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THE PHYSICAL CHARACTERISTICS OF LYOPHILIZED TABLETS CONTAINING A MODEL DRUG IN DIFFERENT CHEMICAL FORMS AND CONCENTRATIONS

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Abstract: Orodispersible tablets, usually prepared using freeze–drying method, are becoming a popular drug formulation for patients who have difficulties swallowing solid dosage forms. The influence of drug solubility and concentration on the physical characteristics of lyophilized tablets composed of mannitol and gelatin was investigated. Phenobarbital and phenobarbital sodium were studied as model drugs. The tablets were analyzed for mechanical strength using a new method employing Instron, a material testing apparatus. For tablets containing phenobarbital in the form of sodium salt, better mechanical strength was demonstrated than for tablets prepared with water insoluble phenobarbital – acid form. Besides, the mechanical characteristics of the tablets indicate that plasticity and porosity were reduced when sodium phenobarbital was incorporated at a higher dose. Lyophilized tablets were not hygroscopic and only a small increase of tablet mass by 1% and 3% was observed after 4 weeks of storage at 40% and 60% RH, respectively. All formulations disintegrated in seconds in water, at a temperature of 37°C.

Keywords: lyophilization; freeze-dried tablets; mannitol; gelatin; phenobarbital

Oral route of drug administration is convenient and preferred by patients and this is why tablets and capsules are the most popular pharmaceutical dosage forms. However, sometimes patients, especially children and elderly people, may have difficulty swallowing solid dosage forms. It is estimated that 50% of population is affected by this problem, which results in a high incidence of non-compliance and ineffective therapy (1). The problem can be solved by producing orodispersible forms (Ph. Eur.), which placed in the mouth, allow to rapidly disperse or dissolve in the saliva and then can be swallowed as a liquid, in the normal way. Such systems in the literature are called: FMTs (fast-melting tablets), ODT (orally disintegrating tablets) or FDDF (fast dissolving/disintegrating dosage forms).

There are three major methods for manufacturing this kind of tablets: 1) freeze-drying, 2) moulding by compression or heat-moulding, 3) direct compression. Because of the high porosity, freeze-dried tablets disintegrate in oral cavity faster than other systems. Unfortunately, lyophilization, as a method of tablet preparation, has also disadvantages: lack of physical resistance, hygroscopicity of the product, as well as high cost of production and low dose of the drug which can be incorporated (2). Typical freeze-dried tablet consists of a drug enclosed in a water soluble matrix made of a hydrophilic structure-forming polymer (usually gelatin) and a filler (saccharide – usually mannitol). Other ingredients of the tablets may be sweetening agents (aspartam), taste-masking additives and preservatives (3). At present, many researchers are studying the possibilities to utilize other matrix forming agents in the FDDF formulations. These are: maltodextrins, different kinds of gelatins, xantan gum and cellulose-derivatives (4). The type and amount of the excipients have a significant influence on the characteristics of the lyophilized tablets, however, the incorporated drug can also modify properties of tablets to a great extend.

The aim of the study was to determine the influence of concentration and chemical form of the drug on physical properties of the lyophilized tablets containing mannitol and gelatin. Phenobarbital and its sodium salt were used as model drugs. Besides, the applicability of a material testing machine Instron to determine the mechanical strength of the tablets was evaluated.

EXPERIMENTAL

Preparation of tablets

Tablets were made by freeze-drying. Gelatin (I.G.G. Eberbach, Germany) and mannitol (POCh

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Gliwice, Poland) were dissolved in purified water at 60°C. Phenobarbital, F (donated by Galenus, Warsaw, Poland) and its sodium salt, FNa (Tarchomin Pharmaceutical Works, Warsaw, Poland) were introduced at various concentrations to the tablet solution with constant mixing. The compositions of different formulations, both with and without drug, are shown in Table 1. FNa dissolved completely at all concentrations, but with F suspension was formed, when the concentration exceeded 0.1% (w/w). The pH of FNa solution was in the range 7.6-9.2 and pH of the F dispersions was 5.1. Freeze-dried tablets were prepared as follows: the wells of PVC blisters (20 mm in diameters) were filled with 2.0 ml of solution or suspension and the blisters were placed immediately on the pre-frozen shelves of the freeze-dryer (Alpha 2-4, Christ, Osterode, Germany). The samples were frozen at – 45°C and kept at this temperature for 60 minutes. Primary drying was performed for 40 h at a pressure of 0.08 mbar with gradual increasing the shelf temperature to 20°C. In the second drying step the shelf temperature was increased to 35°C for 2 hours.

Visual inspection of tablets

Morphological characterization of the freeze-dried tablets comprised of: shape, color, surface and friability analysis. Adhesion of tablets to the blister and the easiness of taking them out were also evaluated.

Mechanical strength testing

A compression testing machine Instron (Model 5543, Instron Corporation, Canton, USA) was used to determine the tablets strength. Each tablet was placed horizontally on the lower support and compressed using a constant speed of 0.22 mm/min to the maximum force of 80 N. Relationship between the load (N) and deformation of the tablets (%) was studied. Tablets containing different amounts of F or FNa as well as tablets lyophilized in different locations on the freeze-dryer shelf were compared. From each formulation 10 tablets were analyzed to evaluate reproducibility of the results.

Stability of tablets at different relative humidity

Tablets with F or FNa (n = 6) were placed in a hygrostat and stored at relative humidities (RH) 45%, 60% and 90% over sulphuric acid solutions (48%, 38% and 17%, respectively) for 4 weeks. Changes in tablet mass and appearance were observed.

Disintegration test

For determination of disintegration time of tablets two different methods were employed. In the

Table 1. The visual characteristics of freeze-dried tablets: placebo and containing phenobarbital (F) or phenobarbital sodium (FNa) as model drugs

Composition of solution or suspension subjected to freeze-drying [%]			Drug content per tablet [mg]	Surface of tablets	Durability of tablets	Removal from the blisters
gelatin	mannitol	drug				
PLACEBO						
0.5				porous, burst	very fragile	-
0.75				porous	fragile	+/-
1.0	**5,0**	-	-	**porous**	**durable**	**+**
2.0				porous	hard	-
2.0	3.0			porous	hard	-
TABLET WITH DRUG						
		0.1 FNa (solution)	2.0	porous, irregular	durable	+
		1.0 FNa (solution)	20.0	porous, irregular	durable	+
1.0	**5**	10.0 FNa (solution)	200	porous, burst	hard and fragile	+/-
		0.1 F (solution)	2.0			
		0.5 F (suspension)	10.0	porous, irregular	stable, hard	+
		1.0 F (suspension)	20.0			

(+) the tablet can be easily taken out from the blister;
(-) the tablet sticks to the blister and can not be removed without damage

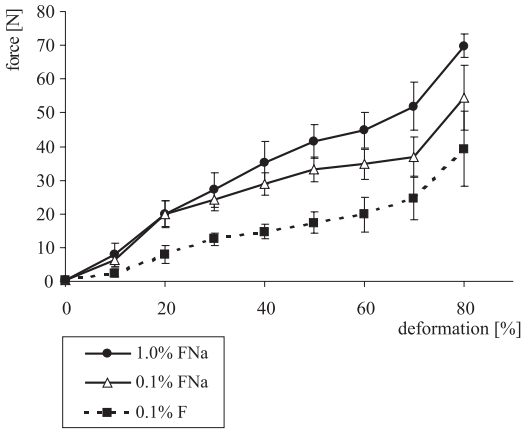

Figure 1. Deformation curves of tablets prepared with phenobarbital sodium, FNa (0.1% and 1.0% solution) and phenobarbital, F (0.1% solution); error bars ± SD (n=10).

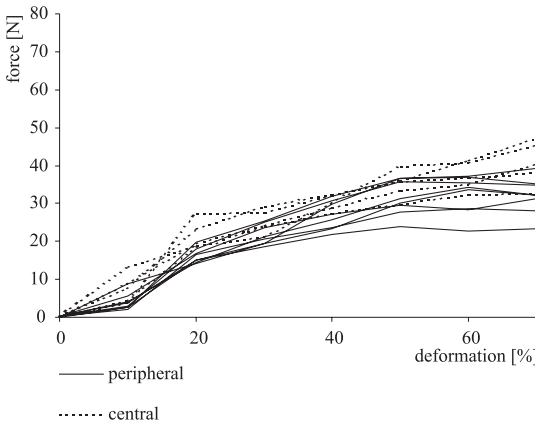

Figure 2. The effect of localization of the blisters on a freeze-dryer shelf (peripheral or central) on deformation curves of tablets containing phenobarbital sodium (0.1% solution).

first one, a Ph. Eur. disintegration apparatus (Pharma Test, Hamburg, Germany) was used. Tablets were placed in cylinders on the bottom mesh, burdened with disks and immersed in water at room temperature or 37°C. The time required for complete disintegration of each tablet was recorded. In the second method, the tablets were placed in a plastic syringe funnel on a blotting paper covered with glass pellets. The time required for 5 mL of water to pass through the syringe was measured.

RESULTS AND DISCUSSION

In the first step of the studies the best ratio of gelatin to mannitol was established in order to formulate freeze-dried matrices of satisfying mechanical characteristics. In Table 1 the investigated compositions of placebo tablets are shown. On the basis of visual inspection and evaluation of adhesion to the blister as well as on the integrity after removing from a blister formulation composed of mannitol and gelatin in ratio 5:1 was chosen as optimum. This composition of structure-forming excipients was used for preparation of lyophilized tablets with F and FNa. All tablets obtained by the lyophilisation process were white and porous, their shape was cylindrical, corresponding to the shape of the blister well. Tablets containing up to 20 mg of F or FNa (14.3% of the total mass) had satisfying appearance, and they did not differ visually. The increase of the amount of FNa to 200 mg per tablet (62% of total mass) resulted in increased hardness and, finally, tablets could not be removed from blister without braking (Table 1).

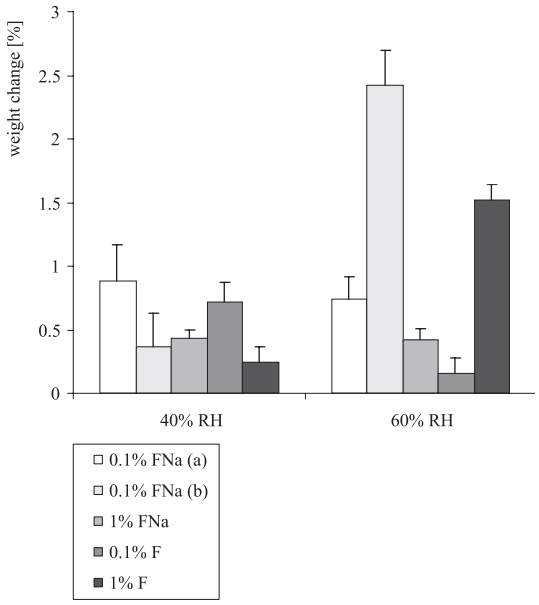

Figure 3. Changes in weight of lyophilized tablets containing different concentrations of model drugs during 4 weeks of storage at room temperature and 40% and 60% RH (error bars ± SD, n=6): F – phenobarbital, FNa – phenobarbital sodium (a and b – two different batches)

A standard hardness tester used for compressed tablets was not appropriate to study strength of the lyophilized tablets since they did not break during the test. This is why the applicability of another instrument, a universal material testing machine Instron, was investigated. The results of the mechanical studies performed with this apparatus are shown in Figure 1. The curves indicate that the matrices are plastic: an increasing

force caused deformation without breaking the tablets.

At the initial step gradual deformation up to 70% was observed with small forces applied, but 30%-50% further increase in the force was required to get 80% deformation. The relationship between force and deformation is described by the curves which are linear in three segments: I – up to 20%, II – between 20% and 70%, III – above 70% deformation. The initial 20% deformation occurs when the fragile lyophilizate structure is crushed, the step II corresponds to the deformation which is caused by compression of the porous matrix, while only at higher loads the structure of a tablet is completely destroyed (step III). The force required for 20% deformation can be a measure of resistance to crushing, and the one responsible for step II can be related to porosity and plasticity of the tablets. The slopes of the curve segments (aI and aII values) were calculated using linear regression analysis. On the basis of these parameters it can be assumed that the chemical and physical form of an active substance influences the mechanical strength and the structure of the lyophilized tablets. The use of F in acidic form resulted in lower mechanical strength (aI=0.38 N/%) in comparison with tablets containing FNa (aI=0.98 N/%), however the compression response at step II was similar: aII=0.31 and 0.34 N/%, respectively. This means that faster precipitation and crystallization of a slightly soluble drug (F) resulted in the structure less resistant to crushing, however the porosity and plasticity of the matrix was similar. For FNa tablets the crushing resistance was similar, independent of concentration (aI=0.98 N/%), but increased drug concentration resulted in a less porous and plastic structure, what can be demonstrated by higher aII values: 0.62 N/% for 1.0% FNa formulation and 0.34 N/% for 0.1% FNa formulation. This indicates that FNa contributes to the structure-forming process. For FNa formulations good reproducibility of the curves was observed (RSD <15%).

The results demonstrate that the Instron apparatus can be suitable for the mechanical analysis of lyophilized tablets. A comparison between the mechanical properties of tablets located at the peripheral and in the central part of the shelf in a freeze-dryer was done. The location of the blister during lyophilization may be important for the properties of tablets because different time of freezing was observed – shorter for tablets in the peripheries. The deformation curves for one batch of tablets containing 0.1% FNa are shown in Figure 2. Small difference in the mechanical behaviour was noted – tablets from the central part of the shelf, freezing slower, were more resistant, however the difference was not statistically significant. Corveleyn and Remon (4) reported that faster freezing results in higher degree of supercooling with the formation of small crystals. Small ice crystals result in a higher surface area and higher degree of porosity after lyophilisation, what can explain a decreased strength of the peripheral tablets.

Lyophilized tablets show significant porosity, and one can expect that they can absorb moisture very easily. To determine hygroscopic properties, the tablets were stored in three levels of the relative humidity – 40%, 60% and 90%. The most intensive water uptake occurred at 90% RH and this resulted in tablet shrinkage. In Figure 3, the changes in tablet weights after 4 week storage at 40% and 60% RH are demonstrated. Only a small increase in moisture content was noted. This increase was higher at 60% RH (2,7%), compared to 40% RH (about 1%). A very small moisture enhancement does not allow for conclusion whether type of the drug and its concentration influences hygroscopic properties of tablets. Besides, the evaluation of two batches of tablets containing 0.1% FNa (a and b, Figure 3) shows that the difference within one formulation can be larger than between different formulations.

All lyophilized tablets rapidly disintegrated in water regardless of the method of analysis. Due to a very short time of the process it could not be possible to define the disintegration time precisely. At 37^{o}C all tablets disintegrated in few seconds and at room temperature disintegration time varied from 14 s to 2.5 min., but no influence of either drug form or concentration was observed. If the syringe apparatus was employed, the jelly structure was formed due to the presence of gelatin, and this stopped the flow of water. This means that a new adequate method for analysis of disintegration time of the freeze-dried tablets should be searched.

CONCLUSIONS

The results demonstrate that the ratio 5:1 of mannitol and gelatin as matrix formers is appropriate to obtain freeze-dried fast dissolving tablets. Chemical form, the concentration of the drug and physical properties of the freeze-dried liquid (solution or suspension), have a significant influence on the mechanical strength of tablets. Even though the lyophilizates were porous, they did not absorb water during at least monthly storage in 60% RH. Further studies should be carried out in order to develop a

new method for determination of disintegration time of lyophilized tablets.

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