Clinical Medicine and Health Research Journal (CMHRJ)
Volume 02, Issue 06, November - December, 2022
Page No. 274-280

**Research Article**

# Formulation Development & Evaluation of Controlled Drug Delivery System: An Overview

**Shimanta Paul[1], Tausif Ahmed[1], Shanzid Hasan[1], Md. Khaledur Rahman Bhuiyan[2], Swapan Kumar Das[2], Nikolaos Symros[3]**

[1]Department of Pharmacy, University of Asia Pacific, Bangladesh

[2]Eskayef Pharmaceuticals Ltd.

[3]Aristotle University of Thessaloniki, Thessaloniki, Macedonia, Greece

**Received: 20 October, 2022 Accepted: 18 November, 2022 Published: 22 November 2022**

## Abstract:

The therapeutic effect is brought about by the drug delivery system dispensing the active medicinal ingredient. Due to fluctuations in plasma drug levels, traditional drug delivery devices have poor bioavailability and cannot generate a continuous release. The drug must also be supplied at a tightly regulated rate and to the correct location for it to be most effective and safe. To solve the problems inherent in the current methods of administering medication, scientists are working on perfecting controlled drug delivery systems. Controlled pharmaceutical delivery systems have come a long way in the last twenty years, from bulk distribution to nanoscale precision to smart, patient-specific dosing. The paper's initial portion provides background knowledge on drug delivery methods, emphasizing pharmacokinetics. The article also discusses the pros and cons of more conventional drug delivery methods. Controlled drug delivery systems' design factors, categorizations, and schematics are also discussed in length. In addition, recent advances in nano-drug delivery, targeted, and innovative drug delivery utilizing stimuli-responsive, intelligent biomaterials are discussed. The limitations of regulated medicine distribution and some possible solutions are discussed at the end of the study.

**Key word: CDDS, Therapeutic Effects, DDS, Formulation development, Crispr Cas9, etc.**

## 1. Introduction

It takes a lot of time and money to develop a new medication compound. Individualizing medication therapy, dose titration, and therapeutic drug monitoring are only a few of the ways that have been tried to increase the safety efficacy ratio of "old" pharmaceuticals. Other extremely appealing strategies have been extensively researched, such as controlled drug delivery [1, 2], delayed drug delivery, and targeted medication delivery. It is fascinating to see the large amount of effort and the large number of papers from the United States and Europe that are produced by Indian researchers [3]. Numerous studies in both animals and humans have bolstered our knowledge of the pharmacokinetic and pharmacodynamic principles that regulate the action and disposition of powerful opioid analgesics, inhalation anesthetic drugs, sedative/hypnotics, and muscle relaxants [4]. Evidence from these investigations points to the possibility that the skin and buccal and nasal mucosa can be used as additional entry points for analgesics and anesthetics. Similar progress with other chemicals has resulted in a multitude of new tools, ideas, and methods that make up what is collectively known as controlled-release technology (CRT). Controlled-release technologies (CRTs) include, but are not limited to, programmable implanted drug-delivery systems, transdermal and transmucosal controlled-release delivery systems, ml6 nasal and buccal aerosol sprays, drug-impregnated lozenges, encapsulated cells, oral soft gels, and iontophoretic devices to administer drugs through skin. Numerous motivating forces are pushing researchers to create innovative tools, strategies, and methods [5]. Although conventional drug delivery methods are used frequently, there are various drawbacks to them that these alternatives may address. When compared to the price tag on creating a brand new medicine, these developments may look appealing. Since the late 1950s, the number of new chemical entities introduced into the market has decreased. This is due to several factors, including rising R&D costs, alternative investment opportunities for drug firms, a decline in the number of firms conducting pharmaceutical research, and the erosion of effective patent life. It is now predicted that it will take over a decade and well over $ 120 million to bring a new medicine through discovery, clinical testing, development, and regulatory approval. It is estimated that by the year 2000, up to forty percent of all drugs sold in the United States will utilize some sort of novel drug delivery mechanism [6].

The purpose of any drug delivery system is to transport the therapeutic dose to the site of action, to rapidly establish and then maintain the therapeutic drug concentration that elicits

the desired pharmacological activity, and to reduce the occurrence and severity of side effects. In order to accomplish this, it would be beneficial and more convenient to stick to a once- or twice-daily dosing schedule [7]. When compared with the standard instant release dosage form, a prolonged release dosage form that is carefully crafted can be a significant improvement in this regard. Over the past two decades, researchers have paid considerable time and energy to perfecting new approaches to medication delivery. Monolithic matricesmatrix tablets continue to be popular despite the availability of other technologies due of their simple processing technologies, repeatability, stability of materials and dosage form, and easy scaleup operation [7].

Due to the rising costs and complexities of bringing new pharmacological entities to market and the acknowledged therapeutic benefits of controlled drug delivery, researchers have been focusing more on developing sustained or controlled release drug delivery systems in recent decades. Numerous benefits make these dosages appealing. It is widely accepted that there already exists a large number of therapeutically useful chemicals for numerous disease states1. However, these medications' efficacy is sometimes capped by their side effects or the requirement that they be administered in a therapeutic setting. The purpose of developing continuous or controlled delivery systems is to lessen the number of times a medicine needs to be administered, boost its efficacy by delivering it directly to the site of action, lower the drug's toxicity, or ensure that all patients receive the same dose [9].

## 2. Controlled Drug Delivery Systems (CDDS)

According to FDA guidelines, an active pharmaceutical ingredient (API) is any substance with the intent to diagnose, cure, mitigate, treat, or prevent disease. The term "drug delivery" refers to a method of administering medication that optimizes localized drug concentration. Any drug delivery system worth its salt will seek to maximize drug exposure while keeping it safe within the sick tissue. Active pharmaceutical ingredients (APIs) and excipients/additives, which are not APIs, are both parts of every dosage form (Figure 1). Active pharmaceutical ingredients are what doctors utilize to treat patients. The goal of any controlled-release medication delivery system is to minimize unwanted side effects while effectively treating or preventing disease in the shortest amount of time possible by the use of the least amount of medicine possible given via the most appropriate administration route. A number of advantages, including as steady dosing, rate control, and precise targeting, are missing from immediate-release drug delivery systems. The ideal method of administering medication would gradually release the substance over the course of the treatment, as determined by the body's requirements.


**Figure 1: Conventional Vs Controlled Drug Delivery System**

## 3. Oral Controlled-Release Drug Delivery: Factors in Their Design

### 3.1 Solubility

Medications with a limited solubility in water aren't very effective when taken orally. Poor choices for controlled/sustained oral dosage forms include drugs that are well soluble in stomach acid. Highly water-soluble drugs tend to leach quickly from the carrier, reducing the loading efficiency of various carrier systems such liposomes and micro particles. Because of shifts in pH throughout the digestive system and dissolving rate, pH-dependent solubility, especially in the physiological pH range, would be another challenge for controlled release formulation. Oral absorption is influenced by three main parameters: solubility, dissolution, and intestinal permeability. The biopharmaceutical classification system makes it possible to assess the impact of each of these characteristics [10].

### 3.2 Drug Stability

Degradation of a medicine in a solid form is significantly more gradual than that of a drug in suspension or solution [11]. To prevent their breakdown in the stomach, medications that are unstable at this pH level may be given in a slow-release dose form that doesn't release the drug until it reaches the intestine. Oral controlled drug delivery systems are not appropriate for drugs that undergo gut-wall metabolism or exhibit small intestine instability [12].

### 3.3 Molecular Size and Diffusivity

The molecular size of a medicine has a negative correlation with its diffusivity, or its capacity to pass across a membrane [13]. The membrane's diffusivity is proportional to the cavity size and shape. Passive diffusion accounts for the absorption of more than 95% of all medicines [14]. A drug's molecular size must exceed 600 Dalton if it is to be effectively diffused passively. Proteins and peptides are two types of medications for which it is challenging to regulate the rate of medication release from the dose form [15].

### 3.4 Partition coefficients

The drug's proportion in the oil phase relative to the aqueous phase is the partition coefficient. It controls the movement of drugs through biological membranes. When a drug's partition coefficient is high, it may readily cross a biological membrane [14]. A drug's ability to diffuse through a rate-limiting membrane or into a matrix system is dependent on a property known as the partition coefficient. For the same reason that medications with a low partition coefficient cannot partition out of the lipid membrane, those with a high partition coefficient cannot be used in an orally controlled drug delivery system [15].

### 3.5 Drug pKa and ionization at physiological pH

Drugs residing predominantly in ionized form are poor choice

for oral controlled release drug delivery system because absorption rate of ionized drug is 3-4 times less than that of unionized form [17]. The pKa range for acidic medicine whose ionization is pH sensitive is about 3.0-7.5 and for basic drug whose ionization is pH sensitive is around 7.0-11.0 are appropriate for optimum positive absorption [16].

### 3.6 Absorption

The point of developing a controlled-release product is to exert some kind of command over the delivery mechanism [19]. In an ideal controlled oral delivery system, all of the medicine would be released at once, and the body would be able to absorb it all. Because of drug breakdown, protein binding, site-specific, dose-dependent absorption, poor water solubility, and a tiny partition coefficient, the proportion of drug absorbed from the system may be lower than anticipated [18].

### 3.7 Distribution

When it comes to drug elimination, drugs having a large apparent volume of distribution are not ideal candidates for oral drug delivery systems [18]. One key metric of medications is their apparent volume of distribution, which characterizes the extent of dispersion and protein binding in the body. Both the steady-state distribution volume and the T/P ratio may be used to analyze the drug's movement through the body [19].

$$\frac{T}{P} = \frac{k_{12}}{K_{21} - b}$$

Here, T = Amount of drug in peripheral compartment;

P=Amount of drug in central compartment;

$K_{12}$=Constant for distribution of

**Figure 2: Equation of apparent volume of distribution [18].**

**Figure 2: Equation of distribution of drug.**

### 3.8 Metabolism

An active drug may undergo metabolism to render it inactive, or an inactive drug may undergo metabolism to render it active. There are two limitations on the design of sustained/controlled medication delivery that stem from the drug's metabolism [17]. Drugs that can induce or inhibit enzyme synthesis are not good choices for controlled delivery systems because of the challenges they present in maintaining constant blood levels during long-term treatment. Sustained/controlled medication administration is not appropriate for drugs with variable bioavailability due to the first-pass impact or intestinal metabolism [18].

### 3.9 Therapeutic index

Therapeutics index, the ratio of the median toxic dose to the median effective dose, can be used to characterize the margin of safety. Controlled-release medication formulation is not appropriate for drugs with a low therapeutic index. By keeping the dosage within the safe therapeutic range, unwanted effects can be kept to a minimum [18].

$$\text{Therapeutic index} = \frac{TD_{50}}{ED_{50}}$$

**Figure 3: Ratio of therapeutic index [10].**

### 3.10 Half- life

The half-life in biology is the determining factor in how long an effect will last. Controlled drug delivery systems work best with drugs that have a relatively long half-life (more than 2 hours). A drug's half-life is affected by its elimination, metabolism, and distribution [10, 18].

## 4. Controlled-release drug delivery system design considerations

Figure 4 is a simplified illustration of the many variables that must be taken into account while constructing a controlled-release drug delivery system. One can categorize the parameters as either formulation-related or drug-related. The biomaterial characteristics, mode of administration, pharmacokinetics, and stability enhancement are the primary considerations under formulation-related parameters. Moreover, the drug's binding effectiveness with plasma proteins, its capacity to overcome biological barriers, and regulatory considerations are the most important factors in developing the dosage form [20].

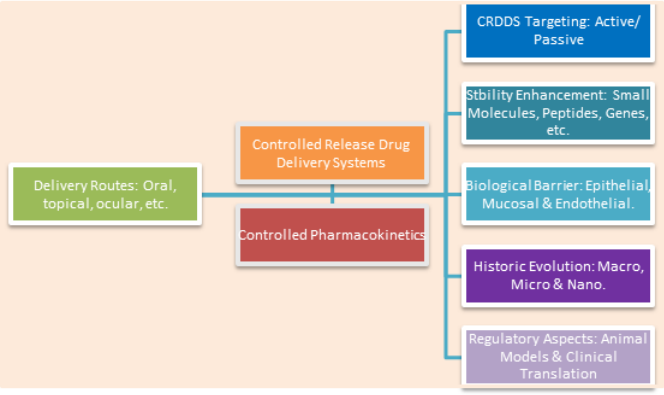


**Figure 4: Guidelines for CDDS Layout [43].**

Biocompatibility, surface chemistry, hydrophilicity, degradation, mechanical, and rheological qualities are just few of the biomaterial characteristics that need investigation. Additionally, the biomaterials' behavior at varying pH and temperatures must be evaluated. When deciding on a biomaterial and formulating a dosage form for a medicine, the routes of administration are paramount. To facilitate drug release following rectal delivery, for instance, the biomaterial

in question must either have a melting point over 37 °C or be soluble at that pH. Stability improvement should be performed during the design of the controlled release carrier for medications that are not stable under extreme conditions. This includes peptides, proteins, genes (DNA), growth factors, and colloidal/non-colloidal particles. To do this, the relevant medications can be integrated into targeted carrier systems [21].

It is crucial to limit the drug's effects to the organ in need of the pharmacological activity for which it was designed. Antibody tagging, ligand attachment, and targeted delivery are all viable options for achieving this goal. Biological barriers prevent precise medicine delivery to organs like the brain, bone, and testicles. Alternatives that can get drugs through barriers and to their intended targets include those that are designed with permeation enhancers and nanocarriers [22]. An optimal in vitro in vivo correlation requires the development of animal models appropriate for each type of delivery mechanism (IVIVC). This helps connect the dots between the findings of in vivo animal studies and those of human clinical trials [23].

**Table 1: Merits & demerits of CDDS [43]**

| Merits of CDDS | Demerits of CDDS |
|---|---|
| Specific Target | High Manufacturing Cost |
| High bioavailability | Poor IVIVC |
| Less dosing frequency | Toxicity Risk |
| Metabolism Protection | Invasive Technique |

## 5. Nanocarriers in CDDS and TDDS

Sub-micron particles, known as nanocarriers, have a high specific surface area, allowing for greater loading or dosing in a given volume. They circulate for considerably longer than the medicine alone, increasing the drug's bioavailability and making it more readily available at the site of disease [33]. They provide effective wayfinding in the chaotic in vivo setting (protects the drug from undue degradation). They are able to establish therapeutic responsiveness at a far lower dose, minimizing drug-related side effects. Nanocarriers' surface chemistry can be easily adjusted to accommodate a wide variety of medicines and targeting compounds. Targeted drug delivery that provides a sustained release of the therapeutic payload is feasible. Nanocarriers allow for a wide range of formulation and delivery options for drugs [35]. In addition to targeting particular cell types, they are also capable of localizing their effects inside defined sub-cellular areas (i.e., the nucleus for gene delivery). In this way, nanocarriers can improve medication intracellular trafficking [38].

If a medicine is to be successful against diseased cells in a certain tissue, it must do so without harming the healthy cells present there. Nanocarriers can safely boost medication concentrations without increasing drug toxicity. Cellular and intracellular targets [39] refer to the specific tissue compartments within cells that receive the medication. Nanocarriers are utilized to transport drugs to areas that they would otherwise have a hard time penetrating, such as those with strong anatomical barriers. Because it operates as a selective barrier to the brain, the blood-brain barrier prevents most drugs from crossing into the brain. Drugs in nanocarriers can be administered to the brain without being broken down by the body's natural defenses, making them effective against a wide range of central nervous system illnesses. There are two ways the nanoparticle can go into the brain: transcellular and paracellular [40]. Drug delivery systems that employ nanocarriers have gained popularity due to their ability to transport drugs to specific tissues while also penetrating barriers such as the blood-brain barrier and reaching distant areas. Therefore, maximizing the therapeutic efficacy of a medicine requires its distribution throughout the body, which can be greatly enhanced by administering the drug linked to nano-structures or nanocarriers.

The goal of the targeted medication delivery system is to bring the pharmacological effects of the treatment to the sick site while reducing systemic side effects [41]. As was previously mentioned, conjugating a drug with a physiologically suitable polymer would improve drug delivery by enhancing solubility, decreasing toxicity, and maximizing the drug's therapeutic window [42].

## 6. Difficulties and Possible Future Paths in CDDS

Over the past two decades, regulated medication delivery systems have seen tremendous development. Despite this, there is room for development to overcome these constraints and open up more opportunities in the future.

### 6.1 Nanomedicine Challenges and Improvements in CDDS

Advantages of nano-drug delivery systems over traditional administration methods include more precise drug distribution and better outcomes for patients. However, safety and toxicity profiles of nanoparticle systems are lacking. Several investigations found that nanoparticles generated inflammation of the liver, lungs, and brain via oxidative stress [24]. This inflammation was caused by nanoparticle uptake by the reticuloendothelial system. The capacity of nanocarriers to pass the blood-brain barrier is useful in treating brain illnesses, but it can lead to neurotoxicity if the brain isn't the intended site of action. Additionally, nanoparticles can cause immunomodulatory effects. To stop the spread of autoimmune diseases like autoimmune encephalomyelitis, scientists have found a way to use nanoparticles' immunomodulatory activity to target inflammatory monocytes across the blood-brain barrier [25]. Due to their ordered mesopores (2-6 nm), tunable size (50-200 nm), and shape, and their ease of surface modification, inorganic mesoporous nanoparticles have attracted a lot of interest in controlled drug delivery because they can be modified to better target the drug and release it from the endosome. Mesopores can be coated with stimuli-responsive polymers to prevent the premature release of pharmaceuticals, so allowing for spatio-temporal control over the release of a specific medication into the cytoplasm of the target cell [26].

### 6.2 Microfluidics in CDDS

Possible future research directions include developing microfluidics devices for implantable and controlled distribution. It is often referred to as lab-on-a-chip (LOC) technology and typically consists of micro-devices with tiny compartments and channels [27]. Improved drug delivery can be achieved with the help of these microdevices by directing the flow of fluids to a targeted area [28]. Some recent research has proposed the creation of synthetic polypeptides by polymerizing -amino acid N-carboxy anhydrides (NCAs), with the goal of organizing these NCAs into nanostructures that may then deliver the medicine to a targeted area. Furthermore, by modifying the chemical and physical features of the polypeptide structure, the release of the pharmacological compounds can be controlled [29]. Microfluidics is also being used for important purposes including finding new antibodies and transporting cells [30, 31].

### 6.3 Intelligent Biomaterials

The potential for the creation of smart biomaterials that can sense their surroundings, automatically adjust to them, and then control the release of drugs is enormous. One possible application is an intelligent hydrogel that can detect changes in blood sugar levels in its environment (via changes in pH or temperature) and then release only the amount of insulin needed to keep glucose levels stable. While producing smaller biosensor hydrogels is necessary, doing so is currently difficult due to the hydrogels' increased fragility and an inability to impart appropriate mechanical strength [29].

### 6.4 CRISPR CAS9 Technology

CRISPR, or clustered regularly interspaced short palindromic repeats, is a family of DNA sequences that functions primarily in prokaryotes as an effector of the adaptive immune system. There have been profound shifts in our understanding of how to modify genes in specific tissues as a result of this [33]. This CRISPR-based delivery method is made up of a single guided RNA (sgRNA) and a Cas9 endonuclease. Cas9 can be targeted to a specific location in DNA or RNA with the help of sgRNA. CRISPR RNA (or crRNA) sequences recognize the precise target. But studies are being done to reduce the off-target consequences of the sgRNA with Cas9 protein combo. Instead of Cas9, any other protein therapeutic ingredient might be delivered using the same approach [32].

### 6.5 Quantum Sensing Drug Delivery

Quantum dots, or QDs, are another breakthrough that have helped pave the way for more precise drug assays using nanotechnology. They are essentially semiconductors made from carbon-based nanoparticles that exhibit great chemical inertness, high specific surface areas, low toxicity imparting capacity, and high solubility [34]. Due to their distinct optical features, such as the quantum confinement effect and the emission of fluorescence when activated by a light source, QDs are promising candidates for use as nano-probes and carriers in biological research. QDs, with their unique spectral properties, can overcome the difficulty of real-time drug tracking that is inherent to most polymer-based drug carriers. Quantum dots can be used to readily track down other drug carriers, as their fluorescent emission is superior to that of organic dyes. In another paper, researchers detailed a method for delivering RNA that utilized QDs and siRNA together [35].

### 6.6 Three-Dimensional Printing in CDDS

The capacity to precisely create the systems with numerous materials and the unequaled potential for printing complex physiological structures and organs have garnered attention in both tissue engineering and drug delivery [36]. For improved therapeutic efficacy, modern 3D-printed pharmaceuticals such as drug-eluting implants and printlets (3D-printed tablets) can be tailored to the patient's specific needs in terms of dose, form, size, and release characteristics [37].

## 7. Conclusion

Drugs and fillers are combined to make the dose form. Excipients create a solid state, increase shelf life, and hide an unpleasant flavor. Typical dose forms include solids, semisolids, and liquids, but they all have drawbacks, including volatility in plasma drug levels, the need for frequent dosing, and low patient compliance. Any drug dose form relies on the drug's bioavailability to have any effect. To increase bioavailability, lengthen drug release, and keep medication plasma levels within the therapeutic window with minimal side effects, controlled drug delivery systems have arisen as an alternative to the traditional kind. Improved drug solubility and stability, as well as selective drug distribution at a controllable pace and mechanism to target organs, tissues, and cells, are all possible thanks to controlled drug delivery. There are many controlled drug delivery systems based on dissolution, diffusion, water penetration, and chemical regulation. Additional medical problems (cancer, infections, etc.) can benefit from stimulus-responsive delivery systems because of their ability to both targets and regulate release. Further, regulated targeted delivery can be achieved by developing nanocarriers with intelligent biomaterials and additive manufacturing processes. Microfluidic, 3D-printed devices and CRISPR cas9-based delivery systems coupled with quantum sensing are at the forefront of personalized medicine.

## Abbreviations

IVIVC = In vitro In vivo Co-relationship
$ED_{50}$ = Effective dose in 50% of subjects
$TD_{50}$ = Toxic dose in 50% of subjects
DDS = Drug delivery systems
CRISPR Cas9 = Clustered regularly interspaced short palindromic repeats
siRNA = Small interfering Ribose Nucleic acid

## Informed Consent Statement

Not applicable.

## Conflicts of Interest

The authors declare no conflict of interest.

## Funding

This research received no external funding.

## References


1. Panchagnula R. Transdermal delivery of drugs. *Indian J Pharmacol*. 1997;29:140–56.
2. Rao PR, Diwan PV. Formulation and in vitro evaluation of polymeric films of diltiazem hydrochloride and indomethacin for transdermal administration. *Drug Dev Indian Pharm*. 1998;24:327–36.
3. Rao PR, Diwan PV. Permeability studies of cellulose acetate free films for transdermal use: Influence of plasticizers. *Pharm Acta Helv*. 1997;72:47–51.
4. Thacharodi D, Rap KP. Development and in vitro evaluation of chitosan-based trandermal drug delivery system for the controlled delivery of propranolol hydrochloride. *Biomaterials*. 1995;16:145–8.
5. Krishna R, Pandit JK. Carboxymethylcellulose-sodium based transdermal drug delivery system for propranolol. *J Pharm Pharmacol*. 1996;48:367–70.
6. Bhat M, Shenoy DS, Udupa N, Srinivas CR. Optimization of delivery of betamethasone - dipropionate from skin preparation. *Indian Drugs*. 1995;32:211–4.
7. Darshana HD, Mangal NS, Sudhakar GD. Design and evaluation of an extended release tables of prochlorperazine maleate. *Indian Drugs*, 2000; 38: 69-74.
8. Ravi kumar NMV, Pranita S, Dutta PK. Effect of swelling on chitosan-amine oxide gel in extended release of drug. *Indian Drugs*, 1999; 36: 393-98.
9. Jeganath. S, Asha. D, Sathesh Kumar. S, Keerthi S Nair, Senthil Kumaran. K. Oral Controlled Drug Delivery System – A Review. *Research J. Pharm. and Tech*, 2018; 11(2):797-804. doi: 10.5958/0974-360X.2018.00151.8.
10. Vyas SP, Khar RK. Controlled drug delivery: Concepts and Advances. 1st ed. Vallabh prakashan; 2002; 156-189.
11. Chien. YW. Novel drug delivery system. Volume 50.
12. Allen LV, Popvich GN, Ansel HC. Ansel's Pharmaceutical dosage form and drug delivery system. 8th ed. 2004; 260-263.
13. Patrick JS. Martin's Physical Pharmacy and Pharmaceutical Sciences. 3rd ed. Varghese Publishing House. Bombay: 1991; 512-519.
14. Kar RK, Mohapatra S, Barik BB. Design and characterization of controlled release matrix tablets of Zidovudin. *Asian J Pharm Cli Res*. 2009; 2:54-6
15. Lachaman L, Liberman HA, Kanig JL.The theory and practice of industrial pharmacy. 3rd ed. Bombay: Varghese publishing house 1987.
16. Jain NK. Controlled and novel drug delivery. *CBS publisher and distribution*. 1997; 1-25.
17. Venkataraman DSN, Chester A, Kliener L. An overview of controlled release system. Handbook of pharmaceutical controlled release technology. *Marcel Dekker Inc*. 2000; 1-30.
18. Modi Kushal, Modi Monali, Mishra Durgavati, Panchal Mittal, Sorathiya Umesh, Shelat Pragna. Oral controlled release drug delivery system: An overview. *Int. Res. J. Pharm*. 2013; 4(3):70-76.
19. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics: Pharmacokinetics. 2nd ed. Vallabh Prakashan, Delhi: 2009; 399-401.
20. Hardenia A., Maheshwari N., Hardenia S.S., Dwivedi S.K., Maheshwari R., Tekade R.K. Basic Fundamentals of Drug Delivery. Elsevier; Amsterdam, The Netherlands: 2019. Scientific rationale for designing controlled drug delivery systems; pp. 1–28.
21. Fenton O.S., Olafson K.N., Pillai P.S., Mitchell M.J., Langer R. Advances in biomaterials for drug delivery. *Adv. Mater*. 2018;30:1705328. doi: 10.1002/adma.201705328.
22. Singh A.P., Biswas A., Shukla A., Maiti P. Targeted therapy in chronic diseases using nanomaterial-based drug delivery vehicles. *Signal Transduct. Target. Ther*. 2019;4:1–21. doi: 10.1038/s41392-019-0068-3.
23. Mitragotri S., Burke P.A., Langer R. Overcoming the challenges in administering biopharmaceuticals: Formulation and delivery strategies. *Nat. Rev. Drug Discov*. 2014;13:655–672. doi: 10.1038/nrd4363.
24. Bartucci R., Paramanandana A., Boersma Y.L., Olinga P., Salvati A. Comparative study of nanoparticle uptake and impact in murine lung, liver and kidney tissue slices. *Nanotoxicology*. 2020;14:847–865. doi: 10.1080/17435390.2020.1771785.
25. Lu L., Qi S., Chen Y., Luo H., Huang S., Yu X., Luo Q., Zhang Z. Targeted immunomodulation of inflammatory monocytes across the blood-brain barrier by curcumin-loaded nanoparticles delays the progression of experimental autoimmune encephalomyelitis. *Biomaterials*. 2020;245:119987. doi: 10.1016/j.biomaterials.2020.119987.
26. Vallet-Regí M., Colilla M., Izquierdo-Barba I., Manzano M. Mesoporous silica nanoparticles for drug delivery: *Current insights. Molecules*. 2018;23:47. doi: 10.3390/molecules23010047.
27. Hassan S., Zhang Y.S. Chapter 10—Microfluidic technologies for local drug delivery. In: Santos H.A., Liu D., Zhang H., editors. Microfluidics for Pharmaceutical Applications. William Andrew Publishing; Amsterdam, The Netherlands: 2019. pp. 281–305.
28. Srivastava A., Yadav T., Sharma S., Nayak A., Kumari A.A., Mishra N. Polymers in drug delivery. *J. Biosci. Med*. 2015;4:69–84. doi: 10.4236/jbm.2016.41009.
29. Mogoşanu G.D., Grumezescu A.M., Bejenaru L.E., Bejenaru C. Chapter 8—Natural and synthetic polymers for drug delivery and targeting. In: Grumezescu A.M., editor. Nanobiomaterials in Drug Delivery. William Andrew Publishing; Amsterdam, The Netherlands: 2016. pp. 229–284.
30. Simutis K., Stonyte G., Mažutis L. Chapter 12—Antibody discovery using microfluidic systems. In: Santos H.A., Liu D., Zhang H., editors. Microfluidics for Pharmaceutical Applications. William Andrew

Publishing; Amsterdam, The Netherlands: 2019. pp. 337–351.
31. Chen R., Sun Z., Chen D. Chapter 11—Droplet-based microfluidics for cell encapsulation and delivery. In: Santos H.A., Liu D., Zhang H., editors. Microfluidics for Pharmaceutical Applications. William Andrew Publishing; Amsterdam, The Netherlands: 2019. pp. 307–335.
32. Wei T., Cheng Q., Min Y.-L., Olson E.N., Siegwart D.J. Systemic nanoparticle delivery of CRISPR-Cas9 ribonucleoproteins for effective tissue specific genome editing. *Nat. Commun*. 2020;11:3232. doi: 10.1038/s41467-020-17029-3.
33. Deng Y., Zhang X., Shen H., He Q., Wu Z., Liao W., Yuan M. Application of the Nano-Drug Delivery System in Treatment of Cardiovascular Diseases. *Front. Bioeng. Biotechnol*. 2020;7:489. doi: 10.3389/fbioe.2019.00489.
34. Subham Jain N., Preeti S., Amit B.P. Application of Quantum Dots in Drug Delivery. *Nanosci. Nanotechnol. Asia*. 2021;11:1–16. doi: 10.2174/2210681211666210211092823.
35. Natarajan J.V., Nugraha C., Ng X.W., Venkatraman S. Sustained-release from nanocarriers: A review. *J. Control. Release*. 2014;193:122–138. doi: 10.1016/j.jconrel.2014.05.029.
36. Beg S., Almalki W.H., Malik A., Farhan M., Aatif M., Alharbi K.S., Alruwaili N.K., Alrobaian M., Tarique M., Rahman M. 3D printing for drug delivery and biomedical applications. *Drug Discov. Today*. 2020;25:1668–1681. doi: 10.1016/j.drudis.2020.07.007.
37. Trenfield S.J., Awad A., Madla C.M., Hatton G.B., Firth J., Goyanes A., Gaisford S., Basit A.W. Shaping the future: Recent advances of 3D printing in drug delivery and healthcare. *Expert Opin. Drug Deliv.* 2019;16:1081–1094. doi: 10.1080/17425247.2019.1660318.
38. Chamundeeswari M., Jeslin J., Verma M.L. Nanocarriers for drug delivery applications. *Environ. Chem. Lett*. 2019;17:849–865. doi: 10.1007/s10311-018-00841-1.
39. Yadav K.S., Mishra D.K., Deshpande A., Pethe A.M. Chapter 7—Levels of Drug Targeting. In: Tekade R.K., editor. Basic Fundamentals of Drug Delivery. Academic Press; Cambridge, MA, USA: 2019. pp. 269–305.
40. Naz F., Siddique Y.H.J.C., Targets N.D.-D. Nanotechnology: Its application in treating neurodegenerative diseases. CNS Neurol. Disord. *Drug Targets*. 2021;20:34–53. doi: 10.2174/1871527319666200916121515.
41. Attia M.F., Anton N., Wallyn J., Omran Z., Vandamme T.F. An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites. *J. Pharm. Pharmacol.* 2019;71:1185–1198. doi: 10.1111/jphp.13098.
42. Shah A., Aftab S., Nisar J., Ashiq M.N., Iftikhar F.J. Nanocarriers for targeted drug delivery. *J. Drug Deliv. Sci. Technol*. 2021;13:102426. doi: 10.1016/j.jddst.2021.102426.
43. Adepu S, Ramakrishna S. Controlled Drug Delivery Systems: Current Status and Future Directions. *Molecules*. 2021 Sep 29;26(19):5905. doi: 10.3390/molecules26195905.

Copyright (c) 2021 The copyright to the submitted manuscript is held by the Author, who grants the Clinical Medicine and Health Research Journal a nonexclusive license to use, reproduce, and distribute the work, including for commercial purposes.

This work is licensed under a Creative Commons Attribution 4.0 International License