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PROLONGATION OF THE RELEASE OF EPHEDRINE HYDROCHLORIDE BY THE USE OF ANIONIC ACRYLIC RESINS

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ABSTRACT

Eudragits S, L, RL and mixture of S and L were employed for prolonging the release of ephedrine hydrochloride from tablets by two different techniques, viz, spray coating and molecular dispersion, The in-vitro dissolution rate evaluation in both acid and alkaline media revealed that, tablets prepared with Eudragit-L showed the most prolonged release with $t_{20\%}$ of 3½ and 4½ hours for spray coating and molecular dispersion methods respectively. Concerning the technique itself; drug-Eudragit molecular dispersion system showed a slower release than spray coating.

Higuchi model for drug release could be applied for the release pattern only for few hours in case of tablets containing coated drug, while it absolutely explains the release from tablets having drug-Eudragit molecular dispersion system. Release was found to proceed according to order kinetics.

INTRODUCTION

Natural and synthetic polymers, wax and some other materials, either alone or combined have been employed for the preparation of sustained release medication[1-5]. Polymers such as acrylates[6] and vinyl acetate[7] are widly used because

of their non-toxicity and harmlessness to humans. Coating technique using Eudragit RS was previously used by El-Sayed et al[4] for sustaining the availability of certain drugs. Eudragit L and S acrylic resins are copolymers, anionic in nature, the carboxyl groups ensure resistance to the gastric acid and allow dissolution in the neutral to weakly alkaline section of the intestine, whereas, Eudragit E dissolves in gastric juice owing to the basic nature of the amino groups. Eudragit RS and RL (Retard), are copolymeric materials based on trimethylammonium ethyl methacrylate[8].

The aim of the present work was to study anionic acrylic resins for producing sustained release tablets of ephedrine hydrochloride via two different techniques: first, by molecular dispersion of the drug in the polymeric matrix, and second, by using the fluidized-bed apparatus for coating the drug-lactose mixture with the organic solution of the Eudragit.

EXPERIMENTAL

Materials:

Ephedrine hydrochloride (Knoll A.G., Ludwigshafen, West Germany).
Eudragit[R] L,S,RL (Rohm Pharma GmbH, Darmstadt, West Germany).
Lactose (El-Nasr Pharmaceutical Co.). All other ingredients are analytical grade.

Equipment:

Uniglatt" Wurster" System, CH-4133, Binzen Haltingen, West Germany.
Tablet Press, Erweka-Apparatebau, G.M.b.H, E.K.O., West Germany.

Erweka tablet Hardness Tester.. USP Disintegration Apparatus, Erweka. Roche Friabilator, Erweka. Unicam Sp 600 UV Spectrophotometer .

Methods:

1. Molecular Dispersion Using Solvent Method:

A- Ratio of 1:1 drug: Eudragit was used throughout all the batches. The calculated amount of Eudragit was dissolved in suitable organic solvents (acetone: isopropyl alcohol,1:1). This was added to the ephedrine hydrochloride-lactose mixture 3:7), mixing in a porcelain dish and evaporating the organic solvents on a steam bath. The mass formed was forced through 1800 um. screen and the granules were dried at room temperature overnight. The dried granules were passed through 630 um. mesh screen and retained over 315 um. mesh screen. The retained granules were compressed into tablets using 2% talc powder as lubricant and 10% potato starch as disintegrant.

2. Spray Coating using Uni-Glatt System:

The calculated amount of Eudragits solutions was divided into two portions. One portion was used for coating the drug-lactose mixture by spraying technique. The second protion was used to granulate the produced coated mixture to produce granules with suitable size for the purpose of compression into tablets.

A- Coating Stage (1st stage):

The drug: lactose mixture was placed in the coating chamber of the Glatt apparatus, kept in motion by the effect of heated air at 60°, directed into the chamber by a blower. In the apparatus, the air passes up through the centers carrying with it the particles that have been coated with the polymer solution which is applied by the atomizing nozzel.

The travelling of the coated powder upward in the air stream helping it to get dry. At the end of the operation, the coated powder was taken out and was subjected to the granulating stage.

B- Granulating Stage (2nd Stage):

Using the second portion of the organic polymer solution, the coated powder was granulated using the granulation chamber of the Glatt apparatus. The method and conditions of granulation were exactly the same as mentioned by Nouh[9]. Final granules were screened using a 315 um. mesh screen and were compressed into tablets under the same previous conditions.

3. Dissolution Procedures:

Using the USP rotating basket method, the dissolution studies were carried out in 0.1 N HCl and in phosphate buffer of pH 7.4 for three hours. The samples were withdrawn at predetermined time intervals, and analyzed spectrophotometrically at 256.5 nm. for the released amounts of ephedrine hydrochloride. The means are of five determinations.

4. Physical Properties:

The tablets were evaluated for the uniformity of weight (B.P. & U.S.P.), uniformity of thickness(micrometer), hardness (Erweka), friability (Roche), and disintegration time (U.S.P.) and drug content.

RESULTS AND DISCUSSION

Figures 1 and 2 show the release profiles of ephedrine hydrochloride from the various polymers used. As evident in these figures, the rate of drug release is a function of both the formulation technique and the type of Eudragit used. The release rate of the drug from the tablets prepared from a coated drug using Glatt air suspension coater, provided higher rates of dissolution (Figure 1). Using the molecular dispersion method resulted in better prolongation of the in-vitro release (Fig. 2). This reflects itself in the T 20% values (Table 1). This is in agreement with findings of Kassem et al[10] that the embedding of phenobarbitone and atropine sulphate in stearic acid, brings about more prolongation of release than coating both drugs in a coating pan. The lower protection of the drug coated with Eudragit in Glatt air suspension coater could be attributable to the physical properties of the tablets prepared by this technique (Table 1). These tablets showed lower hardness values and higher friability precent than those prepared by the other method. It is worthwhile to mention that, all tablets satisfied the USP requirements for weight uniformity (C.V.% ranged from 3.18 - 4.00). The uniformity of thickness was parallel to that of weight. The most interesting point is that, the tablets prepared by molecular dispersion technique showed higher weight valtes than those prepared by the other technique. This may be due to the lower density of granules obtained with the air suspension technique. In a previous work[9], it was found that granules prepared in fluidized-bed were lower in density than granules prepared by wet granulation method, consequently the tablets prepared from the

latter granules exhibited higher weight values. Concerning the influence of Eudragit types ued, it seems that the granules prepared using Eudragit-L exhibited more prolonged release than those prepared by the other types. The precent of ephedrine hydrochloride released from tablets was found to be high from the batches prepared with Eudragit-S. A combination of Eudragit-S and Eudragit-L in 1:1 ratio was intermediate with regard to in release of drug. Gubara et al[11] pointed out that, the incorporation of Eudragit-RS and L as a binder, produced more prolonged release for ephedrine hydrochloride and chloroquine phosphate than other Eudragit types. The role of various types of Eudragit in prolonging the release of drugs was stated by Juslin et al[12] in case of phenazone tablets prepared from precoated pellets with Eudragit-RS using Glatt air suspension coater, and by Ghanem et al[13] in case of tetracyclines copricipitates with anionic and cationic resins. From the results of K (first order rate constant) and $t_{20\%}$ stated in Table 1, for the different batches, it was concluded that tablets prepared with Eudragit-L achieved the greatest prolongation in their release irrespective of the foumulation technique applied.

The value of release rate in acidic and alkaline media from all matrices evaluated in this investigation were plotted as a function of square root of time (Figure 3). The most interesting finding was that, Higuchi equation[14] was found to be valid for the first few hours in case of tablets prepared from coated drug (Figure 3 A), while the equation was valid throughout the time of experiment for tablets prepared by the dispersion technique (Figure 3 B). This indicates that, the diffusion mechanism is working only for a few hours in case of tablets formulated with coated ephedrine hydrochloride, then after this coat is disrupted by the effect of

dispersion, the coat layer surrounding the drug was expected to be more thick and strong as a result of solvent evaporation, and consequently the linear plots (Figure 3 B) appeared to indicate that the drug release in these system is diffusion controlled. For all batches subjected to this investigation, the release of ephedrine hydrochloride was found to follow first-order release pattern (Figures 4&5).

In conclusion, it might be possible to design a prolonged release form by controlling the release rate through both types of anionic acrylic resins and the method of formulation itself. A calculated amount of drug should be incorporated to produce the initial dose which would be released in the first 2 hours in the stomach, with the remaining drug released over the following 4 hours in the intestinal tract.

Table 1: Physical Properties and In-vitro Dissolution Rate of Ephedrine Hydrochloride Tablets

Technique and Type of Eudragit used		*Weight*		*Thickness*		*Friability %*	*Hardness (Kg)*	*Drug Content*	$t_{20\%}$ *(min)*	K_h-1
		Mean	*C.V.%*	*Mean*	*C.V.%*					
Spray Coating	(1)	0.0950	3.57	3.38	0.06	0.188	3.73	93.6	93	0.046
	(2)	0.1141	4.00	3.36	0.15	0.138	7.12	87.8	201	0.030
	(3)	0.1582	2.25	4.41	0.16	0.068	6.34	85.3	147	0.040
	(4)	0.1106	3.89	3.36	0.60	0.166	6.63	85.9	96	0.050
Molecular Dispersion	(5)	0.1812	3.82	5.04	0.12	0.067	8.20	85.8	159	0.025
	(6)	0.1783	3.18	4.94	0.77	0.073	7.71	81.0	255	0.022
	(7)	0.1665	3.60	4.63	0.73	0.019	8.90	86.8	225	0.023
	(8)	0.1660	3.38	4.46	0.07	0.038	8.79	83.7	171	0.026

(1), (5): Eudragit S (2), (6): Eudragit L (3), (7): Eudragit RL (4), (8): Eudragit S + L (1:1)

N.B.: The disintegration time of all batches was more than 3 hours.

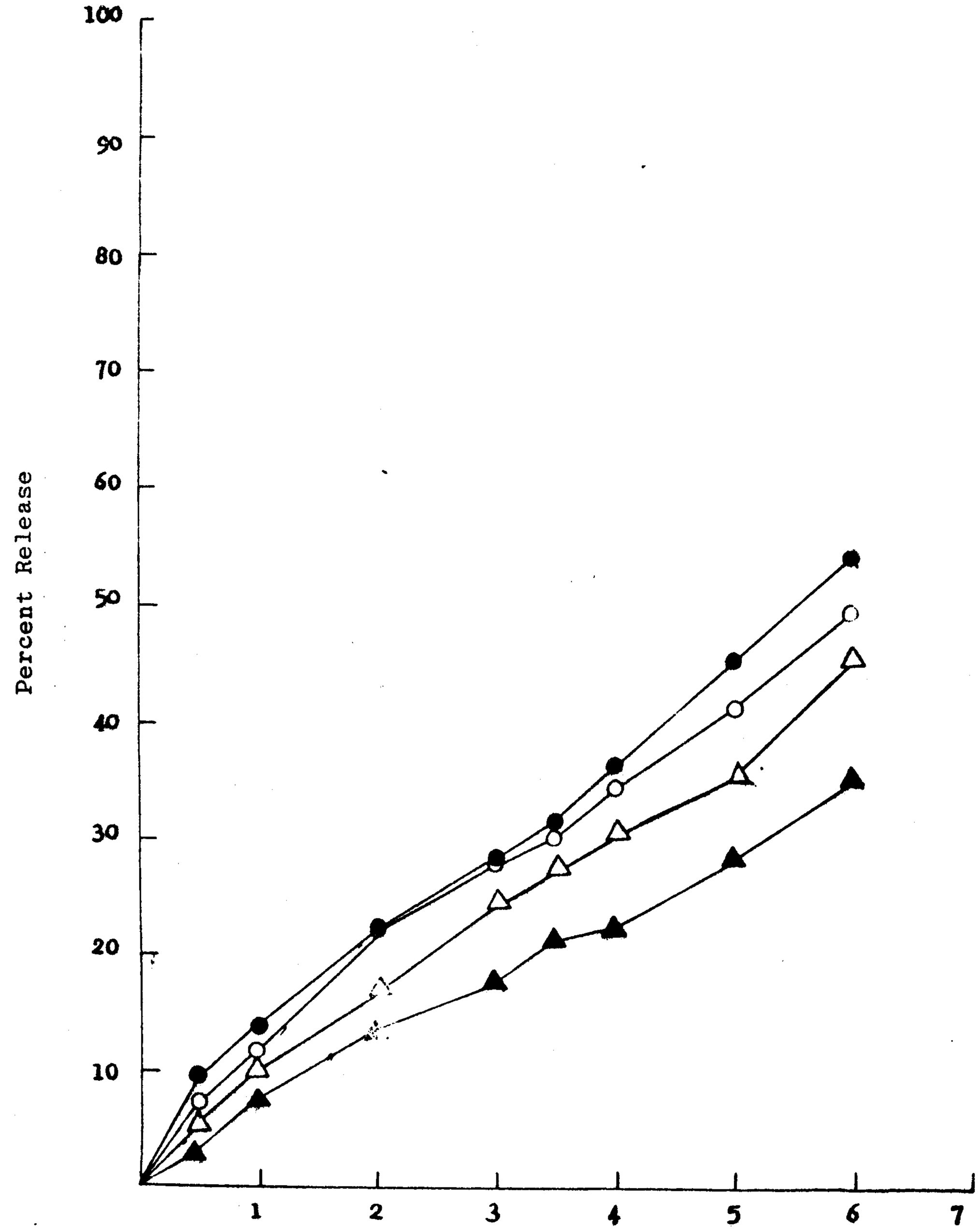

Fig. 1: Dissolution rate of ephedrine hydrochloride from tablets prepared by spray coating using glatt apparatous.

Key : ● Eudragit S ▲ Eudragit L
△ Eudragit RL ○ Eudragit L + S(1:1)

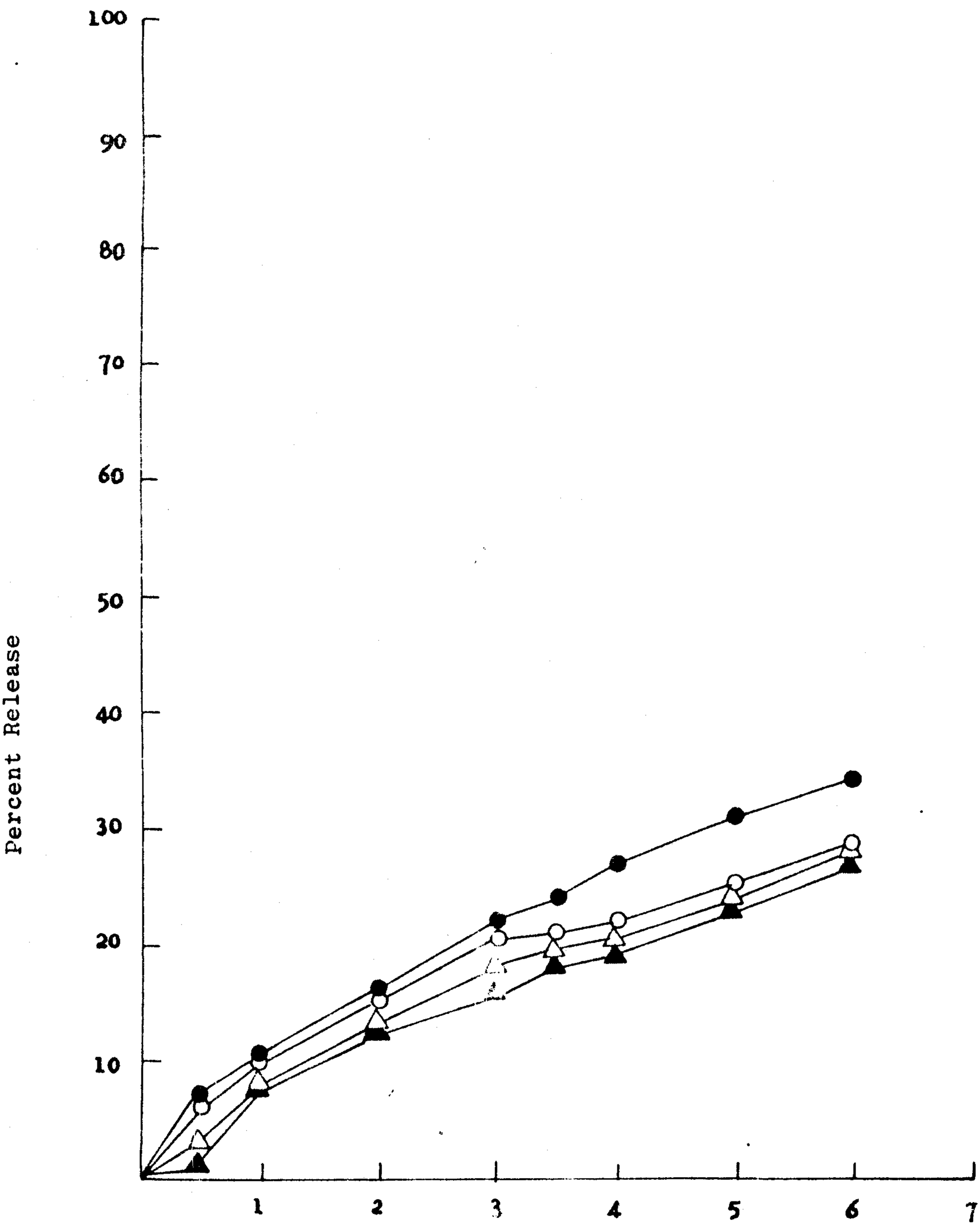

Fig. 2: Dissolution rate of ephedrine hydrochloride from tablets prepared by molecular dispersion technique

Key : The same as Fig. 1.

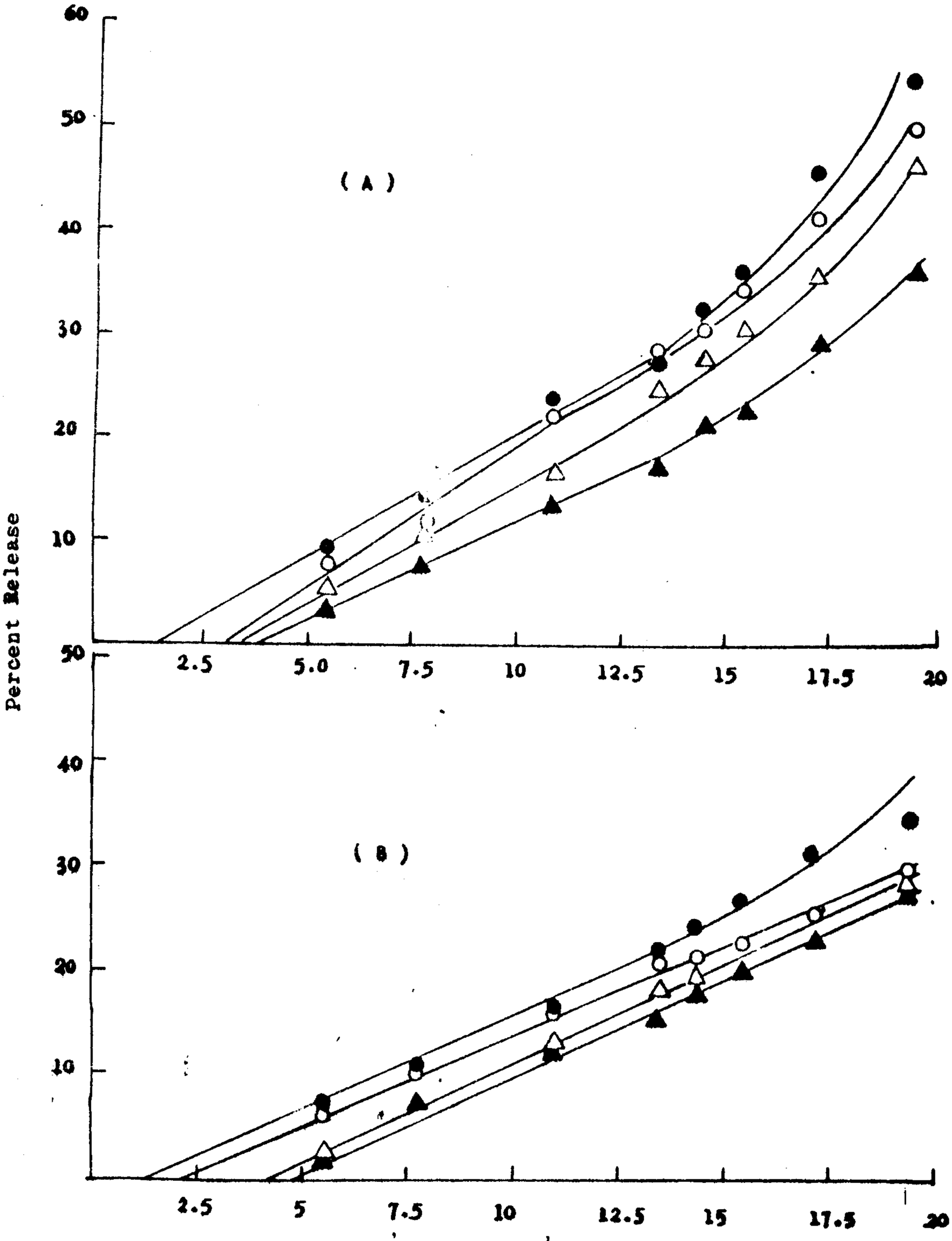

Fig.3: Comparison of percentage release versus $t^{\frac{1}{2}}$ model to the release of ephedrine hydrochloride from tablets prepared by (A) spray coating using glatt apparatus and (B) molecular dispersion technique.
Key: : The same as Fig. 1.

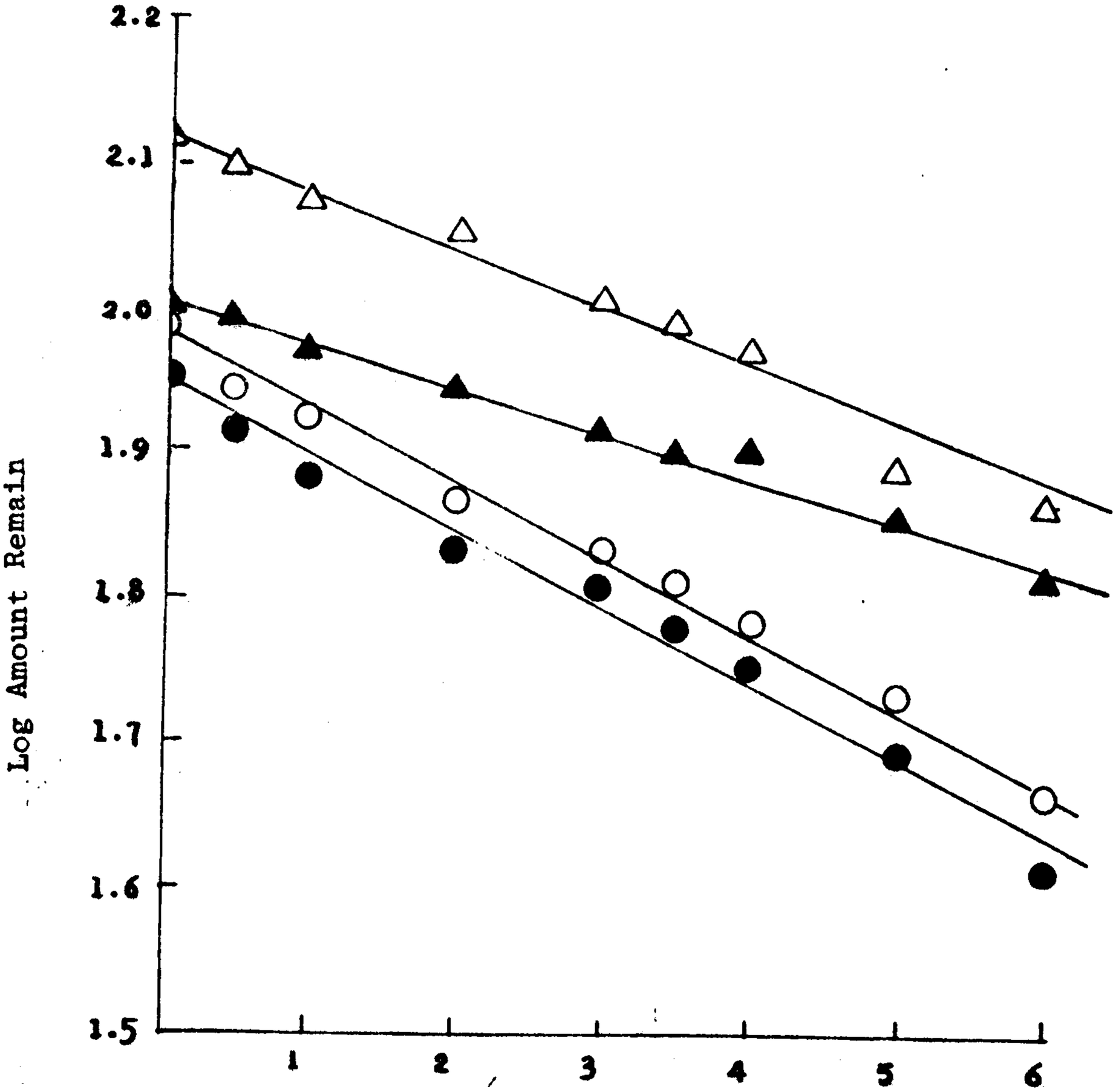

Fig. 4: Apparent first-order release profiles of ephedrine hydrochloride from tablets prepared by spray coating using glatt apparatus.

Key : Same as Fig. 1.

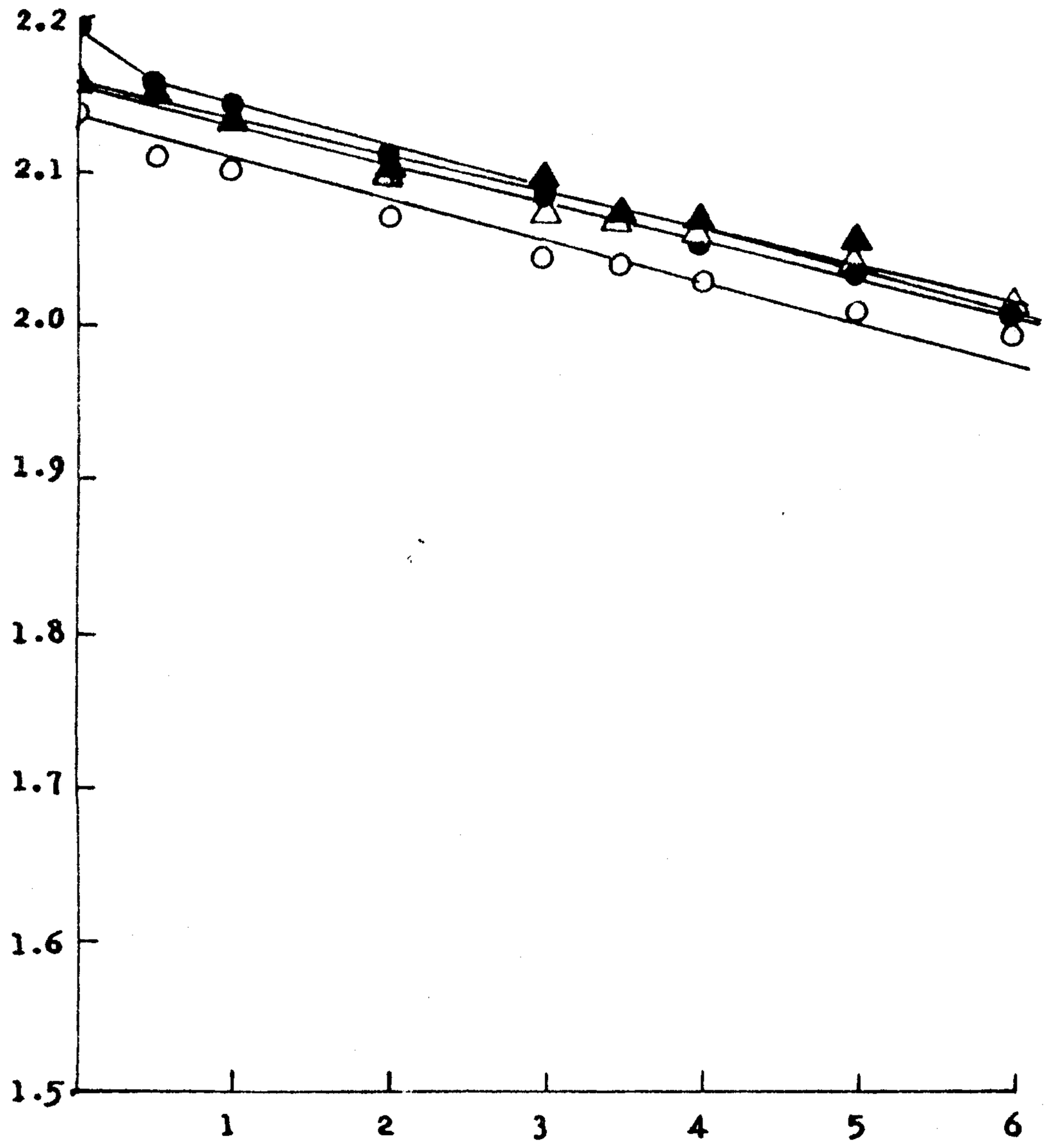

Fig. 5: Apparent first-order release profiles of ephedrine hydrochloride from tablets prepared by molecular dispersion technique.

Key : The same as Fig. 1.

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التوافر الممتد لايدروكلوريد الافدرين بواسطة الايون سالبة الايون

احمد طلعت نوح – محمد على على قاسم – علاء الدين على قاسم – جلال محمد المحروق
قسم الصيدلانيات – بصيدلة المنصورة – صيدلة القاهرة – صيدلة الازهر

تم فى هذا البحث تحضير اقراص ايدروكلوريد الافدرين ممتدة المفعول بطريقتين هما الكسوة بالرش وطريقة التشتيت الجزئيى وذلك باستخدام ثلاثة انواع من الايدراجيت سالبة الايون .

وقد اثبتت الاتاحة المعملية فى الوسطين الحمضى والقلوى ان الاقراص المحضرة بايدراجيت – ل قد اطالت الاتاحة بدرجة كبيرة مما اتاح ٢٠ من المادة الدوائية فى زمن قدرة $\frac{1}{2}$ ٣ ، $\frac{1}{2}$ ٤ ساعة وذلك للاقراص المحضرة بطريقة الكسوة بالرش وطريقة التشتيت الجزئيى على الترتيب .

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