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Study on dissolution release of Ivabradine hydrochloride from its solid oral dosage forms

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ABSTRACT

The study on dissolution release indicates that the percentage release of Ivabradine hydrochloride from finished dosage forms. The aim of the study is to evaluate the percentage release of active substance Ivabradine Hydrochloride present in anti anginal drug formulation. The study reveals the dissolution release pattern of drug substance with the Innovator reference product. The multimedia dissolution profile with 3 different media (pH1.2,water & pH7.4)at various time points (10,20,30 &45 min) are studied for both innovator as well as our product. From the comparative dissolution profile results the difference factor(F1) and the similarity factor(F2) was calculated.

KEYWORDS

Ivabradine hydrochloride Tablets;
Dissolution method development;
In-vitro release estimation;
comparative dissolution Profile;
Anti anginal.

INTRODUCTION

The amount of Drug substance dissolved in a suitable medium at particular time interval is called dissolution release.

Dissolution should form an essential part of pharmaceutical development of solid oral dosage forms and usually suspensions. The media and conditions chosen in the studies will depend on the required release characteristics of the intended product.

For development purposes the generation of dissolution profiles at short intervals such as 10, 15, 20, 30 and 45 minutes in the above media are strongly recommended. This would enable:

- The selection of the formulation, by comparison of the dissolution profiles with that of the innovator product. This should be a basic strategy in pharmaceutical development to maximize the chances of bioequivalence.
- Comparison of the release properties of the pivotal batches to demonstrate in-vitro similarity, which is considered essential for retention of efficacy and safety. Note that bioequivalence studies are done normally only once on a pivotal batch during development. It must therefore be demonstrated that the product retain the release characteristics up to and during commercial production.
- The selection of the dissolution specifications (conditions and acceptance criteria) for product release and stability study purposes. A dissolution specification should be discriminating, implying that it should be able to detect inadequate release properties of the commercial batches.
- Post-approval amendment application. If the amendment is of a major nature and requires bioequivalence studies, in-vitro data may be acceptable, provided

that (1) the profiles of the amendment batch and the current batch are similar and (2) that the dissolution study design is acceptable (preferably the three media and short interval multipoint as mentioned above).

Two scenarios for comparing the profiles obtained multipoint dissolution are operative:

1. If both the test and reference product show more than 85% dissolution within 15 minutes, the profiles are considered similar.
2. Calculate the f2 value. If $f_2 \geq 50$ the profiles are normally regarded similar. Note that only one measurement should be considered after 85% dissolution of both products has occurred and excluding point zero.

In this equation f2 is the similarity factor, n is the number of time points, R(t) is the mean percent drug dissolved of e.g. a reference product, and T(t) is the mean percent drug dissolved of e.g. a test product.

The evaluation of similarity is based on the conditions of

- A minimum of three time points (zero excluded)
- 12 individual values for every time point for each formulation
- Not more than one mean value of > 85% dissolved for each formulation
- That the standard deviation of the mean of any product should be less than 10.% from second to last time point.

In vitro dissolution complementary to a bio equivalence study

The results of "in vitro" dissolution tests, obtained with the batches of test and reference products that were used in the bioequivalence study should be reported. The results should be reported as profiles of percent of labeled amount dissolved versus time.

The specifications for the in vitro dissolution of the product should be derived from the dissolution profile of the batch that was found to be bioequivalent to the reference product and would be expected to be similar to those of the reference product.

For immediate release products, if the dissolution profile of the test product is dissimilar compared to that of the reference product and the invivo data remain acceptable the dissolution test method should be re-evaluated and optimised. In case that no discriminatory test method can be developed which reflects invivo bioequivalence a different dissolution specification for the test product could be set.

It is a requirement of the pre qualification programme to submit comparative dissolution data, including profile comparison and discussion, for the biobatch and innovator biobatch (same batches as used in the bioequivalence). The data from part of the, pharmaceutical development report, but can also be included in the bioequivalence study report.

For extended release products, the same dissolution strategy as for immediate release products can be followed in the development studies, though it is recommended that the analysis points

The term bioavaliability was defined as "the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of absorption" of a test and a reference drug.

Bioavailability and bioequivalence of drug products, and drug subtances selection have emerged as critical issues in pharmacy and medicine during the last three decades. Concern about lowering health care costs has resulted in a tremendous increase in the use of generic drug products; currently about one half of all prescriptions written are for drugs that can be substituted with a generic product. Over 80% of the approximately 10,000 prescription drugs available in 1990 were available from more than one source. With the increasing availability and use of generic drug products, health care professionals are confronted with an ever-larger array of multi source products from which they must select those that are therapeutically equivalent.

This phenomenal growth of the generic pharmaceutical industry and the abundance of multi source products have prompted some questions among many health professionals and scientists regarding the therapeutic equivalency of these products, particularly those in certain critical therapeutic categories such as anticonvulsants and cardio vasculars. Inherent in the currently accepted guidelines for product substitution is the assumption that a generic drug considered to be bioequivalent to a brand-name drug will elicit the same clinical effect. As straight forward as this statement regarding bioequivalence appears to be, it has generated a great deal of controversy among scientists and pro-

fessionals in the health care field. Numerous papers in the literature indicate that there is concern that the current standards for approval of generic drugs may not always ensure therapeutic equivalence.

Before the therapeutic effect of an orally administered drug can be realized, the drug must be absorbed. The systemic absorption of an orally administered drug in a solid dosage form is comprised of three distinct steps:

1. Disintegration of the drug product
2. Dissolution of the drug in the fluids at the absorption site

Transfer of drug molecule across the membrane lining the gastrointestinal tract into the systemic circulation.

Bioavailability Factors related to the dosage form

Physicochemical properties of the drug	Formulation and manufacturing variables
Particle size	Amount of disintegrant
Crystalline structure	Amount of lubricant
Degree of hydration of crystal	Special coatings
	Nature of diluent
Salt or ester form	Compression force

Bioavailability Factors Related to the patient

Physiologic factors	Interactions with other substances
Variations in absorption power along GI tract Variations in pH of GI fluids Gastric emptying rate Intestinal motility Perfusion of GI tract Pre systemic and first-pass metabolism Age, sex, weight Disease states	Food Fluid volume Other drugs

Fastest Availability	Solutions Suspensions Capsules Tablets Coated tablets
Slowest availability	Controlled-release formulations

Aim of the present study

Dissolution test is part of general test specification of solid oral dosage forms (tablets and capsules), oily suspensions, etc. and same is carried out for following purposes.

a) To access batch to batch quality during formulation development and during regular production for batch release.
b) To assist bio-availability and bio-equivalence study. Wherever possible comparison of dissolution studies with these studies is also provided.
c) Dissolution test is also part of stability study to establish shelf life.
d) Dissolution data (3 or 5-media dissolution study) is required for getting new drug formulation approval from local and international authority.
e) To justify scale up and post approval changes (SUPAC) in dosage forms.

Depending upon requirement. single, double or multiple time point dissolution study and single or multiple media dissolution study shall be carried out.

The dissolution results shall be calculated in Microsoft Excel software. The data shall be reported on all the tablets or capsules. Range that include minimum and maximum % dissolution from no. of tablets or capsules at each time point should be reported.

If required. Fl and F2 statistical calculations shall be performed on data obtained from innovator and formulation development sample. Conclusion regarding similarity and dissimilarity of dosage form shall be reported.

In dissolution study, tablet or capsule formulation is placed in polypropylene jar of 1000 ml capacity containing 900 or 500ml of suitable dissolution medium depending upon label claim. The medium is allowed to rotate at certain speed of 50 to 100 RPM by means of a stainless steel rotator Called Paddle or Basket. The time points for dissolution for fixed single or multiple time interval. After specified time, aliquot of samples are withdrawn and analyzed for the amount of drug dissolved in that medium. This indicates drug dissolution capacity in presence of excipients in that medium and thus can be used as quality tool during formulation development and manufacturing.

Following are the parameters that are usually considered during method development for Dissolution.

a. Selection of dissolution medium
b. Selection of apparatus and RPM (Speed)
c. Selection of dissolution time interval (single and multiple point)
d. Selection of other parameters like, media volume, temperature, etc.

Selection of dissolution medium

Selection of dissolution medium depends upon following parameters.

a. Type of formulation (Immediate or modified release).
b. Solubility characteristics of active component.
c. Type formulation design, e. g. Soft gel capsule, Hard gel capsule, Tablets, Oily suspension, etc.

Bio pharmaceutical Classification System (BCS) has classified drug solubility into four categories.

i. Highly soluble and highly permeable substances
ii. Poorly soluble and highly permeable substances
iii. Highly soluble and poorly permeable substances
iv. Poorly soluble and poorly permeable substances

For formulation having active substances that fall in Class-i and Class-iii categories, but are immediate release formulations (uncoated and film coated), 0.1N hydrochloric acid as dissolution medium shall be used. However if formulation of this class is modified release (delayed release, enteric coated and sustained release), in that case 6.8 pH buffer shall be used as dissolution medium. In both the cases, pH 4.5 buffer shall be intermediate media for dissolution profile.

For formulation having active substances that fall in Class-ii and Class-iv categories, but are immediate release formulations of uncoated and film coated tablets, 6.8 buffer as dissolution medium shall be used. For modified release formulation (delayed release, enteric coated and sustained release) of this class, 6.8 pH buffer shall be used as dissolution medium. In both the cases, pH 4.5 buffer shall be intermediate media for dissolution profile.

For formulation of Class-ii and Class-iv category, because of poor solubility of active drug, it I may require to use a surfactant (i.e. Sodium lauryl sulphate) to enhance drug solubility in dissolution media. Concentration of surfactant can be from 0.5 to 2.0%. Higher concentration other than this should be justified.

For formulation of Class-ii and Class-iv category, if all the medias are tried out (0.1 S HCI, pH-6.8, use of surfactant) and if dissolution rate is not satisfactory in required time, in that case Tris buffer pH-9.0as dissolution media shall be used. In such cases justification along with various media trial results should be provided.

For all formulations, if dissolution test is applicable as per guidelines requirement the dissolution test should be provided. In case test is not provided due to any reason, same should be justified and information taken on efforts taken to develop the same should be provided.

For regulatory submission purposes and for comparison with innovators. we also have to carry out dissolution study in additional dissolution media like pH-7.5 buffer (Apart from 0.1 N HCI, pH-6.8, pH-4.5 and water). To compare data with innovators, statistical parameters like Fl and F2 calculated on our and innovators dissolution data is very useful and recommended.

Selection of RPM

The selection of RPM depends upon type of formulation, solubility characteristics of active substances and apparatus used for dissolution study.

For capsules (both soft gel and hard gel), USP-I i. e. Basket apparatus is recommended, rotation speed for paddle shall be 50 to 75 RPM. Use of higher RPM other than this should be justified.

For tablets, USP-II i. e. paddle apparatus is recommended, rotation speed for basket shall be 75 to 100 RPM. Use of higher RPM other than this should be justified.

Any change in apparatus and RPM other than recommended parameters should be justified.

Other apparatus that are mentioned in USP general chapters (e. g. Flow through cell) shall be used for specific formulation.

Selection of dissolution time intervel (single and multiple point)

Dissolution time is defined as the time in minutes at which maximum amount (+80% of label claim) of drug is dissolved.

For immediate release dosage forms, dissolution time from 30min. to 60min. is recommended. In some cases dissolution time may be higher i. e. up to 90min. to l20min. In such cases suitable justification should be provided.

For modified release formulations (delayed release, enteric coated and sustained release), time depends upun design of formulation, site of action and therapeutic

use. Time for such formulations may be from about 6 hrs. to 24 hrs. or may be higher.

In most of the cases, (except in modified release formulations) single point dissolution analysis is sufficient. However in some cases two time point dissolution analysis may be required.

The % release of active components should meet the specification within specified time.

Selection of other parameters like, media volume, temperature, etc.

The volume of dissolution media is ideally 900ml, however if label claim is less than 5mg and if active substances has less absorbance at selected wavelength, then in that case dissolution volume can be reduced to 500ml.

The dissolution media temperature is fixed i. e. 37.0 (±0.5)ºC

Before starting dissolution analysis, ensure dissolution apparatus passes calibration test that can be performed periodically to ensure accuracy and precision of the same. Other factors that are to be checked are centeric position of rotator, wobble test, etc.

Before starting dissolution analysis, ensure that the dissolution media is properly degassed,especially in case of surfactants are used for dissolution media preparation.

Care should be taken during dissolution of tablets and soft gel or hard gel capsule (if paddle apparatus is used) that the same will not float on media surface. In such cases sinker of suitable size can be used.

Clean the dissolution apparatus and jars with suitable detergent, but do not wash with organic solvent.

MATERIALS AND METHODS

Ia)Dissolution system: Dissolution profile for ivabradine tablets 5 mg in pH 1.2 medium (Comparative dissolution with Innovator Product)

Apparatus	: Apparatus II of BP (Paddle)
Medium	: 0.1M Hydrochloric acid (pH1.2) :
Volume	: 900 ml
Time	: 10,20,30 &45 minutes
Speed	: 50 RPM
Temperature	: 37^{o} C ± 0.5^{o} C

b)Standard preparation

Weigh accurately about 0.030 gm of Ivabradine Hydrochloride WS in to a 100 ml volumetric flask, add 70 ml diluents, shake and sonicate to dissolve the contents and make up the volume with diluent. Transfer 2ml of the above solution into a 100 ml volumetric flask and makeup the volume with dissolution medium. Filter the solution through 0.45µm filter.

c)Sample Preparation

Set the apparatus at above condition and place one tablet each in 6-dissolution bowl. Run the apparatus for 45 minutes. Withdraw 10 ml of the sample in the above time intervals from each bowl, replacing the same amount every time with dissolution medium. Filter the solution through membrane filter.

d)Chromatographic condition

Apparatus	:	HPLC
Column	:	C18, 250 x 4.6 mm; 5µm; SS Column (Inertsil ODS 3V)
Wave length	:	210 nm
Flow rate	:	1.0 ml/min.
Inj. Volume	:	10µl
Samle cooler	:	20°C
Column oven	:	25°C
Mobile Phase	:	Filtered and degassed mixture of Buffer and Acetonitrile in the ratio of 700 : 300
Buffer	:	Dissolve 6.8 gm of Potassium dihydrogen ortho phosphate in 1000 ml of water and adjust the pH 4.0 with dilute Ortho phosphoric acid
Diluent	:	Acetonitrile and Water in the ratio of 600:400

e)System suitability

Chromatograph the Standard preparation and record the peak responses as directed under procedure. The theoretical plates for Ivabradine HCl peak should no be less than 2000, tailing factor should not be more than 2.0 and the relative standard deviation for 5 replicate injections should not be more than 2.0%.

f)Procedure

Separately inject 10 microlitres of filtered portion of the Sample preparation and Standard preparation

into the Chromatograph. Record the chromatogram and measure the responses for the major peak. Calculate the release in percentage with respect to label claim by using the following expression.

g)Calculation

$$\frac{AT}{AS}\times\frac{WS}{100}\times\frac{2}{100}\times\frac{900}{1}\times\frac{P}{100}\times 1\times 1000$$
$$\times\frac{100}{5}\times\frac{468.59}{505.05}= \_\_\_\_\_ \%\ \text{release of Ivabradine}$$

Where 'AS' Is The Average Area Of Ivabradine Hcl Peak In Standard Preparations;' AT' Is The Individual Area of Ivabradine Hcl Peak In Sample Preparation'WS' Is The Weight of Ivabradine Hcl WS Taken For Standard preparation in gm; 'P' is percent purity of Ivabradine HCl WS on as such basis; 468.59 is the molecular weight of Ivabradine and 505.05 is the molecular weight of Ivabradine

TABLE 1 : Test sample: Ivabradine hydrochloride 5 mg Tablets

Time points in minutes.	% release In pH 1.2 (0.1 M HCl medium)	% release In Water medium	% release In Phosphate buffer pH 7.4 medium
10	90.70	84.20	96.20
20	100.40	95.20	99.90
30	100.70	97.20	100.20
45	101.10	98.80	98.10

TABLE 2 : Innovator 's Reference product: PROCORALAN

Time points in minutes.	% release In pH 1.2 (0.1 M HCl medium)	% release In Water medium	% release In Phosphate buffer pH 7.4 medium
10	85.22	82.80	88.90
20	100.11	99.70	96.60
30	103.10	100.30	96.20
45	104.24	102.60	98.50

HCl respectively.

The difference factor F1 and the similarity factor F2 is calculated by using the following statistical expression.

$$f1=\{[\Sigma_{t=1}n[Rt-Tt]/[\Sigma_{t=1}nRt]\}*100$$

$$f_2=50.\log\{[1+(1/n)\,\Sigma_{t=1}n(Rt-Tt)^2]^{-0.5}*100$$

Where 'Rt' is the average percentage relase of Reference product(Innovator);'Tt' is the average percentage release of Test product (own formulation) and 'n' is the number of time points tested

TABLE 3 : Innovator's reference product vs Test sample in pH1.2 medium

Time (t) [mins]	Reference ®	Test (T)	Rt-Tt	(Rt-Tt)²	|Rt-Tt|
0	0.00	0.00	0.00	0.00	0.00
10	85.22	90.70	-5.48	30.03	5.48
20	100.11	100.40	-0.29	0.08	0.29
30	103.10	100.70	2.40	5.76	2.40
45	104.24	101.10	3.14	9.86	3.14
	392.67			45.73	11.31
Difference Factor - F1 [Acceptance Criteria : 0 - 15]					2.88
Similarity Factor - F2 [Acceptance Criteria : 50 - 100]					72.64

IIIa) Dissolution System: Dissolution Profile for Ivabradine Tablets 5 mg in Phosphate buffer pH7.4 medium (Comparative dissolution with Innovator Product)

Apparatus	: Apparatus II of BP (Paddle)
Medium	: Water; 900 ml
Time	: 10,20,30 & 45 minutes
Speed	: 50 RPM
Temperature	: 37^{o} C ± 0.5 ^{o} C

b)Standard preparation

Weigh accurately about 0.030 gm of Ivabradine Hydrochloride WS in to a 100 ml volumetric flask, add 70 ml diluents, shake and sonicate to dissolve the contents and make up the volume with diluent. Transfer 2ml of the above solution into a 100 ml volumetric flask and makeup the volume with dissolution medium. Filter the solution through 0.45µm filter.

c)Sample preparation

Set the apparatus at above condition and place one tablet each in 6-dissolution bowl. Run the apparatus for 45 minutes. Withdraw 10 ml of the sample in the above time intervals from each bowl, replacing the same amount every time with dissolution medium. Filter the solution through membrane filter.

d)Chromatographic condition

Apparatus	:	HPLC
Column	:	C18, 250 x 4.6 mm; 5µm; SS Column (Inertsil ODS 3V)
Wave length	:	210 nm
Flow rate	:	1.0 ml/min.

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Inj. Volume	:	10µl
Samle cooler	:	20°C
Column oven	:	25°C
Mobile Phase	:	Filtered and degassed mixture of Buffer and Acetonitrile in the ratio of 700 : 300
Buffer	:	Dissolve 6.8 gm of Potassium dihydrogen ortho phosphate in 1000 ml of water and adjust the pH 4.0 with dilute Ortho phosphoric acid
Diluent	:	Acetonitrile and Water in the ratio of 600:400

e)System suitability

Chromatograph the Standard preparation and record the peak responses as directed under procedure. The theoretical plates for Ivabradine HCl peak should not be less than 2000, tailing factor should not be more than 2.0 and the relative standard deviation for 5 replicate injections should not be more than 2.0%.

f)Procedure

Separately inject 10 microlitres of filtered portion of the Sample preparation and Standard preparation into the Chromatograph. Record the chromatogram and measure the responses for the major peak. Calculate the release in percentage with respect to label claim by using the following expression.

g)Calculation

$$\frac{AT}{AS}\times\frac{WS}{100}\times\frac{2}{100}\times\frac{900}{1}\times\frac{P}{100}\times 1\times 1000$$
$$\times\frac{100}{5}\times\frac{468.59}{505.05}= \text{\_\_\_\_\_}\ \%\ \text{release of Ivabradine}$$

Where 'AS' Is The Average Area Of Ivabradine Hcl Peak In Standard Preparations;' AT' Is The Individual Area of Ivabradine Hcl Peak In Sample Preparation 'WS' Is The Weight of Ivabradine Hcl WS Taken For Standard preparation in gm; 'P' is percent purity of Ivabradine HCl WS on as such basis; 468.59 is the molecular weight of Ivabradine and 505.05 is the molecular weight of Ivabradine HCl respectively.

TABLE 4 : Innovator's reference product vs Test sample in Water medium

Time (t) [mins]	Reference ®	Test (T)	Rt-Tt	(Rt-Tt)²	|Rt-Tt|
0	0.00	0.00	0.00	0.00	0.00
10	82.80	84.20	-1.40	1.96	1.40
20	99.70	95.20	4.50	20.25	4.50
30	100.30	97.20	3.10	9.61	3.10
45	102.60	98.80	3.80	14.44	3.80
	385.40			46.26	12.80
Difference Factor - F1 [Acceptance Criteria : 0 - 15]					3.32
Similarity Factor - F2 [Acceptance Criteria : 50 - 100]					72.52

IIIa) Dissolution System: Dissolution Profile for Ivabradine Tablets 5 mg in Phosphate buffer pH7.4 medium (Comparative dissolution with Innovator Product)

Apparatus	: Apparatus II of BP (Paddle)
Medium	: Phosphate buffer pH7.4; 900 ml
Time	: 10,20,30 &45 minutes
Speed	: 50 RPM
Temperature	: 37° C ± 0.5 ° C

b)Standard preparation

Weigh accurately about 0.030 gm of Ivabradine Hydrochloride WS in to a 100 ml volumetric flask, add 70 ml diluents, shake and sonicate to dissolve the contents and make up the volume with diluent. Transfer 2ml of the above solution into a 100 ml volumetric flask and makeup the volume with dissolution medium. Filter the solution through 0.45µm filter.

c)Sample preparation

Set the apparatus at above condition and place one tablet each in 6-dissolution bowl. Run the apparatus for 45 minutes. Withdraw 10 ml of the sample in the above time intervals from each bowl, replacing the same amount every time with dissolution medium. Filter the solution through membrane filter.

d)Chromatographic condition

Apparatus	:	HPLC
Column	:	C18, 250 x 4.6 mm; 5µm; SS Column (Inertsil ODS 3V)
Wave length	:	210 nm
Flow rate	:	1.0 ml/min.
Inj. Volume	:	10µl
Samle cooler	:	20°C
Column oven	:	25°C
Mobile Phase	:	Filtered and degassed mixture of Buffer and Acetonitrile in the ratio of 700 : 300

Buffer : Dissolve 6.8 gm of Potassium dihydrogen ortho phosphate in 1000 ml of water and adjust the pH 4.0 with dilute Ortho phosphoric acid

Diluent : Acetonitrile and Water in the ratio of 600:400

e)System suitability

Chromatograph the Standard preparation and record the peak responses as directed under procedure. The theoretical plates for Ivabradine HCl peak should not be less than 2000, tailing factor should not be more than 2.0 and the relative standard deviation for 5 replicate injections should not be more than 2.0%.

f)Procedure

Separately inject 10 microlitres of filtered portion of the Sample preparation and Standard preparation into the Chromatograph. Record the chromatogram and measure the responses for the major peak. Calculate the release in percentage with respect to label claim by using the following expression.

g)Calculation

$$\frac{AT}{AS}\times\frac{WS}{100}\times\frac{2}{100}\times\frac{900}{1}\times\frac{P}{100}\times 1\times 1000$$
$$\times\frac{100}{5}\times\frac{468.59}{505.05}= \text{\_\_\_\_\_}\ \%\ \text{release of Ivabradine}$$

TABLE 5 : Innovator's reference product Vs Test sample in phosphate buffer pH 7.4 medium

Time (t) [mins]	Reference ®	Test (T)	Rt-Tt	(Rt-Tt)²	|Rt-Tt|
0	0.00	0.00	0.00	0.00	0.00
10	88.90	96.20	-7.30	53.29	7.30
20	96.60	99.90	-3.30	10.89	3.30
30	96.20	100.20	-4.00	16.00	4.00
45	98.50	98.10	0.40	0.16	0.40
	380.20			80.34	15.00
Difference Factor - F1 [Acceptance Criteria : 0 - 15]					3.95
Similarity Factor - F2 [Acceptance Criteria : 50 - 100]					66.90

Where 'AS' Is The Average Area Of Ivabradine Hcl Peak In Standard Preparations;' AT' Is The Individual Area of Ivabradine Hcl Peak In Sample Preparation'WS' Is The Weight of Ivabradine Hcl WS Taken For Standard preparation in gm; 'P' is percent purity of Ivabradine HCl WS on as such basis; 468.59 is the molecular weight of Ivabradine and 505.05 is the molecular weight of Ivabradine HCl respectively.

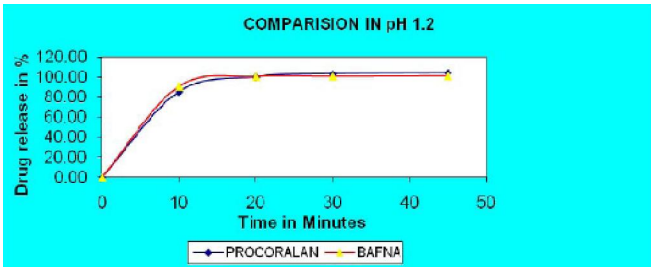

Figure 1 : Comparative dissolution profile Innovator Vs Test product in pH 1.2

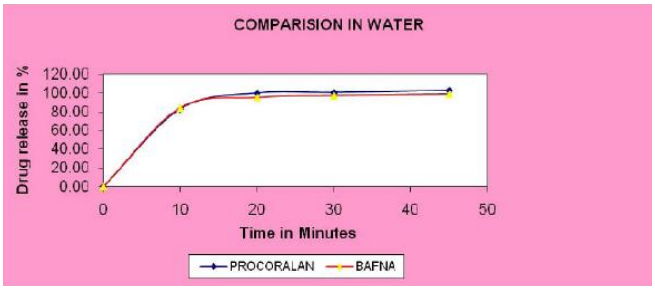

Figure 2 : Comparative dissolution profile Innovator Vs Test product in Water

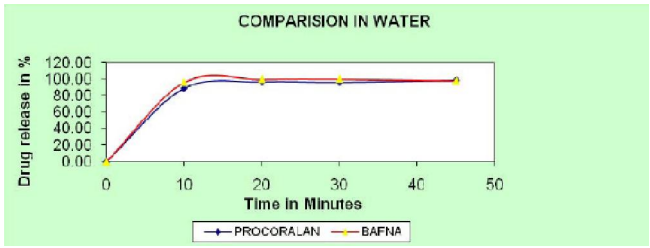

Figure 3 : Comparative dissolution profile Innovator Vs Test product in Phosphate buffer pH 7.4

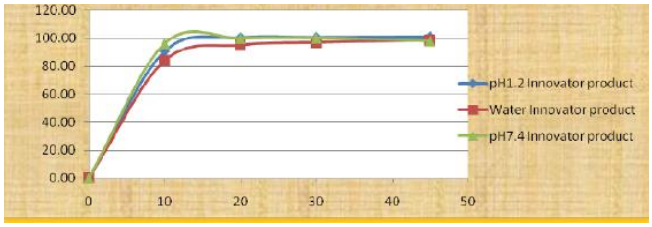

Figure 4 : Comparision of 3 dissolution media release for Test product(pH1.2,Water &pH7.4)

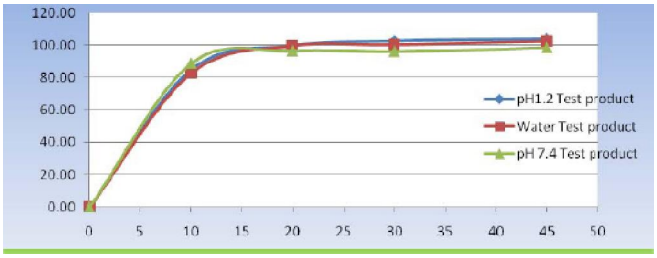

Figure 5 : Comparision of 3 dissolution media release for Innovator(pH1.2,Water &pH7.4)

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RESULTS AND DISCUSSIONS

The similarity factor (F2)and difference factor(F1) was evaluated against Innovator's reference product. The drug product release pattern was studied at variou intervals(10,20,30&45 minutes). The multimedia dissolution in 3 different pH was performed for Innovator product as well as test product for comparision and submission of data to regulatory. Finally the dissolution method by HPLC has develped to estimate the percentage release of Ivabradine hydrochloride present in dosage forms. From the release results obtained among 3 media dissolution the water medium is finalised as release medium.

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