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FORMULATION AND EVALUATION OF BEADS AND MOLDED PREPARATIONS CONTAINING GRISEOFULVIN

F.M.Sakr, A.H.Abd El-Gawad and E.E.Zin El-Din

Pharmaceutics Department, Faculty of Pharmacy, Universi of Mansoura, Mansoura, Egypt.

ABSTRACT

Solid dispersions containing polyethylene glycols (PEG) and different ratios of griseofulvin were made into beads and molded tablets. Beads were prepared by a newly designed technique referred to as the "dry solidification technique" (DST). This was based on dropping the molten drug-polymer mixtures from a syringe needle onto the top of talc powder beds chosen as solidification substrates. Molded tablets were obtained by pouring the molten mixtures into a tablet triturate mold placed on aluminium foil sheets. The formed beads and tablets were examined for their physicomechanical properties and physiological availabilities. Increasing drug contents and PEG mol. Wts. were found to increase beads and tablets hardness while decreased their dissolution rates and resistance to abrasions. The mechanical properties and dissolution rates of the molded tablets were also compared with those of hardly compressed tablets containing ranges of particle size between 125-150 um (A) and 212-250 um (B) of corresponding solid dispersions. Molded tablets were found to be mechanicaly stronger than those of (A) and (B) respectively, however their dissolution rates remained almost the same. Bioavailability results of the different preparations were found to be parallel with those of their dissolution rates; so that maximum urinary excretion of the drug and higher physiological availability were observed in case of beads rather than those of molded or compressed tablets.

INTRODUCTION

Solid dispersion systems may provide a means of increasing dissolution rates and bioavailability of sparingly soluble drugs (1,2). These systems have been investigated extensively since the last two decades regarding their methods of preparations, dissolution and bioavailability, physicochemical properties and stability as well as the introduction of new compounds as advantageous water soluble matrices for many insoluble drugs[1-9]. Studies concerned design and evaluation of solid dispersions in oral dosage forms have been the subject of only scant attention[10].

Polyethylene glycols have proven to be valuable water soluble matrices for many sparingly soluble drugs[2] yet their soft-plastic nature and low melting points (specially the lower mol. wt. grades) were found to produce solid dispersions that could not be easily grinded and consequently made into tablets. Traditional tabletting techniques may also emphasize the need of mixing other excipients with a solid dispersion system before being compressed into tablets. This might affect the desired dissolution rates and bioavailability of such a system.

In the present study, two methods were adopted to prepare beads and molded tablets containing different mol. wts. of PEG-griseofulvin solid dispersions without the need of the too many equipments and handling expenses required in the traditionl tabletting or capsule filling techniques. Griseofulvin was chosen as model drug whose dissolution rate was reported to increase several folds when fused with PEG[2,8]. Beads were prepared by dropping the molten PEG-drug mixtures from a syringe needle onto the top of talc powder beds used as solidification substrates. Molded tablets were obtained by pouring the molten mixtures into a tablet triturate mold. The effect of drug content and PEG mol.

wts. on physicomechanical properties and physiological availabilities of the formed beads and tablets were studied and compared with those of corresponding compressed tablets.

EXPERIMENTAL

Materials :

The materials used were PEG, of mol. Wts. 4000, 6000 and 20.000 (Hoechst A.G. Frankfurt), griseofulvin (Hoechst UK Ltd., Milton Keynes, Bucks, England) and talc powder (Prolabo Chem. Ltd.). The dissolution medium was 0.1 M HCl.

Equipment :-

Tablet hand press (Research & Instrument Co. GB), Tablet hardness tester TB 24, Roche Friabilator RA3R and a Unicam SP 600 UV Spectrophotometer (PYE Unicam, Cambridge, GB).

Methods :-

1- Preparation of beads :-

Physical mixtures were prepared by thoroughly grinding together 2,5 and 10 % griseofulvin and the different mol. Wts. PEG for 5 minutes using a glass pestle and a mortar. Each individual mixture was heated in a porcelain dish few degrees above the melting point of the polymer. The molten mixtures were stirred with a glass spatula for 2 minutes then taken up by a syringe and dropped from a needle (gauge No. 12) onto top of 2 cm thick beds of talc powder chosen as a suitable solidification substrate. Talc powder showed no tendency to stick or adhere with the molten drops before being solidified. The dropping height was kept at 5 cm as it was found suitable for producing the most spherical beads. The solidified drops were sieved and blown with cold stream of air to free them from any traces of the substrate powder.

2- Preparation of molded tablets :

A stainless steel tablet triturate mold was used for preparing the molded tablets. The upper part was flat plate containing raws of equal size holes (diameter 0.5 cm, thickness 0.3 cm).

The molten drug-PEG mixtures were individually poured to overfill the holes of the upper part which was firmly placed on top of aluminium foil sheets. Tablets were allowed to solidify then ejected by pressing them on the cylendrical projections after scrapping off the excess solidified mixtures with a thin hot spatula.

3- Preparation of compressed tablets :

The molten drug-PEG mixtures were allowed to solidify in their procelain dishes before bing scrapped out and grinded in glass morters. The powdered mixtures were individually sieved into size fractions ranging between 125-150 um (A) and 212-250 um (B). Weights from each fraction equivalent to those of corresponding molded tablets were hardly compressed in a hand press tabletting machine to constant packing fractions 1 (i.e.approximately the same as those of the molded tablets). A 0.5 cm flat faced punch and a die set were used for the compression process in order to produce tablets with equal diameters as those of molded ones (80 mg).

All beads, molded and compressed tablets were stored over silica gel in closed containers for a period of two weeks before being tested. This period was supposed to be sufficient for the preparations to attain their stable physical structures and maximum hardness.

4- Evaluation of beads and tablets :-

a- Weight uniformity :-

The test was carried out on 20 randomly chosen beads or tablets from each drug-polymer ratio. The results of the average weights together with their percentage coefficient of variations (C.V. %) are given in Table 1.

b- Beads and tablets hardness :-

The breaking loads of 20 beads from each drug-polymer batch were measured by raising them individually on flat plate fixed to underside of a chemical balance pan[11]. Lead shots required to break or deform a bead were taken as its breaking load.

Tablets hadrness were measured by edgewise pressure in a hardness tester. The test was carried out on 20 tablets and their average hardness values together with the average breaking loads of the beads are presented in Table. 1.

c- Beads and tablets resistance to abrasions :-

The test was carried out on 10 g of beads or 50 tablets. The samples were rotated in a friabilator for a period of 20 minutes then sieved. The residue,expressed as a percent of the initial weight of either the beads or the tablets,was defined as the friability of the sample.

$$\% \text{ Friability} = \frac{\text{Loss in weight}}{\text{Original weight}} \times 100$$ [2]

d- Dissolution study : -

Numbers of beads, molded or compressed tablets equivalent to 20 mg of the drug were used. The samples were individually added into a 2 litres capacity Pyrex glass beaker containing 1L of 0.1M HCl as a dissolution medium. The medium was equilibrated at 37° ± 1 before adding the samples and stirred at a rate of 60 rpm by a 0.5 x 2.5 stirrer blade centered 2 cm above the bottom of the beaker.Two ml samples were withdrawn by a syringe fitted with a membrane filter (Swnnex filters, 0.45 um Millipore USA-Bedford Mass). and analysed spectrophotometrically at 295 nm. The withdrawn volumes were immediately replaced by equal amounts of fresh 0.1 M HCl. The percent of the drug released was calculated on the basis of the total drug content for each number of beads or tablets used in the dissolution study.

e- Bioavailability study :-

Beads, molded and compressed tablets containing the 5% drug-PEG were selected on the basis of their suitable physical and mechanical properties. Twelve healthy male volunteers age between 30-38 years and weighing between 60-80 kg were chosen. All volunteers were refrained from any medication. The beads, molded and compressed tablets equivalent to 120 mg of griseofulvin were individually given on an empty stomach with 200 mls of water. No food was allowed for at least 3 hours after ingestion. Ample amounts of fluids were taken frequently during the day. The volume and pH of urine were recorded at intervals of 0, 1, 3, 6, 12, 24, 36, 48, 60 and 72 hours after adminstration, aliquots were stored in refregirator. The samples were analysed for total 6-demethylgriseofulvin by the method of Rowland and Riegelman (12). Control experiments were run for each subject in the same manner as the test but on hardly compressed tablets containing corresponding physical mixtures. The physiological availability at each time interval was calculated according to Morrison et al.(13).

$$\text{Physiological availability \%} = \frac{\text{\% of dose excreted from test preparation}}{\text{\% of dose excreted from control preparation}} \quad (2)$$

RESULTS AND DISCUSSION

It is clear from the photographic presentation in Fig. 1. that each individual bead or molded tablet was satisfactorily uniform in shape and size indicating the effeciency of the techniques employed for preparing them.

1- Uniformity of weight :-

The weight uniformity results of the beads and molded tablets in Table 1 are in agreement with their shape and size uniformity observed in Fig. 1. Each single bead or molded tablet out of the 20 randomly test ones was found to have very similar

weights with coefficient of variation (C.V. %) between 0.09-0.14 %. These values were found to be little higher (0.17-0.26 %) for compressed tablets probably due to the possible loss of some powdered mixtures during die filling, compression and ejection procedures.

2- Mechanical properties :-

The hardness and the friability results in Table 1 showed that at any drug-polymer ratio, increasing PEG mol. wts. was found to increase beads and tablets hardness but decreased their resistance to abrasions. This could be attributed to the increasing Brinell hardness (14) of the higher mol. wt. PEG rather than those of the lower mol. wt. grades. Previous work[15] showed that the Brinell hardness of the 20,000 mol. wt. PEG was 10. 8N m^{-2} x10^{-6} while that for a lower mol. wt. e.g the 1500 grade was 4.6 N m^{-2} x 10^{-6}. This means that, beads and tablets containing the higher mol.wt. PEG could tend to resist breaking loads rather than those containing the lower mol. wt. grades.

In contrast to the hardness test results, beads and tablets containing the higher mol. wt. PEG were found to be more friable than those containing the lower mol. wt. grades. It was shown[16] that although the 20.000 mol. wt. grade had the highest Brinell hardness than that of the 1500 grade, yet their modulus of elasticity were 4.3 Nm^{-2} x 10^{-8} and 3.5 Nm^{-2} x 10^{-8} respectively. This indicates that the lower mol. wt. grades are less elastic and consequently less brittle,the way by which beads and tablets containing them could resist agitation and mechanical forces that tended to fragment them. Similar findings were observed by Sakr et al.[16] (16), who stated that, incorporating increasing amounts of some non-ionic surfactants (Tweens) with the

rather brittle natured PVP (used as a granulating agent) has found to decrease its Brinell hardness and Modulus of elasticity. This was accompanied by corresponding decrease in tablets tensile strength, yet they became less friable than those containing pure PVP as a binding agent. This phenomena can also be noticed in metallurgy as one can see that cast iron can bear more loads than soft iron but its brittle nature cannot resist agitation or mechanical shocks that soft iron can bear.

Turning next to the effect of drug content on beads and tablets hardness; increasing drug content means corresponding increase in its microcrystalline density within the relatively soft PEG forming the majority of beads and tablets. The net result was the formation of increasing numbers of microcrystal-microcrystal and microcrystal-PEG bonds rather than the formation of the softer PEG-PEG bonds. This intended to enforce beads and tablets structures and thereby increase their hardness. On the other hand, the increased microcrystalline structure may tend to reduce beads and tablets plasticity so that they could not absorb agitation and mechanical shocks during the friability test.

The increased mechanical strength of molded tablets rather than those of corresponding compressed tablets can be explained as that each bead or molded tablet was actually composed of intimate and homogeneous solid units in which molecular bonds could be existing together with the microcystalline bonds after solidification. In the case of compressed tablets only particle-particle bonds were existing by rearrangement, fragmentation and plastic deformation during the compression process[17,18] The last two raws at the lower part of Table 1 are representative results on physical and mechanical properties of some selected tablets prepared from a coarser range of particle sizes

212-250 um (B) of the 5% griseofulvin-PEG 6000 solid dispersions. These tablets were found to be less harder and more friable than corresponding compressed tablets prepared from the finer particle sizes 125-150 um (A).

3- Dissolution results :-

The times taken to release 50 and 95% of the drug from the different preparations are listed in Table 1. It can be seen that at any drug content and PEG mol. wts., beads have shown to exhibit a higher rate of dissolution than molded or compressed tablets. The enhanced drug release from beads can be attributed to their smaller sizes and larger surface area available in the dissolution medium rather than those of corresponding tablets. Representative graphs in Fig. 2. showed the in vitro dissolution profiles of griseofulvin from beads, molded and compressed tablets containing 5% drug-PEG 6000 solid dispersions

Increasing PEG mol. wts. was found to decrease beads and tablets dissolution rates (Table 1). This could be related to the slower water solubility and the increased viscosity of the higher mol. wt. PEG at the diffusion boundary. This increased viscosity could therefore hinder the drug molecules to be released from the diffusion layer thereby reduceing its dissolution rate[2]. On the other hand, the composition of a solid dispersion may have a significant effect on the particle size of its crystallites. If it is made up of a high weight fraction of a drug, an ultra-fine crystallization of the drug may not be obtained. This can be logical if one accept that the higher the dilution of a solid dispersion the finer the crystalline size of its precipitate and consequently the higher will be the dissolution rates. This probably accounts for the decreased values of t_{50}% and t_{95}% of beads and tablets containing higher ratios of griseofulvin.

4- Bioavailability results :-

The urinary excretion rate of griseofulvin was claimed to be directly reflected by its blood level concentration[1,2]. The 72 hours urinary excretion results in Table 2 indicated that the rates of excretion were in the order of beads > molded and corresponding compressed tablets > compressed physical mixtures. Accordingly beads showed the highest physiological availability while those of molded and corresponding compressed tablets showed similar values. The initial urinary excretion rate of total 6-demethylgriseofulvin reflects the relative absorption of griseofulvin and that the cumulative amount ultimately excreted in urine serves as a quantitative index of the extent of absorption. In this case, the obtained data revealed that griseofulvin was absorbed in the following order : beads > molded and corresponding compressed tablets > compressed physical mixtures. This could be explained on the basis of difference in dissolution rate from the different preparations, which is attributed to the influence of particle size, wettability induced by PEG as well as the increased surface area[2].

From the previous studies we can conclude that :

1- Possible oral dosage forms of beads and molded tablets could be directly prepared from fused mixtures of griseofulvin-PEG solid dispersions without the complications associated with solidification, grinding, sieving, filling into capsules or compression in form of tablets. These new techniques could be employed for other drugs-PEG solid dispersions.

2- Molded preparations have shown to be mechanically stronger than those of corresponding compressed tablets whose mechanical properties varied with the initial size fractions of the drug-PEG mixtures used for preparing them.

3- Beads were found to have the highest dissolution rates and physiological availabilities than either molded or corresponding compressed tablets. Both types of tablets produced similar availabilities.

4- Considerations must be paid during the choice of polymers mol. wts. and drug ratios when beads or tablets with certain properties were required.

5- Future size of beads and molded tablets could be constructed according to the therapeutic doses of their incorporated drugs.

Table 1: Physical and mechanical properties of the different beads and tablets.

	Preparations	Weight Mean.mg	Weight C.V.%	Hardness g	Friability %	Dissolution rate t 50%	Dissolution rate t 95%
BEADS	Gris.+PEG 4000						
	2%	16.22	0.09	375	-	9	40
	5%	16.23	0.09	390	-	12	68
	10%	16.45	0.10	425	-	18	88
	Gris.+PEG 6000						
	2%	16.30	0.10	405	0.035	12	50
	5%	16.38	0.11	445	0.058	16	80
	10%	16.42	0.11	460	0.068	23	95
	Gris.+PEG20000						
	2%	16.40	0.10	475	0.065	14	55
	5%	16.53	0.11	500	0.075	19	88
	10%	16.68	0.11	542	0.080	26	108
MOLDED TABLETS	Gris.+PEG 4000						
	2%	79.85	0.13	12.50	0.120	19	76
	5%	79.82	0.13	12.50	0.133	24	108
	10%	79.92	0.15	15.00	0.142	31	120
	Gris.+PEG 6000						
	2%	79.75	0.12	1750	0.135	22	78
	5%	79.82	0.14	2000	0.148	29	116
	10%	79.86	0.14	2250	0.156	36	130
	Gris.+PEG20000						
	2%	79.95	0.11	2250	0.162	24	88
	5%	80.11	0.13	2750	0.178	29	121
	10%	80.21	0.14	3250	0.199	39	140

Table 1: Cont.

COMPRESSED TABLETS (A)	Gris. +PEG 4000						
	2%	79.25	0.17	1100	0.135	20	72
	5%	79.25	0.18	1250	0.151	22	103
	10%	79.33	0.18	1300	0.172	28	115
	Gris. +PEG 6000						
	2%	79.34	0.18	1500	0.152	20	75
	5%	79.31	0.22	1650	0.167	25	110
	10%	79.42	0.25	2250	0.185	34	124
	Gris. +PEG20000						
	2%	79.40	0.22	2100	0.180	26	84
	5%	79.52	0.21	2500	0.192	29	118
	10%	79.45	0.26	3100	0.201	37	136
COMPRESSED TABLETS (B)	Gris. +PEG 6000						
	2%	79.49	0.17	1250	0.165	18	72
	5%	79.55	0.18	1750	0.181	25	100
	10%	79.62	0.17	2100	0.196	30	119

* Could not be accuratly determined

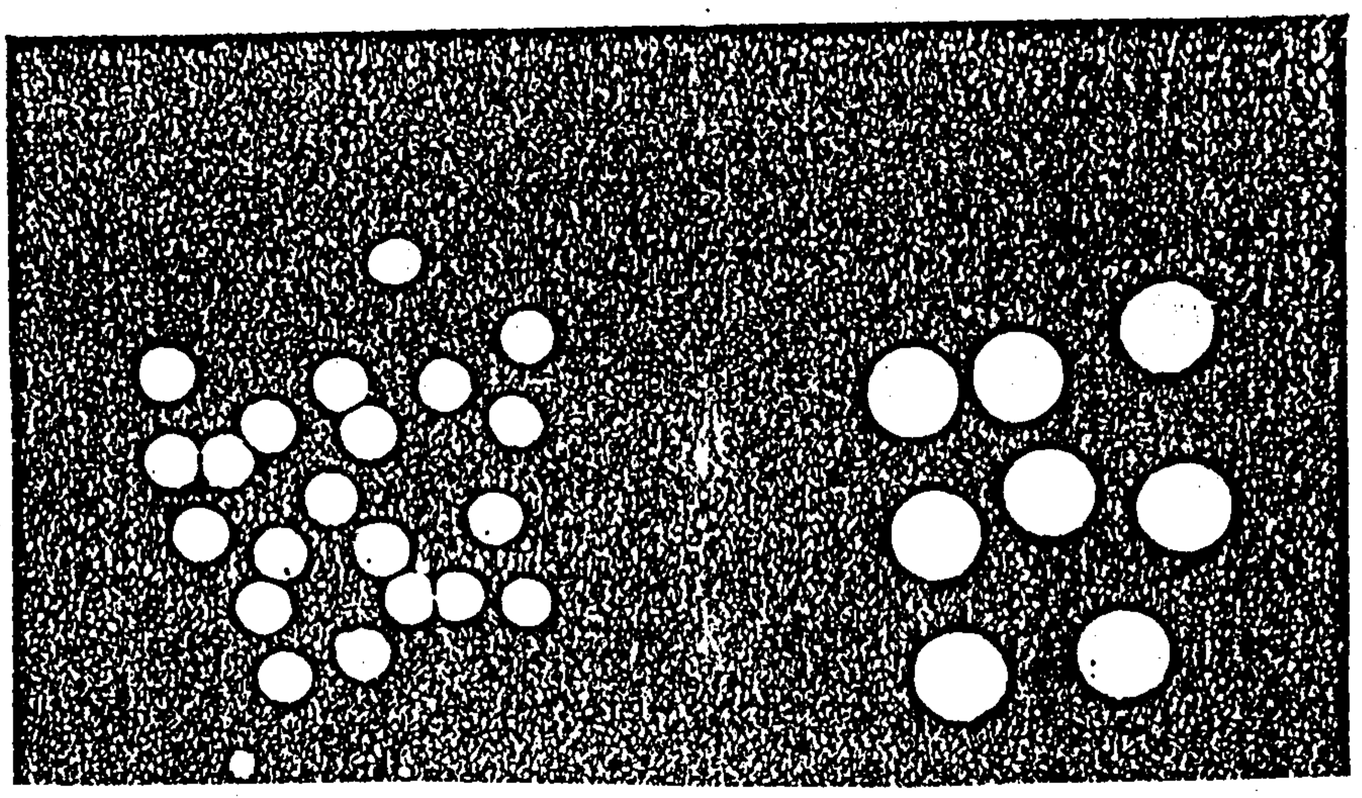
(A)Compressed tablets prepared from the 125-150μm fractions

(B)Compressed tablets prepared from the 212-250 μm fractions.

Table 2: Mean cumulative excretion of 6-demethylgrise ofulvin(A)and percentage physiological availability (B) from beads and tablets.

Time [h]	Physical mixture compressed tablets		Beads		Molded tablets		Solid dispression compressed tablets	
	A	B	A	B	A	B	A	B
1	0.417	0.74	0.815	1.45	0.611	1.09	0.623	1.11
3	2.960	5.29	8.743	15.62	5.851	10.45	6.231	11.13
6	10.871	19.42	18.812	33.61	13.891	24.82	15.980	28.56
8	15.518	27.73	25.820	46.14	21.760	38.89	22.231	39.7
12	23.950	42.80	32.471	58.03	26.250	46.91	28.850	51.5
24	34.980	61.20	45.782	81.82	38.562	68.91	40.842	72.99
36	40.246	71.92	56.230	100.50	49.881	89.15	50.281	89.86
48	46.676	83.41	61.720	110.31	56.252	100.53	56.861	101.62
60	51.450	91.95	69.441	124.11	60.980	108.99	63.120	112.81
72	55.950	100	78.596	140.47	68.252	121.98	69.551	24.30

Formulation and Evaluation of Beads and Molded Preparations Containing Griseofulvin



BEADS MOLDED TABLETS

Fig. 1: Photographic presentations of the formed beads and molded tablets.

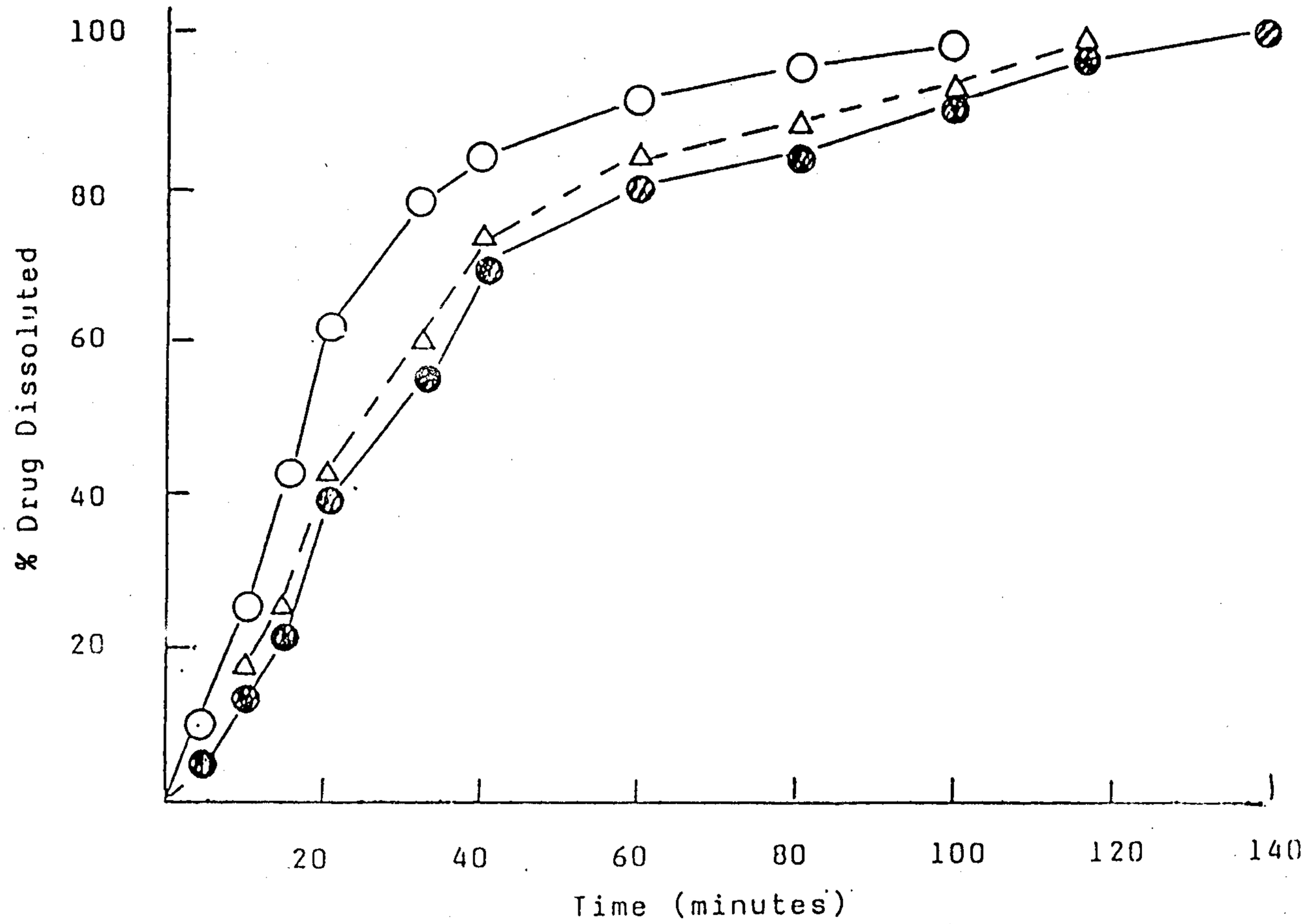


Fig. 2: Dissolution profiles of griseofulvin from beads, molded and compressed tablets containing 5% drug-PEG 6000 solid dispersions.

Key: ○ Beads, △ Compressed tablets, Molded tablets.

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صياغة وتقييم حبيبات ومستحضرات القوالب الصيدلية المحتوية على الجريزوفلفين

فاروق محمود صقر ،عبد الجواد حلمى عبدالحواد ، عصمت السيد زين الدين
قسم الصيدلانيات ـ كلية الصيدلة ـ جامعة المنصورة ـ جمهورية مصر العربية

فى هذة الدراسة تم تحضير حبيبات وأقراص بطريقة القوالب تحتوى على بولى ايثيلين جليكول مع تركيزات مختلفة من الجريزوفلفين على هيئة منتشر صلب . وقد استحدثت طريقة لتحضير الحبيبات (التجفيف الصلب)والتى اشتملت على تنقيط المخلوط المصهور المحتوى على المادة الدوائية مع البوليمر على بودرة التلك من محقنة خاصة اعدت لهذا الغرض ولتحضير الاقراص تم صب المخلوط المنصهر على قالب صب أقراص . وتمت دراسة الخواص الفيزيوكيميائية للحبيبات وللاقراص الناتجة كما قيمت الاتاحه الحيوية .

وقد وجد أنه بزيادة نسبة البولى ايثيلين جليكول وكذا وزنه الجزيئى زادت صلابة الحبيبات والاقراص وقلت معدلات ذوبانيتها ،كما ظهر أن حجم جزيئات المنتشر الصلب قد لعب دورا كبيرا فى التأثير على الخواص الميكانيكية وكذا معدل الذوبانية .

أثبتت تجارب الاتاحه الحيوية أن معدل انطلاق المادة الدوائية فى البول قد أظهر أعلى معدلاته فى حالة الحبيبات أكثر منها فى حالة الاقراص المعده بطريقة القوالب أو مثيلاتها المعدة بطريقة الكبس .

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