REVIEW ARTICLE

ORAL CONTROLLED RELEASE MATRIX FORMULATION DESIGN AND THEIR RATE CONTROLLING FACTORS

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ABSTRACT

The trend of formulation development of controlled release (CR) matrix drug delivery system has been increased to many folds during the last few years. Such CR dosage forms are now considered to be more effective than conventional immediate release dosage formulations due to avoidance of frequent dose administration with precise drug release over an extended time period. A properly formulated matrix based system also offers targeted delivery to a selected organ/tissue where the drug release is controlled at a specific rate. Development of matrix-based tablets with persistent drug release has always been a challenge to the pharmaceutical manufacturers owed to various biological, physicochemical and release limiting factors. In this review, different types of matrix-based systems are discussed in detail. Parameters that greatly influence the release of active pharmaceutical ingredient (API) from the matrix design and would eventually affect the overall performance of such products are also been highlighted.

Keywords: Controlled release, drug release system, matrix design, targeted delivery.

1. INTRODUCTION

1.1. Pharmaceutical Oral Dosage Formulations

Drug delivery through oral route is considered to be the most convenient and extensively utilized option for the general population. Oral dosages offer many benefits including the ease of administration, low cost, and safety of the route resulting in increased patient compliance and adherence to the therapy[1-3]. The oral route covers a wide range of dosage forms for the fulfillment of consumers' need and satisfaction. Immediate release (IR) formulations are one of the used designs that have been commonly prescribed to the patients. Unfortunately, these IR drugs present certain limitations such as frequent administration of daily doses leading to the plasma drug fluctuations[4,5]. To overcome the drawbacks associated with the IR formulations, controlled release drug delivery system (CRDDS) has been introduced. They are basically designed to deliver the drug at a particularly definite rate and to maintain safe and effective drug plasma profile for a period as long as defined by the system. CRDDS results in substantially constant plasma profile of the active pharmaceutical ingredient (API) rather uncontrolled fluctuations observed with conventional IR dosage form[6,7].

2. MATRIX-BASED CRDDS

Matrix formulation design is one of the extensively utilized techniques for controlled delivery of drugs worldwide. The word "matrix" demonstrates the three-dimensional network-based structure containing the combination of active pharmaceutical ingredient (API) and excipients/adjuvants[8]. In this system, API is mixed with an appropriate amount of the retardant(s) that may release the drug in a continuous manner following diffusion or erosion[9]. Various methods have been reported in past to obtain the polymeric network that embedded the drug uniformly. It is commonly done by dispersing the finely divided drug particles with a liquid/viscous

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polymer(s) followed by cross-linking of the polymeric chain or by dispersing the API and the retardant at an increased temperature to obtain the matrix delivery. Alternatively, they could also be manufactured by dissolving the drug and the retardant(s) in a common solvent, followed by solvent evaporation at an elevated temperature and/or under a vacuum[10-12].

2.1. Rationale for Matrix Based CRDDS

Pharmaceutical industries are now being focusing towards the development of matrix-based drug formulations due to the following reasons[10,13]:

- Improved patient convenience and compliance by maintaining therapeutic concentrations over an extended time period.
- Versatile in term of the manufacturing process.
- Made to release high molecular weight compounds.
- Drug toxicity decreases by slowing the rate of drug absorption.
- Improve product stability by protecting the API from hydrolysis.
- Minimize the local and systemic adverse drug reactions (ADRs) and upgrade the efficacy of therapy.
- Less amount of the total drug is utilized.
- Improvement of the bioavailability of some drugs.

2.2. Limitations of Matrix Tablets

Although matrix formulations have been found successful in maintaining the therapeutic drug level at steady state, unfortunately, these systems present certain difficulties which are listed below[14-16]:

- Achievement of zero-order release is difficult at times.
- The remaining matrix must be removed after the drug has been released.
- The drug release rates vary with the square root of time.
- Not all drugs can be blended with a given polymeric matrix.

2.3. Classification of Matrix Tablets

Matrix-based designs are categorized into various classes as shown in Fig. 1.

2.3.1. Lipid matrix system

As the title indicates, this system is based on the lipid waxes or any other lipid-based material. The release rate of incorporated API is found to remain constant during overall drug release period. The release of the medicament(s) depends on an aqueous medium dissolving the matrix forming agent that would leach out from the compact mass resulting in a porous matrix of tortuous capillaries. The API contained by the aqueous medium will diffuse from the matrix network through water-filled capillaries[17, 18].

2.3.2. Hydrophobic or insoluble polymer matrix

As far as the hydrophobic systems are concerned the API is enclosed in an inert retardant which is insoluble in GI fluids. The rate of release is directly related to the diffusion of drug molecules present in the aqueous solution via a tubular network formed in between the compressed polymeric particles. However, the release from the matrix can be modified by changing the porosity and tortuosity of the medium. It has also been found that the pore-forming hydrophilic salts or solutes used as formulation adjuvant have a major impact on the release of drugs[19,20].

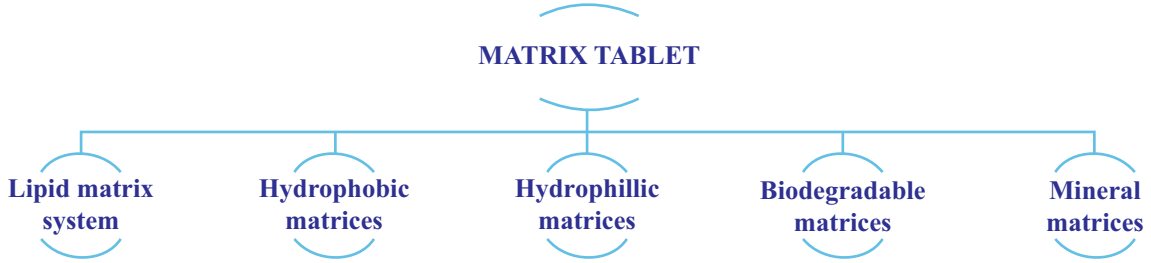

Fig. 1. Types of matrix formulations.

2.3.3. Hydrophilic matrices

This delivery system is also termed as a swellable soluble matrix. This system exhibits swelling, profound gelling, erosion and significant potential of dissolution in an aqueous vehicle. A hydrated matrix layer is formed by hydrophilic colloid through a swelling mechanism that further promotes diffusion of water towards matrix. Moreover, the rate of drug release from layers of the hydrated matrix is controlled by diffusion. Erosion of outer layer is also reported for such components but the degree of erosion is subjected to the nature of a colloid. This type of system has been successfully utilized for rate controlling of aqueous and non-aqueous drugs. Water-soluble matrix formers like soluble cellulose ether derivatives are used to obtain such deliveries[21,22].

2.3.4. Biodegradable matrices

The biodegradable network has been used by many researchers to formulate control release dosage forms[23]. These systems are composed of monomers connected with each other by different functional moieties but have an unbalanced association with the main structure. Biological degradation and erosion of these matrices lead to the respective monomers and oligomers, metabolized or excreted by enzymatic or non-enzymatic procedures[24].

2.3.5. Mineral matrices

This system involves the retardant obtained from the mineral origin including various sorts of seaweeds. Alginic acid is one of the classic examples of these matrices[24].

3. POLYMERS AND THEIR PROPERTIES

General properties of polymers/retardants are discussed as follows:

3.1. Biodegradability

Many naturally occurring and semi-synthetic polymers have proven their biodegradation and biocompatibility[25-27]. When polymer comes in contact with water, polymeric bond degradation takes place by hydrolysis or enzymatic cleavage that results in small fragments of large molecular size polymer leading to bulk erosion[28].

3.2. Biocompatibility

The polymeric material must be non-toxic, non-irritant and non-injurious for human use[29,30].

4. FORMULATION COMPONENTS OF MATRIX-BASED TABLETS

The formulation development of controlled release (CR) dosage forms is considered to be more complicated and challenging than the traditional IR dosage forms. Usually, a matrix-based design is composed of the following components:

- API
- Release controlling agents / matrix formers
- Matrix modifiers (channeling and wicking agents)
- Solubilizers and pH modifiers
- Lubricants and flow enhancers
- Supplementary coating agents

4.1. Release Controlling Agents / Matrix Formers

Matrix formers are basically the hydrophobic moieties with higher melting points (>37°C) responsible to control the release profile at a desirable time frame. A polymer alone or in combination usually constitutes about 20–40% of the total formulation to achieve targeted responses[31]. Commonly used matrix formers include cellulose derivatives of hydroxypropyl methylcellulose (HPMC), methylcellulose (MC) and acrylic polymers of eudragits and carbopols[8]. Others include polyvinylpyrrolidone (PVP K30), kollidon SR and hydrogenated vegetable oils like soybean oil, cottonseed oil, microcrystalline wax and carnauba wax[32].

4.2. Matrix Modifiers

Channeling agents are soluble in GI fluids and are found to form tortuous or convoluted capillaries from which the drug is assumed to be released. Traditionally sugars, sodium chloride, and polyols have been used in the formulation development of various CR products. The choice of the agent depends on the nature of drug and desirable release characteristics. These agents can be incorporated in

20–30% portion of the formulation design.

4.3. Solubilizers and pH Modifiers

Solubilizers are often incorporated in the design to promote dissolution of the drug in vivo. Polyethylene glycols, polyols, and surfactants have been utilized as solubility enhancers. Similarly, if the drug is prone to ionization then the buffers or counterions may be appropriately added to avoid the alteration in absorption and the therapeutic responses. Sodium carbonate[33] and magnesium oxide[34] have been used to alter the pH in formulation development of different dosage forms.

4.4. Lubricants and Flow Enhancers

Anti-adherents, lubricants, and glidants are needed to cope up with the problems related to the adherence, sticking and ejection. Talc and colloidal silicon dioxide improved the flow properties and promote easy ejection of the tablets from the die. Both colloidal silicon dioxide and talc constitute little of the final formulation usually 0.5–1% and 4–6%, respectively[35].

4.5. Supplementary Coating Agents

Supplementary coating chemicals have been used to increase the lag time of the drug release. Such materials are considered to be added especially in the manufacturing of the highly water-soluble drugs or when the active drug is responsible to induce GIT irritation. Under these circumstances, drug release is required to be delayed further till the formulation reaches towards more distal gut part[35].

5. FACTORS AFFECTING THE RATE OF DRUG RELEASE FROM THE MATRIX

There are so many factors that affect drug release from a matrix system. These factors are classified according to their impact on the release of drug into the following[36,37]:

- Release limiting factors
- Biological factors
- Physicochemical factors

5.1. Influence of Release Limiting Factors

There are certain parameters that would directly affect the release of medicaments from the matrix. The effect of such factors is discussed as:

5.1.1. Polymer hydration

Dissolution of a polymer includes absorption/ adsorption of water in more accessible place. It may lead to the rapture of polymer-polymer bonding following the simultaneous formation of water-polymer linkage and separation of polymeric chain, swelling and finally the dispersion of polymer embedded drug in the dissolution medium. The rate of polymer hydration is found to be directly related to the drug release. The polymer methocel K hydrates quickly as it contains methoxy groups hence justify the application of CR matrices. It is also observed that large size fraction of HPMC could be hydrated more rapidly than small size fraction. The initial time of hydration is significant as it corresponds to the time where the protective gel coat is formed around matrices containing HPMC polymers[38-40].

5.1.2. Polymer composition

Polymeric composition and their complex nature play a vital role in the drug release. Cellulose ether is reported to induce many reactions. The cross-linkages and the attached functional groups may induce intermolecular interaction with various species consequently making their structures insoluble and stable. These interactions may affect the release pattern of different drugs[40].

5.1.3. Polymer viscosity or weight

Polymer viscosity is majorly used as a property of the matrix weight. Increase in viscosity or molecular weight of polymeric material in the matrix would increase the viscosity of gel layer and thus slow down the drug dissolution[41]. The viscosity of the gel-forming moiety delays or hinders the primary hydration without any impact on the rate of release[42].

5.1.4. Drug solubility

Hydrophilicity of a drug is the property of its functional group, stereochemistry, and polymorphic form[43]. Drug solubility determination in an aqueous medium at different pH values is significant during the pre-formulation evaluation stage. Solubility

directly influences the rate of drug release from the porous network of polymer[44] but in systems where the drug is poorly soluble, additional control on dissolution rate is not required. With respect to solubility, hydrophilic drugs follows diffusion as a release pattern whereas insoluble drugs follow erosion[30,45-47].

5.1.5. Proportion of polymer

Polymeric fraction also affects the drug release from the matrix design. By decreasing the amount of HPMC with marginally soluble drugs, increase the rate of drug release. The whole phenomenon is dependent upon the proportion and consistency of gel formation[40,43].

5.1.6. Polymer-drug interaction

The assessment of water concentration profile can be determined using HPMC with various molecular weights. Cellulose–ether polymer, when analyzed thermally, showed an interaction between polymer and drug in a gel layer that surrounds the matrix tablet and this partially takes part in drug release modulation. The effect of temperature on the release pattern of the drug from the matrix has also been reported by the researchers in past[40].

5.2. Effect of Biological Factors on Drug Release from the Matrix Tablets

Apart from polymer properties affecting drug release, following biological factors may also be considered:

5.2.1. Biological half-life

Biological half-life mainly presents an elimination rate of the drug in terms of quantity. Drug's biological half-life and duration of action shows its considerable role in the matrix formulation. Drugs with very short half-life and large doses execute a restriction because of the dose size while chemicals with elimination half-life greater than 8 hours are also inappropriate in a matrix-based controlled systems[48].

5.2.2. Absorption

Drugs with slow, irregular and erratic absorption rates are least selective candidates for controlled release formulations. Potent drugs that have aqueous solubility with poor absorption or those drugs that are absorbed through carrier-mediated transport system are also not considered to be suitable for CRDDS[48].

5.2.3. Metabolism

Metabolism of drug molecules results in either inactivation or conversion of an API into its active metabolite. Many tissues are responsible for the metabolism of drugs but the main organ is liver having a variety of enzyme systems. It has been extensively documented that drugs responsible to induce or retards activation of hepatic enzymes are known to exhibit drug-drug interactions[49] and are able to establish poor control release profiles[48].

5.2.4. Protein binding

Drug-protein binding has a profound effect on the pharmacological activity of the drug without considering the type of pharmaceutical dosage forms. Excessive and prolong plasma-protein binding leads to enhanced elimination half-life and erratic bioavailability. Hence these drug candidates are generally not suitable for CR dosage forms as the drug molecule already remains in the body for an extended period of time[40].

5.2.5. Safety considerations and side effects

By formulating CR system the chances of systemic side effects are decreased, as the release rate is controlled by polymeric matrix resulting in lesser amount of the total drug to be consumed. The most extensively utilized parameter for safety consideration of a drug is its therapeutic window, which could be obtained by dividing the value of 50% toxic dose with 50% effective dose. Generally, chemicals having broad therapeutic window presents safety and thus are suitable to formulate CRDDS. However, the drugs with narrow therapeutic index are more potent and therefore not considered fit for CRDDS due to technological limitations[40,50].

5.2.6. Disease state

CRDDS also proved to be better for the management of disease state in various cases. One of the examples is osteoarthritis where the use of tramadol ER has

found to be valuable as it avoids the occurrence of joint stiffness[51,52].

5.3. Effect of Physicochemical Factors on Drug Release from the Matrix Tablets

Some of the important physicochemical factors that influence the release of drugs are:

5.3.1. Dose size

Pharmacological agents with a half-life of less than 2 hours or greater than 6 hours are not suitable in terms of manufacturing as CRDDS. These systems require an excessively large quantity of API to compress and cope up with the duration of action for a prolong period[47,53].

5.3.2. Ionization, pK_a and aqueous solubility

Ionized drug molecules are assumed as poor candidates for CRDDS. Although in unionized drug formulations, the absorption is well defined but permeation is almost negligible. The rate of absorption is found be 3–5 times lesser in ionized species than unionized forms of the API. The value of pK_a for acidic and basic drugs approximately falls in the range of 3.0–7.5 and 7.0–11.0, respectively, while unionized form possesses p*K*a values in the range of 0.1–5.0[54,55].

5.3.3. Partition coefficient

Active moieties with highly lipophilic or hydrophilic nature show extremities in partition coefficient hence demonstrate either low/high flux into the tissues that consequently affect the extent of absorption. However, the rapid flux results in drug accumulation within the tissues. As far as the matrix systems of control formulations are concerned, both these extremities are undesirable [54,56].

5.3.4. Stability

Since most oral CR systems are designed to release their contents in the GIT, drugs that are unstable in the environment of the intestine might be difficult to formulate into prolonged release system[56].

5.3.5. Molecular size and diffusivity

It has been reported that smaller size molecules have shown decreased drug release than the large size drug moieties[22]. Diffusion of the active agent through the rate-controlling matrix membrane is an important factor to consider in relation to diffusion through a variety of biological membranes. The drug diffusivity (D) mainly depends on the size, shape and the weight of API. The value of D for products having a molecular weight between 150–400 mg, via flexible retardants is found to be in the range of 10^{-6} to 10^{-9} cm^2/sec whereas for higher molecular weight (>500 mg) molecules, drug diffusivity is very small even difficult to quantify (10^{-12} cm^2/sec). Thus the high molecular weight drugs are usually related to very slow release kinetics in sustained release devices when diffusion through polymeric membrane or matrix is the release mechanism[11,40]

6. CONCLUSION

In the light of above-discussed details, it is concluded that matrix-based technique is versatile in various aspects of manufacturing and stand economically for both producers as well as consumers. Besides all these benefits, this system has also been associated with certain limitations which are due to biological, physicochemical and release controlling factors. Successful matrix-based formulations could result if the mentioned factors are carefully kept in mind during pre-formulation and formulation stages.

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CONFLICT OF INTEREST

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REFERENCES

1. Siddiqui MN, Garg G, Sharma PK. A short review on a novel approach in oral fast dissolving drug delivery system and their patents. Adv Biol Res. 2011;5:291-303.
2. Martinez ADB, Bellver MVM, ICR Galan. Matrix tablets based on amino acid-derived polyesteramide containing release modifiers. J Drug Dev Sci Technol. 2017;42:307-314.
3. Anselmo AC, and Mitragotri S. An overview of clinical and commercial impact of drug delivery

systems. J Control Release. 2014;190:15-28.
4. DeVane CL. Immediate-release versus controlled-release formulations: pharmacokinetics of newer antidepressants in relation to nausea. J Clin Psychiatry. 2003;64: 14-19.
5. Kaplan R, Parris WC, Citron ML, Zhukovsky D, Reder RF, Buckley BJ, Kaiko RF. Comparison of controlled-release and immediate-release oxycodone tablets in patients with cancer pain. J Clin Oncol.1998;16:3230-3237.
6. Lee HJ, Kim JY, Park SH, Rhee YS, Park CW, Park ES. Controlled-release oral dosage forms containing nimodipine solid dispersion and hydrophilic carriers. J Drug Dev Sci Tech. 2017;37:28-37.
7. Bayomi MA, Al-Suwayeh, SA, El-Helw ARM. Excipient-excipient interaction in the design of sustained-release theophylline tablets: in vitro and in vivo evaluation. Drug Dev Ind Pharm. 2001;27:499-506.
8. Zimmer L, Kasperek R, Poleszak E. Modern polymers in matrix tablets technology. Polim Med. 2014;44:189-196.
9. Qiu Y, Zhou D. Understanding design and development of modified release solid oral dosage forms. J Valid Technol. 2011;17:23-32.
10. Misal R, Waghmare A, Aqueel S, Hattiambire K. Matrix tablets: A promising technique for controlled drug delivery. Indo Am J Pharm Res. 2013;3:1-5.
11. Allen LV, Popovich NG, Ansel HC. Ansel's Pharmaceutical Dosage Forms and Drug Delivery System, 9th ed., Lippincott Williams & Wilkins, Philadelphia, USA, 2011; pp. 236, 258, 260.
12. Chien YW. Novel Drug Delivery Systems, 2nd ed., Marcel and Dekker, Boca Raton, USA, 1992; pp. 139-150.
13. Vyas SP, Khar RK. Controlled Drug Delivery – Concepts and Advances, 2nd ed., Vallabh Prakashan, Delhi, India, 2012; pp. 411-447.
14. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy, 3rd ed., Lea & Febiger, Philadelphia, USA, 1990; p. 346.
15. Jayanthi B, Manna PK, Madhusudhan S, Mohanta GP, Manavalan R. Per oral extended release products, an overview. J App Pharm Sci. 2011;1:50-55.
16. Kayser O, Lemke A, Hernandez-Trejo N. The impact of nanobiotechnology on the development of new drug delivery systems. Curr Pharm Biotechnol. 2005;6:3-5.
17. Abdel-Rahman SI, Mahrous GM, El-Badry M.Preparation and comparative evaluation of sustained release metoclopramide hydrochloride matrix tablets. Saudi Pharm J. 2009;17:283-288.
18. Chandran S, Asghar LF, Mantha N. Design and evaluation of ethyl cellulose based matrix tablets of ibuprofen with pH modulated release kinetics. Indian J Pharm Sci. 2008;70:596-602.
19. Tiwari SB, Murthy TK, Pai MR, Mehta PR, Chowdary PB. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS PharmSciTech. 2003;4:18-23.
20. Sudha BS, Sridhar BK, Srinatha A. Modulation of tramadol release from a hydrophobic matrix: implications of formulations and processing variables. AAPS PharmSciTech. 2010;11: 433-440.
21. Sumathi S, Ray AR. Release behaviour of drugs from tamarind seed polysaccharide tablets. J Pharm Pharm Sci. 2002;5:12-18.
22. Teixeira AZA. Hydroxypropylcellulose controlled release tablet matrix prepared by wet granulation: effect of powder properties and polymer composition. Braz Arch Biol Technol. 2009;52:157-162.
23. Lin M, Meng S, Zhong W, Li Z, Du W. Novel biodegradable blend matrices for controlled drug release. J Pharm Sci. 2008;97:4240-4248.
24. Patel H, Panchal DR, Patel U, Brahmbhatt T, Suthar M. Matrix type drug delivery system: A review. J Pharm Sci Biosci Res.2011;1;143-151.
25. Sriamornsak P. Application of pectin in oral drug delivery. Expert Opin Drug Dev. 2011;8: 1009-1023.
26. Wakerly Z, Fell JT, Attwood D, Parkins D. Pectin/ethylcellulose film coating formulations for colonic drug delivery. Pharm Res. 1996;13:1210-1212.

27. Wakerly Z, Fell JT, Attwood D, Parkins D. Studies on drug release from pectin/ethylcellulose film-coated tablets: a potential colonic delivery system. Int J Pharm. 1997;153:219-224.
28. Siepmann J, Kranz H, Bodmeier R, Peppas NA. HPMC-matrices for controlled drug delivery: a new model combining diffusion, swelling, and dissolution mechanisms and predicting the release kinetics. Pharm Res. 1999;16:1748-1756.
29. Mansour HM, Sohn M, Al-Ghananeem A, DeLuca PP. Materials for pharmaceutical dosage forms: molecular pharmaceutics and controlled release drug delivery aspects. Int J Mol Sci. 2010;11:3298-3322.
30. Sharma K, Singh V, Arora A. Natural biodegradable polymers as matrices in transdermal drug delivery. Int J Drug Dev Res. 2011;3:85-103.
31. Maroni A, Curto MDD, Zema L, Foppoli A, Gazzaniga A. Film coatings for oral colon delivery. Int J Pharm. 2013;457:372-394.
32. Prajapati ST, Patel AN, Patel CN. Formulation and evaluation of controlled-release tablet of zolpidem tartrate by melt granulation technique. ISRN Pharm. 2011;2011:208394.
33. Tran TTD, Tran PHL, Lim J, Park JB, Choi SK, Lee BJ. Physicochemical principles of controlled release solid dispersion containing a poorly water-soluble drug. Ther Deliv. 2010,1:51-62.
34. Hamza YES, Aburahma MH. Design and in vitro evaluation of novel sustained-release matrix tablets for lornoxicam based on the combination of hydrophilic matrix formers and basic pH-modifiers. Pharm Dev Technol. 2010;15: 139-153.
35. Patwekar SL, Baramade MK. Controlled release approach to novel multiparticulate drug delivery system. Int J Pharm Pharm Sci. 2012:4: 757-763.
36. Fuertes I, Caraballo I, Miranda A, Millán M. Study of critical points of drugs with different solubilities in hydrophilic matrices. Int J Pharm. 2010;383:138-146.
37. Maderuelo C, Zarzuelo A, Lanao JM. Critical factors in the release of drugs from sustained release hydrophilic matrices. J Control Release. 2011;154:2-19.
38. Siepmann J, Siepmann F. Modeling of diffusion controlled drug delivery. J Control Release. 2012;161:351-362.
39. Grund J, Koerber M, Walther M, Bodmeier R. The effect of polymer properties on direct compression and drug release from water-insoluble controlled release matrix tablets. Int J Pharm. 2014;469:94-101.
40. Ummadi S, Shravani B, Rao NR, Reddy MS, Nayak BS. Overview on controlled release dosage form. Int J Pharma Sci. 2013;3:258-269.
41. Phaechamud T, Darunkaisorn W. Drug release behavior of polymeric matrix filled in capsule. Saudi Pharm J. 2016;24;627-634.
42. Sujja-Areevath J, Munday DL, Cox PJ, Khan KA. Relationship between swelling erosion and drug release in hydrophilic natural gum mini-matrix formulations. Eur J Pharm Sci.1998;6:207-217.
43. Efentakis M, Al-Hmoud H, Buckton G, Rajan Z. The influence of surfactants on drug release from a hydrophobic matrix. Int J Pharm. 1991;70:153-158.
44. Vaidya MP, Avachat AM. Investigation of the impact of insoluble diluents on the compression and release properties of matrix based sustained release tablets. Powder Technol. 2011;214: 375-381.
45. Nokano M, Ogata A. In vitro release characteristics of matrix tablets, Study of karaya gum and guar gum as release modulators. Indian J Pharm Sci. 2006;68:824-826.
46. Streubel. A, Siepmann. J, Dashevsky A, Bodmeier R. pH-independent release of a weakly basic drug from water-insoluble and -soluble matrix tablets. J Control Release. 2000;67: 101-110.
47. Varma MV, Kaushal AM, Garg A, Garg S. Factors affecting mechanism and kinetics of drug release from matrix-based oral controlled drug delivery systems. Am J Drug Deliv. 2004;2:43-57.
48. Karan S, Jiang Z, Livingston AG. Sub-10 nm polyamide nanofilms with ultrafast solvent transport for molecular separation. Science.

2015;348:1347-1351.
49. Bushra R, Aslam N. An overview of clinical pharmacology of ibuprofen. Oman Med J. 2010;25:155-161.
50. Shargel L, Wu-Pong S, Yu ABC. Applied Biopharmaceutics and Pharmacokinetics, 6th ed., McGraw-Hill Companies, 2012; pp. 473-476.
51. Gana TJ, Pascual MLG, Fleming RRB, Schein JR, Janagap CC, Xiang J, Vorsanger GJ.023 Study Group. Extended-release tramadol in the treatment of osteoarthritis: a multicenter, randomized, double-blind, placebo-controlled clinical trial. Curr Med Res Opin. 2006;22: 1391-1401.
52. Hair PI, Curran MP, Keam SJ. Tramadol extended-release tablets. Drugs. 2006;66: 2017-2027.
53. Cooper J, Gunn C. Powder flow and compaction, In: Carter SJ (Ed.), Tutorial Pharmacy, CBS Publishers and Distributors, New Delhi, India, 1986; pp. 211-233.
54. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics – A Treatise, 2nd ed., Vallabh Prakashan, Delhi, India, 2009; pp. 397-434.
55. Paramar J, Rane M. Tablet formulation design and manufacture: Oral immediate release application. Pharma Times. 2009;41:21-29.
56. Mandhar P, Joshi G. Development of sustained release drug delivery system: A review. Asian Pac J Health Sci. 2015; 2:179-185.