7.4) media. Samples of known weight (10 mg) were exposed to 100 ml of the swelling medium and allowed to swell completely for 24 h to attain equilibrium at 37°C. Adhered liquid droplets on the surface of the particles were removed by blotting with tissue paper and the swollen microspheres were weighed on an electronic balance. The percentage equilibrium water uptake was calculated as[23]:

Swelling ratio = (Final weight-Initial weight) / Initial weight × 100

***In-vitro* drug release study**

In-vitro release of simvastatin IPN microspheres were monitored in phosphate buffer saline (pH 7.4) 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. The aliquots, following suitable dilution, were assayed spectrophotometrically at 238 nm.

RESULTS AND DISCUSSION

Physicochemical characterization of mucilage

After isolation of the mucilage and then further precipitation by ethanol, the total yield of mucilage was found to be 12.5% w/w. The morphological and physical characterization of isolated mucilage shows, it is brownish white powder, with characteristic odour and lustrous in nature. When dissolved in water, it gives neutral, colloidal solution; it is soluble in hot water and practically insoluble in ethanol, acetone, ether and chloroform. Moisture content of mucilage was 8% and was found to be within official limit. The swelling index was found to be 21.5 and ash values as total ash, water insoluble ash and acid insoluble ash 6.0, 2.5 and 3.0% respectively (Table 2). The isolated mucilage was also studied for flow properties such as angle of repose, bulk density, tapped density, carr's index. The angle of repose indicated that the powder was having good flow. The bulk density and tapped density of mucilage was found to be 0.40 and 0.49 gm/cc and carr's index was 18.42% (Table 3). The result of chemical test shows presence of carbohydrate which is the general constituent of mucilage. While the absence of tannins, sulphate, proteins, amino acids, oil and fats indicated the purity of mucilage.

FTIR

FTIR was used to confirm the formation of the IPN matrix. Fig. 1 presented the FTIR spectra of simvastatin, placebo microsphere, drug loaded microspheres respectively. Simvastatin showed that the principle IR peaks at 2929.67 cm^{-1} resulted from C=O (aromatic) stretching and the peak

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at 1697.24 cm^{-1} resulted from C=O (side chain) stretching and a broad peak around 3419.56 cm^{-1}, indicating stretching of hydroxyl groups. All the principal peaks of simvastatin are present in drug loaded IPN microspheres, which confirm the stability of simvastatin in IPN microspheres. In the case of placebo microspheres, a broad band with less intensity compared to both Ls and PVA matrices is due to the presence of very few uncross-linked hydroxyl groups that are hydrogen bonded to various degrees. The bands appearing at 1164.92 cm^{-1} are due to the presence of an acetal group, which formed due to the reaction of glutaraldehyde with hydroxyl groups of both PVA and Ls. Thus, FTIR confirms the cross-linking reaction in addition to the formation of an IPN matrix.

Formation of microspheres and drug entrapment efficiency

In the present study, simvastatin loaded IPN microspheres of Ls and PVA were prepared using glutaraldehyde as a cross-linking agent (Table 1). The microspheres obtained were all spherical in nature with smooth surfaces as demonstrated by SEM images shown in Fig. 2 and they fell in the size range of 20.14±1.11 to 39.73±0.53 μm (Table 4). An increase in size of microspheres was also observed with the increase in ratio of polymer in the microspheres. This could be due to the fact that at higher amounts of polymer, the viscosity of the polymer solution increased, thus producing bigger droplets during emulsification that were later hardened in the presence of GA. Table 4 shows that % drug entrapment efficiency (% DEE) of the microspheres prepared using different formulation variables was in the range 62.43±0.40 to 86.65±0.52 and it depends on the GA concentration and the ratio of Ls:PVA. At lower concentrations of GA, a loose network are formed due to insufficient cross-linking, which results in higher leakage of drug from the polymer matrix, whereas at higher GA concentration, a more rigid network is formed which caused retention of more drug particles during microspheres preparation.

Equilibrium water uptake studies

Equilibrium water uptake of the cross-linked microspheres exerts an influence on their release rates[24]. The percentage equilibrium water uptake data of the cross-linked microspheres presented in Table 4 shows that as the amount of GA in the matrices (Ls:PVA=1:2) increases from 2.5 ml to 4.5 ml, the equilibrium water uptake in pH 7.4 decreases significantly from 209.13% to 154.33%. The reduction in water uptake capacity is due to the formation of a rigid network structure at the higher concentration of cross-linking. Again it was observed that formulations containing higher amounts of polymer showed lower percentages of equilibrium water uptake than formulations containing small amounts of polymer. Formulation F1 (Ls:PVA=1:2) showed higher water uptake capacity than F2 (Ls:PVA=1:3). Similarly, formulation F2 exhibited greater swelling than formulation F3 (Ls:PVA=1:4) due to the hydrophilic nature of Ls, thereby leading to higher water uptake capacity.

***In-vitro* drug release studies**

In-vitro drug release was performed in phosphate buffer saline (pH 7.4) and percentage cumulative drug release vs time data are presented in Fig. 3 to investigate the extent of cross-linking density and the ratios of Ls:PVA on the *in-vitro* release profiles of different IPN based

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formulations. Fig. 4 indicated that the formulation F4 showed a higher release rate than F7 and similarly the formulation F1 showed a higher release rate than F4 (i.e. F1 > F4 > F7). This indicates that the release was slower for those formulations in which a higher amount of GA was used compared to those where lower GA 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. The percentage cumulative drug release vs time for the microspheres prepared with different ratios of Ls:PVA loaded with simvastatin are presented in Fig. 5. The cumulative percentage released is higher in the case of F5 than F6, and similarly F4 shows higher release rates than F5 (i.e. F4 > F5 > F6). This indicates that with increase in the ratio of Ls:PVA, the swelling of the matrix decreases which leads to the slower release of drug from the matrix.

CONCLUSION

It was found that the mucilage can be successfully isolated from *Lepidium sativum* seeds using water based extraction procedure and from the physicochemical characterization it was found that the isolated mucilage can be used as a suspending agent in different pharmaceutical preparations. It was also predicted that the Ls-PVA based IPN microspheres were successfully prepared by the emulsion cross-linking method using glutaraldehyde as cross-linking agent for the effective encapsulation and controlled release of simvastatin. Microspheres with spherical shapes were produced with a narrow size distribution ranging from 20.14±1.11 to 39.73±0.53 μm. FTIR was used to confirm the formation of the IPN network. Microspheres were able to provide drug release for an extended period of time (8 h or more) in phosphate buffer saline (pH 7.4). The amount of cross-linking agent and the ratio of Ls:PVA influences the drug entrapment efficiency and release of simvastatin from microspheres. When prepared with higher extent of GA, the higher level of drug entrapment could be attained in IPN based formulation. The release of simvastatin depends on the extent of cross-linking of the matrix as well as the ratio of Ls:PVA present in the matrix.

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Abbreviations: IPN, Interpenetrating polymer network; **Ls,** *Lepidium sativum*; **PVA,** poly vinyl alcohol; **GA,** glutaraldehyde; **FTIR,** fourier transform infrared; **HMG-CoA,** 3-hydroxy-3-methylglutaryl coenzyme A; **SEM,** scanning electron microscopy; **SEI,** secondary electron image; **UV,** ultraviolet; **V_d,** volume mean diameter.

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Table 1: Formulation codes and different process variables used to prepare IPN microspheres

Formulation code	Gum: polymer ratio	Glutaraldehyde (ml)
F1	1:2	2.5
F2	1:3	2.5
F3	1:4	2.5
F4	1:2	3.5
F5	1:3	3.5
F6	1:4	3.5
F7	1:2	4.5
F8	1:3	4.5
F9	1:4	4.5

Table 2: Physicochemical characteristics of mucilage from the seeds of *Lepidium sativum*

S. no.	Tests	Observations
1	Description	Brownish white powder
2	Solubility	Soluble in hot water, insoluble in ethanol, ether, acetone and chloroform
3	Odour	Characteristic
4	Appearance	Lustrous
5	pH (1%w/v)	Neutral
6	Loss on drying (%)	8%
7	Swelling index	21.5
8	Test for carbohydrate (Mollish test, Benedict's test, Fehling's test)	+ve
9	Test for tannins	-ve
10	Test for gum and mucilage (swelling in H_2O and KOH solution)	+ve
11	Test for oils and fats	-ve
12	Test for proteins and amino acids (Biuret test, Precipitation test)	-ve
13	Test for sulphate	-ve
14	Total ash value (%)	6.0%

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15	Water insoluble ash (%)	2.5%
16	Acid insoluble ash (%)	3.0%

Table 3: Flow properties of isolated gum

S. no.	Parameters	Observations
1	Angle of repose	29.98^0
2	Carr's index	18.42%
3	True density	0.49 gm/cc
4	Bulk density	0.40 gm/cc

Table 4: Effect of cross-linking agent, Ls:PVA ratio on particle size, drug entrapment efficiency (DEE) and percentage equilibrium liquid uptake in pH 7.4 media

Formulation code	% Yield	% DEE (± SD, n=3)	Volume mean diameter (µm) (± SD, n=3)	% Equilibrium liquid uptake study in pH 7.4 media
F1	69.15	62.43±0.40	20.14±1.11	209.13
F2	71.23	69.54±0.65	22.52±0.66	195.33
F3	79.01	73.53±0.63	25.45±1.32	181.66
F4	82.27	76.89±0.16	27.91±1.33	175.33
F5	84.58	77.24±0.24	28.33±1.15	168.00
F6	83.43	79.74±0.84	30.44±0.60	161.66
F7	88.12	80.42±0.23	32.98±0.54	154.33
F8	90.17	83.14±0.66	36.10±0.73	131.66
F9	92.53	86.65±0.52	39.73±0.53	105.33

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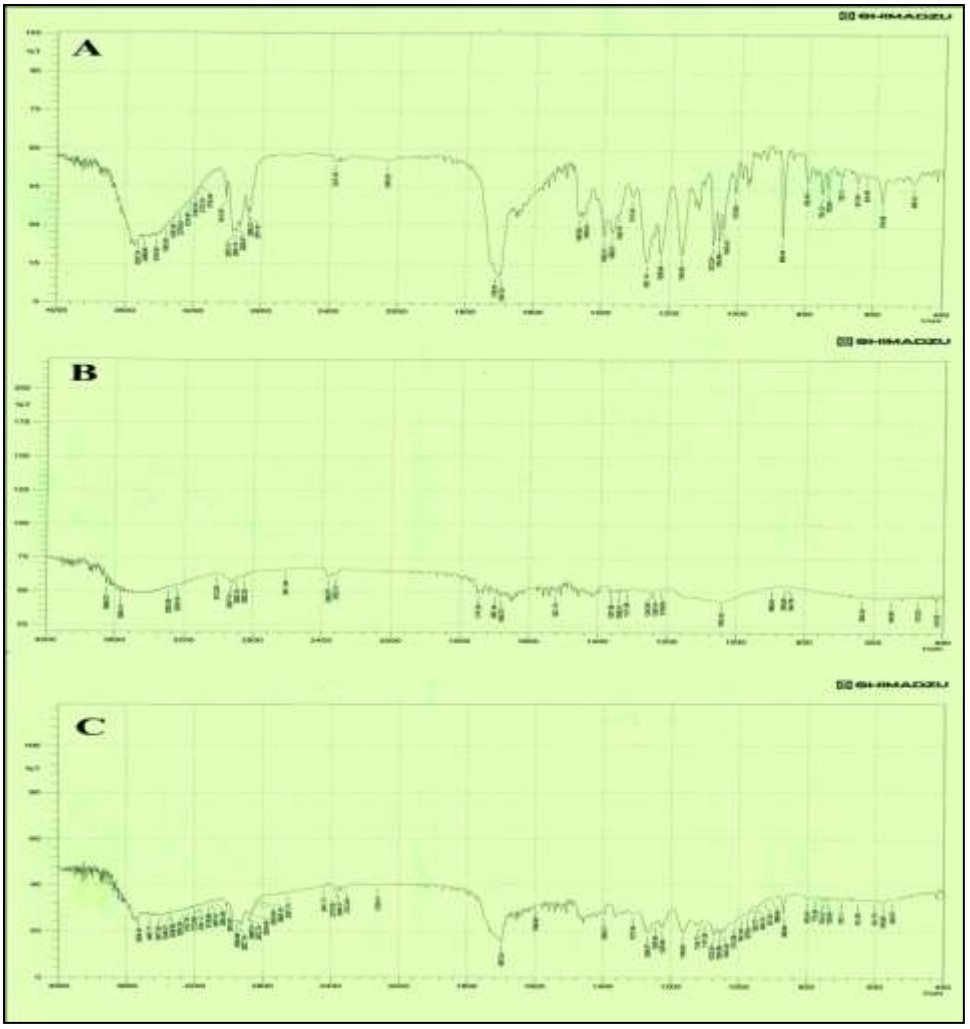

Fig. 1: FTIR spectra of (A) simvastatin (B) placebo microsphere and (C) drug loaded microsphere

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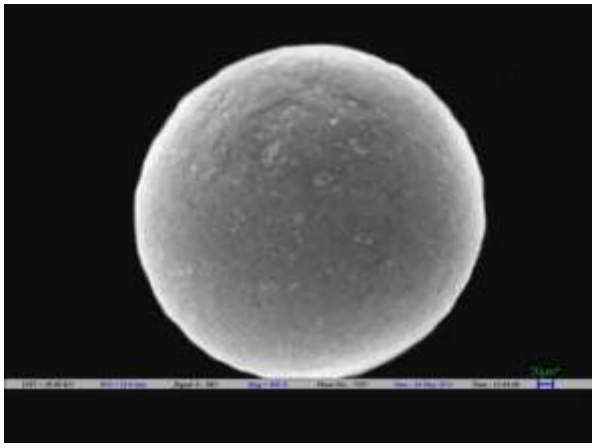

Fig. 2: SEM photograph of IPN microsphere

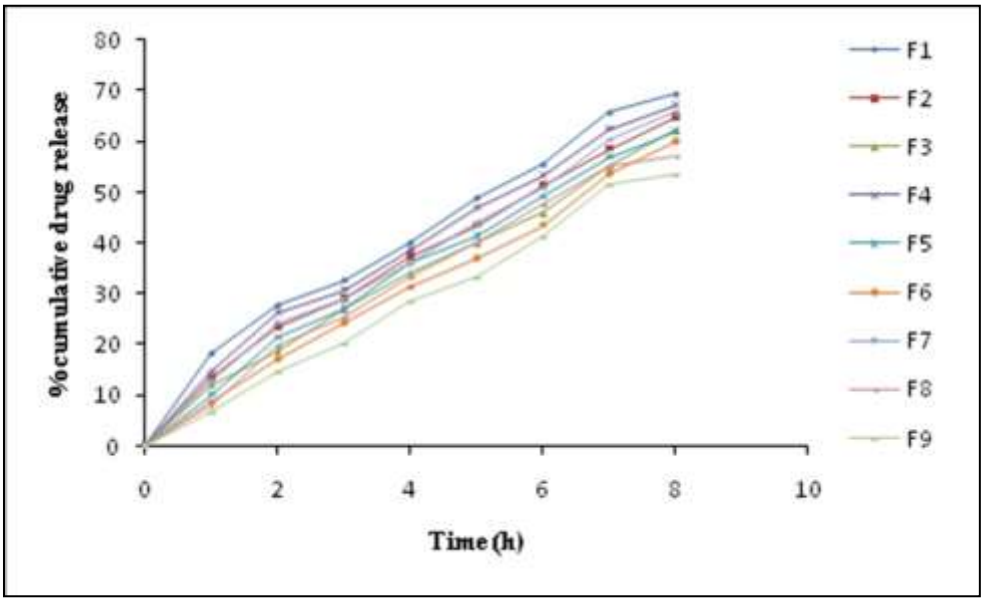

Fig. 3: *In-vitro* release profiles of different IPN formulations in pH 7.4 media

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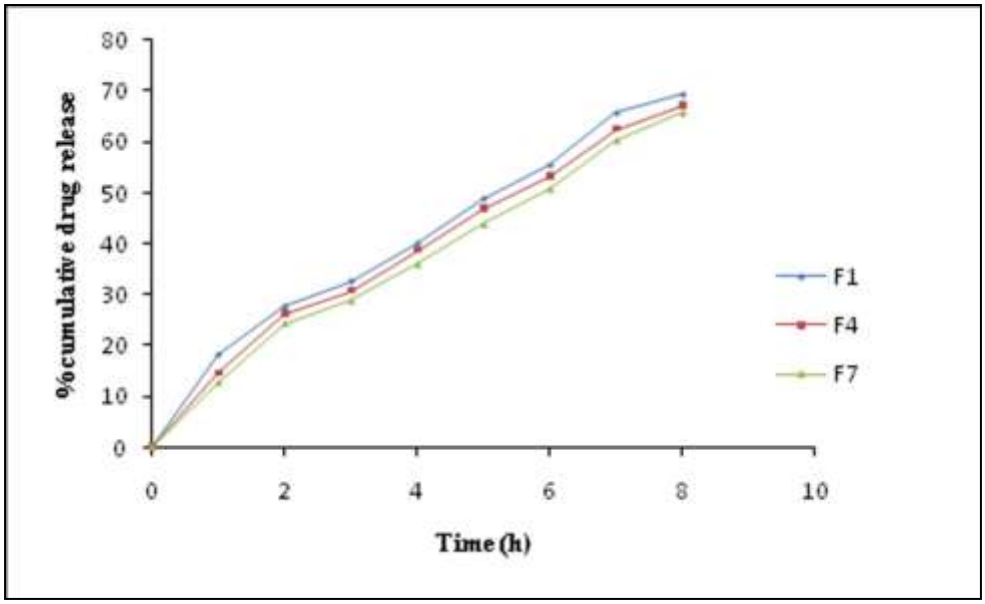

Fig. 4: Effect of cross-linking density on *in-vitro* release profiles of formulations F1, F4 and F7 in pH 7.4 media

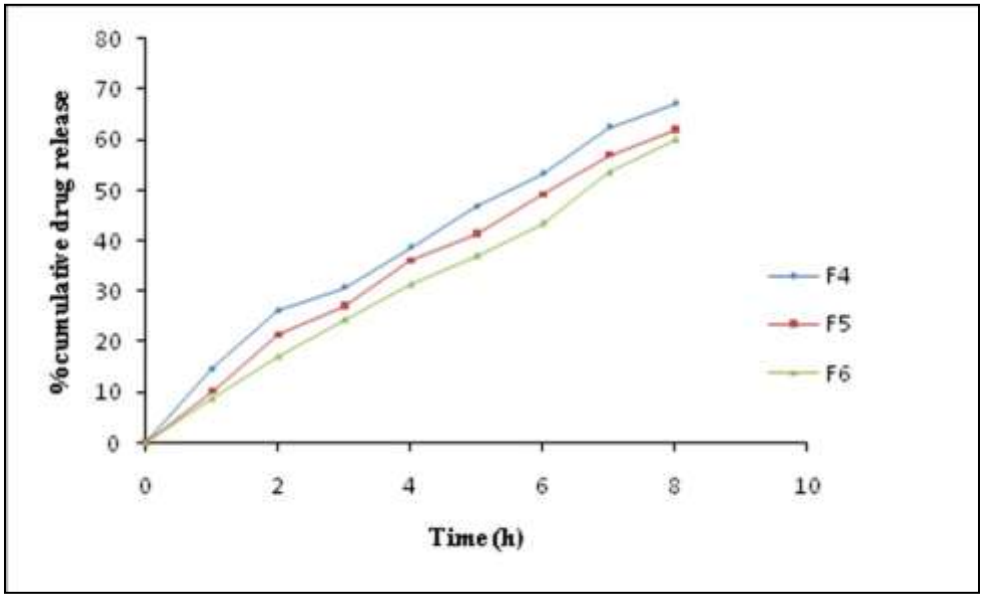

Fig. 5: Effect of Ls:PVA ratios on *in-vitro* release profiles of formulations F4, F5 and F6 in pH 7.4 media

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