Zagazig J. Pharm. Sci., December 1997
Vol. 6 , No. 2 , pp. 70-74.

ISSN 1110-5089

STABILITY OF DIRECTLY COMPRESSED FLUCONAZOLE TABLETS PREPARED BY SUPER DISINTEGRANTS

Mohamed Salama and Hanaa A. El-Ghamry*
Deptaretment of Pharmaceutics, Faculty of Pharmacy ,Zagazig University
Zagazig - Egypt.

ABSTRACT

Fluconazole as drug is used for the treatment of fungal infections, prepared as directly compressed tablets using super disintegrant cross-linked PVP (Polyplasidone XL) alone and in combination with different concentrations of cross-linked carboxymethyl cellulose (Ac-Di-Sol). The prepared tablets were physically evaluated by subjecting to several tests , friability, hardness, disintegration time and dissolution rate. The chosen formulae with the best characteristics was stored at room temperature for one year and re-evaluated for its same characteristics. The results indicated that the tablets prepared with combination of 2.5% cross-linked CMCNa and 6% cross-linked PVP demonstrated good reproducible characteristics prior to and after storage.

INTRODUCTION

The term super disintegrants (Ac-Di-Sol) and (Polyplasidone XL) was described by many investigators interested in tablet formulation by direct compression technique[1]. The addition of disintegrants have been shown to improve the drug bioavailability[2]. The name super disintegrants came from the low concentration (2 to 4%) at which they are completely effective. Since, Ac-Di-Sol is the more efficient disintegrating agent, it is postulated that the rate, force and extent of swelling play an important role in those disintegrants that work by swelling. Crospovidone swells little, but returns to its original boundaries quickly after compression which aids its stability on storage[3-5]. Ac-Di-Sol as a super disintegrant gives superior functionality, rapid drug dissolution and improve drug bioavailability[6].

In this work fluconazole tablets were prepared using Polyplasidone XL at a fixed concentration of 6% alone and in combination with different concentrations of Ac-Di-Sol, and then their characteristics were evaluated.

MATERIALS AND METHODS

Materials:

Fluconazole, cross-linked PVP (Polyplasidone) and starch 1500 (Sta-Rix-1500) were donated by EPICO, 10th of Ramadan, Egypt. Microcrystalline cellulose (Avicel PH101), Croscarmillose sodium (Ac-Di-Sol) and Magnesium stearate were obtained from F.M.E. Corporation, New York, USA. Dibasic calcium phosphate (Emcompress) from Edwiard Mendell Co., New York, USA.

c) Stability of the proposed formulae:

The prepared batches were evaluated and the chosen formulae was subjected to stability testing by storing in tightly closed glass bottle and stored at room temperature for one year then was re-evaluated for certain physical parameters.

Apparatus:

The following equipment were used in the present study: Erweka single punch tablet machine (Germany), was used for tablet comperssion. Hardness was examined using Schleunger-4 M hardness tester (Switzerland). The disintegration, dissolution & friability apparatus used were from Pharma test corporation (Germany). The drug concentration entration was measured using spectrophotometer-UV 160 IPC, Shimadzu Corporation (Japan).

Preparation of Tablets:

Tablets were prepared by mixing the powder of each formulae then compressed into 10-mm diameter, round-flat tablets using Erweka single punch machine adjusted for each excipient to produce 220mg tablets.

Evaluation of the prepared tablets:

a) Physical standards:

All the manufactured tablets were evaluated for the uniformity of weight,hardness, friability and disintegration time.

b) Dissolution profiles:

Dissolution was carried out in 1000 ml 0.1 N HCl equilibrated at 37 ± 0.5°C, stirred at 100 rpm using paddle technique. The withdrawal time interval was arranged as follow: 5, 10, 15, 20, 30 and 45 minutes. The withdrawn samples were replaced with fresh dissolution medium, the withdrawn samples were filtered and measured by UV spectrophotometer at 261 nm. The data obtained are shown in Table 1 and Fig. 1.

RESULTS AND DISCUSSION

Physical evaluation of the prepared tablets (friability and hardness) showed excellent friability and hardness regardless to the increase of Ac-Di-Sol concentration but disintegration and dissolution was changed by the gradual increase of Ac-Di-Sol concentration as shown in table 2 and Fig. 1. These results were attributed to the efficacy of Ac-Di-Sol to increase the rate of dissolution with a smallest increase in its concentration. About 2.5% was found to be very effective to give rapid dissolution and smaller disintegration time [3-6]. It is obvious that Ac-Di-Sol have a good swelling property in the dissolution media 0.1 N HCl than any other super disintegrant[7].

Table (1): Formulation of Tables Using Cross Linked PVP alone and in Combination with Different Concentration of Cross-linked CMCNa.

Ingredients	formulae 1	formulae 2	formulae 3	formulae 4	formulae 5	formulae 6	formulae 7
Fluconazole (mg)	100	100	100	100	100	100	100
Microcrystalline cellulose (Avicel PH101 (mg)	59	52	51	50.5	50	50	50
Dibasic calcium phosphate (Emcompress) (mg)	59	52	51	50.5	50	50	50
Croscarmillose sodium (Ac-Di-Sol) (mg)	-	-	1.1	2.2.	3.3.	4.4.	5.5
Cross-linked PVP (mg)	-	13	13	13	13	13	13
Magnesium stearate (mg)	2	2		2	2	2	2

Table (2): Physical Characteristics for Fluconazole Formulations Containing Different Concentration of Ac-Di-Sol as a Dissolution Enhancer.

Disintegrant	Physical Characteristics				
	Friability* %	Hardness (Kg)	Uniformity# of weight (g)	Disintegration time (min.)	T50▲ (min.)
No Disintegrant	0.13	8.2±0.41	0.22±0.01	0.3	20
0% Ac-Di-Sol	0.17	7.9±0.52	0.219±0.02	7.1	15
0.5% Ac-Di-Sol	0.17	7.9±0.5	0.221±0.01	6.2	15
1% Ac-Di-Sol	0.12	8.1±0.49	0.22±0.02	5.6	15
1.5% Ac-Di-sol	0.19	7.8±0.51	0.218±0.01	4.8	10
2.5% Ac-Di-sol	0.19	8.2±0.61	0.219±0.02	4.3	10

* Carried out on 10 tablets 100r/4min.

Weight of each one of 10 tablets then the total weight of 10 divided on 10.

▲ Time required to release 50% of the drug.

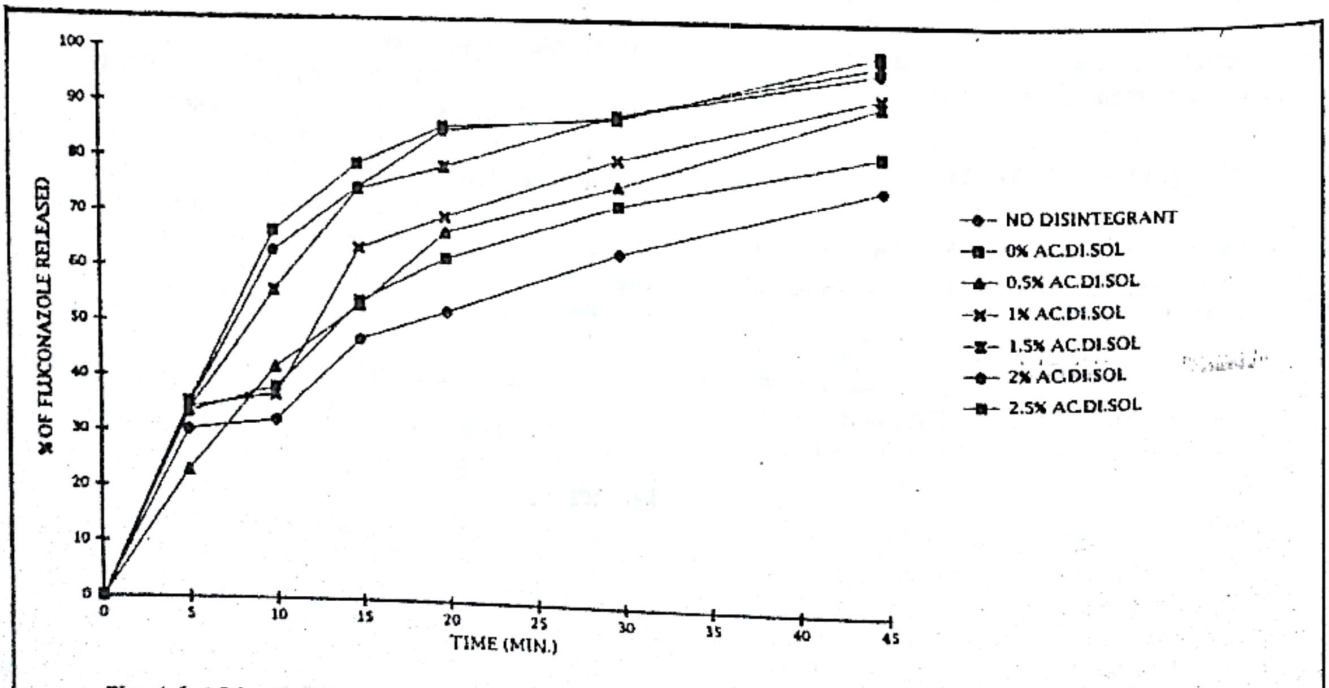

Fig. (1) Dissolution rate of 7 formulations of fluconazole tablets containing different concentrations of Cross-linked CMCNa with fixed conc., of Cross-linked PVP

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The chosen formulae with the best characteristics was the final one with 6% cross-linked PVP and 2.5% Ac-Di-Sol.It was stored at room temperature, and all characteristics were re-evaluated after storage. It was found to be stable and showed no significant difference in all characteristics before and after storage (table 3, 4 and Fig. 2). These results indicate that the drug has good shelf life stability and the two disintegrants used were stable.

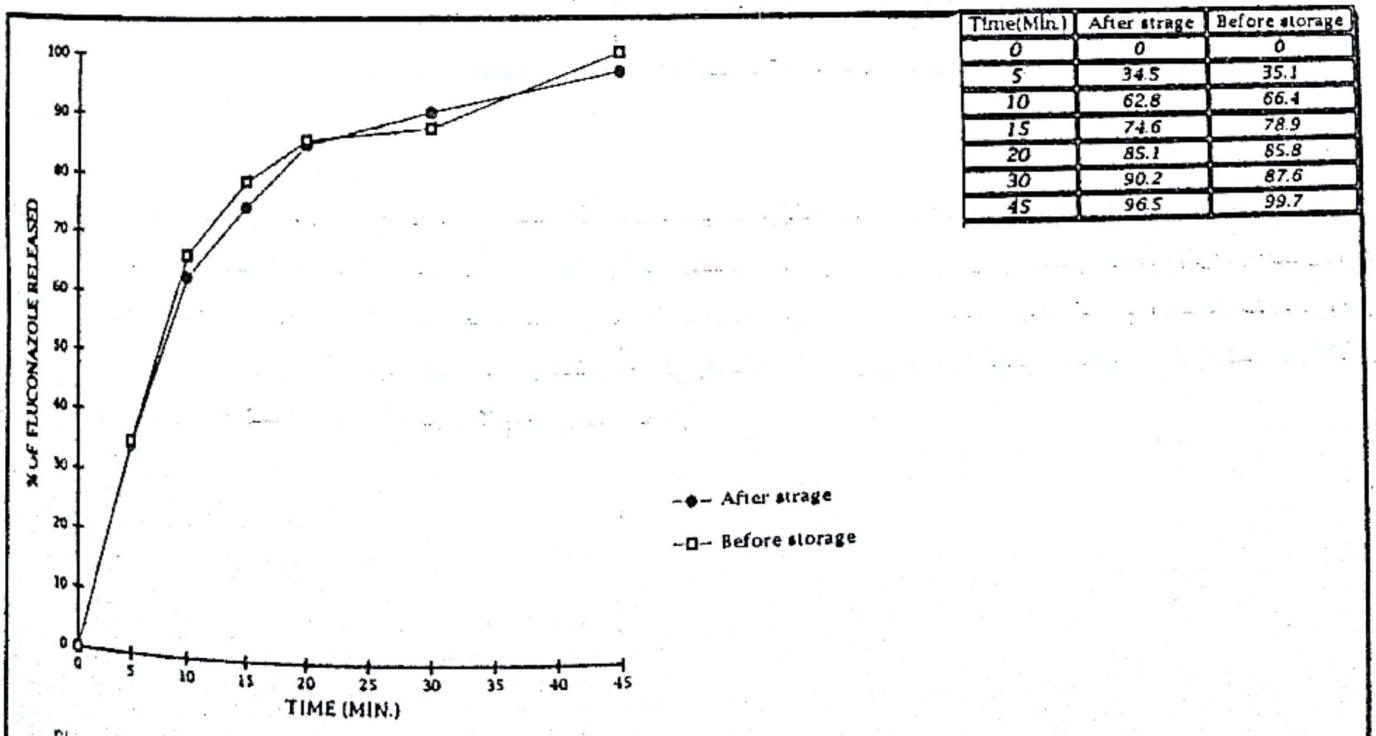
Table (3): Physical characteristics of the best fluconazole tablet formulae after one year storage at room temperature.

Disintegrant	Physical Characteristics				
	Friability* %	Hardness (Kg)	Uniformity# of weight (g)	Disintegration time (min.)	T50▲ (min.)
2.5% Ac-Di-Sol	0.22	7.9±0.56	0.22±0.02	4.1	10

* Carried out on 10 tablets 100r / 4min.
# Weight of each one of 10 tablets then the total weight of 10 divided on 10.
▲ Time required to 50% drug release.

Table (4): The Effect of Gradual Increase of Cross-Linked CMCNa (Ac-Di-Sol)., at a Fixed Concerntration of Cross-Linked PVP on the Release Rate of Fluconazole Tablets.

Time (Min.)	No Disintegrant	0% Ac-Di-Sol	0.5% Ac-Di-Sol	1% Ac-Di-Sol	1.5% Ac-Di-Sol	2% Ac-Di-Sol	2.5% Ac-Di-Sol
0	0	0	0	0	0	0	0
5	30.2	33.3	2.9	33.2	33.7	34.5	35.1
10	32.1	37.9	41.7	36.6	55.6	62.8	66.4
15	47.1	54	53.2	63.5	74.2	74.6	78.9
20	52.4	61.9	66.7	69.5	78.6	85.1	85.8
30	63.5	72.1	75.6	80.4	88.3	88.1	87.6
45	75.8	81.7	90.5	92	97.8	96.5	99.7



Time(Min.)	After strage	Before storage
0	0	0
5	34.5	35.1
10	62.8	66.4
15	74.6	78.9
20	85.1	85.8
30	90.2	87.6
45	96.5	99.7

Fig. (2) Dissolution rate of the chosen fluconazole formulae before and after one year storage

CONCLUSION

It was concluded that the use of Ac-Di-Sol as a disintegrant and dissolution accelerator will favour the efficacy of characteristics of fluconazole tablet. In addition cross-linked PVP with a concentration 6% without Ac-Di-Sol showed slight increase in fluconazole dissolution rate but less than that of Ac-Di-Sol which is added with smaller concentration.

In conclusion, the preparation of fluconazole tablets with the use of 2.5% Ac-Di-Sol and 6% cross-linked PVP produced stable formulae with reproducible characteristics.

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Received: 26 April 1997
Accepted: 22 July 1997

ثبات أقراص الفلوكونازول المحضرة بطريقة الكبس المباشر باستخدام مفتتات عالية الفاعلية

محمد سلامة محمد – هناء عبد الفتاح الغمرى

قسم الصيدلانيات – كلية الصيدلة – جامعة الزقازيق – مصر

يستخدم الفلوكونازول كعلاج لأمراض التنيا وقد تم تحضيره بطريقة الكبس المباشر باستخدام مفتتات عالية الفاعلية مثل عديد فينيل البيروليدون (عديد البلاسيدون) شبكى الاتحاد منفرداً أو مع تركيزات مختلفة من كاربوكسى مثيل السليلوز شبكى الاتحاد (أى-دى-سول) وقد تم تقييم الأقراص المحضرة فيزيائياً لتعيين الهشاشة ودرجة الصلابة وزمن التفتت وزمن الزوبان. وقد تم اختيار أحسن الصيغ لحفظها لمدة عام ومن ثم تقييم خواصها. وقد دلت النتائج على أن الأقراص المحضرة باستخدام ٢,٥ فى المائة من كاربوكسى مثيل السليلوز الصوديوم شبكى الاتحاد و ٦٪ من عديد فينيل البيروليدون شبكى الاتحاد قد أعطيا أفضل النتائج قبل وبعد التخزين .