Journal of Pharmaceutical Investigation
Vol. 40, No. 5, 285-289 (2010)

Zero-order Delivery of Alfuzosin Hydrochloride with Hydrophilic Polymers

Jun-Bom Park, Chang-Hwan Hwang, Hyung-Gon Noh, Yu-Byeong Chae, Jun-Woo Song and Chin-Yang Kang†

College of Pharmacy, Sahm Yook University, Seoul 139-742, Korea

(Received July 21, 2010 · Revised October 11, 2010 · Accepted October 12, 2010)

ABSTRACT − Manufacturing a multi-layered tablet such as Xatral XL® is more complex and expensive than monolayered tablets, but mono-layered tablets may have less favorable release properties depending on the pharmacodynamics and pharmacokinetics of the active ingredient. We therefore sought to develop a monolayer tablet with a similar dissolution profile to the commercial alfuzosin sustained-release triple layered tablet (Xatral XL®). We prepared four different mono-layered alfuzosin tablets with different concentrations of hydroxypropyl methycellulose and PVP K-90. Fomulation III with alfuzosion/ mg-stearate/ HPMC/ PVP K-90 (10/5/110/95 mg/tab) has a similar dissolution rate to Xatral XL®, with a similarity factor score of 81.4. However, the swelling and erosion rates of the two formulations were different, and NIR analysis showed differences in the mechanisms of drug release. Thus, although formulation III and Xatral XL® show similar dissolution rates, the mechanisms of drug release are different.

Key words − Alfuzosin HCl, Xatral XL®, HPMC, PVP, Mono-layered tablet

Alfuzosin HCl is approved for the treatment of benign prostatic hyperplasia and given as 2.5 mg three times a day or as a sustained-release form as 5 mg two times a day. However, the need for repeated administration reduces patient compliance (Jardin et al., 1999; Buzelin et al., 1993; Jardin et al., 1993; Teillac et al., 1992; Jardin et al., 1991). The GEOMATRIX® drug delivery system of sustained-release dosing gives a constant drug release rate and allows for once-a-day dosing. The system uses a triple-layer tablet with a white center layer that contains the active ingredient in an active matrix with two outer yellow layers that can be expanded or eroded to control the hydration and swelling rates of the center layer to give a constant dissolution rate. This drug delivery system produces constant drug dissolution over 18 h and reduces plasma fluctuations, as well as increasing patient compliance (Maggi et al., 2000).

Despite these advantages, producing these multi-layer tablets is both more complex and more expensive. The Jenn-Chiang Machinery Company, which manufactures the tablets, indicates that multi-layer tablet machines are 3-fold more expensive than single-layer tablet machines, and material loss for multi-layer tablets is also 3-fold higher. Manufacturing costs will be reduced if the same dissolution properties can be achieved with a single-layered tablet (JENN-CHIANG MACHINERY Homepage). We therefore sought to produce sustained-release tablets in a mono-layered drug matrix that produces a constant release of drug substance over 18 h.

Materials and Methods

Materials

Alfuzosin HCl was purchased from Farmak (Olomouc, Czech), tetrahydrofuran and sodium chloride from Kanto chemical (Isehara, Japan), and hydrochloric acid and perchloric acid from Junsei (Tokyo, Japan). Magnesium stearate was supplied by Hwa-il chemical (Seoul, Korea), PVP K-90 from BASF (Seoul, Korea), and HPMC from Shin-etsu (Tokyo, Japan). Xatral XL® was obtained from Handok (Seoul, Korea), distilled water, ethanol and methanol graded for HPLC from Burdick & Jackson (Ulsan, Korea). All other materials and reagents were of reagent grade or above.

Tablet manufacturing

With Alfuzosin HCl as the active ingredient, and magnesium stearate, HPMC, PVP K-90 as excipients, the tablet was produced with a Single Rotary Tableting machine (Chamunda Pharma, CPM 03-10) (Ahmedabad, India) with direct compression, with formulations summarized in Table I.

In vitro dissolution study

The dissolution study for tablets containing 10 mg Alfuzosin HCl was performed using a USP 32 apparatus 2 (paddle),

†Corresponding Author :
Tel : +82-3399-1600, E-mail : kangjy@syu.ac.kr
DOI : 10.4333/KPS.2010.40.5.285

Table I. *Compositions and Amounts of the Tablets*

Formulation	Ingredients			
	Alfuzosin HCl	Magnesium stearate	HPMC[a)]	PVP K-90[b)]
Formulation I	10 mg	5 mg	90 mg	115 mg
Formulation II	10 mg	5 mg	100 m g	105 mg
Formulation III	10 mg	5 mg	110 mg	95 mg
Formulation IV	10 mg	5 mg	120 mg	85 mg

a): Hydroxypropylmethylcellulose, b): Polyvinylpyrrolidone

Pharma-Test PTWS-1210 dissolution machine (Hanburg, Germany) equipped with an autosampler. The dissolution media was pH 1.2 HCl according to "Registration specification for finished product". Dissolution media were maintained at 37±0.5ºC and paddle speed was 100 rpm. Samples were filtered through a 40 mm filter and taken at 0, 1, 2, 4, 6, 10, 14, and 18 h. Six samples at each time point were analyzed by HPLC.

HPLC analysis

Alfusozin HCl release was detected by a Beckman HPLC system (Fullerton, USA), consisting of a UV detector (168), C18 column (4.6×120 mm, 5 μm, Waters), pump (126), autosampler (508), column oven (234), and data processor (Karat 32). The analysis method was modified from Alfuzosin HCl (USP 32-NF 27). Briefly, the wavelength of UV detector was 254 nm, column temperature was maintained at 30ºC, the flow rate was 1.0 mL/min, and injection volume was 20 μL. The mobile phase was sodium perchlorate:acetonitrile:tetrahydrofuran = 80:20:1(v/v/v). Sodium perchlorate was made by adding perchloric acid (6 mL) to distilled water (900 mL), adjusted to pH 3.5 with sodium hydroxide, and made to a final total volume of 1000 mL by adding additional water.

Data analysis

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Hadjiioannou et al., 1993). The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1693) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = k_0 t \quad (1)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\mathrm{Log}C = \mathrm{Log}C_0 - kt/2.303 \quad (2)$$

Where, C_0 is the initial concentration of drug and K is first order constant.

$$Q = Kt^{1/2} \quad (3)$$

Where, K is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}t \quad (4)$$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The following plots were made: cumulative % drug release vs. time (zero order kinetic model); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model) log cumulative % drug release vs. log time (korsmeyer model) and cube root of drug % remaining in matrix vs. time (hixson-crowell cube root law)(Shoaib et al., 2006).

Mechanism of drug release

Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer-Peppas model:

$$M_t/M_\infty = kt^n \quad (5)$$

Where M_t/M_∞ is fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in table II for cyclindrical shaped matrices.

Evaluation of dissolution data

Tablet release profiles were compared by calculating a statistically derived mathematical parameter, similarity factor (f_2) (Costa et al., 2001; Moore et al., 1996). Fraction release data was used to normalize the percent drug release values for the labeled amount of alfuzosin HCl in each delivery system. The similarity factor is:

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{j=1}^{n}|R_j - T_j|^2\right]^{-0.5} \times 100\right\} \quad (6)$$

Where R_j and T_j are percent drug dissolved at each time point

for the reference and test product, n the number of dissolution sample times, and t the time sample index. If the two profiles are identical, f_2 is 100. Values of f_2 50 indicate similarity of two dissolution profiles.

Swelling and erosion study

Alfuzosin HCl and Xatral XL® tablets were randomly selected and weighed. We performed the dissolution test for both tablets, weighing and drying them at 1, 2, 4, 6, 8, 10, 12, 16, and 18 h. All swelling and erosion test were performed in triplicate. The swelling rate (weight gain) and erosion rate (weight loss) were calculated as follows (Tahara et al., 1995) .

$$\% \text{ Weight gain } = 100 \times \frac{\text{wet weight-dry weight}}{\text{dry weigght}} \quad (7)$$

$$\% \text{ Weight loss } = 100 \times \frac{\text{original weight-remaining (dry)weight}}{\text{original weight}} \quad (8)$$

Measurement of NIR imaging

Samples were hydrated using a USP apparatus II (USP 32-NF 27) in a Pharma test PTWS 1210 dissolution tester. The dissolution medium was 900 mL of de-aerated stimulated gastric fluid at 37±0.5ºC, with paddle speed of 100 rpm. The hydrated sample was removed from the dissolution bath and deposited in a freeze dryer tube, which was immediately put into a carbon dioxide ice and methanol bath to freeze the sample. Once the condenser temperature was below -40ºC and the pressure below 13 Pa vacuum, the freeze dryer tube containing the sample was attached to a Freezone 1L (Labconco, Kansas City, MO, USA) freeze drier. Water was then removed by sublimation. The dried tablets were subsequently microtomed across the horizontal plane at the middle-point using a Leica EM Trim, to enable imaging of the core and gel layer of the tablet. A Foss Spectrum One NTS FT-NIR spectrometer and Spectrum Spotlight FT-IR Imaging system were used for imaging both formulations and Xatral XL®. Images were obtained for dry tablets, as well as tablets that had been hydrated for 2,8, and 18 h.

Results and Discussion

Dissolution study and kinetic mechanism

Dissolution results of the four mono-layered Alfuzosin HCl tablets and triple-layered Xatral XL® are shown in Figure 1. Formulation I and II are over-released early because of the small amount of HPMC, so did not show zero-order release. However, Formulations III and IV showed similar zero-order drug release as Xatral XL® (Table III) (Vueba et al., 2004). According to the Korsmeyer-Peppas equation, all formulations and Xatral XL® showed diffusional exponent values (n) ranging from 0.54 to 0.64, indicating that the release mechanism of alfuzosin HCl from these matrices is anomalous (non-Fickian) transport, suggesting that both dissolution of the drug in the hydrated matrix and its own erosion modulate drug release. For Formulation III and IV and Xatral XL®, the zero-order kinetic model and Higuchi's model yielded good fits (R^2>0.97).

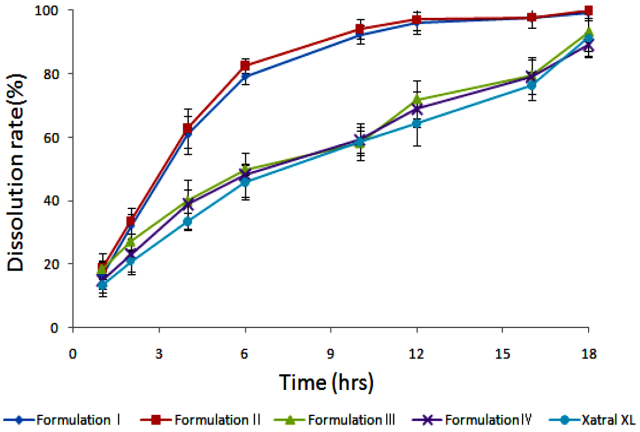

Figure 1. Comparative dissolution rate on Xatral XL® and formulation I~IV (n=6)

Table II. *Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape*

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-Fickian) diffusion
0.89	Case- transport
n > 0.89	Super case- transport

Similarity factor

Although Formulations III and IV and Xatral XL® showed similar dissolution rates, we quantitated this similarity using the f_2 value from equation (1). f_2 values for Formulations I and II were 30.4 and 29.1, respectively, indicating different drug releas profiles. Formulations III and IV had f_2 scores of 81.4 and 79.0, respectively, indicating similar dissolution to Xatral XL®. As shown in Table IV, f_2 values are calculated in dissolution rates based on the interval time stated in equation (1).

Swelling and erosion behavior

Formulation III showed a high f_2 score and was chosen to

Table III. *Fitting of the Experimental Alfuzosin HCl Release Data to Different Kinetic Equations*

Formulation	Zero-order		First-order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
	K_0	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2	K_{KP}	n	R^2
Formulation I	4.451	0.784	-0.083	0.650	26.279	0.899	-0.102	0.700	0.201	0.609	0.853
Formulation II	4.344	0.764	-0.078	0.645	26.721	0.887	-0.097	0.689	0.230	0.575	0.847
Formulation III	4.004	0.974	-0.082	0.883	20.355	0.979	-0.098	0.925	0.186	0.535	0.986
Formulation IV	4.053	0.972	-0.090	0.848	19.767	0.983	-0.104	0.901	0.155	0.601	0.989
Xatral XL®	4.200	0.978	-0.097	0.886	19.173	0.960	-0.111	0.918	0.135	0.644	0.992

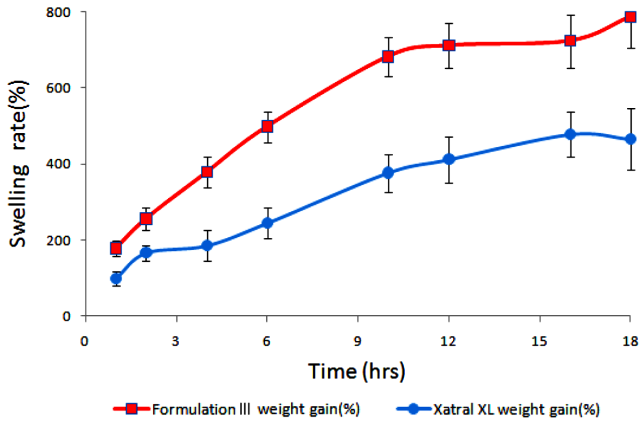

Figure 2. Swelling rate on Formulation III and Xatral XL® (n=3); (■): Formulation III, (○): Xatral XL®

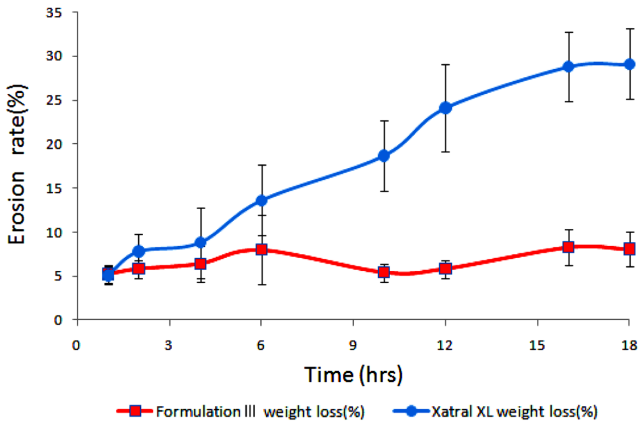

Figure 3. Erosion rate on Formulation III and Xatral XL® (n=3); (■): Formulation III, (○): Xatral XL®

measure swelling and erosion rates with Xatral XL®. Formulation III showed dramatic increases in weight gain (Fig. 2), and both Xatral XL® and Formulation III showed increased swelling, 450% and 800%, respectively, after 18h (Fig. 3). Controlled drug release occurs through the absorption of dissolution fluid and swelling as erosion occurs. The erosion rate was higher for Xatral XL® than Formulation III, indicating that Xatral XL® release is governed by both swelling and erosion,

Table IV. *Similarity Factor on Xatral XL® and Formulations*

	Formulation I	Formulation II	Formulation III	Formulation IV
Similarity factor(f_2)	30.4	29.1	81.4	79.0

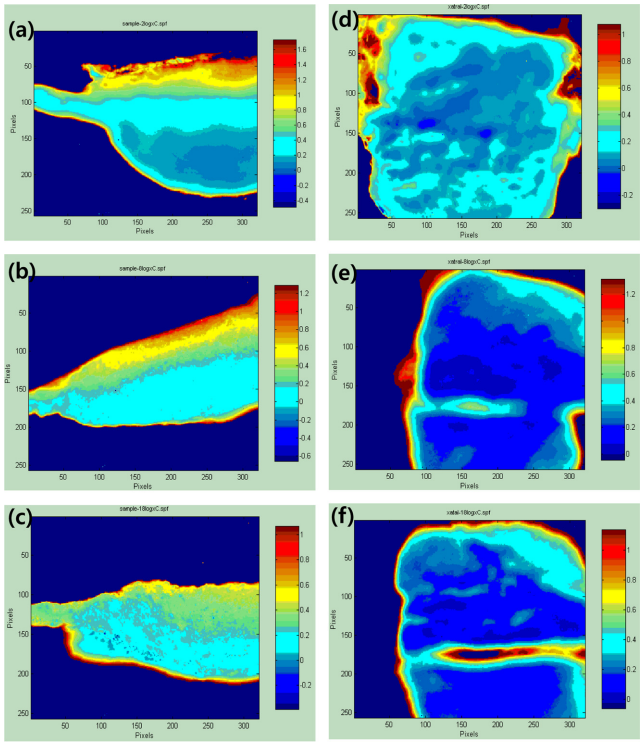

Figure 4. NIR Imaging on Formulation III and Xatral XL® ; (a) : after 2 hr of dissolution on Formulation III, (b) : after 8hr of dissolution on Formulation III, (c) : after 18hr of dissolution on Formulation III, (d) : after 2hr of dissolution on Xatral XL®, (e) : after 8 hr of dissolution on Xatral XL®, (f) : after 18hr of dissolution on Xatral XL®

whereas Formulation III release is controlled by swelling alone.

NIR Imaging

Formulation III showed the highest f_2 value and was chosen

for NIR Imaging after 2, 8, and 18 h of dissolution (Fig. 4). Red areas on the images indicate tablet membranes that form hydrophilic polymers, and both Formulation III and Xatral XL® form them early, which controls drug release initially. However, by 18 h, Formulation III has maintained them hydrophilic polymer membrane, whereas the middle layer of Xatral XL® containing alfuzosin is largely eroded.

Conclusion

We have developed a mono-layered tablet with alfuzosin, a drug for benign prostatic hyperplasia, with similar dissolution properties as Xatral XL®, a triple-layered, sustained-release formulation, using a multi-matrix of HPMC and PVP-k90. In particular, Formulation III showed an f_2 value of 81.4, similar to Xatral XL®. Formulation III, which is easily produced by direct compression with mixed hydrophilic polymers, has potential for cheaper and more efficient manufacturing than Xatral XL®.

References

Bourne DWA, 2002. Pharmacokinetics. In: Banker G.S., Rhodes C.T., Modern Pharmaceutics, 4th ed., marcel Dekker Inc., New York, 67-92.

Buzelin, J.M., Hebert, M., Blondin, P., te Prazalf Group, 1993. Alpha blocking treatment with alfuzosin in symptomatic benign prostatic hyperplasia: comparative study with prazosin, Br. J. Urol. 72, 922-927.

Costa, P., Lobo, J., 2001. Modeling and comparison of dissolution profile, Eur. J. Pharm. 13, 123-133.

Hadjiioannou, T.P., Christian, G.D., Koupparis, M.A., Macheras, P.E., 1993. Quantitative Calculations in Pharmaceutical Practice and Reserarch, VCH Publishers inc., New York, 345-348.

Higuchi, T., 1963. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm.Sci., 52, 1145-1149.

Hixson, A.W., Crowell, J.H., 1931. Dependence of reaction velocity upon surface and agitation (I) theoretical consideration. Ind. Eng. Chem., 23, 923-931.

Jardin, A.H., Bensadoun, H., Delauche-Cavaller, M.C., Attali, P., The BPH-ALF Group, 1993. Long term treatment of benign prostatic hypertropy with alfuzosin: a 12-18 month assessment. Br. J. Urol., 72, 615-620.

Jardin, A.H., Bensadoun, H., Delauche-Cavaller, M.C., Attali, P., The BPH-ALF Group, 1999. Long term treatment of benign prostatic hypertropy with alfuzosin: a 24-30 month survey. Br. J. Urol. 74, 579-584.

Jardin, A.H., Bensadoun, H., Delauche-Cavaller, M.C.., Attali, P., The BPH-ALF Group, 1991. Alfuzosin for treatment of benign prostatic hypertrophy. Lancet 337, 1457-1461.

JENN-CHIANG MACHINERY Homepage http://www.jcmco.com.tw/dh.htm

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P., Peppas, N.A., 1983. Mechanisms of solute release from porous hydrophilic polymers. Int. J. pharm., 15, 25-35.

Maggi, L., Conte, U., Grenier, P., Vergnault, G., Dufour, A., Jarreau, F.X., Rauch-Desant, C., 2000. Tablet with controlled release of alfuzosine chlorhydrate, US Patent 6, 149,940.

Moore, J.W., Flanner, H.H., 1996. Mathematical comparison of dissolution profile, Pharm. Tech. 20, 64-74.

Shoaib, M.H., Tazeen, J., Merchant, H.A., Yousuf, R.I., 2006. Evaluation of drug release kinetics from Ibuprofen matrix tablet using HPMC. Pak. J. Pharm. Sci., 19, 119-124.

Tahara, K., Yamamoto, K., Nishihata, T., 1995. Overall mechanism behind matrix sustained release (SR) tablet prepared with hydroxypropyl methylcellulose 2910, J. Control. Release 35, 59-66.

Teillac, P., Delauche-Cavallier, M.C., Attali, P., The Dualf Group, 1992. Urinary flow assessment after a single oral administration of alfuzosin, a new alpha1, blocker, in patients with benign prostatic hypertrophy, Br. J. Urol. 70, 58-64.

Vueba, M.L., Batista, de Carvalho, L.A.E., Veiga, F., Sousa, J.J., Pina, M.E., 2004. Influence of cellulose ether polymers on ketoprofen release from hydrophilic matrix tablets, Eur. J. Pharm. Biopharm. 58, 51-59.