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Design of Chitosan Based Acrylic Polymer As A Carrier for Water Soluble Drug

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Abstract

Study of drug release from polymeric systems has a significant role in drug formulation and in pharmaceutical dosage determination. Chitosan based membranes have been developed by grafting polymerization of vinyl monomers including acrylic acid (AA) and 2-hydroxyethylmethacrylate (HEMA) onto chitosan using potassium persulphate (K2S2O8), and sodium bisulphite (NaHSO3) as redox chemical initiation system. The grafting polymerization of vinyl monomers onto chitosan was confirmed by Fourier Transform-Infrared Spectroscopy (FTIR) and Scanning Electron Microscope (SEM). Release profile of Paracetamol drug from chitosan grafted vinyl polymers were investigated using gastric and intestinal medium (pH 1.2 and 7.4 respectively) followed by studying the kinetic data for Paracetamol drug release using Koresmeyer – peppas, Higuchi, Zero order and First order equations where the data confirmed that the drug diffusion from chitosan was related to Higuchi model and reached to 90 % drug release at pH value 7.4 for a sample containing high amount of acrylic acid.

Keywords: Chitosan; Grafting; Acrylic acid; 2-Hydroxyethyl methacrylate; Paracetamol; Drug delivery

1. Introduction

Chitosan is considered one of the most important natural polymers which produced from Chitin through N-de-acetylation process in a strong basic medium [1-4].

Recently, the interest of chitosan research development is due to its eco-friendly, low cost, non-poisonous and highly promising properties.

The Presence of two functional groups (amino group and hydroxyl group) in chitosan structure contributes the ease functionalization process by grafting of vinyl monomers onto chitosan surface [5-7].

Grafting polymerization of synthetic polymeric materials onto natural polymers as chitosan aims to embedding side chains with different functional groups. This modification for chitosan surface led to introduce desired characteristics to chitosan and its application fields [8-9].

Grafting polymerization is considered one of the most useful methods to improve the homogeneity between chitosan backbone and surface embedded synthetic polymers. The synthetic polymers attached to chitosan surface functional groups by covalent bonds which led to increase the stability, solubility, adsorption capacity and chelating properties of chitosan [10-12].

Due to the high ability of grafted chitosan for carrying many active biological agents such as drugs and enzymes in addition to sensitivity and biocompatibility of chitosan pH, drug delivery is an important considerable application for grafted chitosan [13-15].

Grafting of vinyl monomers onto chitosan backbone using free radical initiation systems such as ammonium persulphate (AmPS), potassium

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persulphate (PPS), Azobis isobutyronitrile (AIBN) or other chemical initiators was the most common grafting method in the last few decades [16].

The main purpose of using the synthetic polymer grafting chitosan in the drug delivery is to increase the control release of drugs inside the living cells.

Paracetamol drug is one of the most common acetaminophen (Acetyl –P-aminophenol) drug with few metabolic pathways in its biological actions inside the living organism as inflammatory pain [17].

The aim of this work is to modify Chitosan surface using vinyl polymeric materials as a copolymer of acrylic acid and hydroxyethylmethacrylate in order to introduce new functional groups on the chitosan surface for drug delivery application using water soluble Paracetamol as a drug model.

2. Experimental

2.1 Material:

Above 90% de-acetylated chitosan was obtained from Oxford Laboratory. Acrylic acid (AA), 2-hydroxyethylmethacrylate (HEMA) and glutraldehyde were obtained from Merck, Paracetamol as a model for drug was obtained from ALKAN pharmaceutical Co. Potassium persulphate, Sodium bisulphite, hydrochloric acid, potassium chloride, mono-potassium phosphate, sodium chloride, sodium hydroxide, ethanol and glacial acetic acid were all used as laboratory grade chemicals and supplied from El-Nasr Chemical Company, Cairo, Egypt.

2.2. Preparation 2% chitosan stock solution.

2% chitosan solution was prepared by adding 30 g of de-acetylated chitosan to 35 ml glacial acetic acid diluted with 1460 ml distilled water (2% molar concentration) and placed in a necked flask over night with stirring.

2.3. Preparation of Cross-linked Chitosan [2].

10 g of de-acetylated chitosan was dissolved in 200 ml distilled water then 10 ml of glutraldehyde (25%) was added with continuous stirring for 16 h. After filtration process a precipitate was obtained and washed with ethanol.

2.4. Preparation of Redox Initiator.

Redox initiator consists of potassium persulphate (KPS) and sodium bisulfite (NaHSO3) which prepared by adding 2 g of each initiator dissolved in 30 ml distilled water.

2.5. Synthesis of grafting copolymer [14].

2 %(w/v) Chitosan stock solution were prepared using glacial acetic acid aqueous solution 1% (v/v). 200 ml Chitosan stock solution was stirred with 18 ml of equal ratio between potassium persulphate and sodium bisulphite. Acrylic acid and 2-hydroxyethylmethacrylate monomers in two different molar ratios as listed in Table 1 were impeded into the solution with continuous stirring for three h [18]. Ethanol was added to the resulting solutions and dried for 24 h at 65 0C to form polymeric films.

Table 1. Molar ratio of HEMA and AA monomers

Sample	(CS) [a]	HEMA	A.A	KPS	$NaHSO_3$
S1	200 ml	4 ml	2 ml	9 ml	9 ml
S2	200 ml	5 ml	1 ml	9 ml	9 ml

[a] A 2% (w/v) chitosan solution.

2.6. Characterization of Grafting Polymer

2.6.1 Infrared Analysis

The molecular structure of the studied samples were elucidated in the range 4000 to 400 cm-1 by Fourier transform infrared spectroscopy (FTIR), Jasco 6100 type A FTIR spectrometer.

2.6.2 Morphological Properties

Morphological properties of the prepared polymeric films were investigated using scanning electron microscope JEOL Model JSM-T20 SEM.

2.7. In vitro drug load and release studies

Paracetamol was utilized as an inflammatory pain drug. Before the drug release experiment, absorbance values of seven calibration solutions (0–5 mg/L) were measured at 236 nm with a double beam UV Spectrophotometer PG instruments Ltd.

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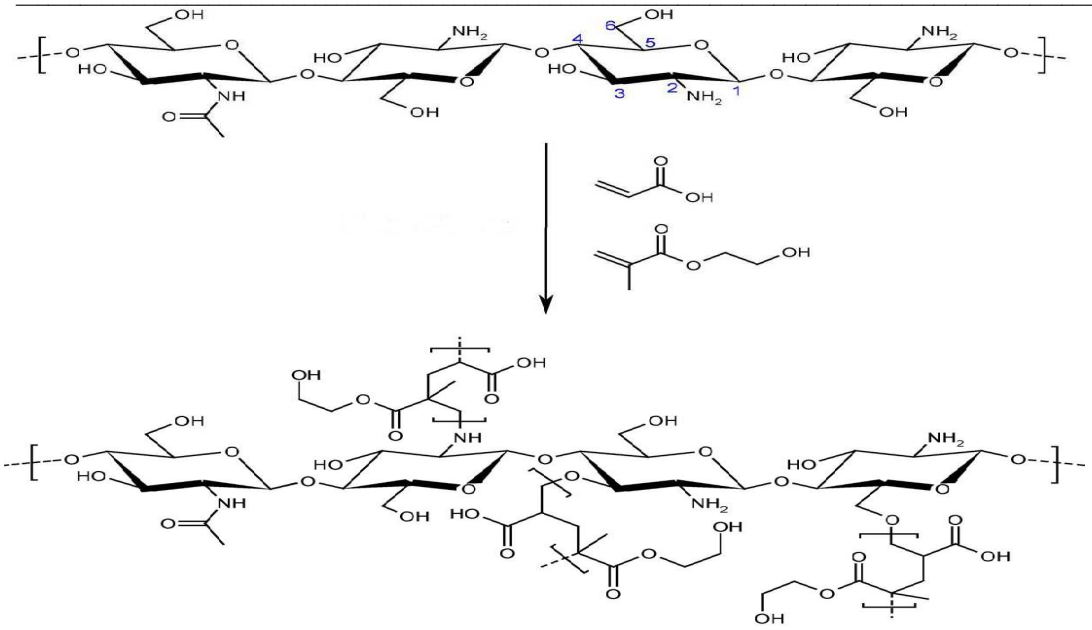

Scheme 1 : Grafting mechanism for acrylic polymers onto Chitosan [18]

2.8. Drug release kinetics.

The kinetics of paracetamol release from the modified chitosan was determined by finding the best fit of the curves (% release against time) to distinct models (Eqs. (1) – (4)) [19].

Ln {Qt/Q∞} = ln k +n ln t [Koresmeyer – peppas] ..... (1)

Qt : Amount of drug released at a given time (t).

Q∞: Amount of drug present initially.

K: A constant comprising the structural and geometric characteristics of the formulation and n is the release exponent.

Qt = KHt1/2 [Higuchi Equation]..... (2)

Qt: Amount of drug released at time (t).

KH: Higuchian release rate constant.

Qt – Q0 = k0t [Zero order equation] ..... (3)

Qt: Amount of drug released in time (t).

Q0 : Amount of drug dissolved at time zero.

k0 : Zero-order release constant.

Ln (Q∞/ Q1) = k1t [First order equation] .....(4)

Q1: Amount of drug remaining at time (t).

Q∞: Total amount of drug present initially.

k1: First-order rate constant.

3. Result and Discussion.

3.1 Fourier Transform Infrared Spectroscopy

Figure 1 represents the FTIR spectra of pure chitosan, acrylic grafted chitosan and acrylic grafted chitosan loaded with Paracetamol. The C=O asymmetric stretching bond of the ester of HEMA is appeared as absorption band at 1720 cm−1. The very intense characteristic band at 1560 cm−1 is due to the asymmetric stretching bond of the C-O carboxylate anion from acrylic acid grafted chitosan. The sharp peak at 1405 cm−1confirfms the carboxylate anion [20]. While for S0 sample, a relatively sharper band for hydroxyl stretching bond has shifted to a lower wavenumber (3440 cm-1) indicating weakening of the O-H bond due to cross-linked reaction. Formation of the imine (C=N) linkage is confirmed by a weak band at (1661 cm-1). The characteristic bands of

amide at (1585 cm-1) responsible for N-H deformation shifted to a lower wave number. FT-IR confirmed the loading of Paracetamol drug to chitosan where C=C band of benzene ring appeared at 1506 cm-1, C-C aromatic bond band appeared at 1605 cm-1 ,C-H stretching aromatic band appeared at 3103 cm-1 and bending band at 708 cm-1[21].

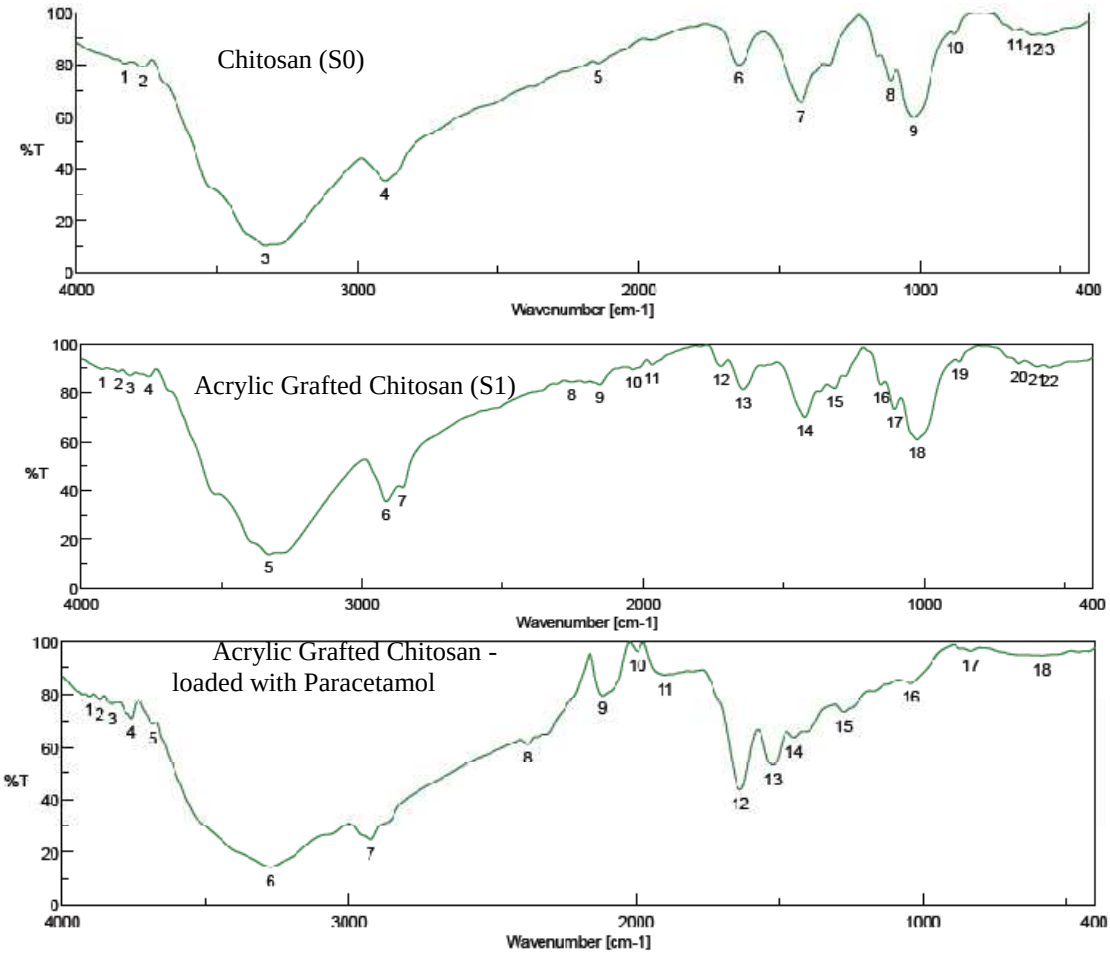

Figure 1 : FTIR for pure chitosan and acrylic grafted chitosan

3.2. Morphological Properties

Figure 2 represents the morphological investigation of pure chitosan and chitosan grafted with acrylic polymers as listed in table 1. From the figure it is obvious that, the pure chitosan has smooth homogenous surface in compared with the surfaces of grafted polymers. Grafted polymer is more homogenous and highly distribution in S1 sample which may be due to the higher acrylic acid contribution in the grafted polymer.

Incorporation of Paracetamol drug is confirmed by SEM where the drug distributed on the surface of chitosan grafted acrylic polymers where the drug was accumulated on the surface of the drug loaded film [22].

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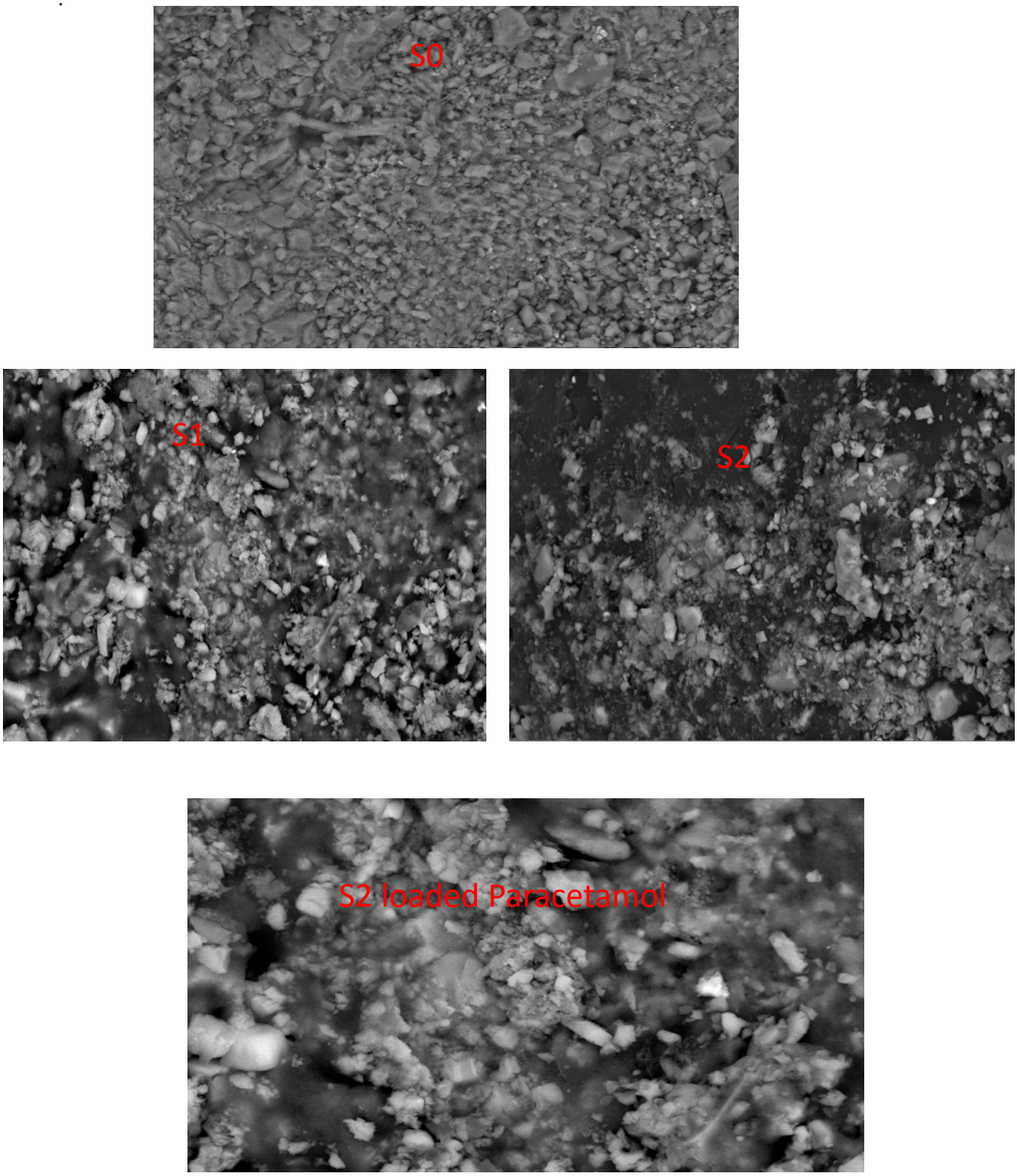

Figure 2: SEM for Pure ChitosanS0, grafted chitosan S1, S2 and S2 loaded drug Samples

3.3. Release of Paracetamol from films.

Figure 3.1 and Figure 3.2 show the release profiles of different samples of grafted chitosan containing of paracetamol. The percent released of sample containing high amount of acrylic acid (S1) is greater than the one containing less amount of acrylic acid (S2) also greater than crosslinked chitosan (S0).

The release of Paracetamol was generally the greatest in sample (S1) from the other samples (S0, and S2). These differences in release percent could be attributed to the amount of acrylic acid.

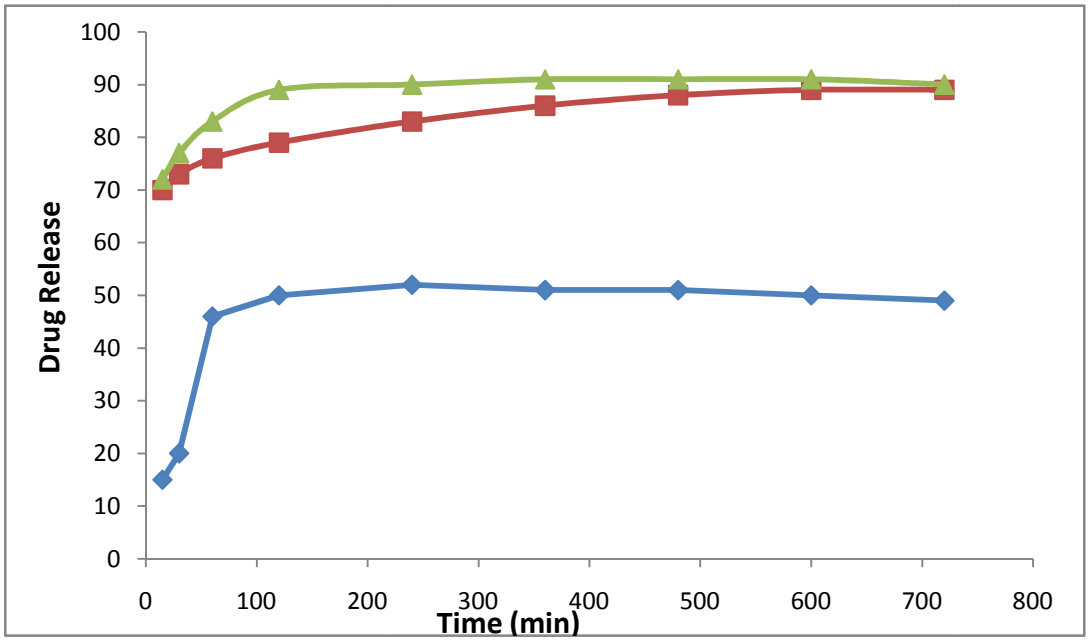

Figure 3.1: Effect of time on % drug release at pH=1.2

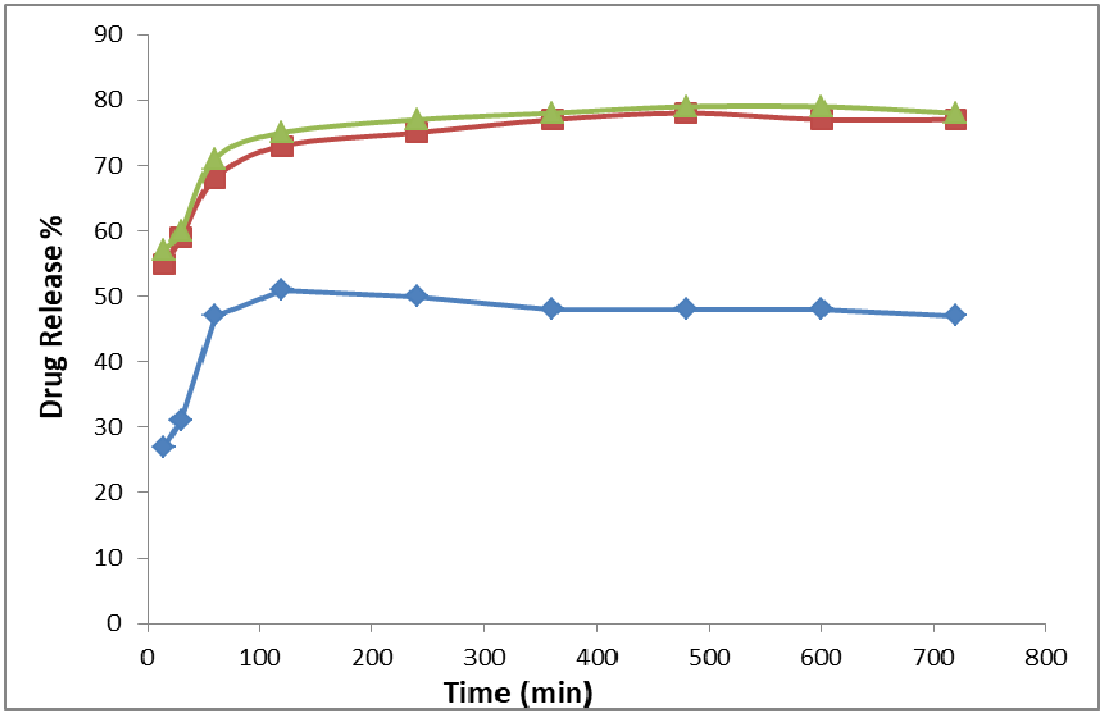

Figure 3.2: Effect of time on % drug release at pH= 7.4

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3.4. Kinetic Study for Paracetamol drug release

The data presents in table 2 according to various kinetic models, it is obvious that. The best linearity was found to be (R^2 = 0.4426, 0.91, and 0.0989) for S0, S1, and S2 respectively related to Higuchi's equation**.**

Table 2: Kinetic data for Paracetamol drug release

	Koresmeyer – peppas		**Higuchi Equation**		**Zero order equation**		**First order equation**	
	R^2	K	R^2	K	R^2	K	R^2	K
S0	0.3252	31.99	0.4426	0.0413	0.289	-0.0011	0.2835	-0.0005
S1	0.582	82.455	0.91	0.0217	0.7371	-0.0006	0.8729	-0.0011
S2	0.1089	69.666	0.0989	0.0106	0.1191	-0.0004	0.1548	-0.0007

4. Conclusion

Graft copolymerization of AA and HEMA onto chitosan improve loading and release Paracetamol comparing with chitosan crosslinked with glutraldehyde. The addition of AA improves the homogeneity of grafted polymers onto chitosan nanoparticles and also increased the drug release profile in both pH values 1.2 and 7.4. Kinetic study of Paracetamol drug was studied using four equations and the results confirmed that the Paracetamol drug diffusion from chitosan polymeric material obeys Higuchi Equation.

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