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A STUDY ON THE STABILITY OF DIRECTLY COMPRESSED OXYTETRACYCLINE HYDROCHLORIDE AND DIIODOQUIN TABLETS

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ABSTRACT

A study on the stability of directly compressed oxytetracycline hydrochloride and diiodoquin tablets was preformed. A comparison was made between diiodoquin tablets prepared by direct compression and those prepared by wet granulation. T½ was determined using the calculated rate of reaction. The tablets were stored in amber coloured bottles for different periods. It was found that directly compressed tablets were more stable than those prepared by wet granulation method.

INTRODUCTION

It has been recognized that there are legal, moral, economic and competitive reasons, as well as those of safety to monitor, predict and evaluate drug product stability[1]. Carstensen[2] reported a review about stability of solids and solid dosage forms.

The decomposition reaction may follow zero and first order reactions, the distinction between them is possible and important. There are of course time where first and zero order cannot be distinguished in anyway. Brownley and Lachman[3] studied the formation of hydroxymethyl furaldehyde from Lactose. Gross[4,5] studied the decomposition of

bacitracin. Haynes et al[6] explained the different kinetics, i.e., dehydration kinetics, two component systems decomposition involving moisture and photolysis.

Haynes et al reported about first order decomposition of chlortetracycline capsules. Enezian[7] showed that tablets prepared by microcystalline cellulose decomposed by a first order pattern and that the rate constant adhered to an Arrhenius equation. Carstensen[8] et al described preformulation screening program. He examined the interaction and the incompatibility that happened between drugs. Lach and others[9,10,17] developed methods for screening by using diffuse reflectance spectroscopy. Johnson et al[18] studied stability of ascorbic acid in various tablet formulations.

Heavy metals such as calcium salts, Magnesium salts, interact and inactivate tetracyclines[19]. The intertablet migration of nitroglycerin could be related to the container used for storage. This may lead to decrease in content uniformity[20]. Photosensitivity reaction have been reported for the tetracycline after exposure of the patient to strong sunlight[21]. The basic mechanism is the photosensitized oxidation of the adsorbate or substrate by molecular oxygen[22,23]

The fading of coloured tablets by light was tested[24]. The intensity of ultra-violet rays contributed mainly to the fading, but visible light also, was responsible. The discolouration of reserpin, dihydralazin sulphate tablets on prolonged exposure to air was reported[25], reserpine was responsible for discolouration of these tablets and it was recommended that discoloured material should not be used clinically[26]

EXPERIMENTAL

Materials and Equipment:

I- Oxytetracycline hydrochloride powder, the same as used in the preparation of tablets.

II- Sodium hydroxide, sodium nitrite, hydrochloric acid, Chloroform which saturated with water, and copper sulphate 0.1% w/v.

III- Directly compressed oxytetracycline hydrochloride and diiodoquin tablets.

IV- Pye unicum SP6-400 U.V. Spectrophotometer.

Method: for directly compressed oxytetracycline hydrochloride tablets.

The method used was colourimetric assay as suggested by Mortada et al[27] in 1975. Tablets under the test were powdered in a porcelain morter and an equivalent weight which contains 1 mg oxytetracycline hydrochloride was used.

The powder was dissolved in 10 ml distilled water in a measuring flask, 25 ml of N hydrochloric acid 2 ml was added. The flasks were left for 10 minutes then they were cooled, 2 ml of 1% w/v sodium nitrite were added. The flasks were left for 15 minutes, then 3 ml sodium hydroxide 20% w/v. were added. The colour developed was measured at 450 nm.The test was carried out on tablets after compression and storage. Blank was performed using distilled water only. K values of reaction rate constant were determined.

The stability of diiodoquin in directly compressed tablets were investigated and compared with that in tablets prepared by the traditional wet granulation method. The procedure used was reported by Carstensen[2] and Chu et al[28]. The procedure

is sensitive for both chloroiodoquin and diiodoquin .

Tablets were powdered in porcelain morter and equivalent amount containing 20 mg medicament was taken. The powder was transfered to a funnel and the medicament was extracted with 3 N hydrochlorice acid, and filtered, 0.5 ml of 0.1% copper sulphate w/v was added to riltrate. The volume was completed to 50 ml by N sodium hydroxide. The solution was extracted by shaking with chloroform saturated with water using 25, 15 and 10 ml respectively. The absorbance was read at 430 nm.

RESULTS AND DISCUSSION

Antibiotics, especially tetracyclines are sensitive to moisture, heat, light, heavy metals and other incompatible materials. They tend to undergo different chemical interactions. They are sensitive and decompose in acidic and alkaline media. Storage also, may lead to degradation. After storage period the percentage of oxytetracycline hydrochloride was calculated and the results are shown in Table 3. Each formulation has its own K. value (reaction rate constant).

With regard to formulations containing Avicel it was found that the increase in actual concentration of the vehicle lead to the increase in K value. On the other hand, Celutab had large value of reaction rate constant especially formula containing actual concentration 32.6% w/w . This may be due tc sugar, humidity interaction during storage and/or the aldhydic group present in sugar, which deteriorates the antibiotic by oxidation. On the other side, STA-R_x produced tablets with the least K value. This may be due to nonabsorbing character of STA-R_x

to humidity. Also, STA-R_x has no aldhydic groups.

The highest values of reaction rate constant, were of tablets produced using Emcompress. The basic nature, and complex interaction of Emcompress were the main reasons of tablets instability. Tablets were blackened and were dark in colour. This due to ability to oxidation of the antibiotic which was accelerated by basic nature of Emcompress.

Tablets prepared using blends of vehicles were also, studied. The smaller values of reaction rate constant were those for tablets containing STA-R_x blends. This can be shown in Table 2. Figure 1 explained the relationship between K values and vehicle concentration. Linear relationship was obtained between the actual vehicle concentration and K values determined • Emcompress showed the largest slope, while STA-R_x showed the least slope.

Table 4 showed the relationship between K values and vehicle concentration used to compress diiodoquin tablets.

STA-R_x1500 when used for the preparation of diiodoquin tablets gave rise to smaller reaction rate constant, the values increase by increasing the actual concentration of STA-R_x in the formula.

On the other hand, blends of Avicel/STA-R_x 1:1, when used for manufacturing diiodoquin tablets. relatively smaller reaction rate constant value was obtained. This may be due to the small affinity of starch and cellulose mixture to absorb moisture.

Tablets prepared using STA-R_x/Celutab 1:1 blends gave the smallest reaction rate constant value. But, tablets produced by traditional wet granulation method showed the highest values. The value was not more than 8.49×10^{-3}. This can be attributed to the effect of moisture and heat

applied during granulation and drying.

Figure 2 explained the relationship between the reaction rate constant values and actual concentration of the different vehicles used

CONCLUSION

From the previous discussion, it can be concluded that

1- The decomposition of oxytetracycline hydrochloride followed the first order reaction.
2- Emcompress(dicalciam phosphate dihydrate) showed the largest reaction rate constant values for oxytetracycline hydrochloride.
3- The least reaction rate values were for formulations containing STA-R_x while oxytetracycline hydrochloride tablets containing Celutab showed high reaction rate constant values but less than that of tablets containing Avicel.
4- STA-R_x blend gave decreased values of reaction rate constant to oxytetracycline hydrochloride, while the blends of Emcompress increased the values of reaction rate constant.
5- The directly compressed diiodoquin tablets had small reaction rate constant than the tablets produced by other techniques.
6- Celutab/STA-R_x 1:1 blends produced tablets with the smallest reaction rate constant-while, high reaction rate constant values were shown for tablets prepared using traditional wet granulation method.

Table 1: Effect of various vehicles on the physical characteristics of oxytetracycline hydrochloride tablets.

Vehicles		Weight (gm)		Thickness (mm)		Hardness (Kg)		Friability (Loss.%)		H.F.R.	D.T. (Minutes)	
Name	Conc.% w/w	mean	C.V.%	mean	C.V.%	mean	C.V.%	mean	C.V.%		Mean	C.V.%
Avicel	0.0	0.1396	1.42	3.17	1.06	5.75	11.95	3.735	20.09	1.53	18.61	12.90
	19.6	0.1228	1.47	2.90	9.02	6.15	12.14	0.8762	7.00	7.01	27.10	7.05
	32.6	0.1156	7.80	2.66	5.90	5.65	7.28	0.769	18.53	7.33	42.88	9.50
	42.0	0.1100	9.26	2.57	1.29	5.87	9.24	0.757	4.25	7.75	53.10	6.54
	49.0	0.1045	6.50	2.57	2.03	6.05	3.25	0.685	38.79	8.82	75.10	23.36
Anhydrous Lactose	19.0	0.0891	6.50	2.22	4.85	4.82	22.12	8.520	16.32	01.565	6.81	9.18
	32.6	0.1226	1.57	2.61	11.85	5.17	10.19	5.585	14.53	0.925	10.95	15.06
	42.0	0.1217	1.53	2.55	9.11	6.10	14.86	5.193	1.923	1.17	8.85	14.67
	49.0	0.1209	7.56	2.54	5.16	6.10	12.09	4.725	1.83	11.11	3.89	17.69
Celutab	0.0	0.1153	3.21	2.70	2.12	5.25	17.53	6.688	11.78	10.784	12.15	7.91
	19.6	0.1246	1.57	2.88	1.25	5.55	15.51	1.1446	25.09	4.84	13.20	5.59
	32.6	0.133851	1.37	2.99	6.80	5.80	8.57	1.1386	15.45	5.09	14.14	9.99
	42.0	0.1145	3.21	2.65	2.94	7.70	10.39	1.069	0.13	7.32	15.76	19.94
	49.0	0.1228	1.840	2.80	1.29	7.60	11.09	1.0826	28.97	7.02	16.83	8.14
Sugartab	0.0	0.1112	3.22	2.39	1.80	7.32	9.10	0.887	11.30	8.24	3.85	17.6
	19.6	0.1204	4.93	2.50	11.77	5.70	6.79	1.253	17.61	4.56	9.[illegible]	23.09
	32.0	0.1252	2.88	2.78	2.84	5.07	3.32	1.2471	22.54	4.06	10.61	28.27
	42.0	0.1045	1.46	2.33	1.65	4.97	12.63	1.445	2.76	3.43	13.95	13.79
	49.0	0.0916	3.13	2.16	22.24	5.02	10.60	1.1550	2.111	4.34	10.02	9.23
STA-R_x	0.0	0.1031	3.86	2.43	2.17	6.19	11.22	1.868	18.26	3.31	4.99	5.78
	19.6	0.1036	3.26	2.49	1.27	6.22	6.12	1.036	3.50	5.99	7.53	9.39
	32.0	0.1066	3.40	2.52	1.98	6.87	11.03	1.332	11.51	4.40	6.24	4.29
	42.0	0.1053	2.11	2.54	5.78	7.02	12.14	1.113	12.03	6.30	5.93	4.29
	49.0	0.1077	3.19	2.58	2.35	7.55	57.98	0.943	16.05	8.004	6.91	4.89
STA-R_x/ Celutab 1:1	0.0	0.066	18.52	2.13	2.6	5.42	9.22	3.78	35.62	1.433	4.09	12.91
	19.6	0.0962	2.75	2.29	2.11	7.42	10.29	0.858	44.93	8.647	4.83	7.41
	32.6	0.1011	1.75	2.39	1.47	8.60	9.41	0.568	8.98	15.122	5.85	5.06
	42.0	0.1063	1.56	2.50	1.45	9.37	6.31	0.539	11.50	17.355	6.52	2.28
	49.0	0.1103	2.24	2.56	1.67	9.85	6.35	0.367	15.29	26.839	8.32	5.60
Avicel/ Celutab 1:1	0.0	0.0960	3.95	2.20	4.05	5.17	11.62	1.630	18.33	3.17	5.83	7.41
	19.6	0.0989	1.71	2.26	1.75	7.32	9.79	1.169	25.16	6.31	9.73	7.74
	32.6	0.101120	0.06	2.31	2.51	8.15	8.27	0.729	14.38	11.16	13.57	6.12
	42.0	0.094550	0.51	2.39	2.38	o.56	6.27	0.536	15.56	16.12	16.19	4.49
	49.0	0.1062	1.22	2.39	1.174	8.85	3.03	0.462	23.65	19.13	16.59	7.27

Table 2 : Effect of various vehicles on the physical characteristics of Diiodoquin tablets:

Vehicles	Conc.%	Weight (gm)		Thickness (mm)		Hardness (Kg)		Friability (Loss.%)		H.F.R.		D.T. (Minutes)	
Name	w/w	mean	C.V.%	mean	C.V.%	mean	C.V.%	mean	C.V.%			Mean	C.V.%
STA-R$_x$ 1500	0	0.0784	3.66	1.66	1.92	1.05	15.06	8.079	24.18	5	0.13	> 120	
	19.6	0.0906	2.17	1.99	0.63	1.60	28.71	4.09	27.23	7	0.39	14.45	8.5
	32.6	0.0957	4.53	2.707	2.41	1.70	21.18	4.64	9.07	4	0.42	10.29	5.16
	42.0	0.1078	1.80	2.31	1.04	2.70	17.34	2.65	15.49	3	1.01	9.14	14.97
	49.0*	0.1101	1.71	2.34	0.73	2.88	15.09	2.08	9.28	3	1.38	9.03	10.38
STA-R$_x$/ Celutab 1:1	0	--	--	--	--	--	--	--	--	--		--	--
	19.6	--	--	--	--	--	--	--	--	--		--	--
	32.6	--	--	--	--	--	--	--	--	--		--	--
	42.0*	0.1132	3.81	2.41	1.03	1.45	19.57	2.11	35.25	15	0.69	13.31	9.40
	49.0	0.1032	2.53	2.32	1.76	2.5	22.53	1.81	37.70	[a]11	1.38	12.99	4.41
STA-R$_x$/ Celutab 3:1	0 *	0.080	5.811	2.045	1.26	0.9	19.42	5.84	4.68	[a]11	0.15	>120	
	19.6	0.0939	1.488	2.103	2.32	1.075	11.33	3.29	14.79	12	0.33	30.24	7.90
	32.6	0.102	2.60	2.24	1.06	1.30	15.16	2.40	8.84	15	0.54	13.80	6.03
	42.0	0.108	0.996	2.31	0.86	1.63	10.87	2.31	25.33	12	0.71	12.48	17.17
	49.0*	0.1164	1.99	2.47	1.57	2.36	7.43	1.91	23.81	7	1.67	1.67	9.08
Avicel/ STA-R$_x$ 1:1	0	0.1019	1.37	2.43	0.59	1.10	11.73	3.27	7.44	13	0.34	>120	
	19.6	0.104	0.985	2.49	1.69	1.48	9.62	3.26	7.42	2	0.45	4.38	9.87
	32.6	0.108	2.12	2.54	1.86	1.77	14.04	2.35	10.32	4	0.75	2.44	20.16
	42.0*	0.119	1.08	2.70	1.29	3.20	8.66	1.90	16.52	0	1.66	1.54	24.76
	49.0*	0.1184	1.513	2.64	0.997	3.84	6.47	1.90	6.55	0	2.40	1.40	6.23

Table 3: Stability characters of oxytetracycline hydrochloride in oxytetracycline hydrochloride tablets after shelf storage.

Name	*Vahicle Actual conc.% W/W*	*Initial conc.%*	*Storage Time in weeks*	*Final conc.%*	*K Values X10^{-4}*
Avicel	49.0	100.32		90.90	19.0
	42.0	95.10		88.00	15.0
	32.6	98.00	52	86.30	24.0
	19.6	103.25		98.17	9.7
	0.0	101.37		98.30	6.0
Celutab	49.0	105.22		97.70	15.0
	42.0	99.24		91.81	16.0
	32.6	95.61	49	81.80	31.0
	19.6	98.41		95.45	6.2
	0.0	98.21		97.60	1.3
STA-RX 1500	49.0	100.81		96.21	11.0
	42.0	99.91		96.31	8.3
	32.6	96.86	44	93.10	9.0
	19.6	98.15		96.30	4.3
	0.0	94.83		93.18	4.0
Emcompress	49.0	98.11		75.00	49.0
	42.0	101.32		74.00	45.0
	32.6	96.16	46	52.50	110.0
	19.6	101.16		90.00	25.2
	0.0	101.32		96.00	12.00
Avicel/ Celutab 1:1	49.0	97.15		93.10	7.6
	42.0	92.35		79.50	27.0
	32.6	98.11	56	79.50	38.0
	19.6	95.12		88.36	13.0
	0.0	103		100.00	5.6
STA-RX/ celutab 1:1	49.0	91.23		81.81	46.0
	42.0	96.15		88.60	15.0
	32.6	98.22	55	97.7	6.7
	19.6	104.31		100.00	7.7
	0.0	101.20		100.00	2.2
Celutab/ Emcompress 1:1	49.0	95.25	53	72.10	51.00
Avicel / Emcompress 1:1	49.0	93.13	53	70.40	52.00
Emcompress/ STA-RX 1500 1:1	49.0	94.23	53	78.12	35.00

Table 4: Stability characters of directly compressed diiodoquin tablets prepared using STA-RX1500 starch and its blends and of that prepared by wet granulation, after shelf storage.

Name	*Vehicle Actual conc.% w/w*	*Initial conc.%*	*Storage Time in weeks*	*Final conc.%*	*K Values X10^{-3}*
	49.0	98.36		90.02	2.17
STA-R-X	42.0	96.40		92.12	1.26
1500	32.6	93.89	48	91.11	1.11
	19.6	92.00		87.85	0.96
	0	90.31		88.00	0.73
	49.0	99.54		93.56	1.72
STA-R-X	42.0	46.63		89.89	1.83
/	32.6	91.44	48	86.12	1.67
Avicel	19.6	90.36		85.89	1.41
1:1	0	90.12		85.50	1.49
STA-RX	49.0	95.02		93.36	0.41
/	42.0	96.08	48	95.00	0.27
Celutab	32.6	----	--	----	----
1:1	19.6	----	--	----	----
	0	----	--	----	----
STA-RX	49.0	99.99		87.09	2.88
/	42.0	98.68		85.97	2.87
Celutab	32.6	96.90	48	85.51	2.60
3:1	19.6	95.91		86.96	2.38
	0	93.93		86.21	2.04

Table 4 Cont:

Formula No.	*Weight (g) Mean*	*C.V.%*	*Thickness Mean*	*C.V.%*	*Hardness (Kg) Mean*	*C.V.%*	*Friability (loss%) Mean*	*C.V.%*	*Initial Conc.%*	*Final Conc.%*	*K x 10^{-3}*
1	0.801	12.16	3.40	11.15	5.10	9.02	0.15	11.81	104.22	91.00	2.82
2	0.820	13.15	2.91	16.21	6.11	9.15	0.11	12.15	105.52	89.23	3.49
3	0.811	12.21	2.88	10.91	8.22	19.13	1.11	10.86	107.11	93.14	3.91
4	0.815	15.16	2.98	21.91	8.12	19.15	0.52	92.15	104.53	89.01	3.35
5	0.816	13.16	3.03	18.12	7.91	10.11	0.88	33.15	101.98	88.00	3.07

* Storage time was 48 weeks.

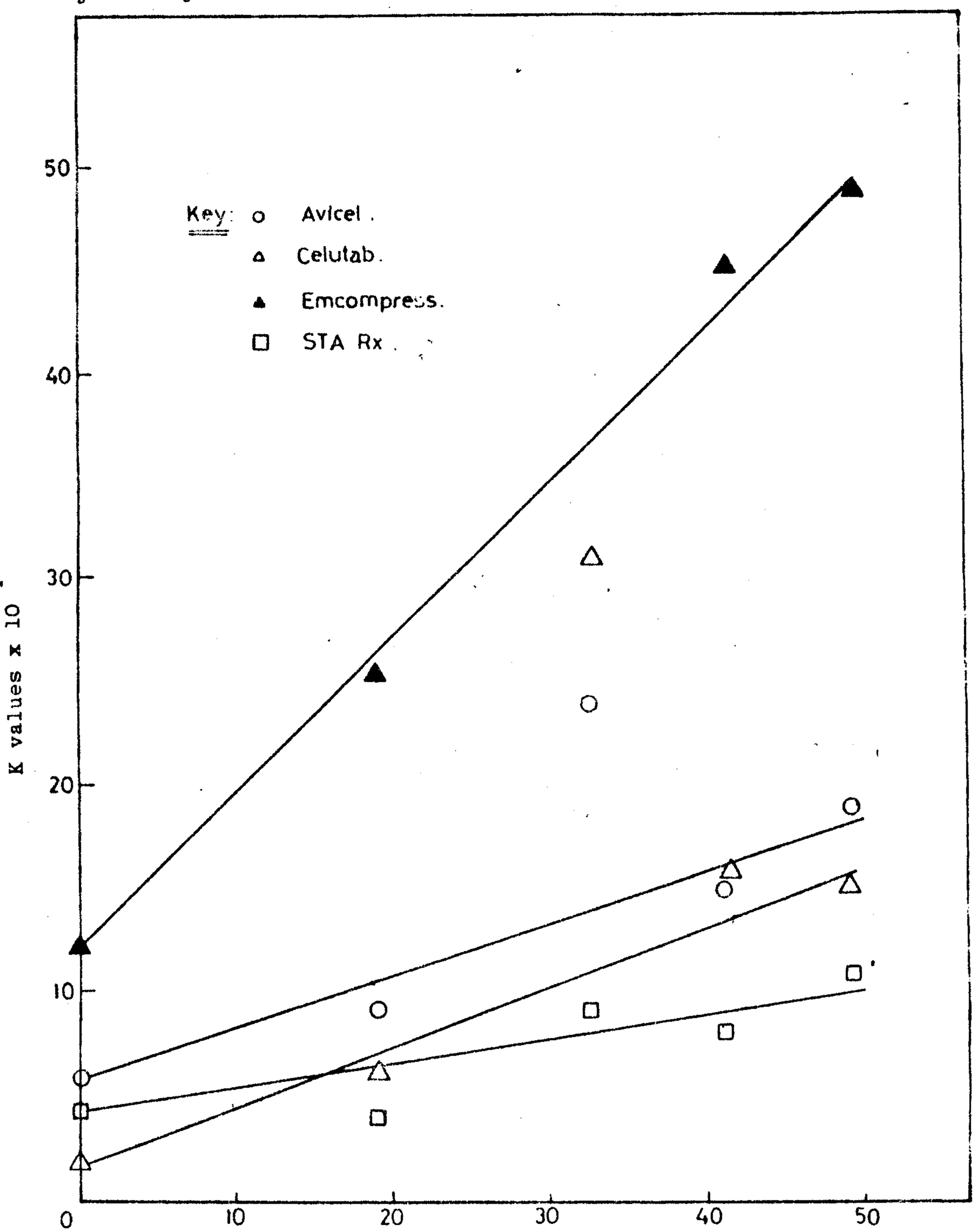

Fig. 1: Effect of vehicles concentration on K values of oxytetracycline hydrochloride .

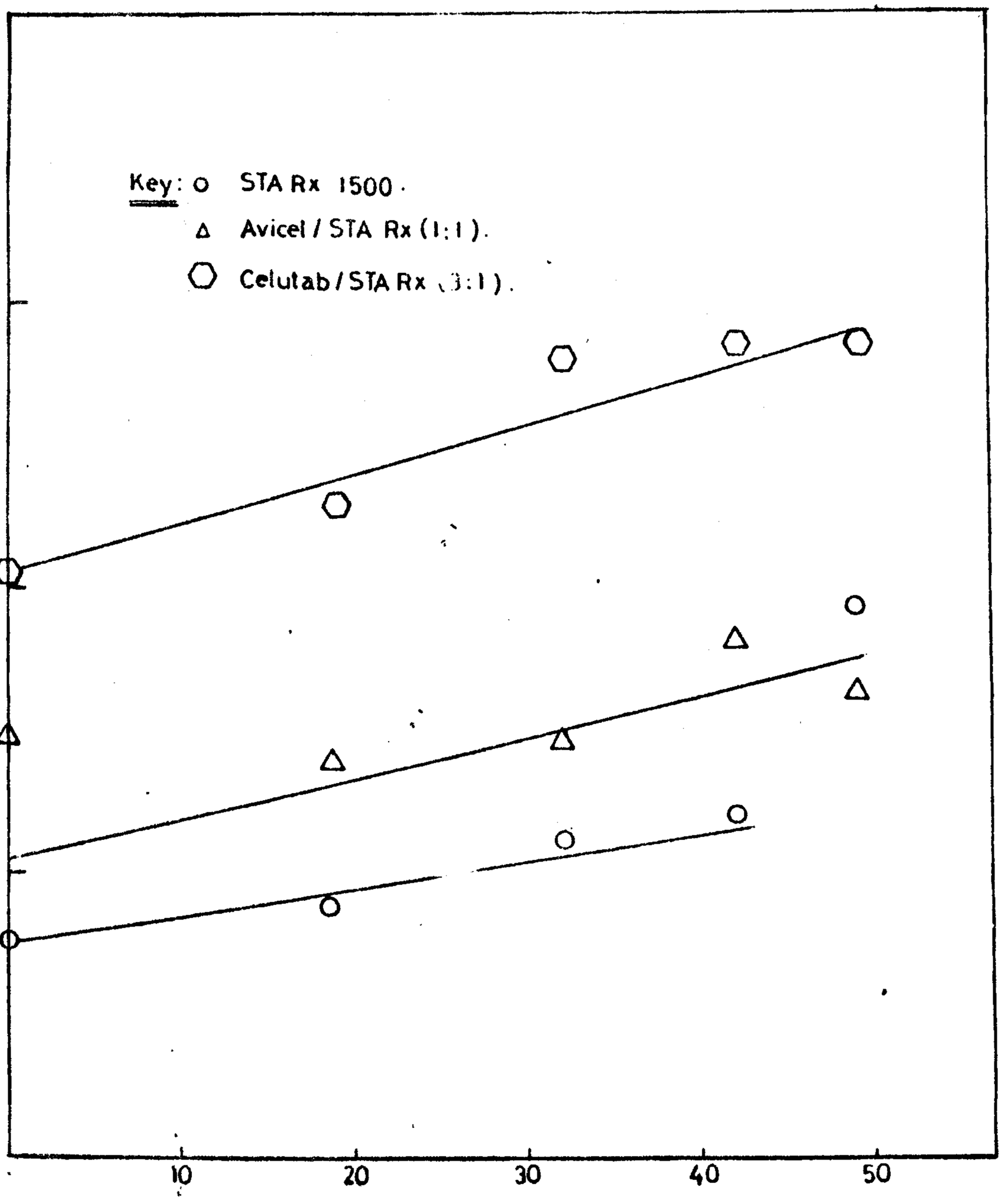

Fig. 2: Effect of direct compression vehicles and their blends on the reaction rate constant of diiodoquin

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دراسة على ثبات اقراص الاوكس تتراسيكلين هيدروكلورايد والداى ايودكيين المحضرة بطريقة الكبس المباشر والتحبب الرطب

احمد السيد ابو طالب - صلاح توت
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تمت دراسة ثبات كل من اقراص الاوكس تتراسيكلين والداى ايودوكين المحضرة بطريقة الكبس المباشر . ولقد اجريت مقارنة بين اقراص الداى ايودوكين المحضرة بطريقة الكبس المباشر وتلك التى حضرت بطريقة التحبب الرطب . ولقد عين نصف الحياه لكل مستعملا فى ذلك حساب معدل التفاعل . ولقد خزنت الاقراص فى زجاجات عنبرية اللون لفترات مختلفة - ولقد وجد ان الاقراص المحضرة بطريقة الكبس المباشر اكثر ثباتا من تلك التى حضرت بطريقة التحبب الرطب .

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