ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES
Published by JK Welfare & Pharmascope Foundation Journal Home Page: https://ijrps.com

Formulation development and *in vitro – in vivo* pharmacokinetic studies of gliclazide colon targeted matrix tablet

Sivakumar Kalidoss[1]*, Kailasam Koumaravelou[2]

[1]Centre for Research & Development, PRIST University, Thanjavur, Tamil Nadu, India
[2]PRIST University, Abhishekapakkam, Puducherry, India

Article History:

Received on: 25.09.2018
Revised on: 16.12.2018
Accepted on: 19.12.2018

Keywords:

Gliclazide,
In vitro kinetic,
In vivo pharmacokinetic,
X-ray image

ABSTRACT

The colonic drug delivery system (CDDS) of Gliclazide was formulated and *in vitro* and *in vivo* pharmacokinetics studies were conducted. The colonic delivery system consists of SR matrix tablets containing Gliclazide were developed by dissimilar grade of HPMC combinations with enteric coating polymers like EudrajitL100 and S100 as coating materials, as an outlet layer, insoluble and impermeable at acidic pH but easily soluble at a pH value higher than 5.5 (EudrajitL100 and S100). *In vitro* results showed the colonic drug delivery system is capable of avoiding drug release in acidic medium for 2 h but the gliclazide drug release in phosphate buffer, pH 6.8, after 3 hrs stage of time and release was up to 24 hrs. The dissolution mechanism of drug release was more definite by Higuchi plots that showed good quality linearity (R^2 values between 0.90 and 0.93), with slope > 0.5, representing that drug release mechanism from the formulations were non-fickian diffusion mechanism. Pharmacokinetic parameters like Cmax, Vd, Ke, t1/2, Cl, AUC0-∞ and MRT were designed for selected (GLZ6) formulations**.** Furthermore, the relative bioavailability (RB) was also found to be high, and therefore it indicates that gliclazide released extra amounts from the tablet formulation and absorbed for blood circulation with a satisfactory plasma concentration. X-ray pictures exhibit that the selected formulation GLZ 6 could be targeted particularly to the colon, without any early drug release in the stomach and small intestine. Therefore, from this study, it had been concluded that Gliclazide matrix tablets might persuade be additional efficient in the management of diabetic patients through CDDS.

* Corresponding Author

Name: Sivakumar Kalidoss
Email: akottaimuthu@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v10i1.1800

Production and Hosted by
IJRPS | https://ijrps.com

INTRODUCTION

The development and also the design of colon specific formulations represent a technological challenge as these indefinite quantity forms should have the higher GI tract in intact form before delivering the drug to the colon. The oral route is taken into account to be most convenient for the administration of medicine to patients. Oral

administration of typical indefinite quantity forms commonly dissolves within the abdomen fluid or intestinal fluid and gets absorbed from these regions of the GI tract (GIT) relying on informed the chemical properties1of the drug (Pirjo Nykanen, 2003). However, colonic drug delivery via the oral route isn't while not its challenges. The colon constitutes the foremost distal section of the GI tract so an orally administered formulation should retard drug unharness within the higher canal regions however unharness the drug promptly on entry into the colon. Due to the dearth of enzymes, the colon is taken into account as an appropriate site for the absorption of varied medication. Over the past 20 years, the foremost challenge for somebody is to focus on the

medication specifically to the colonic region. Earlier colon was thought-about as associate innocuous organ alone to dependable for absorption of water, electrolytes and temporary storage of stools (Sarasija S *et al.,* 2006). However, currently, it's accepted as a necessary site for drug delivery. In the present investigation, gliclazide matrix tablets were developed by wet granulation methodology. Matrix tablets were characterised by *in vitro* drug release, *in vitro* kinetic, *in vivo* pharmacokinetic study and *in vivo* x-ray image studies.

MATERIALS AND METHODS

Gliclazide was received as a gift sample by Bal Pharmaceutical company, India. Eudrajit L 100 D 55, Eudrajit S 100 were received from signet chemicals, Mumbai. Alternate materials utilized in the experiment such as dibasic Calcium phosphate, povidone, aerosil 200, talc and Magnesium stearate were of the pharmacopoeial grade. A tissue tearor (BioSpec Products, Inc., USA) and ultrasonic cell disruptor- Branson Ultrasonics™ Sonifier S-250A Analog Ultrasonic Cell Disruptor/Homogenizer (Branson Ultrasonics™, USA) were used for tissue homogenization. Once sterilized surgical equipment/ instruments such as scissors, forceps, glass syringes, etc. were utilized to during the study. All the previous chemicals were of analytical grade.

Formulation of Gliclazide matrix tablet

Step I: Core Tablets

Take the Gliclazide, Poly ethylene Glycol 6000 and Aerosil 200 through 40 # SS sieve in double lined polybag separately and weigh the HPMC (Methocel K100LV-CR Premium (IF10805), HPMC K4M and Dibasic Calcium Phosphate passed through 40 # SS sieve the above materials were mixed for 5 minutes in the double lined polybag at unidirectional flow for uniform mixing. in a polybag. Povidone K-90 was dissolved into purified water under continuous stirring until to get lumps free clear solution. The prepared binder solution was slowly added to dry mixed materials to get uniform wet granules. The wet mass was sifted using 12 mesh sieve. The above-wet mass was transferred to lab model FBD (Retsch), fixed the product container properly and dry the granulated mass at an Inlet temperature of 50-60°C and Product temp 35-45° C. Checked the LOD at this stage using Moisture Balance. LOD Limit: NMT 1.0-3.0 % (at 105 °C for 5 minutes) and Continued the Drying till required LOD is reached. The dried granules were transferred through Quadro co-mill fitted with 0.457 (018 R) screen at a speed of 1000 RPM. Add talc and magnesium stearate through # 40 mesh Sieve and mixed of 2 minutes. The lubricated blend was compressed using 9.5 mm normal concave circular punches, Rotary Tablet Press.

Step II: Coating

The optimized formulation was coated employing a combination of EudrajitL 100 and S100 by employing a fluidized bed coating equipment. Coating resolution was ready by dissolution of five hundred mg of Eudrajit polymers (L-100 and S-100; 1:1) in ethanol: acetone (2:1) to convey 10% coating. PEG 4000 (1% w/v) was utilized as a softener. The coating solution was applied till there's no drug release in simulated GIT fluid. A 10% w/w increase within the Coating level was chosen as an optimum coating % level (Cheng G *et al.,* 2004).

In vitro dissolution studies

The release rate of Gliclazide SR tablets was determined utilized USP dissolution testing equipment I (basket type). The study was conducted utilized 900 ml of 0.1 N HCl at 37 ± 0.5°C and 100 rpm for first 1 h. Then replace with 7.4 pH phosphate buffer and continual for 12 h. Aliquot volume of 5 ml was withdrawn at regular intervals and replaced with fresh buffer diluted. The samples were replaced with fresh dissolution medium. Once filtration, the amount of drug release was calculated from the standard calibration curve of pure drug.

Kinetic modelling of the drug release profile

The drug release kinetic information was subjected to zero order, first order, Higuchi model (Higuchi *et al.,* 1963), Hixson–Crowell model, Korsmeyer and Peppas model (Korsmeyer *et al.,* 1983) for analyzing the device of medicine release and release kinetics from the dosage form using MS Excel 2007. The model with the best parametric statistic was thought of to be the most effective fitting one (Dorozynski *et al.,* 2004).

Pharmacokinetic studies of gliclazide pure and selected formulation

Animals

Healthy either gender rabbits were selected and conducted pharmacokinetic studies for the selected formulations of Gliclazide (GLZ6) in plasma. Rabbits having 2±0.35 kg of body weight were selected for the study. Rabbits were fed with normal control food and water *ad libitum*. The selected rabbits were housed in normal temperature with humidity as well as non-natural light and dark cycles (12h) before starting the experiment. The selected rabbits fasted overnight earlier to experimentation and water was given. All experimental procedure was permitted by the IAEC (PRRM College of Pharmacy, Utukur, Kadapa, India. (As per

the ref no. CPCSEA/COP/12/04-12-2015) and experiments were conduct in agreement with CPCSEA.

Group I: pure Gliclazide (2.5 mg/day)
Group II: Selected formulation GLZ6 (Gliclazide (2.5 mg)

Pharmacokinetic Analysis

Single dose oral administration of CTDD was prepared for the experiment. The amount of drug in plasma and various organs were calculated at different periods. This study aimed to find the drug character of the selected drug after treatment. Forthe selected CTDD formulations of Gliclazide (GLZ6), the following pharmacokinetic parameters were calculated/ measured:

i. C_{max} (µg/ml) was calculated from the plasma concentration versus time graph.
ii. T_{max}, (hr) was calculated from the plasma concentration versus time graph.
iii. Elimination rate constant (Kel, hr−1) was calculated by least-squares regression method.
iv. t½ e (hr) was calculated from the equation: t½ = 0.693/Kel.
v. Absorption rate constant (Ka, hr−1) and absorption half-life (t½ a, hr) were determinedby using the method of residuals.
vi. The area under the plasma concentration versus time curve (AUC (0-t), µg.h/ml) and the area under the first moment curve(AUMC (0-t), µg.h/ml) from 0 to 24 hours were calculated from the linear trapezoidal method.
vii. The area under the Plasma Concentration versus Time curve (AUC (0-α), µg.h/ml).
viii. The area under the First Moment Curve (AUMC (0-α), µg.h/ml).
ix. Mean Residence Time was (MRT (0-α), hr) from 0 to infinity.
x. The volume of distribution (Vd, L).
xi. Clearance (Cl, L.hr−1)
xii. Relative bioavailability (RB)

The parameters were calculated using follow- ing equations (Hesham Tawfeek M. *et al* 2013, Pandey R *et al* 2003, Abubakr Elgorashi S, 2009, Liu J *et al* 2012, Shargel L, *et al.,* 2004)

i. AUC (0-α) = AUC (0–t) + Fpt/Kel
ii. AUMC (0-α) = AUMC (0-t) + Fpt / Kel + Fpt/Kel^2
iii. MRT (0-α) = AUMC/AUC
iv. Cl = Dose/AUC
v. Vd = $KaFX_0$ / Log A (Ka-Ke)
vi. RB = AUC (0–t) (test)/ AUC (0–t) (reference) × 100%
vii. Where Fpt = Final drug concentration in plasma at time t
viii. Kel = Elimination rate constant;
F = Fraction of drug absorbed
ix. X_0 = Dose administered at starting;
RB = Relative Bioavailability
x. Log A = Y-intercept of the last portion of the plot (i.e. log extrapolated drug concentrationin plasma vs time curve)
xi. AUC o–t (test) = Area under the plasma con- centration versus time curve from 0 to 24 hours for all the three selected formulations
xii. AUC o–t (reference) = Area under the plasma concentration versus time curve from 0 to 24 hours of pure suspension of all three drugs

Analysis of Biological Samples

The pharmacokinetic parameters study, once oral administer selected formulations, GLZ6, (Gliclazide 2.5 mg). CTDD tablets and pure drug of gliclazide 2.5 mg tablets individual cluster of ani- mals. Blood samples (0.2 mL) were taken from themarginal ear vein of rabbits at planned time peri- ods (0, 2, 4, 8, 12, 16, 20, 24, 26 and 30 hours) andpicked up into heparinized tubes. From the sam- ples of plasma and blood obtained was centrifuged at 12000 rpm for 10 minutes at -40C, that was thenpreserved in glass tubes and frozen at −25°C ± 2.0. To 0.5 mL of plasma and tissue samples, 0.2 mL mobile phase, 0.1 mL of 5% v/v HCOOH was added,and the drug was eluted by CH3OH by utilizing solid phase extraction. The extracts were evaporated to dryness at 40^0 C under Nitrogen gas. Resi- dues were then reconstituted in 0.5 mL of mobile phase. The concentration of drug in biological sam- ples was calculated by the developed and valid bi- oanalytical strategies by RP HPLC (Sivakumar Kalidoss *et al.,* 2017).

Pharmacokinetic Data analysis

By using The Math Works, Inc. V2 Demo software non-compartmental analysis was performed for the drug concentration in varied tissues andplasma at the dissimilar time period. Pharmacoki- netic parameters like Cmax, Vd, Ke, t1/2, Cl, AUC0-
∞ and MRT were calculated for selected, ACD5, AM5 and GLZ6, formulations**.** The results of the *in- vivo* pharmacokinetics parameters for selected for- mulations were measured by appropriate statisti- cal tests with P< 0.05 level of significance.

***In vivo* x-ray imaging studies**

The protocol for the *in vivo* X-ray picture experiment was approved by the IAEC of PRRM school of Pharmacy, Utukur, Kadapa, India. (As per the reference no. CPCSEA/COP/12/04-12-2015). Rabbits were selected as an animal model for evaluating the colon-specific delivery

system. Tablets were formulated as per the optimized formula by replacement the drug with the radio-opaque compound BaSO4. After that, the tablets were coated equally to the optimized batch. All the rabbits utilized for the experiment fasted night long with free access to H2O. Once nightlong abstinence, the chosen tablets were treated to the rabbits with fifteen millilitres of H2Or. X-ray pictures of the abdomen of the animal were recorded at varied time intervals to mark out the progress and behaviour of the mini tablet within the GIT of rabbits (Dev RK *et al.,* 2011).

RESULTS AND DISCUSSION

In vitro drug release studies

The cumulative percentage releases of a different formulation of Gliclazide SR tablets were shown in Table 2 and Figure1. The release of Gliclazide from SR tablets varied according to the types and quantity of polymers content in the various formulations. A formulation which shows the mostsatisfactory result is GLZ6, where drug release started after 5 hrs and released maximum 98.92 by 24 hrs. Remaining formulations were respectively, release started and reached maximum, GLZ1- 2hr in 15..24 and 99.34 in 20 hrs, GLZ2-14.62 in 2 hr and 98.42 in 24 hrs, GLZ 3-14.72 in 2hr and 98.22 in 24 hrs, GLZ4 13.98 in 2 hr and 98.42 in 24 hrs and GLZ5 7.04 in 2 hr and 98.37 in 24 hrs. Formulations GLZ1 to GLZ 6 contain HPC different concentration. The amount of HPC increases retardation nature also increased. The period of drug release was slower with formulation GLZ6 was about only 98.92 % in 24 hrs.

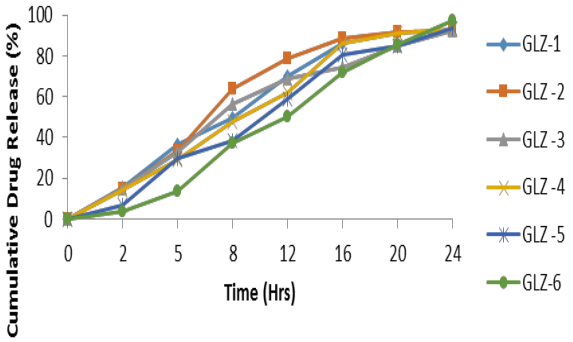

Figure 1: *In vitro* cumulative percentage release of different formulation of Gliclazide colon targeted matric tablets

In-vitro release kinetic for the formulation (glz1 to glz6) of gliclazide

The dissolution information (from the values of 2 to 24 hrs of the release of drug) of all formulations were fitted to first-order, Higuchi, zero-order and Korsmeyer – Peppas models. The formulations didn't follow first-order release kinetics. The correlation coefficient (R^2) was calculated to find the best-fitted model for drug release and their values are provided in Table 3. While the data were plotted in the graph according to a zero-order of reaction equation, the formulations from GLZ2 to GLZ6 have shown good linearity to their regression values 0.980, 0.977, 0.936, 0.964 and 0.981, respectively. The best fit with higher correlation (R^2> 0.93) was found with the Higuchi for GLZ2, GLZ3, GLZ4, GLZ5 and GLZ6 CTTDS tablets. Drug release from hydrophobic matrix tablets involved in pore dissolution and matrix erosion. Dissolution resulted in the complete release of the drug, maybe the coating of a certain fraction of drug by HPMC and HPMC IP K4M coated with EudrajitL100 and Edragit S 100. The release profiles of GLZ2, GLZ3, GLZ4, GLZ5 and GLZ6 might be well clarified by Higuchi model, as the plots showed good linearity and correlation coefficient (R^2) values 0.907, 0.901, 0.912, 0.924 and 0.930 respectively. The dissolution mechanism of drug release was further confirmed by Higuchi plots that showed good linearity (R^2 values between 0.90 and 0.93), with slope > 0.5, indicating that drug release mechanism from the formulations was non-fickian diffusion mechanism (Subhash Chandra Bose P *et al.,* 2011, Apurba Sarker Apu *et al.,* 2012).

In vivo Pharmacokinetic Studies

Oral Route of Administration Conventional Gliclazide Tablet (GLZ) and Selected Formulation (GLZ6) of CTDD Tablet

The mean pharmacokinetic parameters and the plasma drug concentrations vs time profile curve following oral treatment of 2.5 mg of Gliclazide for the (i) conventional Gliclazide tablet (GLZ) and (ii) selected formulation (GLZ6) of colon targeted drug tablet after oral administration in six rabbits for each group are presented in Table 4 &5. The Cmax was not decreased significantly, but Tmax was delayed significantly when compared with the conventional tablet. Moreover, the curve also shows that in the initial hours, the plasma concentration of the drug was maintained statistically (P = 0.13) higher than the conventional tablet. The relative bioavailability was found to be high. Thus, it is confirmed that the maximum amount of Gliclazide was released from the selected formulation of CTDD in the colonic region. In 95 % confidence interval, parameters like ke, Vd, Cl, t½, AUC (0-∞), AUMC (0-∞), MRT (hrs) and relative bioavailability of the selected formulation (GLZ6) was significantly (P < 0.005) improved when compared with a conventional tablet of gliclazide.

Table 4: Plasma Drug Concentration Vs Time Profile for the gliclazide tablet and selected formulation GLZ6

Table 1: Composition of Tablet formulations with different ratios and different grade of HPMC polymers

Ingredients (mgs)	GLZ-1	GLZ-2	GLZ-3	GLZ-4	GLZ-5	GLZ-6
Gliclazide -IP	60.000	60.000	60.000	60.000	60.000	60.000
Dibasic Calcium Phosphate IP	70.000	70.000	65.000	65.000	58.000	56.500
Colloidal silicon dioxide IP (Aerosil 200)	20.000	14.000	12.000	8.000	8.000	7.500
Polyglykol 6000 PF	65.000	64.000	63.000	60.000	60.000	60.000
HPMC (Methocel K100 Premium LVCR	24.000	36.000	48.000	60.000	68.000	72.000
HPMC IP K4M	30.000	26.000	22.000	20.000	20.000	18.000
Povidone (Plasdone K90) ISP	25.000	24.000	24.000	20.000	20.000	20.000
Purified water IP	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc -IP	3.000	3.000	3.000	3.000	3.000	3.000
Magnesium stearate -IP	3.000	3.000	3.000	3.000	3.000	3.000
Target weight / Tablet (mg)	300.000	300.000	300.000	300.000	300.000	300.000

Table 2: The *in vitro* cumulative percentage release study of a different formulation of Gliclazide colon targeted matrix Tablets

Dissolution Media	Time (Hrs)	Formulations (cumulative percentage drug release)					
		GLZ-1	GLZ -2	GLZ -3	GLZ -4	GLZ -5	GLZ-6
Simulated gastric fluid	2	15.24	14.62	14.72	13.98	7.04	3.74
Simulated intestinal fluid	5	36.45	33.43	32.82	28.88	29.54	13.70
Simulated colonic fluid	8	49.34	63.84	56.12	47.42	38.62	36.88
Simulated colonic fluid	12	70.12	78.74	68.46	61.68	58.54	50.44
Simulated colonic fluid	16	86.22	88.84	74.64	85.94	80.56	71.92
Simulated colonic fluid	20	-	91.62	84.86	90.78	84.92	85.31
Simulated colonic fluid	24	-	92.42	92.22	92.82	93.37	97.12

Table 3: In-vitro release kinetics for a different formulation of Gliclazide colon targetted matrix Tablets

Formulation	Zero-order	First order	Hixson-Crowell	Higuchi	Koresmeyars Pappas	
	R^2 Value	R^2 Value	R^2 Value	R^2 Value	R^2 Value	'n' Value
GLZ-1	0.856	0.960	0.845	0.898	0.863	0.673
GLZ-2	0.980	0.701	0.838	0.907	0.502	0.678
GLZ-3	0.977	0.532	0.813	0.901	0.312	0.664
GLZ-4	0.936	0.976	0.795	0.912	0.870	0.612
GLZ-5	0.964	0.689	0.731	0.924	0.500	0.628
GLZ-6	0.981	0.505	0.747	0.930	0.251	0.630

0	0	0
2	511.45	477.94
4	2045.51	709.61
8	1590.98	1006.48
12	--	1359.01
16	--	1522.72
20	--	2350.32
24	--	1031.88
26	--	238.69
30	--	34.17

The pharmacokinetic parameters of the colon targeted drug delivery tablet formulation of Gliclazide also to calculate the relative bioavailability in terms of percentage. Pharmacokinetic analysis results showed a clear and significant difference among the conventional and colon targeted tablet formulations. In the colon targeted tablet formulation, the Cmax was almost significantly ($P = 0.13$) higher, and Tmax was also improved significantly ($P < 0.005$) when compared with conventional tablet dosage form of Gliclazide.

In addition, the curve shows that at the early time periods, the plasma concentration of drug was less because of the presence of polymer the HPMC (K100) and HPMC (K4M) has pH-dependent solubility which retards the release throughout the intestines of rabbits. The release was improved in the colonic region, and hence there was a high plasma concentration of Gliclazide which is because of the high solubility of HPMC K100 and HPMC K4M polymers in the colonic pH. This reduced Cmax initially and at Tmax was delayed and lower plasma concentration of Gliclazide in the

Table 5: Mean pharmacokinetic parameters for the Gliclazide tablet and selected formulation GLZ6

Pharmacokinetic Parameters	GLZ	GLZ6	P – Value
C_{max} (mcg)	2045.51 ±109.54	2350.32 ±136.88	= 0.13
T_{max} (Hrs)	4 ± 0.91	20 ± 0.73	< 0.005
k (hr-1)	0.33 ± 0.06	0.06 ± 0.004	
AUC (mcg.hr/ mL)	9892.93 ± 131.65	31971.14 ± 214.28	
VD (L)	0.76 ± 0.03	1.36 ± 0.51	
Cl (L/ hr)	0.25 ± 0.03	0.08 ± 0.01	
t1/2	2.08 ± 0.91	12.06 ± 1.47	
AUMC	2557 ± 202.46	1187.55 ± 184.62	
MRT	0.26 ± 0.04	0.04 ± 0.007	

early hours from the designed formulation when compared conventional tablet shows that the Gliclazide was only targeted in the colonic region and was not released in the gastrointestinal tract.

The CTDD tablet prepared and characterized by a reduction in the ke and raise in the t½ compared to the conventional Gliclazide tablet. The results indicate the flip-flop phenomenon which is in-line as stated in the literature (Schall R *et al.,* 1992), which is one of the associations either with SR or delayed release formulations. Another suggestion of delayed delivery of Gliclazide from the CTDD tablet is a slower rate of absorption Cmax/ AUC (0-α) and a maximum MRT when compared with the conventional Gliclazide tablet. The volume of distribution (Vd) was maximum and delayed clearance (Cl) from the CTDD tablet formulation, suggesting that the improvement in MRT was because of delayed absorption of Gliclazide. Furthermore, the relative bioavailability (RB) was also found to be more, and therefore it had been indicated that Gliclazide released more amounts from the CTDD tablet and absorbed for blood circulation with a satisfactory plasma concentration.

In vivo x-rays imaging studies

Rabbits were chosen as the animal model since variation within the pH of GIT of rabbits is analogous thereto of humans. *In vivo,* X-ray picture permits the image of *in vivo* functioning of a colon-specific drug delivery system, thereby ascertain the situation of drug release. The results of X-ray picture experimentation are presented in Figure 2. Figure 2a shows that the tablet remains intact within the stomach establishing *in vivo potency* of the coating of 10% w/v EudrajitL100 and EudrajitS 100 in preventing drug release in the gastric milieu. Figure 2b exhibits no significant difference in the integrity of the tablet in comparison to Figure 2b, thereby indicating intactness of the tablet in the small intestine. Figure 2c shows the CTTD tablets in the colon. These pictures demonstrate that the optimised formulation GLZ 6 might be targeted specifically to the colon, with none premature drug release within the stomach and small intestine.

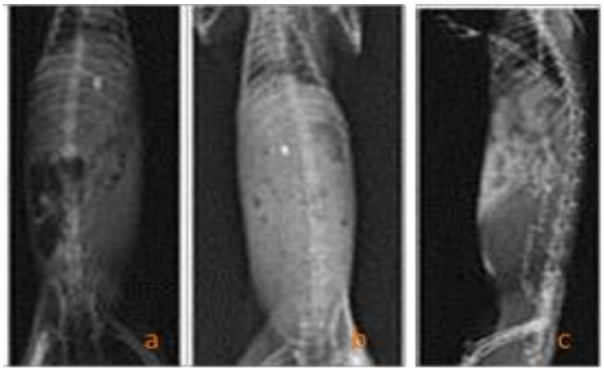

Figure 2: X-ray images of transit of tablet administered through oral route of selected formulation (GLZ6) (a) 1.5 h (stomach), (b) (intestinal colon junction) and (c) 10 h (colon)

CONCLUSION

In this present evaluation, *in vitro* kinetic and *in vivo* pharmacokinetic studies were performed an animal study CDDS. *In vitro* studies showed that this colonic drug delivery system is in a position to stop drug unharness in an acid medium (0.1N HCl, pH 1.2) for two h however the drug Gliclazide release in phosphate buffer medium, pH 6.8) once three h and release were up to twenty-four hrs. The dissolution mechanism of drug release was additionally confirmed by Higuchi plots that showed sensible one-dimensionality (R^2 values between 0.90 and 0.93), with slope > 0.5, indicating that drug release mechanism from the formulations was non-fickian diffusion mechanism. Moreover, the relative bioavailability (RB) was conjointly found to be high, and therefore it indicates that Gliclazide free additional amounts from the CTDD pill formulation and absorbed for blood circulation with an appropriate plasma concentration. The colon targeted matrix tablet of Gliclazide formulation system includes the drug delivery system that achieves slow as extended unharness of the drug over an extended interval of time. Thus, this new colonic drug delivery system is doubtless helpful for oral site-specific drug delivery together with colon targeting.

REFERENCES

Abubakr Elgorashi S. Bioavailability and In-vivo Transdermal Delivery of Haloperidol. Sudan J Med Sci. 4:2009: 47–54.

Apurba Sarker Apu, Fahmida Nashid Afroza, Hossain Md. Mohiuddin, Kanij Fatema, Md. Zakiur Rahman, Md. Amran Howlader. Design, Development and *In vitro* Evaluation of Diclofenac Sodium Matrix Tablet Prepared by Direct Compression Using Methocel K100LV CR Polymer. Int J Pharmaceu Sci Rev Res.13:2012: 121 – 127.

Cheng G, An F, Zou MJ, Sun J, Hao, He YX. Time- and pH-dependent colon-specific drug delivery for orally administered diclofenac sodium and 5-aminosalicylic acid. World J. Gastroenterol. 10:2004: 1769- 1774.

Dev RK, Bali V, Pathak K. Novel microbially triggered colon-specific delivery system of 5-Fluorouracil: Statistical optimization, *in vitro*, *in vivo*, cytotoxic and stability assessment. Int J Pharm. 411:2011:142-151.

Dorozynski P, Jachowicz R, Jasinski A, Kulinowski P, Kwiecinski S, Skorka T, Szybinski K. The polymers for the preparation of hydrodynamically balanced systems: methods of evaluation. Drug Dev.Ind. Pharm. 9:2004: 947–957.

Hesham Tawfeek M. Lornoxicam suppositories: in-vitro formulation and in-vivo evaluation. Int J Pharm Sci Res.4: 2013: 4228–4235.

Higuchi T. Mechanism of sustained release medication: theoretical analysis of the rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci.52: 1963:1145-1149.

Korsmeyer RW, Gurny R, Doelker E, Buri P and Peppas NA.Mechanisms of solute release from porous hydrophilic polymers. Int. J.Pharm. 15:1983: 25-35.

Liu J, Shentu JZ, Wu LH, Dou J, Xu QY, Zhou HL, Wu GL, Huang MZ, Hu XJ, Chen JC. Relative bioavailability and pharmacokinetic comparison of two different enteric formulations of omeprazole. J Zhejiang Univ Sci B.13: 2012: 348–355.

Pandey R, Sharma A, Zahoor A, Sharma S, Khuller GK, Prasad B. Poly (dl-lactide-co-glycolide) nanoparticle-based inhalable sustained drug delivery system for experimental tuberculosis. J Antimicrob Chemother. 52:2003: 981–986.

Pirjo Nykanen. Development of Multiple Unit Oral Formulations for Colon-Specific Drug Delivery Using Enteric Polymers and Organic Acids as Excipients. Division of Biopharmaceutics and Pharmacokinetics Department of Pharmacy, University of Helsinki. Academic Dissertation. 2003

Sarasija S, Hota A. Colon-specific drug delivery systems. Indian J. Pharm. Sci.62:2006: 18.

Schall, R, Luus H. Comparison of absorption rates in bioequivalence studies of immediate-release drug formulations. Int J Clin Pharmacol Ther Toxicol. 30:1992: 153–159.

Shargel L, Wu-Pong S, Yu A. Applied Biopharmaceutics & Pharmacokinetics. 5th Ed, McGraw-Hill Medical; 2004.

Siepmann J Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv. Drug Deliv. Rev.48: 2001: 139-157.

Sivakumar Kalidoss and Kailasam Koumaravelou, Formulation Development and Evaluation of Colon Targeted Matrix Tablets of Gliclazide. Inter. Jour.of pharmaceutics and drug analysis.4:2017: 498 – 507

Subhash Chandra Bose P, Srikanth Reddy P, Valluru Ravi, Sarita D, and Pramod Kumar TM. Formulation and evaluation of sustained release floating tablets of diltiazem Hcl using xanthan gum. Res.Jour.Pharm.Bio.Chem.Sci.2. 2011: 319 – 328.