FORMULATION AND EVALUATION OF DICLOFENAC SODIUM MATRIX TABLETS USING NEW NATURAL POLYMER

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Abstract:

The aim of this work was preparation and evaluation of diclofenac sodium controlled release matrix tablets using various proportions of natural polymer Abelmoschus esculentus mucilage powder (i.e;Drug: Polymer ratio-1:0.25,1:0.5,1:1,1:1.5,1:2) as release controlling factor by Wet Granulation method. The tablets were evaluated for various parameters like friability, weight variation, hardness, drug time, content uniformity. In vitro drug release characteristics of dosage form was evaluated in 6.8 pH phosphate buffer. All the formulations followed zero order kinetics along with diffusion mechanisms.A better sustained drug release (98.7%) was obtained with the matrix tablet (Batch F) of the tamarind gum. Results showed that the drug release from matrix tablets prepared by using natural polymers can be sustained for more than 12 hrs and the drug release vary with concentration of polymer in matrix tablets. A better sustained drug release (50.65%) was obtained with the matrix tablet (Batch C-III) made-up of the carbopol than with the cashew nut tree gum and HPMC. It is cleared through the dissolution profile of Diclofenac sodium from matrix tablets prepared using different polymers were indicated an increase in the polymer ratio retarded the drug release to a greater extent.

1.0 Introduction:

to develop a rate controlled formulation.1 A matrix system can be better defined as a well mixed system comprising of one or more drugs with gelling agent i.e; hydrophilic polymers. Various materials like waxes, hydrophilic polymers, hydrophobic polymers and Gums have been employed in the formulation of matrix tablets. The present work is an attempt to extract and investigate the controlling property of polymer of natural origin i.e; Abelmoschusesculentus, grown as a vegetable crop in tropic, subtropic and warmer area of the temperature zones. The reason for choosing a natural polymer is due to disintegrating property, non toxicity, low cost, free availability, eco-friendly, potentially degradable and compatible. Diclofenac sodium is an effective anti-inflammatory, analgesic and antipyretic categorized under NSAIDs'2. Diclofenac sodium 2-[(2, 6-dichlorophenyl) amino] benzene acetic acid sodium salt is a benzene acetic acid derivative with potent analgesic and anti-inflammatory properties.

Matrix tablets serve as an important tool for oral extended- release dosage forms. Hence, various problems like patient compliance, drug targeting, local side effects, frequent administration and fluctuations in blood concentration levels, associated with their counterparts, therefore the conventional dosage forms restricted. A matrix tablet is the oral solid dosage form in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serve as release rate retardants.1,4 Polymers are high molecular weight compound originate from natural

and synthetic source. Hydrophilic polymer (HPMC K4M) basically the cellulose derivative use of matrices, which satisfy the key criteria of release pattern byswelling property. HPMC is a partly o-methylated and o-(2-hydroxypropylated) cellulose with a molecular weight 10,000-1, 5000,000. Hydrophobic polymer (acacia gum) reduced the rate and extent of drug release due to reduced porosity of matrix. Acacia is a complex loose aggregate of sugars and hemiacetal. It is an acidic polysaccharide containing D-galactose, L-arabinose, L-rhamanose, D-glucuronic acid with a molecular weight of approximately 240,000-500,000.5,6 Both HPMC K4M and acacia gums are cellulose polymer based matrix which forms hydrogel due to simultaneous migration to the matrix

Procurement of drug and other excipients:

Diclofenacsodium was obtained as gift sample from Alchem Laboratories, Baddi India. The Parmacolonial grade of gum acacia was obtained from RFCL Limited, New Delhi, India and microcrystalline cellulose was procured from RANKEM Limited, New Delhi, India.

Preparation of sustained release tablets:

The composition of different formulations of Aceclofenac SR matrix tablets is shown in Table 1. Different tablet formulations were prepared by direct compression technique. All the powders passed through 40/60 mesh sieve. The required quantity of drug, various polymers and other ingredients were mixed thoroughly. Talc and magnesium stearate were finally added as a glidant and lubricant respectively. The blend was directly compressed (10 mm diameter, round flat faced punches) using multiple punch tablet compression machine (Ahmedabad, India). Each tablet contained 200 mg of Aceclofenac.

2.0 Literature review:

[1] R.Sureshkumar, N.Jawahar ,V.Senthil (2010) Sustained release tablets of Diclofenac Sodium were fabricated using Cashew nut tree gum, HPMC and CarbopolThe tablets were evaluated for pre-formulation studies like angle of repose, bluk density, compressibility index and physical characteristics like hardness, weight variation, fraibilty and drug content. In-vitro release of drug was performed in PBS pH 7.2 for twelve hours. All the physical characters of the fabricated tablet were within acceptablelimits. The tablet with HPMC(Batch B-I) and Carbopol(Batch C-I) exhibited greater drug content than those with cashew nut tree gum and other batches of HPMC and carbopol

[2] A. Seetha Devi, MD. Tabasum (2013),Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Regular research is going on infield of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration. The advantages of natural plant based excipients include low cost, natural origin, free from side effects, biocompatible, bioacceptable, renewable source; environmental friendly processing, local availability, better patient tolerance as well as public acceptance.

[3] Dranil Kumar Yadav* and D.A. Jain(2015) The main accusative of the present work was to develop sustained release matrix tablets of Diclofenac sodium for maintaining therapeutic blood

or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects. In the present study, Polysaccharide mucilage derived from the seeds, was investigated as sustained release matrix forming material in tablet formulations. Mucilage extracted from seeds was subjected to physicochemical characterization. Matrix tablets were prepared by wet granulation technique using isopropyl alcohol as a granulating agent in different drug: polymer ratios. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness and in vitro dissolution using paddle method. All the formulations showed compliance with pharmcolonial standards. Tablets prepared with Hydroxypropyl methylcellulose (HPMC 50cps) and Xanthan gum as matrix forming material for the comparative study.

[4] Sujja AJ, Munday DL, and Khan KA.(2013) Controlled release drug delivery systems significantly improved therapeutic efficacy especially as matrix systems which is the innumerable method used to develop a rate controlled formulation.1 A matrix system can be better defined as a well mixed system comprising of one or more drugs with gelling agent i.e; hydrophilic polymers. Various materials like waxes, hydrophilic polymers, hydrophobic polymers and Gums have been employed in the formulation of matrix tablets. The present work is an attempt to extract and investigate the controlling property of polymer of natural origin i.e; Abelmoschusesculentus, grown as a vegetable crop in tropic, subtropic and warmer area of the temperature zones. The reason for choosing a natural polymer is due to disintegrating property, non toxicity, low cost, free availability, eco-friendly, potentially degradable and compatible

3.0 Materials and methods:

Fresh A.E fruits were collected and washed with water to remove dirt and debris. Incisions were made on the fruits & left over night. The fruits were crushed and soaked in water for 5- 6hrs for 30min and left to withstand for 1hr to allow complete release of the mucilage into the water. The mucilage was extracted using a multilayer muslin cloth bag to remove marc from the solution. Acetone (3times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40ºc for 10min, collected, ground, passed through a # 80 sieve and stored in desiccators at 30ºc and 45% relative humidity before use.

Drug-excipient compatibility studies: Infrared (IR) spectroscopy was conducted using a FTIR 8201 PC Spectrophotometer (Shimadzu, Tokyo, Japan) and the spectrum was recorded in the wavelength region of 4000 to 400 cm− 1 . The procedure consisted of dispersing a sample (drug alone or mixture of drug and excipients) in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained

Preparation of diclofenac sodium matrix tablets Matrix tablets each containing 100mg of Diclofenac sodium were prepared by WetGranulation method using A.E mucilage. The tablets prepared were as per the formulae given in the Table 1. Diclofenac sodium, Diluents (lactose) and polymer

(Abelmochusesculentus mucilage powder) in various ratios like 0.25%, 0.5%, 1.1%, 1.5% and 2% were taken accurately and blended thoroughly. The blend was moistened with distilled water to get damp mass. The damp mass was then passed through sieve no 12 and the granular mass obtained were dried in hot air oven at 60º c for 1hr.The dried granules were passed through sieve no 16 to get free flowing and uniform sized granules. The granules were lubricated with 2% talc and 2% magnesium stearate were added which is previously passed through sieve no 100. The resulting mixture was compressed by Cadmac 16 station tablet punching machine to a hardness of 7.5-8 kg/sq.cm using flat punches.

Isolation of seed mucilage: The seeds were washed with water to remove dirt and debris, and dried. The dried seeds were crushed and powdered in ball mill. To 20g of seed powder, 200ml of cold distilled water was added and slurry was prepared. The slurry was poured into 800ml of boiling distilled water. The solution was boiled for 20 minutes under stirring condition in a water bath. The resulting thin clear solution was kept overnight so that most of the proteins and fibers settled out. The material was squeezed from an eight-fold muslin cloth bag to remove the marc from the solution. Acetone was added to the filtrate to precipitate the mucilage in a quantity of three times the volume of the total filtrate. The mucilage was separated, dried in an oven at a temperature < 50 °C, collected, dried-powdered, passed through a sieve (number 80), and stored for further use in desiccators

Release kinetics:

In order to establish the mechanism of drug release the in-vitro drug release data was fitted to four popular exponential equations (zero order, first order, Higuchi, and koresmayerpeppas).The drug release of all the formulations was found to be followed zero order kinetics as correlation coefficient(r 2)values are higher than that of first order kinetics as shown in Table 5. By incorporating the release data in Higuchi and erosion models, the r2 values of Higuchi model were found to be slightly greater than Erosion model. So this indicates drug release from Matrix tablets followed diffusion mechanism. To further confirm the exact mechanism of drug release the data was incorporated into Koresmayerpeppas model and the mechanism of drug release was indicated according to the value of release exponent (n).

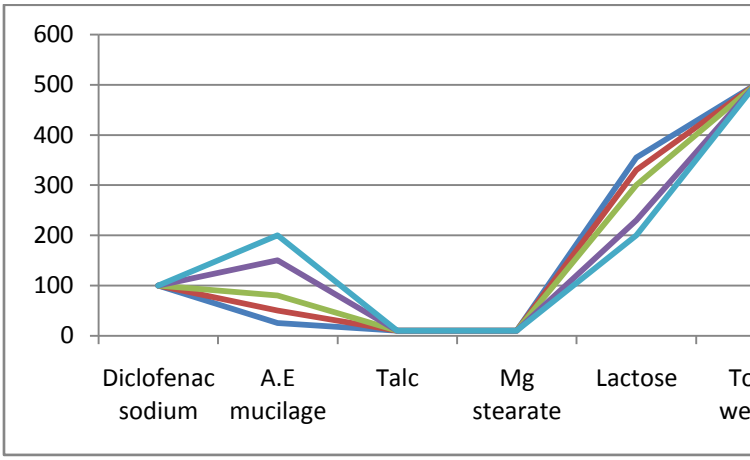
Swelling behavior of SR matrix tablets: The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of diclofenac sodium S.R. tablets based on different matrices was studied. The swelling of matrices was monitored by immersing the tablet into a basket of USP 2 dissolution rate test apparatus containing 900 ml of dissolution medium (pH 6.8 phosphate buffer) maintained at 37±0.5°C for 12 h. at 50 rpm. At the specific time interval, the tablets were withdrawn, soaked with tissue paper, and weighed and the process was continued till the end of 12 h. % weight gain by the tablet was calculated by formula; S.I = {(Mt-Mo) / Mo} X 100, where, S.I = swelling index, Mt = weight of tablet at time't' and Mo = weight of tablet at time t = 0

4.0 Results and discussions

Formulations F1 to F5, were made by taking different proportions (i.e;D:P ratio are 1:0.25,1;0.5,1:1,1:1.5,1:20) of A.E mucilage. In all the formulations, 100 mg of Diclofenac sodium was incorporated and final weight was made up to 500 mg. The granules of different formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The results are shown in (Table 2). Angle of repose values ranged from 19.7°-25.4º indicates good flow property of granules. The free flowing properties of granules were further confirmed by determining carr's index and hausners ratio. The carr's index values and hausner's ratio values were ranged from 19.7-24.2 and 1.19- 1.24. The values of bulk density ranged from 0.496-0.576 gm/cm3 and the values of tapped density range from 0.63-0.665 gm/cm3 were found to be within the limits as per USP. Tablets of all the formulations were subjected to many in-process evaluation parameters such as physical appearance, content uniformity, weight variation hardness and friability tests are shown in the (Table 3). All the tablets were round in shape with no visible cracks and having smooth appearance. The average percentage weight variation of 20 tablets from the average was remained within ±0.1%.This weight variation test revealed that the tablets were within the range of pharmacopoeial limit. Drug content of all batches of tablets were within the range of 98.2 to 99.8% indicating good uniformity among different formulations of the tablets. All the formulations showed reasonably good hardness values ranged from 6.9 to 8.01 kg/cm2. Further, to strengthen these values friability values are also considered. The percentage weight loss of all the formulations was less than 0.8%.This indicates that all the tablets withstand the mechanical shocks during handling

Table: Formulation of Diclofenac Sodium Matrix Tablets

Ingredients	F1 (mg) D:P(1:0.25)	F2 (mg) D:P(1:0.5)	F3 (mg) D:P (1:1	F4 (mg) D:P(1:1.5)	F5(mg) D:P (1:2)
Diclofenac sodium	100	100	100	100	100
A.E mucilage	25	50	80	150	200
Talc	10	10	10	10	10
Mg stearate	10	10	10	10	10
Lactose	355	330	300	230	200
Total weight	500	500	500	500	500



Graph: Formulation of Diclofenac Sodium Matrix variations

Discussions: There must be sufficient polymer content in a matrix system to form a uniform barrier. The barrier protects the drug from immediately

releasing into the dissolution medium. If the polymer level is too low, a complete gel layer may not form,. In most studies, increased polymer level in the formulation results in decreased drug-release ratesBecause hydrophilic matrix tablets containing hydrophilic polymers absorb water and swell, the polymer level in the outermost hydrated layers decreases with time. The outermost layer of the matrix eventually becomes diluted to the point where individual chains detach from the matrix and diffuse into the bulk solution. The polymer chains break away from the matrix when the surface concentration passes a critical polymer concentration of macromolecular disentanglement or surface erosion. The polymer concentration at the matrix surface is defined as the polymer disentanglement concentration

Physicochemical evaluation of sustained release tablets:

The sustained release Aceclofenac tablets were off-white, smooth, and flat shaped in appearance. The results of physicochemical characterizations are shown in Table 3. The thickness of sustained release tablets was measured by vernier caliper and was ranged between 3.2±0.05 and 3.3±0.05 mm. The weight variation for different formulations (F1 to F9) was found to be ±1.90% to ±2.40%, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. The hardness of the Sustained release tablets was measured by Monsanto tester and was controlled between 5.66±0.44 and 5.83±0.25 kg/cm2. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The percentage of drug content for F1 to F9 was found to be in between 97.89±6.56 to 100.59±6.09 of aceclofenac it complies with official specifications.

Conclusions:

To concluded that among all the formulations F4 containing 1.5 % A.E. mucilage powder was found to release the drug in a slow, controlled manner with maximum drug release of 99.8% and found to follow Zero order release kinetics with Non – Fickian diffusion mechanism.his study deals with the investigations carried out with the objective of developing oral sustained release formulations throughformulated matrix tablets of Diclofenac sodium using natural polymer Cashew nut tree gum, HPMC and Carbopol were capable of exhibiting sustained release properties They are thus capable of reducing the dose intake, minimize the blood level oscillations, dose-related adverse effects and cost thus ultimately improve the patient compliance in the therapeutic management of pain and inflammation All characterized parameters of drug were found to be within the satisfactory limit. The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased. The release of drug after a study of the release kinetics model follows zero order and the mechanism of drug release was found to be non- fickian diffusion super casefound to be an optimized formulation which gives better results than the marketed formulation on the basis of in vitro release.

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