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PREPARATION AND CHARACTERIZATION OF pH SENSITIVE HYDROGEL FOR SUSTAINED RELEASE OF METOCLOPRAMIDE

Humaira Sultana[1,2], Rabail Khaliq[2], Sameera Khurshid[2], Sumaira[1]

[1]Department of Pharmaceutics, Faculty of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur Pakistan.
[2]Bahawalpur College of Pharmacy, Bahawalpur Medical and Dental College, Bahawalpur, Pakistan

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ABSTRACT

Objective: The aim of present research work was focus on preparation of PVA/SA hydrogels for Metoclopramide HCl drug release and investigates swelling and release study. **Method:** Chemical cross-linking method was used for the preparation of PVA/SA hydrogels in which glutaraldehyde was used as cross linker. By changing the concentration of polymers and cross linker different samples were prepared. **Results:** Characterization was done by FTIR, Sol gel analysis, swelling studies. Release studied was carried out at λmax $(274nm)$ in pH (1.2-7.5) of phosphate buffer and its absorbance was determined by using UV spectrophotometer. Zero order, 1st order, Higuchi and Korsmeyer- Peppas model were used to evaluate the drug release. **Conclusion:** It was concluded from the study that hydrogel could be one of the best approaches to enhanced sustained release of metoclopramide.

Keywords: Hydrogels, Cross-linking, Sodium alginate, Polyvinyl alcohol, FTIR.

*Corresponding Author. E-mail: madni3570@gmail.com; Mobile No. +923337306404

INTRODUCTION

Three-dimensional, cross-linked network of hydrophilic polymers which swell-up in biological fluids and water are called hydrogels. These polymeric networks have the proficiency to clench water within its porous structure. The hydrophilic groups which are present in the polymeric chains such as (amino, hydroxyl and carboxyl) increase the water holding ability of the hydrogels **[1]**. Hydrogels are categorized into two classes based on physical and chemical nature of the crosslink junction. Polymer networks which are chemically cross linked have permanent junction, while physically cross-linked networks have transient junctions **[2]**. A polymeric network devoid of water is called xerogel. The quantity of water present in the hydrogels may vary from 10% to 1000 times of the weight of xerogel. There are two main factors upon which the water carrying ability of xerogel is dependent. First one is the numbers of hydrophilic groups and second one is the density of the cross linker. Poly (vinyl) alcohol (PVA) was discovered serendipitous in 1924. Hydrogels based on the PVA are prepared by either chemical or physical cross-linking methods. To cross linked PVA difunctional cross linking agent can be used. Formaldehyde, glutaraldehyde, monoaldehydes and acetaldehyde are difunctional cross linking agents which have been used for the preparation of PVA hydrogels. The acetal bridge is formed between the hydroxyl groups of the PVA chains, when these cross-linking agents are used in the presence of acetic acid, sulfuric acid, or methanol. PVA hydrogels are non-carcinogenic non-toxic, and bio adhesive in nature. They have been used for numerous pharmaceutical and biomedical applications **[3]**. Uses of PVA gel for the drug delivery, the lining for artificial heart and contact lenses. PVA is mainly used in topical, ophthalmic and pharmaceutical formulations. It is used as a stabilizer in emulsions (0.5%w/v), as a viscosity increasing agent for viscous formulations such as in topical lotions (2.5%w/v), ophthalmic products (0.25-3.00%w/v) and as a lubricant in transdermal patches, sustained release oral formulations and contact lenses Sodium alginate (SA) is a linear, hydrophilic polysaccharide, which is naturally occurring polymer. Like PVA it is also a water-soluble polymer. SA present in cream color powder. Its solution is prepared by dissolving the desired quantity of SA in distilled water with continuous stirring at 60C◦for 1hr. It is obtained from alginic acid. It has a carboxyl ate group in the side chain **[4]**. It is cross linked ionically by combining of divalent cations such as

(Mg^{2+}, $Ca2^{+}$, $Sr2^{+}$and Ba^{2+}). in aqueous solution to enhance gelation by non-covalent cross links. The gelation time and young modulus are dependent on the alginate and cations concentration. The cation acting as a cross linking agent between the carboxyl ate groups which are present in the alginate molecules. The divalent cations magnesium and calcium are present in solution at concentrations in the range 5-10 M. SA has many applications in pharmaceutical and biomedical and fields.

MATERIALS AND METHODS

Materials

(PVA) (MW-13000-23000g/mol) (Merck Germany) and other polymer was Sodium Alginate (Shanghai China) Glutaraldehyde (Schlaru Chemie S.A). Potassium dihydrogen phosphate, Sodium hydroxide and hydro-chloric acid (Merck Germany) was also used. Chemicals of analytical grade were used.

Methodologies

In this work number of cross linked hydrogels of PVA/SA with various polymeric compositions and cross linking level was prepared. The method used is given below. Calculated amount of PVA was dissolved in predetermined amounts of water under continuous stirring at 150-200 rpm at temperature of 95℃. Desired amount of sodium alginate was weighed and dissolved in water at 60℃ for 1hr with continuous stirring until a clear solution obtained. PVA solution was mixed to the prepared sodium alginate solution and stirring was done for 30 minutes. Gultaraldehyde as a cross linker was added slowly. Distilled water was added to make up the volume to 100 grams **[5]**. The final volume of solution was made 100grm with distilled water. After mixing thoroughly, the final solution was poured into the glass tubes. The capped tubes were placed in water bath and the temperature was gradually increased and maintained at 45℃ for 1h, 50℃ for 2h, 55℃ for 3h, 60℃ for 4h and 65℃ for 12h.

CHARACTERIZATION OF PH SENSITIVE HYDROGEL

Dynamic Swelling Ratio

q =Wh/Wd

Where, Wh = weight of swollen gel disc at time t

Wd = initial weight of dry gel disc

The following formula was used to calculate the dynamic swelling ratio

S (Dyn) % = [$(Wh - Wd)/Wd$] X 100

Equilibrium Swelling Ratios

For studying the equilibrium swelling, same solution was used to keep these samples in it continuously. Until hydrogels became constant in weight these studies were kept on. **[6,7]**.

The given equation was used to calculate these ratios

S (Eq) = Wh/Wd

Where,

Wh = weight of hydrogel in swollen state at equilibrium, $Wd =$ The initial weight of dry hydrogel.

Sol-gel Fraction

The extraction process was used to perform sol-gel analysis this study was done to evaluate uncross linked polymers in gel. After extraction, gel was dried in vacuum oven at 45 ^{0}C to gain constant weight. W_0 and W_1, the initial weights of dried hydrogel and extracted dry gel. Equation used is given below **[8]**.

Sol Fraction (%) = [W_o-W_i/W_o] × 100

Gel Fraction (%) =100-Sol fraction

Drug Loading and Drug Release

Method of Drug Loading and its Determination

For drug loading six samples were selected. Three of them are those in which poly vinyl alcohol concentration was changed while in other samples cross linker concentration was changed. 1% weight/volume of drug solution was prepared in distilled water. For drug loading, disc was immersed in drug solution until equilibrium swelling was achieved. The fully swelled disc was removed from the drug solution and was bolted with filter paper in order to remove the drug solution on the surface. After drug loading the loaded disc were first dried at room temperature and then dried in oven at 40-45C until constant weight was achieved **[9,10]**. Three methods were used for determining the drug loading in hydrogels

First method used the following equation to calculate the amount of drug loaded in hydrogel

Amount of drug = W_D-W_d

Drug loading % = [(W_D-W_d)/ W_d] x 100

Where, W_d and W_D are the weight of dried hydrogel before and after immersion in drug solution.

Drug Release Studies

The paddle apparatus recommended by USP was used to study the release pattern of drug. For this purpose, drug loaded disc were immersed in the dissolution medium maintained at 37 ˚C in order to maintain a uniform concentration of drug in the medium the solution was stirred at 100 rpm. Distilled water was used for dissolution purpose. The dissolution was done for 12 hours with constantly taking the aliquots after specified intervals throughout the procedure while replenishing with fresh distilled water and absorbance was analyzed for studying the release pattern of drug in the UV spectrophotometer and compared with the standard curve of the drug. The amount of drug release from the hydrogels disc was noted by Mα. Mt/Mα denotes the fraction of drug release **[11,12]**.

Table I: Different formulations of PVA/SA based hydrogels for drug delivery.

Samples No.	PVA/100g of solution	SA/100g of solution	Wt. ratio %	GA/100g of solution	GA/wt. %
S_1	3 g	2 g	60/40	0.5 g	3%
S_2	4 g	2 g	67/33	0.5 g	3%
S_3	5 g	2 g	72/28	0.5 g	3%
S_4	4 g	1.5 g	80/20	0.5 g	3%
S_5	4 g	1.3 g	75/25	0.5 g	3%
S_6	4 g	1 g	73/27	0.5 g	3%
S_7	4 g	2 g	67/33	0.42 g	2.9%
S_8	4 g	2 g	67/33	0.45g	2.7%
S_9	4 g	2 g	67/33	0.49 g	2.5%

Table 2: Gel fraction of PVA/SA hydrogels.

Sample No	PVA/SA ratios	Glutaraldehyde	Gel fraction
S_1	60/40	3.0	94.0
S_2	67/33	3.0	94.3
S_3	72/28	3.0	94.5
S_4	80/20	3.0	95.0
S_5	75/25	3.0	88.0
S_6	73/27	3.0	85.0
S_7	67/33	3.5	95.0
S_8	67/33	3.7	96.0
S_9	67/33	3.9	97.0

RESULT

pH Effect on Release and Swelling

Three-dimensional semi IPNs hydrogels were prepared from PVA and SA deploying. These hydrogels were sensitive to the pH due the cationic polymer sodium alginate. However, PVA not sensitive to the pH of the medium because it contains neutral hydroxyl moiety, in this case swells at lower pH because of the influence of the sodium alginate. Although swelling occurs at pH 7.4 but is less then that occurs at lower at lower pH because at lower pH sodium alginate shrinkage and does not release drug. At lower pH PVA swelling is enhanced by the cationic groups due to electrostatic repulsive forces that allow entry of water into the gels which also causes the swelling of PVA due to entrapment of water. As PVA concentration increases the swelling increases, while increases SA concentration resulting decrease swelling **[13,14].**

Sol-gel Analysis

Uncross linked polymer present in the hydrogels was determined by gel analysis. A minor increase in gel portion was observed with increase of PVA concentration and a profound increase in gel portion was seen by increasing the cross linker.

Impact of Concentration on Swelling

Hydrogels with the varying concentration of PVA from three samples were selected (S_1, S_2 and S_3) in these samples swelling increases with increase concentration of PVA. as shown in table 5.3,5.4 and 5.5. This is because of free hydroxyl groups available for swelling and water interaction **[15]**. Among the prepared nine samples three samples (S4-S6) with varying concentration of sodium alginate were selected for the pattern of swelling. These samples showed swelling at pH 7.4. Hydrogels with the varying concentration of cross-linker (2.5, 2.7 and 2.9). Three samples were selected (S7, S8 and S9). In these sample swelling increases with increase cross-linker concentration.

Table 3: Swelling ratio of PVA/SA.

Sr No.	pH 7.4		pH 1.2	
	Q	Eq	Q	Eq
S_1	5.6	11.25	3.2	5.00
S_2	4.2	10.03	3	4.00
S_3	4.0	8.57	2.8	4.28
S_4	5.3	15.5	3.0	5.55
S_5	5.0	13.3	3.2	5.00
S_6	4.6	12.30	3.1	4.61
S_7	5.1	7.27	3.1	4.54
S_8	4.4	8.18	2.9	4.54
S_9	6.3	13.13	3.7	5.55

Table 4: Amount of metoclopramide HCl released.

Sample No	Drug released %	
	pH 7.4	pH 1.2
S_1	88.4	72.43
S_2	94.67	74.37
S_3	96.24	74.41
S_7	88.48	70.43
S_8	78.4	64.43
S_9	75.06	62.01

Mechanism of Drug Release

Drug release happened when the hydrogels imbibe by the absorption of the solvent (water). Entry of water into the hydro-gel results in the dissolution of the drug inside the structure of gel and release occurred when the hydrogels finally swelled. The behavior of loading and release of metoclopramide HCl was directly related to the swelling. In order to study the release order of drug values of "r" were considered, keeping in mind the criteria that model for drug release would best fit for which values of "r" would be near to "1". So, the model that best fit with Metoclopramide HCl release was first order. These values of (K) and (R^2) have been shown in the tables. However, values for "R^2" for Higuchi drug release model have shown diffusion-controlled mechanism for the Metoclopramide HCl release, because the plot was linear when plotted b/w fraction of drug release. The intercept and slope of "In M t / $M\infty$ " in Korsmeyer-peppas have been manipulated to evaluate the value of "n". The results for values of "n" have depicted a non-Fickian release of Metoclopramide, because obtained values were b/w 0.45-1 **[16]**.

FTIR Analysis

The spectra of SA were described as having a broad peak that is caused by C-H stretching vibrations at a wavelength of 2871 cm^{-1}. The amide group's N-H vibration is attributed to the peak at 1585 cm^{-1}.1407 cm^{-1} is stretching vibration of COO-group. Alkoxy bond's C-Stretching in SA comes at 1046 cm^{-1}. OH, stretching at 3300 cm^{-1} occurs in the IR spectrum of PVA. Two peaks at 2938 cm^{-1} and 2907 cm^{-1} show -CH groups stretching in alkanes. Hydrogel displays significant absorption peak at 1161 cm^{-1} because a feature of PVA-derived -C-O stretch. The -COOH groups of SA are responsible for a few prominent peaks visible between 1547 and 1691 cm^{-1}. The presence of drug was confirmed in the SA/PVA hydrogel by its spectra **[17]**.

Table 5: Polymers and crosslinker effect on drug release pattern by employing different kinetics models.

Sample No	PVA/GA composition	pH	Zero-order		First-order		Higuchi model		(n)	R	Release order
			K_o	R1	K_o	R2	K_o	R3			
S1	3	1.2	8.095	0.985	0.095	0.995	18.287	0.990	0.957	0.995	Non-Fickian
		7.4	8.321	0.932	0.139	0.995	23.065	0.993	0.830	0.991	Non-Fickian
S2	4	1.2	8.765	0.954	0.109	0.992	19.894	0.986	0.884	0.988	Non-Fickian
		7.4	8.990	0.956	0.187	0.985	27.011	0.983	0.743	0.979	Non-Fickian
S3	5	1.2	9.948	0.954	0.133	0.992	22.36	0.986	0.647	0.979	Non-Fickian
		7.4	9.234	0.965	0.232	0.996	29.113	0.989	0.565	0.986	Non-Fickian
S7	2.5	1.2	8.090	0.986	0.077	0.984	15.793	0.971	1.226	0.998	N0n-fickian
		7.4	8.223	0.945	0.131	0.978	22.661	0.976	1.041	0.985	Non-Fickian
S8	2.7	1.2	7.193	0.990	0.69	0.992	16.383	0.982	1.006	0.990	Non-Fickian
		7.4	7.32	0.992	0.111	0.990	20.300	0.985	0.948	0.991	Non-Fickian
S9	2.9	1.2	6.794	0.996	0.081	0.993	14.602	0.981	1.093	0.998	Non-Fickian
		7.4	6.987	0.9973	0.150	0.9923	19.244	0.9881	0.913	0.9971	Non-Fickian

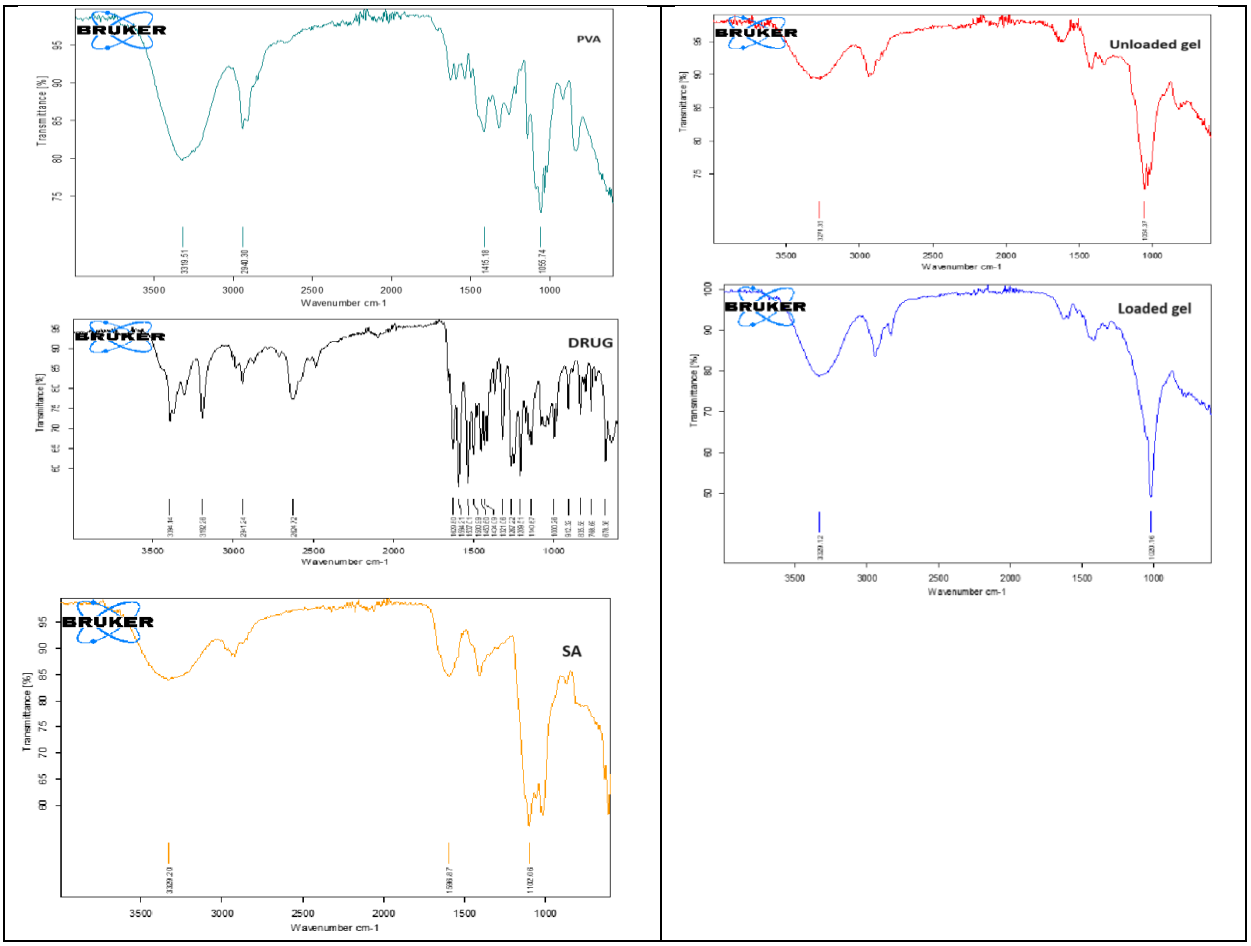

Figure 1: FTIR spectra of (PVA, SA, drug, unloaded hydrogel and loaded hydrogel).

CONCLUSION

The hydrogels have shown the excellent capacity for association of drug metoclopramide using the polymer sodium alginate and polyvinyl alcohol. The objective of this research was to formulate hydrogel by crosslinking method. The prepared hydrogel was characterized by FTIR, Sol gel analysis, swelling studies. Release studied was carried out at λmax ($274nm$) in pH (1.2-7.5) of phosphate buffer and its absorbance was determined by using UV spectrophotometer. Zero order, 1st order, Higuchi and Korsmeyer- Peppas model were used to evaluate the drug release. Results of all parameters were satisfactory and confirmed that prepared hydrogel can be effectively used for enhancing drug release in sustained manner.

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