Preformulation Compatibility Screening of Dika fat-Drug Mixtures Using Differential Scanning Calorimetry

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Abstract

Differential scanning calorimetry (DSC) was used as screening technique for assessing compatibility between dika fat and drug substances. Dika fat was found to be compatible with aspirin, ascorbic acid, paracetamol, sulphanilamide, phenylpropanolamine hydrochloride, bromopheniramine maleate, chlorpheniramire maleate, diazepam, phenobarbital, phenobarbital sodium, phenylpropanolamine hydrochloride and propranolol hydrochloride. It appears that dika fat can be used as a formulation aid in medicinal or veterinary products containing any of these substances. It was found that dika fat may interact with ephedrine hydrochloride, norgestrel and atropine sulphate.

Keywords: Dika fat, Drugs, Compatibility screening, Differential scanning calorimetry

Introduction

These authors first reported the use of dika fat in the formulation of pharmaceutical dosage forms as tablet lubricant (Udeala *et al,* 1980; Onyechi and Udeala, 1990). We also reported the use of the fat in the preparation of sustained release tablets (Onyechi and Udeala, 1988). Other workers have since described the use of dika fat in the formulation of other dosage forms (Ofoefule *et al.,* 1997; Ofoefule and Chukwu, 2001). Since our first report, and despite the increasing use of dika fat as a formulation aid for medicinal and cosmetic products, there has been no report of the study of the compatibility of dika fat with classes of drugs and formulation excpients.

Dika fat is a solid vegetable oil extracted from the kernels of *Irvingia gabonensis* var *gabonensis* and *var excelsia*. Dika fat exhibits excellent storage stability at room temperature (Udeala *et al.,* 1980). The fat is generally used for food and is therefore easily available.

The compatibility of a drug substance with excipients used in pharmaceutical formulations is determined by preformulation studies. Several techniques have been used to study drug-drug and drug–excipent interactions: thin layer chromatography, diffuse reflectance spectroscopy, tristimulus reflectance and quantitative assay after isothermal stress, differential thermal analysis, DTA and differential scanning calorimetry.

A differential scanning calorimeter measures the difference in heat flows to a sample and a reference, which are subjected to the same temperature programme. DSC measurements provide information on thermal effects that are characterized by an enthalpy change and by the temperature range, such as melting behaviour, crystallization, solid-solid transitions and chemical reactions (Bottom, 2001)

In pharmaceutical systems DSC and DTA have been used for the determination and estimation of impurities (Van Doreen and Mueller, 1984), identification of polymorphic forms and solvates (Giron, 1995; Giron, 1998), assessment of molecular interaction between solid components of pharmaceuticals (Mura et al, 1998; McDaid *et al.,* 2003) and for the rapid evaluation of the compatibility of drug substances with excipients (El-Shattaway *et al,* 1982; Botha and Lother, 1990; Mura *et al.*, 2005; Balestrieri *et al.,* 1996). In the present investigation computer mediated differential scanning calorimetry was used to study the compatibility of dika fat with some drugs. We have compared the DSC thermograms of 1:1 mixtures of dika fat and the drugs with those of the components.

Materials and Methods

The following materials were used aspirin (Merck, USA), ascorbic acid (Roche, USA), bromopheniramine maleate (Hexagon, USA), chlorphenirarnine maleate (Hexagon, USA), diazepam (Roche, USA), paracetamol (Halewood, England), phenobarbital (Merck, USA), phenobarbital sodium (Merck, USA), propranolol hydrochloride (Merck, USA), phenylpropanolanine hydrochloride (Merck, USA), sulphanilamide (Merck, USA) norgestrel (Wet, USA), atropine sulphate (Merck, USA) and ephedrine hydrochloride (Sigma, USA).

Differential scanning calorimetry: Thermal analyses were performed on dika fat, pure drug and 1:1 (w/w) physical mixtures of dika fat and named drugs respectively. Samples (2-8 mg) were weighed and after being finely powdered were encapsulated in flat-bottomed aluminum pans with crimped-on lids. Thermal curves were obtained using a Perkin-Elmer DSC-4 differential scanning calorimeter (Perkin-Elmer Corporation, Norwalk, CT, USA) equipped with a Bascom Turner Recorder and Data Acquisition System (Bascom Turner Instruments, MT, USA). A model DSC Intracooler (Perkin Elmer Corporation, Norwalk, CT, USA) provided a convenient means of cooling the sample holder enclosure block of the calorimeter.

Thermograms were obtained at a constant heating range setting of 20 mcal per minute, in an atmosphere of nitrogen and recorded at a constant chart speed of one inch per minute. The individual substances and 1:1 mixtures of drug and dika fat prepared were heated over the temperature range 20 to 220^{0}C.

Results and Discussion

The DSC thermograms of the dika fat samples used in this study are shown in Figure 1. Data from the endothermic profiles are presented in Table 1. The endothermic profiles for unrefined dika fat samples from var *excelsia* (Fig. 1 a) showed a melting endothermic peak with a transition temperature range from 28 – 60^{0}C and an average maximum peak of transition at 46^{0}C. The refined fat sample from the same var *excelsia* (Fig 1b) showed a melting endothermic peak with a transition temperature range from 32 – 52^{0}C and an average maximum peak of transition at 48^{0}C. The endothermic profile for unrefined dika fat from var *gabonensis* (Fig. 1c) showed a melting endothermic peak with a transition temperature range from 28 – 52^{0}C and an average maximum peak of transition at 45^{0}C. The endothermic profile for refined dika fat from var *gabonensis* (Fig. 1d) also showed a melting endothermic peak with a transition temperature range from 32 – 48^{0}C and an average maximum peak of transition at 47^{0}C. Endothermic profiles of dika fat samples derived from var *excelsia* and var *gabonensis* showed no real difference between the two sources.

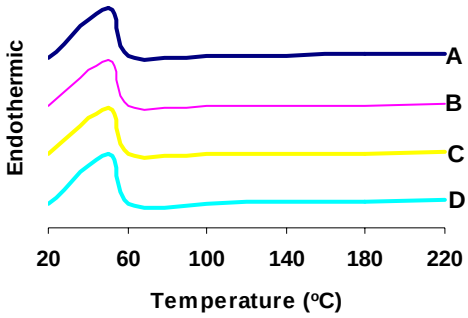

Fig. 1: DSC thermograms for fat from *Irvingia gabonensis* , a, var excelsia (unrefined); b, *var excelsia* (refined); c, *var gabonensis* (unrefined) and d, *var gabonensis* (refined)

DSC thermograms were generated for physical mixtures of processed (refined) and unprocessed (unrefined) samples of dika fat and both aspirin and ascorbic acid. The purpose was to determine the effect, if any, of the purification procedure adopted for dika fat, on the thermal behaviour of either aspirin or ascorbic acid, and the dika fat sample used. Data from the endothermic profiles are presented in Table 2. The endothermic profiles for aspirin showed an endotherm with a transition temperature range from 132 – 150 ^{0}C and an average maximum peak of transition at 145 ^{0}C. This transition peak corresponds to the melting of aspirin. The transition temperature range of 141 – 144 ^{0}C is official in the European Pharmacopoeia (1969). The endothermic profile for dika fat showed a melting endothermic peak with a transition temperature range from 28 – 60 ^{0}C and an average maximum peak of transition at 46^{0}C. The endothermic profile of the mixture of aspirin and both refined and unrefined dika fat combined the features characteristic of the endothermic profiles of each component. No interaction between dika fat and aspirin occurred. Bottom (2001) stated that incompatibility is highly improbable if the endothermic profiles of a mixture are a simple superposition of those of the components.

Data from the endothermic profiles for physical mixtures of ascorbic acid and dika fat derived from both *Irvingia gabonensis* var *excelsia* and var *gabonensis* are also presented in Table 2. The endothermic profile for ascorbic acid showed an endotherm with a transition temperature range from 192 – 204 ^{0}C and an average maximum peak of transition at 198^{0}C. This transition peak corresponds to the melting of ascorbic acid. The melting temperature range for ascorbic acid obtained was 192 – 204^0 C (Merck Index, 1976a; Clarke, 1969). The melting temperature range obtained in this work (192 – 204 ^{0} C) was within the range reported. Endothermic profiles of the mixtures of ascorbic acid with processed and unprocessed dika fat indicated the same double peaked endothermic transitions corresponding to the peaks of the individual components. Incompatibility between ascorbic acid and dika fat is therefore highly improbable. DSC thermograms of dika fat samples derived from the var *excelsia* and var *gabonensis* showed no real difference between the two sources in endothermic profiling per se and with both aspirin and ascorbic acid. Therefore only processed dika fat derived from *Irvingia gabonensis* var *excelsia* was used for subsequent DSC investigations.

Data from the endothermic profiles of other drugs investigated in this study are presented in Table 3. The drugs were: bromopheniramine maleate, chlorphenirarnine maleate, diazepam, paracetamol, phenobarbital, phenobarbital sodium, phenylpropanolamine hydrochloride, propranolol hydrochloride, ephedrine hydrochloride, norgestrel and atropine sulphate.

Bottom (2001) suggested that pharmaceutical preparations can be rapidly investigated by DSC for incompatibility by comparing the results for the individual components and the mixture with each other. If the mixture exhibits thermal effects that are not apparent in the individual components, he suggested that that is an indication of interaction.

The endothermic profile for the mixture of dika fat and bromopheniramine maleate combined the features characteristic of the thermal curves of dika fat and bromopheniramine maleate. Interaction between dika fat and bromopheniramine maleate is therefore improbable.

The endothermic profile for the mixture of dika fat and chlorpheniramine maleate combined the features characteristic of the thermal curves of dika fat and chlorpheniramine maleate.

Table 1: Transition temperature obtained from endothermic profiles of dika fat samples by differential scanning calorimetry

Dika fat sample from	Transition temperature range (^oC)	Average maximum transition peak (^oC)	Remarks
Unrefined *Irvingia gabonensis var excelsia*	28-60	46	Melting endotherm
Refined *Irvingia gabonensis var excelsia*	32-52	48	Melting endotherm
Unrefined *Irvingia gabonensis var gabonensis*	28-52	45	Melting endotherm
Refined *Irvingia gabonensis var excelsia*	32-48	47	Melting endotherm

Table 2: Endothermic profiles of dika fat with aspirin and ascorbic acid combinations using differential scanning calorimetry

Dika fat/drug mixture	Transition temperature range (^{0} C)				
	20-60	**60-100**	**100-140**	**140-180**	**180-220**
Unrefined Dika fat from *Irvingia gabonensis* var *gabonensis*	28-52				
Aspirin			132-150	132-150	
1:1 Aspirin-unrefined dika fat from *Irvingia gabonensis* var *gabonensis* mix	30-56		130-152	130-152	
Refined Dika fat from *Irvingia gabonensis* var *gabonensis*	32-48				
1:1 Aspirin-refined dika fat from *Irvingia gabonensis* var *gabonensis* mix	33-55		132-150	131-151	
Unrefined Dika fat from *Irvingia gabonensis* var *excelsia*	28-60				
1:1 Aspirin-unrefined dika fat from *Irvingia gabonensis* var excelsia mix	29-60		132-150	132-150	
Refined Dika fat from *Irvingia gabonensis* var *excelsia*	32-52				
1:1 Aspirin-refined dika fat from *Irvingia gabonensis* var *excelsia* mix	34-51		134-149	134-149	
Ascorbic acid					192-204
1:1 Ascorbic acid-unrefined dika fat from *Irvingia gabonensis* var *gabonensis* mix	29-60				190-206
1:1 Ascorbic acid-refined dika fat from *Irvingia gabonensis* var *gabonensis* mix	25-60				191-205
1:1 Ascorbic acid-unrefined dika fat from *Irvingia gabonensis* var *excelsia* mix	26-60				189-208
1:1 Ascorbic acid-refined dika fat from *Irvingia gabonensis* var *excelsia* mix	27-56				191-206

Interaction between dika fat and chlorpheniramine maleate is also improbable.

The mixture of dika fat and diazepam exhibited thermal effects apparent in the individual components; this is an indication of no interaction. Donahue (1975) reported a melting endotherm at 128^{0}C for diazepam by DSC. The melting range for diazepam is reported in NF XIII as 131–135 ^{0}C. Therefore, the result obtained in the present investigation showed there was no incompatibility between this drug and dika fat.

The endothermic profile for the mixture of dika fat and paracetamol also combined the features characteristic of the thermal curves of dika fat and paracetamol. Interaction between dika fat and paracetamol is therefore highly improbable.

The endothermic profile for the mixture of dika fat and phenylpropanolamine hydrochloride is a superimposition of the thermal curves of dika fat and phenylpropanolamine hydrochloride. Interaction between dika fat and phenylpropanolamine hydrochloride is therefore improbable.

The endothermic profiles for the mixture of dika fat and propranolol hydrochloride combined the features characteristic of the endothermic profiles of dika fat and propranolol hydrochloride. Interaction between dika fat and propranolol hydrochloride is improbable.

The thermal curve for the mixture of dika fat and phenobarbital sodium combined the features characteristic of the thermal curves of dika fat and phenobarbital sodium. This is an indication of no interaction between dika fat and phenobarbital sodium.

In the endothermic profile of the mixture of dika fat and phenobarital, some changes were discernible when compared with the profiles of the component materials. The first endotherm corresponding to phenobarbital was broadened and was shifted to higher temperatures. This contrasted with the same endotherm on the endothermic profile of pure phenobarbital. The second endotherm indicating the melting of dika fat was still identifiable. Phenobarbital is known to exhibit polymorphism. It is usual practice to subject samples that show polymorphism to some form of pretreatment prior to DSC. This ensures that only a known polymorphic form is present. The sample of phenobarbital used in this investigation was not pretreated. The various polymorphic forms were present in the sample. The changes which occurred in the endothermic profile of the mixture of dika fat and phenobarbital resulted from the presence of the various polymorphic forms of the drug. However, from stability considerations, it is to be assumed that incompatible interaction between dika fat and the drug is probable.

The endothermic profile for pure norgestrel showed a melting endotherm from 205 – 210^{0}C. In the endothermic profile for a mixture of norgestrel with dika fat an endotherm that indicated the melting of dika fat was seen.

Table 3: Data from thermal curves of named drugs and 1:1 physical mixture of dike fat and named drugs

Drug	Transition temperature range in ^{0}Co		Peak transition temperature in ^{0}Co		Remarks
	Pure drug	1:1 Mix of pure drug and dike fat	Pure drug	1:1 Mix of drug and dika fat	
Diazepam	128-140	120-136	130	130	Endothermic transition of 130^0 C indicative of melting. No incompatibility with dika fat.
Bromopheniramine maleate	130-140	138-142	136	136	Endothermic transition of 136^0 C indicative of melting. No incompatibility with dika fat.
Chlropheniramine maleate	132-144	130-144	136	136	Endothermic transition of 136^0 C indicative of melting. No incompatibility with dika fat.
Paracetamol	160-176	160-176	172	172	Endothermic transition of 171^0 C indicative of melting. No incompatibility with dika fat.
Phenobarbital Sodium	190-220	188-220	194	194	Endothermic transition of 130^0 C indicative of melting. Exhibiting polymorphism. No incompatibility with dika fat.
Phenylpropanolamine hydrochloride	188-198	188-200	195	195	Endothermic transition of 195^0 C indicative of melting. Exhibiting polymorphism. No incompatibility with dika fat.
Propanol hydrochloride	160-175	160-175	164	164	Endothermic transition of 195^0 C indicative of melting. Exhibiting polymorphism. No incompatibility with dika fat.
Sulfanilamide	166-174	165-174	166	166	Endothermic transition of 195^0 C indicative of melting. Exhibiting polymorphism. No incompatibility with dika fat.
Norgestrel	200-220	190-220	210	209	Endothermic transition of 200^0 C indicating melting. Melting endotherm shifted to lower temperature in mix with the fat. Probable interaction dika fat.
Atropine Sulphate	196-210	Obliterated	194	Obliterated	Endothermic transition of 194^0 C indicating melting. Melting peak obliterated in mixture with dika fat. Probable interaction with dika fat
Ephedrine hydrochloride	119-140	Obliterated	132	obliterated	Endothermic transition of 194^0 C indicating melting. Melting peak obliterated in mixture with dika fat. Probable interaction with dika

The endotherm corresponding to the melting of norgestrel was also identifiable. However, the transition temperature range was broadened and shifted to lower temperatures. De Angelis (1969) reported that norgestrel showed a sharp endothermic peak indicating melting at 209^{0}C. Melting temperature ranges from 206 - 207^{0}C have been reported (Merck Index, 1976b). The melting temperature range obtained in this work 205 - 210^{0}C is similar to reported values. However the change in thermal behaviour of norgestrel in the presence of dika fat indicated probable interaction between the two under the experimental conditions.

Data from the endothermic profile of a mixture of dika fat and atropine sulphate is included in Table 3. An endotherm indicating the melting of dika fat is shown. The first endotherm corresponding to atropine sulphate was broadened and shifted to higher temperatures. The second endotherm corresponding to the melting of atropine sulphate was completely obliterated. Such a change in the thermal behaviour of atropine sulphate when mixed with dika fat indicated incompatible interaction.

The endothermic profile of a physical mixture of dika fat and ephedrine hydrochloride showed that the first endotherm indicating the melting of dika fat shifted to higher temperatures. The second endotherm corresponding to the melting of ephedrine hydrochloride was completely obliterated. Such a change in the thermal behaviour of ephedrine hydrochloride when mixed with dika fat indicated incompatible interaction.

Overall data presented in Table 3, from the endothermic profiles of mixtures of dika fat with various drugs, enabled a prediction of possible interaction between dika fat and the different drugs.

Conclusion: The drugs investigated in the study fall into three categories. In the first group are drugs which showed no evidence of incompatibility with dika fat. The endothermic profiles of physical mixtures of the drugs with dika fat combined the peaks characteristic of the individual components. The profiles of the mixtures are a simple superposition of those of the components. The drugs in this group included: aspirin, ascorbic, paracetamol, phenylpropanolamine hydrochloride, bromopheniramine maleate, chlorpheniramire maleate and diazepam.

Drugs belonging to a second group did not show conclusive evidence of incompatibility with dika fat. The endothermic profiles of physical mixtures of these drugs with dika fat showed peaks characteristic of each component. However, some of the peaks shifted to either higher or lower temperature regions of the thermogram. Drugs such as norgestrel and phenobarbital belong to this category.

The third group of drugs showed incompatibility with dika fat. The thermal curves of 1:1 physical mixtures of these drugs with dika fat did not represent the curves of the individual components. In the physical mixtures of dika fat and the drugs, the transition peaks of the drugs were obliterated in generated endothermal profiles.

Atropine sulphate and ephedrine hydrochloride belong to this last group.

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