International Journal of Pharmaceutics, 61 (1990) 127–134
Elsevier

IJP 02070

A controlled release delivery system using two hydrophilic polymers

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(Received 19 December 1988)
(Modified version received 27 November 1989)
(Accepted 14 December 1989)

Key words: Dyphylline; Zero order release; Hydroxypropylmethylcellulose; Poly(ethyloxazoline); Erosion; Cube root law; Diffusion; $t^{1/2}$ release.

Summary

In an attempt to modify the release behavior from an HPMC matrix, the release performance of two systems of solid dosage forms containing dyphylline was evaluated. System I and its modifications consisted of an HPMC core matrix whose side wall and one face were press coated with an erodible water soluble polymer poly(ethyloxazoline), i.e., a core in a PEOX cup and System II was a matrix containing HPMC and PEOX. When approx. 80% or greater of the drug content was included in the core, system I displayed an apparent zero order release. When the majority of the drug was included in the cup, the release followed the Hixson-Crowell cube root law of dissolution. The release from System II was found to be a linear function of the square root of time. When a placebo PEOX layer was attached to system II, the release profile obeyed the cube root law of dissolution. The results suggest that the inclusion of an erodible polymer such as PEOX can indeed modify the release behavior and that the modification of release is dependent on the dosage form design. The data indicate that it is possible to design a dosage form (HPMC core in a PEOX cup) capable of delivering a drug at constant rate by a combined diffusion and erosion process.

Introduction

Hydroxypropylmethylcellulose (HPMC), a hydrophilic cellulose ether, has been extensively utilized in investigating drug release from matrices containing both water soluble and sparingly soluble drugs (Lapidus and Lordi, 1966, 1968; Ford et al., 1985a,b, 1987). This polymer is available in various grades of varying molecular weights and viscosities (Dow Bulletin). Among the various grades, HPMC K-4000 is the fastest hydrating and has the weakest gel strength. Drug release from HPMC matrices (Shenouda et al., 1986) was found to follow the Higuchi equation (Higuchi, 1963) of square root of time dependency. Poly(ethyloxazoline), PEOX, is a novel tertiary amide polymer produced by the cationic ring-opening of 2-ethyl-2-oxazoline (Dow Bulletin). This polymer is available in various molecular weights of 50 000, 200 000 and 500 000. The latter two are referred to as medium and high molecular weight (MMW and HMW), respectively. They are water soluble; thermostable and thermoplastic polymers with a glass

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transition of 69–71° C. To date, most of this polymer's applications were directed to the nonpharmaceutical fields.

Because of PEOX's unique physical properties particularly its hydrophilicity and high aqueous solubility, it was decided to explore its use in the development of controlled release dosage forms. The purpose of this study was to investigate the effect of incorporating this polymer in modifying the release of a water soluble drug, dyphylline, dispersed in a HPMC Matrix. The release from two basic types of formulations were studied. PEOX was applied as a press coat to the side wall and one face of the disc (a core in a PEOX cup, System I) or included in the HPMC matrix (system II). The release behavior of some modifications of these basic types were also studied and evaluated.

Materials and Methods

Materials

PEOX (MMW and HMW) was ground and the fraction screened through no. 40 mesh was utilized. Dyphylline (Aldrich), premium grade HPMC K-4000 (Dow), Mannitol (ICI America, Inc.) and zinc stearate (Witco) were used as received.

Preparation of dyphylline solid dispersion in PEOX

Dyphylline (100 g) and HMW PEOX (500 g) were dissolved in a sufficient volume of 50 : 50 absolute ethanol-deionized water, spread as a thin film on aluminium foil and dried under vacuum at 80° C for a period of 5 days. The dried sheet was ground to a powder and used.

Formulations

System I (a dyphylline-HPMC core in a PEOX cup): the core consists of 10% (20 mg) or 50% (100 mg) dyphylline, 20% (40 mg) HPMC K-4000, 1% (2 mg) zinc stearate as a lubricant, and the balance of the weight of the 200 mg tablet is made up of mannitol; the cup consists of 600 mg PEOX either the MMW or HMW type. In this study, when only the core contains the drug it is designated as active core, with the appropriate dyphylline content listed, and placebo cup. When only the cup contains the drug it is designated as active cup, with the appropriate drug content, and placebo core. When both the core and cup contain the drug it is designated active core and active cup with the appropriate drug content following the designation.

System II (dyphylline-PEOX-HPMC matrix) consists of 600 mg dyphylline dispersion (16.67% w/w) in PEOX (HMW), 160 mg HPMC K-4000, 32 mg mannitol, and 8 mg zinc stearate corresponding to a tablet weight of 800 mg.

Preparation of compressed tablets

System I: the ingredients of the core, corresponding to a batch of 200 tablets, were thoroughly mixed and slugged. The slugs were reduced into granules passing through no. 14 mesh. The granules were then mixed with zinc stearate and compressed using 9/32 inch (7.14 mm) round, flat face, beveled edge punches and a die in a Stoke's single punch machine. The die was filled by hand with individually weighed 200 mg of the core formulation and the machine was turned over by hand. The cores can also be made using a Carver press at a setting of 1000 pounds. The average tablet weighed 200.4 ± 1.3 mg ($n = 31$), had an average hardness of 7.3 ± 1.1 kp ($n = 31$) as tested by a Heberlein hardness tester, and measured 3.90 ± 0.07 mm ($n = 44$) in thickness. Using 1/2 inch (12.7 mm) round, flat face, beveled edge punches and a die, the core was then placed on the center of the bottom punch. The latter was lowered to allow the addition of 600 mg of PEOX or PEOX containing the drug, individually weighed, to cover the side wall and one face of the core. Compression was done manually at a predetermined setting to provide a unit which maintains its integrity during handling or by using a Carver press at a setting of 2000 pounds. The pressed unit was visually inspected to check the uniformity of the thickness on the side wall and the centering of the core. These units measured 6.16 ± 0.13 mm ($n = 23$) in thickness. This type of dosage form is illustrated schematically in Fig. 1.

Press coated tablet (I-p.c.): In this system, two different weights of 910 and 956 mg MMW PEOX were selected to give units of different coat thickness. Using 1/2 inch punches and a die, 356 or

TABLE 1

Description of the various modifications of delivery Systems I and II

System modification	Description
I-a	active core, (20 mg), placebo MMW PEOX cup
I-b	active core, (100 mg), placebo MMW PEOX cup
I-c	active core, (100 mg), placebo HMW PEOX cup
I-d	active core, (100 mg), active MMW PEOX cup, (23 mg)
I-e	placebo core, active HMW PEOX cup, (100 mg)
I-f	active core, (20 mg), active HMW PEOX cup, (100 mg)
I-p.c.	active core, (20 mg), placebo MMW PEOX (910 or 956 mg) Coat
II-g	100 mg drug in PEOX-HPMC matrix
II-h	bilayer, 100 mg drug in a PEOX-HPMC matrix with a Placebo PEOX layer

310 mg of PEOX was lightly compressed by hand in a Stoke's single punch machine. The upper punch was then raised while maintaining the bottom punch at its lowest position. The core tablet was then placed on top of the previously compressed layer and manually centered. A 600 mg of PEOX was then added to completely encase the core and the machine was turned over by hand for final compression and ejection. The same units were made in a Carver press by compressing the specified weight of PEOX (356 or 310 mg) at a setting of 1000 pounds. Following the centering of the core and the addition of 600 mg of PEOX, the material was compressed at an applied pressure of 2000 pounds. The measured thickness of the press coated units were 8.63 ± 0.16 mm ($n = 11$) and 9.15 ± 0.11 mm ($n = 12$) for the units utilizing 910 and 956 mg PEOX, respectively. The centering of the core was checked by visually inspecting the split halves of the compressed unit.

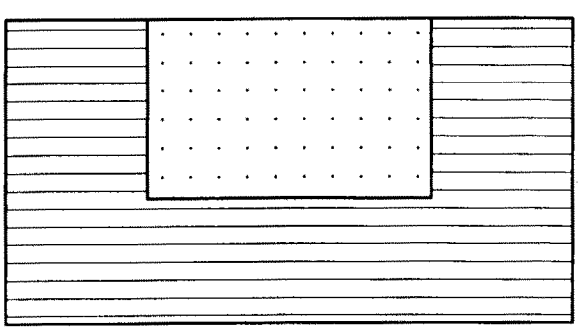

Fig. 1. A cross-section of delivery System I (dimensions in text).

For system I and its modifications, subjecting the core to a second compression with the PEOX has resulted in a decrease in thickness to 3.47 ± 0.05 mm ($n = 17$) and an increase in diameter to 7.62 ± 0.1 mm ($n = 13$), respectively.

System II: the ingredients of this type were thoroughly mixed and compressed using 1/2 inch punches and a die in a Stoke's single punch machine.

Table 1 lists the various modifications of each system studied.

Release Studies

The modified paddle method (Shenouda et al., 1986) was utilized in all release studies. This method utilizes a 10-mesh circular stainless steel screen approx. 7 cm in diameter which is placed on the bottom of the dissolution vessel thus acting as a platform for the dosage form. A volume of 900 ml of deionized water, equilibrated at $37\,^{\circ}C \pm 0.5\,^{\circ}C$, was used as the release medium and all experiments were conducted at 50 rpm. At appropriate time intervals, 10.0-ml samples were withdrawn for analysis and immediately replaced by an equivalent volume of fresh deionized water. Dyphylline was spectrophotometrically analyzed at a wavelength of 273.2 nm, using Perkin-Elmer model Lambda 5. Linearity was established for aqueous solutions of dyphylline in the range of 2–25 μg/ml. The release profiles of a minimum of six tablets from each modification were generated.

Release studies of System I

The release results of each tablet for every modification of a system were evaluated and the average release was plotted in all figures. Table 2 lists a summary of the calculated regression parameters for all modifications of the two systems. The coefficient of variation ranged between 2 and 13%. The upper end of the range was occasionally encountered in System I at sampling intervals during which PEOX was eroding. This might be attributed to slight offcentering of the core and/or uneven erosion of the PEOX.

The release performance of System I-a is shown in Fig. 2. The figure shows a constant release starting at 2 h. Initially, the release occurred from the exposed surface of the core to the release medium. As the PEOX erodes, diffusion through the newly exposed surface of the side wall and the other face of the core occurs resulting in a constant release. From this figure, it appears that the linear portion is preceded by a slower phase. The latter was confirmed upon examination of the release profiles from Systems I-b and I-c shown in Fig. 3. Systems I-b and I-c exhibit a biphasic release with an initial slow but linear phase followed by a faster constant release. Compared to System I-b, the slow phase of system I-c was extended possibly due to a relatively slower rate of hydration of the cup which contained PEOX of higher molecular weight. The biphasic type of release was recently observed (Seta et al., 1988) for Captopril in a bilayer hydroxypropylcellulose core, containing different concentration of the drug in each layer, surrounded by an insoluble cup of ethyl cellulose and carnuba wax. Table 2 lists the various calculated regression parameters of systems I-a, I-b and I-c. In order to achieve an apparent zero order release and to maintain a constant release throughout the period, 23 mg of Dyphylline was included in the MMW PEOX cup (I-d) whose calculated parameters are also listed in Table 2. This modification allowed a constant release up to 6 h (82% released, Fig. 4) beyond which negative deviation occurs due to long diffusional pathlength of the drug. This behavior is expected since the drug in the HPMC core is the only source for release at later times. In order to separate the diffusion and erosion components of release present in I-d, the difference between the total amount released from I-d and I-b was calcu-

TABLE 2

Summary of the calculated regression parameters of release from different modifications of Systems I and II

System	Type of release	Slope ± S.D.	Intercept ± S.D.	Correlation coefficient (r)	Number of tablets
I-a	apparent zero	3.79 ±0.13 mg h^{-1}	−3.96 ±0.63 mg	0.9992	17
I-p.c. (956 mg)	apparent zero	3.41 ±0.16 mg h^{-1}	−7.98 ±0.92 mg	0.9992	11
I-p.c. (910 mg)	apparent zero	3.43 ±0.19 mg h^{-1}	−7.21 ±0.45 mg	0.9991	6
I-b	apparent zero	slow phase: 6.57 ± 0.68 mg h^{-1}	~ 0	0.9998	6
		fast phase: 18.05 ± 1.74 mg h^{-1}	−23.31 ±4.13 mg	0.998	
I-c	apparent zero	slow phase: 5.39 ± 0.7 mg h^{-1}	~ 0	0.9993	6
		fast phase: 17.59 ± 0.41 mg h^{-1}	−31.87 ±4.13 mg	0.999	
I-d	apparent zero	17.62 ±0.75 mg h^{-1}	−3.81 ±0.68 mg	0.999	6
I-e	cube root	0.929 ± 0.050 $mg^{1/3}$ h^{-1}	~ 0	0.9996	6
I-f	cube root	0.931 ± 0.048 $mg^{1/3}$ h^{-1}	~ 0	0.9999	6
II-g	$t^{1/2}$	33.25 ±3.14 mg $h^{-1/2}$	−10.29 ±2.44 mg	0.9999	6
II-h	$t^{1/2}$ (intial*)	24.97 ±1.42 mg $h^{-1/2}$	−5.2 ±1.53 mg	0.9995	6
	cube root (entire period)	0.212 ± 0.01 $mg^{1/3}$ h^{-1}	0.101 ± 0.010 $mg^{1/3}$	0.9996	

Regression intervals in hours: a, 2–5 h; p.c., 3–6; b, 0.5–1.5 and 2–6; c, 0.5–2 and 3–7 hours; d, 0.5–6; f, 0.25–1.0; h*, 0.5–2.2.

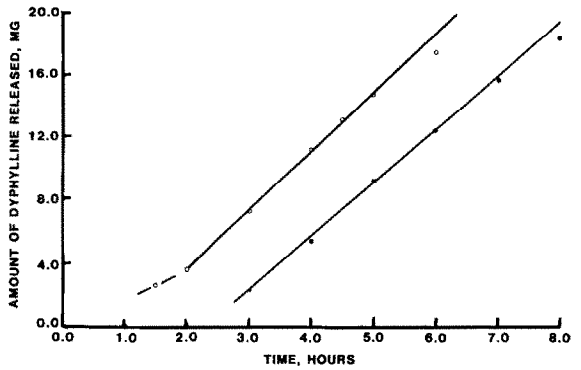

Fig. 2. Average release profile of I-a and I-p.c. delivery systems. (○) I-a, (●) I-p.c. (956 mg MMW PEOX).

lated. The initial erosion rate (up to 2 h) was found to follow the Hixson-Crowell cube root law for dissolution (Hixson and Crowell, 1931) expressed below:

$$W_0^{1/3} - W^{1/3} = kt \qquad (1)$$

W_0 is the initial dyphylline content (23 mg in cup), W is the quantity of dyphylline remaining at time t and k is the cube root dissolution rate constant. The calculated values for k and the correlation coefficient are $0.83(\%)^{1/3}$ h^{-1} and 0.997, respectively. The value of k is comparable to that obtained for system I-e discussed below. For comparative purposes, the calculated erosion data at 0.5, 1.0 and 1.5 hours and the release data (diffusion) obtained in I-b, at the same time, are

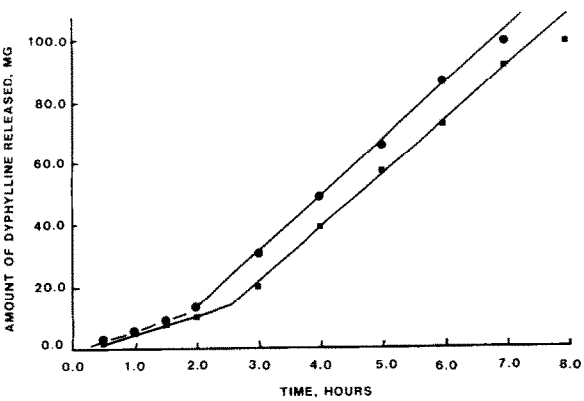

Fig. 3. Average release profile of I-b and I-c delivery systems. (●) I-b, (■) I-c.

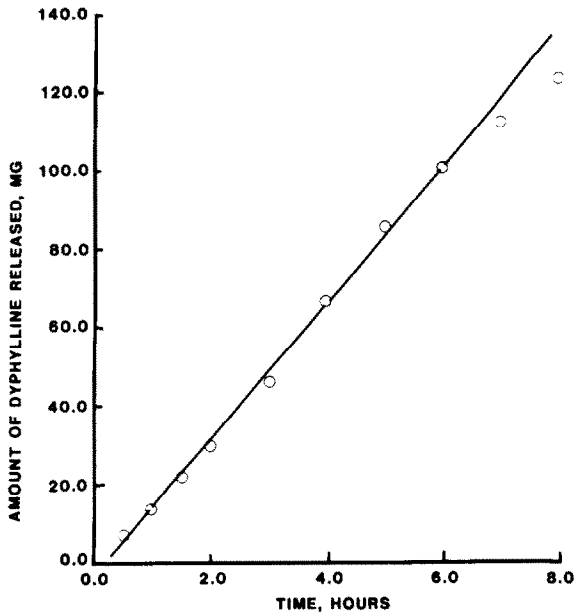

Fig. 4. Average release profile of I-d delivery system.

plotted (Fig. 5). The calculated initial rates are 6.56 and 8.46 mg h^{-1} for both the diffusion and erosion components, respectively. The calculated erosion rate is about 29% faster than the rate due to diffusional processes. It should be emphasized

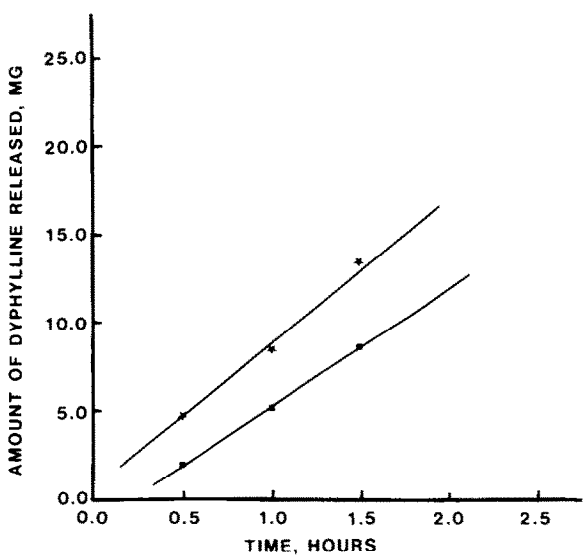

Fig. 5. A plot illustrating the initial diffusion and erosion components of System I-d. (■) Diffusion ($r = 0.9998$), (★) erosion ($r = 0.998$).

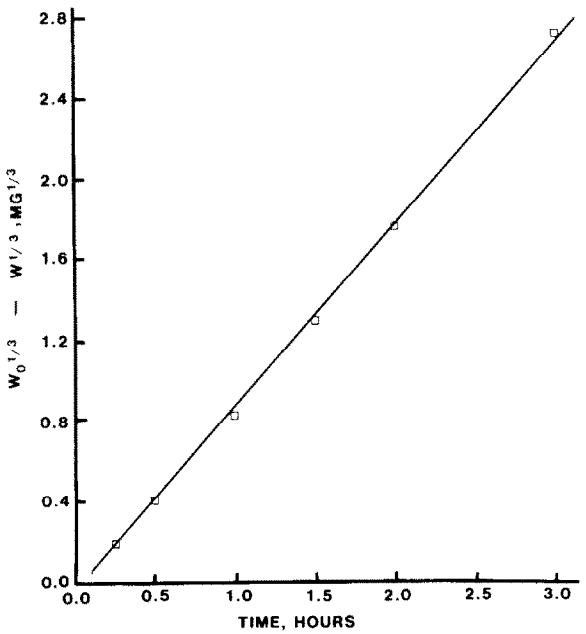

Fig. 6. The average release profile of I-e delivery system; Eqn 1 in text.

that the addition of a small amount of dyphylline in the erodible PEOX cup resulted in an apparent zero order release from this system (I-d) and eliminated the biphasic behavior observed in I-b.

Further release studies of System I

When a system consisting of an active HMW PEOX cup (100 mg dyphylline) surrounding a placebo core (I-e) was evaluated, the release profile followed the Hixson-Crowell cube root law indicating an erosion process (Fig. 6 and Table 2).

The release profile of system I-f was generated and was also found to follow the cube root law for up to one hour. As shown in Table 2, the initial release rate is comparable to that of I-e indicating that erosion of the cup is the predominant source of release. During this period, the diffusional contribution from the core is negligible (System I-a). However, if regression was extended to 2 h, the calculated rate becomes 1.01 ± 0.07 $mg^{1/3}$ h^{-1} ($r = 0.9992$). The increase in the calculated rate is due to diffusional contribution from the core (3.59 mg, Fig. 2, I-a) to the total amount released of 82 mg at 2 h.

To test the predictability of release from system I, the release data generated from I-a, I-e and I-f were utilized. The sum of the average amount released, at various times up to three hours, from System I-a and System I-e were regressed against the average amount released from system I-f at the same sampling times. A slope of 1.05 ($r = 0.9994$) was calculated compared to a theoretical value of unity. This treatment of the data confirms the predictability of release from this system. The inclusion of the data from System I-a containing MMW PEOX did not introduce any error of appreciable magnitude in these calculations due to the minimal and undetectable diffusional contribution to overall release from this system at times less or equal to 1 h. These results further support the separate and independent contributions of both diffusion and erosion to the overall release from System I.

To check whether diffusion occurs only from the exposed portion of the core to the release medium and none occurs through the hydrated clear layer of the PEOX cup, the release from a press coated tablet (I-p.c.) was evaluated (Fig. 2). There was no release of dyphylline at early sampling times and only significant amounts were released at three hours and beyond. In this system, it appears that diffusion occurs directly from the core. Detectable amounts of dyphylline could only be found in the release medium after the majority of the coat was eroded (3 h). Complete erosion of the coat occurred between 3–4 h compared to 2–3

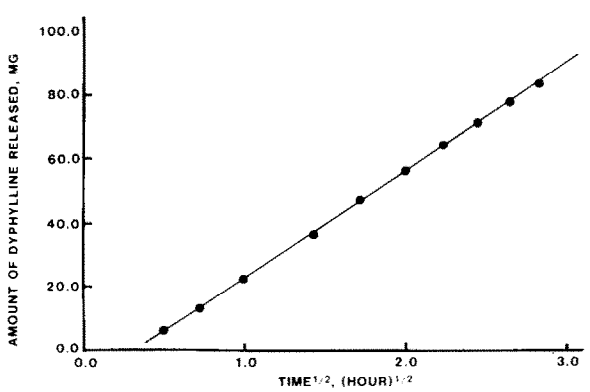

Fig. 7. A plot of the average amount released from system II-g vs $t^{1/2}$.

h observed in I-a. These observations were confirmed visually and photographically. The calculated parameters, listed in Table 2 for I-p.c., are not significantly different for the two press coated tablets prepared with different amounts of PEOX in spite of an increase in thickness of 0.5 mm for the press coated unit prepared with 956 mg PEOX. These results indicate that a difference in thickness of this system has no significant effect on the release parameters. Therefore, it is concluded that the difference in the regression parameters between I-a and I-p.c. and the prolonged erosion time in the latter may be due to the additional surface of PEOX present in the coat (other face) which must erode before a significant amount of dyphylline is detected in the release medium.

Release studies of System II

The release profile of dyphylline from System II-g showed a square root of time dependency (Fig. 7 and Table 2) and was comparable to that reported for a matrix containing only HPMC (Shenouda et al., 1986). System II-g was further studied by pressing 200 mg of PEOX covering one face of the disc to form a bilayer tablet (II-h). The release profile of this bilayer disc is shown in Fig. 8. In this figure, the average amount released was plotted vs $t^{1/2}$. Up to 2 h, the release is linear (Table 2), followed by positive deviation. This behavior may imply that erosion is taking place in this system in addition to diffusion. It is true that erosion of the placebo PEOX layer is occurring during the release process and is normally completed in 2 h. However, its dissolution does not contribute to the overall release since it does not contain any dyphylline. Erosion of this portion of the bilayer results in the exposure of additional surface area of the matrix for diffusion. The newly exposed surface contained a high concentration of the drug in the tablet which provided extra diffusion leading to a change in rate. As a result, the release deviated from the initial $t^{1/2}$ relationship. The overall release could be best described by the cube root law for the entire period (Table 2). The cube root fit of the release from system II-h may be due to the extra diffusion from the previously unexposed surface. This is a reasonable explanation since system II-g (same matrix without placebo PEOX layer) showed a release profile which is $t^{1/2}$ dependent for up to 80% release. The results suggest that the release behavior from system II-h, though best fitted by the cube root law, is different from what appears to be a combined diffusion and erosion release behavior previously observed in (hydroxyethyl) methylcellulose matrix tablet containing either salicylic acid or sodium salicylate-sodium chloride (Touitou and Donbrow, 1982). The release from the latter was also described by the Hixson-Crowell cube root equation.

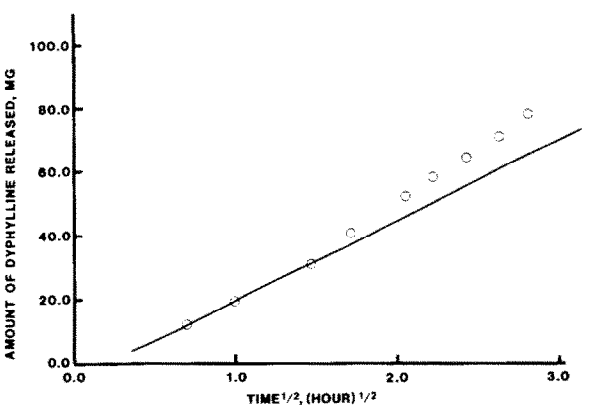

Fig. 8. A plot of the average amount released from system II-h vs $t^{1/2}$.

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