IJFANS INTERNATIONAL JOURNAL OF FOOD AND NUTRITIONAL SCIENCES
ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 3, 2022

STUDY OF VARIOUS PHARMACOKINETIC PARAMETERS O F RITONAVIR

Santosh Ramrao Kanwale*[1] , Ashish Agrawal[2]

1.Research Scholar, Faculty of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, M. P. - 458001
2.Professor, Faculty of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, M. P. -458001
*Corresponding Author Email ID- skanwale@gmail.com

ABSTRACT

AIM- The aim of the present investigation is to study the pharmacokinetic parameters of this ritonavir formulation. **MATERIAL & METHODS-** Ritonavir tablet formulations, F 25 developed in the present study exhibited markedly higher dissolution rates (12-14 fold) and dissolution efficiency values when compared to plain ritonavir tablets. F 25 tablets are formulated respectively with solid dispersion of ritonavir in croscarmallose sodium (1:1) complex. After collecting the zero hour blood sample (blank) the product in the study was administered orally in a capsule shell with 10 ml of water. Blood samples (3 ml) were collected from marginal ear vein at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0 and 12.0 hour after administration. The blood samples collected were immediately centrifuged at 5000 rpm and the plasma separated was collected into dry tubes. All the samples were stored under refrigerated conditions prior to assay. Plasma concentration of ritonavir in the samples was determined by the HPLC method described in methods. **RESULTS-** The elimination rate constant (K_{e1}) for ritonavir was found to be 0.14 h^{-1} and the corresponding biological half life ($t_{1/2}$) was found to be 4.92 h. after the oral administration of ritonavir. The absorption rate constant (K_a) was found to be 0.41 h^{1} following the oral administration of ritonavir. Ritonavir was found to be absorbed relatively slowly when given orally and the peak plasma concentration (C_{max}) of 3.5 µg /ml was observed at 4.0 h following oral administration. **CONCLUSION-** Absorption rate (K_a) and bioavailability (AUC) were markedly increased with these products when compared to ritonavir as such.

KEYWORDS

Pharmacokinetics parameters, Ritonavir, elimination rate constant, biological half life, Absorption rate (K_a) and bioavailability (AUC)

INTRODUCTION

Bioavailability is the most important property of a dosage form. It is the ability of the

dosage form to deliver the active ingredient to its site of action in an amount sufficient to elicit the desired pharmacological response. Bioavailability is defined more precisely as the rate and extent of absorption of a drug from its dosage form in to the systemic circulation (Alsenz *et al*., 2007). It is affected by a number of factors related to the drug, dosage form and patient. Dosage form related factors which can produce profound differences in the drug bioavailability include formulation and manufacturing variables such as particle size, the chemical form, solubility of the drug, the type and quantity of excipient used, the compaction pressure etc (Chavda *et al*., 2010). It is well known that the drug bioavailability and efficacy are severely limited by its poor aqueous solubility and dissolution rate. The drug in a solid dosage form (tablet) must undergo dissolution before it is available for absorption in the gastrointestinal tract. Dissolution forms the rate limiting step in the absorption of drug from solid dosage forms especially when the drug is poorly soluble (Chiou and Riegelman, 1971).

Many of the modern drugs belong to the Class II category under biopharmaceutical classification system (BCS), which are characterized by low solubility and high permeability. These drugs are insoluble in water and aqueous fluids in the pH range of 1.0 - 7.5 and exhibit low and variable dissolution and bioavailability. There is a great need to develop technologies for these 'BCS' Class II drugs for enhancing their dissolution rate and bioavailability. The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug product development (Leuner and Dressman, 2000).

Ritonavir, a widely prescribed anti-retroviral drug, belongs to Class II under 'BCS' and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Ritonavir is practically insoluble in water and aqueous fluids. In our previous study, solid dispersion of ritonavir were prepared and evaluated by the help of various excipient however, the formulation i.e. Ritonavir-Croscarmallose sodium prepared in ratio of 1:1 (F25) had significant dissolution rate. So the aim of the present investigation is to study the pharmacokinetic parameters of this formulation.

MATERIAL & METHODS

Ritonavir tablet formulations, F 25 developed in the present study exhibited markedly higher dissolution rates (12-14 fold) and dissolution efficiency values when compared to

plain ritonavir tablets. F 25 tablets are formulated respectively with solid dispersion of ritonavir in croscarmallose sodium (1:1) complex.

The following two products were tested for in vivo performance.

A.-Ritonavir B.-Ritonavir-Croscarmallose sodium (1:1) solid dispersion (SDS 20) complex.

***In vivo* study protocol**

Healthy rabbits of either sex weighing (1.5-2.5kg) were fasted overnight. Ritonavir and its products were administered at dose equivalent to 10 mg / kg of ritonavir. Each product was repeated 6 times (n=6). The *in vivo* experiments were conducted as a crossover RBD study as per the following design with a wash out period of 2 weeks in between the trails (Sharma and Jain, 2011).

Table 1: *In vivo* study protocol

Animal Species	**Remark**	**Time Period**	
		1	**2**
Rabbit	1,2	A	B
	3,4	B	A
	5,6	B	A

After collecting the zero hour blood sample (blank) the product in the study was administered orally in a capsule shell with 10 ml of water. Blood samples (3 ml) were collected from marginal ear vein at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0 and 12.0 hour after administration. The blood samples collected were immediately centrifuged at 5000 rpm and the plasma separated was collected into dry tubes. All the samples were stored under refrigerated conditions prior to assay. Plasma concentration of ritonavir in the samples was determined by the HPLC method described in methods.

From the time versus plasma concentration data, various pharmacokinetic parameters such as peak concentration (C_{max}), time at which peak occurred (T_{max}), area under the curve (AUC), elimination rate constant (K_{e1}), biological half-life ($t_{1/2}$), percent absorbed

to various times and absorption rate constant (K_a) were calculated in each case (Taylor and Zografi, 1997).

Determination of C_{max} and T_{max}

From the time versus plasma concentration curves peak plasma concentration (C_{max}) and time at which peak occurred (T_{max}) were recorded.

Determination of Elimination Rate Constant (K_{e1}) and Biological Half-Life ($t_{1/2}$)

The elimination rate constant (K_{e1}) was calculated from the slope of the linear line in the elimination phase (the 'best fit' linear regression line for the points in the elimination phase was drawn by the method of least squares).

Determination of Absorption to Times and Absorption Rate Constant (K_a)

Percentages absorbed to various times and absorption rate constant (Ka) were calculated from plasma concentration data by the method described by Wagner and Nelson.

Estimation of Area under the Curve [AUC]

The area under the curve is obtained from time versus plasma concentration by applying trapezoidal rule (Gurunath *et al*., 2014).

RESULTS & DISCUSION

Table 1: Plasma Concentration of Ritonavir Following the Oral Administration of Ritonavir and its Products

Time (h)	Plasma Concentration (µg/ml) of Ritonavir	
	Ritonavir	**Ritonavir – Croscarmellose Sodium (CCS) (1:1), SDF 20**
0.5	1.15 ±0.22	4.56±0.33
1.0	1.82±0.33	15.55±0.55
2.0	2.23±0.21	11.23±0.67
3.0	2.77±0.25	8.38±1.43
4.0	3.61±0.29	7.34±1.57
6.0	2.47±0.32	5.73±0.66
8.0	1.82±0.34	3.11±0.78
12.0	0.92±0.11	1.44±0.66

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 3, 2022

Table 2: Summary of Pharmacokinetic Parameters Estimated Following the Oral Administration of Ritonavir and its Products

Product	Cmax (µg/ml)	Tmax (h)	(AUC) 0-12 h	(AUC)0-□ (µg.h/ml)	Ka (h^{-1})	Percent Absorbed in		Kel (h^{-1})	T1/2 (h)
						0.5 hr	1.0 hr		
Ritonavir	3.22	4.1	22.3	31.33	0.41	22.3	39.9	0.14	4.67
Ritonavir – Croscarmellose sodium (1:1)	15.11	1.1	73.21	81.56	4.66	28.5	99.7	0.18	3.82

Pharmacokinetic parameters estimated following the oral administration of ritonavir and its products are given in Table. The elimination rate constant (K_{e1}) for ritonavir was found to be 0.14 h^{-1} and the corresponding biological half life ($t_{1/2}$) was found to be 4.67 h. after the oral administration of ritonavir (Gupta *et al.*, 2003). The absorption rate constant (K_a) was found to be 0.41 h^{-1} following the oral administration of ritonavir. Ritonavir was found to be absorbed relatively slowly when given orally and the peak plasma concentration (C_{max}) of 3.22 µg /ml was observed at 4.0 h following oral administration (Moore and Flanner, 1996; Vaughan and Tucker, 1976). All the pharmacokinetic parameters of absorption namely K_a, C_{max}, T_{max}, percent absorbed to various times and AUC indicated rapid absorption and higher bioavailability of ritonavir when administered as solid dispersion in croscarmellose sodium (SDF 20) Higher C_{max} and shorter T_{max} values were observed with these products when compared to those of ritonavir as such. Percent drug absorbed in 0.5h was found to be 22.3 % respectively with SDF 20 whereas in the case of ritonavir, it was 22.0%. The absorption rate constant (K_a) was found to be 4.66 h^{-1} respectively with ritonavir croscarmellose solid dispersion SDF 20, Where as in the case of ritonavir, K_a was only 0.41 h^{-1}. (AUC) (extent of absorption) was also much higher in the case of solid dispersion in

croscarmellose sodium (SDF 20) when compared to ritonavir. (AUC) was increased from 31.33 µg.h/ml for ritonavir to 81.56 µg. h /ml for solid dispersion SDF 20 (Ahuja *et al*., 2007; Ali *et al*., 2010).

CONCLUSIONS

Pharmacokinetic studies indicated rapid and higher oral absorption of ritonavir when administered as solid dispersion in croscarmellose sodium (SDF 20). Absorption rate (K_a) and bioavailability (AUC) were markedly increased with these products when compared to ritonavir as such.

REFERENCES

1. Alsenz, Jochem, and Manfred Kansy. "High Throughput Solubility Measurement in Drug Discovery and Development." *Advanced drug delivery reviews* 59.7 (2007): 546–567.
2. Chavda, H, C Patel, and I Anand. "Biopharmaceutics Classification System." *Systematic reviews in pharmacy* 1.1 (2010): 62.
3. Chiou, Win Loung, and Sidney Riegelman. "Pharmaceutical Applications of Solid Dispersion Systems." *J. Pharm Sci* 60.9 (1971): 1281–1302.
4. Leuner, Christian, and Jennifer Dressman. "Improving Drug Solubility for Oral Delivery Using Solid Dispersions." *European journal of Pharmaceutics and Biopharmaceutics*50.1 (2000): 47–60.
5. Sharma, Anshu, and C P Jain. "Solid Dispersion: A Promising Technique to Enhance Solubility of Poorly Water Soluble Drug." *International Journal of Drug Delivery* 3.2 (2011): 149.
6. Taylor, Lynne S, and George Zografi. "Spectroscopic Characterization of Interactions Between PVP and Indomethacin in Amorphous Molecular Dispersions." *Pharmaceutical research* 14.12 (1997): 1691–1698.
7. Gurunath, S, Baswaraj K Nanjwade, and P A Patila. "Enhanced Solubility and Intestinal Absorption of Candesartan Cilexetil Solid Dispersions Using Everted Rat Intestinal Sacs." *Saudi Pharmaceutical Journal* 22.3 (2014): 246–257. Print.
8. Gupta, Manish K, Adam Vanwert, and Robin H Bogner. "Formation of Physically Stable Amorphous Drugs by Milling with Neusilin." *Journal of pharmaceutical sciences* 92.3 (2003): 536–551. Print.

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 3, 2022

9. Moore, Jeffrey W, and Henry H Flanner. "Mathematical Comparison of Dissolution Profiles."*Pharmaceutical Technology* 20.6 (1996): 64–74. Print.
10. Vaughan, D P, and G T Tucker. "An Analysis of the Applications of Dissolution Efficiency."*Journal of Pharmacy and Pharmacology* 28.12 (1976): 932–933.
11. Ahuja, Naveen, Om Prakash Katare, and Bhupinder Singh. "Studies on Dissolution Enhancement and Mathematical Modeling of Drug Release of a Poorly Water-Soluble Drug Using Water-Soluble Carriers." *European Journal of Pharmaceutics and Biopharmaceutics* 65.1 (2007): 26–38. Print.
12. Ali, W, Adrian Christopher Williams, and Clare Frances Rawlinson. "Stochiometrically Governed Molecular Interactions in Drug: Poloxamer Solid Dispersions." *International journal of pharmaceutics* 391.1 (2010): 162–168.