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PHOTODEGRADATION OF PHARMACEUTICALS STUDIED WITH UV IRRADIATION AND DIFFERENTIAL SCANNING CALORIMETRY

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Abstract. Given rapidly increasing concerns about photodegradation of pharmaceuticals, we have applied accurate methods to quantitatively evaluate the drug photostability. The drugs studied were nifedrine, acetylsalicylic acid, acetaminophen, cetirizine, and pantoprazole. UV energy striking a target has been determined by using graphite. Runs were performed by placing each sample in a pan with a quartz lid and exposing it to ultraviolet (UV) light for periods of time ranging from 1 to 120 seconds. Percentage decomposition as a function of time has been determined for each pharmaceutical. Fast differential scanning calorimetry (DSC) in situ was used to evaluate changes in thermophysical behavior of the drugs and possible formation of new phases. The UV degradation rates so determined cover a very wide range, from 0.1 to 20.0 %/s. Factors affecting the photodegradability are discussed.

Keywords: pharmaceutical photostability, UV irradiation, drug DSC analysis, photo-DSC.

1. Introduction

The photostability of pharmaceuticals is an area of growing concern as the number of drugs found to be photosensitive is increasing [1]. Already in 2005 the United States Pharmacopeia listed over 250 drugs that require protection from ultraviolet (UV) and/or visible light [2]. Insufficient photostability can result in a loss of drug potency related to light-initiated reactions with excipients (pharmacologically inactive substances used as a carrier for the active ingredients) as well as unintended biological effects from degradation products, reactions with substrates, or with environmental oxygen [1]. These concerns affect the handling, packing, and labelling of the drugs and vary according to the sensitivity of the compound [3].

Determination of photodegradation is still done by visual inspection, by repeated dissolution studies, or else by chromatographic methods [4]. Needless to say, visual inspection is not accurate while the other two techniques are time consuming. That is why regulatory agencies require more and more information on the photo-stability of drugs [5]. A faster and less cumbersome method for determining the presence of photo-instability and measuring the degree of degradation would be useful to help reduce costs and testing times while providing sufficient accuracy.

Differential scanning calorimetry (DSC) is a useful technique. There exists huge literature on this subject – as for that matter on Materials Science and Engineering in general [6]. Several reviews on DSC explain this technique [7-10]. DSC is also one of the methods of determination of glass transition temperatures T_g and changes of T_g with composition [11-13] – including in drug + encapsulating agent systems [13]. Interesting for our purposes is UV-DSC, or Photo-DSC, that is coupling the calorimeter to a UV source. One takes advantage of the ability of the DSC to detect small changes in the material after irradiation of the sample with UV *in situ*. This technique has been used for fairly long time to study the photo-initiation of curing of thermosets [14]. We have decided to apply the Photo-DSC technique to samples of drugs with a range of photostabilities – from poor to those believed to be "excellent" in this respect.

Giving the criterion of a wide range of photo-stabilities, we have investigated nifedrine, acetylsalicylic acid, acetaminophen, cetirizine, and pantoprazole. Nifedrine is used as a blood pressure lowering drug. Acetylsalicylic acid is better known under the trade name of Aspirine. It is used for the relief of headache and

muscle and joint aches, for reducing fever, inflammation and swelling and thus has been used for treatment of rheumatoid arthritis, rheumatic fever, and mild infection. Acetaminophen is used to relieve mild to moderate pain from headaches, muscle aches, menstrual periods, colds and sore throats, toothaches, backaches, reactions to vaccinations, to reduce fever and also to relieve the pain of osteoarthritis; it is one of the most common medications found in households. Acetoaminophen is thus used for some of the same applications as Aspirin. Cetirizine is used to temporarily relieve the symptoms of hay fever (allergy to pollen, dust, or other substances in the air) and allergy to other substances (such as dust mites, animal dander, cockroaches, and molds). These symptoms include sneezing; runny nose; itchy, red, watery eyes; and itchy nose or throat. Cetirizine is also used to treat itching and redness caused by hives. However, cetirizine does not prevent hives or other allergic skin reactions. Cetirizine (the active ingredient in Zrytec™) is in a class of medications called antihistamines. It works by blocking the action of histamine, a substance in the body that causes allergic symptoms. Finally, pantoprazole (the active ingredient in Protonic™) is used to treat gastroesophageal reflux disease – a condition in which backward flow of acid from the stomach causes heartburn and possible injury of the esophagus (the tube between the throat and stomach).

2. Experimental

Samples of nifedrine, acetylsalicylic acid, acetaminophen, cetirizine, and pantoprazole were obtained from Aldrich-Sigma, St. Louis, Missouri, in purities of 99 % or better. All materials were stored in a dark dry box under nitrogen atmosphere at 278 K. 5–10 mg of a sample was used for each run.

All DSC work was performed in PerkinElmer Diamond DSC with a UV adapter. The UV source was an EFOS Omnicure 2000 with dual fiber optic light guides and a 200–450 nm filter for 1.0 mW/cm^2 of UV. Samples were run in open aluminium pans under 40 cc/min nitrogen purge either isothermally at 298 K and linearly increasing temperature with time – with scanning rates from 20 to 300 K/min. Cooling was supplied by either a PolySci chiller running at 253 K or by the Cryofill liquid nitrogen system. Pyris software's internal trigger was used to turn the Omnicure unit on.

Exploiting the unique design of double furnace DSC to measure energy directly, a graphite target was used to measure the mW of energy striking the sample. Graphite absorbs virtually everything in the UV range we use so the change in energy is proportional to the energy absorbed. The displacement of the baseline when the reference pan is covered gives the energy from the beam actually striking the sample. This ability to exactly measure the light energy applied, with the highly stable isothermally performance and rapid response of this design, make dual furnace DSCs well suited for our purposes.

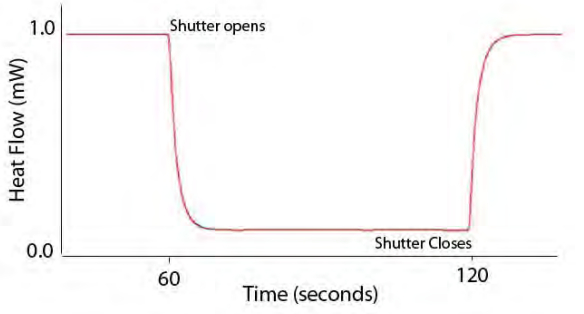


Fig. 1. Calculation of UV energy striking a graphite target for calibration within the DSC

First the energy striking a sample was determined using a graphite target; see Fig. 1.

Photostability runs were performed by placing a sample in a pan with a quartz lid and exposing it to UV light for time periods ranging from 1 to 120 seconds.

3. Results and Discussion

All experiments were run in triplicate and the results averaged.

For brevity we do not include DSC results for all materials studied. In Fig. 2 we present results for nifedrine.

Similarly in Fig. 3 we show results for cetirizine.

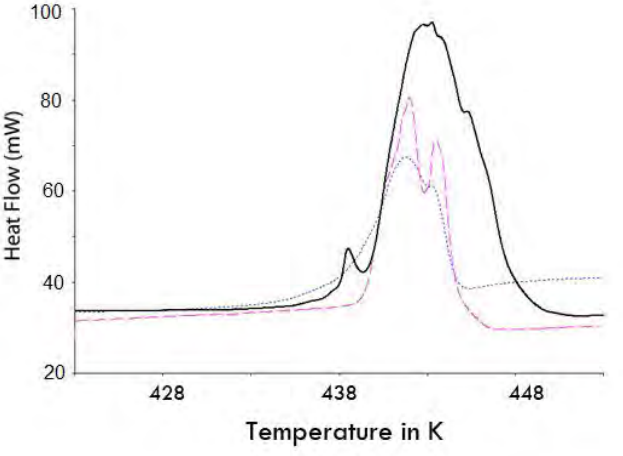


Fig. 2. DSC diagram for nifedrine: no UV exposure (_._._); 1 s exposure (….); 1.5 s exposure(___). Runs made at 20 K/min. Data were not normalized

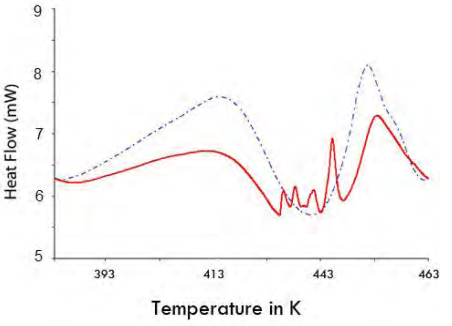


Fig. 3. DSC results for cetirizine: unexposed sample (_._); 5 s exposure (___). Data were not normalized

Figs. 2 and 3 show both formations of new species as a result of UV irradiation. Unlike the degradation shown in Fig. 2 where the material develops some distinct new peaks which then collapse into a single melt, Fig. 3 shows a change to a distinct species. Photo-initiated inter-conversion of polymorphic forms is a known phenomenon [15]. Formation of such new phases is accompanied by *lower* endothermic effects on heating. Other materials investigated have shown similar behavior. Raman spectra or more strictly Raman + DSC combination would enable better characterization of the new phases. Because polymorphic forms are lost in solution, liquid chro-matography would not see these changes.

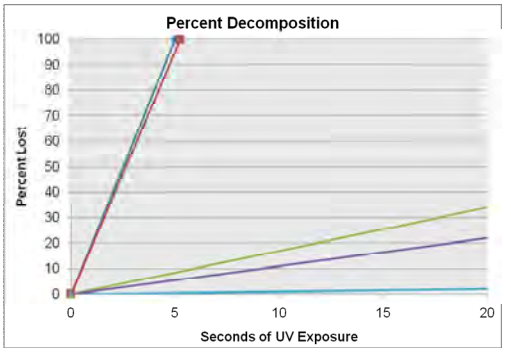


Fig. 4. Decomposition rates as a function of time of UV exposure. Lines from left to right: nifedrine, cetirizine, acetylsalicylic acid, pantoprazole and acetaminophen

On the basis of the DSC results, we have determined the decomposition rates for all five pharmaceuticals. As seen in Figs. 2 and 3, significant changes take place. The data from the original pharmaceutical without exposure to the UV light were analyzed; the resulting peak area was measured and recorded. In the consecutive runs, the peak areas were also determined, compared to the area from the initial unexposed sample and then expressed as a percentage change between the diagrams. This set of information was then analyzed, giving linear changes with time presented in Fig. 4.

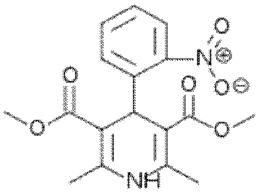
As Fig. 4 shows, our study has indeed covered a wide range of decomposition rates. The lowest degree of photostability is seen for nifedrine, the highest for acetaminophen. Interestingly, while acetylsalicylic acid and acetaminophen are for both used as cures for certain illnesses, the latter shows much higher photostability (Fig. 5). We present the respective numerical values in Table 1.

Table 1

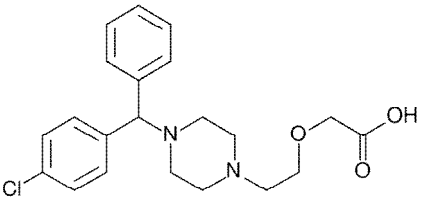
Decompositions per second

Pharmaceutical	Degradation rate per second (%)
Acetaminophen	0.1
Acetylsalicylic acid	1.7
Cetirizine	19.0
Nifedrine	20.0
Pantoprazole	1.1

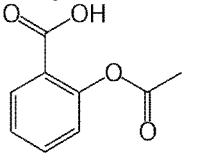
To interpret the results presented in Fig. 4 and Table 1, we need to consider the chemical formulae of the drugs. These are provided in Fig. 5:



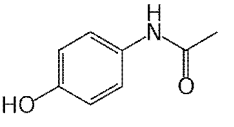
3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate = Nifedrine



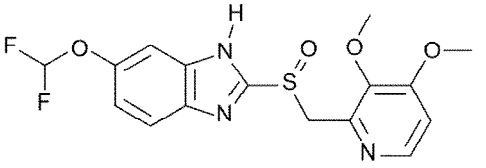
2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid = Cetirizine



2-acetoxybenzoic acid = Acetylsalicylic acid



N-(4-hydroxyphenyl)ethanamide = Acetaminophen



(RS)-6-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-1H-benzo[d]imidazole = Pantoprazole

Fig. 5. Chemical structures of the drugs studied (after Wikimedia Commons)

The degradation rates we have determined are related to the presence – or otherwise – in these molecules of structures such as conjugated double bonds and conjugated hetero-atoms that allow the absorption of UV energy. Compounds with such structures are known to both absorb strongly and to photo-degrade [16]. This provides several pathways for degradation and rearrangement, one of which can be conversion to another polymorphic species [15]. Materials lacking these structures or whose structures allow the absorption and release of energy without splitting the molecule are stable.

We find that these general rules apply well to our results. The lowest degradation rate is found for acetaminophen, a small molecule containing a phenyl ring. The second is pantoprazole, also with phenyl rings and a heterocyclic ring. The third one is acetylsalicylic acid, not much different in its structure from acetaminophen. When we move to cetirizine, we have a dramatic increase in the degradation rate; here the chemical structure is much more complicated and also more open to both rearrangement and degradation as several pathways exist for the molecule to separate into fragments. Finally, the degradation rate of nifedrine is not much larger than that of cetirizine; here also we have an open structure and a number of functional groups that can react easily. Again, the structure allows multiple degradation pathways by either loss of functional groups or fragmentation into radicals.

4. Conclusions

In the beginning of this article we have defined our quest: development of a fast and reliable method of determination of UV irradiation effects on stability of pharmaceuticals. We have noted that the extant methods are either slow or inaccurate, thus practically useless for fast screening. The combination of in *situ* UV irradiation with determination of the resulting effects by DSC does not have disadvantages of earlier methods. We have thus demonstrated that our technique is both reliable and convenient.

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ВИВЧЕННЯ ФОТОДЕГРАДАЦІЇ ЛІКАРСЬКИХ ПРЕПАРАТІВ ЗА ДОПОМОГОЮ УФ-ОПРОМІНЕННЯ І ДИФЕРЕНЦІАЛЬНОЇ СКАНУЮЧОЇ КАЛОРИМЕТРІЇ

Анотація. *Для кількісного оцінювання фотостабільності лікарських препаратів: ніфедрину, ацетилсаліцилової кислоти, парацетамолу, цетиризину і пантопразолу застосовано прецизійні методи аналізу. Опромінення ультрафіолетом вивчено протягом 1–120 с. Для кожного лікарського препарату досліджено залежність відсотку розкладу від часу опромінення. За допомогою диференціальної скануючої калориметрії (ДСК) оцінено зміни теплофізичних властивостей препаратів і можливість утворення нових фаз. Встановлено, що швидкість УФ-деградації коливається від 0,1%/с до 20,0%/с. Розглянуто чинники, що впливають на фотодеградацію.*

Ключові слова: *фармацевтична фотостабільність, УФ-опромінення, ДСК аналіз, фото-ДСК.*