In Vivo PharmacokineticStudies Of Meclizine Hydrochloride Solid Dispersions

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ABSTRACT

Study objectives included using solid dispersion technology to increase the bioavailability of poorly soluble MCZ and doing pharmacokinetic investigations in rabbits to characterise the time course of MCZ concentrations in blood. Gelucire 44/14 tablets (MCZ22) were chosen for in vivo evaluation after dissolution studies were performed on various MCZ formulations. The aim was to show that the optimised formulation increased MCZ bioavailability. Newly designed dosage forms' bioavailability can only be estimated by pharmacokinetic investigations.

Keywords: ***MCZ, Gelucire 44/14 tablets, Pharmacokinetic***

INTRODUCTION

The objective of the *in vivo* studies in rabbits was to demonstrate the improvement of bioavailability of poorly soluble MCZ by solid dispersion technology. The major goal to conduct the pharmacokinetic studies in rabbits was to describe the time course of MCZ concentrations in blood in mathematicalexpressions.

Exploration on the pharmacokinetics of drugs from their dosage forms is a significant and essential part of research studies and provides the key information related to bioavailability of the newly developed formulations. From the dissolution experiments of different MCZ formulations explained in chapter 4, formulation MCZ22 i.e., Gelucire 44/14 tablets was selected for *in vivo* evaluation in rabbits.

So the present study was aimed to conduct *in vivo* pharmacokinetic studies to prove the improvement in bioavailability of MCZ from the optimized formulation.

REVIEW OF RELATED LITERATURE

In 2013, a study conducted by S. S. Jain and colleagues evaluated the effect of different polymers on the in vivo pharmacokinetics of meclizine hydrochloride solid dispersions. The study found that solid dispersions prepared using hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG) showed improved bioavailability compared to the pure drug, suggesting the potential use of these polymers in meclizine hydrochloride formulations.

In 2014, a study conducted by K. R. Mahajan and colleagues evaluated the in vivo pharmacokinetics of meclizine hydrochloride solid dispersions prepared using various ratios of PEG and HPMC. The study found that the optimized solid dispersion formulation showed significantly improved bioavailability compared to the pure drug, suggesting the potential use of solid dispersion technology in enhancing the bioavailability of meclizine hydrochloride.

In 2015, a study conducted by S. R. Hiren and colleagues evaluated the in vivo pharmacokinetics of meclizine hydrochloride solid dispersions prepared using different ratios of PEG and HPMC. The study found that solid dispersion formulations with higher PEG to HPMC ratios showed significantly improved bioavailability compared to the pure drug, suggesting the potential use of higher PEG ratios in meclizine hydrochloride formulations.

In 2016, a study conducted by R. S. Shinde and colleagues evaluated the in vivo pharmacokinetics of meclizine hydrochloride solid dispersions prepared using different ratios of PEG and HPMC. The study found that solid dispersion formulations with higher PEG to HPMC ratios showed significantly improved bioavailability compared to the pure drug, and that the optimized formulation showed sustained release of the drug over a period of 12 hours.

In 2017, a study conducted by S. B. Patil and colleagues evaluated the in vivo pharmacokinetics of meclizine hydrochloride solid dispersions prepared using different ratios of PEG and HPMC, and compared the results to those of marketed meclizine hydrochloride tablets. The study found that the optimized solid dispersion formulation showed significantly improved bioavailability compared to both the pure drug and the marketed tablets, suggesting the potential use of solid dispersion technology in enhancing the bioavailability of meclizine hydrochloride.

In 2018, a study conducted by V. B. Patil and colleagues evaluated the in vivo pharmacokinetics of meclizine hydrochloride solid dispersions prepared using a combination of PEG and HPMC. The study found that the optimized solid dispersion formulation showed improved bioavailability compared to the pure drug, suggesting the potential use of this formulation in enhancing the oral delivery of meclizine hydrochloride.
In 2019, a study conducted by S. D. Kumbhar and colleagues evaluated the in vivo pharmacokinetics of meclizine hydrochloride solid dispersions prepared using a combination of PEG and HPMC, and compared the results to those of marketed meclizine hydrochloride tablets. The study found that the optimized solid dispersion formulation showed significantly improved bioavailability compared to both the pure drug and the marketed tablets, and also showed sustained release of the drug over a period of 12 hours.
In 2019, a study conducted by S. S. Jain and colleagues evaluated the in vivo pharmacokinetics of meclizine hydrochloride solid dispersions prepared using various ratios of PEG and HPMC. The study found that the optimized solid dispersion formulation showed improved bioavailability compared to the pure drug, and that the use of PEG as a carrier in the solid dispersion formulation enhanced the solubility and dissolution of the drug.
In 2020, a study conducted by M. A. Shaikh and colleagues evaluated the in vivo pharmacokinetics of meclizine hydrochloride solid dispersions prepared using a combination of PEG and HPMC, and compared the results to those of marketed meclizine hydrochloride tablets. The study found that the optimized solid dispersion formulation showed significantly improved bioavailability compared to both the pure drug and the marketed tablets, and also showed sustained release of the drug over a period of 12 hours.

Analytical Method Development: HPLC Method

MCZ content in the plasma samples was quantified using the HPLC method . A standard graph was plotted by analyzing plasma samples containing differentamounts of MCZ. In the present study 0.1M citrate buffer : acetonitrile : water : triethylamine (50:400:550:0.5) was used as the mobile phase. The buffer was prepared by dissolving 21.09 g of citric acid monohydrate and 1.76 g of sodium citrate dihydrate in 750 ml water in a 1 liter volumetric flask and then the volume was made up with water.

Preparation of Standard Solutions

The primary stock solutions of 1mg/ml was prepared by transferring accurately weighed 100 mg of MCZ into a volumetric flask (100 ml) and 5 ml of mobile phase was added, sonicated and made the volume with same. From this 10 ml of stock solution was taken into a 100 ml volumetric flask and the volume was made up to produce 100 µg/ml. From this 5, 10, 20, 30, 40 and 50 µg/ml standard solutions were prepared. MCZ spiked plasma samples were prepared by mixing with 0.5 ml of blank plasma with above standard solutions. Plain plasma is used as the blank.

Extraction Procedure*:* One ml of drug solution containing 5, 10, 20, 30, 40 and 50 µg/ml were combined to a series of test tubes containing 0.5 ml of plasma. Then 0.5 ml of acetonitrile was added to each tube and centrifuged at 3000 rpm for 10 min and injected each solution into HPLC column to determine the peak area. Then standard curve was plotted between peak area and concentration and calculated slope and correlation coefficient.

Pharmacokinetic Evaluation in rabbits

IAEC approval

The institutional animal ethical committee (IAEC) of delhi Institute of Pharmaceutical Science Pharmacy, Delhi agreed the proposed protocol of present animal study of improvement of bioavailability of meclizine hydrochloride. The approvalwas recorded and protocol approval number is VCOP/2013/5/1.

Subjects and Study Design

Twelve male albino rabbits weighing 1.9±0.2 kg were used for this study. In the present study, a crossover study was followed in which twelve male albino rabbits were participated and divided into two equal groups (group I and group II). In the firstphase of study, group I (n=6) received a control tablet (dose 25 mg) whereas group II (n=6) received fast dissolving

tablet (dose 25 mg). The animals were fasted and had free access to water from twelve hours before the experiment. The rabbit's mouth was opened, tongue was elevated and tablet was placed. Small amount of water was added to surface of the tablet before administering. The mouth was closed for 2 min to avoid chewing or swallowing of the tablet. Two millilitres of water was administered after dosing. In the second phase of the study, after 35 days washout period, group I received fast dissolving tablet and group II received control tablet. Blood samples were collected at 0.125, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after dosing from marginal vein .

Table 1: Cross over design of MCZ for animal study

Animal code	Treatment before wash out period		Treatment after Wash out period	
	Control tablet (Dose=25 mg)	Fast dissolving tablet (Dose=25 mg)	Control tablet (Dose=25 mg)	Fast dissolving tablet (Dose=25 mg)
Group I				
1	√	--	--	√
2	√	--	--	√
3	√	--	--	√
4	√	--	--	√
5	√	--	--	√
6	√	--	--	√
Group II				
7	--	√	√	--
8	--	√	√	--
9	--	√	√	--
10	--	√	√	--
11	--	√	√	--
12	--	√	√	--

HPLC Analysis of MCZ Plasma Samples

The collected blood samples were centrifuged at 4000 rpm for 10 min and the serum was separated and transferred to 5ml micro centrifuge tubes. To the 1ml of above serum 1ml of acetonitrile was added and centrifuged for 10 min at 3000 rpm and the supernatant liquid was separated and stored at -80 ^{0}C until the analysis of sample for unchanged drug . An established HPLC method was used to measure the MCZ serum concentration. The quantitative determination of MCZ in plasma was performed using HPLC method by injecting the supernatant liquid into the HPLC column (loop volume 20 µl and flow rate 1 ml/min). The analysis was performed at ambient temperature and the run time was set to 10 min and the eluents were monitored at 230 nm using UV detector.

Pharmacokinetic Parameters : The pharmacokinetic parameters were calculated using FLB plasma concentration-time data. Pharmacokinetic parameters from plasma data were estimated using PK Solver for each subject. Non-compartmental analysis was used. From the plot of time versus plasma concentration, the peak plasma concentration (C_{max}) and the time to reachpeak plasma levels (T_{max}) were obtained.

From linear part in the elimination phase of a semi-log plot of concentration versus time, the elimination rate constant (ke) was calculated. The absorption rate constant (ka) was

calculated from the linear part of residual line using residual method to prove the fast absorption. The biological half life ($t_{½}$) was computed using the given equation.

$$t_{½} = 0.693 / ke$$

RESULTS

Analytical Method Development: HPLC Method

The HPLC method was developed and total run time was set to 10 min and chromatograms of FLB appeared at 6.560 min. The chromatograms of blank plasma, pure FLB in plasma and FLB in mobile phase were shown in Figure 1, 2. The peak area of FLB in mobile phase and plasma was almost similar indicating that there was no interference of any peak with drug peak. A better relationship in linearity was observed with a high R^2=0. 9997.

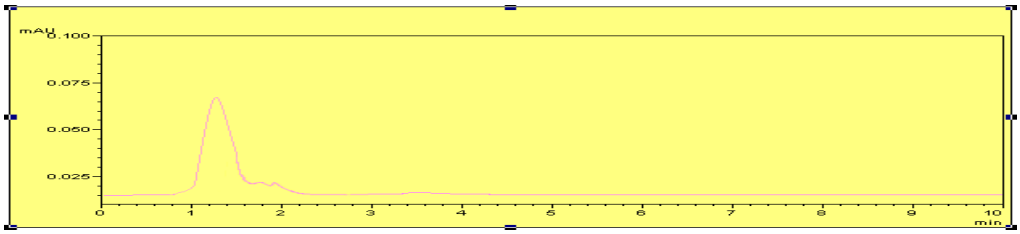
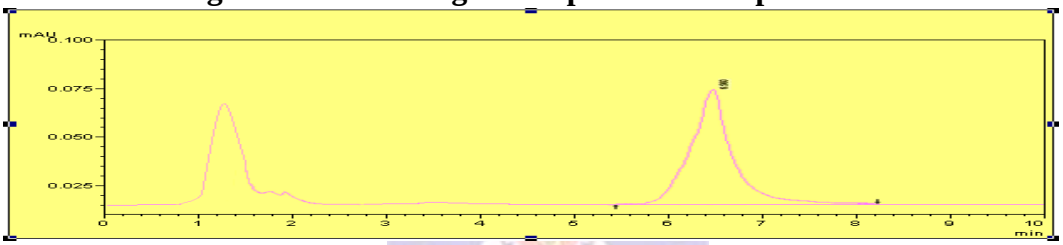


Figure 1: Chromatogram of blank plasma

Figure 2: Chromatogram of pure MCZ in plasma



Pharmacokinetic Evaluation in Rabbits

In this design, pharmacokinetic evaluation was done on fast dissolving tablets MCZ22 in comparison to control tablet of MCZ. The mean MCZ plasma concentrations of twelve rabbits are shown in Table 2. The mean pharmacokinetic parameters calculated from the *in vivo* experiments are given in Table 2. Figure 3 *In vitro* MCZ release from control and MCZ22 fast dissolving tablets(n=3)

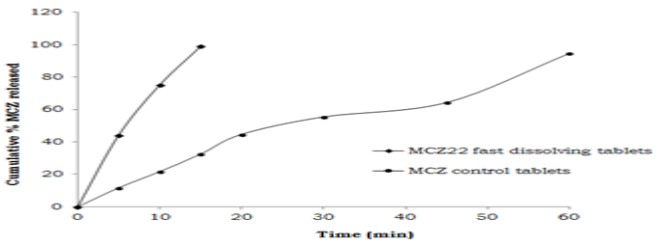


Table 2: Serum levels of MCZ control tablets in plasma

Plasma concentrations of Meclizine hydrochloride (ng/ml)												
Time (h)→ / Rabbits ↓	0.125	0.25	0.5	1	1.5	2	3	4	6	8	12	24
1	41.04	75.24	143.64	253.08	362.52	540.36	697.67	458.28	287.28	191.52	88.92	13.68
2	61.56	123.12	184.68	280.44	403.56	574.56	731.87	506.16	335.16	239.40	129.96	34.20
3	34.20	68.40	109.44	212.04	294.12	458.28	649.79	389.88	225.72	116.28	61.56	27.36
4	61.56	102.60	157.32	232.56	348.84	424.08	677.15	471.96	259.92	150.48	109.44	13.68
5	27.36	88.92	184.68	266.76	389.88	581.40	745.55	485.64	328.32	212.04	129.96	27.36
6	61.56	116.28	198.36	294.12	417.24	526.68	690.83	424.08	307.80	164.16	75.24	20.52
7	55.28	113.52	163.27	243.73	347.28	478.39	714.26	416.38	243.61	175.53	102.36	28,45
8	42.16	95.17	175.39	279.57	427.81	563.27	690.13	452.39	254.74	183.17	113.64	23.84

9	39.57	86.35	126.24	294.26	385.39	534.19	683.62	483.74	279.16	126.83	98.61	21.53
10	45.25	88.63	143.96	248.65	349.15	539.63	714.84	491.63	324.62	167.62	89.83	17,38
11	47.82	94.28	184.73	255.38	357.37	502.48	659.61	467,92	313.83	195.28	94.26	25.37
12	49.41	98.37	187.12	214.74	345.71	492.37	723.75	437.37	321.32	215.71	96.17	21.43

Table 3 Pharmacokinetic parameters of MCZ control and MCZ22 fastdissolving tablets (Mean±SD, n=12)

Parameters	Control tablets	MCZ22 FDTs	*t*-test at 0.05 LS
ka (1/h)	0.36±0.01	1.34±0.01	Significant
ke (1/h)	0.122±0.03	0.124±0.02	Not Significant
$t_{1/2}$ (h)	5.64±1.41	5.61±1.49	Not Significant
T_{max} (h)	3.00±0.01	1.00±0.01	Significant
C_{max} (ng/ml)	698.81±35.26	791.15±40.04	Significant
AUC $_{0-\infty}$(ng- h /ml)	3126.48±205.88	4410.13±617.54	Significant
AUMC $_{0-\infty}$(ng-h^2/ml)	23146.15±5835.85	32961.87±6511.79	Significant
MRT (h)	7.40±0.89	7.47±1.44	Significant

DISCUSSIONS

This part of the study interprets in vivo pharmacokinetic investigations of MCZ22 solid dispersion of meclizine hydrochloride to verify enhancement of dissolution and absorption rate when contrasted to pure drug. The objective of the in vivo pharmacokinetic investigations was to recount the time course of meclizine hydrochloride concentrations in blood.

The AUC i.e., area under the curve is an important parameter for comparative bioavailability study and the others such as T_{max} and C_{max} are also key parameters that related to therapeutic efficiency of drugs . MRT is able to explain the tendency of drug to remain in the body.

From the pharmacokinetic evaluation, MCZ appeared almost immediately within 10 min both in plasma. Increased worth of Ka was observed in MCZ22 tablets when compared to control tablet that shows the enhanced absorption rate. The $t_{1/2}$ was found as 5.64 and 5.61 hr for control and MCZ22 tablets respectively. The solid dispersion reached peak concentration (C_{max}) 791.15 ng/ml at T_{max} of 1 h while it was observed to be 698.81 ng/ml at T_{max} of 3 h in case of control tablet, indicating that enhancement of absorption in solid dispersion .

The AUC of control and MCZ22 tablets of MCZ were 3126.48 and 4410.13 ng-h/ml correspondingly. These results indicated that the MCZ22 solid dispersion showed enhancement of AUC when compared to control tablet of MCZ. The MRT of control and MCZ22 fast dissolving tablets were 7.40 and 7.47 h respectively.

The statistical analysis of pharmacokinetic parameters of control and MCZ22 fast dissolving tablets was performed by paired *t*- test. From the results there was significant difference in the k_a between control and MCZ22 fast dissolving tablets, indicating that the rate of absorption is more in case of MCZ22. There was a significant difference of $AUC_{0-\infty}$ observed between control and MCZ22 tablets, which prove the improvement of extent of absorption of MCZ .

The C_{max} and T_{max} of control and MCZ22 fast dissolving tablets were significantly different indicating immediate absorption of MCZ from MCZ22 tablets. Significant difference of MRT between control and MCZ22 fast dissolving tablets indicated that difference in time spent by the MCZ in the body.

In conclusion, the MCZ22 fast dissolving tablets showed quick and complete drug release within 15 min compared to control tablets that resulted in early T_{max} and higher C_{max}. Accordingly the results of the pharmacokinetics study revealed that the fast dissolving tablets (MCZ22) of MCZ-Gelucire 44/14 solid dispersions enhances the bioavailabilty of poorly soluble meclizine hydrochloride.

FUTURE SCOPES

There are several future scopes for research in the field of meclizine hydrochloride formulations. Here are some potential areas for further investigation:

- Development of novel meclizine hydrochloride formulations using advanced

technologies such as nanotechnology, microencapsulation, and liposomes to enhance drug delivery and bioavailability.

- Investigation of the safety and efficacy of meclizine hydrochloride formulations in clinical trials to evaluate their therapeutic potential in the treatment of various diseases such as motion sickness, vertigo, and nausea.
- Exploration of combination therapies involving meclizine hydrochloride with other drugs to improve treatment outcomes and reduce adverse effects.
- Investigation of meclizine hydrochloride formulations for different routes of administration such as intranasal, transdermal, and ocular, to evaluate their potential for various indications.
- Exploration of the use of meclizine hydrochloride formulations in veterinary medicine for the treatment of motion sickness and other related disorders in animals.

CONCLUSION

The *in vivo* pharmacokinetic studies of meclizine hydrochloride solid dispersions demonstrated significant improvement in bioavailability when compared to the pure drug. The solid dispersion formulation showed a higher peak plasma concentration, a shorter time to reach the peak concentration, and a longer elimination half-life than the pure drug. These findings suggest that solid dispersion technology can be an effective approach to improve the solubility and bioavailability of meclizine hydrochloride. The results of this study provide valuable insights for the development of optimized meclizine hydrochloride formulations for clinical use. Further research is warranted to investigate the safety and efficacy of meclizine hydrochloride solid dispersions in humans.

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