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EVALUATION OF TABLETED CINNARIZINE-MICROCRYSTALLINE CELLULOSE GROUND MIXTURE

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ABSTRACT

Fast release cinnarizine (CN) tablets were prepared by the direct compression of CN-microcrytalline cellulose (1:3) ground mixture. Directly compressed tablets containing either untreated CN or ground CN were also prepared for comparison. Avicel PH 101 was used as the direct compression excipient in each case. The produced tablets were evaluated with regard to their dissolution characteristics, their drug content uniformity and their physical properties including uniformity of weight, hardness, friability and disintegration time. Tablets compressed containing CN-microcrystalline cellulose ground mixture showed good physical properties, better drug content uniformity and superior dissolution characteristics compared to the tablets containing untreated or ground alone CN.

INTRODUCTION

Cinnarizine [1-(diphenylmethyl) - 4-(3-phenyl-2-propenyl) -piperazine] has enjoyed extraordinary popularity for a number of years in the treatment of cerebral and peripheral disorders of the blood circulation and distribution as well as acting as a labyrinthine sedative[1]. This drug is expected to have a dissolution rate limited absorption because of its poor aqueous solubility. Moreover, it has been already reported that the dissolution rate of cinnarizine (CN) differs among commercially available pharmaceutical preparations[2]. This bacame a matter of interest for some authors[2-4] who applied different techniques for solving this problem.

Unfortunately, the literature gives nothing about presenting the modified CN into pharmaceutical dosage forms. In a previous work[5], we found that co-grinding of CN with microcrystalline cellulose (Avicel PH 101) represents an easy and efficient technique for enhancing the dissolution characteristics of this drug. Advantages and mechanisms of such technique have been discussed in detail. The present work deals with the preparation and evaluation of tablets containing CN-Avicel ground mixture.

EXPERIMENTAL

Materials

-Cinnarizine (Advanced Biochemical Industries, Cairo, Egypt).

-Microcrystalline Cellulose, Avicel PH 101 (FMC Corporation, U.S.A.).

-Magnesium stearate (Prolabo, France).

-All other chemicals and solvents used were of analytical grade.

Equipment

-Set of sieves (T G 10, 4188 VEB Metallweberei, Neustadt - Oralla, Germany) and an electric shaker (EML, Labor, Germany).

-Cubic mixer (Erweka Apparatabau, Germany).

-Coffee mill (Radar, type 299.210, France).

-Erweka TBT hardness tester (Erweka Apparatabau).

-Erweka TAB friabilator (Erweka Apparatabau).

-Disintegration test apparatus (Erweka Apparatabau).

-U S P dissolution apparatus 2 (Erwaka Apparatabau).

-Manesty F3 single punch tablet machine (Manesty, England).

-Spectrophotometer (Uvedic 320, Japan).

Methods

-Particle size distribution of CN and Avicel PH 101

The average particle size and the particle size distribution of CN and Avicel were investigated using sieve analysis according to the method described by Bolhuis and Lerk[6].

-Preparation of CN-Avicel ground mixtures

Mixtures of CN-Avicel (1:1, 1:2 and 1:3 W/W) were ground for 5 minutes in the mentioned mill. On the other hand, CN alone was similarly ground. All the ground samples were passed through a 80μ sieve. Random samples from the ground mixtures were spectrophotometrically tested for their CN content.

-Preparation of CN tablets

The formula under test, containing 1% of magnesium stearate, was mixed in the cubic mixer for 10 minutes at 25 r.p.m. Tablets, containing 25 mg of CN were directly compressed using a Manesty F3 single punch tablet machine equipped with 8mm flat punches. Batches, 100 tablets each, were prepared. Avicel PH 101 was used as an excipient in the proportion suitable to give tablets having nearly 4 Kg hardness (Erweka). Accordingly, the average tablet weight was different among the different formulae.

-Evaluation of the prepared tablets

The prepared tablets were evaluated with regard to uniformity of weight, hardness, friability, disintegration time, dissolution profile and drug content uniformity.

Uniformity of weight

Uniformity of weight of tablets was examined according to the U S P XX on 20 randomly taken tablets.

Hardness

Hardness of 10 tablets of each batch was determined using an Erweka hardness tester. The mean hardness (crushing strength) was calculated.

Friability

Loss percentage of preweighed 20 tablets of each batch was deduced after revolving at 25 r.p.m. during 5 minutes. The test was repeated 3 times and the mean loss percentage was calculated.

Disintegration time

The time required for the disintegration of the different batches was determined according to the procedure of the U S P XX.

Dissolution rate

The dissolution rate studies were carried out on tablets of untreated CN, CN ground alone and CN-Avicel ground mixtures. The U S P apparatus equipped with baskets which were rotating at 100 r.p.m. in PH (0.1 N HCl) and in pH 4 (Sorensen's citrate buffer) was used. Temperature was kept at 37°C. One tablet (25 mg CN) was introduced in each of the six baskets. Samples were withdrawn at suitable time intervals by the aid of pipettes with

filter tips. The withdrawn samples were replaced by equal volumes of the dissolution medium. Samples were spectrophotometrically assayed for CN at 252 nm.

Drug content

Ten randomly taken tablets were individually assayed for their content of CN. Tablets were quantitatively dissolved in 0.1 N HCl and spectrophotometrically assayed at 252 nm.

RESULTS AND DISCUSSION

Table 1 summarizes the physical characteristics and the CN content of the produced tablets. All batches showed good weight uniformity with coefficient of variation less than 6% with the exception of those prepared from untreated or ground alone CN. This indicates that the co-grinding technique resulted in a more uniform distribution of the mixed ingredients and led to minimization of the effects of the difference in particle size distribution as shown in Fig. 1. This was also confirmed by the individual assay of the prepared tablets which revealed an excellent CN content uniformity. This reflected that even and efficient mixing of the ingredients was achieved upon co-grinding. Since mixing problems are usually encountered during formulating low dose drugs, the results obtained is of real value.

All batches showed hardness of about 4 Kg (Erweka) except for tablets prepared from CN, ground alone and passed through 80 μ sieve. This may be due to the increased proportion of fines in this case.

All the produced tablets showed low friability values (loss %) even less than 1%.

All the batches showed a fast disintegration time; tablets compressed containing CN in the form of ground mixture (1:3 with Avicel) showed a very fast disintegration time even less than one minute.

All the studied batches showed mean drug content about 91% with a good content uniformity indicated by the low values of the calculated coefficient of variation percentage.

Fig. 2 shows the dissolution profiles for the prepared tablets in 0.1 N HCl. Generally, tablets containing CN-Avicel ground mixture exhibited faster dissolution rate than those containing the untreated drug. This effect could be more easily demonstrated by comparing the values of the relative dissolution rates (RDR) summarized in Table II. RDR is the ratio of the amount of the drug dissolved from the test sample (tablets prepared from ground mixtures) divided by the amount dissolved from tablets containing the untreated drug. Due to the high solubility of CN, a weak base of a pka 7.47[8], in 0.1 N HCl, it seems difficult to descriminate between the CN-Avicel ground mixture tablets based on the ratios of CN:Avicel. Moreover, it could be observed that all the tested tablets, with the exception of those containing untreated CN, showed relatively fast dissolution in 0.1 HCl, releasing more than 60% of its CN content in less than 20 minutes. This seems problemless especially in case of normal young persons. On the other hand, CN is usually prescribed to aged patients who often have a relatively low level of hydrochloric acid in the gastric juice and the pH of their stomach may reach the value 4[1]. Hence, the enhanced dissolution of this drug in higher pH value is very important. Accordingly, it seems reasonable to investigate the release rate of CN tablets in solutions of pH 4. At this pH, tablets prepared containing CN-Avicel ground mixture showed a fast dissolution

rate up to 6 folds higher than those containing the untreated CN as shown in Table II and Fig. 3.

Further look to Table II, it could be observed that, the higher the amount of Avicel ground with CN, the faster the release rate of the drug from the tablets. It is worth mentioning in this respect that although the 1:5 (CN-Avicel) ground mixture showed the fastest release characteristics in our previous study[5], yet its direct compression into tablets is technically difficult due to the higher proportion of excipients required and hence the excessive weight of the produced tablets. The reasons behind the superiority of the dissoultion characteristics of the tablets prepared from CN-Avicel ground mixture over those of the untreated CN may be due to the presence of the drug in a more energetic and less crystalline form in the ground mixtures and so dissolves faster. Other reasons and mechanisms were discussed in detail in our previous article[5]. This is in accordance with Nakai[7] explanation who reported that the dissolution machanism of the ground mixtures is different from that of crystals where drug molecules dissolve from the crystal surface according to concentration gradient.

On the other hand, when particles of the ground mixtures are put in water, water can rapidly penetrate and loose the cellulose net work structure in which the drug molecules are enclosed. This asssumption is true in our case once the tablet disintegrates.

It should be emphasized that grinding of CN alone(≠80μ) followed by mixing with Avicel produced tablets of lower release than those produced from CN-Avicel ground mixtures in the same proportions (Fig. 2 and 3). This confirms that the reduction in the particle size of CN is not the main cause behind the achieved dissolution enhancement upon cogrinding of CN and Avicel.

CONCLUSION

From the results obtained, it could be concluded that co-grinding of CN-microcrystalline cellulose is a suitable technique for the production of fast release CN tablets utilizing the simple and economic, tableting technique, direct compression. Such dosage forms could be administered to aged patient having low hydrochloric acid in the gastric juice as well as for normal patients.

Table I: The physical characteristics and drug content of cinnarizine tablets.

Formula CN : Avicel	Weight mean (g)	c.v.%	Hardness (Kg)	Friability (loss %)	Disintegration time (minutes)	Drug content mean%	C.V.%
untreated	0.1005	10.6	3.85	0.54	2.75	91.8	1.34
ground alone	0.1006	8.0	2.40	0.60	2.88	91.1	2.44
1 : 1 ground mix.	0.1091	1.2	3.75	0.65	3.25	90.7	3.26
1 : 2 ground mix.	0.2060	3.7	4.50	0.40	2.75	91.6	1.93
1 : 3 ground mix.	0.1969	1.8	3.80	0.80	0.79	90.1	2.30

*Each tablet contains 25 mg cinnarizine.

Table II: Relative dissolution rate (RDR) for CN-Tableted Preparation at pH 1 and 4.*

Tableted formulae	pH 1			pH 4		
	RDR	(mimutes)		RDR	(mimutes)	
	10	30	60	10	30	60
CN, untreated	1.0	1.0	1.0	1.0	1.0	1.0
CN, ground alone	1.6	1.2	1.0	1.9	2.1	2.1
CN : Avicel, 1:1, ground mixture	1.4	1.2	1.0	2.8	2.9	2.3
CN : Avicel, 1:2, ground mixture	1.7	1.3	1.1	3.9	3.5	2.7
CN : Avicel, 1:3, ground mixture	2.4	1.4	1.1	6.0	4.2	2.7

* Relative to CN, untreated.

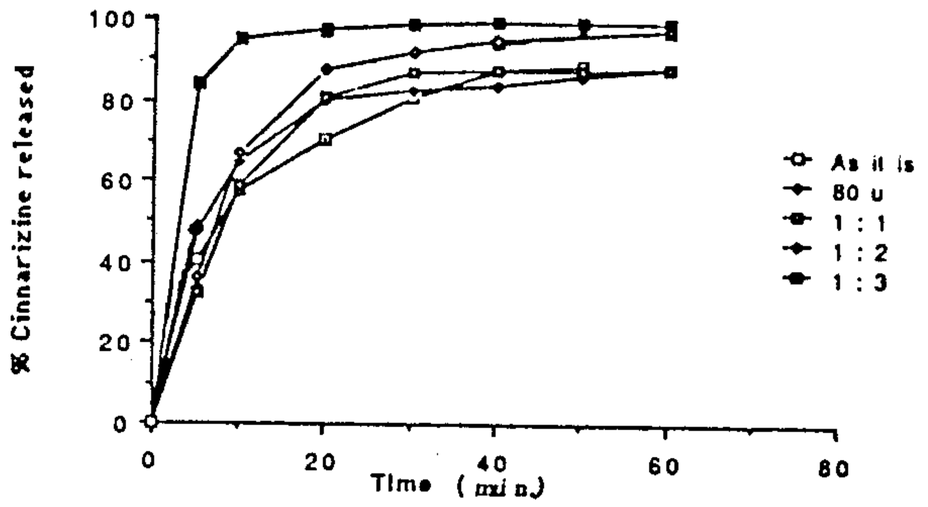

Fig. 2: Dissolution profiles of cinnarizine tablets in 0.1 N HCl.

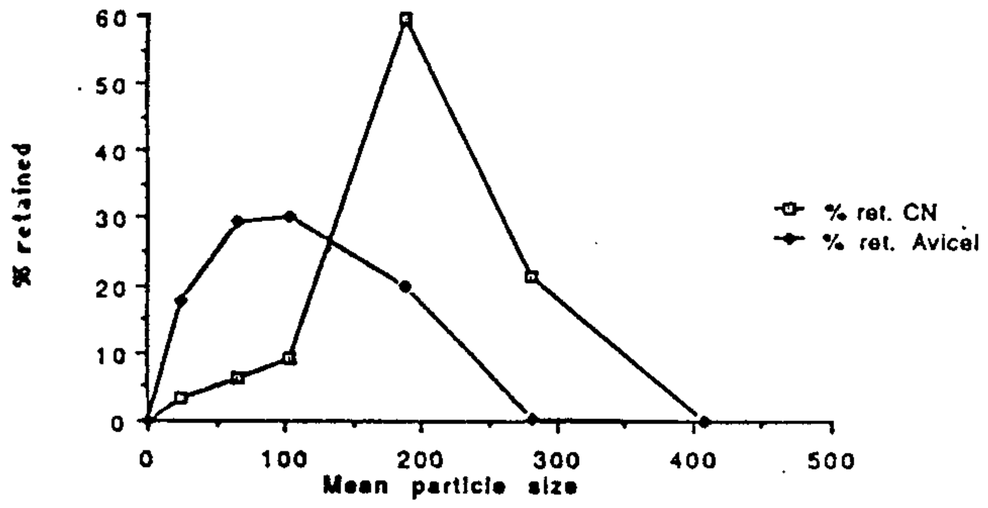

Fig. 1: Particle size distribution of cinnarizine and Avicel.

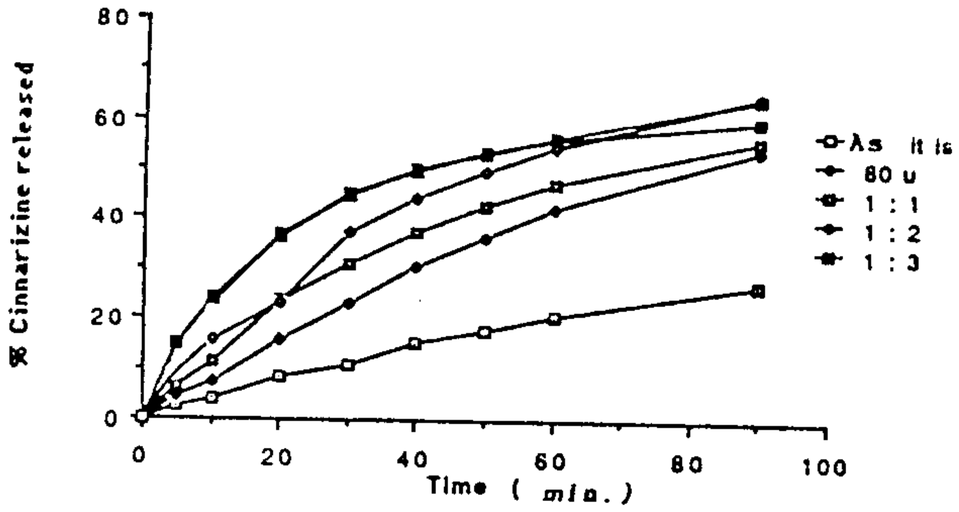

Fig. 3: Dissolution profiles of cinnarizine tablets in buffer solution pH 4.

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تقويم أقراص مطحون السيناريزين مع ميكروكريستالين السليولوز

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تم فى هذا البحث تحضير اقراص مطحون السيناريزين مع ميكروكريستالين السليولوز بنسبة ٣:١ وذلك بطريقة الكبس المباشر ، كذلك تم بنفس الطريقة كبس اقراص تحتوى أما السيناريزين غير المعامل أو السيناريزين المطحون بمفرده للمقارنة. وقد استخدم ميكروكريستالين السليولوز كصواغ فى جميع الحالات. وقد تم تقويم الاقراص المحضرة من حيث صفات الاتاحة ، المحتوى الدوائى وكذلك الصفات الطبيعية التى تشمل انتظام الوزن ودرجة الصلابة ودرجة الهشوشه وكذلك زمن التفتت.

وقد أظهرت الاقراص التى تحتوى على مخلوط السيناريزين مع ميكروكريستالين السليولوز بنسبة ٣:١ تفوقا من حيث محتواها الدوائى وصفات الاتاحة مقارنة بالاقراص التى تحتوى على السيناريزين غير المعامل او الاخرى التى تحتوى على السيناريزين المطحون بمفرده.

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