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Controlled Release Tablet for the Treatment of Type-2 Diabetes Mellitus-A Review

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Abstract

Type-2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder that demands precise and sustained control of blood glucose levels. This abstract discusses the formulation and development of controlled release tablets for the treatment of T2DM. The focus lies on selecting appropriate antidiabetic drugs, designing formulations with controlled drug release mechanisms, and employing polymers and innovative delivery systems to achieve prolonged therapeutic effects. Various strategies, including osmotic pump systems, bilayer tablets, and gastroretentive systems, are explored to optimize drug release kinetics. Emphasis is placed on biocompatibility, safety, and regulatory compliance, ensuring that the developed formulations meet both efficacy and safety standards. The goal is to enhance patient compliance by providing a convenient and effective treatment option for individuals with Type-2 Diabetes Mellitus. The comprehensive approach discussed herein integrates pharmacological principles, formulation science, and regulatory considerations for the successful development of controlled release tablets tailored for the management of T2DM.

Keywords

Controlled release, Tablet formulation, Type-2 Diabetes Mellitus (T2DM), Antidiabetic drugs, Drug release kinetics, Polymers and Osmotic pump systems

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Some key considerations and components for developing controlled release tablets for the treatment of Type-2 Diabetes Mellitus:

1. **Drug Selection:**

Common medications for T2DM include metformin, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors.

The chosen drug's pharmacokinetics and therapeutic window should be considered for sustained release formulations.

2. **Formulation:**

The formulation should be designed to release the drug slowly and consistently over an extended period.

Excipients such as polymers, gelling agents, and release modifiers are often used to control the drug release rate.

3. **Polymeric Matrix:**

Utilizing polymers like hydroxypropyl methylcellulose (HPMC), ethyl cellulose, or polyethylene oxide can help in forming a matrix that controls drug release.

4. **Osmotic Pump Systems:**

Osmotic pump tablets use an osmotic pressure gradient to control drug release. Water influx into the tablet causes the drug to be released through an orifice.

This system can provide a consistent drug release rate independent of gastrointestinal pH.

5. **Bilayer Tablets:**

Bilayer tablets can be designed with an immediate-release layer to provide a quick onset of action and a sustained-release layer for prolonged effects.

6. **Gastroretentive Systems:**

Gastroretentive systems, such as floating or mucoadhesive tablets, can increase the residence time of the tablet in the stomach, allowing for controlled drug release.

7. **Incorporation of Coating:**

Enteric coatings or other coatings can be used to protect the drug from the acidic environment of the stomach, preventing premature release.

8. **Dose Adjustment:**

The controlled release formulation should allow for flexibility in dosing to accommodate individual patient needs.

9. **Biocompatibility and Safety:**

The selected materials should be biocompatible and safe for long-term use.

10. **Regulatory Compliance:**

Ensure that the developed formulation meets regulatory standards for drug development, including bioavailability and bioequivalence studies.

11. **Patient Compliance:**

The formulation should be designed to improve patient compliance by reducing the frequency of dosing and minimizing side effects.

INTRODUCTION TO ORAL DRUG DELIVERY SYSTEM (ODDS) [1]

Oral delivery of drugs is the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. Many of the drug delivery systems available in the market are oral drug delivery type systems.

Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems and historically too, oral drug administration has been the predominant route for drug delivery. It does not pose the sterility problem and minimal risk of damage at the site of administration.

Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:

1) Drugs with short half-life require frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.

3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.

To overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery systems that could revolutionize methods of medication and provide a number of therapeutic benefits.

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms. In recent years, various modified-release drug products have been developed to control the release rate of the drug and/or the time for drug release. The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as 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 as presently recognized".

Advantages Of ODDS

- Appropriate for any patient, whatever the age is.
- The most natural and easiest route for drug delivery
- Economical and safe to the patient.
- No nursing is required, which means the patient can take it with no help.
- Toxicity is delayed due to the late of action which permit easier recovery than in case of the other dosages form.

Disadvantages of ODDS

- Delayed onset of action because, absorption takes time.
- Not suitable in emergency and for unconscious patients.
- Not convenient for a patient with a gastrointestinal disorder such as diarrhoea, constipation, ulceration, and hyperacidity in stomach.
- Not a good choice in case of uncooperative patients as children and infants.
- Not appropriate if the patients suffer chronic vomiting.

Limitation Of ODDS

- Drug absorption may vary.
- Subject to first pass metabolism.
- Oral route not possible in unconscious patients.
- Slow onset of action.

INTRODUCTION TO CONTROLLED RELEASE DRUG DELIVERY SYSTEMS (CRDDS)[1]

More precisely, controlled delivery can be defined as

1) 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.

2) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.

3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.

4) Provide a physiologically / therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

A controlled drug delivery system is usually designed to deliver the drug at a rate. Safe and effective blood levels are maintained for a period if the system continues to deliver the drug. This predetermined rate of drug release is based on the desired therapeutic concentration and the drug's pharmacokinetics.

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action.

Advantages Of CRDDS

1. Overcome patient compliance problems.
2. Employ less total drug
   a) Minimize or eliminate local side effects.
   b) Minimize or eliminate systemic side effects.
   c) Obtain less potentiating or reduction in drug activity with chronic use.
   d) Minimize drug accumulation with chronic dosing.
3. Improve efficiency in treatment
   a) Cures or controls condition more promptly.
   b) Improves control of condition i.e., reduced fluctuation in drug level.
   c) Improves bioavailability of some drugs.
   d) Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bedtime.
4. Economy i.e. reduction in health care costs. The average cost of treatment over an extended period may be less, with lesser frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.

Disadvantages Of CRDDS

1. Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
2. Poor *in vitro – in vivo* correlation.
3. Retrieval of drug is difficult in case of toxicity, poisoning, or hypersensitivity reactions.
4. Reduced potential for dose adjustment of drugs normally administered in varying strengths.

Types of CRDDS: [2]

Controlled drug delivery systems are broadly classified as follows:

- Oral controlled release systems
- Targeted delivery systems
- Dental systems
- Ocular systems
- Transdermal systems
- Vaginal and uterine systems
- Injections and implants.

CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

Most oral controlled release systems rely on dissolution, diffusion, or a combination of both mechanisms to generate slow release of drug to the gastrointestinal milleu.

A. DISSOLUTION CONTROLLED RELEASE

Sustained release oral products employing dissolution as the rate-limiting step are in principle the simplest to prepare.

1. Encapsulation dissolution control:

These methods generally involve coating individuals particles or granules of drug with a slowly dissolving. material. The coated particles can be compressed.

directly into tablets as in Space tabs or placed in capsules as in the Spansule Products. Since the time required for dissolution of the coat is a function of its thickness and aqueous solubility, one can obtain repeat or sustained action by employing a narrow or a wide spectrum of coated particles of varying thickness respectively.

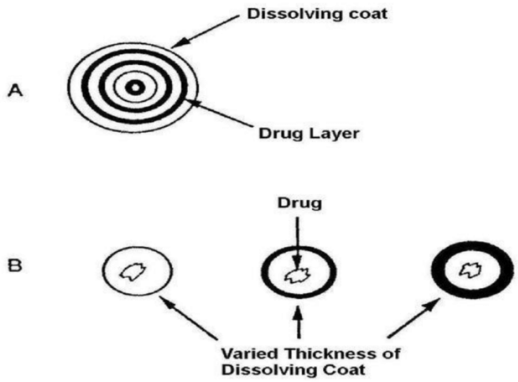

Figure 1: Schematic Representation of Encapsulation Dissolution Controlled Systems

2. Matrix dissolution control:

An alternative approach is to compress the drug with a slowly dissolving carrier of some sort into a tablet form. Here, the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This, in turn, can be controlled by porosity of the tablet matrix, the presence of hydrophobic additives, and the wettability of the tablet and particles surface.

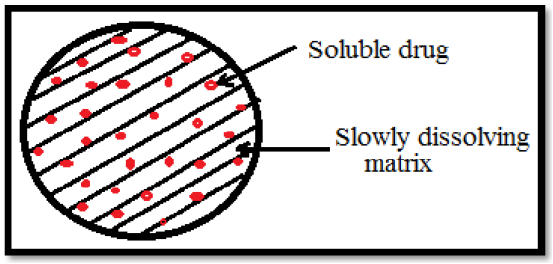

Figure 2: Schematic Representation of Dissolution Matrix System

B. DIFFUSION CONTROLLED RELEASE

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. There are basically two types of diffusion-controlled systems which have boon developed over the past two decades, reservoir devices and matrix devices.

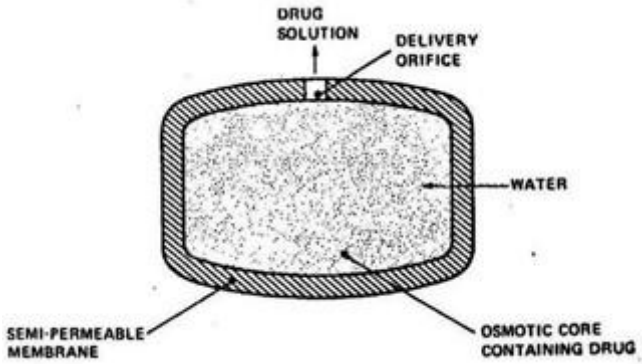

Figure 3: Schematic Representation of Osmotically Controlled Release System

1. Reservoir devices:

In this system, a water-insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the

membrane, diffuse to the periphery, and exchange with the surrounding media.

2. Matrix devices:

In this system, a solid drug is dispersed in an insoluble matrix. The rate of drug release is dependent on the rate of drug diffusion but not on the rate of solid dissolution.

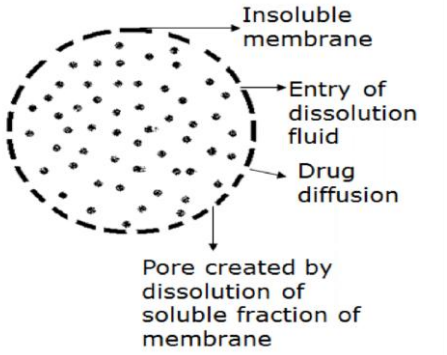

Figure 4: Dissolution and Diffusion Controlled Release System

MATRIX TABLETS (MTs):[3]

Matrix tablets are the type of controlled drug delivery systems, which release the drug in continuous manner by dissolution controlled as well as diffusion-controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug release, retardant material, and additives to formulate a tablet in which the drug is embedded in a matrix of the release retardant. Alternatively, drug and release retardant blend may be granulated prior to compression.

Advantages Of MTs

- Easy to manufacture.
- Versatile, effective, and low cost
- Can be made to release high molecular weight compounds.
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Improvement the bioavailability of some drugs.
- Improvement of the ability to provide special effects. Ex: Morning relief of arthritis through bedtime dosing.

Disadvantages Of MTs

- The remaining matrix must be removed after the drug has been released.
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced using very slow-release rates, which in many applications are indistinguishable from zero-order.
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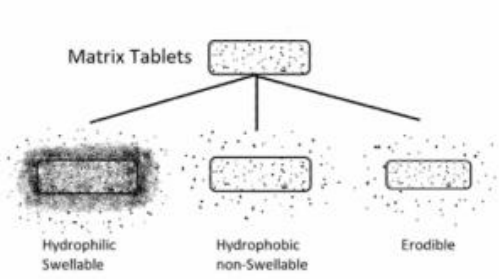

Figure 5: Schematic Representation of Matrix tablets

Polymers Used in MTs:[3]

Table 1: Polymers used as Retardants in Control Release Tablet Formulations:

Matrix characteristics	Materials
Insoluble, Inert	Polyethylene Polyvinyl chloride Methyl acrylate – Methacrylate Copolymer Ethyl cellulose Cellulose acetate. Carnauba wax Stearyl alcohol Stearic acid
Insoluble, erodible	Polyethylene glycol Castor wax Triglycerides Polyethylene glycol monostearate.
Hydrophilic	Methyl cellulose (400cps, 4000cps), Hydroxyl ethyl cellulose, Hydroxypropyl methyl cellulose, {high viscosity grades, K4M, K100M etc}, Sodium carboxy methyl cellulose, Carboxy polymethylene, Galacto mannose. Sodium alginate. Guar gum.
Hydrogels	Polyhydroxy ethyl methyl acrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA)
Soluble polymers	Polyethylene glycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC)
Biodegradable polymers	Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters.
Non-biodegradable polymers	Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).

MECHANISM OF DRUG RELEASE FROM THE MATRIX TABLETS[4]

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the following assumptions:

1) A pseudo-steady state is maintained during drug release.

2) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.

3) The bathing solution always provides sink conditions. The release behavior for the system can be mathematically described by the following equation.

$dM/dh = C0.\ dh - Cs/2$ …… (i)

Where,

dM = Change in the amount of drug released per unit area.

dh = Change in the thickness of the zone of matrix that has been depleted of drug.

C0 = Total amount of drug in a unit volume of matrix.

Cs = Saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory:

dM = (Dm. Cs / h) dt..... (ii)

Where,

Dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix.

dt = Change in time.

By combining equation (i) and equation (ii) and integrating:

M = [Cs. Dm (2C0 –Cs) t] 1/2 ..... (iii)

When the amount of drug is more than the saturation concentration then:

M = [2Cs.Dm.C0.t] 1/2 ..... (iv)

Equation (iii) and eq. (iv) relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

M = [Ds. Ca. p/T. (2Co – p. Ca) t] 1/2 ..... (v)

Where,

p = Porosity of the matrix

t = Tortuosity

Ca = solubility of the drug in the release medium

Ds = Diffusion coefficient in the release medium.

T = Diffusional pathlength for pseudo steady state, the equation can be written as:

M = [2D. Ca .C0 (p/T) t] 1/2 .....(vi)

The total porosity of the matrix can be calculated with the following equation:

p = pa + Ca/ ρ + Cex/pex..... (vii)

Where,

p = Porosity

ρ = Drug density

pa = Porosity due to air pockets in the matrix ρex = Density of the water-soluble excipients

Cex = Concentration of water-soluble excipients for the purpose of data treatment, equation (vii) can be reduced to:

M = k. t 1/2 .....(vii)

Where,

k = constant.

So, the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion controlled.

C. DIFFUSION AND DISSOLUTION CONTROLLED SYSTEMS

The main feature of this system is that the drug core is enclosed with a partially soluble membrane.

Dissolution of part of the membrane allows for diffusion of the contained drug through pores in the polymer coat.

D. ION-EXCHANGE RESINS

Resins are water-insoluble materials containing anionic or cationic groups in repeating positions on the resin chain. The drug-charged resin is prepared by mixing the resin with drug solution either by repeated exposure of the resin to the drug in a chromatographic column or by keeping the resin in contact with the drug solution for extended periods of time. The drug-resin is then washed to remove contaminant ions and dried to form particles or beads. When a high concentration of an appropriately charged ion is in contact with the ion-exchange group, the drug molecules is exchanged and diffuses out of the resin to the bulk solution.

E. pH - INDEPENDENT FORMULATIONS

The granules are designed for the oral controlled release of basic or acidic drugs at a rate that is independent of the pH in the GI tract. (Pederson, A.M, German patent). They are prepared by mixing a basic or acidic drug with one or more buffering agents, granulating with appropriate pharmaceutical excipients, and finally, coating with a gastrointestinal fluid permeable film-forming polymer. When the GI fluid permeates through the membrane, the buffering agents adjust the fluid inside to a suitable constant pH, thereby rendering a constant rate of drug release.

F. OSMOTICALLY CONTROLLED RELEASE

In this type of drug delivery systems, osmotic pressure is the driving force that generates constant. drug release. This system is fabricated by applying a semi permeable membrane around a core of an osmotically active drug or a core of an osmotically inactive drug in combination with an osmotically active salt. A delivery orifice is drilled in each system by laser or by a high -speed mechanical drill.[5]

G. ALTERED DENSITY FORMULATIONS

It is reasonable to expect that, unless a delivery system remains in the vicinity of the absorption site until most, if not all its drug contents is released, it would have limited utility. To this end, several approaches have been developed to prolong the residence time of drug delivery systems in the GI tract. One such approach is the bioadhesion approach.[5] which is based on the adherence of bioadhesive polymers to the mucin on epithelial surface of the GI tract. The other approach is to alter

the formulation's density by using either high- or low-density pellets.[6]

1. High - density approach:

In this approach, the density of the pellets must exceed that of normal stomach content and should therefore be at least 1.4.[7] In preparing such formulations, drug can be coated on a heavy core or mixed with heavy inert materials such as barium sulfate, titanium dioxide, iron powder, and zinc oxide. The weighed pellet can then be covered with a diffusion-controlled membrane.

2. Low-density approach:

Globular shells which have an apparent density lower than that of gastric fluid can be used as carrier of drug for sustained release purposes.[8] Polystyrol, poprice, and even popcorn are all candidates as carriers. The surface of these empty shells is undercoated with sugar or with a polymeric material such as methacrylic polymer and cellulose acetate phthalate. The undercoated shell is then coated by a mixture of drug with polymers such as ethyl cellulose and hydroxyl propyl cellulose. The final product floats on the gastric fluid for a prolonged period, while slowly releasing drug.

WORK REPORTED ON CDDS:

This survey reveals that no such articles were reported on the proposed work and some related articles are mentioned below:

Krishnaiah YSR *et al.,* have designed oral controlled drug delivery system for highly water-soluble drugs using guar gum as a carrier in the form of three-layered matrix tablet and concluded that guar gum is potential carrier in this system for a highly water-soluble drug.

Muhammad A *et al.,* has done the formulation and in-vitro evaluation of Flurbiprofen controlled release matrix tablets using cellulose derivative polymers. The studies showed ethyl cellulose ether derivative polymer was effective release controlling polymer for Flurbiprofen matrix tablet. HPMC also retarded the release rate of drug when combined with ethyl cellulose.

Khan Kamran Ahmad, Zizzadoro Claudia *et al.,* worked on Preparation and In Vitro Evaluation of Controlled-Release Matrices of Losartan Potassium Using Ethocel Grade 10 and Carbopol 934P NF as Rate-Controlling Polymers. All the above considered, the present study suggests that the controlled-release matrices developed by blending Ethocel grade 10 and Carbopol 934P NF showed good results in terms of physicochemical parameters and drug release profiles. The addition of coexcipients such as HPM, CMC, and starch may help in increasing the release rate, and further study might be undertaken to develop optimal concentrations to obtain the desired release rate, therefore achieving the important goal of finely tuning the pharmaceutical cargo to tailor the therapy to the needs of the patients.

Bala P. S.N. Sri, Muskan, Begum Hameeda *et al*., worked on formulation and evaluation of controlled porosity osmotic tablets of valsartan valsartan was effectively incorporated into a controlled porosity osmotic pump-based medication delivery system for the efficient management of hypertension by covering the core tablet with absorbable pore-forming chemicals the creation of micro-porous tablets was sped up and made less expensive by doing away with the need for pricey laser drilling based on the study's findings F6 was determined to be the best formulation overall since it releases 92.35% of the medicine in 12 hours drug release from the porous osmotic tablets was inversely linked to coat weight but directly proportional to the concentration of pore former and osmotic agent the PH. The in vitro drug releases the zero-order graphs regression values were closer to one formulation process that was standardized and proven to be reproducible which indicated that the system.

CONCLUSION AND FUTURE PERSPECTIVES:

Oral drug delivery is the most used mode of drug administration for systemic effects. Because they increased patient compliance, are inexpensive to treat, and are simple to administer therapeutic agents. Because oral drug delivery is non-invasive, patients usually feel more at ease with it than parenteral drug delivery. Due to its many benefits over other delivery methods, including patient compliance, affordability, and safety, oral dosage forms account for most of the drug delivery market.

In conclusion, the development of controlled release tablets for the treatment of Type-2 Diabetes Mellitus (T2DM) represents a multifaceted approach that integrates pharmacological insights, formulation science, and regulatory considerations. The meticulous selection of antidiabetic drugs and the careful design of formulations with controlled drug release mechanisms are pivotal for achieving sustained therapeutic effects. Various strategies, including osmotic pump systems, bilayer tablets, and gastroretentive systems, offer innovative solutions to optimize drug release kinetics.

The incorporation of biocompatible materials and adherence to regulatory standards ensure the safety and efficacy of the developed formulations. This comprehensive approach aims not only to enhance the management of T2DM by providing consistent blood glucose control but also to improve patient

compliance through convenient dosing schedules. The focus on patient-centric formulations, coupled with the flexibility of dosing and minimized side effects, addresses the diverse needs of individuals living with T2DM.

Clinical trials play a crucial role in validating the performance and real-world applicability of these controlled release tablets. The outcomes of such trials provide valuable insights into the overall effectiveness and safety profile of the formulations, guiding their integration into clinical practice.

In essence, the pursuit of controlled release tablets for T2DM underscores a commitment to advancing treatment modalities, fostering patient well-being, and contributing to the broader landscape of diabetes management. This convergence of scientific innovation and patient-centric design heralds a promising future in the ongoing endeavor to combat the challenges posed by Type-2 Diabetes Mellitus.

REFERENCES:

1. G.Jayapal Reddy, J.Venkateshwar Rao and K.R.S. Sambasiva Rao, Enhancement of Bioavailability of Atorvastatin Calcium Through Gastric Resident Formulation Approach, Int. J. Pharm. Biol. Sci., 3 (1), 2013, 636-654.
2. Bechgaar H., Baggeson S., Journal of Pharmaceutical Sciences, 1980; 69 (11): 1327-1330.
3. G. Jayapal Reddy, J. Venkateshwar Rao and K.R.S. Sambasiva Rao, Design and Evaluation of Atorvastatin Calcium Mucoadhesive Microspheres: A Novel Formulation Approach to Enhance the Oral Bioavailability, Int. J. Pharm, Biol and Chem.Sci, 2 (2), 2013, 20-31.
4. Higuchi.T. J. Pharm. Sci., 1971; 60: 1683.
5. Theeuwes, F., Curr. Med.Res.Opin. 1983; 8 (2) 20.
6. Park, K., Chang, H.S. and Robinson, J.R., Recent Advances in Drug Delivery Systems, Anderson and Kimeds, Plenum Press, New York; 1984, p163.
7. Mujoriya Rajesh, Bodla Ramesh Babu; Research Journal of Pharmaceutical Dosage Forms andTechnology, 2012; 4 (1).
8. Jayapal Reddy Gangadi, Venkateshwar Rao Jupally and K.R.S. Sambasiva Rao, Design and Evaluation of a Novel Floating in Situ Gel for Gastroretentive Drug Delivery of The Narrow Absorption Window Drug Atorvastatin Calcium, International Journal of Pharmaceutical Research and Biomedical Analysis, 3 (1), 2014, 14-27.