Comparison of the surface properties of raw, micronized and conditioned lactoses

Abstract

The surface properties of lactose play an essential role for the behavior of these powder in inhalers. The different Inverse Gas chromatography methods are providing very interesting tools for characterizing the surface of lactose powders.

This application note compares the surface characteristics of a same lactose powder different stages of the preparation process in order to be used in inhalers (not milled, milled and conditioned). The determined surface characteristics are: the surface energy, nanoroughness, acid-base character, specific surface area and adsorption energy distribution functions.

The applied treatments are modifying significantly the lactose surface nanoroughness. This seems to be an important parameter for understanding the behaviour of this type of powder.

Keywords

Lactose, IGC at infinite dilution conditions, IGC at finite concentration conditions, surface energy, nanoroughness, acid-base character, adsorption isotherm, specific surface area, adsorption energy distribution functions.

Introduction

The surface properties of pharmaceutical powders are related to variations in their physical properties providing performances variability. However, the characterisation of powders surface properties remains difficult and only few methods are available, each of them having advantages and disadvantages.

In the case of lactose powder, several works have shown the suitability of IGC to differentiate batches or to compare the surface properties of different modified lactose samples. All these studies have been achieved at infinite dilution condition (IGC-ID). This method allows the determination of several characteristics like the dispersive component of surface energy (γ_s^d), acid-base surface characteristics and gives also information about the surface morphology.

IGC-ID involves the use of very low probe amounts (zero coverage) and is very sensitive to any changes occurring at solid surfaces, particularly to those concerning the most interactive adsorption sites. However, this method is not able to provide a quantitative information about the number of these most interactive adsorption sites.

In order, to reach such an information, we are compelled to increase the solid surface coverage. Hence, we are performing IGC at finite concentration conditions (IGC-FC). Applying this method, adsorption isotherms are obtained that allow the specific area and the adsorption energy distribution function determination. The latter provides an interesting picture of the surface energetic heterogeneity from a molecular point of view.

Experimental

Those two methods of the Inverse Gas Chromatography, IGC-ID and IGC-FC, were used to characterise the surface properties of not milled, micronized and micronized-conditioned lactose samples coming from the same batch.

Lactoses

This study is performed on three samples: not milled, micronized and micronized-conditioned lactose called La1, La2 and La3 respectively.

Columns

The columns are build with 1/4” external diameter chromatographic grade stainless steel tubing (4 mm internal Ø). For all the examined samples, the column length is 40 cm.

According to the protocol described by TICEHURST[1], the columns were conditioned at 40°C during 16 hours under a helium flow of about 15 ml/min. in order to “clean” the surface of the lactose particles.

***Table 1** : Lactose IGC columns characteristics.*

Samples	Description	Weight (g)
La1	Not Milled (200 µm)	5.477
La2	Micronized (5 µm)	2.113
La3	Micronized & conditioned (5 µm)	2.137

These columns were used successively for the IGC-ID and the GC-FC measurements.

IGC-ID measurements protocol

The IGC measurements, at infinite dilution conditions, were performed at 30°C, using a helium flow rate of 20 ml/min (precisely measured).

The probes injected at infinite dilution are gathered on table 2.

***Table 2** : Injected probes at infinite dilution.*

Measurementss	Probes
γ_s^d	n-alkanes ($C_5 \rightarrow C_8$)
Nanoroughness	isooctane, 2,2-dimethylhexane, cyclooctane
Acid-Base	chloroform, benzene, acetone, acetonitrile, metylacetate, ether, THF

IGC-FC measurements protocol

The IGC measurements, at finite concentration conditions, were performed at 30°C using n-octane. The carrier gas-flow rate remained close to 20 ml/min and was determined with accuracy.

Results

IGC at infinite dilution conditions (IGC-ID)

Surface energy determination (γ_s^d)

As described in the “IGC-ID sheet”, the dispersive component of the surface energy (γ_s^d) is computed from the slope of the n-alkanes straight line. For this study, the straight line of each lactose sample was obtained by plotting the variation of free enthalpy of adsorption (ΔGa) of n-pentane, n-hexane, n-heptane and n-octane in function of their corresponding carbon atom number. The resulting straight lines are depicted on figure 1.

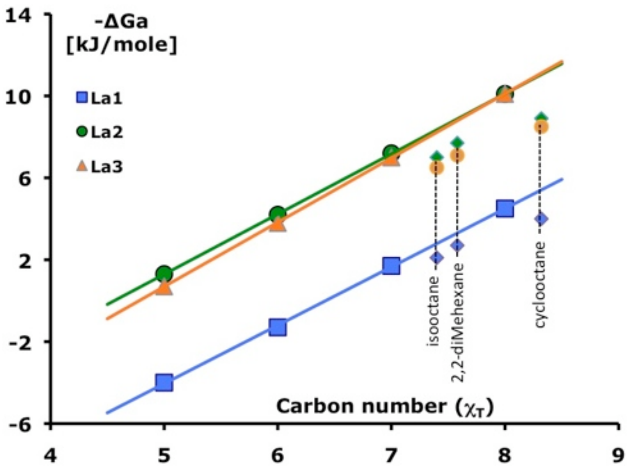

***Figure 1** : n-alkanes straight lines and branched alkanes ΔGa.*

Figure 1 reveals that the not milled sample (La1) straight line and the corresponding ΔGa values are about 5.5 kJ/mole lower than those observed for the micronized (La2) and the micronized-conditioned (La3) samples.

Since the free enthalpy of adsorption variation values (ΔGa) are computed for 1 g of examined solid, this observation is suggesting that the surface area of La1 is lower than those of both micronized samples (La2 and La3). This result should be confirmed by direct surface area determinations, from the adsorption isotherms measured by IGC at finite concentration conditions.

The measured values of the dispersive component of the surface energy are gathered in table 3. The other datas gathered in table 3 indicate that the slope of the straight line, i.e. $\Delta Ga(CH_2)$, obtained for the La1 and the La2 samples are not significantly modified by milling. Since the γ_s^d values are computed from the corresponding $\Delta Ga(CH_2)$ values, no significant difference is observed for those two samples.

***Table 3** : Measured γ_s^d values at 30°C.*

Samples	$\Delta Ga(CH_2)$ [kJ/mol]	γ_s^d [mJ/m^2]
La1	2.88 ± 0.06	**45.4 ± 1.8**
La2	2.91 ± 0.06	**46.5 ± 1.8**
La3	3.15 ± 0.07	**54.3 ± 2.2**

One may note that the γ_s^d values obtained for the La1 and La2 samples are close to those obtained by TICEHURST[1] ($40 < \gamma_s^d < 44$ mJ/m^2), under the same experimental conditions.

The most significant change is observed in the case of the La3 sample, i.e. the conditioned micronized sample. Indeed, the conditioning of the La2 sample increases the γ_s^d from 46.5 to 54.3 mJ/m^2 !

Nanoroughness

The surface roughness was estimated comparing the behaviours of branched and cyclic alkane probes with those of n-alkanes (fig. 1). The method for the morphology index (IM) determination is also described in the “IGC-ID sheet”.

This method gives information about the accessibility of the branched probe to the surface and demonstrates possible “size exclusion effects“. Indeed, if the representative point of a branched (or cyclic) alkane takes place on the n-alkanes straight line, the accessibility to the surface of this probe is identical to those of the n-alkanes molecules. In other words, the surface is smooth at the molecular level. Normal alkanes and branched alkanes have the same accessibility to the surface and the corresponding computed IM value is close to 1.

On the other hand, if the representative point of a branched alkane is located under the n-alkanes straight line, the accessibility to the solid’s surface of this probe is lower to those of the n-alkanes molecules. This reveals that there is some roughness on the examined surface. This surface roughness and the particular structure of the branched molecules reduce their accessibility to the surface. Consequently, the interactions between the surface and the branched alkane probe are reduced and the corresponding IM values are lower than 1.

Figure 1 displays the behaviours of the branched and cyclic alkanes observed on the three lactose samples. The La1 sample exhibits minor size exclusion effects. These effects are increasing from the La2 sample to the La3 sample. These observations are confirmed by the corresponding IM values gathered at table 4 and depicted at figure 2.

***Table 4** : Measured IM index values at 30°C.*

Sampl	Isooctane	2,2-diMeC6	Cyclooctane
La1	0.75	0.77	0.57
La2	0.59	0.64	0.44
La3	0.50	0.52	0.36

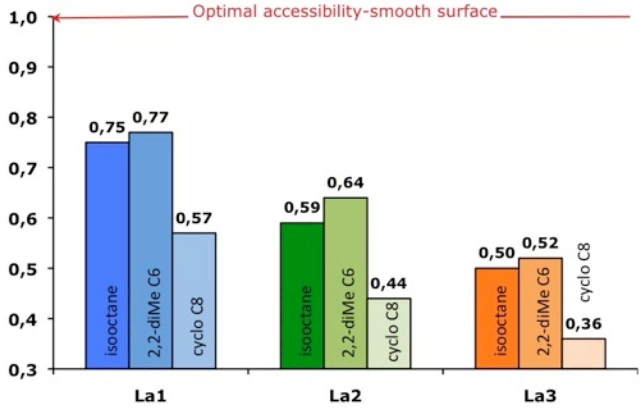

***Figure 2** : Comparison and evolution of nanoroughness (IM).*

The successive treatments applied to the La3 sample increase the surface roughness of the lactose particles. Hence, the γ_s^d increase and lactose surface roughness seem to be related.

Acid-Base character

The above parts are only considering the dispersive, i.e. the non-polar interaction ability of the surface. In this part, polar probes will be used in order to estimate the specific interaction ability (ISP) of the lactose samples. The specific interaction determination method is also described in the “IGC-ID sheet”.

All the computed ISP values measured during this study are gathered in table 5.

***Table 5** : Measured ISP values [kJ/mol].*

Probes	La1	La2	La3
Chloroform[a]	10.3 ± 0.1	10.0 ± 0.2	10.7 ± 0.1
Benzene[a]	5.0 ± 0.1	5.0 ± 0.1	5.3 ± 0.1
Methylacetate[b]	9.5 ± 0.1	10.0 ± 0.2	10.2 ± 0.2
Acetonitrile[b]	14.0 ± 0.1	14.3 ± 0.1	15.3 ± 0.2
Acetone[b]	12.6 ± 0.1	13.2 ± 0.2	14.0 ± 0.2
THF[c]	10.5 ± 0.1	11.2 ± 0.1	11.5 ± 0.5
Ether[c]	7.0 ± 0.1	7.5 ± 0.2	7.8 ± 0.1

[a] acidic, [b] amphoteric, [c] basic

The comparison of the data listed in Table 5 reveals that from La1 to La3, all the ISP values are increasing. In other words, the industrial processes increase the interaction capability of the lactose powder with other polar molecules (as is the case of drugs). A closer examination reveals that for the acidic character (sensed by basic probes) this increase partly occurs already during micronization ; the interaction of the acidic probes (chloroform and benzene) being rather decreased or left unchanged. In contrast the conditioning induce a small increase of both the acidic character and basic character.

IGC at finite concentration conditions (IGC-FC)

The above part of this study was performed by IGC at infinite dilution conditions. In other words, the surface properties of lactose were investigated at very low surface coverage.

For IGC-FC measurements, important probe amounts are injected, in order to achieve a larger surface coverage: close or higher than the monolayer coverage. Hence, desorption isotherms may be obtained. The methods and principles, involved for those determinations, are described in the “IGC-FC sheet”, accompanying the present report.

The isotherms obtained using these probes are exploited applying the BET method[4] for the determination of the monolayer capacity of the solid (i.e. the probe amounts needed to form a monolayer on the surface). Knowing the surface area covered by one probe molecule, the surface area of the solid may then be computed. The BET method allows also the determination of the BET constant that is related to the interaction energy between the surface and the first formed probe layer.

Examples of n-octane isotherms ares given on figure 3, whereas the results of the BET exploitation of the measured isotherms are given in table 6. The end result is the mean value of the results obtained from the exploitation of at least three isotherms.

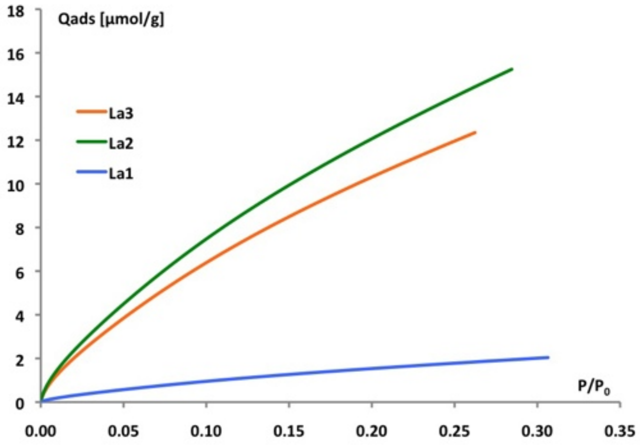

***Figure 3** : Comparison of n-octane adsorption isotherms at 30°C.*

***Table 6** : Measured specific surface area values [m^2/g] on lactose samples.*

Samples	BET Constant [n.u.]	S_{BET} [m^2/g]
La1	5.6	**0.7 ± 0.1**
La2	7.1	**5.5 ± 0.6**
La3	8.1	**4.8 ± 0.5**

The data gathered in table 6 show that the surface area of lactose is, as expected, significantly increased by micronization.. The supplementary treatment applied to the lactose sample (from La2 to La3) induces a slight decrease of the measured surface area value.

The examination of the BET constant shows a progressive increase of the interaction ability of the lactose surface. This observation is in agreement with the results obtained at infinite dilution conditions .

The surface energetic heterogeneity may be assessed from the probe adsorption energy distribution functions[5]. The method of determination of those functions is described in our “IGC-FC sheet”. The resulting adsorption energy distribution functions, calculated for n-octane are presented on figure 4. Again, these functions are the compilation and exploitation of at least three chromatograms.

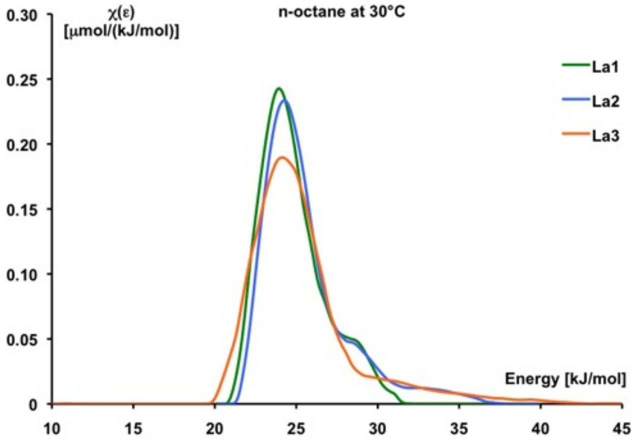

***Figure 4** : Comparison and evolution of nanoroughness (IM).*

The shapes of the functions, obtained from n-octane adsorption measurements, are very different.

La1 displays a large peak centered at 25 kJ/mol and a small peak corresponding to higher energies until 31 kJ/mol. After micronization a new population of high energy sites located between 31 to 36 kJ/mol is added to the previous peaks. After conditioning La3 displays again a different distribution : while the main peak is still centered at 25 kJ/mol, it is visibly broader ; and the sites of higher energy appear to be continuously distributed until 42 kJ/mol without any fluctuation suitable to correspond to the previous peaks. Hence, this population appears to be entirely different from the previous one.

Discussion

It is worth to point out that, in contrast to the liquid state, the surface energy of a solid is not a characteristic of a material. The surface properties of a solid are most complex quantities. Indeed, those properties depend on several factors, like surface chemistry, surface roughness, surface defects (for example in a crystalline structure) or impurities and so on. All these factors, which may act together or separately, are at the origin of the solid surface energetic heterogeneity and therefore influence the solid interaction ability.

Lactose may be regarded as a complex solid. Indeed, amorphous and crystalline lactose forms may coexist. Moreover, the treatments applied to this solid, i.e. micronization and conditioning, are generating heterogeneity. For example, micronization is breaking lactose crystalline particles, therefore creating new surfaces, edges and also surface roughness. The surface hydroxyl density or repartition may be also modified. Moreover, some authors[2,3] suggest that amorphous lactose is also produced through this process.

Inverse Gas Chromatography is highly sensitive to such surface aspects as pointed out by TICEHURST[1]. However, the interpretation of the results remains difficult.

The observed changes, induced by the treatments applied to the original lactose sample (La1), reveal that the micronisation induces only a minor increase of γ_s^d and of the polar interaction ability of lactose. On the other hand, surface area and nanoroughness undergo a significant increase.

When the latter sample is conditioned, γ_s^d and nanoroughness are enhanced, whereas the surface area is slightly decreased.

The analysis of these observations suggests that at the first, the crystalline particles are broken down. During this process, new surfaces are created having edges and other crystalline defects. This is the origin of the detected nanoroughness and of the high energy of the adsorption sites, revealed by the adsorption energy distribution function (see figure 4).

In the case of mineral solids (talc, mica and so on) the same phenomenon are also observed. However, there are often accompanied by a strong γ_s^d increase. In the case of lactose, only a slight increase is observed… Why so ?

Firstly, lactose is an organic solid and therefore much less interactive. Another possibility is the existence of a less surface interactive amorphous lactose layer on freshly milled lactose, which is partially hiding the crystalline lactose, as proposed by NEWELL[2,3] and al.

However, we do not agree with NEWELL about the fact that the surface energy of amorphous lactose should be higher than the one of a crystalline sample. For example, the γ_s^d measured on celluloses having increasing crystalline ratios increase and their nanoroughness too.

According to the evolution of the surface characteristics after conditioning, the amorphous lactose assumption may be right. Indeed, the conditioning (65% RH-drying-cooling) could be considered as a lactose surface recrystallisation operation (same principle as the method used for the determination of crystallisation enthalpy [see NEWELL[3] p48]). This conditioning reduces the surface area and enhances the γ_s^d and the nanoroughness.

Conclusion

This study shows that Inverse Gas Chromatography is an interesting method for the monitoring of the surface properties of lactose following different treatments, like micronization and conditioning. Several authors demonstrated the interest of this method.

During this study, the morphological aspect (accessibility to the surface from the point of view of the molecules) and the determination of the surface heterogeneity was investigated for the first time on lactose using IGC. Indeed, only the surface energy and specific interaction ability were commonly measured up to now.

The consideration of those further surface characteristics has shown that the accessibility of the molecular probe, or of other molecules (drug) are reduced by the milling process and also by the conditioning process. However, our knowledge about how far these surface aspects influence the performance of lactose will remain unknown until a systematic study will be undertaken.

Our suggestions

Inverse chromatography techniques are adapted and sensitive enough to follow the evolution of the surface properties of lactose particles with ageing. This is also valid for active molecules particles.

These techniques are also interesting in order to get answers about the interactions between lactose and active molecules. Of course, since the active molecules could not be used as probes, only indirect information could be obtained. For example by studying the evolution of the lactose at different active molecule coverage ratio.

Inverse chromatography is also able to carry out ‘in situ” modifications of lactose particles, i.e. into the column. For example by exposing the particles to carrier gases having different compositions (%RH) and at different temperatures. This provide an easy way to study the effect of different treatments onto the surface properties of these particles.

EXTRAS

1. GLOSSARY

★ ΔGa:

Free enthalpy variation of adsorption of a probe.

★ γ_s^d:

Dispersive component of the surface energy.

★ Nanoroughness:

Surface roughness at the molecular scale corresponding to all the surface asperities or pores generating exclusion effects of probes.

★ ISP:

Specific interaction parameter that corresponds to ΔGa^{sp}, the contribution of the polar forces to the free enthalpy variation of adsorption of a polar probe onto the surface.

★ Probe(s):

Molecule(s) injected in order to explore the solid surface.

★ Infinite Dilution:

Dilution level that corresponds to an absence of interaction between the injected probes.

★ Finite Concentration:

Concentration level that corresponds to high surface coverage for the measurement of desorption isotherms.

2. HINTS

The origin of the surface energetic heterogeneity may be the surface topology, the nature and the distribution of the chemical functions onto the surface.

The latter could be assessed by varying the properties of the used probes (acidic, amphoteric, basic).

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