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PRECLINICAL PHARMACOKINETIC EVALUATION OF STARCH ACETATE AND CHITOSAN MICROPARTICLES OF GLIPIZIDE

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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) evaluation of microparticles of glipizide 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 glipizide over 12 h. The objective of the present study is preclinical pharmacokinetic evaluation of selected glipizide microparticles (SAF2 and CHF3) in comparison to glipizide pure drug in healthy rabbits (n=6). The products were tested orally at a dose equivalent to 0.4 mg/kg of glipizide. Plasma glipizide concentrations were determined by a reported and revalidated HPLC method. The biological half life ($t_{1/2}$) of glipizide pure drug estimated (3.45 h) was in good agreement with the literature value of 2-5 h. The $t_{1/2}$ of glipizide was slightly elongated with microparticles. The absorption of Glipizide was very rapid when administered as pure drug and was slow from both the microparticles tested. Based on $(AUC)_o^{\alpha}$, the relative bioavailability (BA) of glipizide from microparticles SAF2 and CHF3 was 105.41 % and 113.95% respectively when compared to glipizide pure drug (100%). A good level A correlation was observed between percent drug released (*in vitro)* and $(AUC)_o^{\alpha}$ (*in vivo*) with both the microparticles. Thus, the results of preclinical pharmacokinetic studies indicated that glipizide was absorbed slowly

from microparticles and the plasma drug concentrations were sustained over longer period of time when compared to glipizide pure drug.

KEYWORDS: Glipizide, Microparticles, Chitosan, Starch acetate, Preclinical evaluation, Pharmacokinetics.

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] the preparation and *in vitro* (drug release) evaluation of microparticles of glipizide 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 glipizide over 12 h. 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 Glipizide over 12 hours and were found suitable for oral control release of Glipizide 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 glipizide pure drug in healthy rabbits.

MATERIALS AND METHODS

Materials

Glipizide 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.[7] 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 glipizide were prepared by emulsification solvent evaporation method. Chitosan microparticles of glipizide were prepared by emulsification - desolvation -crosslinking method. The details of the methods are described in our earlier papers.[5, 6]

Preclinical Pharmacokinetic Evaluation

In vivo preclinical pharmacokinetic evaluation was done on glipizide microparticles, SAF2 and CHF3 in comparison to glipizide 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) Glipizide pure drug

(ii) Glipizide microparticles, SAF2

(iii) Glipizide 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 0.46 mg/kg of glipizide. The dose for experimental rabbits was calculated as suggested by Bikash Medhi and Ajay Prakash.[8] 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 a 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, 4, 6, 8, 10 and 12 h) after administration. Blood 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^{o}C prior to assay for drug content on the same day. The plasma concentrations of glipizide were determined by a reported HPLC method[9] 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[10,11] were used for the estimation of various pharmacokinetic parameters.

RESULTS AND DISCUSSION

Preclinical pharmacokinetic evaluation was done on selected glipizide microparticles prepared employing i) starch acetate, a new modified starch (SAF2) and ii) chitosan, a mucoadhesive polymer (CHF3) in healthy rabbits in comparison to glipizide pure drug with a view to evaluate their *in vivo* performance. Plasma concentrations of glipizide observed following the oral administration of glipizide 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 0.202 h^{-1} and 3.43 h respectively for glipizide pure drug. The $t_{1/2}$ of glipizide estimated is in good agreement with the reported[12] value of 2-5 h. The K_{el} and $t_{1/2}$ are 0.158 h^{-1} and 4.38 h respectively for microparticles SAF2 and 0.165 h^{-1} and 4.2 h respectively for microparticles CHF3. The $t_{1/2}$ of glipizide was slightly elongated with microparticles be due to *in vivo* sustained release and slow absorption of glipizide from the microparticles.

Glipizide was absorbed rapidly when administered as pure drug with an absorption rate constant (K_a) of 2.425 h^{-1}. A C_{max} of 3.22± 0.65 µg/ml was observed at 2 h following oral administration of glipizide pure drug. Plasma concentrations were later decreased rapidly.

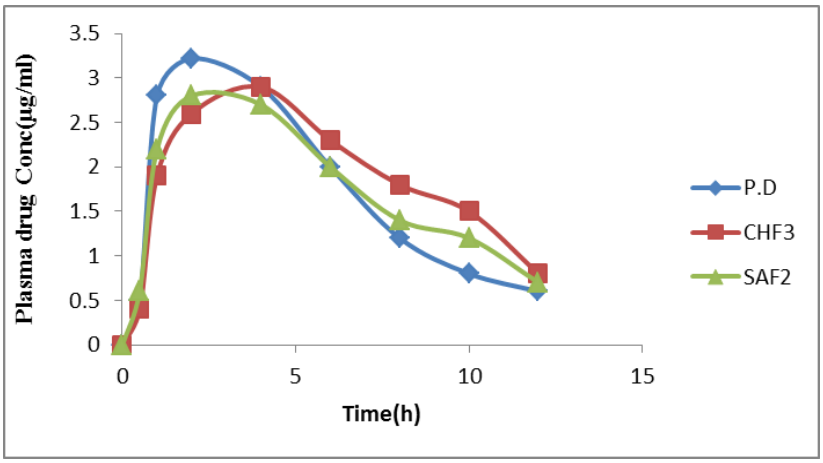

Fig 1: Plasma Concentration Vs Time profiles of Glipizide Estimated Following the Oral Administration of Glipizide and its Microparticles in Rabbits (n=6)

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

Pharmacokinetic Parameter	Glipizide	Microparticles SAF2	Microparticles CHF3
C_{max} (µg/ml)	3.22± 0.65	2.8 ± 0.29	2.9± 0.27
T_{max} (h)	2	2	4
K_{el} (h^{-1})	0.202	0.158	0.165
$t_{1/2}$ (h)	3.43	4.38	4.2
AUC_0^{12} (µg.h/ml)	21.58	21.45	23.12
AUC_0^{α} (µg.h/ml)	24.55	25.88	27.96
K_a (h^{-1})	2.425	1.013	1.006
Rel BA (%)	100	105.41	113.95

Glipizide was absorbed slowly from microparticles SAF2 and CHF3 with an absorption rate constant (K_a) of 1.013 h^{-1} and 1.006 h^{-1} respectively. A C_{max} of 2.8 ± 0.29µg/ml was observed at 2 h with SAF2. A C_{max} of 2.9± 0.27µg/ml was observed at 4 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 glipizide from microparticles SAF2 and CHF3 was 105.41 % and 113.95% respectively when compared to glipizide 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.

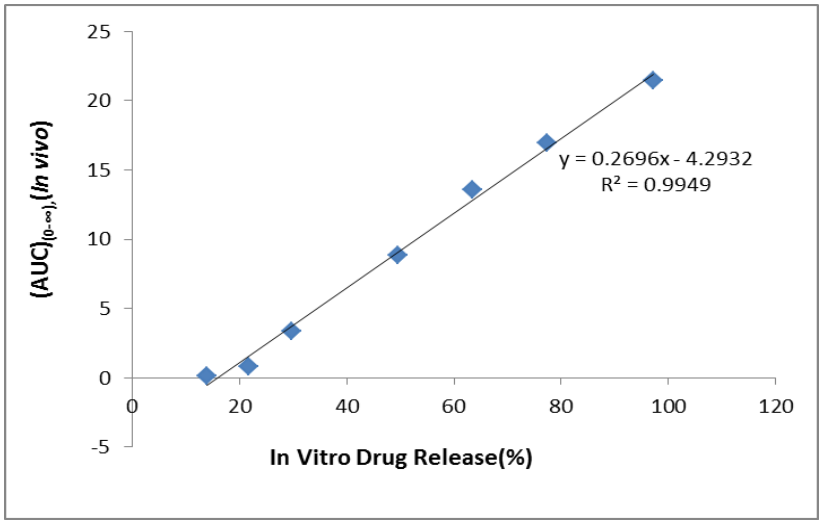

Fig 2: *In vitro- in vivo* correlation of Glipizide microparticles SAF2.

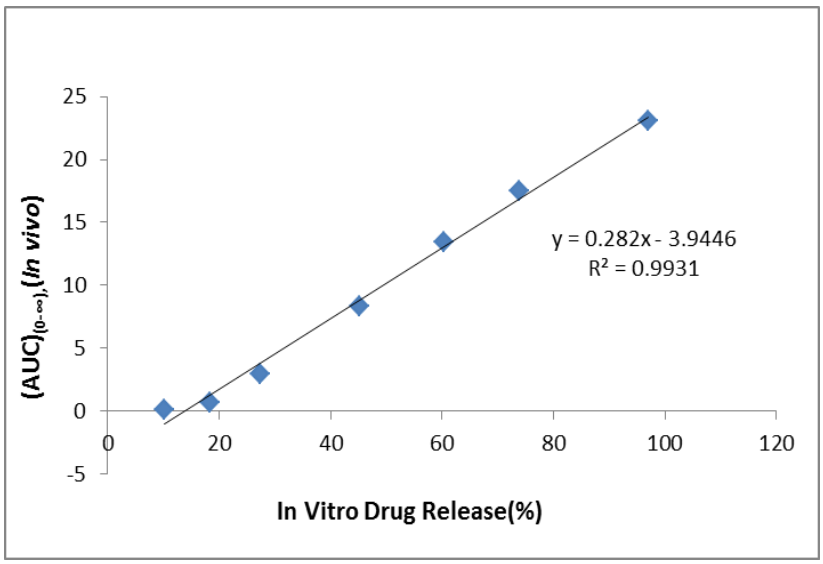

Fig 3: *In vitro-in vivo* correlation of Glipizide microparticles CHF3.

The R^2 values describing the correlation between *in vitro* and *in vivo* results were found to be 0.994 and 0.993 with microparticles SAF2 and CHF3 respectively indicating good level A correlation.

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

CONCLUSIONS

1. The biological half life ($t_{1/2}$) of glipizide pure drug estimated was in good agreement with the literature value. The $t_{1/2}$ of glipizide was slightly elongated with microparticles.
2. The absorption of Glipizide 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 glipizide from microparticles SAF2 and CHF3 was 105.41.0 % and 113.95% respectively when compared to glipizide 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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