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PREFORMULATION STUDIES ON DIRECTLY COMPRESSED TEMAZEPAM TABLETS.

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ABSTRACT

Temazepam, a benzodiazepine derivative, was prepared in directly compressed tablets using Avicel, Anhydrous Lactose (A.H.L.), STA-R_X 1500, Emcompress and Compactrol. It was found that A.H.L. represents the most suitable single vehicle while Avicel : STA-R_X 1:1 blend was the most suitable blend for the preparation of temazepam tablets. STA-R_X 1500 and its blends with the other used vehicles were shown to give the highest dissolution. The most uniform tablets were produced on using Emcompress alone or as a binary blend with Avicel (1:1) as directly compresssible vehicles.

INTRODUCTION

Temazepam is used as a sedative hypnotic drug of a short half life[1]. It is manufactured only in the form of capsules (John Wyth and Brother Limited, Havant, England). The purpose of the present article it to prepare temazepam in the form of directly compressed tablets employing the direct compression techique. It is known that this technique offers several advantages over the traditional wet granulation methods[2].

It was stated that no single directly compressible vehicle has been found to be suitable for all directly compressed formulae. Thus, comparative studies on the efficiency of various directly compressibe excipients with medicaments are very essential to select the most suitable vehicle or mixed ones for each drug.

In this article directly compressed temazepam tablets were prepared using single directly compressible vehicles and their binary blends in 1:1 ratio. The produced tablets were evaluated with regard to their physical standards and uniformity of drug content. The dissolution rate for temazepam was carried out on the prepared tablets.

EXPERIMENTAL

Material :

Temazepam (Chemical Industrial Development Co. CID, Egypt) was used as received. Dibasic calcium phosphate dihydrate; Emcompress (Edward Mendell Co., Carmel, New York, USA), Calcium sulphate dihdrate; Compactrol (Edward Mendell), Microcrystalline cellulose, Avicel PH 101 (F.M.C. Corporation, New York, Delaware, USA), STA-R_X1500 starch (Staley MFG Co. Deeantr, Illenois, USA) and Anhydrous Lactose; A.H.L.(U.S.P. Shiffield Chemical Union, NL, 07033 USA) were used as directly compressible vehicles. Magnesium steatate and stearic acid (CID Co.) were used as lubricating agents.

Equipment :

Korsch single punch eccentric tablet machine (Berlin, west Germany), Erweka hardness tester (Erweka, West Germany), Erweka friabilator, Disintegration apparatus (Berlin, West Germany), Cubic mixer (Berlin, West Germany)

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USP dissolution apparatus (Erweka apparatebou, England) and a micrometer (Bat and Co. Ltd, Sussex, England were the equipments used.

Procedure :

Temazepam powder was used as received from the manufacturer. The tablets were prepared by mixing the drug with certain amount of the tested vehicle and lubricant. The above mentioned directly compressible vehicles[3-9] were used single or in blends of 1:1 ratio for preparing the desired tablets. Different batches of directly compressed temazepam tablets were prepared, each containing 2.5% w/w of temazepam 2% w/v of magnesium stearate and stearic acid and 95.5% w/v of each vehicle or their mixttures. Ordered mixing of the drug with the excipients was done on a paper using a spatula then the powder ingredients were blended in a cubic mixer for 15 minutes at 50 r.p.m. The mixed powder then compressed into 8 mm diameter flattened tablets using an eccentric tablet machine adjusted for each excipient to produce 200 mg tablets containing 5 mg of the drug.

Evaluation of tablets :

a- Physical standards and uniformity of drug content:

All the manufactured tablets were evaluated concerning uniformity of weight, disintegration time (USP 1985), uniformity of thickness, hardness and friability. Also uniformity of drug content for the prepared tablets was carried out according to the USP 1985.

b- Dissolution rate :

The dissolution rate was determined using the USP dissolution apparatus. The tablet was placed in a dry basket (40 mesh cloth) at the begining of each test. The dissolution rate was determined in 500 ml of 0.1 N hydrochloric acid equilibrated at 37 C. The basket was stirred at 100 r.p.m. Samples (5 ml) were with drawn every 5 minutes over 15 minutes, then

every 15 minutes over the total dissolution time of 120 minutes. Fresh dissolution medium was added each time to substitute the withdrawn samples. The content of each sample was assayed spectrophotometrically at 235 nm. The data obtained are shown in Figs. 1-3.

RESULTS AND DISCUSSION

Physical characteristics:

Uniformity of weight and thickness:

The physical characteristics of the produced tablets with regard to their mean, standard deviation and coefficient of variation were calculated and summarized in Tables 1 and 2. The single vehicles were found to produce temazepam tablets which are uniform in weight and complied with the USP 1985 specifications for uniformity of weight. The single vehicles investigated could be arranged considering the standard deviation and the coefficient of variation for their capability to produce weight uniform tablets as follows: A.H.L > Avicel > STA-R_X1500 >Emcompress >Comactrol. The blends of these vehicles in 1:1 ratio were found to produce weight uniform tablets which pass the USP 1985 limitations for weight uniformity. The binary blends of the investigated directly compressible vehicles could be arranged according to the uniformity of tablet content, Table 2, as follows : Avicel: STA-R_X1500 > STA-R_X1500: Emcompress > A.H.L.: Emcompress> A.H.L.: Avicel: Emcompress > STA-R_X1500: A.H.L. > STA-R_X1500: Emcompress > A.H.L.: Compactrol >Emcompress: Compactrol > Avicel: Compactrol.

The uniformity of thickness was found to go side by side in all cases with the uniformity of weight, Tables 1 and 2 .

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Disintegration time :

Data obtained in Tables 1 and 2 illustrate that the disintegration time of the produced tablets was affected by the nature of the excipient. All tablets prepared using a single vehicle were found to pass the USP 1985 disintegration test, except for those batches prepared by Emcompress or Compactrol, as shown in Table 1. These findings may be due to the disintegration properties of STA-R_X [3] and Avicel [10] and the dissolution properties of A.H.L. On using binary blends of these vehicles in 1:1 ratio, it was found that only STA-R_X shortened the disintegration time of those tablets containing Emcompress and Compactrol to comply with the USP 1985 disintegration test, Table 2. These findings can be attributed to the disintegration properties of STA-R_X starch and its water sorption properties which leads to tablet swelling and its disintegration into particles. Avicel also shortened the disintegration time of the tablets containing Emcompress to comply with the USP 1985 test. Avicel which acts as a disintegrant, increases water permeability of water into tablets, resulting in disintegration enhancement.

Hardness :

The hardness values of the prepared tablets are shown in Tables 1 and 2 . Avicel and Emcompress produced the hardest tablets which may be attributed to their cchesion forces arised upon compression and the higher applied force in case of Avicel, while STA-R_X and Compactrol produced tablets with low hardness values which may be due to elastic deformation that took place after compression. This shows that the hardness values of the produced tablets depend upon the type of the excipient. A significant improvement in the hardness values of the produced tablets was obtained especially when Avicel was blended with other vehicles. This may be

due to the approximate equally applied compression force in these batches, as indicated in Table 4. Upon mixing compactrol and STA-R_X with, A.H.L. and Emcompress, the hardness of the produced tablets was significantly improved except for Compactrol : STA-R_X blend which may be due to the elastic deformation that took place in this blend compression.

Friability:

The friability of the produced temazepam tablets, as indicated by percentage loss, is shown in Tables 1 and 2. On using single vehicles, Avicel produced tablets with the lowest friability value while Compactrol produced tablets with the highest value. This may be due to capping produced after relief of the compression force especially for tablets containing Compactrol. The friability of Compactrol based tablets was improved when its blends with other vehicles were used in tablet preparation, as shown in Table 2.

Hardness/Friability ratio (h.f.r.):

This ratio gives an indication of the mechanical properties of tablets[11]. The following was the sequence obtained for the single vehicles-based tablets with respect to the h.f.r. of the produced temazepam tablets: Avicel > A.H.L. > Emcompress > STA-R_X1500 > Compactrol as shown in Table 1. The h.f.r. revealed that Avicel is superior to the other excipients investigated as it improves the mechanical properties of the tablets, as shown in Table 2.

Uniformity of drug content:

The mean percent of drug content, standard deviation and coefficient of variation were calculated for temazepam tablets, as given in Table 3. According to the USP XXI (1985) specification, all batches of temazepam tablets comply with the test,

except for those batches containing STA-R_X and STA-R_X: A.H.L. blend as indicated from Table 3. From these results it is obvious that Emcompress improved the uniformity of drug content when blended with other vehicles, as it gave the least standard deviation and the least coefficient of variation values.

Dissolution rate :

It found that the dissolution rate is significantly affected by the type of the excipient incorporated within the tablets. It was noticed that STA-R_X caused rapid dissolution of temazepam from its tablets, Figures 1-3, which may be due to its disintegration properties, as it leads to the incorporation of excessive quantities of the dissolution fluid into the tablet leading to faster breakdown of the tablet. Avicel and A.H.L. showed repid dissolution of temazepam from their tablets which was pronounced after 45 minutes, as indicated in Fig.1, which may be due to their disintegrating and dissolution properties respectively. On the other hand, tablets prepared using Emcompress and Compactrol exhibited the lowest dissolution rates as shown in Fig.1, which may be due to difficulties in permeation of the dissolution medium into tablet.

The effect of binary blends of vehicles 1:1 on the release of temazepam from the prepared tablets is shown in Figs. 2 and 3. It was found that STA-R_X is superior than the other excipients investigated as it enhanced the dissolution of temazepam especially when it was mixed with other vehicles which is related to its disintegrating properties[3].

Table 1: Physical Properties of Temazepam Tablets Preared Using Single Directly Compressible Vehicles.

Vehicle	Weight (g)(1)			Thickness (mm)(1)			Hardness(Kg)(2)			Friability %Loss(3)	H.F.R.	D.T. (minutes		
	$\bar{X}$	S.D.	C.V.%	$\bar{X}$	S.D.	C.V.%	$\bar{X}$	S.D.	C.V.%			$\bar{X}$	S.D.	C.V.%
Avicel	0.2026	0.0028	1.41	4.18	0.05	1.22	4.4	0.615	13.97	0.32	14.66	3.5	1.075	30.72
STA-Rx1500	0.1995	0.0033	1.66	3.23	0.053	1.66	2.11	0.65	31.09	1.25	1.69	3.33	0.408	12.25
A.H.L.	0.1974	0.0027	1.40	3.01	0.021	0.69	3.6	0.90	25.25	0.50	7.2	7.3	0.27	3.75
Emcompress	0.2002	0.0054	2.73	2.11	0.030	1.42	4.3	1.47	34.53	0.78	5.5	> 120	--	--
Compactrol	0.1954	0.0089	4.60	1.93	0.06	3.13	1.17	0.61	50.46	2.24	0.52	> 120	--	--

(1) Mean of 20 tablets weighed individually and thickness measured.

(2) Mean of 10 tablets determined individually.

(3) Mean of 3 determinations using 20 tablets.

Table (2) : Physical Properties of Temazepam Tablets Prepared Using Binary Blends 1:1 of Vehicles.

Vehicles	Weight gm(1)			Thickness (mm)(1)			Hardness kg(2)			Friability %loss(3)	H.F.E.		D.T. (minutes)		
	$\bar{x}$	S.D.	C.V.%	$\bar{x}$	S.D.	C.V.%	$\bar{x}$	S.D.	C.V.%				$\bar{x}$	S.D.	C.V.%
Avicel:STA.Rx	0.1997	0.0023	1.14	3.55	0.0058	0.25	4.8	0.49	10.27	0.65	7.44	0.58	0.13	22.25	
Avicel: A.H.L.	0.1993	0.0035	1.78	3.36	0.029	0.87	3.86	0.47	12.32	0.39	9.90	1.54	0.37	25.37	
Avicel:Emcompress	0.2003	0.0039	1.84	2.58	0.0027	0.95	4.17	0.64	15.43	0.35	12.08	20	5.36	26.93	
Avicel:Compactrol	0.2025	0.005	2.48	2.68	0.046	1.70	4.85	0.82	16.94	0.70	6.95	97.0	13.04	13.44	
A.H.L.:STA-Rx	0.1992	0.0037	1.86	3.11	0.004	1.41	3.10	0.64	27.18	0.89	3.48	2.7	0.97	26.34	
A.H.L.:Emcompress	0.2012	0.0035	1.76	2.56	0.028	1.12	5.84	0.069	18.32	0.61	9.6	28.6	4.39	15.36	
A.H.L.:Compactrol	0.1999	0.0039	1.99	2.55	0.031	1.24	4.025	1.102	27.38	0.72	5.57	32.2	2.16	6.73	
STA. Rx:Emcompress	0.2003	0.0033	1.63	2.62	0.023	0.90	4.45	0.90	20.32	1.02	4.36	2.85	0.22	7.84	
STA-Rx: Compactrol	0.1979	0.037	1.88	2.57	0.026	0.99	2.01	0.29	14.65	1.31	1.53	1.2	0.11	9.3	
Emcompress: Compactrol	0.2023	0.0046	2.3	2.07	0.048	2.37	0.52	0.82	14.15	0.88	4.24	100	20.0	20.0	

(1) Mean of 20 tablets weighed individually and thickness measured.

(2) Mean of 10 tablets determined individually.

(3) Mean of 3 determinations using 20 tablets.

Table 3 ; Effect of Various Vehicles on the Uniformity of Drug Content of Directly Compressed.Temazepam Tablets.

Vehicle	% Drug Content		
	Mean	S.D.	C.V. %
Avicel	104.4	0.635	7.47
STA-RX	103.38	0.460	8.99
A.H.L.	96.52	0.290	6.03
Emcompress	99.34	0.25	5.03
Compactrol	95.99	0.34	7.27
Avicel: STA-RX (1:1)	100.14	0.29	5.93
Avicel: A.H.L. (1:1)	100.50	0.31	6.23
Avicel: Emcompress	102.48	0.13	2.62
Avicel: Compactrol	107.06	0.39	7.27
STA-RX: A.H.L.	107.26	0.55	10.17
STA-RX: Emcompress	92.94	0.17	3.69
STA-RX: Compactrol	95.12	0.29	6.09
A.H.L.: Emcompress	97.44	0.196	4.025
A.H.L.: Compactrol	93.18	0.217	4.66
Emcompress: Compactrol	103.96	0.27	5.13

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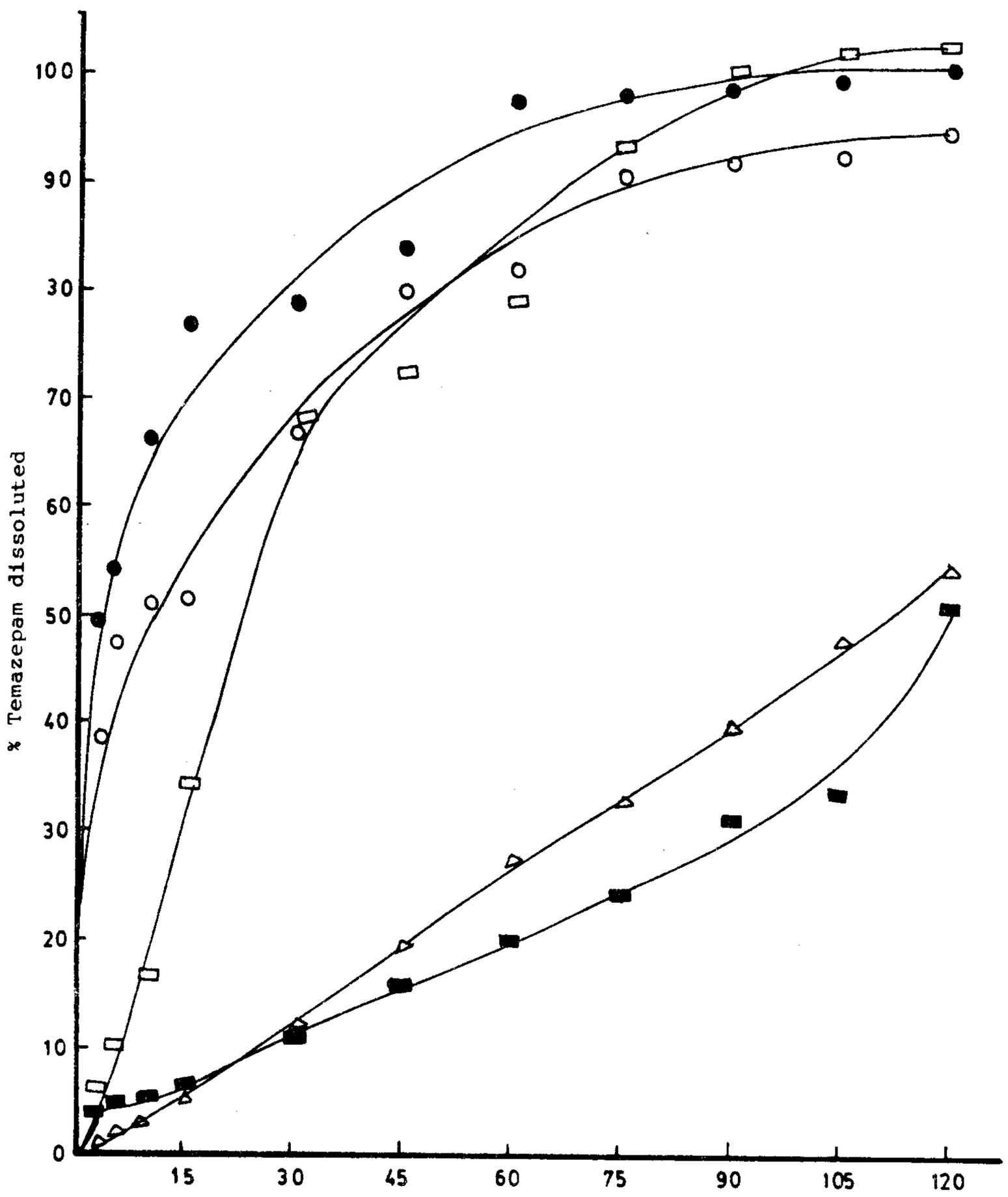

Fig.(1): Effect of single directly compressible vehicles on the dissolution of temazepam from its tablets

○ Avicel ● STA-Rx 1500 ▭ A.H.L.

▬ Ecompress △ Compactrol

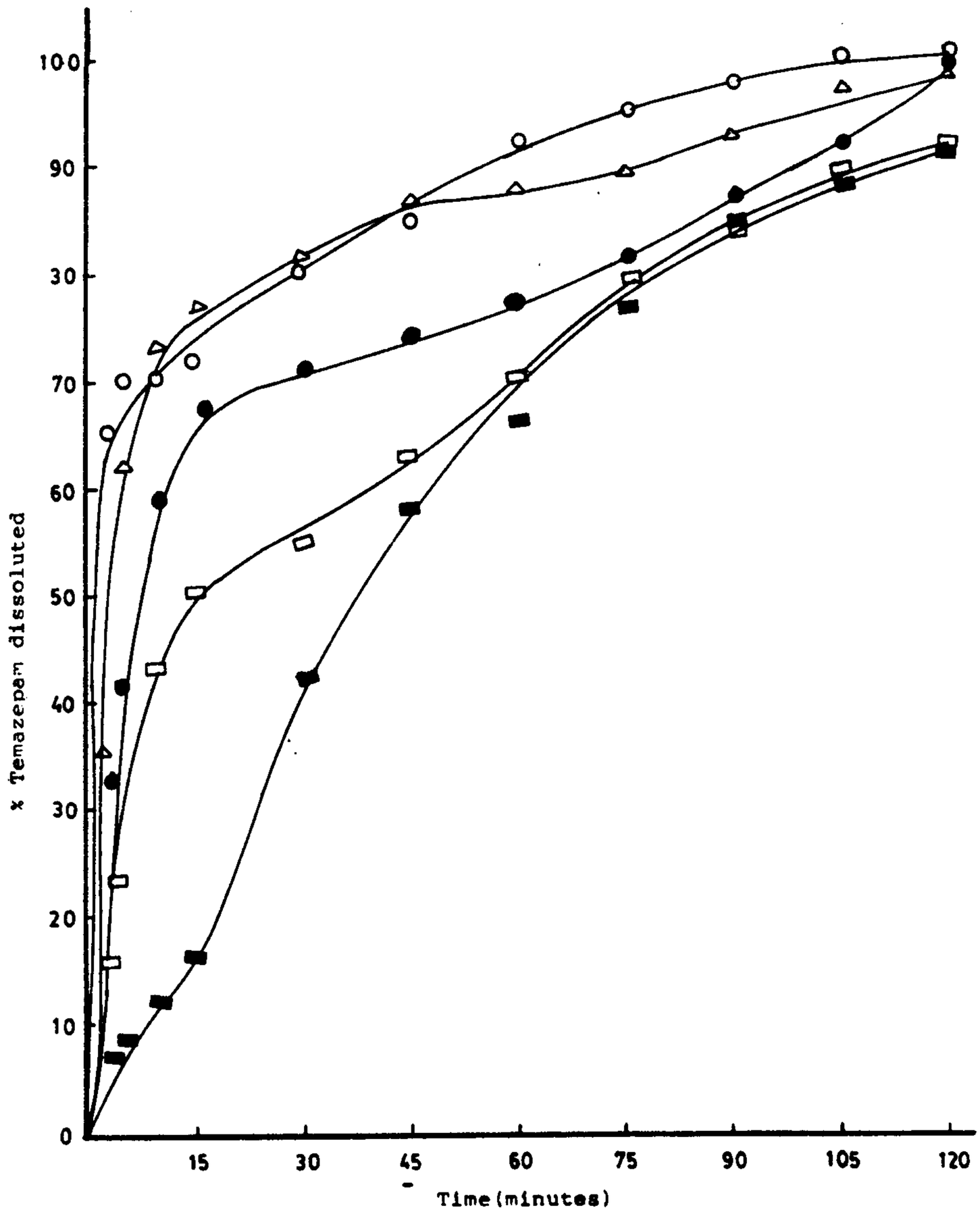

Fig.(2): Effect of binary blends of directly compressible vehicles on the dissolution of Temazepam from its tablets.

○ Avicel : STA-Rx ● Avicel: A.H.L.
□ Avicel : Emcompress ■ Avicel:Compactrol
△ A.H.L.: STA-Rx

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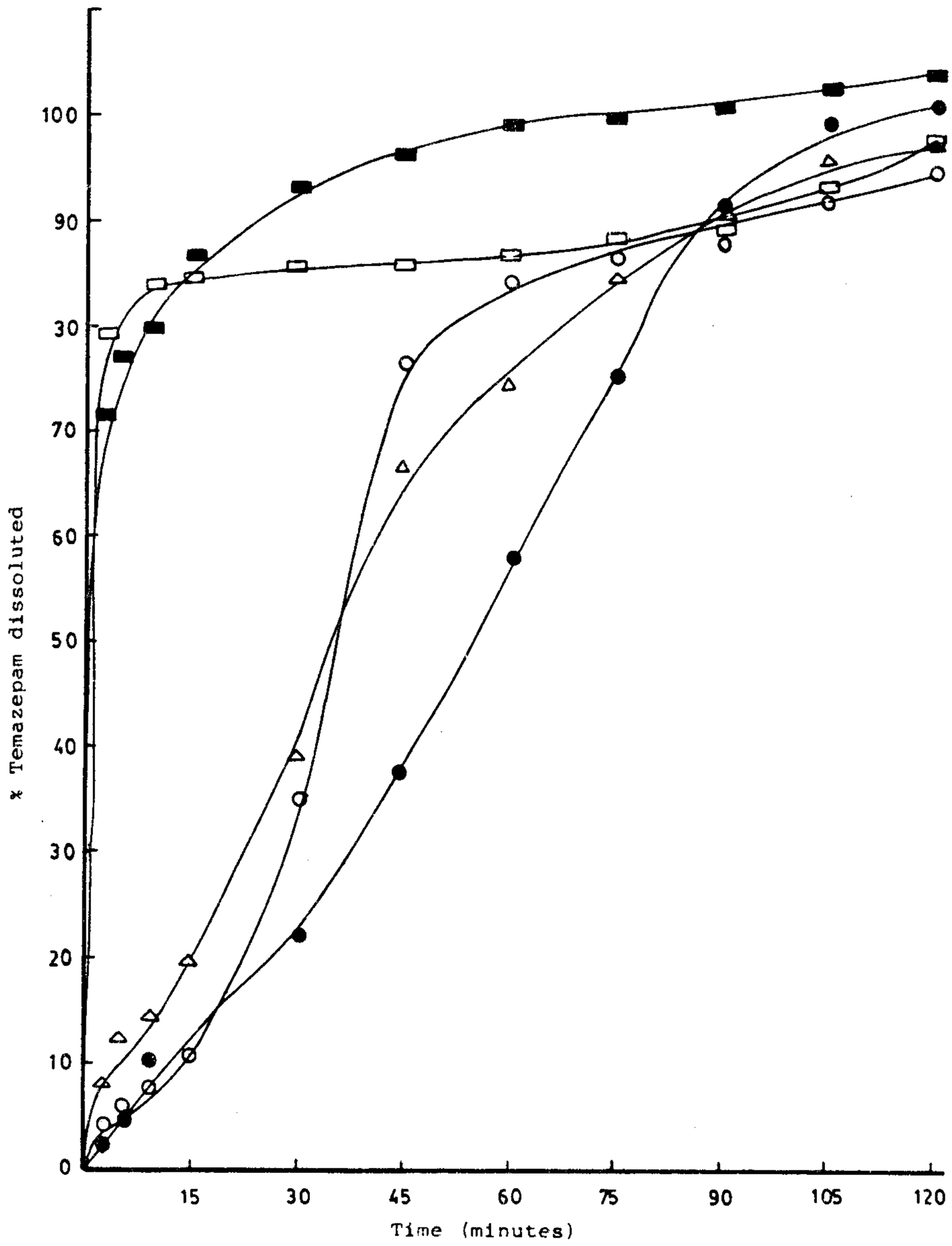

Fig. 3): Effect of binary blends of directly compressible vehicles on the dissolution of temazepam from its tablets.

○ A.H.L.: Emcompress ● A.H.L.:Compactrol ■ STA-Rx:Compactrol

▭ STA-Rx: Emcompress △ Emcompress: compactrol.

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دراسة على صياغة وتقييم أقراص التيمازيبام المحضرة بطريقة الكبس المباشر

أحمد السيد أبوطالب ، على عبد الظاهر عبد الرحمن ، محروس عثمان أحمد
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حضر التيمازيبام-أحد مشتقات البنزود يازيبينات في أقراص بطريقة الكبس المباشر بمساعدة صواغات الكبس المتفردة أوفى مخلوط ثنائى (١:١) من الأفسيل ، سكر اللبن اللاماثى ، نشا أس تى ـ آر ـ آر أكسى ١٥٠٠ ، الامكمبرس والكمباكترول .

ولقد وجد أن سكر اللبن اللاماثى يمثل أفضل صواغ لتحضير أقراص التيمازيبام بطريقة الكبس المباشر أما فى حالة المخلوط الثنائى فقد وجد أن سكر أفسيل ، أس ـ تى ـ آ ـ آر اكس ١٥٠٠ فى مخلوط نسبته ١ : ١ هما أفضل خليط لتحضير الاقراص موضوع البحث.

ولقد أعطى نشا أس . تى آر ار اكس وكذلك مخاليطة مع بقية الصواغات أفضل اتاحة للأقراص المحضرة .

اما عن تجانس المحتوى الدوائى للأقراص المحضرة فقط أعطى الامكمبرس بمفرده أوفى مخلوط ثنائى ١:١ مع الافسيل أفضل تجانس للمحتوى الدوائى للاقراص المحضرة .

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