Bioencapsulation Research Group

Bioencapsulation Innovations

January 2015

CONTENTS

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EDITORIAL

DRUG TARGETING AND ENCAPSULATION

In the past few years, considerable advances of basic and application researches have taken place in the field of pharmaceutics. The newly recognized research thrust on nano- and microencapsulation is expected to have a revolutionary impact on the human health. To do this, considerable interest has been devoted towards the design of new drug delivery systems with the aim to specifically target the drug, such that the drug is released at a controlled rate and at the desired time.

The final aim of site-specific delivery is to minimize or eliminate the undesirable side effects. Targeted drug delivery, also called smart drug delivery, is a method of delivering drugs to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. The goal of a targeted drug delivery system is to prolong, localize, target and have a protected drug interaction with the diseased tissue.

The conventional drug delivery system is the absorption of the drug across a biological membrane, whereas the targeted release system releases the drug in a dosage form. Indeed, in traditional drug delivery systems such as oral ingestion or intravascular injection, the medication is distributed throughout the body through the systemic blood circulation. For most therapeutic agents, only a small portion of the medication reaches the organ to be affected. Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues.

The advantages to the targeted release system is the reduction in the frequency of the dosages taken by the patient, having a more uniform effect of the drug, reduction of drug side-effects, and reduced fluctuation in circulating drug levels. The disadvantage of the system is high cost, which makes productivity more difficult and the reduced ability to adjust the dosages.

To reach this aim, different strategies have been developped. To support them, several innovative drug carriers have been designed like liposomes, polymer-drug conjugates, antibody-drug conjugates, micelles, dendrimers, nanoparticles, nanocapsules, microparticles, microcapsules, nanoemulsions, microemulsions, artificial DNA structures, ... Different techniques of encapsulation have been described using ultrasonic devices, microfluidic systems, (auto)emulsifications, coacervation, ...

The potential of drug delivery strategies involve the use of nano- (micro) carriers for controlling, for instance, the biodistribution of antitumor drugs: passive targeting (through the enhanced permeability and retention effect, EPR effect) and active targeting (including stimuli-sensitive carriers and ligand-mediated delivery).

Finally, the problem of «nano- (micro) toxicity» in cancer treatments has also to be mentioned and studied since at this time there are few studies of the long-term consequences of nano-(micro)particles on human health. In particular, non degradable materials constituting the nano- (micro)carriers can accumulate into the cells and/or organs and exert damage effect as well as their degradation products.

It is important to note that in the literature conflicting results are present. These are likely caused by variations in type, composition, size, shape, surface charge, and modifications of nano- (micro)carriers employed; use of various in vivo and in vitro models (the cell death mode may be also cell type dependent); experimental procedures (different methods to evaluate cell death; materials dose, concentrations and efficiency of cellular uptake, and time of exposure).

Prof. Thierry Vandamme

Strasbourg University, France

CALENDAR

PROGRAM 2015

January

EPNOE : Course - Polysaccharides for health and well-being
January 21-22 , 2015
Wageningen, the Netherlands
http://www.epnoe.eu/Education

International Workshop Polyelectrolytes in Chemistry, Biology and Technology
January 26-28, 2015
Singapore, Singapore
http://www.ntu.edu.sg/ias/upcomingevents/Polyelectrolytes15/Pages/default.aspx

Nano-Poudres, Nano-Materiaux, Nano-Objets : Produits Du Futur De La Molecule Au Consommateur
January 29, 2015
Villeneuve d'Ascq, France
http://www.sfgp.asso.fr/fileadmin/document/Annonces_Journees/2015_01_29-Journee_Genie_du_Produit/Journee_Nanotechnologies_a_Lille_-_29_Janvier_2015.pdf

February

6th AnnualGlobal Drug Delivery and Formulation 2015
February 9 - 11, 2015
Dusseldorf, Germany
http://www.ddfevent.com

February

6th training School on Bioencapsulation
February 23-27, 2015
Strasbourg, France
http://bioencapsulation.net/2015_Strasbourg/

4th Galenus Workshop "Drug Delivery to Human Skin"-
25th – 27th of February, 2015
Saarland University, Germany
http://www.uni-saarland.de/lehrstuhl/lehr-lab.html

March

Biohydrogels Workshop
March 5-6, 2015
Nantes, France
www.univ-nantes.fr/biohydrogels-workshop

April

8th International Conference on Bio-based Materials
April 3 - 15, 2015
Maternushaus, Cologne, Germany
http://www.biowerkstoff-kongress.de

1st European Conference on Pharmaceutics: Drug Delivery
April 13-14, 2015
Paris, France
http://apgi.org/Reims2015.htm

18th Microencapsulation Industrial Convention
April 22-24, 2015
Eindhoven, Netherlands
http://bioencapsulation.net/2015_Eindhoven/

May

Polymerix 2015 : Biosourced polymers
May 28 et 29, 2015
Rennes, France
http://www.cbb-developpement.com/index.php?option=com_content&task=view&id=506&Itemid=666

June

7th International Symposium on Food Rheology and Structure (ISFRS 2015)
June 7 - 11, 2015
Zurich, Switzerland
http://www.isfrs.ethz.ch

18th Gums & Stabilisers for the Food Industry Conference Hydrocolloid functionality for affordable and sustainable global food solutions
Glyndwr Univ., Wrexham, UK
June 23rd - 26th 2015
http://www.foodhydrocolloidstrust.org.uk

Septembre

The 2015 Tissue Engineering Congress
8th -10th September 2015
London, UK
www.regonline.co.uk/Tiss2015

23th International Conference on Bioencapsulation
September 2-4, 2015
Delft, Netherlands
http://bioencapsulation.net/2015_Delft/

PROGRAM 2016

April

10th Workd Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology
April 4-7, 2016
Glasgow, UK
http://www.worldmeeting.org/home/

FUTURE CONFERENCES AND EVENTS SUPPORTED BY THE BRG

7TH TRAINING SCHOOL ON BIOENCAPSULATION

Strasbourg, France
February 23-27, 2015
11 lectures and
3 half days of practical demonstrations
http://bioencapsulation.net/2015_Strasbourg/

18TH MICROENCAPSULATION INDUSTRIAL CONVENTION

Eindhoven, Netherlands
April 22-24, 2015
12 lectures, one exhibition
and hundreds of
one-to-one meetings
http://bioencapsulation.net/2015_Eindhoven/

23TH INTERNATIONAL CONFERENCE ON BIOENCAPSULATION

Delft, Netherlands
September 2-4, 2015
40 oral presentations and
tens of posters
http://bioencapsulation.net/2015_Delft/

International Microencapsulation Society

20TH INTERNATIONAL SYMPOSIUM ON MICROENCAPSULATION

Boston, USA
October 1-3, 2015 -

http://www.northeastern.edu/ims2015/

ARTICLE

PHARMACEUTICAL NANOTECHNOLOGIES: LECITHIN/CHITOSAN NANOPARTICLES

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Nanomedicine has been defined as "the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain and of preserving and improving human health, using molecular tools and molecular knowledge of the human body" (Duncan, 2011). To act at the molecular level, dosage forms of very low size are required. These delivery systems basically derive from a dramatic size reduction of conventional dosage forms to values in the range 1-1000 nm. Pharmaceutical nanotechnologies exploit polymers to build drug-polymer conjugates, polymer micelles or matrix-type nanoparticles, as well as lipids (e.g. liposomes, solid lipid nanoparticles) and also combinations thereof, as in oily-core nanocapsules. Colloidal nanoparticles made of polymers and lipids are considered biocompatible, biodegradable and safe for various administration routes. Nanocarriers protect loaded drugs from degradation, increase their aqueous solubility, promote transmucosal absorption and cellular uptake, overall improving drug bioavailability.

In recent years a colloidal nanoparticle system obtained by interaction between the cationic polysaccharide chitosan and soybean lecithin has been proposed (Fig. 1) (Sonvico F., 2006).

These nanoparticles form spontaneously following a self-assembly process, driven by the electrostatic interaction between the positively charged chitosan and the negatively charged phospholipids of lecithin. Differently from other particles, manufacturing is simple and easily scalable. While chitosan is dissolved in acidic water, lecithin and the hydrophobic drug to encapsulate are dissolved in alcohol. The alcoholic solution is then added to the water phase under stirring to form the nanoparticles. It was demonstrated that 20 parts of lecithin to 1 part of chitosan is the optimal weight ratio to obtain nanoparticles of about 200-250 nm in size with a strong positive surface charge, which stabilizes the colloidal dispersion.

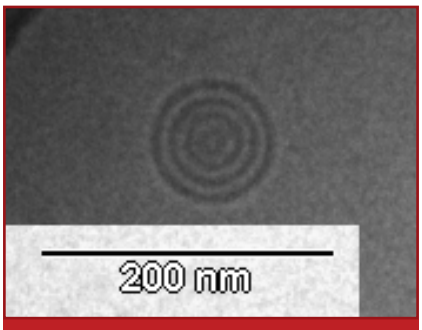

Fig.1. Cryo-TEM microphotograph of a LCN.

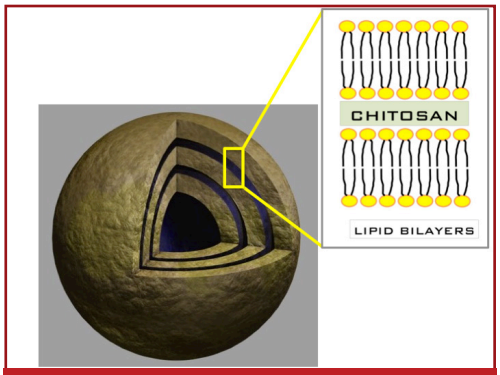

Fig. 2. Representation of the structure of LCNs.

A comprehensive investigation of the physical properties of the system elucidated the particle structure, represented by condensed liposomes with chitosan intercalated between two phospholipid bilayers to increase the particle density (Fig. 2) (Gerelli, 2008). The presence of a polysaccharide-based shell is useful to tailor the surface charge and properties of the nanomaterial, while the lipid core provides the vehicle to solubilize and efficiently encapsulate lipophilic drugs. Particle characteristics (size, charge, morphology) may vary in consequence of the encapsulation of the drug, although without affecting the system's performance and stability.

So far, these lecithin/chitosan nanoparticles (LCNs) have been studied as carriers for drug administration by the oral route (progesterone, tamoxifen citrate) (Sonvico, 2006; Barbieri, 2013), dermal application of corticosteroids (clobetasol-17-propionate, diflucortolone valerate) (SenyiÐit, 2010; Ozcan, 2013), transdermal delivery of melatonin (Hafner, 2011a) and also for functional food applications (Souza, 2014) Initially, progesterone was chosen as model lipophilic drug, showing encapsulation efficiencies up to 60%, although dependent on the amount of drug in the preparation. In contrast, encapsulation of a hydrophilic compound (metoclopramide hydrochloride) was unsatisfactory.

More recently, LCNs loaded with tamoxifen citrate for the oral treatment of estrogen-dependent breast cancer were developed (Barbieri, 2013). Few anticancer drugs are enough water soluble and permeable to allow for their efficient administration per os. Nanocarriers could improve their oral bioavailability, therapeutic efficacy and safety profile, as long as the encapsulated drug is masked within the nanostructure. Indeed, it was shown that enzymes typically present in the gastrointestinal tract (in particular lipase and lysozyme) triggered the in vitro release of tamoxifen citrate from LCNs by degrading the nanoparticle structure. Thus, the drug remained encapsulated and protected in conditions similar to the gastric environment and started being released only in a simulated intestinal fluid with enzymes. Furthermore, ex vivo transport experiments with excised rat intestinal mucosa demonstrated that the nanoparticles enhanced tamoxifen transport across the tissue. In fact, LCNs guaranteed mucoadhesion to the mucosal surface and increased paracellular transport likely owing to chitosan acting on intercellular tight junctions. Interestingly, it was found that it was the direct contact between nanoparticles and mucosa that increased drug permeation. In addition, LCNs allowed the drug to escape intracellular metabolism as tamoxifen mostly diffused in its intact (non metabolized) form.

The corticosteroid clobetasol17-propionate (CP) was encapsulated with very high efficiency (> 90%) in LCNs for dermal application. In vitro transport experiments with pig ear skin showed that the nanoparticle dispersion significantly increased CP accumulation in the skin (particularly in the epidermis,

target site of topical steroidal treatment) in comparison with conventional dosage forms such as a chitosan gel and a commercial cream containing the same drug (Senyiğit, 2010). In order to facilitate the cutaneous application, the CP colloidal formulation was incorporated into a chitosan gel at different ratios without any physical and chemical stability problem. As the carrier significantly accumulated CP into the skin, no significant permeation was observed. This meant that side effects related to topical steroidal treatment could be reduced, improving the risk–benefit balance of these drugs. In contrast, Hafner et al. (2011a) prepared melatonin-loaded lecithin/chitosan nanoparticles showing increased melatonin flux in vitro (1-2 folds) across pig skin compared to an aqueous melatonin solution. In vitro they showed that LCNs can be safely applied to skin cells (human skin keratinocytes and fibroblasts) at concentrations up to 200 mg/ml without inducing cytotoxicity.

As future perspective, these nanoparticles appear interesting for administration also to mucosal tissue such as in the nose. In this regard, the presence of chitosan is advantageous due to its mucoadhesive properties, which may prolong retention within the nasal cavity and enhance drug permeability.

Finally, it must be highlighted that the nanocarrier eventually has to become a finished medicinal product for use in clinical practice. It is likely that for administration purposes, stability issues or patient convenience, the nanoparticles require further transformation into a larger dosage form, even if transitorily. This transformation should be achieved by technologies able to temporarily "mask" the nanoparticles within a bigger structure preserving their original size. This can be done with LCNs as described by Cagnani et. al. (2004) who realized a powder for nasal delivery of the drug-loaded nanoparticles. Spray drying (in the presence of a filler) transformed the nanoparticles into microparticles, which were then agglomerated by tumbling to form coarse soft globules (Fig. 3). After insufflation by a suitable device, these agglomerates broke down into smaller fragments of aggregated microparticles that, upon disintegration in physiological fluids, released intact the original nanocarriers. In this way a solid product containing the nanocarrier can be proposed to build the finished dosage forms to suit different routes of administration, therapies and patients (Buttini, 2012). Recently, lyophilization was also exploited to dry a liquid dispersion of piroxicam-loaded LCNs with a view of stabilizing the system and facilitating its handling during manufacturing of an oral product (unpublished data). Compared to spray drying, freeze-drying seems less effective with respect to restoration of the original size of the nanocarrier upon reconstitution of the powder in water. Stability of lyophilized lecithin/chitosan nanoparticles loaded with melatonin has been evaluated in the short- and long term and resulted dependent on the cryoprotectant used (Hafner, 2011b).

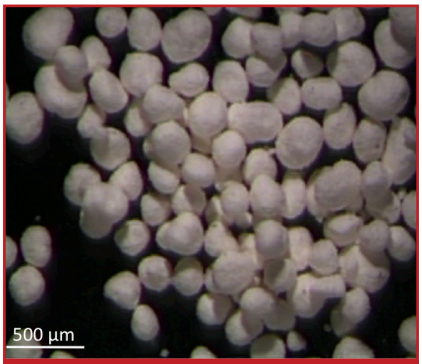

Fig.3. Agglomerates of microparticles, the latter obtained by spray drying LCNs in the presence of a filler.

In conclusion, nanocarriers based on polysaccharide and lipid materials owing to easy manufacturing scale-up, stability, versatility of administration appear very interesting for a rapid technology transfer to novel drug products implementing pharmaceutical nanotechnology into traditional dosage forms.

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Dr. Colombo graduated in Pharmaceutical Chemistry and Technology at University of Parma (Italy) in 2001 after research internships in France and USA. Since 2004 she is Assistant Professor at University of Ferrara (Italy). Her research concerns nasal, respiratory and oral drug delivery, focusing on technological/biopharmaceutical aspects of dosage form manufacturing. She published 41 papers and 4 patents.

ARTICLE

BI-COMPARTMENTAL ENCAPSULATION OF TWO DRUGS WITH DIVERSE SOLUBILITY IN JANUS MICROPARTICLES

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[a, b] University of Strasbourg (UdS), France - [c] Government College (GC) University, Faisalabad, Pakistan.

INTRODUCTION

Active pharmaceutical ingredients are administered by different routes but oral administration remains the most physiological and convenient way of delivering drugs (Delie and Blanco-Príeto, 2005). Different drug delivery systems are used for oral administration but microparticles have added advantages over single unit systems like less chance of dose dumping and local irritation, increased bioavailability, low dependence on gastric emptying time etc. Microencapsulation is used to develop microparticles where active materials are entrapped in a matrix or reservoir for protection and controlled release of drug(s), patient comfort and compliance by reduced frequency of administration (Khan et al., 2013). Conventional microencapsulation methods (emulsion solvent evaporation, emulsion solvent diffusion etc.) show poor drug loading, poly-dispersity and batch to batch variation (Holgado et al., 2008). Microfluidics can overcome these problems by producing microparticles having a very narrow size distribution (Serra and Chang, 2008), high encapsulation efficiency and also particles with diverse morphologies. In general, it is not suitable to incorporate two drugs of dissimilar solubilities in a single particle. So, Janus particles would provide suitable alternative for the aforementioned problems.

FABRICATION OF JANUS

A simple off-the-shelf side-by-side microfluidic device (Fig 1) was used to synthesize Janus particles of poly(acrylamide)/poly(methyl acrylate) encapsulating a hydrophilic sodium fluorescein and a lipophilic ketoprofen as model drug respectively. Two monomer dispersed phases, admixed with the drugs, were injected into a continuous phase (Silicon oil of 500 cSt viscosity) through a fused silica capillary (internal diameter (I.D) 100 µm) placed in an outlet PTFE tubing (I.D. 1.6 or 1 mm or 0.5). Once bi-phasic droplets are generated they are polymerized downstream by UV irradiation having an intensity of 276 mW/cm2 (Hamamatsu Lightningcure LC8) (Fig 1). Janus particle were collected at the exit of the collecting tube and washed with ethyl acetate, dried and stored in glass vials until further use.

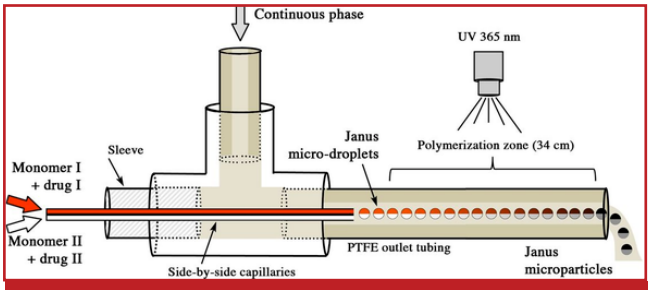

Figure.1: Setup of side-by-side microfluidic device.

Particle size analysis was performed by Hiris version 3 (R & D Vision) software and has shown decrease in size by increasing the ratio of continuous to dispersed phase flow rates (Qc/Qd) in flow focusing arrangement, or by decreasing collecting tube internal diameter. In most cases coefficient of variation was less than 5% except when operated at a high Qc/Qd ratio i.e. 120 & 240, or when the collecting tube internal diameter was 0.5 mm. (Fig 2). Optical and SEM microscopy confirmed Janus structure while Raman spectroscopy confirmed different chemistry on each side of bi-compartmental particles.

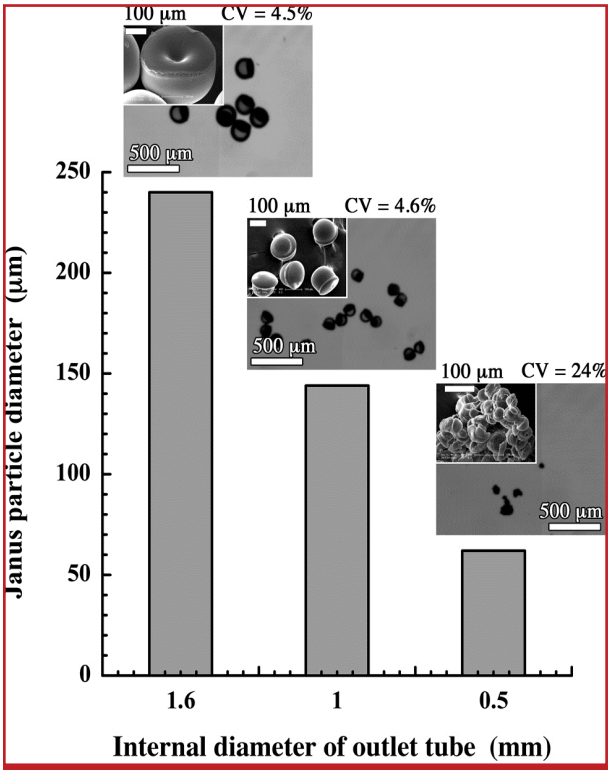

Figure 2: Decrease in Janus particle size with decreasing internal diameter of collecting tube (b) [Adopted from (5)].

FTIR spectra confirmed complete polymerization of bi-phasic droplets by observing the absorbance of C=C double bonds for acrylate at 1636 and 808 cm-1 and for acrylamide at 1605 cm-1 respectively. These peaks were absent in optimized formulation and suggests successful polymerization of two monomers under given conditions. Cytocompatibilty of these particles were carried out in BNL-CL2 cells. These cell lines were observed before and after incubation of different concentration of Janus particles. These particles showed minimal cytotoxicity until 4 mg/mL. LD 50 of Janus particles was found to be around 9 mg/mL (Fig 3). MTT assay results were further analyzed and confirmed by addition of propidium iodide and Calcein AM (acetomethoxy derivate of calcein) which can stain dead and live cells respectively. In the cell population, dead cells appear as red due to the red-fluorescent nuclear and chromosome counterstain propidium iodide, as it is only permeable

ARTICLE

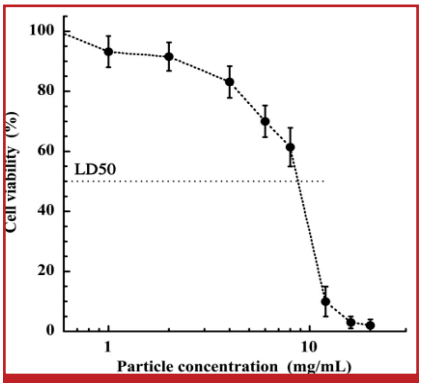

Figure 3: Graph shows cell viability after exposure of BNL-CL2 hepatic cell line to different particles concentrations [Adopted from (5)].

to dead cells. Live cells appear green because nonfluorescent Calcein AM is converted to a green-fluorescent calcein after acetoxymethoxy group is removed by intracellular esterases.

It was found that particles having same composition but different size vary in encapsulation efficiency. Smaller particles have higher efficiency in comparison to bigger particles, for example 144 µm particles have 32 and 30% encapsulation efficiency for ketoprofen and sodium fluorescein respectively, while 244 µm size particles have 30 and 29% encapsulation efficiency for the same drugs. A probable reason is that smaller droplets polymerize faster and prevents the loss of drug in continuous phase and is in agreement with our previous studies on microbeads (Khan et al., 2013).

Drug release studies were carried out at pH 6.8 in USP phosphate buffer solution for two formulations having similar composition but polymerized in different sized collecting tubes. It was observed that formulation having large particle size showed faster drug release as compared to smaller particles. Smaller particles released both drugs in a more sustained release manner. This could be due to variation in uniformity of two particles. SEM micrographs confirmed that the large size Janus particles were dented on one side and lack uniform distribution of the two phases, while smaller particles have more uniform structures (Fig 4a, b).

Furthermore, it was observed that ketoprofen release was higher compared to hydrophilic sodium fluorescein. This release could be due to the following reasons: (1) in all optimized formulations, the concentration of crosslinker and acrylamide in hydrophilic phase was quite high i.e., 6 wt.% and 30 wt.%, respectively. (2) initial loading amount of sodium fluorescein was 1 wt.% as compared to 10 wt.% of ketoprofen. Hence therelease rate of sodium fluorescein was enhanced by decreasing the concentration of crosslinker from 6 to 1.5 wt.%. This resulted in a decrease in crosslinking density and increased the mesh size which allowed more freedom of movement for the solvent and drug molecule.

CONCLUSION

A side-by-side capillary microfluidic device was successfully used to prepare poly(acrylamide)/poly(methyl acrylate) Janus particles for bi-encapsulation of two molecules with diverse solubilities in a single microparticle.. The size of these biocompatible particles were easily tuned by varying the collecting tube internal diameter and flow-focusing arrangement. These particles successfully released two molecules in sustained release manner over 24h by Fickian diffusion. Moreover, in future these particles could be used for targeting various parts of the GIT.

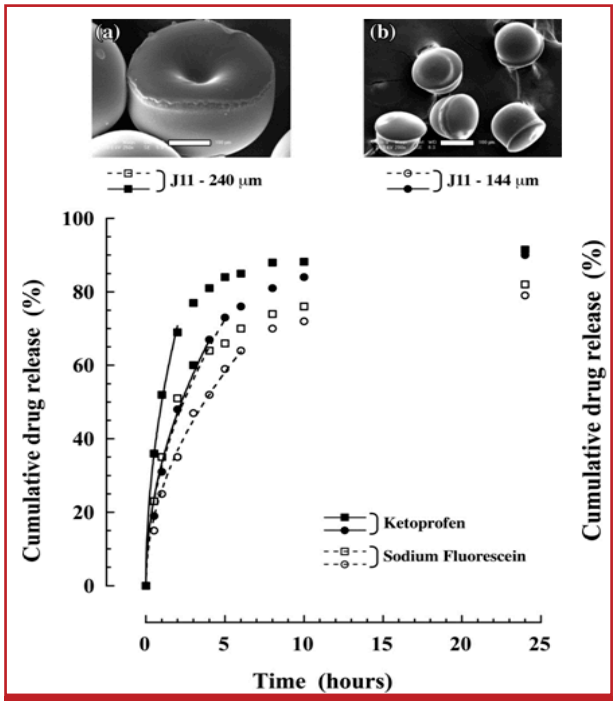

Fig. 4: Sustained release of two active molecules as function of morphology and particle size (a, b). Release curve shows modified Fick's second law of diffusion on first 60% release. Scale bar represents 100 µm[Adopted from (5)].

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ARTICLE

A CASE STUDY: QUANTIFYING THE RHEOLOGICAL PROPERTIES OF A GRANULATION WITH A MIXER TORQUE RHEOMETER TO RESOLVE PRODUCT QUALITY ISSUES IN PRODUCTION

Dr Keith Parry, Caleva Process Solutions Ltd, UK

INTRODUCTION

Wet granulations are an invaluable precursor to many solid dose formulations and are widely used in the pharmaceutical industry (Parker et al. 1990). The difficulties in achieving a pharmaceutical granulation providing the optimum properties to enable an easy and consistent manufacturing process is a well-known issue for both developers of formulations and production managers in the manufacture of pharmaceuticals.

Caleva process solutions ltd
The Spheronization Company

There are several things that can affect the properties of a granulation (Soh et al., 2013), each having a different effect on the level of performance. The actual content of the formulation is clearly important e.g. concentration of active ingredient, but the amount of liquid binder in the mix is generally considered one of the most important variables that can be controlled by the formulator.

The time and intensity of mixing that is given to a granulation is generally considered of less importance. In this case study (which is an undisclosed real example) we hope to show that it can be absolutely critical to achieving an optimal, or even acceptable, product performance.

THE PROBLEM

In this example, a manufacturer of pellets containing venlafaxine was experiencing inconsistent results from the manufacturing line. The resultant product was variable in both usable yield (weight of acceptable pellets as a % of weight of granulation made), and pellet consistency (highly variable dissolution profile). The product was a generic Venlafaxine formulation containing 15% water content.

Since the formulation was already registered, neither the formulation ingredients nor the amount of liquid binder could be easily modified.

It was noted that the texture of the granulation and the extrudate was visually inconsistent but no quantitative assessment of this casual observation had been undertaken. To asses this issue, the rheological properties of the customer's granulation were examined in a quantitative way. From a practical standpoint this was only possible using the Caleva Mixer Torque Rheometer (MTR3).

THE ASSESSMENT

Two key parameters were examined.

An initial trial was performed to look at the effect binder levels might have on the consistence of the formulation. This assessment was made on the bench top with a 20g dry powder sample, using an MTR3 and the results are shown in Figure 1.

In the original development, it is suspected that the optimum binder concentration was determined by the "hand squeeze test" (a subjective assessment and not appropriate for the 21st century pharmaceutical industry!).

The effect of different mixing regimes was examined in a second assessment. Within the registration some flexibility was permitted in the amount and intensity of mixing. There was scope for changes to be made in this area. It appeared that no quantitative assessment had been undertaken of the influence of mixing upon the formulation properties. It was assumed that this factor was of little significance to the final formulation providing it was granulated "enough".

THE RESULTS

For pellet formulations an ideal % binder content is generally somewhere just before the maximum consistency reading is reached. In

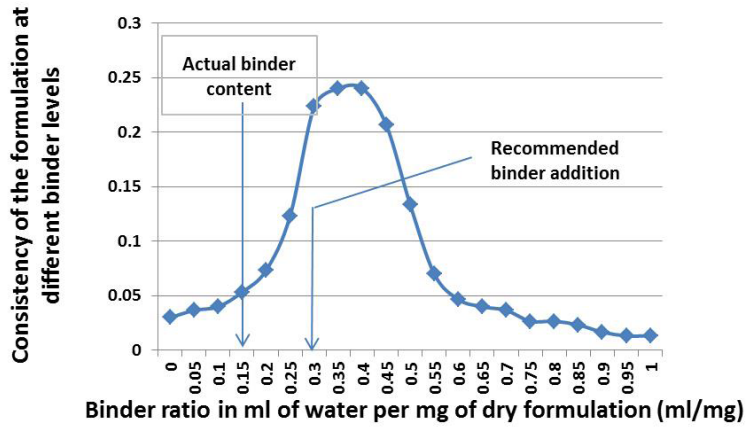

Figure 1 : The consistancy of a venlafaxine formulation with different amounts of liquid binder added

this case the results suggested that a water content of about 35% would be optimum for this formulation, however the product was already registered containing a water content of 15%. At this stage the manufacturer, understandably did not want to change this value.

The second evaluation was undertaken (again using the Caleva MTR) at this (registered) 15% water content but this time looking, at the effect of mixing time on the consistency of the product.

Using a small sample size of 20g of the dry powder with a 15% addition (3ml) of the binder the granulation was mixed continuously and the consistency measured at regular intervals. The results obtained are shown in figure 2.

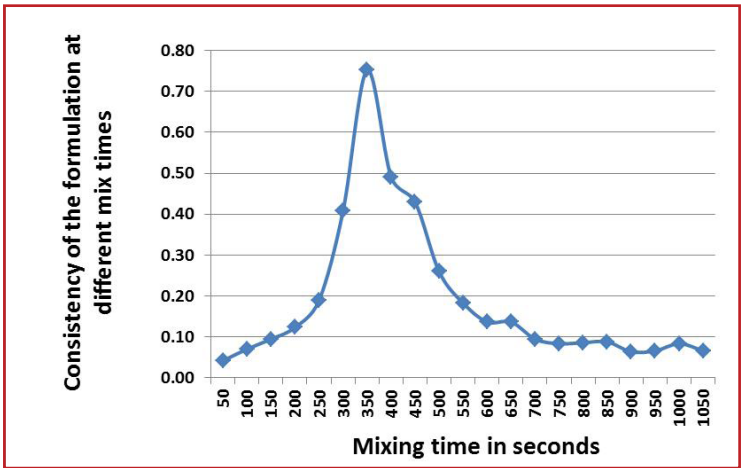

Figure 2 : Changes in consistency of a venlafaxine formulation with increasing granulation time

DISCUSSION

The first results show that the 15% binder content used in this formulation is very likely not to be optimum for this product. The early assessment made using the "hand squeeze test" and without any quantitative data is not optimum. The formulation will never be "optimum" as at this stage the binder ratio cannot practically be changed due to the product registration.

A similar problem was apparent with the granulation time given to the formulation. Once quantified results were obtained it was clear that the granulation regime was of paramount importance if consistent product quality was to be realized in practise. The results showed that the highest levels of consistency were only obtained at a very narrow intensity of mixing. It was easily possible to both over and under mix.

CONCLUSIONS

There are several conclusions that can be drawn from this case study:-

Quantifiable measurements of formulation consistency are a desirable part of formulation development.

Whilst the importance of the percentage of binder liquid added to a formulation is recognised as important to achieve consistent production quality many people who work in formulation development still rely on subjective and non-quantifiable assessments.

The possible sensitivity of the granulation regime is sometimes not appreciated during formulation development. Contrary to this general perception the granulation process should be quantitatively studied as a standard part of product development.

The Caleva Mixer Torque Rheometer is the only instrument that can easily and reproducibly generate the valuable data shown in this case study.

There are three main ways available to determine the optimum ratio and mix time:-

Adding binder and testing by 'eye and hand' to reach an estimated optimum ratio. Obvious limitations and no reproducibility!

The systematic investigation of a range of possible options with subsequent testing of the final characteristics of tablets and spheroids (pellets) produced. A time-consuming and expensive undertaking!

By use of a Caleva MTR3 – the only method that is objective, quantifiable and can be used for scale-up production (Rowe, R. C. and Parker, M.D, 1994).

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Keith is the business development manager for Caleva Process Solutions in the UK. His current focus is working on alternative markets for Caleva's Mixer Torque Rheometer – an instrument widely used in the pharmaceutical industry.
His special interest is in the elemental analysis of, amongst other things, pharmaceutical compounds by use of inductively coupled plasma's (ICP-MS and ICP-OES)
He obtained his Ph.D in Analytical Chemistry from the University of Wales, Cardiff.

ARTICLE

NANO AND MICROENCAPSULATION OF INSULIN: A FUTURE FOR DIABETICS ?

N. Auberval, Y. Frère – Institut Charles Sadron, CNRS UPR22, France

DIABETES

General purpose

With nearly 285 million diabetic people worldwide, diabetes is a disease is which is becoming more prevalent and subsequently worrying health services. It can be defined as a disorder of glucose assimilation, utilization and storage. In healthy people, high levels of plasmatic glucose are regulated to normal levels (1 g/L) by insulin, which is secreted by pancreatic β-cells. In diabetics, insulin is no longer secreted inducing hyperglycaemia. In type 1 diabetes this usually results from destruction of β-cells (autoimmune disease occurring in children), while in type 2 diabetes an overproduction of poor quality insulin (followed by long-term exhaustion of pancreas and insulin injections in middle-aged people) causes the disease. Furthermore, hyperglycaemia induces vascular complications such as microangiopathy damaging the retinas and kidneys; and macroangiopathy leading to myocardial infarction, stroke and peripheral arterial disease both associated with loss of peripheral nerve sensitivity, leading sometimes to amputation of affected limbs.

Treatments

Main diabetic treatments are based on medication. In type 1 diabetes, insulin therapy is realized by subcutaneous injections of insulin with different supports: pens, external or internal pumps. For type 2 diabetic patients, associated to dietary advices, some oral antidiabetic drugs reduce the insulin resistance or improves insulin sensibility. However, insulin therapy can also be necessary for long-term type 2 diabetics, however it can present drawbacks: multiple subcutaneous injections are painful, restrictive and uncomfortable for patients with some risks of hypoglycaemia, lipodystrophy and technical failures (pumps). In account of these problems researchers are developing alternative treatments to these injections.

Eye drops, inhalation sprays, oral tablets and others were studied. Two known developments concern inhaled insulin Exubera® (Pfizer) and oral insulin Oralin® (Generex). However, the increase of side effects and lung cancer; and the lack of reproducibility and tolerance, respectively led to their removal from the market.

THE ORAL ROUTE

Advantages

The oral route is fast, simple and discreet to use, does not require injections or materials, limits severe hypoglycaemia and respects the first hepatic pass, contrary to subcutaneous, intraperitoneal, transdermal, rectal, buccal or nasal delivery routes. For many drugs, the first hepatic pass is a drawback because it decreases the drugs bioavailability. But in the case of insulin, this pass reflects what is happening in physiological conditions and allows the liver to control the insulin release to peripheral tissue and ensures a good control of glucose homeostasis.

Drawbacks

Unfortunately, two major problems are encountered by peptide drugs along the gastrointestinal tract. The stomach and intestine represent chemical and physical barriers. In the stomach, the presence of enzymes (pepsin, lipase) and low pH alter the structure and biological function of drugs. The active compound remaining is then in contact in the intestine with alkaline pH and enzymes (trypsin, chymotrypsin...) inducing the almost total degradation of compounds with a peptide nature. Moreover, passing through the intestine membrane is limited by the size and hydrophobicity of the peptide, which explains the low bioavailability of proteins that administered orally (Pauletti, 1996).

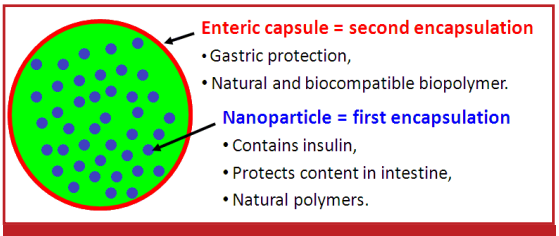

Figure 1: Concept of insulin double encapsulation.

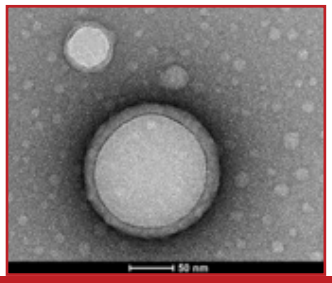

Figure 2: Transmission electron microscopy of insulin nanoparticles.

ORAL ADMINISTRATION OF INSULIN

To solve the problems encountered along the gastrointestinal tract, our team composed of chemists, in partnership with biologists (Centre européen d'étude du Diabète, Strasbourg), have developed a new drug delivery system called pharmaceutical vector, and is based on a double encapsulation procedure (Frère, 2004). This procedure involves successive nano- and micro-encapsulation of the insulin: 1) First encapsulation: synthesis of insulin nanoparticles, to protect the peptide from intestinal fluid and to promote its passage through the intestinal wall until the release of the hormone to the portal vein. 2) Second encapsulation: formulation of an enteric capsule composed of alginate which will contain the insulin nanoparticles (from first encapsulation) and protects them from gastric fluid (Figure 1).

ARTICLE

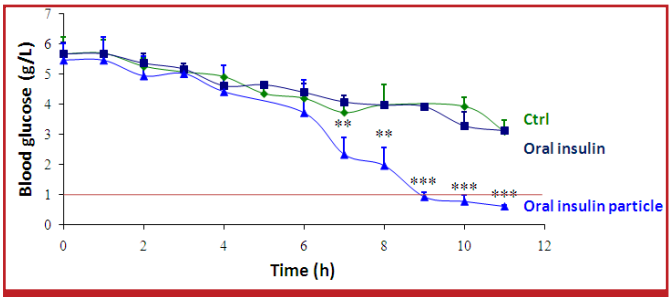

Figure 3: Glycaemia of rats after injection of nanoparticles.

The nanoparticles

They constitute the first encapsulation step. They are synthesized by the method of double emulsion and solvent evaporation, with a biodegradable and bioassimilable polymers (poly (D, L-lactide-co-glycolide)), acid and surfactant. Aqueous insulin is dispersed into the polymer solution to form water/oil emulsion which is then dispersed in the surfactant to obtain a second emulsion of water/oil/water. This multiple emulsion is then added to a surfactant to begin solvent evaporation.

Nanoparticles, negatively charged with a size around 200nm, are spherical (Figure 2), resistant in simulated intestinal fluid, well internalized by enterocytes in culture and have an encapsulation efficiency of insulin of around 95%.

The enteric capsule

The second encapsulation protects insulin nanoparticles from gastric environments. This enteric capsule can be formulated with soft gel capsules, hard-gelatin enteric capsule PCcaps™ coated with Eudragit® (Capsugel, France) or alginate beads, with a final size allowing oral administration to diabetic rats.

Our work is essentially focused on alginate beads. To obtain the whole system, nanoparticles are mixed with alginate solution and calcium carbonate. This aqueous phase is dispersed in pharmaceutical oil with surfactant. Gelation occurs by adding acetic acid (adapted from Poncelet, 1999) and beads are extracted with aqueous solution of calcium chloride. The final size is around 100 to 200µm.

In vivo assays

Insulin nanoparticles are injected in the duodenum of diabetic rats using a catheter (in accordance with the standards and ethics protocols). Encapsulated insulin is significantly more active than free insulin and decreases glycaemia until normal level after 9 hours (Figure 3).

Additionally the gastric resistance of commercial capsules PCcaps™ was also tested (Figure 4). In simulated gastric juice, capsules are resistant and released their entire payload (caffeine) under intestinal conditions.

Insulin lyophilized nanoparticles enclosed in PCcaps™ capsules reduce glycaemia of diabetic rats, however as of yet they do not allow normoglycemia to be achieved after oral administration of the whole system. Currently, the change of second encapsulation from PCcaps™ capsules to alginate beads could be a solution to obtain normoglycemia in diabetic rats after the oral administration.

CONCLUSION / PERSPECTIVES

Drug delivery system through the double encapsulation of insulin with successive nano- and microspheres was proven to be a success: pharmaceutical vectors which are gastric-resistant are obtained and release active insulin nanoparticles in the intestine, which decrease glycaemia in diabetic rats due to a slow insulin profile.

The experiments show the efficiency of oral administration of the developed system. Before human clinical trials, the process of nanoparticle production has to be improved for scale-up and the insulin-loaded nanoparticles must be tested as diabetic treatment on mini-pig.

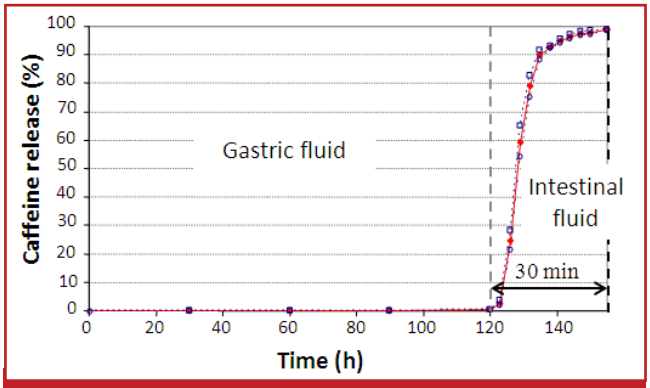

Figure 4: Caffeine release from PCcaps™ in simulated GI fluids.

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After obtaining my PhD (2010) on the prevention of oxidative stress in diabetes using natural antioxidative compounds, both on cells line and type 2 diabetes model of rats, I switched from biology to polymers to manage the project of oral administration of insulin, as postdoctoral research associate with Dr Yves Frère.

ARTICLE

THERAPEUTIC APPLICATION OF MICROENCAPSULATION IN CANCER

Thierry F. Vandamme Université de Strasbourg, Illkirch - France.

INTRODUCTION

The oncology community is on the constant lookout for improvements and advancements in cancer treatments. One of these improvements consists of using different microencapsulation techniques as an novel approach. The interests in microencapsulation lie in the fact that this approach usually consists of a single step process that forms tiny liquid-filled, biodegradable « micro-balloons » containing various drug solutions that can provide for instance, better drug delivery and new medical treatments for solid tumors. In other words, by using microcapsules containing anti-tumor treatments and visualization markers, the treatment can be directed right to the tumor, which has several benefits over systemic treatment such as chemotherapy. The microparticles (microspheres or microcapsules) can be injected into human tumors to actually inhibit tumor growth or can be injected following cryo-surgery (freezing) to improve the destruction of the tumors much better than freezing or local chemotherapy alone. The microparticles can also contain a contrast agent that enables C-T, X-ray or ultrasound imaging to monitor the distribution within the tissues to ensure that the entire tumor is treated when the microcapsules release their drug contents.

At present, invasive and systemic cancer treatment is a necessary evil for many people with the devastating diagnosis. The majority of chemotherapy is done intravenously, but, because the drugs are very toxic and are not targeted, they have a lot of side effects. Therefore the patients endure therapies with ravaging side effects, including nausea, immune suppression, hair loss and even organ failure, in hopes of eradicating cancerous tissues in the body. Another problem with intravenous drugs is that they go everywhere in the bloodstream and do not easily cross the blood brain barrier so little amounts get delivered to the target tumors. To counteract this, generally, high doses are necessary. To avoid these drawbacks, intravenous delivery systems should not be investigated, but localized therapies delivering directly into the tumor site. As an example of localized therapy, we can mention current treatment which includes leaving wafers infused with the anti-tumor agent BCNU in the brain after surgery (figure 1), but when the drugs in these wafers run out, repeating invasive placement is not generally recommended. Moreover, the choice of the drug can be problematic, as for instance, BCNU has a half-life in the body of 15 minutes. Therefore the drug needs protection and to be released with a sustained and prolonged release because of this short half-life. Encapsulation inside biodegradable polymers can solve this problem. With uniform spheres, manufacturers can design the microparticles to precisely control the time of drug release by altering polymer composition. The tiny spheres can also be injected in tissues, through the skull, obviating the need for more surgery.

Figure 1 : Schematic illustrating injection of microcapsules containing anticancer drugs into the brain.
Source: Fattahi P et al. Advanced Materials 25, 4555–4560 (2013).

Obviously, different techniques to make microspheres or microcapsules can be used to encapsulate the drug inside of them. The main problem in these cases lies in the use of solvents. From a pharmaceutical point of view, the organic solvents have to be eliminated after the preparation of the microparticles.

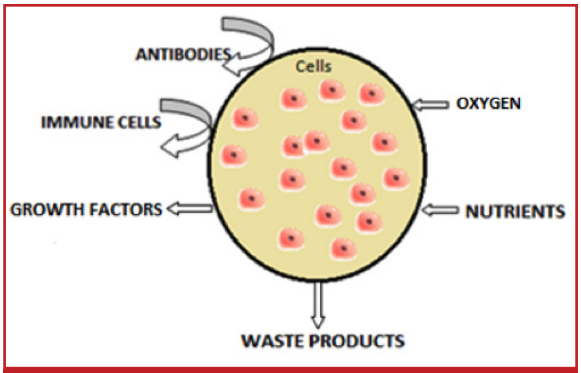

Figure 2 : Schematic illustrating cell microencapsulation

To optimize the drug release kinetics, researchers also examined how the anticancer drug releases from the microparticles. Using mathematic modelling, they established a drug diffusion coefficient for the encapsulation system. This helps in designing how much drug has to be included in each microsphere or microcapsule and how long these microparticles will deliver the required dosage (each drug has its own diffusion coefficient and half-life)

UNIVERSITÉ DE STRASBOURG

MICROENCAPSULATION OF ANTICANCER DRUGS

As mentioned above, microencapsulation can modulate the release kinetics of soluble drugs and contribute to delay the complete release. On the contrary, poor water solubility of many anticancer agents (such as paclitaxel, PCT; camptothecin, CPT; and certain porphyrins like meso-tetraphenylporphine, TPP, used in photodynamic therapy, PDT) hinders their application and complicates direct parenteral administration. Various formulation strategies based on the use of drug carrier systems have been suggested to overcome their poor solubility, low

stability, and toxic side effects (Garcia-Carbonero, R., and Supko, J.G.; Singla, A.K. et al.). Among such systems, we can mention the liposome formulation, cyclodextrin drug carriers, solid lipid nanoparticles, polymeric drug encapsulation delivery systems, self-microemulsifying drug delivery systems, nanocrystals, hydrosol colloidal dispersions, microemulsions, solid dispersions, cosolvent use, dendrimers, polymer-drug conjugates, polymeric micelles, and mesoporous silica nanoparticles which have drawn much attention owing to their easily controlled properties and good pharmacological characteristics. The carriers are attracting increased attention and growing interest for drug targeting, because they can be easily prepared with well-defined biodegradable polymers. Leroux et. al. mention the rationale behind using nanoparticles for cancer therapy, was based on the fact that certain neoplastic cells have been found to exhibit an enhanced endocytotic activity. Therefore the size of the carriers also has a high significance to optimize the release and the targeting of the anticancer drugs into the tumors. Recent studies led by several research teams have shown that encapsulating chemotherapeutic agents in nanoparticles can influence pharmacokinetic parameters and the biodistribution of the drug. Therefore, it's expected to help tumor accumulation with a resulting limitation of adverse effects. High concentration in neoplastic tissues can be obtained based on peculiarities of the vascular system surrounding tumors. Indeed, the vascular system of tumors is highly disorganized and presents an enhanced permeability due to the tumor-increased needs for oxygen and nutrients. This phenomenon called the enhanced permeability and retention (EPR) effect provide an interesting gateway for small nanoparticle to penetrate more readily into tumoral sites. This retention effect is realized further by an impaired lymphatic drainage reducing carrier clearance from the tumor (Leroux et al.). Other carriers like micelles prepared from PEG-diacyllipids conjugates, such as PEG-PE, are of also of particular interest (Lukyanov, A.N., and Torchilin, V.P.).

CELL MICROENCAPSULATION IN CANCER

Although cell encapsulation technologies were originally developed for the treatment of acquired and genetic diseases such as diabetes, they can also be applied to the treatment of a variety of solid tumours. There are a number of strategies aimed at treating tumours with encapsulated cells. Many of these strategies have shown promise in preclinical studies and clinical trials.

Brian Salmons and Walter H. Gunzburg (2010) mention the advantage of using encapsulated cells for the treatment of cancers (but also other diseases). Indeed, in this strategy, therapeutic molecules can be delivered in a sustained manner from implanted cells since the cells are enclosed in microcapsules and are thus protected from host immune rejection (figure 2).

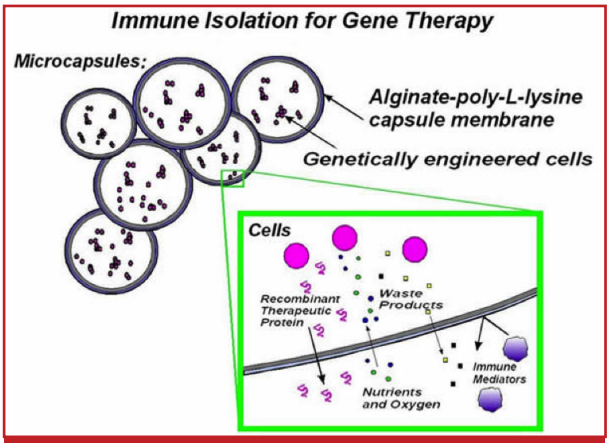

Figure 3 :Schematic illustrating microencapsulation of gene therapy
Source : Mac Master university, http://fhs.mcmaster.ca/gene/

In spite of the advantages of encapsulation of cells for the treatment of tumours, one potential problem that can be encountered is that such cells may show poor in vivo survival rates, due to the highly hypoxic and acidic conditions found inside many tumours. In order to improve the survival of the encapsulated cells in these arduous conditions, several authors and research teams successfully selected a human HEK 293 cell line for its ability to survive in hypoxic conditions and thus this cell line can withstand the hostile environment found in tumours.

Such selected cells may form the basis of a good platform for the treatment of tumours with encapsulated cells, regardless of which anti-tumour factor the cells are producing.

Table 1. Preclinical studies of encapsulated cells for cancer treatment (Brian Salmons and Walther H ; Gunzburg, 2010).

Active Product	Cells	Encapsulation	Tumour type	Reference
Endostatin	HEK293	Alginate	Glioma	Read, 2001
	CHO	Alginate	Melanoma	Teng, 2007 Zhang, 2007
	HEMA-PEG	118	Neutral	
			Leukaemia	Schuch, 2005
Angiostatin	C2C12	Alginate	Melanoma	Cirone, 2003
	C2C12	Alginate		Li, 2006
Endostatin	Porcine	Alginate		
Sol. neutrophilin	Aortic	Alginate		
Thrombospondin-2	Endothelial	Alginate	Renal cell carcinoma	Bartsch, 2008
Cytokines				
TNF-alpha	J558	Alginate	Breast cancer (MCF-7)	Hao, 2005
Interleukin-6	CHO	Alginate	Hepatocellular carcinoma	Moran, 2006
Antibodies				
RM4-TNFalpha	VkCk	Alginate	Colon carcinoma	Shi, 2005
Combination				
Angiostatin				
Fusion protein	C2C12	Alginate	Melanoma	Cirone, 2006

A variety of cells, including HEK 293, CHO and C2C12 cells (Table 1) have been encapsulated and used for the treatment of tumours. These cells have been genetically modified to express products that either directly or indirectly combat tumours (figure 3).

CONCLUSION AND PERSPECTIVES

Regardless of the important therapeutic advances developed over the last number of years for the management of cancer, the fact is that many patients still suffer from a tremendous reduction in their quality of life, due to lack of complete selectivity of conventionally administered chemotherapeutic drugs. In the search for more efficacious tumour-targeted therapies, the use of microencapsulation of cells capable of simultaneous binding to tumour-associated antigens and to an activating receptor, such as CD3, has emerged as, for instance, a promising approach. With the intention to complementing and improving this cancer immunotherapy, human HEK-293 cells have been genetically modified ex vivo to secrete a recombinant anti-CEA (carcinoembryonic antigen)×anti-CD3 bsAb. After encapsulation in alginate-poly-l-lysine microcapsules, bsAb-secreting HEK-293 cells are able to be monitored for several weeks. This system has proved to be feasible for the maintenance of cell growth and recombinant antibody production giving proof-of-concept of its use as immunotherapeutic organoids in cancer treatment. These advances should complete the « conventional microencapsulation » of anticancer drugs even if their release can already be optimized and modulated by their encapsulation in selected carriers like microperes or microcapsules.

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Thierry Vandamme obtained his PhD in Pharmaceutical Sciences in 1994 at the catholic University of Louvain in Belgium. After its PhD thesis, he carried out two post-doctoral training courses, the first one at the University of Stanford in California (1995) in the Laboratory of Dr. Jorge Heller (Laboratory of synthesis of biodegradable polymers) and the second one at the School of Pharmacy in London (1996) in the research team of Professor Ruth Duncan (Laboratory of therapeutic polymers). In 1996, he became lecturer at the University Louis Pasteur of Strasbourg and was promoted Professor in Biogalenics in February 2005 on an employment "Fillon". His research activities are undertaken within the Department of Bioorganic Chemistry (UMR7199) and the main aim of this research activities are based on the developments of new systems of delivery of drugs. His research activities and his laboratory are located in the Faculty of Pharmacy of the University of Strasbourg. He is also the Vice-Dean in charge of research in the Faculty of Pharmacy, Vice-president of the University of Strasbourg and is elected in the research council of the University of Strasbourg..

INDUSTRIAL AND DIVERSIFIED NEWS

Fast dissolving oral drug delivery systems required for effective administration to non-compliant patients

Aptalis Pharmaceutical Technologies (part of Forest Laboratories Inc. acquired by Actavis in July 2014 http://bit.ly/14yMJV2), producers of Diffucaps® and Microcaps® delivery systems, are developing rapid dissolving drug delivery products for challenging patient compliance situations.

More information
http://bit.ly/1FUKcpH

Anabio Technologies develops systems of encapsulation using natural food grade materials, including isolate of whey, pectin, prebiotic, carrageenan, alginate. The company claims the absence of excipient and chemical.

For more information
http://www.anabio.ie

New joint venture aims to develop improved probiotic powders with small particle size and high stability

Bifodan A/S a Danish probiotic ingredient supplier is collaborating with the University of Copenhagen and the Danish Technical Institute to develop microencapsulated probiotic products. The aim, to protect bacteria against the processing conditions of moisture and heat that reduce the viability of probiotic microorganisms and ensure they are stable in gut acid conditions to ensure effective intestinal delivery.

More information
http://bit.ly/1C0retF

Microencapsulated probiotics for soft chews

Vets Plus Inc., a manufacturer of pet health products, has launched its newly developed microencapsulation platform technology to stabilize actives in soft chews. Initially the technology is to be used to protect probiotic bacteria in cold extruded soft chew pet products.

More information
http://bit.ly/1u3Ihdw

Wake up and smell the whiskey

Harris Tweed Hebrides, the hand-woven cloth from Scotland and Jonny Walker Black Label Scotch whiskey, have announced a new collaboration. Working with textile technology experts from Heriot-Watt University the team plan to encapsulate a perfume from Angela Flanders "Aqua Alba" that was inspired by the famous whiskey brand, and incorporate it into the fabrics during the finishing process.

More information
http://bit.ly/1wc9tRy

LESAFFRE Ingredients Services (LIS): with over 50 years of experience in spray-drying process of food grade ingredients, LIS proposed also vacuum drying, granulation and encapsulation technologies, intended to food and feed, cosmetic and pharmaceutical sectors. A full range of services including: pilot plant production, scale-up, production and analysis are provided.

For more information:
http://www.lesaffre-ingredients-services.com/

Microencapsulated for texttiles

Byskin, a French company, proposes a range of industrial textiles containing encapsulated actives (arnica, menthol, hyaluronic acid) which release their contents in the skin contact. They claim offering solutions for warm muscular, refreshment, anti-ageing agents

For more information
http://www.entreprises.ouest-france.fr/article/rezebyskin-surfe-sur-cosmeto-textile-13-10-2014-164201
http://www.byskin-paris.com

Carlina & Genbiotech agreement

Carlina signed a licence agreement with Genbiotech concerning the exploitation of its PEPTIDOTS technology which allows the formulation of peptides or proteins in the form of nanoparticles. The aimed asset having for objective the repair of bones and cartilage in animal health.

For more information
http://www.pharmabiz.com/ArticleDetails.aspx?aid=84982&sid=2

Research and Markets: Global Microencapsulated Phase Change Materials (MPCM) in Textile and Mattress Markets - 2014 Outlook and Trends

The market research publisher has reported on the developing trends in microencapsulated phase change materials particularly the market for their use in smart textiles in active wear.

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OPEN POSITIONS

Postdoctoral Researcher in the field of Mechanical- / Chemical- / Food Engineering
Swiss Federal Institute of Technology Zürich (ETH)

The research area will be related to design, optimization and implementation of new extrusion processes and related equipment development for the functional structuring of food systems.
The work field of interest for the advertised researcher position will mainly deal with the setting up of new processes for coupled micro- and macro-disperse structuring of multiphase food products. Such coupled tailoring of structure building blocs on the micro and macro scale requires detailed knowledge of the structuring mechanisms in the acting process. The process category of major interest will be micro- to macro extrusion flow processes, the treated food material systems will be in a fluid or semisolid state with complex rheological behaviour.
The postdoctoral position will be opened for a 2-year period.
The starting date is planned between Feb.15 to April 15.
Letters of application, CV and main certificate should be addressed to:
Prof. Erich J. Windhab
ETH Zürich, IFNH-LMVT Schmelzbergstrasse 9, LFO E 18
CH-8092 Zürich

erich.windhab@hest.ethz.ch

Postdoctoral Position
Institute of Chemical Process Fundamentals ASCR Prague, Czech Republic

Laboratory of Immobilized Bicatalysts and Optical sensors is seeking Post Doctoral Fellow to assist in the development of a research capability in preparation of organic–inorganic bio-materials and their applications as industrial biocatalysts and optical sensors.
The candidate must hold a Ph.D. or equivalent qualification for less than 2 years. Candidates with a solid background and training in microbiology, biochemistry, biotechnology, chemical engineering, analytical chemistry or another relevant field are encouraged to apply. Knowledge in Czech language is not required but welcome. High level communication skills in English, both written and spoken are required. The monthly salary is 30,637 Kč and might be increased up to 40,500 Kč. The duration will be minimum one year, maximum two years and project start on July 2015
The application must send motivation letter (1 page), CV, PhD and Master certificates, signed copy of declaration of the candidate agreement with the salary conditions and working programme.
Please send your complete application documents before 31st January 2015 by e-mail to:

kuncova@icpf.cas.cz

Spray Drying Manager
Girona, Spain

Main tasks:
Supervision of all new SD equipment installation in Girona plant. Definition of URS.
Definition and optimization of materials and personnel flows. Writing of appropriate SOP procedures.
Design of production, cleaning and campaign set-up procedures. Writing of technical documentation.
Knowledge sharing: training of his team and relevant people inside the organization.
Primary contact with customers regarding SD requirements and technical discussions.
Responsible of development trials and development batches in SD for generics and third-party projects.
Control of SD installations in EQ Plant. Supervisionof SD regular commercial manufacturing operations.
Review of BPRs. Must be in close collaboration with QP Quality person for batch release.

Requirements:
Bachelor Degree in Chemistry, Chemical Engineering or similar
Experience in similar functions and in managing working teams in pharmaceutical sector.

For information or application, e-mail to:

eva.ramiro@solutiaghs.com

Encapsulation systems for slow release of CO_2 and antimicrobial plant extracts

MARINA VEMMER

Supervisor	Prof. Dr. Anant Patel
Date & Place	11-12-2014 – Bielefeld, Germany
Affiliation	Bielefeld Univ of Applied Sc., Germany

My thesis aimed at the development and investigation of slow release systems based on Ca-alginate by means of pharmaceutical and agricultural application scenarios:
1) As several insect pests are attracted by CO_2 there is an interest in CO_2 releasing formulations for use within attract-and-kill strategies. Hence, a formulation based on baker's yeast, starch and the entomopathogenic fungus *Beauveria bassiana* (amylase source and potential biological control agent) was developed releasing CO_2 over as many as 4 weeks and attracting larvae of the western corn rootworm.
2) Antimicrobial thyme extract was encapsulated (EE% ≈ 95 %) and shown to be suitable for the control of the multiresistant skin bacterium *Corynebacterium jeikeium* and of different phytopathogenic fungi. It was further investigated how the bead composition and the surrounding medium influence the release kinetics.

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Vol. 31, Number 7 (2014)

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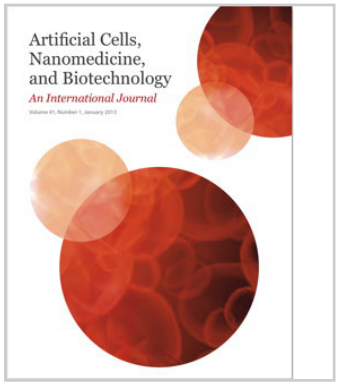

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