Acta Pharmaceutica Turcica
47: 39 – 51 (2005)

Studies on Sustained Release Matrix Systems of Chlorzoxazone

Klorzoksazonun Sürekli Etkili Matriks Sistemleri Üzerine Çalışmalar

Tamer Güneri*, Filiz Taneri, Gökhan Ertan

University of Ege, Faculty of Pharmacy, Department of Pharmaceutical Technology, 35100 Bornova, Izmir

Abstract

In this study, the aim was to prepare matrix tablets of chlorzoxazone to achieve a sustained release profile suitable for peroral administration. Matrix tablets were prepared by means of wet granulation method using Eudragit® RS 100 as the polymer. The effect of formulation factors on drug dissolution and kinetics of drug release were investigated. Matrix tablets prepared from the granules in ratio of 1:0.5:0.8:0.46 (Chlorzoxazone:Eudragit® RS 100:Lactose:Primojel®) and with the particle size of 250 μm, revealed the best release behaviour. Micromeritic investigations were also carried out on chlorzoxazone powder and the granules of the tablets which showed the best release profile. These tablets showed non-Fickian behaviour according to the curve fitting analysis. This study claimed to formulate a delivery system that may optimize the drug release and reduce the side effects by the preparation of matrix tablet formulation of chlorzoxazone.

Key words: Chlorzoxazone, Eudragit® RS 100, matrix tablet, dissolution kinetics, diffusional behaviour, micromeritics

Introduction

Chlorzoxazone, 5-chloro-2-benzoxolinone, is a benzoxazole derivative which inhibits polysynaptic reflexes within the spinal cord and subcortical regions of the brain. It is used to decrease muscle tone and tension and trelievus to relieve spasm and pain associated with muscoskeletal disorders (Remington's Pharmaceutical Press, 1990). Its use is limited depending on side effects such as nausea and vomiting probably due to rapid absorption or gastric irritation (Martindale, 2002).

Eudragit® RS 100 is a copolymer of acrylic and methacrylic acid esters that swell in digestive fluid independently of the pH and becomes permeable. It is frequently preferred in film coating of the tablets, granules and other small particles and can be used also in matrix formulations (Sanghavi *et al.*, 1990; Kırılmaz *et al.*, 1996; Lehman, K., 1997, 2001; Derrar *et al.*, 2004; Ferrero *et al.*, 2003; Pignatello *et al.*, 2001).

Matrix tablets can be prepared with acrylic resins by granulation or direct compression. Pharmacologically inactive substances can be embedded in water-insoluble polymers as a means of retardation; e.g. tabletting together with polymer powder or by extrusion at the softening temperature of the polymers in the range of 120-200 °C. Poly(meth)acrylates are used mainly to regulate the drug release (Lehman, K. 2001).

* *Corresponding author* : e-mail: gunerit@pharm.ege.edu.tr

The aim of the present study was to prepare matrix tablet formulation of chlorzoxazone to achieve a sustained release profile by using Eudragit® RS 100. In the first step, the effect of formulation variables as polymer:drug ratio, particle size distribution and compression pressure, were investigated on the release of drug from the tablets. Afterwards, kinetic and micromeritic evaluations were carried out. Additionally, physical properties of the tablets were investigated.

Materials and Methods

Chlorzoxazone (CZX) was obtained as a gift sample from Cilag AG. (Geel, Belgium). Eudragit RS 100 was supplied from Röhm Pharma. (Darmstadt, Germany), Lactose was purchased from Merck (Darmstadt, Germany) and Primojel was supplied from Westerhorn (Dauenhof, Germany). Other reagents and solvents were of analytical grade.

Preparation of matrix tablets: The matrix tablets of 690 mg each containing 250 mg CZX were prepared by wet granulation method in different CZX: Eudragit® RS 100: Lactose: Primojel® ratios (Table 1). Powder mixtures were kneaded in a mortar using methanol as a binder during the granulation process. The granules were dried then sieved through a combined sieve set (Retsch, Germany) and reduced to particle sizes of 1400-1000,1000-710,710-500 and 500-250 μm. Matrix tablets were produced by compacting the granules under the compaction force of 512, 1025 and 2048 lbf/ft^2 during 10 s.

Table 1. The content ratios and the compaction force values of the matrix tablets

Code	CZX	Eudragit® RS 100	Lactose	Primojel®	Compaction Force (lbf/ft^2)
I	1	0.05	0.80	-	1025
II	1	0.10	0.80	0.40	2048
III	1	0.30	0.80	0.40	2048
IV	1	0.30	0.80	0.46	2048
V	1	0.50	0.80	0.46	2048
VI	1	0.50	0.80	0.46	1025
VII*	1	0.50	0.80	0.46	512

*a, b, c, d: Particle sizes of 1000 μm , 710 μm , 500 μm, 250 μm.

Preparation of hard gelatin capsules: Granules with a ratio of 1:0.5:0.8:0.46 and 250 μm particle size were filled in hard gelatine capsules in order to understand the effect of the tabletting procedure on the dissolution of the granule.

In vitro dissolution studies: In vitro dissolution studies were performed on the matrix tablets and the hard gelatin capsules using USP XXIII apparatus type II (The United States Pharmacopoeia, 2001) at 100 rpm, in 900 mL of simulated gastric and simulated intestinal media (SGM and SIM) maintained at 37 ±0.5 °C. Sampling was performed during 8 h 1 mL aliquot withdrawn at appropriate time intervals was filtered and the amount of drug dissolved was determined spectrophotometrically (Shimadzu UV-160A) at 280 nm in SGM and at 287 nm in SIM, respectively. Half change dissolution study was also carried out on the matrix tablets (V, VI and VII).

Kinetics of drug release

Kinetic evaluations: The in vitro release data of the ideal matrix tablets (VII-d) were evaluated kinetically by $(Bt)^a$, Langenbucher, first-order, zero-order, Hixon-Crowell, RRSBW, $Q\sqrt{t}$, Higuchi, Hopfenberg (spherical, cylindrical, slab) equations and the ideal kinetic models were estimated for drug release. The release constants (k) and determination coefficients (r^2) were calculated by means of a computer program (Ege M. A. *et al.*, 2001).

Curve fittting: Curve fitting was performed using Microsoft Excel 2000 version. The dissolution data were fitted to Equation (1).

$$\frac{M_t}{M_\infty} = kt^n \qquad (1)$$

where M_t/M_∞ is the fraction of drug released at time t, k is the kinetic constant of the system, and n is the diffusional exponent characteristic of the release mechanism. A value of n=0.45 shows that Fickian (Case I) diffusion is observed. A value of n=0.89 indicates Case II transport and the release is directly proportional to time. For values of $0.45<n<0.89$ anomalous (non-Fickian) transport is predominating mechanism (Peppas, 1985). The release exponent and kinetic constant of the system were calculated.

Micromeritic studies: In order to standardize the drug powder and the granule product for industrial applications, the micromeritic properties of the granules (VII-d) were studied by determining their fluff density and weight, tapped density and weight, fluidity, angle of repose and particle size distribution (Voight *et al.*, 1982; Güven, 1987). Hausner ratio and Consolidation (Carr %) index were also calculated by using Equations (2) and (3) to understand flowability rates of the powders and/or granules when tabletting or filling into gelatin capsules (Fassihi *et al.*, 1987; Wells, 1988).

$$\text{Consolidation index \%} = \frac{Tapped\ density - Fluff\ density}{Tapped\ density} x100 \qquad (2)$$

$$\text{Hausner ratio} = \frac{Tapped\ density}{Fluff\ density} \qquad (3)$$

Physical properties of the matrix tablets: Physical parameters of the matrix tablets that revealed the best release profile (VII-d) were characterized by investigating weight deviation, thickness, diameter, hardness and friability (Güven, 1987)

Results and discussion

According to the in vitro dissolution profiles of the pure CZX powder, the drug dissolved completely in 3.5 h in SGM and in 2 h in SIM (Figures 5 and 6). Matrix tablets showed very poor solubility in SIM (Figure 2-I). Dependingly, to achieve a better release profile in SIM, it might be necessary to add soluble and swelling excipients such as starch, Primojel®, Avicel PH 101 to accelerate release rate. Thus, Primojel® was added to the matrix tablets as a disintegrating agent in increasing amounts. Consequently, the dissolution increased, approximately to 90 % both in SGM and SIM where the tablets dissolved very quickly in the first 2 h (Figures 1-IV and 2-IV). For this reason to modulate the drug release, the amount of Eudragit® RS 100 was increased; however, tablets yielded decreased results in SIM (Figure 1-5).

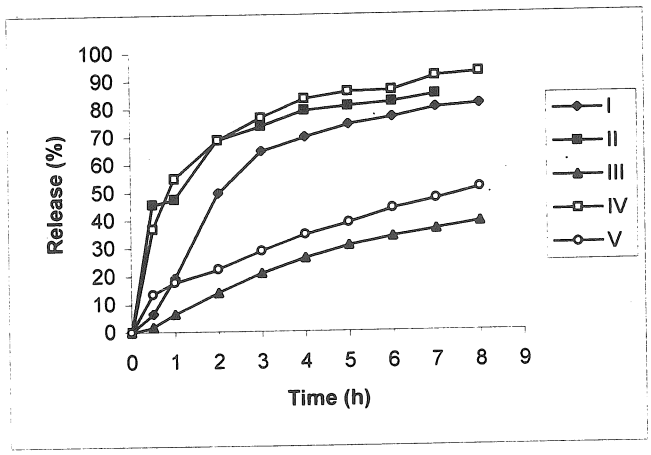

Figure 1. In vitro dissolution profiles of CZX matrix tablets (I-V) in SGM

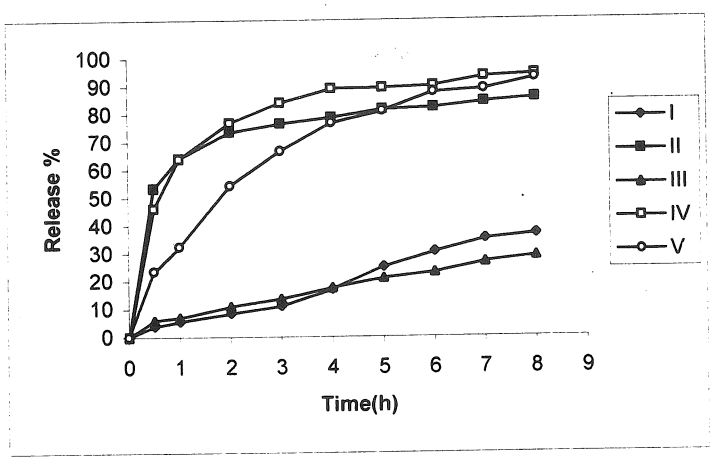

Figure 2. In vitro dissolution profiles of CZX matrix tablets (I-V) in SIM

It was observed that the particle size did not show any considerable effect on the in vitro dissolution profiles of the matrix tablets (Figures 3 and 4).

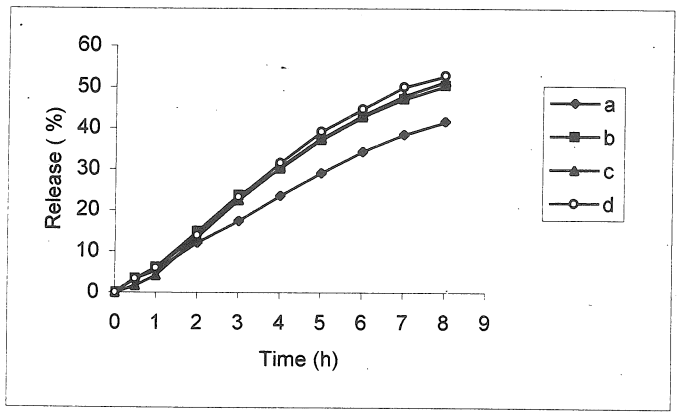

Figure 3. In vitro dissolution profiles of matrix tablets (VII- a, b, c, d) in SGM prepared from the granules with different particle sizes (a- 1000 μm, b- 710 μm, c-500 μm, d- 250 μm)

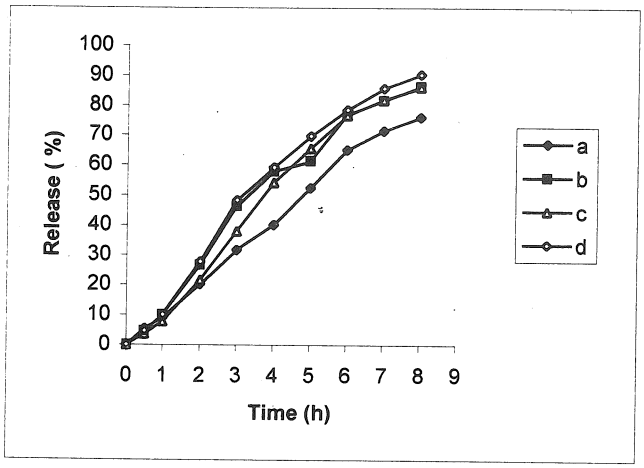

Figure 4. In vitro dissolution profiles of matrix tablets (VII-a, b, c, d) with different particle sizes in SIM (a- 1000 μm, b- 710 μm, c-500 μm, d- 250 μm)

The impact of the applied compaction force on the release profile of CZX from the matrix tablets is also investigated and reflected as in Figures 5 and 6.

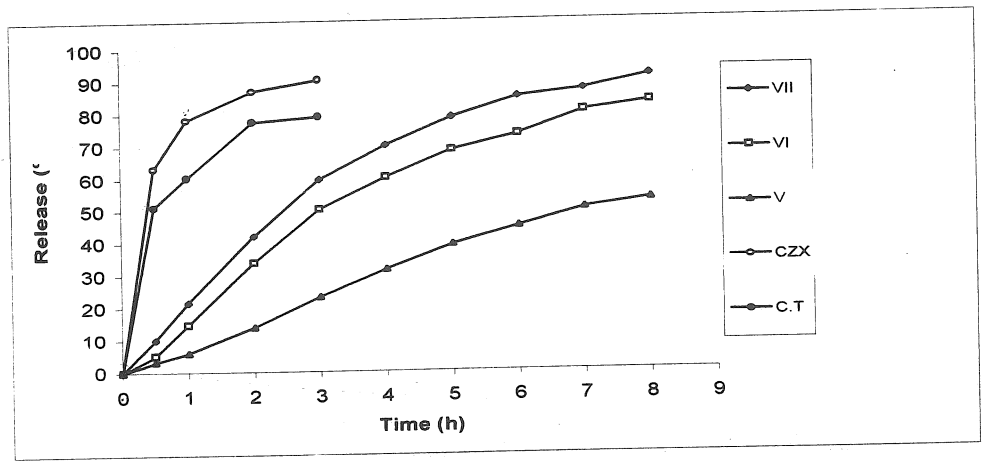

Figure 5. In vitro dissolution profiles of CZX , matrix tablets (V, VI and VII) and commercial tablet (C.T) prepared under different compaction forces in SGM

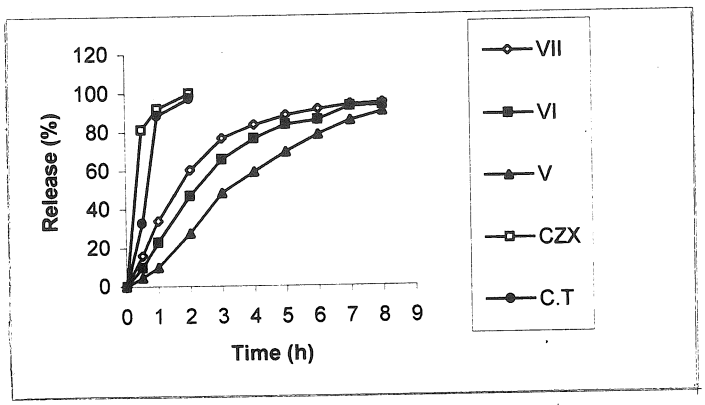

Figure 6. In vitro dissolution profiles of CZX, matrix tablets (V, VI and VII) and commercial tablet (C.T) prepared at different compression pressures in SIM

It was observed that the compaction force was the most important factor on the dissolution of these matrix tablets. According to the results of the half-change dissolution study the best release profile was achieved with the tablets prepared under the compaction force of 512 lbf/f^2 (VII, Figure 7).

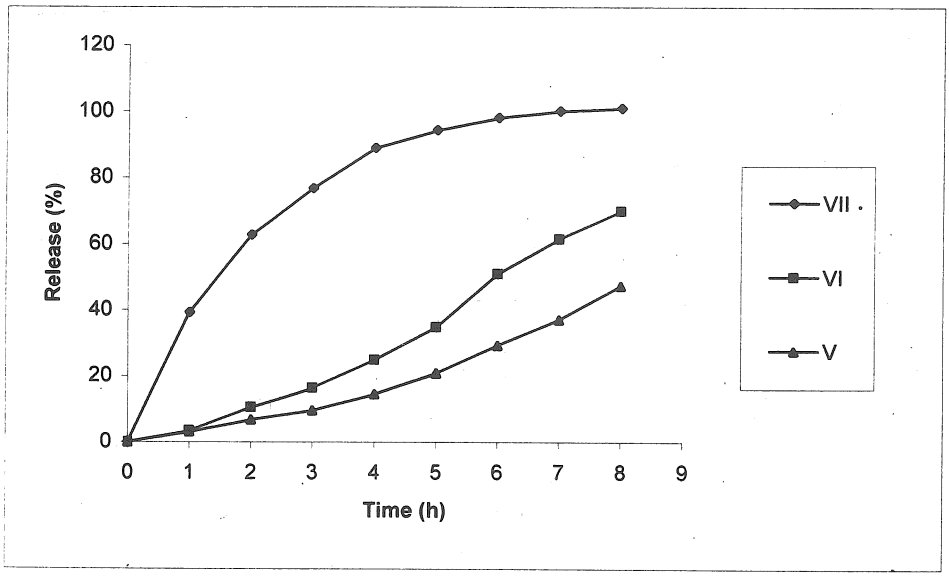

Figure 7. Half change dissolution profiles of the matrix tablets (V, VI and VII) prepared at different compaction forces

As a result of the in vitro dissolution studies, we suggest that the matrix tablets (VII-d) prepared under the compaction force of 512 Ibf/f^2 with the particle size of 250 μm in a ratio of 1:0.5:0.8:0.46 (CZX:Eudragit® RS 100:lactose:Primojel®) revealed an ideal sustained release behaviour, so that the drug release could be extended up to 8 h. In addition, when the results of the in vitro dissolution studies of the hard gelatin capsules were examined, the dissolved % of the drug decreased approximately from 30 % to 10 % in 0.5 h, from 45 % to 20 % in 1 h and from 55 % to 40 % in 2 h with the ideal matrix tablets (VII-d) compared to the hard gelatin capsules. This result showed that the tabletting procedure had considerable effect on the dissolution of the granules (Figures 5, 6 and 8).

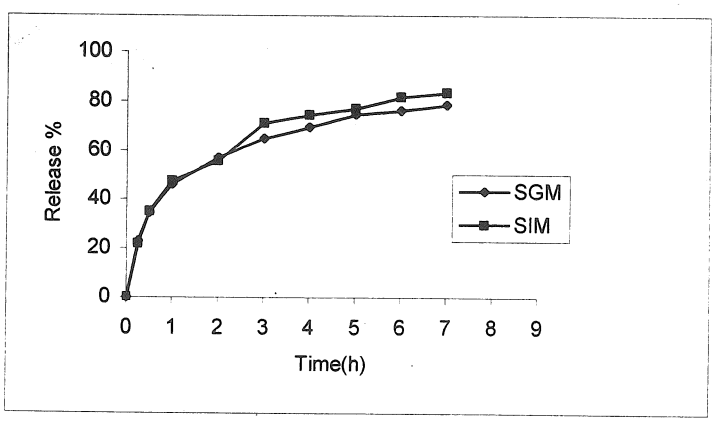

Figure 8. In vitro dissolution profiles of the gelatine capsules in SGM and SIM

The data of in vitro dissolution release of the matrix tablets (VII-d) were examined kinetically; consequently, the highest correlation coefficient and the best kinetic model was observed as first order kinetics in SGM and RRSBW distribution in SIM, respectively. For RRSBW, the shape parameter (β) was found as 1.012 and $t_{63.2\%}$ value as 143.6 min (Table 2, Figures 9, 10)

Table 2. Kinetic evaluations of CZX matrix tablets (VII-d)

	SGM	SIM
(Bt)[a]	A = 1.078 B = 1.398×10^{-3} R = 0.994 r^2 = 0.99	A = 0.878 B = 1.514 r = 0.991 r^2 = 0.983
Langenbucher	r = 0.992 r^2 = 0.984	r = 0.968 r^2 = 0.937
First- order	kr^1 = 0.301 h r = 0.998 r^2 = 0.997	Kr^1 = 0.405 hr^{-1} r = 0.987 r^2 = 0.974
Zero -order	kr^0 = 0.115 mg/h r = 0.957 r^2 = 0.915	Kr^0 = 0.108 r = 0.907 r^2 = 0.823
Hixon- Crowell	r = 0.992 r^2 = 0.984	r = 0.968 r^2 = 0.937
RRSBW	β = 1.183 r = 0.998 r^2 = 0.996	β = 1.012 r = 0.996 r^2 = 0.992
$Q\sqrt{t}$	k = 8.05×10^{-5} r = 0.992 r^2 = 0.984	K = 1.049×10^{-4} r = 0.967 r^2 = 0.936
Higuchi	r = 0.995 r^2 = 0.991	r = 0.983 r^2 = 0.967
Hopfenberg Spherical	k′ = 1.187×10^{-3} r = 0.992 r^2 = 0.984	k′ = 1.323×10^{-3} r = 0.967 r^2 = 0.936
Hopfenberg Cylindirical	k′′ = 1.504×10^{-4} r = 0.985 r^2 = 0.971	k′′ = 1.597×10^{-3} r = 0.954 r^2 = 0.911
Hopfenberg Slab	k′′′ = 1.911×10^{-3} r = 0.957 r^2 = 0.915	k′′′ = 1.806×10^{-3} r = 0.907 r^2 = 0.823

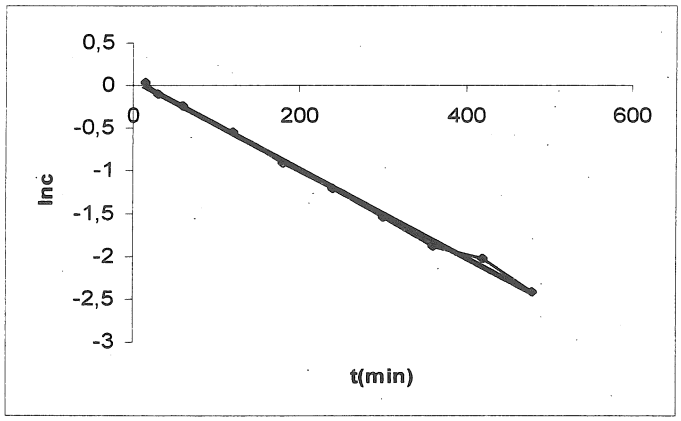

Figure 9. First order distribution of the matrix tablet (VII-d) in SGM

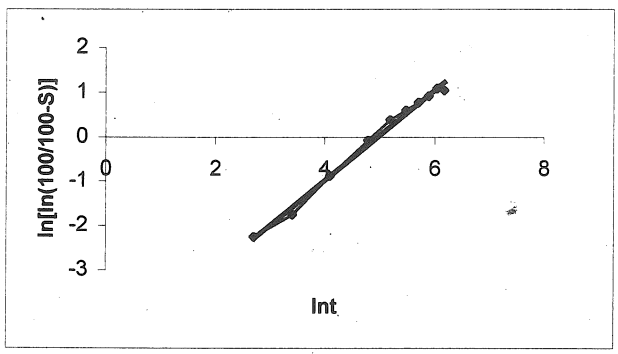

Figure 10. RRSBW distribution of the matrix tablet (VII-d) in SIM

The dissolution data of the matrix tablet (VII-d) were conveniently analyzed using Equation (1). The values of n and k were found as 0.795 and 1.319 for SGM (r^2=0.968); 0.623 and 1.499 for SIM (r^2=0.923), respectively. These values indicated that drug release was regulated through both mechanisms of diffusion and polymer relaxation (Pillay *et al.*, 2000). This type of transport may be observed if there are sites on the polymer or on particles distributed in the gel interacting with the drug molecules and if the drug concentration does not significantly exceed the concentration of sites (Upadrashta *et al.*, 1993).

Depending on the results of the micromeritic investigations accomplished on the pure drug and on the granules (VII-d), it was observed that tapped densities of materials decreased compared to the fluff densities (Table 3) .

Table 3. Micromeritic properties of the pure drug (CZX) and the granule of the matrix tablet (VII-d)

Micromeritic property	Pure Drug (CZX) ± SE	Granule(250μm) ± SE	P (T<= t) tw
Fluff density(mL/g)	2.05 ± 0	1.7 ± 0	$3.5x\ 10^{-29}$
Fluff weight(g/mL)	0.487 ± 0	0.588 ± 0	$3.16x\ 10^{-28}$
Tapped density (mL/g)	0.776 ± 0.0089	0.651 ± 0.0063	0.000312
Tapped weight(g/mL)	1.287 ± 0.014	1.529 ± 0.014	0.000363

Fluidity increased in granulated form compared to the powdered form. Flowability of the granules was found to be excellent (9.68) according to the Carr index of compressibility and good (1.11) according to the Hausner ratio while the results were very poor (37) and poor (1.59) for the pure drug, respectively.
These results were confirmed by the flow time and angle of repose values (Tables 4 and 5). From these results it may be concluded that the process of granulation has significantly increased the flowability of CZX. As it is understood no fluidity problem will occur during the tablet processing and the granules do not need any glidant.

Table 4. Flow time (sec) values of pure drug (CZX) and the granule (VII-d)

Flow time (sec.) Amount	Pure drug (CZX)	Granule	P(T< =t) tw
1g	0.666 ± 0.288	1 ± 0	0.116
2g	13 ± 1.732	1 ± 0	0.00027
4g	29.666 ± 2.081	1 ± 0	1.83×10^{-5}
6g	30.666 ± 3.785	2 ± 0	0.000195
8g	50 ± 15	2 ± 0	0.00518
10g	58 ± 8.504	2 ± 0	0.000329

Table 5. Angle of repose (°) values of pure drug (CXZ) and the granule (VII-d)

Angle of Repose (°) Amount	Pure drug (CZX)	Granule	P(T< =t) tw
1g	36.985 ± 7.924	8.224 ± 3.717	0.00470
2g	36.257 ± 6.943	19.165 ± 3.636	0.00194
4g	44.533 ± 2.724	19.246 ± 1.482	0.000145
6g	50.329 ± 1.613	16.730 ± 2.425	3.705×10^{-5}
8g	49.497 ± 3.879	24.947 ± 1.054	0.000452
10g	53.375 ± 1.505	23.535 ± 1.005	8.956×10^{-6}

Table 6. Weight and relative deviation values of pure drug (CZX) and the granule (VII-d)

Amount	Weight deviation ± SD Relative Deviation		
	Pure Drug	Granule	P (T <=t) tw
1 mL	0.644 ± 0.0205 3.195	0.538 ± 0.022 4.177	0.00383
2 mL	1.228 ± 0.033 2.757	1.109 ± 0.064 5.824	0.0483
4 mL	2.265 ± 0.0223 0.986	2.107 ± 0.063 3.0017	0.0152
5 mL	2.983 ± 0.068 2.284	2.783 ± 0.105 3.807	0.0519
6 mL	3.507 ± 0.05 1.431	3.302 ± 0.087 2.655	0.241

Table 7. Particle size distribution values of the pure drug (CZX) and the granule (VII)

Particle size	Pure drug (%)	Granule (%)
>1400 µm	-	65.5
1400 - 1000µm	-	8.55
1000- 710 µm	-	5.85
710 - 500 µm	0.198	6.24
500 - 250 µm	62.8	5.12
250 - 125 µm	13.4	2.46
< 125µm	21.1	2.3

According to the results of the quality control tests, all the matrix tablets (VII-d) showed acceptable pharmacotechnical properties and the results complied with the specifications for the tested parameters as stated in the USP XXIII (Table 8).

Table 8. Physical parameters of the matrix tablets (VII-d)

Physical parameters	Results
Weight deviation ± SD	0.690 ± 0.00029
Thickness (mm)	5 ± 0
Diameter (mm)	13 ± 0
Hardness (kg / monsanto)	1.4 ± 0.186
Friability (%)	4.022

Conclusion

Beginning from crude materials to packing such as formulation, preparation, in vitro dissolution, kinetics, diffusional behaviour, micromeritic properties including pharmacotechnical properties of the matrix tablets have been investigated. Matrix tablets prepared from the granules in the ratio of 1:0.5:0.8:0.46 (Chlorzoxazone:Eudragit® RS 100:Lactose:Primojel®) and with the particle size of 250 μm, revealed the best release behaviour. The present study demonstrated that a sustained release dosage form of CZX could be prepared and the drug release could be modulated by using Eudragit® RS 100.

Acknowledgements

The authors would like to thank to the Research Foundation of University Ege for financial support given to the project (Prj. No: 96/ECZ/010).

Özet

Bu çalışmada amacımız klorzoksazonun matriks tabletlerini hazırlayarak peroral uygulama için uygun olan sürekli etkili salım profilini elde etmektir. Matriks tabletler polimer olarak Eudragit® RS 100 kullanılarak yaş granülasyon yöntemiyle hazırlandı. İlaç dissolusyonu ve kinetiği üzerinde formülasyon faktörlerinin etkisi ve ilaç salımının kinetiği araştırıldı. 1:0.5:0.8:0.46 (Klorzoksazon: Eudragit® RS 100:laktoz:Primojel®) oranında ve 250 μm partikül büyüklüğüne sahip granülelerden hazırlanan matriks tabletler en iyi salım özelliğini gösterdi. Ayrıca toz ilaç ve en iyi salım profilini veren tabletlerin granüleleri üzerinde mikromeritik araştırmalar yapıldı. Yine bu tabletler eğri uyum analizine göre non-Fickian davranışı gösterdi. Bu çalışma, klorzoksazonun matriks tablet formülasyonlarının hazırlanması ile ilaç salımının optimize edilebildiğini ve ilaç yan etkilerinin azaltılabileceğı bir salım sisteminin formüle edilebileceğini ortaya koymaktadır.

References

Derrar, M. O., Sallam, A., Abd-Elbary, A. and El-Samaligy, M. (2004). Lactic acid-induced modifications in films of Eudragit RL and RS aqueous dispersions. *Int. J. Pharm.* 274:85-96.

Ege, M.A., Karasulu, H.Y., Karasulu, E. and Ertan, G., (2001). A computer program designed for in vitro dissolution kinetics, in vitro-in vivo kinetic correlations and routine application, *4th Central European Symposium on Pharmaceutical Technology, Vienna, Scientia Pharmaceutical Supplement 1 Band* 69, p. 127-128.

Fassihi, A. R. and Kanfer, I. (1987). The effect of compressibility and powder flow properties on tablet weight variation. In: Pharmaceutical Technology, Tableting Technology, M.H. Rubinstein Eds., Vol. I, Wiley, New York, p.189-202.

Ferrero, C., Bravo, I. and Jimenez-Castellanos M. R. (2003). Drug release kinetics and front movement studies from methyl methacrylate (MMA) copolymer matrix tablets: effect copolymer type and matrix porosity. *J. Contr. Rel.* 9, 19, 92(1-2): 69-82.

Güven K.C. (1987). Eczacılık Teknolojisi, Modern Reprodüksiyon, Istanbul, p.272-273.

Kırılmaz, L. and Dündar, Ç. (1996). Studies on the release of oxolamine citrate from matrix tablets prepared with Eudragit®. *Acta Pharm. Turc.* 38 (1):5-8.

Lehman, K. (1997). In Mc. Ginity, J. W. (Ed.), Aqueous polymeric coatings for pharmaceutical dosage forms, 2nd Ed. Marcel Dekker, New York, p. 101-176.

Lehman, K. (2001). Practical course in film coating of pharmaceutical dosage forms with Eudragit. Pharma Polymer. Darmstadt, p. 8-10, 144-147.

Martindale (2002). The Complete Drug Reference, 33rd Ed., Pharmaceutical Press, London, UK.

Peppas, N. A. (1985). Analysis of Fickian and Non-Fickian drug release from polymers. *Pharm. Acta Helv.*, 60 (4): 110-111.

Pignatello, R., Ferro, M., De Guidi, G., Salemi, G., Vandelli, M. A., Guccione, S., Geppi, M., Forte, C. and Puglisi, G. (2001). Preparation, characterization and photosensitivity studies of solid dispersions of diflunisal and Eudragit® RS 100 and RL 100. *Int. J. Pharm.* 218: 27-42.

Pillay, V. and Fassihi, R. (2000). A novel approach for constant rate delivery of highly soluble bioactives from a single monolithic system. *J. Contr. Rel.* 67: 67-78.

Remington's Pharmaceutical Sciences (1990). 18th Ed., Pennsylvania,Mack Publishing Com., p.922.

Sanghavi, N. M., Bijlani, C. P., Kamath, P. R. and Sarwade, V. B. (1990). Matrix tablets of salbutamol sulphate. *Drug Dev. Ind. Pharm.* 16 (12): 1955-1961.

The United States Pharmacopoeia (2001). XXIII, United States Pharmacopoeial Convention, Inc., Rockville

Upadrashta, S. M., Haglund, B. O. and Sundelof, L. O. (1993). Diffusion and concentration profiles of drugs in gels. *J. Pharm. Sci.* 82 (11): 1094-1098.

Voight, R. and Bornschein, M. (1982). Pulver, Puder. In:Lehrbuch der Pharmazeutischen Technologie, Verlag Chemie, New York, p. 157-167.

Wells, J. I. (1988). Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances, Wiley, New York, p.209-214.

Received: 08.01.2004
Accepted:13.02.2004