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Research Article

**Synthesis and Characterization of Polyvinylalcohol
/Cloisite30B (MMT) Nanocomposite for Controlled
Release of Anticancer Drug Curcumin**

Pradyumna Kumar Swain¹, Mira Das², P.L Nayak^{1*}.

P.L.Nayak Research Foundation, Synergy Institute of Technology, Bhubaneswar, India.

²Siksha O Anusandhan University, Odisha, India.

Abstract

In this research program, Polyvinyl alcohol (PVA) /Cloisite 30B hybrid nanocomposites were prepared and characterized by using SEM and XRD analysis. From SEM the data the surface morphology of the composites was determined and from the XRD data it was found that intercalation or partial exfoliation was occurred with significant increase in its properties. Controlled release of curcumin from the above blend was also studied. Its release kinetics were evaluated at different pH medium (acidic, neutral and basic) by taking the values of cumulative release data against the time and the nature of drug release was concluded.

Key words: Polyvinyl alcohol, Cloisite 30 B, Curcumin, Drug delivery, Kinetics.

INTRODUCTION

Drug delivery using a suitable carrier for its controlled release has emerged as a powerful methodology for the treatment of various diseases. The therapeutic index of traditional and novel drugs is enhanced via the increase of specificity due to the targeting of drugs to a particular tissue, cell or intracellular compartment, the control over release kinetics, the protection of the active agent or a combination of the above. Polymer composites were proposed as drug carriers over 30 years ago and have received growing attention since, mainly due to their stability, enhanced loading capabilities and control over physicochemical properties [1-3]. In addition to systemic administration, localized drug release may be achieved using macroscopic drug depots close to the target site [4]. In recent years biodegradable polymers have attracted attention of researchers to be used as carriers for drug delivery systems.

Poly(vinyl alcohol), PVA, is a non-toxic, biocompatible, water-soluble synthetic polymer and has good physical and chemical properties and film-forming ability [5]. In recent years PVA has been used in different medical applications such as

artificial pancreas, hemodialysis, nanofiltration, synthetic vitreous and implantable medical device.

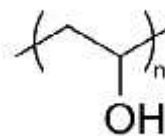


Fig-1 Polyvinyl alcohol

Curcumin (diferuloylmethane), a polyphenol, is a low molecular- weight active principle of the perennial herb *Curcuma longa* (commonly known as turmeric). Recent evidence suggests that curcumin is a highly pleiotropic molecule that interacts physically with its diverse range of molecular targets including transcription factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation and apoptosis. Curcumin possesses antioxidant, anti-inflammatory, anticarcinogenic, and antimicrobial properties, and suppresses proliferation of a wide variety of tumor cells. Several clinical trials dealing with cancer have addressed

the pharmacokinetics, safety, and efficacy of curcumin in humans. Despite extensive research and development, poor solubility of curcumin in aqueous solution remains a major barrier in its bioavailability and clinical efficacy. Being hydrophobic in nature, it is insoluble in water but soluble in ethanol, dimethylsulfoxide, and acetone. To increase its solubility and bioavailability, attempts have been made through encapsulation in liposomes, polymeric and lipo-NPs, biodegradable microspheres, cyclodextrin, and hydrogels [6-11]. In recent years, various controlled delivery forms, such as polymeric micro/nanospheres, liposomes, micelles, parenteral emulsion, and prodrugs have been investigated to increase its solubility, to minimize the side effects as well as to avoid the use of toxic adjuvant.

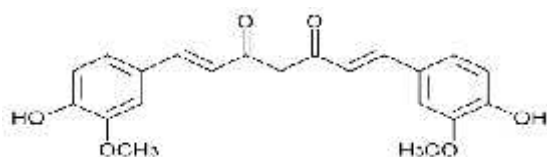


Fig-2: Curcumin structure (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (IUPAC NAME)

In the present research program, we wish to report a novel biomaterial—PVL/ MMT (Cloisite 30 B) hybrid nanocomposite for the control release of Curcumin. The nanocomposites have been characterized by SEM, XRD methods. The drug delivery has been carried out at different pH conditions and the results are encouraging.

EXPERIMENTAL

Materials: Polyvinyl alcohol Samples was purchased from Aldrich Co. (with 99% hydrolyzed, Mw 85,000 - 146,000). The Cloisite 30B was procured from Southern Clay Products; USA. Curcumin was purchased from Dabur, India. All other samples were of Analytical Grade.

Preparation of Nanocomposites

One gram of polyvinyl alcohol was dissolved in 50 ml deionized water and heated at 70°C to obtain a homogeneous solution. Calculated amount of Cloisite 30B (1%, 2.5%) was added to this slurry. The mixture was stirred for 8 hours at room temperature till a homogenate composite is formed. The product was poured into the specially self-made mold and dried at ambient temperature for several days.

Drug Loading

Curcumin-loaded PVL/C30B nanocomposites were prepared by emulsion/solvent evaporation method. In

short, curcumin of different loadings, i.e., 1 wt%, 2.5wt%, 5 wt%, 7.5wt%, 10wt%, and 15% were dissolved in ethanol with (80:20) PVL/ C 30B. The formed solution was poured into a labeled Petri dish and allowed to evaporate the solvent overnight at room temperature. This compound was used for drug delivery purposes.

Dissolution experiments

Dissolution experiments were performed at 37°C using the dissolution tester (Disso test, Lab India, Mumbai, India) equipped with six paddles at a paddle speed of 100 rpm. About 900ml of phosphate buffer solution (pH 5.8, pH 7.0 and pH 7.4) was used as the dissolution media to stimulate gastrointestinal tract (GIT) conditions. A 5-ml aliquot was used each time for analyzing the Curcumin content at a fixed time interval. The dissolution media was replenished with a fresh stock solution. The amount of Curcumin released was analyzed using a UV spectrophotometer (Systronics, India) at the max value of 420 nm.

Drug release mechanism from matrices

From time to time, various authors have proposed several types of drug release mechanisms from matrices. It has been proposed that drug release from matrices usually implies water penetration in the matrix, hydration, swelling, diffusion of the dissolved drug (polymer hydro fusion), and/or the erosion of the gelatinous layer. Several kinetic models relating to the drug release from matrices, selected from the most important mathematical models, are described over here. However, it is worth mention that the release mechanism of a drug would depend on the dosage form selected, pH, nature of the drug and, of course, the polymer used.

(i) Zero - Order Kinetics [14].

$$W = k_1 t \dots\dots\dots (1)$$

(ii) First - Order Kinetics [15].

$$\ln (100 - W) = \ln 100 - k_2 t \dots\dots (2)$$

(iii) Hixon-Crowel's Cube- Root Equation (Erosin Model) [16].

$$(100 - W)^{1/3} = 100^{1/3} - k_3 t \dots\dots (3)$$

(iv) Higuchi's Square Root of Time Equation (Diffusion Model) [17].

$$W = k_4 t \dots\dots\dots (4)$$

(v) Power Law Equation (Diffusion/ Relaxation model) [18].

$$Mt / M = k_5 t^n \dots\dots\dots (5)$$

Mt / M is the fractional drug release into dissolution medium and k_5 is a constant incorporating the structural and geometric characteristics of the tablet. The term 'n' is the diffusional constant that characterizes the drug release transport mechanism. When $n = 0.5$, the drug diffused and released from the polymeric matrix with a quasi-Fickian diffusion

mechanism. For $n > 0.5$, anomalous, non-Fickian drug diffusion occurs. When $n = 1$, a non-Fickian, case II or Zero-order release kinetics could be observed.

Characterization

X-Ray Diffraction (XRD)

The change in gallery height of the blend was investigated by WAXD experiments, which were carried out using a X-ray diffractometer (BEDE D-3system) with Cu K radiation at a generator voltage of 40 kV and a generator current of 100 mA. Samples were scanned from $2\theta = 1-100$ at a scanning rate of 20/min.

Scanning Electron Microscopy (SEM):

The blending of the PVL nanocomposites containing different concentrations was characterized using SEM (440, Leica Cambridge Ltd., Cambridge, UK). The film specimens were placed on the Cambridge standard aluminium specimen mounts (pin type) with double-sided adhesive electrically conductive carbon tape (SPI Supplies, West Chester, PA). The specimen mounts were then coated with 60% Gold and 40% Palladium for 30 seconds with 45 mA current in a sputter coater (Desk II, Denton Vacuum, Moorestown, NJ). The coated specimens were then observed on the SEM using an accelerating voltage of 20 kV at a tilt angle of 30° to observe the microstructure of the PVL composite blends.

Swelling Studies

Water absorption of the polymer-drug conjugates was measured following ASTM D 570-81. The samples were preconditioned at 50°C for 24h and then cooled in a desiccator before being weighed. The preconditioned samples were submerged in distilled water at 25°C for 24h. The samples were removed and dried with a paper towel before weighing. Water absorption was calculated as a percentage of initial weight. The soluble material loss was checked by weighting the specimens after drying them in an oven at 50°C for another 24h. The total water absorption for 24h was calculated including the soluble material loss. Where, W_1 = Weight of Swollen composite after 24 hr., W_2 = Weight of Dry Composite.

$$\% \text{ Swelling} = \frac{W_1 - W_2}{W_2} \times 100$$

Where, W_1 = Weight of Swollen composite after 24 hr., W_2 = Weight of Dry Composite.

RESULTS AND DISCUSSION

X-Ray Diffraction (XRD)

The Wide angle XRD (WAXD) showed different peak regions for C 30B and PVL like $2\theta = 4.8^\circ$ and $2\theta = 40^\circ$ respectively. The weak diffraction peak of PVL proves its amorphous nature. But when PVL blended with C 30B to make PVL/ C 30B nanocomposites the peak remarkably shifted to the region $2\theta = 5.8^\circ$ (Figure 3) indicating that probably an intercalation or partial exfoliation had occurred.

Scanning Electron Microscopy (SEM)

The scanning electron micrograph of a typical drug-loaded PVA blended with C 30B is shown in Figure 4. The composite showed surface cracks probably caused by partial collapsing of the polymer network during drying.

Equilibrium Swelling Studies

The swelling behavior of the composites has been investigated. It is generally known that the swelling behavior of the polymer network depends upon the nature of the polymer, polymer solvent compatibility and degree of cross-linking. However, in the case of ionic networks, swelling behavior depends upon mass transfer limitations, ion exchange and ionic interaction. The swelling behavior of the composites is depicted in Figure 5.

It shows that the swelling increases with time up to a certain level, and then levels off. The swelling parameters are furnished in Figure 5. Due to the hydrophobicity of drug the swelling % increases with increase in the drug loadings. % of Swelling studies of Different Drug Loadings of PVA-C30B nanocomposite.

In-vitro Drug Release

Effect of pH, Time and Drug loading

In order to investigate the effect of pH on the swelling of PVA/C 30B composite (2.5%), we have measured the % cumulative release in both pH 5.8, pH 7.0 and 7.4 media. Cumulative release data presented in Figure 6, 7 and 8 indicate that by increasing the pH from 5.8 to 7.4, a considerable increase in the cumulative release is observed for all composites. From Figure 6, 7, and 8, it can be seen that the 15% drug-polymer composites have shown longer drug release rates than the other composites. Thus, drug release depends upon the nature of the polymer matrix as well as pH of the media. Interestingly, more than 90 wt% curcumin is released from composites at pH 7.4 within 48 hours, whereas less than 70 wt% of the drug is released at pH 5.8 within 48 hours. This suggests that the basic environment is more suitable over the acidic environment for the drug release. Further the electrostatic interaction of composites is more easily broken at pH 7.4 than at pH 5.8 leading to curcumin

being released more rapidly at pH 7.4 than pH 5.8. Release data (Figure 6,7,8) showed that formulations containing highest amount of drug (10%) displayed fast and higher release rates than those formulations containing a small amount of drug loading.

Drug release kinetics

Drug release kinetics was evaluated by plotting the cumulative release data vs. time by fitting to an exponential equation of the type as represented below.

$$M_t / M = kt^n$$

Where

- M_t / M = the fractional drug release at time t,
- k = constant characteristic of the drug-polymer system
- n = empirical parameter characterizing the release mechanism.

The values of n and k were estimated using the least squares procedure, and these data are given in Table 1. The values of k and n have shown a dependence on the polymer content of the matrix and % drug loading. Values of 'k' for composites prepared by varying the amounts of drug containing and keeping

PVA/C 30B (2.5 wt %) constant, ranged from 0.04 to 0.17 in pH 7.4, 0.04 to 0.11 in pH 7.0 and 0.04 to 0.11 in pH 5.8 respectively. However, the drug loaded composites exhibited 'n' values ranging from 0.6 to 1.2 in pH 7.4 and 0.5 to 1 in pH 7.0, 0.6 to 1 in pH 5.8 indicating a shift from erosion type release to a swelling controlled, non-Fickian type mechanism.

CONCLUSION

Controlled release of anticancer drugs by using biodegradable polymers has a significant advantage over conventional drug delivery. In this research program, novel nanocomposites of PVA blended with cloisite 30B were prepared and characterized by X-ray diffraction and scanning electron microscope. The swelling behaviors of the nanocomposites have also been reported. The blend was loaded with different percentage of anticancer drug curcumin to study its release behavior at different time interval and different pH medium. From the data obtained by calculating different kinetic parameters like 'k' and 'n' the drug release mechanism was concluded as a non-Fickian type of mechanism.

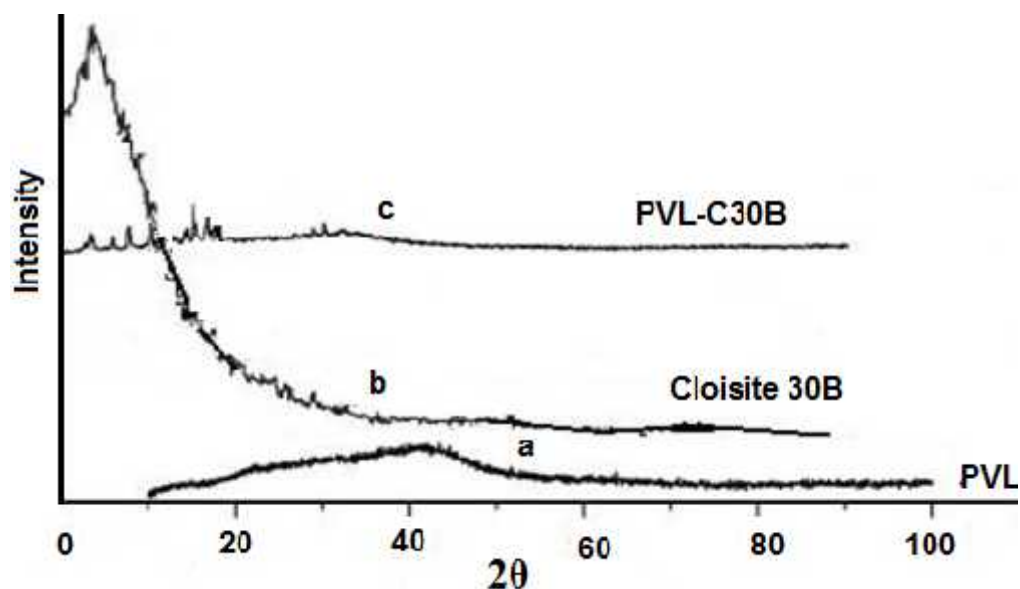


Figure 3
X-ray diffraction of (a) PVL (b) Cloisite30B (c) PVL-C30B



Fig 4
SEM of PVA/C30B

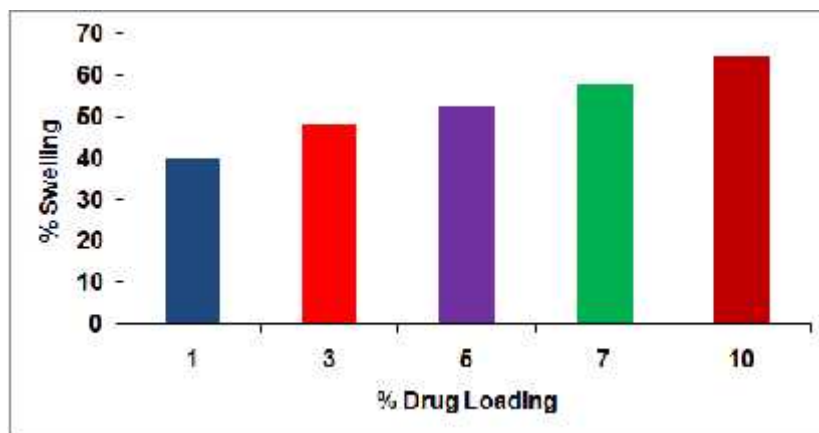


Fig 5
Water Absorption of the PVA-C30B nanocomposites with different % of drug loadings

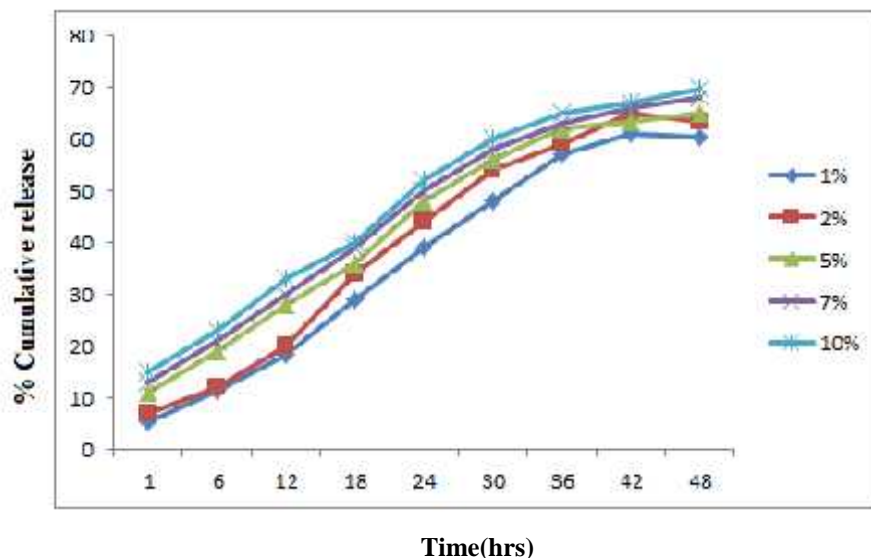


Fig 6
% Cumulative Release vs Time for Different Formulations of Curcumin Loaded in PVA-C30B in pH 5.8 media

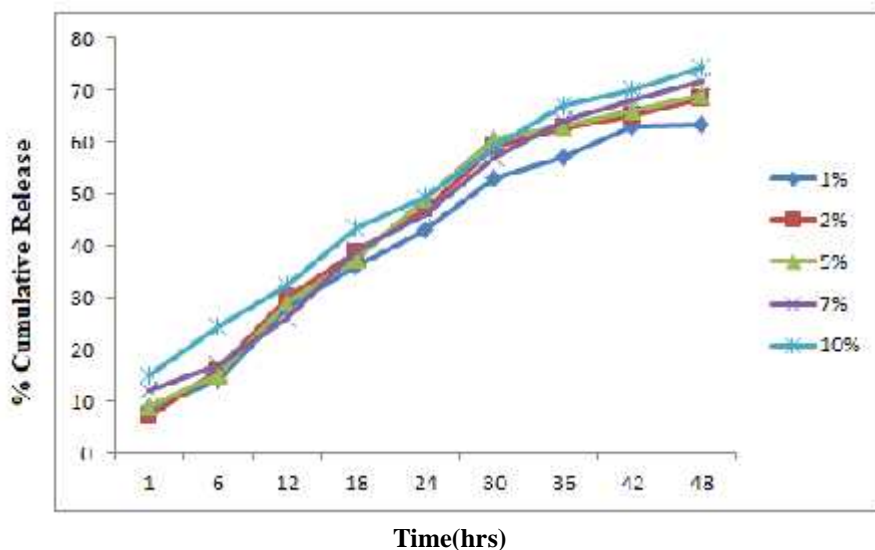


Fig 7
 %Cumulative Release vs Time for Different Formulations of Curcumin Loaded in PVA-C30B in pH 7.0 media

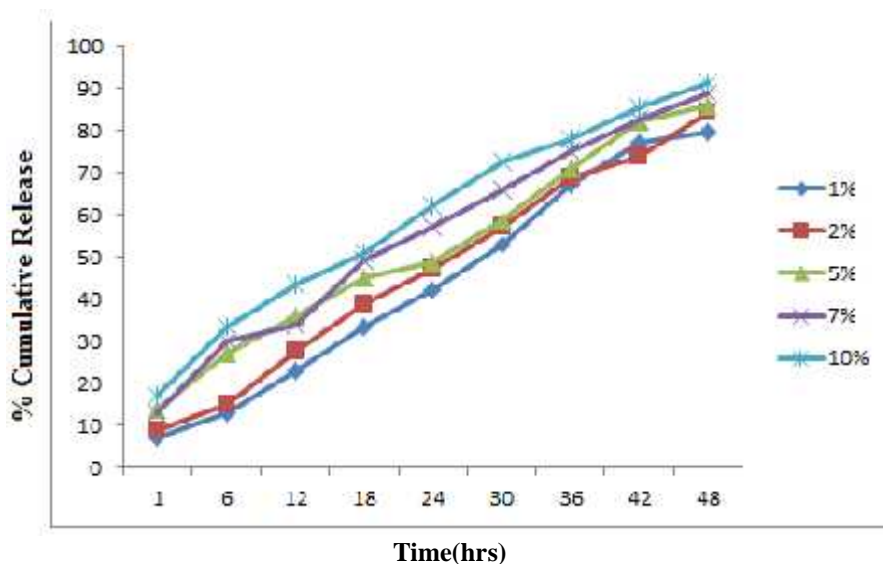


Fig 8
 % Cumulative release Vs. Time for different formulation of curcumin loaded in PVA/C 30B composite film in pH 7.4 media.

Table -1
 Release kinetics parameter of different formulation at pH 5.8, pH 7.0 and pH7.4

Curcumin %	value of "k"			value of "n"		
	pH 7.4	pH7.0	pH 5.8	pH 7.4	pH7.0	pH 5.8
1 wt %	0.07	0.04	0.07	0.6	0.55	0.77
2 wt%	0.04	0.07	0.04	0.8	1	0.8
5wt%	0.11	0.07	0.11	0.7	0.6	0.6
7%	0.17	0.07	0.11	0.7	0.6	0.6
10%	0.11	0.11	0.07	1.2	0.6	1

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