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ENHANCING THE PROPRANOLOL HCL BIOAVAILABILITY IN RATS WITH NARINGIN: A ROLE IN PERMEABILITY GLYCOPROTEIN (P-GP) INHIBITION

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ABSTRACT: Drug transporters altered functions may affect pharmacokinetics, which in turn may affect a drug in blood levels. The maintenance of an appropriate serum concentration of a drug is important to ensure therapeutic efficacy. Bio enhancers, or naturally generated drug absorption enhancers, increase the quantity of unchanged medication in the systemic blood circulation by controlling pre-systemic metabolism and/or membrane permeability. In this study, we have focused on the influence of functional alterations in the intestinal P-glycoprotein (P-gp) on the PK (Pharmacokinetic) of drug by the oral route after pre-treatment with Naringin and verapamil as standard. The interaction between drug and Naringin has been studied using *in-vitro* noneverted sac study, *in-situ* Single-Pass Intestinal Perfusion (SPIP) study, and *in-vivo* oral bioavailability study in rats using Bioanalytical method in RP-HPLC. The bioavailability of drug is improved with Naringin, and this combination is better than verapamil combination of drug, and further studies are needed to confirm the results in patients.

INTRODUCTION: Oral administration is a non-invasive approach that is typically the most popular, safest, and least expensive. There are several transporters that are described that help with the opposite direction of transport by secreting drug molecules back into the intestinal lumen from the inside of enterocytes. Another name for this phenomenon is intestinal drug efflux [1]. P-glycoprotein (P-gp) is the most well-known efflux pump found in the human intestine. P-glycoprotein is a crucial cell membrane protein that expels a variety of foreign materials from cells. P-gp is widely distributed and expressed in the proximal tubule of the kidney, liver cells, and the intestinal epithelium, where it is responsible for pumping xenobiotics (such as poisons or drugs) back into the intestinal lumen.

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Propranolol HCl, a widely used beta-blocker, under-goes extensive hepatic first-pass elimination, after oral dosing with a reported 15–23% systemic bioavailability [2]. Its oral bioavailability varies and is constrained by several elements such as intestinal efflux transporters, like the export pump P-glycoprotein (P-gp). Several therapeutic agents are substrates to P-gp and their bioavailability is lowered or a resistance is induced because of the protein efflux. Hence, Phytochemicals were explored for overcoming multidrug resistance and poor bioavailability problems of the therapeutic P-gp substrates. Bioenhancers, or naturally generated drug absorption enhancers, increase the amount of unchanged medication in the systemic blood circulation by controlling pre-systemic metabolism and membrane permeability [3].

In this study, we focused on the changes in the expression of P-gp in the intestine on the pharmacokinetics of Propranolol HCl, which is a known substrate of P-gp [4]. Naringin, a naturally occurring flavonoid glycoside, is regularly consumed in the human diet.

Naringin inhibits Permeability glycoprotein (P-gp) [5] events associated with tumour initiation, promotion, and progression and has potential cardioprotective effects. Therefore, the present study was to investigate the effect of Naringin on the pharmacokinetics of Propranolol HCl in rats. Intestinal permeability characteristics of were mechanistically investigated using the *in-vitro* non-everted sac and *in-situ* single pass intestinal perfusion methods. To confirm these findings, an *in-vivo* pharmacokinetic study of oral administered Propranolol HCl in rats with or without Naringin pretreatment was performed.

MATERIALS AND METHODS: Propranolol HCl, Verapamil, Naringin was procured from Yarrow chem products (Mumbai, India). Solvents used for quantitative analysis were of HPLC grade (Merck, India) and all other chemicals, reagents which were used in the study are of analytical grade. Male Wistar rats weighing about 220–240 g were used for *in-vitro*, *in-situ* and *in-vivo* pharmacokinetic studies were procured from Systemic research labs, Hyderabad, India. Rats housed in cages were kept in a room under controlled temperature (20–22°C) and 12 h day–night cycle. Animals were used for studies after 1-week acclimatization with access to water and feed. All animal study protocols were approved by Institutional Animal Ethics Committee of Kakatiya University (IAEC/04/UCPSC/KU/2023).

***In-vivo* Pharmacokinetic Study:** In this study rats were randomly divided into four groups of five animals in each group. The rats were allowed free access to food and water, until the night prior to dosing, and were made to fast for 10 h. For the first group, oral Propranolol HCl solution (5.5 mg/kg dissolved in 0.25% w/v of sodium CMC) was administered through feeding needle; the second group low dose of Propranolol HCl (5.5mg/kg) and third group with high dose of Propranolol HCl(10 mg/kg)were pretreated with Naringin (42 mg/kg) and, respectively, for 6 days; and in the fourth group, verapamil (45 mg/kg) was usedBlood samples (1.5 mL) were collected from the retro-orbital plexus at preset intervals of 0, 1/2, 1, 2, 4, 6, 8, 12 hrs after administration of Propranolol HCl and after pretreatment with Naringin and Verapamil. All blood samples were allowed to clot and centrifuged for 10 min at 10,000 rpm. The serum was separated and transferred into clean Eppendorf tubes and stored at −40°C until HPLC analysis. The concentration of Propranolol HCl in the serum samples was estimated by using HPLC [6].

***In-situ* Single-Pass Intestinal Perfusion Study:** The *in-situ* single-pass intestinal perfusion (SPIP) study was performed according to the previously reported methods. The rats were divided into four groups drug alone (control), Naringin pretreatment (test groups) with high and low dose of drug and verapamil pretreatment (standard P-gp inhibitor) groups each consisting of 3 animals. Briefly, rats were anesthetized using Ketamine and Xylazine (80mg/kg and 10mg/kg, ip) and they were placed on a warm pad to maintain normal body temperature. A small midline incision of 2-3 cm was made on the abdomen portion of rats, and an ileum segment of approximately 8-12 cm was isolated using the ileo-caecal junction as a distal marker. Semicircular incisions were made at each end of the ileum, and the lumen was rinsed with normal saline (37 ºC), and the; both ends were cannulated with polyethylene tubing and ligated by using silk suture. Blank perfusion buffer (phosphate buffer saline, pH 7.2) was first perfused for 5 min at a flow rate of 1 mL/min by using a Syringe pump followed by perfusion of phosphate buffer saline (pH 7.4), at a constant flow rate of 0.2 mL/min for a period of 90 min and perfusate was collected at every 10 min interval. After completion of cannulation, the ileum segment was covered with isotonic saline-wet gauzen (37 ºC). The samples were collected and stored at -40 ºC until analysis. Drug concentrations in perfusion samples were analysed by HPLC [7].

Phenol Red Water Flux Correction: The corrected outlet concentration Cout (corr) for Propranolol HCl was calculated from the following equation.

$$\text{Cout (corr)} = \text{Cout} \times \text{Concentration of phenol red in (CPR in)} / \text{Concentration of phenol red out CPR out}$$

Where, Cout (corr) is corrected outlet concentration of the drug, Cout is the outlet concentration of the drug, CRP in is the concentration of phenol red entering the intestinal segment and CRP out is the concentration of phenol red exiting the intestinal segment.

Effective Permeability Coefficient (Peff): The effective permeability coefficient of Propranolol HCl was calculated from the following equation.

$$(Peff) = (-Q*\ln (Cout/Cin) / (2\pi rL)$$

Where, Q is perfusion flow rate , C out is outlet concentration of the drug, C in is inlet drug concentration, r is radius of the rat small intestine, and L is the length of the perfused intestinal segment.

Peff was estimated from the steady-state concentration of compounds which is attained when the concentration of phenol red in the perfusate samples is stable. Generally, the steady-state was reached at 30-40 min after the beginning of the experiment.

***In-vitro* Noneverted Sac (Normal Sac) Study:** Male rats were fasted overnight with free access to water before the experiment. The rats were divided into four groups drug alone (control), Naringin pretreatment (test groups) with high and low dose of drug and verapamil pretreatment (standard P-gp inhibitor) each group consisting of 3 animals.

The rat was exsanguinated after anaesthesia, the small intestine was isolated and cut into segment of equal length (10 cm). The probe drug was dissolved in isotonic phosphate buffered saline (PBS) containing 25 mM glucose. The probe drug solution (1 mL) was filled into the non-everted sac (mucosal side), and both ends of the sac were ligated tightly. Then, the sac was immersed into 40 mL of Phosphate buffer saline containing 25 mM glucose. The medium was pre-oxygenated with 5% CO2/95% O2 and pre-warmed at 37°C for 15 min. Under bubbling with a CO2/O2 mixture gas, the transport of the drug from mucosal to serosal surfaces across the rat intestine was measured by sampling the serosal medium periodically for 90 min. The samples of 2 mL were collected at preset time intervals from the serosal medium and replaced with fresh buffer. The drug transported was measured by using HPLC [8].

Apparent Permeability Coefficient (Papp): The apparent permeability coefficient for Propranolol HCl was calculated from the equation given below [9].

$$Papp = dQ / dt*1 / ACo$$

Where, dQ/dt is the rate of drug transport from mucosal to serosal medium. A is the surface area of the intestinal sac used for the study. C0 is the initial concentration of drug present in the intestinal sac.

Serum and Perfusion Samples Analysis: Propranolol HCl in the serum and perfusion samples was estimated by reverse-phase high-pressure liquid chromatography method.

Analysis of Serum, Intestinal Sac and Perfusion Samples: A Shimadzu HPLC system equipped with a LC- 20AT pump and SPD 20 UV visible detector and RP C18 column (250 mm×4.6 mm ID, particle size 5µm, was used for the HPLC analysis of serum and perfusion samples. The mobile phase used was 50 mM potassium dihydrogen orthophosphate (pH- 3.5): acetonitrile: 50:50, and the elution was monitored at 260 nm with a flow rate of 0.8 mL/min.

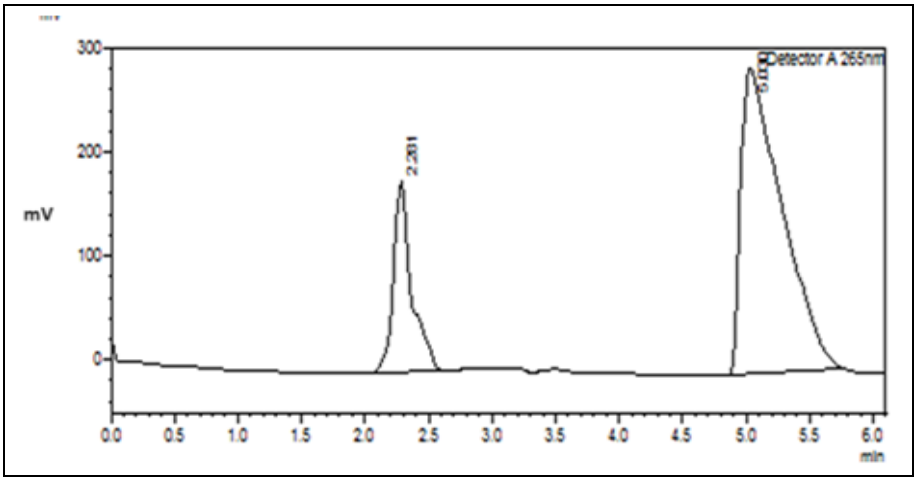

FIG. 1: HPLC CHROMATOGRAPH OF SERUM SPIKED WITH PROPRANOLOL HCL AND METFORMIN. THE RETENTION TIMES OF PROPRANOLOL HCL AND METFORMIN WERE 5.030 AND 2.281 RESPECTIVELY

Sample Preparation: To 100 µL serum, 100µL of Metformin (1mg/ml) was added as internal standard. Add 700 µL of methanol was added to serum samples for protein precipitation and vortexed on a cyclomixer and centrifuged at 13,000 rpm for 10 min. The serum was separated and supernatant is transferred into clean Eppendorf tubes and allow for dryness and add 200 µL mobile phase (ACN: Water pH 3.5; 50:50). The concentration of drug in samples was estimated by using HPLC analysis.

Statistical Analysis: The pharmacokinetic parameters were analysed by using Kinetica software version .Data are presented as means ± SD. Prism 5.0 software (GraphPad) was used for data analysis. Statistical analysis was performed using One-way ANOVA.

RESULTS:

***In-vivo* Pharmacokinetic Study:** The increase in Cmax, AUC, and $t_{1/2}$ of Propranolol HCl (low dose) were found to be 1.00 fold, 1.44-fold and 1.03-fold, respectively, in Naringin - pretreated group compared with drug alone group. The increase in Cmax, AUC, and $t_{1/2}$ of Propranolol HCl (high dose) were found to be 1.56-fold, 2.51-fold, 1.31-folds, respectively in Naringin -pretreated group compared with drug alone.

The increase in Cmax, AUC and t_{max} of Propranolol HCl were found to be 2.13 -fold, 1.24-fold, 1.87-fold, respectively, in verapamil- pretreated group compared with control group. While no significant change was observed in $t_{1/2}$ Propranolol HCl in pre-treated groups compared with drug alone group.

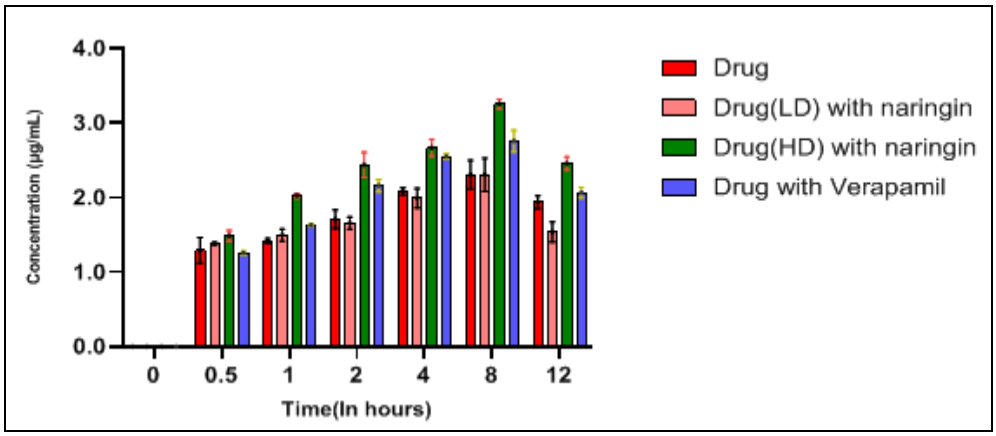

FIG. 2: SERUM CONCENTRATIONS (µG/ML) OF PROPRANOLOL HCL AFTER ADMINISTRATION OF NARINGIN AND VERAPAMIL IN RATS

TABLE 1: MEAN PHARMACOKINETIC PARAMETERS OF PROPRANOLOL HCL AFTER ADMINISTRATION OF NARINGIN AND VERAPAMIL IN RATS

S. no.	PK Parameters	Propranolol HCl	Drug (LD) with Naringin	Drug (HD) with Naringin	Drug with Verapamil
1	C_{max}(µg/ml)	2.133	2.148	3.336	2.603
2	t_{max}	8hr	8hr	8hr	8hr
3	AUC	22.09	31.96	55.56	27.41
4	AUMC	1679.89	1872.87	1926.17	1184.95
5	AUC_{total}	50.03	55.56	77.41	45.90
6	$t_{1/2}$ (hr)	19.58	20.24	25.75	36.65
7	MRT (hr)	15.77	25.93	43.67	53.80
8	Clearance L/hr	214.87	213.37	248.01	176.28
9	Vd ,mL	2578.50	2560.09	2976.19	2115.38

***In-situ* Single-pass Intestinal Perfusion Study:** The intestinal permeability (Peff) of Propranolol HCl was determined in the rat ileum segment by using SPIP technique. Effective permeability values were calculated from the steady state concentration of compounds in the perfusate collected from the outlet. Pretreatment with Naringin for 7 days resulted in significant ($p < 0.05$) increase in effective permeability of Propranolol HCl. The increase in effective permeability was found to be 1.21 -fold, 1.27-fold and 1.01-fold pretreated Naringin with low dose of Propranolol

HCl, high dose of Propranolol HCl and verapamil treated groups compared with the drug alone group.

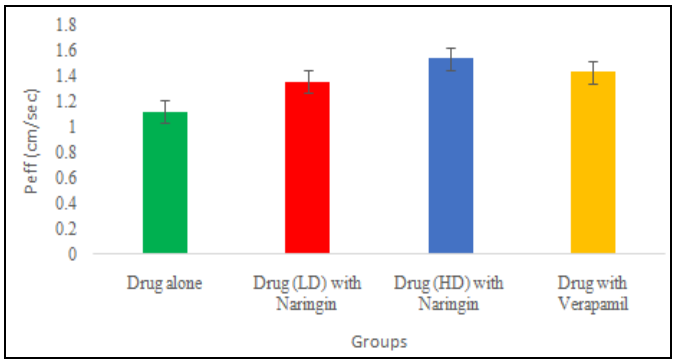

FIG. 3: EFFECTIVE PERMEABILITY OF PROPRANOLOL HCL IN PERFUSION SAMPLE

***In-vitro* Study:** Permeability of Propranolol HCl was determined in rat intestine sac segment using *in-vitro* non-everted sac model and the samples were analyzed by RP-HPLC method and the apparent permeability values were calculated. The permeability coefficient of Propranolol HCl was found to be 0.002071 in a drug alone and 0.002312 in the drug high dose with Naringin which resulted in the significant increase in the intestinal permeability by 1.11 folds (from 0.002071 to 0.002312cm/sec). This is because of decreased p-gp count in conditions resulting in the increased permeability coefficient of drug high dose with Naringin in comparison to drug alone.

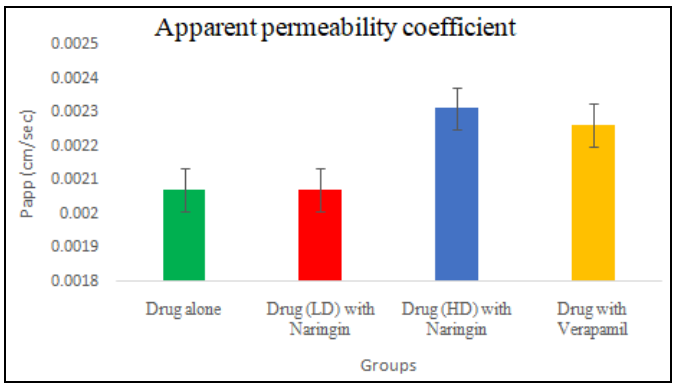

FIG. 4: COMPARISON OF PAPP VARIOUS TREATED GROUPS

DISCUSSION: Dietary supplements containing phytochemicals have the potential to alter the absorption and pharmacokinetics of drugs that could lead to phytochemical-drug interactions and the basic mechanism involved for such interactions is phytochemical mediated modulation of transporters that are responsible for absorption of drug. Furthermore, several phytochemicals were reported to modulate P-gp by directly Interacting with the vicinal ATP-binding site, the steroid-binding site, or the substrate- binding site. Phytochemicals are common component of daily nutrition, are a possible source of interference with absorption processes, due to modulation of efflux transporter P-gp.

P-gp is an energy-dependent efflux pump responsible for decreased drug accumulation in multidrug-resistant cells, and it was found to be concentrated in a small number of species sites. In the intestine, P-gp is located almost exclusively within the brush border on the apical surface of mature enterocytes, and thus significantly restricts Oral absorption and the bioavailability of xenobiotics. The modulation of P-gp has been reported as the cause of drug-drug interactions, when potent P-gp enhancers/inhibitors and P-gp substrates are administered together.

In this study, was used Propranolol HCl as a putative P-gp probe substrate to investigate the possible interaction with naringin in rats by using *in-vitro*, *in-situ* and *in-vivo* models. Moreover, pharmacokinetics of primarily Propranolol HCl depends on the P-gp activity without involvement of metabolism by cytochrome P450. In addition, oral drug absorption was found to be similar in rats and humans. Thus, permeability studies in rat intestine would be more useful for prediction of *in-vivo* absorption of P-gp substrates.

Naringin have enhanced the intestinal transport and oral bioavailability of Propranolol HCl indicating the inhibitory effect on P-gp mediated drug metabolism. In addition, the intake of dietary supplements containing naringin may increase the absorption or oral bioavailability of drugs able to serve as P-gp substrates in addition to Propranolol HCl. Further studies are needed to elucidate the clinical implication of these findings in human volunteers.

CONCLUSION: The present study demonstrates that naringin significantly enhances the intestinal permeability and oral bioavailability of propranolol HCl in rats, most likely by inhibiting the P-glycoprotein (P-gp) efflux transporter. This was consistently supported across the *in-vitro* non-everted sac model, in-situ single-pass intestinal

perfusion, and *in-vivo* pharmacokinetic evaluation, showing improved permeability coefficients and increased systemic exposure (notably AUC and Cmax), with a more pronounced effect at the higher propranolol dose. Overall, naringin appears to act as a promising natural bioenhancer for P-gp substrate drugs such as propranolol; however, these findings also indicate a potential risk of herb/food–drug interactions. Further mechanistic studies and well-controlled clinical investigations in humans are required to confirm the relevance, safety, and therapeutic applicability of this combination.

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CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Catalán-Latorre A, Nácher A, Merino V, Jiménez-Torres NV and Merino-Sanjuán M: In situ study of the effect of naringin, talinolol and protein-energy undernutrition on intestinal absorption of saquinavir in rats. Basic Clin Pharmacol Toxicol 2011; 109(4): 245-52
2. Ryu JM, Chung SJ, Lee MH, Kim CK and Shim CK: Increased bioavailability of propranolol in rats by retaining thermally gelling liquid suppositories in the rectum. J Control Release 1999; 59(2): 163-72.
3. Kesarwani K, Gupta R and Mukerjee A: Bioavailability enhancers of herbal origin: an overview. Asian Pac J Trop Biomed 2013; 3(4): 253-66
4. Sama V, Pagilla B, Chiluka R, Alvala R, Pola RK and Mullangi R: Bioenhancing effects of naringin on atorvastatin. ADMET DMPK 2019; 7(3): 174-182.
5. Mohammad A, Rakesh KP, Hardik P and Sadaf JG: Effect of Naringin co-administration on oral bioavailability of Efavirenz in rabbit. Research Journal of Pharmacy and Technology 2022; 15(4): 1641-7
6. Shaik M and Vanapatla SR: Enhanced oral bioavailability of linagliptin by the influence of gallic acid and ellagic acid in male Wistar albino rats: involvement of p-glycoprotein inhibition. Drug Metab Pers Ther 2019; 34(2).
7. Bedada SK, Appani R and Boga PK: Capsaicin pretreatment enhanced the bioavailability of fexofenadine in rats by P-glycoprotein modulation: *in-vitro*, *in-situ* and *in-vivo* evaluation. Drug Dev Ind Pharm 2017; 43(6): 932-938
8. Salphati L, Childers K, Pan L, Tsutsui K and Takahashi L: Evaluation of a single-pass intestinal-perfusion method in rat for the prediction of absorption in man. J Pharm Pharmacol 2001; 53(7): 1007-13.
9. Athukuri BL and Neerati P: Enhanced oral bioavailability of metoprolol with gallic acid and ellagic acid in male wistar rats: Involvement of cyp2d6 inhibition. Drug Metab Pers Ther 2016; 31(4): 229-34.
10. Athukuri BL and Neerati P: Enhanced Oral Bioavailability of Domperidone with Piperine in Male Wistar Rats: Involvement of CYP3A1 and P-gp Inhibition. J Pharm Pharm Sci 2017; 20: 28-37.
11. Dewanjee S, Dua TK, Bhattacharjee N, Das A, Gangopadhyay M, Khanra R, Joardar S, Riaz M, Feo V and Zia-Ul-Haq M: Natural Products as Alternative Choices for P-Glycoprotein (P-gp) Inhibition. Molecules 2017; 22(6): 871.
12. Bhalani DV, Nutan B, Kumar A and Singh Chandel AK: Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics. Biomedicines 2022; 10(9): 2055.
13. Pope E, Lara-Corrales I, Sibbald C, Liy-Wong C, Kanigsberg N, Drolet B and Ma J: Noninferiority and safety of nadolol vs. propranolol in infants with infantile hemangioma: a randomized clinical trial. JAMA Pediatrics 2022; 176(1): 34–41.
14. Neerati P and BL: Improved bioavailability of linagliptin by resveratrol in rats involvement of permeability glycoprotein (P-gp) inhibition. Int J Pharm Sci & Res 2021; 12(4): 2237-46.
15. Chauhan S, Shekhar R and Tiwari BK: Bioavailability enhancement and characterization of poorly water-soluble drug. Int J Pharm Sci & Res 2024; 15(11): 3182-89.
16. Karthick G, Akiladevi D and Ahamed MI: A Comprehensive review of a new nanosuspension for improving the oral bioavailability of poorly soluble drugs. International Journal of Pharmaceutical and Life Sciences 2022; 3(1): 14-22.

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