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-compliant orally disintegrating tablet formulations (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 or an alkaline buffer, 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) multiparticulate 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 track, a drug will experience varying pHs (for example, stomach: pH 1.2–3.5, duodenum: pH 4.6–6.0, small intestine: pH 4.7–6.5, large intestine: pH 7.5–8.0); varying fluid volumes (for example, 45 mL vs. 686 mL in the stomach, 105 mL vs. 54 mL in the small intestine, and 13 mL vs. 11 mL in the large intestine in the fasted vs. fed states); surface area (stomach: 0.1–0.2 square meter (sq-m), small intestine: 4,500 sq-m, large intestine: 0.5–1 sq-m); and transit times (stomach: 0.25–3 hrs, duodenum: 1–2 hrs, small intestine: 1–10 hrs, large intestine: 4–20 hrs) 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., ondansetron, carvedilol, EUR-1057, nifedipine) based on lag-time coating and (1) use of solubility-enhancing organic acids, (2) solubility-retarding alkaline buffers, and/or (3) use of crystallization-inhibiting polymers (solid-solution approach).

• Eurand’s Diffucaps® technology allows development and commercialization of drug delivery systems of weakly basic drugs with varying but pH-independent solubility profiles (e.g., methylphenidate, propranolol, cyclobenzaprine) for customized delivery as needed, i.e., to deliver drugs in quantities when needed to mimic circadian rhythm variations of disease states.
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 2 mm or less in diameter) obtained by (1) layering drug on inert cores, extrusion-spheronization, controlled spheronization, or granulation-compression, (2) applying 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) capsules2 or blending with rapidly dispersing granules and compressing into orally disintegrating tablets (ODTs)5 (Fig. 1).

- 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 populations6.

- 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) state7.

- 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 compression8.

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 (Fig. 2) providing significant reduction in patient-rated daytime drowsiness8–11.
• Stimulant therapy of school-going children with attention-deficit/hyperactivity disorder (ADHD) with a scheduled drug such as methylphenidate requires the development of a modified-release dosage form to avoid dispensing the drug during the school hours. Metadate CD®, a capsule formulation containing 30% of the dose as IR for rapid onset of action upon dosing at breakfast and the remaining 70% of the dose for continued action until bedtime, is compared with Concerta®, an expensive osmotic device that uses the OROS® technology, in Fig. 312,13.

• 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 (Fig. 4)14,15.

Fig. 2: Plasma Profiles of cyclobenzaprine from Flexeril® (10 mg IR) dosed 3 times daily vs. Amrix® (ER capsule) dosed once daily

- Amrix® with reduced sedation is better tolerated compared to Flexeril®

Fig. 3: Plasma Profiles of Metadate CD® compared to expensive Concerta®

- Metadate CD® containing a scheduled CNS stimulant was initially developed to avoid medication of children with ADHD during school hours as it allows medicating just once daily at breakfast
- The extended-release capsules comprise 30% of the dose as immediate-release (IR) beads for rapid onset of action and 70% of the dose as extended-release (ER) beads for extended effect during the day until bedtime

• 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 (Fig. 4)14,15.
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. 5).\(^7\)

Fig. 4: Plasma Profiles of InnoPran XL vs. Inderal LA

- Chronotherapeutic release formulation specifically designed to coincide with daytime catecholamine levels
  - Administration at bedtime
  - 4 hour delayed release to achieve \(C_{\text{max}}\) in the early morning hours
  - Lower plasma concentration during the night when less is needed
  - Superior bioavailability to Inderal LA\(^8\)

Fig. 5: Plasma Profiles of Ondansetron QD (EUR-1025) vs. Reference (Zofran\(^\text{®}\) IR) Dosed BID

- EUR-1025 achieved similar plasma concentration at 24 hours post dosing v. BID dosing of IR product • \(N = 12\) healthy subjects

- Maximizing the surface area and 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).\(^9\)
• 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. 6 & 7).\(^8,18\).

![Fig. 6: Release Profiles for EUR-1057 Once-daily ODT-CR and CR Capsules](image)

- Patient-friendly once-daily ODT CR also developed to improve patient compliance
- EUR-1057 CR beads are provided with a compressible coating to minimize membrane fracture during tableting
Fig. 7: Plasma Profiles for EUR-1057 QD, 50 mg vs. 25 mg Syrup

- Patient-friendly once-daily ODT-CR1 and CR capsules are bioequivalent
- $C_{\text{max}}$ of 50 mg ODT-CR1 and CR capsules comparable to that of 25 mg Syrup

- 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 tabletting (Fig. 7).

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:


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