An Overview on Controlled Release Drug Delivery System

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Abstract- *Controlled drug delivery systems are used to ensure patient compliance, improve drug effectiveness, and ensure safety. Any drug administration method that achieves a slow drug release over an extended period of time is considered a controlled release system. Less frequent dosage and improved plasma concentration level management are used to achieve this. It can be difficult to successfully market a controlled release formulation since many different elements must be considered, as well as the drug's physiochemical properties, physiological factors, and manufacturing parameters. The goal of developing a medicine's controlled release drug delivery system is to enhance therapeutic benefits while minimizing adverse effects and managing the diseased condition. This article's purpose is to discuss the most recent patents available while thoroughly reviewing drug delivery system design for controlled release.*

Keywords- controlled release, drug delivery device, Drug release rate.

I. INTRODUCTION

The expansion of controlled release drug delivery system (CRDDS) had received a more attention in recent years as the cost and difficulties associated with marketing novel drug entities has increased, along with understanding of the therapeutic benefits of such delivery. The most frequent and favored method for delivering medicines has been oral administration. A perfect controlled drug delivery system is one that delivers the drug locally or systemically at a predetermined rate for a specific amount of time. Unlike the traditional immediate release system, this approach does not depend on the absorption process to control how quickly the medication manifests in the body.To maintain the safe effective medication concentration in the body over an extended period of time, the mechanism for controlled drug release is required. Drug concentrations should be kept in the body above the level at which they are effective and below the level at which they are poisonous in order to get the best results. But when a patient receives a dose of a medication, the body's initial concentration of the medication is above a hazardous level before it is regularly reduced to an ineffective level owing to elimination. A drug delivery system should give the required therapeutic concentration of medication in the plasma and hold it constant during the treatment period. It should do this by delivering the medicine at a rate determined by the body's needs over the period of treatment. The appeal of various dose formulations stems from a number of factors. It is generally acknowledged that a sizable number of therapeutically useful compounds currently exist for many disease states. The effectiveness of these medications, however, is frequently constrained by side effects or the requirement that the molecule be administered in a clinical area. By localising the drug to the site of action, lowering the dosage needed, or ensuring uniform drug distribution, sustained- or controlled-delivery systems are designed with the intention of minimising the frequency of dosing or increasing the effectiveness of the medicine. Two fundamentals would be required to create the ultimate medicine delivery system. First, it would be a single dose for the entire course of treatment, whether it will be for few days or weeks, as in the case of an infection, or for the patient's entire life, as in the case of diabetes or hypertension. Second, it should bring the active entity directly to the site of action, thereby minimising or removing side effects. Delivery to particular receptors, localisation to cells, or localization to certain bodily parts may all be necessary for this. It goes without saying that this ideal delivery system will have varying requirements for various illness conditions and medications. As a result, we want to deliver the therapeutic substance at a particular location at a certain time. In other terms, the goal is to successfully place the medicine both spatially and temporally. Currently, the majority of medication delivery devices can only partially accomplish both of these specific goals(1,2,3,4)

II. ADVANTAGE

- Reduced in frequency of drug administration.
- Uniform drug effect.
- Drug toxicity is reduced.
- Reduced GI side effects.
- Increases the safety margin drug which as high potency. [4, 5]. .

III. DISADVANTAGE

- *In vivo* and *in vitro* correlation is poor.
- Dose dumbing can occur. [4, 5].
- Initiation of pharmacological action is delayed.
- Enhanced first pass metabolism.
- GI residence time of dosage form has greater dependence.
- Compared to conventional doses, the price unit of medication is higher.
- Not all medications can be formulated into extended release(ER) dose forms [5].

VI. FACTORS INFLUENCING THE DESIGN AND ACT OF CONTROLLED RELEASE PRODUCTS

1. physiological properties:

Aqueous solubility:

A substance's solubilized in water is referred to as aqueous solubility. At a temperature of 30°C, the maximum amount of a chemical that will dissolve in clear water.The solid dosage form is a suitable option for controlled release system. Since it has good water solubility and is PH-independent .E.g. Pentoxifylline, has formulated in CRDDS as minimum solubility of 0.1 mg. drug with pH dependent aqueous solubility e.g. phenytoin and without PH dependent aqueous solvent e.g. steroid's for parenteral (IM) route [3, 6, 9]

partition coefficient:

Drug diffusion across the membrane or matrix that Controlsthe rate of diffusion as well as drug penetration via biological Membranes is influenced by partition coefficient. A drug mustdiffuse through a variety of biological membranes, as lipid-like barriers. An important factor is determining adrug can pass through lipid membranes (i.e., it's permeable) isits apparent oil/water partition coefficient[3, 6, 9]

drug stability:

Good candidates for CRDDS include medications that are resistant to enzymatic breakdown, acid/base, and other gastric fluids. Because the drug's bioavailability will diminish if it is metabolized in the stomach and small intestine, it is not suitable for controlled release formulations [3, 6, and 9].

drug pka:

The drug's ionization in the GIT at physiological PH is controlled by pka. The high ionized medicines are often not good choices for CRDDS. Compared to ionized medications, the unionized drug is quickly absorbed from biological membranes. In order for an acidic medicine to ionize, the pH must be between 3.0 and 7.5, and for a basic drug, the pH must be between 7 and 11.

Molecular Weight And Size:

The molecular diffusibility across a biological membrane is significantly influenced by two key variables: molecular size and molecular weight. Drug diffusion is made more difficult by molecule sizes more than 400d as opposed to easier when they are less than 400d. The size and shape of the membrane's cavities affect diffusivity. Passive diffusion is responsible for absorbing more than 95% of medicines. For passive diffusion, a drug's Particle mass must be higher than 600 Dalton.

(2) Biological factor:

Absorption:

It must be consistently delivered from the controlled release mechanism and then uniformly absorbed in order to maintain constant blood or tissue levels of the medication. When determining the CRDDS, uniformity in the rate and degree of absorption is crucial. The rate-limiting stage, however, is the drug's release from the dose form. To avoid dosage dumping, the absorption rate should be higher than the release rate. The different elements that influence how well medications are absorbed, including water solubility, log P, and acid hydrolysis.

Biological half-life ($t_{1/2}$):

The drug generally has a short half-life, requiring frequent doses. This makes it a good choice for controlled release systems. A medication with a lengthy half-life requires administration over an extended period of time. The best candidates for CRDDS are medicines with $t_{1/2}$ of 2-3 hours. Drugs used for controlled release systems but with a $t_{1/2}$ of more than 7-8 hours.

Therapeutic window:

Drugs having a limited therapeutic index are unsuitable for CRDDS. The delivery mechanism would dump doses and ultimately become hazardous if it were unable to manage release.

o **Dose size:**

The CRDDS must have a higher dose than a traditional dosage form because it was designed to do away with recurrent dosing. However, the dose utilized in conventional dosage form provides a guide for the CRDDS dose. The volume of the sustained dosage ought to meet the acceptability requirements.

Distribution:

Since it reduces the concentration of circulating medications and can be rate-limiting in their equilibrium with blood and extracellular fluid, the distribution of pharmaceuticals into tissues can play a significant role in the overall kinetics of drug elimination. Binding of the medication to blood proteins and tissues is one of thecomponentsof this distribution. Example: furosemide, theophylline.

Metabolism:

As provided the rate of metabolism is not excessively high, a medicine that is extensively metabolized can be used in a controlled release system. When the medicine is supplied via several routes, the extent of metabolism ought to be consistent and predictable. An inadequate option for such a product is a medicine that can induce or inhibit metabolism since steady-state blood levels would be challenging to maintain.

Elimination:

A controlled release drug delivery system that has a drug absorption and elimination rate thatis equal over an extended period of time is optimal. The amount of medicine to be included in the controlled release dosage form will be greater the $t_{1/2}$. To maintain the high release rate, drugs with $t_{1/2}$ less than 2 hours need to be taken in much greater doses. Drugs with $t_{1/2}$ between 2 and 4 hours make good CRDDS candidates for, Example: propranolol.

V.CLASSIFICATION OF CONTROLLED RELEASE SYSTEM

1 .Rate pre-programed drug delivery system
2. Activated modulated drug delivery
3. Feedback regulated drug delivery system
4. Site targeting drug delivery system

(1)Rate Pre Programed Drug Delivery System:

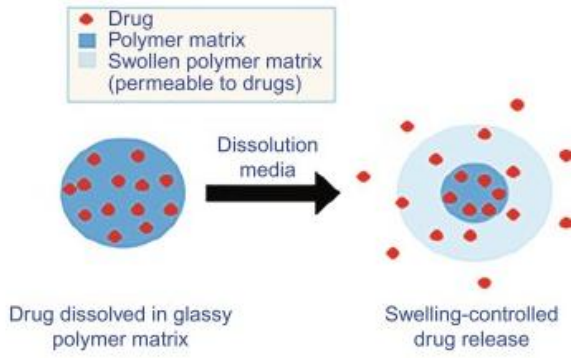
This has a pre-planned drug release from the delivery system with a specific medication Flow rate profile. The system regulates the drug molecules molecular diffusion into, though, or around the delivery system's barrier medium.

(1.1)Dissolution controlled drug delivery system:

Solid matter that has been dissolved in a suitable solvent is referred to as dissolution Process. After liquid diffuses from solid, it's a rate-determining step. The two primary categories of dissolution-mediated controlled release formulation are reservoir and matrix system. The most popular method for regulating release is called as matrix dissolving System, which involves uniformly dispersing the active pharmaceutical ingredient (API) throughout a polymer matrix when the polymer matrix breaks down (7, 18).

(1.2)Matrix Dissolution System:

The "monolithic dissolution controlled device" is generally used to study of matrix dissolution system. Changes to the Tablet's porosity, and reduction in its wetting capacity, and a slower rate of dissolution are used to control its disintegration.



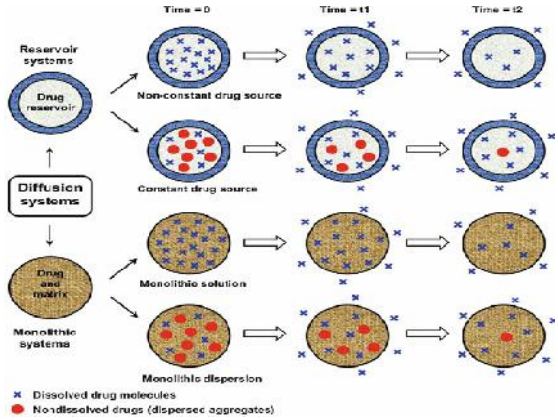
(1.3)Encapsulation Dissolution Control:

These techniques often include coating individual medication particles or granules with a slowly dissolving substance. In the case of products like space tablets or capsule, the coated particles can either be directly compacted into tablets or put inside of capsules. One can achieve repetitive or sustained action by using a limited or wide range of coated particles of varied thicknesses, as the time needed for the coat to dissolve is dependent on its thickness and water solubility, respectively.

(1.4) Diffusion controlled drug delivery system:

It is a significant method for absorption that requires no energy. When equilibrium is reached with this medication, it is directly proportional to the concentration gradient that

crosses the membrane. Drug diffusion from a site of greater concentration to a region with a lower concentration. Its diffusion through a polymer that is insoluble in water determines the dissolution rate in this system. Diffusion controlled system are classified into reservoir and matrix type delivery system. The drug release is covered by Fick's law of diffusion.



(1.5) Hydrophilic Swellable Matrix Diffusion:

It also known as glassy hydrogels is widely known for maintaining the release of Medication that is extremely water soluble. Hydrophilic gums are the materials [19].Natural examples include tragacanth and semi-synthetic: xanthium gum, hpmc, and Cmc. Artificial polyacrylamides examples are Procardia and Glucotrol xl.

(1.6) Micro reservoir partition controlled system:

The drug reservoirs are composed of solid particles suspended in an aqueous solution of a polymer that is water-miscible. High dispersion methods are used to create a Micro-dispersion partition controlled system. In a nutshell, micro-reservoir and matrix Dispersion

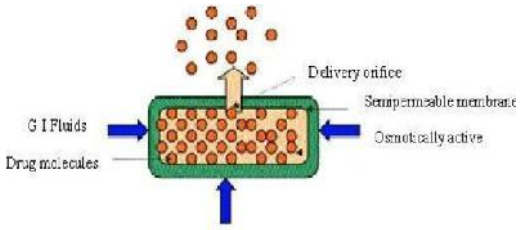
(2)Activated Modulated Drug Delivery System:

In this, a physical, chemical, or biological mechanism, as well as any external energy Source supplied, control or initiate the release of medications from the delivery system. Energy input or any other applied method can regulate drug release. The following Categories apply to this activation procedure.

A) Activation by physical process:

(1) Osmatic pressure activated system:

The most promising strategy based system for regulated medication delivery is osmotic Technology. The movement of water across membrane that is selectively permeable is Known as osmosis and caused by different osmotic pressure in this method of controlled Drug administration, a solution formulation serving as the drug reservoir is housed in a Semi-permeable structure. Under an osmotic pressure gradient, the medication is delivered in solution form at a controlled, stable rate. Drug release rate is constant. Examples: methylene chloride, ethanol, isopropyl alcohol (3, 11, 17, 18,).



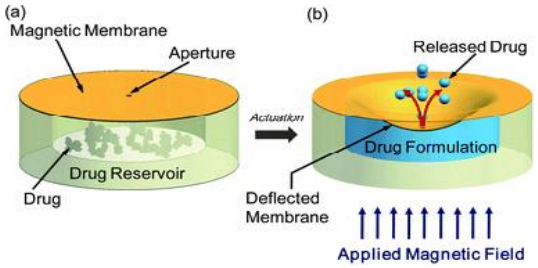
Elementary osmatic pump

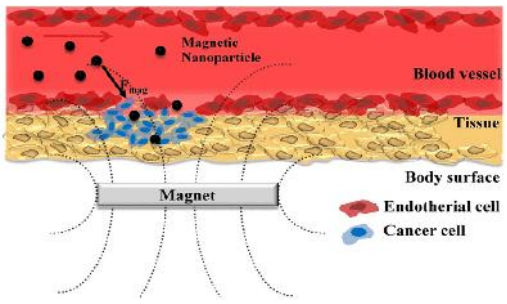
(2) Hydration activated system:

Depends on the hydration included swelling process to activate the release of drug. Drug Dispersed is homogeneously in a hydrophobic polymer .release of the drug is controlled by swelling polymer matrix. Example: diazepam. (6)

(3)Magnetically Activated System:

The principle behind the magnetic drug delivery method is that the medication can either be conjugated on the surface of a magnetic microsphere (or Nano sphere) .an external Peminent magnetic field is applied on the desired area to guide and concentrate the Drug (3, 20).



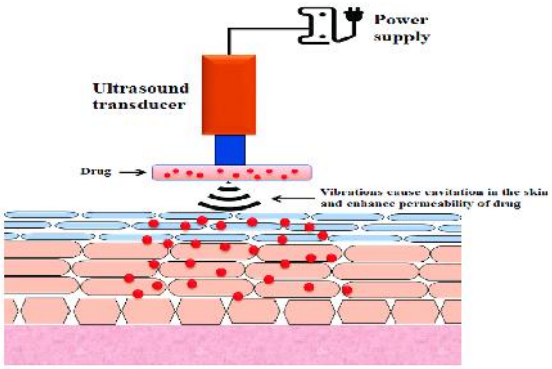


(4)Photochemical waves activated system:

This category of drug delivery device uses covalent bond cleavage that is controlled by Light irradiation to speed up the release of the payload that is enclosed .which upon uv Light irradiation irreversibly cleavage to liberate a free carboxylic acid and o nitrobenzaldehyde is Workhorse for photochemical trigged drug delivery system example: acetone and HCHO(13 ,21).

(5)Sonophoresis activated system:

The activation of medication delivery in this uses an ultrasonic instrument. For the Administration of drugs through the skin, a very low frequency (55 kHz) for a very less Period of time (15 seconds) is utilized. This ultrasonic gadget is a battery-operated handheld system that includes a control unit, an ultrasonically produced horn, a Disposable coupling medium sealed unit, and a return electrode .these gadgets are made of biodegradable and non-biodegradable polymer (13).



(6) Vapor pressured activated system:

In this system, a liquid exists in equilibrium with its vapor phase and pressure of the Independent volume of fluid. One device used to pressure control delivery, device Consist of two chambers, one contains the drug solution and second with a vaporizable Fluid such as fluorocarbon. When a drug is injected, a volatile liquid vaporizes at body Temperature, creating a vapor pressure that compresses the chamber below and delivers the medication in a regulated manner. (13).

(7) Electrically activated system:

This system is used for electrical current to activate and modulate the diffusion of a Charge drug molecule across the skin a facilities rate. Example; dexamethasone sodium Phosphate (13 22).

(8) Mechanically activated system:

A medication reservoir or storage space that has a pumping device that is mechanically triggered. A spray system that utilizes a mechanical drug delivery pumping system delivers a controlled dose of medication into a bodily cavity, such as the mouth or nose. The each pumping spray has a predetermined spray volume of the medicine being administered. For former metered-dose nebulizer lhrh, or luteinizing hormone-releasing Hormone (23 13).

(9) Hydrodynamic pressured activation system:

The source of energy is used for activate the drug release process are also known for Hydrodynamic pressured action system (13).

(10) Photo activated system:

The photo activated approach has sparked a significant deal of scientific interest due to its ability to accurately control the release of pharmacological compounds and the Activation of bio imaging agents. The best photo responsive systems, which are frequentlyUV or visible light-sensitive (13)

B)Activation by chemical press:

(1) pH activated system:

The significance of pH Sensitive Drug Delivery Systems (PSDDS) is growing because these systems produce the medication at precise times in accordance with the pathophysiological requirements of the disease, improving patient therapeutic efficacy and compliance. At acidic pH, cationic polymers containing amino groups are more water soluble than they are at neutral ph. When the pH is basic compared to when it is acidic, anionic polymers having carboxyl groups are more water soluble. These are used for preventing gastric degradation, peptic ulcer, cardiovascular disease Drawbacks of conventional drug formulations, ph-responsive drug-delivery systems have gained increasing attention. This is because these systems can deliver drugs in a Controlled manner at a specific site and time, leading to high therapeutic efficacy (6, 13, and 17).

(2)Ion activated system:

This system is used for resin and contain ion groups .An ion exchange resin is a polymer (often styrene) having electrically charged spots Where one ion can swap places with another. Resins are water insoluble particles containing cationic and anionic groups. These resin used to CR

(controlled release) System Example: Levodopa and carbidopa. [13, 17, 25].

Cation exchange resin:

Positivly charged ions are exchanged by covalently at tached negatively charged functionl groups in cation exchange resins. They are created by copolymerizing styrene and diviny l benzene, andthe majority of them include sulfonic acid group s (SO3H) Example: Morphine sulphate, (17 2).

Anion exchange resin:

Positively charged functional groups are exchanged by negatively charged ions in anion exchange resins. These are made by first attaching CH2Cl groups to the benzene rings of the styrene-divinylbenzene copolymer using chlormethylation, and then inducing these to react. Either triaryl amines, like diethyl amine. For example: chloromethylating. (17).

(3)Hydrolysis Activated System:

Hydrolysis is also known as chemical reaction; the interaction of water with chemical .This uses a microcapsule to enclose the drug reservoir. The implanted device is also a Part of it. These systems are all constructed with biodegradable polymers. The rate of Drug delivery is controlled by the hydrolysis breakdown of the polymer chain, which Activates the release of the medication (6, 13).

C) Activation by Biological Process:

(1) Enzyme activated system:

An enzyme-activated system, the enzymatic process activates the system to release Medications. Liposomes, nanoparticles, prod rugs, micro particles, and other methods of enzymatic drug delivery are available. Drug, nano carrier, promoiety, coated polymer, Ligand, and other substances are the system's primary constituents (23).

(2) Anti body interaction activation system;

Antibody interaction blocks the enzymatic breakdown of the polymer matrix or the Permeability of the medication in the polymeric reservoir (13, 20).

(3) Feedback Regulatory Drug Delivery System:

Bio Responsive DDS:

In this system, the drugs reservoir is contained in a device enclosed by a bio responsive Polymeric membrane whose rug permeability is controlled by concentration of Biochemical agent in tissue where the located in system (13, 18, 23).

Bio Erosion Regulated DDS:

This system is consists of drug dispersed bio erodible from poly (vinyl and ethyl ether) Half ester which is coated with a layer of immobilized urease, in solution with nature ph. Polymer (23).

Self-controlling drug delivery mechanisms:

The reversible and competitive binding mechanism for the activation and release of Medicines controls this mechanism. In this, a polymeric drug reservoir contained within Membrane that is semipermeable. The biological component of activates the drug's Release a tissue. Example: an insulin-sugar-lactin-derived biological complex is Enclosed (23, 24).

(4) Site Targeting Drug Delivery System:

Active targeting:

The foundation of an active targeted drug delivery system is a technique that administers a specific dosage of a therapeutic, diagnostic, or both to a specific location of a damaged Organ in the body (26).

Passive targeting

The drug's efficacy in passive targeting is directly correlated with its circulation time. The Nanoparticle is covered with a coating to accomplish passive targeting. This can be Accomplished by a number of chemicals, one of which being polyethylene glycol (PEG) (23, 25).

VI.CONCLUSION

It has been more than 30 years since controlled-release delivery systems were developed. Controlled release (C.R.) product provides an advantage over conventional dosage forms by enhancing the bio-pharmaceutics, pharmacokinetic, and pharmacodynamics properties of drugs in such a way that it reduces dosing frequency to the point where one dose per day is sufficient for treatment and diagnosis through uniform plasma concentration, providing the maximum utility of drug with a reduction in local and

systemic side effects, and curing or controlling condition in the shortest possible time. The most of the device use on the fundamental principles of dissolution, diffusion, osmosis, ion exchange and etc...For a drug delivery system to be designed in the best possible way, it is necessary to have a better understanding of the release mechanisms, carrier material elements, barrier characteristics, pharmacological effects, and pharmacokinetics of the medicine. This review includes appropriate examples and a detail of the various factors that influence the performance and design of controlled release products.

REFERENCES

[1] M. Prabaharan & J. F. Mano Chitosan-Based Particles as Controlled Drug Delivery Systems. Drug Delivery, .12:41-57.2005

[2] Senthilkumar Murugesan , Byran Gowramma1,* , Kaviarasan Lakshmanan 1 , Veera Venkata Satya-narayana Reddy Karri 2 and Arun Radhakrishnan Oral Modified Drug Release Solid Dosage Form with Special Reference to Design; An Overview .current drug research reviews.12.2020.

[3] Joseph R. Robinson, Vincent H. Lee. Controlled drug delivery fundamentals and applications, second edition .drug and the pharmaceutical science.29.

[4] Kumar Bishwajit Sutradhar & Chandra Datta SumiImplantable Microchip: the futuristic controlled drug delivery system, Drug Delivery, 23:1, 2016

[5] Debjit Bhowmik, Harish Gopinath, B. Pragati Kumar, S. Duraivel, K. P. Sampath Kumar. Controlled Release Drug delivery system. 1:10:2012.

[6] Ramineni Vengamma. Factors affecting drug design and performance of sdds and cdds.2020.

[7] S.Deepu, Molly Mathew and MS. Shaman. Controlled drug delivery system. International journal of Pharmaceutical and Chemical science.3:2014.

[8] N.K.Jain.controlled and novel drug delivery book...2019.

[9] Rnjith kumar at el.Factor influencing the design and performance of oral sustained /controlled release dosage form. International journal science and Nano technology.2:2002.

[10] S.P.Vyas.R.K.Khar targeted and controlled drug delivery novel carrier system

[11] Dr. Mosab Arafat.Approaches To Achieve An Oral Controlled Release Drug Delivery System Using Polymers: A Recent Review.International Journal of Pharmacy and Pharmaceutical Sciences .7:7:2015

[12] Gul Majid Khan. Controlled release oral dosage form: some recent advance in matrix type drug delivery system. Review article .international journal.2001.

[13] Juergensiepmann, Florencesiepmann.modling of diffusion controlled drug delivery. Journal of controlled release.11. 2012

[14] Kumar bishwajit sutradhar and Chandra data sumi. Implantable microchip: the futuristic controlled drug delivery system. Drug delivery. 23.201

[15] Kovanya moodley, Viness pillay, yahya E.Choonara, lisa C. du toit, Valence M. K. Ndesendo, pradeep kumar, shivaan cooppan and priya bawa

[16] Oral drug delivery systems comprising altered geometric. International journal of molecular sciences 13.18.43.2012

[17] Kora Pattabhi Rama CHOWDARY* and Yarraguntla SRINIVASA RAO. Mucoadhesive Microspheres for Controlled Drug Delivery. Biol. Pharm. Bull. 27(11) .1717—1724 .2004

[18] B. Sahilhusen I Jethara Shri .Pharmaceutical Controlled Release Drug Delivery Systems: A Patent Overview. Research gate. 2014

[19] Anand S. Surana and Rakhee K. Kotecha. An Overview On Various Approaches To Oral Controlled Drug Delivery System Via Gastroretention. International Journal of Pharmaceutical Sciences Review and Research. 2:2:2010.

[20] Shivakalyani Adepu and Seeram Ramakrishna .Controlled Drug Delivery Systems: Current Status and Future Directions. Molecules. 26.5905.2021.

[21] Rajendra Jangde. Magnetically modulated Drug Delivery Systems: An Overview. Research J. Pharm. and Tech. 4(11):Nov. 2011

[22] Chase S Linsley et al. Recent advances in light-responsive on-demand drug-delivery systems. PMC. 2017.

[23] Rukkumani Rajagopalan, Jatinder V. Yakhmi. Nano technological approaches toward cancer chemotherapy. Micro and Nano Technologies. Science direct.2017

[24] M. V. Srikanth, S. A. Sunil, N. S. Rao, M. U. Uhumwangho and K. V. Ramana Murthy. Ion-Exchange Resins as Controlled Drug Delivery Carriers. Journalof Scientific Research. 2 (3), 597-611 .2010

[25] Manisha Gahlyan*, Saroj Jain. Oral Controlled Release Drug Delivery System- A Review. PharmaTutor; 2(8); 170-178. 2014.

[26] Takayuki yoshida, Tsz Chung Lai, Glen S Kwon and kazuhiro. Ph and ion sensitive polymers for drug delivery.10 (11):1497 -1513:2013.