

Fysikaalisen farmasian XV vuosittainen symposium: JUHLASYMPOSIUM

21.-22.1. 2004 Helsinki

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**Fysikaalisen farmasian XV vuosittainen symposium:
JUHLASYMPOSIUM**

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OHJELMA JA TIIVISTELMÄT

Toimittanut:
Petra Lehtinen

Fysikaalisen farmasian yhdistys

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OHJELMA

Keskiviikko

9:30		<i>Ilmoittautuminen ja kahvi (postereiden oltava paikoillaan kello kymmeneen mennessä)</i>
10:25	Mikko Koivisto	Symposiumin avaus
10:30	Juhani Posti	Physical Pharmaceutical Test Procedures in the General Chapters of the European Pharmacopoeia
11:10	Hanna Kortejärvi	Novel application of bayesian approach in level A in vitro-in vivo correlation (IVIVC) model
11:40		<i>Lounas ja posteriesittelyt</i>
13:30	Niina Kivikero	Multichamber microscale fluid bed powder processor
14:00	Matti Murtomaa	A novel method for microscale granulation
14:30		<i>Kahvi</i>
15:00	Mikko Koivisto	Yhdistyksen lyhyt historiikki
15:10	Yhdistyksen kunniajäsenet	Paneelikeskustelu fysikaalisen farmasian historiasta ja tulevaisuudesta Suomessa.
16:10	Mikko Koivisto	Keskiviikon päätös
16:30		FYSIKAALISEN FARMASIAN YHDISTYKSEN VUOSIKOKOUS
19:00		Parhaan posterin palkitseminen
19:10		<i>Buffet</i>

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Torstai

9:30	Lasse Kervinen	Process Analytical Technology (PAT) -An introduction
10:15	Niklas Laitinen	An image analysis approach in the PAT framework
10:45		<i>Tauko</i>
11:00	Jukka Rantanen	Process analysis with spectroscopic tools
11:45		<i>Lounas</i>
12:45	Reijo Lappalainen	Spectroscopic techniques for tablets
13:25	Pekka Jarho	Development of Nove Cyclodextrin Containing Formulations for Sublingual Delivery of Cannabinoids
13:55		Symposiumin päätös
14:00		<i>Kahvi</i>

LUENNOT

PHYSICAL PHARMACEUTICAL TEST PROCEDURES IN THE GENERAL CHAPTERS OF THE EUROPEAN PHARMACOPOEIA

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Introduction

Pharmacopoeias (*e.g.*, the European Pharmacopoeia, *Ph. Eur.*, and the United States Pharmacopoeia, *USP*) describe and provide basic operational requirements for numerous different test procedures applicable for testing and studying the properties of drug substances and excipients, and also of finished drug products. By their nature the test procedures may be chemical, physical, technical-functional, or (micro)biological. This variety of test methods also includes physical test procedures relevant to be mentioned and discussed at this Symposium of Physical Pharmacy.

1. Physical and physical-technical test procedures currently described in the Ph. Eur.

Physical test procedures are presented as separate monographs in the general chapters 2.2. 'Physical and Physicochemical Methods' and 2.9. 'Pharmaceutical Technical Procedures' of the Ph. Eur. (the listing below is according to current status of Ph. Eur., 4th Edition (2002) and its Supplements 4.1 to 4.8). Several of the existing test procedures are under revision and harmonisation within the International Conference on Harmonisation procedure (ICH), and also a few new test procedures are under preparation. Co-operating pharmacopoeias in ICH procedures are the Ph. Eur., the USP, and the Japanese Pharmacopoeia, *JP*.

The physical and physicochemical methods listed in chapter 2.2 of the Ph. Eur. also include a number of procedures which, although their underlying principles are physical or physicochemical, are generally conceived as "chemical"-analytical test methods and do hence not belong to the domain of physical pharmacy, for example:

2.2.21. Fluorimetry

2.2.22. Atomic emission spectrometry

2.2.23. Atomic absorption spectrometry

2.2.24. Absorption spectrophotometry, infrared

2.2.25. Absorption spectrophotometry, ultraviolet and visible

2.2.26. – 2.2.30. = various chromatographic methods

2.2.37. X-ray fluorescence spectrometry

2.2.40. Near-infrared spectrophotometry

2.2.43. Mass spectrometry

2.2.48. Raman spectrometry

"Physical pharmaceutical" test procedures described in chapter 2.2 of the Ph. Eur.:

2.2.14. Melting point – capillary method

2.2.15. Melting point – open capillary method

2.2.16. Melting point – instantaneous method

2.2.17. Drop point

2.2.18. Freezing point

2.2.32. Loss on drying

2.2.34. Thermogravimetry

2.2.42. Density of solids

Further general test procedures of Ph. Eur. that basically also belong to the domain "physical pharmacy":

2.2.5. Relative density

2.2.6. Refractive index

2.2.8. Viscosity

2.2.9. Capillary viscometer method

2.2.10. Rotating viscometer method

2.2.49. Falling ball viscometer method

Some of the physical-technical test procedures described in chapter 2.9. 'Pharmaceutical Technical Procedures' of Ph. Eur. are listed below:

2.9.8. Resistance to crushing of tablets

2.9.9. Measurement of consistency by penetrometry

2.9.12. Sieve test

2.9.14. Specific surface area by air permeability

2.9.15. Apparent volume (*of powders: 'bulk' and 'tapped density'*)

2.9.16. Flowability (*of powders through a funnel aperture*)

2.9.18. Preparations for inhalation: aerodynamic assessment of fine particles

2.9.22. Softening time determination of lipophilic suppositories

2.9.23. Pycnometric density of solids

2.9.24. Resistance to rupture of suppositories and pessaries

2.9.26. Specific surface area by gas adsorption

2. Physical and physical-technical test procedures currently described in the USP

In the USP, the corresponding, purely physical or physical-technical test methods are described under the heading 'Physical Tests and Determinations' in section General Chapters (status: USP 27, official from 1 January 2004). For example:

- <601> Aerosols, metered-dose inhalers, and dry powder inhalers (including test procedure for particle size determination by aerodynamic size distribution)
- <616> Bulk density and tapped density
- <651> Congealing temperature
- <695> Crystallinity, as described under *Optical microscopy* (<776>)
- <696> Crystallinity determination by solution calorimetry
- <699> Density of solids
- <731> Loss on drying
- <741> Melting range or temperature
- <776> Optical microscopy
- <786> Particle size distribution estimation by analytical sieving
- <811> Powder fineness
- <841> Specific gravity
- <846> Specific surface area (*by gas adsorption*)
- <891> Thermal analysis (*Transition temperature, Thermogravimetric analysis, and Eutectic impurity analysis*)
- <911> Viscosity
- <941> X-ray diffraction
- <1181> Scanning electron microscopy
- <1241> Water-solid interactions in pharmaceutical systems (*Determination of sorption-desorption isotherms, Rates of water uptake, and Physical states of sorbed water*)

General process of ICH harmonisation of pharmacopoeia monographs and test procedures

The Pharmacopoeial Discussion Group (PDG) with representatives from each of the three concerned pharmacopoeias (Ph. Eur., JP, USP) intends to coordinate and facilitate the ICH harmonisation work carried out by nominated expert groups on the topics selected. The harmonisation may concern a monograph or chapter already included in one or more of the three pharmacopoeias ("retrospective harmonisation"), or also a completely new text may be prepared within the ICH frame ("prospective harmonisation". Prospective harmonisation is

expected to be less problematic a procedure in practice. The ICH harmonisation work starts and proceeds in the following sequence:

Stage 1: Identification. Based on inquiry among its users, PDG identifies subjects to be harmonised among the pharmacopoeias and nominates a coordinating pharmacopoeia for each subject.

Stage 2: Investigation. The coordinating pharmacopoeia collects basic information and prepares a draft monograph or chapter, accompanied by a report giving the rationale for the proposal = Stage 3 draft.

Stage 3: Proposal for expert committee review. The three pharmacopoeias forward the Stage 3 draft to their expert committee for review and comments. The consolidated comments are forwarded to the coordinating pharmacopoeia that prepares a draft harmonised document = Stage 4 draft.

Stage 4: Official inquiry. The Stage 4 draft and the commentary are published in the forum of each pharmacopoeia (Pharmeuropa/Ph. Eur., *Pharmacopoeial Forum*/USP, and corresponding forum of the JP). Comments regarding the draft are to be sent by readers of the forum to their national pharmacopoeial secretariat (*e.g.*, **interested members of the Fysikaalisen Farmasian yhdistys may also comment via the Finnish Authority, NAM!**). Each pharmacopoeia analyses the comments received and submits its consolidated comments to the coordinating pharmacopoeia for its further review and preparation of a draft harmonised document = Stage 5A draft. The Stage 5A draft is sent to the secretariats of the other two pharmacopoeias.

Stage 5: Consensus. A. PROVISIONAL. The stage 5A draft is reviewed and commented by the other two pharmacopoeias, and it is very desirable to reach full agreement already at this stage with a view to reaching a final consensus document. – If a consensus has not been reached, the coordinating pharmacopoeia prepares a revised version = Stage5A/2 for comments of the two other. This review/comment and revision process is repeated (Stage 5A/n) until a consensus is reached or until the coordinating pharmacopoeia considers that "harmonisation by attribute" should be applied (= certain pharmacopoeia specific deviations from the otherwise harmonised text). – B. DRAFT SIGN OFF. When full agreement is reached, the 5B draft is sent by the coordinating pharmacopoeia to the other two for final confirmation.

Stage 6: Adoption. The document is submitted for adoption to each pharmacopoeia. Adopted texts are published by the three pharmacopoeias in the supplements or a new edition, as appropriate.

Stage 7: Implementation. The pharmacopoeias will inform each other of the date of implementation in the particular region; the date of implementation may vary according to the region, but harmonisation is not achieved until the text becomes official in all three pharmacopoeias.

On behalf of the European Pharmacopoeia, the permanent Ph. Eur. 'Group of Experts No 12 – Galenical products' (*Group 12*) and the appointed *ad hoc* expert group 'Working Party – Powder characterisation techniques' (*Group of Experts POW*) annexed to Group 12 are primarily responsible for drafting of physical-technical test procedures, and for cooperation with the corresponding ICH group(s) of the other two pharmacopoeias.

GENERAL CHAPTERS OF THE PH. EUR. AND/OR OF THE USP CURRENTLY IN THE ICH HARMONISATION PROCESS, AND NEW MONOGRAPHS UNDER PREPARATION

1. General chapters of the Ph. Eur. and/or of the USP currently in the ICH process

Chapter title	Coordinating Pharmacopoeia	Harmonisation Stage
Bulk density and tapped density (Ph.Eur. 2.9.34) / <616> USP	Ph.Eur.	3
Density of solids (Ph.Eur. 2.2.42) / <699> USP	Ph.Eur.	3
Powder flow (Flowability) (Ph.Eur. 2.9.36)	USP	4
Particle size analysis by laser diffraction (Ph.Eur. 2.9.31) / <429> Light diffraction USP	Ph.Eur.	3
Optical microscopy (Ph.Eur. 2.9.37) / <776> USP	USP	4
Particle size distribution estimation by analytical sieving (Ph.Eur. 2.9.38) / <786> USP	USP	5A draft
Porosity and pore size distribution of solid materials by mercury porosimetry (Ph.Eur. 2.9.32) / <267> Mercury porosimetry USP	Ph.Eur.	3
Powder fineness (Ph.Eur. 2.9.35) / <811> USP	USP	4
Specific surface area by gas adsorption (Ph.Eur. 2.9.26) / <846> Specific surface area USP	Ph.Eur.	5B draft
Characterisation of crystalline solids by X-ray powder	Ph.Eur.	3

diffraction (XRPD) (Ph.Eur. 2.9.33) / <941> X-ray diffraction USP		
Thermal analysis (Ph.Eur. 2.2.34) / <891> USP *)	Ph.Eur.	2

*) The general chapter 'Thermal analysis' will include techniques such as thermogravimetry, differential scanning calorimetry (DSC), and thermomicroscopy. A text for microcalorimetry (isothermal microcalorimetry, solution calorimetry) will be drafted as a second step. Newer related techniques such as modulated DSC, *e.g.*, will not be included in the general chapter 2.2.34 at this first ICH-harmonisation stage.

Elaboration of a harmonised general chapter or monograph to the concerned three pharmacopoeias is an iterative working procedure and proceeds as outlined on pages 3-4.

2. New general chapters under preparation, to be proceeded according to the ICH procedure

Chapter title	Harmonisation Stage
Gravimetric water sorption (Ph.Eur. 2.9.39)	First draft/Ph.Eur. under preparation
Wettability of porous solids, including powders	First draft/Ph.Eur. under preparation

NOVEL APPLICATION OF BAYESIAN APPROACH IN LEVEL A IN VITRO-IN VIVO CORRELATION (IVIVC) MODEL

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Background

Level A is the highest level of IVIVC representing point-to-point relationship between in vitro dissolution and in vivo input rate [1], [2]. Typically IVIVC models are based on averaged in vivo and in vitro data. Also stochastic IVIVC models have been developed that are based on subject-specific two-stages method or mixed-effect population method [3], [4], [5].

Levosimendan, a proprietary molecule of Orion Pharma, is a novel calcium sensitizer with positive inotropic and peripheral vasodilatory effects [6]. It has been developed for the treatment of congestive heart failure.

In this study the Bayesian approach was applied to level A IVIVC. The theoretical basis of the Bayesian pharmacokinetic approach was introduced in 1979 by Sheiner [7] but to our knowledge, it has not been applied previously in the context of level A IVIVC model.

Material and methods

A) In vitro dissolution USP basket method with 500 ml phosphate buffer, pH 5.8 and a rotation speed of 100 rpm

B) Bioavailability (BA) study I was included to help specify the prior distribution of the model parameters (1 formulation, n=10)

C) BA study II was used as actual observed data (4 formulations, n=9)

D) BA study III was used to test external predictability of the IVIVC model (2 formulations, n=15)

A one-compartment model was used as a convolution technique to predict levosimendan concentrations in plasma.

The Bayesian approach was applied to compute the posterior probability distribution for the one-compartment model parameters. This distribution is obtained by combining the prior information and the likelihood. Likelihood measures how well the model explains the data. Usually in statistical modeling, only likelihood is used. In Bayesian modeling the prior distribution, representing the information about the model not contained in the observed data, can be combined with likelihood to obtain more informative models. Most probable (MAP) values were derived from posterior probability distributions to obtain point estimates, i.e. single values for pharmacokinetic parameters and for levosimendan concentration values in plasma.

Results and discussion

Prediction results were similar when the actual observed data in the IVIVC model consisted of levosimendan concentration data either from two or four formulations.

Histograms of posterior probability distributions for the pharmacokinetic parameter $AUC_{0-\infty}$ and C_{max} are shown in Figure 1. It can be noticed that the MAP values lie near the most probable values of the predicted posterior probability distribution. Also the distributions are narrow, which indicates that there is only a small amount of uncertainty in the model predictions.

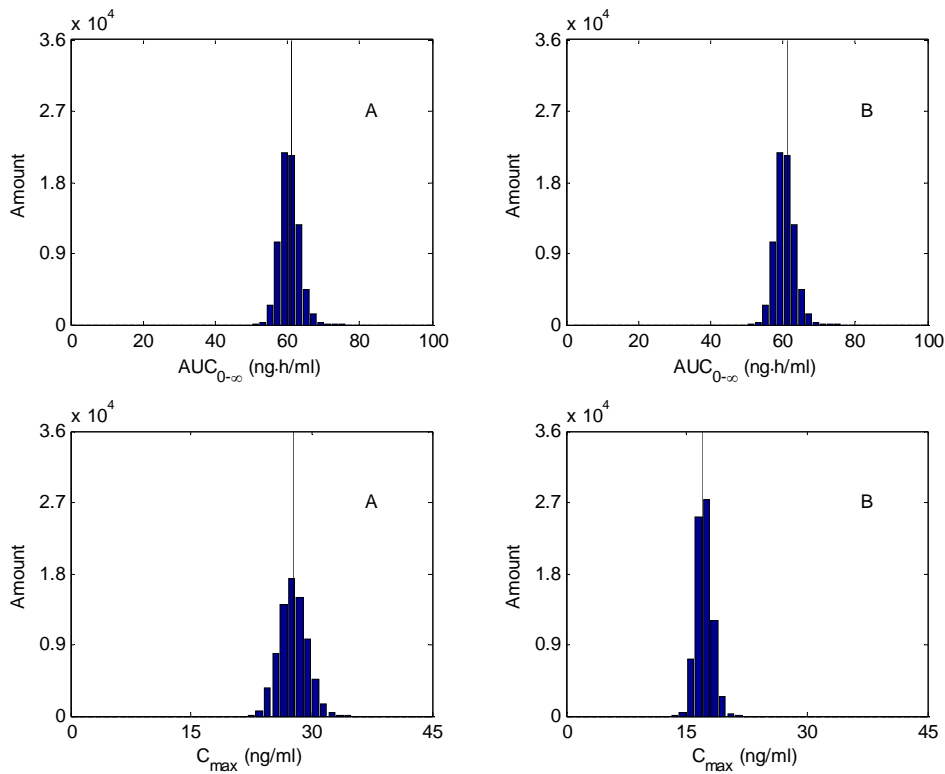


Figure 1. Histograms of the posterior distributions, and MAP values of the pharmacokinetic parameters $AUC_{0-\infty}$ and C_{max} .

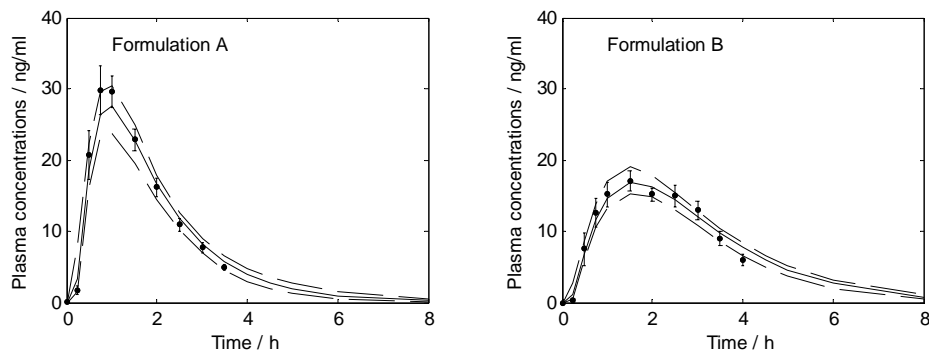


Figure 2. Observed average values of the plasma concentration time profile \pm SEM (dots with error bars), predicted 95% posterior probability interval curves for average plasma concentration time profile (dashed line) and MAP values (continuous line) in IVIVC model for external data set.

The most important result of the modeling is the utilisation of posterior probability distributions. Highly informative posterior probability interval curves for predicted levosimendan concentration time profiles are shown in Figure 2. It can be seen that nearly all the observed values are within predicted 95% posterior probability intervals.

Conclusions

It can be concluded that Bayesian analysis can be used to provide stochastic approach in level A IVIVC modelling. Due to Bayesian approach predictions can be presented as probability distributions. In level A IVIVC modelling evaluating the histograms of posterior probability distributions of predicted parameters and 95% posterior probability curves for predicted concentration vs. time profile curves are very useful. Information about uncertainty related to the level A IVIVC model prediction can be estimated. Another great benefit in Bayesian approach is that data from prior studies can be easily used to specify the prior distribution for model parameters. Secondly relatively small amount of new observed in vivo data is required. However, further studies are needed in order to create criteria to test predictability of level A IVIVC model with Bayesian approach.

References

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MULTICHAMBER MICROSCALE FLUID BED POWDER PROCESSOR

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Introduction

The fluid bed systems are widely used e.g. in the pharmaceutical, metallurgical and chemical industries. Like in all processes it is crucial to understand thoroughly the process behavior. The multichamber microscale fluid bed powder processor (MMFP) (Ariacon Oy, Turku, Finland) gives an opportunity to study different fluid bed processes and materials very fast. The small scale is a real benefit in e.g. in the preformulation stage of a new pharmaceutical product, it reduces material costs and time consumed to the expensive research.

Technical facts

The MMFP contains four conical fluidization chambers. The fluidizing air flow rate (from 0.05ml/s to 2000ml/s) and the temperature of the inlet air (20-90°C) can be adjusted in each chamber independently. The humidity of the inlet air can be controlled (relative humidity 0-70%) by the process air control unit which is connected to MMFP. Process control and monitoring are fully automated and different parameters can be logged e.g. every second. Different processes can be ran simultaneously in the chambers. The air flow is created with a fan and it is measured by a high accuracy meter. The amount of material needed in the process is small, e.g drying experiments need 1-20g of powder.



Fig.1 The fluidizing chambers and the NIR-probe

Research

So far the MMFD has been used for reasearch in different areas e.g. dehydration studies (1.) and electrostatic measurements (2.). Also fluidization behavior characterisation (3.) and fluid bed granulation have been studied.

References

1. Räsänen, E., Rantanen, J., Mannermaa, J.-P., Yliruusi, J., and Vuorela, H., 2003. Dehydration studies using novel multichamber microscale fluid bed dryer with in-line NIR measurement. *Journal of Pharmaceutical Sciences* 92 (10), 2074-81.
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A NOVEL METHOD FOR MICROSCALE GRANULATION

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Abstract

This paper presents a novel method for applying a granulation liquid into a microscale fluid bed. The system is based on an electrostatic atomization process which is briefly presented. The developed method overcomes some of the problems which have previously made microscale granulation process extremely difficult to perform. Some preliminary results are also presented.

Objective

Some of the new drug candidates are extremely expensive, and will be even more so in the future. However, to speed up the expensive drug development phase, formulation studies, such as granulation experiments, need to be performed as early as possible. These issues lead to the fact that the amount of material available for first formulation studies is usually small. It can be concluded that there seems to be a special need for a method which enables one to perform granulation studies with significantly less material than previously. The produced granules should have a controlled size distribution in order to maximize the amount of sample which can be further studied. It can be summarized that an ideal method should fulfill following requirements:

- small amount of powder to be granulated (tens of grams or less)
- high yield
- minimal adhesion of the spray on the walls (controlled spray trajectory)
- adjustable droplet size distribution
- on-line granule size control
- no pressurized air which hampers the sensitive fluidization process
- droplets should travel against the upwards moving gas

Method

Electrostatic atomization is a process in which a high electric charge density is applied on the surface of a droplet. At a certain critical charge density (Rayleigh limit), the coulombic repulsion force exceeds the surface tension. As a result, the initial droplet will break and produce small, highly charged droplets.

When the liquid is placed inside a capillary tube, and an electric field is applied at the tip of the capillary, so called Taylor cone is observed (fig. 1).

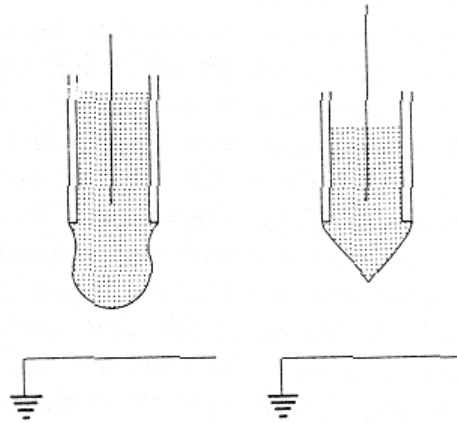


Fig. 1. The tip of a capillary without an applied electric field (left) and with an applied electric field (right). The image on the right hand side shows the formation of the Taylor cone.

Both electric field and the charge density are highest at the sharp point of the Taylor cone. The surface disruption takes place at the tip, and as a consequence small, highly charged droplets are emitted from the cone.

In this study, a small electrostatic atomization nozzle was developed and was used to generate a spray which was used in microscale granulation.

Results

In the preliminary experiments, two parameters; the atomization potential (electric field) and the feed rate, were varied. Laser diffraction studies performed with 20 % (w/w) lactose-water solution showed that droplet sizes between 30 μm and 80 μm were obtained. Fig. 2 presents an example which shows that the droplet size distribution was narrow.

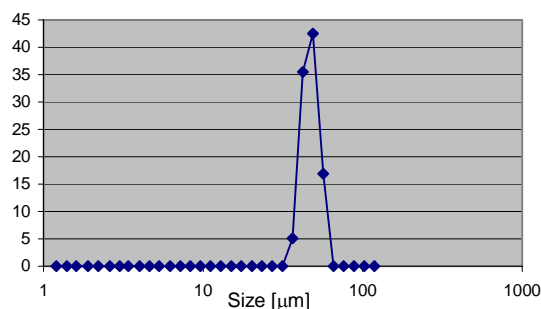


Fig. 2. An example of the size distribution of electrostatically atomized droplets.

Droplets which are generated by electrostatic atomization are highly charged and this property was utilized in targeting PVP-water -solution droplets directly into the fluid bed (Ariacon Oy, Turku, Finland). By applying an appropriate electric field, droplets were guided against the air flow directly into the fluid bed without significant adhesion on the walls. As a result, granules with variable size have been obtained.

Conclusions

Preliminary experiments have given very promising results and it is believed that the requirements stated in the previous page can be fulfilled in the near future. The presented method allows size-controlled microscale granulation without the use of pressurized air. However, more tests and computational modeling is required to optimize the nozzle and the guiding field geometry. It is believed that when the system is running ideally, the yield of this set-up is very high because the adhesion on the walls is negligible, and also because a predetermined granule size distribution can be obtained.

PROCESS ANALYTICAL TECHNOLOGY (PAT) – AN INTRODUCTION

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Traditionally in pharmaceutical industry the quality of a product is tested after batch processing. The release analyses consist of a set of tests that are analysed using a sample taken from the product batch. In other industry areas more attention is paid on process monitoring as well as analyses that are done during the manufacture of intermediate products or the final product. The monitoring procedures used in paper industry are good examples. In addition, the advances of new analysis technology have opened new possibilities for real time analysis. The Food and Drug Administration (FDA) has prepared in co-operation with pharmaceutical industry an initiative in order to emphasize better understanding of manufacturing processes and the importance of real time analysis. This initiative is presented in the draft guideline ‘PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance’, dated August 2003¹. It is expected to be published as the final version in the beginning of 2004.

In the draft guideline Process Analytical Technology (PAT) is defined as *a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality*. In this context the term analytical must be viewed broadly. In addition, the PAT initiative does not restrict to measurements during batch processing. The FDA states strongly that *quality cannot be tested into products; it should be built-in or should be by design*. This is not possible without a sound understanding of the manufacturing processes.

According to the draft guideline PAT framework tools can be categorized as follows:

- Multivariate data acquisition and analysis tools
- Modern process analysers or process analytical chemistry tools
- Process and endpoint monitoring and control tools
- Continuous improvement and knowledge management tools

Pharmaceutical processes are complex multi-factorial systems. Multivariate tools including design and analysis of experiments are required during the development phase in order to

gain deep understanding of the interconnection between the composition and process factors and responses or the quality indicators. Multivariate tools also are needed when the quality attributes of the product is extracted from the vast amount of data gathered during the manufacturing process.

The modern process measurement tools include NIR and Raman spectroscopy, acoustic emission tools and image analysis tools. However, the conventional measurement systems may not be neglected in the PAT framework (temperature, pressure, force, air flow rate, torque etc.). The PAT framework moves focus of modern process analysing tools from off-line measurements in the laboratory to measurements done in the production area. Such measurements are at-line, on-line, in-line or non-invasive measurements. An on-line measurement system is connected to the process using a sample stream. In an in-line measurement the process stream may be disturbed, but in non-invasive measurement the sensor is not in contact with the material (e.g. Raman spectroscopy through a window). One objective of PAT is to establish real time quality assurance, which is enabled by real time measurements during the batch manufacturing. This establishes reduction in the amount of required chemical release analyses.

The critical control parameters of the process must be identified in order to enable effective process control, which is pre-requisite for low variability and high quality of the product. Appropriate process measurement systems have to be established for monitoring the critical parameters. Endpoint control is also an important part of the process control. Finally, a relationship must be found between the quality attributes of the product and the parameters measured during batch processing. Without proper knowledge management tools it is not possible to use efficiently the information gained during the development and production cycle of a product.

Potential benefits of the PAT based manufacturing include^{1,2}:

- enhancing process understanding and reducing process failures
- ensuring quality through optimal design, continuous monitoring, and feedback control
- reducing cycle time to improve manufacturing efficiency
- identifying the root causes of process deviations
- basing regulatory scrutiny on process knowledge and scientifically based risk assessment
- increasing process automation

- facilitating continuous processing

The benefits are obvious. However, the PAT framework raises the question how it should be implemented in practice? The PAT approach sets even more challenges to the development phase than the traditional approach. Strong requirements that there has to be deep understanding of the manufacturing processes emphasize the importance of the product development phase. New technology must be implemented. Both the development laboratory and the production line have to be equipped with the necessary process monitoring techniques. It seems also clear that the PAT approach should be started already during the development phase. Otherwise there will not be enough time for the PAT implementation before the marketing authorization application is submitted.

The first PAT based marketing authorisation applications are under work or evaluation. There is very little published information telling how a PAT based application should be prepared and to which level the measurements during batch processing should be taken in order to justify the reduction of chemical release analyses. The final answers to these questions can hardly be given until the procedure has taken shape and more experience is gained concerning the PAT approach. This requires discussions together with the FDA, other authorities, industry, universities, equipment suppliers and other parties.

The FDA has announced that the PAT approach will not be obligatory. On the other hand, the FDA has taken a very active role in presenting the benefits of PAT and motivating industry. There is a possibility that even though PAT will not be officially obligatory, the new approach has to be adopted in order to ensure that the marketing authorization of a new product will be granted in an optimum time frame.

The process analytical technology will be a part of our future and the pharmaceutical industry has to be prepared to adopt it.

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AN IMAGE ANALYSIS APPROACH IN THE PAT FRAMEWORK

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Introduction

The Food and Drug Administration (FDA) has established guidelines for Process Analytical Technologies (PAT) to facilitate the introduction of new technologies for the pharmaceutical industry [1]. The initiative deals with systems for analysis and control of manufacturing processes based on timely measurements of critical quality parameters and performance attributes of raw and in-process materials. Furthermore, PAT involves processes to assure acceptable end product quality at the completion of the process. The scheme strives to acquire real-time control of processes and aims ultimately at continuous quality assurance and greater understanding of processes. Research contributions aiming to improve the efficiency of pharmaceutical manufacturing processes are evidently needed. The FDA in the US has a high priority initiative to develop PAT strategies. Fortunately also many European pharmaceutical companies and authorities realise the need to introduce new technologies and innovative systems in the manufacturing of drugs. For example, the European Directorate for the Quality of Medicines (EDQM) is working on questions how the European Pharmacopoeia can contribute to regulatory assessment of PAT. To further strengthen the situation in Europe efforts in academia in this field are needed. This presentation demonstrates a novel image analysis approach for analysis and control of different phases of development and manufacturing of pharmaceutical solids. The use of the approach in three manufacturing steps is presented.

Methods

Case 1. At-line monitoring of the granule growth in a fluidized-bed granulation process [2,3,4]. In total 34 granulations were made with a bench-scale fluidized bed granulator (Glatt, WSG 5, Glatt GmbH, Binzen, Germany). The aim was to obtain batches with varying end-point particle mean sizes and the intention was to be able to monitor different kinds of particle growth kinetic profiles. The process conditions were planned using a central-composite experimental design. The process variable ranges were found through previous screening studies. The three process variables were altered on three levels: inlet air (T), (30°, 40°, 50°C), nozzle spraying pressure, (1, 1.5, 2 bar) and granulation liquid flow rate (160, 175 and 190 g/min)). Surface images of samples from 34 granulations were continuously captured during the spraying and drying phases of the process and particle size distributions were determined. A parameter called the grey scale difference matrix (GSDM) was derived

from two surface images taken in controlled illumination conditions. The particle size calculation from the surface images was based on a multivariate Partial Least Square (PLS) model between the GSDM and sieve analysis measurements.

Case 2. Prediction of tableting behaviour using surface images of bulk granules [3]. The image information of the end-point samples was also assessed with respect to tableting behaviour in order to predict further processability of the granules. Tablets of 17 batches were compressed using by an instrumented Korsch (EK-0, Germany) single punch tableting machine using flat-faced 9 mm punches. The target crushing strength of tablets was 100 N and the target weight was 250 mg. From each batch 500 tablets were compressed. The weight variation of the tablets was determined using the relative standard deviation of the upper punch force profiles for each tablet. Principal component analysis (PCA) was used to visualize the 12-fraction particle size distribution generated from the images using Simca software (Simca v. 8.0, Umetrics AB, Umeå, Sweden). PCA was utilised to evaluate whether the surface image information can be used to predict tableting behavior of different granules.

Case 3. Analysis of the quality of film-coated tablets [5,6]. The quality of film-coated tablets were evaluated by calculating a surface roughness parameter. Ten (n=10) images of each tablet batch were taken with a resolution 600x800 pixels. The dimensions of the tablet surfaces in the images were 6.2 mm x 4.6 mm. The roughness was measured from a matrix that is formed by the numerical grey-scale values of the digital image. The principal idea is that smooth surfaces have small variations in grey-scale values and the rougher the surface, the larger the grey-scale value variations. Roughness is the arithmetic average of the absolute values of all points (pixels) of the profile.

Results

The introduced approach was suitable in particle size measurements of granules during all process phases and in the monitoring of different kinds of granule growth behaviour. The visual inspection of the granule samples was powerful, enabling representational batch-to-batch comparisons. The tableting behavior of the granules could be predicted directly from particle size information generated from the surface images. Fast screening of tableting properties can be made using the combination of multivariate visualization and image information PCA as a projection method is efficient in data visualization. Roughness values obtained with the optical method can be used in the evaluation the influence of process variables on film-coating tablets.

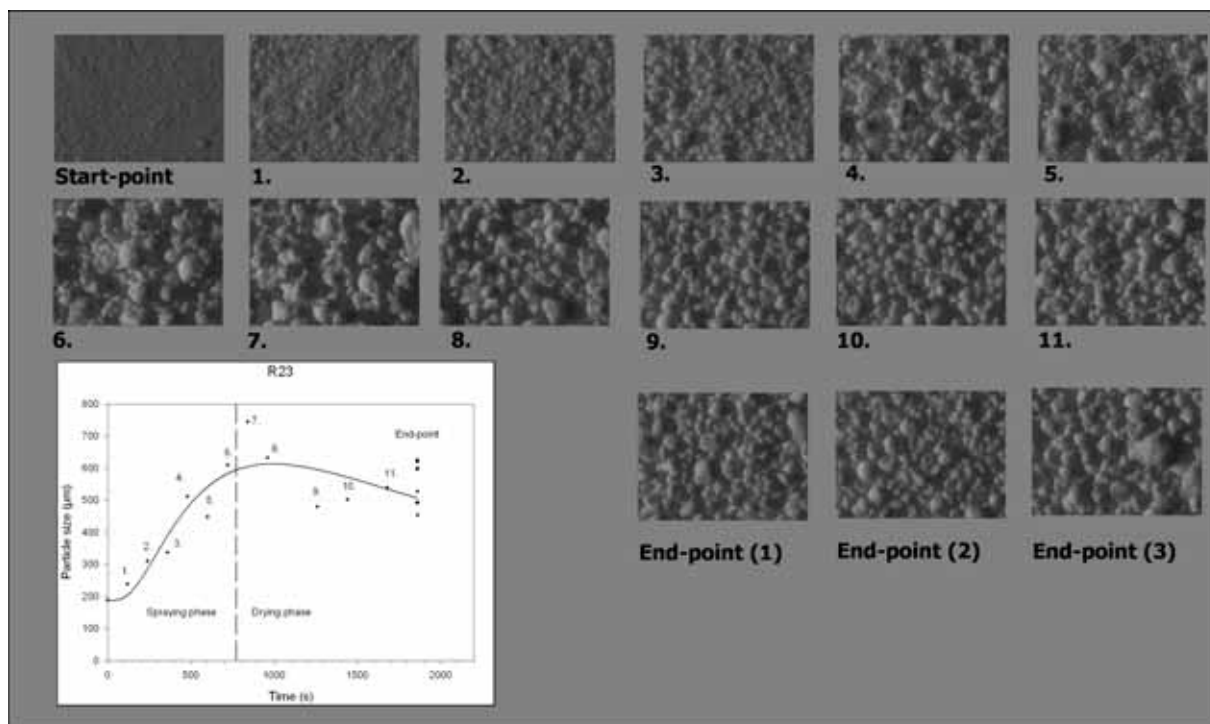


Figure 1. The granule growth of a model batch. Each dot (•) shows the data point for the particle mean size measured from the surface image information. Each numbered dot corresponds to the numbered surface images. Three end-point data points and images are shown together with three replicate data points from end-point sieve analysis (■). The spraying and drying phases of the process are separated with a dashed line (Figure taken from ref. [2]).

In general, the idea of characterization of bulk surface images opens new perspectives for visual characterization of pharmaceutical solids. Development of process analytical technologies aims at improving the efficiency of these processes. The current visual characterization approach can be an effective process analytical tool, once critical quality parameters, and performance attributes of raw and in-process materials are identified. We have shown that the method can be used to assure acceptable end product quality at the completion of the process.

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PROCESS ANALYSIS WITH SPECTROSCOPIC TOOLS

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There is an increasing demand for new approaches to understand the chemical and physical phenomena that occur during pharmaceutical unit operations. Obtaining real-time information from the process opens new perspectives for safer manufacture of pharmaceuticals. However, getting relevant information from these multicomponent systems is not a straightforward task. Recently, U.S. Food and Drug Administration (FDA) has introduced an initiative to address this issue. Process analytical technology (PAT) is a system for developing and implementing new efficient tools for use during pharmaceutical development, manufacturing, and quality assurance while maintaining or improving the current level of product quality assurance [1]. This guideline addresses four critical toolboxes to be utilized:

1. Multivariate data analysis
2. New process analytical tools
3. Process end-point detection
4. Knowledge management

In this presentation, these toolboxes are evaluated in an introductory manner.

Processing-induced changes in the solid-state form can occur during manufacturing for many therapeutic compounds [2]. Most such changes have an impact on product quality or efficacy and there is a growing recognition of the need to detect these physical changes during the manufacturing process. NIR and Raman spectroscopic techniques are well established methods for the discrimination of different solid state forms of drugs and can be easily used for in-line measurements. However, the generation of representative calibration data to produce a quantitative model can be challenging [3-5]. The goal of this research was to investigate the effect of sampling procedure, data analysis methods and instrument configuration on the quality of calibration model, and to compare NIR and Raman spectroscopic methods to X-ray powder diffractometry (XRPD). Dynamic mixing of the powder coupled with a large number of accumulations was required to get a good quality calibration model with spectroscopic tools.

Wet granulation processes are widely used in pharmaceutical industry. Typically, processing is performed with high shear mixer or fluid bed system, and these unit operations are typically complex processes with many interacting process variables. These unit operations

are often “knowledge-based” processes, and a highly experienced operator is needed for successful granulation. Therefore, there is a need for PAT tools in these systems. Near infrared (NIR) spectroscopy has been applied for monitoring different phases of various wet granulation processes [6-10]. In high shear granulation systems, process monitoring has traditionally based on measuring information related to mechanical properties of wet mass, power or torque signal [11]. In this study, NIR spectroscopy together with multivariate data analysis was used to study three phases of high shear granulation. NIR spectroscopy enabled analysis of various phenomena during the high shear granulation process (Fig. 1.). In a multivariate model with spectral information from all process phases, deeper analysis of different phases proved difficult. Three separate models for mixing, spraying, and wet massing were needed to characterize changes during this dynamic process.

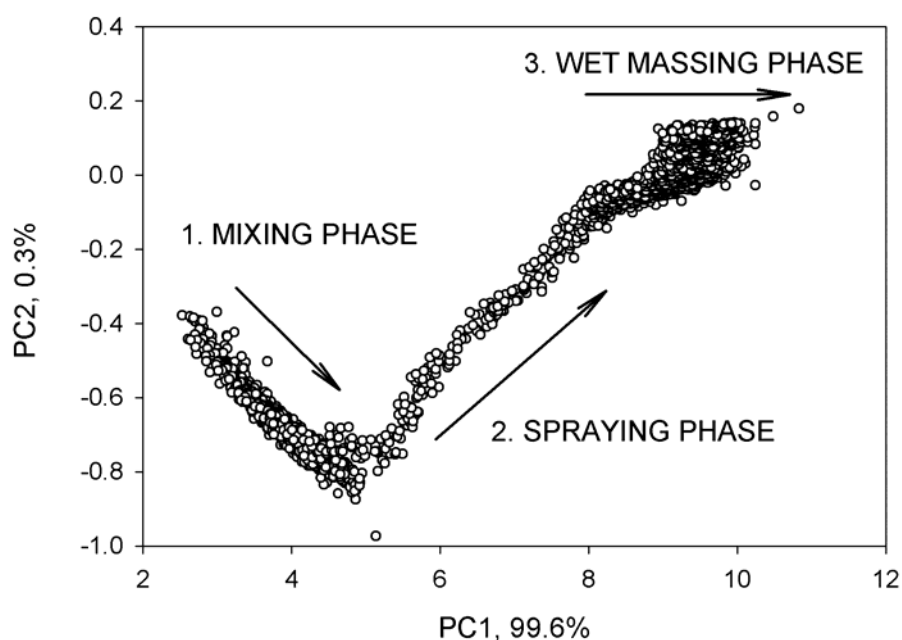


Fig. 1. NIR spectral information during high shear granulation.

While the phenomenon of hydrate formation during wet granulation has been widely documented, the kinetics of the transformation are not well understood and important substance and process variables remain to be elucidated. Furthermore, analytical difficulties often arise due to the need to sample and measure remotely leading to uncertainties regarding the exact kinetic profile. The goal of this work is to address these issues. Firstly, through utilising real-time analytical methods in the form of Raman spectroscopy to obtain representative transformation profiles. Secondly, by comparing and contrasting the behaviour of different hydrates in terms of their intrinsic properties (e.g. solubility, dissolution rate) and the influence of external factors such as seeding and agitation conditions. This approach showed that overall transformation rate from anhydrous to hydrate

form during wet granulation is not only a function of intrinsic properties, but also strongly affected by the history of powder, surface properties, and external factors such as presence of seeds and degree of shear forces.

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SPECTROSCOPIC TECHNIQUES FOR TABLETS

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Several non-destructive and destructive testing techniques can be used to study physical and chemical properties of tablets. In a Tekes COMBIO-project (Varma)¹ our aim is to utilize the data of these methods to build a model for prediction of orally active drug compound releasing from a tablet based on starch acetate.² Of course the model includes many other parameters, e.g. related to particles and compaction method, tablet composition and physicochemical properties of components. The methods utilized in the BioMater Centre include impedance techniques, ultrasound methods, Fourier Transform Infrared Imaging (FTIRI), contact angle and roughness measurements and dynamic mechanical testing. These complementary techniques can provide many parameters and spectra that are related with the structure of tablets and the properties which are relevant in respect to drug release such as a water penetration speed. Based on our preliminary survey with tablets prepared with varying characteristics, the results with new impedance and ultra sound testing setups are reproducible and the data correlate very well with the other parameters of the tablets. Mechanical parameters determined using an Instron 8874 tester are in agreement with the data from a tablet compaction process. Furthermore, contact angle and roughness measurements reveal some relevant surface properties. FTIRI is a very potential technique³ for studying dynamic processes in multi-component systems, because each component can be resolved spatially based on the spectral response. This technique will be utilized especially in the later stages of the project. In this presentation, potential of these different techniques will be discussed with some examples and plans related to process analysis.

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DEVELOPMENT OF NOVEL CYCLODEXTRIN CONTAINING FORMULATIONS FOR SUBLINGUAL DELIVERY OF CANNABINOIDS

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Over the last few years, marijuana or its components, e.g. tetrahydrocannabinol (THC, Fig. 1) and cannabidiol (CBD, Fig. 1), have been reported to counter the symptoms of a broad range of conditions including nausea, pain, various neurological disorders (MS-disease, Parkinson's disease), anorexia, glaucoma and inflammation. The therapeutical use of cannabinoids is, however, limited due to their poor aqueous solubility and high first-pass metabolism. In the present study novel sublingual/buccal formulations for improved delivery THC and CBD were developed by using cyclodextrin technology.

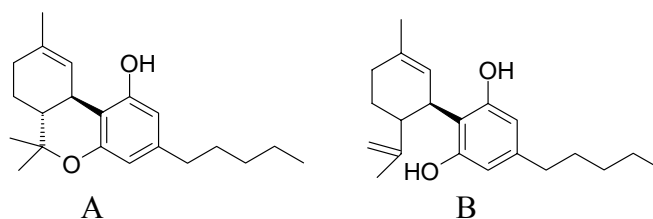


Figure 1: The chemical structure THC (A) and CBD (B).

The complexation of THC and CBD with randomly methylated β -cyclodextrin (RM- β -CD) and natural β -cyclodextrin (β -CD) was studied by using the phase-solubility method. The solid complexes of THC and CBD with cyclodextrins were prepared by freeze-drying (RM- β -CD) or by using the precipitation complexation method (β -CD). The dissolution studies were performed with capsules which all contained 1 mg of THC or CBD. In THC/RM- β -CD and CBD/RM- β -CD formulations the amounts of inclusion complexes equivalent to 1 mg of THC and CBD were 25.7 mg and 12.4 mg, respectively. In CBD/ β -CD formulation the amount of inclusion complex equivalent to 1 mg of THC was 9.1 mg. The in vivo absorption of THC was studied with rabbits. The THC/RM- β -CD-solution (equal to 250 μ g/kg of THC) or THC/ β -CD powder (equal to 250 μ g/kg of THC) was administered sublingually and orally to the anesthetised rabbits. The blood samples were withdrawn at appropriate intervals and the samples were analysed by GC/MS.

The phase-solubility diagrams of THC and CBD with RM- β -CD were classified as Ap-type and the apparent stability constants ($K_{1:1}$, $K_{1:2}$) for 1:1 and 1:2 inclusion complexes were calculated to be $19\,600\text{ M}^{-1}$ and 38 M^{-1} for THC and $484\,000\text{ M}^{-1}$ and 8 M^{-1} for CBD, respectively. With natural β -CD CBD was found to follow B-type phase solubility behaviour, which allowed the preparation of the solid inclusion complexes by using the precipitation complexation method. The dissolution studies showed that from CD containing formulations THC and CBD were fully dissolved in 10-30 minutes. Without CDs the dissolution was significantly slower and THC and CBD were fully dissolved after 3 hours. The in vivo studies showed that sublingual administration of THC/RM- β -CD solution or THC/ β -CD powder increases significantly the bioavailability of THC compared to oral administration. Figure 2 shows the mean plasma concentrations of THC after sublingual and oral administration of THC/RM- β -CD- solution.

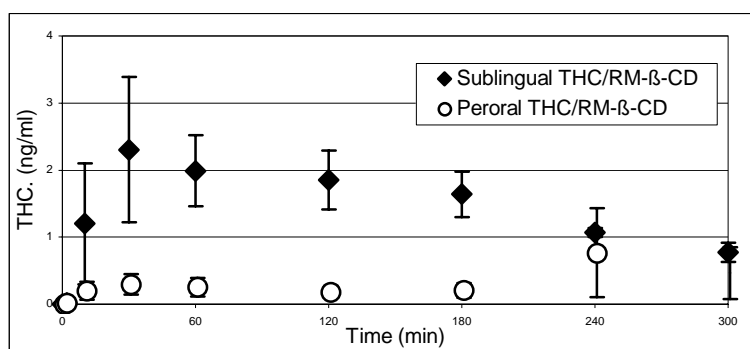


Figure 2. The plasma concentrations of THC after sublingual and oral administration of THC/RM- β -CD-solution (dose equivalent to $250\text{ }\mu\text{g/kg}$ of THC) in rabbits (mean \pm SEM, $n = 4-5$)

The results show that cyclodextrin complexation significantly increases the aqueous solubility and dissolution rate of THC and CBD, which can be used in a development novel sublingual/buccal formulations for cannabinoids. The present study shows also that sublingual administration of THC/RM- β -CD or THC/ β -CD complexes increases substantially the bioavailability of THC compared to oral administration.

POSTERIT

APPLICATION OF GUINIER CAMERA XRPD IN THE QUANTIFICATION OF PHARMACEUTICAL BINARY MIXTURES

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The study of structures of pharmaceutical solids is a very important aspect of pharmaceutical development. X-ray powder diffraction (XRPD) has become the method of choice for the crystallographic characterization of powdered crystalline drug substances. Typical applications of XRPD include qualitative and quantitative phase analysis, evaluation of polymorphism and solvate structures, evaluation of degrees of crystallinity and study of phase transitions. For these applications X-ray diffractometers employing the Bragg-Brentano reflection geometry is the established method.

Another method to measure XRPD patterns is the X-ray powder camera. The method records diffractograms of small powder samples over a wide range of diffraction angles (e.g. $4-100^\circ 2\theta$) simultaneously. An advantageous X-ray powder camera type is the Guinier camera, which employs the transmission geometry and a highly monochromatic $K_{\alpha 1}$ ($\lambda=1.54060 \text{ \AA}$) X-ray beam. These features are to provide better diffraction peak resolution and peak symmetries when compared with the normal $\theta/2\theta$ diffractometers. The small amount of sample required is beneficial for pharmaceutical applications as in most pharmaceutical development phases the amounts produced are small and expensive.

The present study is focused on comparing the Bragg-Brentano method with the Guinier method in the quantification of pharmaceutical phases. In the poster the limits of detection (LOD) for salbutamol sulphate in α -lactose monohydrate formulations are studied. Mixtures of 10, 5, 2, 1 and 0.5 % (w/w) salbutamol and lactose were prepared and measured on Guinier Imaging Plate Camera G670 (Huber) and normal Bragg-Brentano $\theta/2\theta$ geometry diffractometer (Philips) using similar measurement times.

Results show a LOD of ca. 1 % (w/w) of salbutamol for both of the methods. However the sample amount for the Guinier measurement is only 4 % of the amount required for the Bragg-Brentano measurement. According to the results the modern Guinier XRPD camera is a feasible alternative to the traditional diffractometer especially in cases where sample availability is limited.

INTERACTION BETWEEN TWO MODEL DRUGS AND POLY (L-LACTIDE) POLYMER IN NANOPARTICLES

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Introduction

A drug and its polymeric carrier can be either crystalline or amorphous in polymeric nanoparticles, which is determined by preparation method used and interactions between the drug and the polymer [1]. The state of the drug and the hosting polymer affect entrapment, stability and release behavior of the system.

Materials and methods

Nanoparticles were prepared by a modified nanoprecipitation method [2]. The polymer used was poly(l-lactide) (PLA) (M_w 2000 Da) and the model drugs were salbutamol sulfate and beclomethasone dipropionate. The drug:polymer ratio in the nanoparticles was 1:10. Crystalline state and thermal behavior of the pure components and the drug containing nanoparticles were determined by x-ray powder diffraction (XRPD) theta-theta diffractometer and differential scanning calorimeter (DSC), respectively.

Results and discussion

The preparation method and incorporation of drugs into nanoparticles reduced the crystallinity of the polymer (Table 1). Salbutamol sulfate was dissolved in the polymer and acted at least as a plasticizer. There was a probable electrostatical interaction between salbutamol sulfate and the polymer. Beclomethasone dipropionate remained mainly crystalline leading to decreased crystallization of the polymer.

Table 1. Results of XRPD and DSC experiments.

Sample	Crystallinity (%)	Glass transition temperature of PLA (°C) ¹	Melting temperature of PLA (°C) ¹
Polymer	59	43.2	151.9
Empty nanoparticles	54	41.5	151.0
Salbutamol nanoparticles	55 ²	38.9	150.3
Beclomethasone nanoparticles	48 ³	43.4	147.9

¹ Measured by second run after melt quenching of the sample.

² Salbutamol sulfate caused 0 % of the crystallinity.

³ Beclomethasone dipropionate caused 13 % of the crystallinity.

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RAMAN SPECTROSCOPY FOR DETERMINATION OF DRUG RELEASE FROM POLYMER FILM

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The aim of the present study was to develop a rapid and sensitive method for the quantification of a drug released from a polymer film. We explored the potential application of Raman spectroscopy for the rapid quantification of the drug amount.

Sodium salicylate (2,4 % w/w) containing polycaprolactone (PCL) films were prepared by solvent casting, as described earlier¹. The films (ca. 20-35 mg) were incubated in phosphate buffer pH 7,4 at 37°C. Amount of sodium salicylate in the films as a function of incubation time (i.e. a remaining drug content) was measured with a CCD-Raman spectrometer developed by VTT Electronics, Finland². A spectral band centered at 805 cm⁻¹ was chosen for the sodium salicylate determination (Figs. 1-2). The spectra were baseline corrected and band areas were integrated between 792-820 cm⁻¹ and peak area between 895-930 cm⁻¹ was used as a reference. The concentration of the released drug was determined by UV-spectrometer (254 nm).

Our results suggest the drug release from the polymer film may be determined quickly and simply by Raman spectroscopy

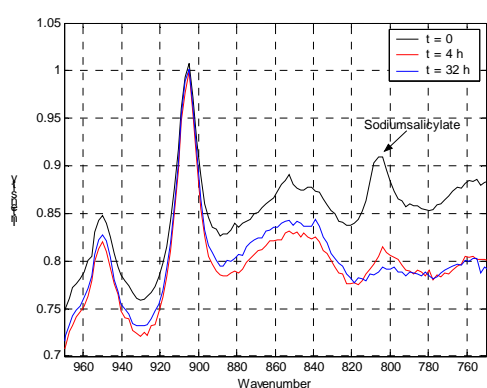


Figure 1. Decrease in sodium salicylate signal intensity as a function of time. The sodium salicylate was mixed with PCL.

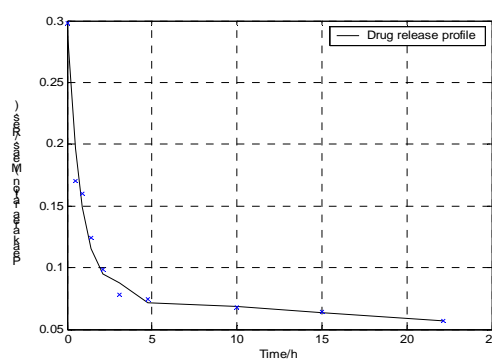


Figure 2. Decrease in amount of sodium salicylate remaining in PCL film as a function of time

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A SIMULATION METHOD TO PREDICT THE PROGRESS OF INTERNAL HUMIDITIES OF POWDER CHAMBERS EQUIPPED WITH A DOUBLE-BARRIER-DESICCANT SYSTEM

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Perhaps the most common and simplest way to protect the product from moisture is to utilize protective packaging material and include a desiccant inside the package, if necessary. The set-up utilized normally is the so-called single-barrier-desiccant system where the desiccant material (normally water-insoluble adsorbent-type) is packed in a very permeable or porous container, which does not constitute any barrier against moisture transfer, and where the desiccant material is in equilibrium with the humidity of the head space of the package. The only barrier against the moisture transfer is the walls of the package itself. However, the set-up has certain disadvantages, one being the fact that the internal humidity of the package will initially be low if dry desiccant is loaded in the package. In addition, the humidity can reach the environmental level (RH_{env}) quite rapidly if the desiccant capacity is exhausted.

A solution to regulate more effectively the internal humidity could be the use of the so-called double-barrier-system where the water molecules have to penetrate through both the powder chamber wall and the desiccant container wall before they will be scavenged by the desiccant. The relative values of the permeabilities for the powder chamber and the desiccant container are crucial, as are their absolute values, and the amount of the desiccant.

In the present study, the simulation method for the system was developed and applied to demonstrate the effects of various parameters on the progress of the internal humidity of the powder chamber (RH_{ch}). On the basis of the simulations, it is easy to estimate the appropriate values for, e.g. the permeabilities of the desiccant container (P_{con}) and the powder chamber (P_{ch}), plus the desiccant amount (m_{desc}), so that the desired humidity can be controlled within a specified range for the defined time (Fig. 1).

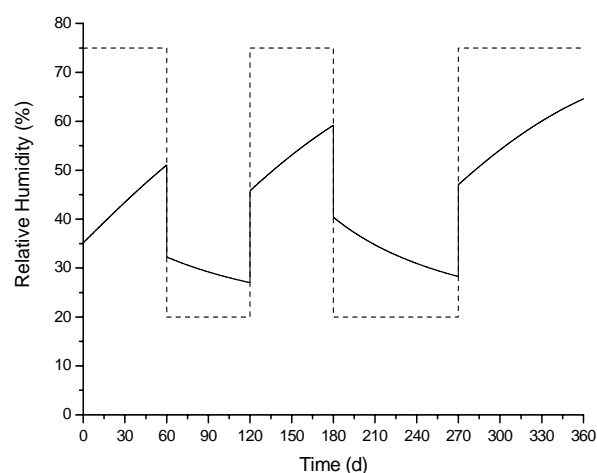


Fig. 1. The regulation effect of the double-barrier-desiccant system on the RH_{ch} (solid line) against the changes in RH_{env} (dashed line) between 20% RH and 75% RH at 25°C when $P_{ch} = 20$ ng/(min %RH), $P_{con} = 40$ ng/(min %RH), $m_{desc} = 500$ mg (not including 9 w-% water) and $V_{ch} = 2.42$ ml.

PHYSICAL CHARACTERIZATION OF ERYTHROMYCIN– CELLULOSE ACETATE PHTHALATE MATRIX FILMS

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Purpose

A number of pharmaceuticals are unstable in the acidic environment of the stomach. Hence, various technological approaches are applied to prevent the degradation of such drugs in the gastric fluid. In this study, the drug–polymer matrix films possessing acid-resistant properties were developed. The physical interactions between a model drug, erythromycin base, and an enteric polymer, cellulose acetate phthalate (CAP), were also investigated.

Methods

For film casting, the calculated amounts of the drug were dissolved in 8% (w/w) polymeric solution to achieve drug loading in the films of 25–55% (w/w). Afterwards, the drug-containing solutions were poured onto Teflon[®] moulds and dried at room temperature (21±2°C) for 24 hours. XRPD, DSC and SEM were used to study the physical properties of the films obtained.

Results

The XRPD data revealed that the drug was transformed in an amorphous form during processing. This was also confirmed by the DSC traces for the films obtained, each of which demonstrated the single T_g in the temperature range of 140–160°C. Morphologically, the films were rather homogeneous.

Conclusions

Erythromycin was found to be molecularly dispersed within the polymeric matrices studied regardless of the drug loading concentrations. This finding suggests that CAP has a potential to inhibit self-association of erythromycin, apparently, as a result of the specific intermolecular interactions between the drug and polymer.

CRYSTALLIZATION INHIBITION OF AMORPHOUS ERYTHROMYCIN IN SOLID DISPERSIONS

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Purpose

A growing interest to amorphous solids in pharmaceutical research is attributed to their useful properties such as increased bioavailability because of their higher water solubility and sometimes improved tableting behavior of the material. However, an amorphous form is known to be metastable in relation to a crystalline form. In this study, the solid dispersions (SDs) of erythromycin base and polyvinylpyrrolidone (PVP) were prepared and the influence of content of PVP on their physical stability was investigated.

Methods

SDs were prepared by co-evaporation method. Evaluation of the properties of the SDs was performed using DSC, XRPD and SEM. For stability study, the representative samples were placed in a controlled temperature cabinet at 25°C (60% RH) and 40°C (70% RH). The physical state of the drug in the SDs was evaluated after 3 and 6 months by DSC and XRPD.

Results

The DSC curves revealed neither endothermic event corresponding to the melting of the drug nor exothermic peak attributable to the recrystallization. Though a wide endotherm due to water evaporation becomes clearly visible in some samples, no peak was appearing in the angle of diffraction in the XRPD patterns for the SDs throughout the storage period.

Conclusions

It was found that PVP has significant inhibitory effect on spontaneous crystallization of the amorphous erythromycin in the solid state at both elevated temperatures and high relative humidity.

Acknowledgements

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PREFORMULATION AND FORMULATION STUDY OF N-ACETYL-D-GLUCOSAMINE

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The aim of this study was to design a site specific, controlled release tablet of a model compound of drug, N-acetyl-D-glucosamine (NAG), by using starch acetate (SA) as a matrix former. The matrices were designed to release NAG in 2-4 hours, starting already in stomach and mainly at the upper part of the small intestine.

Physical and powder properties of NAG and SA were studied by using DSC, FT-IR, UV-Vis, He-pycnometer, SEM, laser diffraction and Karl Fisher titration. NAG release characteristics were determined by USP *in vitro* dissolution method. Dissolution mediums were HCl-solution (pH 1.2) for the first two hours, and water for the next 2 – 24 hours. Plackett-Burman screening design of experiment was used to evaluate the effect of compaction rate, type of compression, tablet porosity, SA particle size, amount of drug in the tablet and tablet mass on release rate and mechanism of NAG. After that, drug release was optimised by using a full 2-level factorial design. The factors studied were the amount of drug in the tablet and tablet porosity.

Based on preformulation studies, NAG was found to be flaky shaped, crystalline and anhydrous material (m.p. 213.1 ± 1.5 °C and particle density 1.48 g/cm³). The physicochemical properties of SA were found to be similar to those reported earlier [1]. No interactions with SA were observed in the stability studies, so it could be concluded that NAG was compatible with SA. The dissolution experiments showed that drug release mechanisms varied from Fickian diffusion to anomalous or even zero-order transport. However, it was not possible to model nor predict the effect of the variables on the release mechanism reliably enough. Instead, the drug release rate could be modelled ($r^2=0.999$) and predicted ($Q^2=0.998$) well. The most significant factors affecting the release rate were the amount of NAG in the tablet ($p<0.01$), the porosity of the tablet ($p<0.01$), the compression speed ($p<0.01$) and the tablet mass ($p<0.01$). Hydroxypropyl methyl cellulose (HPMC) and ethyl cellulose (EC) were also used as matrix formers for comparison.

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THERMOPOROMETRY AS A METHOD FOR DETERMINATION OF DRUG LOAD IN POROUS SILICON

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Porous silicon (PSi) has a wide variety of applications. Recently the PSi biomedical applications have also emerged, e.g. drug delivering vehicle applications. The amount of drug load in PSi can be determined by DSC with employing thermoporometry.

The p⁺-type PSi (100) was electrochemically etched in HF (40 %)- ethanol mixture (HF:EtOH 1:1) with current density of 50 mA/cm². The PSi microparticles were prepared by ball milling and sieved to the appropriate particle size of < 38 μm. After milling the microparticles were rinsed in HF – ethanol mixture to restore hydrogen termination. Post treatments of thermal oxidation or thermal carbonization (850 °C) were also used.

Different drug substances were loaded into PSi microparticles with drug – ethanol solution by one hour elutriation. The suspension was filtered with a teflon membrane filter and dried at suitable temperatures. The amount of loaded drug was measured with Pyris Diamond DSC (PerkinElmer) with a constant heating rate of 2 °C/min. Closed Al-pans and pure nitrogen gas flow were used in the measurements, correspondingly.

The drug substances in crystalline form can be detected from the pores by DSC as shown in Fig. 1. Ibuprofen shows sharp peak when melting from the surface of nonporous Si (curve (a)). When loaded in PSi the melting peak broadens and melting temperature decreases. Different treatments influence on the drug load in pores as shown in figure on curve (b) and (c). Especially the thermally-carbonized PSi seems to suitable for drug loading applications.

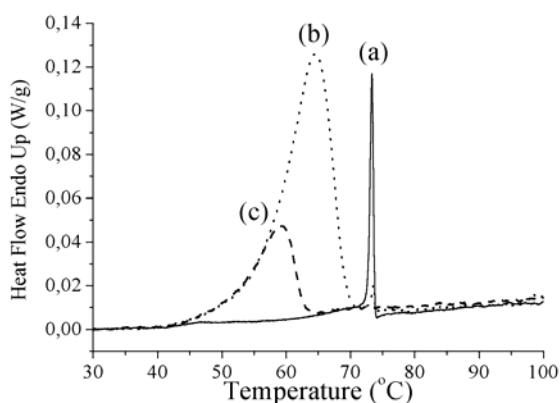


Fig. 1. DSC data from ibuprofen loaded on nonporous Si (a) and in thermally-carbonized PSi microparticles (b) and (c).

FORMULATION OF LOW MOLECULAR WEIGHT PLA NANOPARTICLES BY MODIFIED NANOPRECIPITATION METHOD

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The main focus of this work was in the identification and optimization of the key process variables in formulating the PLA (M_w 2 000 g/mol) nanoparticles by a modified nanoprecipitation method as well as the stability studies of the drug substance during and after the particle formation [1]. As a model drug substance was used sodium cromoglycate. The main variables studied were the amount of the stabilizer (propylene glycol, 25-500 mg), mixing speed (50-400 rpm) and mixing time (1-30 min) during and after the fusion of the inner and outer liquid phases, and the adding method of the inner phase to the outer phase (drop-by-drop, pouring). The stability of the drug substance during and after the particle formation was studied by differential scanning calorimetry (DSC).

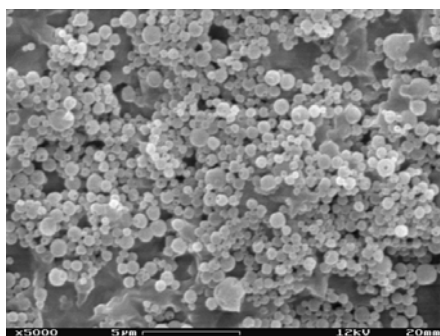


Figure 1. PLA nanoparticles.

This study showed that exact knowledge of materials and process variables is crucial for the successful formation of nanoparticles from the low molecular weight PLA (M_w 2 000 g/mol). Especially, the amount of stabilizer needs to be high enough. Also the viscosity of the inner and outer phases, as well as the mutual diffusional properties of the solvents, which may be affected by solvent selection and mixing conditions, play an important role in

the formulation of nanoparticles. From the stability studies by DSC, it was obvious that both the drug substance, sodium cromoglycate, and the PLA polymer were in unaltered form in the nanoparticle formulation.

ACKNOWLEDGEMENTS

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EFFECT OF THE AMOUNT OF OXAZOLINE LINK ON THE EROSION OF THE 2,2-BIS(2-OXAZOLIN) LINKED POLY- ϵ -CAPROLACTONE

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Our earlier studies have shown that when compared to poly- ϵ -caprolactone (PCL), the erosion of 2,2-bis(2-oxazoline) linked poly- ϵ -caprolactone (PCL-O) is faster in simulated intestinal fluid (SIF) (pH 7.5, pancreatin present) and macromolecule release is accelerated by enzyme enhanced erosion [1]. The aim of this study was to evaluate the effect of the amount of oxazoline link on erosion rate of the solvent casted PCL-O films in SIF and PBS (pH 7.4).

The molecular weights (Mw) of studied polymers varied between 34 800 and 87 500 g/mol. In cases of PCL-O 1000, 5000 and 10 000 polymers, the values represent the number average molecular weights (Mn) of PCL blocks (g/mol). Weight loss of PCL-O films increased in SIF with an increase in amount of oxazoline (Fig 1). The rate of the weight loss was not affected by molecular weight of PCL-O. No substantial weight loss was observed for PCL or PCL-O films during incubation for 1 month in PBS (data not shown). It can be concluded that the erosion rate of PCL-O can be controlled by the amount of the oxazoline link.

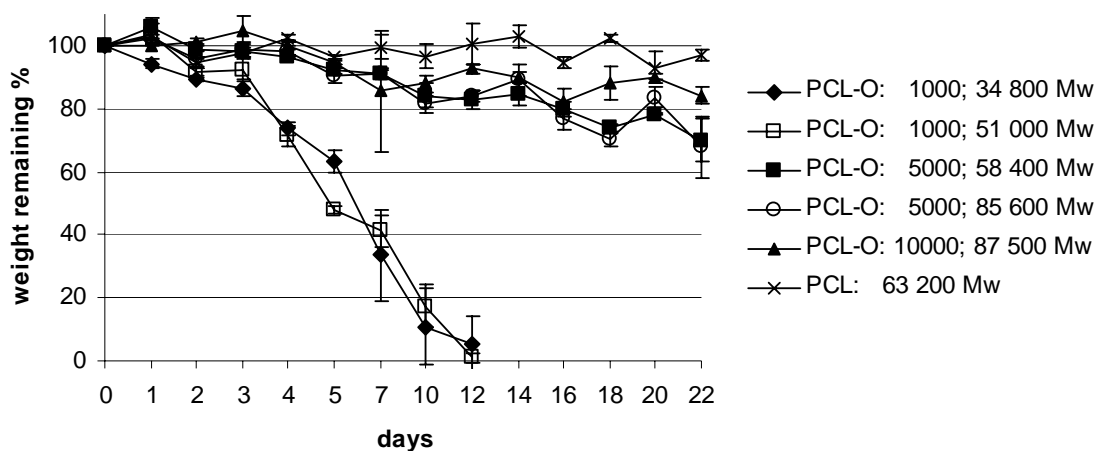


Fig 1. Percentage of remaining weight of PCL and PCL-O films incubated in simulated intestinal fluid at 37 °C. Mean \pm SD are shown (n=3)

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EFFECTS OF INCORPORATED DRUGS ON DEGRADATION OF NOVEL 2,2-BIS(2-OXAZOLINE) LINKED POLY(LACTIC ACID) FILMS

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It is well-known that the physicochemical properties of incorporated drugs strongly affect the degradation rate of poly(lactide). The objective of this study was to evaluate the effects of neutral, basic and acidic drugs on the hydrolytic degradation rate of the novel 2,2-bis(2-oxazoline) linked poly(lactic acid) (PEA), which have been recently introduced for drug delivery.

Three different model drugs (2% w/w; neutral guaifenesin, acidic sodium salicylate or basic timolol) were incorporated into solvent cast poly(*D,L*-lactide) (PDLLA) and PEA films. The degradation study was carried out in PBS (pH 7.4, 37°C); the resulting decrease in molecular weight (M_w and M_n) was determined by size exclusion chromatography and the weight loss of films was measured. Drug releases of guaifenesin, sodium salicylate and timolol from PDLLA and PEA films were examined in PBS (pH 7.4, 37°C).

The results are summarized in the table showing the molecular weights and percent of weight remaining of polymer films after 12 and 26 weeks immersion in PBS (pH 7.4). And also, the amounts of released drug (%) from polymer films in PBS (pH 7.4) after 1, 5 and 10 weeks.

Polymer	Drug	After 12 weeks		After 26 weeks		Drug released in		
		M_w	wt%	M_w	wt%	1 wk	5 wk	10 wk
PDLLA	Drug-free	92 100	88	87 400	90	-	-	-
	Guaifenesin	96 400	94	73 300	93	21.6%	30.7%	34.0%
	Sodium salicylate	53 700	92	22 800	60	38.9%	47.3%	52.5%
	Timolol	17 900	91	11 400	21	1.8%	2.3%	16.6%
PEA	Drug-free	8 900	82	4 900	54	-	-	-
	Guaifenesin	11 400	81	-	-	7.7%	11.9%	80.1%
	Sodium salicylate	17 400	83	8 400	48	50.3%	62.9%	90.3%
	Timolol	20 300	86	7 400	52	3.5%	5.5%	43.6%

As a conclusion, all incorporated drugs enhanced clearly the degradation rate of the PDLLA films. Instead, the degradation rate of the PEA film was affected slightly by incorporated drugs. In fact, the incorporated drugs tended to slow down the degradation of the PEA films.

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