**QD Diffucaps®** Drug Delivery Systems for Weakly Basic Pharmaceutical Actives


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**Abstract**

Lack of compliance to dosing regimens is widespread largely due to complicated regimens (e.g. too many medications, too frequent dosing) and swallowing difficulties. Eurand’s Diffucaps® technology enables the development of once-daily controlled-release (CR) capsules or patient-friendly orally disintegrating tablet (ODT) CR comprising immediate-release (IR), sustained-release (SR), timed pulsatile-release (TPR) or timed sustained-release (TSR) bead populations multicoated with a weakly basic drug, an organic acid, and a solid-solution and then further coated with one or more functional polymers.

**Introduction**

- Complicated regimens (too many medications, too frequent dosing) and physical difficulties in complying (e.g. handling small tablets, swallowing difficulties, timely accessibility to drinks) are often cited as factors responsible for non-compliance or lack of adherence to dosing regimens, which has become a major medical problem in America costing billions of dollars.

- Drug delivery systems such as sustained-release (SR) multi-particulate capsule or matrix tablet formulations, amorphous/nanocrystalline or solid solution formulations, and organic acid- or effervescent-containing formulations have been developed to enhance absorption of the drug throughout the human digestive tract to reduce the frequency of dosing.

- Many pharmaceutical actives are weakly basic and exhibit pH-dependent solubility profiles. Further, in the human digestive tract, a drug will experience varying pHs (e.g., from pH 1.0 in the stomach under fasted conditions to pH ~7.4 in the large intestine) and transit times that depend on factors such as dosage form and fasted/fed conditions. The drug must be released from the dosage form in solution form; otherwise, it is generally not absorbed. Consequently, the ability to apply enhanced absorption systems to develop controlled-release (CR) products has been limited.

- Eurand’s Diffucaps® technology allows development and commercialization of weakly basic drugs with varying pH-dependent solubility profiles (e.g., cyclobenzaprine, propranolol, ondansetron, carvedilol, nifedipine, EUR-1057) based on (1) lag-time coating, (2) use of solubility-enhancing organic acids, and/or (3) use of crystallization-inhibiting polymers (solid-solution approach).

**Experimental Methods**

- Eurand’s Diffucaps® technology involves (1) the preparation of drug-containing cores such as immediate-release (IR) beads, pellets or microtablets (e.g., typically 1.5 mm in diameter) obtained by layering drug on inert cores, (2) controlled spheronization or granulation-compression using one or more coatings with proprietary functional polymers, and (3) combining one or more coated, spherical, multi-layered bead populations (Fig. 1) into hard gelatin or hydroxypropyl methylcellulose (HPMC) capsules or blending with rapidly dispersing granules and compressing into orally disintegrating tablets (ODTs) (Fig. 2).
• In case of weakly basic drugs requiring an organic acid to solubilize the drug prior to its release into the intestine, a drug-containing core (e.g., an acid crystal or an inert core layered with the acid) is coated with a water insoluble polymer to sustain the acid release and to prevent the acid from coming into contact with the weakly basic drug. The SR acid-cores are coated with the drug as well as one or more polymer membranes to produce CR capsules containing IR and/or timed pulsatile-release (TPR) bead populations.

• A weakly basic drug and a crystallization-inhibiting/solubility-enhancing polymer are dissolved in a solvent mixture and coated onto inert cores. The polymer inhibits the drug from returning to crystalline form while maintaining it in the thermodynamically activated (i.e., amorphous) state.

• IR beads containing extremely soluble drugs, such as EUR-1057, are coated with an alkaline buffer prior to coating with functional polymers to create an alkaline pH microenvironment that retards drug release. The polymer coated beads are further coated with a compressible coating to eliminate/minimize membrane fracture during compression.

**Results and Discussion**

• Cyclobenzaprine, freely water soluble, is a novel centrally acting drug administered to relieve skeletal muscle spasm of local origin. Cyclobenzaprine is well absorbed after oral administration with a relatively long half-life, but with a suspected short pharmacological activity. AMRIX® is the first and only FDA approved, once-daily skeletal muscle relaxant providing significant reduction in patient rated daytime drowsiness.

• InnoPran XL®, a chronotherapeutic dosage form designed to be dosed at bedtime, provides therapeutically effective concentrations in the morning hours to prevent or minimize target organ damage from morning cardiovascular events.

• Ondansetron, a serotonin receptor antagonist, is freely soluble < pH 3.0 and is practically insoluble > pH 6.0, thereby making it difficult to develop once-daily (q.d.) formulations. By creating an acidic pH microenvironment within the polymer coated bead to solubilize the drug prior to its release into the hostile pH environment, the formulation has demonstrated its suitability for a q.d. dosing regimen (Fig. 3).
• Maximizing the surface area, optimizing the drug load and polymer coating composition while maintaining the drug in the amorphous state dramatically shifts the poorly soluble drug’s solubility/absorption kinetics, enabling the development of q.d. dosage forms of poorly soluble drugs (e.g., nifedipine).

• EUR-1057, an atypical antipsychotic agent, is extremely soluble in the physiological pH range (e.g., > 700 mg/mL), thereby insufficiently extending drug release/absorption from coated beads under 500 μm to provide patient compliant, once-daily, orally disintegrating tablet formulations. By creating an alkaline pH microenvironment at the drug-alkaline buffer interface within the polymer coated bead, thereby retarding drug’s solubility/release, Eurand could develop alternate bioequivalent dosage forms—CR capsules and ODT CR (Fig. 4).

• For a CR ODT, the most critical parameter is being able to develop a product with reproducible dissolution profiles. Coated beads are typically rigid and encounter breakage issues upon compression into ODTs. The Diffucaps® beads are coated with a compressible coating to eliminate/minimize membrane fracture during tableting.

Conclusion
• Combining one or more Diffucaps® bead populations into CR dosage forms provides therapeutically effective plasma concentration profiles suitable for q.d. dosing regimens.

REFERENCES:


