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PREPARATION AND *IN-VITRO* EVALUATION OF ORAL CONTROLLED-RELEASE MATRIX TABLETS CONTAINING DICLOFENAC SODIUM

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تم فى هذا البحث تحضير أقراص منضبطة الانطلاق تحتوى على ١٠٠ مجم من عقار ديكلوفيناك الصوديوم وذلك بإستخدام زلال البيض وثلاثة مواد أخرى هى كاربوكسى ميثيل سليولوز الصوديوم وهيدروكسى بروبيل ميثيل سليولوز والايودراجيت ر س.

وتم تقييم هذه الأقراص من حيث خواصها الطبيعية ومعدل انطلاق العقار منها وأوضحت النتائج أن جميع الأقراص المحضرة لها خواص فيزيائية مقبولة وقد وجد أن معدل انطلاق العقار يعتمد على نوع المادة المستخدمة لتحضير الأقراص وكذلك على الأس الهيدروجينى للسائل المستخدم فى إجراء تجارب معدل الانطلاق. وقد تم مقارنة معدل الانطلاق للعقار من الأقراص المحضرة لنوعين من الأقراص الممتدة المفعول الموجودة بالسوق والمحتويه على نفس الكمية من العقار وهى أقراص فولتارين ١٠٠ مجم ممتدة المفعول (إنتاج شركة سيبا جايجى - الولايات المتحدة الامريكية) وأقراص ديكلوفين ١٠٠ مجم الممتدة المفعول (إنتاج الشركة المتحدة للأدويه - الاردن). وإتضح من النتائج انه لايوجد اختلاف واضح بين معدل انطلاق الدواء من الاقراص التى تحتوى على زلال البيض أو خليط من زلال البيض وكربوكسى ميثيل سليولوز الصوديوم والمستحضرات المطروحة فى السوق. وإتضح أيضا أن ميكانيكية إنطلاق الدواء من جميع الاقراص تتبع نظام الانتشار المنضبط. وبناءا على النتائج التى تم الحصول عليها فإن إستخدام زلال البيض لتحضير أقراص منضبطة الانطلاق لعقار ديكلوفيناك الصوديوم يكون ذو اهمية.

Controlled-release matrix tablets containing 100 mg-diclofenac sodium were successfully prepared using egg albumin and three matrices forming materials namely, sodium carboxymethyl cellulose (NaCMC), hydroxypropylmethyl cellulose (HPMC) and Eudragit RS. The prepared tablets were evaluated for their physical parameters and the drug release rate. All the prepared tablet formulations showed acceptable physical parameters. The release rate was variable depending on the composition of the matrix tablet and pH of the dissolution medium. The release profiles and the release kinetics were compared with two commercially available sustained-release tablet formulations of diclofenac sodium, Voltaren SR 100 (Ciba Geigy, USA) and Diclofen SR 100 (The United Pharm. Co., Jordan). The drug release data was fitted to various kinetic models. The drug release from all the tested formulations could be described by the diffusion mechanisms. Tablets prepared with either egg albumin or combination of egg albumin and NaCMC gave release kinetics that were not significantly different from the commercial formulations. Based on experimental results, preparation of controlled-release matrix tablets of diclofenac sodium using egg albumin is promising.

INTRODUCTION

Controlled-release dosage forms continue to draw attention in the search for improved patient compliance and decreased incidence of adverse drug reactions. Ideally, a controlled-release dosage form provides a therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval with a reduction in the peak / nodir concentration ratio. One of the least complicated approaches to the manufacture of controlled release dosage forms involves direct compression of the drug blends to form a tablet in which drug is embedded in

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the matrix core of the polymer.[1-5] Also, hydrophilic matrix systems have been paid considerable attention as sustained release formulations for various drugs on exposure to aqueous fluids.[6,7] The tablet surface becomes wet and starts to hydrate to form a viscous gel layer. The release of drugs from the products can be goverened by the diffusion through the hydrogel and its subsequent erosion.[8-10] It has been reported that drug release from matrices is affected by the physical characteristics of the polymer such as polymer viscosity, particle size and drug/polymer ratio.[11-13] Also, the release is affected by the physicochemical properties of drugs, such as solubility, particle size, drug loading and by manufacturing factors, such as compression force, tablet shape, hardness, formulation excipients coating and processing techniques as well as by the testing medium.[13,14]

The popularity in the formulation of sustained-release dosage forms by using swellable and hydrophilic polymers is related to their non-toxic properties, ease of handling, minor influence on processing parameters, and relatively simple manufacturing technology.[15]

Diclofenac sodium is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic activity.[16] Because of its high level of effectiveness, diclofenac sodium has been used clinically in the form of tablets and suppositories.[17,18] Diclofenac sodium is absorbed from oral tablets into the blood circulation within 30 min after administration and reach the maximum blood concentration at about 2 hr. However, its biological half-life is only 1.3 hr.[19] Therefore, a long acting formulations that can sustain the action of diclofenac sodium in blood over an extended period of time would be very beneficial.

The choice of an appropriate formulation for a selected drug may play a significant role in successful drug therapy. Preparation of matrix tablets by direct compression has been gaining increased attention because of the simple and low cost manufacturing process.[20] Egg albumin is a biodegredable drug carrier which has been using in solid dispersion and microencapsulation processes.[21,22] It has been also recently used for preparation of controlled-release matrix tablets.[23,24]

The objectives of this study were:

1. To develop controlled-release matrix tablets containing 100 mg diclofenac sodium by using egg albumin, and three matrices forming materials namely, sodium carboxymethyl cellulose (NaCMC), hydroxypropylmethyl cellulose (HPMC) and Eudragit RS.
2. To evaluate the controlled-release characteristics of the prepared tablets in comparison with two commercially available sustained-release tablets containing 100 mg diclofenac sodium (Voltaren SR and Diclofen SR) by the *in-vitro* dissolution.
3. To investigate the release mechanism of diclofenac sodium from the prepared tablet formulations by fitting the dissolution data to various kinetic models.

EXPERIMENTAL

Materials

Sodium carboxymethyl cellulose (NaCMC) (C.B. H. Lab. Chem. Nottengham. UK). Hydroxypropylmethyl cellulose (HPMC) (Methocel K100M, Ltd., Orpington, UK). Egg albumin (Gainland chem. Comp., Sandy croft, Deeside, UK). Eudragit RS (RÖhm Pharma GMBH, Weiterstadt, Germany). Microcrystalline cellulose (Avicel PH 102), mean particale size 98 μm (FMC Corporation, USA). Diclofenac sodium and talc (a gift from the United Pharmaceutical Manufacturing Co. Ltd., Amman, Jordan). All other chemicals were of analytical grade.

Commercial tablets

Two different marketed sustained-release tablet formulations containing 100 mg of diclofenac sodium were used as reference, Voltaren SR100 (Ciba Geigy, USA, lot No. 35501) and Diclofen SR100 (United Pharmaceutical Manufacturing Co. Ltd Amman/ Jordan, batch No. 70535).

Methods

Preparation of tablets by direct compression

A series of matrix tablet formulations (seven formulations, F1-F7) containing a constant amount of diclofenac sodium (100 mg), Avicel PH 102 (50 mg) and talc (5 mg) were prepared by varying the composition of the matrix forming materials (Table 1). All materials were passed through 125 μm sieve and retained on 90 μm sieve. All the tablet formulations were prepared by direct compression using single flat-faced single punch (10 mm diameter) tabletting machine (Erweka-AR 400 E, Germany). Diclofenac sodium was first mixed with the matrix forming martial for 10 min in a high speed mixer (Erweka Turbula system S27, Germany). Avicel PH 102 and talc were then added and mixing contiued for another 10 min. The machine was adjusted to produce tablets of approximately 305 mg weight and 50-70 N hardness. F1 (150 mg NaCMC), F2 (150 mg HPMC), F3 (150 mg egg albumin), F4 (150 mg Eudragit RS), F5 (75 mg NaCMC and 75 mg HPMC), F6 (75 mg NaCMC and 75 mg egg albumin) and F7 (75 mg NaCMC and 75 mg Eudragit RS).

Evaluation of the prepared tablets

Physical properties

- Uniformity of weight and drug content were determined according to USP/NF 23 procedures.
- Thickness and diameter testing were measured using a micrometer (Mitutoyo, Japan).
- Hardness and friability were determined using Erweka hardness tester (TBH 30) and Erweka friabilitor (GmbH, Germany) respectively.
- Tablet disintegration was performed at 37° in simulated gastric fluid without enzymes using a disintegration tester (Pharma Teast, PTZ-Italy).

In-vitro drug release studies

Diclofenac sodium released from various tablets was determined according to USP 23 paddle method using Hanson dissolution test station (Hanson Research Co. USA). Dissolution tests were carried out on sets of six tablets from each formulation. The test was conducted in 900 ml of dissolution medium maintained at 37° at a

Table 1: Composition of the prepared tablet formulations of diclofenac sodium.

Ingredients	Formulation number and composition (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8*	F9*
Diclofenac sodium	100	100	100	100	100	100	100	100	100
NaCMC	150	-	-	-	75	75	75	-	-
HPMC	-	150	-	-	75	-	-	-	-
Egg Albumin	-	-	150	-	-	75	-	-	-
Eudragit RS	-	-	-	150	-	-	75	-	-
Avicel PH102	50	50	50	50	50	50	50	-	-
Talc	5	5	5	5	5	5	5	-	-
Total weight (mg)	305	305	305	305	305	305	305	305	305

*Commercial sustained – release tablet formulations containing 100 mg diclofenac sodium per tablet: F8 (Voltaren SR 100), F9 (Diclofen SR 100).

paddle rotation speed of 100 rpm. Samples of 5 ml were withdrawn at predetermined time intervals over 8 hr. period and replaced with equal volume of the dissolution medium equilibrated at the same temperature. In order to determine the influence of pH of the dissolution medium on the rate of drug release, dissolution media of different pH values (simulated gastric fluid without enzyme pH 1.2 and phosphate buffers BP pH 3, pH 5 and pH 6.8) were used as dissolution medium for all the prepared tablets formulations and compared with the commercial sustained-release tablets formulations (Voltaren SR and Diclofen SR). The drug concentration of the withdrawn samples was analyzed after filtration (0.45 μm Millipore filter) by UV spectroscopy (Shimadzu UV/vis 1205, Japan) at 276 nm.

RESULTS AND DISCUSSION

Physical properties

Table 2 shows the physical properties of the prepared tablets of diclofenac sodium. It could be observed that all the prepared tablets fulfill the USP/ NF 23 requirements for uniformity of weight, drug content and friability. These tablets showed acceptable tensile strength, uniformity of thickness and diameter values. Tablets containing NaCMC and/or HPMC showed better tensile strength than those containing egg albumin and Eudragit SR. The tensile strength (T) was calculated using the relationship, $T = 2P/HD\pi$. Where T is the thensile strength (N/m^2), H is the thickness of the tablet (mm), D is the diameter of the tablet (mm), and P is the applied force (N). The tensile strength of the prepared tablet can be arranged in the following order: F2 > F1 > F6 > F5 > F7 > F3 > F4. The disintegration time values for all the tested tablets were > 12 hr (Table 2).

Drug release characteristics

The drug release profiles from different controlled-release tablets are shown in Figures 1-9. The drug was gradually released from all formulations and it was noted that all tablets did not disintegrate during the time-course of the release. This leads to that the process of release of drugs from matrix tablets is a complex one. It involves penetration of the dissolution medium into the dry matrix, hydration and gel formation of the polymer (NaCMC, HPMC, egg albumin or Eudragit), diffusion of the dissolved drug into the resultant gel and erosion of the resultant gel layer. This modeling of these processes is further complicated by the swelling of the system and resulting in a slow and controlled-release rate of the drug.[24] The influence of pH on the drug release profiles from different tablets is shown in Figures 1-9. The rate of drug dissolution was noted to be markedly affected by the pH of the dissolution medium, increased with increasing the pH from pH 1.2 to pH 6.8 for all the tested tablets including the commercial tablets (Figures 1-9). This observation could be ascribed to diclofenac sodium which is converted to diclofenic acid (weak acidic drug) being poorly soluble at low pH values. It was observed that the release profiles of diclofenac sodium in phosphate buffer pH 6.8 from all the prepared tablets could be adequately sustained as compared with the release profiles of the commercial tablets.

Drug release kinetics

The goodness of fit of the release data of all the tested tablets in phosphate buffer (pH 6.8) was tested with the main models which have been proposed to describe drug release kinetics from matrices which include:

- Zero-order:[25] $100 - w = k_0$
- First-order:[25] $\log w - \log 100 = -K_1 / 2.303$
- Cub root:[26] $(100)^{1/3} - (W)^{1/3} = k_2 t$
- Square root:[27,28] $100 - w = k_3 \sqrt{t}$

Where (w) is the percentage of undissolved drug at time t and k_0, k_1, k_2 and k_3 are the specific release rate constants. The values of the release constants and the corresponding determination coefficients (r^2) are listed in Table 3. It seemed that the plots of different models were nearly linear as indicated by the high determinaion coefficent ($r^2 > 0.92$) in all cases.

The fit to the different models constitutes evidence that diclofenac sodium release from the

Table 2: Physical properties, mean (CV%), of the prepared tablet formulations of diclofenac sodium.

Parameter	Formulation						
	F1	F2	F3	F4	F5	F6	F7
Weight (mg)	305(3.23)	307(2.81)	302(2.78)	310(4.94)	303(2.24)	304(1.77)	306(2.61)
Friability (%)	0.66(4.29)	0.73(4.03)	0.89(3.85)	0.54(2.86)	0.35(3.81)	0.37(1.99)	0.80(3.25)
Thickness (mm)	4.05(0.37)	3.44(0.44)	3.42(0.60)	4.4(0.14)	4.36(0.22)	3.99(0.38)	3.65(0.27)
Diameter (mm)	10.22(0.20)	10.5(0.09)	10.50(0.90)	10.13(0.19)	10.02(0.15)	10.32(0.19)	10.01(0.15)
Disintegration time (h)	>12	>12	>12	>12	>12	>12	>12
Drug content (mg)	101.00(1.15)	99.50(0.45)	98.90(1.02)	99.20(0.5)	100.10(0.55)	98.70(1.5)	99.25(1.05)
Tensile strength (N/m^2)	515.25(6.5)	622.95(8.5)	454.99(6.7)	445.40(3.50)	505.14(8.50)	511.43(7.9)	503.14(8.6)

Table 3: Release kinetics of diclofenac sodium from the tested controlled- release matrix tablets in phosphate buffer (pH 6.8).

Formulation Code	Release kinetic Models							
	Zero order (100-w) Vs. t		First order Log w Vs. t		Hixson-Crowell $(100)^{1/3} - (w)^{1/3}$ Vs. t		Square root Eq. (100-w) Vs $(t)^{1/2}$	
	r^2	$K_{1\ (\%n)}$	r^2	$K_1\ (h^{-1})$	r^2	K_2	r^2	K_2
F1 (NaCMC)	0.966	11.55	0.98	0.248	0.984	0.291	0.964	39.3
F2 (HPMC)	0.994	10.37	0.923	0.194	0.958	0.239	0.937	34.26
F3 (Egg albumin)	0.988	6.41	0.988	0.151	0.992	0.164	0.984	21.73
F4 (Eudragit RS)	0.895	11.44	0.966	0.245	0.946	0.288	0.958	40.34
F5 (NaCMC/HPMC)	0.975	10.55	0.987	0.226	0.991	0.265	0.975	35.93
F6 (NaCMC/Egg alb)	0.985	8.36	0.933	0.154	0.96	0.191	0.946	29.89
F7 (NaCMC/Eud.)	0.955	11.13	0.991	0.243	0.985	0.283	0.974	38.89
F8 (Voltaren SR)	0.984	7.94	0.99	0.162	0.994	0.195	0.988	27.18
F9 (Diclofen SR)	0.994	8.47	0.954	0.188	0.978	0.219	0.974	28.56

w = Percentage of drug undissolved at time (t).
K = Specific rate constant.
r^2 = Determination coefficient.

Table 4: Determination coefficients (r), Kinetic release constants (k) and diffusion exponents (n) after fitting the release data to the Simple Power Law.

Formulation code	r^2	K (h^{-n})	n*
F1 (NaCMC)	0.962	12.25	0.49
F2 (HPMC)	0.996	6.96	0.51
F3 (Egg albumin)	0.994	16.14	0.50
F4 (Eudragit RS)	0.938	11.47	0.48
F5 (NaCMC/HPMC)	0.972	17.33	0.49
F6 (NaCMC/Egg alb)	0.980	15.32	0.50
F7 (NaCMC/Eud.)	0.965	16.14	0.51
F8 (Voltaren SR)	0.992	24.77	0.50
F9 (Diclofen SR)	0.982	25.74	0.49

*n = The diffusional release exponent, indicative of the mechanism of release. The values of n is <0.45 for fickian release, >0.45 and < 0.89 for non -fickian (anomalous) release, >0.89 for case II release and >0.89 for super II type release.

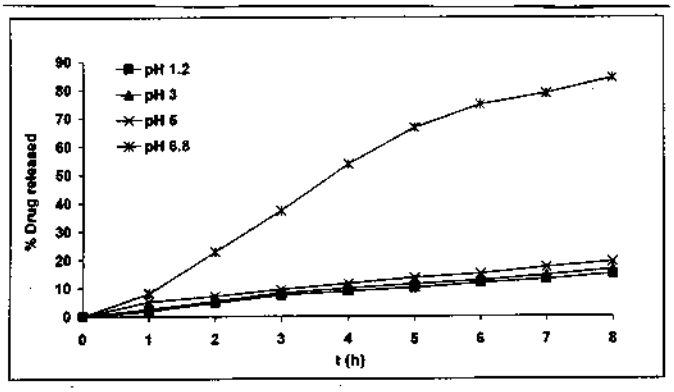

Fig. 1: Effect of pH of dissolution medium on the release of diclofenac sodium from controlled-release matrix tablet prepared with NaCMC (F1).

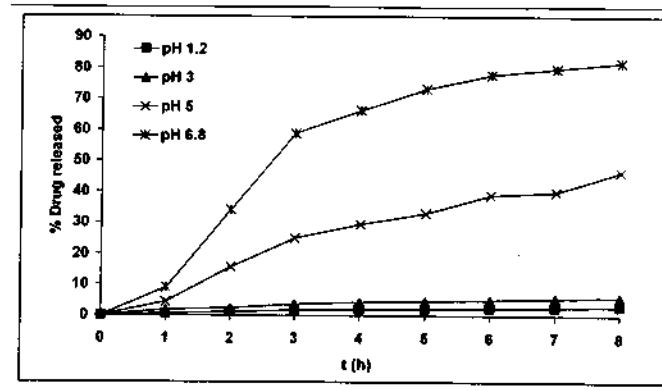

Fig. 4: Effect of pH of dissolution medium on the release of diclofenac sodium from controlled-release matrix tablet prepared with Eudragit RS (F4).

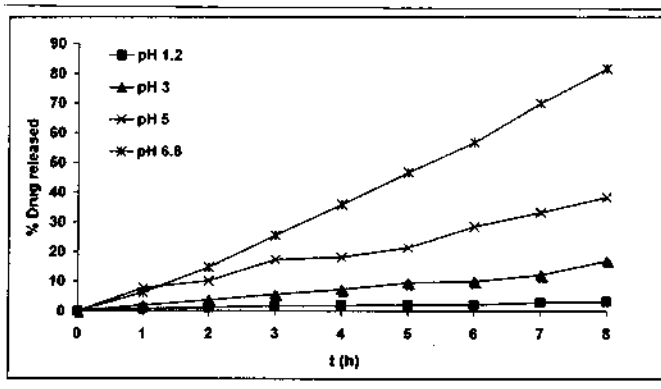

Fig. 2: Effect of pH of dissolution medium on the release of diclofenac sodium from controlled-release matrix tablet prepared with HPMC (F2).

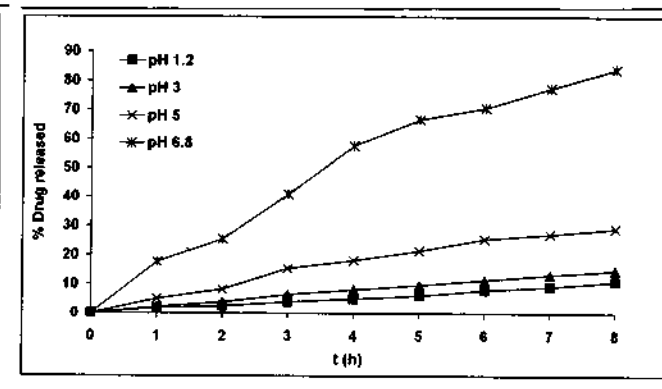

Fig. 5: Effect of pH of dissolution medium on the release of diclofenac sodium from controlled-release matrix tablet prepared with NaCMC/HPMC (F5).

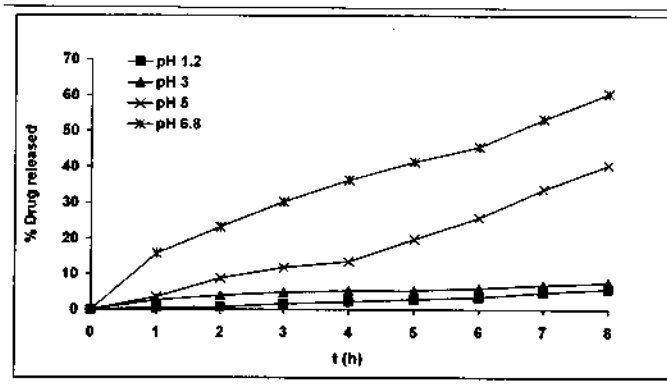

Fig. 3: Effect of pH of dissolution medium on the release of diclofenac sodium from controlled-release matrix tablet prepared with Egg albumin (F3).

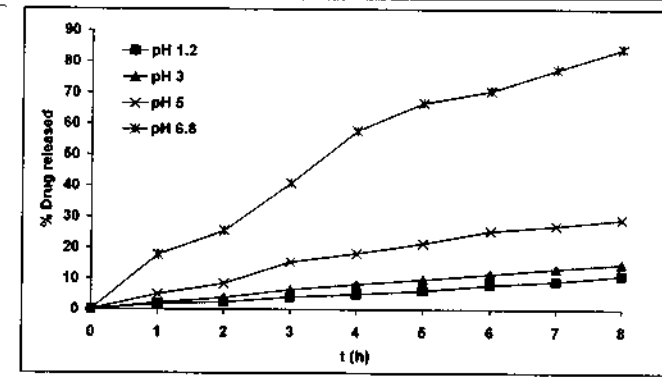

Fig. 6: Effect of pH of dissolution medium on the release of diclofenac sodium from controlled-release matrix tablet prepared with NaCMC/Egg albumin (F6).

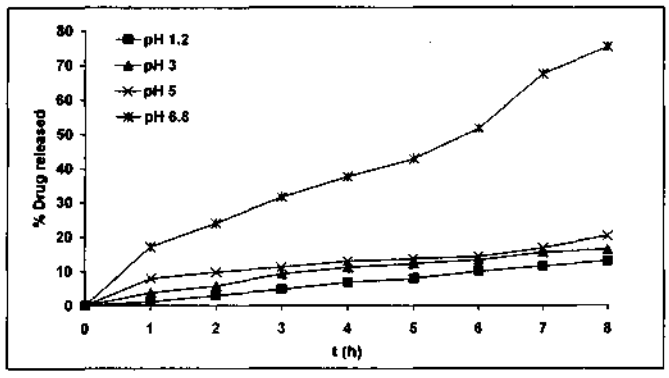

Fig. 7: Effect of pH of dissolution medium on the release of diclofenac sodium from controlled-release matrix tablet prepared with NaCMC/Eudragit (F7).

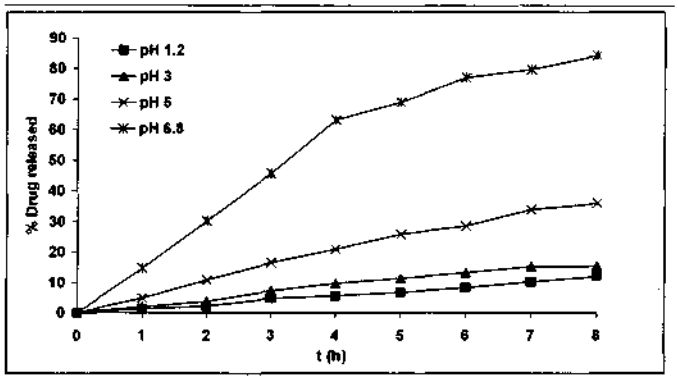

Fig. 8: Effect of pH of dissolution medium on the release of diclofenac sodium from Voltaren SR tablets (F8).

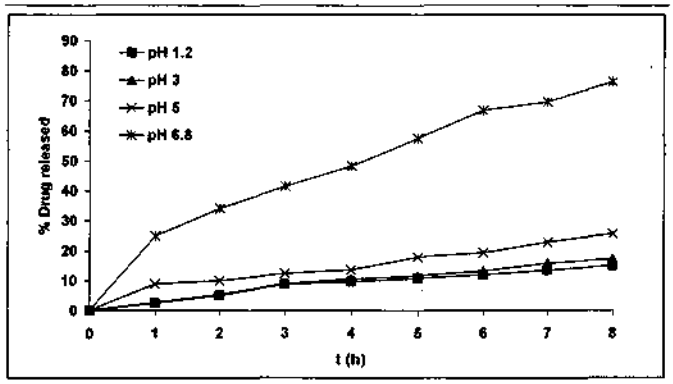

Fig. 9: Effect of pH of dissolution medium on the release of diclofenac sodium from Diclofen SR tablets (F9).

matrices may be due to the simultaneous operation of more than one release mechanism. Alderman[29] described the prolonged release from HPMC matrices and concluded that a gelatinous layer formed when the polymer became hydrated on contact with water, controlled the release of drugs by two mechanisms. Water soluble drugs were released by diffusion out of the gelatinous layer and by erosion of the gel, whereas, poorly soluble drugs were released solely by erosion.[29] Al-Meshal and Bayomi[30] found that the release kinetics from the albumin matrix were anomalous resembling release of drugs from swellable matrices. However, the release rates were further analyzed based on a simple and effective method proposed by Ritger and Peppas[31] who elucidated the possible release mechanism. The Simple Power Low expression shown in the following equation was used to correlate and evaluate the release data of all the tested tablet formulations in phosphate buffer (pH 6.8).

$$\frac{M_t}{M_\infty} = Kt^n$$

Where M_t / M_∞ is the fractional drug released at time t, k is a kinetic constant characteristic of the drug / polymer system and n is an exponent which characterizes the mechanism of drug release. The values of n is < 0.45 for fickian release, >0.45 and <0.89 for non-fickian (anomalous) release, 0.89 for case II release and > 0.89 for super II type release.[32] The determination coefficient (r^2), the release rate constant (K) and the diffusion exponent (n) were illustrated in Table 4. The results of the study displayd that the values of n ranged between 0.48 and 0.51 indicating diffusion release kinetics. This is ascribed to the drug release in swellable matrices is depending on two processes. First, swelling the polymer and second, dissolution and diffusion of the drug out through the swollen polymer matrix.[29] The interpretation has therefore been reduced to the point where one can state that the diffusion of the dissolution medium into the tablet and diffusion of the dissolved drug out or through

the gelled layer are the two main processes involved in limiting the liberation of the drug from the prepared matrix tablets.

According to the above observation egg albumin in the direct compressed tablets behaved like swellable matrices and could be considered as a swellable material to modulate the release rate.

Conclusion

The release of diclofenac sodium from all the prepared controlled-release matrix tablet formulations (F1-F7) was markedly sustained as compared to the commercial formulations. The release of the drug was increased with increasing the pH of the dissolution medium. The release rates and release kinetics of diclofenac sodium from the tablets prepared with either egg albumin (F3) or from a combination of egg albumin and NaCMC (F6) were not different from the commercial sustained-release tablets of diclofenac sodium, Voltaren SR (F9) or Diclofen SR (F8). The release kinetics of diclofenac sodium from the all tested tablets was dependant on the drug diffusion and polymer relaxation. Based on experimental results, egg albumin is a useful direct compressible matrix-forming material for preparation of oral controlled-release tablets of diclofenac sodium.

REFERENCES

1- R. L. Davidson, Ed. Handbook of mater-soluble Gums and Resins. Mc Gram. Hill, New Yourk (1980).
2- R. L. Whistler, Industrial Gums, Academic Press New Yourk (1973).
3- D. E. Zaaske, K. W. Milter, E. L. Strem, S. Auftrian, and P. B. Johnson, J. Am. Med. Assoc., 237, 1453 (1979).
4- F. L. S. Tsse and K. H. Valia, J. Pharm. Sci., 70, 395 (1981).
5- A. Yaob and E. Walega, Oral Sustained Release Formulation Design and Evaluation, Ist ed., Pergamon Press, New York, p. 5 (1988).
6- J. L. Ford, M. H. Rubinstein, F. McCaul, J. E. Hoagan, and P. J. Edgar, Int. J. Pharm., 40, 223 (1987).
7- L. Kabanda, R. A. Lefbvre, H. J. V. Bree and J. P. Remon, Pharm. Res., 11 (11), 1663 (1997).
8- N. H. Shah, A. S. Railkar, W. Phauapradit, F. Zeng, A. Chem, M. H. Infeld and A. W. Mal.Ck. Eur, J. Pharm. Biopharm., 42 (3), 183 (1996).
9- J. L. Ford, M. H. Rabinstein and J. E. Hoagan, Int. J. Pharm., 24, 327 (1985).
10- G. Xu and H. Sunadn, Chem, Pharm. Bull., 43 (3), 483 (1995).
11- S. K. Baveja, K. V. R. Rao, A. Singh and V. K. Gombar, Int J. Pharm., 541, 55 (1988).
12- H. Kurahashi, H. Kami and H. Sunada. Chem. Pharm. Bull., 44 (4), 829 (1996).
13- N. K. Ebuba, A. H. Hikal, C. M. Wyanda, D. C. Beer and A. B. Jones, Pharm. Dev. Technol., 2 (2), 161 (1990).
14- A. Gazzaniga, M. E. Sangalli, U. Conte, C. Caramella, P. Colombo and A. L. Manna, Int. J. Pharm, 91, 167 (1993).
15- L. C. Freely and S. S. Davis, Int. J. Pharm., 44, 131 (1988).
16- P. A. Todda and E. M. Sorkin, Drugs, 35, 244 (1988).
17- United States Patent, Patent Number 4, 948, 581.
18- Y. Hirotani, Y. Arakawa, Y. Maeda, A. Yamaje, A. Kamad and T. Nishiha, Chem. Pharm. Bull., 3049 (1987).
19- P. D. Fowler, Voltarol: diclofenac sodium, Clin. Rheum. Dis., 5, 427 (1979).
20- Y. Kowoslima, H. Takeuchi, T. Hino, T. Nina, T. Lim, F. Sekiguwa and M. Ohya, Int. J. Pharm., 99, 229 (1993).
21- T. Imai, Y. Saito, H. Matsumoto, T. Satoh and M. Otagiri, Int. J. Pharm., 53, 7 (1989).
22- S. I. Zeng, C. P. Martin and C. Mariott, Int. J. Pharm., 107, 202 (1994).
23- A. A. Mohamed and M. A. Bayomi M. A., Drug Dev. It. Pharm., 21 (6), 739 (1995).
24- A. S. Ali, A. M. Ali and F. A. Mohammed, Bull. Pharm. Sci., Assiut University, 20 (2), 141 (1997).
25- K. Singla and D. K. Mediratta, Drug Dev. Ind. Pharm., 14, 1833 (1988).
26- W. Hixson and J. H. Crowell, Ind. Eng. Chem., 23, 923 (1931).

27- T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).
28- W. I. Higuchi, ibid., 51, 802 (1962).
29- D. A. Alderman, Int. J. Pharm Technol. Prod. Mfr., 5, 1 (1984).
30- M. A. Al-Meshal and M. A. Bayomi, Drug Dev. Ind. Pharm., 21 (6) 739 (1995).
31- P. L. Ritger and N. A. Peppas., J. Control Rel., 5, 23 (1987).
32- N. A. Peppas and R. W. Korsmeyer in: N. A. Peppas, N. A. (ed.,) Hydrogels in Medicine and Pharmacy, Volume 3: properties and Applications, Crc, Boca Raton, p. 109 (1986).