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MODIFIED RELEASE OF MEDICATION DELIVERY: A REVIEW

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Abstract:

In terms of drug delivery methods, the oral route is the most popular. However, the traditional dosage form has a few drawbacks that could be fixed by altering the current dosage form. A regulated and sustained drug delivery system prolongs the duration of action by slowing the drug's release rate and maintaining a consistent plasma drug concentration. The matrix tablet is a crucial tool among the numerous formulation options for sustained release tablets. This makes issues like poor patient compliance, multiple doses, and see-saw oscillations simply manageable. A number of hydrophilic or hydrophobic polymers can be used to make matrix tablets using either the direct compression method or the wet granulation method. The main factor controlling how quickly drugs are released from the matrix is pace.

Key Words: Traditional Tablet, Matrix Tablet, Polymer, Sustained Release, Regulated Release.

Introduction:

The terms "sustained release," "sustained action," "controlled release," "extended action," and "timed release dosage forms" are used to describe drug delivery systems created to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time following the administration of a single dose. The phrase "controlled release" has come to refer to those systems that can give therapeutic substances mechanically at set rates over an extended period of time. Yet, the terms "controlled release" and "sustained release" are sometimes used interchangeably.

Sustained Release:

The phrase "sustained release" has frequently been used to refer to a pharmacological dosage form designed to hold back the release of a therapeutic agent such that its occurrence in the systemic circulation is postponed &/or prolonged, and its plasma profile is sustained over time.

Controlled Release:

On the other hand, this term has a connotation that transcends beyond the realm of long-lasting drug activity. The release of the therapeutic ingredient from the controlled delivery system proceeds at a rate profile that is not only predictable kinetically but also reproducible from one unit to the next, which also entails predictability and reproducibility in the drug release kinetics.

Advantages:

- Blood drug levels fluctuate less frequently.
- Decreasing the dosage frequency.
- Increased patient compliance and comfort.
- The highly successful medications now have a larger safety margin.
- A decrease in the overall cost of healthcare.

Disadvantages:

- Lower level of systemic availability compared to standard immediate-release dose formulations.
- Insufficient in vivo to in vitro connection.
- The ability to empty the dosage.
- Getting the medication is challenging.
- Increased formulation costs.

Depending on the Level of Technical Sophistication:

- Drug delivery systems with preprogrammed rates and activation controls
- Site-targeting medication delivery system;
- feedback-regulated drug delivery system

Rate Preprogrammed Drug Delivery System:

This group has a preprogrammed rate profile for the release of the drug molecule from the system. They fall under the category of-

- Drug delivery system with a regulated polymer membrane permeability
- Diffusion-controlled medication delivery method using polymer matrix
- Drug distribution system controlled by microreservior partitions.

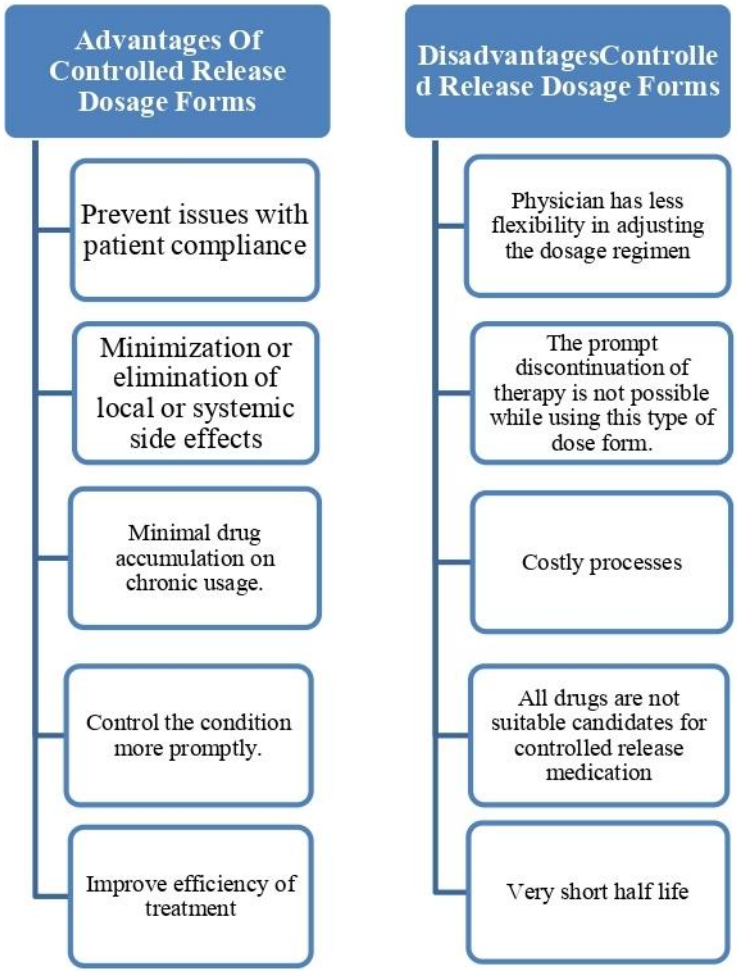

Figure 1: Demonstrate the Merits and Demerits

Drug Delivery System with a Regulated Polymer Membrane Permeability:

This form of drug reservoir contains the drug either completely or partially encapsulated. A rate-controlling polymeric membrane with certain permeability covers its drug release surface. Solid, suspension, and solution forms of the drug reservoir are all possible.

$$Q = \frac{Km/r\ Ka/m\ DdDm}{t\ Km/r\ Dmhd + Ka/m\ Ddhm} \times CR$$

Where, Km/r & Ka/m = partition coefficient of the drug molecule from reservoir to rate controlling membrane & from membrane to aqueous Layer respectively.
Dd & Dm = diffusion coefficient of rate controlling membrane & aqueous diffusion layer respectively.
hm & hd = thickness of rate controlling membrane & aqueous diffusion layer respectively.
CR – drug concentrationin reservoir compartment.
Drug molecules are released by:

- Partition coefficient of the drug molecule.
- Diffusivity of the drug molecule.
- The thickness of the rate controlling membrane.

Diffusion-Controlled Medication Delivery Method Using Polymer Matrix:

This sort of drug reservoir is made by uniformly dispersing drug particles in a matrix of rate-regulating polymer, which can be either lipophilic or hydrophilic in nature. Drug dispersion in the polymer matrix is achieved by one of two methods:

- Mixing a therapeutic dosage of a medicine with a polymer or a very viscous base polymer, then cross-linking the chains of the polymer.
- Mixing rubbery polymer and medication solid at a high temperature.

The rate of the drug release from this system,

$$Q = (2AC_RD_P)^{1/2}/\ t$$

Where, $Q/t^{1/2}$ - rate of release of drug
A – initial drug loading dose in the polymer matrix
CR – drug solubility in polymer

Dp – diffusivity of drug in polymer matrix
Release of drug molecule is controlled by:

- Loading dose
- Polymer solubility of drug
- Drug diffusivity in polymer matrix.

Drug Distribution System Controlled by Microreservior Partitions:

In this type, a biocompatible polymer is used to create a homogenous dispersion by microdispersing an aqueous suspension of the medication. The device can be further coated with a layer of biocompatible polymer to change the drug release mechanism and rate depending on the physicochemical qualities of the pharmaceuticals and the desired drug release rate.
The rate of drug release is defined by,

$$dQ/dt = \frac{D_P D_d m K_P}{D_P h_d + D_d h_P m K_P} * nSp \left[\frac{-D_l S_l (1-n)(1/K_1 + 1/K_m)}{h_l}\right]$$

Where, n = the ratio of drug conc. At the inner edge of the interfacial barrier over the drug solubility in the polymer matrix
m = a/b, a – Ratio of drug solubility in the same medium to drug concentration in the majority of the elution solution.
b – Ratio of drug solubility in the same polymer to drug concentration at the membrane's outermost polymer covering.
K_l, Km &Kp = partition coefficient for, respectively, the drug's interfacial partitioning from the liquid compartment to the polymer matrix, from the polymer matrix to the polymer-coating membrane, and from the polymer coating membrane to the elution solution.
D_l, Dp & Dd = Diffusivities of the drug in the hydrodynamic diffusion layer surrounding the polymer coating membrane, the lipid layer surrounding the drug particle, and the polymer coating membrane enclosing the polymer matrix.
S_l& Sp = drug solubilities in the polymer matrix and liquid compartments, respectively. The technique by which drug molecules are released from this system could be matrix-controlled diffusion or dissolution.
Depending upon the relative magnitude of S_l & Sp. Release of drug molecule is controlled by:

- Partition coefficient
- Diffusivity of drug
- Solubility of drug

Activation Modulated Drug Delivery System:

In this class of controlled drug release systems, a physical, chemical, or biological reaction as well as external energy are used to trigger the release of drug molecules from the delivery system. This activation controlled DDS can be categorised into the following groups according to the process type or energy source used:

A. Activation by Physical Processes

- Osmotic pressure-activated DDS
- Hydrodynamic pressure-activated DDS
- Vapour pressure-activated DDS
- Mechanical force-activated DDS
- Magnetically-activated DDS
- Sonophoresis-activated DDS
- Iontophoresis-activated DDS

B. Activation by Chemical Processes

- pH-activated DDS
- Ion-activated DDS
- Hydrolysis-activated DDS

C. Activation by Biochemical Processes

- Enzyme-activated DDS

Physical Process-Activated DDS:

- **Osmotic Pressure-Activated DDS:** Based on the osmosis principle, osmotic devices release the medication at a predetermined pace that is normally zero. Osmosis is the naturally occurring transfer of a solvent through a semipermeable membrane into a solution containing more solute, bringing the concentration of the solute on both sides of the membrane to the same level. Via a semipermeable membrane, osmotic systems take water from the body into the osmotic substance, where it dissolves and gains volume. This creates osmotic pressure, which causes the medicine to be delivered slowly and evenly through the orifice. Osmotic systems are more intricately designed than DDS based on diffusion and erosion, but they offer better zero-order drug delivery.
- **Hydration/Hydrodynamic Pressure-Activated DDS:** These methods release the medication at a zero-order rate, just like osmotic systems. Nevertheless, it varies from an osmotic system in that the hydrodynamic pressure generating agent, commonly a water-swellable hydrocolloid such as HPMC, is housed in one compartment and the medication solution/dispersion in another compressible reservoir.

Both of these compartments are housed in an impermeable, stiff, and dimensionally stable container. A hydrodynamic pressure is created as the hydrocolloid absorbs water and expands, forcing the drug storage chamber and, gradually and steadily, the drug through the aperture.

- **Vapour Pressure-Activated DDS:** In that the pumping compartment and medication solution/dispersion compartment are divided by a freely movable partition and the complete system is housed in a rigid housing, these systems are identical to hydrodynamic systems. The pump compartment contains a liquefied compressed gas that, when heated to body temperature, vaporises, causing vapour pressure that moves the baffle and forces the medicine into the bloodstream at a steady pace through a set of flow regulators and delivery cannula.
- **Mechanical Force-Activated DDS:** In these systems, the drug reservoir is a solution housed in a container with a pumping system that is mechanically triggered. When manually activating the drug delivery pump system, a metered amount of the drug formulation can be reliably supplied using a spray head into a bodily cavity, such as the nose. The delivery solution's volume is fixed and unaffected by the intensity or length of activation.
- **Magnetically-Activated DDS:** In these systems, a small donut-shaped magnet is positioned in the centre of a biocompatible drug-dispersing polymer matrix that is shaped like a hemisphere, and the outer surface of the medicated polymer matrix is then covered with a pure polymer, such as a copolymer of ethylene-vinyl acetate or silicone elastomers, with the exception of one cavity in the centre of the flat surface of the hemisphere. The uncoated cavity's purpose is to facilitate the peptide drug's release. An external electromagnetic field causes the magnet to oscillate, which causes a diffusion mechanism to release the medicine at a zero-order rate.
- **Sonophoresis-Activated DDS:** A polymeric drug delivery device is activated or triggered by ultrasonic energy in this kind of activation-controlled drug delivery system. Either a bioerodible polymer, such as a poly (lactide-glycolide) copolymer, or a non-biodegradable polymer, such as an ethylene-vinyl acetate copolymer, can be used to create the system.
- **Iontophoresis-Activated DDS:** Similar to passive diffusion under a concentration gradient, but considerably faster, this kind of CRDDS uses an electric current to activate and modify the diffusion of a charged drug molecule over a biological membrane, such skin. The process is painless.

Chemical Process-Activated DDS:

- **pH-Activated DDS:** These systems are developed for acid-labile medications or pharmaceuticals that irritate the gastric mucosa and target their administration to the intestinal tract. It is created by covering the tablet core of a medicine like this with a mixture of an enteric fluid-soluble polymer like HPMCP and an enteric fluid-insoluble polymer like ethyl cellulose. The covering membrane is resistant to breakdown at pH 1-3 in the stomach. A microporous membrane that regulates drug release from the tablet core is created when the intestinal fluid-soluble component in the coated membrane dissolves at a pH above 5 after gastric emptying.
- **Ion-Activated DDS:** This kind of device was created to regulate the distribution of an ionic or ionizable medicine at a constant rate and is based on the idea that the GIT has a reasonably constant amount of ions. An ionizable medication is first complexed with an ion exchange resin to create a CRDDS. Drugs are either complexed with resins containing the SO3 group for cationic drugs or the N(CH3)3+ group for anionic drugs. To slow the rate of swelling when in contact with an aqueous medium, the granules of the drug-resin complex are further treated with an impregnating agent, such as polyethylene glycol 4000. They are then covered with a water-insoluble yet water-permeable polymer membrane using an air-suspension coating method, typically ethyl.
- **Hydrolysis-Activated DDS:** This kind of CRDDS uses a hydrolysis procedure to initiate the drug molecules' release. The drug reservoir in this system is either enclosed in microcapsules or uniformly disseminated in microspheres or nanoparticles made of bioerodible or biodegradable polymers, such as polylactide, poly (lactide-glycolide) copolymer, poly (orthoester), or poly (anhydride). Drug delivery rate is regulated by the rate of polymer degradation, which is initiated by hydrolysis-induced chain breakdown of the polymer matrix.

Biochemical Process-Activated DDS:

- **Enzyme-Activated DDS:** In this kind of CRDDS, the drug reservoir is either chemically attached to polymer chains consisting of biopolymers like albumins or polypeptides, or it is physically trapped in the microspheres. A particular enzyme in the target tissue catalyses the enzymatic breakdown of biopolymers to permit drug release. The creation of albumin microspheres that release 5-fluorouracil in a regulated manner through protease-activated biodegradation is a classic example.

Feedback-Controlled DDS:

In this subset of CRDDS, a trigger, such as a biological component in the body, activates the release of drug molecules through a variety of feedback processes.

- **Bioerosion-Activated DDS:** This CRDDS is made up of a medication that is disseminated in a bioerodible poly (vinyl methyl ether) half ester matrix that is covered in an immobilised urease layer. The polymer gradually degrades in a pH-neutral solution. The drug delivery system's surface urease breaks down urea in the presence of urea to produce ammonia. As a result, the pH rises, triggering a quick breakdown of the polymer matrix and the release of the drug molecules.
- **Bioresponsive DDS:** The concentration of the biochemical agent in the tissue where the CRDDS is located regulates the permeability of the bioresponsive polymer membrane, which encloses the drug reservoir in this CRDDS.
- **Self-Regulating DDS:** A reversible and competitive binding mechanism is used in this kind of feedback-controlled DDS to activate and control drug release. A drug complex enclosed in a semipermeable polymer membrane serves as the drug reservoir. A biological substance from the tissue where the CRDDS is situated permeates the membrane of the CRDDS to activate drug release.

Site-Targeted DDS:

The majority of conventional dosage forms introduce the medication into the body, where it eventually travels via multiple stages of diffusion and distribution to the site of action. The medicine is delivered to non-target tissues in addition to the target site, which may cause toxicity or unpleasant responses. Selective and targeted pharmacological therapy may result in optimal and more successful treatment as well as a sizable decrease in drug doses and expenses. Systems that place a drug at or close to a receptor site or site of action are referred to as targeted or site-specific DDS. Site-targeted DDS can be categorised into three main groups:

- **First-order targeting –** refers to the Mechanism that delivers the medication to the active location or capillary bed.
- **Second-order targeting –** is a term used to describe DDS that transport the medication to a specific type of cell, such as tumour cells, rather than to normal cells.
- **Third-order targeting –** refers to DDS that intracellularly transport the medication.

Site-targeted DDS have also been characterized as –

- **Passive targeting –** refers to the drug carrier's natural or passive disposition as determined by the system's physicochemical characteristics in regard to the body.
- **Active targeting –** targets certain cells, tissues, or organs by altering the drug carrier's natural disposition; examples include the use of ligands or monoclonal antibodies that can specifically target locations.

Drug targeting often requires selective delivery of carriers and can serve the following purposes:

- Protect the drug from degradation after administration;
- Improve transport or delivery of drug to cells;
- Decrease clearance of drug; or
- Combination of the above.

Mechanism of Drug Release from Matrix Devices:

Dissolution Controlled Release:

Sustained release oral products utilising dissolution of medication from the solid surface to the bulk solution through an unstirred liquid film, is the rate limiting stage. , an s.It is possible to include a medication in a tablet with a carrier that dissolves slowly if the medication has a quick rate of dissolution. If the diffusion layer controls the dissolving process, the rate of diffusion is controlled.

$$(Cs - C) \text{ ---------- } (1)$$

Where,

dc/dt = Dissolution rate.

KD = Dissolution rate constant.

Cs = Saturation solubility of drug.

Diffusion Controlled Release:

There are two different sorts of these systems: a. Encapsulation diffusion control A drug core is encased in a water-insoluble polymeric substance in this approach. Drug will interchange with the fluid surrounding the particle or tablet after partitioning into the polymer membrane.

The rate of drug release is given by the equation

$$dm/dt = AdK\Delta c \text{ ---------- } (2)$$

Where,

A = Area

D = Diffusion coefficient

K = The partition coefficient of the drug between the membrane and the drug core

I = The diffusion path length

Δc = The concentration difference across the membrane. An important parameter in the above eq. 2 is the partition coefficient, which is defined as the concentration of the drug in the membrane over the concentration if the drug in core

Polymers in Modified Release:

For the purpose of achieving predetermined clinical goals, modified release dosage forms are created by changing the medication's absorption rate or the location of the drug release. A modified release product may have higher therapeutic efficacy and fewer side effects, increased patient comfort and compliance, optimised performance, and increased selectivity of action. In order to enable drug release modulation, polymers are becoming more and more significant in the design and development of customised drug delivery systems. Polymers are used in a variety of pharmaceutical applications, including binders, solubility modifiers, fillers, coating agents for tablets, and viscosity and flow control agents for liquids, suspensions, and emulsions. The selection of a particular substance and control system for active pharmaceutical has turned into a crucial factor. Drug selection mostly influences the choice of polymeric material.

Cellulosic and acrylic polymers are the main types of polymers utilised in pharmaceutical coating because they both have high film-forming capabilities and can be used to create durable protective coatings. Chitosan may be extensively used in the creation of film dosage forms or as drug delivery systems due to its ability to be processed into film-forms. Before being cast to films, chitosan could be dissolved in organic acids like lactic acid and acetic acid. As a novel, multifunctional excipient for the direct compression tableting technique, starch acetate (SA) polymer has been studied. In order to prevent polymer degradation or dissolution during its active lifespan, elements including the rate of diffusion across the membrane and tablet coating influence the drug release rate.

Physiochemical Properties/Parameters:

Dose Size:

There is a maximum bulk size of the dose that can be supplied for systems that are to be taken orally. For a standard dosage form, a single dose of 0.5–1.0 g is typically regarded as the maximum. The same is true for dose forms with sustained release. Compounds that require big dosages can occasionally be administered in numerous doses or made into a liquid system. The margin of safety associated with administering a medicine in big doses with a limited therapeutic window is another factor to take into account.

Ionization and Pka

Oral SR DDS is not a good option for medications that are primarily in ionised form. Because ionised medications are absorbed 3–4 times less quickly than unionised drugs, their diffusion into the body is far less than that of unionised drugs. The best pKa ranges for optimum positive absorption are 3.0-7.5 for acidic drugs whose ionisation is pH sensitive and 7.0-11.0 for basic drugs whose ionisation is pH sensitive. Drug must have 0.1 to 5.0 percent of the site's workforce unionised.

Partition Coefficient:

The proportion of a medicine in an oil phase to that in an adjacent aqueous phase is known as the partition coefficient. Between the time a drug is administered and when it is eliminated from the body, it must diffuse through a variety of biological membranes, many of which act primarily as lipid-like barriers. Partition coefficient influences both the permeation of the drug across the biological membranes and diffusion across the rate controlling membrane or matrix. The apparent oil or water partition coefficient, which is defined as, is a key factor in determining whether a medicine may pass through these lipid membranes.

$$K=CCow$$

Where,

Co = Equilibrium concentration of all forms of the drug in an organic phase at equilibrium,

Cw = Equilibrium concentration of all forms in an aqueous phase.

Adequate Aqueous Solubility:

The majority of medications are weak bases or weak acids. It will be challenging to include drugs with limited water solubility into the SR mechanism. It can be challenging to slow the dissolving rate of a medication with a high solubility and quick dissolution rate. When compared to a medicine that is less soluble in water, a drug with high water solubility readily dissolves in water or GI fluid, tends to release its dosage form all at once, and is absorbed quickly. This causes the blood drug concentration to rise sharply. When the dose is high, it is frequently challenging to combine a highly water-soluble medicine in the dosage form and delay the drug release. Another issue would be the pH-dependent solubility, especially in the physiological pH range.

Stability:

When taken orally, drugs are subject to enzymatic and acid/base hydrolysis deterioration. It is possible to create a slow-release dosage form for medications that are unstable in the gastric environment, delaying drug release until the dosage form reaches the intestine. Medicines that undergo gut wall metabolism and exhibit small intestine instability are not appropriate for the SR system. In this situation, either an alternative route of administration should be adopted or the drug can be chemically altered to create prodrugs, which may have distinct physicochemical features.

Biological Properties:

Half Life:

An oral sustained-release product's primary objective is to sustain therapeutic blood levels over an extended period of time. The biological half-life is a key factor in the design of the oral SR administration system and has a substantial impact on the duration of action. The elimination, metabolism, and distribution patterns of a drug are factors that affect its biological half-life. Medicines having brief half-lives required frequent dosage to reduce blood level variations. For such medications, SR dose formulations would seem to be particularly desirable. The zero-order rate of release of a drug from its dosage form is directly related to its rate of elimination for a given steady state drug concentration. As a result, medications with extremely short half-lives require faster release rates for only brief periods of time while in dosage form.

Absorption:

Absorption is the transport of a medication from its point of delivery to the bloodstream. The route of delivery affects the pace and effectiveness of absorption. When a medicine is administered intravenously, absorption is complete, meaning the entire dose enters the systemic circulation. Other methods of drug delivery may only result in partial absorption and reduced bioavailability. For instance, the oral route calls for a medicine to dissolve in the GI fluid before penetrating the intestinal mucosa's epithelial cells, but illness conditions or the presence of food may interfere with this process. With uniform and regular drug release as well as absorption, oral SR systems can deliver the constant blood or tissue concentration of the drug.

The maximal half-life for absorption should be around 3–4 hrs if the transit time of dose forms in the absorptive portions of the GI tract is assumed to be 8–12 hours. If not, the dose form will leave the absorptive areas before the medication release is finished. The substances with lower absorption rate constants are therefore not good options. Poor water solubility, a small partition coefficient, protein binding, acid hydrolysis, metabolism, or site-specific or dose-dependent absorption are a few potential causes for the low level of absorption. Oral SR DDS is a poor choice for medications with a high apparent volume of distribution, which affects the rate of drug elimination. A medication that undergoes substantial metabolization is not appropriate for SR DDS. A medication that can trigger.

Approaches for SR/CR oral formulation:

Mechanism for medication delivery with sustained release. Any drug delivery system that distributes medication over an extended period of time without regard to time is included. A sustained dose form is frequently created using a hydrophilic polymer matrix. The optimal drug delivery system's job is to keep the medication's therapeutic range in blood plasma by delivering the correct dose at the right site of action at the right time. Controlled ejection to the.

Additional Measures to Assess Bioequivalence:

Several MR formulations with traditional drug release profiles in vivo have been shown to have bioequivalence, and it is generally accepted that the current regulatory requirements are sufficient in this regard. However, for newer MR products with different drug release mechanisms (such as pulsatile- or chrono-release) or for MR products designed to achieve a rapid rise in drug plasma concentrations (and thus a rapid onset of therapeutic effect) following administration, other measures in addition to the current pharmacokinetic parameters (i.e., AUC and Cmax) may be required for assuring bioequivalence. To determine the influence of a different input rate on therapeutic equivalency, pharmacokinetic/pharmacodynamics (PK/PD) modelling and simulations can be performed to link drug concentrations to their effects (safety or efficacy).

Conclusion:

The procedure or method of providing a pharmaceutical substance to achieve a therapeutic effect in people or animals is known as drug delivery. Nasal and pulmonary routes of medication administration are becoming increasingly significant for the treatment of human diseases. For peptide and protein therapies, these methods offer promising substitutes to parenteral drug administration. For this reason, a number of medication delivery methods have been developed and are being tested for pulmonary and nasal delivery. They include, among others, cyclodextrins, microspheres, gels, prodrugs, liposomes, and proliposomes. The ability to transfer into an aerosol, stability against forces generated during aerosolization, biocompatibility, targeting of specific sites or cell populations in the lung, and release of the drug in a predetermined manner are all requirements that must be met by nanoparticles made of biodegradable polymers.

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