World Applied Sciences Journal 27 (2): 236-249, 2013
ISSN 1818-4952

DOI: 10.5829/idosi.wasj.2013.27.02.81106

Study and Evaluation of *Poly (N-vinyl-2-pyrrolidone)* Hydrogel Swelling, Theophylline Loading and Release

[1]*Sudhair Abbas,* [2]*Bashir Ahmad,* [3]*Zafar Iqbal,* [3]*Shumaila Bashir and* [4]*Javid Ali*

[1]Department of Pharmacy, Abasyn University, Peshawar, KPK, Pakistan
[2]Center of Biotechnology and Microbiology, University of Peshawar, KPK, Pakistan
[2]Department of Pharmacy, University of Peshawar, KPK, Pakistan
[4]PCSIR Laboratories Complex Peshawar, KPK, Pakistan

Abstract: Hydrogels technology has been used by several research workers in the delivery of controlled-release drug systems due to their good tissue compatibility and easy manipulation of swelling degree and therefore, permeability of solute. The desired kinetics, duration and the release rate of theophylline from hydrogels was restricted to certain circumstances, such as properties of hydrogels, incorporated quantity of drug, solubility of drug, drug polymer-concentration and drug-polymer interactions. This research work revealed that the structural and compositional effects of hydrogels on loading, swelling and release and approaches to characterize solute release behavior in a dynamic state. Maximum swelling was observed at pH 7. The theophylline was loaded on the hydrogel discs and the percentage of drug loaded in the hydrogel discs. The hydrogel discs in solution of 0.1 N HCl and phosphate buffer solution showed 34.67 % loading of theophylline respectively. The loading was not significantly different in both media. Mostly release kinetic followed release of theophylline from loaded hydrogel Higuchi model. The drug released was very slow and only 9.5 % from the hydrogel loaded with theophylline in the solution of 0.1 N HCl in 72 hours. While in basic medium release was 95 % from theophylline loaded hydrogel. The analytical solution for network displacement was used to predict solvent intake by swelling hydrogels, solvent efflux from de-swelling hydrogels and changes in pressure, porosity and effective drug diffusivity. The solvents uptake was 86 % by hydrogels with Bis as cross-linker. These in turn influence drug uptake during and after hydrogel swelling and drug release from hydrogel during and after de-swelling. Drug uptake in swelling and drug release from these into a target liquid were investigated here.

Key words: *Poly (N-Vinyl-2- pyrrolidone)* Hydrogel · Theophylline · Drug release · Loading · Buffer solution · 0.1 N Hcl · Dissolution medium

INTRODUCTION

Life is polymeric in the sense that main components of living cell are protein, nucleic acid and carbohydrate which all are polymers. Nature uses these polymers both for as a part of complicated cell machinery as well as for the construction of living organism [1]. Hydrogels are class of polymer having two or multi-component systems composing of three dimensional, physically or chemically cross-linked structures capable to absorb large quantity of water or biological fluid but in which they are insoluble [2]. Hydrogels have ability for absorbing large quantity of water without being dissolved in water or biological fluids. The high quantity of water of these materials improves their biocompatibility, making them more ideal class of synthetic biomaterials. Swelling equilibrium of chemically cross-linked hydrogel ensures, if the osmotic force is forcing the liquids into the hydrogel is balanced reasonable through elastic force of the stretched sub-chain [3]. The osmotic force in case of uncharged structure is located by the solubility of chain in the surrounding media. When hydrogels has been classified as in the group of charged hydrogel, the osmotic force is forcing the amount of solvent into the hydrogel which is

Corresponding Author: Javid Ali, PCSIR Laboratories Complex Peshawar, KPK-Pakistan.

governed by the repulsion of electrostatic forces between charges [4]. Water and other small ions which may be counter ions and additional salt that are unbound salts to enter and come out from hydrogel. The charges is characterized by the permanent charges which are connected to hydrogel chains and they are "charge regulating" as their ionization is related to electrochemical equilibrium (dissociation of protonated moieties will be high in pH however stay un-ionized in low pH) [5].

Hydrogel may be homo-polymers or copolymers, derived from two or more monomers. Generally, there are two classes of hydrogels, physical gels (pseudo-gels), where the chains are attached by hydrogen bonds, hydrophobic interactions, electrostatic forces or chain entanglements and chemical hydrogels (true, permanent) with covalent bonds that link the chains. From cytotoxicity point of view, hydrogel have safe profile, even though mainly toxicity is associated with mostly un-reacted monomers, oligomers and initiators. Therefore, it is important to remove un-reacted monomers with de-ionized water after the reaction is completed [6]. Hydrogels are generally classified by several ways into numerous categories Based on ionic charges, they are classified as, cationic hydrogels, anionic, neutral, or ampholytic hydrogels [7]. On the basis of monomers units, co-polymer, homo-polymers and multi-polymer hydrogels [8]. On the basis of physical structural features, they are classified as, amorphous, semi crystalline, complexation structures or hydrogen-bonded [9].

Theophylline is one of the bronchodilators belongs to methylxanthine group used for asthma and stable chronic obstructive pulmonary diseases. To achieve good efficacy profile should be used in combination with $beta_2$ agonist such as salbutamol and terbutaline methylxanthine include theophylline found in tea, theobromine found in cocoa and caffeine found in coffee. Also present in candy and chocolate. Cola drinks. Contain 86 % theophylline. Aminophylline is one of the theophylline salts. Theophylline is chemically a methyl xanthine derivative recommended to be used in COPD and asthma but its use has been restricted due to its potential for toxicities at very low concentrations. Theophylline naturally occurs in *Camellia sinenses* and *Coffea Arabica*, having close structural resemblance to caffeine, but the concentration present is less than that required for its minimum therapeutic effect. Quantity as greater as 3.7 mg/g have been acknowledged in *Criollo cocoa* beans [10, 11].

MATERIALS AND METHODS

Chemicals: Azo-iso-butyronitrile (AIBN) (Merck chemicals), N-N methylene bis acrylamide (BIS) (Morgan chemicals), Triethylene glycol divinyl ether (DEV-3) (Sigma), Divinyl benzene (DVB) (Fisher scientific), Vinyl pyrrolidone (VP) (Sigma), ethylene dimethacylate (EDMA) (Fisher scientific), Ammonium per sulphate (APS) (Merck chemicals), Theophylline (Sigma) and deionized water. Similarly, bovine serum albumin (BSA), dextran and PVP (Sigma) sample grade.

Buffer Solution: Phosphate buffer solution of pH 6.8 was prepared according to USPXXVI. Dissolved 76 g of tri-basic sodium phosphate in distilled water for preparing 1000 ml of solution. Mixed 250 ml of this solution with 750 ml of 0.1 N HCl and if required, must be regulating with 2 N HCl or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.

Purification of Vp Monomers by Vacuum Distillation: VP monomer was distilled by setting the apparatus with vacuum pump at a pressure of 4.5 mm Hg and the boiling point was maintained in about 80-81°C, pure VP monomer thus achieved was sealed in bottle and stored in freezer.

Instrumentation

UV-Visible Spectroscopy: The double beam UV-Visible spectrophotometer (Shimadzu1606) was utilized for measuring the absorbance of pharmacological substances, of aliquots of dissolution environment drawn at particular time intervals throughout *in-vitro* dissolution testing to investigate the solution theophylline.

High Performances Liquid Chromatography (Hplc) Analysis: High Performance Liquid Chromatography analysis was performed on Perkin Elmer series 200 pump and analytes were distinguished by using U.V-visible detector of Perkin Elmer series 200. The detector response was observed with a chromatocorder 12 (SIC system instrument). S.S (Stainless steel) column filled with ODS C-18 hypersil, 5 ^m, 250 x 2.5 mm (Eka Chemicals AB lab) was utilized for separating the analytes. The column was shielded with the pre column packed Bonda Pak TM C-18 cartridge (Merck KGa A, Germany).

Scanning Electron Microscopy (SEM): Electron microscopy was used for determining the hydrogel pores sizes.

Dissolution Apparatus: USP Dissolution Apparatus II (Pharma Test Germany) was utilized for the investigation of *in-vitro* testing of dissolution.

pH Meter: pH meter Model 420A of Orion company was utilized to evaluate the pH of unlike solutions.

Synthesis of Hydrogel: Different experiments were performed to prepare stable, transparent and rubber like soft and white hydrogels. For this purpose, different concentrations of cross-linkers were used with same procedure and got hydrogel with different swelling ratios and percent conversion. Some of the experiments were as:

Synthesis of *Poly (N-vinyl-2-pyrrolidone)* Hydrogel: 72.8 g vinyl pyrrolidone (VP) was taken in conical flask and 0.560 g crossed linker N-N methylene bis acryl amide was added. This was followed by 0.335 g Azo- isobutyronitrile as initiator. It was degassed with nitrogen to remove oxygen (O_2) which acts as chain terminating agent and put it in test tube, sealed it and heated it on water bath at 50°C for 3 hours, at 60°C for 2 hours, at 70°C for 24 hours and 2 hours at 80°C. Measured hydrogel (Xerogel) and swell it in deionized water to remove any unreacted polymers. The transparent soft rebury like soft hydrogel polymer was obtained. The percentage conversions (CR) were calculated using the following equation:

$$CR(\%\ \text{conversion}) = \left(\frac{M_0}{M}\right) \times 100$$

Where Mo is the weight of monomer + cross linker + initiator and M is the weight of Xerogel.

The % conversion was about 60 %.

Studies of Physical Properties of Hydrogels

Drug Loading: Loading of drug ability of hydrogel disc was considered by using method described elsewhere [12]. Hydrogels were cut in standardized sizes (0.3 cm in thickness and 1.5 cm in diameter), weighed up precisely and soaked in saturated aqueous solution (100 ml) of theophylline for three days in beakers of 250 ml to accomplish swelling equilibrium. The hydrogels disc were then removed from the solution and precisely weighed, the excess of solution from the disc of hydrogel surfaces were removed by the use of filter paper and were kept in freezer for first 2 hours, followed by refrigerating for 12 hours. The substances were then moved to the room temperature for absolute drying.

Table 1: Synthesis of hydrogels from N-vinyl-2 pyrrolidone (VP) cross linked by N, N methylene-Bis- acrylamide (Bis) and with imitator Azo- isobutyronitrile (AIBN).

Monomers	Cross linker	Initiator	% Swelling1 Ratios	% conversion
VP-100	EDMA0.3 mol %	AIBN	96	60
VP-100	Bis 0.25 mol %	AIBN	95.4	66
VP-94.5	BIS 0.25 mol %	AIBN	96	62
VP-96.5	EDMA 0.25 mol %	AIBN	92	61
VP-93.7	Bis 0.25 mol %	AIBN	79	88
VP-90	Bis 0.25 mol %	AIBN	82	60
VP-97	DVE-30.5 mol %	AIBN	90	57
VP-99	DVB 0.25 mol %	AIBN	85	55
VP-75.8	BIS 0.35 mol %	AIBN	87	92

"The amount of drug loaded in the hydrogel was calculated i.e. the amount of drug loaded is equal to weight of dried disc after equilibrating in drug solution minus weight of the Xerogel". It was crossed checked by measuring the concentration and volume of the solutions of the medium before and after the swelling of the hydrogel.

Studies of Drug Release from Hydrogels: The release of drug properties from hydrogel were evaluated under the normal physiological pH conditions of the gastro intestinal tract. The gels, in triplicates were immersed in three different pH conditions, under acidic condition 0.1N HC1, basic atmosphere, phosphate buffer pH 6.8 and under both acidic and basic conditions where gel was first placed under acidic environment (for 2 hours) and then in the basic solution for rest of the time). For this purpose dried gel discs were divided into three groups, GS1, GS2 and GS3, for drug release in 0.1N HC1, Phosphate buffer pH 6.8 and for 0.1N HC1 for first two hr, then washed with water and dried with filter paper and moved to Phosphate buffer pH 6.8 for the rest of time respectively to study the released kinetics of theophylline. The temperature of the medium 250 ml was maintained at 37°C throughout the studies. The sample 1 ml was collected periodically at 0, 0.5, 1, 2, 4 and then after every 4 hours and stored in freezer at -20 °C until analysis. The same volume of the fresh media was replaced after withdrawing of the samples. The amount withdrawn with the samples were compensated by calculation as recommended for dissolution testing of solid dosage forms.

Measurement of Swelling Ratio: The swelling ratio of the hydrogel were measured by immersing the pre-weighed gel discs in de-ionized maintained at 25 °C and after every

one hour it was removed, wiped with moistened filter paper to remove water from the surface and weighed again. The temperature was controlled through thermostatic water bath (Grant precision stirred bath. Grant Instrument Ltd. Cambridge UK) with a precision of ± 0.1 °C. "The swelling ratio is defined as the weight of adsorbed water present in the swollen gel (Ws) divided by dried weight of the gel (Wd)." The percentage of swelling proportion was considered by the use up the below formulation.

$$SR(\%) = \left(\frac{W_s}{W_d}\right) \times 100 \quad (2.1)$$

Measurement of Re-swelling Kinetics: After the hydrogels surface had been wiped with moistened filter paper to remove water and the de-swelling Kinetics of the hydrogels was measured gravimetrically at 60 °C. When the equilibrium is achieved at 25 °C in demonized water, then after the equilibrium, the hydrogels are transferred from demonized water at 25 °C to 60 °C. After the regular interval of time at 60 °C in demonized water the hydrogels are weight water retention is defined as:

$$Wi = \frac{(W_t - W_d)}{W_s} \times 100 \quad (2.2)$$

Where as Wi is weight of hydrogels at certain time period. The swollen hydrogels samples were first freeze-dried for at least 24 hours and the dried gel also known as Xerogel were immersed in demonized water to reabsorb water at 25 °C. During the process of re-swelling, the sample were removed and weighed after being wiped with moistened fitter paper. The water up take was calendared using the following equation.

$$Wup = \frac{(W_t - W_d)}{W_s} \times 100 \quad (2.3)$$

Measurement of De-swelling and Re-swelling Kinetics: The hydrogels de-swelling kinetics was calculated gravimetrically at 60 °C after wiping the sample surfaces had been wiped with moistened filter paper to remove water from the hydrogels surfaces. When the sample of hydrogel reached to equilibrium in de-ionized water at 25 °C and transferred to hot de-ionized water at 60 °C. At regular intervals of time, removed the hydrogels Samples from the de-ionized water and it was weighed. Water retention is defined as:

$$Wi = \frac{(W_t - W_d)}{W_s} \times 100 \quad (2.4)$$

Where Wi is weight of hydrogel at certain interval of time.

Re-swelling kinetics of gel was studied using method described elsewhere [13]. The swollen samples of hydrogel were first freeze-dried for at least 24 hours and then the dried samples of hydrogels were sink in de-ionized water for reabsorbing of water at 25 °C, during the re-swelling course, removed the sample and weighed after being wiped with moistened filter paper. Water uptake was calculated using following equation:

$$Wup = \frac{(W_t - W_d)}{W_s} \times 100 \quad (2.5)$$

***In-vitro* Release Studies:** Evaluation of the *in-vitro* dissolution studies was done by the dissolution apparatus II used as mentioned in US Pharmacopeia. Studies of *in-vitro* release of drug, from the prepared matrix tablets were performed for a period of 12 hours. A six station USP type II apparatus was used at 37 ± 0.5 ℃ and 50 rpm. Experiment was performed in triplicate for 12 hours (initial 2 hours within 0.1N HCl. Rest of 10 hours were in phosphate buffer solution of pH 6.8 under sinks condition. The samples were drawn after every 1-hour from the dissolution medium which was then replaced with fresh medium for maintaining the constant volume. Following filtration and appropriate dilution, the sample solution was analyzed at absorption maxima of 268 nm for theophylline using a UV-Visible spectrophotometer. The concentration of drug present in the samples was determined with the help of appropriate standard curves constructed from reference standards in which the quantity of drug dissolved at specified periods of time was plotted as percent release versus time (hours) curve in y axis and x axis respectively.

Calibration Curve for Theophylline: Standard curves for theophylline was constructed in the range of 2.5 - 34.5 mcg/ml. Different solutions were prepared from the stocked solution using water and methanol as solvent. The absorbance of the solutions was measured against solvent. The regression analysis showed the linear relationship between the concentration and the concentration of theophylline and instrument responses ($R^2 = 0.9967$). The Figure 4 showed that the technique is relatively appropriate for the investigation of the theophylline in this range of concentration.

Data Analysis: The result obtained after the dissolution data obtained for hydrogel discs and matrix tablets were then analyzed and these results were then tested using

different mathematical model. The inner regression was applied for the whole obtained to data in all model to evaluate the released of drugs mechanisms.

Release Kinetics: The release kinetics of theophylline was studied from the matrix tablets, the release data were subjected to the following equations:

Zero Order Equation:

$Qt = KO.$

Where Qt is the percentage of drug released at "t" time and k0 is the release rate constant:

First Order Equation:

ln (100 - Qt) = ln 100-K1.t

Where k1 is the release rate constant:

Higuchi's Equation:

$Qt = kH.t^{1/2}$

Where kH is the Higuchi release rate constant:

Hixson-Crowell:

$$(100 - Q_t)\frac{1}{3} = 100 \times \frac{1}{3} - kHc.$$

Where kHC is the rate constant for Hixson-Crowell equation:

More, in order to distinguish the mechanisms of drug release from hydrogel disc as well as from matrix tablets, the Korsmeyer's-Peppas, semi-empirical form was used:

$$\frac{Q_t}{Q_\infty} = kHP.t_n$$

Where Qt/Q8 is the fraction of drug released at time t, kKP a constant compromising the structural and geometric characteristics of the device and n, the release exponent, which is indicative of the mechanism of drug release [13-16]. For the case of cylindrical geometries such as tablets, n = 0.45 which corresponds to a Fickian diffusion release.

RESULTS AND DISCUSSION

Synthesis of Hydrogels: The changing of monomers into PVP hydrogel with 0.325 g Bis as cross-linker and 0.0115 g AIBN as initiator were more than 92 % in the present preparation. The conversion above 92 % shows complete conversion of monomers [17].The present modified method gave better yield with more than 92 % in the preparation with AIBN as initiator [18]. The reactants were stirred thoroughly and mixture was poured into test tube to obtained polymer disks. The test tubes were sealed to prevent evaporation. After 24 hours, the cross-linked hydrogels were cut into small slabs. The disks were swollen while stirred for 24 hours in distilled water to remove any un-reactant cross-linkers and acids. The water was exchanged many times during this period. Finally the hydrogels were air dried for 24 hours at room temperature followed by a vacuum drying cycle at 50 °C for another 24 hours until a constant weight reached. Gel is swollen system which permits minute particles to move freely and eliminate large particles because of its pore size and size of pores depends upon the monomers or cross-linker concentration. The swelling and de-swelling behavior of the prepared hydrogel was first characterized using aqueous solution. Figure 3.2 and Figure 3.3 showed the swelling and de-swelling ratios and also compared with different cross linkers [19]. The more uptakes was observed for PVP hydrogel prepared with Bis as cross-linker than the other hydrogel prepared with different cross-linking agent and hence can be used for concentrating dilute solution of PVP hydrogel solution and thus proteins [20]. The product obtained was then dried and swelled in de-ionized water for the removal of un-reacted monomers [21], Figures 3.1a, b and tables 3.1, 3.2 showed the percent uptake of water and release of theophylline with various used crossed linkers. However, in some cases good conversion ratios achieved but the swelling ratios were not good. PVP hydrogels prepared through Bis as cross linker as hydrogel micro-carrier were appreciating because these highly crossed linked hydrogels are not dissolved and can be prepared in highly purified form for human use.

Chemical properties of hydrogel like its components, concentration and condition of polymerization was used for the determination of its structure [22]. The degree of hydrogel swelling reduced with enhancing concentration of monomers as well as the extent of cross-linker. However, different researchers have concluded different concentrations of cross-linker and monomers.

EDMA (ethylene dimethacylate), DVE-3(triethylene glycol divinyl ether), DVB (Divinyl benzene), Bis (N, N methylene bis-acrylamide)

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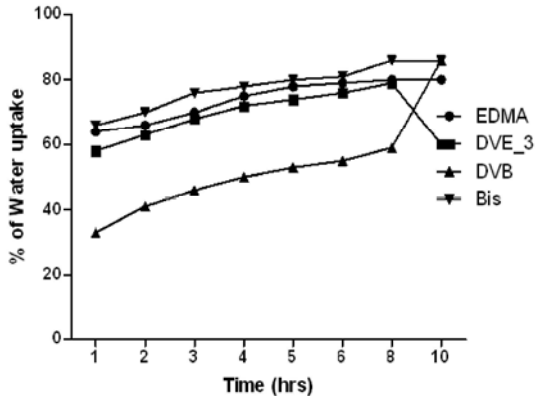

Fig. 1: Swelling behavior variation with time of PVP hydrogel with different cross-linker.

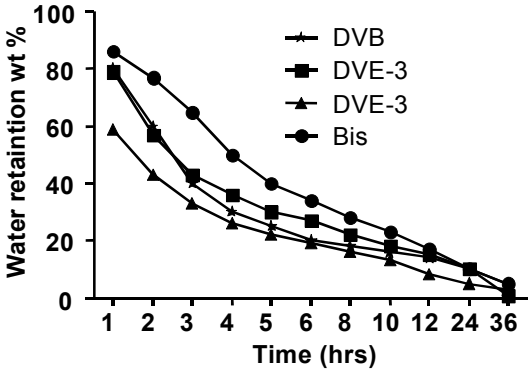

Fig. 2: Graphical representation of deswelling of hydrogel.

Table 2: Effect of cross-linking agents on swelling of PVP.

Time (Hours)	EDMA*	DVE-3**	DVB***	Bis****
1	64	58	33	66
2	66	63	41	70
3	70	68	46	76
4	75	72	50	78
6	78	74	53	80
8	79	76	55	81
10	80	79	59	86

* ethylene dimethacylate), ** triethylene glycol divinyl ether, *** Divinyl benzene, **** N, N methylene bis-acrylamide.

Characterization of Hydrogels: Water in hydrogel exists in two or more different states [23]. Although there was disagreement on the actual structure but it was accepted that water molecules near the polymer segments behave somewhat differently from normal, bulk, water due to interaction with polymer. Water strongly associated with polymer network which bound through hydrogen bonding is often called bound are non freezing water (Wnf) and the normal one, unaffected by the polymeric environment having high degree of mobility referred as free or freezing water (Wf).

In the absence of cross linker the PVP gel dissolved in water, therefore, the cross linking agent Bis, EDMA, DVB and DVE-3 were used in polymerization process to see their ability as cross linker. All PVP samples with Bis, EDMA, DVE-3 and DVB as cross linker were transparent, stable and swollen in the aqueous medium. Table 2 shows percent water up take by Xerogel after different interval of time. After 4 hours % uptake of water by gel with cross linker Bis, EDMA, DVB were 78, 75, 72 and 50 respectively and similarly after 10 hours it reach 86, 80, 79 and 59 showing that cross-linking ability follow the order Bis > DVB > DVE-3 > EDMA as shown in Table 2.

The effect of temperature on the swelling behavior was investigated and variation of equilibrium swelling ratio by the medium temperature showed a continuous decrease unlike sharp discontinuous transition in the equilibrium linear swelling was checked [24]. Here, the equilibrium swelling ratio as a measure of volume swelling was determined based on the gel weight measurement. The curve was reasonably consistent with the previously published results [25] but unlike that of Prazers [26] at the same temperature range with bovine serum albumin. The simple explanation for this was that the usual experimental methods for the determination of linear swelling ratio at any temperature are to measure equilibrium gel diameter at selected points [27]. Also the diameter at one the particular point does not represent the total volume of the sample and only represents the local volume around a particular point [28] thus the sharp transition in the linear swelling curve mean the phase boundary traverses the point at which the measurement is performed. So the proportionality between the linear swelling ratio and the volume swelling ratio breaks down and more gentle volume swelling change are observed relative to change occurred in the linear dimension. Another probability may be that in polymerization system the reactivity of the pendant double of a cross linker is more sensitive to the temperature than the macromolecules.

Swelling of Hydrogels: The dry hydrogels obtained after the polymerization reaction were put into de-ionized water and buffer solution of different pH values (pH 1 to pH 10) in order to check the swelling behavior of prepared PVP hydrogel. First, the hydrogels were cut into equal lengths and diameters i.e.4 mm in length and 2 mm in diameter. Then, the dry hydrogels were weighed and immersed in buffer solution having different pH values i.e. from

Table 3: Weight percent and drug loading of theophylline.

Drug	Medium	Xerogel Weight(grams)	Drug Loaded Weight(grams)	Drug Remaining in solution (%)
Theophylline	HCl (0.1N)	0.00058	0.002	3.60555
	Phosphate buffer (6.8)	0.00153	0.00252	4.5029
	Aqueous solution	0.00721	0.29087	0.20817

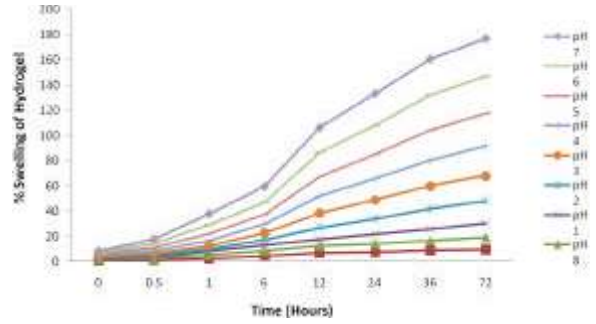

Fig. 3: Graphical representation of percentage swelling of hydrogel in buffer solution having different pH.

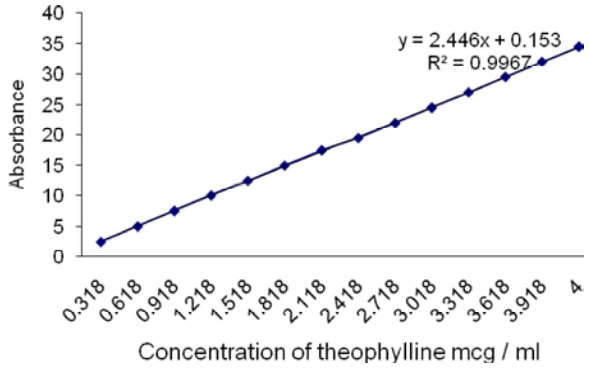

Fig. 4: Calibration curve for theophylline using UV-visible spectrophotometer.

pH 1-10 and at the same time hydrogel was also immersed in de-ionized water. The hydrogels were removed from respective solution after 0.5, 1, 2, 3, 4, 5, 6, 7,8,12, 24 and 36 and 72 hours, dry with filter paper, weighed and again put it into the same solution and weighed till the equilibrium swelling was developed [29]. The maximum swelling was obtained with de-ionized water and solution having pH 7 as shown in Figure 3. The swelling ratio increased with pH up to 7 and then decreased on further increased of pH. Simple explanation for this is that with increasing pH, AA on the hydrogel network chains ionized, resulting in swelling due to osmotic power of the counter ions [30]. Initially, the swelling of hydrogels were very high and after some time the swelling process was decreased and finally achieved equilibrium. Initially the hydrogels were translucent, during the beginning of the swelling phase of hydrogel they became somewhat opaque, which is due to the development of micro-heterogeneities in the hydrogel [31]. However, once the elimination of micro-heterogeneities has been occurred as the hydrogels reached to equilibrium swelling, they come back to full transparency. Such types of these related changes were examined in case of transparency for all hydrogel compositions and agree with the studies of Brazel and Peppas [32]. This swelling of PVP hydrogel is thought to be responsible for controlling the release of drugs. Figure 6 shows the effect on the swelling capacity of cross-linked PVP hydrogels. As this shows there are significant differences between the swelling percentages of this hydrogels in different pHs. In other words this hydrogels is a pH sensitive polymer and well respond to environmental stimuli.

Drug Loading: The study of the hydrogel capability for drug loading of theophylline was carried out in aqueous solution. The hydrogels were cut in uniform size of 4mm in length and 7 mm in diameter, weighed accurately weighed the cut hydrogel disc with the use of physical balance and then placed the weighed hydrogel disc in saturated solution (100 ml) of theophylline (aqueous solution) for 3 days in glass beakers for attaining of equilibrium swelling of the hydrogel disc (maximum swelling) [33]. The hydrogels disc was then removed from the solution and weighed, the excess of solution were removed from the surface of hydrogels disc using filter paper and the loaded hydrogel disc with theophylline was kept for first 2 hours in freezer, then the hydrogel discs were shifted to refrigerator for 12 hours and after which the discs were then removed from the refrigerator and shifted to room temperature for complete drying [33].

The sum of drug loaded in the hydrogels discs was calculated i.e. the degree of drugs loaded is equivalent to weight of the dried hydrogel discs after achieving equilibrium in solution of drug minus the weight of dried hydrogel discs (Xerogel). Simply, the discs of dried hydrogel were swollen to achieve equilibrium in saturated solution of theophylline then dried the hydrogel discs under the similar procedure. The release of drug studies from theophylline hydrogels loaded discs was performed in 0.1N HC1, Phosphate buffer solution of pH 6.8. First both the theophylline loaded hydrogel discs were performed for two hours. The release of theophylline was not greater than 10 % which is acceptable for sustained

release products. The hydrogels discs were then shifted to Phosphate buffer solution of pH 6.8 for the rest of duration for the release of theophylline from hydrogel discs.

Studies of Drugs Release from Kinetic Models: The data obtained was analyzed with the help of First order, Higuchi model, Hixon Crowell models, zero order and Korsmeyer's release models to identify the released mechanism of drugs by which the drugs release from the hydrogels discs.

Drug Loading and Release: Theophylline was loaded into the PVP hydrogel by immersing the dried hydrogel discs into the drug solutions till equilibrium (maximum) swelling achieved. The drug solution was prepared both in 0.1 N HCl as well as in phosphate buffer solution of pH 6.8.

The theophylline was loaded on the hydrogel discs and the percentage of drug loaded in the hydrogel discs is shown in table 3. The hydrogel discs in solution of 0.1 N HCl and phosphate buffer solution showed 34.67 % and 31.77 % loading of theophylline. The loading was not significantly different in both media.

The drugs were loaded in hydrogels in order to evaluate the drug release behavior of these drugs. The slow swelling behavior was observed in the acidic medium for the hydrogel was observed both in the presence and absence of the drug. That may be due to carboxyl moieties of AA are deprotonated in alkaline medium, thus hydrogel swells quickly at higher pH and protonated in the acidic solutions, resulting in shrinkage at acidic pH. The loading capacity of the theophylline was high this may be due to the efficacy of the theophylline for the PVP hydrogel; the high the loading of salicylic acid, the more is its water solubility, in hydrogel consisting of acrylamide and bovine serum albumin, compared with the sodium benzoate. It was also observed that the hydrophilic agents may increase the rate of swelling of the hydrogels [34]. Theophylline being more hydrophilic was deposited at higher rate compared that may be due to hydrogen bonding between polymer and theophylline. Hydrogen bonding may also play important role in the enhanced drug loading. Biodegradation of hydrogels are designed to degrade into biological acceptable and progressively smaller molecules. As the degradation occurred, the imbedded drug is freed into the hosts. In bulk hydrolysis, the hydrogel discs randomly degrade throughout the matrix system. The erosion rate depends upon the volume of the matrix system rather than the thickness of the matrix system and thus the rate of drug release was un-predictable and dumping effect of the dose was usually observed. These systems undergo surface erosion with minimum internal degradation. Therefore, the rate of release is directly related to the degradation rates of hydrogels. Mainly, the general formulations of biodegradable hydrogel materials are micro-particles which used in oral delivery of drug [35].

Drug Release from Theophylline Loaded Hydrogels: The drug released was very slow and only 9.5 % from the hydrogel loaded with theophylline in the solution of 0.1 N HCl in 72 hours [36] that was due to slow swelling of hydrogel in the acidic medium. It is known that the carboxylic acid group of the acrylic acid deprotonated in the alkaline medium and protonated in the acidic medium [37]. In alkaline medium hydration of the hydrogels increased due to the electrostatic repulsive forces among the charged groups of the acrylic acid which lead to swelling of the hydrogel discs while in case of acidic environment electrostatic force vanished among uncharged carboxyl groups [38] and ultimately caused to decrease in the hydration of hydrogel discs as a result of which controlled the theophylline release in the environment of acid. The released mechanisms of drug from the drug loaded hydrogel discs were evaluated by subjecting the dissolussion data into first-order [39], Higuchi's [40], zero order [41], Hixon-Crowell [42] and Korsmeyer's model [43].

The hydrogel loaded discs with theophylline sinked in phosphate buffer solution at pH 6.8 showed that the higher drug release compared with the hydrogel loaded discs in acidic conditions, about 95 % theophylline was released in 72 hours. It was due to the higher swelling rate of the hydrogel in the solution of phosphate buffer at pH 6.8 and it was also because of its better solubility of the theophylline in the basic pH 6.8. When the loaded hydrogels were immersed for the first 2 hours in 0.1 N HCI and then shifted to the solution of phosphate buffer (pH 6.8) for rest of the duration, the theophylline release from loaded hydrogel disc was very low for first 5 hours and then burst release of theophylline was observed [44].

Different mathematical models like Hixon Crowell, first-order, zero order, Higuchi's were used for the analysis of the dissolussion data which was obtained from dissolussion and Korsmeyer's models for understanding the release mechanisms of drug from loaded hydrogels disc. The rate of release kinetic data for all these mathematical models was used for the analysis of dissolussion data by regression coefficient analysis [40] as shown in Table 3 and Table 4.

Table 5: Table showing *in-vitro* release kinetics of theophylline from GS2 theophylline loaded hydrogel full time in basic condition.

						Korsmeyer's	
	Drug Release	Zero Order	First Order	Higuchi Model	Hixon Crowell	----------	
Theophylline	R^2	R^2	R^2	R^2	R^2	N	K
Full time in basic condition	0.9519	0.6093	0.9867	0.9639	0.9729	0.7963	0.5844
0-8 in basic condition	0.9623	0.8982	0.9788	0.9441	0.9339	1.1479	0.6219
8-72 in basic condition	0.8609	0.5518	0.9877	0.9741	0.9565	0.789	0.6697

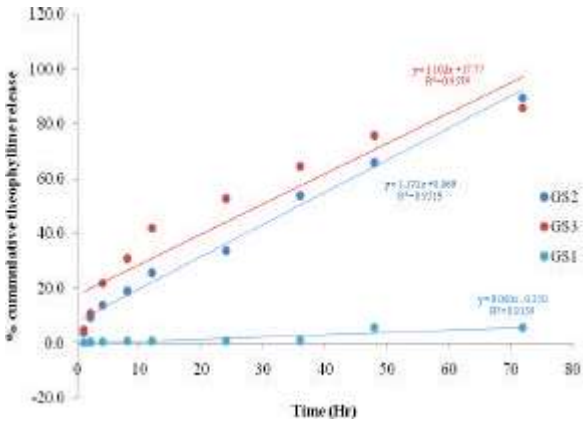

Fig. 5: Zero order plots for in-vitro release profile of theophylline released from theophylline loaded hydrogel.

Release of Theophylline from GS1 Theophylline Loaded Hydrogels: The drug release data was analyzed using regression analysis [40]. The obtained data from the *in-vitro* dissolussion testing were fitted to various mathematical models i.e. Higuchi, First Order, Hixson-Crowell, Zero order and Korsmeyer's Pappas in order to estimate the kinetics and the mechanisms of drugs release from hydrogel loaded disc. Under acidic conditions, it was found that the *in-vitro* theophylline released from the GS1 best fitted to the Higuchi model (Fig. 7) as the R^2 value obtained was the highest (R^2 = 0.9467) indicating the drug release followed Fickian diffusion. Fig. 5 indicated that good linearity (R^2 = 0.9159) was obtained for Zero Order indicating the drug release is independent of drug concentration. However, to know the exact release mechanism of the drug, data was subjected to a kinetic model developed by Korsmeyer's which is usually subjected for the analysis of release mechanism of drug from hydrogel loaded disc. As the (n) value of for the GS1 was 0.3963indicating that the release from the hydrogel followed Fickian release [40].

Release of Theophylline from GS2 Theophylline Loaded Hydrogels: The dissolussion data from the *in-vitro* studies was subjected to various mathematical model *i.e.* First Order, Higuchi, Zero order, Hixson-Crowell and Korsmeyer's Pappas, to predict the kinetics and release mechanism of the drug.

Under basic condition, the higher correlation coefficient was observed for Higuchi model (R^2 = 0.9867, Figure 7) indicating the drug release followed Fickian diffusion. Hixson-Crowell plot for the data was also constructed (Fig. 8), the R^2 value was (R^2 = 0.9639 indicating polymer erosion and dissolution. Fig. 5 indicates that good linearity (0.9519) was obtained for Zero Order indicating that the drug release from hydrogel loaded disc is independent of the concentration of drug. The value of release exponent "n" was 0.7963 by plotting the fraction theophylline released vs. log time (Korsmeyer's-Pappas) indicating that the release of theophylline from hydrogels was non- Fickian diffusion. The results are shown in Table 4. The investigation of the data from dissolution indicates that main mechanism for theophylline release from the hydrogel disc was diffusion but the drug release coupled with erosion also plays an important role [45]. Therefore, data were divided into two portions to analyze the kinetics behavior of theophylline released from hydrogel loaded with theophylline from 0-8 and then from 8-72 hours.

Release of Theophylline from GS2 (From 0-8 Hours): It was interesting to find that in early hours i.e. from 0-8 hours the dissolution data showed good correlation coefficient with Higuchi model as shown in the Table 4.

The *in-vitro* dissolution testing data obtained for the formulation GS2 was subjected to various release kinetic mathematical equations for investigating the kinetics of drug and mechanism of release from hydrogel disc. Values for regression coefficient for the various equations are sum up in Table 4. The maximum value for R^2 (Fig. 7) was obtained for Higuchi Model (0.9788). Fig. 3.10 indicates that good linearity (R^2= 0.9623) was obtained for Zero Order indicating the drug release is independent of drug concentration. Hixson-Crowell plot for the data was also constructed (Fig. 8), the R^2 value was 0.9441indicating erosion and dissolution of the hydrogel disc. Therefore, the data obtained from

Table 4: Table showing *in-vitro* release kinetics of Theophylline from GS1 theophylline loaded hydrogel full time in acidic condition

						Korsmeyer's	
	Drug Release	Zero Order	First Order	Higuchi Model	Hixon Crowell	----------	
Theophylline	R^2	R^2	R^2	R^2	R^2	N	K
Full time in acidic condition	0.9159	0.6903	0.9467	0.8944	0.93729	0.3963	0.3456

Table 5: Table showing *in-vitro* release kinetics of theophylline from GS2 theophylline loaded hydrogel full time in basic condition.

						Korsmeyer's	
	Drug Release	Zero Order	First Order	Higuchi Model	Hixon Crowell	----------	
Theophylline	R^2	R^2	R^2	R^2	R^2	N	K
Full time in basic condition	0.9519	0.6093	0.9867	0.9639	0.9729	0.7963	0.5844
0-8 in basic condition	0.9623	0.8982	0.9788	0.9441	0.9339	1.1479	0.6219
8-72 in basic condition	0.8609	0.5518	0.9877	0.9741	0.9565	0.789	0.6697

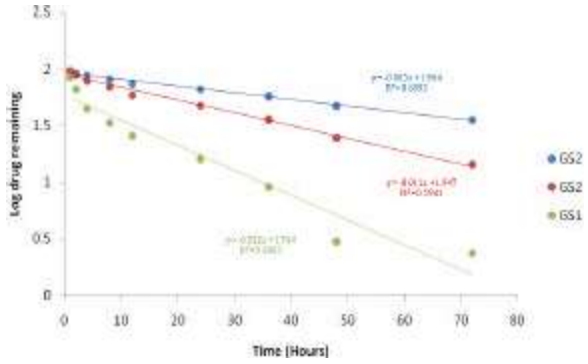

Fig. 6: First order plots for in-vitro release profile of theophylline released from theophylline loaded hydrogel.

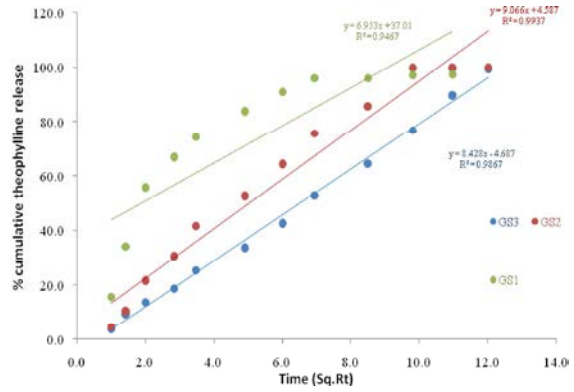

Fig. 7: Higuchi plot for in-vitro release profile of theophylline released from theophylline loaded hydrogel.

dissolussion was also subjected into Korsmeyer's model which is frequently applied for describing the release behavior of drug from hydrogel loaded with theophylline and the diffusion exponent value (n) (1.1479) (Table 4) in Korsmeyer's model indicates the release followed the non-Fickian super case II diffusion phenomena [39]. When the PVP hydrogels disc approaches to contact with the dissolution medium, they become swell by taking water to form a gelatinous hydrogel barrier. In case of PVP with drug loaded, the initial swelling of the hydrogel disc may be possible to assist dissolution of the drug as well as the dissolved drug diffused out of the swollen hydrogel disc barrier to the dissolution environment. Until and unless the erosion of swollen hydrogel disc occurred, further seeping-in of the dissolution medium does not take placed. As a result, the release rate of the theophylline from hydrogel disc depends upon the strength of the loaded hydrogel disc barrier (i.e. the concentration of the hydrophilic hydrogel), hydration rate of loaded hydrogel disc and its viscosity [46].

Release of Theophylline from GS2 (From 08-72 Hours): The drug release from hydrogel loaded with drug above 8 hrs (08-72) hours (Table 4) showed strong correlation coefficient with the Higuchi model (R^2 = 0.9877, Figure 7) indicating the drug release followed Fickian diffusion. Hixson-Crowell plot for the data was also constructed (Fig. 8), the R^2 value was 0.9741indicating polymer erosion and dissolution. However, these kinetic models were not adequate for exploration of the theophylline release phenomena because of combination of both the process swelling phenomena as well as erosion of matrix. Therefore, the *in-vitro* dissolution testing data obtained was also subjected to Korsmeyer's model for understanding the mechanisms of release behavior of theophylline from hydrogel disc [33]. The "n" value of diffusion exponent from Korsmeyer's equation was 0.789 as shown in Table 4.

This studies also demonstrated that the theophylline release rate from PVP loaded hydrogel disc was a complex process and was controlled by dual mechanism i.e. diffusion and erosion process. It was obvious that the degradation of hydrogel was observed at later stage of experiments [46].

Table 6: Table showing *in-vitro* release kinetics of theophylline from GS3 theophylline loaded hydrogel full time in mixed condition.

						Korsmeyer's	
	Drug Release	Zero Order	First Order	Higuchi Model	Hixon Crowell	----------	
Theophylline	R^2	R^2	R^2	R^2	R^2	N	K
Full time in mixed condition	0.9579	0.5941	0.9937	0.9788	0.9692	0.9216	0.3987
0-8 in mixed condition	0.9838	0.8277	0.9389	0.9715	0.9956	0.8975	0.4568
8-72 hrs in mixed condition	0.8609	0.5518	0.9788	0.9937	0.9565	1.5155	0.6697

Release of Theophylline from GS3 Theophylline Loaded Hydrogels: Under mixed conditions (for the first two hrs in acidic condition and then for the rest of time in basic condition), the drug release data of the dissolutions was fitted in Hixon Crowell, Higuchi's, first-order, zero order and Korsmeyer's models to recognize the release mechanisms of theophylline from loaded hydrogel disc. The kinetic of release rate data for all these models was estimated by using the analysis of regression coefficient [47]. It was found that the *in-vitro* theophylline released from the GS3 best fitted to the Higuchi model (Fig. 7) as the R^2 value obtained was the highest (0.9937) indicating the drug release followed Fickian diffusion. Hixson-Crowell plot for the data was also constructed (Fig. 8), the R^2 value was 0.9788indicating dissolution and erosion of hydrogel was observed.

The application of the Korsmeyer's equation [19] showed that the release of theophylline from the hydrogel disc followed the non-Fickian diffusion and the observed value for n was 0.9216. The results are shown in Table 6.

The analysis of the dissolutions data indicates that the major release mechanism for release of theophylline from the hydrogel loaded disc with drug was diffusion but drug release coupled with erosion also plays an important role. Therefore, data were divided into two portions to analyze the kinetics behavior of the theophylline i.e. from 0-8 hours and then from 8-72 hours under mixed condition [44].

Release of Theophylline from GS 3 (From 0-8 Hours): The drug loaded hydrogel was first immersed in acidic solution and then transferred the hydrogel to phosphate buffer solution at pH 6.8. From 0-8 hrs, when this data was subjected to various drug release models, it was found that *in-vitro* release of theophylline from the GS3 best fits to the Zero order model (Fig. 5) as the R^2 value obtained was the highest (0.9838) indicating the drug release is independent of drug concentration. Hixson - Crowell plot for the data was also constructed (Fig. 8), the R^2 value was 0.9715 indicating polymer erosion and dissolution. Fig. 7 indicates that good linearity (R^2 = 0.9389) was obtained for Higuchi Model indicating that the release of theophylline from hydrogel disc followed Fickian

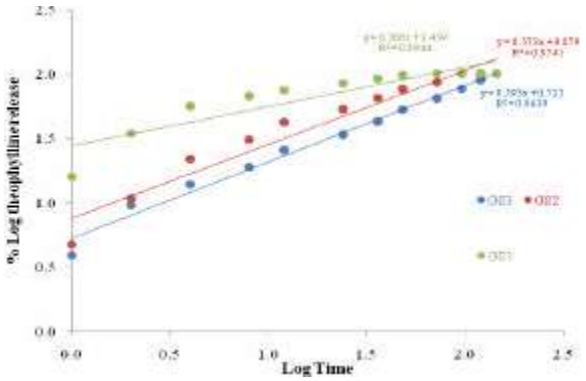

Fig. 8: Hixon-Crowell plot for in-vitro release profile of theophylline released from theophylline loaded hydrogel.

diffusion. The value (0.8975) of release exponent "n", obtained with Korsmeyer's-Pappas equation, suggests that drug release from GS3 formulation followed anomalous transport [44]. Hixson-Crowell plot (Fig. 8) also confirms polymer erosion with the (R^2= 0.9715).

Release of Theophylline from GS3 (From 8-72 Hours): It was interesting to find that Hixon-Crowell model showed best correlation coefficient in above 8 hrs (8-72 hrs). The results were shown in table 3.10. It was found that the *in-vitro* theophylline released from the GS3 best fits to the Hixon-Crowell model (Fig. 8) as the R^2 value obtained was the highest (0.9937) indicating polymer erosion and dissolution. Higuchi model kinetic plot for the data was also constructed (Fig. 7), the R^2 value was 0.9788 Indicating that the release of theophylline from hydrogel disc followed Fickian diffusion. The n value of diffusion exponent was (1.5155) in Korsmeyer's model indicates that the release of drug followed the non-Fickian super case II diffusion phenomena as shown in Table 6. This showed that in early stages the diffusion was dominant process for the release of the theophylline from the hydrogel loaded with drug. However, the erosion may also be one of the important factors in the drug release from PVP drug loaded hydrogel. It showed that in both stages i.e. 0-8 hrs and 8-72 hrs, the diffusion is the major process for the release of theophylline from the hydrogel,

however, zero order also showed very good correlation and indicates complex phenomena of the release of theophylline form the PVP drug loaded hydrogel involving the diffusion and erosion mechanism [44]. Interestingly, we found that it followed the Fickian diffusion and then in latter stage it followed the non-Fickian diffusion known as anomalous release mechanism. Consequently, erosion was coupled with diffusion [44].

CONCLUSION

At present, the *poly (N-Vinyl-2-pyrrolidone)* hydrogel being studied are used extensively in pharmaceuticals to control the release of drug. A result of the present study showed that the loading and release rate of drug is mainly controlled by used solvents.

The release of theophylline usually follow Higuchi model release pattern because the % drug release various with time and hence % drug release is directly proportional to square root of time, in present study The developed poly (N-Vinyl-2-pyrrolidone) hydrogel can be employed to decrease repeated administration and dose-dependent side effects after further *in-vivo* pharmacokinetic studies.

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