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Pharmacokinetic Evaluation of Diclofenac Matrix Tablets Employing Cross Linked Starch-Urea

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ABSTRACT

Modified starches are promising and having good potential as release retardants and rate controlling polymers for controlled release. The controlled release properties of modified starches, generally based on solvent-activation have been intensively investigated. Aim: this aimed to research the in vivo performance of the new polymer (Cross linked starch-urea or CLSU) within the formulation of controlled release dosage forms. Methods: Diclofenac matrix tablets employing CLSU were prepared by gelatinizing potato starch within the presence of urea and salt . 15 mg strength of diclofenac matrix tablets (B) were formulated employing CLSU and pure drug (A) were tested for in vivo pharmacokinetic evolution. Plasma drug concentration of Diclofenac decided by HPLC method. From the time Vs plasma concentration data various pharmacokinetic parameters like peak concentration (Cmax), time at which peak occurred (Tmax), area under the curve (AUC), elimination rate constant (kel), biological half-life (t1/2), percent absorbed to varied times and absorption rate constant (Ka) were calculated in each case as per known standard methods. Results: The absorption rate constant (Ka) was found to be 0.152h-1 for A and 0.817 h-1 for B, and MRT was increased from 9.68 h for A to 14.05 h for B. Tmax raised to 6 h for B from 3 h for A. Based on AUC0 α the relative bioavailability of the diclofenac from CLSU was found to be 124.9% compared to diclofenac pure drug (100%). Conclusion: Thus the results indicated that starch urea cross-linked with salt may be a promising matrix former for controlled release.

Controlled drug delivery is a topic of current interest in pharmaceutical technology and industry. In the last two decades, controlled release dosage forms have made significant progress in terms of clinical efficacy and potential compliance. Controlled release drug delivery systems are those formulations designed to release a lively ingredient at rates, which differ significantly from their corresponding conventional dosage forms. The controlled release drug delivery systems are aimed toward controlling the speed of drug delivery, sustaining the duration of therapeutic activity and / or targeting the delivery of the drug to a tissue. Drug release from these systems should be at a desired rate, predictable and reproducible.

The formation of cross-linked starches with calcium salts is known in polymer chemistry. As the cross-linked polymers generally swell in water and aqueous fluids and form gelatinous matrices suitable for controlled release, it is thought worthwhile to investigate starch urea cross linked with calcium chloride for its application in controlled release.

Diclofenac sodium known as diclofenac is a widely used non-steroidal anti-inflammatory analgesic and anti-pyretic drug. Controlled release formulation is needed for diclofenac because of its short biological half-life9 of 2.0 h. The drug also causes10 gastro intestinal disturbances, peptic ulceration with bleeding if present in large concentration in gastrointestinal tract. Hence, diclofenac is a suitable drug for oral sustained and controlled release and it would be advantageous to slow down its release in gastrointestinal tract not only to prolong its therapeutic action but also to minimize possible side effects of diclofenac.

from M/s Micro Labs Ltd., Pondicherry, Methanol, Potassium dihydrogen phosphate, caustic soda , urea, salt were procured from Qualigens fine chemicals Ltd. Potato starch was procured from Loba Chemie. Crosslinked starch urea (prepared in the laboratory) and all other chemicals used in the study were of analytical grade

Preparation of Cross-linked starch urea polymer: Potato starch (9 parts) was dispersed in purified water (10 parts) to make starch slurry. Urea (1 part), salt (1 part) were dissolved in purified water (40 parts) and therefore the solution was heated to boiling. While boiling, the starch slurry was added and mixed. Mixing while heating was continued for 20 minutes to form CLSU polymer. The mass formed was spread on to a stainless steel plate and dried at 850C for 6-8 h. The dried polymer was powdered and skilled mesh No. 120.

Preparation of matrix Tablets: Matrix tablets of 15mg diclofenac were prepared employing 50% CLSU. The drug and matrix material were mixed in mortar and the binder, water-alcohol (1:1) solution was added and

mixed thoroughly to form dough mass. The mass was skilled mesh No.12 to get wet granules. The dried granules were passed through mesh No.24 to break aggregates. Passed granules were blended with talc 2% and magnesium stearate 2% in a closed polythene bag. The tablets granules were compressed in to tablets on rotary multi-station punching machine

Pharmacokinetic evaluation was done on diclofenac matrix tablets (B) formulated employing CLSU as compared to diclofenac pure drug (A) with a view to guage the discharge retarding and rate controlling efficiency of CLSU in vivo. When the diclofenac matrix tablets formulated employing CLSU were administrated orally at the same dose of 15 mg, the plasma concentrations were found to be lower than those observed with the diclofenac pure drug (Fig. 1) indicating slow absorption of diclofenac from the matrix tablets. A Cmax of 2.9 ± 0.6 µg/ml wasobserved at 6.0 h following the oral administration of matrix tablets. The absorption rate constant (Ka) was found to be 0.152 h-1 . The plasma concentrations were stabilized and maintained within a narrow range for longer periods of time in the case of matrix tablets (Fig. 1). The mean duration (MRT) was increased from 9.68 h for diclofenac pure drug to 14.05 h with the matrix tablets. The MRT value indicated longer stay of drug within the body when administered as matrix tablets. Based on AUC0 α the relative bioavailability of diclofenac from CLSU urea matrix tablets was found to be 124.9 that when compared to diclofenac pure drug (100 %). The elimination rate constant (Kel) for diclofenac was found to be 0.1274 h-1 and the corresponding half- life was found to be 5.44 h following the oral administration of diclofenac. The mean residence time (MRT) was found to be 9.68 h. The adsorption rate constant (Ka) was found to be 0.8172 h-1 . A Cmax of 4.7 ± 1.4 µg/ml was observed at 3.0 h after oral administration of diclofenac pure drug.

The pharmacokinetic evaluation, thus, indicated that diclofenac from the matrix tablets formulated employing CLSU was released slowly and absorbed slowly over longer periods of time in vivo resulting in the maintenance of plasma concentrations within a narrow range over longer periods of time. As such CLSU exhibited good release retarding and rate controlling effect in vivo in the pharmacokinetic evaluation.

Keywords: Diclofenac, Matrix tablets, Cross-linked Starch-Urea, Controlled drug delivery.