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FACTORS AFFECTING RATE OF DISSOLUTION OF PREDNISONE FROM TABLETS

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ABSTRACT

A study was carried out to evaluate some parameters which may have an effect on the dissolution rate of prednisone from tablets. The parameters examined involving formulation were: diluent proportion (Lactose-starch), dissintegrant type (starch, explotab (sodium starch glycolate) type of binder (starch paste, gelatine water solution and PVP alcoholic solution), lubricant, and dye concentration. The Manufacturing variables studied were: method of manufacture (wet granulation, direct compression and double compression), granule size in wet granulation and tablet hardness. dissolution profiles of tablets storaged 2 months at 45°C were compared with those of fresh samples. Tablets prepared with prednisone five years old, tablets with fresh active ingredient and tablets with two different prednisone concentrations (5 and 50 mg per tablet) were used for other evaluations.

In all cases micronized prednisone was used and all batches were physically and chemically evaluated before studying their dissolution following the USP basket method.

The parameters studied that affected significatively dissolution rate of prednisone were: type of binder, lubricant concentration,

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method of manufacture, active ingredient, age and prednisone concentration.

INTRODUCTION

A number of research articles have demonstrated that dissolution is an adequate test to evaluate in-vitro, the bioavailability of many relatively water insoluble drugs.

Prednisone tablets are one of the formulations in which dissolution test has been officialized. Prednisone is a synthetic glico-corticoid with antiinflamatory activity that has shown bioavailability differences among tablets manufactured by different companies (1,2,3,4). On account of this, in the present work prednisone tablets were selected to study the factors affecting their dissolution rate.

EXPERIMENTAL

The experimental work was divided in 3 stages:

-Manufacture of prednisone tablets using different formulations.
-Development of an adecuate analytical method to assay the prednisone in tablets.
-Determination of the percent dissolved of prednisone at different times and statistical evaluation of the differences.

Batches of thousand tablets each were prepared according to Table No. 1, parameters studied in each formula were the following:

Factors related to formulation

Formulas 1, 2, 3	(diluent proportion)
Formulas 1, 4, 5	(binder type)
Formulas 1 and 6	(disintegrant type)
Formulas 1, 7, 8, 9	(lubricant concentration)
Formulas 1 and 10	(dye concentration)

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TABLE NO. 1 Formulations for Prednisone tablets

Formulation	1	2	3	4	5	6	7	8	9	10	16	19
Ingredients:												
Prednisone mic.	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Corn Starch	32.00	83.50	6.40	32.00	34.00	25.60	32.00	32.00	32.00	32.00	----	32.00
Lactose USP	128.55	77.10	154.15	125.00	130.00	128.55	127.00	126.00	124.30	128.50	----	83.55
Magnesium stearate	0.85	0.85	0.85	0.85	0.85	0.85	1.70	3.40	5.10	0.85	2.00	0.85
PVP	3.60	3.60	3.60	----	----	3.60	3.60	3.60	3.60	3.60	----	3.60
Gelatine	----	----	----	6.80	----	----	----	----	----	----	----	----
Explotab	----	----	----	----	----	6.40	----	----	----	----	----	----
Green FD&C No. 3	----	----	----	----	----	----	----	----	----	0.05	----	----
Ahidrous lactose	----	----	----	----	----	----	----	----	----	----	103.00	----
Avicel pH 102	----	----	----	----	----	----	----	----	----	----	60.00	----
Total weigh	170.00	170.00	170.00	170.00	170.00	170.00	170.00	170.00	170.00	170.00	170.00	170.00

NOTE: Formulas 11, 12, 13, 14, 15, 16, 17 and 18 are the same as formula 1. Formulas 11 and 12 have different hardness. Formulas 13, 14 and 15 different granule size. Formulas 16 and 17 were prepared by direct compression and double compression. Formula 18 was prepared using prednisone 5 years old and tablets obtained in formula 1 were set at 45°C for two months.

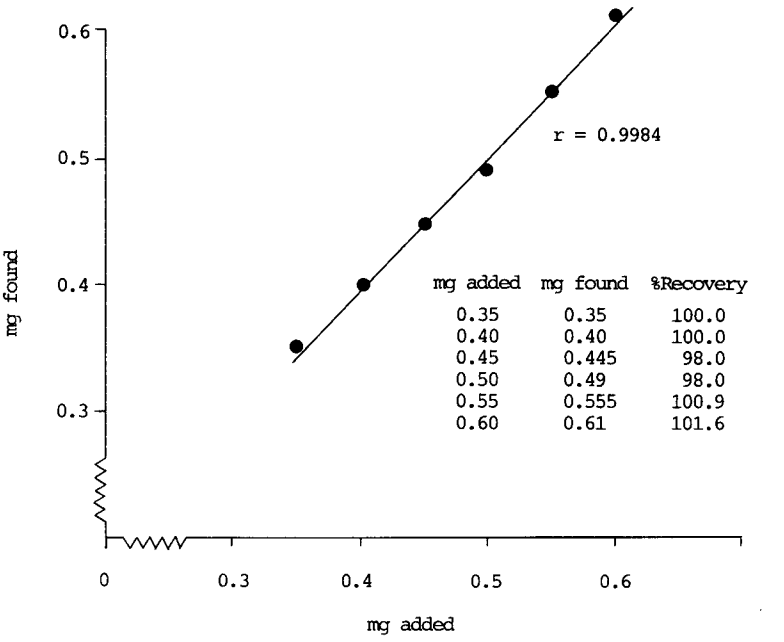

Figure No. 1 Linearity of the analytical method for Prednisone in tablets

Factors related to manufacturing variables

Formulas 1, 11, 12	(tablet hardness)
Formulas 1, 12, 14, 15	(granule size)
Formulas 1, 16, 17	(method of manufacture)

Factors related to the active ingredient

Formulas 1, 18	(age)
Formulas 1, 19	(concentration)

Factors related to storage conditions

Formula 1	(R.T. and 2 months 45°C)

Equipment

Erweka oscillating granulator equipped with stainless steel (304) # 8, 12, 16, 20, 30 and 60 mesh screen. Oven. Hobart mixer 5 Kg

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TABLE NO. 2 Precision and Accuracy for Prednisone in tablets assay
The table shows results obtained in experiments involving spiked placebos. The mean and standard deviation demonstrate the precision and accuracy of the method.

SAMPLE NO.	MG ADDED TO SPIKED PLACEBO	MG FOUND	% RECOVERY
1	0.45	0.44	97.8
2	0.45	0.44	97.8
3	0.45	0.44	97.8
4	0.45	0.44	97.8
5	0.45	0.44	97.8
6	0.45	0.45	100.0
7	0.45	0.45	100.0
8	0.45	0.46	102.0
9	0.50	0.51	102.0
10	0.50	0.48	96.0
11	0.50	0.49	98.0
12	0.50	0.49	98.0
13	0.50	0.48	96.0
14	0.50	0.50	100.0
15	0.50	0.48	96.0
16	0.50	0.48	96.0
17	0.55	0.55	100.0
18	0.55	0.56	101.8
19	0.55	0.54	98.2
20	0.55	0.56	101.8
21	0.55	0.55	100.0
22	0.55	0.56	101.8
23	0.55	0.56	101.8

Mean = 99.2%
Standard deviation = 2.17

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TABLE NO. 3 Hardness, disintegration time and friability for the 19 batches of prednisone tablets. (1) Average of 12 tablets. (2) Average of 10 tablets.

FORMULA	DISINTEGRATION TIME (1) (min)	HARDNESS (2) (UCS)	FRIABILITY (%)
1	3.25	8.54	0.42
2	3.00	6.52	0.33
3	2.75	6.36	0.20
4	6.00	6.90	0.06
5	0.50	7.77	0.14
6	2.75	9.44	0.00
7	2.50	8.15	0.17
8	4.42	6.91	0.72
9	6.00	6.80	0.53
10	3.00	6.76	0.54
11	2.00	4.79	0.26
12	2.92	11.24	0.52
13	3.08	6.96	0.43
14	2.50	6.89	0.90
15	2.42	6.39	0.17
16	6.00	5.79	0.82
17	9.00	8.11	0.46
18	6.50	7.08	0.24
19	4.17	7.97	0.12

capacity. Stokes F single punch tableting machine with flat 8 mm diameter punches.

MANUFACTURING PROCEDURE

Wet granulation

Formulas 1, 2, 3, 4, 5, 6, 7, 8, 9, 18, 19 and 20. Sieve diluents through # 20 mesh screen, blend with prednisone in the Hobart mixer. Add slowly the binder solution and blend for 5 minutes. Granulate through # 8 mesh screen and dry at 50°C to a loss on drying of less than 3%. Pass the dryed granulated material through # 16 mesh screen. Blend the granulate with the disinte-

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TABLE NO. 4 Results of Dissolution from tablets

Factors related to formulation

Formula	% Dissolved * 5'	10'	20'	40'	t_{80} (min.)	DE (%)
Diluent proportion effect						
1	85.5 ± 3.3	91.2 ± 4.4	90.3 ± 4	91.4 ± 3.6	0.29	84.2
2	76.3 ± 4.4	96.5 ± 4.1	99.2 ± 4.1	94.4 ± 4.3	2.83	88.45
3	77.7 ± 6.6	90.0 ± 4.7	94.1 ± 3.3	93.4 ± 1.9	2.92	85.25
Binder type effect						
1	85.5 ± 3.3	91.2 ± 4.4	90.3 ± 4	91.4 ± 3.6	0.29	84.2
4	46.1 ± 4.6	59.3 ± 4.7	85.3 ± 5.1	88.1 ± 4.2	22.60	70.9
5	75.0 ± 4.1	84.2 ± 2.8	85.4 ± 2.1	85.4 ± 4.2	8.50	78.5
Disintegrant type effect						
1	85.5 ± 3.3	91.2 ± 4.4	90.3 ± 4	91.4 ± 3.6	0.29	84.2
6	86.1 ± 4.4	94.1 ± 2.5	93.8 ± 1.4	94.7 ± 2.9	0.40	87.3
Lubricant concentration effect						
1	85.5 ± 3.3	91.2 ± 4.4	90.3 ± 4	91.4 ± 3.6	0.29	84.2
7	72.1 ± 5.3	86.9 ± 4.8	90.2 ± 4.1	94.8 ± 1.7	5.93	82.8
8	46.1 ± 2.2	65.8 ± 4.2	87.3 ± 4.7	93.1 ± 3.1	16.73	74.1
9	25.4 ± 5.5	53.7 ± 7.6	76.4 ± 6.7	86.9 ± 4.2	24.98	63.6
Dye concentration effect						
1	85.5 ± 3.3	91.2 ± 4.4	90.3 ± 4	91.4 ± 3.6	0.29	84.2
10	81.45± 2.25	85.4 ± 2.1	85.2 ± 2.1	86.4 ± 2	0.55	79.85

t_{80} (5) time for dissolving 80% of the drug
DE (6) dissolution efficiency

* $(\bar{X} \pm CI_{95\%})$ 6 tablets average

grant (previously sieved through through # 20 mesh screen) and the lubricant (previously sieved through # 60 mesh screen). Compress using 8 mm diameter flat punches to a weight of 170 mg ± 2% and 7 to 9 USC hardness.

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TABLE NO. 5 Results of Dissolution from tablets

Factors related to Active Ingredient

Formula	% Dissolved * 5'	10'	20'	40'	t_{80} (min.)	DE (%)
Active ingredient age effect						
1	85.5 ± 3.3	91.2 ± 4.4	90.3 ± 4	91.4 ± 3.6	0.29	84.2
18	46.6 ± 3.9	68 ± 3.6	81.2 ± 2.0	83.4 ± 2.1	23.84	69.9
Active ingredient concentration effect						
1	85.5 ± 3.3	91.2 ± 4.4	90.3 ± 4	91.4 ± 3.6	0.29	84.2
19	61.8 ± 3.9	71.3 ± 2.3	76.8 ± 1.8	78.9 ± 1.7	30.94	69.6

* ($\bar{X}$ ± CI_{95}%) 6 tablets average

TABLE NO. 6 Results of Dissolution from tablets

Factors related to manufacturing variables

Formula	% Dissolved * 5'	10'	20'	40'	t_{80} (min.)	DE (%)
Hardness effect						
1	85.5 ± 3.3	91.2 ± 4.4	90.3 ± 4	91.4 ± 3.6	0.29	82.4
11	78.3 ± 5.2	87.6 ± 4.3	88.9 ± 1.5	89.5 ± 2.2	3.35	81.7
12	82.3 ± 3.4	86.9 ± 2.6	90.9 ± 3.4	91.9 ± 2.6	2.18	83.6
Granule size effect						
1	85.5 ± 3.3	91.2 ± 4.4	90.3 ± 4	91.4 ± 3.6	0.29	84.2
13	83.0 ± 1.9	92.5 ± 2.8	91.7 ± 2.2	92.8 ± 2.4	0.67	85.3
14	90.1 ± 4.2	94.7 ± 4.3	94.2 ± 4.2	89.2 ± 2.7	0.48	86.6
15	88.0 ± 3.4	93.3 ± 2.3	92.7 ± 3.2	97.4 ± 3.1	0.06	87.6
Manufacturing procedure effect						
1	85.5 ± 3.3	91.2 ± 4.4	90.3 ± 4.0	91.4 ± 3.6	0.29	84.2
16	60.1 ± 0.9	68.6 ± 1.5	76.7 ± 1.1	81.2 ± 2.7	17.80	69.6
17	29.8 ± 9.2	50.9 ± 6.7	68.8 ± 2.3	77.7 ± 2.2	38.17	58.5

• ($\bar{X}$ CI_{95}%) 6 tablets average

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TABLE NO. 7 Factors related to storage conditions

Results of Dissolution from tablets

	% Dissolved *					
	5'	10'	20'	40'	t_{80} (min.)	DE (%)
Formula 1						
Storage conditions effect						
Initial	85.5 ± 3.3	91.2 ± 4.4	90.3 ± 4	91.4 ± 3.6	0.29	84.2
2 months	90.8 ± 1.7	93.6 ± 2.9	95 ± 1.9	97 ± 2.3	0.04	88.8

* $(\bar{X} \pm CI_{95}\%)$ 6 tablets average

Formula 10

Dissolve the dye in the binder solution and continue as above

Formula 11

Compress to a 4 to 6 USC hardness

Formula 12

Compress to a 10 to 12 USC hardness

Formula 13

Pass the dryed granulated material through # 12 mesh screen and mix only the powder retained in a # 16 mesh screen with the disintegrant and lubricant in the adequate proportion.

Formula 14

Sieve the dryed granulated material through # 16 mesh screen and use only the powder retained in a # 20 mesh screen.

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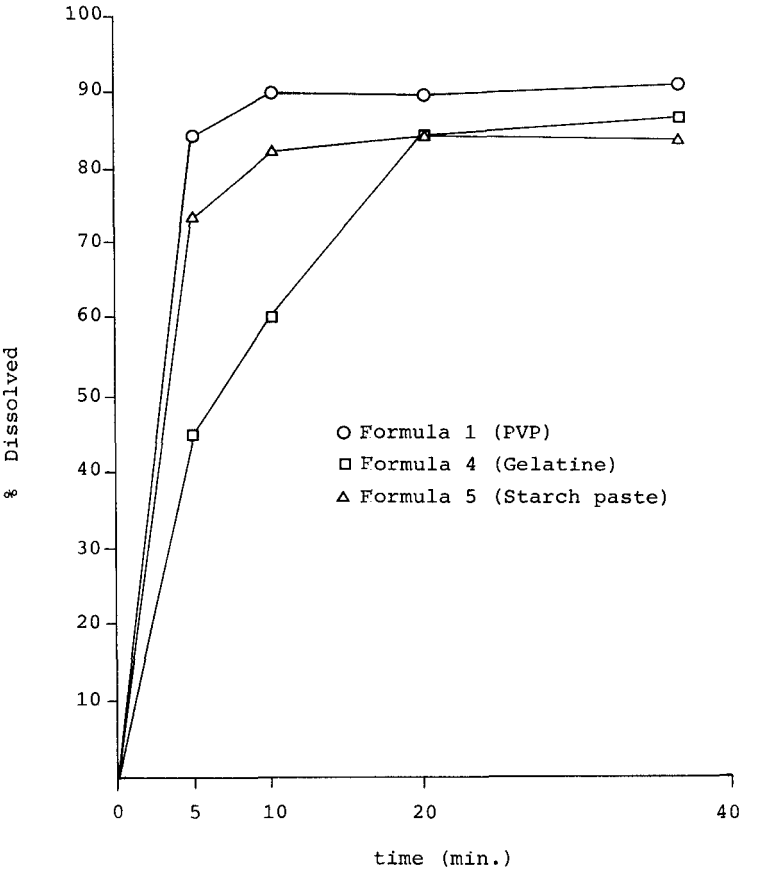

Figure No. 2 Effect of binder on dissolution

Formula 15

Sieve the dryed granulated material through # 20 mesh screen and use only the powder retained in a # 30 mesh screen.

Formula 16 (Direct compression)

Sieve all ingredients through # 20 mesh screen, add prednisone and blend. Pass lubricant throug a # 60 mesh screen before blending.

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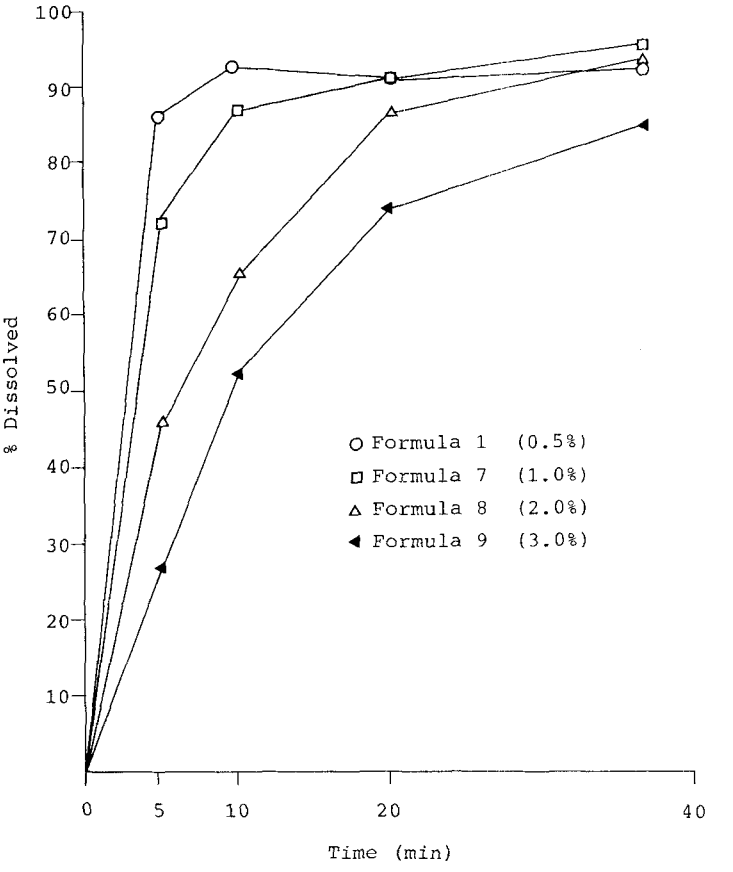

Figure No. 3 Effect of lubricant concentration on dissolution

Formula 17 (Double compression)

Triturated the tablets obtained from direct compression through a # 16 mesh screen and recompress.

ANALYTICAL METHOD FOR THE ASSAY OF PREDNISONE IN TABLETS

Equipment and reagents

Spectrophotometer, TLC equipment, Ethanol: Chloroform 50:50 solvent

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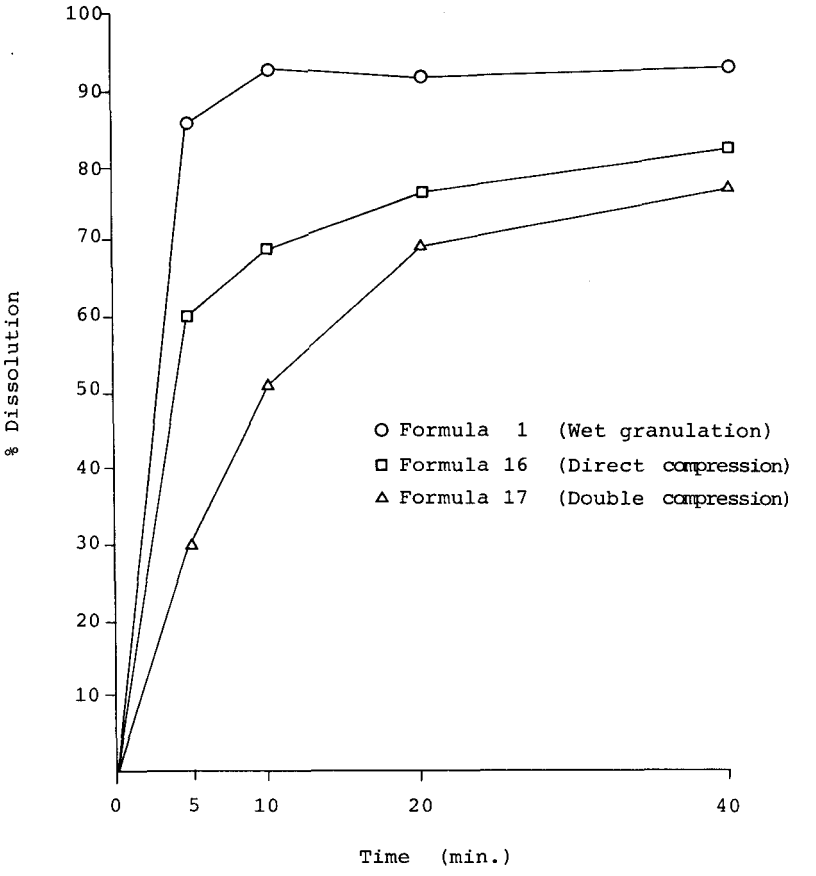

Figure No. 4 Effect of Manufacturing procedure in dissolution

system: Chloroform: Acetone: Ethanol 65:30:5 solution. Prednisone standard solution: 0.5 mg/ml in 50:50 Ethanol: Chloroform Solution.

Procedure

Weight and triturate 10 tablets. Transfer the powder quantitatively to a 10 ml volumetric flask. Dissolve the prednisone in 50:50 ethanol: Chloroform solution using an ultrasonic bath. Apply 100 mcl of this solution to the TLC plate. Develop the plate in the

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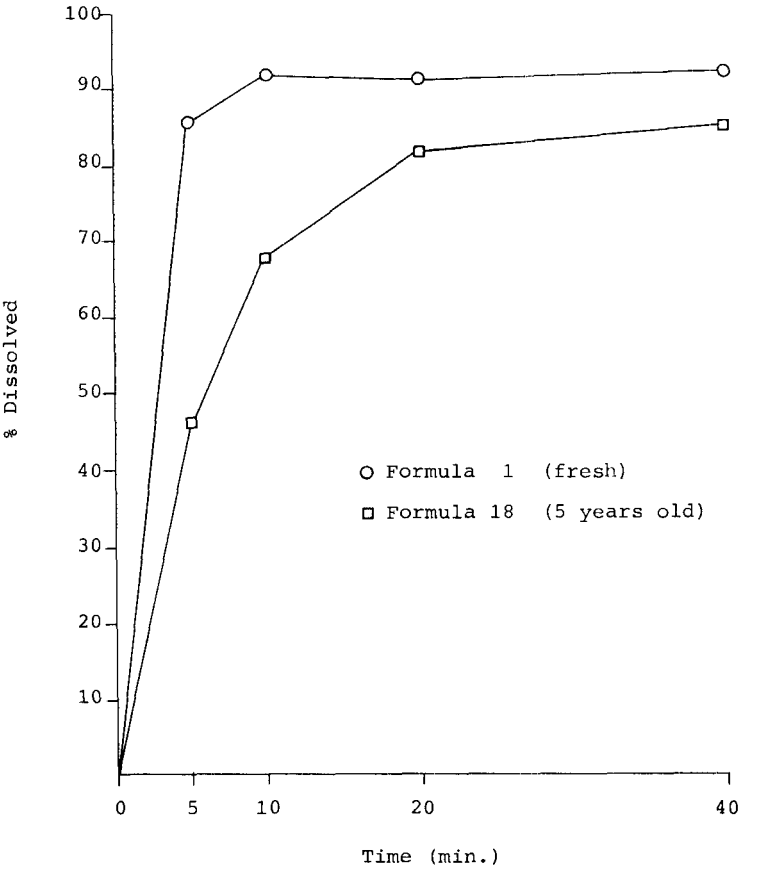

Figure No. 5 Effect of Active Ingredient age in dissolution

chromatographic camera using Chloroform: Acetone: Ethanol 65:30:5 as solvent system and mark the spots in a dark cabinet under a 254 nm UV source. Elute the silica gel with methanol, centrifugate the tubes and measured the prednisone concentration by the ratio of the absorbances of the unknown and the standard sample.

Validation of this method is shown on figures 1 and table No. 2.

Dissolution method

USP basket method was used sampling at 5, 10, 20 and 40 minutes.

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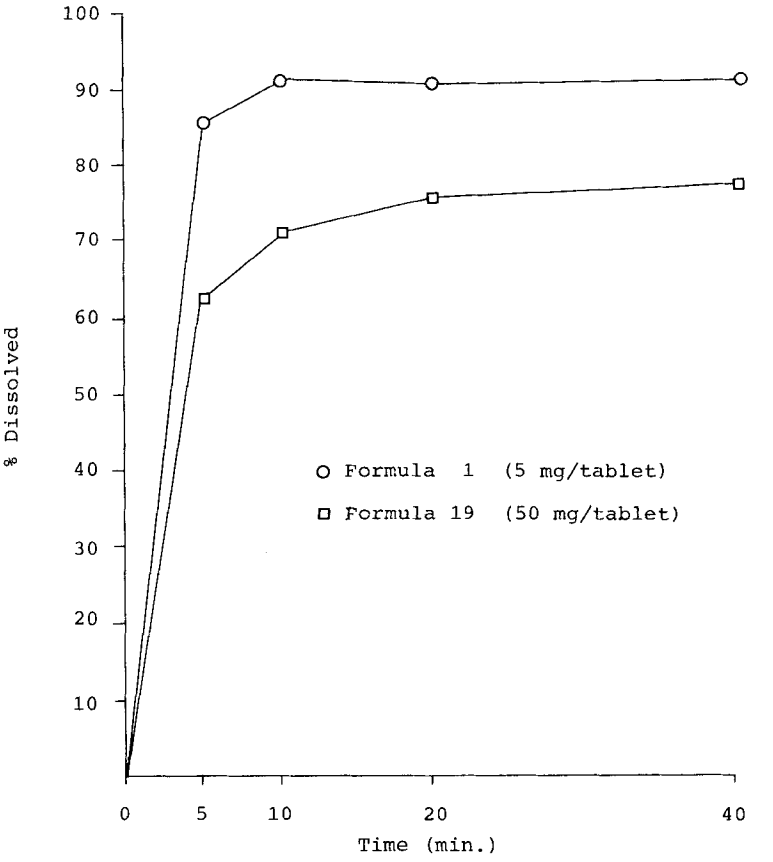

Figure No. 6 Effect of amount of Prednisone in dissolution

Disintegration test: USP XX/NFXV
Hardness test: Schleuniger ZE 110 6 apparatus
Friability: Roche 302165 apparatus

RESULTS AND DISCUSSION

The content uniformity for the different batches was between 96% to 104%.

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The physical constants of the tablets are shown in Table No. 3. Dissolution data can be found in Tables Nos. 4, 5, 6 and 7. Figures 2, 3, 4, 5 and 6 correspond to factors that significantly affected the dissolution rates of the prednisone. Tablets containing PVP show higher dissolution rate than those containing starch paste and gelatine solution. Tablets containing magnessium stearate in concentration above 1% have slower dissolution rate of prednisone. Tablets manufacture by wet granulation had better dissolution profiles than those manufactured by direct compression and by double compression. Dissolution rate was lower in tablets manufactured with five-years-old prednisone. In figure 6 it may be seen that increasing the prednisone concentration to 50 mg per tablet, the dissolution rate is diminished although not as much as could be expected.

Factors such as: diluent proportions, disintegrant type, dye concentration, hardness, granule size and storage conditions did not affect the dissolution rate of prednisone in the tablets tested in this study.

CONCLUSION:

It is suggested that the data presented in this work indicate in a general way the points where we should direct our efforts when we formulate tablets containing a steroid with physical properties similar to Prednisone.

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