Awesh K. Yadav · Keerti Jain *Editors*

Novel Carrier Systems for Targeted and Controlled Drug Delivery

Springer

Novel Carrier Systems for Targeted and Controlled Drug Delivery

Awesh K. Yadav • Keerti Jain
Editors

Novel Carrier Systems for Targeted and Controlled Drug Delivery

Springer

Editors
Awesh K. Yadav
Department of Pharmaceutics
National Institute of Pharmaceutical
Education Research, Raebareli
Lucknow, Uttar Pradesh, India

Keerti Jain
Department of Pharmaceutics
National Institute of Pharmaceutical
Education Research, Raebareli
Lucknow, Uttar Pradesh, India

ISBN 978-981-97-4969-0 ISBN 978-981-97-4970-6 (eBook)
https://doi.org/10.1007/978-981-97-4970-6

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

Novel Carrier Systems for Targeted and Controlled Drug Delivery refers to strategies and the development of novel delivery vehicles that can be administered safely to effectively deliver therapeutics at a controlled rate to the desired site in the body while ensuring minimum to nil toxicity or side effects.

Various methods have been used to construct nanocarriers to deliver the encapsulated drug to the cancer cells. These nanocarriers alter the anticancer drug accumulation and distribution thus producing the best possible therapeutic outcomes. Nano-drug delivery by various drug delivery systems has emerged as a commanding technology for the treatment of various diseases.

Therapeutic drugs have many limitations and low concentrations of therapeutics reach the target organ/cells. Moreover, most of the techniques used in the treatment of various disease are not specific to target cell/organs. To overcome such limitations, researchers are exploring various target-specific novel drug carriers. This book contains 19 chapters including Chapter 1: Influence of drug properties and routes of drug administration on design of sustained and controlled release systems; Chapter 2 : Polymeric materials in controlled drug delivery; Chapter 3: Biopharmaceutics and pharmacokinetic aspects of peroral controlled drug delivery systems; Chapter 4: Parenteral drug delivery; Chapter 5: Transdermal drug delivery system; Chapter 6: Implantable Drug Delivery system; Chapter 7: Proteins/peptides drug delivery system; Chapter 8: Controlled release formulations for alternate routes of administration; Chapter 9 : Regulatory approval pathways involved in controlled release formulations; Chapter 10: Role of controlled release in veterinary formulations; Chapter 11: Fundamentals of targeted drug delivery; Chapter 12: Chemical drug delivery system; Chapter 13: Targeted brain delivery of therapeutics; Chapter 14: Targeted tumour delivery; Chapter 15: Colloidal drug delivery systems: (a) Liposomes and niosomes (b) Solid lipid nanoparticles and nanostructured lipid carriers (c) Polymeric nanoparticles – PLGA, chitosan, albumin, gelatin, alginate, etc. (d) Carbon nanotubes; Chapter 16: Overview of specialized drug delivery systems: transfersomes, ethosomes, layersomes, bilosomes, emulsomes, virosomes, cubosomes, aquasomes, pharmacosomes, dendrimers, polymeric micelles and resealed erythrocytes; Chapter 17: Stimuli-responsive drug delivery systems: magnetically, thermal and pH-assisted drug delivery system; Chapter 18: Theranostics application of controlled release drug delivery systems; Chapter 19: Miscellaneous

targeting approaches: fundamentals of gene delivery, overview of colon, liver, macrophage, mitochondrial and M cells targeting.

Each chapter is an attempt to discuss various aspects of the development of novel and controlled drug delivery systems development, current status, and future prospects of the same. Hope the book shall be a useful compilation to undergraduate, postgraduate pharmacy students and researchers working in the drug delivery field, research and development and National Research Institutes. We are thankful to our research teams that includes Farhan Mazahir, Paul Gajanan Balaji, Amit kumar, Md Imtiyaz alam and Shashi Kashyap (Dr. Awesh K. Yadav) and Parth Patel, Anchal Pathak, Manisha Patel, Gijith KM and Sofiya Tarannum (Dr. Keerti Jain). The inputs and support from them helped us a lot in bringing the book to its present shape. We thankfully acknowledge the support of our respective family who assisted us to their fullest. I (Dr. Awesh Yadav) place on record the motivation of my father and mother, my wife Archana, my daughter, doorva and my son, darsh during the preparation of this book. I (Dr. Keerti Jain) wish to acknowledge the support provided by my familty particularly my husband, Vineet K. Jain, my dear son, Kritansh, my father, mother, sister and brother, Atin Jain. We are also thankful to Springer Nature publisher for their interest and support in quality printing of the book. We realize that feedback, suggestions and inputs from teachers, researchers and students shall help to improve the next edition of the book.

Lucknow, Uttar Pradesh, India — Awesh K. Yadav
Lucknow, Uttar Pradesh, India — Keerti Jain

Contents

Editors and Contributors

About the Editors

Awesh K. Yadav is currently working as Assistant Professor of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER)—India. Dr. Yadav has completed his B. Pharm, M. Pharm and Ph.D. degree from Dr. Hari Singh Gour University, Sagar (MP), India. Dr. Yadav have about 16 Years of experience of Industry as well academic. Dr. Yadav served as Principal at Bhagyoday Tirth Pharmacy College, Sagar (MP), India. Earlier, he served as Assistant Manager in R&D (Formulation) at Ipca Laboratories Limited, Mumbai, India. He has also worked as Research Scientist at Himalaya Drug Company Bangalore, India, and as a Research Assistant at Sun Pharm Advanced Research Centre (SPARC), Vadodara (GJ). Dr. Yadav completed three research projects funded by SERB, New Delhi; DBT, New Delhi and MPCST Bhopal. His research interest is in drug delivery and drug targeting using various drug delivery systems and ligands, i.e. nanoparticles, nanodiamonds, fullerenes, etc.

He has been conferred with various prestigious awards, notably, the Outstanding Teacher Award by APTI MP State Branch and the Best Cited Paper Award by the International Journal of Pharmaceutics (Elsevier Publication). He has served as a reviewer for several international journals, including the *International Journal of Pharmaceutics* and the *International Journal of Biological Macromolecules*, *International Journal of Nanomedicine*, etc.

He has more than 100, i.e. 58 research articles, many review articles in peer-reviewed international journals, 34 book chapters in books from national and international publishers and authored or co-authored and 6 books in national and international publishers. He has also filled three patents. He is a member of many international scientific societies and organizations importantly, Association of Pharmaceutical Teachers of India (APTI), Society of Ethnopharmacology, Society of Pharmaceutical Education and Research, India.

Keerti Jain Assistant Professor, Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER)—Raebareli, earned her M. Pharm. and Doctorate degree from the Department of Pharmaceutical Sciences, Dr. H. S. Gour Central University, Sagar. She previously worked as Associate

Professor in ISF College of Pharmacy, Moga, India, and as Assistant Professor in Delhi Pharmaceutical Sciences and Research University (DPSRU), New Delhi. Dr. Jain did her Post Doctorate from M. S. University of Vadodara, India, as SERB-National Post-Doctoral Fellow. She has about 15 years of research experience on nanomedicine-based drug delivery systems. Dr. Jain has supervised M. Pharm. and Pharm. D. students for their research works which have been published in peer reviewed international journals with good impact factor. Dr. Jain has filed six patents from her innovative research and received funding for research projects from ICMR and SERB, New Delhi. She has edited books with reputed international publishers and contributed many chapters in international books.

She has been awarded with various research fellowships including SERB-NPDF, CSIR-SRF, UGC-JRF, and awarded with many awards for her research work including Pharmaceutical Science Alumni Award-2006, Most Innovative Idea Award in LUFTHANSA impact week and prestigious ICMR—Shakuntala Amir Chand Prize for the year 2019. She has been invited to present her research work at several national and international conferences and enlisted among World's Top 2% Scientists, consecutively for four years from 2020 and 2023 in the field of Pharmacology and Pharmacy, a list created by Stanford University, USA.

Contributors

Wasim Akram Amity Institute of Pharmacy, Amity University Madhya Pradesh, Gwalior, Madhya Pradesh, India

Md Imtiyaz Alam Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER) Raebareli, Lucknow, Uttar Pradesh, India

National Institute of Pharmaceutical Education and Research, Raebareli, Lucknow, Uttar Pradesh, India

Archana Bagre Faculty of Pharmacy, Jagran Lake City University, Bhopal, Madhya Pradesh, India

Lakshmi Narain College of Pharmacy, Karchuri Nagar, Bhopal, MP, India

Shalini Bajaj Faculty of Pharmacy, Jagran Lake City University, Bhopal, Madhya Pradesh, India

Department of Pharmaceutical Chemistry, Truba Institute of Pharmacy, Bhopal, India

Anjali Bisht Department of Pharmaceutical Quality Assurance, ISF College of Pharmacy, Moga, Punjab, India

Kanak Chahar Department of Pharmaceutical Quality Assurance, ISF College of Pharmacy, Moga, Punjab, India

Abhay Singh Chauhan Medical College of Wisconsin, Milwaukee, WI, USA

H. Chaurasiys Quantum School of Health Sciences, Quantum University, Roorkee, Uttarakhand, India

Pranali Chimaniya Arihant School of Pharmacy and Bio Research Institute, Adalaj, Ahmedabad, India

Vinod Dhote Truba Institute of Pharmacy, Bhopal, Madhya Pradesh, India

Sonal Dixit Ravishankar College of Pharmacy, Bhopal, Madhya Pradesh, India

Avinash Dubey Department of Pharmaceutical Quality Assurance, ISF College of Pharmacy, Moga, Punjab, India

Qingping Feng Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada

Ashish Garg Guru Ramdas Khalsa Institute of Science and Technology (Pharmacy), Jabalpur, Madhya Pradesh, India

Rohit Garg Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research-Raebareli, Lucknow, Uttar Pradesh, India

Shweta Garg Sri Ram Institute of Technology-Pharmacy, Jabalpur, Madhya Pradesh, India

Sweta Garg Guru Ramdas Khalsa Institute of Science and Technology (Pharmacy), Jabalpur, Madhya Pradesh, India

Department of Pharmaceutical Chemistry, Shri Ram Institute of Pharmacy, Jabalpur, Madhya Pradesh, India

Rupesh Gautam Indore Institute of Pharmacy, IIST Campus, Indore, Madhya Pradesh, India

Neelam Gupta Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research-Raebareli, Transit Campus Lucknow, Uttar Pradesh, India

Ekta Gurnany Arihant School of Pharmacy and Bio Research Institute, Adalaj, Ahmedabad, India

Tanweer Haider Amity Institute of Pharmacy, Amity University Madhya Pradesh, Gwalior, Madhya Pradesh, India

Alok Pal Jain Sir Atma Ram Institute of Pharmacy and Technology, Jabalpur, Madhya Pradesh, India

Atul Jain Delhi Institute of Pharmaceutical Sciences and Research, Delhi Pharmaceutical Sciences and Research University, New Delhi, India

Deepti Jain School of Pharmaceutical Sciences, RGPV, Bhopal, Madhya Pradesh, India

G. Jain Department of Pharmacy, Shri G. S. Institute of Technology and Science, Indore, Madhya Pradesh, India

Keerti Jain Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Raebareli, Lucknow, Uttar Pradesh, India

Sunil K. Jain Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University) Koni, Bilaspur, Chhattisgarh, India

Surendra K. Jain Truba Institute of Pharmacy, Bhopal, Madhya Pradesh, India

Anchal Karwal National Institute of Pharmaceutical Education and Research, Raebareli, Lucknow, Uttar Pradesh, India

Rameshroo Kewat Nanomedicine and Bioengineering Research Laboratory, Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh, India

Satyam Khare Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India

Aristide Laurel Mokale Kognou Department of Biology, Lakehead University, Thunder Bay, ON, Canada

Amit Kumar Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER) Raebareli, Lucknow, Uttar Pradesh, India

Amrish Kumar Charak School of Pharmacy, Chaudhary Charan Singh University, Meerut, Uttar Pradesh, India

Lakshmi Kumari Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India

Manish Kumar Department of Pharmacy, Madhav University, Pindwara, Rajasthan, India

Shweta Kumar Department of General Medicine, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India

Balak Das Kurmi Department of Pharmaceutical Quality Assurance, ISF College of Pharmacy, Moga, Punjab, India

Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India

Kashid Saurabh Machhindra Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Raebareli, Lucknow, Uttar Pradesh, India

National Institute of Pharmaceutical Education and Research, Raebareli, Lucknow, Uttar Pradesh, India

Akanksha Malaiya Nanomedicine and Bioengineering Research Laboratory, Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh, India

Rahul Maurya National Ayurveda Research Institute for Panchakarma, CCRAS, Ministry of AYUSH, Govt. of India, Cheruthuruthy, Thrissur, Kerala, India

Rashmi Maurya Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India

Farhan Mazahir Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research-Raebareli, Lucknow, Uttar Pradesh, India

Dinesh K. Mishra Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University) Koni, Bilaspur, Chhattisgarh, India

Lopamudra Mishra Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India

Neeraj Mishra Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University of Madhya Pradesh (AUMP), Gwalior, Madhya Pradesh, India

Amity Institute of Pharmacy, Amity University Madhya Pradesh, Gwalior, Madhya Pradesh, India

Puja Nayak Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India

Rishi Paliwal Nanomedicine and Bioengineering Research Laboratory, Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh, India

Shivani Rai Paliwal Nanomedicine and Bioengineering Research Laboratory, Department of Pharmacy, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh, India

Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India

Dheeraj Pandey Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research-Raebareli, Transit Campus Lucknow, Uttar Pradesh, India

Prakash Pandey Guru Ramdas Khalsa Institute of Science and Technology (Pharmacy), Jabalpur, Madhya Pradesh, India

Sharad Prakash Pandey Department of Pharmacy, Shri G. S. Institute of Technology and Science, Indore, Madhya Pradesh, India

Shikha Pandey Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India

Vikas Pandey Amity Institute of Pharmacy, Amity University Madhya Pradesh, Gwalior, Madhya Pradesh, India

Preeti Patel Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Moga, Punjab, India

Rajesh Singh Pawar Faculty of Pharmacy, Jagran Lake City University, Bhopal, Madhya Pradesh, India

Gopal Rai Guru Ramdas Khalsa Institute of Science and Technology (Pharmacy), Jabalpur, Madhya Pradesh, India

Khyati Saini Faculty of Pharmacy, SoPPHI, DIT University, Dehradun, Uttarakhand, India

Abha Sharma Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research-Raebareli, Transit Campus Lucknow, Uttar Pradesh, India

Kangkan Sharma Faculty of Pharmacy, SoPPHI, DIT University, Dehradun, Uttarakhand, India

Rajeev Sharma Amity Institute of Pharmacy, Amity University Madhya Pradesh, Gwalior, Madhya Pradesh, India

Shikha Sharma Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India

Teenu Sharma Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India

Yash Sharma Department of Pharmaceutical Quality Assurance, ISF College of Pharmacy, Moga, Punjab, India

Satish Shilpi Faculty of Pharmacy, SoPPHI, DIT University, Dehradun, Uttarakhand, India

Ajay Kumar Shukla Institute of Pharmacy, Dr. Rammanohar Lohia Avadh University, Ayodhya, Uttar Pradesh, India

T. Shukla Institute of Pharmaceutical Sciences, SAGE University, Indore, Madhya Pradesh, India

Vishal Singh Guru Ramdas Khalsa Institute of Science and Technology (Pharmacy), Jabalpur, Madhya Pradesh, India

Murari Lal Soni Quality Assurance Laboratory, M.P. Council of Science & Technology, Bhopal, Madhya Pradesh, India

S. Soni Department of Pharmacy, Shri G. S. Institute of Technology and Science, Indore, Madhya Pradesh, India

A. Thakar Department of Pharmacy, Shri G. S. Institute of Technology and Science, Indore, Madhya Pradesh, India

S. Upadhyay Department of Pharmacy, Shri G. S. Institute of Technology and Science, Indore, Madhya Pradesh, India

Abhinav Vashishat Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India

Akash Vikal Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India

Awesh K. Yadav Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Raebareli, Lucknow, Uttar Pradesh, India

National Institute of Pharmaceutical Education and Research, Raebareli, Lucknow, Uttar Pradesh, India

Vimal Kumar Yadav Institute of Pharmacy, Dr. Rammanohar Lohia Avadh University, Ayodhya, Uttar Pradesh, India

Influence of Drug Properties and Routes of Drug Administration on Design of Sustained and Controlled Release Systems

Amrish Kumar, Sunil K. Jain, Dinesh K. Mishra, and Rupesh Gautam

Abbreviations

API	Active pharmaceutical ingredient
ATRA	All-trans retinoic acid
BSA	Bovine serum albumin
CODAS	Chronotherapeutic Oral Drug Absorption System
CRDDS	Controlled release drug delivery system
CRS	Controlled release system
CYP	Cytochrome P
DDAVP	Desmopressin
DPP-IV	Dipeptidyl peptidase-IV
EVA	Ethylene-vinyl acetate
HPMC	Hydroxy propyl methyl cellulose
IV	Intravenous
IM	Intramuscular
IUC	Intrauterine contraception
IUS	Intrauterine system
IVR	Intravaginal ring
MCC	Microcrystalline cellulose

A. Kumar
Charak School of Pharmacy, Chaudhary Charan Singh University, Meerut, Uttar Pradesh, India

S. K. Jain · D. K. Mishra (✉)
Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University) Koni, Bilaspur, Chhattisgarh, India
e-mail: dinesh.mishra79@ggu.ac.in

R. Gautam
Indore Institute of Pharmacy, IIST Campus, Indore, Madhya Pradesh, India

A. K. Yadav, K. Jain (eds.), *Novel Carrier Systems for Targeted and Controlled Drug Delivery*, https://doi.org/10.1007/978-981-97-4970-6_1

MEC	Minimum effective concentration
MTC	Minimum toxic concentration
OCAS	Oral Controlled Absorption System
OROS	Osmotic-Controlled Release Oral Delivery System
OTC	Over the counter
OVA	Ovalbumin
PD	Parkinsonism disease
PEG	Polyethylene glycol
PLA	Polylactic acid
PVA	Polyvinyl alcohol
PVP	Polyvinyl pyrrolidone
SR	Sustained release
UDP	Uridine diphosphate

1 Introduction

To efficiently approach the site of action after administration, every therapeutic molecule requires a capable delivery system. In case of freshly developed new chemical entity for therapeutic purpose, the selection and development of suitable dosage form are very critical to get the maximal efficacy for the treatment of target disease. When we opt for traditional drug delivery systems, they generally offer instant release of incorporated drug without any control on the release rate. On the other hand, sustained release and controlled release delivery systems are out-and-out influential for their inimitable benefits, e.g., reduction in dosing frequency, superior bioavailability of incorporated therapeutics, extension of the duration of effective blood-plasma levels, minimal peak-to-trough concentration fluctuation, and reduced side effects associated with conventionally developed formulations.

Still the dominancy of conventional formulations in terms of consumption by the patients is well evident for both, i.e., over the counter medicines as well as for prescriptional medicines. At the same time, a tremendous uplift in the utilization of sustained or controlled release systems has been reported in past decade owing to better efficiency and safety profiles [1]. Considering the increasing demand and their effectiveness on therapeutic front, sustained/controlled delivery systems are in demand nowadays. However, the formulator must compare the pros and cons with conventional system while developing sustained/controlled release delivery system for justifying the appropriate reasons and purpose to opt the comparatively much expensive delivery system.

For the designing of any formulation, a formulator must consider the several factors, i.e., physicochemical properties of the drug, route of drug administration, and pharmacological and biological effects. The safe and effective delivery of medication depends not only on the physicochemical features of the drug but also on how the patient's body reacts to the medication. Pharmacokinetics is the study of the

physiological mechanisms that impact a drug's absorption, distribution, metabolism, and excretion during the biological life of drug.

The role of physicochemical properties of both, i.e., drugs and the excipients, was thoroughly studied as this influences the performance of drug in biological environment. In this, the major properties that hamper the drug activity are solubility, stability, lipophilicity, and molecular interactions. The degree to which a solute may dissolve in a solvent is referred to as its solubility. For a drug absorption by the walls of the intestines, primarily it needs to dissolve at a significantly rapid rate in the biological medium of the body. Because there is often fewer drug content dissolved in water at the absorption site, drug molecules with extremely low aqueous solubility frequently have reduced bioavailability [2].

Drugs having water-soluble concentration of 10 mg/mL are predicted to have impaired bioavailability. Once the medication is ingested, biological fluids in close proximity to a drug particle may affect the medication's stability. Drugs may be subject to metabolic and chemical breakdown, which reduces its efficacy. Drugs with weak acidic stability are able to bypass the acidic stomach when encased with enteric-coated materials, and the GIT drug release will be done at lower rates. Drugs may be resistant to enzymatic breakdown by changing their chemical structure in order to create prodrugs [3].

In summary, it may be suggested that an optimal drug delivery system would provide accurate dosages of a medicine at a set pace to reach the drug level required for managing the ailment. The amount present in the medication will be kept within the therapeutic limits when the drug is released at a zero-order rate for the majority of medicines that clearly correlate concentration and response.

1.1 Concepts and Terminology

To predict the fate of medications after administration, the formulator must be aware of the primary processes through which drug change is conceivable in a biological context.

In the beginning, adsorption of drug from the action site enables compound entrance into the blood stream. After being absorbed, the drug can move across the tissues and intracellular fluids where it is reversibly attached to receptors, and then it may leave the bloodstream. Distribution describes this dispersion. While some medication molecules attach to receptors, others may escape from the receptors and enter the bloodstream once more. Drug metabolization, also known as biochemical alterations or metabolism, can occur in the liver or other tissues as a result of drug particles in the blood stream. The medication and its by-products are then eliminated from the body through feces or urine. Both metabolism and excretion are methods of removing drugs from the body.

Multiple doses must be taken daily in order to attain and sustain optimal therapeutic effective plasma concentrations, which may result in considerable changes in plasma levels. The decrease in drug level below the minimum effective concentration (MEC) or its raising above the maximum safe concentration (MSC) results in

the variations in drug plasma levels. Such may lead to undesirable side effects or a patient who does not receive the anticipated therapeutic benefit.

Although the phrases continuous release and controlled release are commonly used concurrently, they refer to two distinct types of drug delivery systems. Sustained release drug delivery is a way of prolonging the effectiveness of a response by gradually releasing the medication, usually at the cost of a medicine's delayed onset and pharmacological potency. Controlled release dosage forms are developed to disperse the medication at certain release rates within a specific period of time, which is more sophisticated than just prolonging the release rate. Targeted delivery systems are sometimes referred to as controlled delivery systems since they provide spatial control of medicine distribution to a specific location in the body.

1.2 Objective of Controlled/Sustained Release Formulations

CRS is regarded as a delivery system with the objective of therapeutic application of medications at the site of action for a predetermined amount of time at a pre-controlled pace. It is well recognized that the release system formation is mandatory for the proper maintenance of amount of drug in plasma while achieving the necessary therapeutic impact. Studies have demonstrated that the use of CRS has a number of benefits, including better drug exposure control, evaluating drug permeability across the barriers of biological system, assuring that the drug will reach the intended site of action, and preventing early removal of drug compound [4].

The thorough understanding of biological characteristics, including as age, body weight, sex, ethnicity, physiological processes, and pathological condition, that can affect how a medicine is absorbed and removed from the body is another goal of this chapter. For instance, due to their underdeveloped liver function and increased amount of water in the body, newborns must be handled carefully while dosing. Patients who are elderly may experience decreased sensitivity of several receptors, which could result in insensitivity to some medications. It has been discovered that individuals from various ethnic groups react to medications differently. For hypertension Black individuals, beta blockers are preferred to diuretics and calcium channel blockers, but beta blockers are more effective for hypertensive Caucasian patients. By changing the physiological mechanism, pathological alterations may have an impact on the drug's distribution and bioavailability. The clearance of many medications will be impacted by decreased kidney and liver functioning [5].

1.2.1 Merits of Sustained and Controlled Delivery

For a number of reasons, the development of CRS is seen to be an intriguing topic. First, new techniques are now capable of delivering genetically modified products, like as altered amino acid chain, to certain locations of action without triggering the body's immunity or causing them to become biologically inactive [6]. Second, by properly targeting the therapeutic molecule, the dosage for cancer therapies and diseases caused by enzyme deficiencies can be reduced. Many nanomedicines are being developed now, and many of them have a CR profile. These include

formulations based on genetic material, dendrimers, solid lipid nanoparticles, polymeric nanoparticles, carbon nanotubes, and liposomes. To deliver the drug for variety of illnesses, these formulations demonstrated encouraging outcomes [7, 8].

.

1.3 Limitations of Sustained and Controlled Release Dosage Form

The CRS has a number of other drawbacks, including as dosage dumping, toxicity, and greater manufacturing costs. There are certain substantial drawbacks to these delivery methods that must be ignored. One of them is the toxicity that needs to be taken into account when creating CRS. Many medications intended for the sustained or CR recently exhibit possible harm. The dumping of doses is yet another serious issue [9].

For instance, if a single dose of CRS medication is skipped by the cancer patient, it might have serious consequences. In order to insert, implant, or remove many CR-based devices, surgical procedures are required. The surgical procedures are rarely pleasant for patients and can place an additional financial load on the patient. Designing and developing of CRS-based systems can be used strategically in the pharmaceutical sector to extend the unique drug items whose patents get expired [10].

A common situation is changing a medicine formulation that is currently on the market and requires many daily doses to once-a-day dose to maintain command over the generic rivals. Some medications need regulated delivery since fast release dose forms cannot produce the desired pharmacological effect. These involve lipophilic bioactive that require increases in solubility to get satisfactory clinical results, whereas hydrophilic medicines require a softer release and a longer duration of action. Additionally, medications with a short half-life that require regular intake and medications with a non-specific effect that need to be delivered to target areas are some other examples.

1.4 Rationale for the Design of Controlled Release System

Controlled release drug delivery systems (CRDDS) are thought to be fundamentally motivated by the alteration of both pharmacokinetic and pharmacodynamic properties. This can be accomplished in one of two ways: either by utilizing novel drug delivery systems or by changing the drug's molecular structure and/or physiological properties in a way that maximizes its effectiveness while minimizing side effects and treating the disease [11].

Research and studies have typically demonstrated that a drug's pharmacokinetic qualities depend more on the parameters of the delivery mechanism being utilized than they do on the drug itself. The pharmacokinetic and pharmacodynamic profiles of pharmaceuticals which have provided time-based dynamic profiles connecting

the amount of drug and its target, considering it as a necessary process of developing new delivery options [12].

In general, CRS aims at the fulfillment of patients' compliance requirements while ensuring the safety of medications and increased efficacy. Since medications must attain the easy penetration into biological barriers, prevent abrupt waste removal, and be carried to the appropriate targeted site where drug plasma levels must be exceedingly managed throughout timely with the lowest possible dosage frequency in order to achieve those goals [13].

Every drug has a distinct therapeutic plasma concentration (TPC), with lower concentrations resulting in inadequate effectiveness and higher amounts having potentially dangerous adverse effects. Each medicine has a distinct dosage (D) and dosing interval (τ), which distinguishes it from other drugs [4].

The therapeutic efficacy and drug release kinetics are both improved by CRS; as shown in (Fig. 1), an increase in drug levels in the blood is due to stability between the least and most efficacious levels that is known as the effective range. The process by which the product's active ingredient is released is referred to as drug release. Depending on the CRS, the drug release profile, which comprises burst release, lag followed by sudden rupture, zero order, pulsatile, and diffused CR, will be altered (Fig. 2). The zero-order style of release was supplied by ideal CR drug delivery systems. When set in the distributing medium, a majority of preparations released a large amount of the therapeutic ingredient immediately, even before the rate of release of drugs is controlled. In essence, this occurrence is referred to as a "burst release." The burst release phenomenon typically results in a greater initial dose of the medicine being delivered while shortening the lifespan of the delivery device. A release of drug with a well-defined lag time is represented by a pulsatile

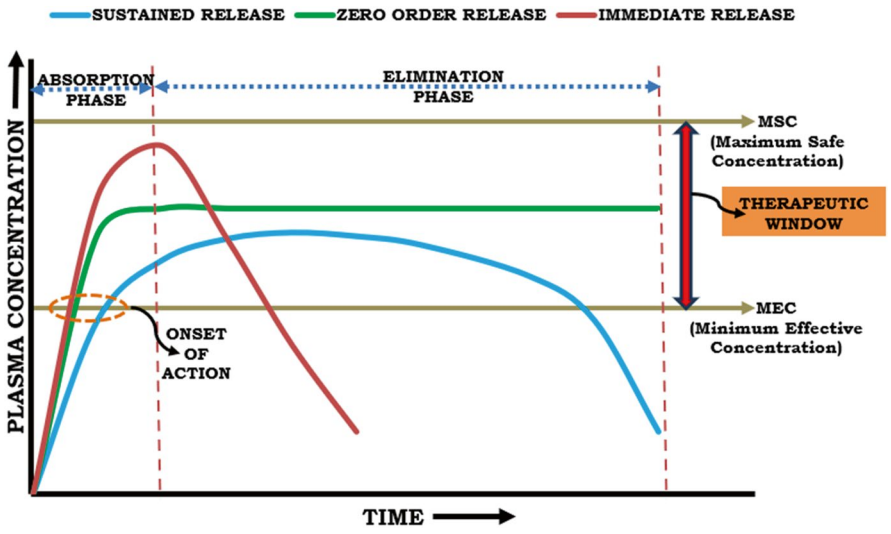

Fig. 1 Plasma drug concentration profile of different delivery systems

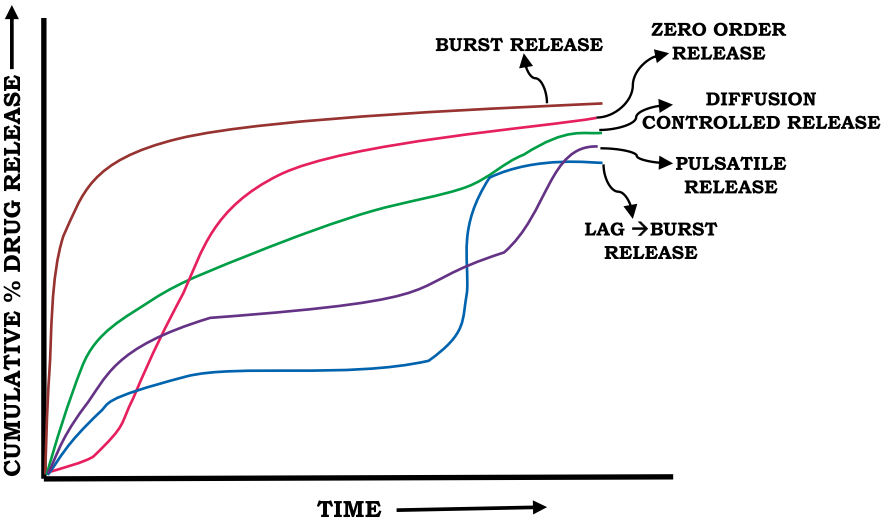

Fig. 2 Plasma profile from different delivery systems

drug release mechanism. It has been established that these systems have advantages over other kinds of systems. The symptoms of several diseased conditions include myocardial infarction, bronchial asthma, hypertension, angina, and rheumatic diseases [14].

The drug molecule that has been dissolved diffuses via the rate-controlling element in a diffusion-controlled drug delivery system. Thus, in such a system, the rate-controlling component is insoluble, nonerodible, and non-degradable. Diffusion is useful in a wide range of controlled drugs administration systems [15]. When a material undergoes from a higher concentration levels to a lower concentration levels, the phenomenon of this movement is known as diffusion mechanism and is also regarded as the primary cause of CRS. Drugs accumulate and subsequently released via this process into a matrix of insoluble polymer of inert water, which is often termed as the reservoir system or, more colloquially, as the polymeric matrix, in the CRS acting by the diffusion mechanism (monolithic systems).

Diffusion CRS can be broadly categorized into four categories depending upon the architecture of the systems and the drug loading technique. There are different forms of diffusion systems, such as monolithic dispersion and monolithic solution, as well as continuous drug source reservoirs and discontinuous drug source reservoirs [16].

The full dose of a medicine enters the general circulation when it is administered intravenously. An intravenous dose of an injection ensures the quick attainment of a higher concentration, which may be necessary for some medications but is not recommended for others and may cause toxicity and side effects. When a medication is taken into its single dose, it keeps the concentration more than the minimal therapeutic concentration for a while, giving the action a finite duration before declining

and having no further therapeutic effect. The medication concentration will exceed the maximal therapeutic concentration if a double dose is given, causing toxicity and undesirable side effects. The release leads to therapeutic concentration stability prolongation within the predetermined range as shown in (Fig. 3) [17].

2 Factors Influencing the Design of Controlled/Sustained Release System

CRS is dependent on their designing procedure on a number of parameters that researchers and formulators need to take into consideration before moving forward with the process of developing CRS-based drugs. The physicochemical characteristics of a medication, including its soluble nature, charge, and partitioning coefficient, as well as its proclivity for protein binding, are among the most critical considerations, since they all perform a significant influence in the development and efficacy of systems. This makes them one of the most important factors [18]. The method by which the medicine is administered is another crucial consideration. The enhancement of the release site and action now makes use of technological ways, which assist the implementation of the correctly functioning. The controlled release system (CRS) is a mechanism or device designed to deliver drugs or therapeutic agents in a controlled and sustained manner over a prolonged period. While CRS offers numerous advantages in drug delivery, certain limitations can affect its performance. These limitations are often associated with physiological factors that influence drug absorption, distribution, and clearance within the body. Some of the

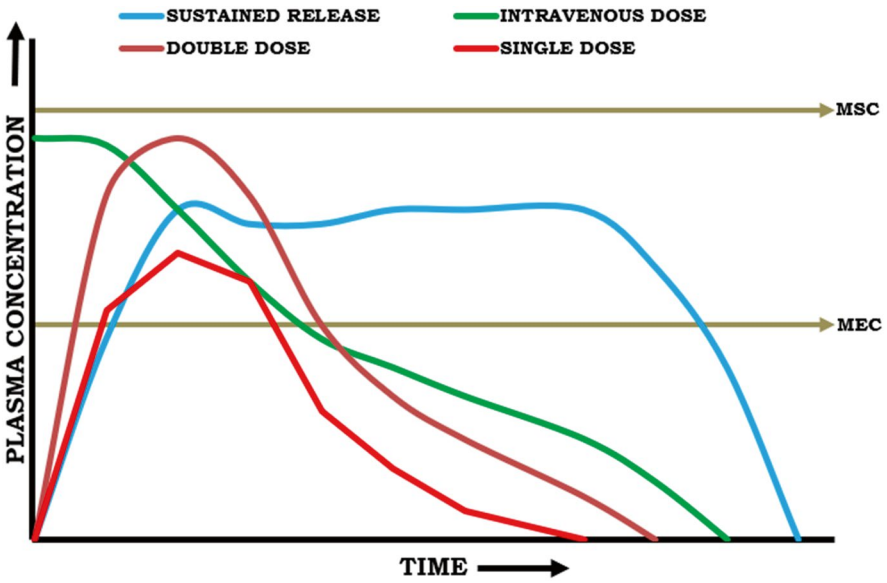

Fig. 3 Plasma profile with different doses/routes

commonly reported limitations include first-pass metabolism, blood supply, the motility of the GIT, and the sequestration mechanism of the small foreign particles [19].

It is vital to increase the proportion of the dose to the maximum at the specific target site of action in order to prevent any potentially negative consequences from occurring. This is something that might be possible to do with the use of locally administered medications, while in other situations, the utilization of carriers might prove to be beneficial. However, as the vast majority of medications have big molecules, they are limited by their impermeability across most surfaces. Because of this, intravascular or intra-arterial administration is the only viable option for delivering these treatments [15, 20].

The anticipated cure, the extent of illness control, and the necessary duration of drug therapy must all be taken into account while creating CRS. These considerations are essential [21]. Furthermore, it was shown that the pathological alterations contributed to the choice of the best drug delivery system designing. When developing the CRS, it may be useful to link clinical symptoms with biochemical indicators of illness, as is the case with specific cancer biomarkers including specific enzymatic expression, lower extracellular pH, and hypoxia. This is the case in the example of the unique tumor biomarkers. It has been demonstrated that several different compounds are capable of producing selective cytotoxicity in hypoxia cells through the process of reductive activation. A few examples of these agents are nitro compounds, quinones, and aromatic N-oxides, such as mitomycin C [22, 23].

The development procedure of CRS has been demonstrated to be impacted by the patient-related factors as well, regardless of whether the patient is fatty or not, mobile or immobile, along with other linked qualities while this remains unaffected by the patients age. For instance, on delivering drug intramuscularly into a mobile patient's body, it is possible that it will behave differently than if it were to be administered subcutaneously into a patient who was bedridden. However, some more elements can be uniquely related with a single patient, in which case variances remain uncontrolled throughout the research phases. On the other hand, other factors are important to be considered during the process of CRS formulation. Our discussion in this chapter is mostly centered on the characteristics of medications and the many ways they might be given to patients, despite the fact that the CR of drug delivery is affected by a wide variety of parameters [15].

The primary subjects of a discussion on the impact of the drug's properties and route of administration on the design of CRS are the activity of the drug in the carrier system, which is also termed as drug release, and both the drug and carrier system activity or their presence at the action site. Initially, it discusses the impact of the drug's physicochemical attributes on the features of its release from the carrier system, whereas the second principle is complex as it highly depends on the drug's pharmacokinetic profile. The features of the drug's release delivery method are what both the basics explain [1].

It is generally agreed that the rate-limiting phase in the administration of pharmaceuticals is the process by which a medication is absorbed across one of the biological membranes of the body, such as the wall of the gastrointestinal tract (GI).

When a CRS is being used, the step that is deemed to be the rate-determining step is not the absorption of the medication but rather the release of the drug from the dosage form. Therefore, rather than absorption, which is a significantly lower rate than the drug's intrinsic absorption rate, bioavailability is determined by the kinetics of drug release [17].

When creating CRS, numerous different methods are utilized, such as dissolving, swelling, diffusing, applying osmotic pressure, ion-exchanging, complexing, and magnetic field application. The relationship that exists between the physiochemical qualities of the medicine and the parameters of the delivery method is what determines the temporal pattern of the drug's release.

3 Physiochemical Properties of Controlled/Sustained Release Systems Influencing Design

The CRS is influenced by a number of physicochemical characteristics as described in Fig. 4.

3.1 Molecular Weight and Diffusion Constant

It has been found that absorption of drugs with lower molecular weights is more quick and complete than those with higher molecular weights. The process of passive diffusion was demonstrated to be responsible for the absorption of around 95% of the pharmacological medicines. One definition of "diffusivity" is "the power of a drug to diffuse within a biological membrane." "Diffusivity" is the term used to describe this capability, which has been proven to be inversely related to the molecule's size [24]. Additionally, drugs that are delivered via sustained release (SR) systems must also be able to diffuse through the biological matrix. When calculating the value of diffusivity, one of the most significant factors that comes into play is the molecular weight of the substances being diffused (D). It has been found that the value of D is connected to features such as the dimensions and contours of the cavities, in addition to the medications themselves. In most cases, the values of the diffusion coefficient for pharmaceuticals with molecular weights ranging from 150 to 400 Da were reported to fall somewhere in the range of 1026–1029 cm^2/s.

On the other hand, the values were found to be extremely low and difficult to quantify for big pharmaceuticals with a molecular weight of more than 500, which is to say that they were less than 10,212 cm^2/s. As a result, it is reasonable to anticipate that medications with high molecular weights will have a very sluggish rate of release from SR devices. In these devices, the release of these medications through the matrix is accomplished by the releasing mechanism [18, 25].

Studies have indicated that medications with larger molecular mass, such as proteins and peptides, are not an ideal choice for oral CRS. This applies to both of these types of molecules. Experiments have also indicated that the maximum molecular weight of 600 Da for medications is developed through passive diffusion for oral

Fig. 4 Physicochemical parameters influencing the formulation and design of sustained/controlled delivery systems

administration. This is the upper limit of the molecular weight range for these drugs. In many polymers, the diffusion coefficient of medications with a molecular weight more than 500 Da is frequently so modest that it is difficult to calculate. This is the case for many types of chemotherapy drugs. Therefore, it is reasonable to anticipate that high molecular weight medications will exhibit extremely sluggish release kinetics in extended release devices that use diffusion across polymeric membrane or matrices as the mechanism for delivering the drug [26].

3.2 Solubility in Aqueous Medium

Due to their high level of solubility in aqueous environments, pH-independent pharmaceuticals become excellent choice for the formulating oral CRS. The minimum solubility limit of pharmaceuticals that are exhibited to be made as CRS has been determined by researchers to be 0.1 mg/mL, and this limit is relatively equivalent to this value. The solubility of a drug is the primary factor that is considered when selecting the appropriate mechanism to be used for CRS. For instance, certain diffusional methods are not appropriate for pharmaceuticals that have a low solubility

in water. The dissolving rate can limit the amount of a drug's absorption that it gets due to its poor solubility profile. Because of this, the device use to control release was unable to exert any influence over the process of absorption; hence, these medications are not considered to be good candidates for such CRS [27]. The biopharmaceutical classification system, also known as BCS, is a technique that makes it easier to determine the relative importance of three parameters that influence oral absorption of medication: solubility, dissolution, and intestinal permeability. According to the BCS, medicines that are placed in class III (high solubility-low permeability) and class IV (low solubility-low permeability) are considered to be poor candidates for being manufactured as a CR dosage form. This is because of the low permeability of the drug [28, 29].

3.3 pH and pKa Values

The pKa values of basic medications range from 7.0 to 11.0, whereas the pKa values of acidic drugs fall somewhere in the range of 3.0 to 7.0. A medication is said to be acidic if the pH affects how it ionizes. For there to be an ideal quantity of absorption, the drugs must be in the unionized form at the required absorption site preferably to the range that varies from 0.1% to 5%. Drugs that are mostly found in their ionized forms are typically considered to be poor choices for developing CRS [30, 31].

3.4 Partition Coefficient

When it reaches different parts of the body, the medicine must be able to pass through a variety of biological matrix so as to get the appropriate therapeutic action. Oral administration of the drug is one method of delivery. It has been demonstrated that these matrixes are generally made up of lipids; hence, it is important to determine the partition coefficient of oil-based medicines as they play crucial role in determining the membrane barrier penetration capacity [15, 32].

It is usual practice to utilize the coefficient of partitioning, denoted by "P," to characterize equilibrium of drug concentration in two phases.

$$P = \frac{\text{The amount of medicinal substance in oil phase}}{\text{The amount of medicinal substance in aqueous phase}} \quad (1)$$

The partition coefficient (P) is calculated using the formula (Eq. 1), where the medicinal substance amount in the oil phase is provided as C_{oil} and the medicinal substance amount in the aqueous phase is given as C_{water}.

If the value of log P is equal to zero i.e., the amount of medicinal substance is equal in both phases, the medicinal substance is said to be lipid-soluble. Likewise, if log $P > 0$, the medicinal substance is said to be lipid-soluble. For instance, diazepam has a log P value of 2.82, and acetohexamide has a log P value of 1.72. If the medicinal substance log $P < 0$, then it is thought to be water soluble. For instance,

acarbose, which has a log *P* value of −6.8, and metformin shows the log P value of −2.6.

3.5 Permeation Ability

The three basic drug characteristics that govern drug penetration by passive diffusion through the intestinal walls are log *P*, expressed lipophilicity, and molecular size [33, 34]. Furthermore, the number of H-bond acceptors and donors on the drug molecule determines the polarity of the therapeutic agent also considered as determining factor for its permeation through the biological barriers.

3.6 The Mechanism Behind Absorption and Its Location

For example, a number of different types of vitamin B aren't ideal choices for the formulating CRS since they are preferably absorbed by carrier-mediated transport. Vitamin B12 is a vitamin that solubilizes in water and is required for a variety of metabolic processes and the avoidance of a variety of medical issues, the most prevalent of which are blood-related illnesses and neuropathies that are related to the spinal cord. When vitamin B12 is consumed in its free (or unbound to proteins) state, it binds to a transporter protein called transcobalamin I or R-binders. Salivary glands in the oral cavity and stomach epithelial cells are both which release this protein. [35]. As the formulators has to control/modify the release rate of the therapeutic agent from CRS, consideration of absorption mechanism and site must kept at the focal point when optimizing the release rate.

3.7 Drug Stability

The existence of physiological fluid in close proximity to a medication molecule may have an impact on the stability of the drug after it has been administered to a patient. It is possible for drugs to undergo chemical degradation owing to metabolic processions as well as degradation due to the enzymatic action depending on its exposure with different biological sites, both of which lead to a reduction in the activity of the drug molecule. Because of the related challenges with bioavailability, it is not possible to develop GI-unstable medicines in form of CRS that are taken orally. For such unstable drugs it is better to utilize an alternative route of administration which provides the better stability of the incorporated drug resulting in better control over the release of drug i.e., topical/transdermal administration. Enteric coating of drugs unstable in gastric pH might bypass the acidic environment of the stomach and instead release the medication in the intestine [36].

Conversely, Gastro-retentive systems might be an effective strategy for the drugs which shows marked instability in intestinal region. Gastro-retentive systems are well capable to prolong the gastric emptying time for maintaining the potency of

incorporated drug in the stomach for better absorption [37, 38]. Modifying the chemical structure of a medication and the process by which it is formed into a prodrug is an additional strategy for preventing the pharmaceuticals from being broken down by enzymes [39, 40].

3.8 Ionization

Many medications are manufactured as weak electrolytes, with the degree of ionization governed mostly by the solution's pKa and pH values. This is because weak electrolytes are more easily dissolved in water. In the scenario of transcellular passive diffusion, the GIT functions as a straightforward barrier of lipophilic properties. In this situation, ionized molecules are thought to be more water soluble and have lower lipid solubility than unionized molecules, which are lipid soluble.

Ionized material => Greater hydrophilicity => Lower transport through biological membranes
Unionized material => Greater lipophilicity => Higher transport through biological membranes

There is evidence that pH levels have an effect on the total partition coefficient of ionized molecules. When it comes to ionized pharmaceuticals, the value of log *P* is determined by the pH of the solution. As a consequence of this, the log distribution coefficient, also known as log *D*, is typically utilized rather than log *P* at various pH values as a method of estimating or predicting the absorptive potential of the drug. When measuring log *D*, it is important to report the values of pH as well. Despite this, it was found that the readings corresponded in a typical way to the determinations that are made at a physiological pH of 7.4 [1, 41]. The log partition coefficient of the drug in the unionized form and at a certain pH is denoted by the notation Log *D*. Log *D* measures how well the drug separates into its components. The relationship between the overall partition coefficient and the distribution coefficient is modelled in the following equation, which is denoted by (2).

$$D = P(1-\alpha) \qquad (2)$$

where, $\propto$ is a variable that represents the degree to which the medication is ionized.

4 Pharmacokinetic Factors Influencing the Design of Controlled/Sustained Release System

When it comes to developing the most effective method of medication administration, pharmacokinetics offers the time course of the interaction between the drug concentration and the target. When examining a drug's pharmacokinetics, the plasma drug concentration lies within the therapeutic window i.e., ranges between the minimum effective concentration (MEC) and the minimum toxic concentration (MTC).

Deviations from this range can cause undesirable side effects or sub-therapeutic effect which prevent the patient from receiving the therapeutic benefits that were intended for them [42]. In order for a drug to be bioavailable, the step that slows down the process the most is absorption; however, in the case of CRS, the step that slows down the process is the release of a drug from its dosage form. CRS is well-known for its capacity to prolong and keep the drug's concentration within its therapeutic range for a longer period of time. This is done in order to increase the drug's exposure to its fullest extent at the site of absorption. It has been demonstrated that well-designed CRS systems exhibit characteristics such as a prolonged/pre-determined residence time that is in line with expectations and controlled drug release mechanisms. In order to design an effective CRS, it is necessary to have in-depth knowledge of the processes of absorption, distribution, metabolism, and elimination of a drug. CRS is essential due to the fact that immediate release dosage forms are unable to produce the desired pharmacological effect. Every pharmacokinetic parameter has a range of values that can be used for the design of a CRS, but once you move outside of that range, it becomes difficult or even impossible to design a CRS. The assumption that the level of drug in blood or body tissue is proportional to the biological activity of the drug will be made throughout the remainder of this discussion [43].

4.1 Absorption

In a CRS, it is necessary to have efficient absorption because the drug releasing rate is the step that is the rate-limiting factor. It is not a good candidate for CRS if a drug is absorbed through active transport, if it is absorbed slowly, or if it is absorbed from a specific region of the GIT. This is because continuous drug release typically results in drug substances that are not absorbed as well as accumulated drug substances. In order to maintain a constant drug levels in the blood, it is necessary for the CRS to release the drug and then absorption of the released drug in an even and consistent manner. For a variety of reasons, including degradation of the drug by solvolysis or metabolism, physical loss, protein bindings, and dose-dependent absorption, the amount of drug that is absorbed from a conventional drug delivery system can be quite low at times [44, 45].

4.2 Distribution

The distribution of drug absorbed into the systemic circulation causes a reduction in the amount of drug which is biologically available for therapeutic action, it is an essential component of the kinetics of drug elimination. Protein binding is the rate-limiting element in the distribution of the medication. This causes a reduction in the free amount of the drug in the blood, which in turn renders the drug inactive in terms of both its distribution and its pharmacological activity. The apparent volume of distribution is a hypothetical volume of the body in which the drug is spread, and it serves as an illustration of how the medication is distributed throughout the body. The apparent volume of distribution has an impact on the concentration of the