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Stability evaluation of tablets containing diclofenac sodium and papaverine hydrochloride and different auxiliary substances in equilibrium relative humidity condition

Ocena trwałości tabletek zawierających diklofenak sodowy i chlorowodorek papaweryny z różnymi substancjami pomocniczymi w warunkach równowagowej wilgotności względnej

INTRODUCTION

The term "stability" refers to the storage time allowed before any degradation product in the dosage form achieves a sufficient level to represent a risk to the patient [13]. According to the requirements of The International Council of Harmonization (ICH), a typical drug stability study consists of 6 months accelerated and at least 2 years (often three or more) of long-term stability testing, where the goal is to ascertain that the product quality is within specified limits [3]. The pharmaceutical solid dosage forms are commonly tested according to the requirements as described in literature [1,7,11].

Methods of rapidly and accurately assessing the physical and chemical stability of pharmaceutical dosage forms with respect to the major degradation mechanisms are generally observed in pharmaceutical development [8, 10, 13]. The most common approach in predicting chemical stability is to predict the degradation rate at long-term stability conditions from stability data obtained at higher temperatures in a short time frame [7].

Tablet moisture is a crucial parameter for stability of the drug and should be kept as low as possible. The physical stability is also important for pharmaceutical dosage forms with respect to its effects on chemical stability. The role of moisture in causing physical changes is related to the water activity of the system rather than the moisture content of either the dosage form or the surrounding air. Water acivity is a thermodynamic term referring to the equilibrium relative humidity (ERH) over a sample. At equilibrium, the water activity of a sample is equal to the ERH of the air surrounding it. Though accelerated aging predictions will generally correlate significantly better using ERH (water activity) than with total water content in the dosage form or absolute humidity in the environment [2,13], correlations are sometimes seen between water content and drug stability using the Carstensen equation [6]. In the report [12], a plot of the logarithm of the degradation rate versus the logarithm

of the water content is linear. In reality, drug product water content will directly correlate with the degradation rate only when the water content correlates directly with the water activity.

Arrhenius modeling can be used for predicting the degradation rate from stress stability data. Two obvious conditions have to be fulfilled with this Arrhenius-type predictions. The first one is that the degradation rates at high temperatures must accurately predict the degradation rate at the long-term stability condition. If this holds stress tests at higher temperatures, it can be used to make a fast prediction of a long-term stability.

The second condition is that the degradation kinetics does not change with time, which allows accurate extrapolation of stability beyond the period, covered by observed stability data [7].

The aim of this study was to evaluate the physical and chemical stability of diclofenac sodium and papaverine hydrochloride in tablets comprising two different formulas of the auxiliary substances by testing the change of shape and weight of tablets at the stress conditions such as various relative humidity and temperatures as well as the quantity of the active substances in ERH.

MATERIAL AND METHODS

S u b s t a n c e s . Diclofenac sodium (DIC) produced by Caesar and Loretz, GmbH, Hilden, Germany, papaverine hydrochloride (PAP) obtained from Galfarm PPH, Cefarm Lublin, Poland, polyvinylpyrrolidone (PVP) K 22, mannitol (M), potato starch (PS), hydroxypropylmethylcellulose (HPMC), microcrystaline cellulose (MC), magnesium stearate (MS), trisodium citrate dehydrate, citric acid monohydrate, methanol and water were the products of Merck, Germany. All other reagents used were of analytical grade (pure for analysis).

T a b l e t s . Composition and preparation of the tablets were presented in the Polish Patent [5]. Tablets 1 (T1). One tablet (T1) consists of 50 mg DIC, 20 mg PAP and excipients as PVP, M and PS to 300 mg of weight. Tablets 2 (T2). One tablet (T2) consists of 50 mg DIC, 20 mg PAP and excipients as PVP, M, HPMC, MC, MS to 300 mg of weight.

Preparation of the solid dosage forms: Tablets were prepared by separate dissolution of DIC and PAP in methanolic solution of PVP, followed by addition of the powdered excipients, evaporation of solvent, granulation of the wet mass (granula machine with a 1.6 mm sieve, Erweka, Germany), then by drying the granulas and tabletting the granulas in the tablet machine (Erweka, Germany).

S t u d i e s o f t a b l e t s . Prepared tablets before and after the storage were weighed by using the analytical balance (Metler Toledo). The diameter and height of the tablets were measured by vernier caliper (Mava, FWP, Poland).

D r u g c o n t e n t . The quantity of active substances was assayed by HPLC method published in a early report [4].The HPLC system consisted of a series of 200 HPLC pump, a series of 200 autosampler equipped with a 200 µl loop, a UV/VIS detector series of 200 set at 278 nm, a vaccum degasser series 200 and a chromatography interface of 600 series LINK, all purchased by Perkin Elmer (USA). The column was a Zorbax SB – C 18, 150 mm x 4.6 mm, 5µm (Agilent, USA). A mobile phase of methanol: water (60:40, v/v) was used at a flow rate of 1.0 ml/min. The accurately weighed tablet was placed into the flask and dissolved with the mixture : methanol: water (60:40, v/v)

and diluted to 100 ml. The solution was filtered using 0.20 μm pore size HPLC filters (Spartan 13/0.2 RC, Aldrich). 10 μl samples were injected into the column by autosampler and chromatogram was developed for a period of 15 min. UV signals were monitored and the peaks were integrated using the software version 6.2.0.0.0:B27. Experiments were performed for six tablets for each of the flow liquid rate HPLC analysis.

S t o r a g e . Tablets without a package were stored in the climatic testing chamber (KBK-65W Wamed, Poland) at temp. 24 °C, 35 °C, 45 °C and relative humidity 50%, 60%, 70%, 80%, 90% (RH) for the period of time needed for an estimation of constant weight of the tablets.

RESULTS

Prepared tablets have white, smooth surface, the average mass of T1 equals 295.92 mg and T2 295.07 mg, respectively, the quantity of DIC 50 mg (± 5%), and PAP 20 mg (± 5%), the hardness ratio larger than 0.1 kG/mm^2, the desintegration time of the tablets in water at 37^{0}C no longer than 15 min and the tablets are consistent with pharmacopoeial requirements [9]. The average diameter of T1 and T2 is 9.1 mm and their heights are 4.28 mm and 3.89 mm for T1 and T2, respectively.

The diagram of the times needed for the achievement of the ERH conditions in tablets at 24°, 35°, 45 °C is shown in Fig. 1.

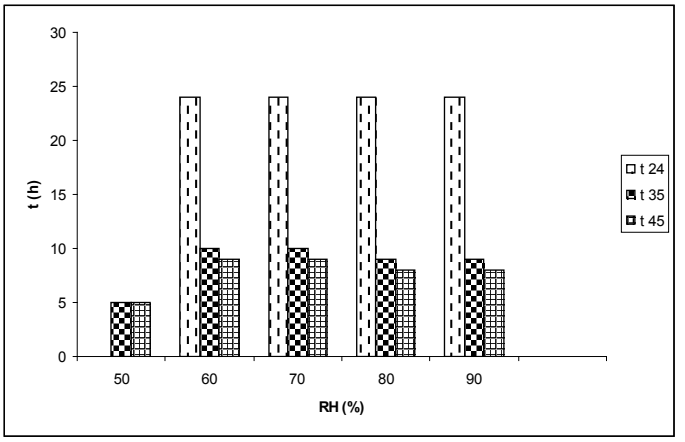

Fig.1. Times needed of achievement of ERH in tablets

The average diameters of tablets after achievement of ERH condition equal 9.5 mm (T1), 9.4 mm (T2) and heights (T1) 4.6 mm and (T2) 4.3 mm. Results of increasing of the weight tablets (m) in the period of storage time (t) are presented in Fig. 2 a–c.

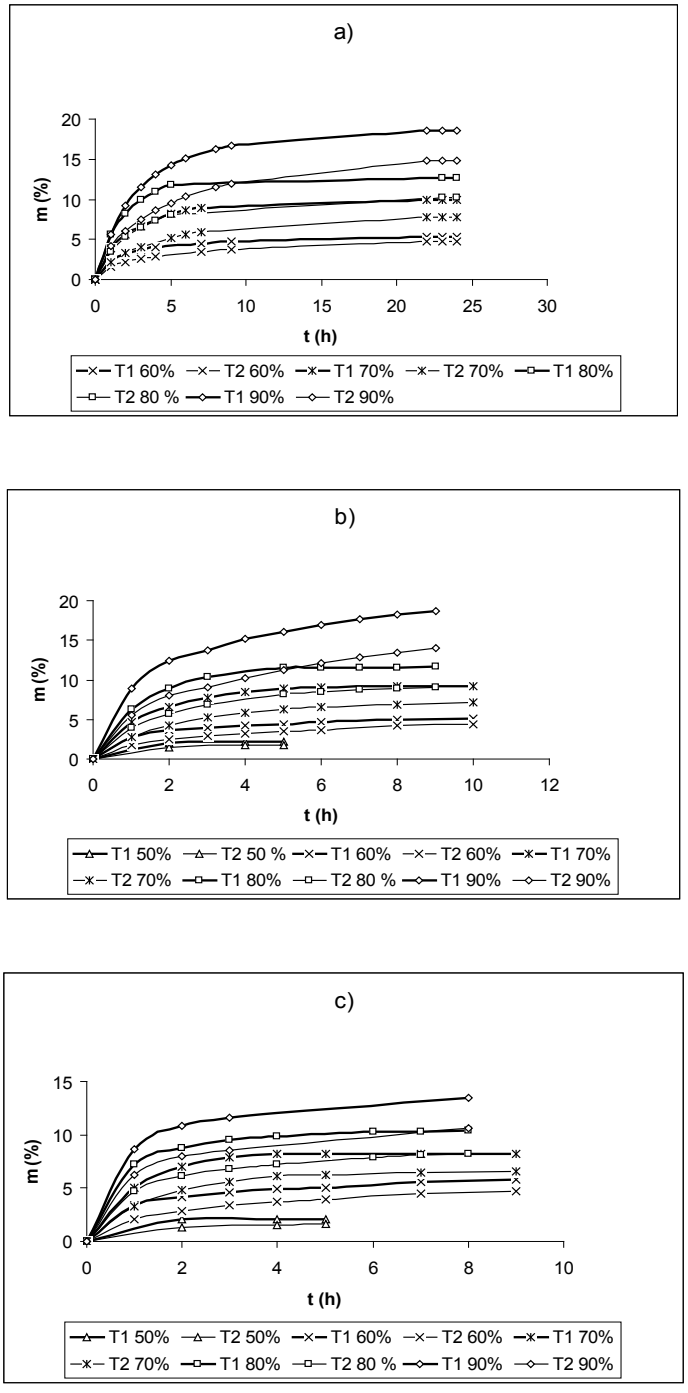

Fig. 2. Increase of the tablets (T1 and T2) weight (m) in different RH in the periods of storage time (t) and temp. a) at 24 °C, b) 35 °C and c) 45 °C

The plots of the logarithm of the moisture content in tablets (ln Ms) in relation to RH during the storage time at all temperatures are presented in Fig. 3.

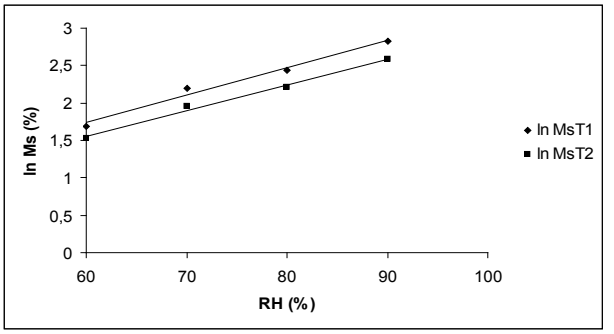

Fig.3. The plots of relationship between the logarithm of increasing moisture content (ln Ms) in T1 and T2 at different RH during the storage in the range from 24 °C to 45 °C

The quantity of the active substances in tablets after all the storage time in different RH and temperatures in ERH conditions are shown in Fig. 4–5.

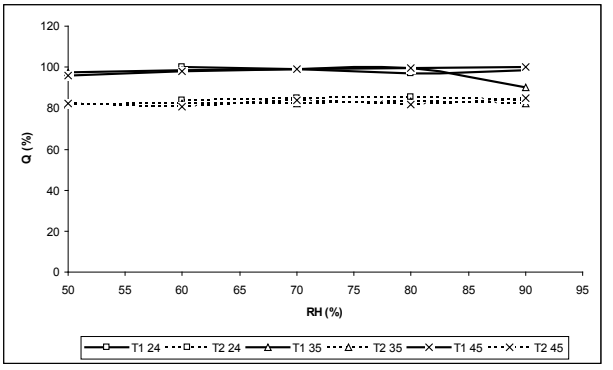

Fig. 4. The quanitity of DIC in T1 and T2 in ERH at 24 °C, 35 °C and 45 °C

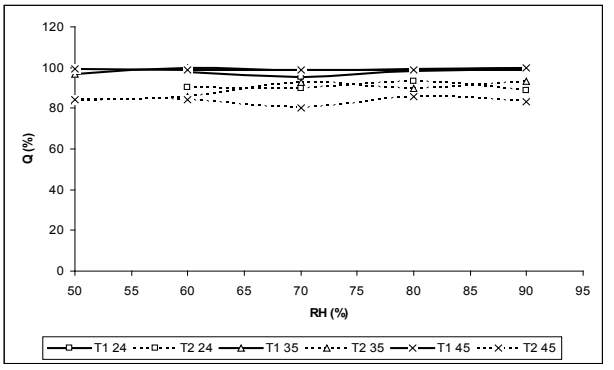

Fig. 5. The quantity of PAP in T1 and T2 in ERH at 24°C, 35°C and 45°C

DISSCUSION

Prepared tablets with DIC and PAP consisting of two formulas of excipients T1 (PVP, M, PS) and T2 (PVP, M, HPMC, MC and MS) were tested before storage and in the periodical time of storage until the constant weight of tablets was achieved. The tablets took the moisture from the surrounding air during the time of storage in different relative humidity and temperatures. The increasing weight of tablets corresponds to moisture contents in the tablet mass. Moisture can be expressed as water percentage or equilibrium relative humidity (ERH) (7). ERH represents the moisture content relative to the saturated moisture content at tested temperatures [13].

As shown Fig. 1 the times needed for the achievement of ERH in both kinds of tablets T1 and T2 are the same and they are 5 h in 50% RH, from 8 h to 10 h in 60% to 90% RH at higher temp. 35 ^{o}C and 45 ^{o}C, but at 24 ^{o}C it is 24 h at the same RH. The time of storage in the tested conditions needed for obtaining the ERH in tablets does not depend on the auxiliary substances which are in mass tablets but only on temperatures in the climatic chamber in the tested RH conditions. As reported by Watermann [13], when the temperature increases, the amount of water in the air for a given relative humidity increases and as a result the tablets uptake the water from the surrounding air in a shorter time.

As shown Fig. 2 a–c, in increase of tablet weights in the storage time corresponds to moisture content in tablets. When the tablets weight does not increase, it can be assumed that the ERH condition in tablets has been achieved. The quantity of the moisture uptaken by tablets was increased with the rise of RH from 50% RH to 90% RH in the climatic chamber as follows 2.16%, 5.41%, 9.04%, 11.52%, 16.91% in T1 and 1.69%, 4.64%, 7.13%, 9.15%, 13.17% in T2 with the difference between the temperatures in given RH from 5% to 4% in T1 and T2, relatively. Formula of T2 compared to T1 uptook less moisture from the air than T1 so in 50% RH 0.5% less and 0.8%, 1.9%, 2.4%, 3.7% in 60% to 90% RH, respectively.

As shown in Fig. 3, a direct linear relationship exists between the logarithm of moisture content in T1 nad T2 and relative humidity which can be decribed by equations: ln Ms T1: $y = 0.0366 \cdot x - 0.455$, $R^2 = 0.9818$ and ln Ms T2: $y = 0.034 \cdot x - 0.48$, $R^2 = 0.9907$.

The addition of excipients used in formula T2 caused that tablets T2 take up less moisture. The auxiliary substances used in T2 are the same with the addition of PVP nad M, but different with HPMC, MC and MS. In formula T1 potato starch (PS) is used which does not protect from the uptake of the moisture by tablets T1.

Studies of sharpe of the tablets present that diameter of tablets after achieving ERH increases on average by 4.4%, height 7.5% in T1 and 3.3% and 10.5% in T2, respectively. Tablets (T1) comprising potato starch changed their shape even within the storage time, but the auxiliary substances such as HPMC, MC and MS in T2 caused a considerable increase in their height, which can be observed as swelling of the tablets.

Results of determination of the quantity of the active substances in tablets after achievement of ERH as in Fig. 5 show that the average quantity of DIC calculated for all temperatures and RH in T1 is 98.61% (± 5%) and PAP 98.48% (± 5%) and in T2 DIC 83.03% (± 5%) and PAP 87.49% (± 5%). A considerable decrease of the quantity of active substances DIC 17% and PAP 12.5% compared to declared doses in tablets T2 show that excipients in the formula of T2 do not ensure the stability

of the active substances in stress conditions such as higher moisture and temperature. However, DIC seems to be more sensitive for moisture content and higher temperature than PAP because the quantity of DIC comparing to PAP decreased by 4.5%. Degradation rates in the tested conditions could not have been predicted with the use of Arrhenius equation because after achieving ERH in tablets T1 was almost 100% of the active substances; however, in T2 after 24 h of storing, they decreased almost 20% of quantity DIC and PAP.

CONCLUSIONS

Studies of the stability of active substances show that different excipients added to the tablets cause difference in the uptake of moisture from the surrounding air during storage time in stress conditions. Potato starch added to the mass tablet T1 joint with PVP and M does not protect the tablets from taking moisture from the air, but a change of shape of the tablets was insignificant and degradation of DIC and PAP does not exist after obtaining ERH condition in tablets. The addition of HPMC, MC and MS in T2 causes an increase of the height of tablets the decrease of the quantity of active substances of approximately 20 %. The test shows that both T1 and T2 the equilibrium relative humidity conditions get in the same time in given RH and temperatures, but T1 tablets take up a higher content of moisture than T2. Bearing in mind the above results, it can be confirmed that the formula of T1 tablets is better for stability of active substances during the storage.

REFERENCES

1. Al-Gohary O.M.N., Al-Kassas R.S.: Stability studies of aspirin-magaldrate double layer tablets. Pharm. Acta Helv., 74, 351, 2000.
2. Heidemann D.R., Jarosz P.J.: Preformulation studies involving moisture uptake in solid dosage forms. Pharm. Res., 8, 292, 1991.
3. International Conference of Harmonization, 2003. Stability testing of new drug substances and products, ICH Q1A (A). WHO working document QAS/06.179, 2006.
4. Kasperek R.: Determination of diclofenac sodium and papaverine hydrochloride in tablets by HPLC method. Acta Pol. Pharm – Drug Res., 65, 4, 403, 2008.
5. Kasperek R.: The tablets containing of diclofenac sodium with analgetic and spasmolytic effect and their preparation. Polish patent No P-380847, 2006.
6. Matsunaga Y., Ohta R., Bando N. et al.: Effects of water content on physical and chemical stability of tablets containing an anticancer drug TAT-59. Chem. Pharm. Bull., 41, 720, 1993.
7. Naveršnik K., Bohanec S.: Predicting drug hydrolysis based on moisture uptake in various packaging designs. Eur. J. Pharm. Sci., 35, 5, 18, 447, 2008.
8. Ohmori S., Kataoka M., Koyama H.: Stability of cyanocobalamin in sugar-coated tablets. Int. J. Pharm., 337, 161, 2007.
9. Polish Pharmacopoeia VIII, Warsaw, 2008.
10. Stulzer H.K., Silva M.A.: Stability studies of coated granules and tablets contained captopril. Acta Pharma. Bonaerense, 25, 497, 2006.

11. Yang Y., Gupta A., Carlin A.S. et al.: Comparative stability of repackaged metoprolol tartrate tablets. Int. J. Pharm., 385, 92, 2010.
12. Vromans H., Schalks E.J.M.: Comparative and predictive evaluation of the stability of different freeze-dried formulations containing an amorphous moisture-sensitive ingredient. Drug Dev. Ind. Pharm., 20, 757, 1994.
13. Waterman K.C., Adami R.C.: Accelerated aging: Prediction of chemical stability of pharmaceuticals. Int. J. Pharm., 293, 101, 2005.

SUMMARY

Two formulas of tablets with diclofenac sodium and papaverine hydrochloride and addition different excipients were prepared and stored in the climatic chamber for stability testing. The studies showed that tablets containing potato starch, polyvinylpirrolidone and mannitol kept their shape and the quantity of active substances does not change after achievement of equilibrium relative humidity condition in tablets.

Keywords: diclofenac sodium, papaverine hydrochloride, stability, moisture, equilibrium relative humidity

STRESZCZENIE

Przygotowano tabletki według dwóch przepisów zawierających diklofenak sodu i chlorowodorek papaweryny z różnymi substancjami pomocniczymi, które następnie przechowywano w komorze klimatycznej w celu zbadania stabilności substancji leczniczych. Badania wykazały, że tabletki zawierające skrobię ziemniaczaną, poliwinylopirolidon i mannitol zachowały swój kształt, niezmienioną zawartość substancji leczniczych po uzyskaniu równowagowej wilgotności względnej w tabletkach.

Słowa kluczowe: diklofenak sodu, chlorowodorek papaweryny, stabilność, równowagowe wilgotności względnej