New Sustained Release Formulation Solutions
Overcome Challenges of Alcohol-Induced Dose Dumping

Introduction
Sustained-released drugs, formulated to release the API in a rate-controlled manner over an extended period of time, can deliver added value to patients. The potential, however, for alcohol-induced dose dumping—and regulatory initiatives to address this threat—present challenges for scientists attempting to formulate compliant sustained-release dosage forms for the marketplace.

Drug companies must evaluate the positives and negatives of sustained-release formulations as they pertain to patient safety (Figure 1). Sustained-release formulations can better control drug absorption, avoid high drug blood levels for APIs with high biological availability, and help avoid fluctuations in drug plasma levels. Moreover, patients can better adhere to treatment plans when less frequent drug administration is required.

Sustained-released formulations can produce negative side effects, in particular the increased risk of toxicity due to dose dumping when the patient consumes excessive amounts of alcohol. Formulation challenges include a poor in vitro-in vivo correlation, a reduced potential for dosage adjustment, and higher cost, explains Christian Becker, regulatory affairs, BASF.

Dose Dumping
“Dose dumping” is the rapid release of the entire amount or a significant fraction of the API of a modified-release dosage form caused by the drug’s interaction with food; the physiological conditions in the gastrointestinal tract, such as the gastric pH and motility; as well as the drug formulation itself (Figure 2).

Dose dumping as a result of simultaneous or deferred consumption of alcohol in relation to drug administration is referred to as alcohol induced dose dumping. If the drug has a narrow therapeutic window, dose dumping can cause a significant risk to patients.

Regulatory Concerns
Potentially fatal adverse reactions, that can occur when sustained release opioids are taken together with alcohol triggered the development of new regulatory guidances in the United States and Europe. In 2005, the FDA requested Purdue Pharma to withdraw Palladone (Hydromorphone) extended release capsules from the market, due to possible serious adverse reactions, that could occur already at the lowest dosage strength, if the drug was consumed with alcohol - against the warning in the package leaflet. In Europe, similar concerns were raised by the Committee for Medicinal Products for Human Use (CHMP) during the approval procedure of a generic oxycodone. Also in this case, a warning in the leaflet was not considered sufficient because a significant percentage of the patients do not abstain from alcohol consumption despite existing warnings.

Meanwhile the FDA has issued separate draft guidances referring to ADD, also for a number of non-opiate APIs and different indications.

Although the guidelines have a common focus on in-vitro testing and risk mitigation through reformulation in case ADD is suspected or observed in-vitro, the requirements
towards the in-vitro test conditions in the EU differ from those in the US. While the EMA guideline remains partly vague towards the in-vitro test conditions, the FDA requires unrealistic high alcohol concentrations of up to 40%. Such high alcohol concentrations do not correlate to physiological conditions and seem to be more relevant in context of a certain form of drug abuse, where dose dumping is induced by intentional excessive alcohol consumption.

As non-harmonized and un-physiological test conditions present a challenge for the pharmaceutical industry, in particular for companies operating in different international regions, a harmonization and consolidation of in-vitro test requirements is required says Becker.

**Current Sustained Release Strategies**

There already are a number of strategies available that can be used to achieve sustained release dosage forms and the desired drug availability rate (Figure 3):

- Coat the drug containing dosage form; Embed API into eroding or non-eroding matrix;
- Modify the API particle size to create coarser particles, leading to reduced dissolution speed of the API;
- Form complexes of the API, e.g. with inorganic or polymer-organic absorbents or ion-exchange resins
  - Form a prodrug;
  - Hot melt extrusion matrix.

Sustained release dosage forms can utilize matrix or reservoir systems as single or multiple units. In addition, matrix systems can include ophthalmic inserts. Implants and transdermal patches can be used as sustained release dosage forms as well.
Standard sustained release coated tablets represent a single-unit reservoir type of sustained-release dosage forms. For multiple unit versions, different matrix granules, pellets, mini-tablets, and multiparticulate systems can be used. There are a variety of release mechanism options for sustained release dosage forms that offer good API solubility:

- Bulk erosion release;
- Surface erosion release;
- Diffusion control release;
- Osmotic pressure control – osmotic pumps.

Solid oral dosage forms for sustained release also include conventional matrix tablets. Among these options:

- An eroding matrix in which size reduction is the driving force;
- A non-erodible hydrophobic matrix, such as BASF’s Kollidon® SR, which retains its size and shape;
- A size-increasing swellable matrix that features a drug-depleted gel layer, and undissolved drug in a glassy inner layer, which is eventually depleted by contact with water.

Reservoir sustained release systems can use a polymeric film as a coating. It can be made in a drug-layering process or as a drug reservoir. The polymeric film is usually a membrane. This membrane can be non-porous, or contain micropores based on a co-formulated soluble material. It can also be semi-permeable.

Other choices for drug release systems include osmotic pumps and openable matrices. Osmotic pumps have a semi-permeable coating along with a drug layer and a push layer. The push layer swells while the drug layer dissolves. Increasing the osmotic pressure in this system releases the drug in a relatively constant, usually zero-order release characteristic. Openable matrices contain a semi-permeable coating that dissolves and releases a drug over a relatively constant period of time.

### Sustained Release Formulation Options

To mitigate risk, drug manufacturers must reformulate their drugs if alcohol-induced dose dumping is suspected or observed in vitro. While this is a significant challenge, options are available for developing alcohol-resistant formulations.

Currently, three ethanol-resistant drug delivery systems are on the market or are described in scientific literature (Figure 4).

#### Matrix tablets

- Tramabeta containing Tramadol HCl, a highly water soluble drug;
- Alfuzosin, containing a highly soluble drug -- Alfuzosin 10 mg;

#### Coated systems

- OROS
- Press-coating

#### Hot melt extrusion

- HPMC/HPC - Meltrix®
- High molecular PEO - INTAC®

- TIMERx® system, which contains xanthan gum and local bean gum, and whose tight gel structure leads to controlled release;

#### Coated systems, such as an osmotic-controlled-release oral delivery system (OROS), i.e. used for Hydromorphone.

Hot melt extrusion systems using materials such as HPMC or high molecular weight polyethylene oxide (PEO). An example here is the Meltrex® delivery platform, i.e. used for Verapamil.

However, conventional HMPC or sodium alginate based matrix tablets do not always meet the latest regulatory requirements.

#### Non-swellable matrix systems

An important option for sustained release formulations are non-swellable matrix systems. Polymers used are Ethyl cellulose or polyvinylacetate/povidone. Polyvinylacetate/povidone, also known as Kollidon® SR, is an attractive retarding agent option with excellent flow properties. It is particularly suitable for the manufacturing of pH-independent sustained-release matrix tablets by direct compression or even hot melt extrusion. Kollidon® SR offers excellent flow properties and extraordinary compactibility, compared with other products (Figure 5). It is a matrix-forming polymer prepared by the spray drying of polyvinylacetate aqueous dispersions, with the addition of 20 percent polyvinylpyrrolidone (PVP). Because it is a spray dried product, the particle shape is nearly spherical, which explains its excellent flow properties. Direct compression of tablets with this material is feasible.

Fusion and a tightening of the polymer matrix take place during the dissolution of Kollidon® SR. This can be explained by a relative low glass transition temperature. This in conjunction with the insolubility in aqueous, ethanol-containing gastric fluids is a very important property because with the tightening of the matrix, soluble high molecular weight polymer
cannot not easily leach out and will inhibit its release in ethanol-containing media.

**In Compliance**

Three formulations of Kollidon® SR are in compliance with regulatory requirements (Figure 6):

- Kollidon® SR with high molecular weight HPMC (e.g. Metolose® 90 SH 15000);
- Kollidon® SR with xanthan gum (e.g. Satiaxane®);
- Kollidon® SR with polyvinyl alcohol (e.g. Parteck® SRP 80).

All of three formulations have good, or at least moderate, flow properties that will result in hard tablets. The tendency for erosion is moderate. The effect of stirring speed was moderate, and release in ethanol containing media is in agreement with FDA or other regulatory authorities’ requirements. All three of these matrix formulations can be used to formulate swellable but not erodible, hard tablets with hardness greater than 200 Newtons. Most important, ethanol has little or no effect on their sustained release.

**References**


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6. FDA, Draft Guidance on Metformin Hydrochloride; Sitagliptin Phosphate (Rockville, MD, July 2014).
