FYSIKAALISEN FARMASIAN VIII SYMPOSIUMI 30.1.1997

APPLICATIONS OF PHARMACEUTICAL PARTICLE TECHNOLOGY

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Posterien abstraktit

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SISÄLLYSLUETTELO

Ohjelma.....1

ESITELMÄT

Particle interactions in dry powders with special reference to electrostatic charging
Geoff Rowley, School of Health Sciences, University of Sunderland.....2

Drug particle design
Esa Muttonen, Orion Pharma.....4

Image analysis in powder characterization
Jouko Yliruusi, University of Helsinki, Pharmaceutical Technology Division.....7

Effect of centrifugal granulating process conditions on total yield, shape, size and size distribution of initial spherical beads based on microcrystalline cellulose
Harum Ar. Rashid, University of Helsinki, Department of Pharmacy, Pharmaceutical Technology Division.....9

A Study on compatibilities of some ingredients in a tablet formulation using microcalorimetry
Mari Rahkola, Vesa-Pekka Lehto and Ensio Laine, University of Turku, Department of Physics.....10

POSTERIABSTRAKTIT

Effect of 2-hydroxypropyl-ß-cyclodextrin on the release of dexmedetomidine from silicone matrices
K.Korhonen, R.Sutinen, P.Paronen and A.Urtti, University of Kuopio, Department of Pharmaceutics.....13

An investigation of the recrystallization of amorphous cefadroxil using image analysis
Satu Parkkali, Vesa-Pekka Lehto and Ensio Laine, University of Turku, Department of Physics.....14

On-line measurement of moisture content in fluidized bed granulation - applicability of near infrared (NIR) reflectance spectroscopic method
Jukka Rantanen, Sakari Lehtola, Pirjo Rämet, Jukka-Pekka Mannermaa and Jouko Yliruusi, University of Helsinki, Department of Pharmacy, Pharmaceutical Technology Division.....15

Mechanical properties of solid tolbutamide/hydroxypropyl-ß-cyclodextrin inclusion complex
Eero Suihko, Ossi Korhonen, Tomi Järvinen, Jarkko Ketolainen, Ensio Laine and Petteri Paronen, University of Kuopio, Departments of Pharmaceutics and Pharmaceutical Chemistry and University of Turku, Department of Physics.....16

A novel unckel tablet-in-die method to estimate friction during tableting
M.V. Velasco, M.R. Jiménez-Castellanos, M.C .Monedero, N. Muñoz and A. Muñoz-Ruiz, Department of Pharmaceutical Technology, Faculty of Pharmacy.....17

Temperature sensitive poly (N-isopropylacrylamide) grafted polyvinylidene fluoride) membrane
Satu Åkerman, Kristiina Järvinen, Bror Svarfvar, Pasi Viinikka, Jan Näsman, Kyösti Kontturi, Arto Urtti and Petteri Paronen, University of Kuopio, Department of Pharmaceutics, Helsinki University of Technology, Laboratory of Physical Chemistry and Electrochemistry and Åbo Akademi University, Department of Polymer Technology.....18

Osallistujaluettelo.....19

Thermometric

TAM™

Isothermal microcalorimetry

a powerful tool in quality control of pharmaceutical solids

The processing of pharmaceutical solids is often associated with large changes in physical properties which may effect the behaviour of the final product. Especially in the manufacture of microcrystalline powders much attention has recently been focused on such changes. According to many scientists, isothermal microcalorimetry has proven to be a superior method to quantify the degree of crystallinity in the final product.

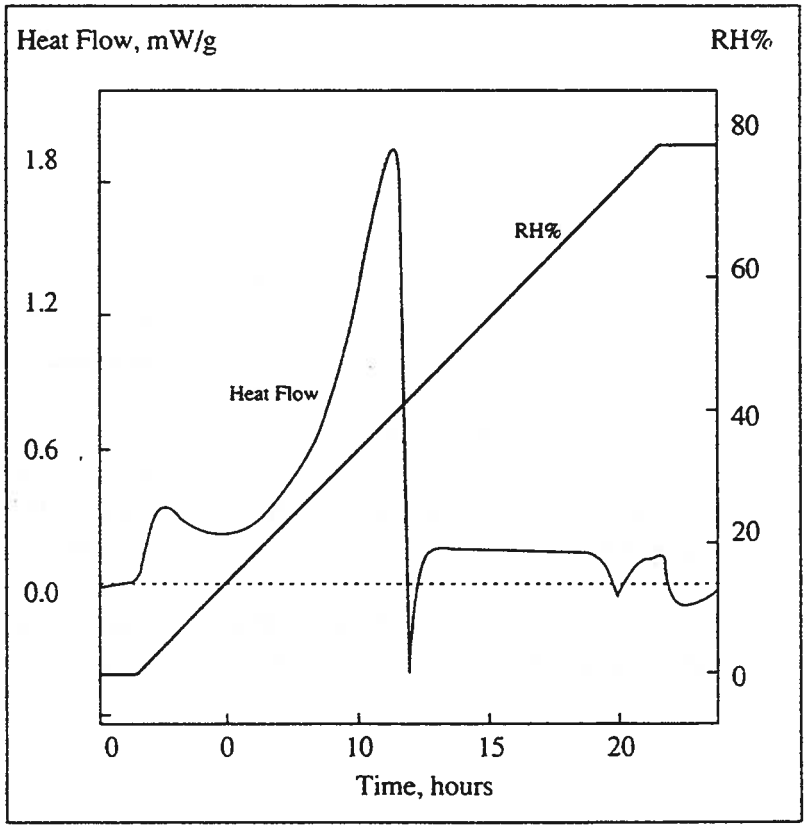

Fig. 1 Heat flow from a micronized pure sample exposed to a continuous constant increase in RH

Bio-Nobile Oy toimii Thermometricin agenttina Suomessa
Tykistökatu 2-4 B, PL 36, 20521 TURKU
P. 02-410 1100, F. 02-410 1123

FYSIKAALISEN FARMASIAN VIII SYMPOSIUMI 30.1.1997

APPLICATIONS OF PHARMACEUTICAL PARTICLE TECHNOLOGY

OHJELMA

09.00	Avaus
09.05	Geoff Rowley, School of Health Sciences, University of Sunderland: Particle interactions in dry powders with special reference to electrostatic charging
10.30	Esa Muttonen, Orion Pharma: Drug particle design
11.15	Keskustelu
11.30	Lounas
12.30	Jouko Yliruusi, University of Helsinki, Pharmaceutical Technology Division: Image analysis in powder characterization
13.15	Harum Ar. Rashid, University of Helsinki, Department of Pharmacy, Pharmaceutical Technology Division: Effect of centrifugal granulating process conditions on total yield, shape, size and size distribution of initial spherical beads based on microcrystalline cellulose
13.45	Mari Rahkola, University of Turku, Department of Physics: A Study on compatibilities of some ingredients in a tablet formulation using microcalorimetry
14.15	Kahvi
14.30	Paneelikeskustelu: Mitä tohtorintutkinnon jälkeen? Puheenjohtajana dos. Juhani Posti, Leiras Oy
16.00 - 18.00	Posterinäyttely ja buffet-iltapala

(1)

TRIBOELECTRIFICATION

PARTICLE PROPERTIES
- surface

CONTACT SURFACE PROPERTIES
- roughness
- contamination
- metal/polymer

TYPE

CONTACT EVENT
- atmospheric

(2)

POWDER HANDLING
- adhesion
- explosion

↓

MIXING
- loss of active due to adhesion

↓

POWDER FILLING
- poor flow
- 'antibiotics in bottle'
- powder transfer ⇄ metal dosator

↓

TABLETTING
- low RH%
- Direct compr. Avicel PH102
- 'muvionat'

↓

DRUG DELIVERY

PARTICLE INTERACTIONS IN DRY POWDERS WITH SPECIAL REFERENCE TO ELECTROSTATIC CHARGING

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(when it comes to mixing ... (granulation))

In general, a decrease in particle diameter leads to an increase in magnitude of interparticulate attractive forces, which far outweigh the separation forces. This is of special significanse in pharmaceutical powder systems which contain particulate active and excipient substances. Agglomeration between particles and adhesion between particles and other solid contact surfaces are phenomena which require detailed consideration in the processing and manufacture of pharmaceutical solid systems.

The lecture will briefly review the role of short range van der Waals forces and long range electrostatic forces in particle/particle and particle/solid interactions. Electrostatic forces and the underlying theory of electrostatic change will be outlined in relation to contact electrification and triboelectrification. Triboelectrification is a special case of contact electrification where charge transfer occurs between solids making contact when sliding, rolling or impact are involved. This type of electrostatic changing will be covered in detail since it is very important in most pharmaceutical powder processing operations.

The complex triboelectrification process depends upon particle properties, contact surface type, contact event and atmospheric conditions. It will be shown that triboelectrification may be involved at all stages from powder raw material preparation to use of the product by a patient.

Particle/powder charge measurement is an important aspect of investigations of interactions between solid surfaces. Two principal techniques, one for bulk powder samples and the other for individual particles will be outlined. Bulk measurements are based on the use of a modified Faraday well which has the advantage of relatively simple apparatus but only provides a net charge value and cannot resolve bipolar charging. Capacitive probes can be employed to measure individual particle charge, however the equipment/technique is more complex.

02 2274543

(3) Part. charge measurement

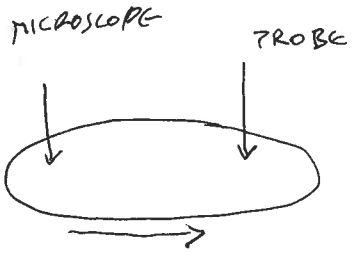
Faraday well

~ cannot resolve bipolar

posit. / negat. almost

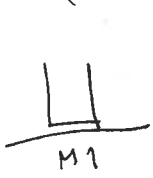
Capacitive probe method

~ more sophisticated



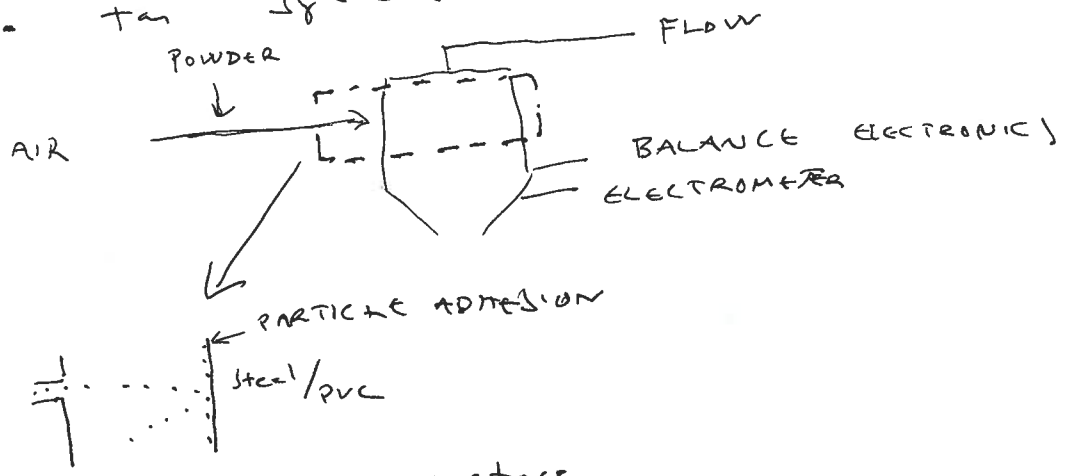
(nC/g) SUORITUS

- tehdään koko prosessi ketju (storage - glove box - Turbula)



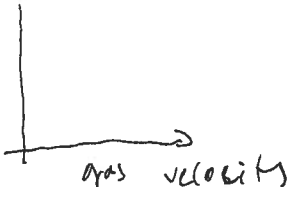
vaa'alle — nitrogen valve

- tai yksikohtaisesti



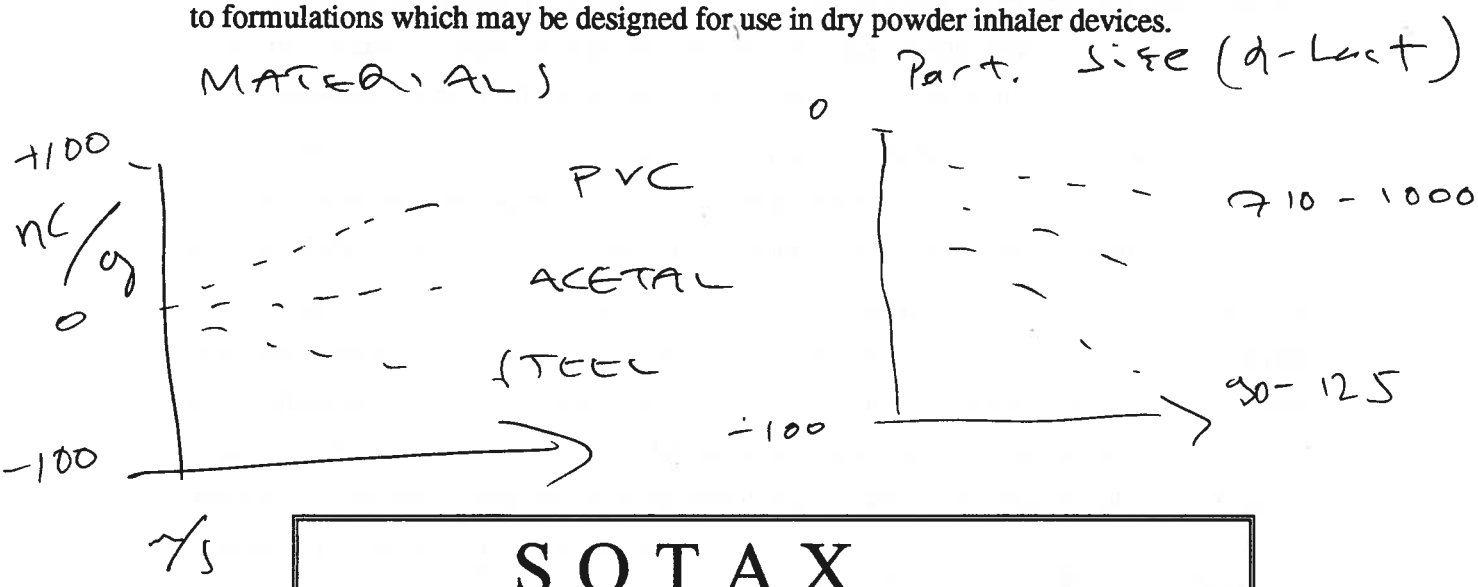
JOKO ① Particle <-> surface

TAI/+ ② Particle <-> particle adhesion



The principal factors affecting the electrostatic charge of powders will be discussed and these include: contact surface type and contamination, surface roughness, particle size and moisture. The effects of these factors will be explained with examples from recent research at Sunderland, in the first instance dealing with carefully classified and characterised single component powder systems. The results show the effects of the principal factors listed above on the propensity for change acquisition of powders using net change measurements and in addition, results for charge decay of pharmaceutical solids obtained from capacitive probe measurements will be discussed.

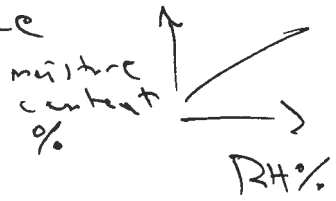
Finally, the triboelectrification of two component powder systems will be discussed with reference to formulations which may be designed for use in dry powder inhaler devices.



Effect of MOISTURE

① Equilibrio ~ moisture

② moisture uptake



③ . Kostendella ei vaikutusta α-Lact charging

DRUG PARTICLE DESIGN

Esa Muttonen, BSc PhD

Development Manager, inhalation products

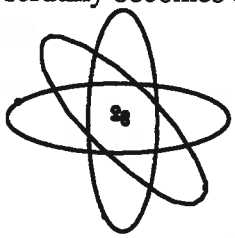
Orion Corporation, Orion Pharma, Espoo, Finland

1. Background

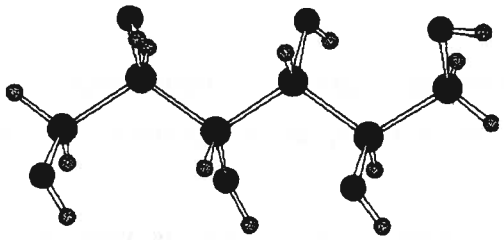
New dosage forms, rapid manufacturing processes and tightening quality requirements introduce growing demands on solid powder materials and especially, on their physical properties. Particle design, a relatively novel approach in pharmacy, has been utilised to study, understand and produce optimal materials for pharmaceutical products.

The key physical characteristics of a solid, crystalline particles are size, habit and crystal form. All these features significant, *e.g.* for processability, dissolution rate and stability of the crystalline material, can be altered by various particle engineering methods.

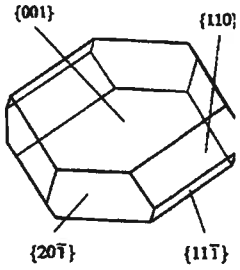
The primary method in production of pharmaceutical materials is batch crystallisation from supersaturated solutions by cooling or by precipitation. The number of properties and complexity of the systems required to be studied, understood and controlled increases rapidly while degrees of freedom also increases. Schematically, this can be illustrated in an ascending series as shown in Fig. 1 where the multiplicity of particulate systems under scrutiny becomes evident.



Elementary particles and atoms



Molecules



Ideal crystals

Real crystals and powders

Fig. 1 Different scales in studying materials.

2. Aims of Particle Design and Crystal Engineering

The primary aims of drug particle design studies are to

- **understand** both particle formation and the target system(s)
- **control** the precipitation process
- **produce** consistently a specified product

3. Conventional Particle Formation Methods

The crystallisation conditions such as solvent properties, initial supersaturation state, rate of cooling, degree of solution agitation, crystalliser geometry and seeding, all affect the physical characteristics of the formed crystals. However, crystallisation is primarily targeted for purification and separation of the solid material.

Particle aggregation and crystal habit can be drastically affected by impurities. Surfactants, foreign ions or other additives can be used for such purposes. For instance, in the case of several primary amides and steroids it has been possible to carry out rational molecular design studies of selected growth inhibitors. The results obtained showed a possibility for controlled morphology modification where 'tailor-made' additives were used to disturb the molecular interactions on a specific crystal face and thus to produce different crystal habits.

In practice, for large industrial scale batch crystallisation vessels, *e.g.* 1 - 2 m^3 volume reactors used in commercial crystallisations, well-controlled conditions are relatively difficult to achieve.

Melt crystallisation, not commonly used for pharmaceutical materials may provide advantages in crystallisation, *e.g.* in controlling the resulting polymorphic form of fatty acids.

Particle formation using supercritical fluids (SCF), such as CO_2 at 100 bar pressure and 40 °C temperature is under intense research by several groups. The published results indicate that the SCF crystallisation method is consistent, it can be well controlled and used to tailor particle size, habit and crystallinity of pharmaceutical materials, such as salmeterol xinfoate.

4. Computational Chemistry and Crystal Engineering

Molecular modeling techniques, utilising lattice energy calculations of molecular crystals introduce a new aspect in crystal engineering, *i.e.* desktop particle design. The power of current computational methods has been proven in several cases, including pharmaceuticals.

In a number of examples molecular modeling has been shown to assist drug particle design studies particularly, by reducing tedious laboratory work needed. Reported successes in additive and solvent selection of and prediction of crystal habit and even polymorphs.

However, for large, relatively flexible organic molecules the present predictive methods are not fully sufficient and thus, these fascinating tools cannot be used for all cases.

5. Examples of Particle Design Studies

Several examples, published in research articles imply that key particle properties, such as flowability, compressibility and mixing propensity can be altered to facilitate the manufacturing process and/or to control the specified features of the end product.

6. Discussion and Conclusion

Particular attention is given to the effect of crystallisation conditions on particle size and crystal form by the regulatory bodies, such as the FDA. In a New Drug Application (NDA), a discussion is expected of the solid state forms of the active ingredient. Consequently, crystal engineering studies are required by the authorities.

In addition, drug particle design, an essential element of pharmaceutical preformulation studies provides an instrument to tailor crystal, particle and powder properties of both raw materials and products.

IMAGE ANALYSIS IN POWDER CHARACTERISATION

Jouko Yliruusi
University of Helsinki, Pharmaceutical Technology Division

Different types of particle size and shape distributions are frequently used in powder characterization. It is well known that many powder properties (flow behavior, aggregation tendency, compression behavior, etc.) are dependent on both particle sizes and shapes. Unfortunately our knowledge - or understanding - of particle sizes and shapes is quite limited. In a matter of fact, we hardly know how these parameters influence in powder systems.

It is evident that image analysis gives great advantages over the other size and shape characterization methods because we can get direct information of particle shapes: we see the particles! However, it seems that the basic philosophy, why and how image analysis should be used in powder characterization, has been forgotten. Let´s take only one example.

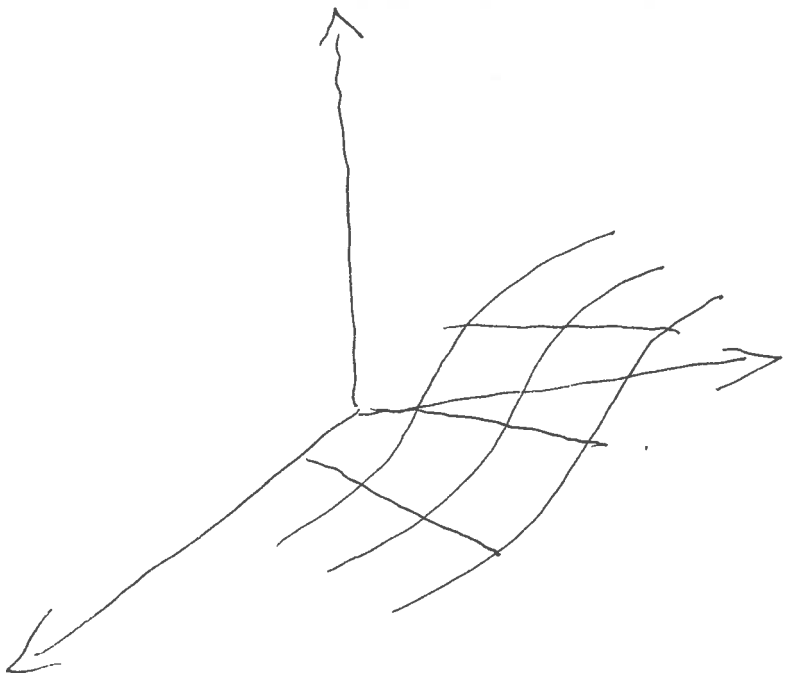
Usually we take an image (or a great number of images) and start semi-interactive image analysis. What is the purpose of our analysis? It should be accurate comparison of different powder populations. However, in normal practise (and also in research) we try to compress the image data. Unfortunately, at the same time we destroy the basic data and also decrease the information content of the fundamental images.

First we typically represent our data by different distributions, which all are rough estimates of the actual powder populations. The next step is to compare those size and shape distributions obtained from different samples. For example, if we have certain shape distributions from ten different granule batches, the comparison problem is difficult. Usually it is impossible to say which one of our distribution is the best one. In such cases, we further simplify the problem. Very often we take only few fractiles of the distributions and make the final evaluations of the particle populations on the basis of these few parameters.

What we have done! The intact images contained the maximum information. The distributions we made are only poor estimates of the images and the final few parameters calculated from

distributions are very weak fingerprints of the real particle populations. We have made terrible over simplifications!

Fortunately, more intelligence methods can be used. With the most modern image analysis techniques it is possible to compare directly the similarities of the images. In such comparisons we might need fuzzy reasoning, which is quite normal technique today. Direct comparison of the intact images is a powerful tool, because then the whole image information can be used. Furthermore, sample preparation will be easier. For example, aggregation of particles is not any longer a problem, but a valuable additional information of particle system.



EFFECT OF CENTRIFUGAL GRANULATING PROCESS CONDITIONS ON TOTAL YIELD, SHAPE, SIZE AND SIZE DISTRIBUTION OF INITIAL SPHERICAL BEADS BASED ON MICROCRYSTALLINE CELLULOSE

Md. Harum Ar. Rashid

Department of Pharmacy, Pharmaceutical Technology Division, P.O.Box 56,
FIN-00014 University of Helsinki

The centrifugal granulation process with its recent modifications has frequently been regarded as the technique of choice in manufacturing multi-layered spherical pellets for oral use. The present study gives a preliminary characterization of a centrifugal granulating system for preparing initial spherical bead cores based on microcrystalline cellulose (MCC). Five independent process parameters of potential importance with respect to final bead core quality were evaluated. The parameters studied were rotation speed of the bottom plate (X_1), slit air volume (X_2), spray air pressure (X_3), spray air volume (X_4) and position of spray nozzle (X_5). Fractional factorial design (FFD 2^{5-2}) was used as the experimental design. Size and size distribution, and shape of the bead cores were characterized by optical microscopic image analysis, and surface morphology by scanning electron microscopy.

Spherical initial bead cores can be prepared by using MCC both as a starting material and as a layering powder, and pure water as a moisturing agent in a centrifugal granulation system. Rotating speed ($p < 0.05$), slit air volume ($p < 0.01$) and spray air pressure were the major process parameters affecting the shape, size and size distribution of MCC bead cores. The expected yield (250-700 μm) reached its maximum (85-90 %) at a low rotating speed and high slit air volume. With respect to the amount of lumps, the slit and spray air volume were the most critical process parameters. The results of this study clearly show the most important process parameters affecting the physical characteristics of MCC beads made in a centrifugal granulator.

A STUDY ON COMPATIBILITIES OF SOME INGREDIENTS IN A TABLET FORMULATION USING MICROCALORIMETRY

Mari Rahkola, Vesa-Pekka Lehto and Ensio Laine

University of Turku, Department of Physics, FIN-20014 Turku

The study of interactions between drug-drug and drug-excipient in the solid state is an important stage during the formulation of new drug candidates or the reformulation of existing products. It is essential to avoid incompatibilities since it has been shown that certain interactions can change the bioavailability or stability of a product.

When considering to carry out a compatibility study the first stage is to choose the most suitable methods for the measurements. This decision is largely done according to the time to be consumed to the study. The number of techniques which can be employed to indicate interactions is wide. It includes chromatography (HPLC and TLC), infrared spectrometry (IR), x-ray diffraction (XRD) and differential scanning calorimetry (DSC). Thermal analysis is in many situations a natural choice since all chemical and physical processes are accompanied by changes in the heat content. Indeed, conventional compatibility studies are mostly performed by using DSC alone or with chromatography where various kinds of accelerated storage tests are utilized. Unfortunately, interpretation of thermograms may be hard and the possibility of making incorrect conclusions does exist. The fact is that the interactions observed at high temperatures may not be relevant under the real storage conditions. Nevertheless, most of the techniques recently employed require plenty of time to obtain reliable data. Therefore, in the present study isothermal microcalorimetry (IMC) was used to evaluate compatibilities. IMC enables the heat rate to be measured at a constant temperature and because of the high detection sensitivity (0.1 μW) of the instrument the measurements can be carried out under ambient conditions or at least near those.

In this study, the compatibilities between three drugs, denoted as drug A, drug B and two different salts of drug C (C_1 and C_2), were investigated in their powder mixtures. Based on the earlier measurements five mixtures of all the possible combinations were chosen to be stored at elevated temperatures for several months. Interactions in those mixtures were studied in various timeintervals by using DSC and XRD. Each experiment comprised at least three samples: in the case of drug A and drug B for instance, both of the pure drugs were measured individually and the third sample was their powder mixture. The weight ratios 1:1 and 1:1:1 were used in the binary and ternary mixtures. Every technique we employed is capable of providing qualitative as well as quantitative data. In this stage, the accelerated storage tests are still going and thus we concentrate on the qualitative analysis available until now. Because of the great number of the samples and achieved data the treatment is performed more closely in the oral presentation.

As an example, the heat flow curves measured from the pure drugs A and C_2 individually and from the 1:1 mixture by IMC at 35°C are shown in Fig. 1a). A strong solid-solid interaction is observed immediately after mixing whereas both the pure components behave stable. DSC thermograms of the same samples are shown in Fig. 1b). Endothermic

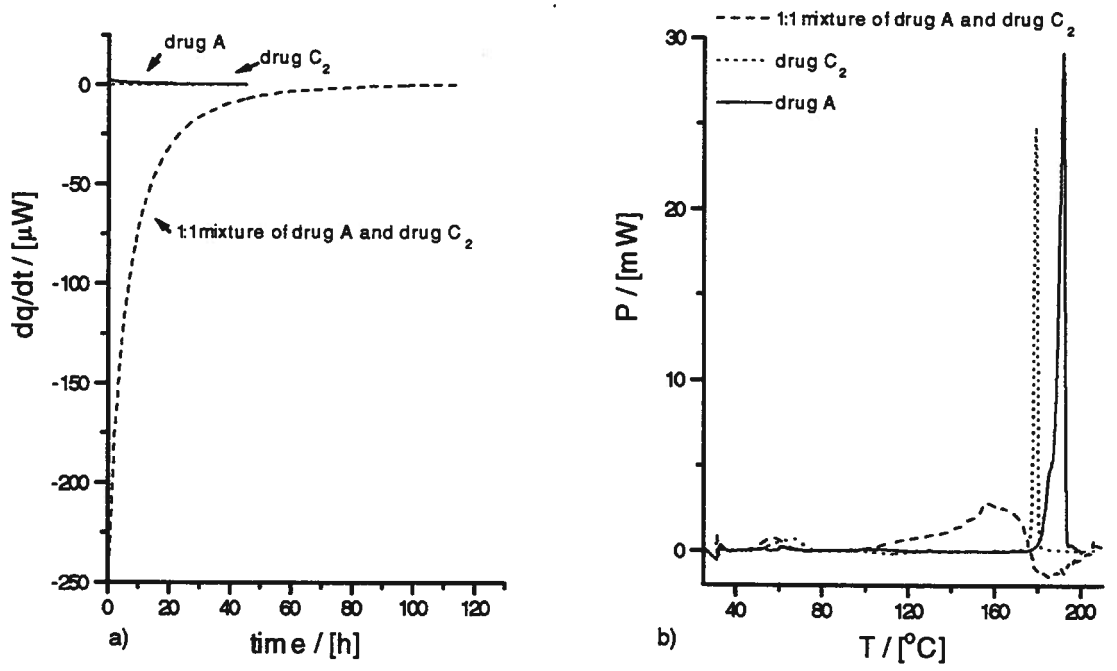


Fig.1. Heat flow curves measured by IMC at 35°C (a) and by DSC (b) from drug A, drug C_2 and their binary mixture.

peaks have disappeared in the case of the binary mixture even though extra thermal effect does exist before the single melting points. This might be caused by the nearly coincident melting of drug A and drug C_2. Consequently, when considering these components incompatible, it is largely done on the basis of information given by IMC.

In conclusion, this study has demonstrated the utility of isothermal microcalorimetry as a method of ascertaining compatibilities in powder mixtures. The application of DSC alone may arise problems when interpreting thermograms and therefore it is recommended to be employed as a back-up method. Moreover, in order to improve the results a compatibility study should always be planned carefully in advance.

EFFECT OF 2-HYDROXYPROPYL-β-CYCLODEXTRIN ON THE RELEASE OF DEXMEDETOMIDINE FROM SILICONE MATRICES

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In water-activated and pH-controlled silicone devices, the fraction of unionized drug and the polymer/water partioning of the drug are increased with suitable buffering agents. At the same time, however, the water solubility of drug is decreased, sometimes drastically. In this case, it may be possible to maintain the dissolution and release rate adequate with cyclodextrins. In this study, we investigated the effect of 2-hydroxypropyl-β-cyclodextrin (CD) on the release of dexmedetomidine from matrix-type silicone transdermal patches.

Silicone matrices were made of a silicone elastomer and the mixtures of dexmedetomidine (DEX), disodium phosphate (DP) and CD using compression molding. CD was added to devices in three different ways: 1) without precomplexation with DEX, 2) using an inclusion complex of DEX-CD prepared by spray-drying, 3) using an inclusion complex of DEX-CD-DP prepared by spray-drying. In vitro release of dexmedetomidine from devices in pH 7.4 phosphate buffer (57 mM) at 32 °C was determed in side-by-side diffusion cells. The drug concentration in the samples was analyzed by RP-HPLC.

Drug release from the silicone matrices followed typically square root of time kinetics. DEX HCl was released well only from the surface of the matrix. This was due to a high loading dose of DEX in the matrix and aqueous channels formed to the hydrofobic matrix during the in vitro release test. Addition of DP did not improve on the release of DEX from the matrix-type devices. In this case, drug particles were effectively separated from each other and from DP by the polymer and DP did not buffer DEX properly. In silicone matrices the largest DEX release enhancement (two folds) was obtained using the DEX-DP-CD inclusion complex prepared by spray-drying since the effects of additives were at their maximum. In addition, CD made spray-drying of DEX with DP possible.

AN INVESTIGATION OF THE RECRYSTALLIZATION OF AMORPHOUS CEFADROXIL USING IMAGE ANALYSIS

Satu Parkkali, Vesa-Pekka Lehto and Ensio Laine
University of Turku, Department of Physics, FIN-20014 Turku

Cefadroxil ($C_{16}H_{17}N_3O_5S$ ($\cdot H_2O$)) is a polymorphic compound which is found in three different crystal forms: crystalline anhydrate, amorphous anhydrate and monohydrate. Different forms have also different physical properties which, for example, is seen as dissimilarities of hydration processes of the anhydrous forms. The aim of this study was to examine the structural changes especially between amorphous and monohydrous forms with image analysis.

The crystalline anhydrous form prepared by industrial methods changes into monohydrous form in humid conditions - water absorbs into crystal structure. Furthermore, the amorphous form can be prepared from the monohydrous form by milling. When milling the the crystalline monohydrous form the hydrogen bonds of the water molecules break up and water molecules evaporate. The other way to prepare amorphous anhydrate is to dry the precipitate obtained from oversaturated monohydrate-methanol solution.

The amorphous anhydrate is very hygroscopic substance unlike the monohydrous form. In humid conditions it absorbs water till it dissolves. After dissolution the monohydrous form crystallizes form the liquid. When observing the previous transformation with optical microscope there was seen a distinct difference between the transformations of two amorphous forms prepared by different methods. The amorphous anhydrate prepared by milling crystallized much faster than the amorphous solid obtained from precipitate.

The transformation of the amorphous cefadroxil under high relative humidity was also recorded to a videotape which was then analyzed by means of Image-Pro Plus -image analysis computer programme. With the programme the progress of crystallization was examined - the growth of surface of the recrystallized area was determined as a function of time. In addition to these methods x-ray diffraction was used to ascertain the different crystal forms.

ON-LINE MEASUREMENT OF MOISTURE CONTENT IN FLUIDIZED BED GRANULATION - APPLICABILITY OF NEAR INFRARED (NIR) REFLECTANCE SPECTROSCOPIC METHOD

Jukka Rantanen, Sakari Lehtola, Pirjo Rämet, Jukka-Pekka Mannermaa and Jouko Yliruusi

Department of Pharmacy, Pharmaceutical Technology Division, P.O.Box 56, 00014 University of Helsinki

Near infrared spectroscopy offers significant advantages over traditional techniques used in chemistry - rapid analysis requires no organic solvents. NIR-spectroscopy has been used in identity and quality testing of raw materials, detection of tablet degradation and testing the powder mixing end-point. In the present study, the applicability of NIR reflectance method as a part of fuzzy logic controlled granulator was determined. The granulations were performed using an automated laboratory-scale fluidized bed granulator (Glatt WSG-5, Glatt GmbH, Germany). Two formulations (one containing only excipients and another containing also drug substance) were used in testing the applicability of NIR measurement. Samples were taken during the granulation and granule moisture content was measured using infrared dryer (Sartorius Thermocontrol YTC01L, Sartorius GmbH Göttingen, Germany) as a reference method. Accuracy of calibration was determined by 'check' granulation. Five different statistic parameters were calculated to describe the quality of NIR-method calibration.

Two calibration curves (spraying and drying phase) were calculated for both formulations. Calibration of spraying phase was performed using seven calibration points and linear fitting for formulation one and logarithmic fitting for formulation two. Calibration of drying phase was performed using nine calibration points and logarithmic fitting for both formulations. Coefficient of determination (R^2-values) were 0.989 and 0.983 for formulation one and for formulation two 0.998 and 0.996 (spraying and drying phase, respectively).

Near infrared reflectance spectroscopic method is suitable for on-line moisture measurement on fluidized bed granulation. It is a promising tool for both lab-scale studies on granule growth kinetics and securing the repeatability on production-scale.

MECHANICAL PROPERTIES OF SOLID TOLBUTAMIDE/ HYDROXYPROPYL-β-CYCLODEXTRIN INCLUSION COMPLEX

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The aim of this work was to study the effect of inclusion complex formation on physicochemical and mechanical properties of tolbutamide and hydroxypropyl-β-cyclodextrin (HP-β-CD) in powder and tablet forms. Solid tolbutamide/HP-β-CD complex was prepared by spray-drying and freeze-drying techniques. Pure tolbutamide and HP-β-CD powders were also spray-dried and freeze-dried. A physical mixture of tolbutamide and HP-β-CD was made. Densification properties of the powders were studied by a compaction simulator. Evaluation of the consolidation mechanism of the powders was based on the Heckel equation. Tensile strength of the compressed tablets were determined.

Yield Pressure (P_y) values, calculated from the Heckel analysis were for tolbutamide, HP-β-CD, physical mixture and inclusion complex 64, 55, 61 and 74, respectively. These P_y values showed that all the studied materials underwent easily densification and were most probably plastically deforming. The inclusion complex had significantly greater P_y than physical mixture. This means that the complexation decreased plastic deformation of tolbutamide and HP-β-CD. The tensile strengths of the compressed tablets were for tolbutamide, HP-β-CD, physical mixture and inclusion complex 1.9, 5.3, 3.7, 2.4, respectively, showing difference between tablets made of physical mixture and inclusion complex. These alterations in studied mechanical properties most propably arise from inclusion complex formation which makes the molecular level structure of the solid complex more rigid and uncapable for strong interparticulate bonding. Consequently, in research and development of solid products which contain cyclodextrins it is of great importance to study the effect of inclusion complex formation on mechanical and physicochemical properties of the solid powder.

A NOVEL UNCKEL TABLET-IN-DIE METHOD TO ESTIMATE FRICTION DURING TABLETING

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A novel method, Unckel tablet-in-die, is proposed for the measurement of force transmission and friction during tablet compression. This method allows the use of a single punch tablet machine to register in continuous the force transmission during the compression of a powder bed. In this study, Maltrin® M510 and M510 have been compressed after the addition of lubricants such as magnesium stearate, sodium stearyl fumarate and glyceryl palmitostearate (1% and 2 minutes of mixing time). Tablets were compressed at three different applied pressures (50, 100 and 200 Mpa). Unckel proposed that the transmisson of an axial force through a powder mass during uniaxial compression in cylindrical dies is exponential and depends on the transmission properties (Poisson´s ratio, ν), friction coefficient (μ) and dimension of the bed (diameter, D, and distance between punches, L).

$$R = e^{-4 \mu \nu L / D}$$

The linear approach to Unckel equation is determined on the basis of the best fit to linear model from consecutive data, obtaining high correlation coefficients. While the slope of the adjustment, that includes the friction coefficient and the Poisson's ratio, distinguished between both malto-dextrins, the corrected intercept did not difference. M510, according to the slope was more sensitive to the addition of the three lubricants than M510. Pressure independent parameters indicative of compression cycle, the slope K and the corrected intercept C are obtained. Also, this approach to Unckel equation provides a parameter, K, that is able to difference between different materials, showing M150 more friction than M510.

TEMPERATURE SENSITIVE POLY(N-ISOPROPYLACRYLAMIDE) GRAFTED POLYVINYLIDENE FLUORIDE) MEMBRANE

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Poly(N-isopropylacrylamide) is a temperature sensitive polymer, which lower critical solution temperature (LCST) is about 32 °C . When temperature is raised above 32 °C poly (NIPAm) srinks and permeability of the polymer decreases. Poly(NIPAm) hydrogels release the drug at temperatures below its LCST, which limits the use in pharmaceutical applications. Drug devices, which release the drug above the LCST has been developed by grafting poly(NIPA)m on the porous matrixes.

In present study, the temperature sensitive membrane was prepared by grafting poly(NIPAm) onto porous poly(vinylidene fluoride) membrane. In this membrane, the polymer is srinking to the walls of the pores at temperatures above the LCST of the poly(NIPAm), which allows drug permeation through the membrane. The effects of temperature and molecular weight of the model compounds on the drug flux across the membrane were studied in side-by-side - diffusion cells.
Temperature did not affect on the flux of the smaller molecule as mannitol (mw 182), while the flux of FITC-dextran (mw 4400) across the 28 *wt%* grafted membrane increased about 30 times when temperature was increasing from 30 °C to 33 °C. At 25 °C the flux of the FITC-dextran (4400) was not detectable. Temperature changes during the study affect on drug flux. Increasing the molecular weight of the FITC-dextran decreased the flux across the membrane at 37 °C.

In conclusion, it was possible to control the flux of the bigger molecules by poly(NIPA)m grafted PVDF -membrane. Present membrane might act as temperature sensitive valve for high molecular weight drugs as peptides and proteins.

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CONTROLLED RELEASE TABLET FORMULATION BY DIRECT COMPRESSION

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Oral administration of active drug substances is the most popular and perhaps considered to be the easiest and the most convenient way to deliver drug to blood circulation and to the active site. However, there is a major problem of drug substances to be dissolved, absorbed etc. in the GI-system due to its rough environmental changes, e.g., pH. Aim of this study was to develope a pharmaceutical tablet, which would release an active substance in a suitable pH conditions in a predetermined rate. Furthermore, the dosage form would be produced by direct compression method, which is considered to be time and energy saving method.

Materials used in this study were starch acetate (degree of substitution; ds., 2.9), which functioned as a matrix former, starch succinate (ds. 2.0), pH depended dissolution agent and theofylline as a model drug. Also some comparisons were made with experimental and commercial formulations. Properties evaluated were drug release (USP-method), tablet disintegration (Ph. Eur-method) and tablet breaking strength.

Results pointed out, that starch succinate behaved well as a pH depended dissolution agent. However, in the case of theofylline the intrinsic solubility of drug released it partially (some 30%) already at the low pH 1.2. This was clearly due to direct compression method, which leaves drug particles free to dissolve on the surfaces of tablet. At the higher pH, starch succinate was acted well releasing drug in a predeterminated rate, and the release rate was able to be controlled by adjusting the amount of starch succinate and compression force.

EFFECT OF pH TO THE FLUID PENETRATION AND DRUG RELEASE FROM STARCH POLYMER TABLETS

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Wetting of surface and penetration of media fluid into tablet are presupposition for disintegration and drug release from tablets. Hydrophilic materials, like celluloses and starches, enhance wetting and disintegration thus accelerating drug release. Hydrophobic materials prevent the penetration and disintegration of tablet and thus sustaine the release of drug substance. Recently it has been shown that novel starch acetates qwn favourable properties to be used as pharmaceutical excipients. Starch succinates qwn pH depended properties and they might be suitable excipients for entero formulations. The aim of this study was to evaluate the effect of pH on the penetration of fluid to the tablets and the release of drug from the tablets consisted of starch acetates and starch succinates. Model drug substance was theofylline anhydrate. Tablets were compressed using an instrumented single punch tablet press. Penetration part of the study was evaluated with the modified Enslin-method and the drug release part with the USP-rotating basket method.

The penetration of fluid was greatly effected by the change of pH. Tablets compressed from plain starch acetate/succinate powders gave an linear increase with every pH studied, and the slight increase in fluid penetration rate was noticed at the pH 5.5. Tablets compressed with drug gave the same kind of an linear increase, until saturation point was reached after 20 minutes. Increase in the penetration rate was also noticed at pH over 5.5. The same kind of a behaviour was noticed when the release of drug was studied. The release rate was significantly increased when pH was above 5.5. Drug substance was totally released within 5 hours at the pH 8.

It was concluded, that the carboxylic acid group of starch succinate acted as a pH-depended drug release substance in tablets. Changing the degree of substitution of starch polymer, the release of drug at different enviroments can be modified.

UTILIZATION OF STARCH ACETATES AS A MULTIPURPOSE DIRECT COMPRESSION EXCIPIENTS

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To be able to save costs and energy in the industrial tablet manufacturing, the direct compression of pharmaceutical materials has become a very important matter. Although a number of widely used commercial excipient materials exists, only a few of them has capability to form solid, enough strong tablets as themselves. Usually several excipient materials are used in the final tablet formulations. Complicated formulations are used consisting of a mixture of particulate materials, each possessing a certain functionality (e.g., flowing, disintegration, binding, controlled release), and thus gaining the desired behaviour to a compressed tablet. The aim of this study was to present properties of a novel group of pharmaceutical polymeric excipients, the starch acetates, and to evaluate the benefits of the use of these materials as a multifunctional excipients (e.g., disintegrant, filler/binder, controlled release substance).

Materials studied, starch acetates, were manufactured from barley starch by Primalco Ltd Polymers. The moiety content of acetate (degree of substitution; ds.) was 0, 0.34, 1.19, 2.1 and 2.9. Model drugs used in this study were propranolol hydrochloride and paracetamol. Drug release test and binding capacity test were performed.

Starch acetates can be used as multifunctional excipient materials in the pharmaceutical tablets. Mechanical properties of the tablets proved to be excellent, and the disintegration depended on the acetate content. The lower moiety content (ds. 0.34 and 1.19) can be used as a tablet disintegrants or binders, and the higher ones are useful with prolonged release tablets. The content of drug, which was capable to be added, was very high with all the starch acetates.