American Journal of Advanced Drug Delivery

www.ajadd.co.uk

Original Article

Microspheres of Poly (vinyl alcohol) and Methyl Cellulose for the Controlled Release of Losartan Potassium and Clopidogrel Bisulphate

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Date of Receipt- 12/6/2014
Date of Revision- 17/6/2014
Date of Acceptance- 21/6/2014

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ABSTRACT

Interpenetrating network (IPN) blend microspheres of poly(vinyl alcohol) (PVA) and methyl cellulose (MC) were prepared to study their controlled release (CR) characteristics of two drugs viz., water-soluble losartan potassium (LK) and water-insoluble clopidogrel bisulphate (CB) that belong to the class of antihypertensive drugs. Microspheres (dia = 1 μm) were prepared by emulsion crosslinking method using glutaraldehyde as the crosslinking agent. Drug-loaded formulations were characterized by Fourier transform infrared (FTIR) spectroscopy to investigate the chemical interactions of drugs with the IPN matrix. The X-ray diffraction (XRD), scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and universal testing machine (UTM) were employed to characterize the developed formulations. Equilibrium swelling of the matrices was performed in pH 7.4 buffer media, while the *in vitro* release was performed in both pH 1.2 and 7.4 buffer media to understand the release profiles of the drugs in simulated stomach as well as intestinal conditions, respectively. The *in vitro* release data were analyzed using empirical equations to understand the mode of transport.

Keywords: Microspheres, Poly (vinyl alcohol), Methyl cellulose, Controlled release, crosslinking, IPN.

INTRODUCTION

In recent years, studies on biodegradable polymeric microspheres have attracted considerable attention due to their potentiality as controlled release (CR) devices for a variety of drugs.[1-4] Among the many polymers used as CR devices, poly(vinyl alcohol) (PVA) has been widely used because of its hydrophilic nature and ease of processability in addition to its pH and temperature stabilities.[5] However, its excessive swelling in the presence of water poses problem, which can be solved by modifying PVA in the form of blend,[6] graft[7] and crosslinked networks.[8] On the other hand, methyl cellulose (MC), a carbohydrate polymer, soluble in water is also biocompatible. It forms aqueous solution and has a unique property to form reversible physical gels due to hydrophobic interactions upon heating. It can also be chemically crosslinked with dialdehyde in the presence of a strong acid to convert into a hydrogel.[9]

Losartan potassium (LK) is a water-soluble having plasma half-life of 1.5-2.5 h[10] and clopidogrel bisulphate (CB) is a water-insoluble with its plasma half-life of 7-8 h. Both the drugs belong to the class of antihypertensitive drugs. Of these, losartan is a specific, nonpeptide angiotensin II receptor antagonist drug used mainly to treat hypertension. The benefit of losartan was greater in patients with atrial fibrillation (AF) than those with sinus rhythm for the primary composite endpoint (cardiovascular mortality, stroke and myocardial infarction) and for cardiovascular mortality alone. CB is an oral antiplatelet agent (thienopyridine class) to inhibit blood clots in the coronary artery, peripheral vascular and cerebrovascular diseases.[11] It helps to keep the blood platelets slippery and discourages the formation of clots, thereby improving the blood flow to the heart, brain and the body. The drug is, therefore, prescribed to reduce the risk of heart attack, stroke and serious circulation problems in people with hardening of arteries or unstable angina (dangerous chest pain) and in people, who have already suffered from heart attack or a stroke (chemical structures of LK and CB are given figure 1). Drugs having relatively short plasma half-life need suitable carrying devices.[8,12] Since, the plasma half-life of LK and CB relatively short and hence requires formulating them as CR devices.

MATERIALS AND METHODS

In this study, CR formulations of LK and CB drugs were prepared using the interpenetrating network (IPN) blend systems[12] of PVA and MC in the form of microspheres. The motivation behind this study is that the CR formulations of both these drugs have not been reported before and there is a need to suggest alternative methods of using different polymers and to develop formulations for the CR of drugs chosen. Hence, the present study attempts to develop CR formulations of LK and CB using the blend IPN microspheres of PVA and MC polymers. The microspheres were prepared by water-in-oil emulsion method and crosslinked with glutaraldehyde (GA). The formulations were characterized for their % encapsulation efficiency, release kinetics, drug polymorphism and physico-chemical interactions of the drugs with the IPN matrices. Their morphology as well as process parameters were used to investigate *in vitro* release profiles in acidic and alkaline pH media. Furthermore, the release kinetics data have been analyzed using the empirical relationships to understand the drug release mechanism.

Materials

Losartan potassium (LK) and clopidogrel bisulphate (CB) were received as

gift samples from a local drug company. Tween-80 was purchased from Loba Chemicals, Mumbai, India. Poly(vinyl alcohol) (MW = 125,000) with its degree of hydrolysis of 86-89 %, methyl cellulose (viscosity, 350-550 cPs), analytical reagent grade glutaraldehyde (GA) aqueous solution 25% (v/v), petroleum ether and liquid paraffin oil were all purchased from s.d. fine Chemicals, Mumbai, India. Water used was of high purity grade after double distillation and deionization.

Preparation of IPN microspheres

IPN microspheres of PVA and MC blends were prepared by taking each polymer in different weight ratios (see table 1) by adopting the emulsion-crosslinking method in presence of GA as a crosslinking agent.[13] Briefly, 2 wt. % of PVA (20 mL) solution was prepared by dissolving the solid PVA powder in doubly distilled deionized water and stirring until a homogeneous solution was obtained. MC was then dispersed into the PVA solution and stirred overnight to obtain a homogeneous solution. After dissolving LK in the above solution, it was slowly added to light liquid paraffin (100 g) containing 1% (w/w) Tween-80 under constant stirring (at 550 rpm) for about 15 min. To this w/o emulsion, GA containing 0.1 N HCl was added slowly and stirred for 3 h to achieve complete crosslinking. The hardened microspheres were separated by filtration, washed repeatedly with petroleum ether followed by water to remove the unreacted GA. Thus obtained solid microspheres were vacuum-dried at 40°C for 24 h and stored in a desiccator before use.

CB-containing microspheres were prepared in 2 % aqueous acetic acid solution instead of double-distilled deionized water as the aqueous phase using the same procedure as used for LK. Different formulations prepared are listed in Table no. 1 and the IPN structure is given in Scheme 1.

Fourier transforms infrared (FTIR) spectral measurements

FTIR was done using Nicolet (Model Impact 410, Milwaukee, WI, USA) to investigate the chemical interactions between the drug and IPN matrices.[14] FTIR spectra of drug-loaded formulations and pure LK as well as CB drugs were scanned between 4000 and 500 cm^{-1}. For FTIR measurements, samples were crushed with KBr and pellets were obtained by applying 600 kg/cm^2 pressure.

Differential scanning calorimetric (DSC)

DSC was performed on placebo microspheres, drug (LK or CB)-loaded microspheres as well as pure LK or CB by heating the samples from 25° to 400°C at the heating rate of 10°C/min under nitrogen atmosphere.[15]

X-ray diffraction (XRD)

Crystallinity of pure and encapsulated drugs was examined by XRD (x-Pert, Philips, UK). XRD profiles were generated for placebo microspheres, drug-loaded formulations as well as pure LK and CB drugs. Scanning was done at ambient temperature (25°C) by varying the angle 2θ up to 50°C.[15]

Scanning electron microscopy (SEM)

SEM images were taken using JEOL model JSM-840A, Japan instrument available at Indian Institute of Science, Bangalore, India. Microspheres were sputtered to form a thin gold coating of 10 nm to make them conducting. Before actual measurements, samples were placed on a copper stub and SEM images were captured at different magnifications by applying a voltage energy of 20 KV.[13]

Encapsulation efficiency

Estimation of drug concentration was made as per the protocol adopted elsewhere.[13]

The LK-loaded microspheres of known weight (~10 mg) were ground to get the powder using an agate-mortar, extracted with 50 mL of 7.4 pH buffer solution and sonicated for 30 min (UP 400s, Dr. Hielscher, GmBH, Germany). The solution was centrifuged (Jouan, model MR23i, France) to remove polymeric debris and washed twice to extract the drug completely. The clear solution was analyzed by a UV spectrophotometer (Secomam, Anthelie, France) at a fixed λ_{max} of 235 nm. Similar protocol was used for estimating the CB concentration at λ_{max} of 236 nm in pH 1.2 buffer media. The % encapsulation efficiency (EE) was calculated as before[13] using:

$$\%\text{Encapsulation efficiency} = \left(\frac{\text{Actual drug loading}}{\text{Theoretical drug loading}} \right) \times 100 \quad \ldots\ldots\ldots (1)$$

The results of % EE for various formulations along with other data are included in Table no. 1.

Swelling experiments

Equilibrium swelling of microspheres at ambient temperature was assessed gravimetrically to measure the extent of swelling in pH 7.4 buffer media.[14] In order to ensure complete equilibrium, samples were allowed to swell for about 24 h and excess surface-adhered liquid droplets were removed by blotting off with soft tissue papers. The swollen microspheres were weighed to the accuracy of ± 0.01 mg on an electronic microbalance (Mettler, AT120, Greifensee, Switzerland) and dried in a vacuum oven at 60°C for 5 h until no further weight gain was observed and % swelling was calculated as described before.[15] Experiments were performed in triplicate, but the average data are considered for graphical display and are included in Table no. 1.

Tensile strength measurements

In order to assess the mechanical strength of IPN microspheres, which could not be directly measured, we have prepared the films of PVA and MC polymers to measure Young's modulus (E) using the UTM (Model H25KS, Surrey, UK). From these results, average molecular weight (M_c) between the crosslinks and average effective crosslink density ($\overline{V}_e$) were estimated.[16] The films were casted on a glass plate in aqueous solutions of PVA and MC as per the compositions given in Table no. 2, peeled off from the glass plate and crosslinked with GA in a bath containing 0.1N HCl for 3 h, which is the same used to prepare the microspheres. The dried films at ambient temperature were used in UTM by cutting appropriate size specimen of 10 mm width and 100 mm length.

In actual measurement, two ends of the specimen were placed between upper and lower jaws of the instrument, leaving a film length of 50 mm in between two jaws. Extension speed of the instrument was maintained at 10 mm/min. Film thicknesses were measured by a micrometer screw gauge, which were found to be 0.2 ± 0.02 mm. The purpose is to measure mechanical properties of the formulations, which cannot be done for microsphere geometry, but to understand closely their stability, we have used films prepared under identical conditions except the addition of GA, as we assume that this would not change the drug release kinetics drastically.

In vitro release experiments

CB is soluble in alcohols, acetic acid and best in methanol, since it has a pH-dependent solubility and almost cannot be dissolved in acetone, ethyl acetate, ether and water. The release of CB was performed in pH 1.2 and 7.4 buffer media, since it is slightly soluble in basic media, resulting in a slower release compared to LK. Drug release

from the IPN microspheres at different % drug loadings, polymer blend compositions and different extent of crosslinking were investigated in 0.1N HCl aqueous media initially for 2 h, followed by phosphate buffer at pH 7.4 until the completion of dissolution process. These experiments were performed in triplicate using a tablet dissolution tester (LabIndia, Mumbai, India) equipped with eight baskets (glass jars) at the stirring speed of 100 rpm.

Weighed quantity of each sample was placed in 500 mL of dissolution media maintained at the physiological temperature of 37°C. At regular intervals of time, sample aliquots were withdrawn and analyzed by a UV spectrophotometer (Secomam, Anthelie, France) at the fixed λ_{max} of 235 nm for LK and 236 nm for CB. The already withdrawn sample media was replenished by adding 5 mL of fresh solvent to maintain the sink condition. Triplicate data were collected and *in vitro* release curves were smoothened through the average experimental points, giving the standard deviations of around ±3 % for all the formulations. % Cumulative Release of drug was calculated using:[16]

$$\% \text{ Cumulative Release} = \left(\frac{\text{Amount of drug released}}{\text{Total amount of drug taken for release study}} \right) \times 100 \quad \ldots\ldots\ldots (2)$$

Drug release kinetics

In order to describe the kinetics of drug release characteristics from the formulations, the following mathematical equations[16,17] were employed:

Korsemeyer–Peppas $M_t/M_\infty = k\,t^n$ (3)

The zero order $Q = Q_0 - K_0 t$ ……. (4)

First order $\ln Q = \ln Q_0 - K_1 t$ …... (5)

Higuchi square root $M_t = K_H\, t^{1/2}$ .. (6)

Hixson-Crowell cube root

$$Q^{1/3} = Q_0^{1/3} - K_c\, t \quad \ldots (7)$$

where Mt and M∞ are the amount of drug released at time, t and at infinite time, respectively; Q is the amount of drug remaining at time, t; Q0 is the amount of drug remaining at t = 0; k, K0, K1, KH and KC are the release kinetics constants obtained from the linear curves of Korsmeyer–Peppas, zero-order, first-order, Higuchi and, Hixson–Crowell cube root equations, respectively.

RESULTS AND DISCUSSION

Fourier transform infrared spectral measurements

FTIR spectra of drug-loaded microspheres and pure drugs (LK or CB) were all taken to investigate the stability of LK or CB after encapsulation. Fig. 2 displays the FTIR spectra of (a) placebo microspheres, (b) LK-loaded microspheres, (c) pure LK, (d) CB-loaded microspheres and (e) pure CB drug. In case of LK, a broad band observed at 3380 cm^{-1} is attributed to N-H stretching vibrations. The two bands observed at 2924 cm^{-1} and 2855 cm^{-1} represent the presence of C-H aliphatic stretching vibrations. The band due to aromatic C=C stretching vibrations is observed at 1634 cm^{-1}; the two bands appearing at 1461 cm^{-1} and 1423 cm^{-1} are assigned to $–CH_2$ and $–CH_3$ bending vibrations, respectively. Aromatic C–N stretching vibrations appear at 1257 cm^{-1} and 1358 cm^{-1}, while the band at 668 cm^{-1} is due to C–Cl bond.

In case of CB, the band due to aromatic C–H stretching vibrations appears at 3119 cm^{-1} and those at 2925 cm^{-1} and 2854 cm^{-1} are due to C-H aliphatic stretching vibrations. The bands at 1401 cm^{-1} and 723 cm^{-1} are the representative of $–CH_3$ and =C-H bending vibrations, respectively. A band at

1613 cm^{-1} corresponds to aromatic C=C stretching, while the region 2500–2550 cm^{-1} is attributed to the stretching vibrations of the bonded N^{+}-H, due to salt formation between ternary nitrogen of clopidogrel and –OH of hydrogen sulphate. A strong band due to C=O stretching vibrations appears at 1751 cm^{-1}, while the band associated with C–O stretching appears at 1187 cm^{-1} and that at 620 cm^{-1} is due to the presence of C–Cl bond.

In case of placebo microspheres, all the characteristic bands of both PVA and MC are observed in addition to a new band at 1018 cm^{-1} due to the presence of acetal group formed from the reaction of GA with hydroxyl groups of MC and PVA. Thus, FTIR confirms the successful crosslinking of PVA/MC IPN matrix with GA.[13] For drug-loaded microspheres, all characteristic peaks of the drugs are observed in addition to bands observed for placebo microspheres, indicating the chemical stability of both LK and CB drugs even after encapsulation, suggesting the absence of chemical interactions between the drugs and the polymer matrix.

Differential scanning calorimetric

Molecular state of drug in the polymer matrix is important to understand its release characteristics. DSC thermograms of (a) placebo microspheres, (b) LK-loaded microspheres, (c) pure LK, (d) CB-loaded microspheres and (e) pure CB are presented in Fig. 3. In the case of pure LK, DSC showed two endothermic peaks at 93°C and 272°C, while for CB, three endothermic peaks are observed at 178°C, 209°C and 227°C. The endothermic peaks after melting are attributed to the thermally-induced decomposition of drugs. Thermogram of the placebo microspheres showed a broad peak at 90°C due to endothermic transition of the polymer matrix.[13] Also, the drug-loaded microspheres exhibit similar profiles as that of placebo, but no characteristic peaks of LK or CB are observed, indicating their amorphous nature even after the formulation.

X-ray diffraction

X-ray diffractograms of (a) placebo microspheres, (b) LK-loaded microspheres, (c) pure LK, (d) CB-loaded microspheres and (e) pure CB are presented in Fig. 4. The LK has many peaks in the region of 2θ =5.85˚ to 27.35˚ in addition to high intensity peak observed at 2θ =13.3˚. However, diffraction patterns of CB have many peaks in the 2θ region of 12˚ to 27˚, while a high intensity peak at 2θ of 21.7˚ is also present due to its crystalline nature. All these peaks disappear in the LK-loaded and CB-loaded microspheres, but only the peaks observed in placebo microspheres are observed, indicating that no crystals of the drugs are found in the drug-loaded formulations because of the absence of crystalline peaks.

Scanning electron microscopic

Typical SEM images of group of microspheres taken at 4,000X and 7,5000X magnifications displayed in Fig. 5 for LK or CB-loaded microspheres are almost spherical with their sizes < 1 μm.

Encapsulation efficiency

To develop drug-loaded formulations, it is important to achieve high EE, to improve the effectiveness of the formulated medication. As reported previously,[18] EE values are dependent on process variables such as drug-polymer ratio, IPN blend composition and extent of crosslinking. Results presented in Table no. 1 display these effects. With decreasing IPN compositions from 90 to 70 wt. % of PVA, at constant LK loading of 10 wt. % and 5 mL of GA, the EE values decrease due to increase in hydrophilicity of the IPN matrix.

A reverse trend is observed in case of CB i.e., EE increased with increasing amount of MC in the matrix due to increase in the size

of the microspheres with increasing MC, offering higher EE values. On the contrary, for IPN composition of 90 wt. % PVA, keeping LK or CB at a constant loading of 10 wt. % and by varying the amount of GA from 2.5 to 7.5 mL, a decrease in EE is observed, due to increase in crosslink density, making the microspheres rigid due to a reduction in free volume space, giving lower EE. Thus, in both the formulations that contained either LK or CB-loaded microspheres, the EE values decrease with increasing % drug loading, suggesting the dependence of EE values on process variables.[19] For all formulations of this study, higher EE values are observed for CB-containing formulations than LK-containing formulations, due to lower solubility of CB in water than LK.

Swelling studies

Drug release rates are influenced by the equilibrium swelling of crosslinked matrices.[20,21] As shown in Table no. 1, with increasing concentration of GA from 2.5 to 7.5 mL, equilibrium swelling decreased significantly from 294 % to 184 % for LK and 316 % to 136 % in case of CB-loaded formulations. Such a reduction in swelling is due to the formation of a rigid IPN matrix at high crosslink density i.e., 7.5 mL of GA. Notice that the formulations containing high amount of MC exhibit high swelling i.e., formulation LK-7 containing 30 wt. % of MC exhibit higher % equilibrium uptake than LK-6 (20 wt. % of MC) and LK-1 (10 wt. % of MC); similarly, formulation CB-7 (30 wt. % of MC) exhibits higher equilibrium uptake than CB-6 (20 wt. % of MC) and CB-1 (10 wt. % of MC), due to increased hydrophilicity of the matrix induced by the presence of MC; the presence of MC in the blend matrix make the matrix sorb higher amount of water than PVA component. In case of water-soluble LK-loaded microspheres, equilibrium swelling increased with increasing drug loading, whereas for water-insoluble CB-loaded microspheres, no systematic variations with respect to drug loading are observed.

Molar mass between crosslinks and effective crosslink density

The average molar mass ($\overline{M}_c$) between network crosslinks and the effective crosslink density ($\overline{V}_e$) of the formulations (F1 to F5) have been calculated[22-24] from Young's modulus ($\overline{E}$) measured on the films of polymers. These data compiled in Table no. 2 suggest that Young's modulus of the blend polymers are affected by the blend ratio and the amount of GA added. For instance, at a constant GA of 5 mL in the blend containing 90, 80 and 70 % PVA and 10, 20, and 30 % MC, Young's modulus decreased, but $\overline{M}_c$ increased systematically, suggesting the effect of added MC in the blend; subsequently, $\overline{V}_e$ values for these blend matrices decrease from 42 to 14. Conversely, keeping the blend ratio constant (90 % PVA + 10 % MC) and increasing the amount of GA from 2.5 to 7.5 mL, Young's modulus increased, but the $\overline{M}_c$ values decreased; however, $\overline{V}_e$ values increased from 34 to 53, indicating the effect of increased concentration GA in the matrix (F5).

In vitro release studies

In vitro release data are influenced by the extent of crosslinking as well as blend ratio of the IPN matrix as discussed under separate headings.

Effect of crosslinking

For assessing the CR trends, IPNs were tested for *in vitro* release of LK and CB drugs. Fig. 6 and Fig. 7 display the plots of % cumulative release of LK and CB in buffer media of pH 1.2 and pH 7.4 at 37°C from the IPNs prepared using the solutions containing 2.5, 5 and 7.5 mL of GA for LK-4, LK-1 and LK-5 as well as CB-4, CB-1 and CB-5 formulations. A clear-cut dependence of drug release is observed on the extent of

crosslinking. For instance, LK-4 and CB-4 formulations having lower concentration (2.5 mL) of GA exhibit higher release than those containing higher concentration (7.5 mL) of GA. The loosely formed IPN network at lower crosslinking released both the drugs much faster than the tightly formed IPN matrices at higher crosslinking. Further, notice that the release of LK during the first two hours is quite moderate, but is much faster (i.e., 80 % of LK was released) in 6-8 h at lower extent of crosslinking. However, at higher crosslinking, the release is much slower with a small amount of drug release up to 60 %. In general, LK was released faster than CB during the early stages followed by a gradual release and leveled off at 8 h for LK and 12 h for CB. Thus, LK or CB-loaded formulations containing different concentrations of GA in the IPN matrix controls the drug release. Notice that with CB-4, CB-1 and CB-5 formulations, cumulative release vs time plots did not attain equilibrium even up to 12 h and the release follows the non-Fickian trend. The % cumulative release of CB is quite lower than LK, due to the insoluble nature of CB.

Effect of blend ratio

The effect of blend ratio on cumulative release of drugs (LK or CB) in pH 1.2 (acidic) and pH 7.4 (alkaline) at 37°C is displayed, respectively in Fig. 8 and Fig. 9. Of the three compositions of IPN matrices, the amount of MC present in the blend IPN controls the release of both LK and CB. In case of LK-1, LK-6 and LK-7 formulations (see figure 8), the release in pH 1.2 media followed a step function up to 2 h, suggesting that the presence of MC in the IPN matrix allows water to penetrate into the IPN producing the first step functional release of LK, while in pH 7.4, the % cumulative release increased up to 5 h at which equilibrium was reached (see figure 8). Here, the hydration force between chains of the two polymers in aqueous media is responsible for the observed swelling and quick attainment of equilibrium by releasing nearly 80 % of LK. However, in case of CB, a gradual swelling of IPN facilitates the release of CB because its diffusion coefficient in the swollen region of the IPN matrix is relatively high, thus showing a continuous release of CB even up to 12 h.

Drug release kinetics and empirical correlations

In order to confirm the release trends of the drugs, *in vitro* release data of Fig. 6-9 have been analyzed by the least-squares method using eqs. (3-7) at 95 % confidence level. The values of n and k along with the estimated correlation coefficients, r are compiled in Table no. 3. For values of n = 0.5, drug diffuses and releases out of the IPN matrix following the Fickian diffusion trend. For values of $n > 0.5$, anomalous or non-Fickian transport is operative. Thus, the magnitude of n characterizes the release mechanism, which depends on the nature of the polymer. In case of solute release from the swellable polymer matrices, if fractional release data gives n = 0.5, then transport is a Fickian. If n = 1.0, transport follows the Case-II, while the intermediary values of n between 0.5 and 1.0 are suggestive of the anomalous transport.[16]

In the present study, n values of LK-loaded microspheres vary between 0.60 and 0.83, while for CB-loaded microspheres, n values vary between 0.52 and 0.70, both suggesting the anomalous transport..

The release of LK and CB described by the diffusion and kinetics models reveals that the kinetics of LK release follows closely to the Higuchi square root equation, indicating the release to be diffusion-controlled, whereas the release of CB follows the first order kinetics, indicating that the rate of dissolution is dependent on the concentration of dissolved drugs. The results

of release kinetics given in Table no. 3 indicate that for formulations containing different amounts of PVA and MC as well as varying amounts of crosslinking agent, no systematic dependence on *n* and *k* values are observed. Also, the release of both LK and CB in the stomach and intestinal stimulated media exhibit different release kinetics.

CONCLUSION

This work reports on the successful development of glutaraldehyde crosslinked IPN microspheres of PVA with MC to encapsulate water-soluble (LK) and water-insoluble (CB) drugs. It is observed that crosslink density of the matrices is significantly affected by the concentration of GA as well as the MC content of the IPN. FTIR confirmed the formation of IPN with no chemical interactions of both LK and CB with either of the individual polymers or the IPN blend matrix. The EE values of 77 % and 97 % are observed, respectively for LK-loaded and CB-loaded formulations. The % swelling results are correlated with crosslink density computed from Young's modulus data. The release of water-soluble LK and water-insoluble CB drugs was described by the diffusion and kinetics models. The kinetics of LK release follows the Higuchi square root equation, indicating the diffusion-controlled process, whereas the release of CB follows the first order kinetics, indicating that transport is dependent on the concentration of the encapsulated drugs.

ACKNOWLEDGMENTS

Miss. A. G. Sullad and Prof. L. S. Manjeshwar thank the University Grants Commission (UGC), New Delhi, India (KU/SCH/UGC/RFSMS/2008-09). Prof. T. M. Aminabhavi thanks the All India Council for Technical Education [AICTE, F.No. 1-51/RIFD/EF(13)/2011-12], New Delhi, India for the award of Emeritus Fellowship.

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Table 1. Formulation parameters of IPNs of PVA and MC, % encapsulation efficiency (EE) and % equilibrium swelling

Formulation Codes	PVA (% w/w)	MC (% w/w)	LK loading (%)	CB loading (%)	GA (mL)	% EE	% Swelling
LK-loaded formulations							
LK-1	90	10	10	-	5	66	197
LK-2	90	10	20	-	5	38	212
LK-3	90	10	30	-	5	33	227
LK-4	90	10	10	-	2.5	77	294
LK-5	90	10	10	-	7.5	56	184
LK-6	80	20	10	-	5	56	218
LK-7	70	30	10	-	5	52	303
CB-loaded formulations							
CB-1	90	10	-	10	5	84	299
CB-2	90	10	-	20	5	48	507
CB-3	90	10	-	30	5	29	177
CB-4	90	10	-	10	2.5	92	316
CB-5	90	10	-	10	7.5	76	136
CB-6	80	20	-	10	5	95	381
CB-7	70	30	-	10	5	97	423

Table 2. Young's modulus (E), molar mass between crosslinks (M_c), effective crosslink density (V_e) data for different blend compositions of IPNs

Formulation codes	PVA (% w/w)	MC (% w/w)	GA (mL)	*E* (MPa)[(a)]	$\overline{M}_c = \frac{3\rho RT}{E}$	$\overline{V}_e = \frac{\rho}{M_c}$
F1	90	10	5	0.314	24	42
F2	80	20	5	0.126	58	17
F3	70	30	5	0.107	68	14
F4	90	10	2.5	0.250	29	34
F5	90	10	7.5	0.390	19	53

[(a)] results are reproducible within $\pm$ 3 % standards errors.

ρ – density of polymer solution; R – molar gas constant; T – temperature in Kelvin

Table 3. Analysis of drug release kinetics using Korsemeyer-Peppas, First order and Higuchi models

Formulation codes[(a)]	n from (eq. 1)	r^2 from (eq. 1)	Higuchi model from (eq. 6)	First order model from (eq. 5)
LK-loaded formulations				
LK-1	0.67	0.940	K_H = 2.741 r^2 = 0.929	
LK-2	0.83	0.967	K_H = 3.273 r^2= 0.926	
LK-3	0.74	0.966	K_H = 3.493 r^2 = 0.939	
LK-4	0.80	0.972	K_H = 3.307 r^2 = 0.949	
LK-5	0.73	0.956	K_H = 2.628 r^2 = 0.896	
LK-6	0.61	0.876	K_H = 2.969 r^2 = 0.913	
LK-7	0.60	0.949	K_H = 3.196 r^2 = 0.948	
CB-loaded formulations				
CB-1	0.60	0.963		K_1 = 0.040 r^2 = 0.992
CB-2	0.63	0.981		K_1 = 0.045 R^2 = 0.993
CB-3	0.70	0.977		K_1 = 0.053 R^2 = 0.994
CB-4	0.60	0.980		K_1 = 0.043 R^2 = 0.991
CB-5	0.53	0.826		K_1 = 0.034 R^2 = 0.984
CB-6	0.63	0.994		K_1 = 0.046 R^2 = 0.990
CB-7	0.52	0.988		K_1 = 0.054 R^2 = 0.983

[(a)]as given in Table no.1

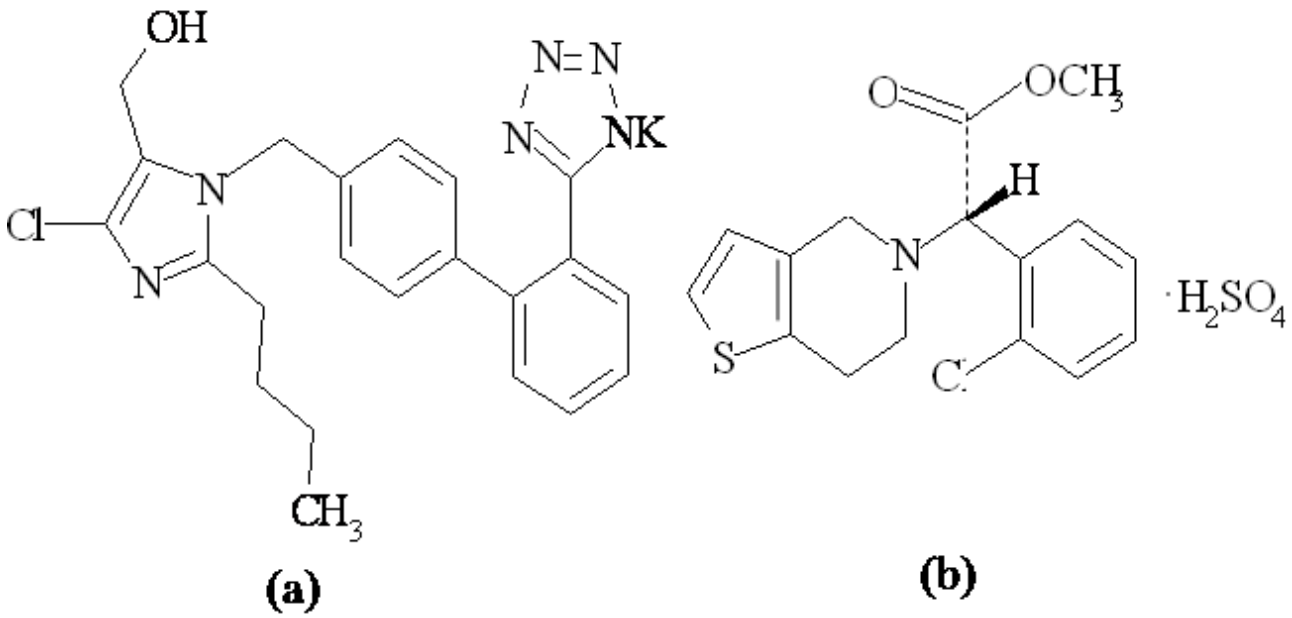


Figure 1. Chemical structures of (a) LK and (b) CB drugs

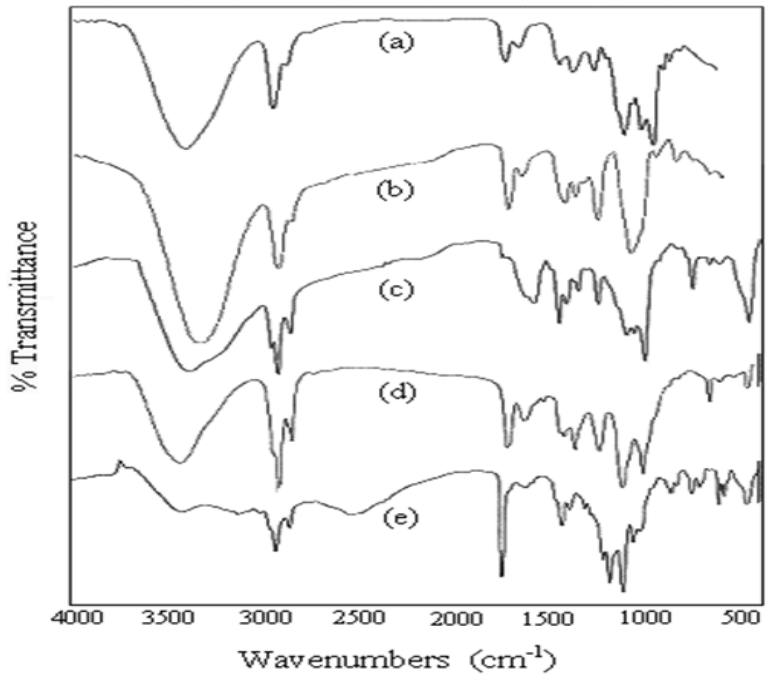


Figure 2. FTIR spectra of (a) placebo microspheres, (b) LK-loaded microspheres (LK-1), (c) pure LK, (d) CB-loaded microspheres (CB-1) and (e) pure CB

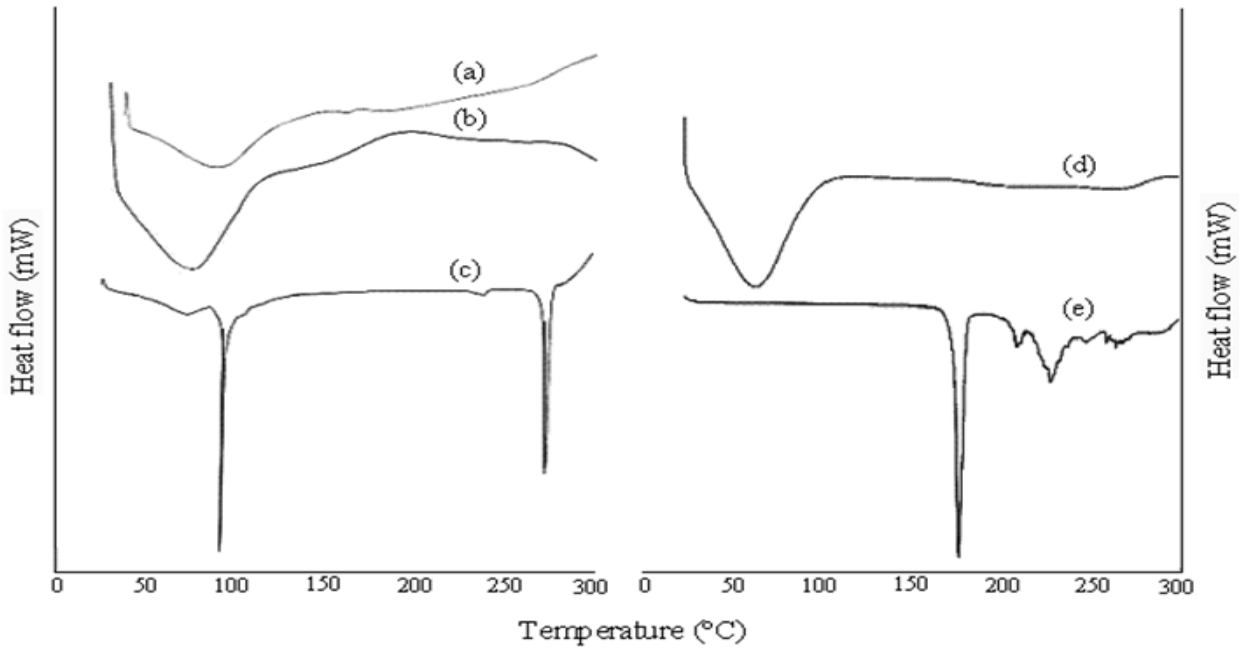


Figure 3. DSC thermogram of (a) placebo microspheres, (b) LK-loaded microspheres (LK-1), (c) pure

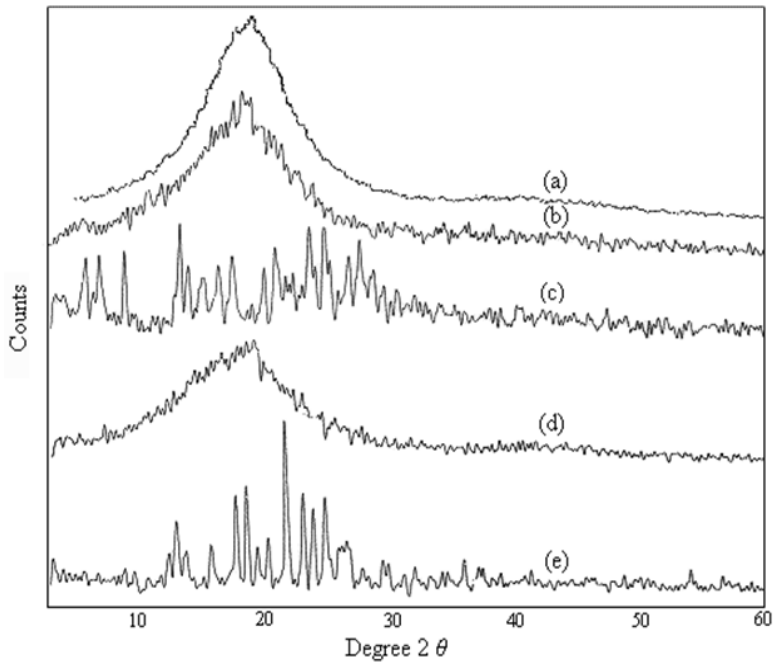


Figure 4. XRD spectra of (a) placebo microspheres, (b) LK-loaded microspheres (LK-1), (c) pure LK, (d) CB-loaded microspheres (CB-1) and (e) pure CB

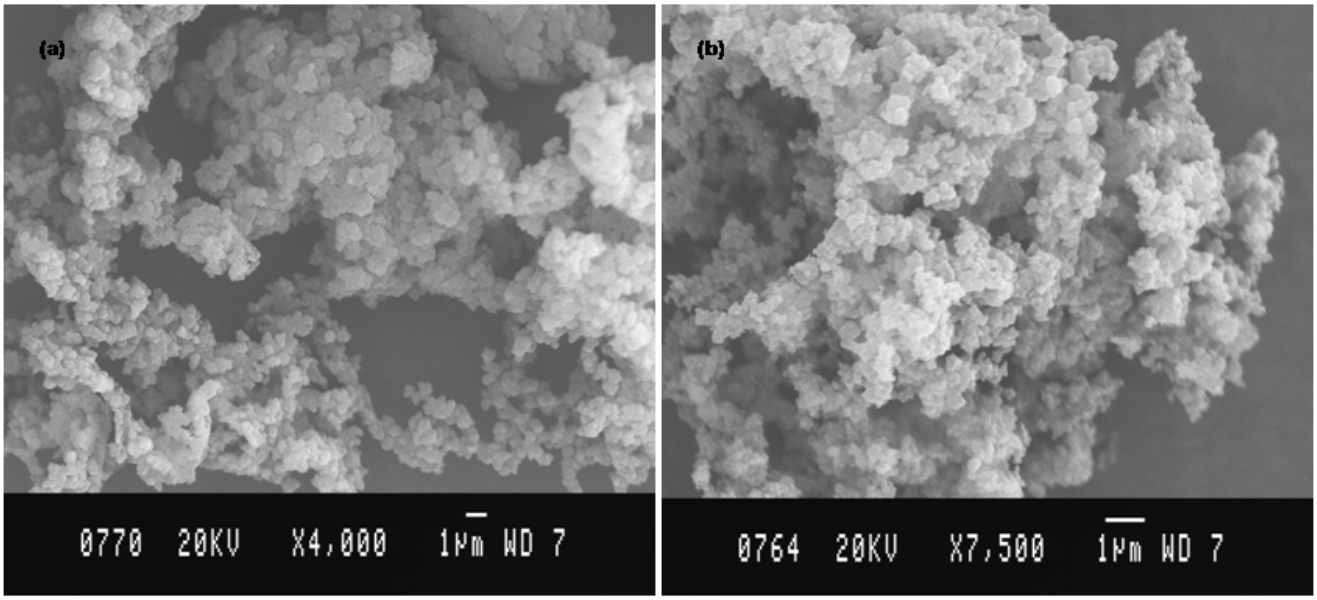


Figure 5. SEM image of (a) group of LK-loaded microspheres (LK-1) and (b) group of CB-loaded microspheres (CB-1)

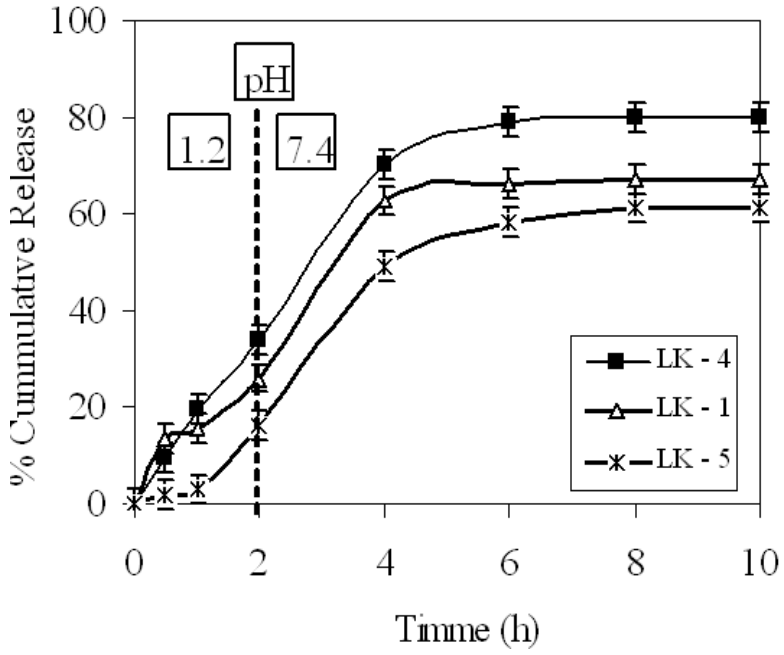


Figure 6. Effect of crosslinking on cumulative release for formulation LK-4 (2.5 mL GA), LK-1 (5 mL GA) and LK-5 (7.5 mL GA) at 37°C

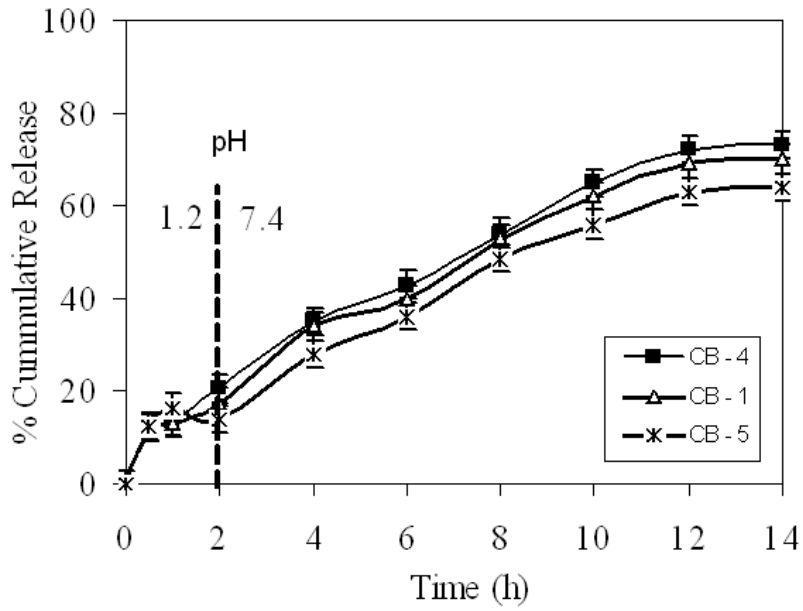


Figure 7. Effect of crosslinking on cumulative release for formulation CB-4 (2.5 mL), CB-1 (5 mL) and CB-5 (7.5 mL) at 37°C

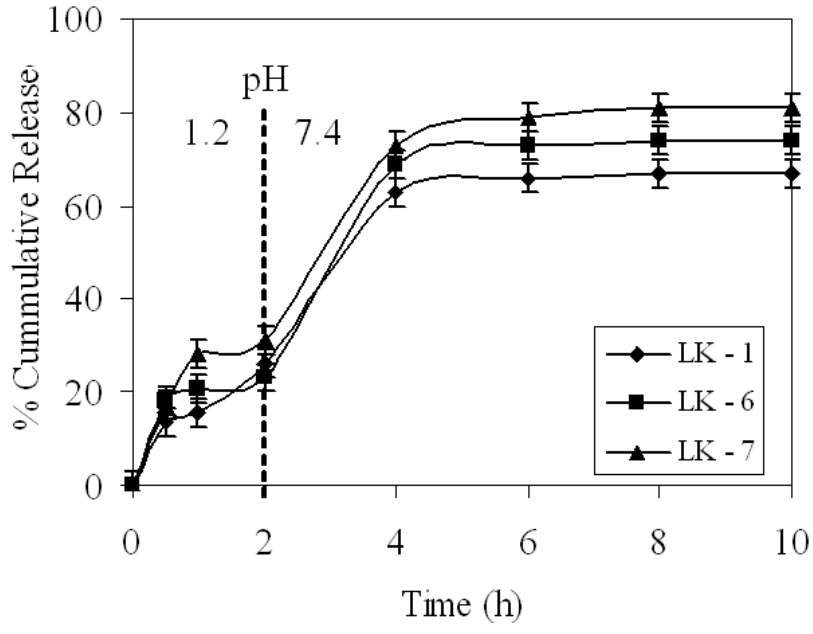


Figure 8. Effect of IPN ratio of drug release for formulation LK-1 (10 wt. % MC), LK-6 (20 wt. % MC) and LK-7 (30 wt. % MC) with constant (5 mL GA) at 37°C

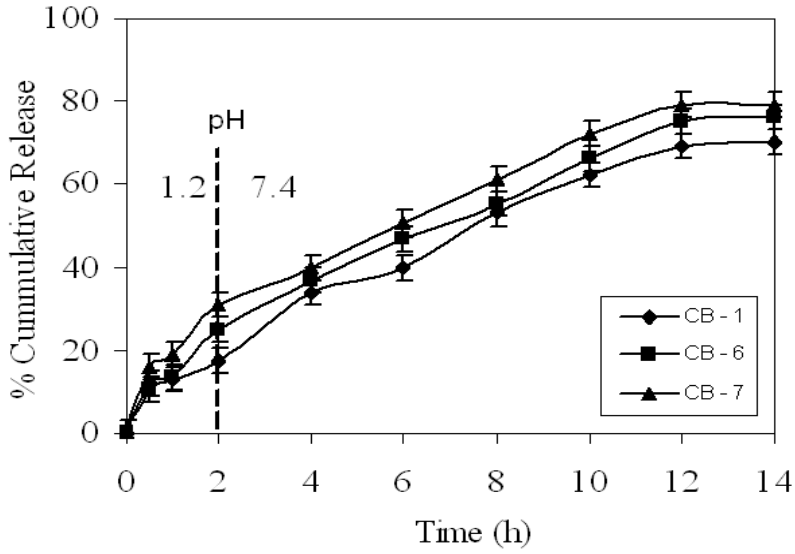
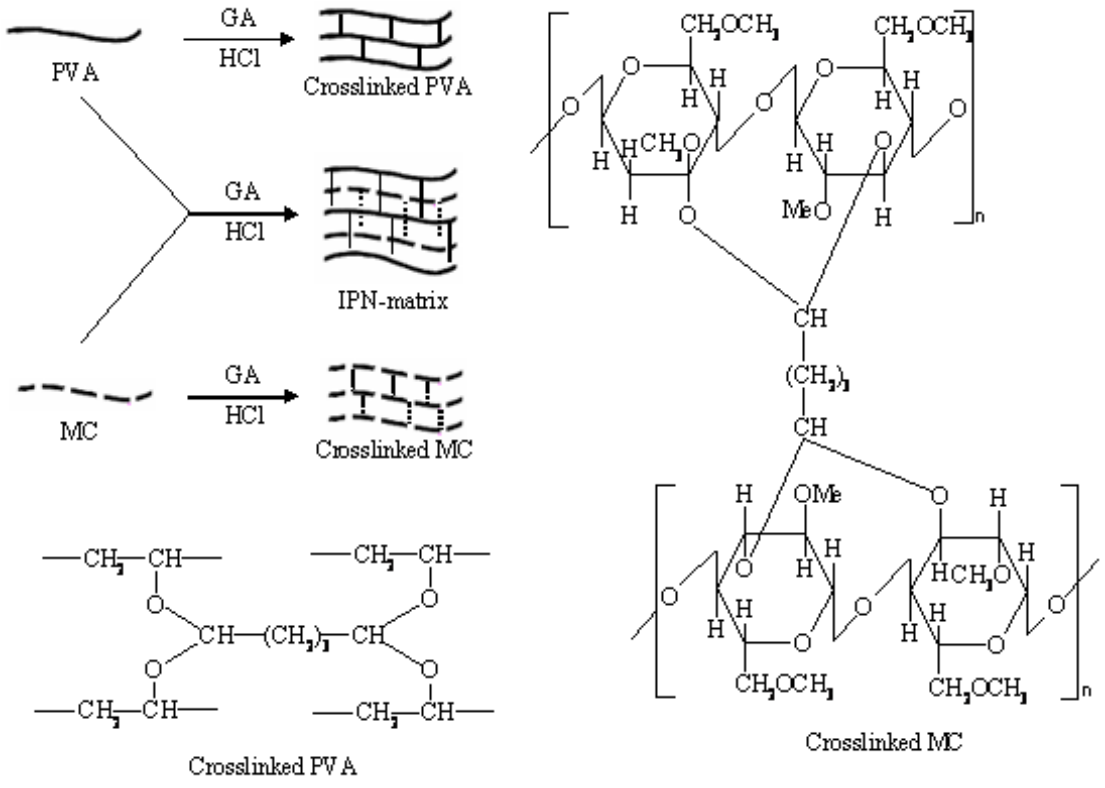


Figure 9. Effect of IPN ratio of drug release for formulation CB-1 (10 wt. % MC), CB-6 (20 wt. % MC) and CB-7 (30 wt. % MC) with constant (5 mL GA) at 37°C



Scheme 1: Formulation of IPN structure