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DISSOLUTION CHARACTERISTICS OF PHARMACEUTICAL EQUIVALENTS

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ABSTRACT

The in-vitro release of diltiazem from pharmaceutical equivalents of sustained release tablets, commercially available in Italy, was studied.

The in-vitro release profiles were determined by means of different methods and apparatus. Paddle, basket, Poole, Diffutest and Stricker methods were compared.

The absorption rates in artificial gastric and enteric juices by means of lipid barriers were calculated.

Some preparations showed a diffusion mechanism, some a first-order release.

The differences among the dissolution profiles of the formulations were enhanced with the Stricker method.

INTRODUCTION

The evolution in the technological field allowed an ever increasing development of novel drug delivery systems. A great variety of new formulations was studied for particular purposes and to decrease the toxicity and side effects of the drugs.

Among all these new preparations, a large number of pharmaceutical equivalents, different in technological characteristics, are available.

Besides the in-vivo tests, required to verify the bioequivalence of these products, some in-vitro methods are employed [1-5]. The standardization of the latter methods allows the observation of significant differences among dissolution profiles of the formula-

TABLE 1

Formulations of diltiazem (mg)

Ingredients	A	B	C	D	E	F
Diltiazem	60	60	60	60	60	60
Polyethylene glycol 6000	20	10	5	20	10	-
Ricinus oil hydrogenated	66	44	22	-	-	1,2
Ethyl Cellulose	-	-	-	-	-	3,6
Microgranular Cellulose	-	-	-	-	100	-
Methyl Acrilate Polymer	-	18	9	20	-	-
Cellulose Acetophtalate	-	-	-	-	5	-
Talc	-	-	-	-	5	113
Magnesium Stearate	4	3	1,5	10	5	4
Lactose	100	245	122,5	240	15	61,2
Starch	-	-	-	-	10	-
Total weight	250	380	220	350	210	243

tions. The use of well known apparatus [6,7] and highly developed te chniques, as for example multi-dimensional topographic analysis [8], is useful for regulatory institutions to control the bioequivalence of the preparations.

In our investigation, all the formulations commercially available in Italy, containing diltiazem, were studied [9]. Their dissolution profiles were determined and compared by different methods.

EXPERIMENTAL

Materials and methods

Six different formulations of diltiazem, commercially available in Italy, were studied. The tablets were composed of 60 mg of diltiazem and several ingredients (Table 1).

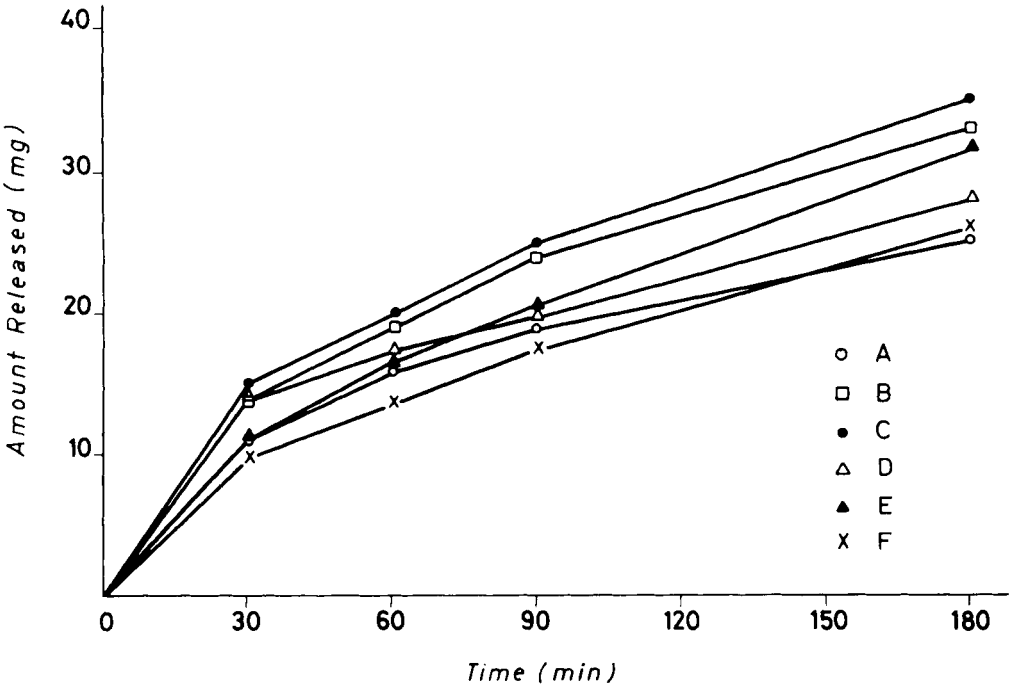

FIGURE 1

Release rate profiles of diltiazem from six tablets in pH 7.4 phosphate buffer, determined by the paddle dissolution apparatus (V.C.=3-5%).

- Dissolution tests

Release rates were determined by means of the following methods and apparatus: paddle method [6,7], basket method [6,7], Poole method (consisting in a flask supplied with a rotating paddle [10,11]), Diffutest apparatus and Stricker method by means of Sartorius apparatus [12].

The first three methods used 1000 ml of 0.1 N hydrochloric acid and pH 7.4 phosphate buffer as dissolution media. The rotational speed of the paddle and the basket was 50 r.p.m.

The Diffutest apparatus consisted of four roundbottom tubes situated at the end of two perpendicular axes, rotating at 30 r.p.m. in a thermostatic chamber. 100 ml of 0.1 N hydrochloric acid and pH 7.4 phosphate buffer were used as dissolution media.

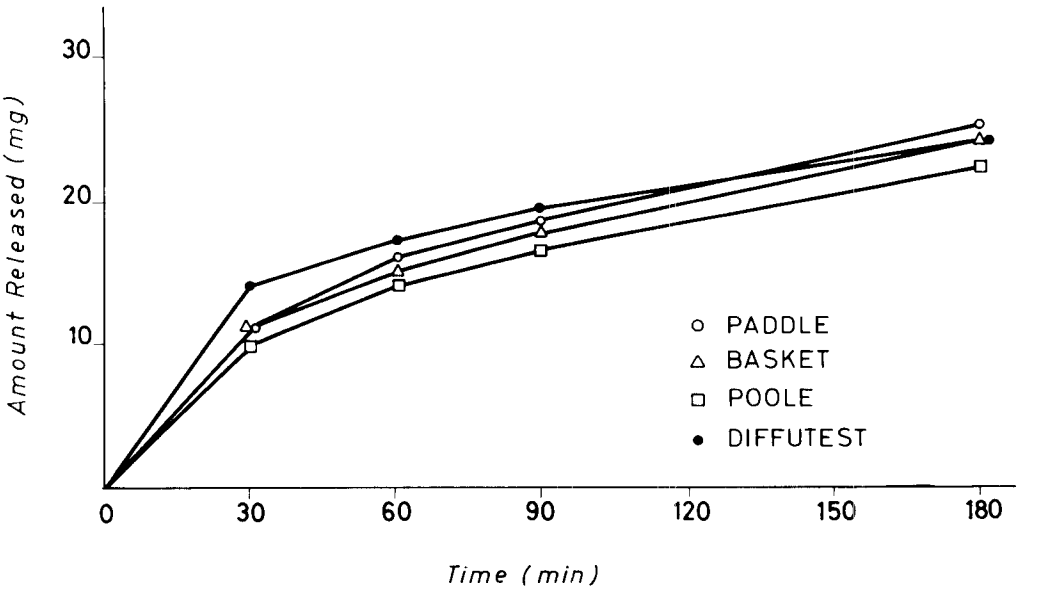

FIGURE 2

Release rate profiles of diltiazem from tablet A in pH 7.4 phosphate buffer, by four different methods (V.C.=3-5% for paddle, basket and Poole methods; V.C.=8-10% for Diffutest apparatus).

Finally, the last method utilized the Sartorius apparatus (SM 16751) that enables solid dosage forms to go into solution under conditions which closely simulate those in the gastrointestinal tract [12]. The pH was increased during the experiment: 0-0.5 hrs. pH 1.2 (0.06 N hydrochloric acid), 0.5-1 hrs. pH 5.7, 1-6 hrs. pH 6.5, and 6-8 hrs. pH 8.1 (phosphate buffers). The volumes of the dissolution media were 100 ml. This method allowed the absorption effect to be taken into consideration [13,14].

In all the methods the temperature was thermostatically controlled at 37.0 ± 0.1°C. Samples were taken at convenient time intervals through membrane filters with 0.8 um pore diameter and assayed spectrophotometrically at 236 nm. The determinations were repeated six times.

- Absorption rates

The absorption rates were calculated, according to the Stricker method, using the Sartorius Absorption Simulator (SM 16750) with

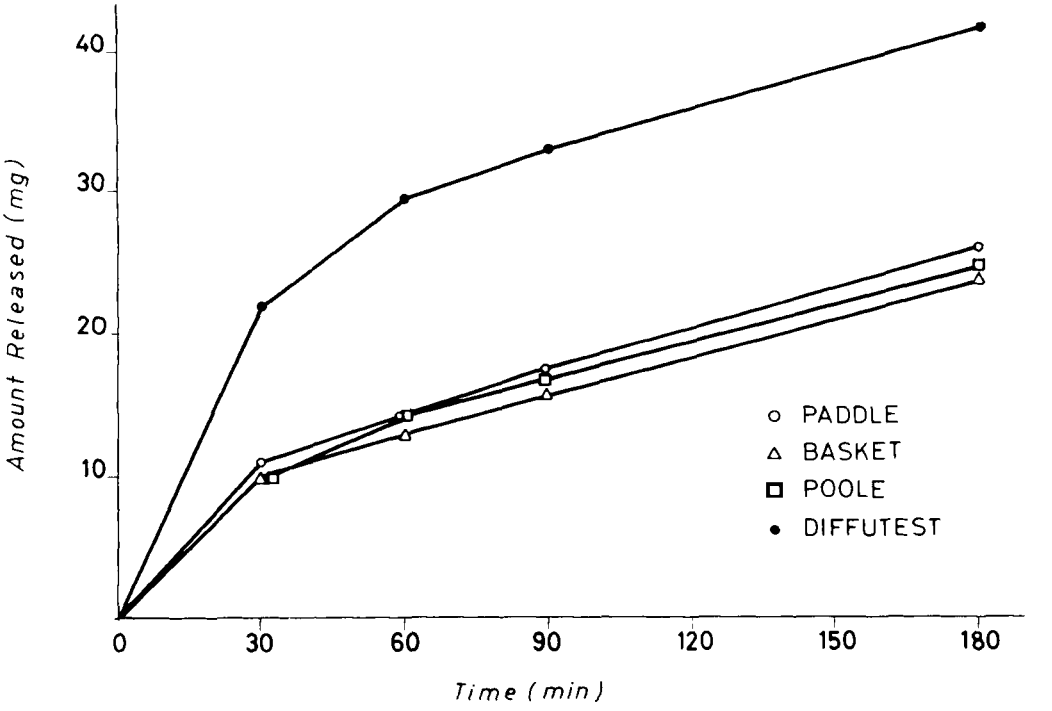

FIGURE 3

Release rate profiles of diltiazem from tablet F in pH 7.4 phosphate buffer, by four different methods (V.C.=3-5% for paddle, basket and Poole methods; V.C.=8-10% for Diffutest apparatus).

two different lipid barriers, 40 cm^2 areas [13,14]. The first one (SM 15701) for the artificial gastric juice (pH 1.1 chloric buffer) and the second one (SM 15702) for the artificial intestinal juices (pH 6.0, 6.5, 7.0 phosphate buffers). In both cases pH 7.5 phosphate buffer was used instead of plasma.

- Hardness

The hardness of the tablets was determined by the Schleuninger apparatus.

- Assay of diltiazem

The samples were assayed by optical assorbance at 236 nm in dilute hydrochloric acid, compared with a reference standard.

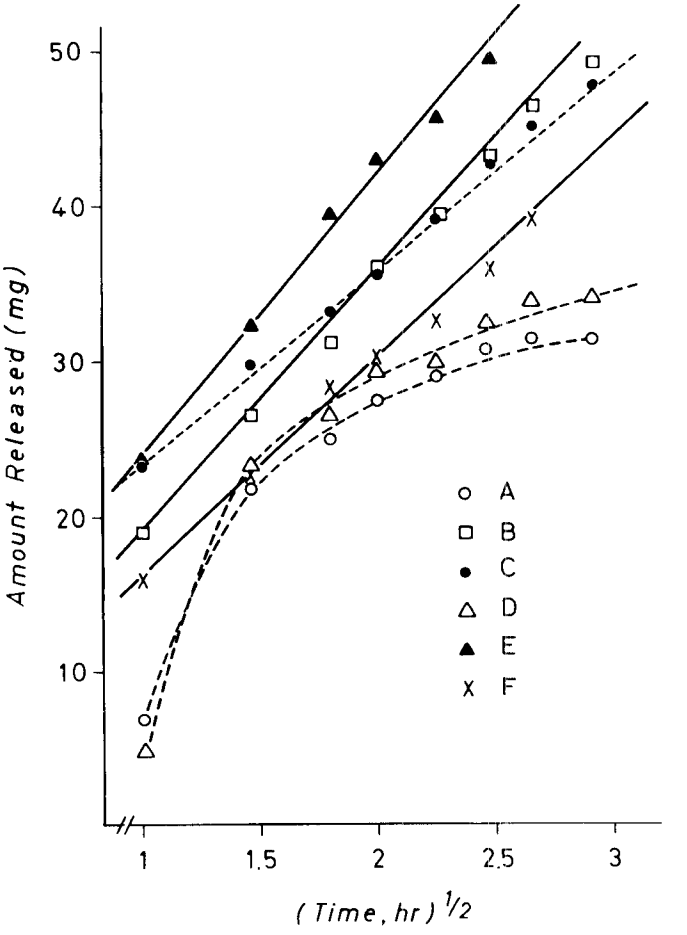

FIGURE 4

Release profiles of diltiazem from six tablets when plotted according to the diffusion model.

- Content Uniformity

Ten units of each preparation were individually assayed for the determination of dose uniformity, as described under "Assay".

RESULTS AND DISCUSSION

No difference was found among the dissolution profiles of the various formulations in acidic dissolution medium, using paddle, ba

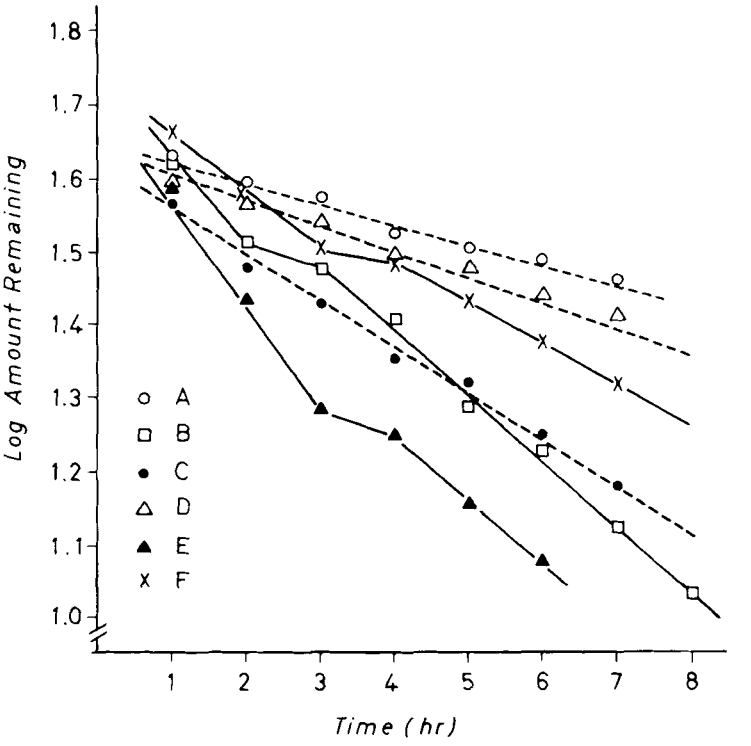

FIGURE 5

Release profiles of diltiazem from six tablets when plotted according to first-order kinetics.

sket, Poole and Diffutest methods: the solubility of the active ingredient in the protonated form was so high to cause the same dissolution profile for all the preparations, in spite of their technological differences.

Different dissolution profiles were observed at pH 7.4. Fig. 1 shows the amount of drug released from each formulation at pH 7.4 by paddle method.

The difference observed in each formulation between the dissolution profiles obtained at pH 1.5 and 7.4 could be mainly attributed to the variuos matrix types utilized to obtain the gradual release. The values of the extent of this matrix effect, calculated after 1 hour, ranged between 30 and 50% of the corrispondent amounts released at pH 1.5 (average amount = 38 mg).

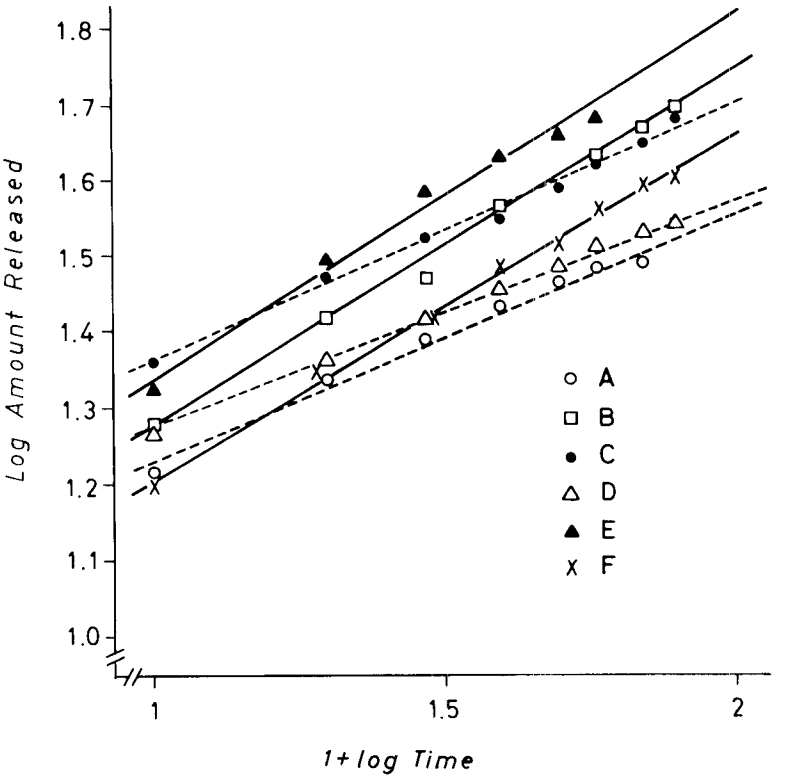

FIGURE 6

Plot of the log of the amount of diltiazem released from six tablets against the log of time.

At pH 7.4 three formulations (A, C, D) had similar dissolution values, using the four mentioned methods; the preparations B, E, F also gave similar results with the first three methods, but showed different dissolution profiles using the Diffutest apparatus. Figures 2 and 3 show dissolution profiles of the preparations A and F which give evidence of these two different behaviours.

Among the equivalent methods, the paddle method was chosen for a kinetic analysis of the drug release from the formulations; the experiments were carried out for eight hours. As shown in Fig. 4, only four preparations (B, C, E, F) presented release profiles described by a linear square root of time dependance. Three formulations (A, C, D) showed linearity between the amount of drug not re

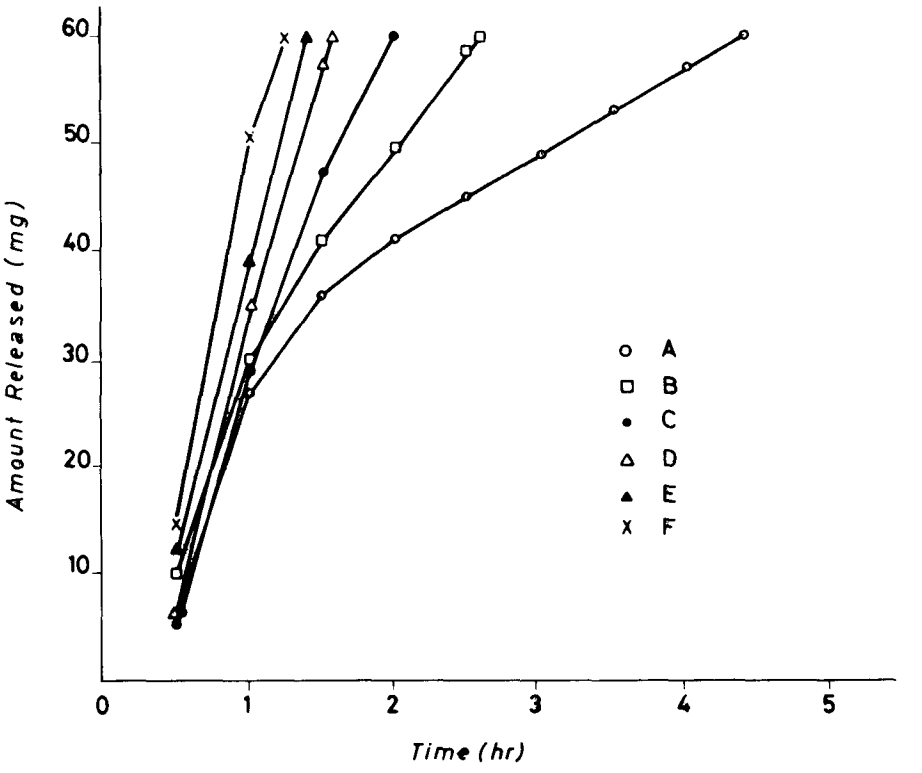

FIGURE 7

Release rate profiles of diltiazem from six tablets, determined by the Stricker method.

leased and the time (Fig. 5). Then the more stringent Higuchi test was developed to distinguish between the diffusion mechanism and the first-order release [15,16]. As shown in Fig. 6, the preparations B, E, F confirmed the release mechanism seen before (Fig. 4), on the contrary the other three formulations (A, C, D) showed a first-order release. Particularly, for the preparation C, the test demonstrated that the first-order release was operative and that a diffusion controlled mechanism, as shown in Fig. 4, was uncorrect. The three formulations which showed a diffusion mechanism were those which presented higher results using the Diffutest apparatus.

Figure 7 shows dissolution profiles determined with the Stricker method. This procedure amplified the behaviour differences among the formulations. These results are more evident in Fig. 8 that

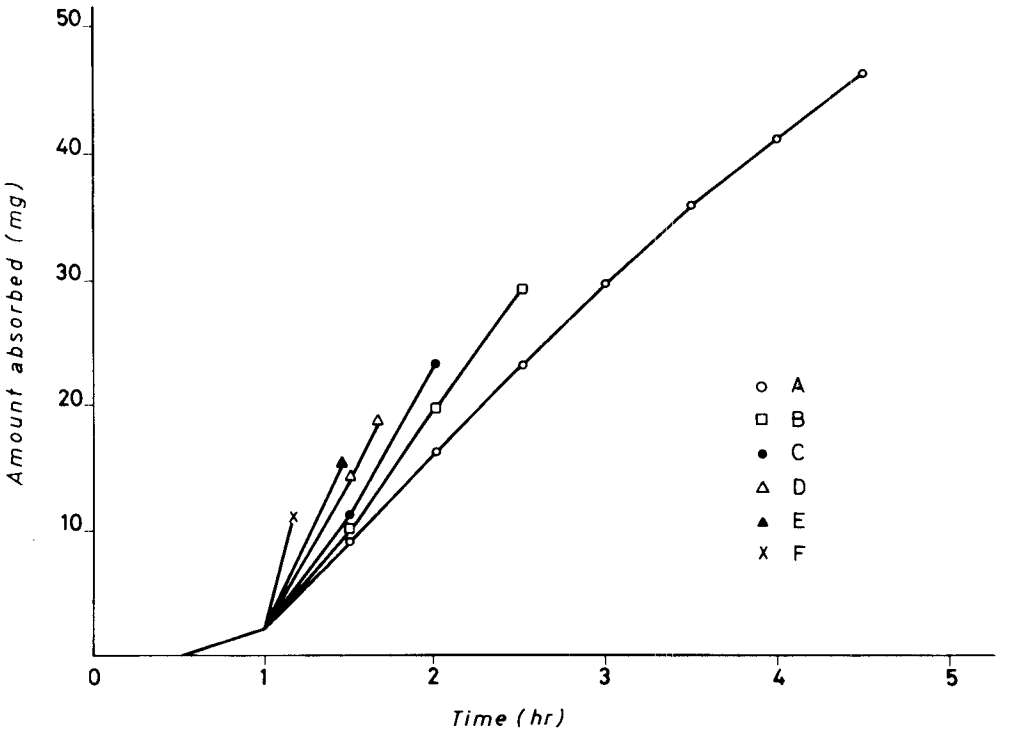

FIGURE 8

Absorption rate profiles of diltiazem from six tablets, determined by the Stricker method.

TABLE 2

Diltiazem content - Hardness

Formulation	Diltiazem content/tablet mg±S.D.(a)	Hardness Kg(a)
A	58.9 ± 1.9	6.0
B	61.4 ± 1.8	7.4
C	59.9 ± 1.4	6.5
D	60.1 ± 1.3	11.4
E	59.5 ± 1.7	10.5
F	58.9 ± 1.7	11.2

(a) Average of 10 determinations.

shows the absorption profiles calculated by means of the mentioned dissolution values, according to the Stricker theory [13,14].

The values for diltiazem content and hardness of tablets are given in Table 2. The formulations showed the uniform distribution of the drug.

CONCLUSIONS

Similar dissolution values of diltiazem from six commercially available sustained-release formulations were obtained, using both official and other well known methods.

Three preparations showed different behaviours using the Diffutest apparatus.

The Stricker method allowed the observation of differences among dissolution profiles of all the examined formulations.

The present results indicate that the official methods were not able to enhance the differences among the preparations.

Several in-vitro methods should be used to pre-evaluate the equivalence before performing in-vivo tests.

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