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# INTERPENETRATING POLYMER NETWORK MICROSPHERES OF POLY (VINYL ALCOHOL)/XANTHAN GUM FOR CONTROL RELEASE OF VERAPAMIL HYDROCHLORIDE

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## ABSTRACT

Xanthan gum(XG) and Poly (vinyl alcohol) (PVA) interpenetrating polymer network(IPN) microspheres were prepared by water in oil emulsion method, loaded with Verapamil Hydrochloride (VMHCl) drug further crosslinked with glutaraldehyde (GA). These microspheres were prepared with various ratios of XG, PVA, drug, cross linker and these were characterized with various techniques. The prepared microspheres with loose and rigid surfaces were evidenced by scanning electron microscopy (SEM).Fourier transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD) analysis confirmed the IPN formation. Differential scanning calorimetry (DSC) study was performed to understand the dispersion nature of drug after encapsulation. *In vitro* dissolution experiments were performed in pH 7.4 buffer medium at 37°C. All the formulations exhibited satisfactory physicochemical and in vitro release characteristics. Release data indicated a non-Fickian trend of drug release from all the formulations. Based on the results, this study suggests that VMHCl loaded XG/PVA IPN microspheres were suitable for sustained release application.

**Keywords:** Xanthan gum, Poly (vinyl alcohol), Interpenetrating Polymer Network, Verapamil Hydrochloride, Glutaraldehyde, Drug Delivery

## 1. INTRODUCTION

Drug delivery research is primarily focused on targeted delivery of the drug to the desired organ system to minimize toxicity and maximize therapeutic efficacy. Polymeric technologies have been refined over past several years and currently great interest has been focused on the development of novel drug delivery systems. In recent years, carbohydrate and biodegradable hydrophilic polymers have been extensively used to develop controlled release (CR) formulations of drugs having short plasma life. Among the various polymers employed, hydrophilic biopolymers are quite suitable because they are non-toxic and acceptable by the regulating authorities [1-3].

Such naturally abundant carbohydrate polymers, though exhibiting some limitations in their reactivity and processibility, have still been used after being modified by crosslinking, blending, etc. The chemical and physical combination methods and properties of multi polymers have been of great practical and academic interest for the controlled release of drugs and proteins [4], because they provide a convenient route for the modification of properties to meet specific needs.

Many studies have been made in the literature to overcome these shortcomings by chemical and physical alterations of such natural carbohydrate polymers. Among the different polymers used to prepare controlled release dosage forms, development of hydrogels and interpenetrating polymer network (IPN) structures have received greater attention as they increase the phase stability and enhance the mechanical properties of the final product [5]. Better mechanical properties of IPN make it suitable for microspheres preparation for the controlled delivery of drugs [6]. 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.

Among the many polymers used as CR devices, PVA, a water-soluble hydrophilic polymer, has been used in many practical applications due to its excellent chemical resistance, good physical properties, biodegradability, biocompatibility, ease of processability in addition to its pH and temperature stabilities [7] It has mechanical strength and high elasticity and swells upon immersion in water.PVA gels crosslinked with glutaraldehyde [8], glyoxal or borate have been proposed as drug delivery

carriers. In these gels, the drug is able to be released fast or slowly due to the gel's high or low swelling ratio upon immersion in water.

Xanthan gum, a natural anionic polysaccharide produced by the bacterium Xanthomonas campestris, is used in, cosmetics, agriculture, textiles, pharmaceutical and petroleum industries [9-10]. On the basis of short-term and long-term feeding studies, XG was cleared by the US Food and Drug Administration (FDA) in 1969 permitting its use in food products without any specific quantity limitations. The primary structure of this naturally occurring polymer consists of 1, 4 linked β-D-glucose residues, having a tri saccharide side chain of β-D-mannose β- D-glucuronic acid-α-D-mannose attached to alternate D-glucose units of the main chain [11].

Verapamil hydrochloride, a calcium channel blocker, is weakly basic in nature and demonstrates poor bioavailability in the small intestine because of pH-dependent solubility (poorly soluble at high pH values, highly soluble at low pH values) [12]. It has been widely used in treatment of arrhythmia, angina and hypertension [13]. The plasma half-life of verapamil hydrochloride is 4±1.5 hrs, which necessitates multiple dosing. It is approximately 90% absorbed from the gastrointestinal tract but is subject to considerable first pass metabolism and its bioavailability is around 20-30% [14].

As there are no reports in literature with regard to VMHCl drug loaded XG/PVA polymer matrix, the authors had chosen the present work for a novel drug release study and their preparation, swelling, in vitro release studies and the results are presented here.

## 2. EXPERIMENTAL

### 2.1. Materials

Xanthan gum (XG, food grade) was obtained from Loba Chemie Private Limited, Mumbai, India. Poly (vinyl alcohol) (1,25,000 M wt), light liquid paraffin oil, glutaraldehyde, Hydrochloric acid, n-hexane all are analar grade samples used and were purchased from SD fine chemicals, Mumbai, India. Double distilled water was used in all the experiments of the present work.

### 2.2. Preparation of IPN microspheres

XG and PVA IPN microspheres loaded with Verapamil hydrochloride were prepared by water-in-oil (w/o) emulsion crosslinking method [15]. A known amount of XG (2 g) and PVA (2 g) was dissolved separately in 100 mL distilled water at constant speed of 500 rpm. These two polymer solutions were mixed in 10:90 composition and allowed for stirring, to this required amount of VMHCl was added and stirring was continued for further 12 h for proper mixing of the drug and the resulting solution was sonicated. The above drug loaded polymer solution was transferred into liquid paraffin oil (w/o) taken in 500 mL beaker to this solution 2 W/V % of Tween 80, 1 mL 0.1 HCl and glutaraldehyde (GA, 5 mL) were added and allowed for stirring using high-speed stirrer (Remi motor, India) at 750 rpm.

This emulsion solution was filtered using vacuum pump (High vacuum pump, Bangalore) and washed repeatedly with n-Hexane and water to remove the oil and excess amount of unreacted GA. Microspheres thus formed dried under vacuum at 40°C and stored in desiccator for further analysis and characterization. These microspheres were designed as XG 1. Repeating the above procedure various formulations were prepared by varying XG/PVA compositions, drug and cross-linker as listed in the table 1.

**Table 1: Various formulation parameters used in the preparation of XG/PVA IPN microspheres**

| Formulation codes | XG% | PVA% | VMHCl loading | GA(ml) |
|---|---|---|---|---|
| XP-1 | 10 | 90 | 10 | 5 |
| XP-2 | 10 | 90 | 20 | 5 |
| XP-3 | 10 | 90 | 30 | 5 |
| XP-4 | 10 | 90 | 10 | 2.5 |
| XP-5 | 10 | 90 | 10 | 7.5 |
| XP-6 | 20 | 80 | 10 | 5 |
| XP-7 | 30 | 70 | 10 | 5 |

### 2.3. Encapsulation efficiency

Specific amount of dried microspheres were vigorously stirred in a beaker containing 10 mL of 7.4 pH phosphate buffer & 0.22% tween-80 (to make the drug soluble in water). The aqueous solution was then filtered and assayed by UV spectrophotometer (Lab India 3000) at a λ max of 275 nm. The results of % VMHCl loading and encapsulation efficiency were calculated using Eqs. 1 and 2, respectively as given below:

$$\% \text{ Drug loading} = \left[\frac{\text{Amount of drug in microspheres}}{\text{Amount of microspheres}}\right] \times 100 \quad \text{--------- (1)}$$

$$\text{Encapsulation efficiency} = \left[\frac{\text{Actual loading}}{\text{Theoretical loading}}\right] \times 100 \quad \text{--------- (2)}$$

### 2.4. *In-vitro* drug release studies

The in vitro drug release studies of drug loaded microspheres were carried out in triplicate at 37±0.1°C using LAB INDIA DS-8000 MUMBAI dissolution apparatus at 50 rpm, in 900 ml of pH 7.4 [16] phosphate buffer solution. An aliquot of the release medium (5 ml) was withdrawn through a sampling syringe at pre-determined intervals of time and an equivalent amount of fresh dissolution medium pre warmed at 37°C was replaced. Collected samples were then analyzed for drug content in the microspheres by measuring the absorbance at 275 nm after suitable dilution using LABINDIA UV3000+ UV/VIS Spectrophotometer [17-18].

### 2.5. Characterization Techniques used in the present study

#### *2.5.1. Fourier Transform Infrared Spectroscopy (FTIR)*

In the present study, FTIR analysis was done using (Bomem model: MB3000, Canada). Polymeric microspheres were finely ground with KBr to prepare pellets under a hydraulic pressure of 400 dynes/$m^2$ and spectra were scanned between 4,000 $cm^{-1}$and 400 $cm^{-1}$.

#### *2.5.2. Differential scanning calorimetry*

Differential scanning calorimetric (DSC) thermo grams of plain drug, drug-loaded microspheres and plain microspheres were recorded using DSC (Model-SDT Q600, USA). Thermograms were recorded between 25°C to 400°C at a heating rate of 10°C/min under nitrogen atmosphere.

#### *2.5.3. X-ray diffraction studies*

X-ray diffraction (X-RD) measurement of plain drug, plain microspheres and drug-loaded microspheres were recorded with diffractometer [Shimadzu Lab X-RD-6000x diffractometer (Japan)], with the help of Nickel-filtered Cu Ka radiation (λ=0.54 nm). Dried samples were mounted on a sample holder, and the patterns were recorded in the range of 10°-60°at the speed of 50°/min to know the crystallinity.

#### *2.5.4. Scanning Electron Microscope (SEM)*

A few microspheres were taken on a copper stub and sputtered with gold for 2 min. These gold-coated microspheres were mounted on the Scanning electron microscopy (SEM) instrument (JSM-6390LV, Jeol, Japan). Representative sections were photographed for evaluation. The acceleration voltage used was 10 kv with scanning electron images as a detector.

## 3. RESULTS AND DISCUSSIONS

### 3.1. FT-IR Analysis

FTIR spectra of Verapamil Hydrochloride (a), Pure PVA (b), pure XG (c), placebo microspheres (d), and VMHCl loaded XG/PVA microspheres (e) are shown in Fig.1.

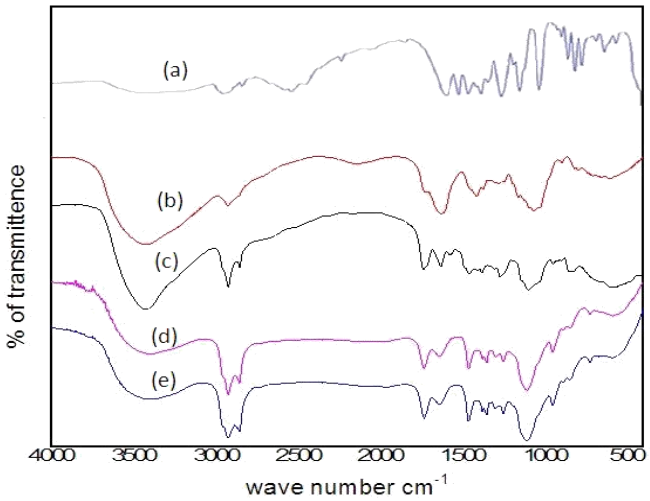


**Fig. 1: FTIR spectra of Verapamil Hydrochloride (a), Pure XG (b), pure PVA (c), placebo microspheres (d), and VMHCl loaded XG/PVA microspheres (e)**

In the FTIR spectra of VMHCl (Fig 1a), showed the C-H stretching vibration of the methoxy group at 2840 $cm^{-1}$, the N-H stretching of the protonated amine group in the range 2800-2300 $cm^{-1}$, and a strong absorption band due to C-O stretching of aromatic ester group at 1262 $cm^{-1}$. Another band at 3000-2950 $cm^{-1}$ represented aromatic C-H stretching, mainly $\upsilon_{=C-H.}$ The FTIR spectra of PVA (Fig 1b) showed a broad peak around 3422 $cm^{-1}$, indicating stretching of hydroxyl groups and peaks at 2925 $cm^{-1}$ is attributed to the stretching vibration of –$CH_2$-. The band at 1097 $cm^{-1}$ indicates the C-O stretching vibration. In the case of XG (Fig.1c), a broad band which appeared at 3423 $cm^{-1}$ is attributed to the presence of a hydroxyl group that is hydrogen bonded to various degrees. The bands appearing at 1610 $cm^{-1}$ and 1420 $cm^{-1}$ indicate the presence of a carboxylate group. The appearance of peaks at1252$cm^{-1}$ in the spectra of XG indicates the presence of a C-O-C group. In the case of placebo microspheres (Fig 1d), a broad band with less intensity compared to both XG and PVA matrices is due to the presence of very few uncross-linked hydroxyl groups that are hydrogen bonded to various degrees. The bands at 1625 and 1420 $cm^{-1}$ are due to the presence of carboxyl groups in XG. The bands appearing at 1126 $cm^{-1}$ are due to the presence of an acetal group, which

are formed due to the reaction of glutaraldehyde with hydroxyl groups of both PVA and XG. Thus, FTIR confirms the cross-linking reaction in addition to the formation of an IPN matrix. On comparison drug loaded microspheres (Fig 1e) with placebo microspheres (Fig 1d) the stretching frequency of COO- group of drug loaded microspheres is shifted to lower wave number due to formation of inter molecular hydrogen bonding between polymer matrix and drug molecule.

### 3.2. DSC analysis

DSC thermograms of pristine VMHCl (Fig 2a), placebo microspheres (Fig 2b), and drug-loaded microspheres (Fig 2c) are displayed in Fig 2.From the DSC thermogram of VMHCl (Fig 2a) a sharp peak is noticed at 145.5°C due to polymorphism and melting, but in case of VMHCl- loaded microspheres (Fig 2c), no such characteristic peak was observed at 145.5°C suggesting that VMHCl is molecularly dispersed in polymer matrix.

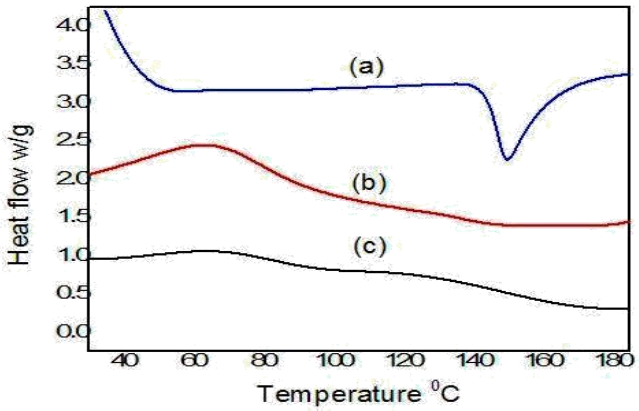


**Fig. 2: DSC thermograms of pristine VMHCl (Fig 2a), placebo microspheres (Fig 2b), and drug-loaded microspheres (Fig 2c)**

### 3.3. Scanning electron microscopic studies

SEM is used to examine the morphology of interpenetrating polymer microspheres, which may provide an evidence for the compatibility and shape. In general, the major component of the IPN forms the matrix whereas the minor component is the dispersion phase. The typical SEM images of group of placebo microspheres (Fig 3a) and drug loaded microspheres (Fig 3b) taken at 500X and 3000X magnifications are shown in Fig 3.

From the SEM photographs of 10% XG+ 90% PVA microspheres (Fig 3a) it is noticed that microspheres are full of cavities, only a limited number of small particles dispersed along the micrograph large number of particles dispersed all over the surface. On the other hand, SEM photograph of drug loaded microspheres (Fig 3b) has been completely improved and become more smoother and all the cavities (big and small) particles are nearly disappeared and replaced by very small particles dispersed homogeneously all over the surface which indicates the drug release nature. A similar observation was reported from the drug release studies by H.M.N.Eldin et al.[19].

The particles which were prepared by Xanthan gum and Poly (vinyl alcohol) only (Fig. 3a) were having smooth surface, whereas the particles in case of drug loaded microspheres (Fig. 3b) reveals a rough surface which indicates their drug release nature.

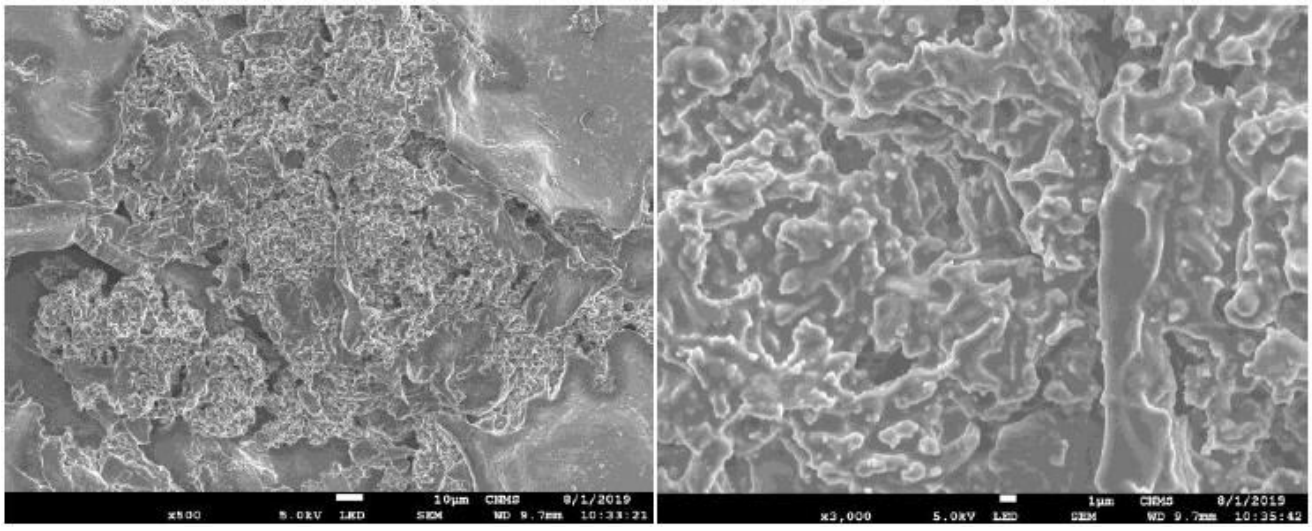

**Fig 3a: XG-PVA microspheres**

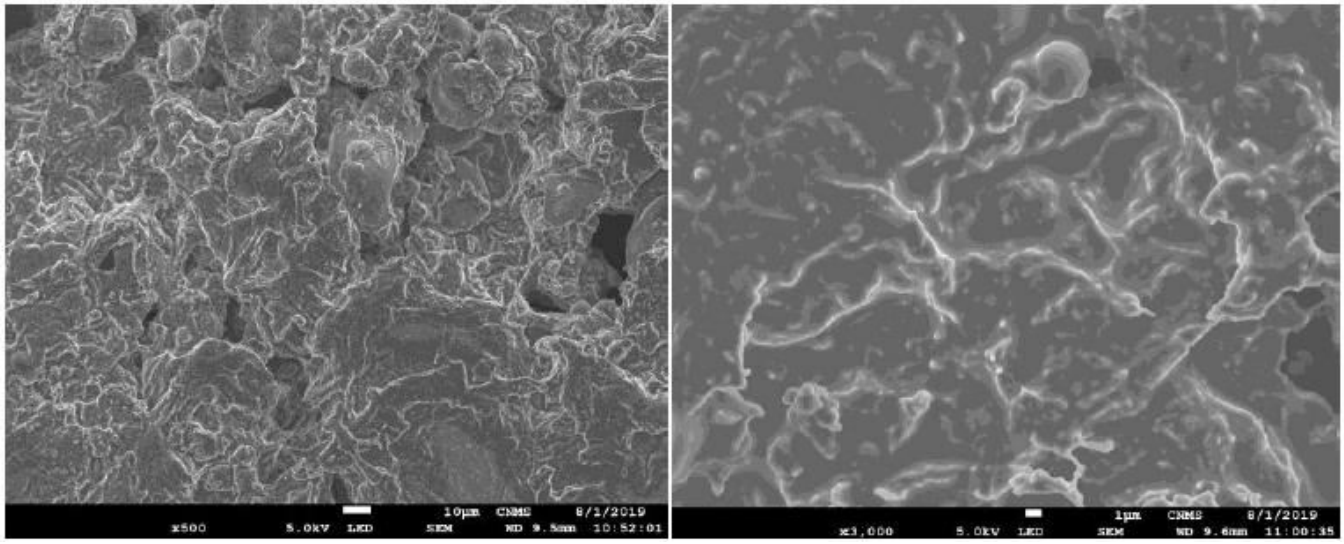

**Fig 3b: Drug (Verapamil Hydrochloride) loaded IPN (XG-PVA) microspheres**

### 3.4. X-RD studies

X-RD analysis can provide a clue for crystallinity of the drug in drug loaded microspheres. X-RD patterns recorded for pure VMHCl drug (4a), placebo microspheres (4b) and VMHCl loaded microspheres (4c) are shown in Fig. 4.

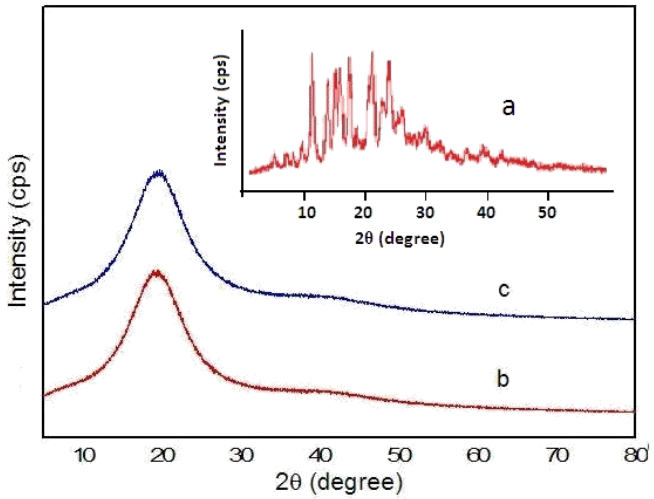


**Fig. 4: X-RD patterns of pure VMHCl (4a), placebo microspheres (4b) and VMHCl loaded microspheres (4c).**

From Fig (4a) the peaks at 2θ of 10°-25° are observed which may be due to drug crystalline nature. These peaks are not found in the VMHCl- loaded microspheres (Fig 4 c) and unloaded microspheres (Fig 4 b). However, other peaks have disappeared in VMHCl loaded microspheres assuring that drug is molecularly dispersed in the polymer matrix. This indicates that drug particles in the polymer matrices are molecularly dispersed, since no indication about the crystalline nature of the drug in drug loaded microspheres.

### 3.5. *In-vitro* release studies

*In vitro* release studies were carried out to study the effect of GA, drug and polymer concentration on drug release experiments.

### 3.6. Effect of cross-linking variation

The cumulative percent of Verapamil Hydrochloride released from the XG-PVA microspheres with cross-linker variation as a function of time is shown in Fig. 5.

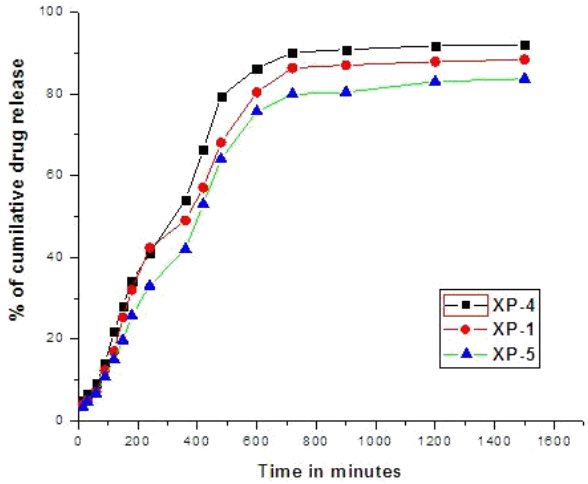


**Fig. 5: % Cumulative release of VMHCl drug through Xanthan gum/poly (vinyl alcohol) microspheres containing different amounts of crosslinking agent**

*(filled circle) 2.5 mL, (filled square) 5 mL, and (filled triangle) 7.5 mL with 10% of VMHCl and (10:90) XG and PVA.*

The extent of cross-linking also showed high impact on the cumulative percentage of drug release from IPN microspheres which is under study. The cumulative % of drug release versus time plots for varying amounts of glutaraldehyde GA (i.e. 2.5, 5, and 7.5) at fixed amount of XG-PVA (10:90) are displayed in Fig. 5.

The loosely formed IPN network at lower cross-linking released the drug much faster (XP-4) than the tightly formed IPN matrices at higher cross-linking (XP-5). The decreasing trend of controlled release of drug at higher concentration of GA due to the formation of rigid polymer structure; this causes the formation of micro voids and also lead to decrease in swelling as well as controlled release. Hence as the amount of GA was increased the drug release was found to be decreased.

### 3.7. Effect of drug variation

The drug variation on Invitro release profile formulations are shown in Fig.6.

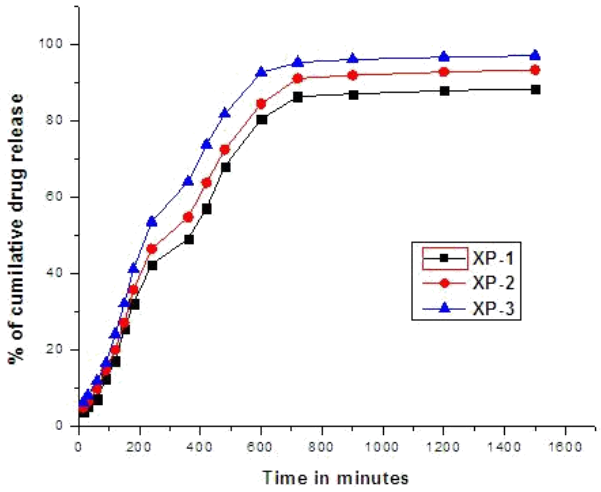


**Fig. 6: %Cumulative release of VMHCl drug through microspheres, containing different amounts of drug 10wt%(XP-1), 20 wt%(XP-2,) and 30 wt%(XP-3).**

Figure 6 shows the drug release profiles of VMHCl loaded XG-PVA blend microspheres(XP-1, XP-2 & XP-3) at different amounts of drug loading (10,20 & 30% respectively) in phosphate buffer solution pH at 37$^0$C. Fig 6 reveals, initially drug release is quite fast for all the formulations, but later it showed slow release. The release data also shows that microspheres containing the highest drug, displayed faster and higher release (XP-3) than those formulations containing a smaller amount of VMHCl (XP-1). Since, drug release from the microspheres is sustained by diffusion mechanism, the release rates are slow at low content of VMHCl due to availability of more free void spaces with lesser number of drug molecules to pass through polymeric matrices. Similar observations were reported in literature [20-21] by different authors. The complete release of VMHCl drug, release in all the above studied formulations was obtained about 10 hours.

### 3.8. Effect of polymer variation

The cumulative percent of Verapamil Hydrochloride released from the XG-PVA microspheres with XG content variation as a function of time is shown in Fig. 7.

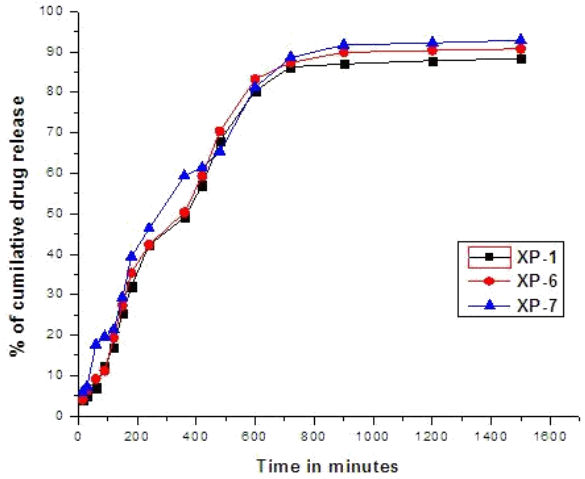


**Fig. 7: Effect of polymer variation on in-vitro release profile formulations**

To understand the release profiles of VMHCl from cross-linked XG/PVA blend microspheres, in-vitro release studies was carried out in pH 7.4 phosphate buffer solution at 37°C. The cumulative percent of Verapamil Hydrochloride released from the XG-PVA microspheres with XG content variation as a function of time shows that the amount of drug released was dependent on the polymer ratio at a fixed cross-linker concentration. The VMHCl release is higher in the case of XP-6 than XP-1, and similarly XP-7 shows higher release than XP-6 (i.e. XP-7>XP-6>XP-1). This can be explained on the basis of hydrophilic nature of XG. XG is more hydrophilic than the PVA and it has more hydroxyl groups, these groups can easily swelled and hence drug release is more for the formulation which has more amount of xanthan gum. A similar observation was reported by Subha et.al [22].

### 3.9. Drug release kinetics

Drug release kinetics was analyzed by plotting the cumulative release data versus time and fitting these data to an exponential type.

$$M_t/M_\infty = kt^n$$

Where $M_t$ and $M_\infty$ are the amount of drug released at time t and at infinite time, respectively; k is a constant incorporating structural and geometrical character of the dosage form and n values denote the diffusion exponent indicative of the mechanism of drug release [23]. Using the least squares procedure, we have estimated the values of n and k for all the seven formulations, and these values are given in Table 2. The correlation coefficients r, values are in the range of 0.973 to 0.992, suggesting a good fit of experimental release data. From the value of 'n' it is conclude that the release kinetics follows fickian transport.

**Table 2: Results of % of release kinetics parameters (k, n, and r) of drug in different blend microspheres formulations**

| Sample code | K | n | $r^2$ |
|---|---|---|---|
| XP-1 | 0.172 | 0.291 | 0.985 |
| XP-2 | 0.221 | 0.258 | 0.992 |
| XP-3 | 0.156 | 0.291 | 0.986 |
| XP-4 | 0.181 | 0.308 | 0.987 |
| XP-5 | 0.212 | 0.482 | 0.973 |
| XP-6 | 0.197 | 0.446 | 0.981 |
| XP-7 | 0.168 | 0.452 | 0.979 |

## 4. CONCLUSION

In this paper, we successfully fabricated verapamil hydrochloride XG-PVA microspheres using water in oil (W/O) emulsion method using GA as cross linker. FTIR analysis confirms the formation of interpenetrating network among polymer, drug and cross-linker. DSC and X-RD result reveals that the drug should be dispersed at molecular level in the microspheres. In vitro drug release studies indicated that the release of verapamil hydrochloride was controlled up to 10 h. The release kinetics data indicated the presence of Fickian transport.

## 5. ACKNOWLEDGEMENTS

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