To Evaluate and Study the Swelling and Drug Release Behavior of Poly (N-Vinyl-2-Pyrrolidone) Gel

Sudhair Abbas, Bashir Ahmad, Javid Ali, Shumaila Bashir, Said Hassan, Sher Mohammad and Abdul Mateen

1Department of Pharmacy, Abasyn University, KPK Pakistan
2Centre of Biotechnology and Microbiology, University of Peshawar, KPK Pakistan
3PCSIR Laboratories Complex Jamrud Road Peshawar, KPK-Pakistan
4Department of Pharmacy, University of Peshawar, KPK Pakistan
5Department of Agricultural Chemistry, University of Agriculture, Peshawar 25130, KPK- Pakistan

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Abstract: The drug loading and drug release efficiency of the P (N-vinyl-2-pyrrolidone) hydrogel was evaluated using the ketotifen as model drugs. The hydrogel was cut into small discs (3 mm thickness and diameter) and immersed in the solutions of the ketotifen for three days to achieve the maximum (equilibrium) swelling. The hydrogel immersed in 0.1 N HCl and phosphate buffers (pH 6.8) showed the 31.828 % and 29.783 % loading of the ketotifen by weight of the dried hydrogel, respectively that was not significantly difference (p was greater than 0.05). However, the slow swelling behavior of the hydrogel in the acidic medium was observed in the absence of the drug. The method of analysis of ketotifen using U.V-visible spectrophotometer and HPLC was developed for the analysis of these components in the dissolution medium. The methods were linear (r² = 0.9967) over the range of 0.1 to 10 µg.ml⁻¹ for ketotifen using U.V Visible spectrophotometer and HPLC respectively. The precision, accuracy and reproducibility of the methods were in an agreeable range to analyze the samples obtained from the dissolution medium. The various parameters for the methods of analysis of the ketotifen using spectrophotometer and HPLC methods were validated. The linearity of the method using UV Visible spectrophotometer and HPLC were (r² = 0.9967). The release of ketotifen from the P (N-vinyl-2-pyrrolidone) hydrogel under acidic condition was only 10 % of the drug released in about 72 hours and followed Higuchi model and drugs were released through Fickian diffusion. The data was best fitted in the Higuchi model (R² = 0.9566) indicating the drug release followed Fickian diffusion. The application of the Korsmeyer’s equation showed that the release of ketotifen release from the hydrogel disc followed the Fickian diffusion. Under basic conditions (pH 6.8), it was observed that the in-vitro release of ketotifen from hydrogel disc GS2 best fitted to the Hixon-Crowell (0.9917) indicating the erosion and dissolution of hydrogel. As the value of (n) for the GS2 was 1.2634, it indicating that the release of ketotifen from hydrogel disc followed non-Fickian super case II release. Under mixed conditions (for the first two hours in acidic condition (pH 0.1N HCl) and then for the rest of time at (pH 6.8), it was found that the in-vitro release of ketotifen from hydrogel loaded disc GS3 best fitted to the Higuchi model (0.9821) indicating the drug release followed Fickian diffusion. The value (0.9216) of release exponent “n” obtained with Korsmeyer’s-Pappas equation suggested that drug release from GS3 formulation followed anomalous transport.

Key words: Drug loading • Swilling ratio • Ketotifen • Kinetic models • SEM

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

Hydrogel was synthesized for the first time from acetylene by Reppe and his associates in the I.G. laboratories, Germany (1939-1941) [5]. Soon this polymer was recognized, due to its properties, as blood plasma expander, dye stripping agent, cosmetic or pharmaceutical thickness and dispersant which made it suitable for application in different fields of life. A number of researchers [6] investigated the synthesis of PVP hydrogel from VP monomer in aqueous system using azo or per oxy catalysts. High yields (92 %) were obtained in aqueous medium. In the field of pharmaceutical sciences and biomedical, because of potential properties of hydrogel and also its properties being biodegrability, inert, non toxic as well as to remove hydrogel from the body without the production of some transitional composite by its self or with any other compounds that are administered with another compound or already present in body or they are considered exclusively in synthesis of different pharmaceutical dosage forms [7]. Other properties like its structure, physico-chemical properties, surface properties, blood compatibility, sustainability properties for different materials and its swelling properties in aqueous solution are being studied very exclusively for biomedical applications [8]. 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. In other words we can say that asthma is the frequent chronic inflammatory disease of the air trunks characterized by changeable and recurring sign and symptoms, reversible airflow 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]. It is one of the antihistamine actions of these medicines or drug is intently related to cromolyne sodium, however this drug or medicines is much less reliable. Cromolyne sodium is not used orally because of its poor absorption and mostly administered through inhalation. Because of good absorption of ketotifen, therefore, used orally and available in tablet dosage form this drug is closely related to allergic reaction which is one of the leading cause for asthma and so many other conditions. The drug inhibits allergic reactions by inhibiting release of histamine from mast cell mostly constrained to bronchial tree consequently this medicines or drug is efficient in asthma and allergic reactions like dermatitis and allergic rhinitis. This medicines or drug give integrity to mast-cell, therefore, will inhibit swelling of mast-cell and release of mediator like histamine [11].

MATERIALS AND METHODS

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 ketotifen. Scanning electron microscopy was used for determining the hydrogel pore sizes.

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 ketotifen. 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.

Evaluation of Gels

Measurement of Swelling Ratio: The swelling ratio of the hydrogels 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.

\[ SR(\%) = \left( \frac{W_s}{W_d} \right) \times 100 \]

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 were 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:

\[ W_i = \left( \frac{W_s - W_d}{W_s} \right) \times 100 \]

whereas 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 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.

\[ W_{up} = \left( \frac{W_i - W_d}{W_s} \right) \times 100 \]

By gradual drugs release in adequate amount to maintain the required therapeutic response for a specific extend period of time and water to avoid the over dose and toxic level in the blood.

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 ketotifen was studied from the matrix tablets, the release data were subjected to the following equations:

Zero Order Equation:

\[ Qt = k_0 \]

where Qt is the percentage of drug released at “t” time and k0 is the release rate constant:

First Order Equation

\[ \ln(100 – Qt) = \ln 100 – K_1.t \]

where k1 is the release rate constant:

Higuchi’s Equation

\[ Qt = k_H.t^{\frac{1}{2}} \]

where kH is the Higuchi release rate constant:

Hixson-Crowell

\[ \left( \frac{100 - Q_t}{Q_0} \right)^{\frac{1}{3}} = 100x \left( \frac{1}{3} - k_HC \right) \]

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:

\[ \frac{Q_t}{Q_\infty} = kKP.\sqrt{n} \]

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 [12-15]. For the case of cylindrical geometries such as tablets, n = 0.45 which corresponds to a Fickian diffusion release.

Ketotifen Standard Preparation: Dissolved accurately weighed reference standard 222 mg, in 100 ml in volumetric flask and added 50 ml 0.1 N HCl and shaken
well for about 30 minutes then made up the volume up to 100 ml with 0.1 ml HCl, dissolved 2 ml of the filtrated up to 100 ml with distilled water and shaked well.

**Ketotifen Sample Preparation:** Dissolved accurately measured powder sample equivalent to 100 mg in 100 ml volumetric flask added 50 ml 0.1 N HCl shook well for 30 minutes then made the volume up to 100 ml with 0.1 N HCl filtered and diluted 2 ml of the filtrated to 100 ml with distillate water. Distilled water as blank and lambda max was (254 nm).

**Ketotifen Testing Method**

**Standard Preparation:** Dissolved accurately weighed 50 mg Ketotifen Fumarate reference standard in 100 ml volumetric flask, added 80 ml methanol, the mixture was dissolved completely by ultrasonic bath made the volume up to the mark with methanol and mixed well. Diluted 10 ml of the above solution to 100 ml with methanol and mixed well. Filtered through 0.45 micron membrane filter.

**Sample Preparation:** Dissolved accurately measured sample equivalent to 5 mg Ketotifen Fumarate in 100 ml volumetric flask, added 80 ml methanol, dissolved completely by ultrasonic bath, made the volume up to the mark with methanol and mix well. Filtered through 0.45 micron membrane filter. The concentration of solution was 50 mcg / ml.

Measured the absorbance of both reference standard and sample at $\lambda_{\text{max}} = 254$ nm.

**Drug Loading and Release:** Ketotifen were 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 ketotifen was loaded on the hydrogel discs and the percentage of drug loaded in the hydrogel discs is shown in Table 3.7. The hydrogel discs in solution of 0.1 N HCl and phosphate buffer solution showed 6.77 % and 5.55 % loading of ketotifen respectively. 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. It was also observed that the hydrophilic agents may increase the rate of swelling of the hydrogels [19]. 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 unpredictable 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 [20].

**RESULTS AND DISCUSSION**

**Validation Process**

**Calibration Curve for Ketotifen:** A standard curve for ketotifen was constructed in the range of 10 - 710 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 ketotifen and instrument responses ($R^2 = 0.9998$). The Figure 1 showed that the technique is relatively appropriate for the investigation of the ketotifen in this range of concentration.

**Precision and Reproducibility:** The precision was determined by analysis of five replicates of the each standard sample containing ketotifen (10 mcg.ml$^{-1}$). The mean concentrations and percentage RSD were calculated. The mean (SD) concentration of ketotifen was $0.588 ± 0.019$ and RSD was $± 3.27 \%$. The reproducibility of method was measured by analyzing five separate dilutions of the sample containing 10mcg.ml$^{-1}$ ketotifen. The mean concentrations and percent RSD were calculated. The mean (± SD) concentration of ketotifen in five separate dilutions of sample was $0.198 ± 0.0084$ and RSD was 4.23 %.

**Repeatability:** Repeatability was determined by measuring the concentration of analysis in five replicates of the same sample of medias of ketotifen gel release. The concentrations of the ketotifen were $0.13 ± 0.002$ mg.ml$^{-1}$ and RSD was 1.54 %.

The analysis of the data for various parameters for the validation of the method of analysis showed very low percentage RSD values and very high recovery, this indicates that the method is good and sufficiently sensitive for the analysis of the drug in the said range and in the similar medium.

The stability of the sample during analysis and within relatively short storage time was evaluated by inter-day and inter-day variations in the samples. The intraday studies were conducted by analyzing the same samples containing 10 mg.ml-1 of ketotifen four times a day at 6:00 am, 12:00 pm and 8:00 pm. The mean concentration was $0.3925 ± 0.0125$ mg.ml-1 and RSD value was below 3.5 %. This indicates the samples are stables at room temperature and storage of the samples will not affect the analytical results.

The inter-day variations in the assay were evaluated by placing the samples containing 10 mg.ml$^{-1}$ of ketotifen in refrigerator (5 - 8°C). The mean (SD) concentration of the ketotifen was $0.39 ± 0.14$ mg.ml-1 and RSD was less than 4 %. The variations in the inter day results were not significant (p was greater than 0.0001).

**Limit of Detection and Quantification:** The limit of detection is the point at which a measured value is larger than the uncertainly associated with it. It is the lowest concentration of analyte in a sample that can be detected but necessarily quantified. The lowest of quantization can be defined as the smallest concentration of analyte that gives a absorbance that can be accurately quantified. Both the USP and ICH guidelines similarly define the LOD and LOQ in ways that are widely accepted the industry. In the most straightforward case, any compound detected with a response at about 3 times the noise response level is concentrated to be its LOD. For the LOQ, the value is very commonly taken as 10 fold the noise response level. The LOD and LOQ values for the present method were found to be 0.01mg.ml$^{-1}$ and 0.1 mg.ml$^{-1}$ respectively showing the suitability of the method for the in-vitro release studies of the ketotifen.

**Scanning Electron Microscope of Hydrogels (SEM):**

The hydrogel interior morphology samples were studied by using scanning electron micrographs (SEM). Figure 2a, Figure 2b, Figure 2c and Figure 2d showed SEM of the hydrogel in their dry state. From the SEM values, one can identify the pores in the hydrogel network and the pores connectivity. The pores connectivity plays a vital role in rapid swelling and deswelling kinetics of the hydrogels [21]. Through these interconnected pores of hydrogel, Water and other solute can enter or leaves. It should be noted that the SEM images of hydrogels largely deviates from those of macroporous network at large cross-linker contents [22] where the structure consists of micro-porous of 2-3µm in diameter.
Drug Release from Ketotifen Loaded Hydrogels: The release studies of ketotifen from hydrogel loaded with drug. Only 6.5% of ketotifen was released in about 72 hours in the acidic medium and low release of ketotifen
was observed because of low swelling activities of hydrogels disc and lower solubility of ketotifen in the acidic conditions. In alkaline medium hydration of the hydrogels loaded with drug increases due to the electrostatic repulsive forces between the charged groups of the acrylic acid and leads to swelling and in acidic environment the electrostatic forces vanish between uncharged carboxyl group which results in the decrease in hydration [23], low swelling and in turn restricts the release of the ketotifen in the medium. Hydrophilic hydrogel schemes are extensively used for oral controlled drug delivery systems due to their high flexibility nature for obtaining a desirable release pattern for various drug profiles, which is mostly cost effectiveness and wide regulatory recognition [24]. The release of drug from hydrophilic hydrogel disc is known to be a very complex interaction between diffusion dissolution and erosion mechanisms. The mechanism of release for drug from these hydrogel disc was estimated by subjecting the data into Higuchi’s [25] (cumulative percentage of drug released verses square root of time), zero order [26] (cumulative amount of drug released verses time) pattern, Hixon Crowell [27] (Wo – Wt versus Time), first-order [28] (log cumulative percentage of drug remaining verses time) and Korsmeyer’s model [29].

The hydrogel loaded with drug immersed in phosphate buffer solution (pH 6.8) showed the higher drug release compared with the hydrogel in acidic conditions, about 85 % ketotifen was released in 72 hours. This was due to the higher swelling rate of the hydrogel in the phosphate buffer at pH 6.8. The loaded hydrogels were first immersed in 0.1 N HCl for 2 hours and then for rest of the time in phosphate buffer (pH 6.8). The release of ketotifen was very low for first 5 hours then burst release of ketotifen was observed [30].
Release of Ketotifen from GS1 Ketotifen Loaded Hydrogels: The data obtained from the in-vitro experiments were subjected to various mathematical model i.e. Higuchi, Hixson-Crowell, Zero order, First Order and Korsmeyer’s Pappas, to calculate the kinetics and release mechanism of the drug. Under acidic conditions, the in-vitro dissolution of drug release obtained for the hydrogel disc GS1 was subjected to various mathematical models to explore the drug kinetics and release mechanism of ketotifen. The values showed best linearity for the Higuchi model (R² = 0.9566). Values for regression coefficient for the various equations are summarized in Table 1. The highest value for R² (Fig. 5) was obtained for Higuchi Model (0.9566) indicating the drug release followed Fickian diffusion followed by zero order kinetics (0.9119) Fig. 6 indicating the drug release is independent of drug concentration. Hixon Crowell kinetic plot for the data was also constructed (Fig. 6) the R² value was 0.9047 Indicating the drug release diffusion and erosion [31]. The application of the Korsmeyer’s equation showed that the release of ketotifen release from the hydrogel disc followed the Fickian diffusion. The results are shown in Table 2. The analysis of the data indicated that main mechanism for the release of the drug from the hydrogel was diffusion. The analysis of the data indicated that main mechanism for the release of the drug from the hydrogel was diffusion [32].

Release of Ketotifen from GS2 Ketotifen Loaded Hydrogels: The drug release from the ketotifen loaded hydrogel discs in solution of phosphate buffer at pH 6.8 was observed for 72 hours. The release was slowly increased with the passage of time. About 55 % of the drug was released in 36 hours while in 72 hours 85 % of the ketotifen was released from ketotifen loaded hydrogel disc. The data taken from the in-vitro dissolution was subjected to different mathematical model i.e. Hixon-Crowell, First Order, Higuchi, Zero order
Table 1: Weight percent and drug loading of ketotifen.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medium</th>
<th>Xerogel Weight (gm)</th>
<th>Drug Loaded Weight (gm)</th>
<th>Drug Remaining in solution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketotifen HCl</td>
<td>0.05745</td>
<td>0.05803</td>
<td>0.269</td>
<td></td>
</tr>
<tr>
<td>Phosphate buffer</td>
<td>0.0121</td>
<td>0.01935</td>
<td>1.52753</td>
<td></td>
</tr>
<tr>
<td>Aqueous solution</td>
<td>0.00723</td>
<td>0.1648</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Table showing *In-vitro* release kinetics of Ketotifen from GS1 ketotifen loaded hydrogel full time in acidic condition

<table>
<thead>
<tr>
<th>Drug Release</th>
<th>Zero Order</th>
<th>First Order</th>
<th>Higuchi Model</th>
<th>Hixon Crowell</th>
<th>Korsmeyer’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketotifen</td>
<td>0.9119</td>
<td>0.7690</td>
<td>0.9566</td>
<td>0.9047</td>
<td>0.9629</td>
</tr>
<tr>
<td>Full time in acidic condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

and Korsmeyer’s Pappas to calculate the kinetics and release mechanisms of release of drug from hydrogel loaded disc.

Under mixed condition the release rate kinetic data for all the models was evaluated using regression coefficient analysis [33]. It was observed that the *in-vitro* release of ketotifen from hydrogel disc GS2 best fits to the Hixon-Crowell (Fig. 6) as the $R^2$ value obtained was the highest (0.9917) indicating polymer erosion and dissolution. Fig.5 indicates that good linearity ($R^2$ = 0.9805) was obtained for Higuchi model indicating that release of ketotifen from hydrogel disc followed Fickian diffusion. Zero order plot for the data was also constructed (Fig. 3), the $R^2$ value was 0.9249 indicating that release of ketotifen from hydrogel disc is independent of the concentration of drug [34]. But, to recognize the exact release mechanism of the drug, data was fitted into a kinetic model developed by Korsmeyer’s which is usually employed for the investigation of drug release mechanism from polymeric matrix systems. As the value of (n) for the GS2 was 1.2634, it indicating that the release of ketotifen from hydrogel disc followed non-Fickian super case II release. Case II type of release from hydrogel disc usually refers to the erosion of the hydrogel chain and anomalous transport (Non-Fickian) refers to a mixture of both diffusion and erosion controlled-release of drug from hydrogel loaded disc release [35]. The (n) values (0.5 < n < 1) showed anomalous release. The data obtained from *in-vitro* dissolution process analysis showed that ketotifen was released by dual mechanism. The diffusion exponents showed that it followed the non Fickian super case-II diffusion.

The analysis of the data indicating that major release mechanism of drug from the hydrogel disc was diffusion however the release of drug coupled with erosion which also plays a significant role. The drug release data were divided into two portions in order to study the suitable release behavior of ketotifen from hydrogel disc. In order to know the ketotifen release from loaded hydrogel disc, the data was divided into two parts [36] according to the curvature in the drug release curve i.e. from 0-8 hours and 8-72 hours in basic condition.

**Release of Ketotifen from GS2 (From 0-8 Hours):** The 85 % release of the ketotifen was observed in phosphate buffer when this data was subjected to various drug release kinetic models. From 0-8 hours, it was observed that the *in-vitro* release of ketotifen from the hydrogel disc GS2 best fits to the Higuchi model (Fig. 5) as the $R^2$ value obtained was the highest (0.9882) indicating the drug release followed Fickian diffusion. Fig. 3 indicates that zero linearity ($R^2$ = 0.9635) was obtained for Zero Order indicating the drug release is independent of drug concentration. Hixon – Crowell plot for the data was also constructed (Fig. 6), the $R^2$ value was 0.9344 indicating polymer erosion and dissolution. The diffusion exponent value (n) was 1.7642in Korsmeyer’s plot that indicating that the release of ketotifen by the combination of both diffusion and erosion of the loaded hydrogel disc with drug and followed the non-Fickian diffusion model as shown in Table 3.

**Release of Ketotifen from GS2 (From 08-72 Hours):** The *in-vitro* dissolution data obtained for the hydrogel disc GS2 above 8 hrs (08-72) hours was subjected to various mathematical models for exploring the kinetic of drug and mechanisms of ketotifen release. The values showed best linearity for the Higuchi model ($R^2$ = 0.9692) indicating the drug release followed Fickian diffusion. Values for regression coefficient for the various equations are summarized in Table 3. The highest value for $R^2$ (Fig. 6) was obtained for Higuchi Model (0.9692) followed by Hixon-Crowell (0.9509) Fig. 6 indicating that the polymer erosion and dissolution. Zero Order plot for the data was also constructed (Fig. 3), the $R^2$ value was 0.9151 indicating that the release of ketotifen is independent of
Table 3: Table showing in-vitro release kinetics of ketotifen released from GS2 ketotifen loaded hydrogel full time in basic condition.

<table>
<thead>
<tr>
<th>Drug Release</th>
<th>Zero Order</th>
<th>First Order</th>
<th>Higuchi Model</th>
<th>Hixson Crowell</th>
<th>Korsmeyer’s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$R^2$</td>
<td>$R^2$</td>
<td>$R^2$</td>
<td>$R^2$</td>
</tr>
<tr>
<td>Full time in basic</td>
<td>0.9249</td>
<td>0.5641</td>
<td>0.9805</td>
<td>0.9917</td>
<td>0.9494</td>
</tr>
<tr>
<td>condition</td>
<td></td>
<td></td>
<td></td>
<td>1.2634</td>
<td>0.6119</td>
</tr>
<tr>
<td>0-8 hrs in a basic</td>
<td>0.9635</td>
<td>0.8769</td>
<td>0.9882</td>
<td>0.9344</td>
<td>0.9911</td>
</tr>
<tr>
<td>condition</td>
<td></td>
<td></td>
<td></td>
<td>1.7642</td>
<td>0.4489</td>
</tr>
<tr>
<td>8-72h in basic</td>
<td>0.9151</td>
<td>0.5916</td>
<td>0.9692</td>
<td>0.9344</td>
<td>0.9646</td>
</tr>
<tr>
<td>condition</td>
<td></td>
<td></td>
<td></td>
<td>0.8018</td>
<td>0.5861</td>
</tr>
</tbody>
</table>

Table 4: Table showing in-vitro release kinetics of Ketotifen from GS3 ketotifen loaded hydrogel full time in mixed condition.

<table>
<thead>
<tr>
<th>Drug Release</th>
<th>Zero Order</th>
<th>First Order</th>
<th>Higuchi Model</th>
<th>Hixson Crowell</th>
<th>Korsmeyer’s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$R^2$</td>
<td>$R^2$</td>
<td>$R^2$</td>
<td>$R^2$</td>
</tr>
<tr>
<td>Full time in mixed</td>
<td>0.9741</td>
<td>0.8621</td>
<td>0.9821</td>
<td>0.9579</td>
<td>0.9764</td>
</tr>
<tr>
<td>condition</td>
<td></td>
<td></td>
<td></td>
<td>0.9216</td>
<td>0.2511</td>
</tr>
<tr>
<td>0-8 hrs in a mixed</td>
<td>0.9441</td>
<td>0.8767</td>
<td>0.9867</td>
<td>0.9639</td>
<td>0.9339</td>
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<tr>
<td>condition</td>
<td></td>
<td></td>
<td></td>
<td>1.1479</td>
<td>0.6219</td>
</tr>
<tr>
<td>8-72h in mixed</td>
<td>0.9685</td>
<td>0.7767</td>
<td>0.9544</td>
<td>0.9955</td>
<td>0.9339</td>
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<tr>
<td>condition</td>
<td></td>
<td></td>
<td></td>
<td>1.1315</td>
<td>0.6219</td>
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</table>

The concentration of drug from hydrogel disc. The “n” value of drug release exponent was 0.8018 (Table 3) by plotting the fraction ketotifen released vs. log time (Korsmeyer’s-Pappas) indicating that the non Fickian diffusion for the release of ketotifen from the hydrogels disc. This showed that in early stages the diffusion was the dominant process for the release of ketotifen from the hydrogel. However, the erosion may also be one of the important factors in the drug release from PVP drug loaded hydrogel [37].

Release of Ketotifen from GS3 Ketotifen Loaded Hydrogels: The data obtained from the in-vitro dissolution testing were subjected to various mathematical model i.e. Hixson-Crowell, First Order, Higuchi, Zero order, Korsmeyer’s Pappas, to calculate the kinetics and mechanism of ketotifen release from hydrogel disc.

Under mixed conditions (for the first two hrs in acidic condition and then for the rest of time in basic condition), it was found that the in-vitro release of ketotifen from hydrogel loaded disc GS3 best fits to the Higuchi model (Fig. 5) as the $R^2$ value obtained was the highest (0.9821) indicating the drug release followed Fickian diffusion. Fig. 3 indicates that good linearity ($R^2 = 0.9741$) was obtained for Zero Order indicating the drug release is independent of drug concentration. Hixson-Crowell plot for the data was also constructed (Fig. 6), the $R^2$ value was 0.9579 indicating polymer erosion and dissolution. The value (0.9216) of release exponent “n” obtained with Korsmeyer’s-Pappas equation suggests that drug release from GS3 formulation followed anomalous transport. Hixson-Crowell plot (Fig. 6) also confirms polymer erosion with the ($R^2 = 0.9579$).

Release of Ketotifen from GS3 (From 0-8 Hours): The drug release data were divided into two portions in order to study the suitable behavior of ketotifen release from hydrogel disc. Initially, the data was best fitted in the

Higuchi Model ($R^2 = 0.9867$). The 85 % release of the Ketotifen was observed in phosphate buffer solution and the data obtained from the in-vitro dissolution testing were subjected to various mathematical model i.e. Hixson-Crowell, First Order, Zero order, Higuchi and Korsmeyer’s Pappas to analyze the kinetics and release mechanism of ketotifen release from hydrogel loaded disc. When these data were subjected to various models for the release of ketotifen, it was found that the in-vitro ketotifen release from the GS3 from 0-8 best fits to the Higuchi model (Fig. 5) as the $R^2$ value obtained was the highest (0.9867) indicating the drug release followed Fickian diffusion. Hixson-Crowell plot for the data was also constructed (Fig. 6), the $R^2$ value was 0.9639 indicating polymer erosion and dissolution. Fig. 3 indicates that good linearity ($R^2 = 0.9441$) was obtained for Zero Order indicating that the release of ketotifen is independent of concentration of drug and diffusion exponent value (n) was 1.1479 in Korsmeyer’s plot that indicates the release of drug by the combination of both diffusion and erosion of the hydrogel and followed the non-Fickian super case II diffusion model.

Release of Ketotifen from GS3 (from 8-72 Hours): It was found that the in-vitro ketotifen release from the GS3 from 8-72 hours best fits to the Hixson-Crowell (Fig. 6) as the $R^2$ value obtained was the highest (0.9955) indicating polymer erosion and dissolution. Fig. 3 indicates that good linearity ($R^2 = 0.9685$) was obtained for Zero Order indicating the drug release is independent of drug concentration. Higuchi model plot for the data was also constructed (Fig. 5), the $R^2$ value was 0.9544 indicating that the release of ketotifen followed Fickian diffusion. The application of the Korsmeyer’s equation showed non-Fickian super case-II diffusion. The release was non-Fickian and it indicates that both erosion and diffusion are evenly responsible for the ketotifen release from hydrogel loaded disc.
REFERENCES


