Investigations in the mechanisms of encapsulating liquid active ingredients via extrusion processing

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List of abbreviations

a	time interval of the recording rate for torque [s]
AA	arachidonic acid
AI	active ingredient
aOT	orange terpene amount within the extrudates [%]
API	active pharmaceutical ingredient
AS	part of amorphous sucrose within the amorphous fraction [%]
aTOC	α-tocopherol amount within the extrudates [%]
a_W	water activity
AWC	added water content [%]
BT	barrel temperature [°C]
cc / CC	crystalline content [%]
c_p	heat capacity
dCAR	decomposition products of carvacrol
DCM	methylene chloride / dichloromethane
DE	dextrose equivalent
$\Delta\delta$	Euclidean distance
Δh	specific enthalpy of fusion [J/g]
ΔH	enthalpy of fusion / melt enthalpy [mJ]
δ_d	dispersion parameter
δ_p	polarity parameter
δ_h	hydrogen bonding parameter
DHA	docosahexaenoic acid
DoE	design of experiments
DSC	differential scanning calorimetry / calorimeter
EO	essential oil
EU	European Union
F_d	contribution to cohesive energy from dispersion forces
FDA	U.S. Food and Drug Administration
F_p	contribution to cohesive energy from polarity
F_h	contribution to cohesive energy from hydrogen bonds
FR	feed rate [kg/h]
GC	gas chromatography
GRAS	generally recognized as safe
GSS	glassy solid solution
GT	Gordon & Taylor (equation)
HDFC	hot die face cutting
HME	hot melt extrusion
HMWC	high molecular weight carbohydrate
i	intensity (for XRPD) or structural group (for solubility parameters)
IU	international unit
IUPAC	International Union of Pure and Applied Chemistry
k	Gordon Taylor constant

LMWC	low molecular weight carbohydrate
m	mass fraction [g or kg]
MC	microcapsule
μ-CT	X-ray micro computerised tomography
MD	maltodextrin
MEC	maximal encapsulation capacity
MSDS	material safety data sheet
n.a.	not analysed
N2	liquid nitrogen
OT	orange terpene content [%]
p	vapour pressure [Pa]
Ph.Eur.	European Pharmacopoeia
PT	product temperature [°C or K]
PVP	polyvinylpyrrolidone
Q^2	coefficient of prediction
r.h.	relative humidity
R^2	coefficient of determination
rAI	retention of the (bio)-active ingredients [%]
RE	refrigeration [2 – 8 °C]
rOT	retention of the orange terpenes [%]
rTOC	retention of α-tocopherol [%]
ρ	density
rLIM	amount of limonene within the retained orange terpene fraction [%]
RP	repeatability
RS	rotation speed [1/s or 1/min]
RT	room temperature [25 °C]
s	solubility of sucrose in 1 g of water [g]
SME	specific mechanical energy [Wh/kg]
SP	solubility parameter
SS	screw speed [min^{-1}]
sTOC	α-tocopherol percentage of the surface [%]
SUC	(crystalline) sucrose [%]
t	process time [s or min]
τ	torque [Nm]
Tg	glass transition temperature [K or °C]
TOC	α-tocopherol content [%]
TSE	twin screw extruder
V	molar volume at the liquid state [cm^3/mol]
w	weight fraction [-]
WC	sample water content [%]
WCA	water content within the amorphous fraction of the sample [%]
XRPD	X-ray powder diffraction

CHAPTER I

Introduction

1. Liquid active ingredients

1.1. Introduction

The term "active ingredient" (AI) is used for a large range of diverse substances and chemicals for various applications. However, it is not clearly defined. Daughton and Ternes (1999) used it for ingredients in pharmaceuticals and personal care products. Additionally the term is applied for substances in crop protection products, herbicides, insecticides, and fungicides (Jeschke, 2004), as well as for flavours, vitamins, minerals, probiotic microorganisms and diverse bioactive compounds in food products (Ubbink and Krüger, 2006). All these products are directly or indirectly used to improve quality of life. The AIs are the main reasons, that these products achieve their significant effects.
The AIs in pharmaceuticals are called "active pharmaceutical ingredients" (API) and are defined in the International Conference on Harmonisation (ICH) Guideline Q7 as follows: "Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body." (ICH Expert Working Group, 2000). A great majority of APIs is delivered to the patient in the solid state as part of a solid dosage form of a marketed product (Morissette et al., 2004). The solid state provide stability and easy handling of the API and the final product. However, there is the minority of liquid APIs, too. Many of these APIs are used as AIs for other applications, too. The processing, handling, and application of these liquid AIs is challenging. Within this thesis a processing technique - extrusion - is investigated to obtain solidified / encapsulated liquid AIs and thus to improve handling and application. But first the group of liquid AIs is described in more detail, beginning with the class of essential oils (EO).

1.2. Essential oils (EO)

1.2.1. Multi component systems and major components

EOs are multi component systems of 20 to 60 substances from plants (Bakkali et al., 2007). Frequently 1 to 3 substances are the major components of an EO with an amount higher than 85 % (Bakkali et al., 2007, Burt, 2004). These ingredients are lipophilic, volatile, of low molecular weight, and own a terpene, terpenoid or phenol-derived structure (Bakkali et al., 2007). Approximately 3,000 EOs are known, whereas about one-tenth is in use for industrial applications (Bakkali et al., 2007, Burt, 2004). EOs are used as flavourings for foodstuffs and as fragrances for perfumes and cosmetics due to their various tastes and odours. Flavours, described as organic substances with a molecular weight of 50 to 300 Da and a high

volatility with boiling points of 20 to 250 °C (Uhlemann & Reiß, 2010) correspond with the molecules found in EOs. Furthermore, for many EOs and their ingredients antibacterial, fungicidal, insecticidal, and antiparasitical effects were proven (Bakkali et al., 2007, Burt, 2004, Hammer et al., 1999). Thus, these EOs are used for pharmaceutical and agriculture purposes, as well as for food protection. Orange terpenes, a multi component EO, and carvacrol, a substance with a defined structure, are selected as liquid model AIs for this thesis.

1.2.2. Orange Oil, orange terpenes, limonene

For decades orange oil has been used for the flavouring of foodstuffs (Anandaraman & Reineccius, 1986). Insecticidal properties were reported, too (Ezeonu et al., 2001). 50 years ago 24 terpenes and sesquiterpenes were identified within cold-pressed orange oil (Hunter & Brogden, Jr., 1965). Nowadays more than 100 natural compounds are identified, whereas 95 volatile components are known. 55 are aroma active (Liu et al, 2012, Högnadóttir & Rouseff, 2003). The monocyclic monoterpene limonene (Fig. 1) is the main ingredient of various types of essential orange oils with amounts higher than 90 % (Högnadóttir & Rouseff, 2003).

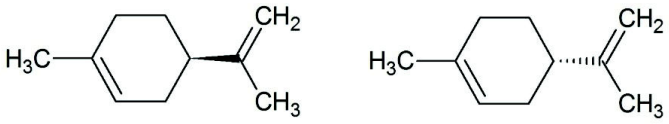

Fig. 1: D-(+)-limonene and L-(-)-limonene (IUPAC: 1-Methyl-4-(1-methylethenyl)-cyclohexene).

Limonene is listed in the EU as flavouring substance in or on foodstuff (EU Commission Decision No 2232/96) and has been used for food applications for years (Chen et al., 1986). Furthermore it was tested for medicinal usage, too (Sun, 2007). Limonene can easily be oxidized, resulting in a strong chemical off-taste (Liu et al., 2012, Uhlemann & Reiß, 2010). The shelf life of a product containing an orange EO is increased by the protection of limonene against oxidation and degradation. The manufacturing process of this product, e.g. extrusion, can lead to limonene degradation, too. The maintaining of the complete limonene amount during and after processing is an important quality feature. Thus, orange terpenes with the main ingredient limonene are a suitable model AI.

1.2.3. Carvacrol

Carvacrol (Fig. 2) is a main component of the EOs of thyme, origanum, savory, and majorana with amounts up to 74.4 % (De Vincenzi et al., 2004).

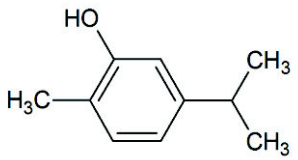

Fig. 2: Carvacrol (IUPAC: 2-Methyl-5-(1-methylethyl)-phenol)

The monoterpenoid phenol is antibacterial (Baydar et al., 2004, Burt, 2004) and has also antifungal, phytotoxic, and insecticidal properties (Kordali et al., 2008). Furthermore antioxidant activity and cyclooxygenase-2 suppression were reported (Hotta et al., 2010, Yanishlieva, et al., 1999). Like limonene, carvacrol is used in the EU in or on foodstuff as flavouring substance (EU Commission Decision No 2232/96) and is additionally listed in the European Pharmacopoeia as reagent (European Pharmacopoeia 7.7). It is used as model for liquid AIs with a defined structure in this thesis.

1.3. Unsaturated fatty acids and vitamins

Besides the essential volatile oils, there are some other liquid non-volatile substances with medicinal effects or biological activity. These are some unsaturated fatty acids and some vitamins like phylloquinone (vitamin K_1), the menaquinone substances (vitamin K_2), and the vitamin E substance group. Relevant unsaturated fatty acids are the ω-3 and ω-6 fatty acids, whereas α- and γ-linolenic acid, linoleic acid, docosahexaenoic acid (DHA) and arachidonic acid (AA) are some of the most important substances. These acids are essential for e.g. cell membrane functions, activity of the central nervous system, and brain growth (Innis, 1991). DHA is important for healthy foetus growth, whereas AA is needed as a precursor for the development of prostaglandins and leukotriene and thus for inflammatory reactions (Horrocks & Yeo, 1999, Needleman et al., 1986). Vitamin K is used for the synthesis of plasma clotting proteins and for the proteins important for bone metabolism (Shearer, 1995). Tocopherols and Tocotrienols belong to the vitamin E substances, whereas α-tocopherol frequently occurs in nature (Meydani, 1995, Pongracz et al., 1995). α-Tocopherol has three chirality centres, leading to eight different stereoisomers. All isomers together are called all-rac-α-tocopherol. The isomer with the highest biological activity is (RRR)-α-tocopherol (Fig. 3).

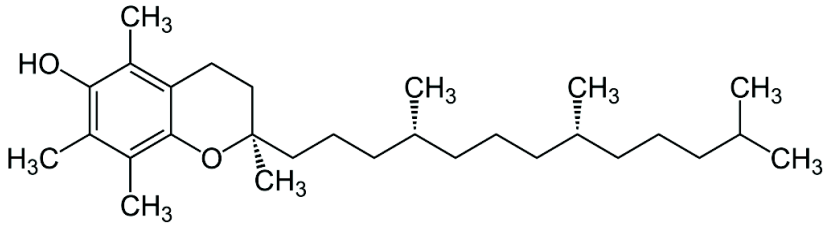

Fig. 3: (RRR)-α-tocopherol

The international unit system (IU) is used for the dosage of the different tocopherol substances. Thereby one IU is congruent with 1 mg of synthetic all-rac-α-tocopheryl acetate, 0.67 mg of the natural (RRR)-α-tocopherol, or with 0.74 mg (RRR)-α-tocopheryl acetate (Institute of Medicine, 2000). Tocopherols are ingredients of the cell membrane and have antioxidant activity (Meydani, 1995, Pongracz et al., 1995). Vitamin E supplementation was investigated for treatment of various chronic and cardiovascular diseases and cancer (Meydani, 1995). However, high dosage supplementation (≥ 400 IU/d) increases all-cause

mortality and should be avoided (Miller et al., 2005). Tocopherols are sensitive to heat and UV exposure (Sabliov et al., 2009). Furthermore processes like cooking extrusion lead to a decreasing tocopherol content (Suknark et al., 2001). Thus all-rac-α-tocopherol is a suitable model AI for non volatile oils. It is selected as third and last AI for this thesis.

1.4. Pharmaceuticals and agrochemicals

Finally, there are some high potential liquid substances, which are used as active ingredients for pharmaceutical and / or diverse agriculture products. Benzyl benzoate is used for treatment of human scabies (Antiscabiosum® 25 % emulsion). The high explosive glycerol trinitrate (Nitrolingual® spray) leads to immediate vasodilation in the event of angina pectoris attacks. The API simethicone (e.g. Espumisan® gold soft capsules, Lefax® extra lemon fresh granules, Simethicon-ratiopharm® 85 mg chewable tablets, Sab simplex® suspension) serves as carminative and degaser, whereas tetrahydrocannabinol (Sativex® spray) is used for treatment of spasticity of multiple sclerosis patients. The fungicides fenpropimorph and propiconazole are approved as plant protection products. Furthermore the chloroacetanilide metolachlor, a mixture of four stereoisomers, and the fatty acid nonanoic acid serve as herbicide. Diverse other liquid substances, like carbosulfan, dichlorvos, disulfoton, and parathion are used as insecticides. None of these high potential AIs is used in this thesis. But in order to provide an almost exhaustive overview about liquid AIs, these pharmaceutical liquids are mentioned, too. To sum up this section, various liquid AIs are available for diverse pharmaceutical, food, agrochemical, and / or personal care applications. Often a solid (dosage) form is desired for the products (see section 3). Thus a solidification of the liquid AI is required and discussed in the next section.

2. Solidified liquid active ingredients

2.1. Advantages of solidification

The handling and application of liquid AIs often is challenging, due to the described (water vapour) volatility, heat sensitivity, sensory changes, and / or poor oxidation resistance of these substances. Products with a short shelf life will be obtained. This disadvantage can be overcome for many fields of application by solidification of the liquid AIs to powders or granules. The final products should provide easy handling, simply dosing, and a long shelf life. The powders and granules should be free flowing. Agglomeration should be prevented. Another main advantage of solidification is the tailoring of the AI release properties, dependent on the desired product properties (Parris et al., 2005, Martin et al., 2010, Sansukcharearnpon, et al. 2010). As described later in section 3, different products require various AI releasing profiles. Some products should release the AI within minutes, whereas others should release the AI continuously during days or weeks. Thus solidification could also lead to new fields of application.

A further advantage of solidification is the improved safety of some AIs, which lead to an easier handling. Some liquids are highly flammable, which can be skipped by solidification (Sansukcharearnpon, et al., 2010). This is also important for this work, due to the properties of the used orange terpenes and the main ingredient limonene (MSDS DL-limonene, 2013). Additionally limonene leads to skin- and / or mucosa irritations, allergic skin reaction, and is environmentally harmful, whereas carvacrol, as a corrosive liquid, could cause skin burns.

All these advantages of solidification lead to a broad range of applications, besides pharmaceutical usage. Solidified liquid AIs are used in home and consumer care products, for insecticides and repellents, for food packaging, in food products and teas, and of cause in pharmaceuticals and dietary supplements, due to their taste, odour and / or pharmaceutical properties or biological activity. A short overview about the different fields of application is given in section 3.

2.2. Structure of solidified liquid active ingredients

The obtained structure of solidified liquid AIs mainly depends on three facts: The AI, the matrix material, and the processing technique. Various types of structures are mentioned in literature depending on the fields of application. For encapsulated food products various terms were reported. Simple, irregular, multi-wall, multi-core, and matrix microcapsules were named by Gibbs et al. (1999). Uhlemann and Reiß (2010) differentiated between matrix particle and microcapsule, whereas Madene et al. (2006) distinguished between a microcapsule and a microsphere where the active compound is dispersed in a polymer network. The illustration of this microsphere resembles the matrix particle of Uhlemann

and Reiß (2010) and the multi-core microcapsule of Gibbs et al. (1999). Furthermore the matrix microcapsule of Gibbs et al. (1999) seems to be one homogeneous phase, whereas the matrix particle of Uhlemann and Reiß (2010) has two phases. Furthermore Zuidam and Shimoni (2010) defined a reservoir and a matrix type of microcapsule. In conclusion there are several arbitrary and overlapping definitions, which were already noted decades ago (Versic, 1988). Formulations in the pharmaceutical field are defined according to IUPAC definitions (Vert et al., 2012). Thus two types of structures are differentiated in this thesis. A microcapsule (MC) is defined as a system of at least two phases. The liquid AI is surrounded by a solid phase of the wall / shell / matrix material. In this thesis the solid phase is generally called matrix material. No distinction is made, if there are multiple cores of AI surrounded by the matrix material or only one core. Also various shapes of the core(s) and the matrix material have no influence on the definition as MC. A schematic MC with multiple circularly cores of liquid AI is plotted in Fig. 4a.

The processed matrix material is not automatically a homogeneous one phase system. Air can be entrapped, due to the applied manufacturing process. Furthermore the matrix could be an amorphous system or partly crystalline, due to the applied excipients. These varieties within the matrix material have no influence on the definition as MC system, too. The other structure is a solid solution. During the process the liquid AI is molecularly dispersed within the matrix material, resulting in a solid product. Thus this system has at least one phase. Entrapped air, for example, can constitute a second phase. A glassy solid solution (GSS) is obtained, if an amorphous matrix material is used and the liquid AI acts as plasticizer on the matrix (Fig. 4b). The term "encapsulation" is incorrect, if a GSS is obtained. Encapsulation implies a two phase system of the AI surrounded by a matrix material. Finally a chimera of a MC and a GSS can also be obtained, if the AI can be molecularly dispersed until a maximal amount within the matrix material. Applying a higher amount of AI will lead to a second phase of pure AI surrounded by a homogenous matrix of an excipient-AI mixture. In chapter IV the structure of solidified carvacrol is discussed in detail.

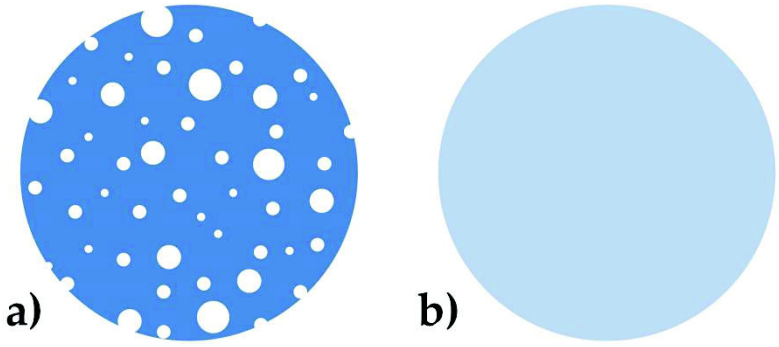

Fig. 4: Schematic figure of a) a microcapsule (MC), where droplets of the liquid AI are surrounded by a solid matrix material and b) a glassy solid solution (GSS), where the AI is molecularly dispersed in the matrix material.

3. Applications of solidified liquid active ingredients

3.1. Home care products

Liquid AIs are used in solid state home care products for cleaning applications as fragrance. Among other products these AIs are used in washing powders, granules or tablets, WC cleaning products like rim blocks, drain cleaner, and water tank tablets, dishwasher and denture cleaning tablets.

The fragrances are added in amounts between 0.2 to 1 % to washing powders because of three reasons: 1) masking of unpleasant odour of the cleansing actives, 2) signalling cleanness performance, and 3) imparting a pleasant smell to the laundry (Quellet et al., 2001). Fragrance released from these home care products during application affects the purchase decision of the consumers (Quellet et al., 2001). Thus many companies promote their products with the fragrance of the incorporated EO or perfume. The fragrance release properties vary between the different products. An immediate release is desired for washing powders or dishwasher tablets, due to applications times below 2 h. Whereas the fragrances should be release retarded from WC rim blocks, due to application for several weeks. In Table 1 some home care products are listed, which are advertised by their smell and are distributed on the German market. Additionally, some home care products with limonene as fragrance are shown in Fig. 5.

Fig. 5: Home care products with limonene as fragrance.

Table 1: Selected home care products with promoted fragrance.

Washing powders / granules	WC rim blocks
Frosch Citrus Voll-Waschpulver (Werner & Mertz GmbH)	Domestos Turbo fresh (Unilever Deutschland Holding GmbH)
Lenor Colorwaschmittel Pulver Blüten Bouquet (Procter & Gamble Germany GmbH & Co Operations oHG)	Meister Proper WC Stein Eucalyptus & Mint (Procter & Gamble Germany GmbH & Co Operations oHG)
Persil Universal Megaperls® Lavendel Frische (Henkel AG & Co. KGaA)	WC Frisch Duo-Duftspüler Citrus oder Bergfrisch (Henkel AG & Co. KGaA)

3.2. Foodstuffs and teas

A pleasant taste and odour are besides appearance, texture, colour, mouth feeling, other sensory aspects as well as nutritional and environmental values, preparation and / or cooking time, costs, and packaging appearance the most important purchasing factors of food products. Today a flavour can be added to nearly all foodstuffs. However, there are two product groups where flavour application is widespread: teas and instant food (powders). Tea is one of the most popular drinks, consumed by 2/3 of the world's population (Sinija et al., 2007). In 1998 tea was cultivated on an area of 2.4 million hectare (Schuchmann & Schuchmann, 2005). The addition of flavours to teas intensifies, duplicates or masks completely or partially the natural aroma of the tea components (Khanijow et al., 2012). Immediate release of solidified flavours is desired, if the tea is prepared by adding hot water. Some flavoured teas on the German market are listed in Table 2 and shown in Fig. 6.

Besides various teas, also many instant teas are market (Table 2). In contrast to teas, many instant teas could be prepared by adding cold water. However, a fast flavour release is desired, too. Thus the structure of solidified flavours for teas and instant teas must not be same, due to different release / dissolution properties in cold and hot water. Instant teas belong to the diverse group of instant food products. Manufacturing methods are described by Schuchmann & Schuchmann (2005) and Sinija et al. (2007). If an additional flavour is used, it has to be added to the production process.

Table 2: Selected teas with flavours.

Teas	Instant teas
Earl Grey (bergamot flavour), Heiße Liebe (raspberry and vanilla flavour), and Pure Lust (strawberry and rhubarb flavour) by Teekanne GmbH & Co. KG as well as Meßmer Earl Grey (natural bergamot, lemon and other flavours), Meßmer Türkischer Bayram (flavour of apple and fig), and Meßmer Wintertraum (flavour of cinnamon and orange) by Ostfriesische Tee Gesellschaft Laurens Spethmann GmbH & Co. KG	Lord Nelson Instant Früchtetee (mango flavour) by Ostfriesische Tee Gesellschaft Laurens Spethmann GmbH & Co. KG, Hansewappen Zitronentee by Zentrale Handelsges. ZHG mbH Food, and Ricola Schweizer Kräutertee (peppermint oil) by Ricola AG

Instant food products (Fig. 6) are widespread and have a high consumer acceptance due to the easy and time-saving preparation, in many cases only by the addition of hot water, low costs, and good taste. The basis of instant food products are food powders. Various techniques can be used to produce food powders, whereby, as a main advantage, the reduction of the water content leads to an increased shelf life (Dhanalakshmi et al., 2011, Schuchmann, 1995). The flavour can be added to the production process of the food powder or can be mixed afterwards with the obtained powder.

Fig. 6: Selected teas and instant food products containing (solidified) flavours.

3.3. Food packaging

EOs are coated on the surface of raw, minimally processed and ready-to-eat fruits and vegetables to improve the shelf life, due to the known antimicrobial and / or antioxidant properties (Lanciotti et al., 2004). However, there is also the possibility to incorporate EOs within the food package. One model AI of this thesis, carvacrol, has already been used for active packaging (Arrieta et al., 2013, Ramos et al., 2012). For this kind of application, it was incorporated in polypropylene (PP) films and edible sodium and calcium caseinate films. The PP films demonstrate some antimicrobial activity whereas only the solid state properties of sodium and calcium caseinate films were investigated (Arrieta et al., 2013, Ramos et al., 2012). The authors have announced further investigations. From my point of view investigations regarding the EO release properties are important, because the release determines the antimicrobial protection period of the food.

3.4. Insecticides and repellents

EOs are widely used as natural insecticides in agriculture and for human and animal protection against mosquitoes (Isman, 2006, Nerio et al., 2010). Research regarding encapsulation and solidification of the volatile substances has been performed for decades in order to improve shelf life, reduce evaporation, and tailoring liberation and bioavailability (Szente et al., 1990). Encapsulated repellents with a retarded release of the EOs and thus a mosquito protection for hours until days are of high interest for humans in all parts of the world. Various manufacturing techniques and products are known. Maji et al. (2007) investigated crosslinked gelatine microcapsules containing limonella oil whereas the company INTERLAC GmbH sales Para'Kito™ EO pellets for wristbands and bag clips. These pellets continuously release the blend of 7 EOs over a period of 15 days.

3.5. Pharmaceuticals and dietary supplements

Two different applications of liquid AIs within pharmaceuticals and dietary supplements are possible. On the one hand they can be used as active pharmaceutical ingredients (APIs) and on the other hand as flavouring and / or taste masking compounds. For example the EO of lavender serves as API in Lasea® (Dr. Willmar Schwabe GmbH & Co. KG) whereas the EOs of eucalyptus, sweet orange, myrtle, and citrus are the APIs in GeloMyrtol® forte (G. Pohl-Boskamp GmbH & Co. KG). The EOs of these drug products are filled in soft capsules to obtain a solid oral dosage form. Thus, the EOs are not solidified within a powder or granule. Parris et al. (2005) encapsulated EOs in Zein nanospherical particles for oral or injectable administration. Topolkaraev et al. (2013) obtained protein microparticles with stabilized carvacrol and other EOs for antimicrobial applications. For most of these applications an immediate release is desired. However, a controlled release could be sometimes reasonable.

α-Tocopherol has to be solidified for dietary supplement granules. As an alternative the solid synthetic α-tocopheryl-acetate can be used. Furthermore some EOs are used as APIs in pharmaceutical instant teas. The manufacturing method should be similar to the instant teas within the food sector. An immediate release in hot or cold water is desired depending on the product. As example served: Harntee 400 TAD® N with anise, citrus, peppermint, juniper berry, and bitter fennel oil (TAD Pharma GmbH) and Heumann Bronchialtee Solubifix® T with thyme oil (Sanofi-Aventis Deutschland GmbH).

Nevertheless, the use of liquid AIs as flavouring is much more significant. All pharmaceuticals and dietary supplements which have to be dissolved in water or which dissolve directly in the mouth need a good taste and thus an immediate release of the flavour (Fig. 7). Otherwise the patients compliance will get lost, the course of disease will be influenced negatively, and / or the product sales decrease. Thus flavourings can be added to

pharmaceuticals to create a pleasant taste and / or to mask the taste of unpleasant or bitter tasting drugs (Sohi et al., 2004).

Fig. 7: Selection of pharmaceutical and dietary supplement granules with flavours.

The content of the flavourings are trade secrets of the manufacturers and often not available to the pharmaceutical companies or consumers (Pawar and Kumar, 2002). Pawar and Kumar (2002) listed more than 60 commonly used flavours for pharmaceutical products. Additionally some market products are promoted with their tastes and flavours, e.g. Aspirin® Complex Heißgetränk with eucalyptus and mint flavour (Bayer AG), Biolectra® Magnesium 300 mg Direkt with orange or citrus flavour (Hermes Arzneimittel GmbH), Lefax® extra Lemon fresh (Bayer AG), Mucofalk® Orange Granulat (Dr. Falk Pharma GmbH), Orthomol Immun Direktgranulat Orange (Orthomol pharmazeutische Vertriebs GmbH).

4. Matrix materials

4.1. Introduction

A broad range of matrix materials is needed to obtain all of the listed products with differing AI release properties. Additionally Kenyon and Anderson (1988) mentioned emulsion stabilizing capabilities, film forming ability, low hygroscopicity, low viscosity, and relative low costs as important properties of suitable matrix materials for food applications. Thus some restrictions must be set for this work. Firstly the investigated products should be used for pharmaceutical and food applications. For this reason only "generally recognized as safe" (GRAS) substances are used (FDA, 2013). Secondly, an application for oral intake with immediate release properties is investigated. Thus four different types of materials, carbohydrates, proteins, lipids, and (synthetic) polymers can be used. In Table 3 some matrix materials are listed, whereas not all (synthetic) polymers meet the criteria for food applications (Madene et al., 2006, Gibbs et al., 1999, Wandrey et al., 2010).

Table 3: Matrix materials for pharmaceutical (and food) applications.

Type	Examples
carbohydrates	Modified starches, maltodextrins (DE < 20), glucose syrups (DE > 20), cyclodextrins, agar agar, gum arabic, maltose, trehalose, sucrose, lactose, fructose, glucose, ...
proteins	Whey proteins, gluten, gelatine derivates, casein, ...
lipids	Phospholipids (lecithin), waxes, glycerides, ...
polymers	Polyvinylpyrrolidone (PVP), polyvinyl acetate (PVAc), polyethylene glycol (PEG), poloxamer, poly(meth)acrylates, ...

In this study mainly carbohydrates are used and thus closely described. The other matrix materials are briefly mentioned only. A comprehensive overview of many matrix materials and their properties is given by Wandrey et al. (2010).

4.2. Carbohydrates

4.2.1. Basic carbohydrates

There are various structures and diverse types of carbohydrates (Table 3). A classification can be done in multiple ways (see Wandrey et al., 2010). In this thesis two groups of carbohydrates are defined. On the one hand "basic" carbohydrates and on the other hand carbohydrates with additional functions. Carbohydrates with emulsifying or complexation properties like modified starches, cyclodextrins, and gum arabic are such carbohydrates with additional functions. These substances are shortly discussed in section 4.2.2. Basic carbohydrates are substances like maltodextrins (Fig. 8) and glucose syrups, as well as

mono- and disaccharides. These carbohydrates are mainly used in this thesis as matrix materials and thus discussed in detail.

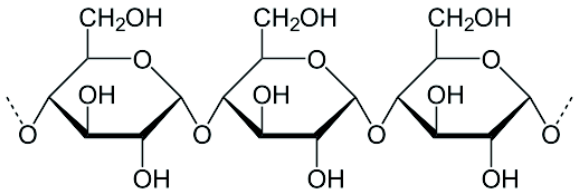

Fig. 8: Section of a maltodextrin consisting of D-glucose, primarily α-1-4-linked.

Maltodextrins and glucose syrups are starch degradation products and thus mixtures of glucose, maltose, oligo- and polysaccharides. These carbohydrates are defined by their dextrose equivalent (DE). The DE is a measure of the degree of hydrolysis of the starch molecule which compares the reducing power of the sugar groups to the reducing power to an equal weight of glucose (Kenyon and Anderson, 1988). Thus increasing DE leads to decreasing molecular weight, increasing solubility, increasing sweetness, increasing hygroscopicity, and corresponds with decreasing viscosity (Kenyon and Anderson, 1988). Glucose has a DE of 100 and starch of 0 - 1, according to this definition. Below a DE of 20 the degradation products are called maltodextrins, whereas the substances with a DE higher than 20 are called glucose or corn syrups (Kenyon and Anderson, 1988, Uhlemann and Reiß, 2010). Uhlemann and Reiß (2010) used eq. 1 to correlate the average molecular weight (MW) of a starch degradation product with the DE.

$$DE = \frac{18016}{\overline{MW}} = 100\ \frac{M_{glucose}}{\overline{MW}} \quad (1)$$

However this equation can only be used as an estimation, due to the practically difficult determinable molecular weights of oligo- and polysaccharides. Kenyon and Anderson (1988) described maltodextrins and low DE glucose syrups as optimal matrix materials due to good film forming properties, low hygroscopicity, fast flavour release, and low costs. However, the definition of film forming properties does not correspond with the pharmaceutical definition nowadays. The authors used this definition to illustrate good barrier properties of the matrix to prevent oxidation and evaporation of the AI during storage. This property was investigated further and correlated with the glass transition temperature (Tg) and the molecular packing of the applied carbohydrate matrix. Above the Tg the amorphous carbohydrate matrix is situated in a rubbery, sticky, and lower viscous state, whereas below the Tg the substance is a glassy solid with hard and brittle properties. Roos and Karel (1991c) reported that the Tg of amorphous carbohydrates depends on the molecular weight and the bound water. It can be predicted applying equation (2), established by Gordon and Taylor (1952):

$$Tg_{mix} = \frac{w_1 Tg_1 + k\, w_2\, Tg_2}{w_1 + k\, w_2} \quad (2)$$

where Tg_1, Tg_2, and Tg_{mix} are the glass transition temperatures [K] of the amorphous substances 1 and 2, corresponding with the used carbohydrate and water, and the binary mixture. Furthermore w_1 and w_2 are the weight fractions of the substances 1 and 2, and k is the GT constant. The Tg of water with a $Tg_{midpoint}$ of 144 ± 1 K was investigated by Johari et al. (1987). Couchmann and Karasz (1978) found out that the GT constant k could be calculated with eq. (3):

$$k = \frac{\Delta c_{p2}}{\Delta c_{p1}} \quad (3)$$

where Δc_p is the change in specific heat capacity at the Tg of substance 1 and 2. Practically more relevant is the estimation of k using eq. (4) defined by Hancock and Zografi (1994).

$$k \approx \frac{\rho_1 Tg_1}{\rho_2 Tg_2} \quad (4)$$

where ρ is the density of substance 1 and 2. However, k is often used as fitting parameter in carbohydrate and food systems (Palzer, 2010).

Eq. (2) was found to be important, because it can be used for every amorphous system containing two substances. Gordon and Taylor (1952) developed this equation based on butadiene / styrene copolymers. Roos and Karel applied it successfully for maltodextrin-water (1991a, 1991c), maltodextrin-sucrose and maltose-water systems (1991a). Hancock and Zografi (1994) used eq. (2) for various pharmaceutical solids.

Long term stabilization of liquid AIs within the rubbery state of an amorphous matrix is not possible. Dependent on the volatility of the AI, the undesired release increased with increasing T-Tg (Gunning et al., 1999). Additionally crystallization of low molecular weight carbohydrates (LMWC), e.g. sucrose occurred in the rubbery state. This increased the release of volatile AIs, further (Gunning et al., 1999, Levi and Karel, 1995). This could lead to the assumption, that a matrix, containing only a high molecular weight carbohydrate (HMWC), e.g. a starch or a low DE maltodextrin with a high Tg, is the best choice for liquid AI encapsulation. However, this assumption is misleading. Yuliani et al. (2009) processed limonene with native corn starch in a cooking extrusion process and obtained a limonene retention below 11 % of the fed AI. Anandaraman and Reineccius (1986) investigated the retention of orange peel oil depending on maltodextrins with different DE values. The authors came to the conclusion that increasing the DE and thus decreasing Tg increased the retention of the AI. Uhlemann and Reiß (2010) and Zuidam and Heinrich (2010) described carbohydrate matrices containing a mono- or disaccharide and a maltodextrin or glucose syrup to receive a high AI load. The increased retention increasing the DE of the maltodextrin or using a mixture of a LMWC and HMWC can be explained with the molecular packing within the matrix. A dense packing and a low free volume are optimal matrix properties of glassy carbohydrates for encapsulation. The use of plasticizers, like water or mono- and disaccharides lead to different molecular structures of the HMWCs. This was mainly investigated in four studies of the Nestlé Research Center (Kilburn et al.,

2004, Kilburn et al., 2005, Townrow et al., 2007, Ubbink et al., 2007). The free volume of maltodextrins is decreased by the sorption of water at water activities below 0.11 at 25 °C (Kilburn et al, 2004, Townrow et al. 2007). Higher water activities lead to a swelling of the matrix, increased mobility of the maltodextrin chains, and an increased free volume (Kilburn et al., 2005, Townrow et al., 2007). LMWCs have not the same plasticizing effect on HMWCs in comparison with water (Kilburn et al., 2005). With increasing maltose content the free volume within the maltodextrin maltose mixture decreases and a denser packing is obtained (Townrow et al., 2007). The dense packing leads to a decreased water uptake in the glassy state, whereas in the rubbery state the opposite is the case (Ubbink et al., 2007). Finally a dense packing decreases the mobility of encapsulated AIs and thus increases shelf life (Kilburn et al., 2005). In conclusion a dense glassy matrix containing a high and low molecular weight carbohydrate is suitable for the encapsulation of liquid AIs. However, the amount of the LMWCs is essential. Increasing LMWC leads on the one hand to increasing matrix density, but on the other hand to a decreasing Tg, which can lead to crystallization of the LMWC and / or to a rubbery matrix.
Therefore water soluble maltodextrins with the DE 12 and 17 as HMWC and sucrose (Fig. 9) as LMWC are selected as matrix materials for this thesis.

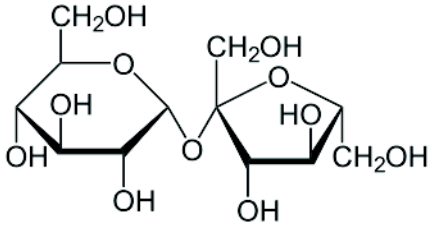

Fig. 9: Sucrose

Sucrose is a disaccharide containing α-D-glucose and β-D-fructose, α,β-1,2-linked. It is also known as table sugar and has a sweet taste and a very good solubility in water. A discrete melting point is not existing. Sucrose decomposes at temperatures higher than approximately 185 °C. The substances turns to a yellow / brown rubbery and sticky mass. This process is called caramelization. The used sucrose substance is a crystalline powder. But sucrose could also appear in the amorphous state (Roos and Karel, 1991b). Amorphous sucrose is not distributed, due to an increasing crystallization rate with increasing water activity (a_w). Roos and Karel (1991b) determined beginning crystallization already at an low a_w of 0.33. Sucrose in mixtures with other excipients has been used for decades for encapsulation of flavours (Blake and Attwool, 1996, Risch, 1988, Zuidam and Heinrich, 2010). However, the formation of amorphous sucrose during the applied processes and its role in encapsulation is not fully investigated. With this thesis this scientific gap should be filled (Chapter II, III, V, VI).

4.2.2. Carbohydrates with additional functions

Additional functions of carbohydrates are emulsification or complexation properties. Typical carbohydrates with emulsification properties are modified starches and gum arabic (also called gum acacia). Westing et al. (1988) compared gum arabic, a low DE modified food starch, and a DE 25 glucose syrup as matrix material in spray drying, regarding the maximal encapsulated amount of orange oil and the shelf life of the products. The carbohydrates with additional functions could stabilize an higher amount of orange oil (17.5 % orange oil using gum arabic and 19.5 % using the modified food starch) in comparison to the glucose syrup (11.4 %). However, the shelf life of the products (stored at 25 °C) was reduced, using an emulsifying carbohydrate (99 days using gum arabic, 57 days using the modified food starch) in comparison to the basic carbohydrate (162 days). This can probably be correlated with the improved barrier properties of the glucose syrup, as discussed in section 4.2.1. This disadvantage was tried to overcome with the combination of modified starches and sugars (Zasypkin and Porzio, 2004) and mixtures of gum arabic, maltodextrin, and a modified food starch (Krishnan et al., 2005). Gum arabic is used in various mixtures with other matrix materials for encapsulation applications till this day (Bouquerand, 2012).

Cyclodextrins are cyclic oligosaccharides with six (α-cyclodextrin), seven (β) or eight (γ) glucose monomer units (Wandrey et al., 2010). They are used to form inclusion complexes with the AI (Marques, 2010). β-Cyclodextrin can be loaded with 6 - 12 % of an essential oil by various techniques (Marques, 2010). The amylose helix of starch has similar properties, too (Maier et al., 1987). The thermostable binding of flavours by various modified and native starches and cyclodextrin was investigated by Maier et al. (1987). The authors found out that cyclodextrin could bind more flavour than the different starches. However, few exceptions were obtained. Furthermore not the full amount of flavour was released from the cyclodextrin, which was investigated via a sensorial test. This disadvantage can be turned into an advantage, if undesired or unpleasant tastes can be masked (Marques, 2010). A mixture of cyclodextrin and maltodextrin can be used as matrix material, too, to combine the advantages of both stabilization mechanisms (Furuta et al., 1994).

4.3. Proteins

The application of proteins as matrix materials is not wide-spread in comparison to carbohydrates. Madene et al. (2006) mentioned the amphiphilic properties, different molecular weights, molecular chain flexibility, solubility, and emulsification properties as advantages for these matrix materials. The research was intensified in the last years. Porzio and Zasypkin (2010) used hydrolyzed gelatine in combination with carbohydrates as matrix material for encapsulation of lemonade flavour, whereas Topolkaraev et al. (2013) used gluten and soy flour as matrix material for the stabilization of thymol and carvacrol,

applicable for antimicrobial products. Proteins are not applied in this thesis and thus not further discussed. However, these matrix materials exhibit a high potential for further research on encapsulation of liquid AIs.

4.4. Lipids

Lipids are a diverse group of substances and molecules. Oils, fats, waxes, and phospholipids, are structural different lipids. Generally lipids are insoluble in water and thus not suitable for a matrix which should exhibit fast disintegration when exposed to water. However, phospholipids, especially lecithin, a main ingredient of egg yolk, have been used for decades for encapsulation applications (Risch, 1988). Lecithin is a mixture of various phosphatidylcholines and their single substances: saturated and unsaturated fatty acids, glycerine, phosphoric acid, and choline. As an example can serve the 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) (Fig. 10).

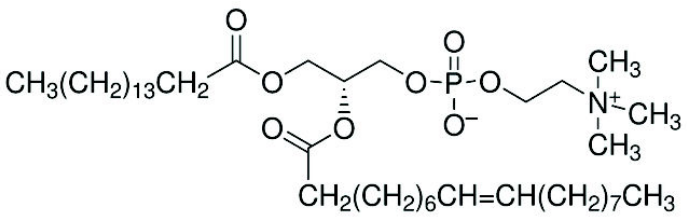

Fig. 10: A substance of lecithin: 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC).

Lecithin has the E-No. 322 and can be used as food additive (European Parliament and Council Directive No 95/2/EC). The amphiphilic structure leads to good emulsifying properties. Thus lecithin, in concentrations between 0.5 and 1.0 %, is widely used as emulsifier in food flavourings (Blake and Attwool, 1996, McIver et al., 2002, Risch, 1988, Subramaniam, 2006). However, the detailed structures of lecithin containing matrices are yet not completely clarified. This has to be done in future to identify the influence of lecithin on encapsulated amount of the used liquid AI.

4.5. (Synthetic) polymers

Various polymers can be used for pharmaceuticals, food packaging, insecticides / repellents, and home care products. The desired release mechanism of the liquid AI from the chosen polymer and the application determines the choice of the matrix material. The release behaviour has been a research topic for years. Peppas and Ende (1997) investigated the controlled release of perfumes like limonene and other essential oil components from glassy polymers like ethyl methacrylate and ethylene glycol dimethacrylate. Varona et al. (2010) compared biodegradable polyethylene glycol (PEG) with a modified starch as matrix material for an agrochemical formulation containing lavandin essential oil. Sansukcharearnpon et al. (2010) encapsulated limonene, among other fragrances, in

ethylcellulose, hydroxypropyl methylcellulose and poly(vinyl alcohol). However, the use of polymers for applications in food is subjected to heavy restrictions. The matrix material, chosen for this thesis, should be applicable for pharmaceuticals and foodstuffs. Thus a suitable synthetic polymer should minimally be listed as food additive (European Parliament and Council Directive No 95/2/EC). Polyvinylpyrrolidone (PVP) (Fig. 11), for example, is mentioned as a food additive (E-No. 1201).

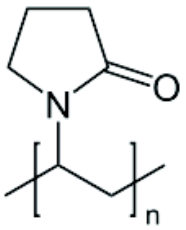

Fig. 11: Section of a polyvinylpyrrolidone (PVP, povidone)

PVP is an amorphous polymer with a molecular weight between 2,000 and 1,500,000 Da (Buehler, 2008). It can be dissolved in many hydrophilic (water) and hydrophobic (butanol) liquids (Buehler, 2008). PVP is plasticized by water, sugars, and amino acids (Buera et al., 1992). Furthermore PVP can form glassy solid solutions with solid APIs (Forster et al., 2001) and it is used in pharmaceutical extrusion - the process of interest - as excipient to enhance drug dissolution (Andrews et al., 2010). Thus PVP is a suitable synthetic polymer for this thesis and detailed investigated in Chapter IV.

5. Encapsulation using extrusion technique

5.1. Introduction

Various technologies, e.g. spray-drying, fluidized bed coating / granulation, spray-chilling / cooling, (melt) extrusion, co-extrusion, freeze or vacuum drying, liposome or alginate entrapment, rotational or centrifugal suspension separation, coacervation, co-crystallization, molecular inclusion, interfacial polymerization, or rapid expansion of a supercritical fluid (RESS), can be used for the encapsulation of liquid AIs. Several authors (Gibbs et al., 1999, Madene et al., 2006, Uhlemann and Reiß, 2010, Zuidam and Shimoni, 2010) summarized and reviewed these techniques for food applications, because the food sector is the largest market for encapsulated liquid AIs. These processes could be applied for pharmaceutical, agrochemical, home care, and other applications, too.
Various product morphologies, particle sizes, and AI loads can be obtained with this broad range of technologies. For example, particles between 10 and 400 µm are obtained using spray-drying, whereas particles between 300 and 5,000 µm are obtained with extrusion (Zuidam and Shimoni, 2010). Thus a desired product structure can probably not be manufactured with every encapsulation method. The retention of the AI and the shelf life of the product are important decision criteria, if the technique is freely selectable. Uhlemann and Reiß (2010) reported that extrusion and fluidized bed coating lead to the lowest distortions of the flavour profile of an eight component strawberry flavour. Westing et al. (1988) compared the shelf life of orange oil encapsulated by spray-drying, extrusion, and molecular inclusion. The products processed via extrusion provided the longest shelf life. Thus encapsulated products of desirable quality are obtained using extrusion. Consequently, the detailed investigation in the mechanisms of encapsulating liquid AIs via extrusion processing is the main aim of this thesis.

5.2. Extrusion

The term extrusion is given by the Latin word "extrudere" which could be translated with thrust. In extrusion a mass is thrusted out of a die. Various types of extruders exist: screw extruders, ram extruders, basket extruders, flat or ring die pelleting presses, and pressurized reactors (Kleinebudde, 2011, Risch, 1988). Nowadays screw extruders are the most common types of extruders for pharmaceutical, food, and other life science applications. The screw extruders can be differentiated into different types: single screw extruders, co- and counter rotating twin screw extruders (TSE), and planetary gear extruders (Schuchmann, 2005). The extrusion process using a TSE is a continuous process. The powder is fed into a (heated) barrel, followed by a transport of the powder through the barrel into the direction of the die. Thereby the powder is transformed to a viscous mass, mixed (with other components), sheared, milled, pressurized, melted, plasticized and/or

cooked (Schuchmann, 2005). Finally the mass is forced through one or more orifices. If the temperature of the mass exceeds room temperature, it cools down, resulting in a solid and texturized product. These extrudates mostly are intermediate products. Downstream processes, like active cooling, drying, cutting, crushing, granulation, milling or spheronization may be applied subsequent to the extrusion process. Nowadays co-rotating TSE are widely used for plastic, pharmaceutical, and many food applications (Breitenbach, 2002, Kleinebudde, 2011, Schuchmann, 2005). Schuchmann (2005) mentioned an efficient mixing and an uniformly conveying as advantages of a co-rotating TSE. Forced conveying will be obtained, using a counter-rotating TSE. Studies comparing these types of extruders are rare. However, some studies were performed for polymer / plastic applications, whereby similar studies should be carried out in the future for pharmaceutical, food, and other applications. Shon et al. (1999) determined a shorter mean residence time and a more narrow residence time distribution for a counter rotating TSE in comparison with a co-rotating TSE. A more rapidly mixing and melting of a polyethylene and polystyrene blend in a counter rotating TSE is reported by Cho and White (1996). Hettema et al. (1999) investigated advantages of a co-rotating TSE for reactive extrusion of polyethylene and polypropylene, due to a higher attainable shear and longer residence time. Even though not all findings from polymer extrusion can be transferred one to one to the extrusion process investigated in this thesis, the use of a counter rotating TSE could have some advantages. Shorter residence times and lower shear rates would decrease the thermo mechanical stress on the used sensitive AIs, whereas a faster melting and mixing could lead to a more homogeneous AI distribution within the matrix material. Thus a counter-rotating TSE is used for the encapsulation process investigated in this thesis (Chapter V, VI). A differentiation between co- and counter-rotating twin screw extruders for encapsulation applications is not carried out and should be performed in future studies.

5.3. Encapsulation via extrusion

5.3.1. Encapsulation via vertical ram extrusion

Encapsulation of liquid AIs using extrusion is widely spread for the manufacturing of solid flavourings. These granules are applied for many foodstuffs, teas, pharmaceuticals, and other products, which have to provide a good taste (see section 2). Approximately 5 % of all solid flavourings are produced via an extrusion technique (Porzio, 2008). Only spray-drying and spray chilling are applied more often. Many companies distribute flavourings encapsulated via extrusion, for example, Durarome® from Firmenich International SA, Evoglass® from Symrise AG, Caplock™ from International Flavours & Fragrances Inc., and FlavorCell® from McCormick & Company. Two extrusion processes are applicable: batch vertical ram extrusion in a pressurized reactor and a continuous process using a TSE

(Porzio, 2008, Uhlemann and Reiß, 2010, Zuidam and Heinrich, 2010), which is introduced in section 5.3.2.

In the patent of Swisher (1957) oil encapsulation via vertical ram extrusion was firstly described. Risch (1988) summarized the further investigations and described the process in more detail (Fig. 12): A carbohydrate melt at 110 to 130 °C with a moisture content of 5 to 10 % was formed in a pressurized reactor. An emulsifier and the flavour were added and mixed vigorously. Then the rubbery mass was forced through a die and solidified in a cold isopropyl alcohol bath. The solid strands were broken into granules and the surface flavour was washed away with the isopropyl alcohol. The granules were recovered, dried and packed. This process is practiced in industry till this day. Among other products the Durarome® flavours are manufactured with this ram extrusion method (Zuidam and Heinrich, 2010).

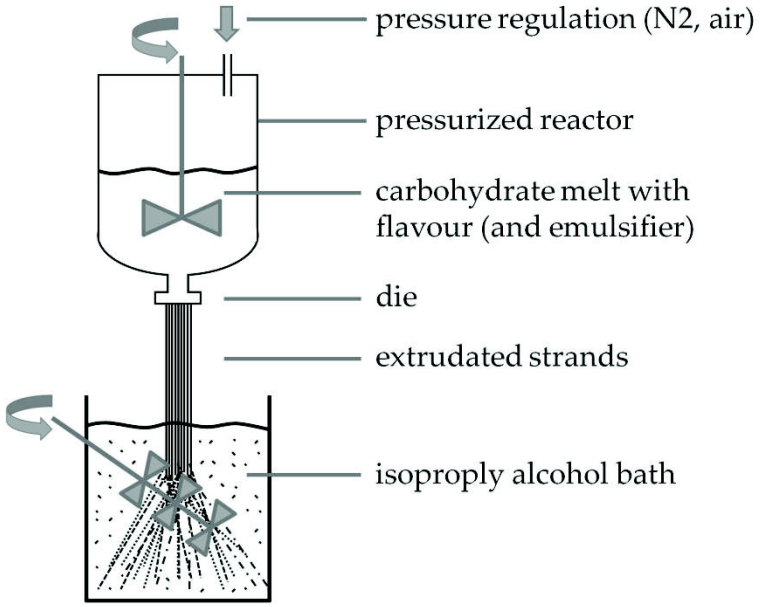

Fig. 12: Schematic figure of a ram extrusion process (modelled after Risch, 1988).

In literature this process is mainly called "melt injection" (Porzio, 2008, Zuidam and Heinrich, 2010). However, this term could be misleading, due to the exact definition of a melt. In this process a moisture content of 5 to 10 % at a temperature of 110 to 130 °C is desired (see above). Melt and dissolution processes could occur in the reactor. Thus the use of the term "vertical ram extrusion" is more exact.

5.3.2. Encapsulation using a TSE

Flavour encapsulation using a TSE arose in the nineties of the last century (Carr et al., 1993, Blake and Attwool, 1996). Today this process (Fig. 13) is the most important extrusion encapsulation process, due to many advantages in comparison with the vertical ram extrusion: it is a continuous process with high production efficiency and an increased choice of various carrier materials while no solvents and chilling baths are required. Furthermore

different shapes of the final products could be obtained, while the flavour load corresponds with the products obtained by vertical ram extrusion (Porzio, 2008).

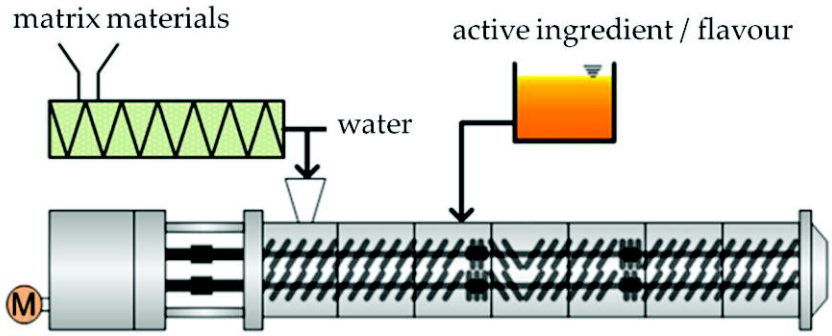

Fig. 13: Schematic illustration of a screw extruder set up for an encapsulation process (set-up from Zuidam and Shimoni, 2010; modified figure with permission from M. Azad Emin).

Porzio (2008) and Zuidam and Heinrich (2010) named this process "melt extrusion". As already mentioned in section 5.3.1. the definition of the term "melt" could be misleading. Water is continuously fed into the extruder as plasticizer for the matrix material (Fig. 13). That is why this definition of melt extrusion is not congruent with the melt extrusion for pharmaceutical applications. During pharmaceutical melt extrusion the conveyed solid powdery mass, at least one component, melts during the process, due to the applied process conditions (Breitenbach, 2002). If a plasticizer like water is added to extrusion processes for pharmaceutical applications the term wet extrusion or in more detail extrusion of wet powder masses is used (Kleinebudde, 2011). In this thesis the term melt extrusion is only used, if the solid matrix material melted due to the process conditions.
The described encapsulation process is commonly used in flavour industry according to various available patents (Blake and Attwool, 1996, Bouquerand, 2012, McIver et al., 2002, Porzio and Zasypkin, 2010). Scientific publications about this process are rare. The available articles and book chapters were mainly published from authors of the industry (Harrington and Schaefer, 2014, Porzio, 2008, Zuidam and Heinrich, 2010). A detailed investigation of the encapsulation of a model flavour has not been published, yet. This is the main aim of this thesis, to investigate the mechanisms of encapsulating liquid AIs via twin screw extrusion technology.

5.4. Batch mixing

The encapsulation process using a TSE is complex. There are various material-, extruder- and process parameters. Some parameters like barrel length and temperature, screw configuration and speed, powder and AI feed rates, die geometry, and location of the AI feeding port can be adjusted directly. Furthermore there are some more process parameters which are affected by the adjustable

process parameters like barrel filling level, the residence time distribution, local residence times, shear stresses, and pressure. It is not possible that one parameter could be varied without influencing many other parameters. This was exemplarily described by Schuchmann (2008) using the example of a food cooking process. That makes it difficult to design and to investigate an encapsulation process using a TSE from scratch.

However, shear and heat treatment, as found in TSE processes, can be simulated in a small scale batch mixing process. For decades these batch mixers (Fig. 14) were used for this purpose in polymer science (Maric and Macosko, 2001, Sundararaj and Macosko, 1995). For the investigation of pharmaceutical extrusion processes batch mixers have been used, too (Liu et al., 2010). The process parameters could be varied independently using this device. Various terms, like torque rheometer, twin-screw counter-rotating batch internal mixer, batch intensive mixer, and internal batch mixer were reported. In this thesis the equipment is called batch mixer.

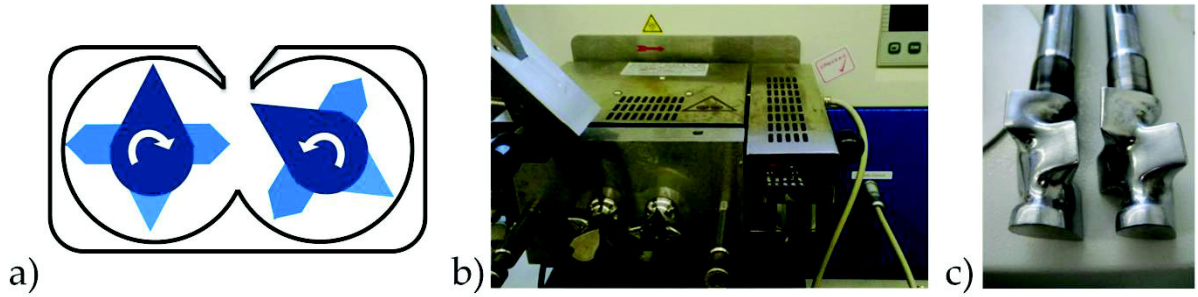

Fig. 14: a) Schematic illustration of a double screw batch mixer, b) a Type 50 Brabender batch mixer, and c) blades.

Torque and product temperature are recorded during the process. Physical processes, like melting, plasticization, crosslinking, degradation and / or solidification could be determined, due to the obtained data (Bousmina et al., 1999). Finally the physical processes could be correlated with the independently varied process parameters like material composition, plasticizer content, chamber temperature and filling level, rotation speed, and process time.

Furthermore the specific mechanical energy (SME) input [Wh/kg], an important indication parameter of extrusion processes, can also be obtained in these batch mixing processes. The SME is used to determine the mean energy input of the screws into the fed mass in processes using a TSE. It is calculated with eq. (5):

$$SME = \frac{power - idle\ power}{feed\ rate_{solids} + feed\ rate_{liquids}} \quad (5)$$

In batch mixing processes the mechanical energy input of the rotating blades acts on the constant amount of material, neglecting the possibly occurring evaporation of gases. With increasing process time the SME increases and can be calculated with eq. (6):

$$SME = \sum_{t\,=\,start}^{t\,=\,end} \frac{a\ RS\ \pi\ (\tau_{t+a} + \tau_t)}{3600\ (m_{solids} + m_{liquids})} \quad (6)$$

where t = process time [s], a = time interval [s] of the recording rate for torque, RS = rotation speed [1/s], τ = measured torque [Nm] and m = weighed-in mass [kg] of the solids and liquids.

Thus a batch mixing process is applied for the first investigations towards the development of the desired extrusion process.

6. Aims of the thesis

The encapsulation process using a TSE is widely applied in flavour industry. However the information on structure development in extrusion and their influence on the encapsulation efficiency and release properties of the AI are either not investigated or not published. For pharmaceutical encapsulation applications the use of a TSE has not been described yet. Therefore, the aim of this thesis is to investigate in the mechanisms of encapsulating liquid AIs using a TSE for pharmaceutical and food applications.

More specifically the aims are:

- To investigate the influence of various process parameters on the solid state properties of the processed carbohydrate powders, containing maltodextrin, sucrose, and water at different ratios. For this study a batch mixing process is applied.
- To identify the physical processes during batch mixing and extrusion, depending on the adjusted process parameters and applied material composition.
- To characterise the solid state (water content, crystalline content, and glass transition temperature) of the processed matrix material with and without liquid AI.
- To analyse the structure of the obtained products, especially to differentiate between AI containing glassy solid solutions and microcapsules.
- To compare the processability and retention of three liquid AIs, orange terpenes, carvacrol, and α-tocopherol.
- To develop a melt encapsulation process using a TSE, based on the batch mixing data.
- To identify the influences of water feeding on the physical processes during extrusion.
- To find the process conditions leading to extrudates with high AI retention.
- To analyse the storage stability of solidified and encapsulated liquid AI and to link data to structures obtained by processing.

7. Outline of the thesis

To date, various excipient mixtures are used as matrix material for extrusion encapsulation processes. Maltodextrin as amorphous high molecular weight carbohydrate (HMWC) and crystalline sucrose as a low molecular weight carbohydrate (LMWC) are selected as matrix materials at the beginning of this work. Mixtures of HMWC and disaccharides have been used for encapsulation of flavours for decades and have been studied widely applying various techniques, including extrusion. The obtained extrudates were described as glassy matrices (Porzio, 2008). Typical extrusion conditions should lead to the loss of the crystalline structure. However, the occurring physical processes during extrusion, depending on the adjusted process parameters and material composition, are not investigated to now. For this reason the excipient mixture should be kept as simple as possible. Thus carbohydrates with additional emulsification or complexation properties, which can possibly provide an increased AI load, are deliberately excluded.

A batch mixing process is chosen to investigate systematically the processability of the selected matrix material (Chapter II). A design of experiments (DoE) is used to study the influences of the sucrose content within the carbohydrate powder mixture, the amount of added water, the process time, and the rotation speed of the blades. Amorphous and partly crystalline samples are obtained. Thus the solid state properties of the obtained samples, like product and glass transition temperature (Tg), crystalline and water content as well as the obtained specific mechanical energy, are correlated with the varied process parameters and material composition to identify the physical processes during batch mixing. As a result plasticization, melting, and caramelization are assigned to specific process conditions.

Subsequently, the application of AIs within the batch mixing process is studied in chapter III. Orange terpenes, carvacrol, and α-tocopherol are selected as liquid model AIs. Adjustable process parameters, e.g. process time and rotation speed are set constant, whereas the material composition, sucrose content within the carbohydrate powder mixture, the amount of added water, and the amount of AI are systematically varied within an applied DoE. Three objectives are pursued: 1) To identify the impact of the process on the stability and retention of the AIs. 2) To analyse the influence of cooling conditions on the solid state properties and on the retention of the AIs. 3) To analyse the AI influence on the matrix material. For objective 1, it turns out, that the process conditions have a high impact on the retention of orange terpenes, whereas carvacrol is minimally and α-tocopherol is not affected. Thus the vapour pressures of the AIs during the processes are calculated. The vapour pressures decreases in order from orange terpenes to carvacrol to α-tocopherol and are finally determined as the critical parameter for the retention of the AIs. Three different cooling methods, from rapid to slowly cooling, are applied for the work on objective 2. But no differences of the solid state properties and the AI retention have been observed. Thus in

the following extrusion process no special cooling device has to be applied. Finally, for objective 3, the determined torque and Tg data lead to the conclusion, that the AIs do not plasticize the carbohydrate material.

The plasticizing or non-plasticizing properties of an AI on the carbohydrate matrix material is studied in chapter IV with the AI carvacrol in more detail. Different techniques and analytical tools, like calculation of solubility parameters, two differential scanning calorimetry methods, and X-ray micro computerised tomography are used to analyse processed and unprocessed carvacrol carbohydrate mixtures. Polyvinylpyrrolidone (PVP) as matrix material is compared to the applied carbohydrates. It turns out that carvacrol acts as plasticizer on PVP, resulting in glassy solid solution instead of a microcapsule system, whereas no plasticizing properties of carvacrol on the carbohydrate material are determined.

Based on the obtained batch mixing data a hot melt extrusion (HME) process using a counter-rotating twin screw extruder is investigated in chapter V. Orange terpenes and α-tocopherol are selected as model AIs. A downstream process is not applied. Before starting the investigation of the process a suitable screw for melting of the carbohydrate mixture and for mixing of the AIs with melted mass is configured. The following parameters are investigated, beginning with the adaption of the maltodextrin : sucrose ratio, due to the absence of additionally fed water. Then the die geometry and process parameters like screw speed and feed rate are studied methodically, before the AIs are applied for the encapsulation process. The volatility of the oranges terpenes, when the hot product left the die, leads to a decreased retention (absolute value 6.0 %) in comparison to α-tocopherol (9.2 %). The temperature of the product turns out to be the critical value for the encapsulation of volatile AIs.

The product temperature can be decreased drastically from temperatures of approximately 140 °C to approximately 80 °C, if water is additionally fed into the barrel, which is studied in chapter VI. The constant and continuous dosing of this plasticizer is challenging and calls for a precise control system. Both sucrose and water act as plasticizers. A too high amount of both plasticizers causes a low viscous matrix, which sticks together after leaving the die. A too low plasticizer content causes high viscosity, increasing torque and finally an emergency shutdown of the extruder due to the exceeding of the torque maximum. Thus a statistical variation of both substances in wide ranges is not possible. Again orange terpenes are selected as model AI and additionally hot die face cutting is applied as downstream process. The loss of crystalline sucrose during extrusion is investigated and compared to HME process. It turns out, that melting of the carbohydrates during this process does not occur, whereas the loss of crystalline sucrose is assigned to a dissolution process in available water and in the plasticized maltodextrin, respectively. Whether an amorphous or a partly crystalline matrix will be obtained, depends on the amount of water, the obtained product

temperature, and the applied maltodextrin : sucrose ratio. Amorphous matrices exhibited the highest AI retention with an absolute value of 4.1 % Finally the reasons of the decreased AI load in comparison with the HME process are discussed.

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CHAPTER II

Solid state of processed carbohydrate matrices from maltodextrin and sucrose

The following research paper with the title "Solid state of processed carbohydrate matrices from maltodextrin and sucrose" (DOI: 10.1016/j.jfoodeng.2014.01.003) has been published in the year 2014 by the Journal of Food Engineering (Impact factor of 2.576 in the year 2013) in Vol. 129 on pages 30-37.

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Author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Markus W. Tackenberg	0	40	100	60	40
Markus Thommes	70	60	0	30	15
Heike P. Schuchmann	10	0	0	0	15
Peter Kleinebudde	20	0	0	10	30

SOLID STATE OF PROCESSED CARBOHYDRATE MATRICES FROM MALTODEXTRIN AND SUCROSE

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ABSTRACT

Various mixtures of maltodextrin, sucrose, and water, as typical compounds of food matrices used for flavour encapsulation via extrusion, were processed in a batch mixing process. Plasticization, melting and caramelization just as the formation of amorphous sucrose were studied. All matrices were plasticized within 2 min, resulting in a loss of crystalline sucrose. Melting occurred due to water loss higher than 55%. Caramelization could be correlated to a specific mechanical energy input higher than 300 Wh/kg. The glass transition temperature of the caramelized matrices could not be fitted with the Gordon Taylor equation, based on the used compounds. Increasing sucrose content in the preblended powder mixture combined with increasing sample water content increased the crystalline fraction within the matrix. These findings enable a systematically investigation of matrices for encapsulation of flavours within the batch mixing process, which can help to transfer the flavour encapsulation to an extrusion process.

KEYWORDS

Encapsulation; Sucrose; Maltodextrin; Plasticization; Melting; Caramelization

HIGHLIGHTS

- Processing of maltodextrin and sucrose with water in a batch mixing process.
- Correlation of plasticization, melting, and caramelization to process conditions.
- Investigation of the formation of amorphous sucrose via a design of experiments.
- Quantification of crystalline sucrose down to < 4% via X-ray powder diffraction.
- Specific mechanical energy above 300 Wh/kg led to caramelization.

CHAPTER III

Orange terpenes, carvacrol and α-tocopherol encapsulated in maltodextrin and sucrose matrices via batch mixing

The following research paper with the title "Orange terpenes, carvacrol and α-tocopherol encapsulated in maltodextrin and sucrose matrices via batch mixing" (DOI: 10.1016/j.jfoodeng.2014.03.010) has been published in the year 2014 by the Journal of Food Engineering (Impact factor of 2.576 in the year 2013) in Vol. 135 on pages 44-52.

The research presented in this article has been conducted in the context of AIF ZIM project (KF2256805WZ1): "Entwicklung eines neuartigen Verfahrens zur Verkapselung von funktionellen Inhaltsstoffen in amorphen kohlenhydratbasierten Matrizes im gegenläufigen Doppelschneckenextruder"; subproject: "Optimierung eines skalierbaren Verkapselungsprozesses in einem gegenläufigen Doppelschneckenextruder auf Basis von (bio-) chemischer und (thermo-) physikalischer Analyse von Rohstoff- und Produkteigenschaften" in cooperation with the company HB-Feinmechanik GmbH & Co KG.

According to the valid legal situation, only the abstract is published in this thesis. The full text research article can be purchased at:

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Evaluation of the authorship:

Author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Markus W. Tackenberg	10	60	80	50	50
Andreas Marmann	0	0	20	10	5
Markus Thommes	60	40	0	30	10
Heike P. Schuchmann	15	0	0	0	15
Peter Kleinebudde	15	0	0	10	20

ORANGE TERPENES, CARVACROL AND α-TOCOPHEROL ENCAPSULATED IN MALTODEXTRIN AND SUCROSE MATRICES VIA BATCH MIXING

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ABSTRACT

Orange terpenes, carvacrol and tocopherol were used as model substances for flavours, essential oils and lipophilic liquid (bio)-active ingredients (AI). They were encapsulated via a batch mixing process in various carbohydrate matrices containing maltodextrin and sucrose. Plasticizing properties of the AIs, independently from their concentration (4.5 - 8.8%), on the matrices were not obtained. Furthermore the AIs did not affect the solid state properties, especially the crystalline content, of the carbohydrate matrix. An AI retention between 6 and 100% correlated inversely with the vapour pressure of the pure AI. At a mixing time of 5 min a vapour pressure of higher than 70 kPa led to a almost completely loss of the AI. The AI retention and the solid state of the matrices were not affected by applying different cooling conditions. These results can be used to adjust the parameters of an extrusion process to receive high AI retention.

KEYWORDS

Encapsulation; Flavour; Batch mixing process; Maltodextrin; Sucrose; Tocopherol

HIGHLIGHTS

- Orange terpenes, carvacrol and tocopherol were encapsulated in a batch mixing process.
- The active ingredients had no plasticization effect on the carbohydrate matrices.
- Increasing vapour pressure decreased the retention of carvacrol and orange terpenes.
- Various process conditions had no effect on the retention of tocopherol.
- Solid state properties of the matrices were not affected by different cooling rates.

CHAPTER IV

Mechanistic study of carvacrol processing and stabilization as glassy solid solution and microcapsule

The following research paper with the title "Mechanistic study of carvacrol processing and stabilization as glassy solid solution and microcapsule" (DOI:10.1016/j.ijpharm.2014.12.012) has been published in the year 2015 by the International Journal of Pharmaceutics (Impact factor of 3.785 in the year 2013) in Vol. 478 on pages 597-605.

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Evaluation of the authorship:

Author	Idea [%]	Study design [%]	Experi-mental [%]	Evalua-tion [%]	Manu-script [%]
Markus W. Tackenberg	30	40	50	60	40
Carola Geisthövel	0	10	40	20	5
Andreas Marmann	0	0	10	10	5
Heike P. Schuchmann	15	0	0	0	10
Peter Kleinebudde	15	0	0	0	10
Markus Thommes	40	50	0	10	30

MECHANISTIC STUDY OF CARVACROL PROCESSING AND STABILIZATION AS GLASSY SOLID SOLUTION AND MICROCAPSULE

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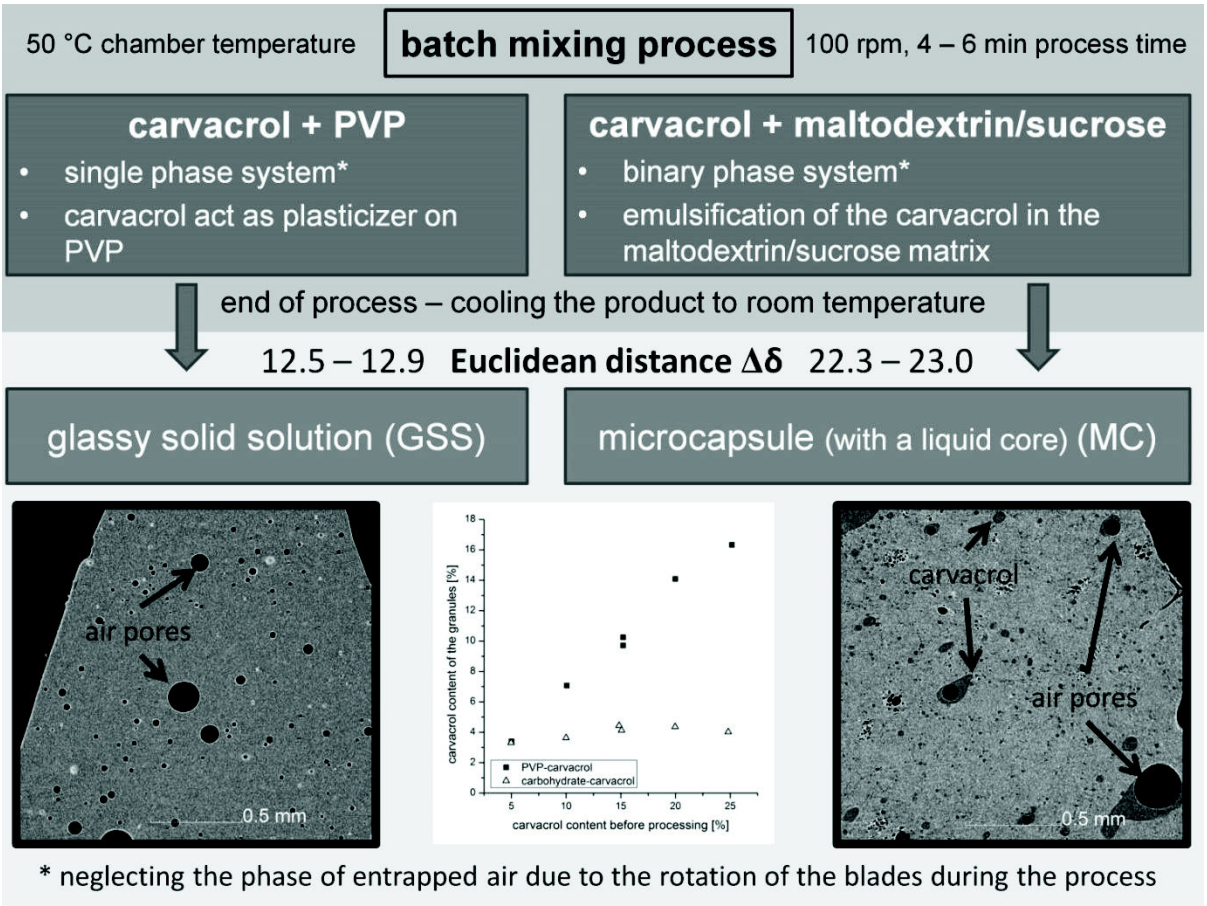
GRAPHICAL ABSTRACT



ABSTRACT

Essential oils and other liquid active pharmaceutical ingredients (APIs) are frequently microencapsulated to improve shelf life, handling, and for tailoring release. A glassy solid solution (GSS), a single-phase system, where the excipient is plasticized by the API, could be an alternative formulation system. Thus this study focuses on the investigation of two formulation strategies using carvacrol as a model compound, namely a microcapsule (MC) and a glassy solid solution (GSS). Applying the solubility parameter approach, polyvinylpyrrolidone (PVP) was chosen as a suitable matrix material for a GSS system, whereas maltodextrin and sucrose served as excipients for a microcapsule (MC) system. Differential scanning calorimetry (DSC) measurements of the excipients' glass transition temperatures and the melting point of carvacrol verified plasticizing properties of carvacrol on PVP. Batch mixing processes, as preliminary experiments for future extrusion processes, were performed to prepare GSSs and MCs with various amounts of carvacrol, followed by crushing and sieving. Maximally 4.5% carvacrol was encapsulated in the carbohydrate material, whereas up to 16.3% were stabilized as GSS, which is an outstanding amount. However, grinding of the samples led to a loss of up to 30% of carvacrol.

KEYWORDS

Carvacrol; Microencapsulation; Plasticization; Glassy solid solution; Carbohydrates; PVP

CHEMICAL COMPOUNDS

Chemical compounds studied in this article: Carvacrol (PubChem CID: 10364), Maltodextrin (PubChem CID: 107526), Methylene chloride (PubChem CID: 66344), Polyvinylpyrrolidone (PubChem CID: 6917), Sodium hydroxide (PubChem CID: 14798), Sucrose (PubChem CID: 5988)

CHAPTER V

Encapsulation of liquids using a counter rotating twin screw extruder

The following research paper with the title "Encapsulation of liquids using a counter rotating twin screw extruder" (DOI:10.1016/j.ejpb.2014.11.017) has been published in the year 2015 by the European Journal of Pharmaceutics and Biopharmaceutics (Impact factor of 4.245 in the year 2013) in Vol. 89 on pages 9-17.

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According to the valid legal situation, only the graphical abstract and the abstract are published in this thesis. The full text research article can be purchased at:

http://www.sciencedirect.com/science/article/pii/S0939641114003440

Evaluation of the authorship:

Author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Markus W. Tackenberg	20	50	40	80	50
Ralph Krauß	20	20	50	0	5
Andreas Marmann	0	0	10	10	5
Markus Thommes	20	30	0	5	10
Heike P. Schuchmann	20	0	0	0	15
Peter Kleinebudde	20	0	0	5	15

ENCAPSULATION OF LIQUIDS USING A COUNTER ROTATING TWIN SCREW EXTRUDER

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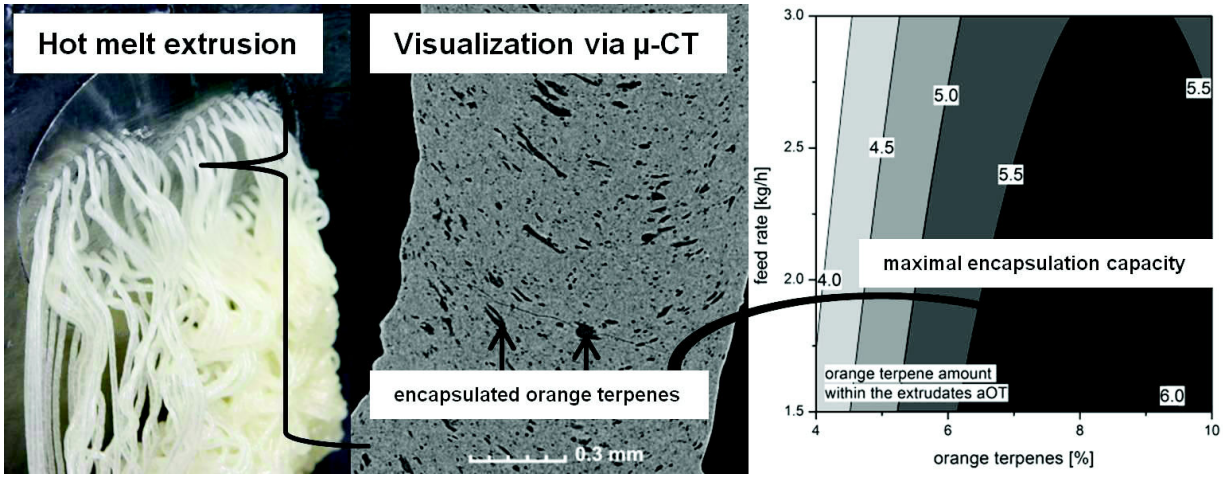
GRAPHICAL ABSTRACT



ABSTRACT

Until now extrusion is not applied for pharmaceutical encapsulation processes, whereas extrusion is widely used for encapsulation of flavours within food applications. Based on previous mixing studies, a hot melt counter-rotating extrusion process for encapsulation of liquid active pharmaceutical ingredients (API) was investigated. The mixing ratio of maltodextrin to sucrose as matrix material was adapted in first extrusion trials. Then the number of die holes was investigated to decrease expansion and agglutination of extrudates to a minimum. At a screw speed of 180 min^{-1} the product temperature was decreased below 142 °C, resulting in extrudates of cylindrical shape with a crystalline content of 9 - 16%. Volatile orange terpenes and the non volatile α-tocopherol were chosen as model APIs. Design of experiments were performed to investigate the influences of barrel temperature,

powder feed rate, and API content on the API retentions. A maximum of 9.2 % α-tocopherol was encapsulated, while the orange terpene encapsulation rate decreased to 6.0 % due to evaporation after leaving the die. During 12 weeks of storage re-crystallization of sucrose occurred, however, the encapsulated orange terpene amount remained unchanged.

KEYWORDS

Hot melt extrusion; Encapsulation; Orange terpenes; α-Tocopherol; API retention; Volatility; Sucrose; Maltodextrin; Storage stability

HIGHLIGHTS

- Liquid APIs are encapsulated by a hot melt extrusion process.
- The process was transferred from batch kneading to counter rotating twin-screw extrusion.
- Process parameters are optimized for the used carbohydrate matrix.
- Encapsulation efficiency was studied by using DOE.
- A two phase system is visualized by X-ray tomography.

CHAPTER VI

Encapsulation of orange terpenes investigating a plasticization extrusion process

The following research paper with the title "Encapsulation of orange terpenes investigating a plasticization extrusion process" (DOI:10.3109/02652048.2015.1035686) has been posted online on June 8, 2015 by the Journal of Microencapsulation (Impact factor of 1.878 in the year 2013). It is not yet published in a printed version.

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Evaluation of the authorship:

Author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Markus W. Tackenberg	10	40	40	100	65
Ralph Krauß	30	60	60	0	5
Heike P. Schuchmann	30	0	0	0	10
Peter Kleinebudde	30	0	0	0	20

ENCAPSULATION OF ORANGE TERPENES INVESTIGATING A PLASTICIZATION EXTRUSION PROCESS

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ABSTRACT

Extrusion is widely used for flavour encapsulation. However, there is a lack of process understanding. This study is aimed at improving the understanding of a counter rotating twin screw extrusion process. Orange terpenes as model flavour, maltodextrin and sucrose as matrix materials, and a water feed rate between 4.0% and 5.7% were applied. Product temperatures < 80 °C and specific mechanical energy inputs < 260 Wh/kg resulted. Amorphous and partly crystalline samples were obtained. The loss of crystalline sucrose was linked to a dissolution process of the sugar in the available water amount. Melting of the excipients did not arise, resulting in a plasticization extrusion process. Maximally 67% of the flavour was retained (corresponding to a 4.1% product flavour load). The flavour loss correlated with insufficient mixing during the process and flavour evaporation after extrusion. Based on these results, recommendations for an improved encapsulation process are given.

KEYWORDS

Flavour encapsulation; Melting; Maltodextrin; Plasticization; Sucrose; Twin screw extrusion

CHAPTER VII

Conclusion and future perspectives

1. Batch mixing

1.1. Advantages of batch mixing

The batch mixer proved to be a useful tool for pre-extrusion studies. The advantages clearly outweighed the disadvantages like loss of water and AI, due to a non hermetically sealing during the process and a lower shear gradient in comparison to extrusion. The benefits are convincing: Firstly, the physical changes in the matrix material caused by a combined shearing and heating process could be identified. Secondly, the solid state properties of the obtained processed material were correlated with these physical changes, the adjusted process parameters, and applied material compositions. Thirdly, the retention and stability of three different liquid AIs during mixing, shearing, and heating could be studied. Finally, the AI matrix structure could be analyzed in detail.

1.2. Physical changes during processing

The flavour encapsulation via extrusion using carbohydrate matrix material is described in literature as a melt process (Porzio, 2008, Risch, 1988, Zuidam and Heinrich, 2010). However, in the batch mixing experiments, three different physical processes occurred, depending on the adjusted process parameters and the chosen material composition: plasticization, melting, and caramelization. If water was added to the process, the carbohydrate mixture was plasticized, whereas the sucrose (partly) dissolved in the free water. The water loss due to evaporation during the process led to an increased viscosity, torque, product temperature, and finally melting. With prolonged operation time melting changed to undesired caramelization. Plasticization and melting were then transferred to two different extrusion processes within this thesis.

1.3. Solid state of AI free matrices

Porzio (2008) defined the physical state of commercial extruded flavours as glassy solids. Re-crystallization of the used disaccharides led to decreased storage stability (Gunning et al., 1999). The presence of partly crystalline extruded matrices has not been reported, yet. Amorphous and partly crystalline samples were obtained with the performed batch mixing experiments. The crystalline content was determined precisely by an investigated XRPD quantification method. Applying designs of experiments the amount of crystalline sucrose within the matrices was correlated with the selected process parameters and material compositions. The crystalline content could be estimated with an equation based on the solubility of sucrose in the water content of the processed mass at the determined product temperature, if only plasticization occurred during batch mixing.

The glass transition temperatures (Tg) of the amorphous fractions within the matrices were determined using DSC. It was shown in Chapter II, that the Tg could be calculated by applying the Gordon Taylor (GT) equation. As already described in literature, amorphous sucrose and water act as plasticizer on the maltodextrin. However, caramelization led to carbohydrate degradation products and thus to lower Tgs than predicted. That is why GT equation had to be rejected if caramelization occurred during the process. The cooling process of the matrices after sampling had no influence on the crystalline content as well as on the amorphous state.

1.4. Processing of the selected active ingredients

Three liquid lipophilic AIs, orange terpenes, carvacrol, and α-tocopherol served as model AIs for flavours as well as for essential and fatty oils with biological and/or pharmaceutical activity.

The batch mixer could not be closed hermetically during the process which led to evaporation of the AIs. The AI retention within the obtained samples correlated inversely with the calculated vapour pressures of the AIs at the obtained product temperatures. The highest amount of evaporation was determined for the AI orange terpenes.

The stability of the AIs during batch mixing was investigated, too. The findings were congruent with the investigations regarding the AI retention. α-Tocopherol remained completely stable, whereas the limonene amount within the orange terpenes was decreased from approximately 96 % to minimally 6 %, depending on the process conditions. Thus orange terpenes, the most sensitive AI towards various process conditions, was primarily used for the extrusion experiments.

1.5. Matrix structure containing AIs

All three AIs were processed during batch mixing with varying carbohydrate matrix compositions. However, no influence of the AIs on the processing of the matrix material was obtained. Torque and glass transition temperatures of the obtained matrices were not affected by varying AI concentrations. This was not generally expected, due to the observations of Yuliani et al (2009). These authors investigated torque decreasing and increasing effects of limonene on a starch matrix during extrusion processing.

The batch mixing results led to the assumption, that the AIs did not plasticize the carbohydrate matrices, which was investigated in detail and proofed using the AI carvacrol in chapter IV. Finally, the microcapsule structure was visualized using X-ray micro computerised tomography.

A totally different system, a glassy solid solution, was obtained using polyvinylpyrrolidone (PVP) as matrix material instead of carbohydrates. The used model AI carvacrol acted as plasticizer on PVP, which led to molecular dispersion of the AI within the matrix material.

An up to 3.7 times higher amount of carvacrol (absolute value: 16.3 %) was stabilized in PVP. However, the synthetic PVP as matrix materials cannot be used for all food applications, which was desirable for this thesis. Thus the universal applicable carbohydrates were used for the extrusion studies. Certainly the glassy solid solution system needs to be investigated in further studies, especially for pharmaceutical applications.

2. Extrusion

2.1. Hot melt extrusion

The evaluation of the batch mixing studies led to the conclusion, that melting as well as plasticization could be induced by extrusion processing. A counter-rotating TSE was used for the realization. Both processes resulting in matrices containing encapsulated AIs.

In literature a hot melt extrusion (HME) process for encapsulation of lipophilic liquid AIs has not been described before. Based on the batch mixing studies the HME process was designed for the encapsulation of various active liquids in a maltodextrin sucrose matrix. Partly crystalline carbohydrate extrudates containing maximally 6.0 % orange terpenes and 9.2 % α-tocopherol were obtained. The decreased encapsulated orange terpene content in contrast to α-tocopherol was due to evaporation of the AI, after the hot mass left the die. Amorphous matrices could not be obtained, due to the adjusted process parameters. Storage at 25 °C / 60 % r.h. led to water sorption and re-crystallization of amorphous sucrose, but not to a significant release of encapsulated orange terpenes. Storage at 40 °C / 75 % r.h. led to collapsed rubbery matrices due to Tgs lower than storage temperature. However, AI release was not detected. This was surprising, due to different reports in literature (e.g. Gunning et al., 1999).

2.2. Plasticization extrusion

In literature encapsulation of flavours using extrusion technique is often called melt extrusion (Porzio, 2008, Zuidam and Heinrich, 2010). However, water is fed into the extruder barrel and mixed with the carbohydrate powder. Within this thesis the mixing process during extrusion was analysed and defined as a plasticization and dissolution process. Melting of the carbohydrate matrices was not determined. Amorphous matrices were obtained, if sucrose amounts lower than 40 % of the preblended powder mixtures were applied. Using powder mixtures with higher amount of sucrose led to partly crystalline products. It was shown, that the crystalline content of the obtained samples can easily be estimated, adopting the equation used in the batch mixing process for the same purpose. The adjustment of the water feed rate was technically challenging in the industrial set-up used in this study, due to the continuous feeding of very low amounts of water (< 280 g/h). The water feed rate has to be adjusted to the amount of sucrose within the powder mixture. A too high amount of both plasticizers led to a sticky, rubbery, and low viscous mass, which left the die, whereas a too low amount led to an emergency shutdown of the extruder, due to the exceeding of the torque maximum. Finally, extrudates with maximally 4.1 % encapsulated orange terpenes were obtained. This decreased AI amount, in comparison to HME, was assigned to insufficient mixing during the process and to

increased evaporation of the AI after the product left the die, due to the downstream applied hot die face cutting.

2.3. HME vs. plasticization extrusion

In comparison, both extrusion processes have specific advantages and disadvantages. Using HME, high energy input in the product will be obtained, due to the absence of an additional plasticizer. This led to an increased product temperature and to a different mixing behaviour of the AI within the matrix material in comparison to plasticization extrusion. A high product temperature is a disadvantage, if volatile AIs have to be encapsulated. However, the HME process led to products with increased AI content in comparison to plasticization extrusion, due to the improved mixing behaviour of AI and matrix during the process. Additionally the glass transition temperature of the obtained products was much higher (50 - 57 °C in comparison to 19 - 41 °C), due to the missing additional plasticizer water. This led to an improved storage stability (Gunning et al., 1999). It should certainly be noted, that the products with minimal water contents are sensitive to water sorption during storage which lead to decreasing Tgs. This can be prevented by hermetically sealing. Furthermore the HME process is easier to handle in an industrial environment and systematically / statistically evaluable. However, with the use of water amorphous or partly crystalline products can be obtained, whereas only partly crystalline samples have been received using HME. Amorphous products obtained by plasticization extrusion contained an increased AI content in comparison to partly crystalline samples obtained by the same extrusion process. Thus an HME process leading to amorphous products should be investigated in the future. Summary of the results of this thesis: Based on batch mixing studies, liquid lipophilic AIs were encapsulated in maltodextrin sucrose matrices applying a novel hot melt and precisely characterised plasticization extrusion process for pharmaceutical and food applications.

3. Some critical considerations

Some critical points need to be addressed at this point. A major disadvantage of both processes is the determined maximal encapsulation capacity below 10 % AI, for volatile AIs even below 6 %. In literature the encapsulated flavour content of extrudates is given with 8 - 12 % (Porzio, 2008). During both investigated processes the liquids periodically squirted out of the die when an AI feed rate of 10 % (or lower) was applied. The encapsulation capacity can be improved by increasing the droplet break-up and/or decreasing the droplet coalescence. This can be done in multiple ways e.g. modifying the material composition, thermal and mechanical energy input. In the patent literature many additives are listed, which are used by the flavour companies to increase the liquid AI load: various emulsifiers like lecithin (Blake and Attwool, 1996), modified starches and pectin (Porzio and Popplewell, 1997), agar agar (McIver et al., 2002), and special dextrins like Nutriose® FB as well as gum arabic (Bouquerand, 2012). Thus this work can only be the beginning of detailed research for improving the maximal encapsulation capacity.

4. Future perspectives

As discussed before, the matrix composition can be varied in multiple ways. As a logical next step sucrose can be replaced by a lower melting carbohydrate or similar matrix material. This would decrease the energy input and the product temperature during HME, and in terms of technical realisation and robust processes caramelization will be prevented. Probably amorphous matrices will be obtained, too. The low water feeding rates during plasticization extrusion can be replaced by conditioning the preblended powder mixtures at a higher relative humidity.

The viscosity of the processed masses at various process conditions should be investigated in detail to draw conclusions regarding the desired AI droplet break-up and the undesired droplet coalescence, to adopt screw configuration and matrix composition.

The use of emulsifiers should be considered. For choosing a suitable additive and concentration batch mixing studies, applying design of experiments, are recommended. The interactions between matrix and emulsifier as well as between emulsifier and AI should be investigated. Probably the obtained solid state system(s) differ(s) from the investigated microcapsule system.

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CHAPTER VIII

Summary

Until now the encapsulation of liquid AIs / APIs using a twin screw extruder (TSE) has not been described for pharmaceutical applications. However, for years the encapsulation of flavours using a TSE has been a common technique in the food sector. A lot of patents were registered and some products are successfully distributed. Nevertheless the extrusion process itself is only described rudimentarily in a few publications.

Thus it was the main aim of this thesis to investigate the mechanisms of encapsulating liquid AIs via extrusion processing, applicable for life science products (drug products and food). Maltodextrin and sucrose were selected as matrix materials. For years this combination has been described in literature for similar applications.

A batch mixer was used for the first studies, due to the complexity of a continuous extrusion process. The influences of different process parameters and material compositions on the process and on the solid state of the obtained samples were investigated. Three different physical processes during batch mixing were identified. Firstly the maltodextrin sucrose mixture got plasticized by the added water. Secondly, after a variable process time, the mass started to melt. Finally, the melt process turned into caramelization.

In a further study three model AIs orange terpenes, carvacrol, and α-tocopherol were added individually to batch mixing processes of the carbohydrate matrices. Varying AI contents were determined in the obtained products. The retained AI contents were successfully correlated with the calculated vapour pressures of the model substances. Finally the AIs had no influence on the process as well as on the solid state properties of the obtained matrices.

This observation was further investigated using carvacrol as model AI. Various methods, calculation of solubility parameters, DSC, and μ-CT measurements were used to characterise the carvacrol matrix structure. Therefore the known carbohydrate matrix was compared to polyvinylpyrrolidone (PVP) as an alternative matrix material. Finally a microcapsule structure was identified using the carbohydrates, whereas a solid glassy solution was obtained by using PVP.

Further, a hot melt extrusion process was developed, based on the identified melting process during batch mixing. Matrix composition, die geometry, and different process parameters were investigated to obtain cylindrical extrudates. Finally, maximally 6 % orange terpenes and 9.2 % α-tocopherol were microencapsulated in the obtained extrudates. The stability of some orange terpene extrudates was investigated at two different storage conditions. Water sorption, crystallization, and a partly collapse of the cylindrical extrudates occurred. However, the AI content remained constant.

In the final study the plasticization process during batch mixing was used to develop a plasticization extrusion process. It turned out, that the water feeding rate had to be adjusted

inversely to the amount of sucrose within the applied powder mixture in order to receive a solid cylindrical extrudate. Maximally an amount of 4.1 % orange terpenes could be encapsulated. Moreover, amorphous and partly crystalline products were received, depending on the amount of sucrose within the powder mixture. Thus a wider spectrum of solid states can be obtained with this extrusion process in comparison to HME, where always partly crystalline matrices were received.

In summary, based on batch mixing studies, two different extrusion processes for encapsulation of liquid AIs were systematically developed and characterised. Both processes are applicable for pharmaceuticals and foods. Finally this thesis can be used to investigate the physical processes during various extrusion encapsulation processes, which may help to improve extrusion and the obtained products.

CHAPTER IX

Zusammenfassung

Die Verkapselung von flüssigen "aktiven Substanzen" / Arzneistoffen mittels eines Zweischnecken-Extruders ist für pharmazeutische Anwendungen noch nicht beschrieben worden. Allerdings ist die Verkapselung von Aromen mittels Extrusion eine im Lebensmittelbereich seit Jahren gängige Technik. Vieles wurde patentiert und einige Produkte werden erfolgreich vermarktet. Trotzdem ist der Prozess an sich nur schematisch in wenigen Publikationen beschrieben worden.

Aus diesem Grund war es Ziel dieser Arbeit, basierend auf dem Wissen der Aromenextrusion, die Mechanismen des Verkapselungsprozesses von flüssigen Wirkstoffen für Anwendungen im Bereich Life Science (Arznei- und Lebensmittel) zu identifizieren und detailliert zu untersuchen. Als Matrixmaterial wurden Maltodextrin und Saccharose gewählt, welche in Kombination bereits häufig für ähnliche Zwecke verwendet wurden.

Auf Grund der Komplexität eines kontinuierlichen Extrusionsprozesses wurden erste Untersuchungen mit einem Batch-Kneter durchgeführt. Dabei wurden die Auswirkungen verschiedener Prozessparameter und Materialzusammensatzungen auf den Prozess und den festen Zustand der erhaltenen Proben untersucht. Drei verschiedene physikalische Prozesse wurden identifiziert. Zu Beginn wurde die Maltodextrin-Saccharose-Mischung durch das zugesetzte Wasser plastifiziert. Je nach gewählten Parametern kam es unterschiedlich schnell zu einem Schmelzen der Kohlenhydrate mit anschließender Karamellisierung.

In einer weiteren Studie wurde das Batch-Knet-Verfahren mit den drei ausgewählten Modellsubstanzen Orangenterpene, Carvacrol und α-Tocopherol durchgeführt. Die gewonnen Proben enthielten einen unterschiedlichen Wirkstoffgehalt, was mit den berechneten Dampfdrücken korreliert wurde. Außerdem beeinflussten die Wirkstoffe weder den Prozess noch die Matrix.

Dies wurde mit Carvacrol näher untersucht. Verschiedene Methoden, wie die Berechnung von Löslichkeitsparametern, DSC Messungen und µ-CT Aufnahmen wurden eingesetzt, um die Carvacrol-Matrix-Struktur zu charakterisieren. Dabei wurden die Kohlenhydrate verglichen mit Polyvinylpyrrolidon (PVP) als alternativer Matrixsubstanz. Letztendlich wurde eine Mikrokapselstruktur bei Verwendung der Kohlenhydrate und eine glasartige feste Lösung bei Verwendung von PVP identifiziert.

Der im Batch-Knet-Verfahren festgestellte physikalische Schmelzvorgang wurde in einer weiteren Studie auf einen Schmelzextrusionsprozess bei Verwendung eines gegenläufigen Doppelschneckenextruders übertragen. Dabei wurden die Matrixzusammensetzung, Düsengeometrie und unterschiedliche Prozessparameter untersucht, um zylindrische Extrudate zu erhalten. Maximal 6 % Orangenterpene bzw. 9.2 % α-Tocopherol wurden dabei mikroverkapselt. Anschließend wurde die Stabilität ausgewählter Orangenterpen-

Extrudate bei unterschiedlichen Lagerungsbedingungen getestet. Dabei kam es zwar zur Wassersorption, Rekristallisierung und teilweisem Kollabieren der zylindrischen Extrudate, allerdings nicht zu einem Verlust des Wirkstoffes durch Verflüchtigung.

In der finalen Studie wurde der im Batch-Kneter identifizierte Plastifizierungsprozess ebenfalls in einen Extrusionsprozess umgesetzt. Dabei musste die dosierte Wassermenge immer auf den verwendeten Saccharosegehalt in der Pulvermischung eingestellt werden, um ein zylindrisches Extrudat zu erhalten. Die Extrudate enthielten maximal 4.1 % Orangenterpene. Im Gegensatz zum Schmelzextrusionsprozess wurden mit diesem Plastifizierungs-Extrusionsprozess neben teilkristallinen auch amorphe Proben erhalten.

Zwei verschiedene Extrusionsprozesse wurden auf Basis von Batch-Knet-Studien zur Verkapselung von flüssigen Wirkstoffen systematisch entwickelt und charakterisiert. Diese beiden Prozesse sind sowohl für pharmazeutische als auch lebensmitteltechnische Applikationen anwendbar. Somit wurde durch die vorliegende Arbeit eine Basis geschaffen, um die physikalischen Prozesse in diversen Extrusions-Verkapselungsverfahren besser zu verstehen und somit die Verfahren und die Produkte weiter optimieren zu können.

CHAPTER X

Original publications and contributions to meetings

1. Original publications

M.W. Tackenberg, M. Thommes, H.P. Schuchmann, P. Kleinebudde, Solid state of processed carbohydrate matrices from maltodextrin and sucrose. J. Food Eng. 129 (2014) 30-37.

M.W. Tackenberg, A. Marmann, M. Thommes, H.P. Schuchmann, P. Kleinebudde, Orange terpenes, carvacrol and α-tocopherol encapsulated in maltodextrin and sucrose matrices via batch mixing. J. Food Eng. 135 (2014) 44-52.

M.W. Tackenberg, C. Geisthoevel, A. Marmann, H.P. Schuchmann, P. Kleinebudde, M. Thommes, Mechanistic study of carvacrol processing and stabilization as solid solution and microcapsule, Int. J. Pharm. 478 (2015) 597-605.

M.W. Tackenberg, R. Krauss, A. Marmann, M. Thommes, H.P. Schuchmann, P. Kleinebudde, Encapsulation of liquids using a counter rotating twin screw extruder. Eur. J. Pharm. Biopharm. 89 (2015) 9-17.

M.W. Tackenberg, R. Krauss, H.P. Schuchmann, P. Kleinebudde, Encapsulation of orange terpenes investigating a plasticization extrusion process. J. Microencapsul. posted online on June 8, 2015.

2. Poster presentations

M.W. Tackenberg, M. Thommes, P. Kleinebudde, H.P. Schuchmann, Untersuchungen zur Verkapselung von Aromastoffen in amorphen Matrices durch Formgebende Extrusion für Anwendungen im Bereich Life Sciences, Annual meeting of the Research Association of the German Food Industry (FEI), Karlsruhe, Germany, 2013.

M.W. Tackenberg, M. Horvat, M. Thommes, P. Kleinebudde, H.P. Schuchmann, Identification of factors affecting the sorption isotherms of spray dried binary carbohydrate mixtures containing maltodextrin and sucrose, Annual meeting of the Germany Pharmaceutical Society (DPhG), Greifswald, Germany, 2012.

M.W. Tackenberg, M. Horvat, M. Thommes, P. Kleinebudde, H.P. Schuchmann, Investigation of glassy and rubbery spray dried ternary carbohydrate blend compositions, 8th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Istanbul, Turkey, 2012.

M.W. Tackenberg, M. Hirth, M. Thommes, P. Kleinebudde, H.P. Schuchmann, Untersuchungen zum Einfluss der Prozessparameter auf die Löslichkeit und das Freisetzungsverhalten von (koch)extrudierten Stärkematrices am Beispiel von Vitamin B1, Annual meeting of the ProcessNet section groups Agglomeration and Bulk Solids Technology & Crystallization, Wittenberg, Germany, 2012.

M.W. Tackenberg, M. Horvat, P. Kleinebudde, H.P. Schuchmann, Influence of water activity and matrix composition on the glass transition temperature of amorphous biopolymeric blends produced for the encapsulation of liquid aromas, European Congress of Chemical Engineering/Applied Biotechnology, Berlin, Germany, 2011.

M. Hirth, F. Gmoser, V. Radu, M.W. Tackenberg, M. Horvat, J. Le Grandois, D. Werner, E. Marchioni, H.P. Schuchmann, Incorporation of labile bioactives into ready-to-eat cereals by high-speed extrusion processing, European Congress of Chemical Engineering/Applied Biotechnology, Berlin, Germany, 2011.

3. Oral presentations

M.W. Tackenberg, A. Marmann, M. Thommes, P. Kleinebudde, H.P. Schuchmann, Stabilisierung von Orangenölaroma in kohlenhydratbasierten Granulaten mittels eines gegenläufigen Doppelschneckenextrusionsprozesses, Annual meeting of the ProcessNet section group Food Technology at the German Institute of Food Technology, Quakenbrueck, Germany, 2013.

M. Hirth, E. Mayer-Miebach, J. Le Grandois, D. Werner, M.W. Tackenberg, M. Horvat, H.P. Schuchmann, Hohe Energieeinträge bei kurzen Verweilzeiten: Stabilität von Polyphenolen in stärkebasierten Produkten im Kochextrusionsprozess, Annual meeting of the ProcessNet section group Plant based Extracts – Products and Processes, Clausthal-Zellerfeld, Germany, 2012.

M.W. Tackenberg, M. Horvat, C. Rüfer, P. Kleinebudde, H.P. Schuchmann, Untersuchungen zur Verkapselung von Carvacrol in amorphen Matrices mittels Formpressung für Anwendungen im Bereich Life Sciences, Annual meeting of the ProcessNet section groups Agglomeration and Bulk Solids Technology & Drying, Hamburg-Harburg, Germany, 2011.

CHAPTER XI

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