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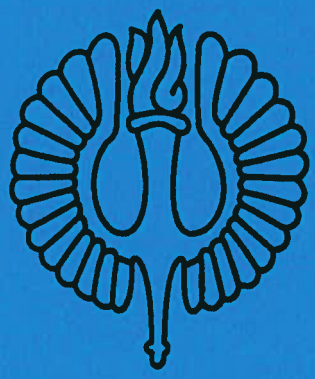

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OHJELMA

9.30	Ilmoittautuminen ja tulokahvi
	I istunto, puheenjohtaja Matti Mäkelä
10.00	Kirsti Saarnivaara: Symposiumin avaus
10.15	prof. John N. Staniforth: The importance of physico–chemical interactions in medicines design
12.00	Lounas
13.00	Posterisessio
	II istunto, puheenjohtaja Petteri Paronen
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15.00	Isabelle Husson: Physical characterisation of free films prepared from polymers used in sustained release coating
15.30	Jukka Arppe: Inhaloitavien salbutamolisulfaattivalmisteiden radioaktiivisesta leimauksesta
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16.00 – 16.15	Loppukeskustelu

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A. KUTSUTUT ESITELMÄT

NEW MEDICINES DESIGN FOR ORAL, IMPLANTABLE AND PULMONARY DRUG DELIVERY

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Introduction

The design of a given type of medicinal presentation, irrespective of route of administration, is most dependent on the physical and physico-chemical characteristics of the component materials, their manipulation and their interactions. Although drugs are responsible for therapeutic activity it is a *medicine* and not a *drug* which a patient receivs for the treatment of an illness. The difference separating a medicine from a drug is the presence in medicines of pharmacologically inert ingredients or *excipients* which modify a whole variety of physical and physico-chemical properties, which can influence the biopharmaceutical performance of the drug.

The attributes required for a given combination of drug and excipients will be wholly dependent on the functionality of the medicine, and consequently dictates the manner in which physical and physico-chemical characteristics are manipulated. For example, a mixture of salbutamol and lactose powders will need to have very different physical characteristics and interactions for optimal functionality in a tablet, compared with a dry powder inhaler medicinal presentation.

It is this type of design consideration, to fit similar materials for different medicinal functionalities, which will be discussed below. The medicinal forms considered will begin with the simplest types of unmodified release tablets and range through modified, controlled and chronotherapeuric release oral sytems, to implants having controllable release characteristics. The design of dry powder presentations of medicines for inhalaion will also be considered. Throughout, emphasis will be placed on understanding physical and physico-chemical interactions, in order to produce optimal medicines design.

Design of Formulations for Unmodified Release Oral Presentations

The key inert ingredient of a tablet formulation is the principal excipient (sometimes referred to as the diluent). It is the characteristics conferred on the drug powder by this material, which controls the requirement for and concentration of other (minor) excipient components. For example, a principal excipient which confers adequate compactibility, flowability, friability resistance, lubricity, fast disintegration and immediate dissolution characteristics, on the drug has achieved virtually all the requirements of an unmodified release tablet presentation: the formulation is complete. The principal excipient which comes closest to realising these ideals is probably microcrystalline cellulose (mcc). Various workers have published assessments of the beneficial characteristics of mcc as a principal tableting excipient, including: highest excipient compactibility; high ductility; non-destructive recoverable deformation; high dilution potential; rapid disintegration; good lubricity; good blending characteristics.

However, a number of these beneficial characteristics can be easily reduced or lost as the result of formulation or process changes influencing physico-chemical interactions. These

changes occur because of the sensitivity of mcc , whether at a molecular, microfibrillar or microcrystalline level, to changes in surface contacts. We have carried out studies at molecular and macroscopic levels which show that changes in solid or liquid-state contacts can adversely influence the characteristics of mcc, in either direct compression or wet granulation systems.
In direct compression processing of mcc, it has been found that 4 main process variables merit consideration when devising a design strategy. Firstly, reducing the mixing time of a lubricant such as magnesium stearate with mcc to just a few minutes, can restore tablet toughness by up to 50%. Use of low-shear blenders can also help conserve compactibility and homogeneity can be improved by use of 2-stage blending. Lastly, use of extrinsic lubrication as a process step, removes lubricant-mcc interactions in the body of the tablet.
In addition, or as an alternative to formulation changes, it is possble to conserve mcc functionality through appropriate formulation development strategy. Firstly, reduction of lubricant levels; secondly, addition of a toughness restoring additive; thirdly, use of process-protected enrobed mcc and lastly, substiturtion of non-sensitizing lubricants, such as sodium stearyl fumarate.
In wet granulation systems, the major problem in loss of functionality arises through addition of an aqueous granulation fluid. Again modification of process variables, such as granulation time, granulation speed, wet granule storage, drier type and drying process, all influence the performance of the finished medicine. In wet granulation processing, 2 specific formulation variables should be considered: aqueous component concentration and substitution of non-aqueous fluids.
The reasons for these effects has been studied using XRD, FT Raman spectrometry, FTIR, Solid State C 13 CP/MAS NMR, Optical IR, ATR IR and Calorimetry.

Design of Medicines for Modified Release Oral Presentations.

Probably the most efficient method for presenting drugs in a modified release form to the gi tract, is using a diffusion-controlled matrix system. For a number of years, matrix systems which were either hydrophobic, or hydrophilic in nature were used to provide simpe first order drug release kinetics. However, a requirement to produce more sophisticated release profiles such as zero order, or more recently multi-phasic profiles (for chronotherapeutic purposes) generally lead to non-matrix systems being used.
Interactions between polysaccharides and water, such as those described immediately above can also be useful in modifying the behaviour of hydrogel systems for controlled release.
Specifically, we have found that 2 polysaccharides, one a heteroploysaccharide and the other a homopolysaccharide, interact synergistically in the presence of water to produce a hydrogel whose structure and drug release characteristics can be designed to change with time according to manipulation of the physical interactions.
Such manipulations can be carried out by modifying concentration ratios of the 2 polysaccharides, and/or drug/polymer ratios. More complex profiles can be produced or matched by selection of third component materials capable of providing ionic species which zip or unzip polysaccharide chains over particular periods. Alternatively,

viscolyzers, hydrogen-bond promoters or destroyers can be used to modify interactions within the matrix.
As with mcc interactions, studies have been carried out in order to provide an understanding of such interactions at both a molecular and maccroscopic level. Quantitative image analysis, using a confocal microscope; magnetic resonance imaging; environmental scanning electron microscopy and cryogenic scanning electron microscopy, have all been used to determine the movement of solvent and solution fronts together with gel structuralization during dissolution. In addition, studies are continuing using fluorescence and esr spin probes to determine microviscosity changes during drug diffusion.
It has however, been possible to produce single phase (first or zero) as well as multi phasic (chronotherapeutic) profiles using as little as 3 component matrix systems.

Design of Controllable (Implant) Medicinal Presentations

The simplest method for providing a controllable, either by pre-determined changes or through full-feedback control, is using electrically-modulated release. The method considered here uses physiologically-acceptable low power electrophoresis. Our studies of this technique have showed that electrode polarity changes can be used to control drug transport across a p-HEMA membrane. Additionally and in a rectilinear fashion, changes in transport current can also be used to vary the rate of drug electro-diffusion . Such changes are super-imposable on basal release rates related to drug size and gel structure and governed by parameters such as total monomer concentration and cross-linker concentration in the polymerized gel barrier. Our results show that feedback control is possible, and shows the potential of this type of system as an artificial gland.

Design of a Dry Powder Inhaler Medicinal Presentation

Although dry powder inhaler (DPI) systems offer many advantages over conventional pressurized metered dose aerosols for therapeutic use, there are a number of formulation-related aspects of functionality which can significantly reduce DPI performance.

The work carried out by ourselves has a number of implications in the design of efficient DPI aerosols. The findings related to particle-wall and particle-particle interactions run counter to considerations normally applied to powders used in tableting.

In design of medicines for pulmonary use, the following main interactions in DPI systems should be considered:

1. Entrainment of coarser powder is dependent on mean air velocity and independent of tube diameter.

2. Entrainment of finer powder is more dependent on tube diameter and pressure drop observed at the site of entrainment.

3. Entrainment of coarser powder occurs at lower flow velocities and is complete within a small velocity spread.

4. Optimum salbutamol/lactose homogeneity was achieved with single contact surface blending.

5. A second (different) contact surface should be considered as a source of possible de-stabilization for salbutamol and lactose blends.

CONTROL OF DRUG RELEASE FROM TRANSDERMAL DELIVERY SYSTEMS

Riitta Sutinen

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Transdermal delivery of drugs is a feasible alternative route of drug administration for several drugs. Due to the wide inter- and intraindividual variability of skin permeability (Southwell et al., 1984), the rate limiting factor in transdermal delivery should be drug release from the transdermal device, not permeation through the skin (ie. drug release from the transdermal system should be slower than its permeation through the skin) (Guy and Hadgraft, 1992).

Typically, the transdermal delivery systems are based on non-porous polymers that determine the rate of drug release and they can be categorized into two main types: matrix systems and reservoir systems (Merkle, 1989) (Fig. 1).

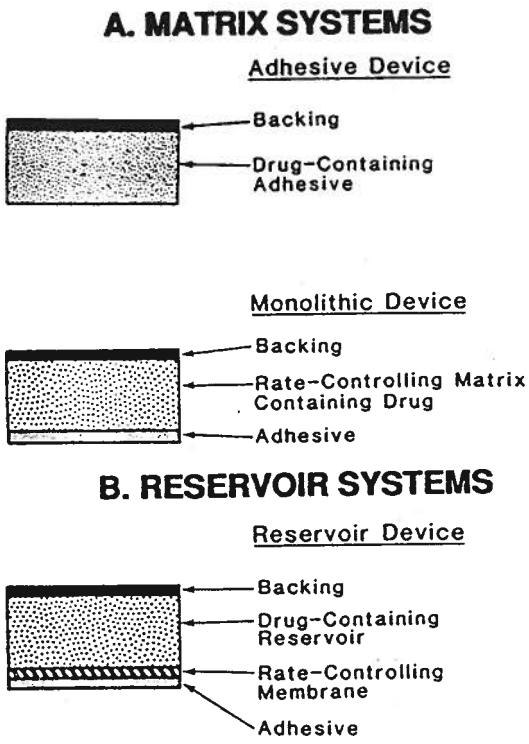

Fig. 1. Categories of transdermal delivery systems (Baker and Heller, 1989)

In matrix systems (Fig. 1 a), drug is homogenously dispersed in a diffusion controlling polymeric matrix. The rate of drug release is proportional to the diffusion coefficient and solubility of the drug in the polymer and the initial drug dose in the matrix (Baker and Lonsdale, 1974). The rate of drug release from the matrix type systems is not constant but it follows square root of time relationship (Merkle, 1989). With the insoluble matrix devices, the constant rate of drug release may be achieved by altering the geometry of the device or by formulating a multilayer matrix in which the dose and the particle size of drug is different in each layer. Matrix devices are easy to formulate and compared to reservoir devices their production is less expensive.

In reservoir systems (Fig. 1b), drug is in the device as solid particles or as a suspension in a reservoir from which it migrates through a rate-controlling membrane to the absorption site. The reservoir systems have the advantage that a zero-order rate of drug release can be achieved (Baker and Lonsdale, 1974). Rate of the drug release from the reservoir is dependent on the thickness of the membrane, its permeability to the drug (ie. the ability of the drug to partition to the rate-limiting polymer and its diffusivity in the polymer), drug loading in the reservoir and the device configuration (Baker and Lonsdale, 1974; Chien, 1985).

Suitable polymers to form the rate-limiting membrane or polymeric matrix of the transdermal device include silicones, polyisobutylene, poly(vinyl chloride), polypropylene, poly(ethylenevinyl acetate), polyurethane and polyhydroxyethyl metacrylate (Baker and Heller, 1989). In most transdermal systems that are currently on the market ethylene-vinyl acetate copolymers and silicones are used.

Ethylene-vinyl acetate copolymers have been used as membranes in transdermal devices principally because it is easy to alter their permeability by adjusting the vinyl acetate content of the polymer (Baker and Heller, 1989). The changes in the permeability are related to changes in the glass transition temperature and crystallinity of the polymer. Pure polyethylene is a rigid glassy polymer with relatively low permeability, but a small fraction of copolymerized vinyl acetate makes the copolymer more rubbery and hence more permeable.

Silicones are hydrophobic and non-porous polymers that are suitable for controlling the release of non-polar and lipophilic drugs from therapeutic systems but they are releatively impermeable to hydrophilic and ionic compounds (Rankin and Aguadisch, 1987). Permeability of silicones to polar molecules is improved by using polar or

osmotic additives in the polymer (Carelli et al., 1986; Rankin and Aguadisch, 1987) or by convering the impermeable ionized drug into a more permeable unionized form with pH-adjusting additives (Sutinen et al., 1990). Drug permeability in silicones can also be altered by modifying the silicone backbone structure (Lee et al., 1986) or by synthesizing silicone-organic block and graft copolymers (Ulman et al., 1989a; Ulman et al., 1989b).

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AQUEOUS ENTERIC COATING SYSTEMS BASED ON NEUTRALIZED CELLULOSE ESTERS

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Since the early of 1970s, increasing interest has been focused on aqueous-based film coatings of oral solid dosage forms. The major advantages of the aqueous film coating technique over e.g. the more traditional organic-solvent-based film coating include a non-explosive coating process, lack of solvent residuals (product safety), environmental considerations and economic benefits. For enteric film coating (i.e. gastric-resistant coating), aqueous latex and pseudolatex systems of various polymers have been used for many years. These coating systems do, however, suffer from certain drawbacks related to coalescence of the dispersion particles and some operational problems such as pneumatic nozzle blockage and adhesion to tablets.

In the early 1980's, Stafford (1982) introduced a simple method of producing aqueous solutions of enteric coating systems from cellulose ester derivatives by neutralizing the free acid groups of the polymers with ammonium hydroxide. In this technique, ammonia ionises the free acid moiety on the polymer. An enteric film is formed when the coated drug preparation is exposed to acidic medium due to the transformation of the salt into the acid form. So far, there are only few reports in the literature on neutralized (ammoniated) cellulose ester derivatives, and little is known about their physico-chemical and enteric properties (e.g. true gastric resistance, drug permeability and dissolution properties).

In the Pharmaceutical Technology Division at the University of Helsinki, the enteric properties of cellulose ester films prepared from ammoniated aqueous and organic-solvent-based solutions have been evaluated with special reference to drug permeability, permeability to hydronium ions, mechanical film properties and short-term storage stability. For characterisation of the

effects of various film formulation factors on film properties, free isolated films and/or film-coated drug products have been evaluated. Cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT) and hydroxypropyl methylcellulose phthalate (HPMCP) have been studied as cellulose ester enteric coating materials.

On the basis of our results, enteric films prepared from neutralized aqueous cellulose ester solutions showed higher permeability to basic drug (caffeine) and hydronium ions than organic-solvent-based (acetone) enteric films. Consequently, and for the reasons mentioned above, it would be reasonable to assume that inclusion of a hydrophobic adjuvant in neutralized aqueous enteric coating formulations is necessary with respect to their gastric resistance capacity. As regards the mechanical properties, ammoniated aqueous enteric films were shown to be somewhat weaker than the corresponding films prepared from organic-solvent-based (acetone) solutions. Aging under stress storage conditions changed clearly the permeability and the mechanical properties of neutralized aqueous enteric films, especially based on CAT or CAP.

In our experiences, reformulation (neutralization) of organic-solvent-based cellulose ester enteric coating systems to aqueous-based enteric coating systems is a very promising technique in many ways. More research is, however, needed in order to clarify the physico-chemical, pharmaceutical and biopharmaceutical properties of enteric products prepared from neutralized aqueous solutions.

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PHYSICAL CHARACTERISATIONS OF FREE FILMS PREPARED FROM POLYMERS USED IN SUSTAINED RELEASE COATING

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The use of a rate-controlling membrane, applied by film-coating, is one of the most common methods used to develop sustained release dosage forms. The normal course of development of such products requires several experimental products to be prepared and evaluated. The formulation and process variables play an important role in the film-forming properties of coating polymers. Thus, prior knowledge and experience with specific film formers is extremely valuable to better understand the factors affecting the film formation and properties. The principle objectives of the characterisation of free films physical properties is to gain insight into the nature of the polymer/plasticiser interactions as a means for formulating films for optimum performance in pharmaceutical applications.

Pharmaceutically acceptable polymers used in film-coating of solid dosage forms are primarily based on acrylic or cellulosic polymers. Many of these polymers present brittle properties under normal ambient temperatures and humidity conditions. The incorporation of a plasticiser is necessary to obtain effective coating without defects such as cracks, edging or splitting. The degree of plasticisation of a polymer is dependent to a large extent on the amount of plasticiser in the polymeric film and the interactions between the plasticiser and the polymer. Therefore, thermal analysis of polymers and free polymeric films is important, since such determination as the Tg reflects the polymer's behaviour under ambient and coating conditions (1).

Physical-mechanical testing permits to evaluate and compare the effect of plasticisers in free films as a function of formulation compatibility, type, and level. It can be useful guide in predicting not only film coating performance but also further processing (e.g., compression of coated beads) and storage (2). The mechanical properties (such as tensile stress, percentage elongation at beak and elastic modulus) of polymeric films are mainly affected by the thermomechanical properties of the polymer, such as glass transition or softening temperature, and by film additives such as plasticisers and fillers (1). Lately, some studies comparing the mechanical properties of dry and wet polymeric films have shown that the mechanical properties of dry and wet films cast from aqueous colloidal dispersions were significantly different and were strongly influenced by the types of polymer dispersion and plasticiser. The mechanical properties of wet polymeric films should also be taken into consideration when formulating sustained release dosage forms (2, 3).

Finally, permeation kinetics through free films may also be useful to predict the permeability of the coating (4) and even the drug release kinetics from coated dosage forms such as pellets (5). However, in the cases where the drug can dissolve in the coating solvent during spray-coating, it is not possible to easily find a correlation with the results of permeation kinetics through free films, as the drug may be embedded in the coating membrane and alter the film coating properties , e.g. the drug may act as a plasticiser (6).

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RADIOLABELLING OF INHALED SALBUTAMOL SULPHATE FORMULATIONS

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Radiotracer techniques are commonly used to evaluate the pulmonary deposition of inhaled drug particles after drug delivery from metered dose inhalers (MDI), powder devices and nebulizers. The labelling methodology of in vivo deposition studies is based on either chemical or physical incorporation of the gamma emitting component in the particles observed. However, direct measurements of pulmonary deposition of inhaled drugs by means of gamma camera detection are usually impossible, because drugs rarely contain an element that can be substituted by a gamma emitting radionuclide. Therefore, in deposition studies of inhaled dosage forms, either inert Teflon particles or drug particles to which a radiotracer is physically bound, have been used. In these studies, ^{99m}technetium (^{99m}Tc) is the most commonly used radionuclide, which is not chemically bound to the active drug but acts only as a marker for the active drug component in the formulation.

In this study, a gamma labelling method for incorporating the radionuclide to salbutamol sulphate (Ph. Eur.) particles before preparing the final formulation has been developed. The labelled particles can be used for preparing either MDIs or inhalation powders [1].

In the labelling process ^{99m}Tc was eluted from a radionuclide generator as pertechnetate ($^{99m}TcO_4^-$) in saline and placed in a glass test tube. One drop of ammonia and one drop of an aqueous 5% tetraphenylarsonium chloride were added. The radioactivity was partitioned into the organic solvent by shaking the water solution with chloroform. Micronized salbutamol sulphate particles were suspended to chloroform phase and homogenized. The suspension was sprayed into a hot air stream, and the airborne particles were collected.

The size and shape of the labelled and unlabelled salbutamol sulphate particles were compared from scanning electron micrographs.

The MDIs were prepared by using halogenated hydrocarbons as propellants and lecithin as a surfactant. In the powder preparation, lactose was used as a carrier material. The amount of drug per dose was analyzed with an HPLC method, and the radioactivity of the corresponding dose was analysed with a dose calibrator. The correlation between radioactivity and drug concentration was determined by cascade impactor (Andersen 8-Stage Non-Viable Sampler - air flow 28.3 l/min) to ensure that the radioactive tag was homogenously distributed in different particle size fractions. In addition, the aerodynamic behaviour of the labelled and unlabelled salbutamol preparations was compared by the cascade impactor.

In vivo trials have showed the suitability of this labelling method for studying the lung deposition of salbutamol sulphate particles administered both from MDIs and powder dosage forms. Studies with a novel multiple-dose powder inhaler showed a similar pulmonary deposition as achieved with a conventional MDI both in healthy subjects and asthmatics **[2, 3]**.

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APPLICATION OF 2^3 AND 3^3 FACTORIAL EXPERIMENTAL DESIGNS AND MULTIVARIATE DATA ANALYSES IN STUDYING FLUIDIZED BED GRANULATION PROCESS

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Fluidized bed granulation is typically a multivariate process with a large number of variables affecting the quality of granules. Therefore, fluidized bed granulation process studies give promising possibilities for applying different experimental designs and data analysing techniques. In this study the effect of three fluidized bed granulation variables (inlet air temperature, atomizing air pressure and binder amount) on mean granule size were studied using 2^3 and 3^3 experimental desings. Also the effect of replicated experiments was evaluated. The dependence of mean granule size on granulation variables was explained using regression analysis and neural networks. In neural network modelling a network with one hidden layer was tested. A standard back propagation learning rule was used to change the weights of a net in learning. The results show that both experimental design and technique applied for the generation a regression model affect the accuray of regression model. In every case neural network modelling gave more accurate results than corresponding regression models.

B. POSTERIABSTRAKTIT

AN EVALUATION OF YOUNG'S MODULUS OF PHARMACEUTICAL POWDERS WITH THREE DIFFERENT BEAM BENDING TESTS

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For predicting the behaviour of pharmaceutical powders under compression, the materials have been classified according e.g. to the Young's modulus E, yield pressure P_y and strain rate sensitivity SRS parameter values. All these parameters typically require experimental evaluation. Beam bending techniques have been under consideration for last decade and proven to be accurate techniques to measure the Young's modulus of pharmaceutical powders. The Young's modulus describing the intrinsic elastic property of particulate materials has to be typically considered from solid, homogeneous, and to the zero porosity state compressed compacts or casted samples. However, in practise with pharmaceutical powders it is not possible to reach the absolute intact structure using conventional compression methods. Thus extrapolation techniques have be gained from data of compacts of different porosities.

The three- and four-point bending tests have been the most used methods in evaluation of elastic properties pharmaceutical powders. In this study these tests and also the two-point bending test were performed using microcrystalline cellulose samples compressed to rectangular beams with dimensions of 60x6x2mm. The bending of the beam as well as the stress pattern induced inside the beam were evaluated using double-exposure holographic technique.

The displacement of the beam and the induced stress patterns in each bending technique were evaluated using the fringe spacing data gained from holograms. The displacement of the sample beams was calculated at every point continuously and thereby the experimental displacement curves were gained and compared to theoretical displacement curves. It was found that the three- and four-point bending techniques gave very linear stress pattern in the middle section of the beam, from where the needed displacement for the Young's modulus is usually measured. However, the two-point bending technique created distortion inside the beam structure especially at fixing point of the beam and thereby nonlinearity to the stress pattern.

FRICTIONAL WORK DURING DOUBLE-SIDED TABLET COMPRESSION.

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The present paper deals with the frictional work in compression by double-sided profiles (rotary press). The equation of Järvinen and Juslin (Järvinen and Juslin, 1974) for use in the calculation of the frictional work in single punch tablet compression has been applied to single sided sawtooth displacement profiles accomplished in a compaction simulator. An equation for friction work calculations in double-sided compression was derived. Quantities of powder to produce tablets of 1.5 mm and 0.75 mm thicknesses at zero theoretical porosity in the one sided sawtooth profiles were manually filled in the die. Similar double-sided sawtooth profiles were accomplished using an amount of powder to produce 3 mm thickness tablet (null porosity). Furthermore, an asymmetrical profile with the amplitude of the sawtooth of upper punch double than that of the lower punch has been used with a quantity of powder to obtain 2.25 mm thickness at zero theoretical porosity. Compression speed was 7.5 mm/s in all cases except in the asymmetrical profile the compression rate of the upper punch was, however 15 mm/s. The materials used were dibasic calcium phosphate and granular lactose. For each profile tablet batches of both materials were done at 100, 200 and 300 MPa of applied pressure. Breaking strength of tablets was measured with a CT5 0.5 Tonne Testing Machine.

Frictional work has been calculated using a deduced equation for symmetrical and asymmetrical double-sided compressions. In the symmetrical compression the equilibrium point was assumed to be in the halfway between the punches and at a distance proportionally to the amplitude of the sawtooth profile in the asymmetrical compression. Frictional work calculated using proposed equation for double-sided profiles was close to the theoretical values estimated with the Järvinen and Juslin equation for single sided profiles. The novel equation seems to open new possibilities for the evaluation of friction phenomenon in rotary press tabletting. Crushing strength of tablets were independent of profiles, being similar for tablets obtained with single or double sided.

PHYSICAL PROPERTIES OF THEOPHYLLINE MONOHYDRATE AND POLYMORPHS OF ANHYDROUS FORM

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Theophylline has been reported to exist in monohydrate and anhydrous forms. It has been also reported that anhydrous form of theophylline has two polymorphs, which might affect the dissolution behaviour and bioavailability of theophylline. The aim of this study was to characterize the physical properties of theophylline monohydrate and anhydrous forms I and II using differential scanning calorimetry (DSC), solution calorimetry and scanning electron microscopy.

Theophylline monohydrate was recrystallized from distilled water. Anhydrous form II was prepared from monohydrate by drying at 110°C for 24 h and form I was prepared by heating anhydrous form II at 260°C for 1 h.

The water contents of the monohydrate and anhydrous form II, determined with Karl Fischer titrimeter, were 9.16 and 0.16 %, respectively. X-ray powder diffraction patterns of anhydrous theophylline forms I and II and monohydrate were significally different. The extrapolated onset temperature and enthalphy for the dehydration of monohydrate, determined with DSC, were 55°C and 47.3 kJ/mol, respectively, and the extrapolated onset temperatures for the fusion of monohydrate, anhydrous forms I and II were 271.1, 271.7 and 266.2°C, respectively. The heats of solution for the theophylline monohydrate, anhydrous forms I and II, determined with solution calorimeter, were 28.6, 17.4 and 19.4 kJ/mol, respectively. The scanning electron micrographs from the surface structures showed that monohydrate had smaller surface area than anhydrous forms. The mean particle sizes with standard deviations, determined also from micrographs, of monohydrate, anhydrous forms I and II were 29±18, 11±12 and 11±12 μm, respectively. The enthalphy of polymorphic transition for the anhydrous form was found to be very small (1-2 kJ/mol).

Dissolution differences between monohydrate and anhydrous forms I and II can be explained with differences in the surface areas and particle sizes as well as with differences in crystal packing and intermolecular hydrogen bonding of different forms of theophylline.

EVALUATION OF MECHANICAL PROPERTIES OF FREE FILMS BASED ON AQUEOUS POLYMERIC DISPERSION OF ETHYLCELLULOSE USING TENSILE TESTER OF J. J. LLOYD

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Determination of mechanical properties of free films gives an important information for example from the release kinetics and plasticizer efficiency.

In the present study free films were prepared by casting method using three types of Surelease®-dispersions differing from each others by the type of plasticizer and presence or absence of anti-adherent. Films were coalesced using three different temperatures, namely 40, 50 and 60°C. The coalescence time used was 24 hours. The samples were stored for 12 weeks in different storage conditions (temperature, humidity) to find out the stability of the films.The mechanical properties of the films were evaluated after storage periods of 4, 8 and 12 weeks using tensile tester of J. J. Lloyd.

The coalescence temperature, plasticizer and anti-adherent had an important effect on mechanical properties of the free films. Tensile strength, elastic modulus and elongation increased with increasing coalescence temperature. The DBS (dibutyl sebacate) plasticized films were weaker and softer than the GTC (fractionated coconut oil) plasticized films, so DBS is more effective plasticizer. The anti-adherent (fumed silica) had a detrimental effect on mechanical properties, expect on elastic modulus.

The storage in different conditions didn't change reciprocal order of the different types of film, but there were changes in test results between different time points. Because of large deviations it is impossible to say were the changes significant or not without statistical analysis.

EVALUATION OF THERMAL BEHAVIOUR OF PLASTICIZED ETHYLCELLULOSE FILMS BY MEANS OF DIFFERENTIAL SCANNING CALORIMETRY

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Differential scanning calorimeter (DSC) is a powerful tool in evaluation of plasticizer efficiency in polymer materials. It also can reveal poor mixing of components.

Ethylsellulose films were cast from ethanol solutions differing from each other by the type and amount of plasticizer. The plasticizers used were dibutyl sebacate (DBS), triethyl citrate (TEC), triacetin, Myvacet®and diethyl phthalate (DEP).

Films were analyzed with Perkin Elmer 7 DSC.The glass transition temperatures are listed in table 1. Also a softening trasition was obtained. In case of three plasticizers (TEC, triacetin and DEP) insufficient mixing was revealed by obtaining two different glass transitions.

	$T_g \pm sd$ (°C)				
	DBS	TEC	Triacetin	Myvacet	DEP
0%	142.9 ± 0.3	142.9 ± 0.3	142.9 ± 0.3	142.9 ± 0.3	142.9 ± 0.3
10%	73.6 ± 1.7	74.0 ± 1.0	84.5 ± 1.3	74.5 ± 2.0	92.7 ± 2.7
20%	42.5 ± 1.5	70.4 ± 1.9	87.5 ± 0.8	45.0 ± 0.6	81.5 ± 4.0

Table 1 : Glass transitions of films tested

The results clearly indicate that DBS and Myvacet® are the two most efficient plasticizers for ethylcellulose. A high correlation between glass transition temperatures and mechanical properties was obtained.

ACOUSTIC COMPACTION STUDIES ON MICROCRYSTALLINE CELLULOSE

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Acoustic studies have been performed, both during the roller compaction of the microcrystalline cellulose powder and on single tablets after the compaction of the powder by a single-punch tablet machine, via air using a microphone with a flat frequency response up to 20 kHz. Both of the compaction units are instrumented for the measurement of applied compressive force. So the acoustic emissions from the material during (or after) compaction can be detected as a function of applied (or maximum) compressive force.

The microcrystalline cellulose roller compacted using compressive forces below 30 kN shows a quite normal compaction behaviour but the product compacted at this force splits into two and turns to yellow by its edges. This "capping" phenomenon is indicated by an enhancement of acoustic emission in the region of about 17-23 kHz in time-averaged acoustic emission spectra. Acoustic emissions from single tablets seem to appear as wave packets consisting in very many frequency components that may, in addition, be time-varying. However, there seem to be some characteristic frequency components of these transient sounds.

Further investigations using two-channel detection in order to increase the signal-to-noise ratio of the detection are in progress. The background (noise) signal from the compaction machine can be subtracted from the signal containing the acoustic emissions from the material under investigation. Furthermore, instrumentation and analyzing procedures for real-time acoustic tabletting studies are in progress.

A STABILITY AND TRANSFORMATION STUDY OF SOME TRIGLYCERIDE-BASED PRODUCTS

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Triglycerides and commercial fats have three main crystal forms: α, β' and β. The polytypism, or one-dimensional polymorphism, is caused by temperature activation. The most stable form is β and, before long, most products reach this form. The β-form is usually the unwanted form because its large crystal size causes "sandy taste" in foodstuffs and poor solubility in pharmaceuticals. The most stable form in practice depends on the fat content.

Triglycerides are long-chain molecules and the crystal lattice has two characteristic features: long spacing(s) (30-50 Å) which tells about the molecule length and longitudinal packing, and short spacings (3-6 Å) which describe the lateral distances in the lattice. Short spacings are used when the three polymorphic forms are identified. The long spacings depend on the molecule length and are not used when identifying the polymorphic forms.

The stability and transformations of two pure triglycerides (tripalmitin and tristearin) and a margarine product was studied as a function of preservation temperature. The methods were thermodiffractometry (TXRD), differential scanning calorimetry (DSC) and microcalorimetry (MC).

DSC showed a clear transition α→β for triglycerides prepared originally in the α-form. TXRD showed clear transition processes (α→β or β'→β) for all three fats. The polymorphism was more obvious for pure triglycerides than for the margarine product as the x-ray diffraction patterns of triglycerides were more "crystalline". MC gave equal transition enthalpy for the α→β transition of tripalmitin according to measurements made at constant temperatures as DSC in a scanning measurement. This provides that the thermally activated α→β transition consist of two consecutive reactions (endothermal and exothermal) that can not be separated when concerning the bulk sample, not one crystal. These two reactions are hence simultaneous at the temperatures below the transition temperature obtained with DSC. The transition rates were studied using the Arrhenius equation. The activation energy of tripalmitin obtained with TXRD and MC was 455 kJ/mol and 410 kJ/mol, respectively.

COMPARISON OF KINETIC STUDIES OF CAFFEINE MADE WITH X-RAY DIFFRACTION AND MICROCALORIMETRY

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Stability studies are essential in drug research for many reasons. Uncontrolled structural changes during the storage of raw materials, manufacturing or storage of the final product can drastically impair the quality of product. Therefore, physical study of structural changes is important. This study deals with the suitability of x-ray diffraction and microcalorimetry for the determination of the polymorphic transformation kinetics of anhydrous caffeine. Polymorphism is very common among the drug substances so that this kind of study is often needed.

The anhydrous caffeine has two polymorphic forms. The transformation temperature between the low-temperature II- and the high-temperature I-modification is about 140°C. The form I is not stable but transforms into the form II at room temperature. The activation energy of the process is however so high that transformation happens quite slowly.

The results show that these methods combined give an exact picture of the transformation process. X-ray diffraction is almost irreplaceable method for the study of polymorphism and quantitative analysis can be used to analyze the concentrations of phases in polymorphic mixture. Polymorphic transformations can be so sluggish or the heat of transformation can be so small that ordinary thermoanalytical methods are not useful. Only microcalorimetry is sensitive enough to measure the energetic changes in anhydrous caffeine when it turns slowly from metastable form I into stable form II. However, to get consistent kinetic results with x-ray diffraction is one kind of problem as the principles of these two methods are totally different. With diffraction one can observe one physical change, i.e., the increase of the stable phase while microcalorimeter measures the energy related to all parts of reactions concerning phase transformation of anhydrous caffeine, e.g., sublimation, nucleation and growth of crystals.

STABILITY STUDIES OF FLUTAMIDE

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The purpose of this work was to make physical characterization of flutamide and to study if some environmental factor causes the growth of particle size. Preliminary studies were carried out with two samples. One sample was just micronized and the other contained needle-like particles after storage at room conditions. Differential scanning calorimetry (DSC) and x-ray powder diffractometry (XRD) were used to study the presence of possible polymorphs. Both preliminary samples had also equal moisture content. The only observed change involving physical stability of flutamide was growth of particle size. It was observed that specific surface areas of preliminary samples were considerably different. Because of that we regarded specific surface area measurement with BET-method as an useful tool in this case.

BET-method is based on gas adsorption. The surface area is measured by determining the quantity of a gas that adsorbs as a monomolecular layer. Specific surface area is determined as surface area of sample per sample weight and it is dependent on particle size. When particle size grows specific surface area decreases. By studying the decrease of specific surface area one can estimate whether the particle size has grown or not.

Micronized flutamide was stored under different environmental conditions to accomplish growth of particle size. After storage specific surface areas were measured with BET-apparatus. The specific surface area of flutamide decreases after storing at elevated temperatures. Visual examination with optical microscope shows that particle size has grown. This agrees with BET-results. Because BET-method does not give direct information of particle size we are going to expand this study to particle size analysis.

PHYSICAL MATERIALS RESEARCH PROJECT 1989-1994 – OBJECTIVES, RESULTS AND SELF EVALUATION

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The essential goals of physical drug research within the last five years have been to build up physical knowledge and research facilities for the pharmaceutical technology. Exact information found from the physical measurements has promoted the development of production conditions and helped the reasonable choice of raw materials. In detail, the determination of hygroscopicity of powder samples has become feasible with the development of the gravimetric system. X-ray powder diffraction and its applications formed an essential tool for the study of physical structures and structure transformations. Acquisition of automated powder diffractometer systems with modern software enabled besides routine structure determinations, also quantitative analysis of phase fractions in solid mixtures. Shape analysis of x-ray diffraction line profiles at best offered information on the microstructure of crystalline materials. With a temperature and humidity chamber accessory it has been possible to follow structure transformations also in varying ambient conditions. Modern x-ray analysis on single crystals has enabled deepgoing studies of crystal and molecular structures.

What has been the outcome of the studies? 1) Physical characterization of drug materials has consolidated it's position as a part of drug formulation and development. 2) Systematic investigations have figured out the effect of external circumstances. Temperature, humidity and mechanical treatment have come up as relevant parameters. 3) Novel techniques have been introduced. E.g., a study of acoustic emission during powder compaction and its frequency spectral analysis represents a brand-new way of approach to compression technology. 4) Examination of physical stability has been enabled by introducing different accelerated processes as well as a modified microcalorimeter that follows the stability under real storage conditions. Therefore, we would like to say that the Pharmaceutical Physics Research Group has become one of the leading service and research centers in the field of pharmaceutical physics. A clear indication of significance will be a new minilaboratorium in the rebuilding of the department of Physics that will be brought into use within two months.

EMULSIOVOITEEN STABIILIUDEN SEURANTA MÄÄRITTÄMÄLLÄ VARASTO MODULUS JA PALLOSKOKOJAKAUMA AJAN FUNKTIONA

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Voiteilla on havaittu tapahtuvan konsitenssin muutoksia ajan funktiona. Riippuen valmisteesta ja olosuhteista muutosnopeudet vaihtelevat. Tässä työssä tarkoituksena oli tutkia emulsiovoiteen fysikaalista rakennetta ja sen kehittymistä heti valmistuksen jälkeen ja säilytettäessä +25°C:en lämpötilassa. Rakenteen määrittämiseen käytettiin sekä reometristä menetelmää että valomikroskoopilla laskettua palloskokojakaumaa. Tutkittavaksi valmisteeksi valittiin ö/v emulsiovoide, jota tutkimuksessa seurattiin ajankohtina 1, 3, 7, 14, 21, 28, 56, 112 vuorokautta valmistuksen jälkeen.

Emulsiovoiteen fysikaalista rakennetta mitattiin oskilloivalla reometrillä (StressTech). Mittaussysteeminä käytettiin cone and plate -menetelmää. Mittapään halkaisija oli 40 mm ja kulma 4°. Mittaus suoritettiin +25°C:ssa. Tässä työssä päädyttiin tarkastelemaan Oscillation stress sweep -testiä. Testissä voima (stress) suureni 0,06 Pa:sta 50 Pa:iin frekvenssin ollessa vakio 1 Hz. Näytteen antaman vasteen (strain) perusteella saatiin elastisuutta kuvaava G´ (storage modulus, Pa) lineaariselta elastisuusalueelta. Valomikroskoopin (Nikon) avulla määritettiin emulsiopallosten kokojakauma käyttäen 400X suurennusta.

Mittauksista nähtiin, että emulsiovoiteen G´ suureni ensimmäisenä kahtena viikkona valmistuksen jälkeen. Sen jälkeen G´ lähti pienenemään. Emulsiopallosten kokojakauma oli kapea ja lähes muuttumaton ensimmäisenä kolmena viikkona valmistuksen jälkeen. Palloset olivat jakaantuneet pääasiassa kahden pienimmän fraktion (<2.5µm ja 2.5µm) alueelle. Kolmen viikon jälkeen toiseksi pienimmän fraktion osuus alkoi kasvaa samalla, kun pienimmän fraktion osuus väheni. Molemmat määritykset osoittivat emulsiovoiteen rakenteen stabiiliuden lähteneen heikkenemään säilytyksen aikana.

Tutkimus osoitti, että emulsiovoiteen reologiset ominaisuudet muuttuvat valmistuksen jälkeen ja ovat mitattavissa. Vastaavaa muutosta ei pystytty näkemään pelkästään palloskokojakaumaa tarkastelemalla. Jakauma antoi viitteitä rakenteen muutoksesta vasta 28 vrk jälkeen. Nämä kaksi eri menetelmää täydensivät toisiaan ja auttoivat ymmärtämään emulsiovoiteessa tapahtuvia rakenteellisia muutoksia.