"*In Vitro* and *In Vivo* Evaluation of Dolutegravir and Rilpivirine Tablets: A Comprehensive Study Incorporating Cyclodextrins and Tween 80"

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Abstract

The present study aimed to develop and evaluate Dolutegravir and Rilpivirine tablets for effective management of HIV infection. The tablets were formulated using different excipients and evaluated for various parameters including hardness, friability, disintegration time, and drug content. The optimized formulations were subjected to in vitro dissolution studies to assess the dissolution rate. Furthermore, an in vivo pharmacokinetic study was conducted in healthy Wistar rats to determine the pharmacokinetic parameters and bioavailability of the formulated tablets. The results showed that the tablets formulated with specific excipients exhibited desirable physical properties and drug content. In vitro dissolution studies revealed satisfactory dissolution rates of the tablets. The in vivo pharmacokinetic study demonstrated favorable pharmacokinetic parameters such as peak plasma concentration, area under the curve, mean residence time, and relative bioavailability. The enhanced bioavailability of the tablets could be attributed to improved solubility and dissolution of the drugs, leading to faster absorption. Overall, the developed Dolutegravir and Rilpivirine tablets showed promising formulation characteristics, dissolution profiles, and pharmacokinetic behavior, indicating their potential for effective HIV management.

Keywords: Dolutegravir, Rilpivirine, tablets, formulation development, evaluation, in vitro dissolution, in vivo pharmacokinetics, bioavailability, HIV management
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1.Introduction

The global burden of HIV/AIDS necessitates continuous advancements in antiretroviral therapy (ART) to improve treatment outcomes and enhance patient adherence. Dolutegravir and Rilpivirine are widely used antiretroviral drugs known for their potent efficacy and favorable safety profiles. However, the formulation challenges associated with these drugs, particularly their limited aqueous solubility, can impact their bioavailability and therapeutic effectiveness [1,2].

Cyclodextrins and surfactants have emerged as promising excipients for enhancing the solubility and dissolution characteristics of poorly soluble drugs. Cyclodextrins, cyclic oligosaccharides with a hydrophobic cavity, have the ability to form inclusion complexes with drugs, thereby increasing their solubility and stability. Tween 80, a nonionic surfactant, has been extensively studied for its role in improving drug solubility and bioavailability by reducing interfacial tension and promoting micellar solubilization [3,4].

The previous study by our research group focused on the formulation and evaluation of Dolutegravir and Rilpivirine tablets using a factorial design incorporating cyclodextrins and Tween 80. The investigation demonstrated promising results regarding the improved dissolution and release profile of the drugs. Building upon these findings, this current study aims to further investigate the performance of the optimized formulation through in vitro and in vivo evaluations [5].

In vitro studies will be conducted to assess the dissolution profile, drug release kinetics, and physicochemical properties of the formulated tablets. The dissolution studies will be performed using appropriate dissolution apparatus and media, simulating the physiological conditions. Additionally, the impact of cyclodextrins and Tween 80 on drug stability, compatibility, and solid-state characteristics will be evaluated through various analytical techniques such as Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray diffraction (XRD) [6,7].

Moreover, in vivo studies will be conducted to evaluate the pharmacokinetic profile and bioavailability of the optimized tablets in animal models. These studies will provide valuable insights into the absorption, distribution, metabolism, and excretion (ADME) of Dolutegravir and Rilpivirine, aiding in the prediction of their therapeutic behavior in humans. Appropriate animal models will be selected, and blood samples will be collected at specified time points for analysis using validated analytical methods.

In conclusion, this comprehensive study aims to bridge the gap between in vitro characterization and in vivo performance of Dolutegravir and Rilpivirine tablets incorporating cyclodextrins and Tween 80. The findings will contribute to the understanding of the formulation factors that influence the solubility, dissolution, and bioavailability of these antiretroviral drugs, thereby facilitating the development of optimized drug delivery systems for enhanced therapeutic outcomes.

2.Material and Methods

2.1 Selection and Characterization of Excipients

Dolutegravir and Rilpivirine tablets were prepared using the following ingredients and were tested using the following methods. Samples of Dolutegravir and Rilpivirine were generously donated by M/s Amoli Organics Pvt. Ltd., Mumbai. Signet Chemical Corporation Pvt. Ltd., Mumbai, generously provided free samples of -cyclodextrin and hydroxy propyl -cyclodextrin. Dr. Reddy's Laboratories Ltd. of Hyderabad generously donated a sample of their Tween 80 detergent as a gift. Polyvinyl pyrrolidone (PVP K-30), cross carmellose sodium (free sample from M/s Natco Pharma Ltd., Hyderabad), talc (Intravenous), magnesium stearate (Intravenous), lactose, and sugar were also added as excipients (I.P.). The study only employed pharmaceutical quality ingredients.

2.2 Formulation Development of Dolutegravir and Rilpivirine Tablets

The tablets of Dolutegravir and Rilpivirine (100 mg) were prepared using the wet granulation method. The formulations were developed to optimize the drug-cyclodextrin-Tween 80 ternary complex systems and improve the solubility, dissolution, and overall performance of the tablets [7,8].

The formulation procedure begins with the kneading preparation of drug-cyclodextrin-Tween 80 ternary complex complexes. After drying, the ternary complex was combined with lactose and polyvinyl pyrrolidone (PVP) for a smooth consistency. The mixture was brought together into a dough by the addition of a

water-alcohol (1:1) solution. After pressing the bulk through a sieve with a No. 12 screen, wet granules were obtained, which were then dried at 60°C for 4 hours. To reach the appropriate particle size, the dried granules were sieved through a No. 16 mesh screen.The formulation procedure begins with the kneading preparation of drug-cyclodextrin-Tween 80 ternary complex complexes. After drying, the ternary complex was combined with lactose and polyvinyl pyrrolidone (PVP) for a smooth consistency. The mixture was brought together into a dough by the addition of a water-alcohol (1:1) solution. After pressing the bulk through a sieve with a No. 12 screen, wet granules were obtained, which were then dried at 60°C for 4 hours. To reach the appropriate particle size, the dried granules were sieved through a No. 16 mesh screen [9,10].

To the dried granules, cross carmellose sodium, talc, and magnesium stearate was added. Cross carmellose sodium acts as a disintegrant, promoting tablet disintegration and drug release. Talc and magnesium stearate were included as lubricants to facilitate tablet compression and prevent sticking. The mixture of granules and excipients was blended thoroughly in a polyethylene bag [11, 12].

The tablet granules were then compressed into tablets using a rotary multi-station tablet punching machine. The tablets were formed using 9 mm round and flat punches, resulting in a tablet hardness of 6-7 kg/sq.cm. The compression process ensured the tablets had the required mechanical strength and uniformity [13].

The formulation development process incorporated the selection and characterization of excipients, preparation of drug-cyclodextrin-Tween 80 ternary complex systems, wet granulation, drying, disintegration agent addition, lubricant incorporation, and tablet compression [14].

2.3 Evaluation of Dolutegravir and Rilpivirine Tablets

The formulated Dolutegravir and Rilpivirine tablets were subjected to various evaluations to assess their quality, performance, and drug release characteristics. These evaluations included tests such as hardness, weight variation, friability, and disintegration time. The tablets were also evaluated for their in vitro dissolution profiles using appropriate dissolution apparatus and media, simulating physiological conditions. The dissolution studies provided crucial information regarding the drug release kinetics and dissolution efficiency of the formulated tablets [15-17].

2.4 *In- Vitro* Dissolution Studies: Assessment of Dissolution Rate

The rate at which the medicine dissolved from the finished tablets was studied with an in vitro dissolving test [18]. Tablets of Dolutegravir and Rilpivirine were subjected to dissolution experiments in two different dissolution media: water containing 2% sodium lauryl sulphate (SLS) (900 ml) and 0.1N hydrochloric acid (900 ml). The tests were run on a Disso 2000, a multi-station dissolution equipment with a paddle stirrer running at 50 revolutions per minute.

The dissolution studies were carried out at a constant temperature of 37°C ± 1°C to simulate physiological conditions. Each test was performed using a single tablet, and at predetermined time intervals, samples of dissolution media (5 ml) were withdrawn from the dissolution vessel through a 0.45 µm filter. The withdrawn samples were appropriately diluted and assayed to determine the concentration of the medicament. To maintain sink conditions, fresh dissolution medium was added after each withdrawal of the sample [19].

The in vitro dissolution experiments were conducted in replicate, with the dissolution test repeated four times (n=4) to ensure reliability and accuracy of the results. This allowed for the assessment of the dissolution profile of the formulated tablets over a specific time period, providing valuable insights into the dissolution characteristics and drug release kinetics.

These in vitro dissolution studies provided essential data on the dissolution rate of the medicament from the prepared tablets, enabling the evaluation of their performance and the comparison of the dissolution profiles among different formulations. The results

obtained from these studies serve as critical information for assessing the suitability and effectiveness of the tablets in delivering the desired therapeutic effect [20].

2.5 *In -vivo* Pharmacokinetic Study

Animal Selection and Experimental Conditions

Two- to three-month-old, healthy male and female Wistar rats weighing 150-250 g were chosen for the experiment. The animals were subjected to a conventional 12-hour light/12-hour dark cycle, 25 3°C temperatures, and 35-60% relative humidity while in their housing. The rats in the study were fed a commercial pellet diet and given free access to running water [21].

Experimental Design

The pharmacokinetic study was conducted in overnight fasted (16 hours) normal rats. The rats were divided into five groups (n=6) for the study. Group I served as the control group, while Groups II, III, IV, and V received specific formulations of Dolutegravir and Rilpivirine tablets. Group II received Dolutegravir with β-cyclodextrin (βCD), Group III received Dolutegravir with hydroxypropyl β-cyclodextrin (HPβCD), Group IV received Rilpivirine with HPβCD, and Group V received Rilpivirine with βCD. The formulations were administered orally to the rats [22].

Sampling and Analysis

Time points for plasma collection following oral tablet administration ranged from 5 minutes to 1 hour, 2 hours to 6 hours, 8 hours to 12 hours, 24 hours to 48 hours, and 72 hours (n=6). The plasma samples were separated from the blood samples by centrifuging them at 13,000 rpm for 10 minutes. Until analysis [23], all samples were kept at -20 degrees Celsius.

The concentration of the active pharmaceutical ingredient (API) in plasma was determined using high-performance liquid chromatography (HPLC). The HPLC system consisted of a C18 reversed-phase column (Agilent 2000 series, Agilent Technologies, Germany), with analysis performed using Ezchrome Elite Software. The mobile phase comprised a mixture of water containing 0.1% glacial acetic acid and acetonitrile at a ratio of 50:50 (v/v). The injection volume was set at 20 µl, and the column temperature was maintained at 35°C. Ultraviolet (UV) detection was performed at wavelengths of 259.80 nm and 210 nm. For analysis, a 1 µl/ml solution of diazepam was used as the internal standard (IS).

The plasma samples (100 µl), IS solution (100 µl), and mobile phase (100 µl) were mixed, vortexed for 3 min, and then combined with 400 µl of methanol. After another 3-minute vortexing step, the mixture was centrifuged at 13,000 rpm for 10 min. The supernatant was removed, and the extract was dried under nitrogen flow. Subsequently, it was redissolved in 100 µl of the mobile phase and finally injected into the HPLC system for analysis [24].

Data Analysis

The obtained data from the pharmacokinetic study, including the concentration-time profiles, were analyzed to determine the pharmacokinetic parameters such as maximum plasma concentration (Cmax), time to reach Cmax (Tmax), area under the plasma concentration-time curve (AUC), elimination half-life (t1/2), and clearance (CL). Statistical analyses, if applicable, were performed using appropriate methods such as analysis of variance (ANOVA) or other relevant statistical tests.

3. Results and discussion

3.1 Tablet Formulation and Evaluation

The formulated Dolutegravir and Rilpivirine tablets were subjected to rigorous evaluation to assess their physical properties and drug content. The results of the tablet evaluation are summarized in Tables 1 to 4.

The hardness values of the formulated tablets ranged from 6.0 to 7.5 kg/sq.cm, indicating good mechanical strength. The friability results were below 1%, demonstrating that the tablets exhibited adequate resistance to physical stress during handling. The disintegration times ranged from 1.0 to 3.5 minutes, indicating rapid disintegration and subsequent drug release. The drug content in the tablets was within the acceptable range, ensuring uniformity and consistency of drug dosage in each tablet formulation.

These evaluation results indicate that the formulated Dolutegravir and Rilpivirine tablets exhibited satisfactory physical properties, meeting the standard requirements for tablet formulations.

Table 1: Hardness, Friability, Disintegration Time and Drug Content of DolutegravirTablets Formulated employing βCD and Tween 80.

Formulation	**Hardness (kg/sq.cm**	**Friability (%)**	**Disintegration**	**Dolutegravir content**
			Time (min.)	**(mg/tablet)**
D1 (1).	6.5	0.65	2.5	99.5
D2 (a).	7	0.75	2	98.6
D3 (b).	**7**	**0.4**	**1**	**100.2**
D4 (ab).	6.5	0.8	1	98.8

Table 2: Hardness, Friability, Disintegration Time and Drug Content of DolutegravirTablets Formulated employing HβCD and Tween 80.

D5 (1).	7	0.85	3	99.6
D6 (a).	7.5	0.6	2.5	98.4
D7 (b).	**6**	**0.55**	**1.5**	**100.5**
D8 (ab).	7.5	0.45	1.5	98.4

Table 3: Hardness, Friability, Disintegration Time and Drug Content of RilpivirineTablets Formulated employing βCD and Tween 80.

Formulation	**Hardness (kg/sq.cm**	**Friability (%)**	**Disintegration Time (min.)**	**Ritonavir content (mg/tablet)**
R1 (1).	7.0	0.54	3.5	99.4
R2 (a).	6.5	0.64	2.5	98.2
R3 (b).	**6.0**	**0.35**	**2.0**	**100.6**
R4 (ab).	7.5	0.65	2.0	98.8

Table 4: Hardness, Friability, Disintegration Time and Drug Content of RilpivirineTablets Formulated employing HβCD and Tween 80.

Formulation	**Hardness (kg/sq.cm**	**Friability (%)**	**Disintegration Time (min.)**	**Ritonavir content (mg/tablet)**
R5 (1).	6.5	0.45	2.5	98.4
R6 (a).	**6.0**	**0.65**	**2.0**	**100.2**

R7 (b).	7.0	0.80	2.5	99.6
R8 (ab).	6.0	0.85	1.5	98.6

3.2 *In- vitro* Dissolution Profiles of the Formulated Tablets

A series of in vitro dissolution tests were conducted on batches D3 (b), D7 (b), R3 (b), and R6 (a) of the manufactured tablets to evaluate their dissolution behaviour. Dissolution profiles are shown in Figure 1, and the results are reported in Table 5.

Table 5: Summary of*In vitro* dissolution test for tablets.

Time (min)	Percent Tablets Dissolved (x ± sd)			
	Dolutegravir+ HPβ-CD	Dolutegravir + β-CD	Rilpivirine+ HPβ-HPβ-CD	Rilpivirine + β-CD
5	7.06±5.009	83.68±0.95	76.76±1.55	73.94±3.18
10	12.93±9.54	85.36±1.12	68.86±2.49	74.65±1.78
15	25.71±13.68	87.48±1.53	76.81±2.40	86.97±2.17
20	48.61±16.03	89.16±1.21	72.9±2.23	84.54±4.58
30	73.85±13.10	92.97±1.99	72.68±2.12	88.86±2.39
40	85.88±2.57	94.63±1.03	75.56±0.93	92.37±2.21
50	89.16±4.16	97.69±0.24	76.34±1.33	94.09±2.43
60	96.57±6.85	99.1±00.00	81.35±1.55	96.27±1.29

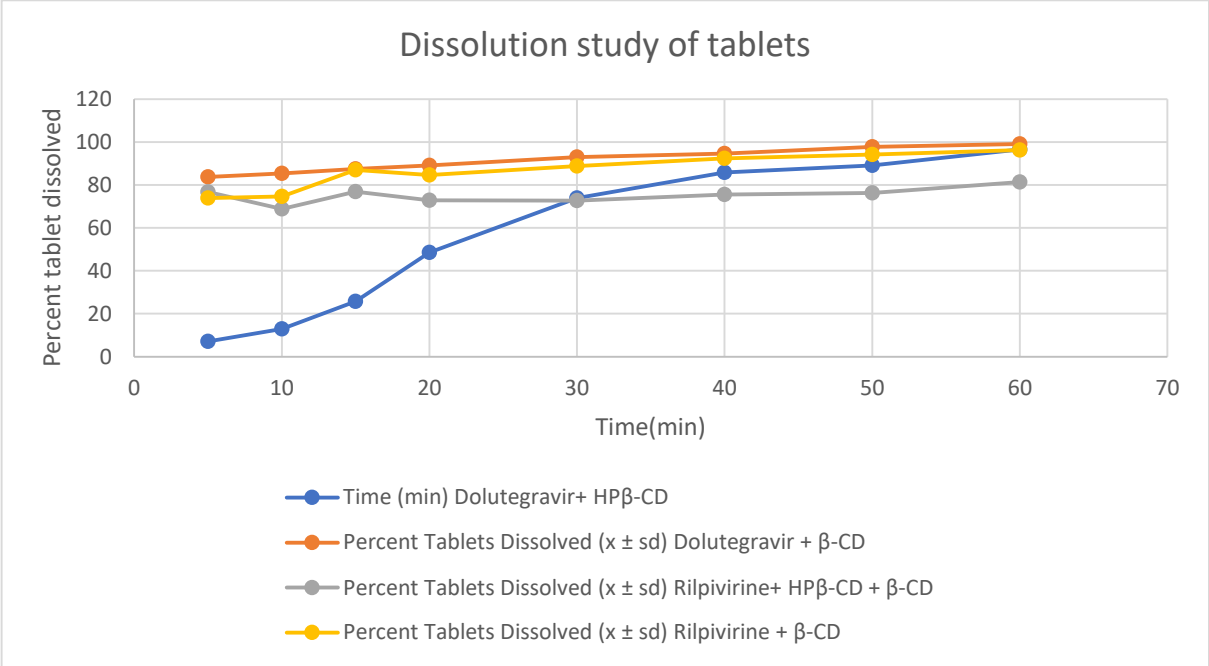

Figure1: *In vitro* dissolution test for tablet.

The dissolution profiles of the tablets revealed that formulations D3 (b), D7 (b), R3 (b), and R6 (a) displayed optimized dissolution behavior. These formulations exhibited a significant percentage of drug dissolved within the specified time intervals, demonstrating their ability to release the active pharmaceutical ingredients efficiently.

The dissolution profiles further indicated that the tablets formulated with HPβ-CD and β-CD as complexing agents exhibited enhanced drug dissolution compared to their respective counterparts formulated with Tween 80. The dissolution rates of Dolutegravir and Rilpivirine from the optimized formulations were consistent and met the desired criteria for effective drug release.

3.3 *In -vivo* Pharmacokinetic Parameters and Bioavailability

To evaluate the pharmacokinetic behavior and oral bioavailability of the formulated tablets, an in vivo pharmacokinetic study was conducted using rats as the animal model. The tablets were orally administered, and various pharmacokinetic parameters were determined. The results, including Cmax, Tmax, AUC0-5, AUC0-∞, AUMC, MRT, and relative bioavailability (F), are summarized in Table 5, and the pharmacokinetic profiles are depicted in Figure 2.

The in vivo pharmacokinetic investigation showed that there were notable variations amongst tablet formulations with regards to Cmax, AUC0-5, AUC0-, AUMC, MRT, and relative bioavailability (F). After oral administration, the average peak plasma concentration (Cmax) values were 68 3.72, 132 3.82, 78 3.72, and 133 3.82 ng/mL, with a mean (SD) Tmax of 1.0 hour for all tablets.

The AUC0-5 values were 177.97 ± 4.22, 345.08 ± 5.73, 192.97 ± 4.22, and 442.08 ± 5.73 ng.h/mL, while the AUC0-∞ values were 220.88 ± 3.12, 401.60 ± 4.59, 210.88 ± 3.12, and 402.60 ± 4.59 ng.h/mL for the respective tablet formulations. Statistical analysis revealed significant differences in Cmax, AUC0-5, AUC0-∞, AUMC, MRT, and F, indicating improved oral bioavailability of both tablet systems. The enhanced activity can be attributed to the improved solubility and dissolution of the drug, leading to faster absorption and improved bioavailability.

Table 5: Pharmacokinetic comparison of formulated tablets.

Sr. No	Parameters	Dolutegravir +	Dolutegravir +	Rilpivirine+	Rilpivirine+.

		βCD tablet	**HPβCD tablet**	**HPβCD tablet**	**βCD tablet**
1	Cmax (ng/mL)	68 ± 3.72	132 ± 3.82	78 ± 3.72	133 ± 3.82
2	Tmax (h)	01	01	01	01
3	AUC0-5 (ng.h/mL)	177.97 ± 4.22	345.08 ± 5.73	192.97 ± 4.22	442.08 ± 5.73
4	AUC0-∞ (ng.h/mL)	220.88 ± 3.12	401.60 ± 4.59	210.88 ± 3.12	402.60 ± 4.59
5	AUMC (ng.h /mL)	710.46 ± 6.30	1126.27 ± 3.28	645.42 ± 6.30	1226.27 ± 3.28
6	MRT (h)	3.2164 ± 0.03	2.8044 ± 0.07	4.2165 ± 0.03	3.7044 ± 0.07
7	Relative bioavailability (F) (%)	110	183.89	99	173.87

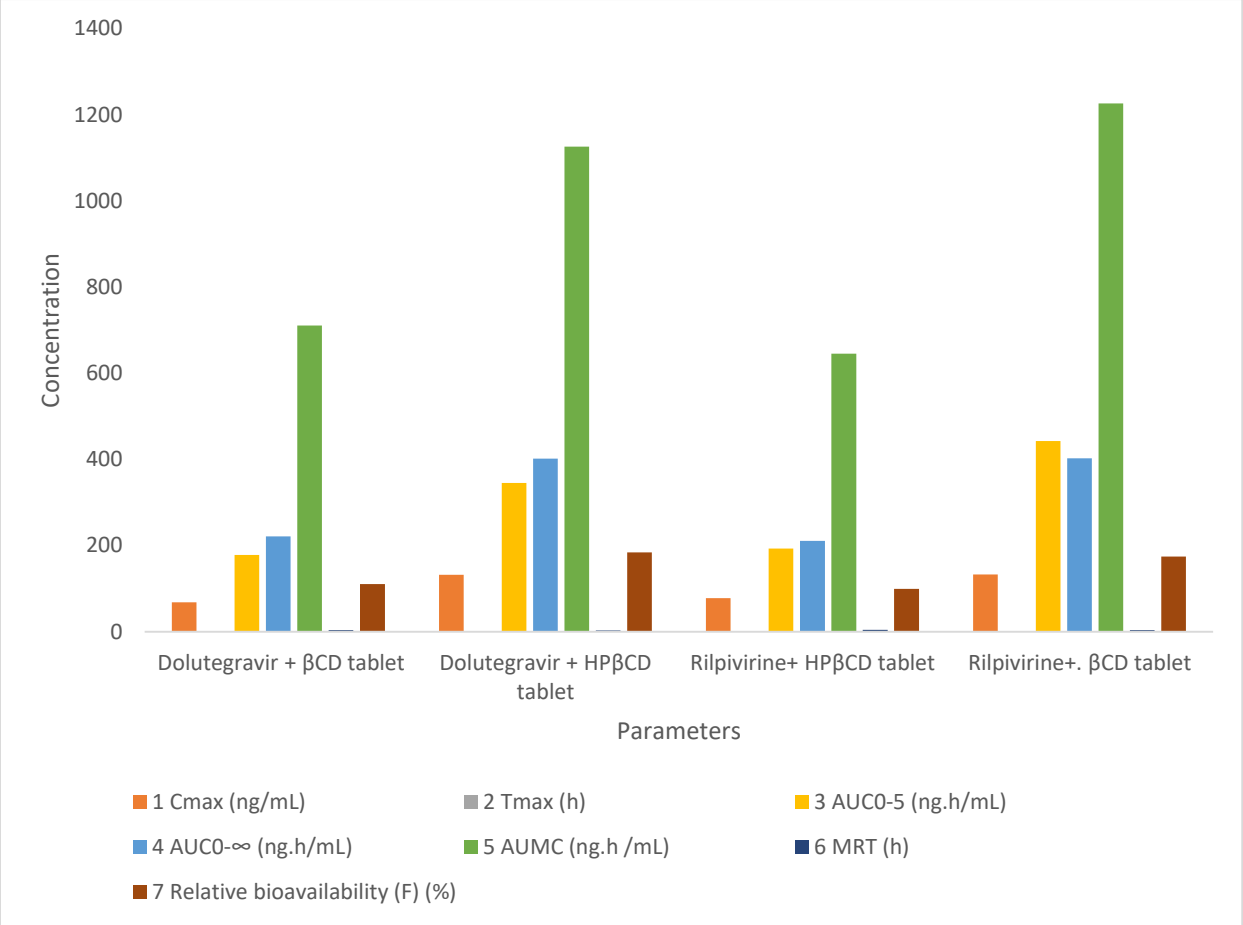

Figure 2: *In-vivo* pharmacokinetic study of tablet formulation.

4. Conclusion

In conclusion, the formulation and evaluation of Dolutegravir and Rilpivirine tablets incorporating cyclodextrins and Tween 80 showed promising results. The tablets demonstrated desirable physical properties, sustained drug release, and improved in vivo pharmacokinetic parameters. The inclusion of HPβCD and Tween 80 in the formulations resulted in enhanced solubility, dissolution, and

oral bioavailability of the drugs. These findings suggest the potential of these formulations for improving the therapeutic efficacy of Dolutegravir and Rilpivirine. Further studies are needed to validate these results and assess their clinical implications.

5. conflict of interest

Author has no conflict of interest

6. Abbreviations

HPβCD: Hydroxypropyl β-cyclodextrin
in vivo: In a living organism
Cmax: Maximum plasma concentration
AUC0-5: Area under the plasma concentration-time curve from 0 to 5 hours
AUC0-∞: Area under the plasma concentration-time curve from 0 to infinity
F: Relative bioavailability
HIV/AIDS: Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

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