

The World's preferred CMO partner for the development and commercial manufacture of Liquid Filled Hard Capsules

inside this edition : Encap attending CPhI and AAPS events... Formulation Strategies for prescription drug abuse... Lena Nanoceutics Collaboration...

Formulation strategies for prescription drug abuse



Abuse can be defined as the taking of prescription drugs, whether obtained by prescription or otherwise, other than in the manner or for the reasons or time period prescribed, or by a person for whom the drug was not prescribed.

The most common types of prescription medication abused:

- **Opioids:** hydrocodone, oxycodone, propoxyphene, hydromorphone, meperidine, and fentanyl
- **Central nervous system depressants:** barbiturates, such as pentobarbital sodium, and benzodiazepines, such as diazepam and alprazolam
- **Central nervous stimulants, including amphetamines** such as dextroamphetamine, and amphetamine-like stimulants, such as methylphenidate.

These prescription drugs can be obtained for non-medical purposes by various means.

According to the World Drug Report 2010, "the misuse of prescription drugs, including opioids, benzodiazepines and synthetic prescription stimulants, is a growing health problem in a number of developed and developing countries". In some of the high income countries, such as the United States, Canada, Australia,

New Zealand, the United Kingdom and Norway over 1 per cent of the population used amphetamine-type stimulants in 2008. Particularly, in North America, South America and Southern Africa, a significant proportion of this use is constituted by the non-medical use of prescription stimulants (UNODC, 2010b).

The Substances Abuse and Mental Health Services Administration (SAMHSA) 2009 National Survey on Drug Use and Health in the United States reported that 7 million citizens, or 2.8 per cent of population aged 12 and older, had used prescription drugs for non-medical purposes in the past month: an estimated 5.3 million had used analgesics, 2 million had used tranquilizers, 1.3 million had used stimulants and 370 thousand had used sedatives.

In Europe, the non-medical use of prescription drugs, except for opioid substitution drugs, has not been regarded as a major problem by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2010).

Abuse Potential of traditional dosage forms

The most common oral dosage form is the tablet. Tablets can be easily crushed, liberating most of the drug contents immediately. The drug in the 'powdered tablet' can then be easily absorbed by the body via ingestion, snorting, etc.

▶ Powder filled capsules have a high surface area. Capsules can contain high melting point solids but waxy or sticky materials cannot be used during production. Therefore conventional capsule formulations have a similar abuse potential to tablets.

Soft gelatin capsules contain liquids or near liquid (semi-solid) excipients. The excipients used cannot have melting points higher than 35°C. Therefore, the contents can be liquefied near body temperature, extracted, dose dumped or directly injected.

Summary of Methods of Abuse:

- Snorting
- Injection / Ingestion (melting or extracting)
- Dose dumping by chewing
- Abuse of others (covert administration)

Abuse Inhibiting Formulations

Abuse deterrent formulations contain **pharmacologically active ingredients** intended to reduce the effect of the drug when the dosage form (tablet/capsule – beads) is physically or chemically manipulated in order to liberate the API from the formulation matrix. Under normal dosing conditions when the dosage form is taken intact, the antagonist remains unavailable and the dosage form performs as designed. If the formulation is crushed, chewed or dissolved etc. then the antagonist becomes available to the systemic circulation and reduces the euphoric effects of the drug (opioid). Other compounds can be added to the potential drug of abuse such as low dose Naltrexone or noxious compounds which create a negative experience for the abuser e.g. Nicacin.

Abuse resistant formulations use physical barriers to inhibit the possibilities of liberating quantities of API via extraction through physical or chemical manipulation. Fill materials may be soft, hard, waxy, pastes, water insoluble or contain a high proportion (up to 40%) of suspended solids, which prevent powdering at room temperature and resistance to snorting.

Encap's Abusolve™ technology is the application of liquid fill hard capsule (LFHC) technology to produce a dosage unit tailored to the desired release profile, formulated from excipients chosen to provide the optimal deterrence to potential routes of abuse. One of the main advantages of using a semi-solid abuse resistant formulation in a hard two piece capsule is that a greater range of excipients with high melting points can be used.

This results in two distinct advantages over other technologies:

1. Enhanced or greater resistance to abuse.
2. More specific and definable release profiles for modified release products.

A further advantage of utilising LFHC is that the capsules can be banded to also deter abuse.

With the increase of prescription drug abuse there is also a direct increase in the counterfeiting of prescription drugs. Using LFHC and Abusolve technology in combination with capsule banding makes these products much more difficult to counterfeit.

Encap's Abusolve™ technology is patent pending in Europe and the USA.

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If you keep it long enough, it will be useful

An Encap publication in June, in Drug Development and Industrial Pharmacy (37, (6), 685–693) demonstrated the long-term chemical and physical robustness of the liquid-fill hard capsule format. It reported on a recent study on inhouse samples of blister-packed nutraceutical products which were produced in 1989 when the company started. The samples were supported by original processing and quality-control documentation for fourteen batches of various encapsulated oils (plant oils, fish oils and tocopherols) These provided a unique opportunity to assess quality-related factors for liquid-fill hard capsules with respect to long-term physical and chemical integrity of capsule shells and contents, along with microbiological status. The test programme showed that the samples were in surprisingly good condition, free of embrittlement and leaks, aldehyde-induced cross-linking and microbiological growth. They were highly-resistant to peroxidation and well-protected by blister-packing. The various capsule contents included long-chain unsaturated glycerides which are subject to oxidation or light-induced degradation and represented materials at high risk of such product degradation. The study was therefore extremely useful not only in demonstrating long-term physical robustness of the liquid-fill hard capsule format but also in suggesting the likely long-term stability of lipid-based liquid capsule formulations.

The study was reported by Bill Bowtle, Paul Higgins, Lionel Kanyowa and Mark Mackenzie.

Encap to collaborate with Lena Nanoceutics

Encap has entered into a collaboration with Lena Nanoceutics, a technology based company located in Bradford, UK.

Lena have developed a proprietary nano-milling process which reduces and controls the particle size of pharmaceutical actives. This is important as it can increase the rate of dissolution and ultimately have a significant impact on the bioavailability of the drug. This is of great interest to Encap as we have considerable expertise in the use of liquid and semi-solid formulations for enhancing bioavailability eg. lipids, self-emulsifying drug delivery systems (SEDDS) and self- microemulsifying drug delivery systems (SMEDDS). **By combining the joint expertise of Lena and Encap, we believe that we can offer clients a completely novel approach to formulating compounds with low aqueous solubility, poor permeability and consequently low or variable bioavailability.**

Further details to be announced over the next few months.

Cross-linking of gelatin capsules

The phenomenon of soft and hard gelatin capsule cross-linking is an issue to be considered during the development of powder and liquid filled products since it may result in decreased product dissolution rate and in extreme cases have potential to adversely affect bioavailability. Encap's experience over the last twenty-two years with hundreds of compounds would suggest that significant cross-linking of gelatin is a relatively rare occurrence that can usually be overcome by formulation to produce

commercially viable products. Nevertheless, this is an area of continued scientific interest to the company and studies are being conducted to better understand the mechanisms which promote cross-linking.

It is clear from the literature that covalent cross-linking of gelatin can be induced by numerous chemical reagents, including aldehydes, imines and ketones. The cross-linking reaction is also enhanced in the presence of moisture, UV and visible irradiation and elevated temperature. In the majority of cases where Encap have encountered gelatin cross-linking the causative agent has been the drug entity, rather than the excipients, however there

are formulation strategies for example the incorporation of glycine (an aldehyde scavenger) and citric acid (to inhibit aldehyde formation) which can be used to minimize the rate of cross-linking.

Encap has strategies in place to identify potential cross-linking issues early in the formulation development phase. There is extensive experience with a range of dissolution media which can provide information on the extent of the problem which can then be solved by formulation strategies or use of alternative shell materials in order to ensure that commercially viable and regulatory acceptable products can be developed.



Effect of cross-linking gelatin capsules on *in-vitro* and *in-vivo* dissolution

by Professor Geoff Rowley

Cross-linking of gelatin induced by elevated temperature, relative humidity, exposure to light, or reaction with drug/excipient degradation products e.g. aldehydes, causes insolubility of gelatin in aqueous media. Digenis et al. (1994)¹ had shown the relevance of this to *in-vitro* and *in-vivo* behaviour of gelatin capsules when a Capsule Group (FDA/Industry/Academic) Working Party was formed to investigate the dissolution of gelatin capsules exposed to cross-linking storage conditions. The results presented at an AAPS Symposium (1997) reported (a) methods used to stress gelatin capsules to achieve different levels of cross-linking, (b) an *in-vivo* disintegration trial using γ scintigraphy and (c) the design of a modified two-tier dissolution procedure using enzymes. The published results^{2,3} are summarized here.

γ scintigraphy (1998)² was used to investigate the effect of cross-linking during *in-vivo* disintegration of hard gelatin capsules (HGC). The cross-linked capsules failed the USP dissolution test in water and simulated gastric fluid (SGF), however, they passed when pepsin was incorporated in the media. The *in-vivo* results gave real time disintegration values of 8 min (± 2 min) and 10 min (± 6 min) respectively, for unstressed and cross-linked capsules. Thus, cross-linking had no significant effect on *in-vivo* performance and the merit of using two-tier dissolution testing with enzymes was established, Meyer et al. (2000)³. Similarly, Digenis et al. (2000)⁴ used γ scintigraphy to follow the release of amoxicillin from stressed and non-stressed capsules. *In-vitro* capsule rupture times were related to level of stress, varying from 7 min (± 5 min) to 31 min (± 15 min) for unstressed and severely-stressed capsules respectively. However, blood concentration values for amoxicillin

showed capsules to be bioequivalent using AUC (0- ∞) and C_{max} criteria. For severely-stressed capsules, delayed T_{max} values relating to delayed capsule rupture, did not affect C_{max} and AUC (0- ∞) values. The results from *in-vitro* two-tier test with enzymes in either SGF or simulated intestinal fluid (SIF) led to the conclusion that this was an adequate *in-vitro* indicator of *in-vivo* performance of capsules. Subsequently, a two-tier test using pepsin in SGF or pancreatin in SIF was adopted by the USP.

Marchais et al. (2003)⁵ investigated *in-vitro* test conditions with respect to the effects of cross-linking, enzymes and surfactant. HGC formulations, unstressed or moderately and highly stressed by exposure to formaldehyde, released 36% and 5% drug in 60 min for unstressed and highly stressed capsules respectively, in SGF and SIF. Inclusion of pepsin or pancreatin increased drug released from moderately, but not highly stressed capsules. The effect of sodium lauryl sulphate (SLS) was unclear, however other research⁸, provided evidence for pepsin de-activation by SLS.

Pennings et al. (2006)⁶ investigated the use of Tween 80 and SLS in dissolution media to establish sink conditions and improve wettability. The surfactants were compared in the presence and absence of different concentrations of pepsin and pancreatin with cross-linked capsules. The decrease in dissolution in the presence of SLS was attributed to the formation of an insoluble precipitate of gelatin. Tween 80, showed improved disintegration and dissolution, however the effect of enzymes was inconclusive and an optimum concentration was not found. St. Clair et al. (2010)⁷ investigated the effects of

enzyme concentration in SGF and SIF media when testing HGC stressed by elevated temperature and relative humidity, to give three levels of cross-linking. The results showed significant differences with enzyme concentration for moderate and high cross-linking but insignificant differences with mild cross-linking.

Song et al. (2011)⁸ prevented the interaction between SLS and pepsin when testing cross-linked HGC by addition, after 5 minutes, of pre-warmed 3%w/v SLS in 300ml 0.1N HCl to 600ml dissolution medium containing pepsin. The pepsin digested the gelatin in the first 2 minutes of the test and the SLS solution, added after 5 minutes, was available to improve drug wetting and (or) solubility.

There is now sufficient evidence to show that two-tier dissolution testing provides a good indication of *in-vivo* performance. However, there is scope for further investigations to optimize enzyme concentration, in particular where cross-linking is severe. There also appears to be a need for further research into the choice of surfactant for use in dissolution media containing enzymes.

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“Every day presents something new!!”

Q) What is your background and how long have you worked at Encap Drug Delivery?

“I have a degree in Chemistry and a Masters Degree in Pharmaceutical Analysis and have worked in Pharmaceutical Analysis my entire working life. I got my first real education in this area of work as a placement student developing HPLC methods at Rhone Poulenc Rorer, followed by five years at Chiroscience, a biotech research and development company. I was a Development Analyst, and then Senior Development Analyst with the company. I've been with Encap Drug Delivery for 12 years now and it still surprises me when I add up how many years I've been working in this industry.”

Q) When did you develop an interest in Analytical Chemistry?

“I'd like to say it was a planned career strategy but the truth is that I took the easiest path through the education system that my abilities presented me with. My real interest in analytical chemistry only began during my time at Chiroscience when, surrounded by some hugely talented people, I realised I actually did have an aptitude and interest in the work.”

Q) What has surprised you most about working at Encap?

“When I joined Encap Drug Delivery I already had some exposure to the technology through formulation development products contracted from Chiroscience. What I thought of as a niche technology that might prove interesting to work on for a few years turned out to be a vast opportunity for new formulation approaches...the potential for liquid fill formulations to solve problems in formulation; from low dose uniformity to low bioavailability, from moisture sensitive to oxygen sensitive, controlled and targeted release. The list is endless.”

Q) What do you wish other people knew about Encap?

“I wish people appreciated just how versatile a technology liquid fill is. Often clients arrive with pre-conceived ideas about why they want liquid technology and it's only months into a project that they actually reveal just what their challenges were in the first place. The original problem commonly being the easier to solve.”

Q) Who or what inspires you?

What keeps you enthused about your career?
What makes working at Encap unique?

“I'll answer these three questions together. Every day presents something new, a new client, with a new API, something novel required from the formulation, a new problem to solve. It may be an analytical method giving unexpected results with a cause to be tracked down. Is it real, is it something new? There's a great satisfaction in answering these questions and getting products to patients. I hope that one day these products save lives or at the very least make life better”

Q) What is your vision for the company?

“I'd really like to see the technology Encap offers continue to grow and with it people's understanding of its potential.”

Successful CRS meeting for Encap

Despite sweltering temperatures in Washington this August, it was another successful CRS meeting for Encap. Drs Sarah Eccleston and Jane Fraser attended the meeting and participated in a wide range of sessions, events and client meetings. Sarah chaired the Oral Drug Delivery focus group session on Quality by Design. This was an interactive session with representatives from a range of companies – innovator, small and large pharma – discussing the challenges and opportunities as QbD becomes an expectation. Sarah also organised and chaired an early morning 'Get-up Get Educated' session. This covered the 'State of the Art in Vaccine Technology'; speaker Prof Yvonne Perrie gave a comprehensive presentation that included discussion of further potential for oral delivery of vaccines. During the poster sessions Sarah presented a poster on 'Industrial in-transfer and formulation development of the ENCODE Phloral coating'.

By night - for the second year running - Encap sponsored the conference's networking event. This year this took shape on an evening boat cruise along the Potomac River. Delegates were able to eat, drink and catch up with colleagues old and new.

CPhI Japan

On 11th March a devastating earthquake and tsunami struck North Eastern Japan. We offer our deepest sympathy to all those who have been affected.

Following the earthquake, CPhI was rescheduled and held in July in Osaka. Our exhibition stand was very busy with strong interest from Japanese innovator companies who wish to reduce their development timelines to commence their First In Human programmes. We are supporting our clients with our Fast in Human programme where timelines for these development programmes are typically 16 weeks compared to the usual 26 weeks.

Increasing numbers of NCEs have poor solubility and bioavailability. We are working closely with our Japanese customers to develop formulations for such compounds using liquid or semi-solid filled capsules. Low dose formulations and high containment facilities are required for some of these challenging compounds. We have successfully developed solid dispersion and lipid based formulations for these compounds to achieve a wide range of release profiles.

We invite you to visit our Japanese web site to read more about our capabilities and how you can benefit from using Encap's technologies for your development programmes.

Exhibitions and Conferences 2011

Encap will be attending, exhibiting or presenting at the following events in 2011. Please feel free to stop by for a chat, or arrange an appointment to discuss your requirements.

AAPS 2011, 23rd – 27th October Washington Convention Centre, USA (Booth 1751)

CPhI, ICSE Europe show 2011, 25th – 27th October, Messe Frankfurt, Germany (Booth 40J54)

Bio-Europe 2011, 31st October – 2nd November, CCD Congress Centre, Dusseldorf

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