



CDT® Controlled Delivery Technologies Platform

Why utilize a controlled release technology?

Without controlled release technologies, people end up taking numerous doses of drugs, OTC products and nutritional supplements to realize the maximum benefits. At times this may result in potentially undesirable side effects that may negate the benefits derived from the drugs or products. Controlled release (Extended, sustained and others) address these concerns by optimizing bioavailability of active ingredients while reducing adverse side effects, improving dosing compliance and maximizing overall product effectiveness.

Controlled release technologies enable precise control over the timing and amount of active ingredients released. Few of these technologies are capable of providing near zero order kinetics over 24 hours; a feature which is difficult, if not impossible, to attain with first generation technologies. SCOLR Pharma has developed and advanced a series of controlled release technologies that offer tangible improvements over other approaches and technologies available today.

How Does CDT® work?

SCOLR's platform of patented CDT® technologies enable delivery of active pharmaceutical, OTC, and nutraceutical ingredients from a tablet or capsule over an extended time period. These technologies originated in the mid 1990s during extensive research in the pharmaceutical laboratories of Dr. Reza Fassihi, B. Pharm., Ph.D. at [Temple University School of Pharmacy](#). Since then, this research has led to the development of a wide platform of patented controlled delivery technologies that are the exclusive intellectual property of SCOLR Pharma.

The CDT® platform is founded on the art of matrix hydration and erosion, changes in gel thickness, electrolyte ionization, and ionic interactions. These simple systems lead to carefully controlled delivery of the active ingredients in a predictable, programmable manner with consistent reproducibility. Previously, this has not been achievable with first-generation delivery systems. This technology provides the opportunity for formulation across various classes of drugs: [Class I](#) (high permeability/high solubility) and [Class II](#) (high permeability/low solubility). SCOLR has also demonstrated formulations with certain [Class III](#) drugs (low permeability/high solubility), which are historically very problematic.

Self-Correcting Matrix Delivery Systems (CDT® Technology)

Novel drug delivery technologies can be applied to meet many of the challenges that we face in life-cycle management of both old and new drugs. They can also enable the advancement of new drugs that would not be feasible without the ability to improve and control delivery. An optimal drug delivery system would lend itself to formulation flexibility and cost-effective production of a large range of dose variants and individualized dosage regimens that may potentially arise for the purpose of patent extension, product differentiation, or to satisfy regulatory approval requirements.

Oral dosage forms represent the vast majority of the drug-delivery market in the United States and Europe because of the safety, efficacy, economics, and consumer compliance and preference advantages as compared to alternative routes of delivery. Transdermal, injectible, and inhalation routes all possess significant regulatory, technical and compliance barriers to their economical application.

Over the last two decades, the pharmaceutical market has demonstrated an increasing preference for modified oral dosage forms that allow for controlled release (CR) rather than immediate-release (IR). Increased patient compliance, patent extension, product differentiation, heightened safety and efficacy, and a greater return on investment represent significant motivations for the application of CR formulations to new and existing drugs.

While currently available modified oral dosage forms are an extremely diverse group in terms of mechanisms used to control drug delivery and the complexity of manufacture, matrix technologies have proven the most economical because of their simple manufacturing processes, high level of reproducibility, greater stability of the raw materials and the finished dosage form, ease of scale up operation and well-established *in-vitro*-*in-vivo* correlations.

Whereas simple matrix delivery systems have been classically limited to first order release kinetics, SCOLR Pharma has employed materials science, colloid chemistry and biopharmaceutics in the formulation of simple monolithic matrices collectively referred to as "self-correcting matrix delivery systems." These approaches use conventional tableting technology to form swellable, erodible matrix tablets, caplets or capsules that can yield first-order, bimodal and zero-order drug release profiles.

SCOLR Pharma has developed a series of technologies applicable to modified oral dosage forms, each focusing on overcoming specific barriers to optimize drug administration. The common rationale underpinning all these systems is the ability to dissociate or modify the site, duration and magnitude of drug action from the inherent physical limitations and chemical properties of the drug molecule itself.

SCOLR Pharma's CDT® delivery systems utilize the ionic interaction between selected polymers and additives to preferentially hydrate and influence peripheral hardening of the gel matrices with a progressive shift in gel formation toward the central core, thus controlling erosion and dissolution. The release rate from these systems is less adversely affected than competing technologies by ionic strength outside of the tablet, tablet hardness, pH, hydrodynamics and other physiological parameters of the gastrointestinal tract as have been determined by USP dissolution methods, surrogate dissolution techniques, and erodability studies. Such analyses ensure the highest possible success of clinical trials based upon these *in-vitro* examinations.

Each technology may be specifically applied to a given product depending on the physical characteristics of the drug, such as solubility, flow properties, and drug load. The desired duration of release can be programmed from four to twenty-four hours. This allows the finished dosage form's release profile to be manipulated by alterations in the formulation itself, rather than through manufacturing-dependent changes in tablet geometry, layering or coating.

CDT® Platform Summary

Dual Polymer Platform

The first patent within the technology, referred to as the *Dual Polymer* platform, was developed specifically for the controlled release of highly soluble actives, and involves the simple granulation of an active pharmaceutical ingredient (API) with one or more polymers or gums of differing swelling characteristics. The combination of differential hydration rates of each polymer and the relative charges they carry may be combined to suppress the diffusion of the drug for up to 24 hours. This method of controlled release results from ionic interactions between the API and the polymer matrix, which is initiated once the dosage is taken by the patient and exposed to hydration in the gastrointestinal tract.

APIs with poor flow properties may be combined with better flowing controlling polymers and excipients during the granulation step to yield a more manufacturable tablet. APIs with poor compression characteristics or those formulations that require a large drug load to be therapeutically effective may also be combined with more compressible materials and high-viscosity polymers to allow for the manufacture of a lower-volume dosage form than is possible with other matrix technologies.

Electrolyte Platform

The second patent - referred to as the *Electrolyte* platform - employs the colloidal chemistry phenomenon of "salting-out" to moderate the swelling and erosion kinetics of the polymer matrix containing the API and one or more electrolytes or "salts." The presence of these ionizable salts allows for non-collapsible diffusion channels enabling stable and consistent diffusion of the drug. The electrolytes also contribute to a contracting micro-environment within the tablet, whose pH is mediated by the pKa of the electrolyte, thus either enhancing or suppressing the solubility of the API itself. As the matrix hydrates, the electrolytes and polymer compete for available water, resulting in a programmable rate of release.

The result is a system which is capable of zero-order, pH-independent release of an API for up to 24-hours, without regard to the solubility of the API itself. Because the system consists of a non-covalently bonded matrix, the manufacturing process is fundamentally a two-step process of simple dry-blending and direct compression. This two-step process allows for the manufacture of a monolithic tablet with cost advantages comparable to a simple wax-matrix, yet provides release profiles comparable to an osmotic pump or multi-layer tablet.

Amino Acid Platform

Three patents encompass the technology referred to as the *Amino Acid* platform which has applied theories of colloidal chemistry in the formulation of a matrix comprised of an API granulated with one or more amino acids, within a secondary dry-blended matrix composition. The ionic interaction between the granulated and dry-blended constituents allows for the controlled release of an API over 24-hours, independent of its solubility.

SCOLR's *Amino Acid* platform employs the colloidal chemistry technique of "salting in," that offers improvements on the solubility of BCS Class III compounds inside the tablet matrix without compromising the controlled release characteristics of the delivery system.

Ibuprofen Platform

The remaining and most recent patents represent the application of SCOLR's formulation experience to a specific drug, ibuprofen. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) available in both OTC and Rx products, either alone or in combination with other drugs, such as cough-cold medicines or opiate-analgesics. SCOLR's *Ibuprofen* platform employs a novel hydrophilic polymer matrix to control the release of ibuprofen from a tablet core. This matrix provides a bimodal delivery profile generating both an immediate release "burst" of ibuprofen for the onset of pain relief and continues to deliver drug over 12-hours.

SCOLR's *Ibuprofen* platform was the first technology platform developed independently at SCOLR, but shares many of the valuable characteristics of the other CDT® technologies – dry-blend and direct compression manufacturing, novel use of commonly utilized excipients – and employs them to produce the first commercially-viable extended-release 12-hour ibuprofen formulation for the US market. The novel matrix technology employed in SCOLR's *Ibuprofen* platform has been successfully produced at commercial volumes in excess of 1200kg per batch without any "picking" or "sticking" that is commonly seen with other ibuprofen products. This enhanced manufacturability results in a very cost-effective product candidate for the OTC market. This matrix technology is flexible and we anticipate that it can be combined with other drugs to create both OTC and Rx combination products, and thus represents a significant opportunity for line extensions beyond the current 12-hour ibuprofen product.

CDT® Technology Compared to Other Controlled Release Drug Delivery Systems

The opportunities for increased patient compliance, patent extension, product differentiation, and improved safety and efficacy offered by extended release (ER) technologies have resulted in the development of multiple delivery platforms to address the wide range of APIs and their physiochemical characteristics such as solubility, compressibility and flowability. While all of the delivery technologies discussed herein may be classified as "sustained" or "extended" release, their effectiveness in controlling drug release varies widely.

Each broad category of delivery technology - diffusion, reservoir, coated-bead and multi-particulate, pore-forming wax, and geometric-physical devices - has traditionally been limited in the specific types of pharmacokinetic release profiles that may be obtained. Few delivery technologies are capable of 24-hour near-linear release; this is often as dependent upon the physical characteristics of the delivery system as upon the characteristics of the API itself.

Diffusion tablet systems rely on hydrophilic polymer swelling for control of drug release, and may then be coated with diffusion barriers to further control drug release. These systems often employ granulation steps to incorporate the drug in a single polymer such as polyethylene oxide or hydroxypropyl methylcellulose; the diffusion barriers are often formed from film-forming polymers such as acrylic resins or ethyl cellulose. These granulation and coating processes add extra processing steps, variability and cost to manufacturing. While such have yielded acceptable sustained release patterns for short durations, it is difficult to produce a linear release over 12 to 24 hours.

SCOLR Pharma's monolithic matrix systems offer an advantage over single polymer diffusion systems by employing additional materials that work with the physical properties of the API and polymer to further control tablet hydration and the release of the drug. These systems have produced linear release profiles over durations up to 24 hours without the need for multiple layers within the tablet.

Reservoir devices usually consist of a semi-permeable barrier that is involved in the release of the API from a core site within the tablet. The manufacturing process may involve incorporating laser-bored orifices in the semi-permeable membrane. Although capable of producing a linear release pattern, factors such as the complexity of design, necessary manufacturing processes, and specialized equipment, may result in producing an unbalanced cost-benefit ratio.

SCOLR Pharma's monolithic matrix systems eliminate the need for costly manufacturing processes such as creating coating membranes with precise release orifices; in the case of the *Electrolyte* platform, a simple two step process of dry blending and direct compression is all that is necessary. A matrix system is less susceptible to tablet damage that may alter release rate of the drug, and lead to dose dumping, than a semi-permeable membrane system; a coated reservoir system may develop leaks if the membrane is compromised after manufacture. Further, osmotic systems are often limited to low doses of drugs due to size limitations of the tablet. **SCOLR Pharma's** electrolyte patent has proven to be effective for high doses of drugs; in some cases with little controlling excipient necessary so the overall tablet size is minimized.

Coated-bead and multi-particulate systems often employ pH-sensitive, enteric, or sustained release coatings upon aggregate granules or “beads” of the API. These granules/beads may then be packaged in a capsule or compressed with additional excipients to form a tablet. The API may also be blended or granulated with polymers before coating to provide an additional level of control; these systems may also appear as a blend of coated-beads with differing release rates for extended release or pulsatile release formulations. Regardless of the manner of manufacture, coated bead systems are extremely complex to produce, requiring large numbers of excipients, use of solvents and multiple manufacturing steps.

SCOLR Pharma's monolithic matrix systems employ the tablet matrix itself as the rate-controlling mechanism instead of complex coating processes, and because the drug is incorporated into the matrix itself, there is no need for a bead template to shape or build upon. **SCOLR Pharma's** matrix technologies are as flexible as multi-particulate systems, allowing formulations as both capsule and tablet dosage forms with fewer manufacturing steps.

Pore-forming wax systems incorporate the API into a wax base via tableting and rely upon the rate of erosion to control the release of the drug. The API and a water soluble excipient (such as a polymer or salt) are introduced into a wax or wax-like compound (such as paraffin) and then placed in an aqueous environment in order to allow the water soluble polymer to dissolve out of the wax, resulting in the formation of pores. Upon contact with the gastrointestinal fluid, the pores facilitate erosion of the wax and the subsequent release of the active ingredient. This erosion is often non-linear - the accuracy and efficacy of the resulting rate of release is often of insufficient precision for many pharmaceutical products. It is rarely capable of controlling drug release in a near-linear fashion over 24 hours, because the high volume of controlling excipient required for such a duration often results in a significant portion of the drug remaining trapped in the wax matrix.

SCOLR Pharma's monolithic matrix systems employ both diffusion and erosion to mediate drug release from the tablet, thus exhibiting far more reproducible release than non-linear erosion systems. The self-correcting nature of the ionic gel matrices controls both polymer hydration and erosion, this allows for near-linear release throughout 24 hours as gel formation progresses toward the dry central core and erosion continues at the outer boundary of the gel layer. The use of electrolytes and/or amino acids as channelization agents within the gel layer ensures the complete hydration of the matrix and corresponding release of the drug in a stable and controlled manner.

Geometrical-physical systems incorporate the active ingredient into a layer or core, which is then formed into a pellet and altered by physical means to effect and control the rate or erosion or dissolution of the dosage form. Surface-area modifications are often employed to retard the burst release of highly soluble actives or increase the extent of the release of actives from tablet cores that possess diffusion limitations. The physically-altered pellet may then be incorporated alone or in combination with other modified pellets and excipients into a capsule or tablet. These systems can be quite simple, such as an enteric-coated tablet, or highly complex. Many of the physical-geometric delivery system designs are intentionally complex so as to remain distinctive and proprietary while also providing a significant degree of flexibility in formulation and a wide range of available release profiles. Because the rate and extent of release is dependent upon the how the physical alteration to the tablet is affected *in vivo*, variations in the coatings or barriers dramatically affect the release of the active ingredient and may result in a high degree of *in vivo* release variability.

SCOLR Pharma's monolithic matrix systems allow for highly reproducible release *in vivo* because of a reliance upon the uniform hydration of the entire dosage form rather than a select portion of the tablet, as is often the case with physical-geometric systems. The lack of intricate physical manipulation during production minimizes the cost of manufacture, but the patents covering **SCOLR Pharma's** platforms allow for such manufacturing efficiencies without sacrificing the proprietary nature of the technologies.

CDT® Technology Comparison Summary Table

| Technology | Advantages | Disadvantages |
|---|---|---|
| SCOLR Pharma CDT® Controlled Delivery Technologies | <ul style="list-style-type: none"> • Simple low cost manufacturing (only 2-3 steps) • Capable of near-linear release • Reproducible <i>in vivo</i> • Amenable to capsules and tablets • High payloads without dose dumping concerns • Long-life patents • Cost-effective reformulation of existing ER products • Commercialized nutraceuticals and late-stage OTC drugs | <ul style="list-style-type: none"> • May require granulation depending on the nature of the API and overall goals of the formulation. • Not suitable for drugs that suffer from a high degree of first pass metabolism. |
| Diffusion | <ul style="list-style-type: none"> • Inexpensive • Easy to achieve first-order release | <ul style="list-style-type: none"> • Difficult to achieve near-linear release or other complex profiles • Often require granulation and/or coating • Potential dose dumping concerns • Numerous patents, Difficult to protect with IP |

CDT® Technology Comparison Summary Table (continued)

| Technology | Advantages | Disadvantages |
|--------------------------------|---|--|
| Reservoir | <ul style="list-style-type: none"> • Zero order release possible • pH-independent and ion-independent release possible • Release may be independent of drug solubility | <ul style="list-style-type: none"> • Complex to manufacture • Multiple manufacturing steps (Estimated at 18-36 steps or more) • Low drug load • Rapid transit • Incomplete release • Ghost present • Potential dose dumping concerns |
| Coated-bead, Multi-particulate | <ul style="list-style-type: none"> • Capable of near-linear and pulsatile release • Amenable to capsules and tablets • May incorporate bio-adhesion • Lowest <i>in-vivo</i> variability | <ul style="list-style-type: none"> • Multiple manufacturing steps (Estimated at 18-36 steps or more) • Low drug load • Incomplete release • Potential dose dumping concerns |
| Pore-forming Wax | <ul style="list-style-type: none"> • Inexpensive • Rugged | <ul style="list-style-type: none"> • Dependent on non-linear erosion • Incapable of near-linear release over 24h • Incomplete release • Non-proprietary • Ghost present • Potential dose dumping concerns |
| Physical-Geometric | <ul style="list-style-type: none"> • Capable of near-linear and unique release profiles • Proprietary Design | <ul style="list-style-type: none"> • Complex manufacturing • Multiple manufacturing steps (Estimated at 18-36 steps or more) • Low drug load • Incomplete release • Potential dose dumping concerns • Variability <i>in vivo</i> Incomplete release Ghosts present |

Key Benefits of CDT®

How can CDT® benefit your material delivery technique?

- **Extremely flexible design and dosing** — Capable of releasing ingredients in one of many different types of profiles in order to maximize performance based on the needs of the drug. Can also accommodate multiple ingredients in order to satisfy the need for combination products.
- **Highly programmable** — Releases a precise quantity of active ingredient each hour for up to 24 hours. Protracted delivery is possible because CDT® tablets and capsules are floatable in the digestive tract. Can be designed to release at a specific pH and thus be delivered to a specific point in the digestive tract where the ingredient is most efficacious.
- **Easy to manufacture** — Because the core technology relies on dry blends and direct compression, active substances incorporating CDT® do not require specialized expertise, manufacturing equipment or facilities. Fewer processing steps reduce manufacturing time and decrease risk of batch failure.
- **Cost effective** — Because CDT® can be manufactured in existing high-volume facilities, with only 2-3 manufacturing steps; it significantly lowers the cost of production.
- **High payload** — CDT® enables the use of fewer excipients and more active ingredients in each tablet or capsule compared to other delivery technologies.
- **Strong patent protection** — Long patent life and easy identification of infringement. Allows pharmaceutical companies to extend the patent life for their valuable market franchise