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IN VIVO PHARMACOKINETIC STUDY OF GASTRO RETENTIVE FLOATING MATRIX TABLETS OF NICARDIPINE HYDROCHLORIDE PREPARED BY SINTERING TECHNIQUE

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ABSTRACT

The present work involved *in-vivo* pharmacokinetic evaluation of sintered gastro retentive floating matrix tablets (GRFT) of Nicardipine Hydrochloride in comparison to Nicardipine pure drug and unsintered GRFT of Nicardipine. The objective of the present investigation was to study the effect of sintering technique in development of controlled release dosage form. The pure drug, both formulated unsintered and sintered controlled release GRFT of Nicardipine HCL were tested for *in-vivo* bioavailability study in healthy male New Zealand rabbits (n=3). The plasma concentrations of Nicardipine HCL drug were determined by a validated HPLC method. From the time versus plasma drug concentration data, various pharmacokinetic parameters (C_{max}, T_{max}, AUC, K_E and $T_{1/2}$) were estimated. T_{max} for pure drug, unsintered and sintered tablets was found to be 1h, 2hr and 4h with C_{max} values of 119.33 ± 4.72 ng/ml, 96.33± 3.05 ng/ml and 63.66 ± 2.51 ng/ml respectively**.** Increase of T_{max} values in sintered tablets suggested slow absorption of drug from the formulated sintered tablets and the availability of drug at a controlled manner. An increase of the Elimination half-life ($T_{1/2}$) and decrease in elimination rate constant (K_E) of drug in sintered matrix tablet in comparison to the that of unsintered tablets and pure drug was also observed, indicating the prolonged and controlled systemic availability of drug in biological system. The investigated sintered gastro retentive floating matrix tablets exhibited a remarkable increase in bioavailability due to prolonged plasma residence and could maintain constant plasma level of Nicardipine HCL for more than 16 hr

in rabbits.

KEYWORDS: *In-vivo*, Sintering, Pharmacokinetic Parameters, Gastro retentive floating tablet (GRFT), Nicardipine HCL.

INTRODUCTION

Nicardipine Hydrochloride (NIC) is a dihydropyridine calcium-channel blocking agent used to treat high blood pressure and angina. After oral administration Nicardipine has an extensive hepatic first pass metabolism with systemic bioavailability ranging from only 20 to 33%. Because of extensive hepatic first pass effect and short biological half-life (2-4 hr), the drug needs to be administered frequently (30 mg, thrice daily). Moreover, NIC is absorbed only in stomach and upper part of GIT because of its good solubility at low pH. Hence to extend the gastric residence time and to prolong the drug release, the design of gastro retentive floating tablets of Nicardipine is desirable.[1]

The concept of sintering in pharmaceutical sciences is relatively new, but the research interests related to this process have been growing continuously. In powder metallurgy, sintering is defined as bonding of adjacent particle surfaces in a mass of powder or in compact, by the application of heat. Conventional sintering technique involves the heating of compact at a temperature below the melting point of the solid constituent in controlled environment under atmospheric pressure.[2,3] In the pharmaceutical science, sintering has been described as the mechanism for the strengthening of the mechanical properties of consolidated pharmaceutical powder at elevated temperature, for solid-bond formation during tablet compression, and for thermal curing of polymer-latex film coating. The sintering process has been used for the fabrication of sustained- release matrix tablets for the stabilization the dug permeability of film coatings derived from various pharmaceutical lattices.[4] The sintering technique has been used for the fabrication of matrix tablet for sustained release and retardation of release of drug from various systems. The thermal sintering method involves fusion of polymer particles or formation of welded bond between particles by exposing the polymer matrix to the temperature above the glass transition temperature of the polymer. The entrapment of drug particles in the welded bond leads to controlled release of drug.[5,6]

Earlier We reported[7] the design of thermally sintered gastro retentive floating tablets (TSGRFT) of Nicardipine Hydrochloride employing HPMC K 100 M as matrix former and

sodium bicarbonate as the gas generating agent. The aim of the present study was to assess the relative bioavailability i.e., rate and extent of absorption of formulated sintered and unsintered gastro retentive floating matrix tablets of Nicardipine Hydrochloride with that of the pure Nicardipine Hydrochloride drug solution to study the effect of sintering technique in development of sustained release floating matrix tablets.

MATERIALS AND METHODS

Materials

Nicardipine HCL (NIC) was obtained as Gift sample from DR. Reddy's Laboratories ltd, Hyderabad. Sodium bicarbonate and Magnesium stearate were procured from Lobachem Pvt Ltd Mumbai. HPMC K100M was provided by Aurobindo Pharma Ltd, Hyderabad. Methanol used were of HPLC grade, while all chemicals and other reagents used for the study were of analytical grade.

Preparation of sintered gastro retentive floating tablets (SGRFT) of Nicardipine HCL for rabbits

Doses for rabbits were calculated based on BSA using the formula, Animal dose (mg/kg) = HED (mg/kg) x Conversion factor, where conversion factor for animal rabbit is 3.08.[8,9] Floating tablets for rabbits containing 5 mg (at a dose level equivalent to 40 mg of human dose) of Nicardipine HCL were prepared by direct compression method, using HPMC K100M as matrix former at 58% strength in the formulae and sodium bicarbonate (15%) as gas generating agent. Magnesium Stearate were added as glidant. Sintering of tablets was done by using Hot air oven. The prepared matrix tablets were placed on aluminium foil and exposed to thermal treatment at 70^0C for 3 hr in hot air oven. The temperature of the oven was maintained within a degree Celsius. After the exposure to temperature and time the tablets were removed, cooled to room temperature and were stored in desiccators till further use.

In-vivo pharmacokinetic studies

Both unsintered and sintered controlled release matrix tablets of Atenolol were subjected to *in vivo* pharmacokinetic studies. Nine healthy male New Zealand rabbits (2.5 to 3kg) were used for these studies. The *in vivo* pharmacokinetic studies were performed with the permission of Institutional Animal Ethical Committee, Guru Nanak institutions technical campus-School of pharmacy, Hyderabad, India (CPCSEA Registration Number: 1374/PO/Re/S/10/CPCSEA). The protocol for the animal experiment was approved by the

IAEC (Approval no.03/GNIP/CPCSEA/IAEC/2019). All the rabbits were fasted overnight with impromptu access to water on the penultimate day before the experimentation. After an initial period of acclimatization for one week to laboratory conditions, rabbits were randomly divided into 3 groups with each group comprised of 3 rabbits. The first group received reference standard (Nicardipine HCL drug solution), second group was administered with unsintered gastro retentive floating matrix tablets of Nicardipine Hydrochloride and third group was administered with sintered gastro retentive floating matrix tablets of Nicardipine Hydrochloride. 5 mg of pure Nicardipine Hydrochloride drug (plain drug) dissolved in distilled water was administered orally to the first group of rabbits through the oral tube. Few ml of distilled water was shoved through a syringe, (without needle) to ascertain that all the Nicardipine Hydrochloride reaches the stomach. The unsintered and sintered gastro retentive floating matrix tablet formulations containing 5 mg of NIC were administered orally at the end of the throat to the second and third groups of rabbits respectively by using an oral tube. After receiving the oral dose, immediately 10 ml of distilled water was administered through the tube to facilitate the accession of the tablets and to stop it from protruding to the rabbit's throat. Animal were accessed to food after 4 h of administration of dose. Blood samples (1.0 ml) were collected from marginal ear vein at time intervals of 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20 and 24 hr after administration, into heparinized eppendorf tubes. Plasma was separated by centrifugation of blood at 4000 rpm for 15 min and stored in a freezer until the samples were analyzed.

Instrumentation and chromatographic conditions

The HPLC system (Make: Shimadzu, Spinotech pvt ltd.) consisted of a UV-Vis detector (Shimadzu, Model: SPD-20 A), C-18 column (4.6 x 150 mm, particle size 5 µm). The mobile phase was composed of acetonitrile and 0.02 M potassium dihydrogen phosphate solution in the ratio of 60:40 v/v. Both acetonitrile and 0.02 M KH_2PO_4 solution were filtered before use through 0.45-µm membrane filter, was run at a flow rate of 1 ml/min. The injection volume was about 20µl and the run time was fixed for 10 min. The column temperature was maintained at 40º C and the eluents were monitored at 239 nm.[10]

Preparation of standard stock solutions and calibration solutions

Standard stock solutions of nicardipine hydrochloride and the internal standard (nifedipine) were prepared by dissolving 100 mg of the compounds in 100 mL volumetric flask containing 70 mL of methanol and vortexed for about 15 min, then made up to volume with

methanol. Daily working standard solutions of drug (Nicardipine hydrochloride) were prepared by suitable dilution of the stock solution with the mobile phase.

For the estimation of nicardipine hydrochloride in plasma samples, a calibration curve was constructed by analyzing plasma samples containing different amounts of nicardipine hydrochloride. Five sets of plasma samples with different drug concentrations were prepared by spiking drug free plasma with 100 µL of a known amount nicardipine hydrochloride to yield concentrations of 5, 10, 20, 50, 100 and 150 ng/0.5mL of plasma along with 100 µL of 0.1 µg/0.5mL of internal standard (nifedipine) solution.

Sample preparation

Plasma samples (0.5 mL) was accurately measured into a 10-mL glass tube, followed by the addition of 100 µL of 0.1µg/0.5mL of internal standard (nifedipine) solution. To the above plasma samples 5 mL of extracting solvent ethyl acetate was added, vortexed for 5 min and then centrifuged at 3,000 rpm for 10 min. The organic layer was separated, dried under vacuum evaporation and the residue was reconstituted with 0.1 mL of acetonitrile. 20 µL of the resultant solution was injected into the column for HPLC analysis.[10]

***In Vivo* Data Analysis**

The pharmacokinetic parameters, namely, maximum plasma concentration (Cmax) and time to reach maximum plasma concentration (Tmax) were obtained directly from the observed values. The AUC (area under the plasma concentration-time curve) from the time of administration to the last observed concentration at time t ($AUC_{0–t}$) was calculated by the trapezoidal rule from the observed values. The value of Overall elimination rate constant (K_E) was calculated using the least-squares regression analysis of the terminal portion of the log plasma concentration versus time curve. The AUC of the plasma concentration–time curve extrapolated to infinitive time ($AUC_{0-\infty}$) was calculated by dividing the last measurable plasma drug concentration with the elimination rate constant (K_E) and adding the result to the $AUC_{0–t}$. The Elimination half -life (T1/2) was calculated by dividing 0.693 with K_E.[11]

RESULT AND DISCUSSION

The HPLC chromatograms of blank rabbit plasma, plasma spiked with Nicardipine HCL and Internal Standard (nifedipine) are shown in figures 1 & 2. Satisfactory sharp peaks of the drug and IS, markedly resolved with widened separations were observed. It was also observed that blank plasma has no endogenous interference with analyte or internal standard.

Drug (NIC) and IS (nifedipine) appeared on the chromatogram in 6.499 and 4.918 min respectively with no interfering peaks.

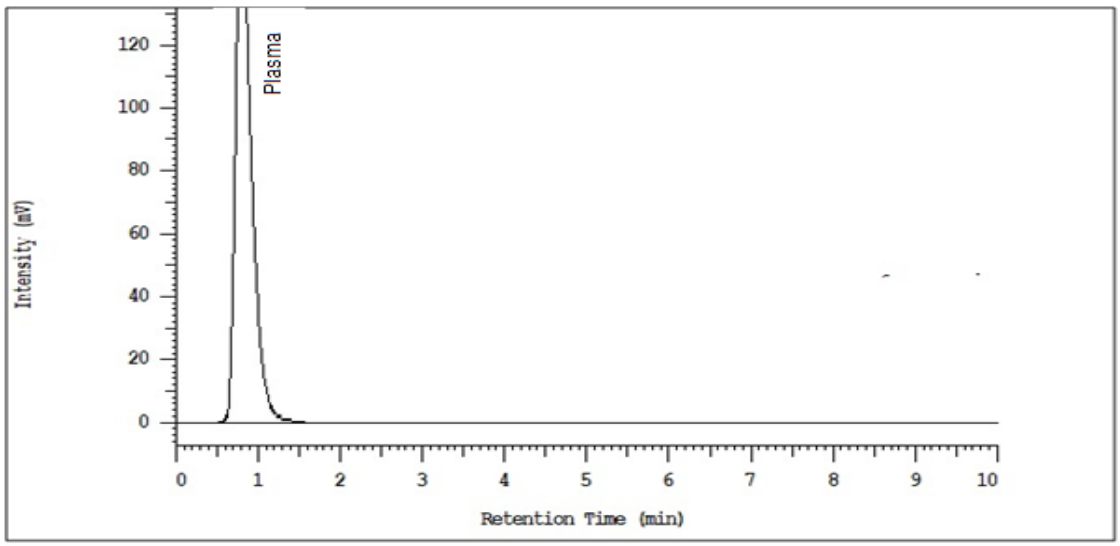

Figure 1: Chromatogram of blank rabbit plasma.

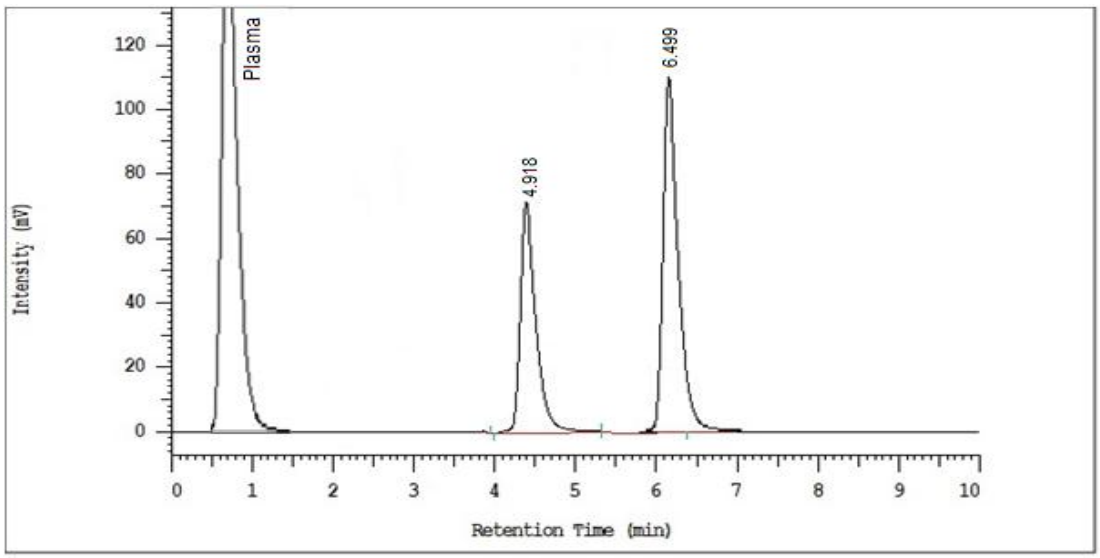

Figure 2: Chromatogram of rabbit plasma spiked with internal standard Nifedipine (Rt-4.918 min) & analyte Nicardipine Hydrochloride (Rt-6.499 min).

The standard calibration curve of drug Nicardipine Hydrochloride (NIC) in rabbit plasma was constructed by plotting the peak area ratios of NIC and IS on the Y-axis and the respective concentrations of NIC on the X-axis. The calibration curve demonstrated linearity over the range of 5–150 ng/ml. The linearity of results was depicted in Figure 3.

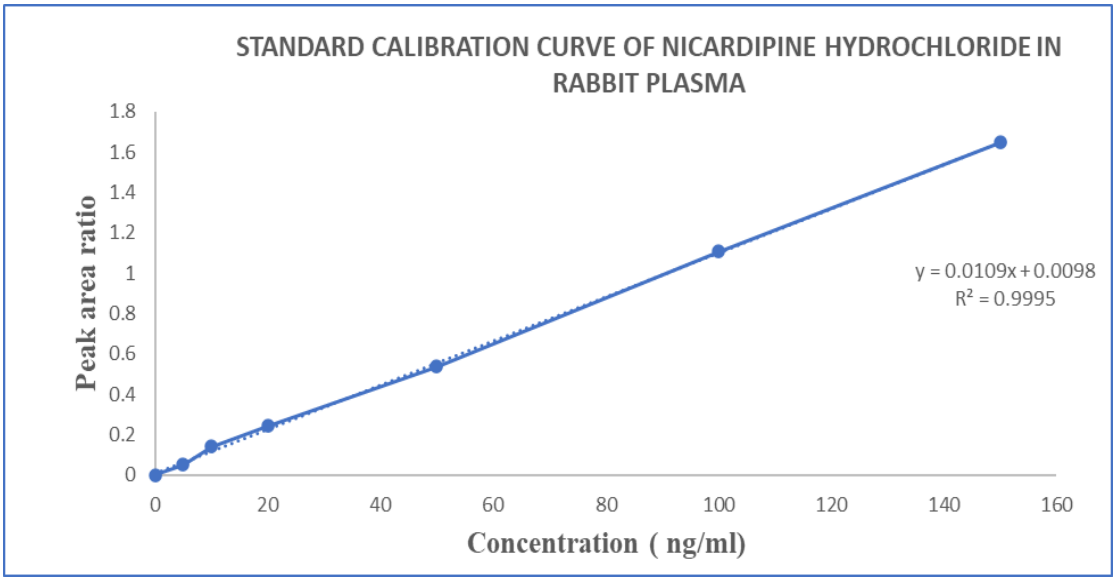

Fig 3: Standard Calibration Curve of Nicardipine hydrochloride in Rabbit Plasma.

The regression equation was found to be y = 0.0109x + 0.0098 with a regression coefficient of 0.9995, where 'y' is the peak area ratio and 'x' is the concentration of Nicardipine Hydrochloride in rabbit plasma. This equation was used to estimate the amount of Nicardipine Hydrochloride in plasma.

Comparative plasma NIC drug concentration profile after oral administration of a 5 mg pure drug, both formulated unsintered and sintered GRFT of NIC to 3 groups of 3 healthy rabbits are shown in Tables 1 and Figure 4.

Table 1: In vivo pharmacokinetic parameters of pure drug Nicardipine HCL and its formulated unsintered & sintered gastro retentive floating tablets in Rabbits.

Pharmacokinetic Parameters	Nicardipine HCL pure drug	Formulated unsintered GRFT of Nicardipine HCL	Formulated sintered GRFT of Nicardipine HCL
C_{max} (ng/mL)	119.33 ± 4.72	96.33± 3.05	63.66 ± 2.51
T_{max} (hr)	1 hr	2 hrs	4 hrs
K_E (hr^{-1})	0.349	0.241	0.154
$T_{½}$ (hr)	1.98	2.87	4.50
AUC_{0-t} (h.ng/mL)	388.49	447.33	612.41
$AUC_{0-\infty}$ (h.ng/mL)	443.87	528.90	662.15

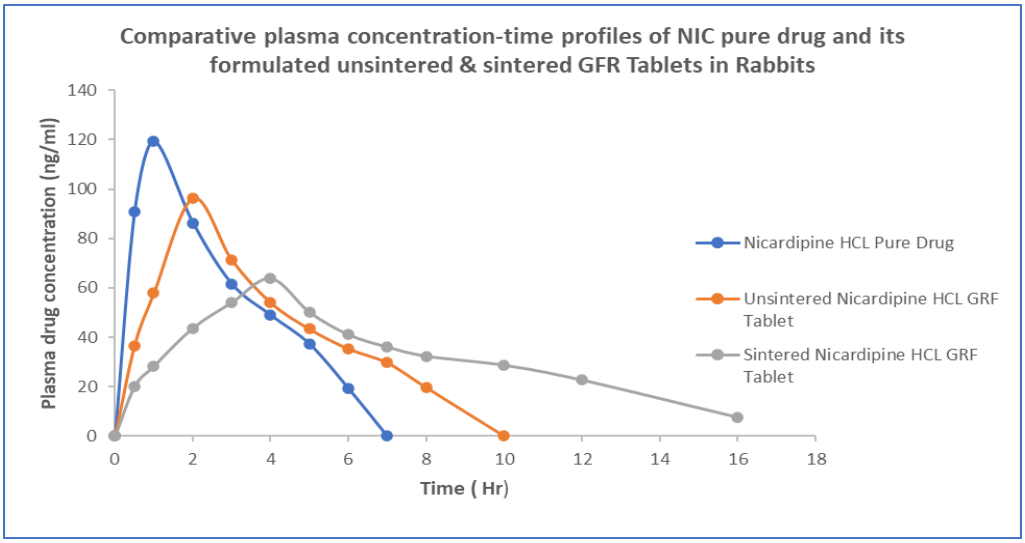

Fig 4: Comparative plasma concentration-time profiles of Nicardipine HCL pure drug and its formulated unsintered & sintered gastro retentive floating tablets in Rabbits.

The results showed that nicardipine hydrochloride administered as plain drug alone reached peak plasma concentration (C_{max}) of 119.33 ±4.72 ng/ml after 1 hr of administration. Whereas the C_{max} of 96.33 ± 3.05 ng/ml at 2 hr and C_{max} of 63.66 ± 2.51 ng/ml at 4 hr were observed after oral administration of unsintered and sintered tablets, respectively. C_{max} of the prepared gastro retentive floating tablets was found to be comparatively less to that of pure drug solution.

NIC drug solution was found to be rapidly absorbed as T_{max} was reached in about 1 hr and for unsintered tablets it was relatively more (T_{max} in 2 hr), whereas in case of sintered tablets the C_{max} had achieved very slowly (T_{max} in 4 hr) and the drug availability was found to be prolonged. Increase in T_{max} value of sintered tablets is the indication the availability of drug at a controlled manner.

The elimination constant (K_E) for drug NIC in the prepared sintered gastro retentive floating matrix tablet was found to be 0.154/h, while for unsintered tablets and pure drug it was found to be 0.241/h and 0.349/h respectively. Based on the elimination constant values, the biological half-life was calculated and was found to be 4.50 hr for the sintered tablet, 2.87 hr for unsintered tablets and 1.98 hr for the pure drug solution.

An increase of the half-life and decrease in elimination rate constant of drug in sintered tablet in comparison to the that of unsintered tablets and pure drug indicates the increased residence time, prolonged and controlled systemic availability of drug in biological system.

The AUC_{0-t} of pure drug solution and unsintered tablet was found to be 388.49 h.ng/mL and 447.33 h.ng/mL respectively. AUC_{0-t} in sintered formulation was found to be increased to around 612.41 h.ng/mL, which clearly suggests the enhanced *in-vivo* drug availability.

As evident from the pharmacokinetic parameters, the sintered gastro retentive floating tablets of Nicardipine HCL showed prolonged release and were able to release the drug effectively at a rate-controlled manner for a prolonged period for more than 16 hr in rabbit.

CONCLUSION

A new controlled release sintered gastro retentive matrix tablets of Nicardipine HCL has been developed and evaluated for its *in vivo* drug release. The investigated sintered matrix tablets were capable of maintaining constant plasma level of NIC for more than 16 hr in rabbits. The sintering condition markedly affected the *in vivo* drug absorption characteristics from the sintered tablets. The sintered matrix tablets showed a distinguished increase in bioavailability due to prolonged plasma residence of the drug. Formulated product prepared with sintering technique displayed prolonged release with reduce plasma drug fluctuations in comparison to the Pure drug and formulated product prepared without using sintering technique. Thus, from the results of the present study, we may conclude that simple technique of thermal sintering may be used in the design gastro retentive floating tablets of Nicardipine HCL to reduce dosing frequency, dose-related adverse effects, the dose intake to minimize the fluctuations in plasma drug concentration and ultimately improve the patient compliance in the drug therapy management.

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