A Review on PREPARATION OF DICLOFENAC SODIUM MATRIX TABLETS

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ABSTRACT

Diclofenac sodium (DS) is a sodium [2(2,6 dichloroanilino) phenyl] acetate-based non steroidal anti-inflammatory and analgesic. It has been used to treat osteoarthritis and rheumatoid arthritisonalong-term, symptomatic basis. The prevention or decrease of negative effects brought on by dosage dumping or excessive plasma drug concentrations. Lower dosage leads to an improvement in patient compliance. Products should be chewed or crushed because doing so can cause toxicity and a loss of the gradual release features of the product. The type of substituents that make up the polymer, such as their molecular structure or level of substitution, determine how quickly HPMC hydrates. DS was weight using a Denver electronic balance (swiss made), and all of the excipients were properly combined to ensure consistent mixing before being sieved using a 60mesh screen. The funnel method was used to calculate the angle of repose. The IP was used to determine the medication content.

KEYWORDS- osteoarthritis, gradual, viscosity, demonstrate, hydroxypropyl methylcellulose, ionicstrength.

INTRODUCTION

Diclofenac sodium (DS) is a sodium [2(2,6dichloroanalio) phenyl] acetate-based non-steroidal anti-inflammatory and analgesic. It has been used to treat osteoarthritis and rheumatoid arthritis on a long-term, symptomatic basis. The typical oral dose ranges from 75-150 mg per day in divided doses, Once per day. A sustained-release tablet matrix containing 100 mg of Diclofenac sodium is administered.[1,2]Incorporating a tablet drug delivery system into a matrix system is one of the most often utilized ways to modulate tablet medication release. Matrix structure, release kinetics, controlled release qualities (diffusion, erosion, swelling), and the chemical makeup and characteristics of the materials used are all taken into consideration when categorizing matrix systems.[3] the three basic categories for matrix

systems are hydrophilic, inert, and lipidic. Because of its benign properties, ability to withstand high amounts of drug loading, and lack of pH dependence HPMC, a semisynthetic nonionic cellulose ether is frequently employed in controlled-release dosage forms. A hydrated viscous layer that forms at the tablet's edge function as a barrier to drug release and regulates the release of drug from hydrophilic matrix tablets.[4] several factors, including tablet form, size, and surface area, may have an impact on the amount of drug released from HPMC matrix tablets.[5] Extended-release dosage forms are frequently created using hydrophilic matrices, commonly utilized as gel-forming agents, cellulose ethers like hydroxypropyl methylcellulose (HPMC) are sometimes referred to as the swellable matrix.[6,7]

Advantages

1. Due to the drug's extended duration of release compared to normal tablets, the frequency of dose is reduced.[8] for example, high pain management in terminally ill patients, this is very helpful for individuals with chronic illnesses that require plasma concentrations a prevent break through symptoms.[9]
2. The prevention or decrease of negative effects brought on by dosage dumping or excessive plasma drug concentrations.[10]
3. Lower dosage leads to an improvement in patient compliance.
4. Improve the rapeutic medication concentration control.
5. Cost-effective manufacturing since fewer pills is required for each patient than in its traditional form.

Disadvantages

1. Cost of development: some controlled release formulations may need pricey specialized equipment and inert substance.
2. Release rate: food and gastric transit time might affect the drug's release rate causing a change in release rate between doses.
3. Products should be chewed or crushed because doing so can cause toxicity and a loss of the gradual release features of the product.

POLYMER USED IN SODIUM DICLOFENAC TABLET MATRIX

Hydroxypropyl methylcellulose (HPMC)-

A non-ionic derivative of cellulose ethers is called HPMC.[13] It is stable between PH 3.0 and 11.[14] HPMC, or Hydroxypropyl methylcellulose, is a semi-artificial polymer.[15,16,17]As it offers a reliable mechanism for the regulated release of the medication and a range of viscosity grades, it is chosen as the primary option for the formulation of a hydrophilic matrix system. Because it is non-ionic, interaction issues in electrolytic, acidic, or basic systems are minimized and the release profiles are repeatable. Additionally, it is economical. [18,19] The type of substituents that make up the polymer, such as their molecular structure or level of substitution, determine how quickly HPMC hydrates.[20]

Various grades of HPMC-

Additionally, HPMC comes in a variety of viscosity grades. Chemistry also illustrates. The chemistry of the kind of cellulose ethers is identified by the first letter; the letter designated various HPMC products. One of the most popular ingredients for the formulation of controlled release medication second (m.pa.s) grade of viscosity for the product measured in 2%aqueous solutions at 20°c is also indicated by the number that follows the initial letter. a centipoise is a unit of measure for a milli pascal second (cps). The letter that comes after viscosity. The letter M denotes a multiplied by 1000 number and the abbreviation LV stands for unique low viscosity items. Grades of controlled release are identified by the term CR.[21] Due to its quick hydration excellent compression and gelling properties. HPMC is considered to have been the most commonly utilized swellable polymer for delaying drug release. Additionally, it is generally easily available for use and has a relatively low level of toxicity. As a result, when utilized as a carrier in a medication release system it has proven substance of tremendous significance.[22]

Mechanisms of diffusion-

According to Alderman (1984), a gel layer forms around a tablet when hydrophilic matrices are submerged in aqueous solutions, I.e. the polymer hydrates and swells in gastrointestinal fluids growing in size as a result. After some time, the matrix erodes or dissolves, allowing the release of the medication. The insoluble portion of the medication is released through tablet disintegration, whilst the soluble portion is released through diffusion through the gel layer.[23,24] According to studies, the amount of medication released from swellable hydrophilic matrices depends on how thick the hydrated layer is when the polymer is hydrated. The pace of drug release is determined by the degree of swelling; the slower the rate of drug release the thicker the gel layer. [25] The definition of viscosity is the measure of a fluid's resistance to flow. The molecular weight of the polymer has an impact on the Viscosity of a polymer solution. The hydrogen

bonding of oxygen atoms in ether links, which causes them to expand and form relatively open random coils is what gives polymers solution their viscosity. The hydrated coils keep forming hydrogen bonds with new water molecules trapping them inside the coils. Therefore the degree of drug release from hydrophilic matrices can be influenced by viscosity.

Utilizing the non-steroidal anti-inflammatory medication diclofenac sodium, the viscosity grades of the HPMC matrix system were investigated as oral controlled-release drug delivery systems. All HPMC viscosity, including K100M, K15M, K4M, and K100LV, were utilized. The finding shows a clear distinction between the drug release profile from various Matrices. Incomparison to the lower viscosity grade K100LV, the medication release from K100M was slower. Diclofenac sodium prolonged the time in the HPMC K100M Matrix allowing it to avoid harmful effects on the gastrointestinal tract. the viscosity classes of HPMC had a substantial impact on the release rate, with low viscosity HPMC showing a statically significant increase in drug release.

Factors affecting drug release-Effects of pH-

Under fed and fasted settings, the gastrointestinal (GI) PH, one of the key characteristics of GI fluids, differs significantly along the digestive tract. It can have an impact on the production of gel layers and the dynamic of the HPMC hydrophilic matrix system.[26] the viscosity of HPMC polymers is typically stable over a broad pH range of 3-11. This is because of their non-ionic nature. Accordingly, if a drug's solubility depends on PH, so will its release from the HPMC matrix.[27] additionally Tritt-Goc, and Kawalczuk (2005) conducted a study to examine the impact of PH and molecular mass on the hydra of HPMC. The study produced images of HPMC swelling at various intervals using magnetic resonance imaging (MRI). Images of HPMC grades under acidic conditions are displayed. It demonstrates how the gel layer thickens overtime, leading to an increase in polymer diameter and a decrease in the dry core. This study supports the idea that low-viscosity HPMC releases drugs more rapidly in acidic environments (such as the stomach) because the gel layer is thinner, allowing for water penetration.

Effects of ionic strength-

Another important characteristic of GI fluid is ionic strength, which has an impact on how quickly drugs are released from HPMC Matrices. The ionic strength in the fasted condition is roughly 0.11 M, however, the fed condition might vary depending on the type of consumed. Due to water and ion secretion the jejunum ionic concentrations are kept constant and in a fasting condition. The remainder of the digestive tract is predicted to be around 0.14M. In both the fed and fasted stages. GI tract ionic concentration strength typically ranges from 0 to 0.4M. Examined how ionic strength affected theophylline release from tablets made of HPMC matrix. It was discovered that the amount of theophylline produce increased along

with the ionic strength. The ionic concentration strength, 0.2 M for low food content and 0.4M for high food content, stimulates the probable impact of food. The results showed that the release pattern of K100 LV matrices was significantly influenced by ionic concentrations. High viscosity grades are the greatest options for creating controlled release profiles that are less impacted by food, as evidence by the fact that K100M Matrices created a strong gel layer and have the lowest drug release rate.

Sodium carboxy methylcellulose (NaCMC)-

This is an ionic cellulose derivative made from polyelectrolytes that is sensitive to variations in PH.[28] One of the primary processes by which this polymer release medication has been identified as gel erosion.[29]

Alginate-

Alginate is a natural polymer that is found in brown sea algae and is employed in a variety of industries, including the food industry as binders and tablets disintegrate during tablet manufacturing. Alginate is employed in the controlled-release formulation because it can hydrate to create a gel. Sodium alginate (NaAlg) was tested by Liew and colleagues (2006) utilizing 17 distinct grades with various particle sizes, viscosities, and chemical composition as a drug-release modifier in matrix tablets. They concluded that sodium alginate has a special property that allows gel formation in both neutral and acidic conditions, and that this property needs to be used when creating a controlled-release formulation. Giunchedi and colleagues (2006) investigation looked atalginate compressed matrices as a method for extended-release. They discovered that sodium alginate polymer can be employed successfully as a drug-release modifier in matrix tablets. The contribution of a cation (mostly calcium) has produced mixed results in each of the investigations listed, suggesting that this would interaction is an important factor in drug release.

Effects of Cations -

Al^{3+}, ca^{2+}, Zn^{2+}, and Mg^{2+} are examples of polyvalent cations that have been utilized to cross-link alginate molecules.[30,31] bridge can form between the anionic polymer chains in a matrix containing alginate, creating a hydrogel network. The link can also be referred to as the "egg-box model", which depicts the two-dimensional bonding between alginate and adivalent cation (such as ca^{2+}, Zn^{2+}).[32] In contrast, because they have an additional Valence available for bonding, aluminum ions would interact with alginate molecules differently. Due to aluminum ions' higher positive charge per unit of surface than divalent cations, cross-linking can occur to a greater extent. It has been employed in microspheres, beads, and film coating to modify drug release from sustained release formulation. They are also widely employed in Matrix tablets to protect the matrix structure and delay the matrix's early breakdown.

However, the amount of cation present has a significant impact on how soon or slowly the medication is released.

METHOD OF PREPARATION

Beximco pharmaceutical limited provided a free sample of Diclofenac sodium (DS). Methocel (HPMC 15 cps) and PEG 600 were procured from colorcon in the USA as the reagent. A sample of kollidon SR, Lactose, and maize starch was provided as gifts by loba chemie PVT. ltd. in India. As well as magnesium stearate from Hanna chemical Ltd., Talc was purchased (Japan). The only other chemicals used were all of drug store quality.

Preparation of DS matrix tablets by direct compression techniques-

DS was weight using a Denver electronic balance (Swiss made), and all of the excipients were properly combined to ensure consistent mixing before being sieved using a 60 mesh screen. Following adequate mixing, the combined ingredient was put into a tablet punch machine (Jagur, India) for direct compression using hand pressure. Different sets of die and punches were used to create tablets in a variety of shapes. Formula mode using the direct compression procedure was designated with the codes FDC-1 and FDC-2.

Preparation of DS matrix tablets by wet granulation techniques-

The binder solution was created by dissolving lactose and maize starch in ethanol Separately, DS and polymer were homogenized. After that, a wet mass was created by gradually adding the binder solution to the drug-polymer mixture. Once more, the wet mass was run through a filter with the necessary mesh size before being ground into granules and combined with talc and magnesium stearate. The combination was then ingested using a tablet punch machine. Wet granulation was used to manufacture tablets in a variety of forms. Formula mode using the wet granulation method was designated with the codes FWG-1 and FWZ-2.

Characterization of bulk drugs-

All three bulk pharmaceuticals were identified using several official identification tests, and their aqueous medium analysis was conducted using the Jasco UV visible Method at 276mm with a spectrophotometer (model 7800, Tokyo, Japan). The situation of DFS, CFH, and TPL (271mm in the case of DFS). The IR spectrum obtained was compared to the reference spectrum using a Jasco IR report 100 infrared spectrophotometers (Tokyo, Japan). It also investigated how different Formulation excipients, such as talc, magnesium stearate, and ethyl alcohol, affected the stability of the medication.

Preparation of Matrix- Embedded tablets-

These medication-controlled release matrix- embedded tablets were made individually through the wet granulation process utilizing various EC ratios. Drugs that had been ground up independently were combined with EC, granulated will 100%ethyl alcohol, and dried at 55° c in a tray dryer. The nal granules were compressed in a single station for punch tablet press (cadmach, Ahmedabad, India) with 1% talc and 0.5% magnesium stearate. For each of the three medication formulations, three batches of tablets were previously prepared. There was 100mg of DFS, 500mg of CFH, and 200mg of TPL in each pill of DFS, CFH, and TPL.

Physical characterization of Design tablets-

Each batch of the manufactured pill was tested for drug content. Twenty tablets from each batch were removed, weighed, and finely powdered. This powder was precisely weight, appropriately dissolved and diluted in triple-distilled water before being subjected to an ultraviolet spectrophotometric analysis at 276nm (DFS and CFH) and 271nm (for TPL). 20 tablets were weighed using an electronic scale (Alcoset, type ER 1892A, Japan) to ascertain the weight variance. A Monsanto (standard type) tablet hardness tester was used to measure the hardness of 10 tablets. 10 tablets were used in a combell electronic friabilator for 5 minutes at 25rpm to test friability.

Release Rate Studies-

Utilizing the paddle Method and a usp xxlll type 2 dissolution apparatus, experiments on release rate were conducted in 900ml of triple-distilled water at a temperature of 37.5, 0.5c, 75 rpm was used as the stirring speed. A 5ml sample was taken out and replaced up to 12 hours later with brand-new dissolving media at predefined intervals. The sample was examined following the necessary dissolution. The mean of three pills from three distinct batches of each drug was used in the data analysis and the cumulative percentage of drug release was calculated.

Batch Reproducibility and stability on storage-

Each formulation was made in three batches, and under identical conditions, the individual dissolving rates of each batch were assessed. The effect of storage in ambient settings affected the stability and release properties of DFS, CFH, and TPL the best formulation of each type (DFS4, CFH2, and TPL2) was examined after six months and a year. The tablets were kept in ambient condition (25°c, 75% relative humidity) with imperious cellophane packages.

Preparation of matrix tablets- DS was sieved through the mesh, combined with avicel, magnesium stearate, hydroxyethyl cellulose(HEC), and avicel in a glass bottle, and then pressed in a tablet press with content pressure. Components A and B of the DS Matrix tablets contain 20% and 30%, respectively. As stated in

the tablet. In a Wurster apparatus operating at 50°c, matrix tablets were coated with a film made of 7.5 g of Eudragit L 100, 2.2g of dibutyl phthalate, and 3.75g of talc suspension in 130g of isopropanol.

Ingredients(mg)	Formula(A)	Formula(B)
Diclofenac sodium	100	100
Hydroxyethylcellulose	40	60
Avicel	56	36
Magnesiumstearate	4	4

Kinetics modeling of drug release-

All of the batches were in vitro dissolved for eight hours, and then the results were processed using the zero-order equation[33] and the Higuchi equation[34].

$M_t = M_0 + K_0 t$ ..... (1)

$M_t = M_0 - K_H t^{1/2}$ ..... (2)

In this equation M0 represents the dose of the drug included in the delivery systems. The rate constants for the Higuchi model and zero order are K_0 and KH, respectively. These models fell short in explaining the drug release mechanism because swelling (following hydration) and gradual matrix erosion were prevented. Them doing so. The well-known Korsmeyer kinetic equation was therefore fitted to the dissolution data to determine how the drug is released.[35,36]

$\text{Log } (M_t/M) = \log K + n \log t$ ..... (3)

Where K is the release rate constant that take into account the structural and geometric properties of the tablets; Mis the amount of drug released after an infinite length of time; and

Indicating the drug release mechanism. For a cylindrical tablet, form the Ficken diffusion phenomenon predominates when n is less than 0.45 and n between 0.45 and a strange transport is 0.89.(non - fickan diffusion), frequently referred to as first-order release. The release can be classified as case ll and super case ll transport after the n value reaches 0.89 and above, meaning the drug release rate does not fluctuate over time and the release is zero order is a characteristic. The erosion and degradation in its situation dominate the medication release.

FORMULATION AND EVALUATION TEST FOR DICLOFENAC SODIUM MATRIX TABLETS

Evaluation of granules-

- The angle of repose- the funnel method was used to calculate the granules' angle of repose. We permitted the granules to go through the ready funnel to the top.
- Bulk density- the following formulas were used to determine and compute the densities of the loose and tapped bulks. LBD is the powder's weight divided by the packing volume. TBD is the powder's weight divided by the packing's tapped volume.
- Compressibility index- Carr's compressibility index was used to get the granules' compressibility index.

Carr's index (%)= [TBD - LBD]×100/ TBD Evaluation of tablets-

- Average weight- Twenty tablets of each formulation were weighed using an electronicbalance(sartoriusIndia,limited)toevaluate weightvariance,andthetestwasconductedfollowing theIndianpharmacopoeia.
- Drug content- the medication was extracted using a PH 6.8 phosphate buffer after fivepillswereindividuallyweight.TheIP was usedtodeterminethemedicationcontent.
- Hardness and friability- the Monsanto hardness tester (codmach, Ahmedabad, India) and determine the hardness and device for assessing friability (Indian items, Mumbai,India),correspondingly.

CONCLUSION

In this study, DS matrix tablets were created utilizing various polymers in varying ratios. Whencombined with kollidon SR, polyethylene glycols (PEG) and hydroxypropyl methylcellulose(HPMC) demonstrate various unique release properties in the DS matrix tablets. The production process is straightforward and easily customizable in standard tablet manufacturing facilities. Carbopol could display prolonged release characteristics. To promote patients' compliance in the therapeutic management of pain and inflammation, they are therefore able to decrease dose intake,limit blood level oscillations, dose-related side effects, and cost.

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