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How Does Long-Term Storage Influence the Physical Stability and Dissolution of Bicalutamide from Solid Dispersions and Minitablets?

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Abstract: The stability of amorphous drugs is among the main challenges in the development of solid dosage forms. This paper examines the effect of storage conditions (25 °C/60% RH and 40 °C/75% RH) and different packaging materials, i.e., polystyrene containers and PVC/Al blisters, on the crystallinity and dissolution characteristics of solid dispersions containing bicalutamide and polyvinylpyrrolidone. The results confirmed drug amorphization upon milling and improved dissolution resulting from the lack of a crystal lattice. These properties varied with time regarding sample composition, storage conditions, and packaging material. The most resistant to storage conditions was the 1:1 solid dispersion packed into blisters. Based on the obtained results, the 1:1 solid dispersion was formulated into minitablets, which were then tested after tableting and then packed into PVC/Al blisters and stored for six months in the same conditions as solid dispersions. We proved that efficient stabilization of amorphous bicalutamide depends on the barrier properties of packaging materials and that a properly chosen material protected the drug substance from the influence of unfavorable storage conditions such as elevated temperature and humidity.

Keywords: bicalutamide; milling; polyvinylpyrrolidone; amorphous solid dispersions; minitablets; stability study

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1. Introduction

Poor aqueous solubility and limited bioavailability of active substances (APIs) are currently among the most important issues in the pharmaceutical field. The most successful approaches reported on this topic are amorphous solid dispersions or cocrystals [1], and solid nanoparticles [2]. Amorphization leads to an increase in the molecular mobility of the drug, which is responsible for reaching supersaturation and a higher dissolution rate. Among the drug-processing technologies allowing to obtain amorphous drug substances, hot-melt extrusion (HME), patented melting-based method KinetiSol®, spray-drying, supercritical fluid technology, and milling have been reported. To select an appropriate method, the nature of the active substance and the properties of the final product need to be taken into consideration [3].

Milling is a first-line strategy that is applied to improve dissolution characteristics of a drug. Milling induces particle size reduction, which causes an increase in surface area, leading to an improved dissolution rate and bioavailability. The mechanical force applied during the process may lead to thermal decomposition of the material, accumulation of

defects in crystals, chemical reactions, formation of metastable polymorphs, and amorphization [4]. The advantages of using solid dispersions containing poorly water-soluble drugs obtained by milling are illustrated by products introduced into the market, e.g., tablets containing sirolimus Rapamune® (Pfizer, NYC, NY, USA), or everolimus Certican® and Zortress® (Novartis, Switzerland) [5].

Given the instability of amorphous drug substances and the tendency toward recrystallization, the choice of an appropriate manufacturing technique and the selection of a suitable stabilizer are extremely important. This should include an in-depth analysis of the mechanism of stabilization, and possible drug–carrier interactions, including behavior upon drug dissolution under both in vitro conditions and after administration, as well as upon storage, especially regarding the prolonged impact of elevated temperature and humidity [3]. Hydrophilic polymers, such as macrogols, poloxamers, hydroxypropyl methylcellulose (HPMC), and polyvinylpyrrolidone (PVP), are among the most commonly used stabilizers. They improve the wettability of the solid dispersion, leading to enhanced dissolution [6]. However, their hygroscopicity may undermine the improved dissolution performance of amorphous drugs. Due to the absorption of water, which acts as a plasticizer, drug glass transition temperature (Tg) is reduced and its recrystallization proceeds [7]. To minimize this effect, polymers of high Tg, which increase the glass transition temperature of the mixture and reduce molecular mobility, such as PVP (Tg = 167 °C) [8] are frequently used [9]. Although the solubility of many solid drugs in PVP is quite low, high miscibility provides sufficient stabilization of amorphous solid dispersions containing active substances at high concentrations [10]. Stabilization of the amorphous phase may occur not only due to the antiplasticizing effect of the carrier but also by specific complexation with the active substance [11,12]. Storage of the prepared solid dispersions below the glass transition temperature improves stability by reducing molecular mobility, so it inhibits the active substance crystallization kinetics [13]. Apart from hydrophilic carriers used to stabilize the amorphous active substance, porous silica-based materials such as Syloid® or Neusilin® are also applied. They have been proven to be a suitable method to improve the dissolution rate [14].

The compaction of solid dispersions into tablets increases the therapeutic functionality [15]. Some important limitations need to be taken into consideration during the development of such dosage forms [16]. The main issues are the limited physical stability of the active substance in the amorphous phase, changes in the dissolution rate after compression, and an unfavorable tablet size resulting from the composition of solid dispersion, i.e., low drug loading. Additionally, spontaneous crystallization of amorphous drug upon compression may limit its applicability [17].

Among the solid dosage forms, minitablets have gained particular attention in recent years. They offer the advantages of a multi-particulate system and leverage the benefits of tablets. Their small size and diameter of less than 3 mm make them easier to swallow. Other advantages of minitablets include higher physical, chemical, and microbiological stability and also better dosing accuracy, and easier modulation of the active substance release profile as compared to granulates or pellets [18]. However, due to the unique shape and size of minitablets, there are particular considerations regarding their design, including hardness, and disintegration time. From a technological point of view, there are some benefits in manufacturing minitablets in comparison with pellets, such as reproducible size, weight, and smoother surface. Current studies showed better tabletability and compatibility of minitablets. Tablets containing microcrystalline cellulose expressed the lowest yield pressures and showed more plastic deformation [19,20].

In the work presented herein, we use bicalutamide (BCL) as a model drug that is a non-steroidal anticancer substance. Bicalutamide belongs to BCS class II [21,22]. Bicalutamide is a highly hydrophobic substance (logP = 2.92), characterized as slightly soluble (3.7 µg/mL). Several papers on the formation of solid dispersions containing BCL, by complexation with β-cyclodextrin [23] and preparation of nanodispersion [24], have been published. PVP K29/32 was chosen as the carrier because of its beneficial properties. PVP K29/32 is an

amorphous water-soluble excipient physiologically compatible, nontoxic, inert, resistant to temperature, and stable over a wide range of pH [25]. The glass transition temperature (Tg) of PVP K29/32 is 167 °C [8].

The aim of this study was to evaluate the stability of minitablets containing amorphous solid dispersions of bicalutamide and PVP K29/32 upon storage in different packaging materials. The solid dispersions of weight ratios, i.e., 1:1, 2:1, 4:1, and 10:1, were obtained by ball milling. Based on our previous studies, we chose PVP K29/32 as the carrier [26,27]. Solid dispersions were packed in polystyrene containers and PVC/Al blisters, and stored for twelve months under the following conditions: 25 °C/60% RH, and 40 °C/75% RH, according to ICH (International Conference on Harmonization) guidelines. At a predetermined time, changes in the appearance of the samples, the crystalline structure of the drug substance, and the dissolution were analyzed. Based on the stability study results, the appropriate drug-to-carrier ratio and packaging material were selected to formulate minitablets containing solid dispersions and to examine their stability. The influence of both types of storage conditions on the properties of minitablets was analyzed after six months of storage.

2. Materials and Methods

2.1. Materials

Bicalutamide (BCL, 99.8%, Hangzhou Hyper Chemicals Limited, Hangzhou, Zhejiang, China) was used as a model drug and PVP K-29/32 (Ashland, Covington, KY, USA) as a carrier. Cellulose microcrystalline type 102 (JRS Pharma, Rosenberg, Germany) was used as a filler, sodium starch glycolate (DFE Pharma, Goch, Germany) as a superdisintegrant, and magnesium stearate (Merck, Darmstadt, Germany) as a glidant. Sodium lauryl sulfate (SLS, BASF, Ludwigshafen am Rhein, Germany) was used to prepare the medium for dissolution studies.

2.2. Methods

2.2.1. Ball Milling

Bicalutamide mixed with PVP K-29/32 in the weight ratios 1:1, 2:1, 4:1, and 10:1 was milled using a Pulverisette 7 Classic Line planetary ball mill (Fritsch, Weimar, Germany) to obtain solid dispersions. Each substance was weighted using a Vibra AJ 620CE (Shinko Denshi, Tokyo, Japan) balance, and its characteristics are as follows max. 620 g, min. 0.1 g, e = 0.01 g, d = 0.001 g. During the milling operation, two zirconium oxide milling jars (a volume of 45 mL) were filled with seven zirconium oxide balls (15 mm in diameter). The 4 g of API and carrier mixture were introduced into the milling jars. The process was carried out at room temperature using the following parameters: 400 rpm, 20 min milling periods, 10 min pauses (to avoid overheating of the milled materials), and reverse mode. The number of milling cycles was equal to 35, and the total milling time was 17.5 h.

2.2.2. Final Blend Preparation and Characterization

The weighted amount of solid dispersions containing bicalutamide and PVP K29/32 in a 1:1 weight ratio was mixed with cellulose microcrystalline as filler, sodium starch glycolate as superdisintegrant, and magnesium stearate as glidant. The percentage of each ingredient was 58.8%, 37.6%, 2.8%, and 0.7%, respectively. The 1:1 weight ratio was chosen to obtain minitablets based on an optimal active substance to carrier quantity. The bulk, tapped density, and angle of repose were according to the Ph. Eur. requirements to evaluate the flowability of the final blend. A weighted amount of the final blend was loaded into a cylinder of 100 mL volume. The bulk density was calculated as the mass of the powder divided by the bulk volume. The tapped density was determined as the mass of powder divided by the volume after tapping. Based on the obtained results, the Hausner ratio and the compressibility index were calculated according to the Ph. Eur. requirements. The angle of repose was determined as a three-dimensional cone-like angle formed by the final blend

during the measurement, measured after the blend passed through a sieve on a polished surface 60 mm in diameter.

2.2.3. Preparation of Minitablets by Direct Compression and Evaluation of Their Properties

The final blend was compressed using a single-punch tableting machine (Korsch EK0, Berlin, Germany) equipped with round flat punches, 3 mm in diameter. After compression, the mechanical properties of the minitablets such as mass, resistance to crushing, and disintegration time were according to the Ph. Eur. requirements. The parameters such as thickness and hardness were verified using a hardness tester apparatus (VenKel VK200, Varian, Inc., Cary, NC, USA). Disintegration time was measured in distilled water at 37 °C using an Electrolab ED-2 SAPO (Electrolab, Mumbai, India).

2.3. Stability Evaluation

2.3.1. Storage of Solid Dispersions and Minitablets

Solid dispersions were packed into either polystyrene containers or PVC/Al blisters. The samples were stored in climate chambers of the HPP type (Memmert GmbH + Co. KG, Büchenbach, Germany) under long-term conditions (25 °C/60% RH) and accelerated conditions (40 °C/75% RH). Samples were visually and instrumentally analyzed immediately after preparation, after two weeks, and after one, three, six, nine, and twelve months of storage. The minitablets were packed into PVC/Al blisters and subjected to stability tests for six months, under both long-term and accelerated conditions.

2.3.2. Visual Inspection of Sample Appearance

Each sample was visually inspected after being taken out of the climate chamber. The changes in color and agglomeration of the powdered samples were examined.

2.3.3. Laser Diffraction Measurements

A Malvern Mastersizer 3000 (Malvern Panalytical Ltd., Malvern, UK) equipped with a HydroEV unit was used to determine the particle size distribution of raw bicalutamide and solid dispersions. The samples were analyzed using the wet method using cyclohexane (reflective index, RI = 1.426) as a dispersant. Fraunhofer diffraction theory was applied to find the relationship between the particle size and the light intensity distribution pattern. The reported data are the averages of ten series of measurements of each sample.

2.3.4. Powder X-ray Diffraction (XRPD)

An X-ray diffractometer (Rigaku Mini Flex II, Tokyo, Japan) was used to study the crystallinity of the samples. All samples (solid dispersions and minitablets) were scanned within the angular range from 3° to 43° at a scanning speed of 5°/min. Monochromatic Cu Kα radiation (λ = 1.5418 Å) was used.

2.3.5. Dissolution Studies

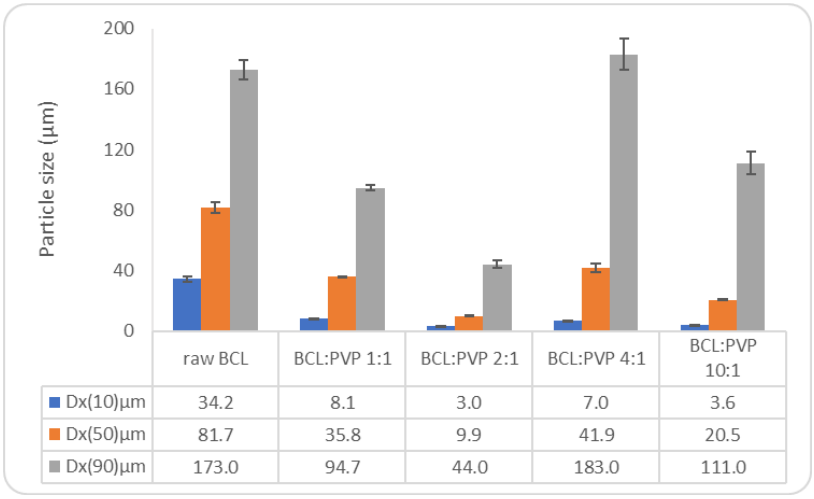
Dissolution studies of BCL from solid dispersions and minitablets were performed according to the procedure recommended by the FDA for BCL tablets. This study was conducted in Ph. Eur. No. 2 apparatus (paddle). Vision G2 Elite8 (Hanson Research, Chatsworth, CA, USA) was used, equipped with a Vision G2 AutoPlus autosampler. The dissolution medium, i.e., 1000 mL of 1% SLS, was maintained at 37 $\pm$ 0.5 °C, and the paddle speed was settled at 50 rpm. Milled solid dispersions or minitablets were introduced into the beakers. Each sample analyzed contained 50 mg of the drug substance. During the dissolution studies, the sink conditions were maintained (the solubility of BCL in 1% SLS is ca. 150 µg/mL). The amount of dissolved bicalutamide was determined online at 272 nm using a UV-1800 spectrophotometer (Shimadzu Corporation, Kyoto, Japan) equipped with flow-through cuvettes. The results were presented as the average of three measurements (n = 3) with their standard deviations (mean $\pm$ SD).

3. Results and Discussions

3.1. Bicalutamide and PVP K29/32 Solid Dispersions

3.1.1. Appearance of the Samples

After the solid dispersion preparation, each of them was white, free-flowing powder, regardless of the composition. However, differences were observed in particle size and morphology. Our previous studies showed that the median particle size of raw bicalutamide measured using a laser diffraction method, namely the Dv(50) value, was equal to 81.7 µm, and the Dv(90) value, representing the size of 90% of the total volume of material in the sample, was 173.0 µm. After milling, the Dv(50) of the solid dispersions did not exceed 42 µm. The maximum Dv(90), equal to 183 µm, was noticed for the 4:1 solid dispersions; and for the other samples, the Dv(90) was less than 111.0 µm (Figure 1) [26].



	raw BCL	BCL:PVP 1:1	BCL:PVP 2:1	BCL:PVP 4:1	BCL:PVP 10:1
Dx(10)µm	34.2	8.1	3.0	7.0	3.6
Dx(50)µm	81.7	35.8	9.9	41.9	20.5
Dx(90)µm	173.0	94.7	44.0	183.0	111.0

Figure 1. Particles sizes of raw bicalutamide, 1:1, 2:1, 4:1, and 10:1 solid dispersions. The results were obtained for freshly prepared powder samples.

The appearance of the samples was assessed immediately after taking them out of the stability chambers (Table 1). After 12 months of storage in long-term conditions (i.e., 25 °C, 60% RH), the samples were still white, regardless of the active substance to carrier weight ratio and packaging materials. Some agglomerates occurred in the samples, but they were easy to pulverize. The impact of storage was more pronounced for samples stored under accelerated conditions (i.e., 40 °C, 75% RH). However, the PVC/Al blister was a sufficient barrier to protect all the solid dispersion samples from temperature- and humidity-driven changes within two weeks of study. Elevated temperature and humidity induced changes in the appearance of the 1:1 and 2:1 solid dispersions stored in the polystyrene jars—after two weeks, changes in color and agglomeration were observed—while samples stored in blisters remained unchanged. After six months, slight yellowing and agglomeration were observed. However, the samples were still easy to pulverize by shaking, using mortar or spatula. With time, the color of the solid dispersions stored in accelerated conditions turned yellowish; and became beige after 12 months storage. This was attributed to the hygroscopic nature of PVP K29/32, which absorbs moisture when exposed to a humid environment [12]. Samples containing a higher amount of PVP K29/32 were more susceptible to humidity-related changes than those containing a higher amount of the drug compared to the polymer. Importantly, such behavior was observed for both types of packaging materials.

Table 1. Appearance of BCL:PVP solid dispersions after storage.

Time (Months)	Storage Conditions	BCL:PVP Weight Ratio	Polystyrene Container	PVC/Al Blister
			Properties	
0.5	25 °C/60% RH	1:1	White, free-flowing powder	White, free-flowing powder
		2:1		
		4:1		
		10:1		
	40 °C/75% RH	1:1	Yellowish-beige, agglomerated	White, free-flowing powder
		2:1	Slightly beige, agglomerated (less than 1:1)	
		4:1	White, free-flowing powder	
		10:1		
1	25 °C/60% RH	1:1	White, free-flowing powder	White, free-flowing powder
		2:1		
		4:1		
		10:1		
	40 °C/75% RH	1:1	Beige, compacted, rubbery	Agglomerated, brittle, easy to pulverize
		2:1	Slightly beige, lumpy powder	White, free-flowing powder
		4:1	White, free-flowing powder	
		10:1		
3	25 °C/60% RH	1:1	White, free-flowing powder without clods	White, free-flowing powder without clods
		2:1		
		4:1		
		10:1		
	40 °C/75% RH	1:1	Beige, agglomerated, rubbery	Yellowish, agglomerated
		2:1	Slightly beige, agglomerated	White, free-flowing powder
		4:1	White, free-flowing powder	
		10:1		
6	25 °C/60% RH	1:1	White, free-flowing powder	White, free-flowing powder
		2:1		
		4:1		
		10:1		
	40 °C/75% RH	1:1	Beige-yellow, agglomerated, rubbery, difficult to pulverize	Beige-yellow, agglomerated, rubbery, difficult to pulverize
		2:1	White, slightly agglomerated, easy to pulverize	White, slightly sticky lumps
		4:1	White, slightly sticky, pulverize after shaking	White, slightly sticky, pulverized after shaking
		10:1		
9	25 °C/60% RH	1:1	White, free-flowing powder	White, free-flowing powder
		2:1		
		4:1		
		10:1		
	40 °C/75% RH	1:1	Beige-yellow, agglomerated, rubbery, difficult to pulverize	Beige-yellow, strongly agglomerated, rubbery, difficult to pulverize
		2:1	White, slightly sticky, easy to pulverize by spatula	White, slightly sticky, easy to pulverize by spatula
		4:1	Slightly agglomerated, easy to pulverize	Slightly agglomerated, easy to pulverize
		10:1		

Table 1. *Cont.*

Time (Months)	Storage Conditions	BCL:PVP Weight Ratio	Polystyrene Container	PVC/Al Blister
			Properties	
12	25 °C/60% RH	1:1	White, slightly agglomerated, easy to pulverize	White, slightly agglomerated
		2:1		
		4:1	White, free-flowing powder	
		10:1		
	40 °C/75% RH	1:1	Yellowish, sticky, rubbery, hardly to pulverize	Beige, sticky, rubbery, hardly to pulverize
		2:1	Beige, agglomerated, pulverize by mortar	Beige, agglomerated, easy to pulverize by spatula
		4:1	White, slightly agglomerated, easy to pulverize	Yellowish, slightly agglomerated
		10:1	White, free-flowing powder	Yellowish, agglomerated, easy to pulverize by spatula

3.1.2. X-ray Analysis

The diffraction studies were performed to analyze the impact of storage conditions on the molecular order of solid dispersions. The analysis of diffractograms presented in Figure 2 indicates amorphization of bicalutamide upon milling since no Braggs peaks characteristic for bicalutamide crystals are visible for the 1:1, 2:1, and 4:1 freshly analyzed solid dispersions. The amorphous halo is seen instead. Given that an amorphous system was obtained even if the content of PVP K29/32 was as low as 20%, a high potential of the polymer was confirmed in stabilization of the molecularly disordered state was confirmed [25]. Only for the 10:1 solid dispersion, the drug remained crystalline as indicated by the well-resolved diffraction pattern (Figure 2). Differences in the diffraction patterns between samples stored at 25 °C and 60% RH in either polystyrene jars or PVC/Al blisters were almost negligible for 9 months (Figure 3a,b). After 12 months, the diffraction patterns of the samples stored in polystyrene containers exhibited more intense peaks than those stored in blisters (Figure 3c,d). Storage in polystyrene jars under the same conditions induced bicalutamide recrystallization as manifested by the presence of low-intensity Braggs peaks superimposed on the amorphous halo in the diffractograms presented in Figure 3c. The 10:1 solid dispersion was crystalline, regardless of the packaging material. For these samples, none of the tested conditions induced any changes in the crystalline structure after 12 months storage (Figures 2 and 3a–j). Given the hygroscopic nature of PVP K29/32, one can expect that samples stored in packaging materials, which do not prevent water permeation, would exhibit a tendency to recrystallization upon moisture absorption and plasticization. Although some traces of recrystallization occurred, the results indicated that the tested packaging materials were able to inhibit water penetration in long-term conditions to the extent that they prevented nucleation and crystal growth. Due to the high glass transition temperatures of the solid dispersions, near 100 °C provided by PVP K29/32, the amorphous samples exhibited satisfactory stability over 12 months storage. The samples packed into PVC/Al blisters were more resistant than those in polystyrene containers.

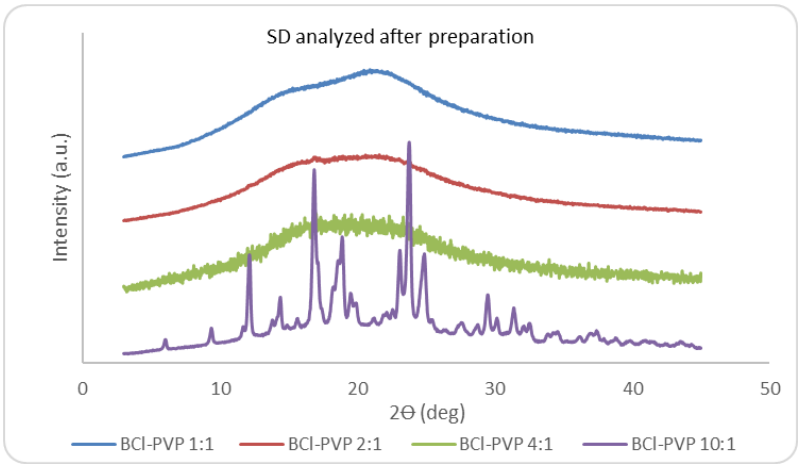
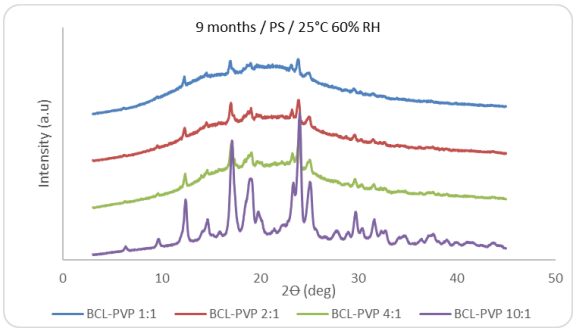
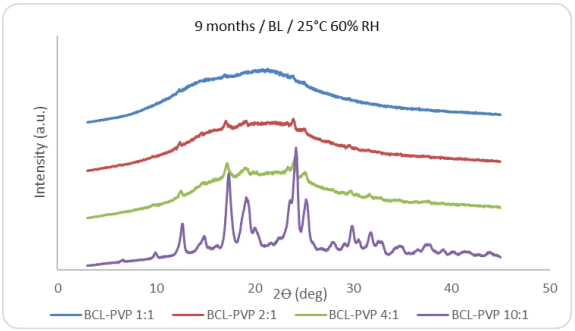


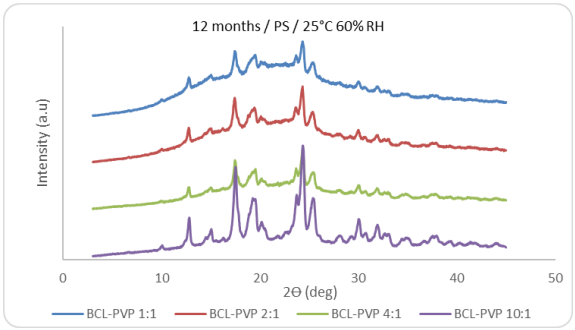
Figure 2. X-ray pattern of bicalutamide from the 1:1, 2:1, 4:1, 10:1 solid dispersions. The results were obtained for freshly prepared powder samples.



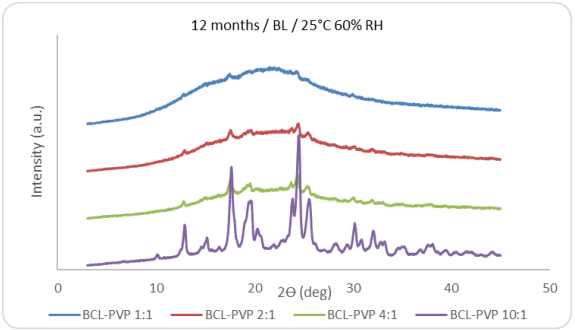
(**a**)



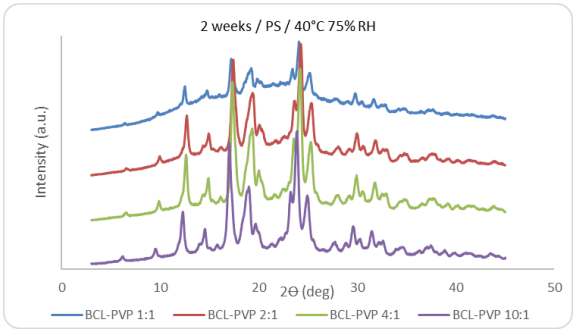
(**b**)



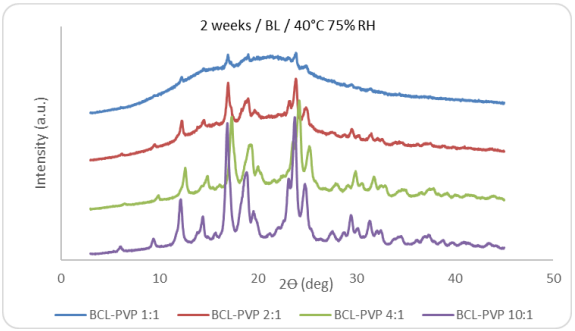
(**c**)



(**d**)



(**e**)



(**f**)

Figure 3. *Cont.*

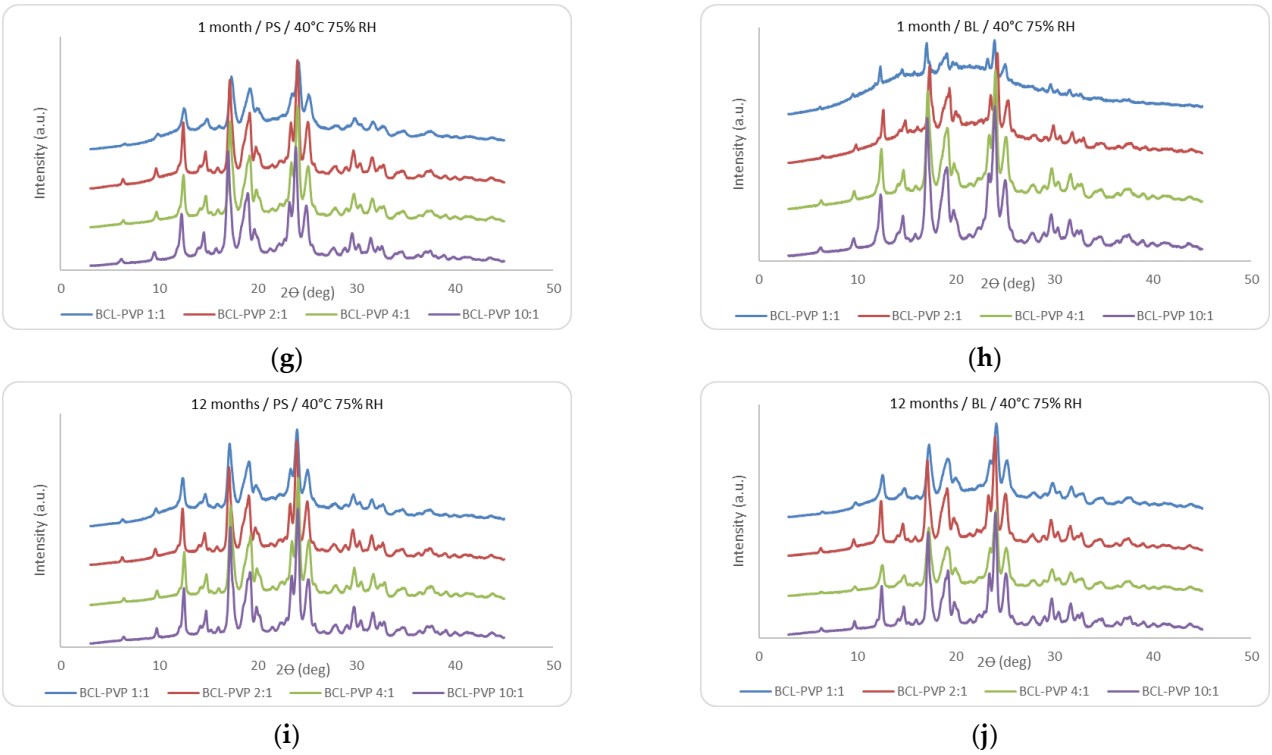


Figure 3. X-ray pattern of bicalutamide from the 1:1, 2:1, 4:1, 10:1 solid dispersions packed into polystyrene containers (PS, left panel) and PVC/Al blisters (BL, right panel)after storage in long-term conditions (25 °C, 60% RH), for 9 months (**a**,**b**), and 12 months (**c**,**d**) and accelerated conditions (40 °C, 75% RH) for 2 weeks (**e**,**f**), 1 month (**g**,**h**) and 12 months (**i**,**j**).

The accelerated conditions (i.e., 40 °C 75% RH) caused the recrystallization of all the samples stored in polystyrene containers within the two weeks of storage (Figure 3e). Those packed into blisters showed the same behavior, except for the 1:1 solid dispersion, which was partially amorphous at this time (Figure 3f) and recrystallized after one month of storage (Figure 3,h). This indicates that only moisture insulation can prevent the recrystallization of samples stored at elevated temperature and high humidity.

3.1.3. Dissolution of Bicalutamide from Solid Dispersions

The formation of amorphous solid dispersion is a method of the improving of dissolution of poorly water-soluble drugs. Since the miscibility of many active compounds with polymer is limited, a high amount of the macromolecular compound is usually added to solid dispersions to provide good stability and favorable dissolution characteristics [28]. In the presented paper, our goal was to monitor how the dissolution changes upon storage of solid dispersions in two types of packaging materials and to correlate those changes with the rearrangement of crystal structure triggered by different environmental conditions.

The results showed that freshly prepared amorphous solid dispersions (i.e., 1:1, 2:1, and 4:1 systems) exhibited a 10-fold improvement in drug dissolution in comparison with crystalline bicalutamide, reaching c.a. 80% in all he samples after one hour. Only, dissolution from the 10:1 solid dispersion, which was crystalline, was 5-fold greater than from raw bicalutamide and equal to 43% (Figure 4).

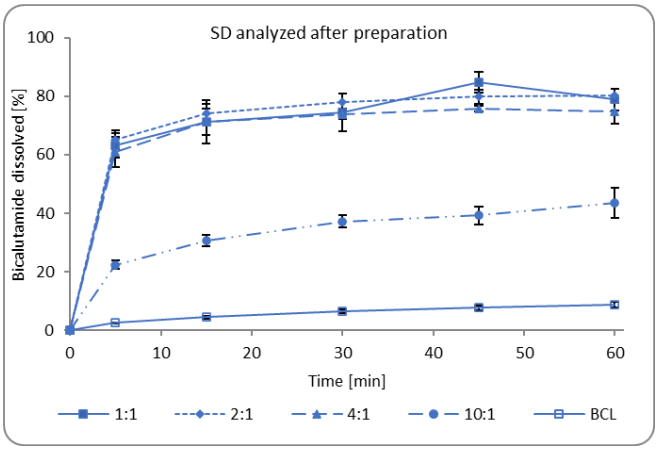


Figure 4. Dissolution of bicalutamide from the 1:1, 2:1, 4:1, 10:1 solid dispersions and for raw substance. The results were obtained for freshly prepared powder samples.

The results of the dissolution study indicate that the 1:1 and 2:1 solid dispersions were the most resistant to storage conditions. After 12 months of storage at 25 °C and 60% RH, the amount of bicalutamide dissolved from the 1:1 solid dispersion remained unchanged, regardless of the type of packaging material (Figure 5b). The 2:1 solid dispersions packed into PVC/Al blisters exhibited unchanged dissolution characteristics after 12 months storage. However, the sample packed in polystyrene containers exhibited a slight decrease in dissolution—73% dissolved after 1 h (Figure 5b). Interestingly, despite the partially amorphous characteristic of the 4:1 solid dispersion, a decrease in drug dissolution was observed in both the PVC/Al blisters and the polystyrene containers (Figure 5b). In comparison with the freshly analyzed solid dispersion sample, it was 1.4- and 1.8-fold lower, respectively (Figure 4). The 10:1 solid dispersion was resistant to storage conditions (Figure 5a) only for one month, and only when packed in a PVC/Al blister. A gradual decrease in drug dissolution was then observed. In this sample, after 12 months, the amount of the active substance dissolved was 8% after 1 h. This was comparable to the value measured for raw bicalutamide [4].

Regarding accelerated conditions (40 °C, 75%RH), after 12 months storage, the 1:1 and 2:1 solid dispersions exhibited only small fluctuations in the amount of dissolved bicalutamide, regardless of the type of packaging material (Figure 5d). The results obtained after 12 months for the 4:1 solid dispersion packed into blisters and polystyrene jars showed a 2-fold decrease in the amount of bicalutamide dissolved in comparison with freshly analyzed solid dispersion (Figure 5d). This decrease in dissolution occurred just after two weeks of storage, and is related to drug recrystallization, as revealed by XRD studies (Figure 2d). Interestingly, similar to the samples stored at 25 °C 60% RH, a gradual decrease in the amount of the active substance dissolved was noticed for the 10:1 solid dispersion. After 12 months storage, the amount of bicalutamide dissolved after 1 h was 3.5-fold lower in comparison with sample analyzed immediately after preparation (Figure 5d).

Based on the results of the storage of solid dispersions in different bicalutamide to carrier weight ratios, packed into polystyrene jars and PVC/Al blisters under long-term and accelerated conditions, the 1:1 solid dispersion was chosen to formulate minitablets. We determined the protective influence of PVC/Al blisters on 12 months storage. The X-ray results showed that the insulation properties of the packaging material from moisture can prevent the recrystallization of the active substance during storage. This result corresponds to dissolution studies—the amount of the active substance dissolved from the 1:1 solid dispersions packed into PVC/Al blisters remained unchanged after 12 months storage, regardless of the storage conditions.

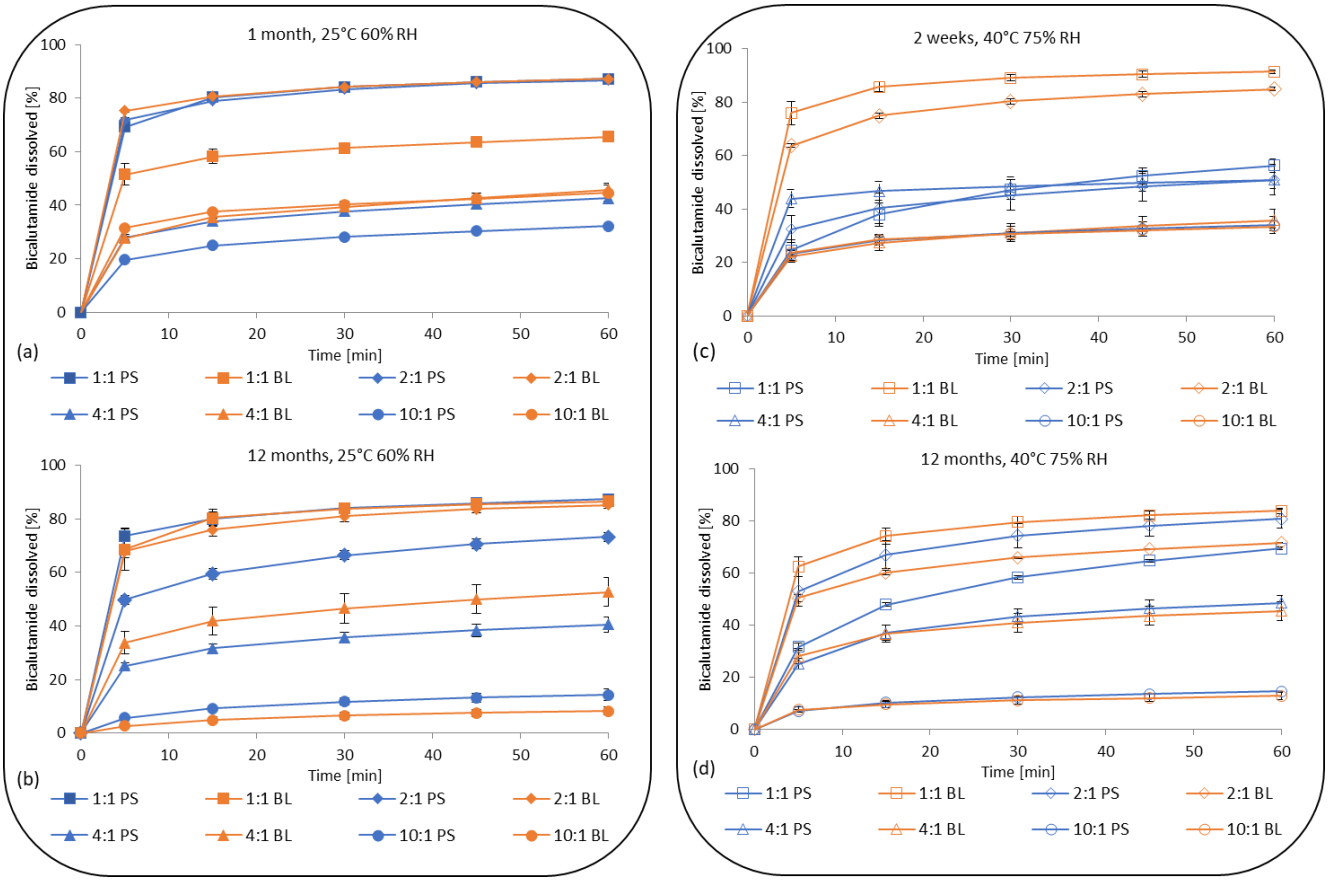


Figure 5. Dissolution of bicalutamide from the 1:1, 2:1, 4:1, 10:1 solid dispersions packed into PVC/Al blisters (BL) and polystyrene bag (PS) after storage in long-term conditions (25 °C/60% RH, left panel) for 1 month (**a**) and 12 months (**b**), and accelerated conditions (40 °C/75% RH, right panel) for 2 weeks (**c**) and 12 months (**d**); the errors bars represent the standard deviation.

3.2. Final Blend and Minitablet Characterization

3.2.1. Physical Characteristics of the Final Blend and Minitablets

The final blend was prepared by mixing the 1:1 solid dispersion with the weighed amount of excipients, including microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The properties of the final blend were established according to the Ph. Eur. requirements, the results are presented in Table 2.

Table 2. Properties of the final blend.

Attribute / Sample	Angle of Repose (°)	Hausner Ratio	Compressibility Index
Final blend	55	1.43	30.1

Based on the angle of repose, the flowability of the final blend was classified as poor. The same characteristic of flowability was defined by the Hausner ratio and the compressibility index. However, despite the poor flow properties of the final blend, the tableting operation went smoothly. The dosage of a single minitablet was equal to 5 mg, which means that 10 minitablets were the equivalent of one tablet containing 50 mg of bicalutamide. The minitablets were packed into PVC/Al blisters (10 minitablets per blister slot) and stored in the climate chambers, both under long-term and accelerated conditions. The physical properties of the obtained minitablets, such as mass uniformity, hardness, thickness, and disintegration time were assessed just after the preparation of the minitablets and after six months of storage (Table 3).

Table 3. Physical properties of minitablets analyzed immediately after preparation and after six months of storage in long-term (25 °C, 60% RH) and accelerated (40 °C, 75% RH) conditions.

Parameter / Minitablets	Mass (mg)	Hardness (N)	Thickness (mm)	Disintegration Time (min:s)
Immediately after preparation	16.3 ± 0.7	38.95 ± 2.94	2.01 ± 0.03	14:29
Long-term conditions	16.0 ±1.1	5.20 ± 0.49	2.93 ±0.02	4:33
Accelerated conditions	17.3 ± 0.5	26.29 ± 3.83	2.95 ± 0.09	4:25

The results presented in Table 3 indicate that the storage conditions influenced the properties of minitablets. However, the mass of tablets stored in the long-term stability chamber remained unchanged (Table 3). After storage under accelerated conditions, the mass of the tablets increased from 16.3 to 17.3 mg. Temperature and humidity in both the long-term and accelerated conditions affected hardness, thickness, and disintegration time. In comparison with the result obtained immediately after the preparation of minitablets, the hardness decreased from 38.95 N to 5.20 N and 26.29 N, respectively. This was the effect of humidity uptake. Moreover, the increase in thickness from 2.01 mm to 2.93 mm and 2.95 mm was noticed. The data obtained correspond to the results for the disintegration time, which is c.a. 3-fold shorter after storage under both conditions. The observed effects resulted from moisture absorption by hygroscopic PVP K29/32, in agreement with previously presented results collected for solid dispersions in powder form.

3.2.2. X-ray Diffraction Studies

The X-ray diffraction analysis of minitablets performed immediately after preparation showed that the drug existed in the amorphous state since no Braggs peaks were visible in the diffraction pattern (Figure 6). Neither the long-term nor the accelerated conditions influenced the molecular arrangement of bicalutamide (Figure 6). The results obtained for the minitablets differ from those obtained for solid dispersions in powder form, which recrystallized after one month of storage in blisters under accelerated conditions. This may result from the fact that the contact of moisture with the active substance in the amorphous phase was limited due to the compact structure of minitablets, which slow down water penetration into the sample. This also confirmed the high stabilizing efficiency of PVP K29/32. Water uptake and inhibition of crystallization tendency may also be limited by addition of the excipients.

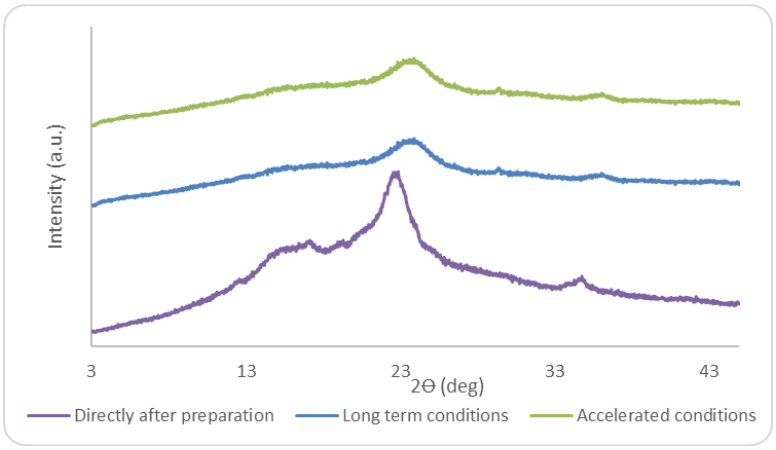


Figure 6. X-ray diffraction of minitablets after six months of storage in long-term (25 °C/60% RH) and accelerated (40 °C/75% RH) conditions.

3.2.3. Dissolution of Bicalutamide from Minitablets

The release of bicalutamide from minitablets was comparable with that reported for solid dispersions in powder form analyzed immediately after preparation. After six months of storage under both long-term and accelerated conditions, the amount of released bicalutamide decreased. After five minutes of dissolution study, the amount of the active substance released was equal to 18.11 ± 6.93% and 19.99 ± 8.64% for minitablets kept in long-term and accelerated conditions, respectively. It is worth mentioning that the amount was 50.19% ± 6.63% for the minitablets analyzed immediately after the preparation, which means that there was a 2.5-fold decrease. The amount of bicalutamide released after 1 h also decreased and reached 49.69 ± 0.54% for minitablets stored at 25 °C and 60% RH and 46.09 ± 3.80% for minitablets stored under accelerated conditions (Figure 7). The amount of bicalutamide dissolved after one hour from freshly prepared minitablets was equal to 85.94 ± 1.11%. This decrease might result from the absorption of moisture and swelling of the PVP K29/32 matrix, which hindered matrix disintegration and slowed down drug release. This indicates that PVC/Al blisters are not suitable as packaging material to protect minitablets against the influence of humidity.

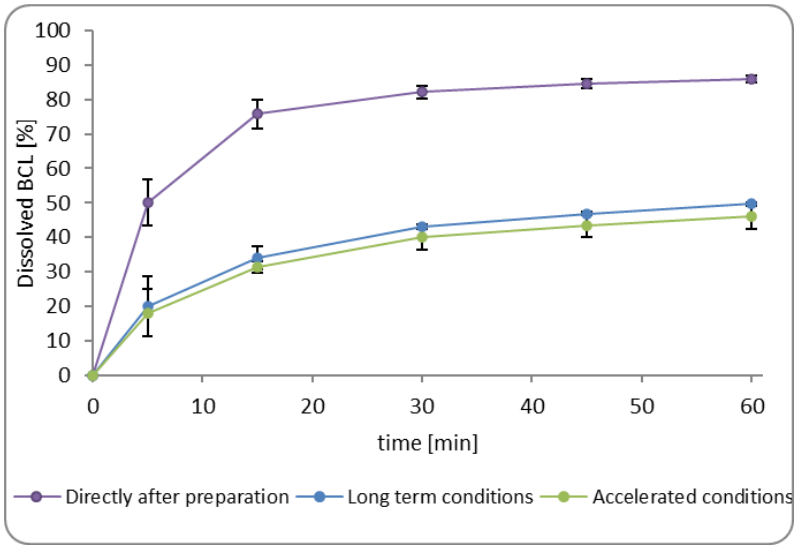


Figure 7. The dissolution profile of bicalutamide from minitablets analyzed immediately after preparation and after six months of storage in long-term (25 °C/60% RH) and accelerated (40 °C/75% RH) conditions. Minitablets were packed into PVC/Al blisters; the errors bars represent the standard deviation.

3.2.4. Kinetics Data

The kinetics of drug release from minitablets was analyzed using open source software, KinetDS 3.0. with standard settings [29], and the best fits were obtained for the Korsmeyer–Peppas and Weibull models, respectively. The Korsmeyer–Peppas model is given as $M_t/M_\infty = A \cdot t^n$, where n is release exponent indicating the mechanisms of drug release, and A is a constant representing a geometric and structural characteristic of dosage form. The Weibull model is given as $M = M_0 [1 - e^{-(t/a)b}]$, where M_0 is the total amount of drug released, a denotes a scale parameter that describes the time dependence, and b is the shape of the dissolution curve progression. The values of the equation constants presented in Table 4 confirmed that the mechanism of dissolution did not change substantially during storage (n value). However, changes in the dissolution rate were observed (A value).

Table 4. Kinetics data calculated for minitablets analyzed immediately after preparation and after six months of storage in long-term (25 °C/60% RH) and accelerated (40 °C/75% RH) conditions.

Kinetic Model / Minitablets	Korsmeyer–Peppas			Weibull		
	A	**n**	**R^2**	**a**	**b**	**R^2**
Immediately after preparation	2.81	1.04	0.9956	1.98	1.06	0.9973
Long-term conditions	1.52	1.01	0.9971	5.31	1.02	0.9978
Accelerated conditions	1.42	1.01	0.9972	5.81	1.02	0.9978

A, **n**—parameters of the Korsmeyer–Peppas model. **a**, **b**—parameters of the Weibull model. **R^2**—coefficien of determination.

4. Conclusions

The performed studies examined the stability of solid dispersions containing bicalutamide and PVP K29/32 on 12 month storage.

The results revealed that the active substance was amorphized upon milling when mixed with PVP K29/32 in 1:1, 2:1, and 4:1 weight ratios. Only in the 10:1 solid dispersion did bicalutamide remain crystalline. The formation of amorphous solid dispersions led to a 10-fold improvement in drug dissolution in comparison with crystalline bicalutamide.

Analysis of diffractograms of samples after storage under long-term conditions (25 °C/60% RH) showed the influence of the packaging materials on the stability of the active substance. After 12 months, the diffraction patterns of the samples stored in polystyrene containers exhibited more intense Braggs peaks than those stored in blisters. The changes in crystal structure correspond to the dissolution characteristics of solid dispersions. The amount of bicalutamide dissolved from the 1:1 solid dispersion remained unchanged. For other samples, a decrease in drug dissolution was observed.

In the case of the samples stored under accelerated conditions (40 °C/75% RH), the solid dispersions packed into polystyrene containers recrystallized within two weeks of storage. The solid dispersions stored in blisters showed similar behavior, except from the 1:1 solid dispersion, which was partially amorphous after two weeks and completely recrystallized after one month of storage. Samples packed in either polystyrene containers or blisters exhibited fluctuations in the amount of bicalutamide dissolved. For the 4:1 and 10:1 solid dispersions, a decrease in the amount of the dissolved active substance was observed, regardless of the type of packaging.

Taking into account the results obtained, the 1:1 solid dispersion was chosen as optimal, and that system was further used to formulate minitablets. PVC/Al blisters were chosen as the packaging material for minitablets. Freshly prepared minitablets contained an amorphous drug and exhibited dissolution characteristics similar to solid dispersions. After six months of storage, both physical properties and dissolution characteristics were altered. However, this did not affect the crystal structure of bicalutamide. This may result from the fact that the contact of moisture with the amorphous sample was limited due to the compact structure of minitablets, which slow down water penetration into the sample. Although bicalutamide existed in an amorphous form, the amount of bicalutamide dissolved from minitablets was reduced by 2-fold, regardless of storage conditions. This might be an effect of moisture absorption and swelling of the PVP K29/32 matrix, which hindered matrix disintegration and slowed down drug release.

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