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DSC AND PHYSICO-CHEMICAL PROPERTIES OF A SUBSTITUTED PYRIDOQUINOLINE AND ITS INTERACTION STUDY WITH EXCIPIENTS

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The 4,6-*bis*[2'(diethylamino)ethoxy]2,8,10-trimethylpyrido[3,2-g]quinoline (BG 637) is one of the compound from the pyrido[3,2-g] quinolines family. This compound had in vitro activity against the resistant cells and can reverse the multidrug resistance developed during the chemotherapeutic treatments.

To characterize BG 637, techniques such as differential scanning calorimetry (DSC), Fourier transform infrared spectrometer (FTIR), ultra violet spectrophotometry (UV), gas chromatography coupled with mass spectrometry (GC/MS), nuclear magnetic resonance (NMR) and X-ray powder diffraction (XRPD) were used. Several of them were also used to show the stability of the drug during various storage conditions.

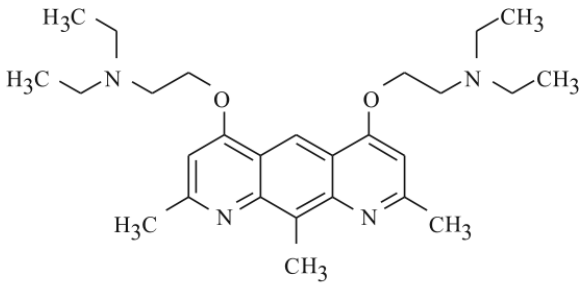
DSC, FTIR and UV were used as screening techniques for assessing the compatibility of BG 637 with several commonly used pharmaceutical excipients. We compared the properties of the pure drug with those of binary mixture drug/excipient. Studied excipients were lactose monohydrate, microcrystalline cellulose, polyvinylpyrrolidone, sodium croscarmellose and magnesium stearate. Melting temperature and enthalpy of BG 637 in binary mixtures were similar to theoretical values. These results showed that BG 637 is a very stable compound and compatible with several pharmaceutical excipients.

Keywords: *BG 637, DSC, excipients, interactions, physico-chemical properties, stability*

Introduction

In the last years, in chemotherapy, some cures failed because of the appearance of a new phenomenon known as the multidrug resistance (MDR). It is one of the main obstacles to successful cancer chemotherapy and antimicrobial treatments. It can be the result of a variety of mechanisms, which are not all fully understood [1, 2]. The most important one is the alteration of the membrane transport either by decreased drug uptake or by increased drug efflux. One of the methods which were proposed to inhibit it, is the use of a high concentration of cytotoxic drugs to overcome the effects of cell extrusion [1, 3]. Another one consists of a combination of two or more drugs whose aim is to reduce the resistance [3]. Many drugs can inhibit this resistance. These molecules generally are lipophilics, amphiphilics and heterocyclics. Verapamil is the first one found to reverse multidrug resistance in vitro [4]. The phenomenon of MDR led to the necessity to discover new molecules. Thanks to organic chemistry, several molecules were discovered that have a reversal property such as the trimethyl pyridoquinolines [5]. Some of them present a good activity at a concentration lower than the reference (verapamil, in vitro).

We were interested by one of them. This compound was 4,6-*bis*[2'(diethylamino)ethoxy]2,8,10-trimethylpyrido[3,2-g]quinoline in the following referred to as BG 637 (Fig. 1). Its synthesis and biological activity were investigated by Matias *et al.* [5].



$C_{27}H_{40}N_4O_2$

M.W.: 452

Fig. 1 Chemical structure of BG 637

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In this paper, we proposed a study of physico-chemical properties of this drug, with the aim to establish its properties according to the European Pharmacopoeia. This study was performed by the use of different methods such as differential scanning calorimetry (DSC), Fourier transform infrared spectrometry (FTIR), X-ray powder diffraction (XRPD) considered generally as reference methods and classical methods as ultra violet (UV) and nuclear magnetic resonance (NMR) spectrometries and gas chromatography coupled with mass spectrometer (GC/MS).

The stability of the compound was also investigated in different conditions of storage, according with the International Conference of Harmonization guidelines [6].

For the present work, we selected different excipients in order to realise direct compression formulation with a good free-flowing excipient.

Furthermore, we carried out compatibility studies, mainly by DSC, between BG 637 and several excipients, in order to evaluate physical and chemical interactions and then chose the most proper excipients, with the aim to establish a formulation of tablets.

The study was executed with different excipients [7], which are the following:

- Sodium starch glycolate and sodium croscarmellose, mostly used as disintegrants for tablets,
- Lactose hydrate and mannitol, used as diluents,
- Microcrystalline cellulose widely used as binder and diluent in tablets,
- Hydroxypropylmethylcellulose and polyvinylpyrrolidone (PVP), mostly used as binder,
- Magnesium stearate, working as lubricant during compression,
- Talc was also evaluated that is widely used both as lubricant and diluent.

We analysed drug-excipient mixtures (50:50 mass/mass) stored for different times: time zero, one week, one, two, three, six, twelve and twentyfour months. This work constituted the preformulation study, the necessary step for the preparation of one of the known dosage form of a drug.

Experimental

Physico-chemical characterisation of BG 637

Differential scanning calorimetry (DSC)

The majority of DSC tests were carried out with the use of a DSC Setaram 92 (Scientific and industrial Equipment, Caluire/France) apparatus. Temperatures of DSC cell and enthalpy measurements were calibrated by using indium, tin, bismuth and lead. Samples of about 20 mg were weighed in open aluminium pans and scanned under static air over a temperature range of 20 to 600°C and a heating rate of 2°C min^{-1}. Pyrolyzed kaolin was used as thermally inert reference product. Any variation of BG 637 placed in experimental crucible was observed by the baseline modifications. Determined temperatures (°C) were: T_{max} (bottom of the peak), T_{onset} (extrapolated). Enthalpy variation was determined for melting peak (ΔH in J g^{-1}) by linear integration according to Setaram software. Temperature accuracy was 0.1°C for melting point and 1°C for other endothermic or exothermic peak.

A second and new apparatus was used (Netzsch DSC 200F3): samples of about 10 mg in an aluminium pan with a lid scanned under static air over a temperature range of 20 to 600°C and various heating rates (1 to 10°C min^{-1}). An empty aluminium pan with a lid was used for reference. Calibration was done as described above. Any difference was not found by authors in the use of open pans and covered pans.

Ultraviolet spectrophotometry (UV)

The UV spectrum was recorded by a Shimadzu UV 2401 apparatus, with 1 cm quartz cell in ethanol solution (Carlo Erba reagent, ACS - for analysis) in the wavelength range of 200 to 400 nm.

Fourier transform infrared spectrometry (FTIR)

FTIR spectrum was recorded on ATI Mattson, Genesis1 spectrophotometer, by mixing the drug with KBr and placed in a cup for diffuse reflectance analysis in the range of 4000–500 cm^{-1}, with a resolution of 4 cm^{-1}. The spectra were scanned by averaging 30 scans for each spectrum.

Gas chromatography coupled to a mass spectrometer (GC/MS)

GC/MS analysis was performed on trace GC DSQ (ThermoFinnigan apparatus). We operated in the electron impact mode under standard conditions (electron energy 70 eV). A thermoTR-5MS column 60 m long×0.33 mm i.d.×0.25 μm film thickness was used with helium as a carrier gas at a linear velocity of 1.5 mL min^{-1}. The injector temperature was set at 250°C. 1 μL of solution (1 g L^{-1} in methanol) was injected. The column temperature program was monitored from 100 to 300°C at 15°C min^{-1}. Analysis was realized in triplicate.

Nuclear magnetic resonance (NMR)

^{1}H and ^{13}C nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) spectra were recorded in $CDCl_3$ using ARX200 and ARX300 Brüker spectrometer. ^{1}H and

^{13}C nuclear chemical shifts were referred to $CDCl_3$ (7.24 and 77.0, respectively) as internal standard.

X-ray powder diffraction (XRPD)

XRPD was obtained with an INEL CPS 120 apparatus. The same batch of BG 637 was analysed in different conditions: the first one without any manipulation, the second one, after pulverisation and the third one, after crystallization.

Laser granulometry

This measurement has been performed using a Mastersizer laser granulometer. The sample was placed in the cell which contained water. The particles size between 0.05 to 880 μm, were detected by the lens (300 RF).

Stability study

BG 637 was placed in a hermetic flask according:

- with International Conference of Harmonization (ICH) conditions of storage:
  * accelerated: at 40°C under 75% relative humidity during six months,
  * long term: at 5°C during 12 months,
- and out of ICH conditions:
  * at 25°C without any conditions of relative humidity,
  * under light (150 Watts), solar radiations and daylight.

Analyses by NMR and UV were done every month during one year and GC/MS after synthesis and at 6 and 12 months. The corresponding spectra and chromatograms were compared with the first one done.

Interaction study between BG 637 and excipients

The study of the interactions of excipients with drug is the essential step in the preformulation stage for the development of all dosage forms. The physical and chemical interactions between the active substance and excipients can affect the chemical nature, the stability and the bioavailability of drug and consequently its therapeutic efficacy and safety.

Excipients have been classified according to the functions they perform in a formulation, although many excipients perform multiple functions. Diluents, for example, can form a large proportion by mass of a formulated product [8]. Disintegrants tend to swell when wetted, so they are good candidates for the dosage form like granules and powder particles [9, 10]. Binders provide cohesiveness to a powder mixture to ensure that a tablet formulation will be compressible [11, 12]. Lubricants usually are hydrophobic substances that act by coating particles to prevent sticking of the tablet into the tableting machine [12, 13].

DSC is a rapid analytical technique commonly used for evaluating drug-excipient interactions. Any shift of endothermic or exothermic peak and/or variation in the enthalpy values reflects a possible interaction [14]. The interpretation of the thermal data is not always straightforward. To avoid misinterpretation of DSC result, the use of other analytical techniques such as UV and FTIR, as complementary tools, is advisable. We compared the new UV and/or IR spectrum with the spectrum of BG 637 alone and any changes in the first one could be the result of interactions [15].

We have chosen eight excipients which have different functions (two binders, two disintegrants, two diluents and two lubricants). They are described in European Phamacopeia [16] and usually used in pharmaceutical process technology. Some of them have two different functions. Commercial names, functions and suppliers are presented in Table 1. The mixtures of drug/excipient (200 mg BG 637/200 mg excipient) were stored at 25°C and 60% relative humidity under different conditions of light [10, 17].

Samples were analysed by DSC, UV and FTIR, at different times: zero, one week, one, two, three, six,

Table 1 Pharmaceutical excipients used in the interaction study

Excipient	Commercial name	Function	Supplier
Hydroxypropylmethylcellulose (HPMC)	Methocel E15 LV	Binder	Colorcon
Talc	No name	Lubricant and diluent	Cooper
Mannitol	Pearlitol DC 400	Diluent	Roquette
Crospovidone	Kollidon CL	Binder and diluent	BASF
Lactose monohydrate	Supertab spray dried	Diluent	Seppic
Sodium starch glycolate	Primojel	Desintegrant	Unipex DMV
Magnesium stearate	No name	Lubricant	Cooper
Polyvinylpyrrolidone	Kollidon PVP K 90	Binder	BASF
Polyvinylpyrrolidone	Kollidon PVP K 30	Binder	BASF
Sodium croscarmellose	AcDiSol	Desintegrant	FMC Europe

twelve and twentyfour months, after making the mixture, in order to observe an eventual interaction [18, 19].

Results and discussion

Physico-chemical characterisation of BG 637

DSC analysis

Some attempts were carried out in different heating rates of 1, 2, 5 and 10°C min^{-1} in order to search any impurities or polymorphic forms. In each test, we performed a first heating, followed by a cooling and at least by another heating. The DSC curve of BG 637 (Table 2 and Fig. 2) shows one endothermic peak corresponding to the fusion. The T_{onset} is constant but the T_{max} increases with an increasing heating rate. The average T_{onset} of the four tests is 139.3°C; the standard deviation is 0.746°C and the relative standard deviation is 0.569%. Similar values were obtained with each DSC apparatus.

UV spectrophotometry analysis

The maximum absorption wavelength was obtained at 256 nm. This analysis was repeated three times with three different batches of the BG 637. Six diluted aqueous standard solutions of BG 637 (1.0 to 6.0 mg L^{-1}) were prepared twice a day during three days. Experimental data measured at 256 nm were used to determine the required analytical parameters such as selectivity (against excipients), range (1.0 to 6.0 mg L^{-1}), linearity (r=0.997 in the range 1.0 to 6.0 mg L^{-1}), repeatability (CV=1.13%) intermediate precision (CV=1.92%) and accuracy (101.2±1.5%) [16].

Table 2 DSC data of BG 637: temperature and enthalpy values of melting (heating) and crystallisation (cooling)

	Tests	1	2	3	4
	Heating rate/ °C min^{-1}	1	2	5	10
1st heating	T_{onset}/°C)	139.7	138.7	140.1	140.2
	T_{max}/°C	142.6	142.7	144.2	145.1
	ΔH/J g^{-1}	–35.7	–34.5	–35.6	–37.1
Cooling	T_{max}/°C	135.0	136.2	134.7	133.2
2nd heating	T_{onset}/°C)	139.3	138.8	139.2	138.0
	T_{max}/°C	142.1	142.3	144.1	145.0
	ΔH/J g^{-1}	–33.3	–32.3	–34.5	–36.3

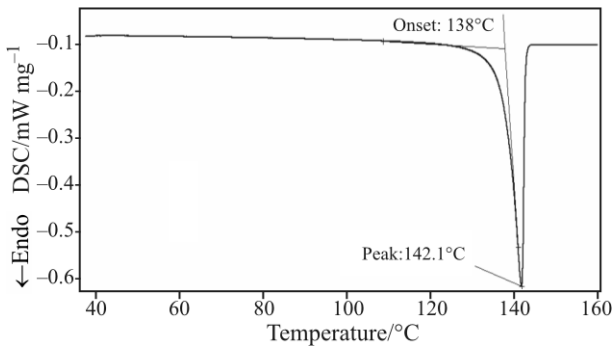

Fig. 2 DSC curves of BG 637 (test done on Netzsch apparatus; heating rate 2°C min^{-1}; heating range 30–160°C; sample 11.6 mg; under static air)

FTIR analysis

The FTIR analysis shows specific peaks: 2600–3000, 1625, 1300–1050 cm^{-1} correspond to CH_2 and CH_3 aliphatic and CH_3 aromatic, to C=C aromatic and C–O aromatic, respectively (Fig. 3).

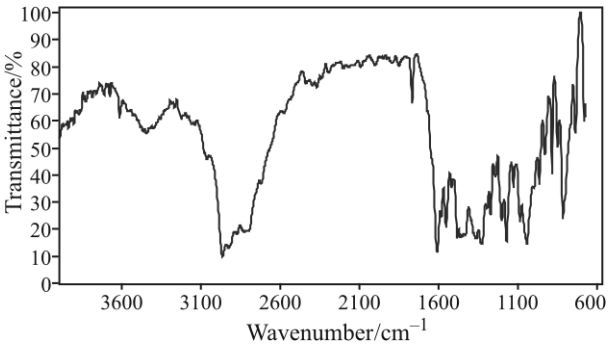

Fig. 3 FTIR spectrum of BG 637 by diffuse reflectance analysis

GC/MS analysis

The chromatogram shows only one peak corresponding to our sample with a retention time of 20.80 min. The mass spectrum (Fig. 4) was characterized by two major m/z peaks: 86 and 100 corresponding respectively to the lateral chains $[CH_2N(C_2H_5)_2]$ and $[CH_2CH_2N(C_2H_5)_2]$. The molecular structure allows the fragmentation of the lateral chain with two possibilities.

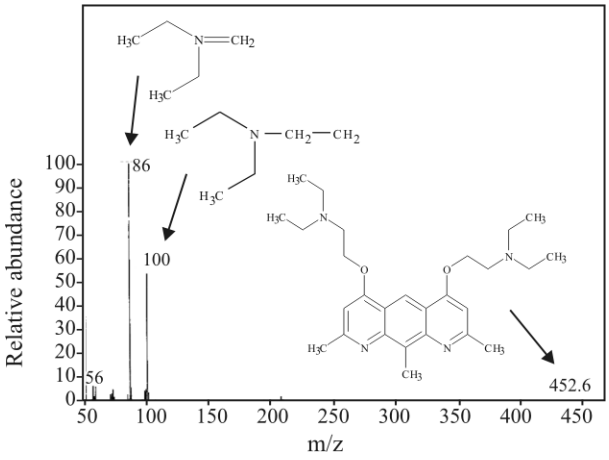

Fig. 4 Mass spectrum of BG 637

Nuclear magnetic resonance (NMR) analysis

The results were:

- for ^{1}H NMR ($CDCl_3$): 1.10 (t, 12H, J=7.1, CH_3); 2.70 (m, 14H, 8H CH_2, 6H, CH_3); 3.10 (t, 4H, J=6.1, CH_2–N); 3.30 (s, 3H, CH_3); 4.25 (t, 4H, J=6.1, 0-CH_2); 6.55 (s, 2H, H Ar); 8.85 (s, 1H, H Ar).
- for ^{13}C NMR ($CDCl_3$): 12.26 (CH_3); 12.55 (10-CH_3); 26.87 (2.8-CH_3); 48.07 (CH_2); 51.36 (CH_2–N); 67.30 (O–CH_2); 99.35 (C-3, C-7); 112.90 (C-5); 118.10 (C-5a, C-5b); 132.36 (C-10); 146.45 (C-10a, C-10b); 160.32 (C-2, C-8); 162.01 (C-4, C-6).

These chemical shifts confirmed the structure of BG 637.

X-ray powder diffraction (XRPD)

The sample treatment does not exert any visible effect on XRPD pattern (Fig. 5). The result suggests that firstly the active substance didn't change and secondly the BG 637 does not form polymorphs.

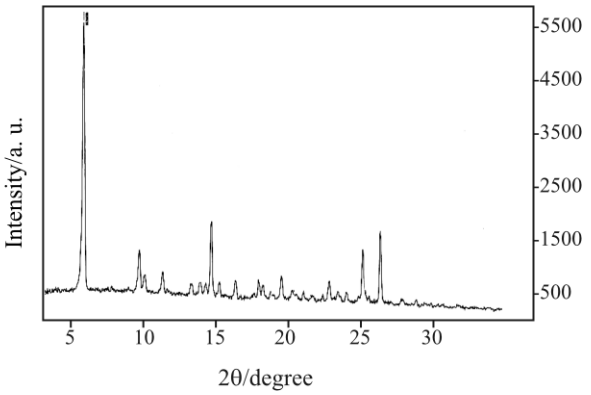

Fig. 5 X-ray powder diffraction pattern of BG 637

Stability study

By the use of NMR, we observed that BG 637 never changed during its stocking as well as at 40°C and at 75% relative humidity and at 4°C in the dark, at 25°C or under solar radiations and daylight. The comparison between the ^{1}H NMR spectra shows the same spectra as the first one established. So BG 637 seems to be stable in the studied conditions. These results were confirmed, first by the UV analysis in the same conditions where the spectra were superimposable with the first one established, and secondly by GC/MS where only one peak was observed in every case the same retention time.

The water content was always less than 3% and residual solvents were always less than International Conference Harmonization recommendation Q3C (R3) [20].

Laser granulometry analysis

The average size of particles is 422.86 μm (D [v, 0.5]) and D [v, 0.9] is 695.95 μm). The graph corresponding to this analysis is a Gaussian curve, confirming the dimensional homogeneity of particles. Some of them can reach 878.67 μm.

Interactions study between BG 637 and excipients

DSC analysis

DSC tests were carried according to two steps. First, we analysed all the excipients by DSC at heating rate of 2°C min^{-1}. Results presented in Table 3, concerned the excipients chosen for formulation. The DSC curve of lactose shows an endothermic peak corresponding to the dehydration (bound water) at T_{max} 144.2°C and ΔH= –72.0 J g^{-1}, a small exothermic event due to the crystalline transition (peak temperature T_{max} at 169.8°C, ΔH<1 J g^{-1}), and a melting point at T_{onset} 189.4°C, followed by a beginning of oxidation at 224°C. The DSC curve of microcrystalline cellulose, of polyvinylpyrrolidone PVP K30, of sodium croscarmellose and of magnesium stearate show a broad endothermic peak due to the dehydration (humidity loss) at T_{max}=81.7, 75.6, 70.8 and 73.2°C, respectively.

Based on structural data, it is currently assumed that commercial magnesium stearate consists of either crystalline hydrates (di- or trihydrate, or a mixture there of), or a poorly crystallised anhydrate [15, 21–23]. Even commercial magnesium stearate

Table 3 Peak temperature and enthalpy values of excipients (tests done on Setaram apparatus; heating rate 2°C min^{-1})

Excipients	Characteristic peaks
Lactose monohydrate	Endothermic peak (dehydration): T_{onset}=136.5°C, T_{max}=144.2°C, ΔH=–72.0 J g^{-1} Exothermic peak: T_{onset}=167.0°C, T_{max}=169.8°C, ΔH=+0.81 J g^{-1} Endothermic peak (fusion): T_{onset}=189.4°C, T_{max}=206.3°C, ΔH=–134.6 J g^{-1}
Microcrystalline cellulose	Endothermic peak (humidity): T_{max}=81.7°C, ΔH=–52.9 J g^{-1}
Polyvinylpyrrolidone PVP K 30	Endothermic peak (humidity): T_{max}=75.6°C, ΔH=–161.8 J g^{-1}
Sodium croscarmellose	Endothermic peak (humidity): T_{max}=70.8°C, ΔH=–107.9 J g^{-1}
Magnesium stearate	Endothermic peak (dehydration): T_{max}=73.2°C, ΔH=–13.2 J g^{-1} Endothermic peak: T_{onset}=95.6°C, T_{max}=105.3°C, ΔH=–13.3 J g^{-1}

contains several hydrates (mono-, di- or trihydrates). Each water molecule is volatilised from about 60 to 110°C. DSC curve shows a second endothermic peak at T_{max}=105.3°C. In our case, none of observed peak could be due to melting.

For microcrystalline cellulose, polyvinyl- pyrrolidone PVP K 30, sodium croscarmellose and magnesium stearate, we observed a thermal oxidation at 270, 175, 213 and 155°C, respectively.

Each DSC binary mixture BG 637/excipient test (about 20 mg) was carried out like described above. The values of the melting peak temperature and enthalpy, of other peaks for the studied binary mixtures are listed in Table 4. DSC curves show the endothermic peak of humidity in the range of 50 to 71°C, excepted for the lactose. After homogenization of binary mixtures, a part of the moisture volatilized, so this endothermic peak had decreased.

For the mixture BG 637/lactose monohydrate we obtained T_{max}=141.7°C and ΔH= –55.0 J g^{-1} of the 1st endothermic peak corresponding to the half of the sum ΔH BG 637+ΔH lactose monohydrate (–72.0–34.5)/2= –53.3 J g^{-1}). This observed theoretical mean value of –53.3 J g^{-1} is near of that obtained practically for the mixture (–55.0 J g^{-1}). So, no interaction between lactose and BG 637 could be observed at about 141°C. The 2nd endothermic melting peak temperature and enthalpy are lower than the pure lactose monohydrate, due probably to a eutectic formation.

BG 637 in binary mixture (50:50) with the other excipients shows ΔH values (–17.8 to –21.0 J g^{-1}) near of the theoretical value of –17.3 J g^{-1}.

We can conclude that the BG 637 was not degraded and its molecular structure was not changed. Interactions between BG 637 and chosen excipients were not observed. These data will be completed with UV and FTIR analyses.

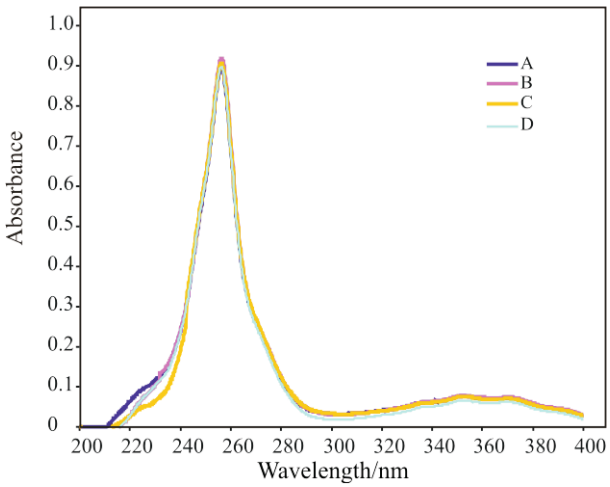

Fig. 6 UV spectra of binary mixture BG 637/mannitol during time (A=time zero, B=after one week, C=after one month in light, D=after one month in darkness)

UV spectrophotometry analysis

For the UV curves obtained in absolute alcohol at time zero, no change was observed with the UV spectrum of BG 637 during two years. These samples were stored and analysed during the storage. The absorption maximum of binary mixture spectra was the same of pure BG 637 (at 256 nm), even with another sugar like mannitol (Fig. 6). There is no degradation peak and no secondary peak appeared.

FTIR analysis

FTIR is one technique used in drug investigation, and has significance in investigations of interactions be-

Table 4 Temperature and enthalpy values of binary mixture BG 637/excipients (lactose, microcrystalline cellulose, polyvinylpyrrolidone PVP K30, sodium croscarmellose, magnesium stearate) (tests done on Setaram apparatus; heating rate 2°C min^{-1})

Binary mixture	Lactose monohydrate	Microcrystalline cellulose	Povydone PVP K30	Sodium croscarmellose	Magnesium stearate
Endothermic peak (humidity)					
T_{max}/°C	none	51.5	70.9	52.7	70.6
Endothermic peak					
T_{onset}/°C	136.8	136.8	137.5	137.1	137.4
T_{max}/°C	141.7	142.6	142.5	142.4	141.0
ΔH/J g^{-1}	–55.0	–19.1	–17.8	–21.0	–21.0
Endothermic peak					
T_{onset}/°C	186.8	none	none	none	none
T_{max}/°C	191.5				
ΔH/J g^{-1}	–16.7				
Exothermic peak					
T_{onset}/°C	196.0	none	137.5	none	none
T_{max}/°C	198.4		176.0		
ΔH/J g^{-1}	+29.6		+3.0		

tween drugs and excipients in pharmaceutical formulations. Appearance of new IR absorption band(s); broadening of band(s); alteration in intensity are the main characteristics which provide interactions between drug and excipients. We proceed like it was described above. For each sample mixture (in light and darkness), we obtained a specific spectrum. For each mixture, the spectra were superimposed with BG 637 spectrum in order to see the changes. There is no new IR absorption band, no alteration in intensity or other changes observed.

Conclusions

A review of the literature on drug-excipient interactions shows that the mechanism of the interaction is often not clear. Excipients have traditionally been thought to be an inert support for drugs, but this is outdating, because they often contain reactive functional groups. These functions can involve some chemical transformations. The physical interactions can affect the speed of dissolution or the uniformity of the dosage of a solid formulation. The chemical interactions can involve the degradation of the active substance, with formation of impurities, for example [19, 24]. For example, lactose with alcohol functions could interact with amine functions of the BG 637. DSC curves, UV and FTIR spectra showed no changes. No interactions between the BG 637 and the chosen excipients were observed. So, these studied compounds could be integrated in a tablet formulation.

The physical characterization of the active substance is crucial to the successful development of the final drug. The full characterization of the active substance is necessary in order to understand the chemical and physical properties of the material [25]. The spectroscopic techniques became an integral part of the physico-chemical characterization of pharmaceutical solids [26].

Studies of drug-excipients compatibility represent an important step in the formulation stage for the development of all dosage forms (ICH Q8) [27]. The success of the formulation depends not only on the physical and chemical properties of the active substance but also on the excipients, which are typically the major component of any solid-state formulation. Different excipients were tested for their compatibility with the active substance. The results confirmed how useful can be DSC for evaluating the drug-excipient interactions at the earliest stage of formulation studies. The presence of solid-solid interaction does not necessarily indicate pharmaceutical incompatibility, the use of other analytical techniques, such as FTIR helps in the interpretation of DSC results, in order to confirm the interpretation, of the DSC results.

In the present case the DSC results, supported by UV and FTIR analyses, showed that all the tested excipients are compatible with BG 637. Interaction studies between drugs and excipients are more and more performed by thermal analysis techniques [28, 29].

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References

1 E. Teodori, S. Dei, S. Scapecchi and F. Gualtieri, Il Farmaco, 57 (2002) 385.
2 M. Volm and J. Mattern, Crit. Rev. Oncog., 7 (1996) 227.
3 P. Olliaro, Pharmacol. Ther., 89 (2001) 207.
4 T. Tsuruo, H. Iida, S. Tsukagoshi and Y. Sakurai, Cancer Research, 41 (1981) 1967.
5 C. Matias, A. Mahamoud, J. Barbe, B. Pradine and J. C. Doury, Heterocycles, 43 (1996) 1621.
6 ICH Harmonised Tripartite Guideline, Stability Testing of New Drug Substances and Products, ICH Q1A(R2). The European Agency for the Evaluation of Medicinal Products (CPMP/ICH/2736/99), 2003.
7 R. C. Rowe, P. J. Sheskey and P. J. Weller, Handbook of Pharmaceutical Excipients, 4th Ed., Pharmaceutical Press (PhP) and American Pharmaceutical Association (APhA), London and Chicago 2003.
8 A. R. Gennaro, Ed., Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Company., Easton PA 1990.
9 A. E. Aboutaleb, A. M. Attia and F. S. Habib, Pharmazie, 38 (1983) 473.
10 H. A. Liebermann, L. Lachman and J. B. Schwartz, Pharmaceutical Dosage Forms: Tablets, 2nd Revised and Expanded Ed., 1996.
11 O. A. Itiola and N. Pilped, Int. J. Pharm., 31 (1986) 99.
12 S. Y. Lin, J. Pharm. Sci., 77 (1988) 229.
13 Z. T. Chowhan, Pharm. Technol., 17 (1993) 72.
14 P. C. Mora, M. Cirri and P. Mura, J. Pharm. Biomed. Anal., 42 (2006) 3.
15 A. A. Araujo, S. Storpirtis, L. P. Mercuri, F. M. Carvalho, M. dos Santos Filho and J. R. Matos, Int. J. Pharm., 260 (2003) 303.
16 EDQM and European Directorate for the Quality of Medicines and Health Care, European Pharmacopoeia, 6th Ed., Council of Europe, Strasbourg 2008.
17 I. I. Jivraj, L. G. Martini and C. M. Thomson, Pharm. Sci. Technol. Today, 3 (2000) 58.
18 United States Pharmacopoeia-National Formulary, USP 30 - NF 25, Rockville 2007.
19 C. L. Winek, Drugs Pharm. Sci., 103 (2000) 59.

20 ICH Harmonised Tripartite Guideline, Impurities: Residual Solvents, ICH Q3C(R3). The European Agency for the Evaluation of Medicinal Products (CPMP/ICH/283/95), 1997.
21 P. Bracconi, C. Andres, A. N'Diaye and Y. Pourcelot, Thermochim. Acta, 429 (2005) 43.
22 P. Bracconi, C. Andres and A. N'Diaye, Int. J. Pharm., 262 (2003) 109.
23 S. Sharpe, M. Celik, A. Newman and H. Brittain, Struct. Chem., 8 (1997) 73.
24 P. Crowley and L. Martini, Pharm. Technol. Eur., 13 (2001), 26–28 see also 30–32, 34.
25 S. Byrn, R. Pfeiffer, M. Ganey, C. Hoiberg and G. Poochikian, Pharm. Res., 12 (1995) 945.
26 H. G. Brittain, S. J. Bogdanowich, D. E. Bugay, J. DeVincentis, G. Lewen and A. W. Newman, Pharm. Res., 8 (1991) 963.
27 ICH Harmonised Tripartite Guideline, Pharmaceutical Development, ICH Q8. The European Agency for the Evaluation of Medicinal Products (CPMP/ICH/167068/04), 2005.
28 G. G. G. Oliveira, H. G Ferraz and J. S. R. Matos, J. Therm. Anal. Cal., 79 (2005) 267.
29 M. Laszcz, B Kosmacinska, K. Korczak, B. Simigielska, M. Glice, W. Maruszak, A. Groman, H. Beczkowicz and L. Zelazko, J. Therm. Anal. Cal., 88 (2007) 305.

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