AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Study on drug release and stability of matrix tablet contained monoammonium glycyrrhizinate

Otgonsuren.D[1], Davaasuren.Ts[1],Enkhtuul.B[1], Davaadagva.D[1], Jambaninj.D[1*]
1.Department of pharaceutical technology, School of Pharmacy, Mongolian National University of Medical Sciences

ABSTRACT

Monoammonium glycyrrhizinate was determined it has anti-viral activity in case of hepatitis A, B, C, D. We have developed matrix tablet contained monoammonium glycyrrhizinate by previous study. The objective of the study was to evaluate drug release of matrix tablet *in vivo* and determinate its stability. In the present study was evaluated *in vivo* drug release of the matrix tablet. Stability testing was 230 determinated by long term and accelerated method by such criteria's: appearance, weight variation, biological active compound, hardness, friability, dissolution and microbiological contamination. The C_{max} (µg/ml), T_{max} (h), AUC_{0-t} (µg h/ml) of Glycyron tablet and Licozinat matrix tablet were determined *in vivo*. Stability of the matrix tablet was determined. Licozinat matrix tablet was released drug by prolonged time by *in vitro*. *In vivo* pharmacokinetic study in rabbits confirmed the prolonged release by showing increase in bioavailability for matrix tablet compared to Glycyron tablet. Licozinat matrix tablet was stable for 12 months. Stability testing of matrix tablet is continuing by long term method.

Keywords: Monoammonium glycyrrhizinate, matrix tablet, *in vivo* drug release, stability

*Corresponding Author Email: jambaninj@mnums.edu.mn
Received 01 October 2019, Accepted 08 October 2019

Please cite this article as: Jambaninj D *et al.*, Study on drug release and stability of matrix tablet contained monoammonium glycyrrhizinate. American Journal of PharmTech Research 2019.

INTRODUCTION

In Mongolia, the morbidity rate of gastro intestinal diseases has ranked in the 2nd place of which liver diseases were primary reason. From the statistical data of 2018, chronic hepatitis, which is the main cause of cancer were 41.7 percent of liver diseases. In 2009, liver diseases were 131 and 158(man and woman) in 10000 people. It increased to 152 and 212(man and woman) by 16 to 34 percent in 2018.[1]

Cost of the drugs used for the treatment of the liver diseases is high and most of them imported in Mongolia. It needs to develop drugs for the treatment of liver diseases from domestic raw materials. Monoammonium glycyrrhizinate was determined it has anti-viral activity in case of hepatitis A, B, C, D. We isolated and purified monoammonium glycyrrhizinate from the Licorice root grown in Mongolia.[2,3] Extended release tablets are usually administrated once a day with benefits to the patient and lower discontinuation of therapy.[4-6] We aimed to develop matrix tablet with hepatoprotective effect and provide domestic drug market, introduce technology of the matrix tablet in the field pharmaceutical factory. In the present study was evaluated *in vivo* drug release and stability of the matrix tablet contained monoammonium glycyrrhizinate.

MATERIALS AND METHOD

The technological study of the developed matrix tablet *Licozinat* was conducted in the Laboratory of Technology and Chemistry, School of Pharmacy, Mongolian National University of Medical Sciences.

Hydroxypropyl methylcellulose (HPMC) K4M was bought from Shandong Liaocheng Hua Pharmaceutical Co.,LTD, China, glycine from Hubei provincial Bafeng Pharmaceuticals and Chemicals share Co.,LTD, DL- methionine from Zhangjiagang Huachang Pharmaceutical Company Limited, China. Polyvinylpyrrolidone K-30, glucose, lactose, microcrystalline cellulose (MCC), talc, and magnesium stearate (Thianjin Well-Real Chemical Technology Co.ltd, China). All chemicals were of analytical reagent grade.

Glycyron tablets(Lot No:17060, produced in Minophagen Pharmaceutical Co.,Ltd, Japan) were used *in vivo* study. Glycyron tablets contains monoammonium glycyrrhizinate 35mg, glycine 25mg and DL-methionine 25mg in each tablet.

Formulation of matrix tablets:

Tablets were prepared by wet granulation method. We prepared 5 formulations and formulation F5 was determined the appropriate design by previous study.[7] Each prepared tablet contained three active pharmaceutical ingredients (APIs) such as: monoammonium glycyrrhizinate 140 mg;

glycine 50 mg; LD-methionin 50 mg. In the present study was used formulation F5 by material of study.

Stability testing:

The stability of matrix tablet determined by long term method for 12 months and by accelerated method for 6 months according to standard MNS 6439:2014. For long term method tablets were stored in the condition with temperature 25 ±2°C and relative humidity 60±5%. For accelerated method tablets were stored in the condition with temperature 40±2°C and relative humidity 75±5%.[8]

Evaluation quality criterias of the matrix tablet for stability testing:

The quality of the prepared tablets was evaluated according to Mongolian National Pharmacopoeia's[9] methods by criterias such as appearance, average weight, weight variation, hardness, friability,[10] microbiological contamination and *in-vitro* dissolution study.

Determination of monoammonium glycyrrhizinate:

Monoammonium glycyrrhizinate was determined from the studied tablets by a spectrophotometric[11] and HPLC method.[12,13,14]

Methodology of high performance liquid chromatography:

Chromatographic system and system suitability: Column C18 as the stationary phase and a mixture of methanol: glacial acetic acid: 0.2 mol/L ammonium acetate's solution (67:1:33) as the mobile phase. As detector a spectrophotometer set at a wavelength of 250 nm. calculated with the reference to the peak of glycyrrhizinic acid. Flow rate:1ml/min, retention time is 10.3 min.

Reference solution: Weigh accurately 10mg of glycyrrhizinic acid CRS in 50 ml volumetric flask, add 45 ml of the mobile phase, ultrasonicate to dissolve, cool, add the mobile phase to volume and shake well (containing 0.2 mg/ml of monoammonium glycyrrhizinate, equal to 0.1959 mg of glycyrrhizinic acid per ml).

Test solution: 20 matrix tablets were powdered in mortar. Weight accurately 35,7 mg of powdered tablets in 50 ml volumetric flask, add 45 ml of the mobile phase, ultrasonicate to dissolve, cool, add the mobile phase to volume and shake well and filter.

Procedure: Inject accurately 10 µl of each of the reference solution and the test solution into the column, respectively, calculate the content.

Doses of matrix tablets for rabbits in vivo

Doses for rabbits were calculated using following formula of Gosh.[15] According to the dose calculated for rabbits (21.56 mg), the same formula was proportionately reduced and compressed into tablets using 2.5 mm flat punch.

Rabbit dose=0.07 x human dose

where, human dose = 140 mg, rabbit weight = 2.2 kg and rabbit dose = 21.56 mg. The rabbit dose was found to be 1.5 times the observed value.

***In vivo* pharmacokinetic study**

An in vivo pharmacokinetic study was conducted in accordance with the ethical guidelines for investigations in laboratory animals. All procedures and care of the rabbits were in accordance with institutional guidelines for animal use in research. Fourteen Rabbits (New Zealand, White) weighing 2.10 ± 0.14 kg (divided into two groups) were fasted overnight. Tablets were administered orally via gastric intubation. The first group received Glycyron tablet while the second group received Licozinat matrix tablet. Rabbits were held in rabbit restainers during blood sampling. Blood samples were collected from ear veins at predetermined intervals of 0.75, 1, 2, 4, 8, 12, 16 and 24 h into blood tubes. Plasma samples were obtained following centrifugation of blood at 3700 rotation/min for 10 min at 4^0C and kept frozen at -80^0C until analysis.[16]

Analysis of plasma Glycyrrhizic acid concentration using UPLC

The UPLC system consisted of (ACQUITY UPLC) was used. Separation was achieved on a reverse-phase column (2.1 x 100mm, ACQUITY UPLC, BEH Amid 1.7 µm) fitted with a column inlet filter. The mobile phase consisted of acetonitrile-water-acetic acid (36:64:0.5, v/v) for Glycyrrhizic acid. The mobile phase was used at a flow rate of 0.4 ml/min. The column was maintained at room temperature and the chromatograms were monitored at a wavelength of 251 nm throughout the experiments. Data processing was handled by a Waters (Millipore) 745 integrator.[17]

Statistical Analysis:

In this study, continuous data were described as means and standard deviations (SD) and followed by analysis of variance. Categorical data analyzed by multiple comparison test and described as percent. All reported p-values are two-tailed, and p-value<0.05 were considered to be significant. All statistical analyses were performed using Stata version 12.0 for windows.

Ethical consideration:

Statement of ethics approval was received from the Medical Ethics Committee of MNUMS in 2017(№2017/3-2017-01).

RESULTS AND DISCUSSION

The result from previous studies, F5 design of matrix tablets released drug at 0.75 and 24 hours by 15.28%±0.11, 99.86%±0.52 was determined to be the appropriate design and it released the drug in a prolonged way during the *in vitro* testing. Further F5 design was used *in vivo* study.

In vivo pharmacokinetic study:

The plasma concentrations of Glycyron tablet (dosage 140 mg) and Licozinat matrix tablet (dosage 140 mg-F5) over time are presented in Figures 1 and 2 respectively. The pharmacokinetic parameters of Glycyron tablet and Licozinat matrix tablet are presented in Table 1.

The absorption was rapid with Glycyron tablets as indicated by low Tmax value (1.0 h) in comparison with Licozinat matrix tablet which exhibited delayed absorption as demonstrated by high Tmax (4 h) values. Cmax value of Glycyron tablet was high compared with Licozinat matrix tablet F5 (Table 3). The low area under the curve (AUC) was observed with Glycyron tablets where as the sustained release formulation showed high AUC values indicating increased bioavailability of the drug in the matrix tablet. The results of the in vivo bioavailability test indicate that drug release from matrix tablet is sustained thereby providing prolonged drug delivery.

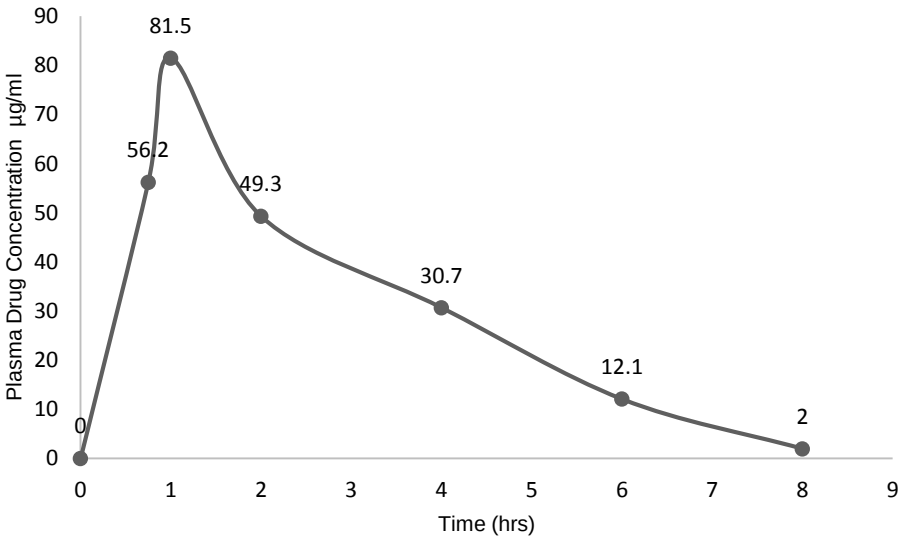

Figure 1. Plasma concentration-time curve for Glycyron tablet.

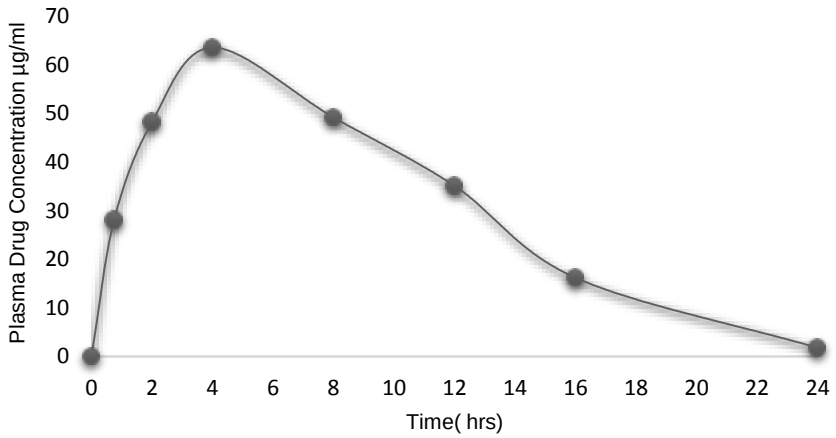

Figure 2. Plasma concentration-time curve for Licozinat matrix tablet (F5).

Table 1. Pharmacokinetic parameters from the plasma concentration- time curve (results expressed are mean of seven rabbits).

Parameters	Glycyron tablet	Licozinat matrix tablet (F5)
C_{max} (µg/ml)	81.50 ± 8.74	75.60 ± 7.36
T_{max} (h)	1.0 ± 0.0	4.0 ± 0.0
AUC_{0-t} (µg h/ml)	436.788 ± 17.23	738.986 ±24.44

All values are expressed as Mean ± SD, n=5, P=0.001

Stability studies:

The stability of Licozinat matrix tablet evaluated according to Mongolian National Pharmacopoeia methods by criteria's by long term method for 12 months and by accelerated method for 6 months according to standard MNS 6439:2014[20]. The quality of tablet was controlled by criteria's such as appearance, average weight, weight variation, amount of biological active compound, friability, hardness, dissolution, and microbiological contamination. The results are shown in table 2 and 3.

Table 2. Stability study of Licozinat matrix tablet (long term method 25 ±2°C, 60±5%)

Specification		Appearance	±5%	Biological active compound	Friability	Hardness	Dissolution, %			Microbiological contamination		
							60 min	240 min	600 min	Total aerobic bacteria	Mould	*E.coli Coliform*
Criterias		**Whitish, flat, bevelled edged**	**0.475-0.525**	**Monoammonium glycyrrhizinate, 0.066-0.073 g**	**Not less than 97%**	**4.58-12.23 kg/cm2**			**Not less than 75%**	**For 1g sample not more than 10^3 CFU**	**For 1g sample not more than 10^2CFU**	**For 1g sample Not reported**
Time, months	0	complied	0.5± 0.0007	0.069 ±0.002	99.3 ±0.01	5.3± 0.22	22.69 ± 0.035	46.48 ±0.056	79.95 ± 0.043	Not more than10^3	Not reported	Not reported
	3	complied	0.501± 0.001	±0.0007	±0.03	5.38± 0.27	22.74 ±0.034	46.87 ± 0.066	80.14 ±0.109	Not more than10^3	Not reported	Not reported
	6	complied	0491± 0.005	0.068 ± 0.003	99.088 ±0.094	5.16± 0.24	22.78 ± 0.025	46.55 ± 0.035	79.96 ±0.046	Not more than10^3	Not reported	Not reported
	9	complied	0.501±0.002	0.069 ± 0.001	99.32 ±0.051	5.38± 0.25	22.67 ± 0.034	46.2 ± 0.15	79.96 ± 0.085	Not more than10^3	Not reported	Not reported
	12	complied	0.502±0.002	0.068 ± 0.002	99.22 ± 0.076	5.2± 0.23	22.78 ± 0.083	47.06 ± 0.093	80.16 ±0.17	Not more than10^3	Not reported	Not reported

All values are expressed as Mean ± SD, n=5, P≥0.05

In this study, continuous data were described as means and standard deviations (SD) and followed by analysis of variance. Categorical data analyzed by multiple comparison test and described as percent. All reported p-values are two-tailed, and p-value<0.05 were considered to be significant. No significant difference was observed in the release profile of different batches and within batches indicating that the process employed to tablet producing was reliable and reproducible. All statistical analyses were performed using Stata version 12.0 for windows.

Table 3: Stability study of Licozinat matrix tablet (accelerated method 40±2°C, 75±5%)

Specification		**Criterias**	**Time**								
			0 month			**3 months**			**6 months**		
			T-20171006	**T-20171101**	**T-20171214**	**T-20171006**	**T-20171101**	**T-20171214**	**T-20171006**	**T-20171101**	**T-20171214**
Appearance		Whitish, flat, bevelled edged	complied	complied	complied	complied	complied	complied	complied	complied	complied
±5%		0.475-0.525 г	0.5 ±0.002	0.49 ± 0.012	0.49 ± 0.007	0.49 ± 0.007	0.5 ±0.009	0.502 ± 0.002	0.49 ± 0.007	0.49 ± 0.011	0.5 ± 0.001
Biological active compound		Monoammonium glycyrrhizinate, 0.066-0.073 g	0.069 ±0.002	0.069 ± 0.001	0.07 ± 0.0003	0.068 ± 0.001	0.069 ± 0.001	0.07 ± 0.001	0.068 ±0.001	0.068 ±0.0008	0.069 ±0.0007
Friability		Not less than 97%	99.33 ±0.01	99.47 ± 0.27	99.26 ± 0.16	99.17 ± 0.31	99.33 ±0.19	99.14 ± 0.38	98.99 ± 0.05	99.5 ±0.24	6.88 ± 0.14
Hardness		4.58-12.23 kg/cm2	5.2 ±0.25	5.80 ± 0.16	5.92 ± 0.12	5.52 ± 0.23	5.66 ± 0.19	5.87 ± 0.19	5.26 ± 0.31	5.76 ± 0.1	26.30 ± 0.45
		60 min,	22.48 ± 0.35	24.63 ± 0.29	26.1 ± 0.53	22.35 ± 0.61	24.75 ±0.38	26.4 ± 0.45	22.85 ± 0.21	24.82 ± 0.14	26.3 ± 0.45
		240 min,	46.11 ±0.22	49.56 ±0.47	55.96 ±0.37	49.29 ± 0.57	49.33 ± 0.61	55.97 ±0.38	46.2 ± 0.45	49.68 ± 0.13	55.91 ± 0.21
		600 min, Not less than 75%	79.32 ±0.43	83.68 ± 0.39	85.74 ± 0.65	79.98 ± 0.28	83.68 ± 0.53	85.79 ± 0.42	81.19 ± 0.54	83.57 ±0.47	85.96 ± 0.42
Microbiological contamination	Total aerobic bacteria	For 1g sample not more than 10^3 CFU	Not more than10^3	Not more than10^3	Not more than10^3	Not more than10^3	Not more than10^3	Not more than10^3	Not more than10^3	Not more than10^3	Not more than10^3

	Mould	For 1g sample not more than 10^2CFU	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
	E.coli Coliform	For 1g sample Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

All values are expressed as Mean ± SD, n=5, P≥0.05

In this study, continuous data were described as means and standard deviations (SD) and followed by analysis of variance. Categorical data analyzed by multiple comparison test and described as percent. All reported p-values are two-tailed, and p-value<0.05 were considered to be significant. No significant difference was observed in the release profile of different batches and within batches indicating that the process employed to tablet producing was reliable and reproducible. All statistical analyses were performed using Stata version 12.0 for windows.

From the stability testing results by both long term and accelerated method, Licozinat matrix tablet was stable for 12 months. Stability testing of matrix tablet is continuing by long term method.

Nowadays Glycyrrhiza uralensis root is clinically used by various types of drug forms, which meets to traditional Eastern and Western medicine.

Japanese researchers have been corroborated by pre-clinical and clinical studies that biological acompounds from Glycyrrhiza uralensis root has considerable influence on immunostimulation, human cells protection and acts as anti-viral.[2]

There are a number of glycyrrhiza uralensis root containing products manufactured by Mongolian pharmaceutical companies and have been used in the treatment of respiratory inflammation diseases and urinary tract inflammations.

Japanese researchers have purified glycyrrhizinate from Glycyrrhiza root as monoammonium glycyrrhizinate to produce Stronger neominophagen 20ml injection, as well as sugar-coated tablet "Glycyron" to treat numerous diseases, such as, allergy, viral infection, viral-induced chronic hepatitis, fatty liver, liver fibrosis, liver enlargement, viral-induced myocarditis, leukemia, and psoriasis.[2]

The active pharmaceutical ingredient of Glycyron tablet is monoammonium glycyrrhizinate 35 mg, and amino acids glycineand methionine, each 25 mg, additionally. However, the tablet Licozinat which we produced during our current research contains 140mg of monoammonium glycyrrhizinat, and 50mg of each glycine and methionine.

Furthermore, tablet "Glycyron" is sugar-coated and is suggested to take 2-3 tablets 3 times a day after meal in adults, and one tablet 3 times daily in child, as intake of multiple medicines in a day. Such application could be complicated for patients and lead to skip dosage. This could further resulted as reduced medical outcome due to low concentration of drug in blood plasma and increased drug side effect.

In this project, we obtained a sustained release matrix tablet Licozinat and could bear pharmacological advantages over Glycyron. Due to sustained release of active ingredient, its concentration would be constant in blood plasma, hence the drug side effect could be reduced.

Moreover, higher concentration and slow release of active substance have significant influence on the reduced application frequency and lowered daily dose, which means 2 tablets of Licozinat are equal to 9 tablets of Glycyron.

In order to produce Licozinat tablet, we have purified monoammonium glycyrrhizinat in laboratory from locally collected *Glycyrrhiza uralensis* roots.

Moreover, we have determined following parameters are pivotal for sustained released tablet: choosing an appropriate proportion of matrix former and filler, select appropriate propotion of lubricant and concentration of binder. As results of testing the various combination, we have concluded that 20% of HPMC-K4M as matrix formation, lactose as filler and 5% solution of PVP-K30 as binder is the most appropriate quantity of excipients in matrix tablet Licozinat.

Many researchers such as Madhusmruti Khandai,[18] Santanu Chakraborty Ch. Chandana,[19] Nagaich U,[4] Pushkar R, they obtained controlled release matrix tablets contained propranolol, metoprolol succinate, diclofenac sodium and aceclofenac used different kind of hydroxyprorylmethylcelluloses (HPMC K4M, K15M and K100M) as a matrix former. We prepared 5 formulations contained monoammonium glycyrrhizinate using different ratio of HPMC K4M as a matrix former for the purpose of obtaining controlled release matrix tablet and evaluated by drug release.

From the result of our study, F5 formulation of matrix tablets released monoammonium glycyrrhizinate at 2, 4, 6, 8, 10, 12, 16, 24 hours by 34.14%±0.25, 46.48%±0.17, 58.6%±0.24, 66.98%±0.22, 79.95%±0.08, 84.42%±0.21, 92.12%±0.11, 99.86%±0.52 *in vitro*. Thus, F5 formulation was the appropriate design, which used 20% of HPMC K4M and lactose as a matrix former and diluents. Sharma Ankita and et all obtained matrix tablet contained Aceclofenac using 13.8% of HPMC K15M and determined drug release. From the result of their study, the matrix tablet released drug at 2, 4, 6, 8, 10, 12, 16, 24 hours by 14.69%, 24.65%, 68.98%, 82.42%, 92.12%, 99.86%.[20] The drugs release of our matrix tablets were released twice as much as at 2 and 4 hours of drug samples from Sharma Ankita and released approximate at 8,12,16,24 hours. After administration our matrix tablet reaches to therapeutic dose at short time (at least 2 hours) and hold on effective concentration for extended time. It is very important criteria for prolonged release drugs, which holds serum concentration of active ingredients for extended time constantly to improve therapeutic efficacy. The results of the in vivo bioavailability test indicate that drug release from Licozinat matrix tablet is sustained thereby providing prolonged drug delivery.

Our study and controlled release matrix tablet differs from other studies by using natural substance isolated from plant source, while most of the researchs have been done on the tablet

containingsynthetic active ingredient. In addition, we conducted bioavailability test and hepatoprotective effect *in vivo* of Licozinat tablet.

The stability of Licozinat matrix tablet has been determined by two different methods. The long term method has been performed for 12 months and the accelerated method was for 6 months, according to national standard MNS 6439:2014. For the long term method, tablets were stored in the condition with temperature 25 ±2°C and relative humidity 60±5%[21]. And during this time, appearance, stability, dissolution, mean weight, quantity assay and microbiological studies have performed constantly on the tablets at 0,3,6,9, and 12th months. For accelerated method, tablets were stored in the condition with temperature 40±2°C and relative humidity 75±5% for 6 months. The same stability parameter tests were performed at 0,3, and 6th months. In consequence, the Licozinat tablet was concluded as stabile .Additional drug stability study for longer time period is in progress. Furthermore, we have planned to perform clinical study on Licozinat tablet in the future.

CONCLUSION

Controlled release "Licozinat" matrix tablets were prepared by wet granulation method. *In vitro* study result showed Formulation (F5) containing 20% HPMC K4M released desired manner and was determined to be the appropriate design. *In vivo* study in rabbits confirmed the prolonged release by showing increase in bioavailability for matrix tablet compared to Glycyron tablet. Licozinat matrix tablet was stable for 12 months. Stability testing of matrix tablet is continued by long term method.

REFERENCES

1. Health indicators -2018. Center for health development. Ulaanbaatar 2018; 59-61, 68-71, 83-84.
2. Rossum T.G.J. Van. "Glycyrrhizin treatment for chronic hepatitis C" Japan 2000.
3. Altantuya E, Badamjav S, Davaadorj D. A systematic study of stronger neominophagen on B virus induced chronic hepatitis. Diagnosis journal 2013; 02 (57): 99-103.
4. Nagaich U, Bharti Ch, Kumar Pal A, Gulati N. Diclofenac Sodium Loaded Sustained Release Matrix Tablet Possessing Natural and Synthetic Polymers: Formulation and *in vitro* Characterization. Indian Journal of Pharmaceutical Education and Research 2014; 48 (supplement): 49-55.
5. Atul Kuksal, Ashok K. Tiwary, Narendra K. Jain, and Subheet Jain. Formulation and In Vitro, In Vivo Evaluation of Extended- release Matrix Tablet of Zidovudine: Influence of

Combination of Hydrophilic and Hydrophobic Matrix Formers. AAPS Pharm SciTech 2006; 7 (1): E1-9

6. Kiattisak Saeio, Yanee Pongpaibul, Helmut Viernstein, Siriporn Okonogi. Factors Influencing Drug Dissolution Characteristic from Hydrophilic Polymer Matrix Tablet. Scientia Pharmaceutica (Sci. Pharm) 2007; 75: 147-163
7. Otgonsuren.D, Davaasuren.Ts, Enkhtuul.B, Davaadagva.D, Jambaninj.D. Formulation and evaluation of Licozinat matrix tablet. Journal of Developing Drugs 2018; 7:2.
8. General requirements of stability testing active pharmaceutical ingredients and fi nished pharmaceutical products.MNS 6439:2014
9. Mongolian National Pharmacopoeia. The first edition. Ulaanbaatar 2011; 470-473.
10. Jambaninj D. Technological study of preparing new drug formulations of *Cacalia hastata* L. Dissertation for Ph.D degree in Pharmacy. Ulaanbaatar, HSUM; 2012
11. SK. Patil, VR. Salunkhe and SK. Mohite. Development and validation of UV Spectrophotometric method for estimation of Glycyrrhetinic acid in hydro-alcoholic extract of Glycyrrhiza Glabra. International Journal of Pharmaceutical, Chemical and Biological sciences 2012; 2(4): 617-621
12. Chinese Pharmacopoeia. Volume II 2010; 488-490.
13. British Pharmacopoeia Volume II, 2015; 241-42.: Volume V, Appendix XVII N V:508-519.
14. United States Pharmacopoeia. 2005; 3, 31, 909.
15. Ghosh S, Barik B. Preparation and evaluation of Aceclofenac sustained release formulation and comparison of formulated and marketed product. International Journal of Medicine and Medical Sciences 2009; 1 (9): 375-382.
16. Sharma P.R, Lewis Sh.A. Design and *in vitro/in vivo* evaluation of extended release matrix tablets of Nateglinide. Journal of Young Pharmacists 2013; 5: 167-172.
17. G.Cantelli-Forti, F.Maffei, P.Hrelia et al. Interaction of Licorice on Glycyrrhizin Pharmacokinetics. Environmental Health Perspectives 1994, v.102 (9): 65-68
18. Madhusmruti Khandai, Santanu Chakraborty, Anuradha Sharma, Debashisha Panda, Nazia Khanam et all. Development of Propranolol Hydrochloride Matrix Tablets: An Investigation on Effects of Combination of Hydrophilic and Hydrophobic Matrix Formers Using Multiple Comparison Analysis. International Journal of Pharmaceutical Sciences 2010; 1(2): Article 001: 1-6

19. Ch.Chandana, Y.Ganesh Kumar, Y.Vamshi Vishnu, M.Minnu Madhuri. Metoprolol Succinate Sustained Release Matrix Tablets- Formulation Development And In vitro Evaluation. International Journal of Pharmacy and Pharmaceutical Sciences 2014; 6(7) :481-486
20. Sharma Ankita, Shukla Tarkeshwar, Indoria Manish Dev, Jha Sajal Kumar. Design, Development and Evaluation of Aceclofenac Sustained Release Matrix Tablets. International Journal of Drug Development & Research 2011; 3 (1): 307-313

AJPTR is

- **Peer-reviewed**
- **bimonthly**
- **Rapid publication**

Submit your manuscript at: editor@ajptr.com