



PRECLINICAL PHARMACOKINETIC EVALUATION OF STAVUDINE TABLETS FORMULATED BY DIRECT COMPRESSION METHOD

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ABSTRACT

Stavudine tablets formulated by direct compression method employing new excipients developed (Lubritose-MCC, Starch phosphate, PGS-PVP) gave very rapid dissolution fulfilling all the official specifications with regard to drug content, friability, hardness, disintegration time and dissolution rate. The objective of the present study is preclinical pharmacokinetic evaluation of stavudine tablets formulated using the new excipients developed by direct compression method to assess their *in vivo* performance in comparison to a market product. With all the four products tested stavudine was found to be absorbed rapidly and peak concentration is achieved in 2 h and later the plasma concentrations were also decreased rapidly. All the pharmacokinetic parameters estimated namely K_{el} , $t_{1/2}$, MRT, K_a and AUC are similar with all the four products. There was no significant difference in each case ($P > 0.05$). Thus, the pharmacokinetic evaluation indicated that the stavudine tablets formulated employing new excipients (commercial and laboratory made) are comparable to the market product with regard to *in vivo* performance.

Keywords: Stavudine tablets, Direct compression, Preclinical, Pharmacokinetic evaluation

INTRODUCTION

Direct compression is the preferred method for the preparation of tablets¹. It offers several advantages^{2,3}. Notable among them are (i) It is economical compared to wet granulation since it requires fewer unit operations (ii) More suitable for moisture and heat sensitive APIs since it eliminates wetting and drying steps (iii) Changes in dissolution profile are less likely to occur in tablets made by direct compression method on storage than in those made from granulations⁴. This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms⁵. Disintegration or dissolution is the rate limiting step in absorption in the case of tablets of poorly soluble API prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution. Formulation of tablets by direct compression method requires an excipient with good flow and compressible characteristics. Though several directly compressible excipients are available commercially there is a continued need for development of new efficient and cost effective excipients for direct compression. We have earlier reported^{6,7} preparation and evaluation of directly

compressible vehicles by co-processing method. The newly developed excipients were suitable for formulation of tablets by direct compression method. Formulation and *in vitro* evaluation of stavudine tablets by direct compression method is also reported⁸ earlier. Stavudine tablets formulated by direct compression method employing new excipients developed gave very rapid dissolution fulfilling all the official specifications with regard to drug content, friability, hardness, disintegration time and dissolution rate. The objective of the present study is preclinical pharmacokinetic evaluation of stavudine tablets formulated by direct compression method to evaluate their *in vivo* performance in comparison to a market product.

EXPERIMENTAL

The following products were tested for *in vivo* pharmacokinetic evaluation

1. Formulation SF3 (stavudine tablets formulated employing Lubritose – MCC)
2. Formulation SF4 (stavudine tablets formulated employing Starch Phosphate)
3. Formulation SF7(stavudine tablets formulated employing PGS-PVP co-processed excipient)
4. Market Product (VIROSTAV 30 Tablets of Ranbaxy Laboratories, New Delhi)

In-vivo study protocol:

The study was conducted as a crossover RBD in healthy rabbits of either sex ($n = 6$) with a wash out period of one month. The *in vivo* protocols were approved by Institutional Animal Ethics Committee. Healthy rabbits of either sex weighing 1.5 – 2.5 Kg were fasted

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over night. The products were administered at a dose of 30 mg of stavudine per rabbit (i.e., one tablet formulated). After collecting the zero hour blood sample (blank), the product in the study was administered orally with 10 ml of water. Blood samples (2 ml) were collected from marginal ear vein at 0.5, 1, 2, 3, 4, 6, 8 and 12 h after administration. Samples were collected in heparinized tubes and were centrifuged at 10000 rpm for 10 min. The plasma separated was collected into dry tubes and the samples were stored under refrigerated conditions at 4-5° C prior to assay for stavudine on the same day. Plasma concentrations of stavudine were determined by an earlier reported⁹ HPLC method with certain modifications as follows.

Instrumentation: The following instrumentation system was used

The HPLC system (make: M/s Shimadzu Corporation, Japan.) consisted of UV – Visible detector (Shimadzu, model: SPD – 10 AVP), C – 18 column (Phenomenex, DESC: Gemini 5 μ C18 110A, Size: 250 x 4.6 mm, S/No: 288063 – 23), 2 pumps (Model: LC – 10 ATVP) and a micro syringe of capacity 25 μ l (Model: Microliter[®] # 702, Mfd. by: M/s Hamilton). The mobile phase consists of a mixture of methanol and water (15:85 v/v). The mobile phase was filtered through 0.45 μ membrane filter before use and was run at a flow rate of 1ml / min. The column effluent was monitored at 265 nm.

Estimation of Stavudine in Plasma:

For the estimation of stavudine in plasma samples, a calibration curve was constructed initially by analyzing plasma samples containing known amounts of stavudine as follows. To a series of tubes containing 0.4ml of plasma in each, 0.1 ml drug solution containing 1, 2, 4, 6 and 8 μ g of stavudine were added and mixed. To each tube 1 ml of acetonitrile was added, mixed thoroughly and centrifuged at 5000 rpm for 20 min. The organic layer (0.5 ml) was taken into a dry tube and the acetonitrile was evaporated. To the dried residue 0.5ml of mobile phase (a mixture of methanol-water 15:85 v/v) was added and mixed for reconstitution. Subsequently 20 μ l were injected into the column for HPLC analysis. In the pharmacokinetic studies plasma (0.5 ml) was analyzed for stavudine as described above.

From the time Vs 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_{el}), biological half-life ($t_{1/2}$), percent absorbed to various times and absorption rate constant (K_a) were calculated in each case as per known standard methods^{10, 11} assuming one compartment model.

RESULTS AND DISCUSSION

Pharmacokinetic evaluation was done on stavudine tablets formulated by direct compression method employing Lubritose – MCC (SF3), Starch Phosphate (SF4) and PGS-PVP co-processed excipient (SF7) with a view to evaluate their *in vivo* performance in comparison to a market product. Plasma concentrations of stavudine following the oral administration of stavudine tablets formulated and Market Product in rabbits (n = 6)

are shown in Fig.1. A summary of the pharmacokinetic parameters estimated following the oral administration of stavudine products tested is given in Table 1. The elimination rate constant (K_{el}) for stavudine was found to be 0.3119 h^{-1} , 0.3202 h^{-1} , 0.3165 h^{-1} and 0.3128 h^{-1} respectively following the administration of SF3, SF4, SF7 and Market product. The corresponding half - life was found to be 2.22 h, 2.16 h, 2.17h and 2.21h respectively. The mean residence time (MRT) was found to be 3.97 h, 3.98 h, 3.85 h and 3.92h respectively with SF3, SF4, SF7 and Market product. The absorption rate constant (K_a) was found to be 1.1020 h^{-1} , 1.045 h^{-1} , 1.0985 h^{-1} and 1.1030 h^{-1} respectively with SF3, SF4, SF7 and Market product. With all the four products tested stavudine was found to be absorbed rapidly and peak concentration is achieved in 2 h and later the plasma concentrations were also decreased rapidly. Based on AUC_0^∞ the relative bioavailability of stavudine from formulations SF3, SF4 and SF7 was found to be 94.13, 101.02 and 93.59 % respectively when compared to Market product (100%).

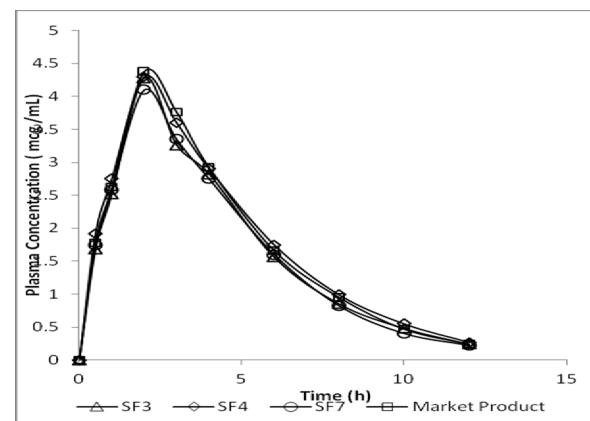


Fig.1: Plasma Concentrations of Stavudine Following the Oral Administration of Stavudine Tablets Formulated and Market Product in Rabbits (n = 6)

Table 1: Summary of Pharmacokinetic Parameters Estimated Following the Oral Administration of Stavudine Tablets Formulated and Market Product in Rabbits (n = 6)

Pharmacokinetic Parameter	SF3	SF4	SF7	Market Product
C_{max} (μ g/ml)	4.28±0.22	4.30±0.21	4.10±0.21	4.38±0.32
T_{max} (h)	2.0	2.0	2.0	2.0
K_{el} (h^{-1})	0.3119	0.3202	0.3165	0.3128
$t_{1/2}$ (h)	2.22	2.16	2.18	2.21
$(AUC)_0^{24}$ (μ g.h/ml)	26.85	28.45	26.92	28.25
$(AUC)_0^\infty$ (μ g.h/m ¹)	27.63	29.65	27.47	29.35
K_a (h^{-1})	1.1020	1.1045	1.0985	1.1030
MRT (h)	3.97	3.98	3.85	3.92
BA (%)	94.13	101.02	93.59	100.0

CONCLUSION

The pharmacokinetic evaluation indicated that the stavudine tablets formulated employing new excipients (commercial and laboratory made) are comparable to the market product with regard to *in vivo* performance.

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