Pharmaceutical Sciences and Drug Design
ISSN: 3062-4428
2024, Volume 4, Page No: 26-34

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Galaxy Publication

Advances in Controlled Drug Release Systems: Current Trends and Future Prospects

Kinam Park[1*]

[1]Departments of Biomedical Engineering and Pharmaceutics, Purdue University, West Lafayette, IN 47907, USA.

***E-mail** ✉ kpark@purdue.edu

Received: 04 March 2024; **Revised:** 20 May 2024; **Accepted:** 29 May 2024

ABSTRACT

Controlled-release drug delivery systems regulate the plasma drug concentrations through predefined release patterns over a specified period. The release rate directly affects drug absorption and systemic levels. These formulations help in reducing the frequency of daily dosing. This review examines the essential criteria, advantages, characteristics, and strategies for the development of controlled-release formulations to enhance drug delivery. These systems ensure the administration of the drug at a controlled rate for a fixed period, either locally or systemically. By utilizing drug-encapsulating technologies, controlled-release methods offer several advantages over conventional approaches, such as customized release rates, drug stability, and improved patient compliance. They maintain steady plasma drug levels within the therapeutic window, reducing side effects and dosing frequency. Oral sustained-release formulations enhance drug utilization by optimizing pharmacokinetics, minimizing adverse effects, and ensuring faster recovery or management of the condition. Advances in drug delivery technology have transformed medication administration, enabling multiple and single-dose regimens. Oral controlled-release drug delivery (CRDD) ensures consistent drug release with predictable kinetics over a set period, targeting specific gastrointestinal regions for localized or systemic effects. This approach reduces the frequency of dosing while maintaining stable drug concentrations in the bloodstream, thereby enhancing therapeutic efficacy.

Keywords: Dosing frequency, Controlled release, Drug concentration, Zero-order, Plasma concentration

How to Cite This Article: Park K. Advances in Controlled Drug Release Systems: Current Trends and Future Prospects. Pharm Sci Drug Des. 2024;4:26-34. https://doi.org/10.51847/m708A2Qw3b

Introduction

Controlled drug delivery systems help maintain optimal drug levels but also present challenges such as potential toxicity, undesirable by-products, the need for surgical procedures, patient discomfort, and side effects [1]. Although these systems tend to be more costly than conventional drugs, an ideal controlled-release system should be stable, biocompatible, efficient, user-friendly, and safe while ensuring prolonged drug availability.

The effectiveness of a polymer-based delivery system depends on balancing swelling, erosion, and dissolution. However, maintaining a consistent gel layer for extended drug release is challenging due to complex polymer dynamics, including relaxation, disentanglement, and erosion [2, 3]. By ensuring steady drug concentrations at the absorption site, these systems help minimize side effects and reduce dosing frequency [4, 5].

Sustained-release formulations are designed to either extend the duration of drug action, reduce the required dose, or improve localization at the target site. While these systems prolong drug administration, controlled-release formulations provide precise therapeutic regulation. Increasing research in this field has led to advancements aimed at enhancing patient adherence and minimizing drug misuse [1, 6].

The development of once-daily oral formulations has introduced new challenges related to testing and clinical evaluation. This review examines extended-release products, their theoretical foundations, formulation techniques, and existing obstacles in the field [1].

Historically, buffers or alkaline compounds have been used in oral formulations of acidic drugs to enhance dissolution and absorption [7]. However, there is still no widely adopted approach for a simple, compressible, monolithic controlled-release system with zero-order kinetics that minimizes dependence on gastrointestinal conditions and pH solubility [8].

This paper discusses key aspects of controlled-release formulations, including essential design requirements, advantages, properties, and formulation strategies, focusing on delivering drugs at a consistent rate for a defined period, either locally or systemically.

Results and Discussion

Controlled-release dosage forms

According to the United States Pharmacopeia (USP), modified-release dosage forms are designed to alter drug-release profiles, offering therapeutic advantages or improved convenience over standard formulations [9]. Extended-release drugs reduce dosing frequency, often requiring half as many doses as immediate-release forms, thereby enhancing patient adherence. Most commercially available extended-release oral formulations utilize one of two primary technologies: matrix systems (hydrophilic, hydrophobic, or inert) and reservoir systems (coated formulations). These technologies regulate drug release through diffusion, erosion, or osmotic mechanisms, in which a polymer membrane surrounds the drug core to control its release rate [10, 11].

Role of polymers in controlled drug delivery

Polymers are essential components of drug delivery systems, acting as binders in tablets and modifying viscosity in liquid formulations, suspensions, and emulsions [12]. Additionally, they function as protective film coatings to mask taste, enhance drug stability, and modulate release characteristics. In controlled drug delivery (CDD), polymers are combined with active pharmaceutical ingredients to achieve a precise and consistent release pattern. This controlled mechanism helps maintain stable drug levels, minimizing the risks of fluctuations that could lead to under- or overdosing **(Figure 1)** [4, 13].

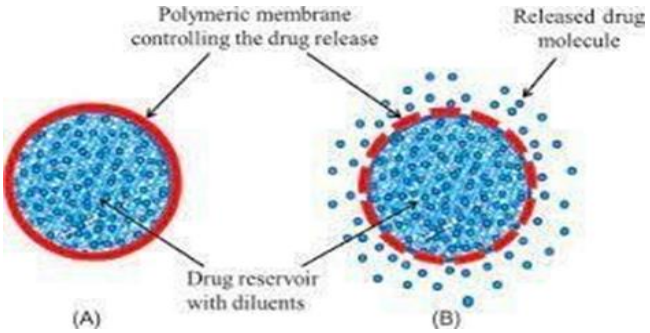


Figure 1. Polymer-controlled drug delivery.

Characteristics of drugs suitable for controlled release

Drugs designed for controlled-release formulations should possess specific characteristics to ensure optimal performance. Ideally, they should have moderate absorption and excretion rates, allowing for a steady therapeutic effect without rapid elimination [14]. Additionally, they must exhibit uniform absorption throughout the gastrointestinal (GI) tract to maintain consistent drug levels in the bloodstream [15]. The drugs used in controlled-release systems are typically administered in relatively small doses to prevent excessive accumulation in the body [16]. Moreover, they should have a wide safety margin to minimize the risk of toxicity and adverse effects [17].

Advantages of controlled-release drug delivery

Controlled-release drug delivery systems offer several benefits. One key advantage is the reduction in both dosage and administration frequency, improving patient adherence and convenience [18]. These systems help stabilize drug concentrations, reducing fluctuations that could lead to inefficacy or toxicity [19]. Additionally, by

maintaining steady drug levels, they minimize local and systemic complications associated with drug therapy [20]. Another benefit is the decreased accumulation of drugs in the body, lowering the risk of long-term adverse effects [21]. Furthermore, these systems can reduce the activity of chronic medications, preventing excessive drug exposure over time [11].

Disadvantages of controlled-release drug delivery

Despite their advantages, controlled-release formulations come with certain limitations. Sustained-release dosage forms (SRDS) are often more expensive and provide limited flexibility for dosage adjustments, making them less suitable for individualized treatment plans [22]. There is also a risk of dose dumping, where a large amount of the drug is released at once, potentially leading to toxicity. Additionally, these formulations may have reduced drug absorption, delayed onset of action, and susceptibility to first-pass metabolism, which can impact drug effectiveness [23]. The manufacturing process for controlled-release drugs is more complex and costly, requiring specialized equipment and production methods. Furthermore, these formulations may not be suitable for drugs that need to be absorbed at specific points in the GI tract [13]. Another challenge is that effective drug release is influenced by gastrointestinal transit time, which varies among individuals. Controlled-release systems are generally designed for the average population, without considering disease states or patient variability [24, 25]. Moreover, enzymatic degradation and potential product failure can complicate the use of antidotes, making it difficult to counteract drug effects in case of overdose or adverse reactions [26, 27].

Types of controlled drug delivery systems

Controlled drug delivery systems are categorized into various types based on their application and method of administration. These include oral controlled-release systems, which provide sustained drug release through the digestive system [28]. Another category is targeted drug delivery systems, designed to direct the drug specifically to affected tissues or organs for increased efficacy [29]. Dental drug delivery systems focus on localized treatment in the oral cavity, while ocular systems are formulated for controlled drug release in the eye [30, 31]. Transdermal systems deliver medication through the skin, offering a non-invasive alternative for continuous drug administration [32]. Other specialized systems include vaginal and uterine drug delivery for reproductive health treatments [33] and injectable and implantable drug delivery systems, which provide long-term controlled drug release directly into the body [34].

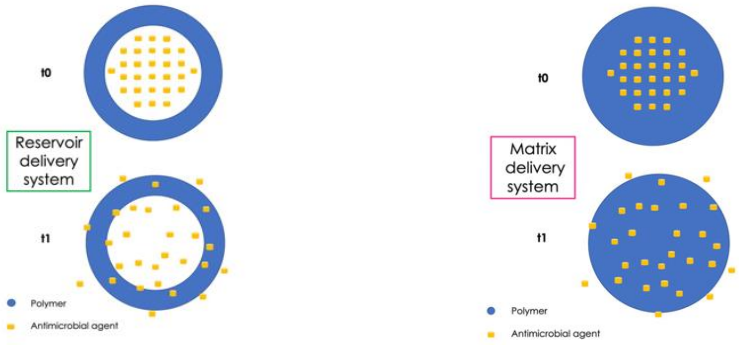
Classification of controlled drug delivery systems

Controlled drug delivery systems are designed to achieve sustained and regulated drug release through various mechanisms [35]. These systems are broadly classified based on how they control the drug release process.

Diffusion-controlled systems

Diffusion-controlled systems regulate drug release by allowing drug molecules to move from areas of higher concentration to lower concentration, following Fick's law of diffusion. The release rate is primarily influenced by the drug's ability to diffuse through a membrane barrier [36].

- Reservoir-type systems: These systems function similarly to a reservoir, where the drug is enclosed within a polymeric membrane that controls its release [37]. The release occurs gradually, ensuring a sustained therapeutic effect. In this mechanism, the rate-limiting step is the partitioning of drug molecules across the polymeric barrier, which determines the overall drug release kinetics in different formulations **(Figure 2)** [38, 39].
- Matrix systems: In a matrix-based system, the drug is uniformly dispersed within a polymeric network. The drug is released at a controlled rate over a specified duration, ensuring sustained plasma levels and optimized therapeutic effects **(Figure 2)** [40]. These systems are designed to achieve predictable drug release profiles, making them a preferred choice for long-term medication management.



a) b)

Figure 2. Schematic diagram of reservoir and matrix systems

Dissolution-controlled systems

Dissolution-controlled systems are used for drugs that are highly soluble in aqueous environments and often encounter challenges with dissolution rates [41]. These systems regulate dissolution by slowing it down, often by incorporating the drug into an insoluble polymer or coating it with polymer materials [42]. In these systems, the rate-limiting step involves the diffusion of the drug through the aqueous boundary layer [43, 44].

- Encapsulation systems: In these systems, drug particles are coated or encapsulated with slow-dissolving polymers through microencapsulation techniques [45, 46]. The release rate is determined by the solubility and thickness of the coating, which controls how quickly the drug dissolves and is released.
- Matrix systems: One of the most widely used techniques for controlled drug delivery, matrix dissolution systems involve dispersing the active pharmaceutical ingredient (API) evenly within a polymer matrix [47]. As the polymer dissolves—typically through erosion—the drug is gradually released into the surrounding medium, ensuring consistent delivery over time [48].

Water penetration-controlled systems

Water penetration-controlled systems regulate the release rate by controlling how water penetrates the system, which triggers the release of the drug [49].

- Swelling-controlled systems: These systems absorb body fluids, causing the polymer to swell. The increased solvent content and expansion of the polymer mesh allow the drug to diffuse through the swollen network [50, 51]. The swelling process is crucial for controlling the rate at which the drug is released, offering a sustained delivery over time.
- Osmotic controlled release systems: Osmotic delivery systems consist of an osmotic core surrounded by a semi-permeable membrane that controls the movement of water into the core [52]. These systems only have one small opening through which the drug is released as a solution. They are effective only for drugs that are soluble in water and follow zero-order release kinetics, providing a consistent drug release rate over time **(Figure 3)** [53, 54].

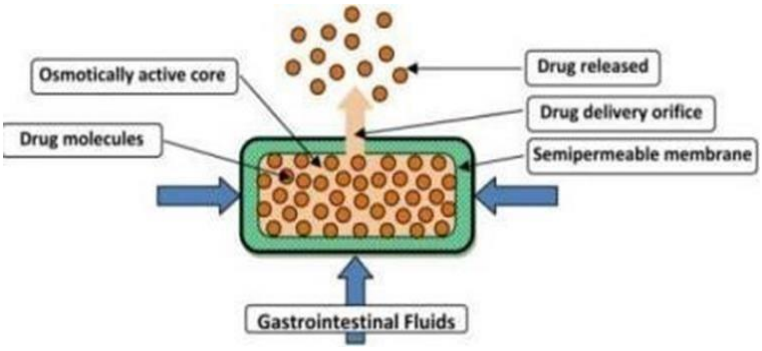


Figure 3. Schematic diagram of EOP osmotic system.

Applications of controlled-release drug delivery systems

Controlled-release drug delivery systems provide significant benefits for individuals with chronic conditions, such as diabetes [55], hypertension [56], asthma [57], epilepsy [58], and neurological diseases like Alzheimer's and Parkinson's [59, 60]. These systems also play a crucial role in hormone replacement therapies [61], managing chronic diseases [62], and improving pain management [63]. They allow for a steady release of pain-relieving drugs [64], reducing side effects and enhancing control over symptoms [65].

In broader medical applications, controlled drug delivery systems are also used in treating cancer [66], eye conditions [67], neurological disorders [68], heart diseases [69], and infections requiring antibiotics [70]. Additionally, these systems are effective in hormone replacement [71], transplantation [72], and pediatric care [73]. They offer the advantage of prolonged therapeutic effects [74], reducing the need for frequent dosing, and minimizing risks such as dependency. Targeted drug release, for instance, helps in tumor treatment by improving effectiveness while reducing harmful side effects [75].

Polymers in controlled drug delivery systems

Polymers play a critical role in controlled-release drug systems because they can adjust drug release rates, target specific tissues, and protect drugs from degradation [75]. Below are some types of polymers commonly used in these systems:

1. Biodegradable polymers: These polymers break down into harmless byproducts in the body, offering a controlled and gradual release of the drug. Examples of biodegradable polymers include polylactic acid (PLA), polyglycolic acid (PGA) and their copolymer, and poly lactic-co-glycolic acid (PLGA) [76-78].
2. Hydrogels: Hydrogels are networks of hydrophilic polymers capable of absorbing and retaining large amounts of water. They respond to environmental factors such as pH and temperature changes, causing them to swell and release the drug. Common examples include polyethylene glycol (PEG) and poly(N-isopropylacrylamide) (PNIPAM) [77, 79, 80].
3. Micelles: Micelles are formed when amphiphilic block copolymers self-assemble in aqueous solutions. These structures encapsulate hydrophobic drugs in their core and release them in a controlled manner. Poly(ethylene oxide)-b-poly(propylene oxide) (PEO-PPO) copolymers are a common example of micellar systems used for drug delivery [81, 82].
4. Liposomes: While not technically polymers, liposomes are made from phospholipid bilayers and can carry both hydrophilic and hydrophobic drugs. Surface modifications with polymers like PEG can enhance their circulation time and improve drug delivery efficiency [83-85].
5. Dendrimers: Dendrimers are highly branched, tree-like polymers with highly organized structures [86]. These polymers can either encapsulate drugs within their core or bond drugs to their surface, allowing for controlled and consistent drug release at specific rates [87]. An example of these dendrimers is polyamidoamine (PAMAM) dendrimers.
6. Polymeric microspheres/nanoparticles: These systems are composed of solid or porous polymeric particles, in which drug molecules are dispersed or encapsulated [88]. They are designed to release drugs using various methods, including diffusion, degradation, or a combination of both. Polylactide-co-glycolide (PLGA) microspheres and nanoparticles are often used in these systems [89].
7. Natural polymers: Natural polymers such as chitosan, alginate, and hyaluronic acid are widely studied for their use in drug delivery systems, due to their excellent biocompatibility and biodegradability [90]. Modifying their molecular weight, composition, and structure [91] allows these polymers to be customized for controlled drug release, targeted delivery, and minimized toxicity [92].

These controlled-release systems provide notable advantages over traditional drug formulations, including improved patient adherence, fewer side effects, and enhanced therapeutic outcomes [93].

Conclusion

Dosage forms are designed to combine drugs with excipients to improve their stability, taste, and overall effectiveness. Conventional dosage forms often face challenges with fluctuating plasma drug levels, which result in higher dosing frequencies and increased patient compliance issues. Controlled drug delivery systems address these challenges by enhancing bioavailability, optimizing drug release, and maintaining consistent plasma levels while minimizing side effects. These systems operate through various mechanisms such as dissolution, diffusion,

water penetration, and chemical control. Additionally, stimuli-responsive delivery systems show great promise in treating specific disease conditions.

Looking ahead, the future of drug delivery will likely focus on personalized therapies using advanced technologies like microfluidic-based systems, 3D printing, and CRISPR-Cas9 techniques. Modern approaches, particularly targeted drug delivery, have transformed oral controlled delivery, offering substantial benefits over traditional forms. This not only optimizes drug properties but also reduces dosing frequency, ensuring a consistent plasma concentration and maximizing therapeutic benefits. This makes controlled drug delivery a preferred and more convenient option for many patients.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Bhowmik D, Gopinath H, Kumar BP, Kumar KS. Controlled release drug delivery systems. Pharm Innov. 2012;1(10):24-32.
2. SBSPMS B. An innovative approach: controlled release drug delivery system (CRDDS) (doctoral dissertation, department of pharmaceutical sciences, Mohanlal Sukhadia University, Udaipur).
3. Deepu S, Mathew M, Shamna MS. Controlled drug delivery system. Int J Pharm Chem Sci. 2014;3(3):636-41.
4. Wani MS, Polshettiwar SA, Chopade VV, Joshi RN, Dehghan MH, Gadkari AA. Controlled release system-a review. Pharm Rev. 2008;6(1):41-6.
5. Robinson JR, Gauger LJ. Formulation of controlled-release products. J Allergy Clin Immunol. 1986;78(4):676-81.
6. Fara J, Urquhart J. The value of infusion and injection regimens in assessing efficacy and toxicity of drugs. Trends Pharmacol Sci. 1984;5:21-5.
7. Niraj VK, Srivastava N, Singh T, Gupta U. Sustained and controlled drug delivery system-as a part of modified release dosage form. Int J Res Pharm Nano Sci. 2015;4(5):347-64.
8. Patil S, Agnihotri J. Formulation development, optimization, and characterization of antifungal topical biopolymeric film using a noisome approach. Int J Sci Res Arch. 2023;8(1):194-209.
9. Malinowski HJ. Biopharmaceutics aspects of the regulatory review of oral controlled release drug products. Drug Dev Ind Pharm. 1983;9(7):1255-79.
10. Weiner M, Shapiro S, Axelrod J, Cooper JR, Brodie BB. The physiological disposition of dicumarol in man. J Pharmacol Exp Ther. 1950;99(4):409-20.
11. Ratnaparkhi MP, Gupta Jyoti P. Sustained release oral drug delivery system-an overview. Terminology. 2013;3(4):10-22.
12. Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics. Vallabh Prakashan; 2019.
13. Ratilal DA, Gaikwad Priti D, Bankar Vidyadhar H, Pawar Sunil P. A review on sustained release technology. Int J Res Appl Pharm. 2011;2:1701-8.
14. Vyas SP, Khar RK. Controlled drug delivery concepts and advances. Vallabh Prakashan. 2002;1:411-7.
15. Lee VH. Controlled drug delivery: fundamentals and applications. CRC Press; 1987. 30 p.
16. Swarbrick J, Boylan JC. Encyclopedia of pharmaceutical technology. New York: Marcel Dekker, Inc.; 1996.
17. Haranath C, Reddy CS, Sowmya C. An overview of SR tablets and their technology. Int J Pharm Drug Anal. 2014:740-7.
18. Crank J. The mathematics of diffusion. New York; 1979.
19. Leon L, Herbert LA. Pharmaceutical dosage forms. New York: Marcel Dekker; 2002.
20. Theseus's F. Elementary osmotic pump. J Pharm Sci. 1975;64(12):1987-91.

21. Mamidala R, Ramana V, Lingam M, GannuRand Rao MY. Review article factors influencing the design and performance of oral sustained/controlled release dosage form. Int J Pharm Sci Nanotechnol. 2009;2:583.
22. Shah N, Patel N, Patel K, Patel D. A review on osmotically controlled oral drug delivery systems. J Pharm Sci Bio Res. 2012;2:230-7.
23. Thombre NA, Aher AS, Wadkar AV, Kshirsagar SJ. A review on sustained release oral drug delivery system. Int J Pharm Res Sch. 2015;4(2):361-71.
24. Tripathi K, Kumar N, Singh M, Singh RK. Fungal siderophore: biosynthesis, transport, regulation, and potential applications. In: Kumar V, Prasad R, eds. Rhizosphere microbes: soil and plant functions. Singapore: Springer; 2020. p. 387-408.
25. Ravi Y, Najmuddin M, Dewalkar HV. Development and evaluation of theophylline microballoons drug delivery system. Int Res J Pharm. 2012;3(5):241-5.
26. Kumar S, Kumar A, Gupta V, Malodia K, Rakha P. Oral extended release drug delivery system: a promising approach. Asian J Pharm Tech. 2012;2(2):38-43.
27. Rathore AS, Jat RC, Sharma N, Tiwari R. An overview: matrix tablet as controlled drug delivery system. Int J Res Dev Pharm Life Sci. 2013;2(4):482-92.
28. Chugh I, Seth N, Rana AC. Oral sustained release drug delivery system. Int Res J Pharm. 2012;3(5):57-62.
29. Vinay K, Prajapati SK, Girish CS, Mahendra S, Neeraj K. Sustained release matrix type drug delivery system. Int Res J Pharm. 2012;1(3):934-60.
30. Parashar T, Soniya SV, Singh G, Tyagi S, Patel C, Gupta A. Novel oral sustained release technology: a concise review. Int J Res Dev Pharm Life Sci. 2013;2(2):262-9.
31. Hemnani M, Patel U, Patel G, Daslaniya D, Shah A, Bhimani B. Matrix tablets: a tool of controlled drug delivery. Am J Pharm Tech Res. 2011;1(4):127-43.
32. Ankit B, Rathore RPS, Tanwar YS, Gupta S, Bhaduka G. Oral sustained release dosage form: an opportunity to prolong the release of drug. Int J Adv Res Pharm Bio Sci. 2013;3(1):7-14.
33. Chowdary KPR, Kalyani GS. Recent research on matrix tablets for controlled release – a review. Int Res J Pharm Appl Sci. 2013;3(1):142-8.
34. Gennaro AR. Remington: the science and practice of pharmacy. 20th ed. Vol. 1. New York: Lippincott Williams & Wilkins; 2000. p. 905-6.
35. Zalte HD, Saudagar RB. Review on sustained release matrix tablet. Int J Pharm Bio Sci. 2013;3(4):17-29.
36. Neetu K, Ajay B, Kumar KM, Ankit G. Patented pharmaceutical oral controlled release matrix system. J Biol Sci Opin. 2013;1(3):263-70.
37. Patel H, Panchal DR, Patel U, Brahmbhatt T, Suthar M. Matrix type drug delivery system: a review. J Pharm Sci Biosci Res. 2011;1(3):143-51.
38. Dash TR, Varma P. Matrix tablets: an approach towards oral extended release drug delivery. Int J Pharma Res Rev. 2013;2(2).
39. Rieder A. Awareness and control of hypertension in Austria. J Human Hypertens. 2004;18(8):535-7.
40. Tanira MOM, Balushi KA. Genetic variations related to hypertension: a review. J Human Hypertens. 2005;19(1):7-19.
41. Wai-Yip Lee T, Robinson JR. Remington's the science and practice of pharmacy. 20th ed. Maryland: Lippincott Williams & Wilkins; 2000. p. 1069-70.
42. Harsh M. The kidney and lower urinary tract. In chapter 19, textbook of pathology: 4th ed. New Delhi: Jaypee brothers medical publishers; 2000. p. 670-2.
43. Neal L, Benowitz MD. Anti-hypertensive agents. In: Katzung BG, editor. Basic and clinical pharmacology. 6th ed. Norwalk (CT): Appleton & Lange; 1995. p. 165–6.
44. Appel LJ. ASH position paper: dietary approaches to lower blood pressure. J Clin Hypertens. 2009;11(9):358-68.
45. Tripathi KD. Essentials of medical pharmacology. 5th ed. New Delhi: Jaypee Brothers medical publishers (P) Ltd; 2008. p. 778-9.
46. Smith DHG. Comparison of angiotensin II type 1 receptor antagonists in the treatment of essential hypertension. Drugs. 2008;68(9):1207-25.
47. Abraham I, MacDonald K, Hermans C, Aerts A, Lee C, Brie H, et al. Real-world effectiveness of valsartan on hypertension and total cardiovascular risk: review and implications of a translational research program. Vasc Health Risk Manag. 2011;7(1):209-35.

48. Babu GD, Sagar KC, Bhoot MR. Design and evaluation of valsartan transdermal patches. Int J Res Ayurveda Pharm. 2012;3(3):461-4.
49. Lakade SH, Bhalekar MR. Formulation and evaluation of sustained release matrix tablet of anti-anginal drug, influence of combination of hydrophobic and hydrophilic matrix former. Res J Pharm Technol. 2008;1(4):410-3.
50. Shanmugam S, Ramya C, Sundaramoorthy K, Ayyappan T, Vetrichelvan T. Formulation and evaluation of sustained release matrix tablets of losartan potassium. Int J Pharmtech Res. 2011;3(1):526-34.
51. Krishnaiah YSR, Karthikeyan RS, Satyanarayana V. A three-layer guar gum matrix tablet for oral controlled delivery of highly soluble metoprolol tartrate. Int J Pharm. 2002;241(2):353-66.
52. Akhlaq M, Khan GM, Wahab A, Hussain A, Khan A, Nawaz A, et al. Formulation and in-vitro evaluation of Flurbiprofen controlled release matrix tablets using cellulose derivative polymers. Pak J Pharm Sci. 2010;23:23-9.
53. Tabandeh H, Mortazavi SA, Guilani TB. Preparation of sustained-release matrix tablet of aspirin with ethyl cellulose, eudragit RS100 and studying the release profiles and their sensitivity to tablet hardness. Iranian J Pharm Res. 2003;2:201-6.
54. Kumar GP, Battu G, Lova R, Kotha NS. Preparation and evaluation of sustained release matrix tablets of lornoxicam using tamarind seed polysaccharide. Int J Pharm Res Dev. 2011;2(12):89-98.
55. Hamza YE, Aburahma MH. Design and in vitro evaluation of novel sustained-release double-layer tablets of lornoxicam utility of cyclodextrin and xanthan gum combination. AAPS PharmSciTech. 2009;10(4):1357-67.
56. Nayak RK, Narayana Swamy VB, Dave M, Senthil A, Lad T, Mahalaxmi R. Formulation and evaluation of sustained release matrix tablets of iornoxicam. Indo Global Res J Pharm Sci. 2011;1(3):92-9.
57. Uddin M. Development of sustained release tablet of Valsartan. World J Pharm Sci. 2015;3(5):1196-05.
58. Sharma V, Sharma S, Khokra SL, Sahu RKR, Jangde R, Singh J. Formulation, development and evaluation of pregabalin sustained release matrix tablets. Pharm Lett. 2011;3(5):326-31.
59. Madhavi N, Sudhakar B, Ravikanth PV, Mohon K, Ramana Murthy K. Formulation and evaluation of phenytoin sodium sustained release matrix tablet. Bioequivalence and bioavailability. J Bioequiv Availab. 2012;4(7):128-33.
60. Katare VB, Bhutkar MA, Kumbhar AP, Pol SK, Katare PB. Formulation and evaluation of sustained release matrix tablets of pregabalin. Res J Pharm Technol. 2013;6(11):1190-94.
61. Ali MS, Singh S, Kumar A, Singh S, Ansari MT, Pattnaik G. Preparation and in vitro evaluation of sustained release matrix tablets of phenytoin sodium using natural polymers. Int J Pharm Pharm Sci. 2010;2(3):174-9.
62. Subramaniam K, Rangasamy M, Kugalur G, Parthiban KN, Senthil NK. Formulation and evaluation of sustained release tablets of Aceclofenac using hydrophilic matrix system. IJPRIF. 2010;2(3):1775-8.
63. Tehseen N, Rao V, Mohammed AH. Design and characterization of twice daily mini-tablets formulation of pregabalin. Int J Pharm Pharm Sci. 2013;5(1):168-75.
64. Emami J, Tajeddin M, Ahmadi F. Preparation and in-vitro evaluation of sustained release matrix tablets of flutamide using synthetic and naturally occurring polymers. Iran J Pharm Res. 2008;7(4):247-57.
65. Saiful I, Fariba K, Reza-ul J. Sustained release theopylline matrix tablets prepared by direct compression 1: effect of hydrophobic excipients. Bangladesh Pharm J. 2010;13(1):1-6.
66. Moin A, Shivkumar HG. Formulation of sustained release diltiazem matrix tablets using hydrophilic gum blends. Trop J Pharm Res. 2010;9(3):283-91.
67. Ulla SN, Roy AK, Kulkarni M, SM VK. Formulation and evaluation of sustained release matrix tablets of Lornoxicam. Int J Drug Dev Res. 2011;3(1):31-44.
68. Sharma VK. Meloxicam loaded floating sustained release matrix tablet. J Adv Pharm Educ Res. 2012;2(1):18-24.
69. Rao TV, Kumar GBK, Ahmed MG, Vedamurthy J. Development and evaluation of chitosan based oral controlled matrix tablets of losartan potassium. Int J Pharm Investig. 2012;2(3):157-61.
70. Crowley MM, Schroeder B, Fredersdorf A, Obara S, Talarico M, Kucera S, et al. Physicochemical properties and mechanism of drug release from ethyl cellulose matrix tablets prepared by direct compression and hot-melt extrusion. Int J Pharm. 2004;269(2):509-22.
71. Patel RP, Patel MH, Prajapati BG, Baria AH. Formulation and evaluation of sustained release matrix tablet of tizanidine hydrochloride by direct compression technique. E-J Sci Technol. 2011;6(1):69-81.

72. Ahmad QJ, Hariprasanna RC, Patil BS, Rabbani G. Fabrication and development of once-daily lornoxicam bi-layer matrix tablets: for the effective treatment of arthritis. J Appl Pharm. 2011;04(03):376-88.
73. Rao BS, Kulkarni SV, Patil P, Surpur C. Design and characterization of sustained release aceclofenac matrix tablets containing tamarind seed polysaccharide. Asian J Pharm Tech. 2011;1(1):17-21.
74. Siddiqui N, Husain A, Chaudhry L, Alam MS, Mitra M, Bhasin PS. Pharmacological and pharmaceutical profile of valsartan: a review. J App Pharma Sci. 2011;1(4):12-9.
75. Ainley W, Weller PJ. A handbook of pharmaceutical excipients. 2nd ed. London: Pharmaceutical press, American pharmaceutical association; 1994. p. 71-3.
76. Illango R, Jayakar B, Kavimani S. Chitosan as a new pharmaceutical excipient. Eastern Pharm. 1998;41:47-9.
77. Liberman H, Lachman L. The theory and practice of industrial pharmacy. 3rd ed. Bombay: Verghese publication house; 1991. p. 171-93.
78. Sultana H, Kiran Kumar GB, Acharya A, Ahmed MG. Development and evaluation of chitosan based oral controlled release matrix tablets of pregabalin. World J Pharm Pharm Sci. 2015;4(06):1306-19.
79. Jadhav GY, Galgatte UC, Chaudhari PD. Estimation of dimenhydrinate in bulk and pharmaceutical dosage form. Indo Am J Pharm Res. 2013;3(8):7001-7.
80. Sharma YR. Elementary organic spectroscopy, principles and chemical application. 1st ed. S. Chand Publication; 2001. p. 81-2.
81. Martin A, Micromeretics I, Martin A, ed. Physical pharmacy. Baltimores, MD: Lippincott Williams and Wilkins; 2001. p. 423-54.
82. Martin A. Physical pharmacy-physiochemical principles in the pharmaceutical sciences. 4th ed. New Delhi: B.I Waverly Pvt. Ltd; 1996. p. 313-6.
83. Bhowmik D, Chiranjib B, Krishnakanth P, Chandira RM. Fast dissolving tablet: an overview. J Chem Pharm Res. 2009;1(1):163-77.
84. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13(2):123-33.
85. Ahmed MG, Choudhari R, Acharya A. Formulation and evaluation of in situ gel of atorvastatin for the treatment of periodontitis. RGUHS J Pharm Sci. 2015;5(2):53-60.
86. ICH Q1A (R2). Stability testing guidelines: stability testing of new drug substances and products. [Online]. [Cited 2008 Nov 10]
87. Mohanty S, Dev A, Tripathy S. Formulation and evaluation of losartan potassium sustained release tablets. Int J Pharm Pharm Sci. 2012;4(3):390-2.
88. Viswanath V, Chandrasekhar U, Rao BN, Prakash KG. Development and evaluation of sustained release matrix tablets of losartan potassium. Int J Appl Pharm Sci Res. 2016;1(04):127-32.
89. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release. 2000;63(3):235-59.
90. Rahamathulla M, Alam MD, Hani U, Ibrahim Q, Alhamhoom Y. Development and in vitro evaluation of effervescent floating matrix tablet of neritinib: an anticancer drug. Pak J Pharm Sci. 2021;34(4):1297-303.
91. Mohamed R. Development of floating matrix tablets of losartan potassium: in vitro and in vivo evaluation. J Drug Deliv Sci Technol. 2013;23(6):611-7.
92. Azharuddin M, Kamath K, Panneerselvam T, Pillai SS, Shabaraya AR. Formulation and evaluation of controlled release matrix tablets of antihypertensive drug using natural and synthetic hydrophilic polymers. Res Biotechnol. 2011;2(4):26-32.
93. Gupta BM. Self medication behaviour in hypertensive patients in a tertiary care hospital. J Adv Med Dent Sci Res. 2019;7(2):65-7.