# Design and Development of Mucoadhesive Gastroretentive Tablets Using Novel Derivatives of Xyloglucan

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**ABSTRACT**

Main aim of this study was to prepare and evaluate mucoadhesive gastro retentive glipizide tablets using xyloglucan (XG) and its conjugates. Carboxy methyl (CMXG) and cysteine conjugates (CysXG) were prepared and tablets were prepared by combining these with HPMC by direct compression method. XG-HPMC formulation were optimized using $3^2$ full factorial design to realize set goals for % release at 8hr and mucoadhesion and were evaluated for performance parameters. Optimum formulations were then reproduced by replacing XG with its conjugates. *Invivo* muco adhesion and bioavailability from optimized formulations for prepared tablets are performed. Significant and synergetic effect was found on % drug released and muco adhesion with trial runs. Tablets with CMXG and CysXG showed higher mucoadhesion, drug retardation compared to optimized XG formulation and less swelling index with CysXG containing formulations. *Invivo* study showed that thiomer containing tablets was retained in stomach of rabbit at the end of $8^{th}$ hr and showed good bioavailability with shorter $T_{max}$ of 5hr and higher total AUC 1065.39 mg/l than XG, CMXG tablets. So muco adhesive gastroretentive glipizide tablets can be successfully prepared with better release retardation and muco adhesion with thiomer of xyloglucan over XG and CMXG.

**Keywords:** Thiomers, Xyloglucan, Mucoadhesive, Gastroretentive, Factorial design, Tablets.

## INTRODUCTION

Various approaches to formulate Gastro retentive drug delivery system (GRDDS) are explored and mucoadhesion is one of them. GRDDS is suitable for drugs with an absorption window in the stomach or the upper small intestine, for drugs which act locally in the stomach and for drugs that are poorly soluble or unstable in the intestinal fluid.[1]
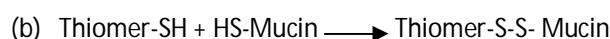
Numerous attempts have been undertaken to improve the adhesive properties of mucoadhesive polymers such as use of linear poly (ethylene glycol) as adhesion promoter for hydrogels[2], the neutralization of ionic polymers[3], mucoadhesion by a sustained hydration process[4] and the development of polymer–adhesin conjugates[5] providing a specific binding to epithelia and ionic interactions.

However these approaches are found to be insufficient to guarantee the localization of drug delivery system at stomach mucosa for prolonged time. This led to evolution of new generation of mucoadhesive polymers called thiolated polymers or "thiomers".[6] Thiomers form disulfide linkages with cysteine-rich subdomains of mucus glycoprotein linkages based on thiol/disulfide exchange reactions and/or a simple oxidation process.[7,8] This mimics the natural mechanism of secreted mucus glycoproteins, which are also covalently anchored in the mucus layer by the formation of disulfide bonds. The mucoadhesive properties of all the polymers where immobilization of thiol groups was done were significantly improved.[8]

(a)　Thiosmer-SH +Mucin -S-S- Mucin ⟶ Thiomer-S-S- Mucin + Mucin –SH

oxidation
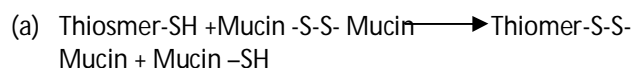
(b)　Thiomer-SH + HS-Mucin ⟶ Thiomer-S-S- Mucin

Mechanism of disulfide bond formation between thiomers and mucus glycoprotein (a) thiol/disulfide exchange reaction, (b) simple oxidation process.

Xyloglucan (XG) is a natural mucoadhesive polymer derived from the seeds of *Tamarindus indica* Linn., and used as thickening, stabilizing and gelling agent in the food industry. The polysaccharide is composed of glucose, xylose and galactose units present in the ratio of 2.8:2.25:1.0.[9] Glipizide is an antidiebetic agent with, half-life of elimination ranges from 3.4 ± 0.7 hours so frequent dosing that is 5 - 20mg once or thrice a dayis required. To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of glipizide isdesirable.[10] Carboxymethyl-XG shows more stability against microbes than plan XG and derivatization has been reported in the literature.[11]

Present study describes formulation and evaluation of tablets of xyloglucan, carboxymethyl xyloglucan (CMXG) and cysteine thiomer of xyloglucan (CysXG) for the purpose of improving gastric retention and bioavailability of model drug glipizide.

## MATERIALS AND METHODS

### Materials

Glipizide provided by Shri Krishna pharma, Ltd. Ahmadabad, India. HPMC K4100M by Loba Chemicals, Mumbai, India; Tamarind seed polysaccharide by Encore polymer Pvt. Ltd, Mumbai; Cysteine Hydrochloride by Sigma lab, Nashik, India.

### Methods

#### Preparation of thiomer of xyloglucan[12]

Xyloglucan (2g) was dissolved in 250 ml of de-mineralized water under constant mechanical stirring for 15 min. This solution was stirred for 30 min and cysteine hydrochloride (4g) was added to reaction mixture in a weight-ratio of 1:2 (polymer: cysteine). Reaction mixtures were incubated for 3h under continuous stirring. After precipitation with acetone, the reaction product was rinsed with acetone: water (1:1) in order to remove unreacted moieties and finally washed with acetone before drying at room temperature followed by drying in a vacuum oven (-600 mm of Hg, $40^{o}C$, 24 h).

#### Experimental design

A full factorial design using three levels each of the two factors viz. HPMC (A) and xyloglucan(B) was adopted, the factor levels were suitably coded as required by the design (Table 1). The translation of coded factor level as amount of ingredient was low(-1), intermediate(0) and high(1) level of HPMC factor 1 was 20, 30 and 40 mg respectively and that for xyloglucan factor 2 was 40, 50 and 60 mg respectively.

**Table 1:** Factor combination as per the experimental design for glipizide tablets

| Formulation Code | Trial No. | Coded Factor Level | |
|---|---|---|---|
| | | Factor 1 | Factor 2 |
| F1 | 1 | -1 | -1 |
| F2 | 2 | -1 | 0 |
| F3 | 3 | -1 | 1 |
| F4 | 4 | 0 | -1 |
| F5 | 5 | 0 | 0 |
| F6 | 6 | 0 | 1 |
| F7 | 7 | 1 | -1 |
| F8 | 8 | 1 | 0 |
| F9 | 9 | 1 | 1 |

The general formula for the formulation optimization of glipizide tablets was glipizide 20mg, HPMC(20-40mg), xyloglucan (40-60mg). The response variables which were considered for optimization included the amount of drug released in 8 h ($rel_{8\,h}$) and mucoadhesive strength.

#### Preparation and evaluation of tablets

#### Preparation of tablets:

Tablets were prepared by direct compression. All the product and process variables (other than the concentration of two polymers) like mixing time and hardness were kept constant. Physical mixtures of glipizide, HPMC and xyloglucan were sieved through # 80. All material was weighed, mixed and subsequently compressed into tablets using flat faced punches of 12mm diameter using RimekMINI PRESS-II MT. The tablets containing CysXG and CMXG in place of XG were also formulated in similar fashion. Also the optimized tablet formula was reproduced replacing XG with CyXG and CMXG. The placebos containing barium sulphate of these tablets were formulated in similar fashion for *in vivo* mucoadhesion time study.

Stat Ease Design Expert 9.0 software was used to prepare design matrix for two factor 3 level design comprising nine runs (table 1). The factors chosen were content of XG and HPMC whereas the responses optimized were mucoadhesion and release at 8 h. The data was analyzed and second-order polynomial equation generated with added interaction terms to correlate the studied responses with the examined variables. The polynomial regression results were demonstrated using 3-D graphs and contour plots. The tablets were evaluated for performance parameters such as thickness, hardness, friability, uniformity of weight and content using methods reported in literature.[13]

#### Mucoadhesion study[14]

Mucoadhesive force was evaluated using a texture analyzer (Make-Brookfield Engineering Labs, Inc., Model Texture Pro CT V1.4 Build 17).

Fresh sheep intestinal mucosa was obtained from a local slaughter house and was used within 2 h of slaughtering. The mucosal membrane was washed with distilled water and then with phosphate buffer pH 6.8 subsequently it was carefully attached to a 10-mm cylindrical probe (TA 3/100probe) by a biadhesive tape.

The tissue inholder was immersed in simulated gastric fluid maintained at 37°C. The designed tablet was attached to the probe (stainless steel cylindrical probe with 10 mm diameter) using double sided tape.

The probe was lowered at a speed of 0.5mm/s until the tablet made contact with mucosal tissue. A constant force of 1 N was applied for 60 s, after which the probe was withdrawn at a speed of 0.5 mm/s to the distance of 15 mm and maximum detachment force (N) was determined for each sample with data rate 15 points/sec. For each new sample, a different mucosa sample was used. The test was conducted in triplicate.

*Swelling index*[15]

Tablets ($T_1$, $T_2$, $T_3$) were weighted individually (designated as $w_1$) and placed separately in Petri dishes containing 10 ml of 0.1N HCl. At regular intervals (0.5, 1, 2, 3, 4, 5, 6 h), the samples were removed from the petri dish and excess water was removed carefully by using filter paper. The swollen tablets were reweighed ($w_2$). The swelling index of each system was calculated using the following formula :

$$\text{Swelling Index} = \frac{w_2 - w_1}{w_1} \qquad (1)$$

*In vitro release study*[16]:

Drug release studies (n=3) were conducted for all the formulation combinations using dissolution test apparatus (DA-6D USP Standard). 0.1N HCl (900 ml) was taken as the release medium at 100rpm and 37±1°C employing USP II paddle method. Aliquots of 5 ml were periodically withdrawn and the sample volume replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 276 nm. The data obtained from *in vitro* dissolution were analyzed using the PCP Disso software.

The values of drug release at end of 8 h and mucoadhesion were determined and numerical optimization was resorted by applying suitable criteria and the suggested solution was arrived upon based on desirability function. The tablets were formulated using the chosen optimal composition and evaluated for dissolution performance and mucoadhesive strength. Plots between predicted and observed responses were critically compared, the residual graphs plotted and the percent error calculated with respect to the observed responses.

Using same optimized formula, by replacing XG with its conjugates tablets were prepared and evaluated for tablets parameters, drug released, mucoadhesion and swelling index.[17]

*Invivo evaluation of formulations.*[18]

The study protocol was approved by Institutional Animal Ethics Committee, AISSMS College of pharmacy. AISSMS/IAEC/11-12/01-18, protocol approval no. CPCSEA/IAEC/PT-04/12-2K11.

*Bioavailability studies in rabbits*

Female rabbits with a weight of 2.5 kg were used, total 8 rabbits divided into 4 groups. The animals were housed individually under environmental conditions (25°C, 12hrlight and dark cycle). The rabbits were fasted overnight and allowed free access to water only. The formulations were administered orally by placing the tablet in hollow polyethylene tube. The tube was inserted into the mouth of rabbit and blown using rubber bulbs. For last group glipizide0.04mg was dispersed in 5ml of distilled water and administered orally to the rabbits by gastric intubation method.

Blood sample from marginal ear vain of the rabbit was collected in screw capped EDTA tubes at predetermined time intervals (1,2,3,4,5,6,7,8 hr). After collection, blood samples were immediately centrifuged for 10min at 4000rpm and separated plasma was stored in screw capped polypropylene tubes at -5°C till analysis. To each tube was added 5ml ethyl acetate as liquid-liquid extracting solvent. The contents of the tube were vortexed, mixed for 3 min and then centrifuged for 3 minutes at 3000 rpm. The organic layer was collected in glass tubes and evaporated to dryness on water bath at 40°C under a nitrogen stream. The contents of the tubes were then reconstituted with 50 μL of methanol and 20 μL of each was injected into HPLC system. Chromatographic analysis was done using Agilent C18 column (250 x 4.6 mm, 5 μ) protected with guard column, using isocratic pump, mobile phase was Methanol : Water (90:10 v/v) at 1 ml/minute, 20 μl sample was injected and analyzed at wavelength of 238 nm.

*Roentographic studies for determination of invivo residence time*

Evaluation of *invivo* residence time of barium sulphate containing optimized XG tablet, CysXG tablet and CMXG tablet was carried out in rabbits. Rabbits of either sex weighing (2.2-2.6 kg) were fasted overnight before administration of tablet but allowed free access to water throughout the study. The institutional animal ethical committee approved the protocol for this study (IESCEA). The tablet was administered by using endotrachial tube and the rabbit was anesthetized and x-ray was taken at 0, 2, 4 and 8hr intervals.

## RESULTS AND DISCUSSIONS

*Preparation of thiomer of xyloglucan (CysXG)*

The thiomer was formed by covalent attachment of cysteine moiety to the hydroxyl groups of xyloglucan by ester bond.

SH-CH2-CHNH2-COOH + OH-POLYMER ⟶ SH-CH2-CHNH2-COO-POLYMER
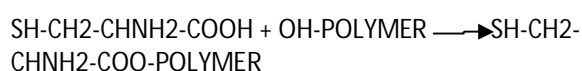
*Evaluation of tablets:*

Appearance of resulting tablets was found to be white, uncoated, circular , biconcave, plain on both side. All nine batches displayed adequate thickness in mm (2.97 ± 0.15 to 3.19 ± 0.08), hardness (5.3 to 5.7 kg/cm$^2$), friability (<0.34%), the weight were within specified range (±5% of average) and content of glipizide in % was within range (97.81±0.39 to 99.45±0.28).

A full factorial design using three levels each of the two factors was adopted for further investigation as required by the design and the factor levels were suitably coded.

The application of an optimization technique consisting of statistical design to pharmaceutical formulation

development provides an efficient and economical method to acquire the necessary information to understand the relationship between controllable (independent) variables and performance dependent variables or responses. The technique of optimization has been employed in our earlier work for development of microspheres of thiomer[15]. The data provided to software could provide a statistical model which was significant and through multiple linear regression analysis it provided equations which represented the type and quantum of influence of variables on responses while the 3D response surface provided a visual representation of interaction and effects of variables.

The Model F-value of 7.08 implies the model is significant. There is only a 2.63% chance that an F-value this large could occur due to noise. Values of "Prob> F" less than 0.0500 indicate model terms are significant.
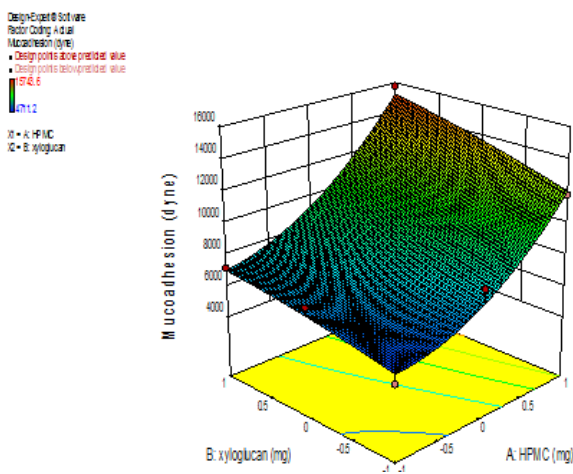


**(A)**
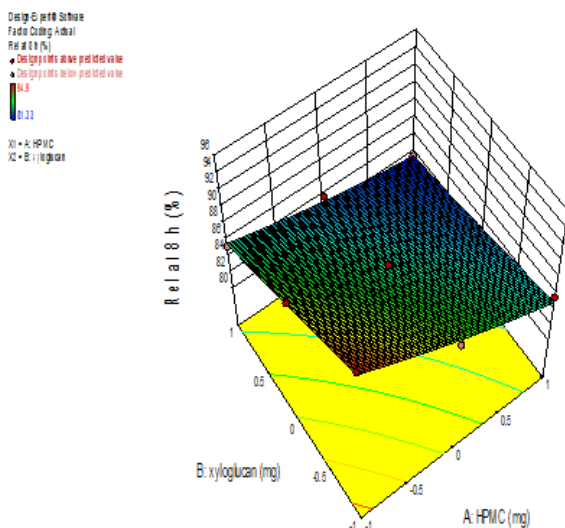


**(B)**

**Figure 1:** Response surfaces (A) Effect of XG conc. and

HPMC conc. on Mucoadhesion (B) Effect of XG conc. and HPMC conc. on % drug released at 8hr.

Drug release at 8 hr= $86.1-3.46X_1-3.16X_2+1.32X_1X_2+0.47X_1^2+0.16X_2^2$--- Eq 2

Mucoadhesion= $8527.43+732.63X_1+1221.85X_2+377.12X_1X_2+1565.03X_2-184X^2$---- Eq 3

The equations 2 & 3 for release at 8hr along with the response surface between xyloglucan and HPMC gives an insight into effect on drug release and Mucoadhesion. The HPMC and XG has similar influence on the drug release whereas for Mucoadhesion the XG had an overwhelmingly pronounced effect on the adhesion and they show a synergism when at high concentrations together which might be due to the chain entanglement and increased viscosity of both polymers.
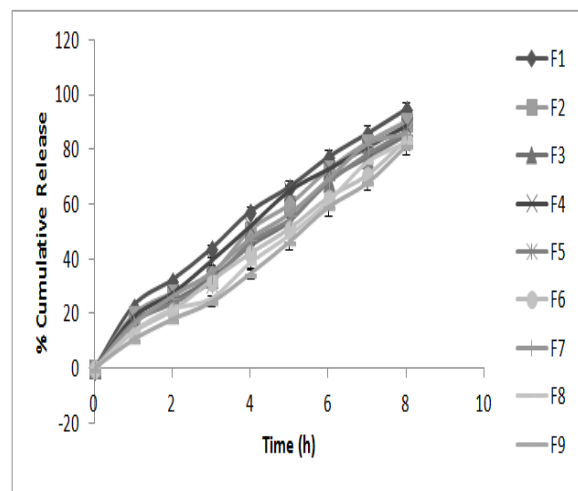


**Figure 2:** *In vitro* drug release studies form trial runs of design matrix

Cumulative released profile showed (fig.2) that with increase in amount of HPMC drug retardation was increased but it was higher with XG, at the end of 8hr almost 95 % of drug released for $F_1$ batch containing minimum amount of both polymers, 85% release for batch $F_3$ containing high HPMC and low XG only 81 % released for $F_9$ batch with higher amount both polymers.

For all five optimized formulations, physicochemical parameters were found to be within limits. Predicted and experimental value showed $R^2$ 0.912 and 0.926 for mucoadhesion and release at 8hr respectively, shows linear co-relation between the predicted and observed response variables, indicating a good co-relation. Upon comparison of the observed responses with that of the anticipated responses, the prediction error varied between -1.68% and +1.42% (table 2). Thus, the low magnitudes of error as well as the significant values of $R^2$ in the current study indicate a high prognostic ability of the software.

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*Validation of response surface methodology*

**Table2:** comparison of observed and predicted response parameters of optimized batches

| Formulation code | Composition HPMC/Thiomer | Response property | Predicted value | | Experimental value | | % error | |
|---|---|---|---|---|---|---|---|---|
| O1 | 35.77/ 60.00 | R1:Mucoadhesion R2:Release 8 hr | 2.997 | 82.00 | 2.8 | 83.13 | -1.03 | 1.359 |
| O2 | 35.13/ 59.99 | R1:Mucoadhesion R2:Release 8 hr | 2.994 | 82.12 | 3.0 | 82.79 | 1.419 | 0.811 |
| O3 | 31.48/ 59.99 | R1:Mucoadhesion R2:Release 8 hr | 2.977 | 82.78 | 3.0 | 83.58 | 0.766 | -1.47 |
| O4 | 25.76/ 60.00 | R1:Mucoadhesion R2:Release 8 hr | 2.949 | 83.84 | 2.9 | 84.97 | -1.68 | 1.34 |
| O5 | 34.80/ 60.00 | R1:Mucoadhesion R2:Release 8 hr | 2.293 | 82.17 | 2.3 | 83.35 | 0.304 | 1.42 |

*Preparation and evaluation of optimum glipizide tablets*

Three batches were prepared $T_1$ $T_2$ $T_3$, HPMC amount remain same in all batches i.e 34.80mg and 60 mg of XG, CM-XG, Cys-XG in $T_1$ $T_2$ $T_3$ respectively. Replacing XG from optimised glipizide formulation with that of its conjugate ($T_1$ , $T_2$ and $T_3$) was evaluated for physicochemical parameters and were found to be within limit. Further, was evaluated for % released at end of $2^{nd}$ 24.17%, 22.85%, 18.69% and $8^{th}$ hr 83.96%, 81.41%, 80.35% these values shows that the release was more retarded with CysXG compared to CMXG and plain XG containing formulation and overall profile was also showing much uniform and sustained released with CysXG conjugate this might be due to increased in cross linking with thiomer. And all the three formulations were follows Peppas Kinetic model with anomalous type of release with both diffusion and erosion of polymer with $r^2$ 0.9933, 0.9921 , 0.9911 and n 0.7521, 0.8627 , 0.7162 respectively.

*Mucoadhesion studyand Swelling Index study for $T_1$, $T_2$, $T_3$*

Mucoadhesion was significantly improved for CysXG (2.95, 3.12 and3,42 gm for T1, T2 and T3 respectively) containing tablets while swelling index was more for CMXG(62.41%) compared to XG(57.69%) and lowest for CysXG(37.4%) containing tablets, this might be due to presence of ionized group on XG which is immobilized with CM in CMXG and which is further replaced with cysteine in CysXG. The increase in mucoadhesion of thiomer despite of reduced water uptake can be attributed to the covalent bonding of thiol group with mucin.

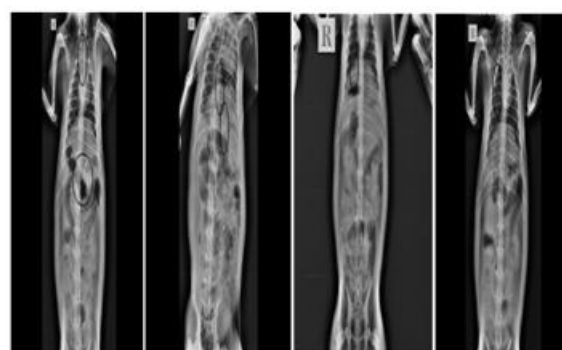*Roentographic studies for determination of in vivo residence time*

It was seen that (fig 3) the time of *in vivo* retention of XG and CMXG tablet in rabbit was similar and CysXG tablet had a higher retention time in stomach (up to 8hr) which is a clear indication of influence CysXG can exert through its covalent disulphide linkages.
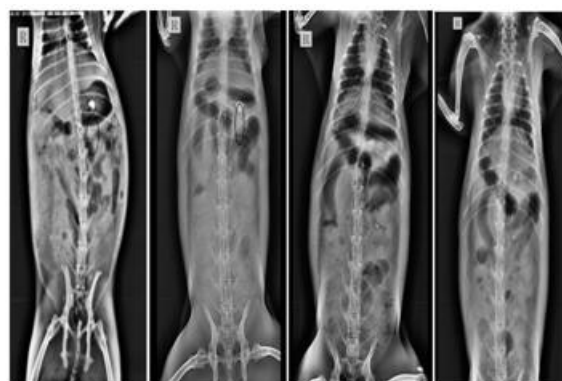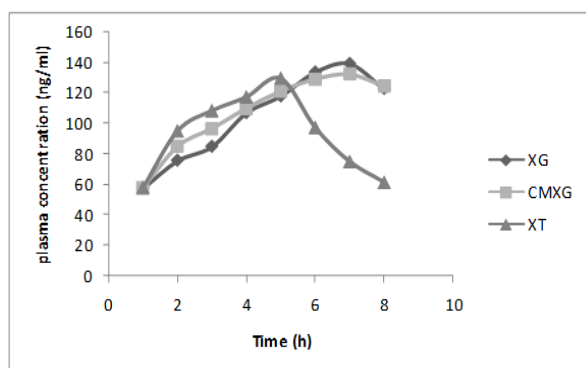


(A)
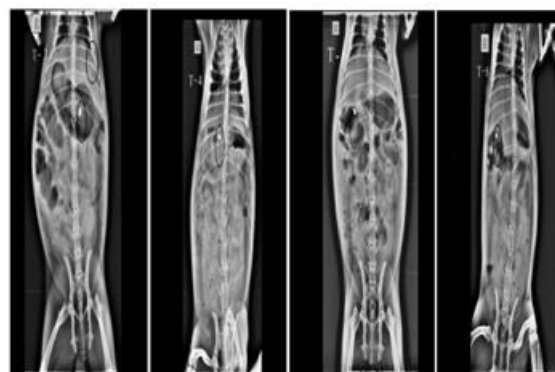


(B)



(C)

**Figure 3:** *In vivo* residence time for placebo tablets of A) XG B) CysXG and C) CMXG

*In vivo bioavailability studies in rabbits*



**Figure 4:** Plasma concentration time profiles for XG, CMXG and CysXG(XT) tablets containing glipizide.

Fig4 indicates the plasma concentration time profile of glipizide through XG, CMXG and CysXG tablets. The CysXG tablets exhibited faster $T_{max}$ of about 5h whereas the profiles of XG and CMXG tablets were similar and displayed $T_{max}$ of about 7 hours. The $C_{max}$ (130ng/ml) was bit less than that of CMX and CysXG but the AUC as calculated by trapezoidal rule was much higher. The AUC t-∞ obtained by dividing last concentration by $K_{el}$ obtained from plot of lnC vs time[16] was added and AUC total was arrived at 1065.39mg/L (Table3). The increased residence time in stomach and other effects of thiomer such as increase in tight junctions openings and inhibition of PgP efflux might have contributed to increased bioavailability.[17]

**Table 3:** Summary of pharmacokinetic parameters of XG, CMXG and CysXG tablets

| Tablet | $C_{max}$ | $T_{max}$ | AUC 0-t Hour*mg/L | AUC t-∞ Hour*mg/L | AUC total Hour*mg/L |
|---|---|---|---|---|---|
| XG | 139.5 | 7 | 286.3 | 419.01 | 705.31 |
| CMXG | 129.79 | 7 | 295.73 | 428.44 | 724.17 |
| CysXG | 132.54 | 5 | 466.34 | 599.05 | 1065.39 |

## CONCLUSION

Swellable, mucoadhesive glipizide tablets with HPMC-XG were successfully prepared by using $3^2$ full factorial design. The prepared tablets exhibited good physicochemical properties. Glipizide release from XG-HPMC tablets was controlled and extended for 8 hr & it is significantly depend upon concentration of both the polymers. More retardation was found with thiomer batch. Mucoadhesive property was found to be improved for glipizide-thiomer tablets over glipizide-XG tablets while swelling index was found to be more for Glipizide-CMXG tabs compared Glipizide thiomer tablets. X rays for retardation of tablets in stomach of rabbit showed 4hrs of retardation with XG and CMXG while 8hrs for thiomer containing tablets. Bioavailability showed that less $T_{max}$ 5hrs and more total AUC 1065.39 mg/l for thiomer containing tablets than XG, CMXG tablets.

Hence the CysXG-HPMC tablets were suitable for gastroretentive and controlled release effect for 8 hr after oral administration of glipizide.

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