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A MICROCALORIMETRIC STUDY ON THE ROLE OF MOISTURE IN PHOTOLYSIS OF NIFEDIPINE POWDER

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Abstract

A well-known photolabile substance, nifedipine, was used as a sample material to test self-constructed irradiation cells and demonstrate their usefulness in photostability studies. The devices were made as accessories for a commercial isothermal microcalorimeter. Several powder samples containing various amounts of moisture were irradiated with monochromatic light as a scan measurement from 700 to 280 nm, and the heat flow evolved in the photodegradation of nifedipine was determined. According to the results, light does not affect the nifedipine molecule directly, but the photodegradation is a result of the combined effects of moisture and light.

Keywords: isothermal microcalorimetry, pharmaceutical substance, photochemistry, photolability

Introduction

One of the most important concerns during the formulation of a medical product is to determine the stability of the drug product under influence of a variety of environmental conditions. Determination of all the external factors that might interfere the stability (e.g., temperature, moisture, oxygen, pH, excipients, metal ions and light) of the product is expensive and time consuming. Furthermore, if the test parameters do not simulate the real conditions well enough the results may be fallacious and erroneous conclusion can be drawn. It should be also borne in mind that although an external factor is determined not to cause instability alone, the factor could be calamitous together with another external factor. Thus, it would be advantageous to have the basic information on the stability behaviours of the components in the product, and the product itself, at the early stage of formulation to reduce the costs in the later long term stability studies. In many cases, isothermal microcalorimetry serves these purposes in the best possible way.

Although utilizing the isothermal heat conduction microcalorimetry in determining the effects of external factors on pharmaceuticals has increased significantly during the last decade [1-13] light has been a stumbling-block in these experiments until these days. In our previous paper [14] we introduced an experimental novelty that

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covers this gap in the instrumental possibilities of stability studies. The method enabled the real time detection of photolability of pharmaceutical solution and solid samples calorimetrically by means of self-constructed irradiation cells made as accessories for a commercial isothermal calorimeter, TAM 2277 (Thermometric AB, Sweden). As a reference, it could be mentioned that some guidelines concerning accelerated tests for photostability of pharmaceuticals are given in [15].

In the present study, nifedipine powder is used as a model drug because it is extremely photosensitive and decomposes concurrently to four components under daylight and UV light [16–18]. The photodegradation depends on the spectral energy distribution and intensity of the light source. Also, the physical state (powder *vs.* solution) of nifedipine affects photolysis. Nifedipine has been reported to be stable down to the wavelength of 475–500 nm [19] which is in agreement with our previous results [14]. The molecule has also been reported to be stable below 290 nm [14, 19]. In this work, the influence of moisture content of nifedipine powder on photodegradation is studied. The dry conditions in the sample vessels are produced with continuous synthetic air flow in the modified irradiation cells.

Experimental

Materials

Nifedipine powder was purchased from Sigma. The weighted powder samples (ca 100 mg) were stored in desiccator above various saturated salt solutions to produce the desired humidity conditions [20]. After the storage in desiccator, the samples were quickly transferred in the calorimetric sample vessels and the samples were sealed hermetically immediately. When dry powder was under study, the powder sample placed in the sample vessel was perfused with synthetic air (<5 ppm H_2O) for days before the measurement, and also during the measurement itself. All the samples were prepared and handled in darkened room under red light.

Methods

The device employed with the samples stored at various relative humidities (RH) prior to the measurements has been introduced elsewhere [14] in detail. In the case of dry powder samples the modified irradiation cells (Fig. 1), which enable perfusion of the sample during the measurement, were used. All the other parameters concerning light scan measurements were as stated previously [14]. The commercial RH perfusion unit was employed in moisture adsorption studies. All the microcalorimetric measurements were made at 25°C with a synthetic air flow of 100 ml h^{-1} if any.

The moisture uptake, or the equivalent moisture content, was determined gravimetrically at 97% RH with the apparatus introduced in [21]. The powder sample was moved quickly from a desiccator containing silica gel in the measurement position of the apparatus and the mass increase was recorded at time intervals of 30 s. The measurements were made at 25°C.

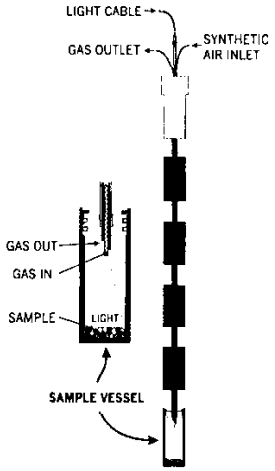

Fig. 1 Diagrammatic presentation of the irradiation cell with the facility for perfusion

Results and discussion

Nifedipine powder was found quite hydrophobic substance as it dissolves very sparingly in water and adsorption of moisture is modest. Adsorption studies were performed calorimetrically as described in [13] as subsequent RH steps. The RH values were set equal to the prestorage conditions of the samples used in the light scan measurements. The run was made in duplicate and the averages are listed in Table 1 together with the gravimetric adsorption result at 97% RH. As the mass increase was quite minor, the standard deviation was relative high (0.03%). However, it is clearly seen that the adsorption behaves quite linearly at lower RH values and even 97% RH does not make any big exception in that series.

During a scan measurement two separate and technically identical irradiation cells are positioned in the sample sides of two separate calorimetric units. One irradiation cell serves as a reference cell giving response for absorption of light in the reference material, i.e., radiant power is determined irrespective of the reactions in the sample, and the energy Q_{irr} fed in the sample can readily be calculated by integration. The other irradiation cell is employed as the actual photocalorimetric reaction vessel giving response for both the thermally active reactions and absorption of light. As the optical parameters of the irradiation cells differ from each other (practically impossible to get them identical) and the heat flow signals obtained with empty vessels are different, the reference runs must be performed so that the correction parameters to get the signals for absorption equal can be calculated (cf. [14]).

A typical scan measurement for nifedipine powder stored at 97% RH is shown in Fig. 2. The heat flow signal from the reference cell has been corrected mathematically to correspond the intensity and wavelength changes of the irradiation in the sample cell during the scan. The thermal response caused by the photoinduced deg-

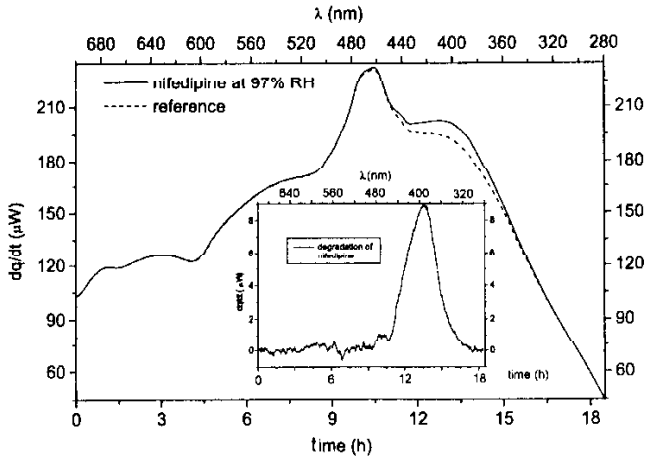

Fig. 2 A typical scan measurement for the degradation of nifedipine powder prestored at 97% RH. ——— represents the heat flow signal from the sample cell and --- from the reference cell (irradiant power). In the inserted figure, the subtraction of the two signals stands for the degradation of nifedipine

radation of nifedipine, which has been represented in the inserted graph (Fig. 2), is obtained as the heat flow signals from the sample and reference (after mathematical correction) cells have been subtracted from each other. Integration of the peak gives the heat of degradation Q_{degr} during the irradiation. The irradiation heat Q_{irr} absorbed by the sample during the scan is calculated by integration of the heat flow signal from the reference cell.

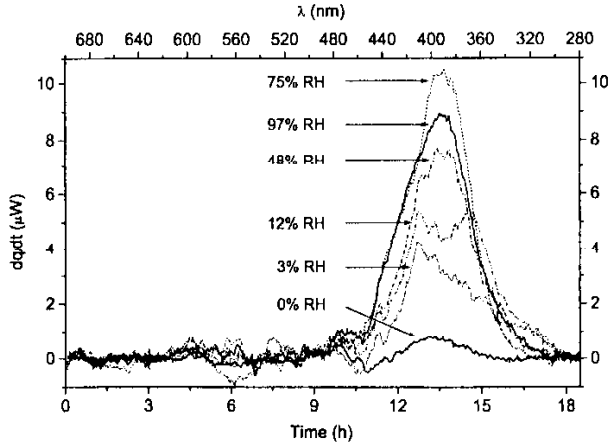

Fig. 3 The heat flow signals for the photodegradation of nifedipine powder under various humidity conditions

Similar scan measurements were made with the samples stored at various relative humidities, and the degradation curves are represented in Fig. 3. The peak areas obtained by integration are summarized in Table 1. The heats or the energy values correspond to the extents of the degradation. Photodegradation of nifedipine seems to depend on the moisture content of the powder and the degradation signal approaches zero at 0% RH. The threshold wavelength for the degradation is fairly obscure (from 500 to 460 nm) but the heat flow signal start to climb strongly at 460 nm. The maximum is reached at 390 nm. The wavelength values differ tens of nanometers from those reported for ethanol solution [14], and the degradation peak has been shifted to shorter wavelengths now. The irradiation intensity varies from one measurement to another due to the ageing of the optical components and changes in optical arrangements thus affecting the extent of degradation during a scan measurement. The values for irradiation energy are also listed in Table 1. Different results obtained with solution and powder samples could be due to the difference in the formation energies of, for example, hydroxyl radicals in ethanol and water.

Table 1 Thermal characteristics for the nifedipine powder at various relative humidities. The mass increase or equivalent moisture content at 97% RH is determined gravimetrically

RH/%	Q_{ads}/J g^{-1}	Δm/%	Q_{degr}/mJ	Q_{irr}/J
97	0.545	1.7	102	9.94
75	0.271		107	9.96
48	0.197	–	84.2	9.99
12	0.089	–	76.3	9.99
3	0.042	–	47.2	10.0
0	0	0	6.0	8.73

Subsequent scans with the same powder samples are also performed. The degradation peaks tend to decrease in size and shift to longer wavelengths. This result suggests that water is not just catalyzing the degradation reaction but takes part in the process presumably via radicals produced by irradiation.

The results presented are under speculation as the analytical assays were rejected to accomplish the measurement in decent time. For example, one pitfall could be the possible evaporation of the photodegradation products in the measurements where the irradiation cells with the possibility for perfusion are employed. Chemical assays should also be made to validate the method.

Conclusions

The results show the usefulness and valuableness of the utilized method in detection of photosensitivity of pharmaceuticals. The threshold value of the wavelength for the photodegradation and effects of external factors on the extent of degradation can readily be determined with the light scan measurements. As microcalorimetry has not yet been used in photostability studies to the day, this method offers an en-

tirely new possibility to utilize microcalorimetry in stability studies and makes the isothermal microcalorimetry more versatile than ever.

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