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PRECLINICAL PHARMACOKINETIC EVALUATION OF STARCH ACETATE AND CHITOSAN MICROPARTICLES OF GLICLAZIDE

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Abstract:

Recently much emphasis is being laid on the development of microparticles because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying. The preparation and in vitro(drug release) and in vivo Pharmacodynamic evaluation of microparticles of gliclazide using i) starch acetate, a new modified starch and ii) chitosan, a new mucoadhesive polymer are reported earlier. The microparticles prepared using both the polymers exhibited good in vitro controlled release of gliclazide over 12 h and in vivo hypoglycemic effect over longer periods of time following their oral administration. The objective of the present study is preclinical pharmacokinetic evaluation of selected gliclazide microparticles (SAF2 and CHF3) in comparison to gliclazide pure drug in healthy rabbits (n=6). The products were tested orally at a dose equivalent to 3 mg/kg of gliclazide. Plasma gliclazide concentrations were determined by a reported and revalidated HPLC method.

The biological half life ($t_{1/2}$) of gliclazide pure drug estimated was in good agreement with the literature value. The $t_{1/2}$ of gliclazide was slightly elongated with microparticles. The absorption of Gliclazide was very rapid when administered as pure drug and was slow from both the microparticles tested. Based on $(AUC)_0^{\alpha}$, the relative bioavailability (BA) of gliclazide from microparticles SAF2 and CHF3 was 85.81 % and 117.14 % respectively when compared to gliclazide pure drug (100%). A good level A correlation was observed between percent drug released (in vitro) and $(AUC)_0^{\alpha}$ (in vivo) with both the microparticles.

Thus, the results of preclinical pharmacokinetic studies indicated that gliclazide was absorbed slowly from microparticles and the plasma drug concentrations were sustained over longer period of time when compared to gliclazide pure drug.

Key Words: *Gliclazide, Microparticles, Chitosan, Starch acetate, Preclinical evaluation, Pharmacokinetics.*

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INTRODUCTION:

The design of microparticulate drug delivery systems (microparticles) is an efficient technique to provide the sustained and controlled delivery of drugs over long periods of time. Microparticulate drug delivery systems [1] consist of small particles of solids or small droplets of liquids surrounded by walls of natural and synthetic polymer films of varying thickness and degree of permeability acting as a release rate controlling substance and have a diameter upto the range of 0.1µm-200µm**.** Microparticulate dosage forms [2] are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into capsules, encapsulated or compressed into a tablet. Microparticulate drug delivery systems contain discrete particles that make up a multiple-unit system. They provide many advantages over single-unit systems because of their small size. Multiparticulates are less dependent on gastric empty time, resulting in less inter and intra-subject variability in gastrointestinal transit time. They are also better distributed and less likely to cause local irritation [3]. Recently much emphasis is being laid on the development of microparticulate dosage forms in preference to single unit systems because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying [4]. Design of microparticulate drug delivery systems requires a suitable polymer to serve the intended purpose. We have earlier reported [5,6,7] the preparation and *in vitro*(drug release) and *in vivo* Pharmacodynamic evaluation of microparticles of gliclazide using i) starch acetate, a new modified starch and ii) chitosan, a new mucoadhesive polymer. The microparticles prepared using both the polymers exhibited good *in vitro* controlled release of gliclazide over 12 h and *in vivo* hypoglycemic effect over longer periods of time following their oral administration.

Microparticles SAF2 prepared using a core :coat (Starch acetate) ratio of 8:2 and microparticles CHF3 prepared using a core: coat (chitosan) ratio of 8:2 gave slow, controlled and complete release(100%) of Gliclazide over 12 hours and were found suitable for oral control release of Gliclazide over 12 hours for b.i.d administration . The objective of the present study is preclinical pharmacokinetic evaluation of these microparticles (SAF2 and CHF3) in comparison to gliclazide pure drug in healthy rabbits.

MATERIALS AND METHODS:

Materials:

Gliclazide was a gift sample from M/s Micro Labs, Pondicherry. Chitosan, 75-85 percent deacetylated was obtained from Central Institute of Fisheries Technology, Cochin, India. Starch acetate with a percent acetylation of 28.38 % and a degree of substitution (DS) of 2.75 was prepared in the laboratory as per the method described earlier [8]. Sodium tri polyphosphate (Sigma), Acetic acid (Qualigens), Chloroform (Qualigens) and Soyabean oil were used. All other materials used were of pharmacopoeial grade.

Methods:

Preparation of Microparticles:

Starch acetate microparticles of gliclazide were prepared by emulsification solvent evaporation method. Chitosan microparticles of gliclazide were prepared by emulsification - desolvation -crosslinking method. The details of the methods are described in our earlier papers.

Preclinical Pharmacokinetic Evaluation:

In vivo preclinical pharmacokinetic evaluation was done on gliclazide microparticles, SAF2 and CHF3 in comparison to gliclazide pure drug in normal healthy rabbits of either sex with a view to evaluate their *in vivo* performance.

***In vivo* study protocol:**

The following products were tested for *in vivo* pharmacokinetic evaluation

(i) Gliclazide pure drug
(ii) Gliclazide microparticles, SAF2
(iii) Gliclazide microparticles ,CHF3

Microparticles SAF2 are prepared using a core: coat (Starch acetate) ratio of 8:2 and microparticles CHF3 are prepared using a core: coat (Chitosan) ratio of 8:2.

The products were administered orally at a dose equivalent to 3 mg/kg of gliclazide. The dose for experimental rabbits was calculated as suggested by Bikash Medhi and Ajay Prakash [9]. The in vivo study protocols were approved by Institutional Animal Ethics Committee (No. CPCSEA/CH/ORG/2017-091). The *in vivo* study was conducted as per crossover RBD (n=6) in each case. Healthy rabbits weighing 2.0 -2.5 Kg were used. The washout period was one month.

After collecting the blank blood sample, the product in the study was administered orally with 10 ml of water. Blood samples (1.0 ml) were collected from marginal ear vein at different times (0.5, 1, 2,3,4,6,8,10 and12 h) after administration. Samples were collected into heparinized test tubes and were centrifuged for 15 min

at 15,000 rpm. The plasma samples were stored under refrigerated conditions at 4-8°C prior to assay for drug content on the same day. The plasma concentrations of gliclazide were determined by a reported HPLC method [10] after revalidation.

Estimation of Pharmacokinetic Parameters:

Assuming one compartment open model, various Pharmacokinetic parameters such as C_{max}, T_{max} $(AUC)_{(0\text{-}12h)}$, $(AUC)_{(0\text{-}\infty)}$, K_{el} $t_{½}$ and K_a were estimated from the Plasma drug concentration data in each case. Standard known methods [11], [12] were used for the estimation of various pharmacokinetic parameters.

RESULTS AND DISCUSSION:

Preclinical pharmacokinetic evaluation was done on selected gliclazide microparticles prepared employing i) starch acetate, a new modified starch (SAF2) and ii) chitosan , a mucoadhesive polymer (CHF3) in healthy rabbits in comparison to gliclazide pure drug with a view to evaluate their *in vivo* performance. Plasma concentrations of gliclazide observed following the oral administration of gliclazide and its microparticles, SAF2 and CHF3 are shown in Fig: 1.The pharmacokinetic parameters estimated are summarized in Table 1.

The elimination rate constant (K_{el}) and biological half life ($t_{1/2}$) were 0.0852 h^{-1} and 8.13 h respectively for gliclazide pure drug. The $t_{1/2}$ of gliclazide estimated is in good agreement with the reported [13] value of 10±2 h. The K_{el} and $t_{1/2}$ are 0.0529h^{-1} and 13.1h respectively for microparticles SAF2 and 0.046 h^{-1} and 15.06 h respectively for microparticles CHF3. The $t_{1/2}$ of gliclazide was slightly elongated with microparticles be due to *in vivo* sustained release and slow absorption of gliclazide from the microparticles. Gliclazide was absorbed rapidly when administered as pure drug with an absorption rate constant (K_a) of 2.34h^{-1}. A C_{max} of 17.6 ± 1.62µg/ml was observed at 2 h following oral administration of gliclazide pure drug. Plasma concentration were later decreased rapidly.

Table.1: Pharmacokinetic Parameters of Glipizide Estimated Following the Oral Administration of Gliclazide and its Microparticles in Rabbits (n=6)

Pharmacokinetic Parameter	Gliclazide	Microparticles SAF2	Microparticles CHF3
C_{max} (µg/ml)	17.6± 1.62	12.2± 1.45	12.6± 1.65
T_{max} (h)	2	3	3
K_{el} (h^{-1})	0.0852	0.0529	0.046
$t_{1/2}$ (h)	8.13	13.1	15.06
AUC_0^{12} (µg.h/ml)	225.3	152.37	200.47
AUC_0^{α} (µg.h/ml)	254.64	218.53	298.29
K_a (h^{-1})	2.34	1.22	1.215
Rel BA (%)	100	85.81	117.14

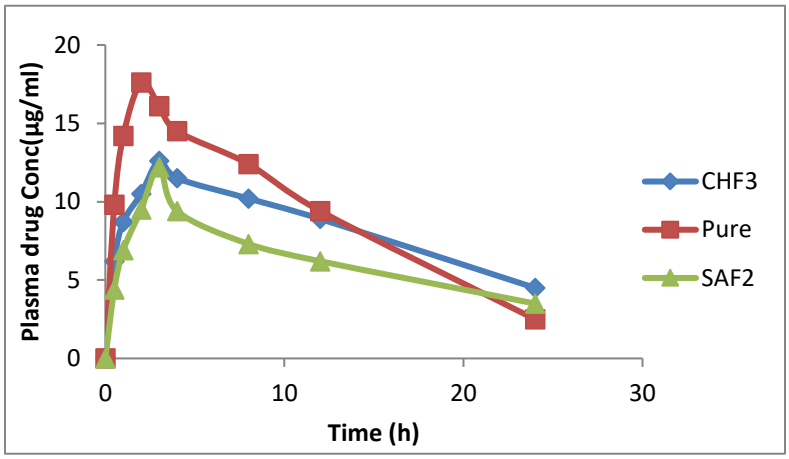

Fig 1: Plasma Concentration Vs Time profiles of Gliclazide Estimated Following the Oral Administration of Gliclazide and its Microparticles in Rabbits (n=6)

Gliclazide was absorbed slowly from microparticles SAF2, CHF3 with an absorption rate constant (K_a) of $1.22h^{-1}$ and $1.25h^{-1}$ respectively. A C_{max} of 12.2± 1.45 µg/ml was observed at 3 h with SAF2. A C_{max} of 12.6± 1.65 µg/ml ml was observed at 3 h with CHF3. The plasma drug concentrations were sustained within a narrow range for extended period of time in the case of both the microparticles.

Based on $(AUC)_o^{\alpha}$, the relative bioavailability (BA) of gliclazide from microparticles SAF2 and CHF3 was 85.81 % and 117.14 % respectively when compared to gliclazide pure drug (100%).

A good level A correlation was observed between percent drug released (*in vitro)* and $(AUC)_o^{\alpha}$ (*in vivo*) as shown in Fig 2 and Fig 3.

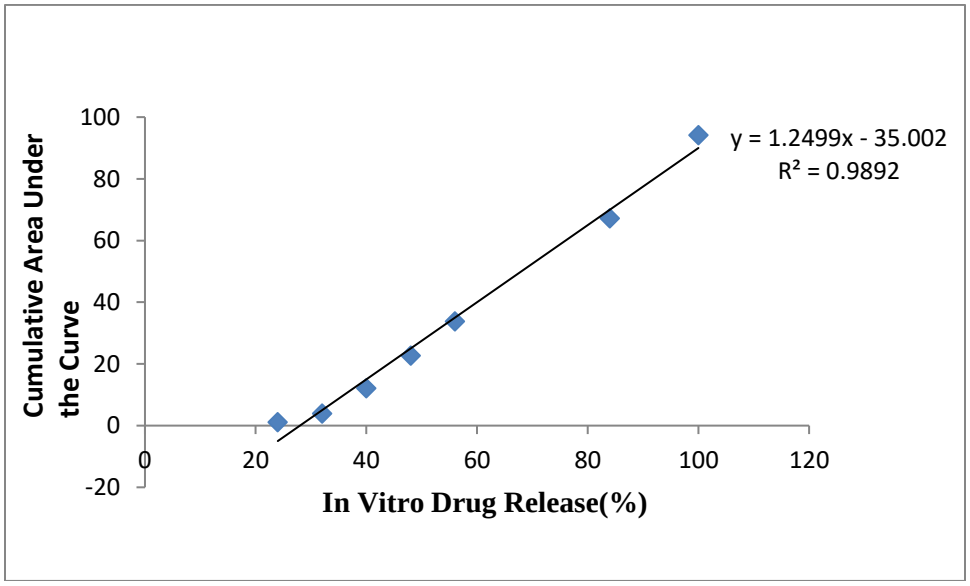

Fig 2: *In vitro- in vivo* correlation of Gliclazide microparticles SAF2

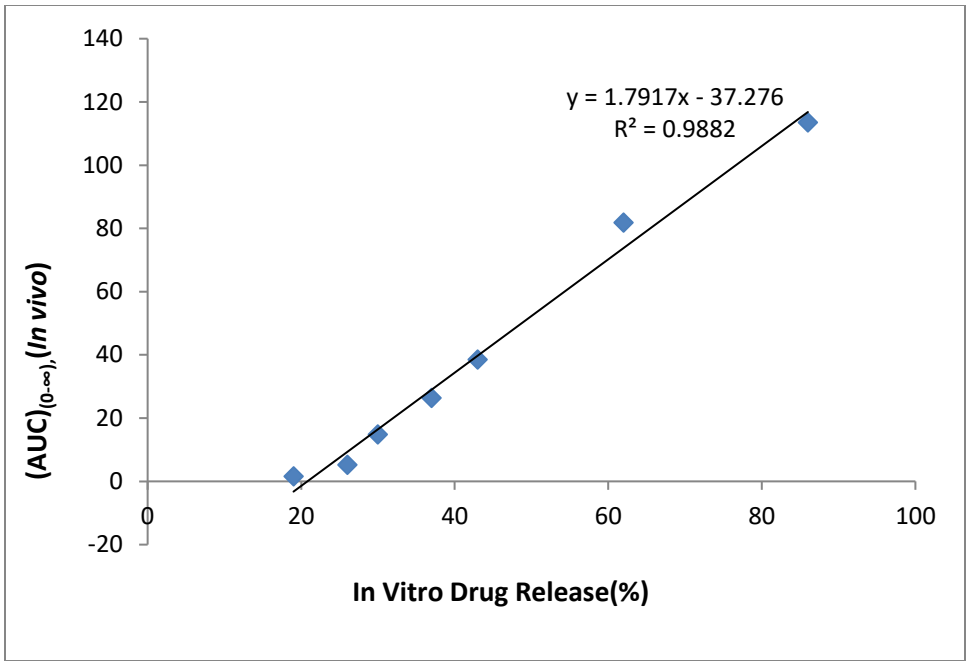

Fig 3 : *In vitro-in vivo* correlation of Gliclazide microparticles CHF3

The R^2 values describing the correlation between *in vitro* and *in vivo* results were found to be 0.989and 0.988 with microparticles SAF2 and CHF3 respectively indicating good level A correlation.

Thus, the results of preclinical pharmacokinetic studies indicated that gliclazide was absorbed slowly from microparticles and the plasma drug concentrations were sustained over longer period of time when compared to gliclazide pure drug. Microparticles also exhibited higher bioavailability when compared to gliclazide pure drug.

CONCLUSIONS:

1. The biological half life ($t_{1/2}$) of gliclazide pure drug estimated was in good agreement with the literature value. The $t_{1/2}$ of gliclazide was slightly elongated with microparticles.
2. The absorption of Gliclazide was very rapid when administered as pure drug and was slow from both the microparticles tested.
3. Based on $(AUC)_o^{\alpha}$, the relative bioavailability (BA) of gliclazide from microparticles SAF2 and CHF3 was 85.81 % and 117.14 % respectively when compared to gliclazide pure drug (100%).
4. A good level A correlation was observed between percent drug released (*in vitro)* and $(AUC)_o^{\alpha}$ (*in vivo*) with both the microparticles.

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