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BIO ANALYTICAL METHOD FOR QUANTITATIVE ESTIMATION, PHARMACOKINETIC AND BIOEQUIVALENCE STUDY OF NIZATIDINE NOVEL RAFT GASTRO RETENTIVE FORMULATION USING REVERSED-PHASE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

Objective: This study presents for the development and validation of reversed-phase high-performance liquid chromatography method for the determination of nizatidine in rabbit plasma.

Methods: The method was used to perform a pharmacokinetics and bio-equity study to compare a raft gastro-retentive formulation of nizatidine with a marketed formulation. Nizatidine is a competitive H2 receptor antagonist that is prescribed for the treatment of different disorders connected with gastric acid production, mainly for nocturnal acid secretion. Twelve New Zealand white rabbits were divided into two groups: One of them receive the new raft formulation that is made up of novel ingredients and the second one receive the marketed raft formulation.

Results: The results indicated that the novel raft formulation significantly enhanced the bioavailability of nizatidine, with higher C_{max} (230.28±0.61 ng/mL) and area under the curve $(AUC)_{0-\infty}$ (1826.17±2.38 ng•h/mL) compared to the marketed formulation (Cmax: 210. Mean C_{max} values for esomeprazole were 8±4.5 ng/mL, and C_{max} for the metabolite were 6.5±1.9 ng/mL $AUC_{0-\infty}$ was 619.1±21, 14 ng•h/mL.

Conclusion: Furthermore, the physical characterization demonstrated that, for the raft formulation, the mean resident time was higher (7.22±0.014 h) than that of the marketed product (3.17±0.07 h) and suggested a sustained release product. A strong *in vitro in vivo* correlation R^2 = 0.9162 was confirmed to the predictability of the raft formulations performance.

Keywords: *In vivo* pharmacokinetic study, Nizatidine, Bio-analytical method, Bioavailability, Bioequivalence, *In vitro in vivo* correlation.

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INTRODUCTION

The proton pump inhibitors are of first when treating gastric acid-related problems. However, in spite of their potent anti-secretary activity, they are unable to control gastric secretion during nighttime [1]. During night excessive acid secretion is mainly mediated by histamine release (nocturnal acid). It was also observed acid secretion in the night more compared to day time and therefore patients feels discomfort and pain more in night than that of day [2].

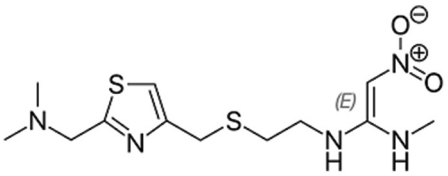

Fig. 1: Structure of nizatidine

Histamine plays an important role in gastric acid secretion during nighttime. Histamine stimulates parietal cells to release the acid. Histamine is also known to react with other stimulants such as gastrin and acetylcholine involved in gastric acid secretion. Second-generation histamine receptor antagonists such as nizatidine are known to completely suppress basal nocturnal acid. Histamine is considered the final common chemical mediator at the oxyntic cell [3].

Nizatidine is a competitive H2R inhibitor, i.e., it competes with histamine for binding H2R present on the parietal cell's basolateral membrane, resulting in the decrease of basal and nocturnal gastric acid secretions. Nizatidine is an anti-secretory drug used in the treatment of many gastric region-related ailments, especially such as hyperacidity, gastric ulcers, and gastro-oesophageal refluxes [4-6]. The drug is known to inhibit acid secretion due to histamine.

Absorption of drug is rapid with bioavailability exceeding 70%. Its apparent volume of distribution accounts for 0.8–1.5 L/kg with a clearance value of 40–60 L/h. Nizatidine (Fig. 1) has a duration of action of up to 10 h. It is eliminated primarily by the kidneys; 90% of the administered dose (65% as an unchanged drug) is recovered in the urine within 16 h [7].

Several methods have been reported in the literature regarding the quantitation of nizatidine in various pharmaceutical and bulk formulations such as the liquid chromatography method for estimation nizatidine in oral solution [8], reverse phase (RP) liquid chromatography method of quantitative determination of drug in pharmaceutical formulations [9], simultaneous estimation of nizatidine using high-performance liquid chromatography (HPLC) in commercial product [10], a stability indicating method for estimation of nizatidine using HPLC with diode array detection in bulk and capsule formulations [11]. There are no specific methods have reported for the estimation of nizatidine biological samples so far. In the present work, investigations were done to explore *in vivo* comparative studies of nizatidine in biological fluid, rabbits were chosen as animal model to carry out studies. Plasma samples were considered biological sample. The preclinical study protocol was approved by an ethical committee,

namely Centralized Experimental Animal Division of Shadan Institute of Medical Sciences Hyderabad. The approval number was recorded as Approval No: IAEC-03/SES/2020/003.

METHODS

Materials

Nizatidine was obtained from Dr. Reddy's Laboratories Ltd., Hyderabad, Amlodipine Sun Pharmaceuticals, Acetonitrile, perchloric acid, dihydrogen phosphate, 1% carboxymethyl cellulose (CMC), diethyl ether. Were procured from SD Fine Chem, India. All the reagents used were of analytical grade.

Methods

The study was carried out with pre-approval of the ethical committee decision with all necessary documentation. The name of institution, "Centralized Experimental Animal Division of Shadan Institute of Medical Sciences Hyderabad" The approval number was recorded as Approval No: IAEC-03/SES/2020/003.

For the study, white rabbits, New Zealand breed were selected. 12 rabbits were taken of either gender. To carry out the study, the animals were divided into two groups A and B. Group A is treated with a novel formulation and Group B was treated with marketed formulation. The rabbit surface area was taken to calculate dose (Equation 1), rabbit surface area was considered as 0.2 m^2 and compared with the human area as 1.6 m^2 Based on the conversion factor we got rabbit dose as 18.75 mg, the given below [12,13].

$$\text{Animal dose} = \frac{\text{The surface area of animal}}{\text{The surface area of human}} \text{Human dose} \ldots \quad \text{Equation 1}$$

To carry out the study, the rabbits were placed in observation in separate cages. The animal room was maintained at 25°C temperature and Relative Humidity 45° with continuous entry 100% fresh air. The animals were exposed to alternative 12 h day and night cycles. The animals were deprived of any sort of medications prior at least for 15 days with a standard diet and subjected to overnight fasting before the experimental day with free approach to water. On the day experiment animals were given pre decided dose of the drug using their feeding tube and avoid any physical restriction the animals were anesthetised for a short period using diethyl ether.

Group A was given marketed formulation according to its body surface area, for ensuring complete consumption, the market formulation was blended with 1% CMC and fed with 20 mL of water. Group B was given a novel raft formulation.

On the completion of dosing, animal blood samples were collected. The marginal ear vein was selected for withdrawing the blood sample. The blood samples were collected in container containing heparin to avoiding any clotting of sample. The pre-determined timings were at 0.5, 1, 1.5, 2, 2.5,3, 4, 6, 8, 12, 16, 20, 24 h. The plasma was separated by centrifuging (Remi-M-12C); the blood samples at 4000 rpm for 10 min and separated plasma was placed at storage (−20°C) until their further study.

The analytical method adopted here was RP-HPLC (WATERS HPLC 2695 With 2996 PDA detector, Germany). Separation and quantitation done using octadecyl silane RP-18 column (250 × 4.6 mm, 5 µm particle size). For nizatidine in rabbit plasma [14,15], the detector wavelength was set at 239 nm. 0.01 M di hydrogen phosphate adjusted to pH 3.5 and acetonitrile in a ratio of 63:37 V/V mobile phase maintained at 1.5 mL/min flow rate.

10 µg/mL concentration of nizatidine was prepared using the mobile phase. The standard calibration curve of Nizatidine was obtained by diluting the above stock solution analyzed using 10 µg/mL amlodipine as an internal standard. A standard calibration curve was established in plasma by adding 100 µL aliquot of prepared dilutions of nizatidine and amlodipine with 100 µL blank plasma. Both the solutions were run in HPLC to determine retention time. The plasma calibration curve was obtained by taking the concentration of the analyte on the x-axis and the peak area on the y-axis.

Quantitative estimation of drug

The concentration of nizatidine in the blood sample was estimated for linearity, range, specificity, accuracy, precision, limit of detection (LOD), and limit of quantification (LOQ).The evaluation of *in vivo* pharmacokinetic parameters helps in comparing the marketed formulation with that of the optimized formulation. The study was conducted to evaluate the pharmacokinetic parameters such as C_{max}, T_{max}, Ke, and area under the curve (AUC) in rabbits using the HPLC method [16].

In vitro in vivo correlation (IVIVC)

IVIVCs are established when a new oral dosage form has been developed. These correlations are predictive quantitative models that describe the relationship between *in vitro* dissolution parameter oral formulations with their relevant *in vivo* response. There are three levels of responses designed for different dosage forms. In these studies, one can investigate the level of correlation between *in vitro* dissolution parameter with that of *in vivo* pharmacokinetic performance of dosage forms [17-20]. The level A type of correlation helps to correlate the entire *in vitro* dissolution profile with that of *in vivo* pharmacokinetic properties. The level B type of correlation is based on "statistical moment theory," which compares the mean of any dissolution *in vitro* parameter with *in vivo* mean residence time (MRT) of the drug. The level C types of correlations are based on point-to-point correlations. In these types of correlations, anyone *in vitro* dissolution property can be correlated with anyone *in vivo* performance. e.g. Time to release 50% or 90% drug of *in vitro* dissolution can be correlated with C_{max} or T_{max} or AUC of the *in vivo* parameter.

In this current research study, an attempt was made to IVIVC using level C by comparing *in vitro* dissolution time with *in vivo* performance. The correlation between mean *in vitro* release of the drug with a MRT of the *in vivo* study.

RESULTS AND DISCUSSION

Linearity and range

The concentration range used was 5–200 ng/mL and curve linearly over this range. The regression coefficient equation $y=0.0098x+0.0064$ and $R^2=0.9997$ (Table 1). The peak area ratios of nizatidine and internal standards reported proportional as presented in chromatogram Fig. 2.

Specificity

To investigate any interfering peak due to the presence of other endogenous compounds in blood plasma, random samples were spiked into HPLC to know its effect in chromatogram (n=6) Fig. 3.

Table 1: Standard calibration curve of nizatidine in rabbit plasma

S. No	Concentration (ng/mL)	Peak area (M±SD)
1	5	0.0501±0.00
2	10	0.0998±0.01
3	25	0.2503±0.00
4	50	0.4968±0.00
5	75	0.7474±0.01
6	100	1.0081±0.04
7	125	1.2371±0.02
8	150	1.4935±0.00
9	200	1.9455±0.01
	n=3	

SD: Standard deviation

Accuracy

Accuracy determination was done at 50, 100, and 150 ng/mL concentrations as low, medium, and high. The determinations were done 3 times for each concentration. The accuracy was expressed in percentages. Percent accuracy was found to be 99.39–100.40% with relative deviation varying from 0.926 to 0.66.

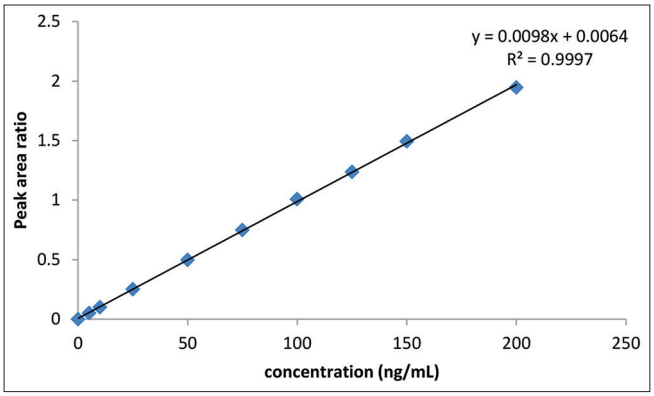

Fig. 2: Standard calibration curve of nizatidine in rabbit plasma

Precision

Precision measurement was performed on the medium concentration 100 (ng/mL). The % relative standard deviation of 1.83–0.82 LOD and LOQ, along with 96.61–101.40% and 89.38–91, 26 inter and intra-day precision were obtained. The lowest concentration of analyte that is sufficient to provide a peak with a signal-to-noise ratio larger than 3:1 for LOD and 10:1. LOD and LOQ were found to be 4 ng/mL and 40 ng/mL, respectively, and their concentration was the lowest reliable limit. Figs. 4-7 show the typical chromatogram of blank plasma spiked with nizatidine with internal standard demonstrating retention time.

Pharmacokinetic results nizatidine-optimized raft formulation

The HPLC chromatogram of blank plasma, drug, and IS are found at 2.6 min and 4.13 min as per the developed method (Fig. 8-10).

Pharmacokinetic data of nizatidine

Nizatidine concentrations in plasma following oral administration of nizatidine marketed product and nizatidine optimized raft formulation

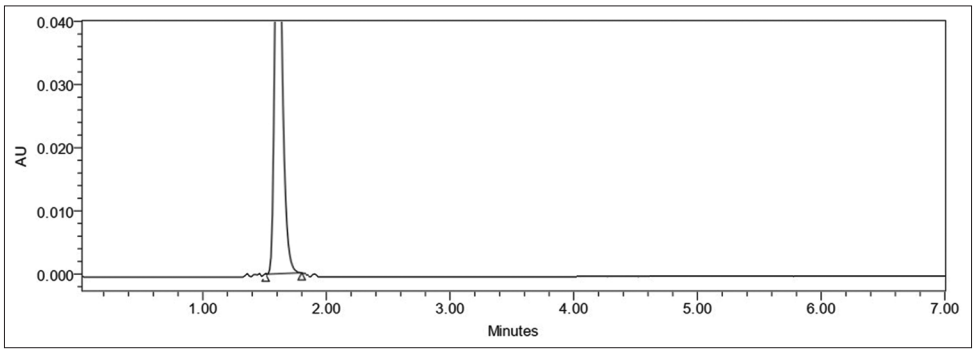

Fig. 3: High performance liquid chromatography chromatogram of blank rabbit plasma

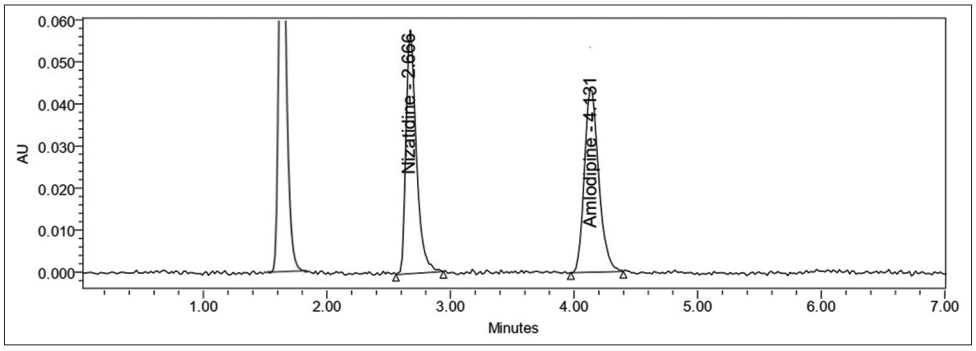

Fig. 4: Standard high performance liquid chromatography chromatogram of Nizatidine and amlodipine in rabbit plasma

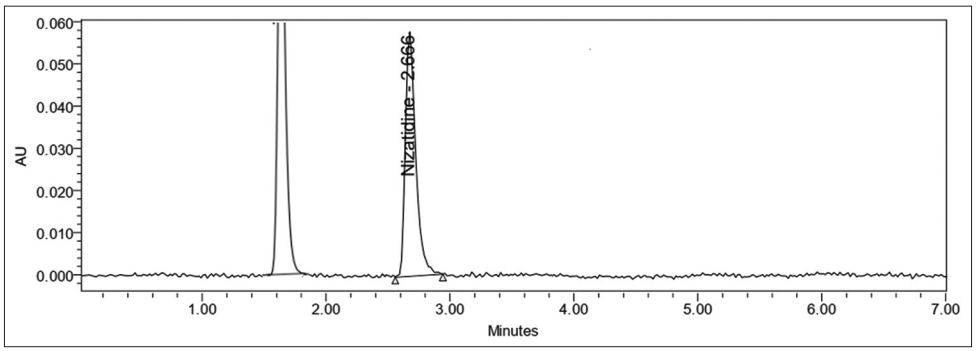

Fig. 5: Standard high performance liquid chromatography chromatogram of Nizatidine in rabbit plasma

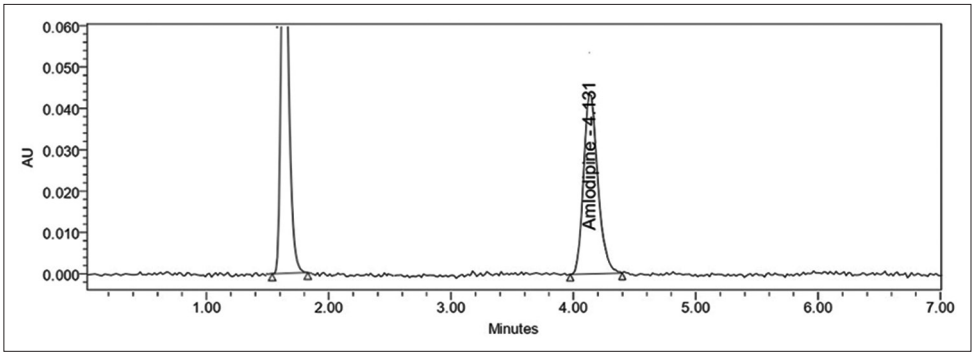

Fig. 6: Standard high performance liquid chromatography chromatogram of internal standard amlodipine in rabbit plasma

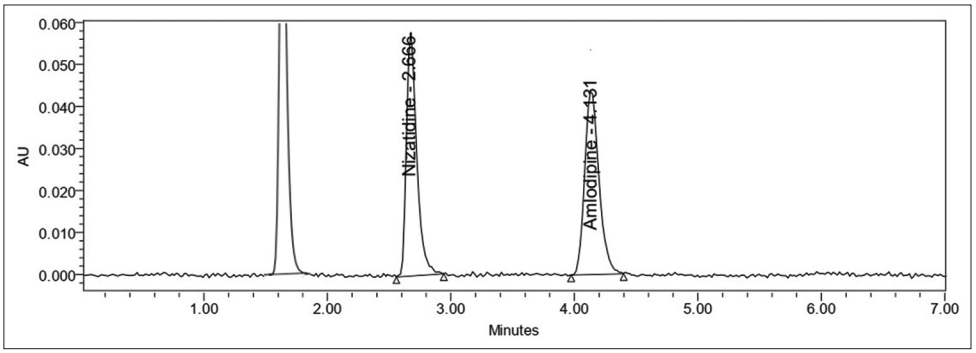

Fig. 7: Standard high-performance liquid chromatography chromatogram of nizatidine and amlodipine in rabbit plasma

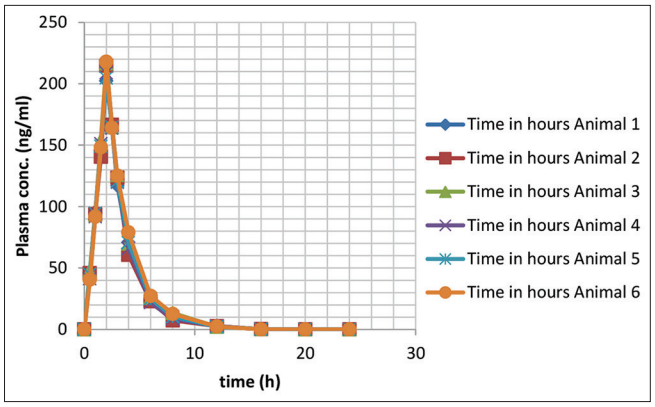

Fig. 8: Plasma conc. versus time profile of nizatidine marketed product in rabbit plasma

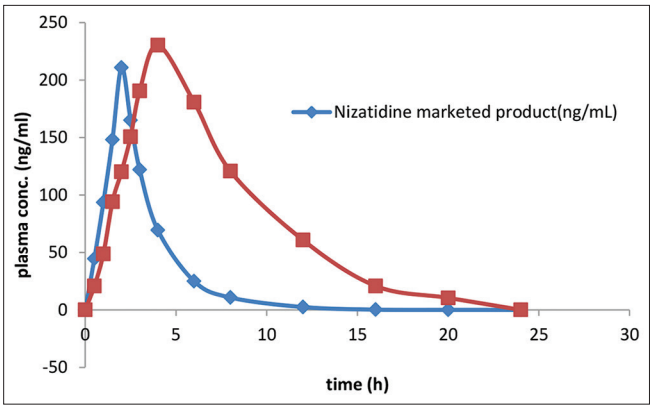

Fig. 10: Plasma conc. versus time profile of nizatidine optimized raft and marketed product in rabbit plasma

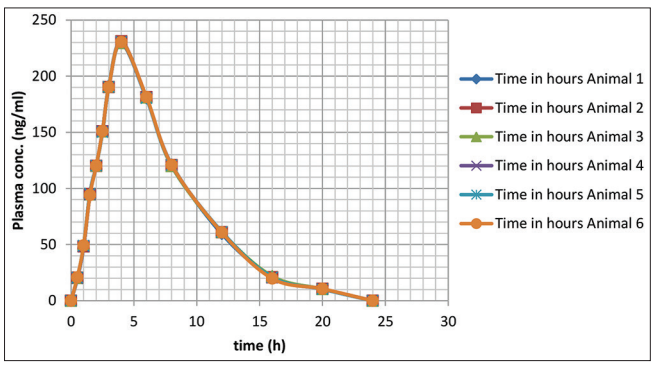

Fig. 9: Plasma conc. versus time profile of Nizatidine optimized raft optimized in rabbit plasma

are given in Table 2 and respective plasma concentration-time curves are shown in Figures.

Figure shows the plasma concentration versus time profile in rabbits after one dose of nizatidine optimize raft formulation and nizatidine marketed product. At observed time points, the nizatidine plasma concentrations in rabbits with optimized raft formulation were considerably more than those with nizatidine marketed product. The PK of nizatidine after ingestion of the two formulations in rabbits is shown in Table 2.

The C_{max} of the optimized raft formulation is 230.28±0.61 ng/mL compared to the nizatidine marketed product formulation 210.8±6.5 ng/mL. $AUC_{0-\infty}$ for the optimized formulation was found to be 1826.17±2.38 ng. h/mL whereas for the marketed nizatidine product formulation 619.1±21.14 ng.h/mL which indicates

Table 2: Plasma conc. versus time of nizatidine marketed product and optimized formulation in rabbit plasma

Time (h)	Plasma conc. Nizatidine marketed product (ng/mL)	Plasma conc. Nizatidine RAFT formulation (ng/mL)
0	0±0	0
0.5	44.48±2.94	20.35±0.40
1	93.44±1.59	48.70±0.62
1.5	148.16±4.65	94.83±0.69
2	210.8±6.50	120.15±0.09
2.5	164.96±1.03	150.68±0.39
3	121.9±3.42	190.43±0.39
4	69.42±6.08	230.28±0.61
6	24.96±2.19	180.68±0.46
8	10.7±2.32	120.68±0.47
12	2.44±0.28	60.74±0.65
16	0.2±0.10	20.82±0.75
20	0±0	10.41±0.13
24	0±0	0

n=3 (Mean±SD) SD: Standard deviation

Table 3: Statistical treatment of Pharmacokinetics of the marketed and novel raft formulations of nizatidine in rabbit plasma (mean±SD, n=6)

Pharmacokinetic Parameter	Marketed formulation	Nizatidine raft formulation	Calculated "t" value
C_{max} (ng/mL)	210.8±6.5	230.28±0.61	7.035*
t1/2 (h)	1.43±0.07	3.336±0.01	67.250*
Kel (h^{-1})	0.485±0.2	0.207±0.001	27.650*
$AUC_{0-\infty}$ (ng h/mL)	619.1±21.14	1826.17±2.38	140.826*
$AUMC_{0-\infty}$(ng h/mL)	1964.31±109.27	13191.55±41.45	247.844*
$MRT_{0-\infty}$ (h)	3.17±0.07	7.22±0.014	139.493*

Null hypothesis (H_o): It states. There should not be a multivariate difference between both formulations at Table t value 4.28 with 5 degrees of freedom at 0.05 level

Result: The obtained t-values are much higher compared t-stat value hence null hypothesis is denied. The obtained result indicates there is an inconsequential difference exists between the prepared (optimized) formulation and marketed formulations

*t-test: paired two samples for means. Statistical study student t-test, SD: Standard deviation, c_{max}: Peak plasma concentration, t_{max}: Time to reach c_{max}, AUC_{0-24}: Area under the curve from 0 to 24 h, $AUC_{0-\infty}$: Area under the curve from 0 h to infinity, $MRT_{0-\infty}$: MRT from 0 h to infinity

more amount of drug is available in the plasma. The pharmacokinetic parameters, including C_{max} and $AUC_{0-\infty}$, provide essential insights into the systemic exposure and bioavailability of the drug. The optimized formulation and marketed formulation pharmacokinetic results were statistically analyzed using a paired "student *t*-test" The comparison between the optimized raft formulation and the marketed nizatidine product formulation reveals significant differences in these parameters.

Plasma concentration was attained rapidly in the case of the marketed formulation whereas in the case of the optimized formulation, there was a slow release of the drug during its entire duration.

The higher C_{max} and $AUC_{0-\infty}$ values for the optimized raft formulation suggest enhanced bioavailability. This could result from improved drug solubility, dissolution, or absorption, indicating that the raft formulation facilitates more efficient delivery of nizatidine into the bloodstream.

The MRT was found to be 2 for the marketed formulation whereas in case of optimized formulation, it is 7.22±0.014 which showed significantly increase. With the same dose drug, the AUC_{0-inf} value is 3 fold increased in comparison to marketing. Statistically, the AUC_{0-inf} of the optimized raft formulation was significantly higher (Table 3) as compared to the nizatidine-marketed product formulation.

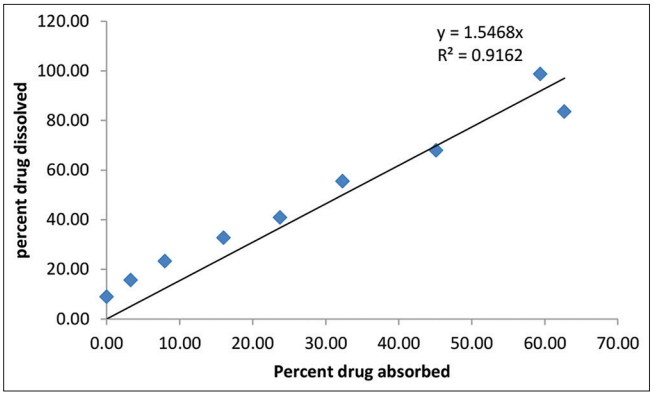

Fig. 11: Percent drug absorbed versus percent drug dissolved plot of nizatidine raft

IVIVC studies of nizatidine optimized raft formulation

These IVIVC are predictive models which mathematically estimate to describe the relationship between *in vitro* dissolution and *in vivo* response of drugs based on pharmacokinetic parameters.

In the present study, correlations are developed by plotting the percentage of drug *in vitro* dissolution with the percent drug absorbed systemically for the entire duration of the drug which directly indicates the amount of drug absorbed from the formulation. For correlating straight-line equations are drawn and the correlation coefficient was calculated to explain IVIVC. From the correlation coefficient, it was found R^2 value 0.9162 profile indicates a study under consideration with IVIVC

CONCLUSION

The aim of this research study was to develop and validate a bioanalytical method by RP-HPLC for the quantitation of nizatidine in rabbit plasma. The application of the method to a pharmacokinetic and bioequivalence study of a novel raft gastro- retentive formulation of nizatidine was successful. The results showed the novel formulation to be more effective than the marketed formulation.

It was found that the new raft formulation of nizatidine enhances significantly its bioavailability. This was evidenced by the higher C_{max} (230.28±0.61 ng/mL) and AUC0-∞ (1826.17±2.38 ng•h/mL) values obtained for the raft formulation compared to the marketed product (C_{max}: 210.$AUC_{0-\infty}$: 619.1±21.14 ng•h•mL). The pharmacokinetic characteristics generated from studies on nizatidine administration in the raft formulation illustrate a more effective administration and prolonged systemic distribution.

Furthermore, the MRT for the new formulation was markedly greater (7.22±0.014 h) than that of the marketed formulation (3.17±0.07 h), indicating a sustained release profile. The unique gastro-retentive properties of the raft formulation contributed to this sustained release of the drug. The study also made a good attempt in developing the *in vitro and in vivo* relationship for new formulation with the correlation coefficient 0.9162 (Fig. 11**)**. These strong positive correlations suggest a direct and stable relationship between *in vitro* dissolution and *in vivo* absorption of the drug which in turn provides support for the effectiveness of the raft formulation.

The novel raft gastro-retentive formulation of nizatidine is found to offer great promise in improving the bioavailability and pharmacokinetic profile of the drug with which the gastro-retentive system has been combined. This formulation may lead to better therapeutic outcomes for subjects with gastric acid-related disorders, especially those with nocturnal acid secretion. The validated RP-HPLC method and the proven IVIVC provide a solid foundation for future research and drug delivery development of other gastro-retentive systems.

AUTHOR CONTRIBUTION

The research work was done Shanti Sagar, and Rajeshwar Vodeti. The manuscript editing, preparation, and statistical study were carried out by Nerella Mounika and Ramgopal Appani.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR FUNDING

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