A Comprehensive Review of Controlled Drug Release Delivery Systems: Current Status and Future Directions

Kalam Mary Swarnalatha[1], Vangala Tulasi Iswariya[1*], Banoth Akash[1], Sneha Bhandari[1], Ramavath Shirisha[1], Tadikonda Ramarao[1]

[1]Department of Pharmaceutics, CMR College of Pharmacy, Hyderabad, Telangana, India.

ABSTRACT

Controlled-release systems regulate drug plasma concentration after administration through pre determined patterns over a fixed period. The release rate should determine drug absorption and concentration. These formulations reduce daily dosing frequency. This article discusses ideal requirements, advantages, properties, and approaches for developing controlled-release formulations to improve drug delivery. This involves delivering drugs at a pre-set rate for a limited period, either locally or systemically. This method, utilizing drug-encapsulating devices, offers advantages over traditional methods, including tailored release rates, drug protection, and increased patient comfort. Controlled-release drug delivery systems maintain a uniform plasma concentration within the therapeutic range, minimizing side effects and administration frequency. Oral sustained release (SR) products optimize drug properties, reducing dosing frequency and ensuring maximum drug utility, reduced side effects, and quicker cure or control conditions. Technological advancements have revolutionized medication methods with controlled drug delivery systems, offering benefits like multiple dosing and single dosing. Oral CRDD provides continuous oral delivery of drugs at predictable kinetics for a predetermined period, targeting specific regions within the gastrointestinal tract for local or systemic action. This technique reduces drug administration frequency and maintains constant drug levels in the patient's bloodstream, increasing its therapeutic effectiveness.

Key Words: *Controlled release, Dosing frequency, Drug concentration, Plasma concentration, Zero order*

eIJPPR 2024; 14(2):24-30

HOW TO CITE THIS ARTICLE: Swarnalatha KM, Iswariya VT, Akash B, Bhandari S, Shirisha R, Ramarao T. A Comprehensive Review of Controlled Drug Release Delivery Systems: Current Status and Future Directions. Int J Pharm Phytopharmacol Res. 2024;14(2):24-30. https://doi.org/10.51847/d6pncGCouf

INTRODUCTION

Controlled drug delivery systems offer benefits such as desired drug levels. However, they also face potential disadvantages such as toxicity, undesirable by-products, surgery, patient discomfort, and potential side effects [1]. Controlled-release systems are expensive compared to traditional pharmaceuticals, but ideal systems should be motionless, biocompatible, powerful, comfortable, safe, easy to administer, and aiming to maintain high drug levels over time.

The ideal polymer balances swelling, erosion, and dissolution processes. However, achieving high gel-state viscosity and maintaining a constant gel layer for linear drug release over prolonged periods remains a challenge due to various dynamic phases in polymer relaxation, disentanglement, and erosion [2, 3]. Controlled-release drug delivery systems maintain plasma concentration within the therapeutic range, minimizing side effects and administration frequency by providing uniform drug concentration to the absorption site [4, 5].

Sustained release systems aim to reduce dosing frequency or increase drug effectiveness by localizing at the action site, reducing the required dose, or providing uniform drug delivery. These systems provide medications over extended periods, while controlled release systems provide therapeutic control. Sustained-release dosage forms are increasingly being studied for better patient compliance and decreased misuse. Research in this field has yielded numerous discoveries, with new and sophisticated

Corresponding author: Vangala Tulasi Iswariya
Address: Department of Pharmaceutics, CMR College of Pharmacy, Hyderabad, Telangana, India.
E-mail: ✉ iswariyapharma@gmail.com
Received: 03 February 2024; **Revised:** 02 June 2024; **Accepted:** 05 June 2024

controlled release and sustained release delivery systems always being developed and tested [1, 6]. The introduction of orally administered once-daily products raises concerns about testing and clinical assessment. This presentation provides an overview of extended-release products, their theoretical base, typical formulation approaches, and current issues in the field [1].

Historically, alkaline compounds or buffers have been used in solid oral formulations of acidic drugs to overcome dissolution rate-limited absorption [7]. However, no strategy has been developed for a simple, compressible, monolithic, and controlled-release system with zero-order kinetics, primarily aimed at minimizing gastrointestinal tract and pH solubility dependency [8].

Controlled release dosage form

The USP defines modified-release forms as those that use drug release characteristics to achieve therapeutic or convenience not offered by conventional dosage forms [9]. Extented release dosage forms allow for a two-fold reduction in dosing or a significant increase in patient compliance. Most marketed monolithic oral Extented release dosage forms fall into two technologies: hydrophilic, hydrophobic, or inert matrix systems, and reservoir (coated) systems. These systems involve simple diffusion/erosion systems or osmotic systems, where the drug core is enclosed within a polymer membrane [10, 11].

Polymers used in control drug delivery system

Polymers play a crucial role in drug delivery, serving as binders in tablets, viscosity. Flow controlling agents in liquids, suspensions, and emulsions [12]. They can also be used as film coatings to disguise drug taste, enhance stability, and modify release characteristics. Controlled drug delivery (CDD) involves combining a polymer with a drug or active agent to release the active agent in a predesigned manner, achieving more effective therapies and reducing under and overdosing **(Figure 1)** [4, 13].

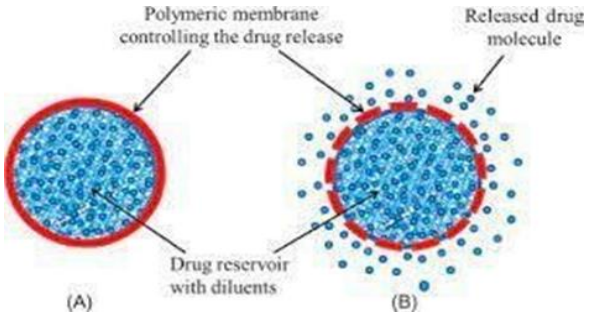


Figure 1. Polymer-controlled drug delivery.

Characteristics of drugs suitable for controlled release

1. Exhibit moderate rates of absorption and excretion [14].
2. Uniform absorption throughout the GI tract [15].
3. Administered in relatively small doses [16].
4. Possess a good margin of safety [17].

Advantages

1. Reduced dose and frequency [18].
2. Reduce fluctuations [19].
3. Effect of less drug minimizes local and systemic difficulty [20].
4. Decrease drug accumulation [21].
5. Reduce chronic drug activity [11].

Disadvantages

1. Sustained release dosage forms (SRDS) has drawbacks like increased costs and less flexibility in dosage adjustments [22].
2. Risk of dose dumping, reduced drug absorption, delayed action onset, and potential for first-pass clearance [23].
3. They also require more costly manufacturing processes and equipment and cannot be used for drugs absorbed at specific times in GIT [13].
4. Effective drug release in oral formulations is influenced by gastrointestinal resistance time and is designed for normal populations [24].
5. However, disease states and interpatient variability are not considered [25].
6. Enzymatic breakdown and product failure can make effective antidotes difficult to use [26, 27].

Types of controlled drug delivery systems

Controlled drug delivery systems are broadly classified as follows:

1. Oral controlled release system [28]
2. Targeted delivery system [29]
3. Dental systems [30]
4. Ocular systems [31]
5. Transdermal systems [32]
6. Vaginal and uterine systems [33]
7. Injections and implants [34].

Classification

The mechanism to obtain sustained and controlled release of drugs [35], they are classified as follows:

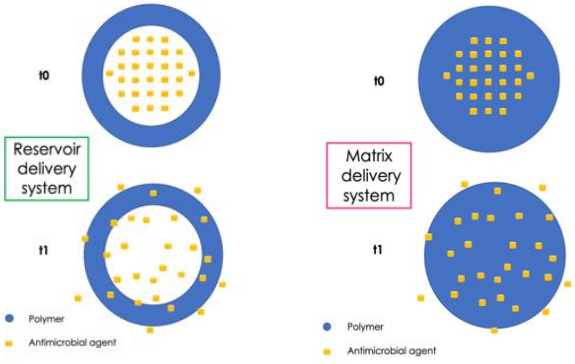
- *Diffusion- controlled systems*

The diffusion process involves drug molecules moving from higher to lower concentration, as per Fick's law. The release charge of a drug depends on diffusion past the membrane barrier [36].

Reservoir type: Delivery systems akin to reservoirs are manufactured [37]. This guarantees that the medication exits the delivery vehicle gradually. The partitioning of the drug molecules within the polymeric membrane is

the rate-limiting step during the release process in various kinds of delivery systems **(Figure 2)** [38, 39].

Matrix: The controlled release matrix system delivers drugs at a predetermined rate at specified time, aiming to achieve therapeutic plasma levels through desirable delivery profiles **(Figure 2)** [40].



a) b)

Figure 2. Schematic diagram of reservoir and matrix systems

- *Dissolution-controlled systems*

High aqueous solubilized drugs that face dissolution rate [41]. Controlling dissolution can be achieved by slowing it down, incorporating it in an insoluble polymer, or coating it with polymeric materials [42]. The rate-limiting step is diffusion across the aqueous boundary layer [43, 44].

Encapsulation systems: By using slow-dissolving polymers, microencapsulation procedures coat or encapsulate drug particles [45, 46]. The coating's thickness and solubility determine how quickly it dissolves.

Matrix systems: Matrix dissolution systems are the most commonly used technique in controlled delivery system and involve the API being homogeneously distributed throughout a polymer matrix [47]. As the polymer matrix dissolves (typically via an erosion-mediated process), drug molecules are released into the external environment [48].

- *Water penetration-controlled systems*

It rates control is obtained by the penetration of water into the system [49].

Swelling-controlled systems: Swelling-controlled release systems absorb body fluids and swell, increasing solvent content and polymer mesh size and allowing drug diffusion through swollen networks [50, 51].

Osmotic controlled release systems: Every osmotic medication delivery method has an osmotic core and a semi-permeable membrane that regulates water flow [52]. They only have one orifice, and the medication is only ever released as a solution [53]. Only works with medications that dissolve in water. Drug release has kinetics [54] that are zero-order **(Figure 3)**.

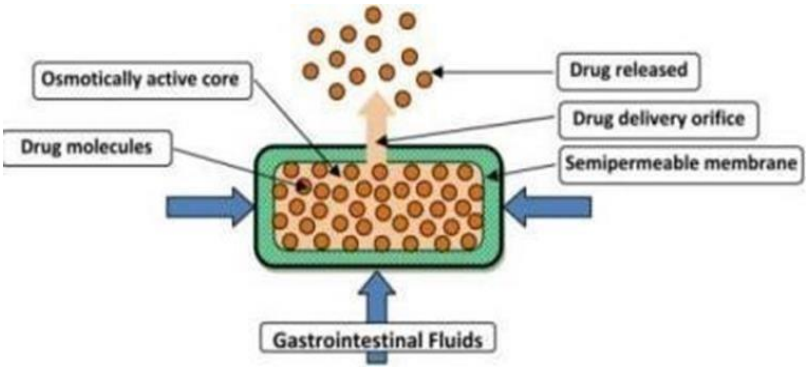


Figure 3. Schematic diagram of EOP osmotic system.

Applications

Controlled-release medications are beneficial for patients with chronic diseases such as diabetes [55], hypertension [56], asthma [57] and epilepsy [58], as well as neurological disorders like Alzheimer's and Parkinson's [59, 60]. They are also used in hormone therapy [61], chronic disease management [62], and pain management [63], providing sustained release of pain-relieving medications [64] for improved control and reduced side effects [65]. Controlled drug delivery systems (CDDS) are used in various fields, including cancer treatment [66], ophthalmology [67], neurological disorders [68], cardiovascular diseases [69], antibiotic therapy [70], hormone replacement therapy [71], transplantation medicine [72], and pediatric medicine [73]. CDDS provide prolonged relief [74], reduce the need for frequent dosing, and minimize the risk of addiction. They target tumors, improve treatment efficacy, and minimize systemic side effects [75]. CDDS are also used in ophthalmology for sustained drug release, neurological disorders like Parkinson's disease and epilepsy, and in antibiotic therapy for localized infections [76].

Polymers

Polymers play a significant role in controlled drug delivery systems due to their versatility in modulating drug release rates, targeting specific tissues, and protecting drugs from degradation [75]. Here are a few common types of polymers used in controlled release drug delivery:

1. *Biodegradable polymers:* These polymers break down into harmless byproducts in the body over time, gradually releasing the drug [77, 78]. Examples include polylactic acid (PLA), polyglycolic acid (PGA), and their copolymer poly (lactic-co-glycolic acid) (PLGA).
2. *Hydrogels:* are three-dimensional networks of hydrophilic polymers capable of absorbing and retaining large amounts of water [79]. They can swell in response to changes in environmental conditions (e.g., pH, temperature) and release drugs accordingly [77, 80]. Examples include polyethylene glycol (PEG) and poly(N-isopropylacrylamide) (PNIPAM).
3. *Micelles:* are self-assembled colloidal structures formed by amphiphilic block copolymers in aqueous solutions [81]. They can encapsulate hydrophobic drugs within their core and release them in a controlled manner. Examples include poly (ethylene oxide)-b-poly (propylene oxide) (PEO-PPO) copolymers [82].
4. While not strictly polymers, liposomes are composed of phospholipid bilayers and can encapsulate both hydrophilic and hydrophobic drugs [83, 84]. Surface modifications with polymers like PEG can prolong circulation time and enhance drug delivery efficiency [85].
5. *Dendrimers:* are highly branched polymers with well-defined structures [86]. Dendrimers can encapsulate drugs within their interior or conjugate drugs to their surface, allowing for controlled release kinetics [87]. Examples include polyamidoamine (PAMAM) dendrimers.
6. Polymeric microspheres/nanoparticles are solid or porous polymeric particles with drug molecules dispersed or encapsulated within them [88]. They can be designed to release drugs through diffusion, degradation, or a combination of both. Examples include polylactide-co-glycolide (PLGA) microspheres and nanoparticles [89].
7. Natural polymers like chitosan, alginate, and hyaluronic acid have been extensively investigated for drug delivery applications due to their biocompatibility and biodegradability [90].

These polymers can be tailored in terms of molecular weight, composition [91], and structure to achieve specific release profiles, site-specific targeting, and reduced toxicity [92]. Controlled-release drug delivery systems offer numerous advantages over conventional dosage forms, including improved patient compliance, reduced side effects, and enhanced therapeutic efficacy [93].

CONCLUSION

Dosage forms combine drugs and excipients to enhance stability and taste. Conventional dosage forms struggle with fluctuating plasma drug levels, requiring high dosing frequency and patient compliance. Controlled drug delivery systems improve bioavailability, release, and maintain plasma levels with minimal side effects. These systems include dissolution, diffusion, water penetration, and chemically controlled delivery. Stimuli-responsive delivery systems are useful in disease conditions. Future drug delivery focuses on patient-specific therapy using microfluidic-based, 3D printed devices, and CRISPR cas9-based systems. Modern technologies, including targeted concepts, have revolutionized oral controlled delivery, offering advantages over conventional dosage forms. This optimizes drug properties, reduces dosing frequency, and maximizes drug utility through uniform plasma concentration, making it a popular and convenient delivery method.

Acknowledgments: The authors are thankful to the management of the CMR College of Pharmacy, Medchal, Hyderabad for their support and encouragement.

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).
[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. IJPCS. 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. Rhizosphere Microbes: Soil and Plant Functions; 2020. pp.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. IRJP. 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 Phar 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's. pharmaceutical science. 20thEdn. Lippincott Williams and wilkini publishing co, Newyork. 2000;1:905-06.
[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 extentded 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 Edn., Lippincott Williams and Wilkins, Maryland, USA. 2000:1069-70.

[42] Harsh M. The kidney and lower urinary tract. In chapter 19, Texbook of pathology: 4th edition. New Delhi: Jayppe Brothers Medical Pubhlishers; 2000:670-2.
[43] Neal L, Benowitz MD. Anti- hypertensive agents. In chapter 11, Basic and clinical pharmacology, 6th edition, editor Bertram G. Katzung Appleton and Lange: 1995;147:165-6.
[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. 5 [sup] th ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd. 2008:778-9.
[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;7:209-35.
[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 hydrophlic 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. IJPRIF. 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 asprin 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. Pharmaceutical press, American pharmaceutical association. 1994;2:71-3.
[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 edn. 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;4:1306-19.
[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).
[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.