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# EVALUATION AND STUDY OF ANTI ANGINAL TABLET (IVABRADINE)

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**Abstract:** *Ivabradine is a selective and specific inhibitor of the hyperpolarization-activated, mixed sodium/potassium inward If current, which contributes importantly to SAN pacemaker activity.3 In animal studies, at therapeutic concentrations, ivabradine has had little action on other cardiac ionic currents or cardiac action potential shape. This may account for the drug's lack of significant effects on myocardial contractility. All Marketed Tablet were found to be good without capping and chipping. Among all the 9 Marketed Tablet T9 formulation is optimized, as it shows maximum drug release at the end of 8hrs which suits the buccal drug delivery system criteria as per our studies. Post compression parameters of Ivabradine HCL were within the limits according to IP standards. Optimized formulation (T9) displayed that it follows zero order release kinetics and drug release follows non- Fickian diffusion mechanism.*

**Keyword:** Angina Pectoris, Anti Anginal, Ivabradine, Procoralan

## INTRODUCTION

Stable angina pectoris is common and disabling, affecting 30 000 to 40 000 per 1 million people in Europe and the United States[1]. Angina often seriously limits everyday activities and frequently leads to premature retirement from work[2]. Angina results from an imbalance between myocardial perfusion and myocardial metabolic demands[3]. Heart rate reduction can alter both elements of this imbalance beneficially[4]. The resulting increase in diastolic filling time should improve myocardial perfusion; myocardial oxygen demand varies directly with heart rate[5]. Ivabradine (Procoralan) is a member of a new class of selective heart rate–lowering agents that act specifically on the sinoatrial node (SAN)[6]. Ivabradine selectively and specifically inhibits If, a primary SAN pacemaker current, reducing heart rate at rest and during exercise in experimental animals and in healthy human volunteers[7]. Therefore, the efficacy and safety of 3 doses of ivabradine for relieving angina and underlying ischemia and the relation between drug-induced heart rate slowing and ischemia relief were explored in patients with stable angina[8].

Ivabradine hydrochloride is a novel medication used for the symptomatic management of stable angina pectoris[9]. Ivabradine acts by reducing the heart rate in a mechanism different from beta blockers and calcium channel blockers, two commonly prescribed anti-anginal drugs. It is classified as a cardiotonic agent[10]. The plasma half-life is about 2 hrs, and bioavailibility is 40%.

## MATERIALS AND METHOD

A variety of methods are used for the evaluation of tablets or conducting quality control tests of tablets. All of the quality control tests of tablets or evaluation tests oftablets are classified into three categories:

**(a) Non-Pharmacopoeial or Non-Official Tests or In-House Tests of Tablet:**

**Appearance/ Description:** The appearance of a tablet is crucial for patient compliance and identification. The control of the appearance of a tablet includes the measurement of a number of attributes such as a tablet's shape, surface texture, diameter, thickness, color, absenceor presence of an odor, taste, physical flaws and consistency, scoreline, and legibilityof any unique identification markings such as embossed or engraved with a logo or letter(s).

**Thickness and Diameter:** The thickness of the tablet is the only dimensional variable related to the tablet compression process. Generally, it is measured with a micrometer. The thickness should control within ±5% variation of a standard value and must control for patient acceptance and make the tablet packaging easier.

The diameter and shape of the tablets should control by the diameter and shape of thedie and punches during the compression process. USFDA recommends that the diameter of the tablet should be 8 mm or less than 8 mm and should not exceed 22 mm. Generally, tablet shapes are round, oval, oblong, caplet, cylindrical, triangular etc. The upper and lower surfaces of tablets may be flat, round, concave, or convex to various degrees. The diameter and shape of the tablet influence esophageal transit,administration techniques.

**Hardness:** The breaking force of tablets is commonly called "hardness" in the pharmaceutical literature. Certainly, tablets require a definite amount of hardness to withstand mechanical shocks of handling in manufacture, packaging, and transportation without affecting the disintegration limit. Generally, oral tablets have a hardness of 4 to 10 kg. However, ODT tablets and chewable tablets have less hardness and often sustained-release tablets are much harder.

**Organoleptic properties:** Organoleptic properties mean properties that can be sense by sensory organs like color, odor, and taste. These properties are important for patient acceptance.

**(b) Pharmacopoeial or Official Tests of Tablets**

**Identification Tests:** The identification test is specified in a product monograph as an aid to confirm that the tablet contains the labeled drug substance by providing positive identification of the active substance(s) and identification of specific excipient(s), such aspreservatives in a drug product. Methods used to orthogonally confirm the identity ofthe active ingredient are HPLC, TLC, NMR, FTIR, Raman Spectroscopy among others.

**Friability Test:** Friability testing is used to test the durability of tablets during transit (packing, transportation). Measurement of tablet friability supplements other physical strengthmeasurements, such as tablet breaking force. It is a pharmacopoeial test for the evaluation of tablets or quality control tests of tablets. A maximum weight loss (obtained from a single test or from the mean of three tests) of not more than 1.0% is considered acceptable.

**Disintegration Test:** Disintegration is the process by which a solid oral dosage form such as a tablet breaksdown into smaller particles or granules. The tablets must disintegrate and all particlesmust pass through the 10-mesh screen in the time specified.

**Weight Variation Test:** A weight variation test is performed to determine the consistency of formulated preparations. It is a pharmacopoeial test for the evaluation of tablets or quality controltests of tablets.

**Uniformity of Dosage Unit Test:** The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. To ensure the consistency of dosage units, each unit in a batch should have drug content within a narrow

range around the label claim.

**Dissolution Test:** In vitro, dissolutiontesting measures the extent and rate of solution formation from a dosage form (the amount of percentage of the drug substance in a dosage form such as tablets, or capsules to go into solution) within a specific time under a specified set of conditions.The terms dissolution and drug release are used interchangeably. The USP dissolutiontest in the monograph is related to Bioavailability and Bioequivalence study only when closely allied with a sound regulatory determination. Without this association,the dissolution test should be regarded solely as a quality control test for batch release[4]. It is a crucial pharmacopoeial test for the evaluation of tablets or quality control tests of tablets.

The volume of the dissolution medium is generally 500, 900, or 1000 ml. The use ofa hydro-alcoholic medium is discouraged. Certainly, conduct all dissolution tests forIR dosage forms at 37±0.5°C.

**Assay Test:** The assay is a specific and stability-indicating test to determine the potency (content)of the drug product. The assay of tablets expresses in the terms of grams, milligrams,or micrograms of drug per tablet. It is a crucial pharmacopoeial test for the evaluationof tablets or quality control tests of tablets. The assay limit is mentioned in the individual product monographs.

**Impurities Test:** Impurities in tablets are specified in an individual product monograph or maycalculate by ICH Q3B(R2) guidelines.

**(c) Specific Pharmacopoeial Tests of Tablets**

**Microbiological Examination of Tablets:** This test is used to determine the absence or limited occurrence of specified micro- organisms that may be detected under the conditions described. Some liquid oral products can be subject to extreme microbiological control, and others require none.

**Acid-Neutralizing Capacity:** Acid-Neutralizing Capacity is a pharmacopoeial test for the evaluation of tablets or quality control tests of tablets. Certainly, this test is applicable only to measure the acid-neutralizing capacity of an antacid tablet. NLT 5 mEq of acid

**Quality test of Splitting Tablets with Functional Scoring:** This test indicates that the label claim of the split portions should be a simple fractional part of the claim for the intact tablet based on the number of scores and thesize of the split portion. NLT 28 of the 30 tablets is acceptable.

**Water content:** The water content of tablets before and after stability study at specified temperaturesand humidity for a fixed time may determine to find out moisture impact on tablets. Generally, water content calculated by using the method is Karl Fischer titration

**RESULT AND DISCUSSION**

**Identification of drug Ivabradine**

**FT-IR study:** The spectrum of Ivabradine shows the following functional groups at their frequencies shown in Figure:

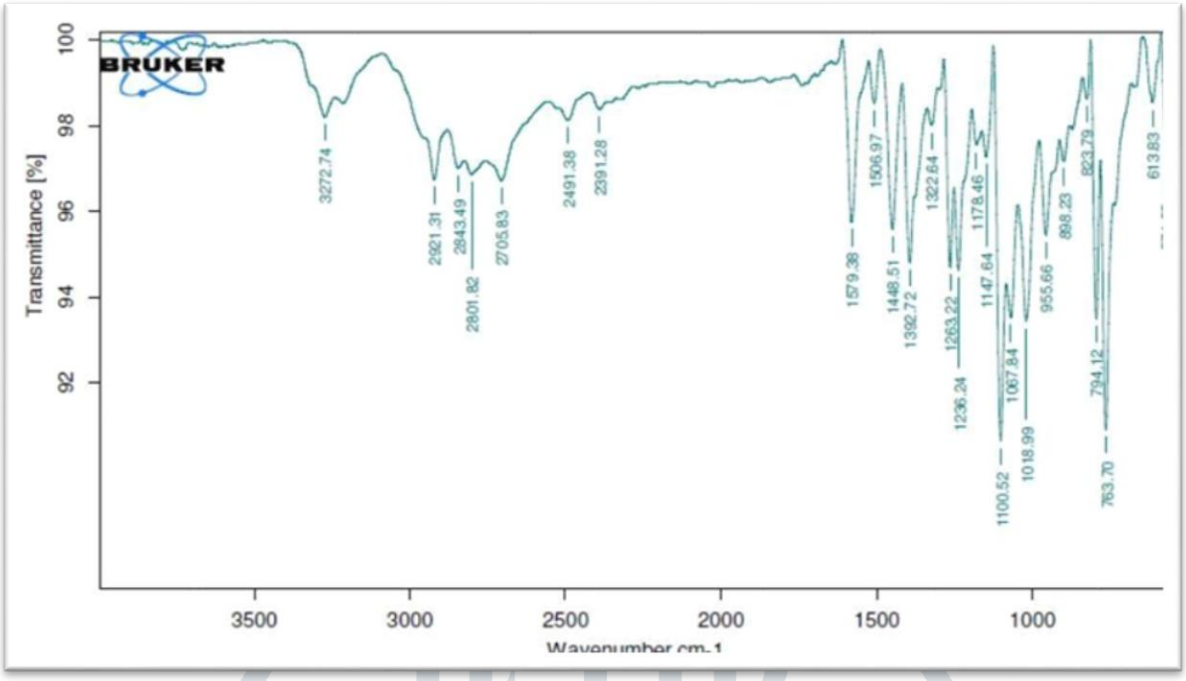


**Figure 1: FTIR spectrum of Ivabradine**

**Standard Calibration Curve in 6.8 pH phosphate buffer** Standard graph ofIvabradine in pH 6.8 phosphate buffer shows linearity in the concentration range of 5-30µg/ml with correlation coefficient of 0.999. Table 6.6 gives data of the standard graph.

**Table 1: Data for calibration curve of Ivabradine in pH 6.8 at 292nm**

| Concentration (µg/ml) | 0 | 5 | 10 | 15 | 20 | 25 | 30 |
|---|---|---|---|---|---|---|---|
| Absorbance | 0 | 0.167 | 0.305 | 0.468 | 0.602 | 0.768 | 0.899 |

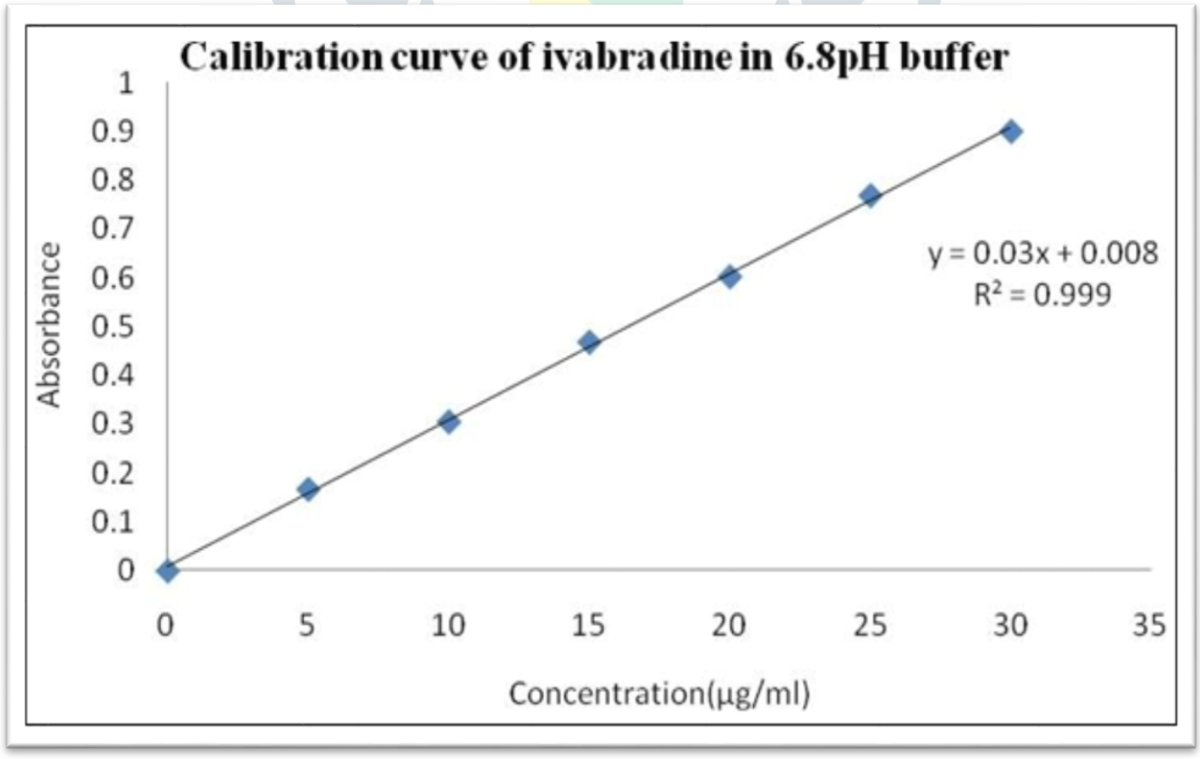


**Figure 2: Data for calibration curve of Ivabradine in pH 6.8 at 292nm**

**Evaluation of nine Marketed Tablet of Ivabradine**

**Table No. 2: pre compression Evaluation of nine Marketed Tablet of Ivabradine**

| Code | Angle of Repose ± SD | Bulk Density (g/ml) | Tapped Density(g/ml) | Carr's Index. (%) | Hausner's ratio |
|---|---|---|---|---|---|
| T1 | 28.16±0.03 | 0.458±0.26 | 0.521±0.45 | 12.09±0.26 | 1.14±0.26 |
| T2 | 29.30±0.26 | 0.453±0.23 | 0.521±0.56 | 13.05±0.23 | 1.15±0.35 |
| T3 | 27.02±0.15 | 0.354±0.12 | 0.41±0.14 | 13.66±0.15 | 1.16±0.14 |
| T4 | 28.16±0.45 | 0.376±0.02 | 0.432±0.23 | 12.96±0.48 | 1.15±0.52 |
| T5 | 29.41±0.53 | 0.371±0.14 | 0.429±0.64 | 13.52±0.51 | 1.16±0.85 |
| T6 | 25.16±0.63 | 0.363±0.52 | 0.416±0.74 | 12.74±0.26 | 1.15±0.74 |
| T7 | 27.50±0.15 | 0.452±0.63 | 0.516±0.85 | 12.40±0.32 | 1.14±0.63 |
| T8 | 26.15±0.47 | 0.395±0.25 | 0.468±0.54 | 15.60±0.46 | 1.18±0.12 |
| T9 | 26.03±0.56 | 0.386±0.42 | 0.448±0.26 | 13.84±0.85 | 1.16±0.20 |

**Table No. 3: Post- compression Evaluation of nine Marketed Tablet of Ivabradine**

| Code | Hardness (kg/cm2) | Thickness (mm) | Weight variation | Friability (%) | % Drug content(CV) | Surface pH | SI (after 8h) | Mucoadhesiv sterngth (gm) |
|---|---|---|---|---|---|---|---|---|
| T1 | 6.6± 0.15 | 2.03± 0.04 | 149± 0.30 | 0.51±0.26 | 92.26±0.76 | 6.26±0.02 | 21.16±2.26 | 4.01±0.15 |
| T2 | 6.7± 0.26 | 2.23± 0.09 | 151± 0.50 | 0.12±0.14 | 94.14±0.86 | 6.66±0.16 | 35.02±1.52 | 4.06±0.25 |
| T3 | 7.1± 0.51 | 2.02± 0.13 | 148± 0.63 | 0.26±0.52 | 93.52±1.02 | 5.98±0.41 | 46.42±1.15 | 4.26±0.16 |
| T4 | 6.1± 0.89 | 2.16± 0.05 | 149± 0.25 | 0.16±0.65 | 95.63±1.46 | 6.15±0.15 | 19.15±1.23 | 4.13±0.02 |
| T5 | 6.0± 0.85 | 2.21± 0.06 | 150± 0.40 | 0.41±0.15 | 94.15±0.89 | 6.16±0.56 | 39.46±2.12 | 4.29±0.15 |
| T6 | 6.1± 0.49 | 2.15± 0.04 | 149± 0.10 | 0.52±0.41 | 96.45±1.10 | 6.02±0.47 | 47.85±1.15 | 4.44±0.41 |
| T7 | 7.1± 0.74 | 2.20± 0.08 | 150± 0.20 | 0.36±0.02 | 93.12±0.36 | 6.15±0.26 | 26.52±1.20 | 4.36±0.52 |
| T8 | 6.4± 0.89 | 2.17± 0.09 | 148± 0.25 | 0.14±0.06 | 95.16±0.52 | 5.63±0.89 | 41.16±1.23 | 4.51±0.26 |
| T9 | 6.6± 0.84 | 2.13± 0.04 | 149± 0.40 | 0.16±0.04 | 97.14±1.15 | 5.98±0.74 | 50.02±2.15 | 4.66±0.18 |

**Table No. 4: *In vitro* dissolution data of Marketed Tablet T1 to T9**

| Time (hrs) | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 0.5 | 29.86 | 26.18 | 20.78±0.52 | 27.56±0.26 | 23.18±0.61 | 10.36±0.02 | 19.26±0.51 | 15.05±0.26 | 8.96±0.18 |
| 1 | 35.16 | 30.1 | 26.48±0.63 | 32.18±0.25 | 28.62±0.85 | 19.26±0.23 | 25.18±0.32 | 20.56±0.35 | 15.02±0.15 |
| 2 | 57.16 | 50.16 | 39.26±0.14 | 52.63±0.36 | 31.05±0.42 | 27.26±0.25 | 46.96±0.56 | 32.18±0.18 | 30.56±0.25 |
| 3 | 79.18 | 68.2 | 59.28±0.5 | 76.18±0.14 | 59.18±0.15 | 36.18±0.14 | 62.59±0.48 | 39.15±0.52 | 46.28±0.56 |
| 4 | 98.15 | 82.62 | 73.48±0.26 | 89.26±0.52 | 71.28±0.32 | 48.62±0.58 | 79.18±0.52 | 47.26±0.14 | 59.86±0.14 |
| 5 | | 97.16 | 86.18±0.85 | 98.05±0.56 | 85.15±0.39 | 69.48±0.56 | 86.17±0.01 | 69.48±0.56 | 72.61±0.85 |
| 6 | | | 98.42±0.45 | | 98.17±0.26 | 82.62±0.32 | 97.08±0.26 | 85.18±0.99 | 80.56±0.15 |
| 7 | | | | | | 99.18±0.14 | | 97.12±0.51 | 89.17±0.35 |
| 8 | | | | | | | | | 98.36±0.26 |

**Drug release kinetics**

**Zero Order:** The *in vitro* dissolution data for best formulation T9 were fitted in different kinetic models i.e, zero order, first order, Higuchi and Korsemeyer-Peppas equation. Optimizedformulation T9 shows $R^2$ value 0.986. As its value nearer to the '1' it is confirmed as it follows the zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 <n < 0.89 is for anomalous behavioror non-Fickian transport, n = 0.89 for case II transportand n >0.89 for Super case II transport.

The mechanism of release is anomalous, that is both diffusion and erosion are involved and the data was shown in the table 5.

**Table No. 5: Drug release kinetics**

| | **$R^2$ values** | | | | **n values** |
|---|---|---|---|---|---|
| **Formulation** | **Zero order** | **First order** | **Higuchi** | **Korsmeyer – Peppas** | **Korsmeyer-Peppas (n)** |
| T9 | 0.986 | 0.834 | 0.96 | 0.67 | 0.982 |

**CONCLUSION**

Ivabradine is a selective and specific inhibitor of the hyperpolarization-activated, mixedsodium/potassium inward If current, which contributes importantly to SAN pacemaker activity.3 In animal studies, at therapeutic concentrations, ivabradine has had little actionon other cardiac ionic currents or cardiac action potential shape.5,6 This may account forthe drug's lack of significant effects on myocardial contractility.

From the present study, the following conclusions can be drawn:

- Mucoadhesive Marketed Tablet of Ivabradine HCL can be prepared by direct compression method using Sodium CMC, HPMC K100M and Karaya gum as mucoadhesive polymers.
- All the marketed Tablet were found to be good without capping and chipping.
- IR spectroscopic studies indicated that there are no drug- excipient interactions.

- Post compression parameters of Ivabradine HCL were within the limits according to IP standards.
- As the amount of polymer in the tablets increases, the drug release rate decreases, whereas swelling index and mucoadhesion strength increase.
- Among all the 9 Marketed Tablet T9 formulation is optimized, as it shows maximum drug release at the end of 8hrs which suits the buccal drug delivery system criteria as per our studies. These Marketed Tablet have displayed good bioadhesion strength (4.66 gm)
- Optimized formulation (T9) displayed that it follows zero order release kinetics and drug release follows non- Fickian diffusion mechanism

**CONFLICTS OF INTERESTS**

There are no conflicts of interests

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