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A review on future aspects of hydration based drug delivery systems

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Abstract
In spite of making tremendous achievements in drug delivery through various routes such as the parenteral, transdermal, Trans mucosal; the oral route remains the most favourite route because of its ease of administration, patient compliance and economic well-being. out of the various oral drug delivering technologies hydration or hydrolysis based process is one most sort after as drug taken comes directly in contact with GI fluids causing disintegration and dissolution of the drug system. In hydration based process disintegration and dissolution are controlled by the use various types of polymers and osmotic agents. Thus delivering the dose at zero order. Various processes include drug embedded or disperse in reservoir, matrixes and hybrids and physically controlled process such osmotic and hydrodynamic pressure creation. This term paper report aims at reviewing the numerous techniques that has been designed till date for optimizing hydration based drug delivery.

Keywords: polymers, osmotic agents, hydrodynamic pressure, matrixes reservoir, hybrid systems

Introduction
The United States Pharmacopoeia (USP) defines the modified-release (MR) dosage form as "the one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms. One class of MR dosage form is an extended-release (ER) dosage form and is defined as the one that allows at least a 2-fold reduction in dosing frequency or significant increase in patient compliance or therapeutic performance when compared with that presented as a conventional dosage form (a solution or a prompt drug-releasing dosage form). The terms "controlled release (CR)", "prolonged release", "sustained or slow release (SR)" and "long-acting (LA)" have been used synonymously with "extended release". The commercial branded products in this category are often designated by suffixes such as CR, CD (controlled delivery), ER, LA, PD (programmed or prolonged delivery), Retard, SA (slow-acting), SR, TD (timed delivery), TR (timed release), XL and XR (extended release).

Material and Methods
Matrix systems: These consist of a rate controlling polymer matrix through which the drug is dissolved or dispersed.

Reservoir (coated) systems: Where drug-containing core is enclosed within polymercoatings. Depending on the polymer used, two types of reservoir systems are considered.

Simple diffusion/erosion systems: Where a drug-containing core is enclosed within hydrophilic and/or water-insoluble polymer coatings. Drug release is achieved by diffusion of the drug through the coating or after the erosion of the polymer coating.

Osmotic systems: where the drug core is contained within a semi-permeable polymer membrane with a mechanical/laser drilled hole for drug delivery. Drug release is achieved by osmotic pressure generated within the tablet core.

Hydrodynamic pressure systems: Where a liquid drug is placed inside a collapsible, impermeable container to form a drug reservoir compartment. this is then contained inside a rigid, shape retaining housing. a laminate of an absorbent layer and a swell able hydrophilic layer is sandwiched between the drug reservoir compartment and the housing. in the GItract, the laminate will imbibe the GI fluid through the annular openings at the lower end of the housing and become swollen this generates a pressure in the system which causes drug to be release through annular openings.

Table 1: polymers commonly used in hydration based drug delivery technology

Hydrophilic Polymers	
Ethyl cellouse Meth ylcellulose HPMC Hydroxypropylcellulose (HPC) Hydroxyeth ylcellulose (HEC) Sodium carboxymethylcellulose (Na-CMC) Noncellulosic: gums/polysaccharides Sodium alginate Xanthan gum Carrageenan	Ceratonia (locust bean gum) Chitosan Guar gum Pectin Cross-linked high amylose starch

Advantages of hydration based controlled release drug delivery systems
Patient compliance: Lack of compliance is generally observed with long term treatment of chronic disease, as success of drug therapy depends upon the ability of patient to comply with the regimen. Patient compliance is affected by a

combination of several factors, like awareness of disease process, patient faith in therapy, his understanding of the need to adhere to a strict treatment schedule. Also the complexity of therapeutic regimens, the cost of therapy and magnitude of local and or systemic side effect of the dosage form. The problem of lack of patient compliance can be resolved to some extent by administering controlled release drug delivery system.

Reduced see saw fluctuation: Administration of a drug in a conventional dosage form [except via intravenous infusion at a constant rate] often results in 'see – saw' pattern of drug concentration in the systemic circulation and tissue compartments. The magnitudes of these fluctuations depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' or 'peak and valley' pattern is more striking in case of drugs with biological half-lives of less than four hours, since prescribed dosing intervals are rarely less than four hours. A well designed controlled release drug delivery system can significantly reduce the frequency of drug dosing and also maintain a steadier drug concentration in blood circulation and target tissue cells.

Reduced total dose: Controlled release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

Improved efficiency in treatment: Optimal therapy of a disease requires an efficient delivery of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A controlled release dosage forms leads to better management of the acute or chronic disease condition.

Result and Discussion

Disadvantages of hydration based controlled release drug delivery systems

Dose dumping: Dose dumping is a phenomenon where by relatively large quantities of drug in a controlled release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index e.g. Phenobarbital.

Less flexibility in accurate dose adjustment: In conventional dosage forms, dose adjustments are much simpler e.g. Tablet can be divided into two fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.

Poor in *vitro-in vivo* correlation: In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so called 'absorption window' becomes important and may give rise to unsatisfactory drug absorption in vivo despite excellent in-vitro release characteristics.

Patient variation: The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

Criteria to be met by drug proposed to be formulated in controlled release dosage forms:

A) Desirable half-life.
B) High therapeutic index
C) Small dose
D) Desirable absorption and solubility characteristics.
E) Desirable absorption window.
F) First past clearance.

Desirable half-life: The half-life of a drug is an index of its residence time in the body. If the drug has a short half-life (less than 2 hours), the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half-life of eight hours or more are sufficiently sustained in the body, when administered in conventional dosage from, and controlled release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of three to four hours.

High therapeutic index: Drugs with low therapeutic index are unsuitable for incorporation in controlled release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities e.g. Digitoxin.

Small dose: If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release is seriously undetermined. This is chiefly because the size of a unit dose controlled release formulation would become too big, to administer without difficulty.

Desirable absorption and solubility characteristics: Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into controlled release formulations is therefore unrealistic and may reduce overall absorption efficiency.

Desirable absorption window: Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the 'absorption window'. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as controlled release dosage form are unsuitable.

First pass clearance: As discussed earlier in disadvantages of controlled delivery system, delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release forms.

Future aspects of hydration based drug delivery systems

MODAS: Multi porous Oral Drug Absorption System (Élan Corporation, Ireland) is surrounded by a non-disintegrating, timed-release coating, which after coming in contact with gastrointestinal fluid is transformed into a semipermeable membrane through which the drug diffuses in a rate-limiting manner. The tablet consists of a core of active drug plus excipients. This is then coated with a solution of insoluble polymers and soluble excipients. After ingestion, the fluid of the gastrointestinal tract dissolves the soluble excipients in the outer coating leaving just the insoluble polymer, thereby forming a network of tiny, narrow channels connecting fluid from the GI tract to the inner drug core of water-soluble drug. This fluid passes through these channels into the core, dissolves the drug and a resultant solution of drug diffuse out in a controlled manner to the outside. The addition of excipients, such as buffers can help produce a microenvironment within the tablet that facilitates more predictable release rates and absorption. Examples of MODAS products developed by Élan include Bron-12 (a 12-hour multicomponent over-the-counter [OTC] cough and cold product) and once-daily potassium chloride.

SCOT: Single Composition Osmotic Tablet System (Andrx Pharmaceuticals, USA) is also based on osmotic principles and utilizes various osmotic modulating agents as well as polymer coatings to provide a zero-order release of a drug.

Portab System: (Andrx Pharmaceuticals) utilizes an osmotic core, typically containing a water-soluble drug. The core includes a water-soluble component and a continuous polymer coating. The purpose of the soluble agent is to expand the core and thereby create micro porous channels through which the drug is released.

ZER-OS: tablet technology (add drug delivery technologies AG, Switzerland): It an osmotic system developed specifically for the delivery of lipophilic compounds. The tablet consists mainly of a core of poorly water soluble drug along with gel forming agents and standard excipients. The gel-forming agent, after coming in contact with water, forms a gel of an appropriate viscosity, and a suspension of a poorly water-soluble agent is formed and is pushed out of the orifice at a controlled rate. Tegretol XR, a successful product on the US market, is based on this technology as well.

Multipor technology (Ethical Holdings Plc., UK): A tablet core of an active drug, which is surrounded by a water insoluble polymer membrane. The membrane consists of minute water-soluble particles that, after coming in contact with water, dissolve and form pores from which the drug is released. This technology also can be applied to pellets, granules, or mini tablets. One or more drug substances also can be incorporated into the membrane, which can provide an immediate release layer.

DPHS or delayed pulsatile hydrogel system (Andrx Pharmaceuticals): It is designed for use with hydrogel matrix products that are characterized by an initial zero-order release of drug followed by rapid release. This release profile is achieved by the blending of selected hydrogel polymers to achieve a delayed pulse.

DUREDAS or dual release drug absorption system (Élan Corporation): It utilizes bilayer-tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct-compression steps that combine an immediate-release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet. The controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner. A further extension of the Duredas technology is the production of controlled- release combination dosage forms whereby two different drugs are incorporated into the different layers, and the drug release of each is controlled to maximize therapeutic effect of the combination. Again both immediate- release and controlled-release combinations of the two drugs are feasible.

TIMERX (Penwest Pharmaceuticals Co., USA): It is a controlled-release drug delivery technology applicable to a broad range of orally administered drugs. This technology is based on an agglomerated hydrophilic matrix. The matrix consists of two pharmaceutically acceptable polysaccharides, locust bean gum and xanthan gum. Interactions between these components in an aqueous environment form a tight gel with a slowly eroding core from which the drug is released at a controlled rate for an extended period of time. Slofedipine XL (nifedipine) and Cystrin CR (oxybutynin) are based on this technology and are marketed in Europe.

KV Pharmaceuticals (USA) has developed technologies for controlled delivery of drugs that includes KV/24, which is a multi-particulate technology that can combine several different drug compounds, each requiring its own unique release profile, in a single tablet form that can be taken orally once every 24 hours.

Meter Release is a twice-a-day dosing, polymer rebased drug delivery system that offers different release characteristics than KV/24 and is used for products that require a drug release rate of 8 to 12 hours.

Symatrix is a micro particulate formulation that employs smaller particles than KV/24 and Meter Release. Symatrix encapsulates therapeutic agents that improve a drug's absorption in the body when precise release profiles are less important.

Spheroid combines equipment technology with formulation expertise. Each particle has its own matrix as the rate-controlling mechanism for the release of its contents. These particlescan be filled into hard gelatin capsules or can be compressed into tablets.

Orasert is designed as a solid oral dosage system that possesses bio adhesive and controlled release properties.

Orasiteis a controlled release muco-adhesive delivery system administered orally in solid or liquid form.

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