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Review on Oral Osmotic Tablet

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Abstract: ***Traditional oral medication delivery methods provide the drug with an immediate release and an efficient concentration at the intended location. Such a dosage regimen could lead to unexpected, ever-changing plasma concentrations. As a result, numerous regulated medication delivery systems are created. Among these, osmotic drug delivery systems (ODDS) and pulsatile drug delivery systems (PDDS) are becoming more and more significant because they improve patient treatment efficacy and compliance by delivering the medicine at precise times based on the course and physiological requirements of the disease. They regulate the drug's delivery by using the osmotic pressure theory.To a significant extent, the drug's release is unaffected by GIT physiological variables. Both targeted and systemic medication delivery are possible with these methods. The theoretical idea of drug delivery, various oral osmotic drug delivery system types, factors influencing the drug delivery system, benefits and drawbacks of these delivery systems, fundamental osmotic system components, evaluation parameters, difficulties, and emerging technologies in oral controlled drug delivery are all "highlighted" in this review.***
Keywords: osmotic Drug delivery system, osmosis, controlled release drug delivery system, polymers.

I. INTRODUCTION

Since the oral route offers the largest active face area of any medicine delivery medium for the administration of different specifics, it's the most popular and practical option. In traditional oral medicine delivery styles, the medicine is released incontinently, and large quantities can be administered desultorily to produce an effective attention at the target point. Variations in remedial tube attention caused by this type of lozenge pattern can sometimes affect in conspicuous adverse goods. Likewise, a number of physiological factors, including the presence or absence of food, the pH of the gastrointestinal tract, the motility of the gastrointestinal tract, the presence of excipients, and the physicochemical characteristics of the medicine, can all significantly affect the rate and extent of medicine immersion from conventional lozenge forms. Oral, intravenous, and transdermal systems are the three primary orders of controlled- release medicine delivery styles. Bibulous pressure is used by oral osmotically controlled release(CR) delivery bias to administer active constituents in a controlled manner. By acclimatizing the features of both the medicine and the system, it's doable to modulate the release characteristics. The release of medicines from these systems is largely independent of pH and other physiological parameters. The first oral bibulous pump was created by Alza Corporation R of the United States(1). Significant progress has been made in the field of innovative medicine delivery systems over the last several decades, particularly in the fields of biopharmaceutics, pharmacokinetics(PK), and pharmacodynamics(PD). To insure efficacity and minimize adverse goods, the medicine cure and dosing intervals are calibrated in a typical conventional remedy authority to keep medicine attention within the remedial window. In general, it has been set up that giving cases further than formerly or doubly a day significantly lowers their compliance. As a result, in recent times, a lot of focus has been placed on creating innovative medicine delivery systems that offer regulated release over time.The drug release from these traditional controlled release bias can be Impacted by a number of variables, including pH, the presence of food, and other physiological parameters.The main benefit of this kind of device is that the drug release is substantially innocent by pH and other physiological factors. As a result, it enables the modulation of the release characteristic through the optimization of medicine and system parameters(2)

A. History

Oral osmotic pumps have undoubtedly advanced, and their market presence is valuable due to the variety of goods that are accessible using this technology and the numerous patents that have been issued in recent years. In 1955, Australian pharmacologists Rose and Nelson created the first and most important medication delivery device that applied the concepts of osmotic pressure. They created two implantable osmotic pumps: one that provided 0.5 mL/day for four days and another that delivered 0.02 mL/day for 100 days.Pharmacological study made advantage of both of these (Santus and Baker, 1995). Stolzenberg created a different osmotic system in 1971 that functioned very similarly to Rose and Nelson's method.

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However, these two systems were only employed in laboratory-scale studies. As a result, its practical application in large-scale production was limited. Higuchi and Leeper proposed a number of modifications to the Rose-Nelson pump in the 1970s.
In 1972, Theuwes created the first osmotic pump. With a technique known as OROS, Alza Corporation of the USA is the industry leader in osmotic pump drug delivery systems and was the first to design an oral osmotic pump.In order to relieve pain, researchers have also created controlled porosity osmotic pump tables of diclofenac sodium and optimized them through experiment design. To distribute diclofenac sodium, researchers have employed a variety of formulation and delivery methods, including iontophoresis, solid lipid nanoparticles, and ethosomes (Kigasawa et al., 2009). In addition to the previously reported solid lipid nanoparticles (Shah et al., 2014, 2015) and solid dispersions (Potluri et al., 2011; Shamma and Basha, 2013), researchers have also reported the development of self-emulsifying osmotic pump tablets for lipophilic drugs like carvedilol. This is an additional development for optimal delivery of carvedilol[2].

B. Devices For Osmotic Medication Delivery

1) Implantable Osmotic Pump

An osmotic engine, a substantially toroidal compartment that is positioned at least partially around the osmotic engine, and a piston inside the compartment make up an implantable osmotic pump that administers medication to a patient. When the pump is installed in an aqueous environment, the osmotic engine is used to force the piston to move within the compartment and release the active substance inside. The Alzet and Duros miniosmotic pumps are among the several varieties of implantable osmotic systems, as are the Rose and Nelson pump, the Higuchi Theeuwes pump, and the Higuchi Leeper pump.

2) Oral Osmotic Pump

An oral osmotic pump is an osmotic device used to administer an active component to patients' oral cavities. The semi-permeable membrane that connects the device's exterior to the active agent compartment allows the agent to be delivered from the device into the oral cavity. Oral osmotic pumps are categorized according to their chambers as either single chamber (e.g., elementary osmotic pump, or EOP) or multi chamber (e.g., push pull osmotic pump, or PPOP) or osmotic pumps with nonexpanding second chamber.

3) Specific Types

A number of specialized osmotic pump systems, including liquid OROS/liquid oral osmotic system, controlled porosity osmotic pump (CPOP), and osmotic bursting osmotic pump (OBOP), have been developed recently. Telescopic capsule, OROS CT, sandwiched osmotic tablets (SOTS), monolithic osmotic system, osmat, multi particulate delayed release systems (MPDRS), pulsatile delivery based on expandable orifice, pulsatile delivery by a series of stops, lipid osmotic pump, L OROS hard cap, L OROS soft cap, and delayed liquid bolus delivery system[3].

II. CONTROLLED RELEASE DRUG DELIVERY SYSTEM

The fundamental idea behind a controlled release drug delivery system is to maximize a drug's utility by minimizing side effects and curing or controlling a disease condition as quickly as possible with the least amount of drug administered via the most appropriate route. This is achieved by optimizing the drug's biopharmaceutics, pharmacokinetics, and pharmacodynamics propertiesCertain aspects, such as site targeting, regulated release rate, and dose management, are absent from the immediate release drug delivery method. Over the course of a prescribed treatment time, the optimal drug delivery system should administer the medication at a rate determined by the body's needs[4]. Although some people prefer rapid release, controlled release drug delivery solutions are made to release the active ingredient in vivo over a longer length of time in a predictable pattern. The overall goal of a controlled release system's design is to create a machine that can continuously release drugs at zero order for an extended amount of time. Patients benefit greatly from lower dose frequency in addition to the therapeutic advantages of decreased variation in medication blood levels. Since the methods for creating such products have advanced significantly and numerous vendors are marketing excipients for controlled release, an increasing number of oral products are being developed and marketed as controlled release products. For drug administration to bodily orifices, controlled release products are also common. This is especially true for ocular products, where distribution requirements to various eye components may vary. However, the goal is frequently to use nanoformulations to improve absorption. In situ gels, implants, or nanocarrier systems can all induce prolonged ocular retention and release. Therefore, the optimal formulation should deliver therapeutic drug levels to the ocular surface or into anterior and posterior ocular tissues, have a high precorneal residence time, and have minimal non-specific drug tissue accumulation. It may also be able to replace invasive injection-based drug administration. Parenteral medication administration is frequently

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Although parenteral medication delivery is frequently linked to quick drug absorption, it would be better to decrease the frequency of injections and get systemic drug levels within the therapeutically effective drug concentration over a longer time frame. For medications with a limited therapeutic index or low bioavailability, this may be especially crucial. Particular care must be taken in the creation and formulation of parenteral controlled release systems as long-acting injectable medicines. Polylactic acid and co-glycolic acid-based depot dose formulations exhibit good in vivo biodegradability[5].

Temporal and/or local control over drug release can be provided by controlled release drug delivery systems. Therefore, the most popular method for regulating the release of medications taken orally is the oral controlled release drug delivery system. Numerous benefits of this approach have been documented, including preventing changes in plasma drug levels, decreasing the frequency of drug administration doses, increasing drug bioavailability, boosting patient compliance, and reducing drug toxicity and adverse effects.

To create a suitable oral controlled release medication delivery system, the drug dosage form must be designed. Characterizing the drug's permeability through biological membranes and its capacity to first pass metabolic effects before entering the bloodstream are both part of the design process. The drug's controlled release dosage form ought to be designed so that changes in the constituent parts result in predictable changes in the release profiles[6].

A. Post-operative complications and pharmacotherapy:

Although most surgeries are successful, unintended post-operative complications can cause a great deal of stress for both patients and medical staff, as well as prolong recovery and hospital departure. Faster post-operative recovery can be achieved with better management of post-operative pain, inflammation, and infection through the controlled administration of pharmaceutical therapy. Medicines in CR dosage forms can keep drug levels within the therapeutic range for extended periods of time, which enhances treatment effectiveness and lessens side effects.

Particularly, after being formulated into CR dosage form, opioids, local anesthetics (Las), strong non-steroidal anti-inflammatory medications (NSAIDs), corticosteroids, and antibiotics can and do help with post-operative pharmacotherapy.

1) Pain

After surgery, between 50 and 70 percent of patients have moderate to severe discomfort that usually lasts for a few days. Common medications used to treat pain after surgery include opioids, non-steroidal anti-inflammatory medicines (NSAIDs), and local anesthetics (Las). Opioids are quite effective, but because of their short elimination half-lives, conventional dosage forms need to be administered often in order to provide long-lasting pain relief, which causes variations in plasma concentrations. In addition to their potential for abuse and addiction, opioids are linked to systemic adverse effects such sleepiness, respiratory depression, and gastrointestinal and bladder malfunction, which has prompted active search for alternative therapy options.Commonly used either alone or in combination with other analgesics, NSAIDs are potent analgesics. However, in addition to their effects on the renal system, NSAIDs can cause irritation to local tissues and the stomach mucosa whether administered locally or systemically. Although Las are frequently employed as nerve-blocking drugs to stop pain signals from damaged tissue from being sent, their short half-lives restrict how long they work.

2) Inflammation

Cortisol, catecholamines, acute phase reactants, and cytokines are among the inflammatory modulators that are systematically released following surgery due to changes in the neuroendocrine, metabolic, and immunological systems. To encourage wound healing and tissue repair, pro-inflammatory and anti-inflammatory modulators must be properly balanced. Exaggerated anti-inflammatory or pro-inflammatory reactions might be lethal if they are severe enough to prolong the recovery from surgery. Corticosteroids, Las, and NSAIDs are all useful for reducing inflammation. The BPain^ section has covered CR formulations to administer NSAIDs and Las, which are utilized for a combination of analgesic and anti-inflammatory actions. Corticosteroids are very effective anti-inflammatory medications that are utilized after oral, dental, and ocular surgery.

3) Infection

Because the body's natural defenses are weakened before and after surgery, there is a higher chance of infection. Surgical site infections (SSIs) impact about 2% of surgical patients, though incidence rates differ depending on the type of surgery. An estimated $10 billion is spent on SSI treatment each year in the United States. Because they dramatically raise mortality and morbidity, the emergence of antimicrobial-resistant microorganisms is a major issue.

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Antimicrobial-resistant types of infections are frequently very difficult to treat, which ultimately lengthens hospital stays and raises treatment expenses. To attain and maintain minimum inhibitory concentrations (MICs) in the target tissues, large dosages of antibiotics either orally and/or parenterally must be administered frequently during surgery.

B. Challenges And Promises Of Translating Technologies Into Post-Operative Care

There has been little progress in moving innovative CR systems from the lab bench to the bedside, despite the fact that research into these systems is still expanding. Technology drives a lot of research without the necessary emphasis on therapeutic applications. Due to technological issues or their inability to prove efficacy and safety, the development of numerous innovative CR formulations is stopped before they reach the clinic. For instance, despite being well tolerated by patients, ThermoDox®, a thermosensitive doxorubicin-containing liposomal formulation, was discontinued following phase II and phase III clinical studies because the life span increase fell short of the necessary threshold. Cost-benefit analysis is necessary to support the commercialization effort.Technical obstacles like practical and repeatable validation and scale-up also hinder the seamless integration of these CR technologies. Notwithstanding these obstacles, some innovative CR formulations do make it from the lab bench to the patient's bedside and provide fascinating new advantages. In 2012, Farra and colleagues reported the successful clinical trial of a microchip-based implant carrying hPTH in humans. In order to treat osteoporosis in a group of postmenopausal women, the release of hPTH was monitored remotely[7].

III. WHAT IS OSMOSIS?

The passage of solvent molecules across a semipermeable wall from a low concentration to a high concentration is known as osmosis. It is caused by a differential in the solute concentration across the membrane, which permits water to pass through while rejecting all other molecules or ions. Osmotic pressure is the force that stops water from moving across a semipermeable membrane in a highly concentrated solution.

A. Principle of Osmosis

Although Pfeffer obtained the first quantitative estimates in 1877, Abbe Nollet was the first to identify an osmotic impact in 1748. In Pfeffer's experiment, a sugar solution is separated from pure water using a membrane that is impermeable to the sugar solute but permeabil to water. After that, water starts to flow in a sugar solution that cannot be stopped unless pressure is applied. The osmotic pressure of the sugar solution, as demonstrated by Pfeffer, is precisely related to both the solution's concentration and its absolute temperature[8].

B. Role of Semipermeable Membrane

The semipermeable membrane is an essential component of the osmotic drug delivery system. Thus, the choice of polymeric membrane is crucial for the formulation of osmotic administration. Osmotic devices can be coated with any polymer that is impermeable to solutes (drugs and excipients) yet permeable to water. For example, cellulose esters such as ethyl cellulose, cellulose triacetate, cellulose acetate butyrate, cellulose acetate, and eudragits. For semi-permeable membranes, cellulose acetate is frequently utilized. It comes in various acetyl contents, such as 32% and 38%, which are commonly utilized.

The membrane needs to meet specific performance requirements, like:

1) The membrane ought to be stable in the device's internal and external conditions.
2) For the material to maintain its dimensional integrity during the course of the device's operational lifespan, it must have adequate wet strength (10-5 Psi) and wet modules.
3) In order to achieve water flux rates (dv/dt) within the intended range, it must have enough water permeability. Water flux rates can be estimated using the water vapour transmission rates.
4) In order to maintain its dimensional integrity during the device's operational lifetime, it needs to be sufficiently rigid to withstand the pressure inside the device.
5) In order to prevent osmogent from being lost through membrane diffusion, it should also be somewhat impermeable to the dispenser's contents.
6) It must not swell.
7) It must be biocompatible[9].
8) One semi-permeable polymer that is frequently used to create osmotic pumps is cellulose acetate.
9) There are two distinct acetyl contents available: 32% and 38%.

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10) Amylase triacetate, poly-(vinyl-methyl)-ether copolymers, agar acetate, and selectively permeable poly-(lactic-acid) and poly-(glycolic-acid) derivatives are examples of polymers that can be utilized as semi-permeable film-forming material[10].

C. Ideal Properties of Semi Permeable Membrane

1) For the material to maintain its dimensional integrity during the course of the device's operation, it must have adequate wet strength and wet modulus.
2) The membrane's water permeability is adequate to maintain the desired water flux rate. The water flux rate can be estimated using the water vapor transfer rates.
3) The limiting value of unity should be approached by the osmotic agent's reflection coefficient and leakiness. Regretfully, polymer membranes with higher water permeability are also typically more osmotic agent permeable.
4) Additionally, the membrane needs to be biocompatible.
5) The semi-permeable membrane needs to be stable in the device's internal and external environments[11].

D. Zero Order Release Kinetic

The following equation was used to fit the release data in order to investigate the zero order release kinetics: dQ/dt = K0 where "t" is the release time, "Q" is the drug release amount, and "K0" is the zero order release rate constant. The percentage cumulative drug release (% CDR) is displayed against time in the graph.

E. First Order Release Kinetic

The release rate data are fitted into the subsequent equation in order to investigate the first order release kinetics: K1 Q = dQ/dt where "t" is the release time [12].

IV. CLASSICAL PHARMACEUTICAL POLYMERIC EXCIPIENTS: SUPER/DISINTEGRANTS, BINDERS, AND DILUENTS

Different kinds of tablets and capsules are the most often used forms of solid oral medication preparations. Generally speaking, tablets and capsules are solid dosage forms with a fairly long shelf life that release the API immediately if no conscious attempt is made to alter the drug's release rate. Tablets are solid pharmaceutical dose forms made by compression techniques that contain the active ingredients along with excipients (with or without sugar or polymer film covering).

To achieve desired dosage form parameters, including uniformity of weight, uniformity of content, drug content, hardness or crushing strength, disintegration time, friability, tensile strength, and dissolution time, polymeric excipients combined with an API are processed using various techniques. For example, wet granulation of the APIs using a specific combination of common polymeric excipients, such as powdered cellulose, maize starch, pregelatinized starch, and sodium starch glycolate, allowed for the reproducible continuous line production of tablets using the fluid bed granulation and drying production method.

A. Polymer Diluents

Diluents are frequently used as bulking agents or fillers in pills or capsules. When the amount of API in a solid dosage form is relatively low, the main purpose of fillers is to increase its bulk. In order to enable practical manufacture, accurate measurement, and convenient administration, excipients are added to increase volume and bulk. Appropriate bulking agents ought to be affordable, tasteless, and compatible with the formulation's other ingredients.

B. Polymer Binders

Binders for tablets or capsules enable the powders to stick together. Granulation binders are employed in graduation procedures to facilitate the agglomeration and cohesiveness of the granules, hence fostering suitable compactibility and free-flowing characteristics.

Solid drug delivery systems use a variety of polymer binders, both synthetic and natural. Alginates, carbomer, microcrystalline and powdered cellulose, cellulose derivatives (sodium carboxymethyl cellulose sodium [CMC], ethyl cellulose [EC], methyl cellulose [MC], hydroxyethyl cellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose [HPMC]), chitosan, gelatin, copovidone, crospovidone, maltodextrin, polyethylene glycol (PEG), polycarbophil, polydextrose, polyvinyl pyrrolidone (PVP), starch, and pregelatinized starch are a few notable examples.

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C. Polymeric Disintegrants

To maximize medication release in the GI tract's aqueous environs after oral ingestion, disintegrants are needed to encourage breakdown into fragments, ideally to primary particles. Since disintegration can occasionally be the rate-limiting stage in the absorption process, disintegrating agents can have a significant impact on the release profiles of the API from the tablet and the plasma drug profile.

The original granules from which the tablets were crushed are frequently released when granulated pills disintegrate. The disintegrant inside the granules further breaks these granules up into small particles. Tablet and capsule disintegrants mostly work by wicking and swelling, however deformation recovery, particle repulsion, heat of wetting, and gas evolution mechanisms may also be important in the disintegration process.

D. Polymeric Superdisintegrants

Super disintegrates are new-generation polymeric disintegrants that accelerate the disintegration of tablets in small quantities, increasing the drug's rate of dissolution. Modified polymers are typically used as superdisintegrant excipients; notable examples are sodium starch glycolate, crospovidone, and croscarmellose sodium, which is sodium CMC's inter-nally cross-linked version[13].

1) *Osmotic Agents:* There are two types of osmogents: inorganic and organic. In certain situations, a medicine that dissolves in water can also act as an osmogent. Magnesium sulphate, sodium chloride, potassium chloride, and sodium bicarbonate are a few examples of inorganic water-soluble pollutants. Polyethylene oxide, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethyl cellulose, methyl cellulose, and polyvinyl pyrollidine are a few examples of organic polymeric osmogents[2].
2) *Coating Solvent:* Inert solvents that can be used to make polymeric solutions for osmotic device walls don't damage the wall, core, or other components. Water, cyclohexane, methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, and carbon tetrachloride are examples of common solvents. It is also possible to use solvent mixes such as methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3), acetone-methanol (80:20), acetone-ethanol (80:20), and acetone-water (90:10).

E. Formulation of Osmotic controlled delivery system:

The wet granulation process was used to create the osmotic core tablets. The non-aqueous (IPA) granulation method was used to create the granules. All of the excipients, including Lornoxicam, have previously gone through a #60 sieve. Then, using the formulas listed in Table 1-2, Lornoxicam was combined with every excipient—aside from the binding and solubilizing agents. The combination was granulated using a PVP K-30 (binder) in isopropyl alcohol (IPA), a solvent for wet granulation, and wetting/solubilizing agents after being combined for ten minutes in a polybag.To get a loss on drying (LOD) value between 1% and 1.2%, the granules were dried at 50 C for 15 minutes after the resultant wet mass was run through a no. #25 sieve. They were then run through a no. #30 sieve and compressed using a tablet machine.

F. Evaluation Parameters are as Follows:

1) *Hardness:* A Schleuniger tablet hardness tester was used to measure the diameter and crushing strength of randomly chosen tablets.
2) *Friability test:* A friability (Roche friabilator) was used to rotate 20 tablets from each formulation for four minutes. After that, the tablets were reduced and weighed again. The proportion of weight loss used to calculate the friability.
3) *Effect of pH:* An in vitro investigation is conducted in various mediums in order to observe the impact of pH on formulation formation.
4) *Effect of Osmotic Pressure:* A study of the release mechanism is conducted at various osmotic pressures to observe how it affects formulation.
5) *In-vitro Evaluation:* In vitro, a traditional USP paddle and basket type of equipment is used to release the drug from an oral osmotic system. The standard parameters, which are as follows for oral controlled drug delivery systems, are also valid for oral osmotic pumps. Typically, the dissolution media consists of distilled water and simulated stomach fluid (for the first two to four hours) and intestinal fluids (for the hours that follow)[14].

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G. Advantages of Osmotic drug Delivery System

Compared to other controlled medication delivery systems, osmotic drug delivery systems for oral and implantable usage offer unique and practical benefits. Osmotic medication delivery techniques have become more appealing due to the following benefits.

1) An osmotically regulated medication delivery system can achieve a zero-order drug release rate.
2) It is possible for delivery to be delayed or pulsed.
3) Comparing osmotic systems to traditional diffusion-controlled drug delivery systems, higher release rates are achievable.
4) By adjusting the release control settings, osmotic systems' highly predictable release rate may be programmed.
5) Drug release in oral osmotic systems occurs regardless of the pH and hydrodynamic conditions of the stomach.
6) Food in the gastrointestinal tract has very little effect on the osmotic system's ability to release drugs.
7) Osmotic systems exhibit a high degree of in vivo-in vitro correlation (IVIVC).

H. Disadvantages

1) Expensive.
2) A poorly managed coating process increases the possibility of film flaws, which can lead to dumping.
3) Minimize the possibility of dosage modifications.
4) A higher chance of receiving a first pass clearance.
5) In genera, systemic availability is poor.
6) The size of the hole is crucial[15].

I. Limitations and Adverse Effects

Numerous treatment fields have shown notable clinical improvements from osmotic delivery systems. While some systems have reduced the negative effects of their active ingredients, others have improved therapeutic efficacy by making things more convenient for consumers. Nevertheless, a few instances involving the drawbacks and restrictions of these kinds of systems have been documented.

Several batches of nifedipine GITS tablets were found to exhibit distinct drug release patterns during quality control. To assess the GITS tablets, magnetic resonance imaging (MRI) was utilized. It was discovered that variations in release patterns among batches were caused by nonuniform coating around the tablet, which resulted in varying membrane thicknesses[16]. GI obstruction has occasionally occurred in persons taking nifedipine GITS tablets for the treatment of hypertension who already had peptic ulcer disease and restrictions.It was hypothesized that this negative event might be caused by the tablet's inactive constituent, which stays intact after passage through the GI tract and is often eliminated in the stool. Osmosin (indometha-cin OROS), which was first made available in the UK in early 1983, was the subject of another case report. Osmosin was removed in August 1983 because the Committee on the Safety of Medicines noticed numerous instances of severe gastrointestinal reactions a few months after it was introduced.

The effects of potassium chloride (osmotic agent) used In the formulation, the potential for high local concentrations of indomethacin and potassium chloride released from the device in the guts of patients with GI stasis, the adhesive qualities of the hydrophilic color coating, the mechanical effects of the device itself, or a combination of several such factors were some of the explanations offered for the apparent toxicity associated with Osmosin. When the adverse reaction profile of Osmosin was compared with that of other indomethacin-containing products, it was discovered that serious GI reactions (hemorrhage and perforation) were more common with Osmosin than with other indomethacin-containing products[17].

V. CHALLENGES AND NEW TECHNOLOGIES IN ORAL CONTROLLED RELEASE DRUG DELIVERY

A. Limiting Factors for Oral Controlled Release Formulations

For medications with low water solubility, creating controlled release formulations presents a number of difficulties. Drugs that are poorly soluble therefore require both solubilization and release profile tailoring. In addition, a lot of novel treatments are being developed, including vaccines, proteins, peptides, and oligonucleotides.

However, unlike small molecule medications, the physical, chemical, and biopharmaceutical properties of such high molecular weight components necessitate the development of novel controlled release technologies to reduce oral delivery barriers such poor absorption and GI tract instability. As a result, the topic of oral distribution of peptides and proteins offers numerous chances for research, development, and innovation. The primary drawback of current controlled release principles is that they are only appropriate for medications that dissolve in water.

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Other obstacles are present in drugs that are absorbed in specific regions of the gastrointestinal system. As a result, novel approaches are needed to address the problems of gastrointestinal transport, drug release mechanisms, and drug absorption processes.

1) Dose dumping: Dose dumping is a situation where a potentially harmful amount of a drug is swiftly released into the systemic circulation from a relatively large dose of the drug in a controlled release formulation. Furthermore, with strong medications that have a narrow TI, dose dumping turns out to be lethal.
2) Less flexibility in accurate dose adjustment: Because a tablet can be separated into two portions, dose modification is easy with conventional dosage forms. It is more difficult in the case of controlled release formulations, though. If the dosage form breaks, the controlled release property can be lost.
3) Poor in vitro in vivo correlation: The rate of drug release is intentionally lowered in controlled release dosage forms in order to achieve drug release, most likely over a wide area of the gastrointestinal system. In this case, the so-called absorption window becomes significant and could result in poor drug absorption in vivo even when the in vitro release characteristics are great.
4) Increased potential for first pass clearance: The process of hepatic clearance is saturated. The medication enters the liver through the portal vein following oral administration. The amount metabolized depends on the drug's concentration when it enters the liver. The amount needed to saturate an enzyme surface in the liver increases with drug concentration. On the other hand, the likelihood of saturating the enzyme surface decreases with decreasing concentrations linked to controlled release and sustained release dosage forms. Therefore, compared to conventional dose forms, controlled release and sustained released formulations have a higher chance of decreased drug availability due to first pass metabolism.
5) Patient variation: The amount of time required for the medicine released from the dosage form to be absorbed may vary from person to person. Each patient has a different residence duration in the gastrointestinal tract, presence or absence of meals, and coadministration of other medications. Additionally, this results in differences in the patients' clinical outcomes.

B. Key formulation considerations in oral sustained release Dosage forms

1) Biological factors

a) Biological Half Life: Maintaining the therapeutic drug's plasma level over an extended period of time is the primary goal of the oral sustained release dosage form. The medicine must enter the bloodstream at the same rate that it is removed in order to achieve this goal. The therapeutic moiety's half-life (t1/2) determines how quickly the drug is eliminated. Because they require fewer doses, substances with short half-lives are typically great candidates for sustained release formulation. In general, medications with shorter half-lives (less than two hours), such levodopa or furosemide, are not good choices for formulations with sustained release.
b) Absorption: Creating a prolonged release product often aims to reduce the rate of medication release relative to the rate of drug absorption. The majority of medications have a transit time of 8–12 hours in the GI tract's absorptive regions, and the maximum half-life needed for absorption is 3–4 hours; if this isn't the case, the device will exit the possible absorptive regions before the drug release is finished. A minimal apparent absorption rate constant of 0.17~0.23 h21 can be linked to this. As a result, the medicine must be absorbed at a somewhat constant pace throughout the small intestine. For many therapeutic moieties, this isn't the case, though.
c) Metabolism: Some medications have reduced bioavailability from sustained release dosage formulations because they are metabolized in the intestinal lumen or tissue prior to absorption. As a result, medications that are poorly soluble in water cannot be made into sustained-release dose forms. To increase the drug's solubility so that it can be created as a sustained release dosage form, an appropriate mechanism is needed. However, when a medication enters the systemic circulation, it may experience crystallization. For this reason, every effort should be made to keep the medication from crystallizing.

C. Physicochemical factors

1) Partition Coefficient

A medication that is given to the GI tract crosses several biological membranes to exhibit a therapeutic effect in certain bodily regions. Since lipids make up these membranes physiologically, the partition coefficient of medications that are soluble in oil is essential for figuring out how well they penetrate membranes. Lipophilic substances are maintained in tissues for a long time, have a high partition coefficient, and are poorly soluble in water. Compounds with a low partition coefficient find it more difficult to pass across the membrane, which lowers their bioavailability .Diffusion across polymeric membranes is equally susceptible to the partitioning effect. Diffusion-limiting membranes typically rely on the drug's partitioning characteristics.

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2) Dose size

There is a cap on the maximum dosage that can be given for systems that are taken orally. For a traditional dosage form, a single dose of 0.5–1.0 g is typically regarded as the highest; this generally holds true for extended release dosage forms. Sometimes, medications that must be taken in big dosages might be administered in numerous doses or in liquid dosage forms. Another consideration when evaluating a medicine for a sustained release dosage form is the administration of a larger dosage with a limited therapeutic window.

3) Stability

Drugs taken orally undergo enzymatic degradation as well as acid-base hydrolysis. Solid state pharmaceuticals often have a slow rate of degradation, making them the perfect composition for long-term drug delivery. A drug's transport across the entire GI tract is prolonged by an unstable dosage form in the stomach. It is therefore advantageous for a sustained release method that lasts until the dose form enters the small intestine. When given in a sustained release dose form, medications that are unstable in the small intestine may show reduced bioavailability. In the end, this impact leads to drug deterioration, necessitating a high dosage of the medication. Two notable examples of this group are propentheline and probanthine.

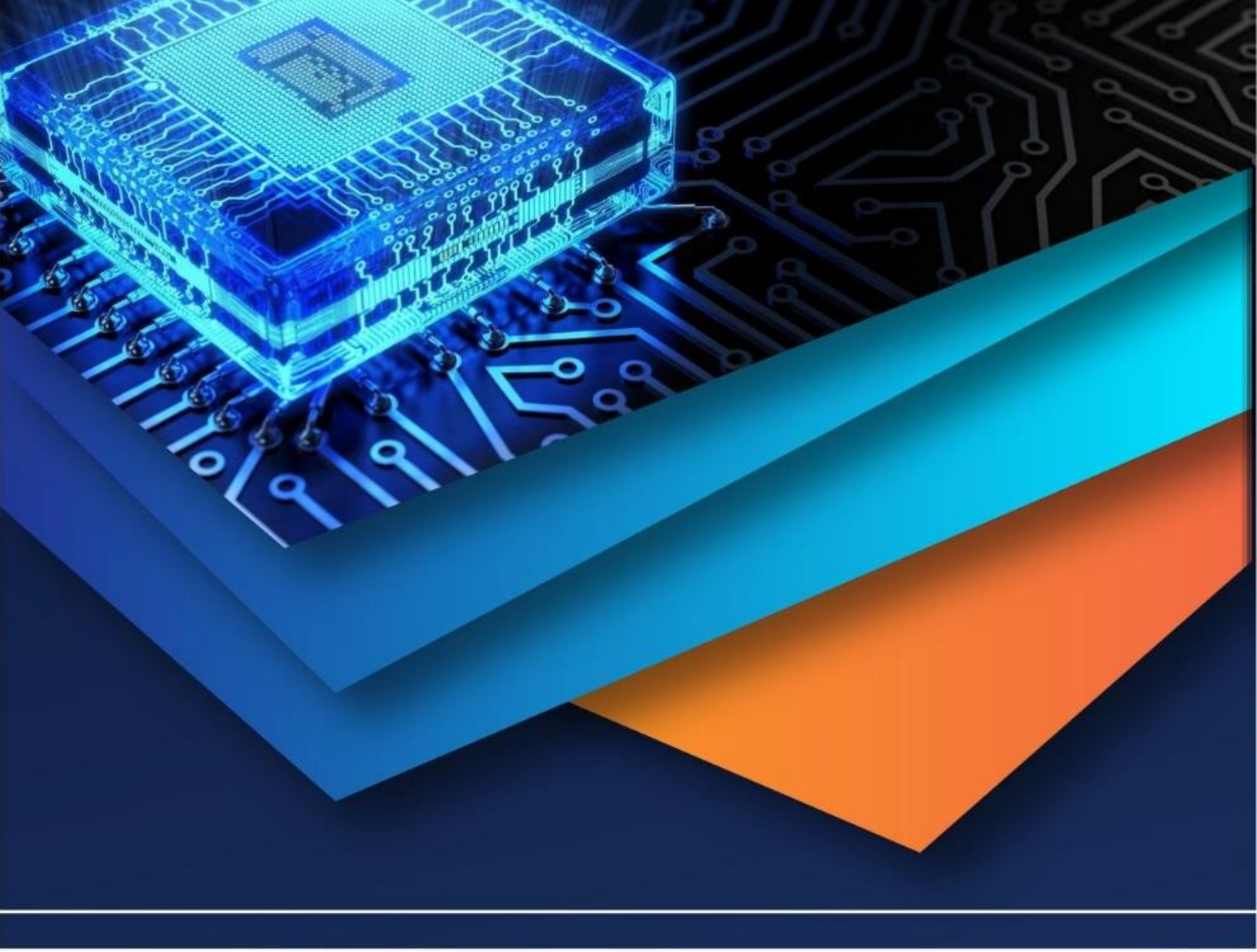
4) Ionization, pKa, and aqueous solubility

Most medications are weak bases or acids. Given that a drug's unaltered form can pass across lipid membranes with satisfactory efficiency, the relationship between the compound's pKa and the absorptive environment must be taken into account. For drug penetration, it is advantageous to supply the medication in its unaltered state. However, a drug's aqueous solubility and unionized form are inversely correlated. Drug solubility is also necessary for delivery systems that rely on diffusion or dissolving. Such dose forms should therefore function in a pH-changing environment (the small intestine's pH is close to neutral, while the stomach's pH is acidic). Low solubility compounds (0.01 mg/mL) are mostly sustained release since the drug's dissolution will limit their release over an extended length of time in the GI tract[18] .

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