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Preparation and Evaluation of Directly Compressed Medazepam Hydrochloride Tablets.

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Summary

Medazepam, the well known benzodiazepine derivative used as a transquillizer and in alcohol withdrawal, was prepared in directly compressed tablets. The directly compressible vehicles which were used singly or in binary blends 1:1, were Avicel, Lactose, STA-R_x 1500 Emcompress and the recently introduced vehicle compactrol. It was found that Avicel and Emcompress represent the most suitable single vehicles used for the preparation of Medazepam hydrochloride tablets. In case of binary blends it was found that the best quality batches were prepared using Avicel : Emcompress blend 1:1. Physical characteristics including uniformity of weight, thickness, hardness, friability were investigated for the prepared batches. The effect of directly compressible vehicle variation on the uniformity of drug content and the dissolution rates of Medazepam hydrochloride tablets was also studied.

Introduction

Medazepam, used in treatment of anxiety, tension, and alcoholism, is manufactured in the form of capsules (F. Hoffman-La Roche, Basle Switzerland). The present work aimed to prepare directly compressed Medazepam hydrochloride tablets.

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The direct compression technique offers several advantages over the traditional wet granulation methods. These include reduced costs, improved product stability and increased product reliability[1]. 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 compressible excipients with medicaments are very essential in formulation to select the most suitable vehicle or mixed vehicles for each drug.

In this project directly compressed Medazepam hydrochloride 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; in order to evaluate the direct compression as a technique for preparing Medazepam hydrochloride tablets. The dissolution rate of the prepated tablets was also investigated in order to study the effect of various vehicles on the availability of Medazepam from the prepared tablets.[2]

Experimental

Materials :

Medazepam hydrochloride. [1] Dibasic calcium phosphate dihydrate (Emcompress) [2], calcium sulphate dihydrate (Compactrol) [2], Microcrystalline cellulose (Avicel pH 101)[3], STA-R_x 1500 Starch [4] and Lactose [5] were used as directly

1-Hoffman-La Roche & Co. Ltd. Basle, Switzerland.
2-Edward Mendell Co., Carmel, New York U.S.A.
3-F.M.C. Corporation, New York Delware
4-Staley MFG Co. Deeantr, Illinois U.S.A.
5-U.S.P. Shiffield Chemical Union, NL, 07033 U.S.A.

compressible vehicles. Magnesium stearate and stearic acid[1] were used as lubricating agents.

Equipments:

Korsch single punch eccentric tablet machine[2], Erweka hardness tester[2], Erwerka friabilator, Disintegration apparatus[2], cubic mixer[2], U.S.P. dissolution apparatus[3], micrometer[4], and SP6 -400 spectrophotometer[5] were the equipments used.

Procedures :

Medazepam hydrochloride 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 last mentioned directly compressible vehicles were used singly or in blends 1:1 ratio for the preparation of the desired tablets. Different batches of Medazepam hydrochloride directly compressible tablets were prepared, each containing 2.5% w/w) Medazepam hydrochloride, 2% w/w magnesium stearate and stearic acid, 95.5% w/w of each vehicle.[3-9] The powder ingredients were blended in a cubic mixer for 15 minutes at 50 r.m.p. . 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.

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1 - Chemical Industrial Development, CID. Co., Egypt.
2 - Berlin, Western Germany.
3 - Erweka apparatebou, Heusentamm.
4 - Bat & Co. Ltd., Sussex, England.
5 - Pye Unicam, England.

Evaluation of Tablets :

(a) Physical standards :

All the manufactured tablets were evaluated for uniformity of weight (B.P. 1980), uniformity of thickness, hardness, friability and disintegration time according to the previously published procedures.[3-9]

(b) Uniformity of drug content :

Ten tablets from each batch were individually assayed for its drug content . The absorbance was read at 254 nm using 1 cm cell. The mean drug content, the standard deviation and c.v % are given in Tables 1&2.

(c) Dissolution Rate :

The dissolution rate was determined in 500 ml of 0.1 N hydrochloric acid equilibrated at 37 $\pm$ 0.5^{o}C, stirred at 100 r.p.m. Samples were withdrawn every 5 minutes over 15 minutes, then every 15 minutes over total dissolution time of 120 minutes. Fresh dissolution medium were added in each time to substitute the withdrawn samples. Samples were analyzed according to the procedures of McGinity & Hill . The drug contents were assayed spectrophotometrically at 254 nm using 1 cm cell. Data obtained were shown in Figs. 1-3.

Results and Discussion

Uniformity of weight and thickness :

All the manufactured tablets fullfilled the requirements of the B.P. 1980 for weight uniformity

Table (1): Physical Properties of Medazepam hydrochloride Tablets prepared by single directly compressible vehicles.

Vehicle	Weight(g)(1)			Thickness(1) (mm)			Hardness(2) (kg)			Friability(3) % loss	H.F.R	D.T. (minutes)			(4) $T_{50\%}$ (min)	Drug content(2) (mg)		
	$\bar{X}$	S.D.	C.V.%	$\bar{X}$	S.D.	C.V.%	$\bar{X}$	S.D.	C.V.%			$\bar{X}$	S.D.	C.V.%		$\bar{X}$	S.D.%	C.V.%
STA-R_x1500	0.1988	0.004	2.06	3.27	0.12	3.74	Immeasurable			23.4	0	1.96	0.18	9.60	4	4.5	0.66	15.5
Avicel	0.2014	0.003	1.45	3.87	0.028	0.72	3.77	0.46	12.4	0.38	9.92	1.75	0.15	9.03	3	4.98	0.48	8.71
Emcompress	0.1975	0.004	2.25	2.086	0.027	1.33	2.85	0.86	30.19	0.63	4.52	>120	-	-	60	4.5	0.67	12.0
Lactose	0.1977	0.006	3.04	2.87	0.07	2.54	1.08	0.25	23.19	13.90	0.078	6.16	0.75	12.2	15	5.93	0.73	12.4
Compactrol	0.1941	0.007	4.00	2.94	0.064	2.18	1.08	0,26	24.90	2.21	0.48	>120	-	-	30	5.84	0.57	9.84

(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.

(4) Time of 50% release, mean of 3 determinations.

Table (2): Physical properties of Medazepam hydrochloride tablets prepared by binary blends of directly compressible vehicles.

Vehicle	Weight (g)(1)			Thickness (mm)(1)			Hardness (kg)(2)			Friability % loss(3)	H.F.R	D.T. (minutes)			(4) $T_{50\%}$ (min)	Drug content (mg)(2)		
	$\bar{X}$	S.D.	C.V.%	$\bar{X}$	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	0.2026	0.004	2.20	3.54	0.014	0.40	3.725	0.50	13.50	0.80	4.65	0.56	0.102	18.27	2	5.4	0.72	13.48
Avicel-lactose	0.2019	0.005	2.75	3.12	0.026	0.84	4.775	0.59	12.35	0.30	15.92	0.54	0.102	18.8	5	6.78	1.03	15.19
Avicel:Emcompress	0.1980	0.003	1.70	2.69	0.017	0.66	3.66	0.42	11.42	0.4	9.15	0.83	0.13	15.55	4	5.13	0.40	7.86
Avicel:compactrol	0.1967	0.005	2.88	2.61	0.033	1.30	2.45	0.37	15.12	0.75	3.26	0.96	0.40	20.72	5	5.50	0.69	12.23
Lactose:Emcompress	0.2040	0.006	3.01	2.52	0.057	2.28	3.35	0.69	20.6	2.64	1.26	32.33	2.25	6.96	30	5.89	1.13	19.15
Lactose:compactrol	0.1953	0.002	1.23	2.37	0.023	0.95	1.08	0.51	47.62	4.28	0.25	10.29	0.43	4.18	12	5.14	0.61	11.83
Lactose:STA-Rx	0.1966	0.004	1.89	2.98	0.045	1.53	3.14	0.49	15.85	0.40	7.85	4.25	0.27	6.44	5	5.25	1.01	19.24
STA-Rx-Emcompress	0.1962	0.004	2.02	2.62	0.048	1.83	2.33	0.51	22.03	0.77	3.03	0.99	0.14	14.43	2	5.25	0.38	7.42
STA-Rx:compactrol	0.1938	0.005	2.43	2.57	0.032	1.25	0.78	0.63	79.89	1.61	0.48	1.15	0.12	10.28	3	5.43	0.67	12.48
Emcompress: compactrol	0.1983	0.004	2.28	1.97	0.042	2.15	2.15	1.12	51.95	3.75	0.57	>120	-	-	60	5.89	0.64	10.82

(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.
(4) Time of 50% release, mean of 3 determinations.

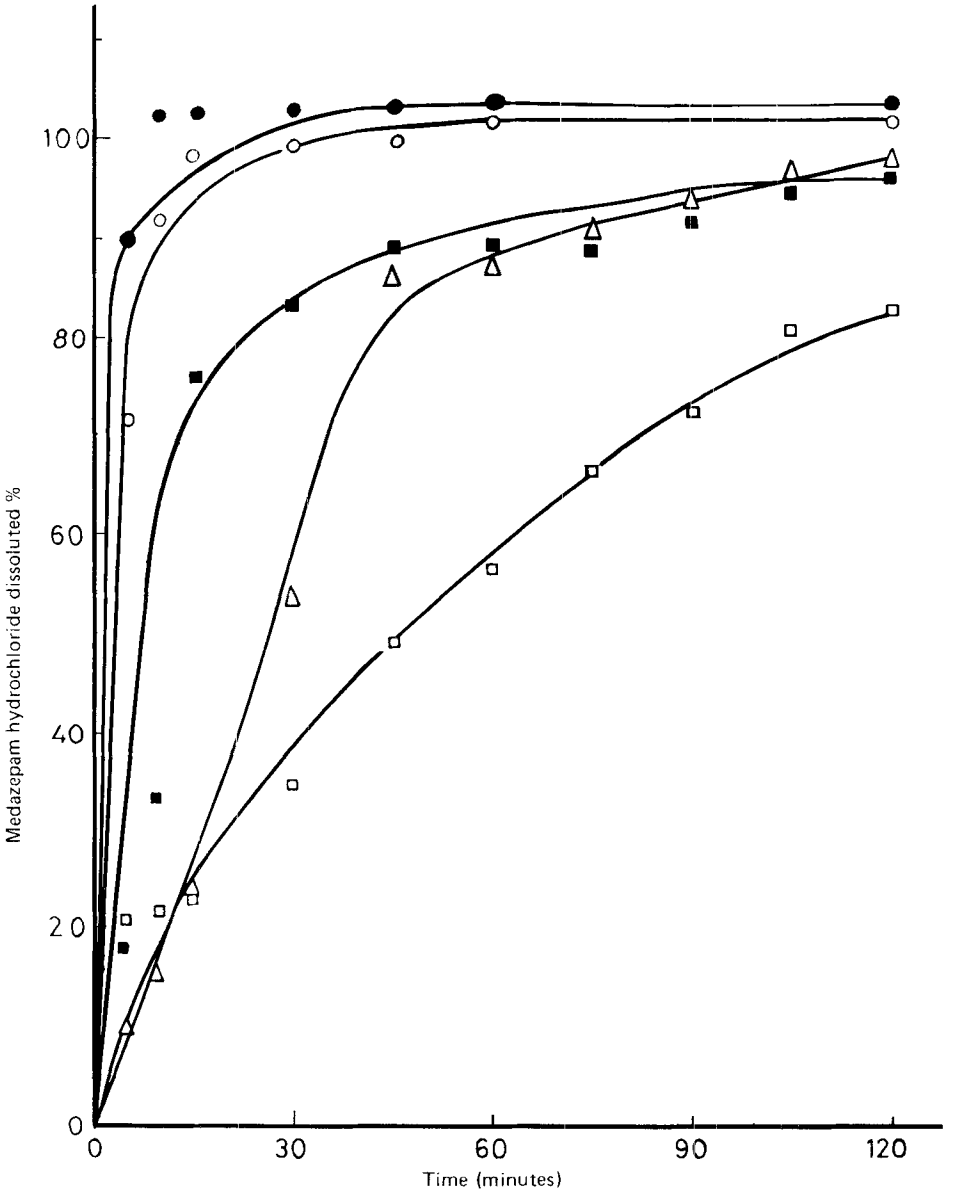

Fig.(1): Effect of single directly compressible vehicles on the dissolution of Medazepam hydrochloride tablets.

○ Avicel ● STA-Rx 1500
□ Emcompress ■ Lactose △ Compactrol

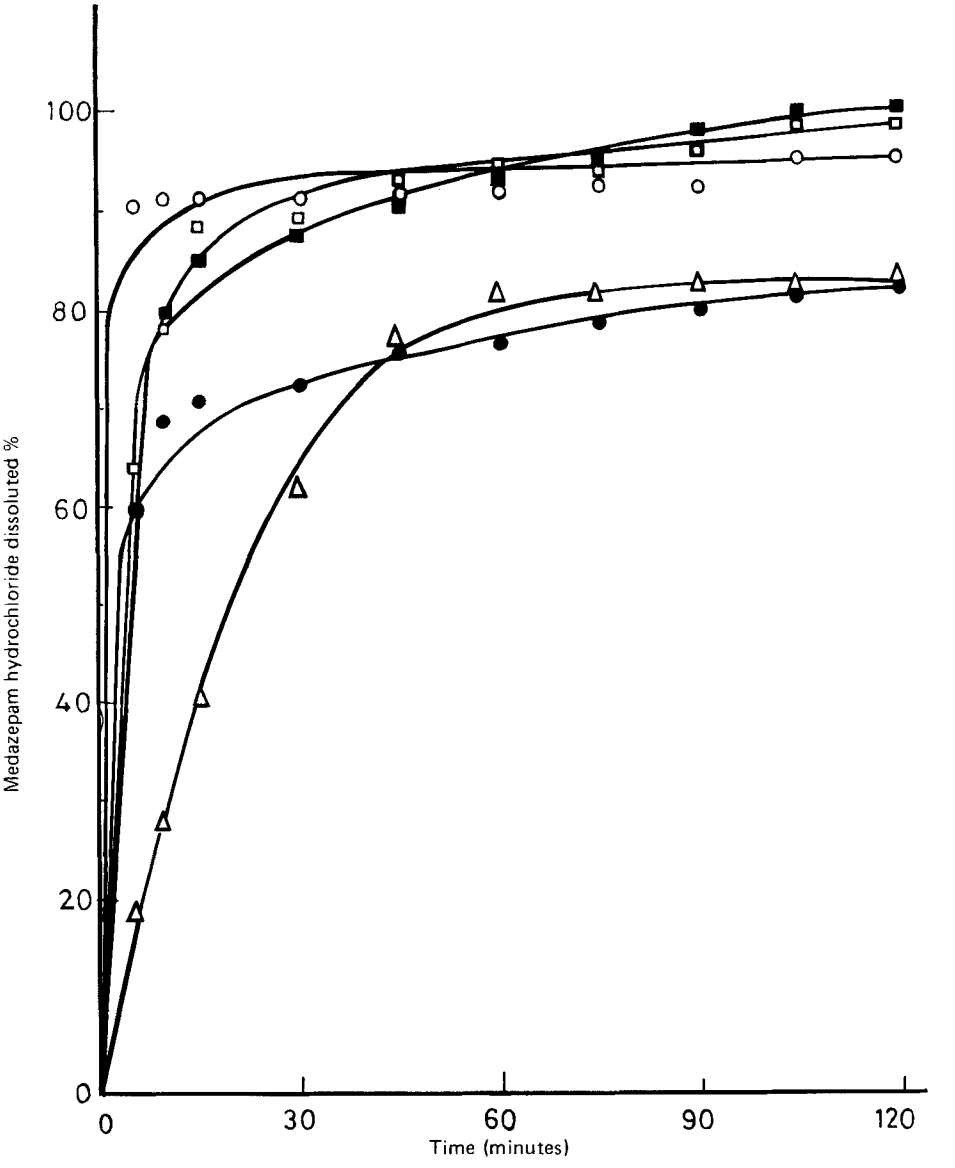

Fig.(2): Effect of blends of directly compressible vehicles on the dissolution of Medazepam hydrochloride tablets.

○ Avicel : STA-Rx ● Avicel:lactose

□ Avicel : Emcompress ■ Avicel: compactrol

△ Lactose : Emcompress

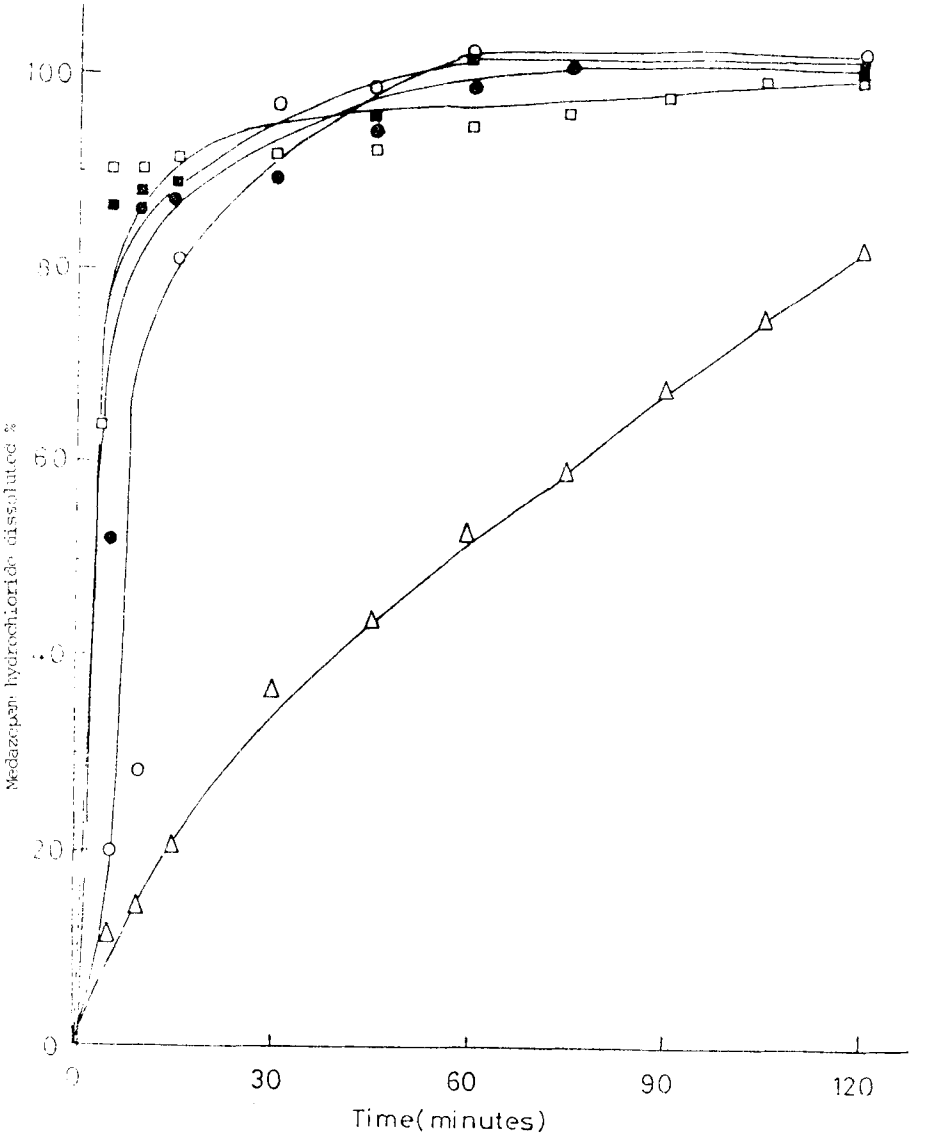

Fig.(3): Effect of blends of directly compressible vehicles on the dissolution of Medazepam hydrochloride tablets.

○Lactose : Compactrol ●lactose : STA-Rx

□STA-Rx : Emcompress ■STA-Rx: Compactrol

△Emcompress : Compactrol.

regardless of the type of the excipient. The physical characteristics of the batches produced using various single vehicles[10-13] and their blends are given in Tables 1 & 2. The excipients investigated can be arranged in a descending order regarding their capability of yielding weight and thickness uniform tablets as follows: Avicel > Emcompress > STA-R_x 1500 > Lactose > Compactrol. For their blends in 1:1 ratio they can be arranged as follows : Avicel : Emcompress > Lactose : Compactrol > Lactose : STA-R_x1500 > Emcompress : STA-R_x1500>Avicel: STA-R_x1500 > Encompress: compactrol > STA-R_x1500 : compactrol> Avicel : Lactose> Avicel : Compactrol> Lactose : Emcompress. The coefficient of variation, shown in Tables1 & 2 is considered as a measure for the last observed uniformity. The weight and thickness variation of the produced tablets are a function of the powders flowability.

Mechanical Properties :

The mechnical properties of the produced tablets were tested. The results are shown in Tables 1 & 2. From the obtained results, it is clear that Avicel produced the hardest tablets while STA-R_x1500 did the reverse, till the immeasurable extent. The friability results obtained, Table 1, confirmed those of the hardness; Avicel produced the lowest friability value for the tablets while STA-Rx produced the highest friability value.

In binary blends, Avicel: Encompress blend produced the highest hardness value and the lowest coefficient of variation percent value , whereas STA-R_x1500: compactrol blend produced the lowest hardness value and the highest coefficient of variation percent value.

The hardness values depend on the type of the excipient used. Thus the hardness of the produced tablets can be arranged as follows : Avicel > Emcompress > Lactose compactrol > STA-R_x-500, while for blends : Avicel: Emcompress> Avicel : Lactose> Avicel : STA-R_x1500 > Lactose : Emcompress> Lactose : STA-R_x1500> Avicel : Compactrol> STA-R_x1500 : Emcompress> Emcompress : Compactrol> Lactose : Compactrol > STR-R_x1500; Compactrol.

Friability values of the produced tablets also depend upon the type of excipient used. Thus we can arrange the friability values as follows : Avicel > Emcompress > Compactrol > Lactose > STA-R_x1500. While for mixed vehicles we have the following order : Avicel: Lactose > Avicel : Emcompress > Lactose : STA-R_x1500 > Avicel : Compactrol > STA-R_x : Emcompress > Avicel : STA-R_v1500 > STA-R_x1500: Compactrol > Lactose : Emcompress > Emcompress: Compactrol > Lactose : Compactrol. Comparison on the hardness-Friability ratio revealed that Avicel is superior to all other excipients investigated, as it improves the mechanical properties of Medazpam hydrochloride tablets as shown in Tables 1 & 2.

Disintegration Time :

Medazepam hydrochloride tablets prepared by Avicel, STA-R_x1500 and Lactose comply the B.P. 1980 disintegration test, the reverse is true for the tablets prepared by Emcompress and compactrol, as shown in Table 1. Tablets prepared by blend of vehicles comply the test for disintegration stated by the B.P. 1980 except the blends of Emcompress: Lactose and Emcompress: Compactrol produced tablets which did not comply the test, Table 2. The last findings revealed the role of Avicel and STA-R_x1500 in improving the disintegration time for Emcompress and compactrol, in blends, to be within 15 minutes. Such results may be explained on the basis that Avicel and STA-R_x1500, being starch in nature, act as disintegrants; this property being obvious at higher proportions.[14]

Uniformity of drug content :

The drug contents of Medazepam hydrochloride tablets prepared by various investigated directly compressible vehicles is shown in Tables 1 & 2. It was found that all the prepared batches were uniform in drug contents and passed the allowance of the B.P. 1980 in this respect, except those tablets prepared by lactose and compactrol in blend which deviated. This can be attributed to segregation which may occur during mixing and compression due to differences in particle size and bulk density as well as the angle of repose between the particles of Lactose and compactrol.

The obtained results indicated the possibility of producing directly compressed Medazepam hydrochloride tablets having reasonable uniformity of drug content. Hence upon choosing the suitable vehicles and adjusting the conditions of mixing, the difficulty of manufacturing tablets containing small doses of active medicaments by direct compression technique can be overcomed.

Dissolution behaviour :

The obtained dissolution data were treated diagramatically in Figs 1-3. The T_{50}% of the prepared Medazepam hydrochloride tablets were shown in Tables 1 & 2 . The Figures represent the plot of cummulative drug release percent or drug dissoluted percent against time in minutes. Dissolution results revealed that the dissolution rate is greatly affected by the type of the excipient incorporated within the tablets. This may be due to the decrease in the disintegration time of the produced tablets, perhaps due to absorption of excessive quantities of the dissolution fluid by the tablets, leading to faster breakdown of the tablet structure[15]. Tablets prepared by STA-R_x1500 and Avicel showed the highest dissolution rate among the obtained tablets with the smallest T_{50}% as shown in Tables 1 & 2 and Figs. 1-3. This may be due to the increased capillary which promots the penetration of the dissolution medium into the tablets.

Tablets prepared by Emcompress and compactrol exhibited low dissolution rates of dissolution among the

obtained tablets with the highest T_{50}% ; This may be due to the difficulty of the dissolution medium to pentrate into tablets.[15]

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