

Review Article

Osmotic controlled drug delivery system (OSMO technology) and its impact on diabetes care

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Received: 14 October 2020

Accepted: 18 November 2020

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ABSTRACT

Recently, focus on the development of controlled release drug delivery system has increased, as existing drugs exhibit certain pharmacokinetic limitations. The major goal of designing sustained release formulations is to improve the drug performance by prolonged duration of drug action, decreased frequency of dosing and reduced side effects by using smallest quantity of drug administered by the most suitable route. Osmotic-controlled release oral delivery system (OSMO technology) is the most promising strategy based system for sustained delivery of drug. Drug can be delivered in a controlled manner over a long period of time by the process of osmosis. Osmotic drug delivery system appears to be a promising solution for the limitations of conventional extended release formulations by virtue of their distinguished technological features. The present review describes briefly about various controlled drug delivery systems with special focus on advantages of osmotic-controlled release oral delivery system related to diabetes therapy and improved compliance.

Keywords: Osmo technology, Controlled drug delivery, Sustained release, Metformin gastrointestinal intolerance, Adherence

INTRODUCTION

Oral route is the most commonly and widely utilized route of administration among all the routes for systemic delivery of drugs. The reasons for such widespread use of oral route are its ease of administration, better patient acceptance and cost-effective manufacturing process. As compared to parenteral route, it is regarded as the most

natural, uncomplicated, convenient and safer route of drug administration.¹ Lot of research is going on the development of controlled release drug delivery system as existing oral drug delivery systems exhibit certain pharmacokinetic limitations and moreover there is risk increased side effects due to multiple drug therapy in chronic diseases like diabetes. Delivering drug at controlled rate, slow delivery, targeted delivery are other

very attractive methods and have been pursued vigorously. Though various technologies used in drug formulations to control the rate of delivery seem similar in achieving delayed drug delivery, there are technological differences which make each one these technologies different from each other. As these technological differences in controlled release drug delivery system result into different outcomes, it is necessary to understand the mechanism of these technologies and their benefits. The key objective of this comprehensive review is to highlight the key features of various technologies used for providing sustained release of drug with focus on osmotic controlled drug delivery system and impact it can have in clinical practice.

CONVENTIONAL ODDS

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. Drugs for oral delivery are mainly categorised into immediate release or conventional drug delivery systems and controlled release systems. Conventional oral drug delivery systems are designed for immediate release of drug for rapid absorption. Bioavailability of drug from these formulations may vary significantly depending on factors like physicochemical properties, presence of excipients, physiological factors like presence of food, pH, gastrointestinal (GI) motility, etc.²

These immediate release dosage forms have some limitations such as: frequent administration, poor patient compliance, difficulty in attaining steady state plasma concentration-time profile, and increased side effects due

to fluctuating drug levels. Thus, to overcome these disadvantages, controlled drug delivery systems have been developed.¹

CONTROLLED DRUG DELIVERY SYSTEMS

Controlled drug delivery systems are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue. Controlled drug delivery can be defined as: sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects; targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type; and provide a physiologically/therapeutically based drug release system.¹

Controlled drug delivery or modified drug delivery systems are divided into four categories: delayed release, sustained release, site-specific targeting, and receptor targeting.³⁻⁶

The main aim of developing sustained release (SR) formulations is to prolong duration of drug action, decrease the dose and frequency, reduce side effects and improve overall drug performance. SR dosage forms provide sustained drug release pattern to maintain therapeutic level for a certain predetermined time.⁷

Advantages of SR: less frequency of dosing, reduced fluctuation in steady-state drug levels, maximum utilisation of the drug, increased safety margin of potent drug, shorter treatment period, overall reduction in health care costs, improved patient compliance, and overall better treatment outcomes.⁷

Table 1: Classification of sustained release drug delivery systems.

Classification	Types
Diffusion systems	Reservoir devices
	Matrix devices
	Hydrophobic matrix system
	Hydrophilic matrix system
	Fat-wax matrix system
Dissolution sustained systems	Soluble reservoir system
	Soluble matrix system
	Dissolution sustained pulsed delivery system
Ion exchange resins sustained release systems	
Methods using osmotic pressure	Elementary osmotic pump (EOP)
	Push pull osmotic pump
	Osmotic pump with non-expanding second chamber
	Controlled porosity osmotic pump
	Osmotic bursting osmotic pump
	OROS-CT
	Multi particulate delayed release systems
	Liquid oral osmotic system (L-OROS)
Mineral matrices	Macro porous systems

Continued.

Classification	Types
	Micro porous system
	Non-porous system
pH Independent formulations	
Altered density formulations	
Swelling and expansion systems	
Floating systems	
Bio adhesive or mucoadhesive systems	
Biodegradable matrices	

OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEMS

Osmotic drug delivery system, is the most promising strategy-based drug delivery system to enhance drug bioavailability.⁸

Osmotic systems are based on the principle of osmosis. Such systems release the drugs at a constant zero order rate. These systems are popularly known as osmotic-controlled release oral delivery system (OROS). The system consist of a drug core and an osmotically active substance (osmogen) like mannitol surrounded by a semipermeable membrane coating with an orifice of 0.4 mm made by laser beam to facilitate drug exit. When exposed to gastrointestinal fluid, water flows through semipermeable membrane and under the influence of osmotic force of osmogen, the drug release is facilitated via orifice.⁹

Classification of osmotic drug delivery systems

Osmotic drug delivery devices fall in two categories: implantable and oral.^{10,11}

Implantable osmotic drug delivery devices

Implantable pump is composed of three layers: innermost layer is of the drug reservoir which is surrounded by an osmotic sleeve having the osmotic agent and outermost layer contains the rate controlling semi permeable membrane. Water enters through semi permeable membrane and acts with the osmotic agent thereby displacing the drug through its reservoir. These pumps are available with variety of delivery rates between 0.25 to 10 ml per hour and delivery duration between one day and four weeks.^{11,12}

Oral osmotic drug delivery devices

The most widely accepted osmotic drug delivery system is OROS. The most important feature is that this system is independent of the physiological factors of the gastrointestinal tract and can be utilized for systemic as well as targeted delivery of drugs.¹³⁻¹⁵

Oral osmotic pump are of various types: single chamber osmotic pump - elementary osmotic pump; multi chamber osmotic pump - push pull osmotic pump and osmotic

pump with nonexpanding second chamber; and specific types of osmotic pumps i.e. controlled porosity osmotic pump, osmotic bursting osmotic pump, liquid OROS, delayed delivery osmotic device, telescopic capsule, OROS colon targeting (CT), sandwiched oral therapeutic system, monolithic osmotic systems, and osmotic matrix tablet (OSMAT).

From the original 'elementary' osmotic pump to the push-pull system and consequently the advanced longitudinally compressed tablet (LCT) multilayer formulation, OSMO technology has developed through the years.¹³ All these technologies utilize the semi-permeable membrane which controls the rate of drug delivery.¹⁶ There are some differences in these various types of osmotic pumps. Covering the details of each type is beyond the scope of this article and only two commonly used technologies i.e. push pull technology and monolithic system are described in detail.

Multi chamber osmotic pump- push pull osmotic pump

The push-pull osmotic tablet designed with a bilayer or trilayer core consists of a drug layer and excipients and a push layer containing a hydrophilic expanding compartment which are osmotically active, it resembles a standard bilayer coated tablet.^{13,16} This push layer generates a hydrodynamic pressure pushing the drug through single or multiple passage ways.¹⁶ Thus, upon ingestion, both layers of the tablet facilitate absorption of water from the GI tract, forming a suspension or a solution in the drug layer. Since the drug can be delivered via suspension, this system is capable of delivering drugs with varied solubility, including water-insoluble drugs.¹³ Figure describes about the different layers of the tablet, containing an over coat of the drug, then a semipermeable membrane, underneath which contains another drug layer over a layer of osmotically activated push layer (Figure 1).¹⁰

Monolithic osmotic systems

The main principle used in this system is dispersion of water-soluble agent in a polymer matrix. In the monolithic system, there is a reservoir on the interior consisting of mixture of drug, osmotic agent, gelling agent and wetting agent. This is surrounded by a polymer matrix layer. Absorption of water ruptures polymer matrix capsule thus liberating the drug to the exterior (Figure 2).¹⁰

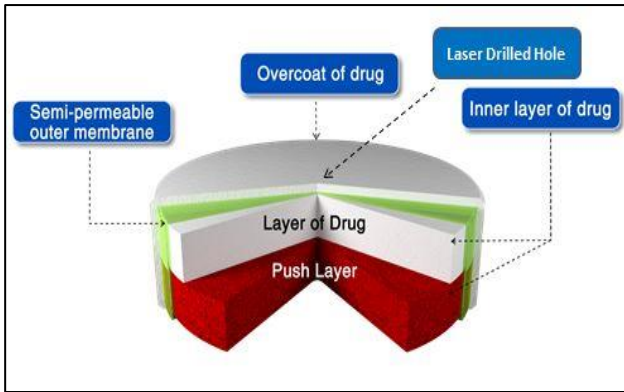


Figure 1: Push-pull osmotic tablet.

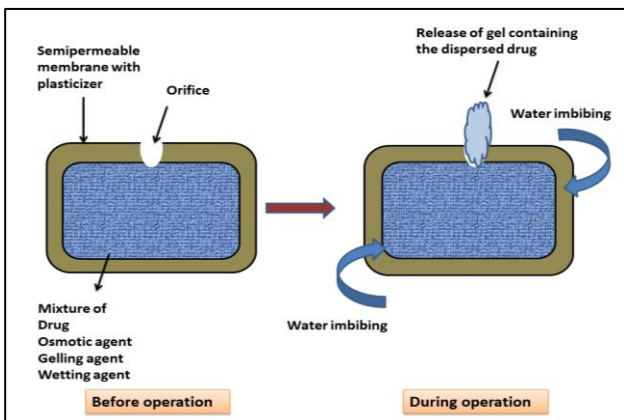


Figure 2: Monolithic osmotic system.

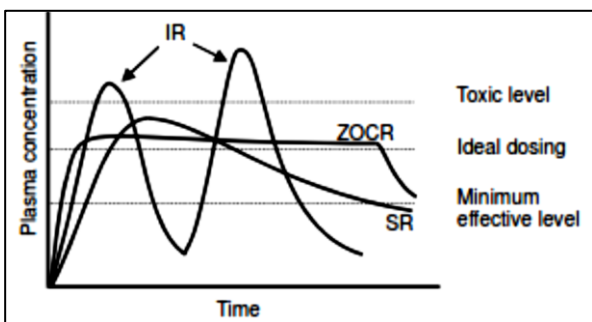


Figure 3: Graphical representation of plasma concentrations of a conventional immediate release (IR), a sustained release (SR) and an idealized zero-order controlled release (ZOOCR) drug delivery systems i.e. OROS.

Advantages of osmotic drug delivery systems

The following advantages have resulted in the popularity of osmotic drug delivery systems: zero-order drug delivery rate, delivery of drug may be delayed or pulsed, as per requirement, drug release is independent of gastric pH and hydrodynamic state, highly predictable drug release rate, and a high degree of in vivo-in vitro correlation (IVIVC).^{10,17}

MARKETED OROS PRODUCTS

The products that have been developed and marketed based on osmotic drug delivery technology cover primarily the following four therapeutic areas: cardiovascular (35%), neurological (25%), seasonal (25%) and metabolic disorders (15%). In the cardiovascular therapeutic area, this system has been developed for two calcium channel blockers; nifedipine and verapamil; in the field of endocrinology, for sulfonylurea glipizide; in urology for doxazosin which is used for the treatment of the symptoms of benign prostatic hyperplasia (BPH), and oxybutynin for the treatment of overactive bladder; in the central nervous system (CNS) therapeutic area, the stimulant methylphenidate, combined with the advanced LCT multilayer delivery formulation, and a new psychotropic drug called paliperidone ER.¹³

DIABETIC CARE: PROBLEM OF MEDICATION NON-ADHERENCE

Plethora of oral antidiabetic medications are available today for diabetes management including metformin, sulfonylurea, dipeptidyl peptidase inhibitors-4 (DPP4) inhibitors, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, Glucagon-like peptide (GLP) analogues, etc. However they are challenged by non-adherence. Medication non-adherence is multifactorial with various factors contributing such as age, medication information, perception and duration of disease, size of tablet and complexity of dosing regimen, polytherapy, inability to maintain/track health records and monitor treatment, psychological factors, safety, tolerability, comorbidities and cost.¹⁸ The World Health Organization (WHO) has shown that adherence to long-term therapy for chronic illnesses in developed countries averages only around 50%.¹⁸ Ensuring patient compliance is one of the most challenging issues in chronic diseases like diabetes mellitus.

Diabetes mellitus (DM) is a complex, chronic, heterogeneous endocrine disorder wherein medication adherence is extremely crucial so as to achieve better therapeutic outcomes and the drug regimen is such that makes compliance challenging.¹⁹ Data suggests that 70% type 2 diabetes patients reported non-adherence to antidiabetic medications.²⁰ In a study of 2,38,000 type 2 DM (T2DM) patients; adherence rate was found to be 47% with DPP4 inhibitors, 41% with sulphonylureas and 37% with thiazolidinediones.²¹ Non-adherence to anti diabetic medication is associated with inadequate glycemic control, increased morbidity and mortality and overall increased costs. These include costs of outpatient care, emergency room visits, hospitalization and managing complications of diabetes.^{20,22,23} Data suggests that at least 45% of patients with T2DM fail to achieve adequate glycemic control (HbA1c <7%) and one of the major contributing factors is poor medication adherence.²⁴

Frois and colleagues showed that serial non-adherence is sizable and is a key predictor of subsequent non-adherence which consequently results in incrementally higher medical care costs, elevated risk for hypoglycemia and poor patient outcomes compared with medication adherence.²⁵ A longitudinal 4 year study with 740,195 T2DM patients found that nonadherent patients can have annual inpatient costs 41% higher compared to adherent patients.²⁶ A study with 15984 T2DM patients reported that treatment noncompliance was associated with a significant ($p < 0.001$) 1.6 fold increase in all-cause mortality.²⁷

There exists an inverse relationship between OHA adherence and HbA1c level. The statistics reveal that each 10% increase in OHA adherence is associated with a decrease of 0.1% in HbA1c level. This indicates that level of adherence is a significant predictor of HbA1c, implying that improved adherence results in better glycemic control.¹⁸

CAN OSMO TECHNOLOGY INCREASE MEDICATION ADHERENCE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS?

Most of the oral anti-diabetic drugs are available either in the immediate or extended release forms and these dosage forms result in increased probability of side effects, and complex dosage regimens which results into poor compliance.⁸

Sulfonylureas are among the first-line treatments because of their long history of proven efficacy and safety. The longer-acting and the short-acting sulfonylureas differ in their pharmacokinetic and pharmacodynamic profiles and, therefore, produce different therapeutic and side-effect profiles. Shorter-acting sulfonylureas, such as IR glipizide, are found to be more effective in improving meal-stimulated insulin secretion and generally have a lower risk of hypoglycemia, but twice daily dosing (half-life 3-7 hours) is needed. Glipizide was designed as an ER preparation using the OROS technology to deliver once-daily administration. Maximum plasma drug concentrations are attained by approximately 9 hours post dosing with OROS glipizide. With subsequent once-daily dosing, effective plasma concentrations are maintained throughout the 24 hour dosing interval with less peak-to-trough fluctuation as opposed to the IR formulation. Furthermore, the once-daily regimen has proven to improve adherence and persistence to therapy compared to the twice-daily dosing of the IR formulation.¹³ Many other antidiabetic drugs like metformin, glibenclamide, gliclazide, glimepiride, pioglitazone, some GLP-1RA are available as extended release formulations.²⁸

METFORMIN GI INTOLERABILITY AND OSMO SOLUTION

Metformin is the first line agent for T2DM patients but it is associated with gastrointestinal effects, including

abdominal discomfort, nausea, and diarrhea, although these can be minimized by slow titration and administration with food.²⁹ In a study conducted by Blonde et al percentage of patients with individual GI adverse events with metformin-XR and immediate-release metformin, respectively, were as follows: diarrhea (6.77 versus 7.59%), nausea (2.26 versus 3.80%), dyspepsia (1.61 versus 1.27%), abdominal pain (1.61 versus 0.63%), constipation (0.97 versus 0.63%), vomiting (0.65 versus 0.63%), abdominal distension (0.32 versus 0%), fecal abnormality (0.32 versus 0.63%), blood in stool (0 versus 0.63%), and flatulence (0 versus 0.63%).³⁰ This indicates that still many patients suffer from intolerable GI side effects which are not addressed by currently available extended release formulations. Also, many patients who would otherwise benefit from metformin up-titration therapy discontinue treatment because of gastrointestinal symptoms, typically during the first few weeks of treatment.²⁹ Extended release formulations offer various benefits to the patients thereby enhancing patient compliance. However, all these formulations are not similar because of different technology used. These technological differences in extended release formulations may impact patient compliance and safety. Therefore, a differentiated sustained release technology i.e. osmotic push pull technology which differs from many available technologies used for manufacturing of extended release formulations offers distinct clinical advantages to the patients with T2DM. Push pull technology ensures predictable therapeutic plasma concentrations thereby minimizing the risk of GI side effects. The lesser incidence of GI side effects with an osmotic drug delivery system will have a beneficial role to improve patient adherence to metformin therapy. This will help patients with T2DM to achieve their glycemic goals and eventually translate into better patient outcomes.

BETTER PHARMACOKINETICS AND PHARMACODYNAMICS USING OSMO TECHNOLOGY

Vildagliptin shows promising properties amongst the DPP-4 inhibitors with established safety and efficacy in patients with T2DM. Dose of vildagliptin needs to be halved to 50 mg once daily in patients who are on SU or have moderate to severe renal impairment or ESRD. Considering higher prevalence of chronic kidney disease (CKD) in diabetes and the fact most patients uncontrolled on SU need addition of DPP4 inhibitor for better glycemic control, large number of patients need to be started on vildagliptin 50 mg once daily instead of twice daily. This may deprive from achieving prolonged glycemic control in these patients. Pharmacokinetic studies have shown that vildagliptin 50 mg in sustained-release dosage form through OSMO technology provide gradual release of the drug and thereby can achieve prolonged DPP-4 inhibition without compromising safety in these patients. Vildagliptin SR tablet 50 mg showed above 80% DPP-IV inhibition for 20 hours and vildagliptin IR tablet 50 mg reported up to 13 hours. Weighted average percentage

DPP-IV inhibition (0-18) and (0-24) was 91.0, 87.4 with vildagliptin SR and 85.1, 72.5 with vildagliptin IR, respectively. Drug was found to be safe and well tolerated.³¹

Another study with metformin PR OSMO tablet versus metformin MR tablet showed that there is prolonged therapeutic action upto 24 hours, smoother uptitration and 30% lower Cmax thus less gastrointestinal intolerance with metformin PR OSMO tablet.³²

CONCLUSION

Better understanding of pharmacodynamics and pharmacokinetics has demonstrated the need for newer drug delivery systems so as to achieve a constant, pulsatile, controlled, and triggered drug delivery. Osmotic drug delivery system is one such novel system that helps to deliver drugs in a controlled manner, provides predictable plasma concentration resulting into lesser side effects, and provides prolonged duration of action thereby improving the medication adherence in various disease conditions.

The clinical benefits have opened new perspectives for the future developments of newer oral delivery drugs. Osmotic drug delivery system appears to provide promising clinical benefits with antidiabetic medications by virtue of sustained therapeutic action and minimizing the side effects. Translation of these pharmacokinetics and pharmacodynamics benefits of osmotic drug delivery system into better clinical outcomes in practice needs to be evaluated in robust randomized controlled clinical trials.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Rajput R, Kumar KMKP, Arya DS, Das AK, Zargar AH, Tiwaskar M, et al. Osmotic controlled drug delivery system (OSMO technology) and its impact on diabetes care. *Int J Res Med Sci* 2021;9:303-9.