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Synthesis of Cross Linked PVP Hydrogels and its Use for the Control Release of Anti-Asthmatic Drugs

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Abstract: In the present study, PVP hydrogels with different compositions were prepared, characterized and used as carrier for different of drugs. Three different formulations were prepared. The released of drug from polymeric hydrogels followed both diffusion and erosion. The theophylline was compacted with PVP hydrogel with various concentrations (drugs-hydrogel concentrations 1:2, 1:1 and 1:3). Subsequent to compaction, the compressed matrix tablets were subjected into dissolution apparatus to test out the mechanism of theophylline released from matrix tablets as well as the time of its release. The theophylline sustainability (1:1) was 5.5 hours and the drug release from matrix tablets was 99 %. The sustainability of theophylline (1:2) was 8 hours and the release of theophylline from compressed tablets was 95 %. The obtained result at 1:3 was 89% of theophylline released after 13 hrs. The current research work showed that drugs and hydrogel with 1:3 concentrations was proficient for supporting the theophylline for greater time with comparable to other drug/polymer concentrations (1:2 and1:1).

Key words: Theophylline % Sustained Release % PVP Hydrogels % Dissolution Environment

INTRODUCTION

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. When water is used as medium for gel, term “hydrogel” is used. 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. According to these networks, 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 cyto-toxicity 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 [2]. In dry state the hydrogel is called a “Xerogel”, without considering the characteristics of its swelling media. Therefore,

Xerogel + Water ------- Hydrogel

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 [3]. On the basis of monomers units, co-polymer, homo-polymers and multi-polymer hydrogels [4, 5]. On the basis of physical structural features, they are classified as, amorphous, semi crystalline, complexation structures or hydrogen-bonded [6, 7].

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Asthma is one of a persistent inflammatory infection of air way, air trunk differentiated by coughing, wheezing, tightness or pain in chest and difficulty in breathing. This is due to narrowing of air ways which is due to spasm of muscle, secretion of mucous and swelling of mucosa which may also be due to various allergic reactions, or even various drugs are also responsible [8]. In other words we can say that the asthma is frequent inflammatory persistent infection of the air trunks differentiated by changeable and persistent sign and indications, revocable flow of air obstruction and broncho-spasm. Sign and symptoms comprise of coughing, wheezing, tightness or pain in chest and shortness of breath shortening. Pharmacologically or clinically asthma is categorized according to the frequency of sign and indications, enforced expiratory volume in 1 second (FEV1) and rate of peak expiratory flow. Possibly asthma could as well be categorized as non-atopic (intrinsic) and atopic (extrinsic, so as to occur in atopic individual mean which are hypersensitive) [9, 10].

MATERIAL AND METHODS

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

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. The experiment was as:

Experiment: A weight of 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 de-ionized water to remove any un-reacted polymers. The transparent soft rebury like soft hydrogel polymer was obtained. The % conversions (CR) were calculated using the following equation:

$$CR\ (\%\ conversion) = (Mo / M) \times 100 \quad (1)$$

Where Mo is the weight of monomer + cross linker + initiator and M the weight of Xerogel.
The % conversion was about 60 %.

Physical Characteristics of Tablets and Granules
Evaluation of Tablets: Assessment of matrix tablets for physical properties like weight variation, hardness, friability and *in-vitro* dissolution study were carried out.

Uniformity of Weight: In a batch every individual tablet was in uniform weight and in within acceptable limits. The uniformity of weights of compressed tablets was established within ±1mg. By using Sartorius balance was used for measurements, control of matrix tablets weight was based on a sample of 20 tablets.

Dimensions: Digital vernier calipers were utilized for the measurement of the dimensions (Thickness and diameter) to within ± 0.01 mm.

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

Monomers	Cross linker	Initiator	% Swelling Ratios	% conversion
VP-100	EDMA0.3 mol %	AIBN	96	60
VP-100	Bis 0.25 mol %	AIBN	96.4	66
VP-97.5	BIS 0.25 mol %	AIBN	94	62
VP-97.5	EDMA 0.25 mol %	AIBN	90	61
VP-100	Bis 0.25 mol %	AIBN	89	88
VP-90	Bis 0.25 mol %	AIBN	85	60
VP-95	DVE-30.5 mol %	AIBN	85	57
VP-100	DVB 0.25 mol %	AIBN	89	55
VP-72.8	BIS 0.35 mol %	AIBN	89	92

Hardness: Tablets hardness testing apparatus (Monsanto Type) was used for the determination of the hardness of the tablets. Tablet hardness was about 5-6 kg is believed to be sufficient for its mechanical strength. Hardness of matrix tablets was measured in triplicate.

Friability: Roche friabilator was used for the determination of the friability of the tablets. Known weight of matrix Tablets (W0) or a sample of 50 matrix tablets was dedusted in a drum for a time period (4000 revolutions) and again weighed precisely (W). Percent friability was computed from weight loss as in equation below. The loss of weight must be less than 1 percent.

% Friability = $W_1 – W_2/W_1 * 100$

Evaluation of Granules: Most powders do not flow freely that produces problems like weight variation, thickness, hardness and friability of the tablets during production that affect the disintegration and dissolution which ultimately effect the bioavailability of drug for this reason to overcome this problem powders are converted into granules that are free-flowing and can be easily compressed into tablets. Therefore the granules were evaluated for the following physical properties.

Angle of Repose: The fixed funnel method was utilized to measure angle of repose [11]. The accurately pre-weighed granule was moved to a funnel having an orifice of 8 mm, protected with its tip at a specified height "h", on top of a circular dish of radius "r". The powders/granules were acceptable for flow freely through the funnel onto the surface until the apex of the conical pile just touches the tip of the funnel. The granules/powder cone diameter was calculated and angle of repose was measured according to the subsequent equation.

$$\tan q = h/r \quad (2)$$

Bulk Density: Both tapped bulk density (TBD) and loose bulk density (LBD) were calculated for the granules before compression [12]. 3 grams of granules from each formulation, evenly shaken in order to break any agglomerates if formed, was poured into a 10 ml graduated cylinder. The initial volume was noted and then the cylinder was permitted to fall on a hard surface from a height of 2.5 cm at 2 second intervals of time. The tapping was carried out until no further change was observed in its volume [13]. The tapped bulk density and loose bulk density were computed by the use of below formulas:

LBD = weight of the powder / volume of the packing
TBD = weight of the powder / tapped volume of the package

Compressibility Index: Carr's compressibility index was used for the measurement of compressibility index of the granules by the following equation [14].

$$carr's\ index(\%) = (TBD - LBD) \times \frac{100}{TBD} \quad (3)$$

Drug Content of Granules and Tablets of Theophylline: Weighed precised number of tablets containing 100 mg of theophylline were finely ground with the help of mortar and pestle and suspended in 100 ml methanol by mechanical stirrer (EZ Stir) for 10 minutes to extract the theophylline. The suspension was filtered through watt-man filter paper. The filtrate was diluted to a concentration of 20 µg/ ml with methanol and the content of theophylline was determined spectrophotometricaly at 285 nm in comparison with a standard theophylline solution having the same concentration of USP theophylline SR in the same medium using UV/Visible spectrophotometer (Lambda 25, Perkin Elmer) [15].

Preparation of Matrix Tablets: To fabricate the different formulation of tablets various drug-hydrogel ratios were used. Matrix tablets were then subjected to different physical (friability, weight variation and hardness thickness) and chemicals tests (assay and content uniformity) for their evaluation. The following process was utilized for compaction of the drug and hydrogel to prepare tablets. The triturating of dried hydrogels was carried out in a porcelain mortar and pestle followed by their passing through mesh No. 20. Theophylline was passed through the mesh No. 20. In order to keep the amounts of theophylline constant, the powder drug and hydrogels were then mixed with the concentration of 1:3, 1:2 and 1:1. Compression of the mixture was done by the use of tablet compression machine. The machine had equipped with 6 mm and 8 mm round punches for the concentration of 1:3, 1:2 and 1:1 correspondingly.

***In-vitro* Drug Release Studies:** Evaluation of the *in-vitro* dissolution testing was done by the USP dissolution apparatus II used as mentioned in US Pharmacopeia. Studies of *in-vitro* release of drug, from the manufactured compacted tablets were performed for 12 hours. USP type II six paddles apparatus was used at 37 ± 0.5°C and 50 rpm. Experiment was performed in triplicate for 12 hours (initial 2 hours within 0.1N HCl. Rest 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 contents present in the samples was determined with suitable standard curves plotted from reference standards in which the quantity of drug dissolved at particular periods of time was plotted as percent release versus time (hours) curve in y axis and x axis respectively.

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 were studied from the matrix tablets, the release data were subjected to the Higuchi's equation, Hixson-Crowell, Zero order equation, First order equation and Qt/Q8 = kKP. tn [16, 17]. 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 [18].The present modified method gave better yield with more than 92 % in the preparation with AIBN as initiator. 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 unreactant 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 [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 deionized water for the removal of unreacted monomers [21]. 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 [23].

Physical Characteristics of Tablets and Granules/ powder: Matrix tablets of theophylline were yellowish in color. In all formulations, the tablets were round with same diameter and thickness i.e. 10 mm and 12 mm respectively. All the batches of tablets prepared with hydrogels were passed for the entire physical test like weight variation tests, thickness, hardness and friability. The tablets of different formulations were subjected to various evaluation tests were performed on the various formulation of tablets, such as friability, weight variation of matrix tablets, thickness, contents of drug, hardness, diameter and *in-vitro* testing of dissolution. All the prepared matrix tablets illustrated uniform thickness as well as weight variation test, the pharmacopoeial limit (USP) in a weight variation test of matrix tablets for the percentage deviation of more than 350 mg is ± 5 %. For all the tablet formulations the average percentage deviation was established to be within the limit as stated above and hence, as per official requirements all the formulations of tablets passed the test for uniformity of weight. The data also showed that the flow characteristics as well as compressibility property of hydrogels and drug were fall in acceptable range [24]. Therefore, on the basis of above data all the different formulations showed that physical parameters were within control limit.

Evaluation of Granules/powders: The physical properties like LBD, TBD, compressibility index, angle of repose and drug content of the granules were investigated to estimate prior to compression, the results of which are summarized in Tables 2.

Table 2: Physical properties of the theophylline granules/powders prepared by using PVP hydrogels as a sustaining agent.

	Formulations		
Properties	1a	1b	1c
Angle of repose	28.33±0.04	29.37±0.07	28.38±0.09
Loose bulk density(LBD) (g/ml)	0.44 ± 0.05	0.46 ± 0.04	0.48 ± 0.02
Taped bulk density(TBD) (g/ml)	0.47 ± 0.03	0.53 ± 0.02	0.52 ± 0.02
Compressibility index (%)	12.56±0.05	14.35±0.05	16.54±0.05
Drug content of granules (%)	98.61±0.05	97.94±0.03	98.22±0.02

All values represent mean ± SD (n = 3).

Table 3: Physical properties of theophylline tablets prepared by using PVP hydrogels as a sustaining agent.

	Formulations		
Properties	1a	1b	1c
Hardness (Kg)	6.5 ± 2.37	7 ± 2.68	8 ± 3.43
Friability (%)	0.21 ± 0.04	0.29 ± 0.02	0.31 ± 0.03
Thickness (mm)	5.3 ± 0.03	6 ± 0.03	7.15 ± 0.03
Weight (mg)	400± 3.05	600 ± 3.09	800 ± 3.10
Drug content (%)	98.84±0.05	99.54±0.02	98.45±0.06

All values represent mean ± SD (n = 20)

One of the important parameters for the assessment of granular flow properties are the angle of repose and compressibility index. Assessment of flow of the granules is mandatory for hardness, uniformity in weight and thickness of the tablets. Conformation to these physical tests will assist in acquisition of results of the chemical tests within the specified limits. The granules fall into the category of having excellent flow if their angle of repose is < 30° and compressibility index value is up to 21 %. Another extrinsic property that affects the compressional properties of granules is the bulk density. The more spherical shape a granule has, the greater will be the bulk density. The greater, the size of granule the lesser will be the bulk density. For better and easier compression, the granules must have greater bulk density. Therefore, the granules having small size and spherical shape can be easily compressed as compared to the granule having large size and irregular shape. Increase in polymer concentration will increase the cohesive forces due to which the granules will assume a more spherical shape than an irregular one. Due to this reason, the tapped and lose bulk density will also increase which means better compressional properties. Similarly the values of angle of repose and compressibility index may also be increases. The drug content of all the formulations were in the range 98-100 % this indicates the uniform distribution of drug in granules. The results indicated that the produced granules have optimum flow, compressibility index and drug content [25].

Evaluation of Matrix Tablets: The compression weight of the tablets was calculated on the bases of drug content of the granules and then compressed. These tablets were then evaluated for thickness, hardness, friability, weight variation and drug content and weight variation, as summarized in Table 3.

To prevent tablets from capping, chipping and other manufacturing defects, they must have appropriate tensile strength and hardness [26]. Generally the release rate of the drug is inversely related to the tablet hardness. So hardness is a physical parameter that affects the bioavailability in immediate release as well as slow release tablets. PVP hydrogels was used as release sustaining agent in tablet manufacturing. Tablets were then subjected to hardness test. The inter-tablet variation in hardness was not significant because $P > 0.05$ tablets were also subjected to another physical test known as the friability test, the results of which are shown in Table 3. Friability of the tablets was found to be in the acceptable limits. Its results were also non-significant as the P value was more than 0.05 with the exception of 1c formulation that was statistically significant P value was less than 0.005. This was the proof of tablets to remain intact during its shelf life. Other physical test such as the thickness and weight variation of the tablets for all formulations were within the limits with the results being significant due to the value of $P < 0.005$ [27]. The percentage of drug in the tablets was in order of 98.84 ± 0.05 % to 99.54 ± 0.02 %. These fall within the limits

[28, 29]. Hence the drug was uniformly distributed in the granules and consequently in tablets.

Drug Release from the Tablets

Drug Release from Compressed Tablets Containing Theophylline and PVP Hydrogel: When the surface of matrix tablet becomes wet and hydrated to develop a layer of gel, the drug release from these matrix system occurred initially by the dissolution of drug and penetration of water into the matrix tablets. In general the release of drug from these matrices is governed by matrix system hydration, formation of gel layer and diffusion of drug into the layer of gel as well as also to the dissolution medium [30]. Erosion of matrix system also may be possible to play a key function in the release of drug from these matrix tablets [31]. These considerations indicating that the hydrophilic hydrogels have the capability to prolong the drug release from matrix tablets. For the controlled release of a matrix-tablet which is under investigation and consisting of drug as well as hydrophilic hydrogel, the drug release from matrix tablets must precede 3 stages. The 1st stage in this process is the diffusion of dissolution liquid in the compressed matrix tablet. The 2nd stage in this process is the swelling of matrix tablets with concomitant or consequent erosion or *in-vitro* dissolution of the compacted tablets while in the 3rd step, this process is the transportation of the drug which is being dissolved, moreover during the hydrated matrix or from the various components of the eroded tablets, to the adjacent dissolution environment [32].

The PVP hydrogel and theophylline were pulverized and compacted to the matrix tablets with 3 various fractions (concentrations). These concentrations were 1:2, 1:1 and 1:3 of theophylline and PVP hydrogel. The hardness of matrix tablets were ranged from 6.5-8 Kg with mean ± S.D = 0.8635 and with RSD = 0.18 % and thickness ranged from 5.3-7.5 mm with S.D = 0.23002 and with RSD = 0.23 %. The tablets were good and weight variations tests was 400-800 mg with mean ± S.D = 2.18789 and with RSD = 2.18 % and results are given in the table 3. Various mathematical kinetic equations (first order, zero order equations were used for understanding the rate of release of theophylline from matrix tablets. Correlation coefficient and goodness of fit values were calculated for each formula. The obtained data from dissolussion testing release from matrix tablets were subjected to Higuchi equation, Hixson Crowell, first-order and the Korsmeyer's model was also developed to compute the release of theophylline mechanisms from these compressed tablets formulations.

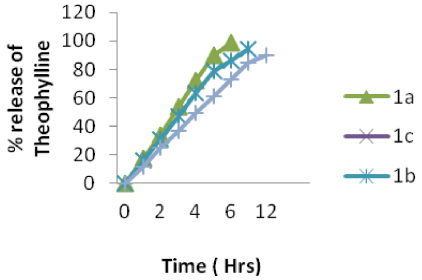

Fig. 1: Graphical representation of an in vitro release profile of theophylline sustained release of tablets containing theophylline and P (N-vinyl-2-pyrrolodone) hydrogel (1: 1), (1: 2) and (1: 3).

The following plots were made, Higuchi equation, first order kinetic model, zero order kinetics, Hixson-Crowell cube root law and Korsmeyer's model.

The release characteristics of theophylline from matrix tablets were considered by the use of USP apparatus-II. The speed of paddles were preset constant at 50 rpm that provided categorized data obtained from *in-vitro* dissolussion testing amongst different matrix tablets formulations [33].

Release of Theophylline from 1a Formulation: The release summary of theophylline matrix tablets compacted with ratio of 1:1 was extremely rapid and 99 % theophylline was released from matrix tablets within 5.5 hrs (Figure 1). This indicating that the hydrogel compressed with theophylline in 1:1ratio was incapable for maintaining the drug for extended period of duration [34]. The matrix tablets hardness was 6.5 ± 2.37 kg with RSD = 0.18 % and thickness was 5.3 ± 0.03 mm and RSD = 0.23 % of the tablets was good and weight variations tests was 400 ± 3.05 mg with RSD = 2.18 % [35]. The rate of theophylline release from the compressed tablets increased with the reduction in hydrogel quantity due to decrease in the strength of hydrogel and in the development of a gel film with a small diffusion path [36]. As consequences, this could have caused an increase in the significant increased in coefficient of diffusion of theophylline and, consequently, an increased in the rate of released of drug from matrix tablets [37]. Water Penetration into the matrix tablets, swelling of matrix tablets and dissolution of drug, diffusion of drug and erosion of matrix tablets is retarded by the hydration of matrix tablets that produced barrier for gel through which diffusion of the theophylline from matrix tablets occurred [38].

Table 4: *In-vitro* release kinetics of Theophylline from 1a, 1b and 1c formulation.

						Korsmeyer's		
	Drug Release Time (hr)	Zero Order	First Order	Higuchi Model	Hixon Crowell			
Drug Polymer Ratio	Theophylline	R^2	R^2	R^2	R^2	R^2	N	K
1:1	0-6	0.9675	0.8833	0.9846	0.9777	0.944	1.1479	1.3627
1:2	0-9	0.9794	0.8933	0.9877	0.9577	0.9666	1.0241	1.265
	0-4 hrs	0.9935	0.8772	0.9798	0.9121	0.9569	1.4793	1.0351
	4-9 hrs	0.9591	0.8933	0.9696	0.9315	0.9566	1.7451	1.0351
1:3	0-6	0.9535	0.8772	0.9798	0.9396	0.9369	1.1093	1.0351
	6-13 hrs	0.9987	0.8772	0.9801	0.9666	0.9469	1.4793	1.0351
	0-13	0.9794	0.8933	0.949	0.9596	0.9566	1.772	1.0351

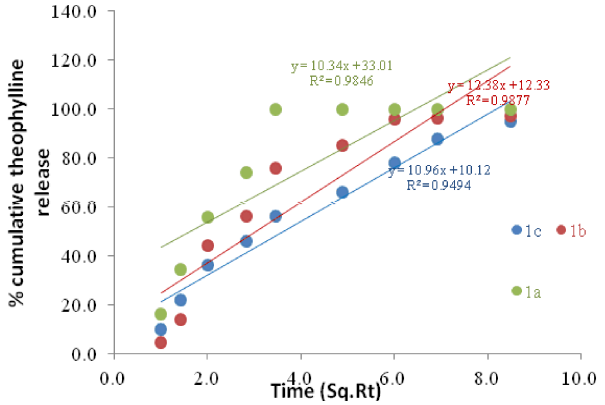

Fig. 2: Higuchi plot for in vitro release profile of theophylline sustained released tablets.

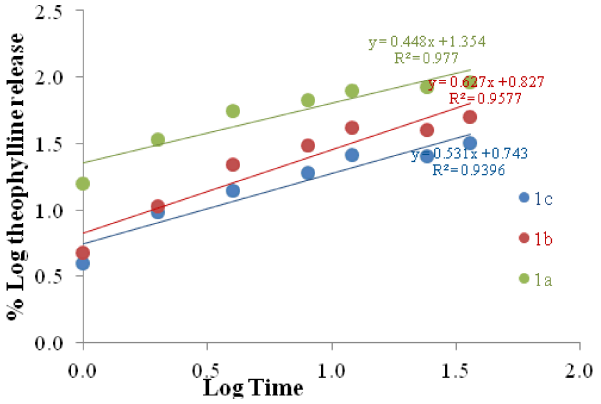

Fig. 3: Hixon Crowell plot for in vitro release profile of theophylline sustained released from tablets.

The drug release rate from the compressed tablets increases with a decrease in the proportion of hydrogel due to decrease in the strength of gel and the development of gel layer with a large diffusion path [39]. The obtained data from *in-vitro* dissolution testing were subjected to various mathematical models i.e. First Order, Hixson-Crowell, Zero order, Higuchi and Korsmeyer's Pappas to identify the drug kinetics and the mechanisms of theophylline release from matrix tablets [40]. The rates of release kinetic data from *in-vitro* dissolution testing for all the equations by the use of regression coefficient exploration are given in table 4.

The dissolution testing of theophylline release obtained for the formulation 1a was subjected to various mathematical models for exploring the drug kinetics and the release mechanisms of theophylline from compressed tablets. The values showed best linearity for the Higuchi model (R^2= 0.9846). Values for regression coefficient of the various equations are summarized in Table 4. The highest value for R^2 (Fig. 2) was obtained for Higuchi Model (0.9846). Hixson-Crowell plot for the data was also constructed (Fig. 3), the R^2 value was 0.9777 indicating hydrogel erosion and dissolution. However, for explaining the theophylline released phenomena, these mathematical models were not adequate to explain the release mechanisms because of combination of both swelling and erosion of matrix tablets [41]. Consequently, the *in-vitro* dissolution testing data was also subjected into Korsmeyer's model which is often used to explain the behavior of drug release from matrix tablets and the diffusion exponent (n) value was (1.1479) in Korsmeyer's model indicating that the release of theophylline followed the non-Fickian super case II diffusion phenomena [42].

Release of Theophylline from 1b Formulation: The drugs release profile of theophylline from matrix tablets containing *P* (*N-vinyl-2- pyrrolodone*) hydrogel (1:2) demonstrated improved results as compared with the matrix tablets which consists of drug and hydrogels with 1:1 ratio. The formulations 1b prolong the theophylline release for 8 hours where 95 % of the drug was released from compressed tablets. While in 3.5 hours up to 55 % of theophylline was released as shown in figure 3.1. The better release may be possible due to the larger quantity of the hydrogel compared with the first formulation.

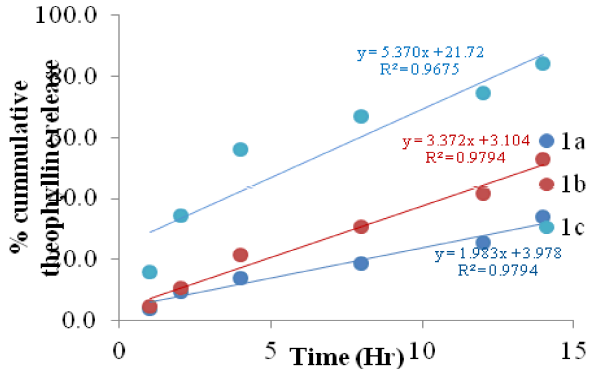

Fig. 4: Zero Order plot for in vitro release profile of theophylline sustained released from tablets. systems. Methods of Molecular Biology, 437: 217-243.

The hardness was 7.9 ± 0.2 kg and RSD = 0.20 and thickness was 6.3 ± 0.23002 mm and RSD = 0.23 %. The tablets were good and weight variations tests was 600 ± 2.02 mg and RSD = 2.18 %.

The mechanism of drug release from these formulations was evaluated by fitting the data into Hixon Crowell [43], Higuchi's [44], first-order [45], zero order [46] and Korsmeyer's model [47].

The behavior of theophylline release from matrix tablets was evaluated using various mathematical equations as demonstrated for the matrix tablets containing drug and hydrogels with 1: 1 ratio. The table 4 showed the correlation coefficient obtained from various models.

It was found that the *in-vitro* theophylline released from the 1b best fits to the Higuchi model (Fig. 2) as the R^2 value obtained was the highest (0.9877) indicating the drug release followed Fickian diffusion. Fig. 4 indicates that good linearity (R^2= 0.9794) was obtained for Zero Order indicating the drug release is independent of drug concentration. As the (n) value for the 1b was 1.0241, it indicates that the release from these matrix tablets followed non-Fickian super case 11 release. In acidic environment electrostatic force vanished between uncharged carboxyl groups [48] and caused the decrease in the hydration, low swelling behavior was observed for matrix tablets and as result of which restricted the theophylline release from matrix tablets in the environment of acidity [49]. The n value of diffusion exponent was 1.0241 indicating that the theophylline release from compressed tablets was super Case II which is generally refers to a both the mixture of erosion and diffusion of matrix tablets [50].

Release of Theophylline from 1c Formulation: The drug release profile using the Theophylline and hydrogel (1: 3) released about 22 % of its substances in first 2 hrs and 60 % in six hrs and 89 % was released in 13 hours as in figure 3. This ratio (1: 3) retarded the theophylline release for 13 hours and the hardness was 8 Kg with S.D = 0.18635 and RSD = 0.18 % and thickness was 7.6 mm with S.D = 0.23002 and RSD = 0.23 %. The tablets were good and weight variations tests was 800 mg with S.D= 2.18789 and RSD = 2.18 %.

The mechanism of drug release from these formulations was evaluated by fitting the data into first-order [43], Higuchi's [44], zero order [45], Hixon Crowell [46] and Korsmeyer's model [47].

The release behavior of drug was calculated by the use of regression coefficient [31] as in table 4. It was found that the *in-vitro* theophylline release from the 1c best fits to the Zero-order (Fig. 4) as the R^2 value obtained was the highest (0.9794) indicating the drug release followed Fickian diffusion. Hixson-Crowell plot for the data was also constructed (Fig. 3), the R^2 value was 0.9596 indicating erosion of polymer and dissolution. The value (1.1093) of release exponent "n" obtained with Korsmeyer's-Pappas equation, suggests that release of drug from 1c formulation followed anomalous super case II transport [50].

CONCLUSION

The main idea of this work was to manufacture and to develop controlled released tablets of anti asthmatic drugs. For this reason one drug was selected that is theophylline. The conversion of monomers to PVP hydrogels in the present methods was very high. Desired pore size of the hydrogel was prepared by changing the concentration of monomers and cross-linkers. Monomers above 15 % T and cross-linkers above 4 % C are not advisable because of turbidity for the preparation of PVP hydrogel and finally hydrogels who's swelling are sensitive to temperature. The selected preparation were analyzed for different parameters like TBD, angle of repose, LBD, compressibility index, thickness, content uniformity for the granules and friability, hardness, uniformity of weight and drug content for tablets according to official procedures. The kinetic studies were carried out for the *in-vitro* release pattern of the drug from various polymers as well as their mechanism of release were determined by applying different models like zero order, first order, Higuchi, Hixson-Crowell and

Korsmeyer's. Mostly the release of drugs like theophylline whether from from compressed tablets followed Higuchi release kinetic model. Similarly stability studies were also carried out for the successful formulations at normal and at accelerated conditions that showed satisfactory results. The preparation of matrix tablets containing drug and polymers with the ratio of 1:1, 1:2 and 1:3 were prepared. The drug polymers ratio with 1:3 sustained the release of both theophylline and drug was mostly release through mixed and complicated mechanisms which may be diffusion, relaxation and erosion process through non-Fickian diffusion process. The kinetic studies were carried out for the dissolussion testing of the drug from various polymers as well as their mechanism of release were determined by applying different models like Hixson-Crowell, Higuchi, first order, zero order and Korsmeyer's. The study revealed that the theophylline formulations containing PVP hydrogels as sustaining materials were the suitable candidates for retarding the drug release for 13 hours at drug to polymer ratio of 1:3. The formulations prepared by solvent evaporation method showed constant release and small fluctuation compared with the formulations prepared by wet granulation method. The present study showed that PVP hydrogels can be a good agent that can be used for controlled drug release.

In conclusion compressed tablets formulations with drug to PVP ratio 1:3 sustained the release of drugs and also showed good *in-vitro* release for both theophylline and ketotifen for 14 hours and can be use clinically as once a day dose.

REFRENCES

1. Saptarshi, D. and S. Mukul, 2009. Modified release dosage form and drug delivery. Journal of pharmacy Research, 2(11): 1728-1729.
2. Liu, C.H., Y.H. Kao, S.C. Chen, T.D. Sokoloski and M.T. Sheu, 1995. "In-vitro and in-vivo Studies of the Diclofenac Sodium Controlled-release Matrix Tablets," Journal of Pharmacy and Pharmacology, 47: 360-364.
3. Langer, R. and N.A. Peppas, 2003. Advances in biomaterials drug delivery and bio-nano-technology. Alche Journal, 49(12): 2990-3006.
4. Estroff, L.A. and A.D. Hamilton, 2004. Water gelation by small organic molecules. Chemical Review, 104: 1201-18.
5. King, M.W., R.L. Ornberg, Y. Marois, G.R. Marinov, R. Cadi, J.H. Southern, S.J. Joardar, S.L. Weinberg, S.W. Shalaby and R. Guidoin, 2000. Partially bioresorbable bicomponent fibers for tissue engineering: mechanical stability of core polymers, 533. Sixth World Biomaterials Congress. Kamuela, Hawaii, pp: 15-20.
6. Shah and Shelat, 2010. Design and Evaluation of Matrix Tablets Containing a Natural Polysaccharide as a Carrier to Optimize Active Drug's (Nsaid) Absorption Profile for Bedtime Administration (Chronotherapeutic Delivery) International Journal of Pharmaceutical Research, 2(1): 52-61.
7. Kudela, V. and V. Kudela, 1987. Hydrogel in Ed. Encyclopedia of Polymer Science and Engineering. New York, NY: Wiley, 7: 703-807.
8. Walter, M.J. and M.J. Holtzman, 2005. A centennial history of research on asthma pathogenesis. Am. J. Respir Cell Mol Biol, 32: 483-489.
9. Graham, N.B. and M.E. McNeill, 1984. Hydrogels for controlled drug delivery. Biomaterials, 5: 27-36.
10. Tiwari, S.B., T.K. Murthy, M.R. Pai, P.R. Mehta and P.B. Chowdary, 2003. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS Pharm Sci Tech, 4: 31.
11. Peppas, N.A., R. Gurny, H.E. Juninger and N.A. Peppas, Eds, 1993. Fundamentals of pH and temperature sensitive delivery systems In Pulsatile Drug Delivery. Wissenschaftliche Verlagsgesellschaft, Stuttgart, pp: 41-56.
12. Lu, H.H., J.A. Cooper, F.K. Ko, M.A. Attawia and C.T. Laurencin, 2001. Effect of polymer scaffold composition on the morphology and growth of anterior cruciate ligament cells.
13. Lee, P.I. and N.A. Peppas, 1987. Prediction of polymer dissolution in swellable controlled release systems. Journal of Controlled Release, 6: 207-215.
14. Peppas, N.A., P. Bures, W. Leobandung and H. Ichikawa, 2000. Hydrogels in pharmaceutical formulations. European Journal of Pharm. Biopharm50, pp: 27-46.
15. Bell, C.L. and N.A. Peppas, 1995. Biomedical membranes from hydrogels and interpolymer complexes. Adv. Polym. Sci., 122: 125-175.
16. Zafar Iqbal, Roohullah, Bashir Ahmed and Obaid ullah, 2003. Preparation of pharmacetamol tablets using PVP-K and K 90 30 as binder. Acta pharmaceutic Turcica 45: 137-45.

17. Brannon, P.L. and N.A. Peppas, 1991. Equilibrium swelling behavior of dilute ionic hydrogels in electrolytic solutions. J. Controlled Release, 16: 319-330.
18. Brannon, P.L. and N.A. Peppas, 1991. Time-dependent response of ionic polymer networks to pH and ionic strength changes. Int. J. Pharm, 70: 53-57.
19. Peppas, N.A. and A.R. Khare, 1993. Preparation, structure and functional behavior of hydrogels in controlled release. Adv. Drug Deliv. Rev, 11: 1-35.
20. Anseth, K.S., A.T. Metters, S.J. Bryant, P.J. Martens, J.H. Elisseeff and C.N. Bowman, 2002. In situ forming degradable networks and their application in tissue engineering and drug delivery. J Control Release, 78: 199-209.
21. Edsman, K., J. Carlfors and R. Petersson, 1998. Rheological evaluation of poloxamers as an in situ gel for ophthalmic use. Eur J Pharm Sci., 6: 105-12.
22. Brannon-Peppas, P., 1990. Preparation and characterization of crosslinked hydrophilic networks, in: L. Brannon-Peppas, R.S. Harland (Eds.), Absorbent Polymer Technology, Elsevier, Amsterdam, pp: 45-66.
23. Dillow, A.K. and A.M. Lowman, 2002. Micro-patterning biomimetic materials for bioadhesion and drug delivery. in Biomimetic Materials and Design: Biointerfacial Strategies Tissue Enginering and Targeted Drug Delivery, Eds. Dekker, New York, pp: 443-470.
24. Bashir Ahmad, Faryal Jehan, Shumaila Rauf and M. Hassan, 2006. Bisazo dyes sorption on to cross linked poly (n-vinyl-pyrrolidone), gels jamal.chem..soc.pak., 29(1): 64.
25. Dong, L.C. and A.S. Hoffman, 1991. A novel approach for preparation of pH sensitive hydrogels for enteric drug delivery. Journal Controlled Release 15: 141-152.
26. Dvornik, P.R. and D.A. Tomalia, 1996. Recent advances in dendritic polymers. Curr. Opin. Colloid Interface Sci., 1: 221-235.
27. Sunil, K., G.D. Gupta and O. Jagmohan, 2009. Matrix Tablets: An important Tool for Oral Controlled release Dosage Forms. A Review. Pharmainfo.net, 7: 6.
28. Peppas, N.A., P. Bures, W. Leobandung and H. Ichikawa, 2000. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm., 50: 27-46.
29. Bashir Ahmed, M. Hassan, Shumaila Bashir and M.B. Auglin, 2004. Chemically cross linked vinyl-2-pyrrolidone/2 hydroxyethyle methacrylate for release of oligopaptide. Turk.J.chem., 28: 1-7.
30. Peppas, N.A. and A.R. Khare, 1993. Preparation, structure and diffusional behavior of hydrogels in controlled release. Adv. Drug Deliv, 11: 1-35.
31. Horie, K., M. Báron, J. Fox, R.B. He, M. Hess, J. Kahovec, T. Kitayama, P. Kubisa, E. Maréchal, W. Mormann, R.F.T. Stepto, D. Tabak, J. Vohlída, l.E.S. Wilks and W.J. Work, 2004. "Definitions of terms relating to reactions of polymers and to functional polymeric materials (IUPAC Recommendations 2003)". Pure and Applied Chemistry, 76(4): 889-906.
32. Peppas, N.A., 2001. Gels for drug delivery in Encyclopedia of Materials: Science and Technology. Elsevier, Amsterdam., pp: 3492-3495.
33. Shumaila Bashir, Zafar Iqbal and Bashir Ahmad, 2003. Super sorbent P (NIPA-co-AA) gel for separation of protein dilute aqueous solution. Jour.chem.soc.pak., 25(3): 192.
34. Matsuda, T., 2002. Device-directed therapeutic drug delivery systems. J. Control Release, 78: 125-31.
35. Miyazaki, S., F. Suisha, A. Kawasaki, M. Shirakawa, K. Yamatoya and D. Attwood, 1998. Thermally reversible xyloglucan gels as vehicles for rectal drug delivery. J Control Release, 56: 75-83.
36. Jaber, E., T. Mona and A. Fatemeh, 2008. Preparation and *In-VitroIn Vitro* Evaluation of Sustained-Release Matrix Tablets of Flutamide Using Synthetic and Naturally Occurring Polymers Iranian Journal of Pharmaceutical Research, 7(4): 247-257.
37. Yeole, P.G., U.C. Galgatte, I.B. Babla and P.D. Nakhat, 2006. Design and evaluation of Xanthan gum-based sustained release Matrix tablets of Diclofenac sodium. Indian Journal of Pharmaceutical Sciences, 68(2): 185-189.
38. Merkus, F.W.H.M., 1986. Controlled and rate-controlled drug delivery, principal characteristics, possibilities and limitations, in Struyker-Boudier, HAJ. (eds), Rate- Controlled Drug Administration and Action, CRC Press, Boca Raton, FL, USA, pp: 15-47.
39. Liu, J., S. Lin, L. Li and E. Liu, 2005. Releases of theophylline from polymer blend hydrogels. International Journal of Pharmaceutics, 298: 117-125.

40. Cardinal, J.R., R.S. Langer and D.L. Wise, 1984. Medical Applications of Controlled Release Matrix systems Volume 1, Classes of Systems, CRC Press, Boca Raton, FL, USA, pp: 41-67.
41. Liu, J., S. Lin, L. Li and E. Liu, 2005. Releases of theophylline from polymer blend hydrogels. International Journal of Pharmaceutics, 298: 117-125.
42. Lordi, G., 1990. Sustained Release Dosage Forms, in Lachman, L, Lieberman, HA, Kanig, JL, The Theory and Practice of Industrial Pharmacy. Varghese Publishing House, Bombay, edi 3rd, pp: 430-456.
43. Gao, P., P.R. Nixon and J.W. Skoug, 1995. Diffusion in HPMC gels. Prediction of drug release rates from hydrophilic matrix extended-release dosage forms. Pharm Res, 12: 965-971.
44. Higuchi, T., 1961..Rate of release of medicaments from ointment bases containing drugs in suspensions, J. Pharm. Sci., 50: 874-875.
45. Shah, N., G. Zhang, V. Apelian, F. Zeng, M.H. Infeld and A.W. Malick, 1993. Prediction of drug release from hydroxypropylmethylcellulose (HPMC) matrices: effect of polymer concentration. Pharm Res, 10: 1693-1695.
46. Siepmann, J., K. Podual, M. Sriwongjanya, N.A. Peppas and R. Bodmeier, 1999. A new model describing the swelling and drug release kinetics from hydroxypropyl methylcellulose tablets. J Pharm Sci, 88: 65-72.
47. Dos Santos, J.F.R., R. Couceiro, A. Concheiro, JJ Torres-Labandeira, Alvarez-C and Lorenzo, 2008. Poly (hydroxyethyl methacrylate-co-methacrylated-beta-cyclodextrin) hydrogels: Synthesis, cytocompatibility, mechanical properties and drug loading/release properties. Acta Biomater, 4: 745-755
48. Talukder, M.M., A. Michoel, P. Rombaut and R. Kinget, 1996. Comparative Study on Xanthun Gum and Hydroxypropylmethylcellulose as Matrices for Controlled-Release Drug Delivery. Int. J. Pharm, 129: 231-241.
49. Sandip, B.T. and R. Ali, 2008. Extended-release oral drug delivery technologies: monolithic matrix Fig1: Graphical representation of an in vitro release profile of theophylline sustained release of tablets containing theophylline and *P* (*N- vinyl-2-pyrrolodone*) hydrogel (1: 1), (1: 2) and (1: 3).
50. John E.H., 1975. Edt; Remington, s Pharmaceutical sciences, Mac Publishing Co; Easton Pa; USA, 15 edi, pp: 1621.