Preliminary analysis of the hemispherical directional reflectance of Alugastrin tablets after 14 days of storage at 40°C

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European Journal of Medical Technologies
2022; 1(31): 15-22

www. medical-technologies.eu
Published online 1.05.2022

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Abstract

Background: Drug stability is one of the key components of the efficacy of oral solid dosage forms. In a medicinal product stored under conditions that are inconsistent with the manufacturer's recommendations in terms of temperature, humidity, and light, adverse changes may occur. In consequence, these changes may affect the physicochemical properties of the drug form as well as the pharmacological activity of the drug. Reflectance together with transmission and absorption is described when radiation is falling on a surface. We assumed that the measurement of the reflectance may be helpful in the observation of changes in the composition of the tested tablets without damaging them. Thus, the present study aimed to examine the usefulness of the hemispheric directional reflectance in assessing the stability of the solid form of the drug as well as the roughness of the tablets surface during storage under stressful conditions.

Materials and methods: Ten chewable tablets of Alugastrin (Polfa Łódź, Poland) containing sodium dihydroxy aluminum carbonate were analyzed. The tablets were randomly selected from a given series and they were carefully measured and weighed. Reflectance was measured using a 410-Solar Visible (Surface Optic Corporation, San Diego, USA) directional reflectometer within seven radiation subbands from 335 nm to 2500 nm. After the measure at 0 days, the tablets were placed in an incubator under 40^{0}C. After 14 days, another reflectance measurement was made. In addition, transmittance (T), total

Key words:

hemispherical directional reflectance, drug stability, solid dosage forms

integrated scatter (TIS), as well as mean squared deviation of the height of the roughness (σ) were calculated based on the obtained reflectance values in each wavelength range. Data before and after exposure under the stress conditions were analyzed using Statistica 13.0 (StatSoft, USA).

Results: The highest mean total reflectance was observed for the wavelength of 590-720 nm while the lowest mean total reflectance was found for 1700-2500 nm both at the begging of the experiment as well as after exposure of the tablets to 40^{0}C. For all investigated wavelength bands, the total reflectance differed significantly between the tablets before and after exposure to stressful conditions ($p<0.001$). Total reflectance decreased significantly during storage within five of the analyzed spectral bands while it increased for the remaining two spectral bands, i.e. 1000-1700 nm and 1700-2500 nm. In addition, tendencies to increase values of σ after 14 days of storage for 335-380 nm, 400-540 nm, 590-720 nm, 1000-1700 nm, and 1700-2500 nm bands were also observed which may suggest surface changes resulting from the exposure to stressful conditions.

Conclusion: The obtained results suggest that some physicochemical changes could have happened in the Alugastrin tablets during storage at 40°C. The change in reflectance may be used to determine the stability of a solid drug form. However, further studies are needed.

Introduction

Drug stability is one of the key components of the efficacy of oral solid dosage forms. In a medicinal product stored in conditions inconsistent with the manufacturer's recommendations, adverse changes occur under the influence of environmental factors such as temperature, humidity, and light, affecting the pharmacological activity of the drug [1]. The physicochemical properties of the drug form are also changing [2]. Therefore, it is extremely important to properly control finished pharmaceutical preparations in terms of maintaining their chemical and physical properties

One of the less popular, but promising methods of testing a solid form of a drug is the measurement of its reflectance. It can make it possible to observe changes taking place on the tested surface, which may have a direct impact on the quality of a given form of the drug.

The reflection frequency is the quantity describing the light beam reflected on the border to the stripes of the beam incident on the border [3]. It depends on the existing condition, the type of material as well as the roughness of the surface, and its slope.

According to the conservation of energy principle, energy is equal to the sum of the reflected (R) energy and transmitted (T) energy:

$$R + T = 1$$

assuming that there is no loss of radiant energy due to light absorption in the medium [3].

The effects of the interaction of light with the medium may be as follows: absorption of electromagnetic radiation, reflection, refraction, polarization, scattering, or secondary emission, because the mentioned processes are interdependent. However, it cannot be described with just one of the concepts mentioned. Depending on the wavelength and the type of object, some of them may be dominant while others will be minimal [3].

The reflectance value ranges from 0 to 1. The reflectance values can be higher than 1, especially for highly reflective forward surfaces such as snow [4].

The unevenness of the tablet surface affects the quality of the finished preparations. It affects the friability of the tablet, and also affects the porosity of the tablet, which is associated with the disintegration of the tablets. Optimal tablet disintegration is a key element that influences the availability of the active substance in the tablet. Changing the porosity of tablets

may have a negative effect on the pharmacotherapeutic treatment. Historically, stylus instruments have been used to evaluate tablet surface roughness. Classic methods of its evaluation are: optical microscopy, laser profilometer, scanning electron microscopy, atomic force microscopy, or UV imaging. Most of the methods used are time-consuming and costly.

The development of methods for measuring the roughness of film-coated tablets may help to better understand the impact of its changes on the stability of this drug form [5].

The methods that use the phenomenon of light scattering to assess surface unevenness are called scatterometric methods. The basic methods include those based on the measurement of the intensity of the reflected light, the intensity of scattered light, the total intensity of scattered light, and the angular distribution of the scattered light. The advantages of the described methods include their high sensitivity and speed of measurements. Control using these methods is most often used in the precision, automotive, optics, and electronics industries [6].

In the present study, we aimed to examine whether the directional reflectance may be useful in assessing the stability of the solid form of the drug as well as the roughness of the tablets surface during storage under stressful conditions.

Tablets containing sodium dihydroxy aluminum carbonate were selected as a model preparation. This preparation is used in the symptomatic treatment of hyperacidity of gastric juice. It has a protective effect on the mucosa of the esophagus, stomach, and duodenum and relieves pain associated with excessive acidity of gastric juice.

Materials and methods

Tablets selected for analysis

The chewable Alugastrin tablets were selected as model preparation for the present analysis (POLFA Łódź, Poland). The tablets contain 340 mg of dihydroxy aluminum sodium carbonate. The choice of the preparation was mainly driven by the limitations of the equipment used for measurements, i.e. a diameter greater than 130 mm. 10 tablets were randomly selected for the study.

Evaluation of the tablets

All tested tablets were carefully evaluated. They were accurately measured and weighed using a caliper (with an accuracy of 0.1 mm), and analytical balance, respectively. Their external appearance was also assessed. To simulate the stressful conditions in which the tablets may be stored, they were placed at a temperature of 40°C in the thermal chamber with forced air circulation (Memmert, Germany) for 14 days.

Images of the tablets

The images of the Alugastrin tablets were taken under visible and UV lights using Olympus Tough camera with a Dermlite attachment (Olympus Europa Se & Co. KG, Germany).

Reflectance measurement

Each tablet was measured using a SOC-410 Solar reflectometer (Surface Optics Corporation, San Diego, USA). With this device, it is possible to measure total reflectance in seven radiation subbands in the wavelength range from 335 nm to 2500 nm, i.e. from ultraviolet, through visible light, to near-infrared. The results for Total, Diffuse, and Specular reflectance were obtained for the beam at an angle of 20°. The tested tablets were placed on the reflectometer outlet, completely covering the aperture, which is a prerequisite for the correct measurement. Measurements were taken on the first day of analysis, and then after 14 days of storage at a higher temperature of 40°C.

Parameters calculated based on reflectance

In the study, the following parameters i.e. transmittance (T), total integrated scatter (TIS), as well as mean squared deviation of the height of the roughness (σ) were calculated based on the obtained reflectance values in each wavelength range.

TIS is the ratio of diffuse reflectance to total reflectance:

$$TIS = \frac{Rd}{Rt}$$

where: Rd – diffuse reflectance; Rt – total reflectance;

Transmittance was calculated from the equation:

$$R + T = 1$$

where: R – total reflectance; T – transmittance

In addition, TIS may be used to calculate σ from the following equation:

$$\sigma = \frac{\lambda}{4\pi \cos\Theta i} \sqrt{TIS}$$

where: λ – wavelength; Θi – beam angle; TIS – total integrated scatter.

Statistical analysis

The obtained results before and after exposure to stress conditions were statistically analyzed using the Statistica 13.0 software (StatSoft; Statistica, Tulsa, OK, USA). Data were expressed as means (M) and standard deviations (SD). The normality of the distribution of quantitative data was evaluated by the Shapiro – Wilk W test. The student's T-test was used to analyze the data showing a normal distribution while Mann-Whitney's U test was used for those data that did not show a normal distribution. The time-dependent continuous variables (i.e. day 0, day 14) were analyzed using ANOVA with repeated measures.

Results

Characteristics of the tablets

All tablets were cylindrical with flat top and bottom surfaces. The tablets did not have any discoloration, impurities, chips, or cracks visible to the naked eye. All edges were preserved, with no visible damage.

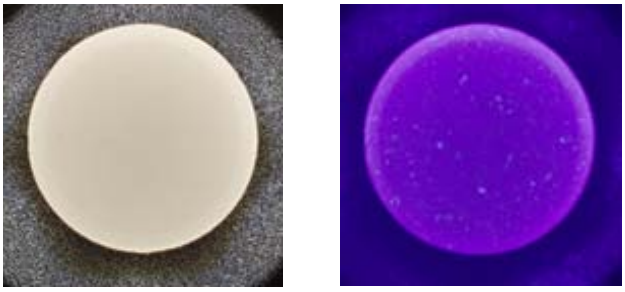

Fig. 1.
Images of the Alugastrin tablet in visible and UV light

Reflectance analysis at the beginning of the experiment (0 days)

For the tested Alugastrin tablets, the highest mean total reflectance was observed for the wavelength range of 590-720 nm while the lowest mean total reflectance was found for the 1700-2500 nm range at the begging of the experiment (Table 1). On contrary, transmittance was the highest for the 1700-2500 nm range while the lowest for the 590-720 nm range. Statistical analysis showed that there was a significant difference in total reflectance between all analyzed wavelength ranges ($p < 0.001$). In turn, the TIS parameter was the highest for the spectral band of 335-380 nm while the TIS values were comparable for the remaining bands ($p = 0.029$).

Changes in total reflectance of Alugastrin tablets during storage at 40°C

During the storage at 40°C the mean total reflectance decreased significantly within the following spectral bands: 335-380 nm, 400-540 nm, 480-600 nm, 590-720 nm and 700-1100 nm. For the remaining spectral bands, i.e. 1000-1700 nm and 1700-2500 nm the total directional reflectance increased significantly during storage (Table 2). Similarly to the beginning of the experiment, the highest reflectance was observed for the wavelength range of 480-600 nm and 590-720 nm while the lowest values of total reflectance were observed for 1700-2500 nm (Table 2).

The percentage differences in total directional reflectance for all analyzed wavelength bands were calculated by taking the mean reflectance of the Alugastrin tablets at the beginning of the study as 100 percent. The highest and the lowest differences in the mean directional reflectance were 106.11% and 93.56% which were observed for the spectral range of 1700-2500 nm and of 335-380, respectively (Fig. 2).

Table 1.
Characteristics of the analyzed Alugastrin tablets at the beginning of the study (0 days)

λ range [nm] / Variable	335-380	400-540	480-600	590-720	700-1100	1000-1700	1700-2500
Total reflectance [a.u.], M±SD	0.944±0.021	0.977±0.002	0.992±0.001	0.995±0.001	0.967±0.001	0.777±0.002	0.419±0.004
Transmittance [a.u.], M±SD	0.056±0.021	0.023±0.001	0.008±0.001	0.005±0.001	0.033±0.001	0.223±0.002	0.581±0.004
TIS, M±SD	1.007±0.048	0.995±0.001	0.995±0.001	0.994±0.001	0.995±0.003	0.995±0.001	0.993±0.001
σ, M±SD	30.384±0.719	39.716±0.019	45.630±0.022	55.301±0.022	76.053±0.012	114.012 ±0.054	177.332±0.089

M-mean; SD-standard deviation; TIS- total integrated scatter.

Table 2.
Changes in total reflectance of the Alugastrin tablets during storage at 40°C (0 days, 14 days)

λ range [nm] / Time of storage	335-380	400-540	480-600	590-720	700-1100	1000-1700	1700-2500
0 day, M±SD	0.944±0.021	0.977±0.002	0.992±0.001	0.995±0.001	0.967±0.001	0.777±0.002	0.419±0.004
14 days, M±SD	0.883±0.034	0.963±0.003	0.981±0.002	0.989±0.001	0.964±0.001	0.785±0.002	0.445±0.005
p	**0.004**	**<0.001**	**<0.001**	**<0.001**	**0.0003**	**<0.001**	**<0.001**

M – mean; SD – standard deviation; Significant differences are in bold.

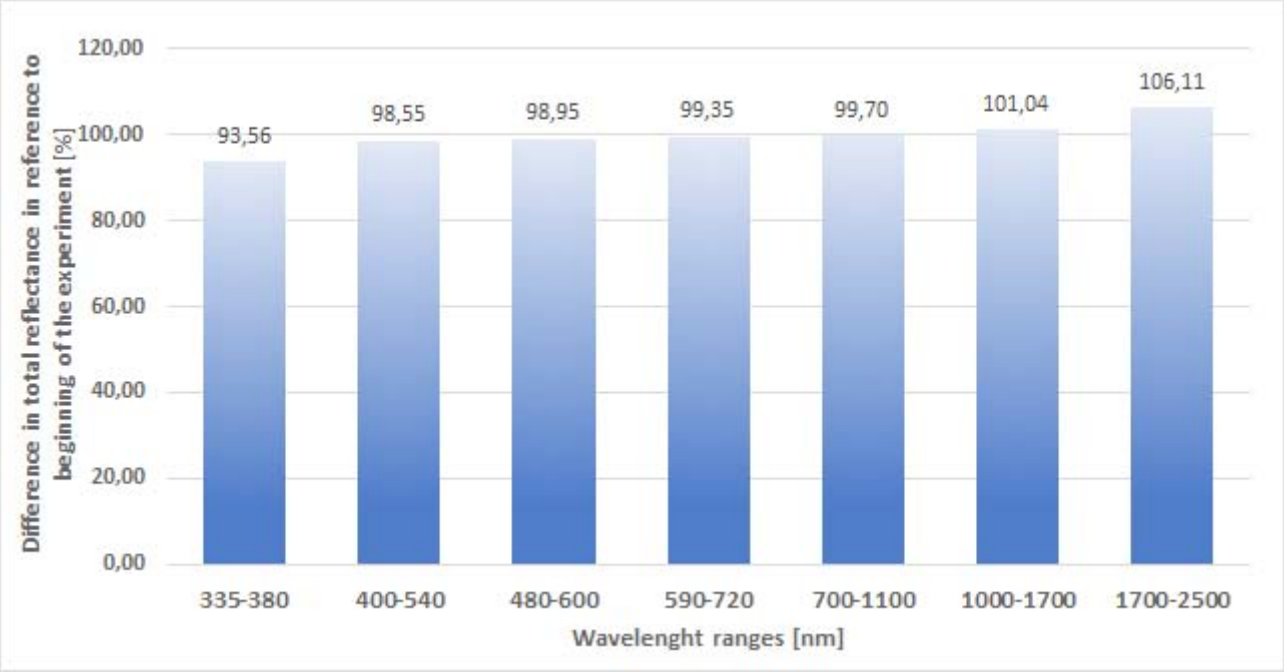

Fig. 2.
Percentage differences in total reflectance after 14 days in all spectral bands compared to the results obtained at the beginning of the experiment.

Changes in TIS parameter of Alugastrin tablets during storage at 40°C

For the TIS parameter, no significant changes during storage for all spectral bands were observed (Table 3). However, the mean TIS on the 14th day of the experiment for the 335-380 nm band was significantly higher compared to other spectral bands (p=0.006).

Changes in mean squared deviation of the height of the roughness (σ) of Alugastrin tablets during storage at 40°C

Similarly to the TIS parameter, the σ parameter did not change significantly during storage (Table 4). However, tendencies to increase values of σ after 14 days of storage were found for 335-380 nm, 400-540 nm, 590-720 nm, 1000-1700 nm, and 1700-2500 nm bands which may suggest surface changes resulting from the exposure to stressful conditions. On the other hand, for the 480-600 nm band decreased value of σ was observed during storage.

Discussion

In recent years, many portable devices have been developed to enable rapid drug analysis not only in the laboratory but also in the field. Many of these devices are able to perform both quantitative and qualitative analyses. Portable devices can help detect low-quality and substandard drugs, including counterfeit and out-of-date drugs. Research is currently underway on many aspects of the use and implementation of these devices for drug quality control [7-18]. Zambrzycki *et al* tested twelve technically diverse devices, from disposable single use tests to portable spectrometers [19]. All tested devices were characterized by high sensitivity (from 91.5 to 100.0%) in identifying medicines that did not contain any active pharmaceutical ingredient (API) or contained the wrong API. According to Wang *et al*, NIR spectroscopy has great potential for use in screening [20].

Research is still needed to evaluate various portable devices and to optimize the selection of the most appropriate technology for medicine quality screening. Portable devices for medicine quality should be

Table 3.
Changes in TIS parameter of the Alugastrin tablets during storage at 40°C (0 days, 14 days)

λ range [nm] / Time of storage	335-380	400-540	480-600	590-720	700-1100	1000-1700	1700-2500
0 day, M±SD	1.007±0.048	0.995±0.001	0.995±0.001	0.994±0.001	0.995±0.003	0.995±0.001	0.993±0.001
14 days, M±SD	1.042±0.060	0.996±0.001	0.994±0.001	0.994±0.001	0.995±0.001	0.994±0.001	0.994±0.001
p	0.274	0.078	0.506	0.688	0.722	0.602	0.102

M – mean; SD – standard deviation.

Table 4.
Changes in σ parameter of the Alugastrin tablets during storage at 40°C (0 days, 14 days)

λ range [nm] / Time of storage	335-380	400-540	480-600	590-720	700-1100	1000-1700	1700-2500
0 day, M±SD	30.384±0.719	39.716±0.019	45.630±0.022	55.301±0.022	76.053±0.012	114.012±0.054	177.332±0.089
14 days, M±SD	30.907±0.881	39.745±0.019	45.622±0.025	55.327±0.019	76.056±0.026	114.068±0.035	177.406±0.104
p	0.274	0.078	0.506	0.688	0.722	0.602	0.102

M – mean; SD – standard deviation.

easy to use, export data and require minimal sample preparation and consumables.

This study explores the feasibility of using Directional Hemispherical Reflectometer combined with analysis and image processing methods for assessing the stability of a solid oral dosage form. Our study demonstrated that during storage mean total reflectance decreased significantly within five of the analyzed spectral bands. For the remaining two spectral bands, i.e. 1000-1700 nm and 1700-2500 nm the total directional reflectance increased significantly during storage. In addition, we observed tendencies, but not significant to increased values of σ after 14 days of storage for 335-380 nm, 400-540 nm, 590-720 nm, 1000-1700 nm, and 1700-2500 nm bands which may suggest surface changes resulting from the exposure to stressful conditions.

At present, there are no data in the available literature that would describe the possibility of using this technology in studying the stability of various drug forms. In fact, data on usage Directional Reflectometer in the analysis of solid dosage forms are scarce. In the studies by Wilczyński *et al*. this method was used to distinguish real Viagra® from counterfeit tablets [21]. The authors investigated the possibility of using reflectance to quickly test drugs for falsification. They analyzed the reflectance of 6 genuine Viagra pills and 24 counterfeit pills within 6 spectral bands. The results showed the statistically significant difference between the directional light reflectance of the original Viagra® and the counterfeit tablets [21].

With the results of reflectance, tablet surface roughness may also be assessed. Previously, Previously, an analysis of surface parameters based on the measurement of total surface scattered radiation power (TIS) was described by Jaglarz *et al* [22]. Other method for assessing tablet surface roughness is optical coherence tomography. Markl *et al* investigated the use of this method to detect defects in the core and shell of a coated tablet. According to authors, the method could be used to detect defects in both the core and coating of a tablet in one test. The authors also found that the test performed could be carried out during the tablet manufacturing process [5].

The present study has several limitations. First, the number of analyzed tablets is low. Second, it is a pilot study that is in progress. We are planning subsequent measurements of reflectance of tablets after a longer time of storage. We also intend to include other parameters during storage that may be important for tablets stability, i.e. UV radiation and humidity. Third, comparing the results from the reflectance analysis with the results of other analyzes is necessary to obtain more obvious results.

Conclusion

The measurements of the reflectance carried out in the present study show that some physicochemical changes could have happened in the Alugastrin tablets during storage at higher temperature as a result of the stressful conditions. In consequence, these changes may affect the effectiveness of the therapy. Our study is a pilot research suggesting that the changes in reflectance can be used to determine the stability of a solid drug form. Further studies are however needed.

Funding: *The research was funded by Medical University of Silesia in Katowice, Poland (project number PCN-1-097/N/1/F).*

Conflicts of Interest: *The authors declare no conflict of interest.*

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