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COMPARISON OF THE IN VITRO RELEASE CHARACTERISTICS OF A WAX MATRIX AND A HYDROGEL SUSTAINED RELEASE DICLOFENAC SODIUM TABLET

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ABSTRACT

Two types of sustained release tablets of diclofenac sodium were formulated, such that one released drug via the pores of a wax matrix (DWM), and the other relied upon the swelling of a hydrogel (DHG). The in vitro release characteristics of these two were compared using USP XXI Dissolution Apparatus I and II as well as an intrinsic dissolution technique at various speeds of rotation. Employment of the release exponent 'n' as a method of ascertaining the release mode showed that DWM exhibits classic diffusion-controlled release of drug down tortuous pores. This was confirmed by scanning electron microscopy.

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Release is relatively independent of rotation speed, except when unprotected from abrasion. DHG tablets exhibited near zero-order release, a dynamic equilibrium existing between rate of gel swelling and erosion. This was true up to a point where high rotational speeds upset this equilibrium by increasing erosion. This was confirmed by gel thickness measurements.

INTRODUCTION

The therapeutic advantages of sustained release oral dosage forms are well documented (1-4). They include patient compliance due to decreased dosing frequency, and the ability to maintain plasma drug levels within the therapeutic range for longer. Sustained release oral dosage forms are now a major part of annual prescriptions (5). They are both medically and economically important and much pharmaceutical research is dedicated to their formulation and subsequent testing. This paper investigates the release characteristics of two different formulations of a diclofenac sodium sustained release tablet by various dissolution methods as well as observations of physical characteristics.

The two sustained release tablets were formulated so that one released drug via the pores of a wax matrix (DWM), and the other relied upon the swelling of a hydrogel (DHG).

In vitro release was studied by three methods; USP XXI Apparatus I (basket), Apparatus II (paddle) and an intrinsic dissolution apparatus (IDA) which exposed one flat surface of the tablet to

dissolution medium. The rotational speed of the dissolution shafts used in each of these three methods was varied so that the effect of changing flow characteristics of the medium over the tablet could be studied. From these dissolution results, the n value was calculated (6) which relates release rates to mode of transport. Solvent penetration, amount of swelling, erosion and electron microscopy were all used to establish the physical characteristics of both formulations after dissolution.

MATERIALS

Diclofenac sodium was purchased from Secifarma, Milan, Italy, the following excipients were used: Microtal D.C.E (Tate and Lyle - Croydon UK), Povidone 25 BP (BASF - Preston UK), Colloidal Anhydrous Silica (Aerosil) BP (Degussa - Frankfurt West Germany), Cetostearyl Alcohol BP (BDH - Poole UK), Hydroxypropylmethylcellulose (HPMC) 15cps (Colorcon - Orpington UK), and Magnesium Stearate BP (Wilfrid Smith LTD - Middlesex UK).

METHODS

Formulation of Tablets

DWM; A mixture of diclofenac sodium (34.2%), sucrose (51.4%), povidone (2.06%) and aerosil (1.02%) was screened through a 500 micron sieve and warmed to 60°C. Molten cetostearyl alcohol

(10.3%) was added and stirred. The cooled mixture was screened through a 500 micron sieve with magnesium stearate (1.02%).

DHG: Diclofenac sodium (24.9%), HPMC (74.6%) and magnesium stearate (0.5%) were passed through a 500 micron sieve and mixed well.

Both formulations were compressed on a Dartec Universal Testing Machine at 15KN force, using 10mm flat face tooling. DWM was compressed at 292mg average weight and DHG at 400mg to produce tablets with a nominal strength of 100mg of diclofenac sodium for use in the USP dissolution tests. Thicker tablets of both formulations were compressed for use in the IDA (approximately 600mg), so as to prevent the exhaustion of drug which might affect the release pattern. Tablets were weighed and measured before use.

Dissolution Methods

All dissolutions were performed (at least in triplicate) in 1000ml pH 6.8 phosphate buffer BP 37°C at rotational speeds of 25-250 rpm, with continuous monitoring at 308nm in a Philips P86209 spectrophotometer and analysis on a Compac Deskpro using Philips software.

The IDA described by Bain et. al. (7) has a central 10mm hole throughout the entire length which allowed a tablet to fit into the base flush with the lower face and a PTFE tape-coated stopper in the other end to prevent solvent contamination from the back

face of the tablet. The tablet was removed after dissolution by expelling it gently with a plunger.

Calculation of n Values

Modes of transport of drug from within the tablets were quantified by means of the n value, which is the exponent characteristic of the mode of transport, described by Korsmeyer and Peppas (6) in 1983. The fraction of drug released (from dissolution data) M_t/M_∞ is expressed as a power function of time t.
Equation 1 shows how n can be derived from these parameters when k' is a constant characteristic of the system.

$$M_t/M_\infty = k't^n \qquad (1)$$

When n approximates 0.5, a Fickian/diffusion-controlled release is implied, whereas the value of n approaching 1 suggests zero-order release (6-9).

Physical Characteristics

After intrinsic dissolution, the tablets were carefully expelled from the apparatus, the DWM tablets were dried at room temperature and prepared for scanning electron microscopy (SEM). The surface

and the core of the DWM tablets were observed under the SEM both before and after dissolution.

DHG tablets were assessed by measuring the gel thickness then peeling it off and weighing the remainder. The 'amount which had been hydrated' was then calculated by subtracting the dry residue weight and the weight of drug released, from the original tablet weight.

RESULTS AND DISCUSSION

DICLOFENAC SODIUM SUSTAINED RELEASE WAX MATRIX TABLETS (DWM)

Figures 1, 2 and 3 show the release of diclofenac sodium from DWM tablets at rotational speeds from 25 to 250 rpm, using the IDA, USP XXI Apparatus I (basket), and USP XXI Apparatus II (paddle) respectively. Generally, higher rotational speeds resulted in faster drug release.

Table 1 shows the n values calculated using Equation 1 from dissolution data on DWM for all three dissolution systems. It can be seen that values of approximately 0.5 implying Fickian/diffusion-controlled release are obtained for both USP systems from the slowest speed up to 150 rpm. At the higher speeds of rotation (200 - 250 rpm) values of n approximating 0.7 are noted, suggesting a deviation from the Fickian/diffusion-controlled release towards zero-order.

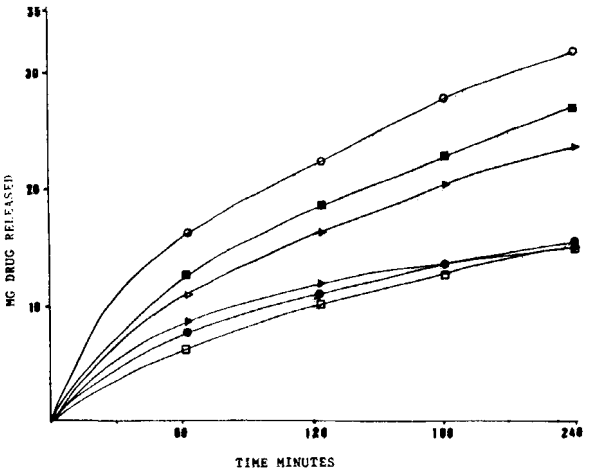

FIGURE 1
Intrinsic Dissolution Of DWM Tablets At Rotational Speeds 25 rpm (□), 50 rpm (▶), 100 rpm (●), 150 rpm (▷), 200 rpm (■) and 250 rpm (○).

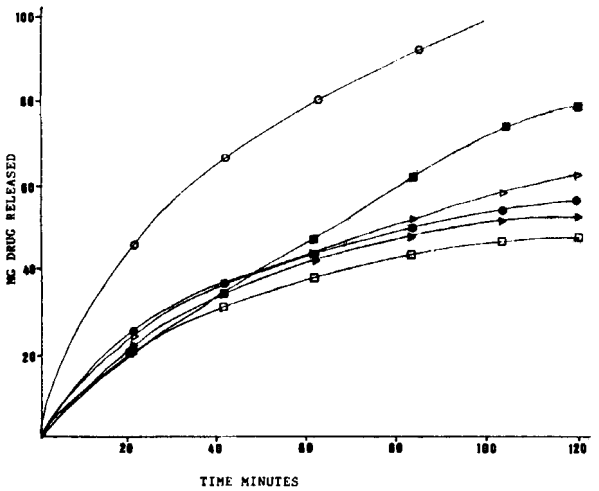

FIGURE 2
Dissolution Of DWM Tablets Using USP XXI Apparatus I At Rotational Speeds 25 rpm (□), 50 rpm (▶), 100 rpm (●), 150 rpm (▷), 200 rpm (■) and 250 rpm (○).

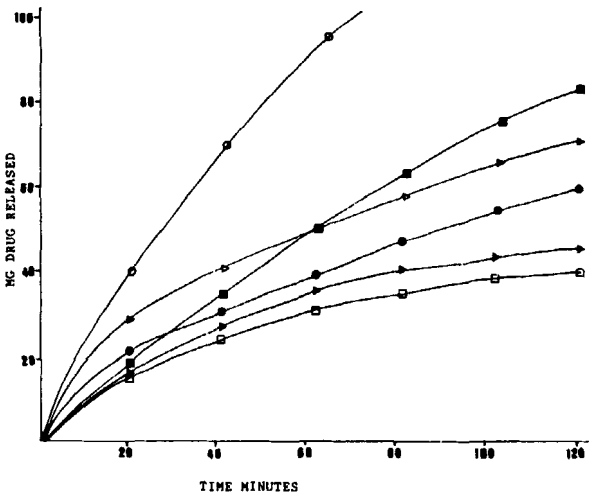

FIGURE 3
Dissolution Of DWM Tablets Using USP XXI Apparatus II At Rotational Speeds 25 rpm (□), 50 rpm (▶), 100 rpm (●), 150 rpm (▷), 200 rpm (■) and 250 rpm (○).

TABLE 1

Values of n Calculated From USP I, II and IDA Dissolutions of DWM Tablets At Various Speeds of Rotation.

	n VALUE AT THE ROTATIONAL SPEED INDICATED RPM					
APPARATUS	25	50	100	150	200	250
USP I	0.67	0.52	0.52	0.48	0.70	0.65
USP II	0.53	0.43	0.51	0.48	0.73	0.71
IDA	0.50	0.61	0.64	0.56	0.50	0.49

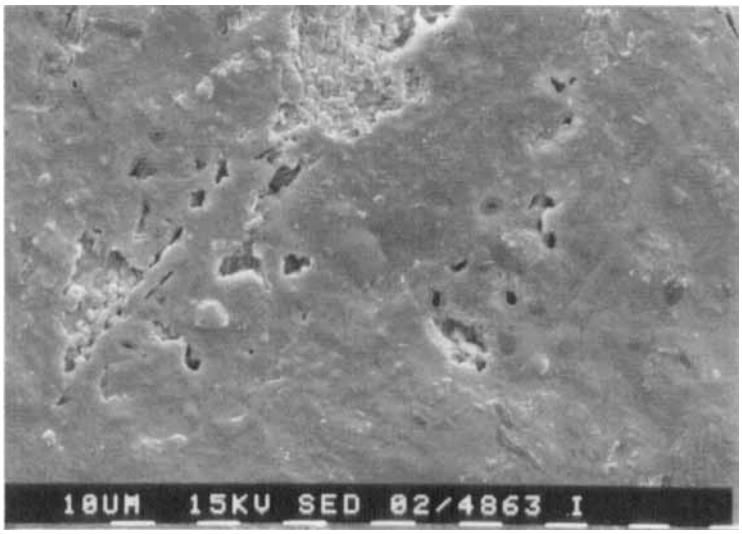

FIGURE 4
SEM : Surface Of A DWM Tablet

It was observed throughout these high rotational speed dissolutions, that DWM tablets either bounced around inside the basket or moved about vigorously under the paddle, resulting in increased tablet surface erosion. The combination of diffusion of drug through tortuous pores (causing increase in pore volume), with the erosion of the matrix surface (causing a shortening of diffusional path lengths) would help to explain such a change in mode of transport. Data from the IDA appears to confirm this theory with values of n close to 0.5 irrespective of the speed of rotation. Since the design of the IDA protects the tablet from excessive erosion, it allowed only the flow of medium over a single flat surface to affect drug release.

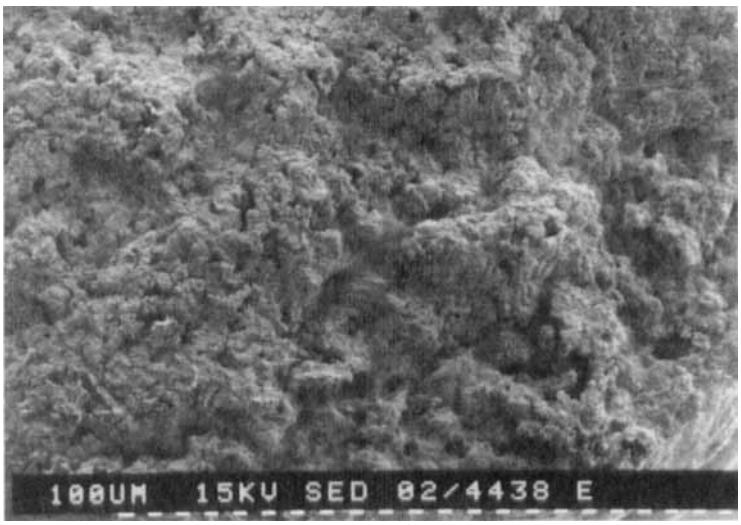

FIGURE 5
SEM : Surface Of A DWM Tablet After Four Hours Intrinsic Dissolution At 200 rpm

The photomicrograph shown in Figure 4 indicates the presence of some small pores on the flat surface of a DWM tablet before dissolution. However, after 4 hours dissolution testing in the IDA at 200 rpm, the tablet surface had become very uneven in nature and covered with numerous pores (Figure 5). Observation of the interior of the tablet before and after dissolution in the IDA (Figures 6 and 7 respectively) similarly showed the initial presence of small pores which increased in size and number during dissolution. It appears that at the onset of dissolution, solvent entered the pores present on the tablet surface and progressively dissolved accessible soluble drug and excipients which then moved out of the tablet by diffusion in the resultant enlarged pores.

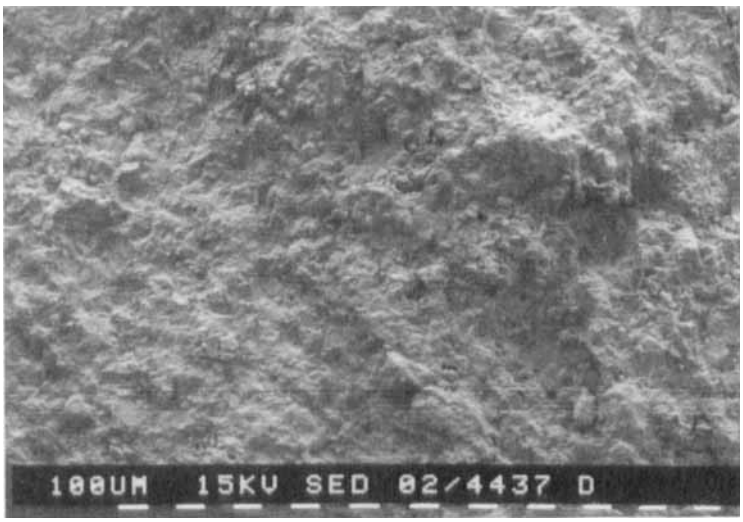

FIGURE 6
SEM : DWM Tablet Interior

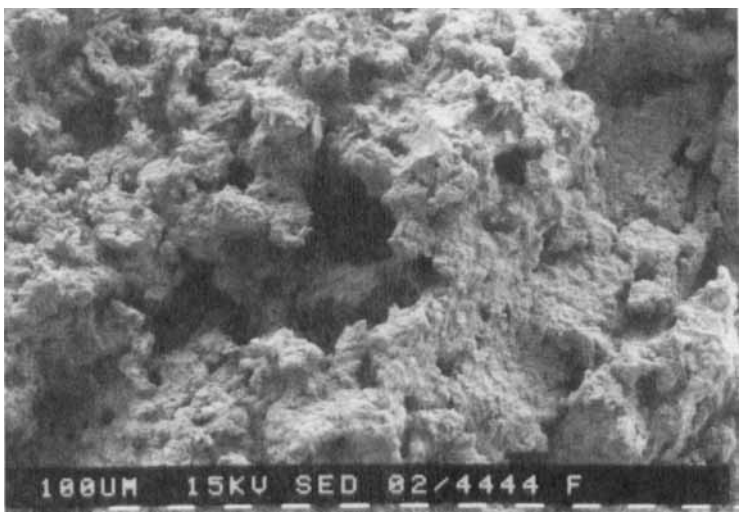

FIGURE 7
SEM : DWM Tablet Interior After Six Hours Intrinsic Dissolution At 50 rpm

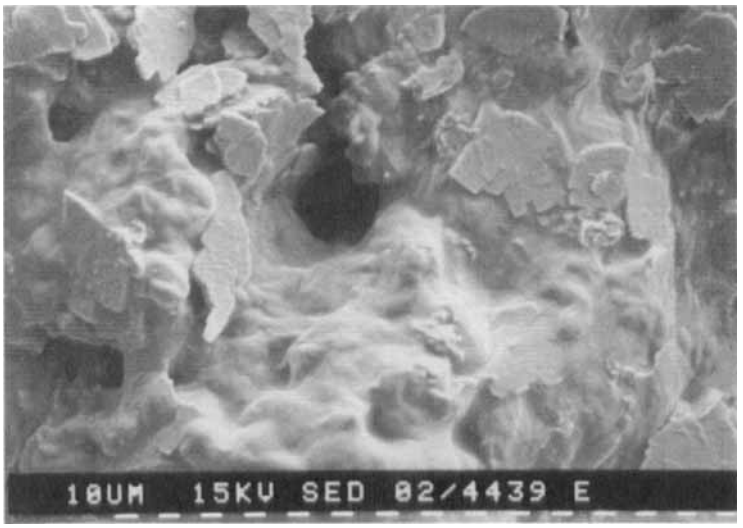

FIGURE 8
SEM : DWM Tablet Surface After Four Hours Intrinsic Dissolution At 200 rpm

Release patterns obtained from such a system therefore exhibit diffusion-controlled release characteristics since diffusional path length is a controlling factor. Figure 8 shows a pore on the surface of a DWM tablet after 4 hours intrinsic dissolution at 200 rpm. The enlarged 'waxy' pore can be seen as well as the flat diclofenac crystals which had dissolved in the dissolution medium, diffused out of the pore and recrystallised on the pore entrance when the tablet was dried.

Evidence showing the increase in size and number of pores is depicted in Figure 9. At the tablet surface, where the drug and excipients have been solubilised by the dissolution medium, numerous large pores are observed whilst the interior of the tablet remains relatively dry and nonporous.

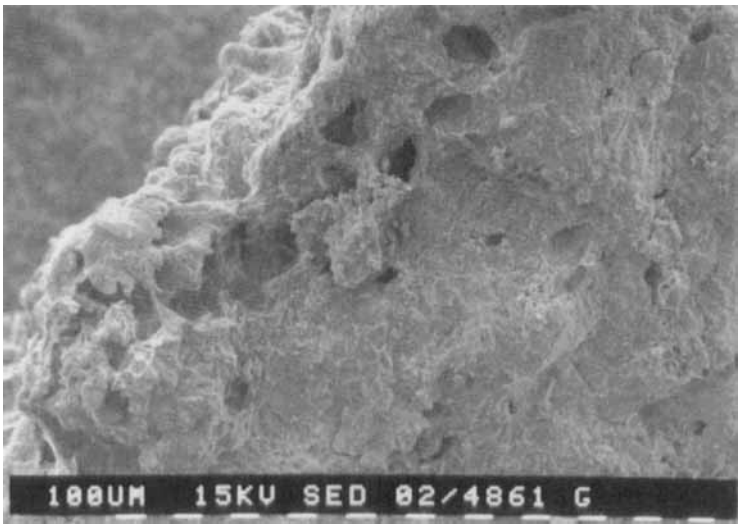

FIGURE 9
SEM : DWM Tablet Interior And Edge After Four Hours Intrinsic Dissolution At 250 rpm

DICLOFENAC SODIUM SUSTAINED RELEASE HYDROGEL TABLETS (DHG)

Dissolution of DHG using the IDA and two USP methods show a similar effect to DWM in that higher rotational speeds resulted in faster drug release (Figures 10, 11 and 12). Table 2 shows the n values calculated for DHG from the three dissolution techniques. Whilst there was some variation in the values of n based on the USP tests, the most frequent value in both cases appeared to be around 0.8 indicating a mode of drug transport nearer to zero-order than Fickian.

DHG tablets are less prone to abrasion than DWM at higher rotational speeds, probably because their gel-like surfaces tend

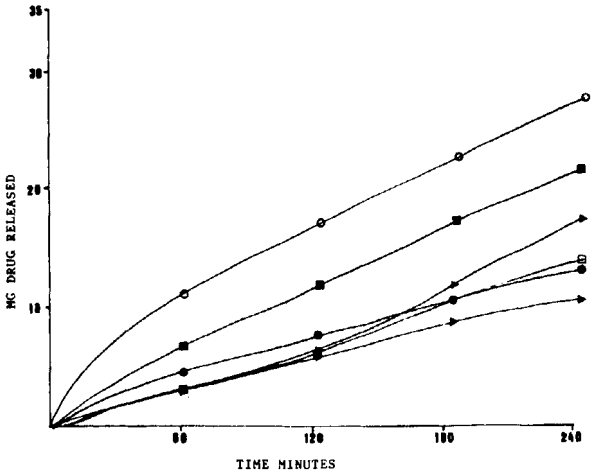

FIGURE 10
Intrinsic Dissolution Of DHG Tablets At Rotational Speeds 25 rpm (□), 50 rpm (▶), 100 rpm (●), 150 rpm (▷), 200 rpm (■) and 250 rpm (○).

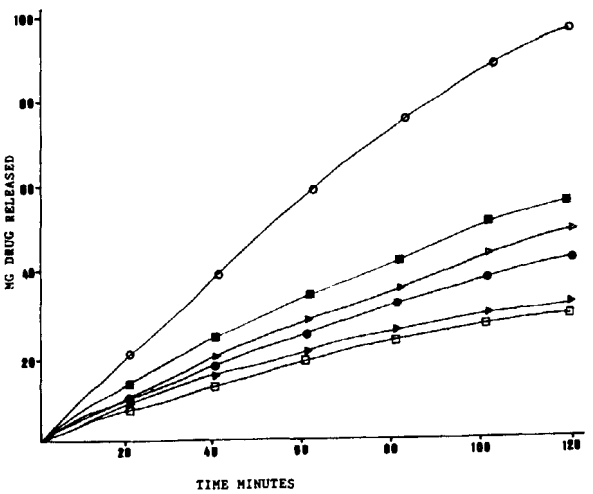

FIGURE 11
Dissolution Of DHG Tablets Using USP XXI Apparatus I At Rotational Speeds 25 rpm (□), 50 rpm (▶), 100 rpm (●), 150 rpm (▷), 200 rpm (■) and 250 rpm (○).

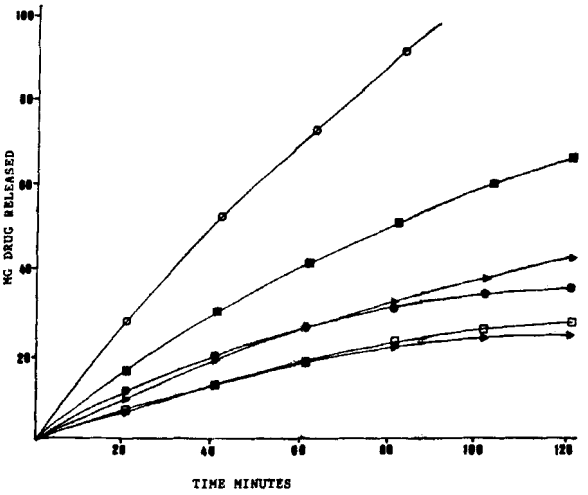

FIGURE 12
Dissolution Of DHG Tablets Using USP XXI Apparatus II At Rotational Speeds 25 rpm (□), 50 rpm (▶), 100 rpm (●), 150 rpm (▷), 200 rpm (■) and 250 rpm (○).

TABLE 2

Values of n Calculated From USP I, II and IDA Dissolution of DHG Tablets At Various Speeds of Rotation.

	n VALUE AT THE ROTATIONAL SPEEDS INDICATED RPM					
APPARATUS	25	50	100	150	200	250
USP I	0.88	0.83	0.76	0.77	0.86	0.89
USP II	0.83	1.09	0.59	0.74	0.81	0.87
IDA	0.85	0.98	1.33	1.34	0.90	0.60

TABLE 3

Gel Characteristics of DHG After Four Hours Intrinsic Dissolution In pH 6.8 Phosphate Buffer.

	SPEED OF ROTATION					
	25	50	100	150	200	250
GEL THICKNESS mm	1.5	1.9	2.6	2.5	1.6	0.7
DRY WEIGHT OF HYDROGEL HAVING UNDERGONE HYDRATION mg	45	56	41	55	75	76

to stick to the basket or the vessel bottom. Results for the IDA of rotational speeds up to 200 rpm yielded n values of approximately 1 implying near zero-order release. It appears that under these conditions, the diffusional path lengths and gel layer thickness remain fairly constant brought about by similar rates of gel formation and its erosion/solubilisation. Data from the IDA at 100 and 150 rpm show values of n to be greater than 1, this has also been noted by other workers (9, 10). Some have postulated that this is due to the high swelling nature of the hydrogel used (10). It is interesting to note that at the very high rotational speed of 250 rpm, there is a decrease in the value of n to 0.6.

This may be explained in terms of pronounced gel layer erosion under such conditions. Table 3 shows both the gel thickness and the weight of hydrogel which has been hydrated and either remains as a gel layer or has dissolved and left the tablet.

It is apparent from Table 3 that at the relatively high rotational speeds of 200 and 250 rpm, a significant amount of hydrogel has been hydrated compared to the lower rotational speeds. But the actual residual gel thickness of the former after dissolution is in fact significantly lower due to excessive erosion of the hydrogel matrix at the higher rotational speeds.

For DHG a dynamic equilibrium exists between hydrogel hydration and its erosion at rotational speeds below 200 rpm. This results in a constant diffusional path length and consequently near zero-order drug release. At rotational speeds greater than 200 rpm, severe tablet erosion occurred which disturbed this equilibrium. This is reflected by the deviation from near zero-order release, perhaps to a regime almost entirely controlled by erosion.

CONCLUSIONS

It is evident from this work that release of diclofenac sodium from sustained release DWM and DHG tablets is governed by different controlling factors. The DWM system exhibits classic diffusion-controlled release of drug down tortuous pores and is

relatively independent of rotational speeds when the tablets are free from abrasion (as they are in the IDA). DHG tablets exhibit near zero-order release where a dynamic equilibrium exists between rates of swelling and erosion, up to a point where very high rotation speeds upset this equilibrium by increasing erosion.

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