ORIGINAL ARTICLE

Verapamil Hydrochloride Nanosuspension and Assessment of Cardioprotective effect in Experimental Model of Myocardial Infarcted Rats

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Abstract

Aim and Objective: Verapamil, a calcium channel blocker, has a restricted bioavailability (20–30%) due to substantial hepatic first-pass degradation. Therefore, the main goal of this work was to use nanosuspension with high shear homogenization and ultrasonication techniques to improve the oral bioavailability of verapamil. **Method:** Animals used in experiments were given a myocardial infarction. Verapamil nanosuspension was used in an in vivo pharmacological investigation and to evaluate cardiac damage indicators. **Results:** When compared to free medications, in vivo pharmacokinetic studies showed greater t1/2, area under the curve from zero to infinity, and C_{max}, suggesting improved bioavailability. Oral verapamil nanosuspension treatment improved nearly all hemodynamic parameters studied in the isoproterenol induced myocardial necrosis model, including cardiac damage indicators and left ventricular end-diastolic pressure. **Conclusion:** These positive outcomes highlight the created verapamil nanosuspension's excellent oral administration capabilities, which may enhance the therapeutic effect.

Key words: Isoproterenol, myocardial infarction, nanosuspension, pharmacokinetics, verapamil

INTRODUCTION

One well-known medication with antiarrhythmic, antianginal, and antihypertensive properties is verapamil, which is categorized as an L-type calcium channel blocker.[1,2] The heart's energy consumption and oxygen requirements are reduced when vascular resistance is reduced because the heart must push against less force.[3] Verapamil, a BCS Class I medication, has a systemic bioavailability of just 20–35% but a significant absorption (≤90%) from the gastrointestinal barrier when taken orally. Nanosuspensions are known to improve the plasma profiles and oral bioavailability of a number of medications.[4,5] Nanosuspensions are submicron colloidal dispersions comprising nanoscale drug particles stabilized by a surfactant.[6] The drug, which is poorly soluble in water, is suspended in a matrix-free nanosuspension.[7] Poorly soluble drugs can be injected intravenously without blocking blood arteries due to the reduced particle size. Lyophilizing the suspensions to create a solid matrix is an additional choice.[8,9] The primary objective of the research was to develop a verapamil nanosuspension as a potential formulation to enhance its oral bioavailability through intestinal lymphatic transport. This work was driven by the lack of thorough research, especially with regard to the *in vitro* and *in vivo* study of enhanced verapamil nanosuspension. These new and creative solutions have the potential to significantly increase oral bioavailability.[10,11] The nanosystems prevent luminal enzymes from degrading drugs during gastric

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transit.[12] The *in vivo* animal investigation was evaluated using an experimental model of isoproterenol (ISO)-induced myocardial infarction.

MATERIALS AND METHODS

Yarrow Chemicals in Mumbai provided the verapamil hydrochloride, stearic acid, glyceryl monostearate, and poloxamer 188. The remaining compounds were all of analytical quality.

Induction of experimental myocardial infarction

Experimental design

Four sets (n = 6) of rats were randomly selected. Group I, a normal control, was given a vehicle orally (2 mL/kg/day) for 14 days before receiving 0.3 mL saline subcutaneously every 24 h on days 13 and 14. Group II rats were given a vehicle orally (2 mL/kg/day) for 14 days. On days 13 and 14, ISO (85 mg/kg) was given subcutaneously at 24-h intervals. Rats in Group III received verapamil (10 mg/kg/day) orally for 14 days, while ISO (85 mg/kg, s.c. every 24 h) was given simultaneously on days 13 and 14. Group IV rats were given verapamil-nanosuspension (10 mg/kg/day) orally for 14 days in addition to ISO (85 mg/kg, s.c. every 24 h) on days 13 and 14. Throughout the investigation, the body weights, food intakes, and water consumption patterns of the animals in each group were monitored on a regular basis. Hemodynamic data were obtained following the surgical operation, as was previously described. After hemodynamic parameters were recorded, all animals were killed to obtain the cardiac histopathological tests.

Estimation of cardiac injury markers

The Creatine Kinase Myocardial Band (CK-MB) isoenzyme technique was performed utilizing a Logotech Kit (Delhi, India) detection kit. By measuring absorbance at 340 nm every 60 s for at least 3 min, the enzymatic content in IU/mg protein was calculated.

In vivo studies of verapamil nanosuspension

We bought male Wistar albino rats from our institute's experimental animal facility that weighed between 150 and 200 g. They were kept at a temperature of 22 ± 1°C, a relative humidity of 55 ± 10%, and a 12-h light/dark cycle. Water and a typical pellet chow meal were given to each animal. Every safety measure was implemented in compliance with the guidelines set forth by the Indian government's Committee for the Control and Supervision of Experiments on Animals. The experimental protocol was approved by the Institutional Animal Ethics Committee.

Pharmacokinetics studies

Two groups of rats (n = 6) were present. The test animals were given a dose of verapamil nanosuspension based on their body weight, whereas the control group was given 10 mg/kg of plain verapamil nanosuspension in sodium carboxymethyl cellulose (0.5%). Blood samples were taken from each animal using the tail vein technique at predetermined intervals of 0.5, 1, 2, 4, 8, 12, and 24 h. The non-compartmental pharmacokinetic model was used to determine the drug and formulation's serum concentration versus time profile, and Kinetica software, version 5.0, was used to analyze the parameters. Thermo Fisher Scientific, USA. The plasma drug profile was used to estimate the pharmacokinetic profile, which included peak plasma concentration (C_{max}), time to acquire C_{max} (T_{max}), and area under the curve from zero to infinity (AUC0-∞).

RESULTS AND DISCUSSION

Verapamil's effect on cardiac injury indicators

Table 1 shows the lactate dehydrogenase (LDH) and CK-MB isoenzyme activity in the hearts of rats administered ISO and vehicles. The activity of CK-MB and LDH was considerably ($P < 0.05$) lower in rats treated with ISO than in rats given a vehicle. When given before ISO therapy, at 10 mg/kg, verapamil nanosuspension significantly ($P < 0.05$) restored normal levels of all cardiac diagnostic marker enzymes. The verapamil-NS+ISO-treated group showed a notable improvement in left ventricular measures and cardiac injury indicators when compared to the verapamil ISO-treated group.

Table 1: Effect of V-SLNs, on cardiac injury markers in ISO, induced Myocardial infarction in rats

Treatment group	LVEDP (mmHg)	CK-MB (IU/mg protein)	LDH (IU/mg protein)
Vehicle control	2.1±10.45	141.17±20.22	90.18±7.20
ISO-control	6.7±13.21**	99.73±13.38**	52.18±13.36**
Verapamil (10 mg/kg)+ISO	4.9±15.70	125.70±13.20	68.25±8.56
Verapamil Nanosuspension (10 mg/kg)+ISO	3.5±4.80##, $	135.26±18.73##, $	87.88±8.52##, $

V-SLNs: Verapamil hydrochloride-loaded solid lipid nanoparticles, SLNs: Solid-lipid nanoparticle, LVEDP: Left ventricular end-diastolic pressure, CK-MB: Creatine Kinase Myocardial Band, LDH: Lactate dehydrogenase, ISO: Isoproterenol. Data are expressed as mean ± SD (n = 6). Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparison test. **$P < 0.01$ compared with the Vehicle Control group. ##$P < 0.01$ compared with the ISO Control group. $$P < 0.05$ compared with the Verapamil (10 mg/kg) + ISO group.

Table 2: Pharmacokinetic profile of plain verapamil and verapamil nanosuspension

Parameter	Verapamil	Verapamil nanosuspension
C_{max} (ng/mL)	61±9.1	83±15.72
T_{max} (h)	3.581±0.20	13.52±1.1
$t_{1/2}$ (h)	3.491±0.22	13.53±1.2
AUC0-∞ (ng.h)/mL	255.4±55.4	1020.22±95.6

AUC0-∞: Area under the curve from zero to infinity

In vivo studies of verapamil nanosuspension

In vivo animal study

Pharmacokinetic study

After the unit dose of free verapamil and verapamil nanosuspension is administered, the plasma profile shows the drug concentration for 24 h over its therapeutic level. On the other hand, it was demonstrated that the free drug was removed from circulation in 8–12 h. Based on the information, the C_{max} and T_{max} of the drug-loaded nanosuspension were substantially different from the free drug's plasma profile. The K el of the free drug was greater than that of solid-lipid nanoparticle (SLNs), indicating a longer t1/2 for the latter. Furthermore, compared to free medication, the mean residence time and AUC0-∞ of SLNs are significantly ($P < 0.001$) improved [Table 2].

CONCLUSION

There are many benefits to the verapamil nanoformulation, from increased solubility to better product stability and delivery effectiveness. *In vivo* pharmacokinetic studies showed that oral verapamil nanosuspension raised the pharmacokinetic parameters, indicating a better bioavailability. *In vivo* investigations showed that verapamil nanosuspension improved cardioprotection and prevented hemodynamic changes. Verapamil nanosuspensions' increased effectiveness points to better disease management and a decrease in dosage and side effects. Therefore, we think that verapamil nanosuspension may be a useful technique for boosting the pharmacological bioactivity and oral bioavailability of medications that are only weakly soluble in water.

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