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Notes

Explosive properties of a nitroderivative compound (ITF 296), in bulk and mixed with anhydrous dibasic calcium phosphate: involving a formulation approach

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Abstract

The explosive and explodibility parameters of a new organic nitrate drug, ITF 296, have been studied. ITF 296 does not possess explosive properties, as determined by European Community standard testing methods (heat, impact and friction tests). The decomposition and auto-ignition temperature, determined by differential scanning calorimetry, are substantially higher than the working temperature which can be achieved with this compound. However, the explodibility properties of ITF 296, as determined by a hot-wire ignition method (Hartmann modified apparatus) and a heat oven auto-ignition method, place ITF 296 in Dust Hazard Class 1. The addition of anhydrous dibasic calcium phosphate strongly attenuates the explodability properties of ITF 296 and, consequently, the need for expensive anti-explosion measures in the development and production environment.

Keywords: ITF 296; Anhydrous dicalcium phosphate; Explosion; Explodibility; Exothermic reaction; Preformulation

1. Introduction

An aspect to be explored in the characterization of a new drug is the evaluation of its explosive properties and the physico-chemical parameters of exothermal decomposition; this helps to predict and prevent possible dangerous accidents in the successive working steps.

It is well known that the explosive behaviour of compounds, such as glyceryltrinitrate and isosorbide dinitrate, may be strongly reduced by adding an inert compound, such as sodium carbonate, sodium hydrogen carbonate, or adsorbing on to non-explosive materials, such as lactose. Moreover, explosions due to thermal decomposition may be simply avoided by working at a temperature below the decomposition temperature.

The explodibility of such compounds (that is the explosion of a powder cloud when exposed to a primer source) is frequently neglected during the characterization of a drug. Dangerous explosions, due to the explodibility of dusty materials, have sometimes occurred while handling compounds which are commonly used in pharmaceuticals;

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sugar (sucrose) is a typical example. A nitrogen atmosphere can render the material inert and consequently permit its safe handling. Moreover, use of anti-static equipment and other apparatus, which prevents raising of a primer source, can also increase the prevention measures.

Information regarding the thermal decomposition, explosive and explodibility parameters can therefore play an important role in preformulation. The choice of suitable excipients and process conditions may facilitate the resolution of problems resulting from thermal behaviour and explosive properties of the compound.

A novel nitroderivative drug (Levi et al., 1992), ITF 296 (3-[2-(nitrooxy)ethyl]-2H-1,3-benzoxazin-4-(3H)-one, CAS number 143248-63-9) was investigated at Italfarmaco Research Center. The decomposition parameters and explosive properties have been determined in the characterization study of ITF 296. Moreover, explodibility limits of the drug were evaluated both as bulk powder and in mixture with anhydrous dicalcium phosphate (Dicafos) at different weight ratios.

The choice of a suitable excipient, such as Dicafos, allows the reduction of the hazardous behaviour of the drug and therefore minimizes the safety operations required for the handling of the product.

2. Materials and methods

ITF 296 was synthesized by Italfarmaco Laboratories. Anhydrous dibasic calcium phosphate (Dicafos, type C52-12) was purchased by Faravelli (I-Milano).

The explosive properties of ITF 296 were determined by heat, impact and friction tests, as described in Directive 97/69/EEC, Part A, Method A14 (Official Journal of the European Communities, 1992).

Koenen test apparatus (Type 785-000 Haake, D-Karlsruhe), fall hammer (Type 782-0005 Haake) and friction test apparatus (Type 781-0260 Haake) were used for the determination of sensitivity to heat, impact and friction, respectively.

A material is said to possess explosive properties if a positive result is recorded in any one or all of these tests.

Differential scanning calorimetry was performed using a DSC 7-1020 Thermal Analysis System (Perkin-Elmer, I-Monza). A quantity, 1.5 mg, of ITF 296 was placed in an aluminium pan and studied over a temperature range from 30 to 200°C, at a scan rate of 1°C/min and 30 ml/min nitrogen flux. Indium was chosen as a reference substance. Temperature correction, using the slope of the thermal event peak (onset), was always applied.

ITF 296 and Dicafos, previously sieved at 300 pm, were mixed at different weight ratios with a Multigel Mod. MP-2 powder mixer (Senesi, I-Firenze) in a 3 l cylinder. The explodibility of a powder cloud of ITF 296/Dicafos physical mixtures was evaluated by the following methods.

The first method employed a Hartmann modified apparatus. The reactor was a closed steel cylinder (volume 2.3 dm^3), equipped on the base with an air or oxygen/nitrogen mixture inlet, and in the center with a metallic spiral wire as primer source.

The powder was poured on the base of the reactor, dispersed by an air or O_2/N_2 mixture to form a cloud, and primed with the white-hot wire. The pressure due to the explosion was detected by an appropriate pressure transductor and recorded.

The system allows determination of:

(1) the explosion parameters (explosion pressure, maximum and average speed of pressure increase (dp/dt);
(2) the lower concentration limit of ignition (explodability limit) of a powder cloud (the powder is considered ignited when an increase of pressure is detected);
(3) the minimum oxygen concentration required for explodability, evaluated by decreasing the oxygen percentage in an O_2/N_2 mixture until no explosion is detected.

The second method employs an oven (diameter, 36.5 mm; height, 220 mm) with an internal quartz wall. It was equipped with an air inlet and was maintained at a pre-determined temperature.

The powder was poured into a shuttle and dispersed into the oven by an air stream to form a cloud, where it could autoignite. The resulting explosion was evaluated by an internal mirror, which allowed observation of the cloud ignition.

Table 1
Explosion tests according to EEC directive 92/69

Heat test	negative
Impact test	negative
Friction test	negative

This system permits the determination of the auto-ignition temperature. The experiment was performed in successive steps, decreasing the temperature by 10°C, until explosion was no longer observed (auto-ignition temperature).

3. Results

In the explosion tests, ITF 296 was found not to possess explosive properties in the sense of the EEC Directive 92/69 (Table 1).

No reaction was observed following release of a 10 kg weight from 0.4 m height (impact test). No reaction or sparking was detected by applying a friction loading force up to 360 N; an orange glow, attributed to the apparatus, was noticed at this force. No explosion was recorded on heating; ITF 296 burned, starting between 10 and 31 s.

The DSC thermogram (Fig. 1) of ITF 296 shows a melting peak at 52.5–54.5°C, as previously reported (Dobetti et al., 1995), and a remarkable exothermic event, due to the decomposition of the drug, which begins above 115°C and whose onset temperature is at 130°C. Furthermore, the decomposition enthalpy (197 ± 5 kJ/mol) indicates a strongly exothermic degradation.

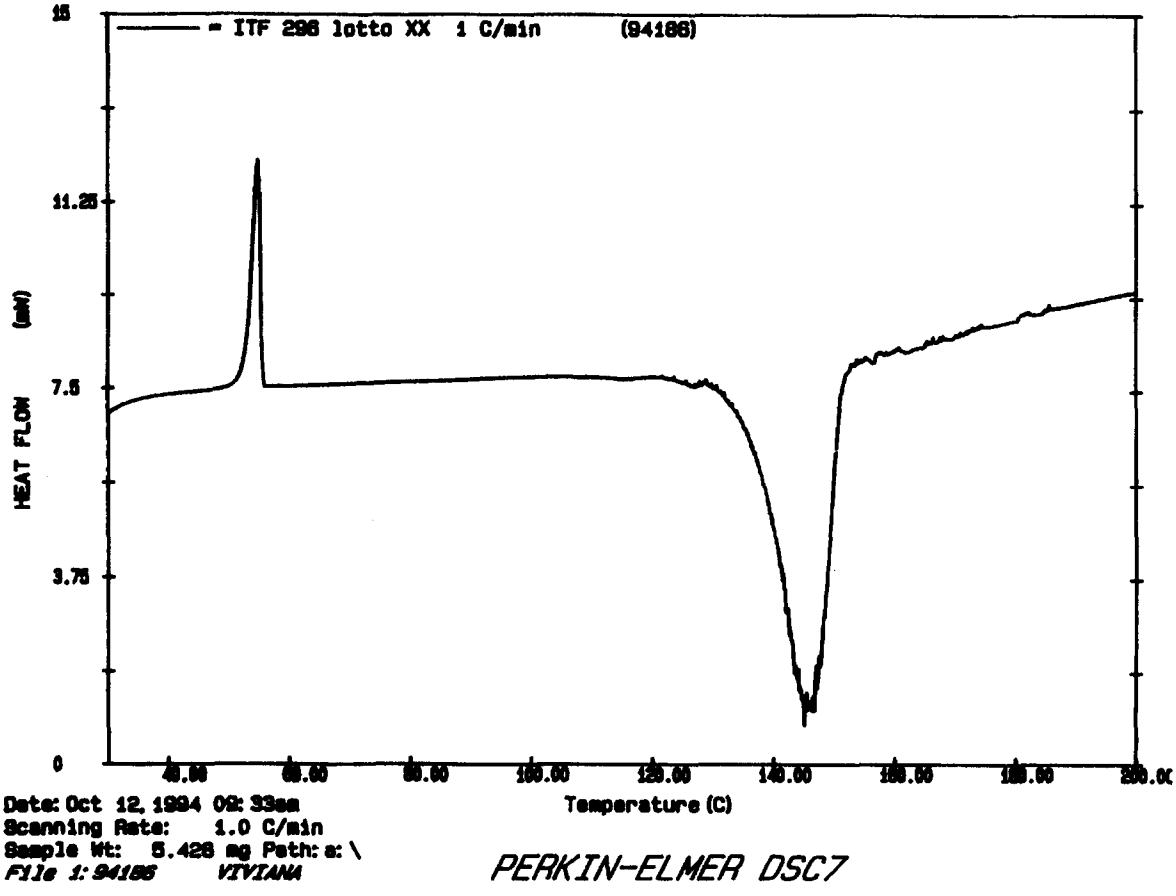

Fig. 1. Thermogram of ITF 296.

Table 2
Kinetic parameters of the decomposition reaction of ITF 296

Decomposition temperature (°C)	T_d	130 ± 1
Decomposition enthalpy (kJ/mol)	ΔH_d	197 ± 5
Frequency factor (1/s)	$\ln K_o$	87.3 ± 2.9
Energy of activation (kJ/mol)	E_d	313 ± 13
Order of reaction	n	0.90 ± 0.02

A decomposition temperature of 165–167°C was previously observed (Dobetti et al., 1995), performing the DSC analysis at 10°C min scan rate. It is known (Ford and Timmins, 1989) that lower decomposition temperatures may result from reduction of the scan rate during thermal analysis.

The kinetic parameters, calculated from DSC analysis and given in Table 2, show that the decomposition of ITF 296 is a first order reaction ($n = 0.90$) with an activation energy higher than 300 kJ/mol. The latter value suggests fairly good thermal stability of the drug up to a temperature close to the decomposition limit.

ITF 296 exploded as a powder cloud at a concentration higher than 60 mg/l in the presence of an ignition source. The minimum oxygen concentration required to allow explosion was 6%. The explodibility parameters of the drug, as bulk and in physical mixture with Dicafos at different weight ratios, are reported in Table 3.

The presence of Dicafos as an inert support appreciably reduces the explodibility of the physical mixture. The minimum percentage of oxygen for powder cloud explosion to occur rises to 15.5% with 81% Dicafos, and explosion is never observed at 90% Dicafos. Moreover, the auto-ignition temperature is increased by adding the inert excipient and reaches 420°C for a physical mixture with 90% Dicafos.

Table 3
Explodibility parameters of ITF 296 mixed with Dicafos at ranging percentage

	100%	30%	19%	10%
Explodibility limit (mg/l)	60	370	500	-
Minimum oxygen (%)	6	n.d.	15.5	-
Auto-ignition temperature (°C)	180	270	330	420
Explosion parameters				
Maximum pressure (atm)	4.8	3.7	2.2	-
$(dp/dt)_{maximum}$ (atm/s)	206	71	18.7	-
$(dp/dt)_{average}$ (atm/s)	83	27	8.9	-

n.d., not determined; -, not detected.

4. Comments

ITF 296 does not possess explosive properties and so does not require the particular care used when handling other nitro-derivative drugs (isosorbide mononitrate, isosorbide dinitrate, glyceryltrinitrate), classified as explosive compounds.

Although the thermal stability of ITF 296 is fairly good, it is sensitive to degradation by water, like the similar nitroderivative drug nicorandil (Nagai et al., 1983; Nagai et al., 1984). This effect is accentuated by increasing temperatures, as found in a previous study (Dobetti et al., 1995). Therefore, the strongly exothermic decomposition at 130°C and the explosion due to the auto-ignition temperature (180°C) do not present an obstacle to the industrial handling of the molecule, since the working temperature must be strictly maintained below 40°C, so as to avoid the formation of degradation products.

As seen in the results section, ITF 296 possesses explodibility properties when it is in the form of a powder cloud in the presence of an ignition source. The explosion parameters taken into account in this study (explodibility limit, minimum oxygen required for the explosion, explosion pressure) demonstrate that the compound may be placed in Class 1 in the Dust Hazard Class (National Fire Codes-Subscription Service, 1989a and National Fire Codes-Subscription Service, 1989b).

Study of the Class 1 list shows that ITF 296 is comparable, as regards the risk of explodibility, to many products widely used in the pharmaceutical industry (sucrose, starch, lactose, sodium stearate), and even less hazardous than cellulose and some others (National Fire Codes-Subscription Service, 1989a and National Fire Codes-Subscription Service, 1989b).

Phosphate salts are commonly used both as fire-extinguishers and as inert supports mixed with an explosive compound to reduce the explosive

properties and promote safe handling of the material (Field, 1982; Nagy and Verakis, 1983; Bartknecht, 1989).

This is confirmed by our results using Dicafos; a reduction of the explodability of ITF 296 is observed when the drug is mixed with an inert support. This reduction is strongly influenced by increasing the amount of Dicafos: explosion never occurs at an excipient concentration of 90% or higher.

Substances which are classified as explosive or can produce strongly exothermic reactions in uncontrolled conditions must be handled with particular care. For this reason, precautions to prevent explosions are planned in advance for such compounds. On the other hand, prevention measures are not anticipated for products which have not demonstrated explosive properties and must, anyway, be handled at low temperature, as is the case with most pharmaceutical materials.

The explodibility parameters of drugs are normally evaluated only during the scale-up phase or just before the start-up of manufacturing, when the pharmaceutical formulation is already defined. At that point the safety of the plant can be ensured only by acting on manufacturing processes (nitrogen atmosphere, anti-static equipment). In our example, however, a pharmaceutical excipient which markedly attenuates the explodibility properties of the compound has already been identified in the pre-formulation plan. This has two beneficial effects: first, that some formulative approaches may be followed, which otherwise would have been excluded because of explodability risk; second, that the need for anti-explosion measures in the manufacturing environment may be reduced, provided that ITF 296 is always present as a mixture with Dicafos.

This will ultimately result in economic benefits, avoiding the high cost of prevention measures, such as nitrogen atmosphere and anti-static equipment, which render the compound inert or markedly reduce the risk of explosions.

5. Conclusions

ITF 296 does not possess explosive properties. Its working temperature (below 40°C) is substantially lower than the decomposition and auto-ignition temperature.

When present as powder cloud, ITF 296 exhibits explodability characteristics, and should be classified as a Class 1 Dust Hazard.

The addition of Dicafos to the drug reduces the explodability and, at a support concentration above 90%, renders the physical mixture completely inert. This eliminates the need for anti-explosion measures in the manufacturing environment, with accompanying savings in production costs.

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