RESEARCH ARTICLE

Development of Sustained-Release Aceclofenac Tablets: Optimization of Polymer Matrices for Controlled Drug Delivery

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ABSTRACT:

Background: Aceclofenac is a widely used non-steroidal anti-inflammatory drug requiring frequent administration, making it a suitable candidate for a sustained-release formulation to improve patient compliance. **Objective:** This study aimed to formulate and evaluate sustained-release tablets of Aceclofenac using different polymer matrices to achieve a prolonged drug release profile. **Methods:** Tablets were formulated with varying concentrations of Carbopol, Kollidon SR, Eudragit L100, and their combinations using the wet granulation technique. The prepared granules were evaluated for flow properties (bulk density, tapped density, Hausner ratio, Carr's index, angle of repose). The resulting tablets were assessed for thickness, hardness, friability, weight variation, and content uniformity. *In vitro* drug release studies were conducted for 12 hours in 0.1 N KOH and phosphate buffer (pH 6.8) using USP apparatus II, and the drug release data were fitted to various kinetic models. **Main Outcome:** The primary outcomes were the physicochemical properties of the granules and tablets, and the drug release kinetics from the formulated matrix systems. **Results:** All formulated granules demonstrated acceptable flow properties, and the tablets complied with official limits for evaluated physicochemical parameters. The drug release from the optimized formulation U18 (Kollidon SR with Eudragit L100) best fitted the Higuchi model, while formulation U20 (Kollidon SR with Carbopol) followed zero-order release kinetics. **Conclusion:** The study successfully developed sustained-release Aceclofenac tablets. The optimized formulations U18 and U20, based on their distinct release kinetics, were identified as suitable matrix systems for providing sustained drug release.

Keywords: Aceclofenac, Sustained Release, Matrix Tablet, Drug Release Kinetics, Wet Granulation.

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1.1. Introduction

1.1. Oral controlled delivery system

Tablets are more accepted drug delivery system for oral administration. To ensure safety and to improve efficacy of drugs as well as patient compliance, are the main objectives of controlled release drug delivery systems. So, they are formulated to maintain the desired drug concentration and to provide a therapeutic amount of drug on the specific-site of absorption [1]. In most of cases, these conventional dosage forms are designed to release their drug rapidly for absorption, leading to wide fluctuation in plasma drug level after a multiple dose administration. Such fluctuations are unsatisfactory particularly for drugs with narrow therapeutic indexes. Increasing the dosing frequency especially for a drug with a short biological half-life may reduce these fluctuations, but this may lead to patient inconvenience and poor compliance. Sustained release dosage forms are thus designed with the aim to overcome these short comings.

Sustained release products always give an immediate release of drugs that produces the desired therapeutic effect, followed by gradual increase of additional amounts of drug to maintain this effect over a predetermined period of time. Sustained release delivery systems are specialized for chronic treatment and with narrow therapeutic indexes. Different techniques have been used in formulating controlled release products. Controlled release formulations can be divided into different categories based on the mechanism of drug [2].

1.2.1. Ion exchange resins

Ion exchange resins are cross-linked water-insoluble polymers carrying ionizable functional groups. The resins have been used in various pharmaceutical applications, primarily for taste masking and controlled release systems. In tablet formulations, ion exchange resins have been used as disintegrants because of their swelling ability. It forms irreversible complex with ionizable drugs upon prolonged exposure of the drug to the resin. A resin bound-drug is removed when appropriate ions are in contact with ion-exchanged groups. The amount of cross linked polymer, and the area and length of diffusion pathway governs the rate of drug release.

1.2.2. Dissolution controlled release

Dissolution controlled release system involves two processes, the detachment of drug molecules from the surface of their solid structure to the adjacent liquid interface, followed by their diffusion from the interface into the bulk liquid medium. The amount dissolved per unit of time from dissolution controlled release system and the rate of dissolution can be calculated using Noyes-Whitney equation (1987). In this type of controlled release system, the active ingredient diffuses through the polymeric material. Such type of systems mainly includes two types of systems reservoir and the matrix system.

1.2.4. Reservoir system

The reservoir system consists of a coating membrane (the diffusion barrier) and a core (the reservoir). In this system the active ingredient diffuses from the reservoir through the coating membrane. In reservoir system, the drug is depot which is surrounded by a polymeric hydrogel membrane. Fick's first law of diffusion can be used to define drug release through the membrane [3]. A matrix system consists of active and inactive ingredients that are homogenously dispersed and mixed in the dosage form. However, this is the most common prolonged release system because of their effectiveness, ease of manufacturing and low cost [4]. In matrix tablets, the drug compound is either suspended physically or dissolved molecularly as a particle mixture into the surrounding excipient [5] [2]. In this simplest form the matrix tablet consists of a single-unit and can be referred to as monolithic. It is the most famous technique used for oral controlled release technology, the popularity of the matrix systems defines various factors. The release from matrix type formulations governed by Fick's first law of diffusion:

$$J = dQ_t / dt = -D \; Dc/dx$$

Where, J is flux or rate of diffusion; Q is the amount diffused per unit time t and D is diffusion coefficient. Mainly most of the matrix release formulations utilize either hydrophobic or hydrophilic matrix system in which the drug is homogeneously distributed or dissolved in the polymeric matrix.

1.2.6. Hydrophobic matrix system

Hydrophobic systems are the only systems which don't require the use of polymer to provide controlled drug release, although insoluble polymers have been used. As the name suggests, the primary rate-controlling components of hydrophobic matrix are water insoluble in nature. These ingredients include glycerides [6], waxes [7, 8], acrylate copolymer [9, 10], fatty acids and polymeric materials such as ethyl cellulose , methyl cellulose (Makhija and Vavia, 2002; Crowely et al, 2004). For modulation of drug release, it is very important to incorporate soluble ingredients into the formulation such as lactose. During drug release the presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix. The corresponding release characteristic can be defined by Higuchi equation known as square root of time release kinetic [11] and the diffusion of the active ingredient from the system is the release mechanism [12]. The hydrophobic matrix system is not appropriate for insoluble drug because the concentration gradient is too low to render adequate drug release. As such, depending on actual ingredient formulation design or properties, incomplete drug release within the gastrointestinal transit time is a potential risk and need to delineate during the development. Within the developing needs of optimization of therapy, matrix system giving programmable rates of delivery become more important. Constant rate of release in delivery always has been one of the primary targets of controlled release system especially for drug with narrow therapeutic index.

1.2.7. Hydrophilic matrix system

The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell on contact with aqueous solution and form a gel layer on the surface of the system. When the release medium (i.e. water) is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process, due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since the diffusion path is lengthened by matrix swelling. Moreover, it has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release [13]. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms [14]. The enhanced motility of the polymeric chain favors the transport of dissolved drug. Polymer relaxation phenomena determine the swelling or volume increase of the matrix. Depending on the polymer characteristics, the polymer amount in the rubbery phase, at the surface of the matrix, could reach the disentanglement concentration; the gel layer varies in thickness and the matrix dissolves or erodes. The concentration at which polymeric chains can be considered disentangled was demonstrated to correspond to an abrupt change in the rheological properties of the gel. In turn, they affect drug release rate in the case of poorly soluble drugs. Swelling controlled release systems are based upon these principles. Due to the viscoelastic properties of the polymer which are enhanced by the presence of cross-linked network, anomalous penetrant transport can be observed. This behavior is bound by pure Fickian diffusion and case II transport. Therefore, transport can be reduced to three driving forces. The penetrant concentration gradient, polymer concentration gradient and osmotic force behavior are observed as a result of polymer network. Appropriate polymer can counterbalance normal Fickian diffusion by hindering the release of embedded drug, leading to an extended period of drug delivery, and possibly zero-order release [15]. Drug release from swellable matrix tablets can be affected by glassy-rubbery transition of polymer (as a result of water penetration into the matrix where interaction among water, polymer and drug or fillers is considered as the primary factor for release control) and the various formulation variables, such as polymer grade and type, drug to polymer ratios, drug solubility, drug and polymer particle sizes, compaction pressure and presence of additives or excipients in the final formulation. Lotfipour [16] investigated the effect of various polymers, fillers, and their concentration on the release rate of atenolol form polymeric matrix. They concluded that, the release rate and mechanism of atenolol releases from hydrophobic and hydrophilic matrices are mainly controlled by the drug to polymer ratio. The results also showed that an increase in the concentration of fillers resulted in an increase in the release rate of the drug from matrices and hydrophilicity or hydrophobicity of the fillers had no significant effect on the release profile. Regarding the mechanism of release, the results showed that in most cases the drug release was controlled by both diffusion and erosion depending on the polymer type and concentration. On the other hand, incorporation of water soluble fillers like polyethylene glycol, lactose and surfactant into gel forming matrices can improve phenomenon of insufficient drug release, because these excipients can enhance the penetration of the solvent or water into the inner part of matrices, resulting in drug release from the matrices [17].

1.2.8. Osmotic driven devices

In osmotic controlled release preparation, the function is based on either comparison or difference in osmotic pressure between two compartments which are separated using semi permeable membrane [18] [19, 20]. The basic concept of the osmotically active core consisting of the drug compound or an excipient draws surrounding liquid into the preparation; this creates a forceful pressure resulting the drug compound to diffuse out from a specially designed orifice. The principle based on the above theory is marketed by ALIZA Corporation for delivery of drugs having very low and high solubility. The advantages of this system include suitability for compounds having water solubility from moderate to extreme level, achievement of uniform drug release and a functionally regardless of the surrounding environment, i.e. changes in pH, ionic strength and microbiological activity [19]. However, due to their functionality is sensitive to deviations in their manufacture, due to their delicate structure and furthermore they may be considered to be expensive to mass produce [19].

1.2.9. Chemically controlled system

In chemically controlled systems, the drug is chemically controlled and is further dividing into two types, pendent chain system and bioerodible system. In bioerodible system the drug is uniformly distributed throughout the bioerodible polymer. The erosion of the bioerodible polymer carry out the release of the drug dissolved or dispersed in the bioerodible polymer. In second type of chemically controlled system, i.e. pendent chain system the drug is chemically bound to the polymer backbone chain and is released by either hydrolytic or enzymatic cleavage. The polymer system may be soluble or insoluble. The soluble forms are mainly used for transport functions such as cell targeting, insoluble forms are more appropriate for long term controlled release implants. The drug may be directly attached through the spacer pump or it may be attached to the polymer. In this aspect, the spacer group is used to affect the rate of release and hydrophilicity of the system.

1.2.10. pH controlled system

A pH controlled system had been developed to target delivery of drug only in the intestinal tract, not in the stomach, for a drug that is labile to gastric fluid.

1.2.11. Floating system

Floating drug delivery systems (FDDS) or hydro-dynamically balanced system have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time, without affecting the gastric emptying rate and the drug is released slowly at a desired rate from the system, results in an increase in the Gastric Residence Time (GRT) and a better control of fluctuations in the plasma drug concentrations and after complete release of the drug.

1.2.12. Ion exchange controlled system

These systems consist of a cross linked insoluble polymer backbone these polymers carry ionisable functional groups, drug is attached to these ionisable functional groups in an ionic form [20-22]. Ion exchange resins have many advantages as they provide uniform drug release, their function in the GI is robust, in theory, ion exchange resins are immune to enzymatic attack [20, 22]. In GI tract the pH and ionic strength give variations among different parts and they always show deviations among individuals. In these systems, the drug is released by diffusion [18] these systems have the capability to exchange the attached drug compound with ions from the surrounding liquid.

1.2.13. Enzymatically controlled system

In enzymatically controlled system the drug reservoir is chemically bounded to polymer chains fabricated from biopolymers, such as polypeptides or albumin. In this system the drug may be physically entrapped in the microspheres for their release mechanism. The release of drug is governed by enzymatic hydrolysis of biopolymer by a specific enzyme in the target tissues. The main example of this is the development of albumin microspheres that release 5-flourouracil in a controlled manner by a protease activated biodegradation.

1.2.14. Hydration-Activated drug delivery system

In this system, the release of drug is governed, activated and modulated by hydration induced swelling of the polymer matrix. When an oral tablet of hydrocolloids absorbs the gastric fluid and hence activated to form a colloid gel matrix surrounding the tablet surface [23]. Hydration activated drug delivery system drug reservoir is homogenously dispersed in a swellable polymer matrix fabricated from a hydrophilic polymer.

1.3. Advantages and disadvantages of controlled release dosage form

Within the inherited constrains of the gastrointestinal physiology involves development of oral controlled release dosage forms of a given drug involves optimization of the dosage form characteristics [24, 25]. Controlled release delivery systems have many advantages over immediate release dosage form. These include reduction in dosing frequency by administering the drug once or twice in a day [7]. Since, the patient compliance can be improved, administration can be convenient and the frequency of drug administration is reduced [17] because of reduction in gastrointestinal side effects [26]. Controlled release dosage form also leads to more uniform drug effect less fluctuation of plasma drug level and lesser total dose.

On other aspect, controlled delivery system also have some disadvantages which include, poor in vitro/vivo correlation, reduced bioavailability, higher cost, unpredictable, and subjected to increased first pass metabolism for certain drugs. A number of factors must be considered such as pH, differential absorption, motility, and ionic strength of luminal content are considered to exert control over the rate of the drug release, as well as movement of the dosage form through the gastrointestinal tract [27].

1.3. Preparation of sustained release matrix tablet

Matrix system is prepared by using different methods wet granulation as reported and documented in various studies [28-30].

1.3.1. Wet granulation

The wet granulation method of tablet production is essentially a process of size enlargement, sticking particles of drug and excipient together using an adhesive to produce a granular product that improves flow properties and an increased ability to cohere under pressure. A flow cycle of the process is shown in figure.

1.4. Aceclofenac

The aceclofenac is a white, crystalline, odorless compound. The Chemical name is [2-2-2-(2, 6-dicholorophenyl) amino] phenyl] acetyl] oxacetic acid. There molecular formula is $C_{16}H_{13}NO_4$.

1.4.5. Pharmacokinetics

Aceclofenac is well absorbed from the gastrointestinal tract; peak plasma concentrations are reached 1 to 3 hours after an oral dose. Aceclofenac is more than 99% bound to plasma proteins.
The plasma-elimination half-life is about 4 hours. About two thirds of a dose is excreted in the urine, mainly as hydroxyl metabolites. A small amount is converted to diclofenac. It has been suggested1 that low concentrations of diclofenac, a minor metabolite, may account for some of the actions of Aceclofenac [31].

1.4.6. Dose

The recommended starting dose of aceclofenac extended release tablet is 30mg given or a 60mg.

1.4.7. Mechanism of action

A mechanism of action usually includes mention of the specific targets to which the drug binds, such as an enzyme or receptor. Receptor sites have specific affinities for drugs based on the chemical structure of the drug, as well as the specific action that occurs there.

The mechanism of action of aceclofenac involves irreversible inhibition of the enzyme cyclooxygenase, therefore suppressing the production of prostaglandins and thromboxanes, therefore reducing pain and inflammation [31].

1.4.8. Adverse effects

The commonest adverse effects of aceclofenac are generally gastrointestinal disturbances, such as gastrointestinal discomfort, nausea, and diarrhea; these are usually mild and reversible but in some patient's peptic ulceration and severe gastrointestinal bleeding may occur. It is generally agreed that inhibition of cyclo-oxygenase- 1 (COX-1) plays an important role in the gastrointestinal effects of NSAIDs; the selective inhibition of COX-2 improves gastrointestinal tolerance. CNS-related adverse effects include headache, vertigo, dizziness, nervousness, tinnitus, depression, drowsiness, and insomnia. Hypersensitivity reactions may occur occasionally and include fever, angioedema, bronchospasm, and rashes. Hepatotoxicity and aseptic meningitis, which occur rarely, may also be hypersensitivity reactions. Some patients may experience visual disturbances.

Haematological adverse effects of aceclofenac include anemias, thrombocytopenia, neutropenia, eosinophilia, and agranulocytosis. Inhibition of platelet aggregation is reversible with other aceclofenac. Some NSAIDs have been associated with nephrotoxicity Such as interstitial nephritis and nephrotic syndrome; renal failure may be provoked by NSAIDs especially in patients with pre-existing renal impairment. Haematuria has also occurred. Long-term use or abuse of analgesics, including NSAIDs, has been associated with nephropathy.

Fluid retention may occur, rarely precipitating heart failure in susceptible patients. Other cardiovascular adverse effects are also shown in patients using aceclofenac.

Other adverse effects include photosensitivity. Alveolitis, pulmonary eosinophilia, pancreatitis, Stevens- Johnson syndrome, and toxic epidermal necrolysis are other rare adverse effects. Induction or exacerbation of colitis has also been reported. Further details concerning the adverse effects of the individual NSAIDs may be found under their respective monographs.

Most licensed product information recommends avoiding of aceclofenac in pregnancy. In many cases published data on use of the drugs in pregnancy is scantly or absent making an informed decision difficult. Use of aceclofenac during pregnancy may delay the onset of labour and increase its duration. Use of aceclofenac during the third trimester of pregnancy may result in the premature closure of fetal ductus arteriosus [31].

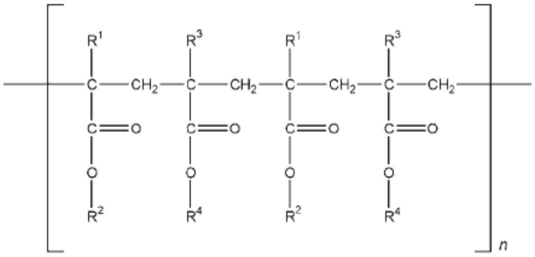
1.4.9. Drug interaction

Interactions involving aceclofenac include enhancement of the effects of oral anticoagulants and increased plasma concentrations of lithium, methotrexate, and cardiac glycosides. The risk of nephrotoxicity may be increased if given with ACE inhibitors, cyclosporine, tacrolimus, or diuretics. Effects on renal function may lead to reduced excretion of some drugs. There may also be an increased risk of hyperkalaemia with ACE inhibitors and some diuretics, including potassium sparing diuretics. The antihypertensive effects of some antihypertensives including ACE inhibitors, beta blockers, and diuretics may be reduced. Convulsions may occur due to an interaction with quinolones. Aceclofenac may increase the effects of phenytoin and sulfonylurea ant diabetics. Use of more than one NSAID together (including aspirin) should be avoided because of the increased risk of adverse effects. The risk of gastrointestinal bleeding and ulceration associated with aceclofenac is increased when used with corticosteroids, the SSRIs, the SNRI venlafaxine, the antiplatelets clopidogrel and ticlopidine, iloprost, erlotinib, sibutramine, or, possibly, alcohol, bisphosphonates, or pentoxifylline. There may be an increased risk of haematotoxicity if zidovudine is used with aceclofenac. Ritonavir may increase the plasma concentrations of aceclofenac. Licensed product information for mifepristone advises of a theoretical risk that prostaglandin synthetase inhibition by NSAIDs or aspirin may alter the efficacy of mifepristone. There have been occasional reports of increased adverse effects when aceclofenac was given with misoprostol although such combinations have sometimes been used to decrease the gastrointestinal toxicity of Aceclofenac [31].

1.5. Eudragit L 100 (E L100):

Eudragit is also called Methacrylic acid copolymers. There Chemical name is Poly(methacrylic acid, methyl methacrylate) 1 : 1. There molecular mass of about 135 000. Eudragit L 100 is an anionic, white free flowing powder. It is used as Film-forming agent; tablet binder; tablet diluents.

1.5.3. Structural formula:



Where, R1, R3 = CH_3**;** R2 = H**;** R4 = CH_3

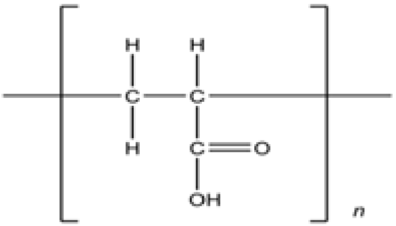
1.5.9. Application in pharmaceutical preparations:

Eudragit L 100 is used for enteric coating. Larger quantities (5–20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct compression processes in quantities of 10–50%. These polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration [32].

1.6. Carbopol:

1.6.1. Chemical description: High molecular weight non-linear polyacrylic acid crossed-linked with polyalkenyl polyether. Its physical appearance is white colored, 'fluffy', acidic, hygroscopic powders with a slight characteristic odor. The Bulk density is 1.76-2.08 g/cm and tapped density is 1.4g/cm.

1.6.3. Structural formula:



1.6.6. Moisture content: Normal water content is up to 2% w/w. however, carbopols are hygroscopic and a typical equilibrium moisture content at 25°C and 50% relative humidity is 8-10% w/w. the moisture content of a carbopol does not affect its thickening efficiency, but an increase in the moisture content makes the carbopol more difficult to handle because it is less readily dispersed.

1.6.7. Solubility:

Soluble in water and, after neutralization, in ethanol (95%) and in glycerin. However, they are described as 'soluble', carbopol do not dissolve but merely swell to a remarkable extent, since they are three dimensionally cross linked micro gels. Packaging in aluminum tubes usually requires a formulation to have a pH less than 6.5, and packaging in other metallic tubes or containers necessitates a pH greater than 7.7 to prolong carbopol stability.

1.6.8. Applications:

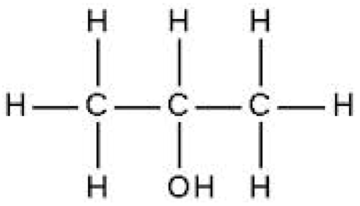
These are mainly used in liquid or semi-solid formulations as suspending or viscosity-increasing agents. Formulations include creams, gels and ointments for use in ophthalmic, rectal and topical preparations. Carbopol grades, even with low residual benzene content, such as carbopol 934P, are no longer included in the PhEur 2005. However, carbopol having low residuals only of other solvents than the ICH-defined 'Class I 0VI solvents' may be used in Europe.

Carbopol having low residuals only of ethyl acetate, such as carbopol 971P and 974P, may be used in oral preparations, in suspensions, tablets, or sustained release tablet formulations. In tablet formulations, carbopol are used as dry or wet binders and as a rate-controlling excipient. In wet granulation processes, water or an alcohol-water blend is used as the granulating fluid. The thickness of the wet mass can be reduced with the addition of certain cationic species to the granulating fluid or, in the case of water, with talc or magnesium stearate in the formulation. Carbopol resins have also been investigated in the preparation of sustained release matrix beads, as enzyme inhibitors of intestinal proteases in peptide containing dosage forms, as a bioadhesive for a cervical patch and for intranasaly administered microspheres, in magnetic granules for site-specific drug delivery to the esophagus and in oral mucoadhesive controlled drug delivery systems. Carbopol are also employed as emulsifying agent in the preparation of oil-in-water emulsions for external use. For this purpose, the carbopol is neutralized partly with sodium hydroxide and partly with a long chain amine such as stearylamine. Carbopol 951 has been reported as a viscosity-increasing aid in the preparation of multiple emulsion microspheres. Carbopol are also used in cosmetics. Therapeutically, cabopol gel formulations have proved efficacious in improving symptoms in moderate to severe dry eye syndrome [32].

1.7. Isopropyl alcohol:

The Empirical Formula is C_3H_8O and molecular weight is 60.1g. It is used as disinfectant solvent.

1.7.4. Structural Formula:



1.7.6. Description:

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

1.7.7. Solubility:

It is miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt solutions. Forms an azeotrope with water, containing 87.4% w/w isopropyl alcohol (boiling point 80.378C).

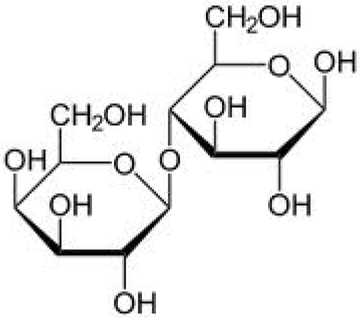
1.7.8. Applications in Pharmaceutical Formulation or Technology:

Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations primarily as a solvent in topical formulations. It is not recommended for oral use owing to its toxicity. Although it is used in lotions, the marked degreasing properties of isopropyl alcohol may limit its usefulness in preparations used repeatedly. Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation. It has also been shown to significantly increase the skin permeability of nimesulide from carbomer 934. Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting [32].

1.8. Lactose:

The Chemical Name is O-b-D-Galactopyranosyl-(1-4)-a-D-glucopyranose, molecular weight is 360.31 and empirical formula is $C_{12}H_{22}O_{11}.H_2O$. It is used as Binding agent; diluent for dry-powder inhalers; tablet binder; tablet and capsule diluent.

1.8.4. Structural Formula:



1.8.6. Description: In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. alactose monohydrate, b-lactose anhydrous, and a-lactose anhydrous. The stable crystalline forms of lactose are a-lactose monohydrate, b-lactose anhydrous, and stable a-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; a-lactose is approximately 20% as sweet as sucrose, while b-lactose is 40% as sweet.

1.8.9. Applications in Pharmaceutical Formulation or Technology:

Lactose is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluent in dry-powder inhalation. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently. Other applications of lactose include use in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions. Direct-compression grades of lactose monohydrate are available as granulated/agglomerated a-lactose monohydrate, containing small amounts of anhydrous lactose.

Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation. Other directly compressible lactoses are spray-dried lactose and anhydrous lactose [32].

1.9. Kollidone SR-100:

The Synonyms is E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer and empirical formula is $(C_6H_9NO)n$. Its molecular weight is 2500–3 000 000 and used as a Disintegrant; dissolution aid; suspending agent; tablet binder.

1.9.6. Description:

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.

1.9.9. Solubility: freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

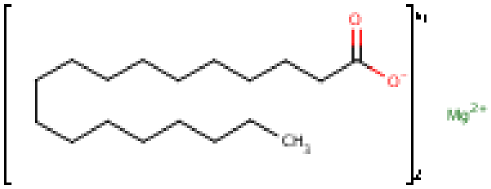
1.9.10. Applications in Pharmaceutical Formulation or Technology:

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wetgranulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.(4–6) Povidone solutions may also be used as coating agents. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone. Special grades of pyrogen-free povidone are available and have been used in parenteral formulations [32].

1.10. Magnesium stearate:

The Synonym is Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt. The chemical name is Octadecanoic acid magnesium salt. Its empirical Formula is $C_{36}H_{70}MgO_4$ and molecular weight is 591.34 and used as a tablet and capsule lubricants.

1.10.4. 1.10.5. Structural Formula:



1.10.7. Description:

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin. Its Solubility is practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

1.10.10. Applications in Pharmaceutical Formulation or Technology:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams [32].

1.11. PVP (polyvinyl pyrollidone)

The Synonyms is E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer. Its empirical formula is $(C_6H_9NO)_n$ and molecular weight is 2500–3 000 000. It is used as a Disintegrant; dissolution aid; suspending agent; tablet binder.

1.11.6. Description:

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates. It is freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

1.11.10. Applications in Pharmaceutical Formulation or Technology:

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wetgranulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.(4–6) Povidone solutions may also be used as coating agents. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone. Special grades of pyrogen-free povidone are available and have been used in parenteral formulations [32].

Methodology:

3.2.1. Preparation of matrix tablet containing carbopol

The drug, aceclofenac, was kept constant and concentration of carbopol was varied. For the development of matrix tablet accurately weighed amount of carbopol, lactose, PVP and magnesium stearate were taken. The quantities are given in table 1. Weighed amount of lactose was added in the mortar followed my weighed amount of carbopol. In the end drug was added. For the granulation purposes IPA was added drop wise along the walls of mortar. The material was then triturated slowely. For 7 to 10 minutes. The wet mass was then passed through sieve no.20. Dried the wet granules in hot air oven for 60 minutes. The granules were then used for pre compression tests and tablets were made [33, 34].

3.2.2. Preparation of matrix tablet containing kollidone SR

The drug, aceclofenac, was kept constant and concentration of kollidone SR was varied. For the development of matrix tablet accurately weighed amount of kollidone SR, lactose, PVP and magnesium stearate were taken. The quantities are given in table 2. Weighed amount of lactose

Table 3.1: Formulation of aceclofenac sustained release matrix tablet using carbopol as polymer

Formulation	Drug (mg)	Polymer (mg)	Lactose (mg)	PVP (mg)	Mg.stearate (mg)	IPA (ml)	Total weight

							(mg)
U1	6	0.75	6.900	0.01	0.01	q.s	500
U2	6	2.25	6.150	0.01	0.01	q.s	500
U3	6	3.00	5.400	0.01	0.01	q.s	500
U4	6	3.750	4.650	0.01	0.01	q.s	500
U5	6	4.500	3.900	0.01	0.01	q.s	500
U6	6	5.250	3.150	0.01	0.01	q.s	500

was added in the mortar followed my weighed amount of kollidone SR. In the end drug was added. For the granulation purposes IPA was added drop wise along the walls of mortar. The material was then triturated slowly for 7 to 10 minutes. The wet mass was then passed through sieve no.20. Dried the wet granules in hot air oven for 60 minutes. The granules were then used for pre compression tests and tablets were made .

3.2.3. Preparation of matrix tablet containing Eudragit L100

The drug, aceclofenac, was kept constant and concentration of Eudragit L100 was varied. For the development of matrix tablet accurately weighed amount of Eudragit L100, lactose, PVP and magnesium stearate were taken. The quantities are given in table 2. Weighed amount of lactose was added in the mortar followed my weighed amount of Eudragit L100. In the end drug was added. For the granulation purposes IPA was added drop wise along the walls of mortar. The material was then triturated slowly. For 7 to 10 minutes. The wet mass was then passed through sieve no.20. Dried the wet granules in hot air oven for 60 minutes. The granules were then used for pre compression tests and tablets were made [35].

3.3. Physicochemical tests performed on Aceclofenac matrix tablets

3.3.1.1. Bulk density

Apparent bulk density was determined by placing pre-sieved drug excipient blend in to a graduated cylinder and measuring the weight and volume [36].

Bulk density= mass/ bulk volume

3.3.1.2. Tapped density

Tapped density was determined by USP method II tablet blend was filled in 100ml graduated cylinder of tap density tester which was operated for fix number of taps until the powder bed volume has reached a minimum, thus was calculated by a formula [36],

Tapped density = mass/ tapped volume

Table 3.2: Formulation of aceclofenac sustained release matrix tablet using kollidone SR as polymer

Formulation	Drug (mg)	Polymer (mg)	Lactose (mg)	PVP (mg)	Mg.stearate (mg)	IPA (ml)	Total weight (mg)
U7	6	0.75	6.900	0.01	0.01	q.s	500
U8	6	2.25	6.150	0.01	0.01	q.s	500
U9	6	3.00	5.400	0.01	0.01	q.s	500
U10	6	3.750	4.650	0.01	0.01	q.s	500
U11	6	4.500	3.900	0.01	0.01	q.s	500
U12	6	5.250	3.150	0.01	0.01	q.s	500

Table 3.3: Formulation of aceclofenac sustained release matrix tablet using Eudragit L100 as polymer

Formulation	Drug (mg)	Polymer (mg)	Lactose (mg)	PVP (mg)	Mg.stearate (mg)	IPA (ml)	Total weight (mg)

U13	6	0.75	6.900	0.01	0.01	q.s	500
U14	6	2.25	6.150	0.01	0.01	q.s	500
U15	6	3.00	5.400	0.01	0.01	q.s	500
U16	6	3.750	4.650	0.01	0.01	q.s	500

3.3.1.3. Angle of repose

Angle of repose was determined by using funnel method. Tablet blend were poured from funnel, that can be raised vertically until a maximum cone height h was obtained diameter heap D, was measured. The repose angle q was calculated by formula [36],

$$\tan \theta = 2h/D$$

Where, h=height; D=diameter of the cone

3.3.1.4. Hausner ratio

Hausner ratio was calculated using the following formula,

$$H = V_0/V_f$$

Where, V_0: initial volume; V_f: final volume

3.3.1.5. Carr's index or compressibility index

The Carr's index of the granules was determined by measuring both the bulk volume and tapped volume of a powder, it is calculated by using following formula [36],

$$\text{Carr's index} = 100 x V_0 - V_f / V_0$$

Where, V_0: initial volume; V_f: final volume

3.3.2. Post-compression

3.3.2.1. Thickness

The thickness of the tablets was determined using a thickness gauge five tablets from each batch were used, and average values were calculated.

3.3.2.2. Weight variation

This is an important in-process quality control test to be checked frequently. Corrections were made during the process of compression. According to USP-NF 20 tablets were weighed individually. Average weight was calculated from the total weight of all the tablets. The individual weight was compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±7.5).the percent deviation was calculated by the following formula [37].

Percentage deviation = (individual weight - average weight/average weight) × 100

3.3.2.3. Hardness test

Hardness is a force required to break a tablet across the diameter. The force is measured in kilograms. The hardness was tested using Monsanto tester. Hardness factor is the average of the six determinations was determined and reported.

3.3.2.4. Diameter

The diameter of the tablets was determined using a diameter gauge five tablets from each batch were used, and average values were calculated.

3.3.2.5. Friability

Roche friabilator was used to measure the friability of the tablets. It was rotated at the rate of 25 rpm. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the fraibilator the tablets were exposed to rolling, resulting in free fall of tablets within the chamber of the fraibilator. After 100 rotations the tablets were taken out of the fraibilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%.the percent friability was determined by using following formula [37].

Percentage friability= $(W_1-W_2)/W_1 \times 100$

Where, W_1: weight of tablets before test; W_2: weight of tablets after test

3.3.2.6. Content uniformity

20 tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in the mortar and the powder equivalent to 100mg drug was transferred to 100ml volumetric flask. The powder was dissolved in 5ml of 70% methanol and the volume was adjusted with phosphate buffer pH 6.8.the sample was mixed thoroughly and filtered through a Whitman filter paper, the filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer at 276nm [37].

3.3.2.7. *In vitro* disintegration time

The in-vitro disintegration time was determined using disintegration test apparatus (Eureka Alpha/Numerous disintegration tester). A tablet was placed in each of the six tubes of the apparatus and a disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no discernible mass remaining in the apparatus was measured.

3.3.2.8. *In vitro* dissolution study

The study was carried out using 0.1N KOH and phosphate buffer 6.8 using the USP apparatus type II. The total volume of dissolution medium was 900ml maintained at 37 ± 0.5°C. The absorbance was at measured 273 nm on UV spectrophotometer. The dissolution study was carried out for 12 hrs.

3.4. Release rate kinetic

From time to time, several authors and researchers gave different types of drug release mechanisms from matrices. Several kinetics models like zero order, first order, Higuchi and Peppas model were used to determine the release kinetic. Equation used for zero-order release model [38], first-order model, Higuchi model [11] and Peppas model [39] were given below from Eqs. i to iii respectively,

$Q = k_1 t$ -- i

$Q = 100(e^{k2t})$ -- ii

$Q = k_3 t^{1/2}$ --iii

Where, Q is % drug released at time t; k_1, k_2 and k_3 are release rate constants, depending on the kinetic model used; k_4 is a constant incorporating the structural and geometric characteristics of the tablet.

The term ‘n’ is the diffusion constant that characterizes the drug release transport mechanism. When n=0.45 or 0.45<n<0.89 or n>0.89, indicates fickian diffusion or anomalous transport or case II transport kinetics respectively.

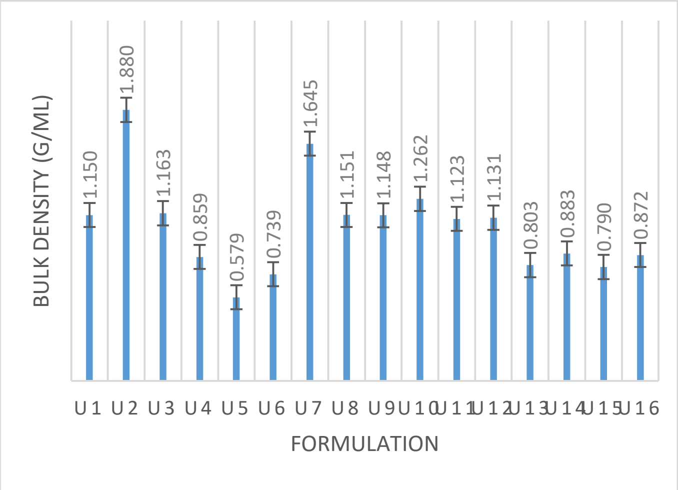
3. Result and discussion

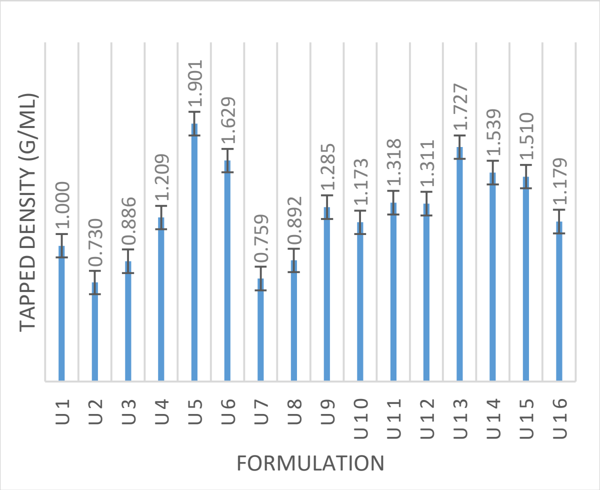
3.1. Precompression studies of Aceclofenac sustain release tablet

The results of bulk density is given in table 3.1 and shown in figure 3.1. The values ranged from 0.579 g/ml to 1.880 g/ml. The maximum density was seen in U2 and minimum was estimated in U5. Bulk density depicts the passive filling of powder into a measuring vessel (USP-NF, 2012). Bulk density mainly depends on particle shape; spherical particles have higher density as compared to particles with irregular shape.The result of tapped density is given in table 3.1 and demonstrated in figure 3.2. The minimum tapped density was seen in U2 with a value of 0.730 g/ml where as maximum tapped density was seen in U5 with a value of 1.901 g/ml. The tapped density was a limiting density attained after tapping down a powder in a volumetric measuring cylinder (USP-NF, 2012). The Hausner ratio obtained for different formulations is given in table 3.1 and depicted in figure 3.3. An excellent flow rate was obtained in U3, U4, U5, U8 and U16 with Hausner ratio of 1.030, 1.039, 1.101, 1.027 and 1.029 respectively. A good flow property was seen in U1 formulation with Hausner ratio of 1.150. The flow rate was fair in U6, U7 and U15 with values of 1.203, 1.249 and 1.193 respectively. A poor flow property was obtained in U2, U13 and U14 with a ratio of 1.372, 1.387 and 1.360 respectively where as very poor flow rate was seen in U9, U10, U11 and U12 with a value of 1.475, 1.481, 1.480 and 1.483 respectively. It was thus observed that formulation containing Carbopol gave excellent to fair flow properties with different polymer concentrations. The flow property improved from poor to excellent when concentration of Eudragit L100 was increased. The formulation containing Kollidon SR gave very poor flow property when the concentration of polymer was increased. The result of Carr's index is given in table 3.1 and compared in figure 3.4. The results depict that an excellent flow rate was obtained in U3, U4, U5, U8 and U16 with values of 2.913, 3.738, 9.167, 2.644 and 2.778 respectively. A good flow rate was obtained in U1 with value of 13.025. The flow rate was fair in U6, U7 and U15 with Carr's index of 16.901, 19.920 and 16.154 respectively. A poor flow rate was seen in U2, U12 and U13 with values of 27.094, 27.891 and 26.460 respectively. The flow rate was very poor in U9, U10, U11 and U12 which had Carr's index of 32.226, 32.459, 32.450 and 32.566. The Carr's index and Hausner ratio are measures of tendency of a powder to be compressed. The interparticulate interactions that influence the bulking properties of a powder also interfere with powder flow so a comparison of the bulk and tapped densities give a measure of the relative importance of these interactions in a given powder. Such a comparison was used as an index of the ability of the powder to flow (USP-NF, 2012). The values of angle of repose are given in table 3.1. All the formulations showed improved flow properties after addition of magnesium stearate as a lubricant and thus angle of repose depicted excellent flow rate according to USP-NF (2012). The tablets were thus compressed by singe punch machine.

3.2. Post compression studies of Aceclofenac sustain release tablet

The result for tablet thickness is given in table 3.2 and depicted in figure 3.5. Thickness of tablets varied between 5.6 mm to 7.7 mm with minimum thickness observed in U1 and maximum thickness was seen in U7. Lower value of standard deviation (S.D.) ensures that thickness of the tablets were consistent with negligible variation. Tablet thickness is consistent if the tablet granulation is adequately constant in particle size, particle size distribution, if the punch tooling is of consistent length if the tablet press is clean and in good working condition.





References

1. Longer, M.A. and J.R. Robinson, *Sustained-release drug delivery systems.* Remington's pharmaceutical sciences, 1990: p. 1676-1693.
2. Tang, Y.-D., et al., *Sustained release of hydrophobic and hydrophilic drugs from a floating dosage form.* International journal of pharmaceutics, 2007. **336**(1): p. 159-165.
3. Lin, C.-C. and A.T. Metters, *Hydrogels in controlled release formulations: network design and mathematical modeling.* Advanced drug delivery reviews, 2006. **58**(12): p. 1379-1408.
4. Abdul, S. and S. Poddar, *A flexible technology for modified release of drugs: multi layered tablets.* Journal of controlled release, 2004. **97**(3): p. 393-405.
5. Skoug, J.W., et al., *Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms by measurement of polymer release.* Journal of controlled release, 1993. **27**(3): p. 227-245.
6. Freiberg, S. and X. Zhu, *Polymer microspheres for controlled drug release.* International journal of pharmaceutics, 2004. **282**(1): p. 1-18.
7. Hayashi, T., et al., *Formulation study and drug release mechanism of a new theophylline sustained-release preparation.* International journal of pharmaceutics, 2005. **304**(1): p. 91-101.
8. Vergote, G., et al., *Wax beads as cushioning agents during the compression of coated diltiazem pellets.* European journal of pharmaceutical sciences, 2002. **17**(3): p. 145-151.
9. Azarmi, S., et al., *Thermal treating as a tool for sustained release of indomethacin from Eudragit RS and RL matrices.* International journal of pharmaceutics, 2002. **246**(1): p. 171-177.
10. Krajacic, A. and I.G. Tucker, *Matrix formation in sustained release tablets: possible mechanism of dose dumping.* International journal of pharmaceutics, 2003. **251**(1): p. 67-78.
11. Higuchi, T., *Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices.* Journal of pharmaceutical sciences, 1963. **52**(12): p. 1145-1149.
12. Kincl, M., S. Turk, and F. Vrečer, *Application of experimental design methodology in development and optimization of drug release method.* International journal of pharmaceutics, 2005. **291**(1): p. 39-49.
13. Sujja-Areevath, J., et al., *Relationship between swelling, erosion and drug release in hydrophillic natural gum mini-matrix formulations.* European journal of pharmaceutical sciences, 1998. **6**(3): p. 207-217.
14. Tahara, K., K. Yamamoto, and T. Nishihata, *Application of model-independent and model analysis for the investigation of effect of drug solubility on its release rate from hydroxypropyl methylcellulose sustained release tablets.* International journal of pharmaceutics, 1996. **133**(1): p. 17-27.

15. Cox, P.J., et al., *Development and evaluation of a multiple-unit oral sustained release dosage form for< i> S</i>(+)-ibuprofen: preparation and release kinetics.* International journal of pharmaceutics, 1999. **193**(1): p. 73-84.
16. Lotfipour, F., et al., *The effect of hydrophilic and lipophilic polymers and fillers on the release rate of atenolol from HPMC matrices.* Il Farmaco, 2004. **59**(10): p. 819-825.
17. Nokhodchi, A., et al., *The effect of various surfactants on the release rate of propranolol hydrochloride from hydroxypropylmethylcellulose (HPMC)-Eudragit matrices.* European journal of pharmaceutics and biopharmaceutics, 2002. **54**(3): p. 349-356.
18. Florence, A.T., D. Attwood, and D. Attwood, *Physicochemical principles of pharmacy*. 2011: Pharmaceutical Press.
19. Verma, R.K., D.M. Krishna, and S. Garg, *Formulation aspects in the development of osmotically controlled oral drug delivery systems.* Journal of Controlled Release, 2002. **79**(1): p. 7-27.
20. Venkatraman, S., et al., *An overview of controlled release systems*. 2000: Marcel Dekker, New York.
21. Pongjanyakul, T. and S. Puttipipatkhachorn, *Xanthan–alginate composite gel beads: molecular interaction and in vitro characterization.* International journal of pharmaceutics, 2007. **331**(1): p. 61-71.
22. Anand, V., R. Kandarapu, and S. Garg, *Ion-exchange resins: carrying drug delivery forward.* Drug Discovery Today, 2001. **6**(17): p. 905-914.
23. Chien, Y.W. and S. Lin, *Drug delivery: Controlled release.* Encyclopedia of pharmaceutical technology, 2002. **1**: p. 811-833.
24. Dube, V., S. Payghan, and J. D'souza, *Development of colon targeted Lornoxicam matrix tablet.* International J of Pharmaceutical Research and Development, 2011. **3**(6): p. 226-232.
25. Abdelraziq Abdelkareem Adam, F., *Design And Evaluation Of Prolonged Release Gliclazide Matrix Tablets*. 2007, Universiti Sains Malaysia.
26. Hosny, E.A., S.S. Abdel-Hady, and K.E. El-Tahir, *Formulation, in-vitro release and ex-vivo spasmolytic effects of mebeverine hydrochloride suppositories containing polycarbophil or polysorbate 80.* International journal of pharmaceutics, 1996. **142**(2): p. 163-168.
27. Gupta, P.K. and J. Robinson, *Oral controlled release delivery.* Treatise on controlled drug delivery", Kydonieus, A.(ed.), Marcel Dekker, New Jersey (1992) 255, 1992. **310**.
28. Huang, Y., et al., *Effects of manufacturing process variables on in vitro dissolution characteristics of extended-release tablets formulated with hydroxypropyl methylcellulose.* Drug development and industrial pharmacy, 2003. **29**(1): p. 79-88.
29. Kavanagh, N. and O.I. Corrigan, *Swelling and erosion properties of hydroxypropylmethylcellulose (Hypromellose) matrices—influence of agitation rate and dissolution medium composition.* International journal of pharmaceutics, 2004. **279**(1): p. 141-152.
30. Iqbal, Z., et al., *Preparation and in-vitro in-vivo evaluation of sustained release matrix diclofenac sodium tablets using PVP-K90 and natural gums.* Pakistan journal of pharmaceutical sciences, 2011. **24**(4).
31. Martindale, *The Complete Drug Reference*. 36th ed. 2009, 1 Lambeth High Street, London SEl 7JN, UK: Pharmacuetical press. 3709.
32. Raymond C Rowe, P.J.S.a.M.E.Q., ed. *Handbook of Pharmaceutical Excipients*. 6th ed. 2009, Pharmaceutical Press: 1 Lambeth High Street, London SE1 7JN, UK. 888.
33. Bhupendra Prajapati, R.P., Dhaval Patel, Payal Shah, *Metformin hydrochloride sustained release tablet using different matrixing tablet.pdf.* e-Journal of Science & Technology (e-JST), 2013. **4**(8).
34. Sandhiya.K. M , s.S.a.v.T., *DESIGN AND DEVELOPMENT OF AMBROXOL HYDROCHLORIDE SUSTAINED RELEASE MATRIX TABLETS.* International Journal of Pharmacy and Pharmaceutical Sciences, 2011. **3**(3).
35. Md. Saiful Islam, F.K., Reza-ul Jalil, *Sustained release Theophylline Matrix Tablets Prepared by direct compression; Effect of Polymers.* Bangladesh Pharmaceutical Journal, 2010. **12**(1).
36. Atram Sandeep C., R.P.N., Syed Faizi M, Bobade Nishan N, Deshmukh Abhishek D., *Influence of different polymers in the formulation and in-vitro evaluation of chlorzoxazone extended release matrix tablet.* International Journal of Pharmacy and Pharmaceutical Science Research, 2013. **3**(1).
37. Suresh V Kulkarni, N.P., Someshwara Rao B, Pratik Kheni, and A.A. Patel Priti, *Formulation and In Vitro Evaluation of Sustained Release Matrix Tablet of Zolpidem Tartrate.pdf.* International Journal of PharmTech Research, 2011. **3**(2): p. 858-863.

38. Xu, G. and H. Sunada, *Influence of formulation change on drug release kinetics from hydroxypropylmethylcellulose matrix tablets*. Chemical & pharmaceutical bulletin, 1995. **43**(3): p. 483-487.
39. Ritger, P.L. and N.A. Peppas, *A simple equation for description of solute release II. Fickian and anomalous release from swellable devices*. Journal of Controlled Release, 1987. **5**(1): p. 37-42.