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A REVIEW: FORMULATE AND EVALUATE DISPERSIBLE TABLET OF ACECLOFENAC FOR ENHANCEMENT OF BIOAVAILABILITY

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ABSTRACT

Pharmaceutical companies are focusing of new drug delivery systems for existing drug with an improved efficacy and bioavailability[1]. The oral route of administration is the most important method of administering drugs for systemic effects. Drug absorption is determined by physicochemical properties of drugs, their formulations, and routes of administration. When drug is administered orally. Dispersible tablets are uncoated tablets intended to be dispersed in water before administration giving a homogeneous dispersion. Typically a dispersible tablet is dispersed in about 5-15 ml of water and the resulting dispersion is administered to the patient. Aceclofenac is a non-steroidal agent with analgesic and anti-inflammatory properties; it provides symptomatic relief in a variety of painful conditions.

Aceclofenac may increase plasma concentrations of lithium, digoxin and methotrexate increase the activity of anticoagulant inhibits the activity of diuretics, enhance cyclosporin nephrotoxicity and precipitate convulsions when co-administered with quinolone antibiotics.

KEY WORDS: DispersibleTablet, Aceclofenac Anti-inflammatory, Wet granulation.

1. INTRODUCTION:

1.1 ORAL DRUG DELIVERY SYSTEM: Oral drug delivery system has been in demand fodecades as the most preferred route of administration. For the past two decades, there has been enhanced demand for more patient compliant dosage forms. As a result, the demand for their technologies has been increasing three fold annually. Since the development cost of a new chemical entity is very high, pharmaceutical companies are focusing of new drug delivery systems for existing drug with an improved efficacy and bioavailability[1]. The oral route of administration is the most important method of administering drugs for systemic effects. This route is preferred due to its manifold advantages including: ease of ingestion, pain avoidance, versatility, patient compliance and accurate dosing[2-3].Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules. Solid oral dosage forms are most convenient from patient as well as from manufacturing chemist's perspective. They ensure uniformity of dosage, are more robust, have less microbiological issues compared to liquid dosage forms.

1.2 ORAL DRUG ABSORPTION

Drug absorption is determined by physicochemical properties of drugs, their formulations, and routes of administration[5]. When drug is administered orally, it gets absorbed into the circulatory system and then excreted through kidney or may be excreted as metabolites.

1.2.1 Gastrointestinal Tract and Different Sites of Drug Absorption

Oral mucosa: The oral mucosa has a thin epithelium and a rich vascularity that favors absorption, but contact is usually too brief, even for drugs in solution, for appreciable absorption to occur.

Stomach: The stomach has a relatively large epithelial surface, but because it has a thick mucous layer and the time that the drug remains there is usually relatively short, absorption is limited.

Small intestine: The intestine mucosa is characterised by the presence of villi that constitute

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the anatomical and functional unit for nutrient and drug absorption[10]. The small intestine has the largest surface area for drug absorption in the G.I.T.

1.2.2 Factors Affecting Oral Drug Absorption

Amongst all pharmacokinetics processes, G.I. absorption is the most amenable parameter influenced by myriad factors. These are:

a. Gastrointestinal pH and pKa of drug
b. Gastric emptying process
c. Intestinal motility
d. First pass extraction
e. Food
f. Disease states and other factor

1.2.3 Factors Altering the Rate of Drug Absorption

1) Physicochemical Characteristics of Drug
a. Number of Nitrogen and Oxygen
b.< 5-NH's –OH groups enhances absorption
c. 10 –O, -N, Hydrogen bond acceptors, reduced absorption
d. Molecular weight (< 500)
e. Log P (< 5)
2) Formulation Factors and Physicochemical Properties of Formulations
a. Drug solubility, Particle size, Salt formation
b.Disintegrants(s), Diluent(s), Inert filler(s), Granulating agent(s), Lubricant(s)

1.2.4 Absorption from Various Dosage Forms

- **Absorption from solution**: A drug given orally is subjected to numerous G.I secretions and, to be absorbed, must survive encounters with low pH and potentially degrading enzymes. Usually, even if a drug is stable in the enteral environment, little of it remains to pass into the large intestine.

- **Absorption from solid forms**: Most drugs are given orally as tablets or capsules primarily for convenience, economy, stability, and patient acceptance. These products must disintegrate and dissolve before absorption can occur[14].

1.3 TABLETS

Tablets are defined as the solid dosage forms containing medicinal substance with or without suitable diluents, and they may be prepared by compression or by molding[15-18].

1.4 DISPERSIBLE TABLETS:

Dispersible tablets are uncoated tablets intended to be dispersed in water before administration giving a homogeneous dispersion[19-22]. Typically a dispersible tablet is dispersed in about 5-15 ml of water and the resulting dispersion is administered to the patient, as indicated in Table1.4. Dispersible tablets are required to disintegrate within 3 min in water at 15-25°.

1.4.1 Advantages of Dispersible Tablets

Dispersible tablet should have:
a. Easier to swallow than drugs in solid dosage forms (like tablet, capsule etc.)
b. Quick on set of action
c. Improved bioavailability
d. Good chemical stability
e. Ease of use in ambulatory treatment. It can be easily administered to geriatric, pediatric and mentally disabled patients
f. Accuracy of unit dosage form
g. Rapid dispersion of excipients
h. Taste masking
i. Increases surface area which may increase dissolution rate
j. Improve the texture and appearance
a. Best suited to large scale production
b. Low manufacturing cost

1.4.2 Methods used for Manufacturing Tablet[23]

A tablet with good characteristics is not made on a tablet press; it is made in the granulation process. Joining particles within a given granulation process will improve flow and compression characteristics, reduce segregation, improve content uniformity, and eliminate excessive amounts of fine particles.

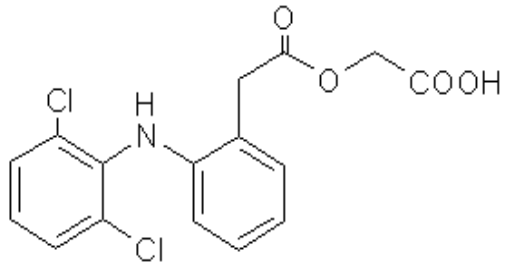
- **Wet granulation:** Wet granulation is the process of adding a liquid solution to powders to form granules. The process can be very simple or very complex depending on the characteristics of the powders. The liquid solution can be either aqueous based or solvent based (dries). Once the solvent has been dried and the powders have formed a more densely held mass, then the granulation is milled.

- **Dry granulation:** The dry granulation process is used to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders.

1.5 BIOPHARMACEUTICS CLASSIFICATION SCHEME (BCS) In order to be absorbed into systemic circulation, the drug(s) must be hydrophilic enough to be solubilized (i.e., soluble), yet lipophilic enough to get across the G.I. membrane (i.e., permeable)[24].

1.5.1 DRUG & EXCIPIENT PROFILE: Aceclofenac

Structure :



Synonyms: Aceclofenacum, Acecloenaco, Aceklofenak, Aceklofenak

ChemicalName:[[[2-[(2,6-Dichlorophenyl)amino] phenyl]acetyl]oxy]acetic acid.

Molecular Formula: $C_{16}H_{13}Cl_2NO_4$

Molecular Weight: 354.2

Description: A white to almost white crystalline powder.

Category: Non-steroidal anti-inflammatory drug (NSAIDs), Analgesic

Melting point: 149° to 150°

Solubility: Soluble in alcohol and methyl alcohol, freely soluble in acetone and dimethylformamide

Identification: I. R, Identification test and U.V

Aceclofenac is a non-steroidal agent with analgesic and anti-inflammatory properties; it provides symptomatic relief in a variety of painful conditions. In patients with osteoarthritis of the knee, the drug decreases pain, reduces disease severity and improves the functional capacity of the knee to a similar extent to diclofenac, piroxicam and naproxen. Aceclofenac reduces joint inflammation, pain intensity and the duration of morning stiffness in patients with rheumatoid arthritis.

Dose and Administration: The usual dose of aceclofenac is 100 mg given twice daily by mouth, one tablet in the morning and one in the evening. There is no evidence that the dosage of aceclofenac needs to be modified in patients with mild renal impairment, but as with other NSAIDs caution should be exercised.

Adverse Drug Reaction: Aceclofenac is well tolerated, with most adverse events being minor and reversible and affecting mainly the GI system. Most common events include dyspepsia, abdominal pain, nausea, diarrhoea, flatulence, gastritis, constipation, vomiting ulcerative stomatitis, pancreatitis. Dermatological side effects include pruritus and rash. Abnormal hepatic enzyme levels and raised serum creatinine have occasionally been reported. Other adverse effect, which is not common such as dizziness, vertigo and rare cases: par aesthesia and tremor.

Drug Interactions: Aceclofenac may increase plasma concentrations of lithium, digoxin and methotrexate increase the activity of anticoagulant, inhibits the activity of diuretics enhance cyclosporin nephrotoxicity and precipitate convulsions when co-administered with quinolone antibiotics. Furthermore, hypo or hyperglycaemia may result from the concomitant administration of aceclofenac and antidiabetic drugs, although this is rare. The co-administration of aceclofenac with other NSAIDs of corticosteroids may results in increased frequency of adverse event.

Contraindications

a. Active Peptic Ulcer.
b. Bleeding from the stomach or intestines.
c. Moderate to severely decreased kidney function.
d. People in whom aspirin or other medicines in this class (NSAIDs), asthma, itchy rash (urticaria) or nasal inflammation (rhinitis).
e. Suspected peptic ulcer.

Precautions: Aceclofenac should be administered with caution to patient with symptoms indicative of gastrointestinal disorders, peptic ulceration, ulceration colitis, Crohn's disease, hepatic porphyria and coagulation disorders. Patients suffering from severe hepatic impairement must be monitored. Aceclofenac should not be administered during pregnancy and lactation period, unless there are compelling reasons for doing so.

Storage: *Store in airtight container at above 25°, protect from light.*[25-27]

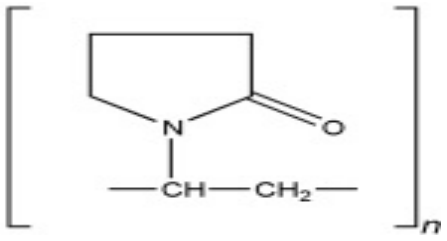
1.5.2 CROSPOVIDONE:

Synonyms: Crosslinkedpovidone, Kollidon, PolyplasdoneXL;

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer [9003-3-8]

Empirical Formula and Molecular Weight: $(C_6H_9O)_n$>1000000

Structural Formula:



Description: Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Solubility: Practically insoluble in water and most common organic solvents.

Typical Properties:

Acidity/alkalinity: pH = 5.0-8.0 (1 % w/v aqueous slurry)

Density: 1.22 g/cm^3

Moisture content: Maximum moisture sorption is approximately 60 %

Functional Category: Tablet disintegrant[28]

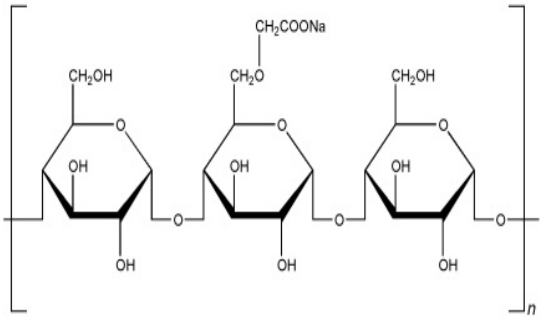
1.5.3SODIUM STARCH GLYCOLATE[29]:

Synonyms: Carboxymethyl starch, Sodium starch; Explosol; Explotab; Glycolys; Primojel; Starch carboxymethyl ether, Sodium salt; Tablos; Vivastar P.

Chemical Name: Sodium carboxymethyl starch [9063-38-1]

Molecular Weight: 5×10^5–1×10^6.

Structural Formula



Description: Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder.

Solubility: Sparingly soluble in ethanol (95 %); practically insoluble in water. At a concentration of 2 % w/v sodium starch glycolate disperses in cold water and settles in the form of a highly hydrated layer.

Typical Properties:

Acidity/alkalinity: pH = 3.0-5.0

pH = 5.5-7.5 for a 3.3 % w/v aqueous dispersion

Melting Point: 200º

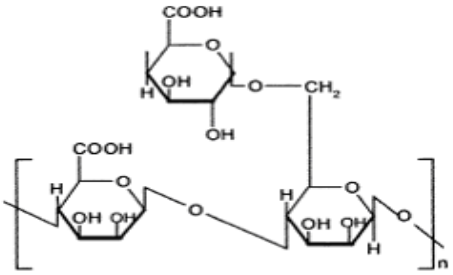
1.5.4 GUAR GUM[30]:

Synonyms :*Galactosol; Guar flour; Jaguar gum; Meyprogat; Meyprodor; Meyprofin*

Chemical Name: *Galactomannan polysaccharide [9000-30-0]*

Empirical Formula and Molecular Weight: *(C6H12O6)n ≈ 220 000*

Structural Formula



Description: *Guar gum occurs as an odorless or nearly odorless, white to pale yellowish white powder with blend taste.*

Solubility: Practically insoluble in oils, grease, hydrocarbons, ketones, esters and ethanol (95 %). Dispersible in hot and cold water and form colloidal solution, slightly soluble in water in water and insoluble in organic solvents.

Typical Properties

Acidity/alkalinity: pH = 5.0-7.0 (1 % w/v aqueous dispersion)

Density:1.492 g/cm^3

1.5.5 ISPAGHULA[31]:

Synonyms: Flea, Ispaghua, Spogel, PlantagoPsyllium, Isaphgol, Plantago sp., Isabgula

Description: *Ispaghulaoccursodourless, pale-buff-coloured husk with blend mucilaginous taste.*

Solubility: Practically insoluble in water, freely soluble in acetone and soluble in methanol.

Typical Properties:

Total Ash: 4 % Maximum

Acid Insoluble Ash: 1 % Maximum

Moisture: 10 % Maximum

Swell Volume: Not less than 65 ml/g

PsylliumMucilloid Content: 99 % Minimum

Chemical Constituents: *Mucilage mainly composed of arabinose, xylose, galacturonic acid, semi drying fatty oil and small amount of aucubin.*

1.6 CONCLUSION:

Direct compression method was found to be more effectiveness in the preparation of dispersible tablet. Disintegration time and dissolution rate was

found to be faster in direct compression as compared to wet / dry granulation. In case of natural disintegatants the formulation with Guar-Gum shows more release than the tablet with Ispagula, while in case of synthetic disintegrants the formulation with Crosspovidone shows more releases than the tablet Sodium Starch Glycolate.Direct compression method has a good pharmaco-economic advantage over the wet/dry granulation by reducing the production cycle time , man power required and ultimately enabling more productivity . The indirect benefits include the minimization of error contribution due to reduction in the number of processing steps, assuring quality compliance.

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