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Research Paper

A study on formulation and assessment of heart rate lowering agent ivabradine orally tablets

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ABSTRACT

Background: Ivabradine is a heart-rate-lowering drug used for the symptomatic treatment of chronic stable angina pectoris in patients with coronary artery disease, normal sinus rhythm, and a heart rate above 72 bpm, and for chronic heart failure. Film-coated tablets that are easy to swallow can improve patient compliance and dosage uniformity.
Objective: To develop and evaluate film-coated ivabradine tablets prepared by dry granulation, and to establish a method for quantifying ivabradine in the formulation.
Methods: Tablets were prepared by dry granulation. The F5 formulation used starch, anhydrous lactose, and microcrystalline cellulose PH 102 as diluents/binders, croscarmellose sodium to modify tablet strength, and sodium starch glycolate as the disintegrant. Purified talc and colloidal silicon dioxide were used as glidants, and magnesium stearate as the lubricant. The film coat contained hydroxypropyl methylcellulose (HPMC) 6 cps as the film-forming polymer, polyethylene glycol (PEG) 6000 as the plasticizer, and titanium dioxide as the opacifier. Tablets were evaluated for friability (%), thickness, hardness, disintegration time, drug content, and in vitro dissolution.
Results: Dry granulation gave satisfactory results for the F5 formulation. The tablets showed a drug content of 99.94% and in vitro drug release of 99.89%.
Conclusions: Film-coated ivabradine tablets with good drug content and complete in vitro dissolution were successfully prepared by dry granulation using the F5 formulation, which is a suitable approach for ivabradine delivery.

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1. INTRODUCTION

The compound known as ivabradine HCl is the earliest illustration in Figure 1., 3-(3-{[((7s)-3,4-Dimethoxybicyclo [4.2.0] octa-1,3,5-trien-7-yl) methyl] methylamino} propyk)-1,3,4,5 tetrahydro-2H-3-benzazepin-one, hydrochloride [1]. It dissolves as white powder in organic solvents such ethanol, DMSO, and dimethyl formamide and has a molecular weight of 468.6g /mol, the chemical formula C27H36N2O5, and a melting point between 135 and 1400C. Ivarabradine lowers heart rate. In April 2015, the FDA authorised ivabradine, a new cardiovascular medication, to help stable, symptomatic cardiovascular disease patients avoid hospitalization [2].

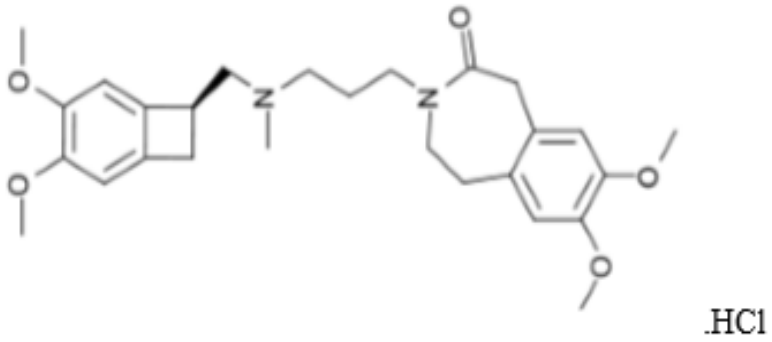


Figure 1. Ivabradine Hydrochloride's Structure

Ivabradine hydrochloride treats stable angina pectoris symptoms in a unique way. The drug must lower heart rate to work. Contrary to beta-blocking drugs, ivabradine does not appear to dilate inotropic characteristics in animal studies [3]. Ivabradine disables cardiac pacemaker IF (also called "clever channels") depending on dosage. Ivabradine metabolites are excreted in urine and faeces. Beta-blockers must be avoided or taken at maximally tolerated dosage [4].

2. RELATED WORK

Formulation and evolution of Ivabradine Hydrochloride orally Tablets has been significant research. In stable, symptomatic chronic heart failure patients with a left ventricular ejection fraction ≤ 35%, sinus rhythm, and resting heart rate ≥ 70 beats per minute, ivabradine, a hyperpolarization-activated cyclic nucleotide-gated channel blocker, reduces the risk of hospitalization due to worsening heart failure [5].

- **Angle of Repose (θ):** Fixed height funnels measured angle of repose. The equation determined the angle of repose, the funnel height was 2 cm (h), the circle diameter (D) was measured, and Table 1 listed the flow type. Tan θ= h/r (Or) θ= $\tan^{-1}$ (h/r), Let, θ = Angle of Repose, h = Heap height, r = Heap Radius.

Table 1. Angle of Repose

'Angle of Repose'	'Type of Flow'
<20	Excellent
20-30	Good
30-40	Fair
>40	Poor

3. METHODOLOGY

Ivabradine Hydrochloride, Anhydrous Lactose, Starch, Croscarmellose sodium, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Microcrystalline Cellulose PH102 were obtained as kind gift Sample from Alves Health care Pvt. Ltd. Baddi,. Purified Talc, Magnesium Stearate, Titanium Dioxide, Polyethylene

glycol 6000, Hydroxypropyl Methyl Cellulose 6 CPS, Purified Talc were obtained as kind gift Sample from Neptune Life Sciences Pvt. Ltd. Baddi,. All the materials were used as an analytical grade.

3.1 The Standard Calibration Curve in Phosphate Buffer with a Ph of 6.8 [5]

In the 5-30µg/ml concentration range, the standard Ivabradine graph in pH 6.8 phosphate buffer exhibits linearity with a correlation coefficient of 0.999.

3.2 Blend Estimation before Compression [5], [6], [7], [8]

- **Bulk Density (Db):** Volume was measured from 10 grammes of various powder mixtures in a 100 ml measuring cylinder. This formula determined bulk density. Db = m/Vo Where, m = mass of the powder, Vo = bulk volume of powder
- **Tapped Density (Dt):** A single 100-millilitre measuring cylinder held the sample powder. The cylinder was tapped 100 times. After recording the final volume, the following calculation determined the tapped density. Dt = m/Vi Where, m = mass of the powder, Vi = tapped volume of powder
- **Compressibility/Carr's Index:** Powder flowability can be assessed by comparing bulk density (Db), tapped density (Dt), and packing down rate. The Compressibility Index is calculated using: Compressibility index (%) = Dt – Db/Dt x 100, Where, Db = Bulk density, Dt = Tapped density

Table 2. Significance of Carr's Index

'Carr's Index'	'Types of Flow'
05-12	Excellent
12-16	Good
18-21	Fair
23-35	Poor
35-38	Very poor
More than 40	Extremely poor

- **Hausner's Ratio:** Divide bulk density by tapped density. Is given by: The Hausner ratio = Dt / Db. Let, Dt = Tapped density, beyond 1.25.Db = Bulk density. A Hausner's ratio below 1.25 indicates superior flow properties compared to a ratio

3.3 Making Tablets Containing 5 mg of Ivabradine [9], [10]

Tablets containing 5mg of Ivabradine were made via dry granulation technique with film coating.

Table 3. Preparation of Tablet Content

Sr. No.	Ingredients	Formulation (mg) F1	Formulation (mg) F2	Formulation (mg) F3	Formulation (mg) F4	Formulation (mg) F5
1.0	Ivabradine Hydrochloride	5.39	5.39	5.39	5.39	5.39
2.0	Anhydrous Lactose	8.00	75.61	8.00	75.61	75.61
3.0	Microcrystalline cellulose PH 102	75.61	8.00	74.00	70.00	74.00
4.0	Starch	74.00	74.00	75.61	12.00	8.00
5.0	Croscarmellose sodium	6.00	6.00	6.00	6.00	6.00
6.0	Sodium Starch Glycolate	7.00	7.00	7.00	7.00	7.00
7.0	Colloidal Silicon Dioxide	1.00	1.00	1.00	1.00	1.00
8.0	Purified Talc	1.00	1.00	1.00	1.00	1.00
9.0	Magnesium Stearate	2.00	2.00	2.00	2.00	2.00

Core tablet Average weight		180.00	180.00	180.00	180.00	180.00
10.0	Titanium Dioxide	2.00	2.00	2.00	2.00	2.00
11.0	Polyethylene glycol 6000	1.00	1.00	1.00	1.00	1.00
12.0	Hydroxypropyl Methyl Cellulose 6 CPS	1.50	1.50	1.50	1.50	1.50
13.0	Purified Talc	1.00	1.00	1.00	1.00	1.00
14.0	Purified Water	21.00	21.00	21.00	21.00	21.00
Coated tablet Average weight		185.50	185.50	185.50	185.50	185.50

3.4 Dry Granulation Methodology

Maximum relative humidity was 55% and temperature was 25°C during production.

- **Step I:** Given material Ivabradine Hydrochloride, Anhydrous Lactose, Starch, Microcrystalline cellulose PH 102, Croscarmellose sodium, Sodium starch glycolate, Colloidal Silicon Dioxide and Purified talc shifting were done using a 40mesh size. Independently shift Magnesium Stearate using a 60mesh size while maintaining a separate position.
- **Step II:** Ivabradine Hydrochloride, Anhydrous Lactose, Starch, Microcrystalline cellulose PH 102, Croscarmellose sodium, Sodium starch glycolate, Colloidal Silicon Dioxide and Purified talc and it should be blended for a duration of 20 minutes.
- **Step III:** Sifted Magnesium Stearate in step II and blend for 5 minutes.
- **Step IV:** The Lubricated Blend Was Moved for Compression.
- **Step V:** Utilized was an 8.0 mm, upper punch and lower Punch plain, round standard concave punch was used. The in-process parameter for the standard weight is 180.0 mg. The individual weight variation is 180.0 mg with a tolerance of +7.5%. The weight variation of 20 tablets is 3.600g with a tolerance of +5%. The thickness should be 3.8+0.3mm. The hardness should be 6.5+4Kp. The friability should not exceed 1.0%. The disintegration time should not exceed 15 minutes. Description- Round, biconvex, white to off-white, uncoated tablet with plain on both sides.
- **Step VI:** The in-process parameter of coated tablets for the standard weight is 185.50 mg. The individual weight variation is 185.50 mg with a tolerance of +7.5%. The weight variation of 20 tablets is 3.710g with a tolerance of +5%. The thickness should be 3.9+0.3mm. Weight Gain in % was not more than 3.0%. Description- Round, biconvex, white to off-white, film coated tablet with plain on both sides.

3.5 Tablet Characteristics after Compression [9], [10]

- **Thickness and Diameter In-Process Parameter:** Tablet diameter and thickness were measured with Vernier callipers.
- **Weight Uniformity In-Process Parameter:** After random selection, all twenty tablets were weighed for weight variance.

Table 4. Weight Uniformity Specifications

As per IP	
Avg. wt. of tablet	**% Deviation**
80 mg or <80	10
>80 mg to 250 mg	7.5
>250 or more	5
As per USP	
130 mg or less	±10
>130 mg and <324 mg	±7.5
324 mg or more	±5

- **Weight Variation In-Process Parameter:** The weight of the tablet was ascertained using a digital weighing balance. The average weight was calculated for each batch of 10 tablets.
- **Friability In-Process Parameter:** Shock and abrasion were applied to the tablets in a 25-rpm plastic chamber with a Roche friabilator separating them by six inches. Twenty pre-weighed tablets were rotated 100 times in the Friabilator. Tablets are weighed again after dusting. Traditional compressed tablets are suitable for weight loss under 1%.

$$Friability\ (\%) = \frac{initial\ weight - final\ weight\ x100}{Initial\ weight}$$

- **Hardness In-Process Parameter:** To endure mechanical shocks during manufacturing, packing, and delivery, tablets must be robust and resist friability. Tablet hardness was tested with a Monsanto hardness tester. The hardness of each batch's tablets was measured in kg/cm^2.
- **Disintegration Time Test In-Process Parameter:** The disintegration tester handled one pill each tube. Insert a disc into each tube. The assembly was suspended in the clean water beaker. After then, the gadget maintained a temperature of 37.0°C ± 0.2°C. The compressed tablet should breakdown after 15 minutes.
- **Measuring Drug Content [10]:** Twenty weighed, powdered tablets. Fill a 100-ml volumetric flask with 10 mg ivabradine tablet powder. Add 60 ml methanol. After 10 minutes of sonication and 15 minutes of shaking. To compensate for volume, use methanol. Whatman filter paper should filter this mixture.
- **In-Vitro Dissolution Study [9]:** A USP dissolving test apparatus Type II Paddle type, 500 mL of 0.1 M HCL, and 45 minutes were used for an in-vitro release investigation. The paddles spin 500 rpm. Medium temperature was 37 ± 0.50 C. After one minute, a 10-mL aliquot of the solution was removed from the dissolving equipment and replaced with new media. The extracted components were analysed at 285 nm with a hydrochloride acid buffer pH 1.2 as a blank using a Lab India UV spectrophotometer. At least one centimetre from the vessel wall and halfway between the spinning basket and the dissolving solution, aliquots were taken at one-minute intervals.

4. RESULTS AND DISCUSION

4.1 Ivabradine's Standard Calibration Curve

Table 5. Data for Ivabradine pH 6.8 Calibration Curve at 292nm

Concentration (µg/ml)	Absorbance
0	0
5	0.163
10	0.307
15	0.470
20	0.601
25	0.771
30	0.903

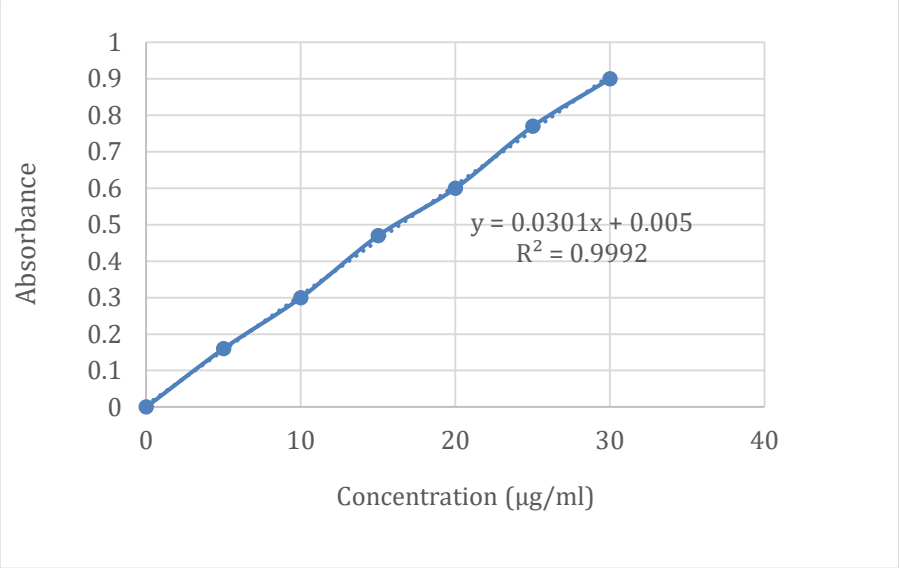


Figure 2. Ivabradine's Standard Curve

Table 6. Assessment of Pre-compression Blend

Formulations	'Angle of Repose' (degree± SD)	'Bulk Density' (g/mL± SD)	'Tapped Density' (g/mL± SD)	'Compressibility Index (%)' (%± SD)	'Hausner's ratio' (%± SD)
F1	24º.11±0.07	0.392±0.07	0.456±0.09	21.41±0.07	1.13±0.08
F2	23º.52±0.09	0.414±0.09	0.563±0.05	14.64±0.09	1.18±0.05
F3	26º.19±0.05	0.362±0.07	0.488±0.07	11.11±0.05	1.19±0.06
F4	25.28±0.09	0.408±0.06	0.503±0.05	13.51±0.08	1.11±0.05
F5	26º.71±0.08	0.582±0.09	0.669±0.08	11.88±0.09	1.13±0.09

Table 7. Assessment of Uncoated Tablets

Formulations	'Weight Variation' (mg)	'Hardness'(kg/cm²)	'Thickness' (mm)	'Friability' (%)	'Disintegrating time' (minutes)
F1	136±1.26	5.35±0.71	3.61±0.21	0.16±0.09	9 min 54 Second
F2	138±0.69	5.50±0.46	3.62±0.41	0.24±0.12	7 min 48 Second
F3	135±0.68	5.60±0.53	3.61±0.11	0.14±0.13	6 min 38 Second
F4	134±0.94	4.80±0.32	3.65±0.21	0.21±0.09	5 min 16 Second
F5	135±0.61	5.5±0.16	3.60±0.10	0.11±0.07	3 min 57 Second

4.2 Estimating the Drug Content

The ivabradine medication concentration was 89.10–99.94, within the permitted range.

Table 8. Estimating of % Drug

Formulation Code	%Drug Content
F1	89.10
F2	93.11
F3	96.17
F4	97.79
F5	99.94

4.3 In Vitro Drug Dissolution Investigations

Shown in Figure 3. In vitro drug release was 99.89%.

Table 9. In vitro Drug Dissolution

Time	In-Vitro Dissolution (%)
0	0
5	49.76
10	67.17
15	76.92
30	89.73
45	99.89

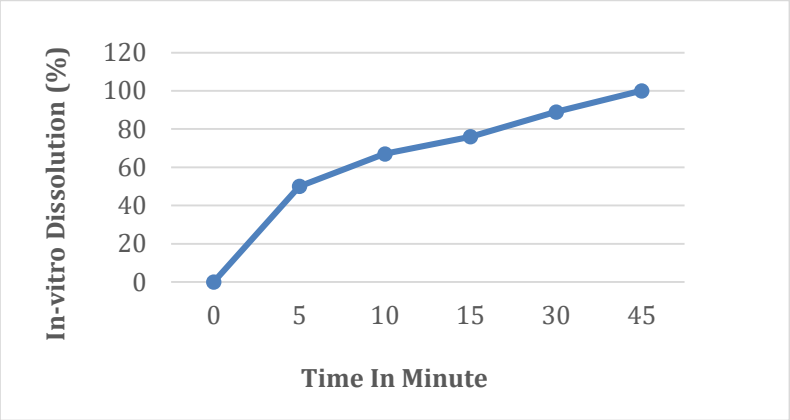


Figure 3. The In-Vitro Drug Release Profile of a Manufactured Tablet

5. CONCLUSION

Using the dry granulation process, 5 MG of Ivabradine film coated tablets were created. Microcrystalline Cellulose PH102, Anhydrous Lactose and starch were utilized as the main diluents in formulation. The parameters of individual weight variation, hardness, thickness, friability, and disintegration time for Ivabradine film coated tablets were assessed and determined to be adequate. Drug content was found 99.94% and in-vitro dissolution found 99.89% of formulated tablets.

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Author Contributions Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Dr. Virendra Kumar	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Informed Consent

All participants were informed about the purpose of the study, and their voluntary consent was obtained prior to data collection.

Ethical Approval

Not Applicable.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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