Formulation of Taste Masked Orodispersible Tablets of Tramadol Hydrochloride and Comparative In Vitro Dissolution Profile With Market Product

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Abstract:

In this study a taste masked orodispersible tablets of Tramadol Hydrochloride were prepared and evaluated for comparative *in vitro* dissolution profile with commercially available market product**.** In this study to assess the bioequivalence of two different product of Tramadol Hydrochloride using in vitro multipoint dissolution profile study by using UV-Visible spectrophotometry. Dissolution medium were purified water & three buffer solutions of different pH like pH 1.2 (hydrochloric acid solution), pH 4.5 (acetate buffer solution), and pH 6.8 (phosphate buffer solution). The Test and Reference tablets were also evaluated to general quality test of dispersible tablets like weight variation, hardness, friability, disintegration time or dispersion time water absorption ratio, wetting time and assay. Both Test & Reference product were complied with the official specification for uniformity of weight, friability and disintegration time and Assay. The dissolution profiles showed there are no significant change in drug release of Test and Reference product of Tramadol Hydrochloride Tablets. The tablets were further analysed for similarity between the dissolution profile of Test and Reference product through determination of difference factor (*f1*), similarity factor (*f2*) by calculating the dissolution results of both Test and Reference product at multi time point after 5, 10, 15, 30, 45 minutes. The results similarity factor shows that the both Test and Reference product tablets in this study were bioequivalent.

Keywords: Dissolution profile, Similarity factor *(f2)*, Tramadol Hydrochloride.

INTRODUCTION

Tramadol hydrochloride, a centrally acting opioid analgesic is used in acute, moderate as well as severe pain [1]. Arthritic as well as neuralgic patients require tramadol routinely for longer duration [2]. Various dosage forms of tramadol hydrochloride available in market for systemic administration. Tramadol hydrochloride used for numbers of conditions like trauma, renal or biliary colic, and pain during labor. Chronic pain of malignant or non-malignant origin and mostly recommended in neuropathic pain [3]. Tramadol is available in many dosage forms like drops, tablets, injection and capsules [4]. The half-life of tramadol hydrochloride is 5.5 hours [5]. The oral bioavailability of tramadol hydrochloride is approximately 75% [6]. Plasma protein binding of tramadol is about 20%. A serum concentration of 100–300 ng/mL is usually effective [7]. The main purpose of oral solid dosage formulations is to make a drug available so that the drug can produce pharmacological effects [8.] The process of dissolution have important role in release of a drug from its dosage form and making it available for subsequent gastrointestinal absorption. Therefore, dissolution performance of oral solid dosage forms is a very important test of product quality and it can be used as a sensitive method

for differentiating between formulations of the same therapeutic agent. Bioavailability of drugs from a given formulation altered in many conditions, oral solid dosage forms did not give the same therapeutic effects. This is happen due to the improper dissolution and improper absorption of the drug from the GIT [9]. So many factors may impact the dissolution of drug from its dosage forms. Not only physiochemical property of drug but design and manufacturing process of formulation can affect the dissolution of drug [10]. Dissolution tests are most useful to guide the new dosage form development. So it necessary to determine dissolution profile at different time points to adequately characterize the *in vitro* performance of the drug product [11]. Dissolution profiles of the product in different dissolution medium can perform and then be compared with reference using model-independent or model dependent methods. The model-independent similarity factor *(f2)* approach widely accepted method for comparing dissolution profiles. In fact, many regulatory authorities require the use of the *f2* test for this purpose. FDA and the European Agency for the Evaluation of Medicinal Products (EMEA) by the Committee for Proprietary Medicinal Products (CPMP) has been adopted Similarity factor *f2* and use to compare the dissolution profile of two different medicinal product [8]. The different dissolution profile medicinal product consider identical when f_2=100. If the *f2* value in between 50-100 this indicates that the similarity between two different product dissolution profiles. For *f2* determination condition required the drug release profile at exclude zero minimum three time point of 12 individual value for every time point for each product and having 10% less mean of the standard deviation from the second to last time point [12].

MATERIALS & METHODS:

Test Sample

Test sample prepared by an accurately weighed amount of DRC equivalent to 50 mg of drug and directly compressible excipient pearlitol 200 SD were geometrically mixed for 25 min followed by sieving through sieve no. 40.The remaining diluents (sodium carbonate, anhydrous citric acid, tartaric acid and talcum), lubricant (sodium stearyl fumarate), sweetener (aspartame), disintegrant (crospovidone / Ac-Di-Sol / Kyron T-314 / sodium starch glycolate) and flavoring agent were blended with the binary mixture. Different batches of orodispersible tablets were prepared by compressing different blend of powders on a 10 station rotary compression machine (Mini Press 11 DL, Karnavati Engineers Ltd, India) equipped with 10 mm diameter flat faced punches to give a tablet weight of 380 mg.

Reference Sample

Tramadol hydrochloride dispersible tablets 50 mg (Contramal DT) manufactured by Abbott Healthcare Pvt ltd was purchased from market.

Assay

Absolute drug content: Crushed the pre-weighed 10 tablets of Test or Reference**.** Take a quantity of tablets powder equivalent to 100 mg of tramadol hydrochloride and transferred in 100 ml volumetric flask then add 50 ml water and sonicate for 20 minutes and finally make up the volume up to 100 ml of mark. Take 2 ml from this solution in 100 ml volumetric flask and volume make up to 100 ml of mark. The solution was filtered through whatman filtered. The absorbance of solution was measured at 271 nm. The amount of tramadol hydrochloride was determined by compare the absorbance [13].

Determination of uniformity of weight: Take twenty tablets from Test and Reference sample and weigh accurately on balance. Divide the total weight by 20 and calculate the average weight. Weight each tablet individually select minimum & maximum weight and detect variation [14].

Hardness test: Digital tablet hardness tester (Thermonic) was used to determine the hardness. Hold tablets firmly on the edge. Set zero on the screen of instrument. Put the tablets between the stationary and moving jaws

and rotate the knob anti clock wise direction till the tablets breaks. When the tablets break the force applied is display on the screen was recorded. Five tablets of Test and Reference were used to determine the hardness.

Friability test: Take a sample of whole tablets corresponding as near as possible to 6.5 gm of Test and Reference product. Tablets were carefully dedusted prior to testing. Accurately weigh the tablets sample and place the tablets in the drum. Rotate at 25 rev/min for 4 min or 100 rotations. The tablets were then weighed and compared with their initial weights and percentage friability was obtained [15].

Water absorption ratio: The ability of orodispersible tablets to absorb water was determined by placing tablets over five circular tissue papers kept one above to another in a petri dish containing 10 ml water-soluble red color amranth dye solution. Time taken by tablet to become complete red was noted. Tablet weight was determined before and after wetting. The water-absorption ratio (WR) was determined according to the following formulae [16].

$WR = 100\ (Wt_a - Wt_b)/Wt_b$.

Where Wt_a and Wt_b are the tablet weights after and before wetting.

Disintegration test: Disintegration time of orodispersible tablets was evaluated under bio-relevant condition of oral cavity. Three tablets of Test and Reference product were randomly selected and kept in 6 ml simulated salivary fluid pH 6.8 maintained at 37 ± 2 °C respectively [17]. Disintegration time was noted until tablets fragmented into fine particles.

Dissolution test: The dissolution test was undertaken using tablet dissolution tester (DS14000$^+$, Electrolab, India). Take 12 tablets of Test and Reference product and transferred the one tablets individually in 12 vessel containing 900 ml dissolution medium, previously equilibrated to the temperature of 37 ±0.5°C. Dissolution medium were buffer solutions of pH 1.2 (hydrochloric acid solution), pH 4.5 (acetate buffer solution), and pH 6.8 (phosphate buffer solution) and water. The medium was maintained at 37±0.5°C. In all the experiments, 5 ml of dissolution sample was withdrawn after 5, 10, 15, 30 and 45 min and replaced with equal volume to maintain sink condition. Samples were filtered and assayed by UV-Visible method.

Data analysis

The uniformity of weight was analyzed with simple statistics – percentage deviation while the dissolution profiles were analyzed with difference factor (*f1*), similarity factor (*f2*).

RESULTS AND DISCUSSION

Both Test and Reference tablets were smooth, flat and round in appearance. The percentage weight variation for both Test and Reference was within Indian Pharmacopeia limit ± 5% of average weight [18]. Hardness of both Test and Reference was varied from 60 Newton to 68 Newton for Test and 70 Newton to 80 Newton for Reference. Both Test and Reference passed the friability test (friability < 1%) indicating good mechanical resistance of tablets (Table 1). In present study, both Test and Reference tablets disintegrated within 3 min fulfilling the official requirements (≤ 3 minutes) for dispersible tablets as defined in European Pharmacopoeia [18]. Test formulation had provided faster dispersion (25.65 ± 1.22 sec) of tablet compared to Reference (45.89±2.13) as well complies with US FDA guidelines i.e. orodispersible tablets should have *in vitro* disintegration time of ≤ 30 sec. [19] Test formulation had Higher water absorption ratio (80.74±0.67%) than Reference formulation, smaller wetting time (20.30 ± 0.98 sec) and dispersion time (25.65 ± 1.22 sec) for Test formulation indicated ready dispersibility of orodispersible tablet in mouth in comparison to Reference product. The results of dissolution profile studies in different medium are given table 2-5 and graphically represented in Figure 1-4. It can be seen from the results of dissolution profile data. The Reference product shows the higher drug release in all dissolution medium except phosphate buffer pH 6.8 in comparison to Test product. Both

Test and Reference product shows drug released 82% or above in acidic media (pH 1.2) within 15 minutes. Higher amount of drug release was observed in pH1.2, phosphate buffer pH 6.8 and Water from both Test and Reference product in comparison to acetate buffer pH 4.5 dissolution medium. This is due to the low solubility of tramadol hydrochloride in acetate buffer pH 4.5. Tramadol hydrochloride is highly soluble at pH 1.2 then phosphate buffer pH 6.8 and water. So in these three medium drugs release was higher side from dosage form.

Analysis of dissolution data

Dissolution profile of Test and Reference product in different dissolution medium is compared were compared using model-independent approach using a similarity factor by calculation the difference factor *f1* and similarity factor *f2* from using the following formulas:

$f_1 = \{[\sum_{t=1}^{n}|R_t - T_t|] / [\sum_{t=1}^{n} R_t]\} \times 100$

$f_2 = 50 \times \text{Log}\{(1+(1\backslash n \Sigma_{t=1}^{n} (R_t - T_t)^2\}^{-0.5} \times 100\}$

Where n is the number of time points, R_t is the dissolution value of the reference at time t, and T_t is the dissolution value of the test at time t. [11]. In the similarity factor *(f2)*, n is the number of multiple time point observation, Rt and Tt is the average percentage of drug dissolved from test and reference product. [12]

The dissolution profiles in different medium of Test and Reference products were compared using difference *(f1)* and similarity *(f2)* factors. Table 2-5 shows the *f1, f2* values of Test and Reference product in different medium. The *f1* and *f2* was calculated from the data obtained from dissolution profile of Test and Reference product in different dissolution medium (pH 1.2, Water, phosphate buffer pH 6.8 and acetate buffer pH 4.5). The observed values in all medium for *f2* are more than 50 and values for *f1* are less than 15. So, this represent that Test product give similar drug release profile in all dissolution medium with respect to drug release profile of Reference product in all dissolution medium.

Table 1: Physiochemical Evaluation of Test & Reference product

S. No	Evaluation Parameter	Test Product	Reference Product
1	**Description**	Off white colored, round, flat uncoated tablets	White colored, round, flat uncoated tablets
2	**Tablet weight (in mg)**	380±2.25	350±3.92
3	**Thickness (in mm)**	5.19±0.78	4.0 mm ±0.85
4	**Hardness(In Newton)**	60 to 68	70 to 80
5	**Friability (in %)**	0.291	0.162
6	**Water absorption Ratio (in %)**	80.74±0.67	63.34±0.78
7	**Wetting time (in sec)**	20.30±0.98	36.29±1.31
8	**Dispersion time (in sec)**	25.65±1.22	45.89±2.13
9	**Assay**	98.14%	99.67%

Table 2: Percentage Drug release, Similarity factor and Difference factor of Test and Reference product in pH 1.2.

Time (In min)	Test product (Drug release)	Reference Product (Drug release)	Similarity Factor *(f2)*	Deference Factor *(f1)*
5	16%	22%	69	4
10	45%	49%		
15	77%	80%		
30	97%	99%		
45	99%	99%		

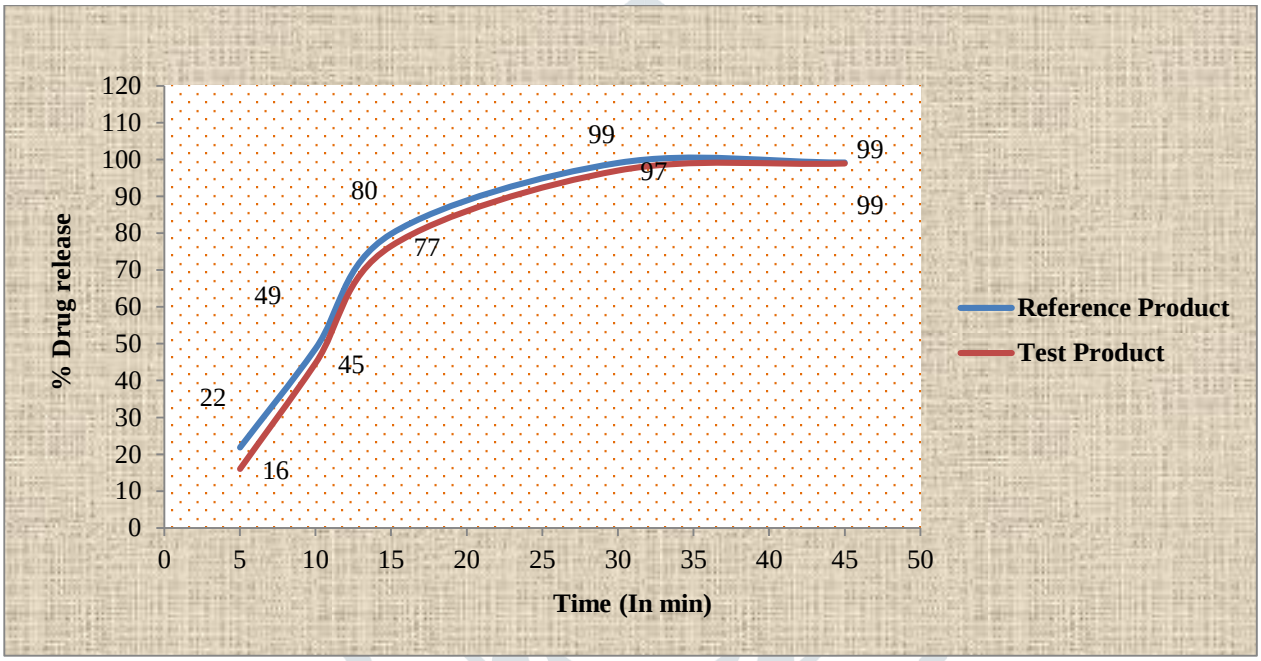

Figure 1: Percentage drug release versus time of Test and Reference product in pH 1.2.

Table 3: Percentage Drug release, Similarity factor and Difference factor of Test and Reference product in phosphate buffer pH 6.8.

Time (In min)	Test product (Drug release	Reference Product (Drug release)	Similarity Factor *(f2)*	Deference Factor *(f1)*
5	10%	12%	60	8
10	37%	30%		
15	74%	69%		
30	96%	87%		
45	98%	98%		

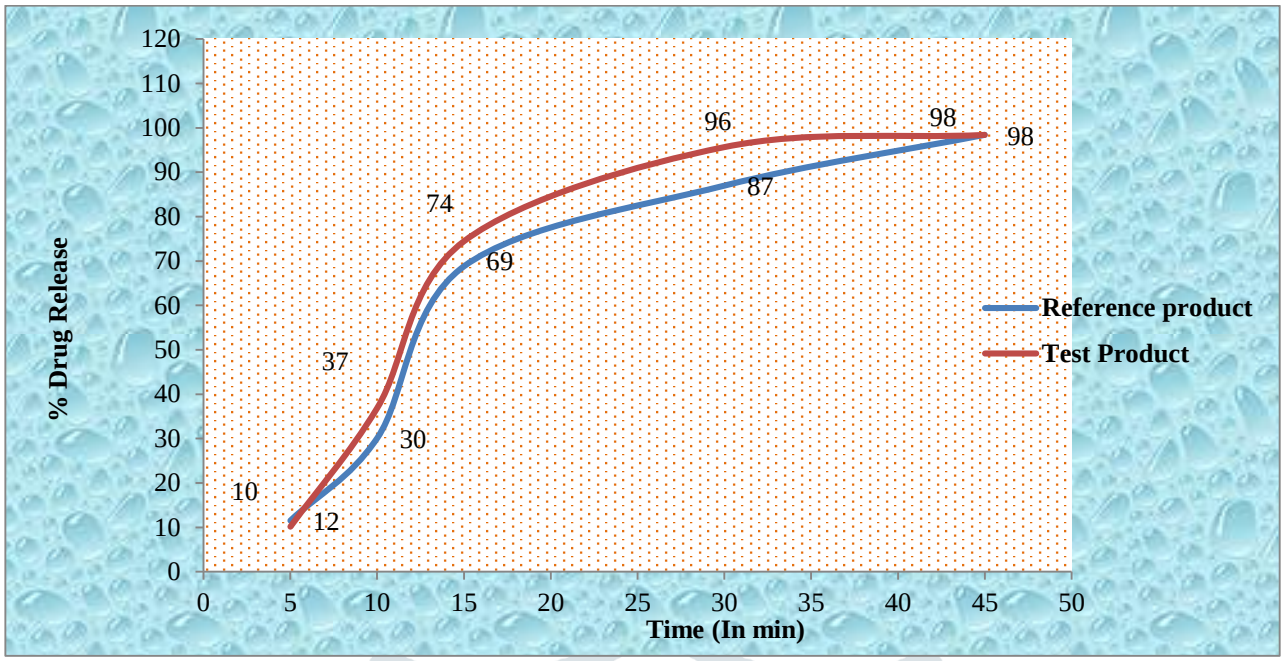

Figure 2: Percentage drug release versus time of Test and Reference product in phosphate buffer pH 6.8.

Table 4: Percentage Drug release, Similarity factor and Difference factor of Test and Reference product in acetate buffer pH 4.5.

Time (In min)	Test product (Drug release)	Reference Product (Drug release)	Similarity Factor *(f2)*	Deference Factor *(f1)*
5	9%	10%	80	4
10	23%	24%		
15	40%	42%		
30	75%	78%		
45	94%	98%		

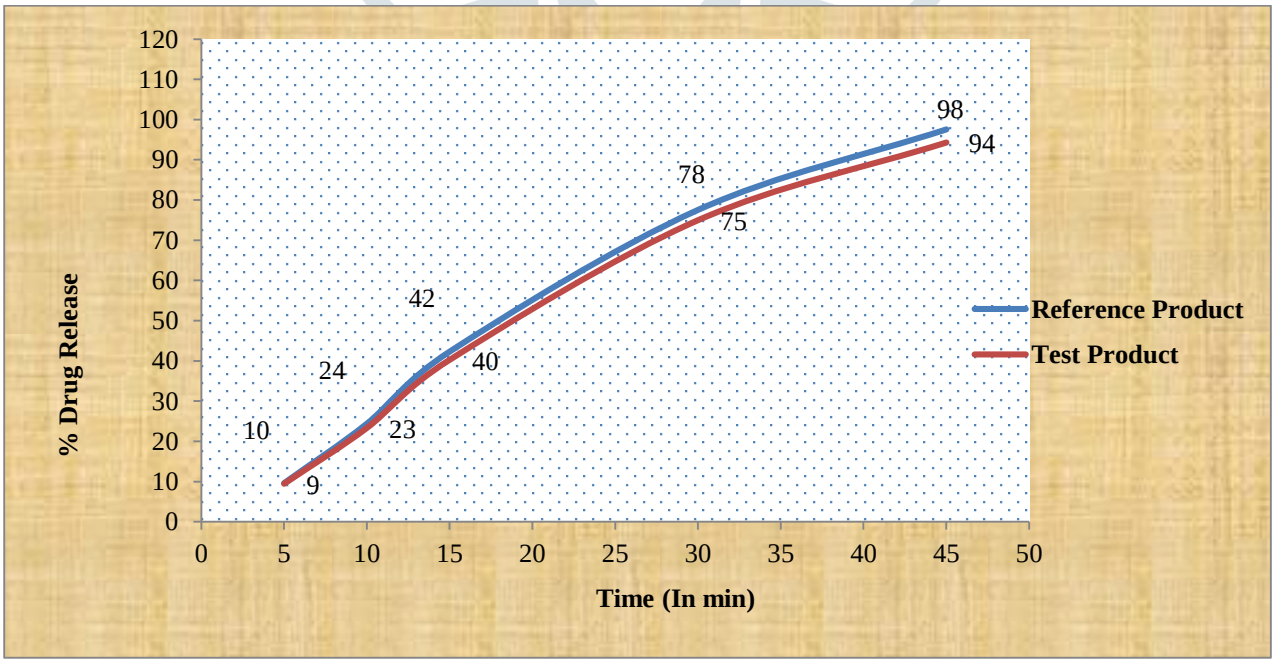

Figure 3: Percentage drug release versus time of Test and Reference product in acetate buffer pH 4.5

Table 5: Percentage Drug release, Similarity factor and Difference factor of Test and Reference product in purified water.

Time (In min)	Test product (Drug release)	Reference Product (Drug release)	Similarity Factor *(f2)*	Deference Factor *(f1)*
5	14%	18%	60	7
10	39%	42%		
15	72%	79%		
30	86%	94%		
45	98%	99%		

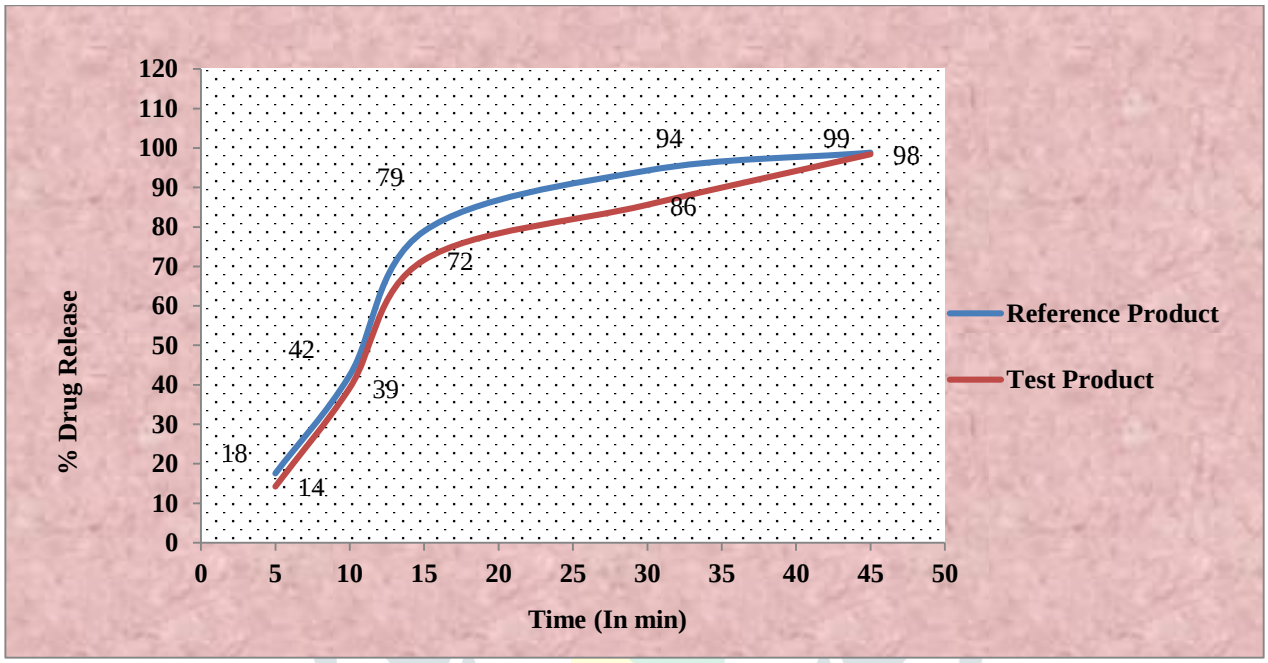

Figure 3: Percentage drug release versus time of Test and Reference product in water

CONCLUSION:

The in vitro dissolution study indicated that both Test and Reference product seem have very good bioavailability in buffer of pH 1.2. The data obtained from dissolution profile in all dissolution medium indicate that the Test product shows similar drug release profile with respect to Reference product drug release profile. The Test product can be considering bioequivalent with the Reference product.

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