IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION DEVELOPMENT OF FILM COATED IVABRADINE TABLET

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Abstract:

Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate ≥ 70 bpm. Treatment of chronic heart failure. In this investigation film coated tablet were prepared by using Povidone as a polymer. By using polymer film coated tablet were prepared by wet granulation method. Prepared tablets were evaluated for thickness, hardness, friability, weight variation, Disintegrating time, drug content and invitro drug release.

Keywords: Povidone, Ivabradine HCL, film coated tablet.

Introduction

Heart failure is characterized by the heart's inability to pump an adequate supply of blood to the body. Without sufficient blood flow, all major body functions are disrupted. Heart failure is a condition or a collection of symptoms that weaken your heart. In some people with heart failure, the heart has difficulty pumping enough blood to support other organs in the body. 9It can be either an acute (short-term) or chronic (ongoing) condition. In acute heart failure, the symptoms appear suddenly but go away fairly quickly. This condition often occurs after a heart attack. Symptoms of heart failure may include excessive fatigue, sudden weight gain, A loss of appetite, persistent coughing, irregular pulse, Heart palpitations, Abdominal swelling, Shortness of breath, Leg and ankle swelling and Protruding neck veins. The most common cause of heart failure is coronary artery disease (CAD), a disorder that causes narrowing of the arteries that supply blood and oxygen to the heart. Evaluation for ischemic heart disease is warranted in patients with heart failure, especially if angina is present, given that coronary artery disease is the most common cause of heart failure. [1]

Materials and methods

Materials

Ivabradine was obtained as gift sample from Ind-swift Laboratories Ltd. The Microcrystalline cellulose and Croscarmellose sodium was purchased from Dupond Nutrition. Povidone was received from BASF-SE. Colloidal silicon dioxide was purchased from Cabot Sanmar Ltd. Magnesium Stearate was purchased from Valtris Specialty Chemicals. Opadry pink was purchased from Colorcon Asia Pvt. Ltd. All other materials used were of analytical grade.

Methods

Preparation of standard curve of Ivabradine HCL: [2]

Ten tablets are taken from each batch were accurately weighed and crushed in mortar and pestle, and tablets powder equivalent to 5 mg Ivabradine was taken and first dissolved in 5 ml of 0.1N HCL and volume was made up to 10 ml by using 0.1N HCL. Then 0.1 ml of this solution was diluted up to 10 ml using 0.1N HCL. This solution was measured using UV Visible spectrophotometer (Shimadzu 1800) at 285 nm against blank reagent.

Drug excipient compatibility studies:

Excipients are integral components of almost all pharmaceutical dosage forms. Excipients are integral components of almost all pharmaceutical dosage forms. Drug excipient interaction was studies by FTIR spectroscopy. The spectra were recorded for pure Ivabradine HCL and with excipient mixture. Drug excipient interactions were studied by FTIR spectroscopy. The scanning range was 400-4000 cm -1.

Formulation development:

Preparation of film coated tablets by wet granulation: [3]

Seven different formulations were prepared by wet granulation method by different type of film coated polymers. These polymers forming a thin layer on to the tablet thereby it improve appearance, organoleptic properties, or to facilitate swallowing. Functional film coats can also be used as a part of the product's stabilization strategy.

Film coated Ivabradine tablet was formulated by using matrix forming polymer.

Table No. 1. Composition of film coated Ivabradine tablets

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7
1	Ivabradine HCL (Crystalline)	5.390	5.390	5.390	5.390	5.390	5.390	5.390
2	Microcrystalline cellulose (Avicel PH-101)	87.610	87.610	87.610	87.610	87.610	87.610	87.610
3	Croscarmellose sodium (Ac-Di-Sol)	-	-	1.500	2.500	1.500	-	1.420
4	Sodium Starch Glycolate	-	1.000	3.000	-	-	3.000	-
5	Povidone	3.000	2.000	1.500	2.500	1.500	3.000	1.500
6	Colloidal silicon dioxide (200/M-5P)	1.500	1.500	1.500	-	3.000	3.000	1.580
7	Croscarmellose sodium (Ac-Di-Sol)	1.500	1.500	-	2.500	-	-	1.500
8	Magnesium Stearate	1.000	1.000	1.000	1.000	1.000	1.000	1.000
9	Opadry 21K540036 pink	3.00	3.00	3.00	3.00	3.00	3.00	3.00
10	Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Average weight		103.0	103.0	103.0	103.0	103.0	103.0	103.0

Note: all quantities were taken in milligrams.

Evaluation of pre-compression parameters of granules: [3]

Prepared lubricated blend of Ivabradine, were evaluated for their flow properties. Various parameters such as angle of repose, bulk density, tapped density, hausner's ratio, and compressibility index were determined.

Table No. 2. Standard Parameters of compressed tablet

Parameters		Standard
Dimension:	**Length:**	8.4 mm to 8.7 mm
	Width:	4.1 mm to 4.4 mm
Friability:		NMT 1.0% w/w
Wt. of 20 tablets:		2.000 g ± 3.0% (Limit: 1.940 g to 2.060 g)
Avg. wt. of tablets:		100.0 mg ± 3.0% (Limit: 97.00 mg to 103.00 mg)
Uniformity of weight:		Not more than 2 of the individual weights deviate from the average weight by more than ± 7.5% and none deviate by more than ± 15.0%.
Thickness:		2.8 mm ± 0.4 mm (Limit: 2.4 mm to 3.2 mm)
Hardness:		NLT 6.0 kp
Disintegration time:		NMT 15 min

Table No. 3. Standard parameters of coated tablets

Parameters		Standard
Wt. of 20 tablets:		2.060 g ± 3.0 % (Limit: 1.998 g to 2.122 g)
Avg. wt. of tablets:		103.000 mg ± 3.0 % (Limit: 99.910 mg to 106.090 mg)
Dimension:	**Length :**	8.5 mm to 8.8 mm
	Width:	4.2 mm to 4.5 mm
Uniformity of weight:		Not more than 2 of the individual weights deviate from the average weight by more than ± 7.5% and none deviates by more than ± 15.0%.
Thickness:		2.9 mm ± 0.4 mm (Limit: 2.5 mm to 3.3 mm)
Disintegration time:		NMT 30 min.

Coating:

Coating solution preparation:

Purified water was transferred into a clean SS vessel and Opadry Pink added with constant stirring and kept the solution under stirring for about 45 min. Then coating solution filtered through 80#.

Coating process:

Through front opening of pan compressed tablets were loaded into the perforated coating pan. Then inlet and exhaust air started. Tablets were dried for 15 min to de-dust the tablets. Pre warmed the tablets at 40 to 60°C inlet temperature and pan in inching mode. After weight gained (Limit: % wt. gain 2.5 % to 3.5 %) of pre-warmed core tablets, tablets were kept for drying at 50°C to 70°C inlet temperature for 5 min with pan in inching mode. Coating was continuing till desired weight gain is achieved. 20 tablets were withdrawn during coating process to check weight gain at each interval. Then tablets were checked for uniform coating.

Table No. 4 Standard parameters of coated tablets

Parameters		Standard
Wt. of 20 tablets:		2.060 g ± 3.0 % (Limit: 1.998 g to 2.122 g)
Avg. wt. of tablets:		103.000 mg ± 3.0 % (Limit: 99.910 mg to 106.090 mg)
Dimension:	**Length :**	8.5 mm to 8.8 mm
	Width:	4.2 mm to 4.5 mm
Uniformity of weight:		Not more than 2 of the individual weights deviate from the average weight by more than ± 7.5% and none deviates by more than ± 15.0%.
Thickness:		2.9 mm ± 0.4 mm (Limit: 2.5 mm to 3.3 mm)
Disintegration time:		NMT 30 min.

Evaluation of tablet [3, 4]

All the prepared core tablets were evaluated for the following official and unofficial tests described in pharmacopoeia or in standard text books or research articles.

General Appearance: The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. Includes tablet size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape: The size and shape of the tablet can be dimensionally described, monitored and controlled.

Friability: The ability of the tablet to withstand abrasion in packaging, handling and shipping. Friability was determined by the using USP friabilator apparatus. A number of tablets are weighed and placed in the apparatus where they were exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Friability is expressed in percentage.

$$\% \text{ Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Tablet thickness: Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Thickness of tablet should be recorded by using digital vernier caliper. It is expressed in mm.

Hardness (Crushing strength): Hardness indicates the ability of the tablet to withstand mechanical shocks while handling. Hardness of the tablet recorded by Monsanto hardness tester. It is expressed in kg/cm^2 or kp

Weight variation:

Twenty tablets are selected randomly from each batch and weighed individually to check weight variation. Calculate average weight and comparing the individual tablet weights the average. The tablet meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. A little variation is allowed in weight of a tablet. The following percentage deviation shown in table No. 7.5 in weight variation is allowed.

Table no. 5 Weight variation parameters

Average weight of tablet	Percentage deviation
130 mg or less	±10
>130 mg and <324 mg	±7.5
324 mg or more	±5

In all the formulations, the tablet weight is 290 to 310 mg, hence ±7.5% maximum difference allowed.

Disintegration test:

In disintegration testing apparatus introduced 1 tablet in each tube. Then disc added in each tube. Assembly was suspending in the beaker containing purified water. Then temperature of apparatus maintained at 37.0°c ± 0.2°c. Compressed tablet should disintegrate within 15 min.

Drug content

Drug content of prepared film coated tablet was determined by UV Spectrophotometric method for more accurate results as follows:

Spectrophotometric conditions [5]

Apparatus : UV Spectrophotometer. SHIMADZU (1800).
Wavelength : 285 nm for Ivabradine.

Preparation of sample solution:

Ten tablets are taken from each batch were accurately weighed and crushed in mortar and pestle, and tablets powder equivalent to 5 mg Ivabradine was taken and first dissolved in 5 ml of 0.1N HCL and volume was made up to 10 ml by using 0.1N HCL. Then 0.1 ml of this solution was diluted up to 10 ml using 0.1N HCL. This solution was measured using UV visible spectrophotometer (Shimadzu 1800) at 285 nm against blank reagent.

Calculation of drug content:

From the calibration curve the unknown concentrations of sample solutions were calculated. Same procedure was followed for each batch.

In-vitro Dissolution Studies [6, 7]

Details of Dissolution Test:

Dissolution test apparatus : USP apparatus Type II
Speed : 50 rpm
Stirrer : Paddle type
Volume of medium : 500 mL
Sample withdraw at each time intervals : 10 mL
Medium used : 0.1 M HCL
Temperature : 37 ± 0.5 ^{0}C

In-vitro release study was carried out (USP dissolution test apparatus Type II Paddle type) using 500 mL, 0.1 M HCL for 45 min. The Paddle are rotated at 500 rpm. The medium was set at 37 ± 0.5^0 C. Aliquot (10 mL) of the solution was collected from the dissolution apparatus after 1 min and was replaced with fresh dissolution medium The withdrawn samples were analyzed by an UV spectrophotometer (Lab India) at 285 nm using hydrochloride acid buffer pH 1.2 as a blank. Aliquots were withdrawn at one min interval from a zone midway between the surface of dissolution medium and the top of rotating basket not less than 1 cm apart from the vessel wall.

Result and discussion:

Physiochemical Parameters of drug:

Description: White to off white powder, hygroscopic
Solubility: Ivabradine HCL is freely soluble in dimethyl sulphoxide and methanol; soluble in water and methylene chloride.
Melting point: Melting point of Ivabradine HCL measured by using digital melting point apparatus, it matches with the standard value.

Table No. 6 Melting Point Determination

Drug Name	Ivabradine
Standard	135 - 140 ºC
Observed	138 ºC

Flow property of drug:

Table No. 7 Powder characterization of pure drug

Parameter	Ivabradine
Bulk Density (g/ml)	0.0365
Tapped Density (g/ml)	0.408
Carr's Index (%)	11.4
Hausner's ratio	1.129
Angle of repose	32.43

There was need to increase the flow properties of drug because from the above data it was concluded that these drug have poor flow properties. Ivabradine drug has angle of repose 32.43 is passable according to standard values.

Characterization of drug:
Identification of drug was carried out by UV spectroscopy, IR spectroscopy and melting point determination.

UV spectroscopy:

UV spectrum of Ivabradine in 0.1N HCL.

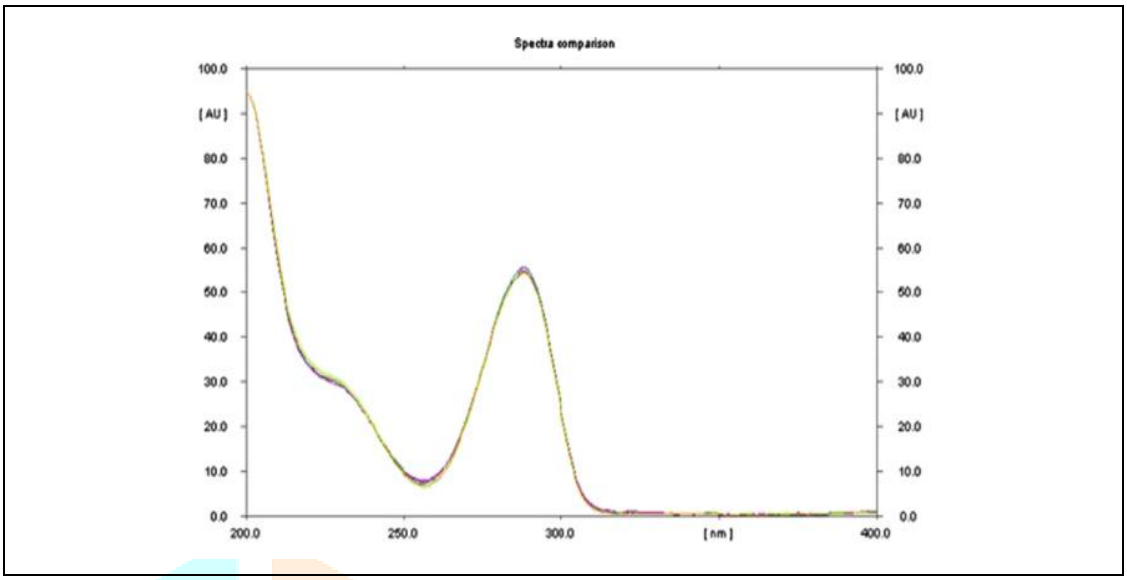

Figure No. 1 UV spectrum of Ivabradine in 0.1N HCL

Table No. 8 Absorption maxima of drugs

Drug	Solvent	Absorption maxima (nm)
Ivabradine	0.1 N HCL	285

Standard calibration curve of Ivabradine in 0.1N HCL

Solvent : 0.1N HCL
Wavelength : 285 nm
Equation for standard curve : y=0.019x-0.010
Correlation coefficient (R^2) : 0.998

Table No. 9 Calibration curve of Ivabradine

Sr. No.	Concentration (mcg/ml)	Absorbance
1	10	0.21
2	20	0.39
3	30	0.604
4	40	0.81
5	50	0.98

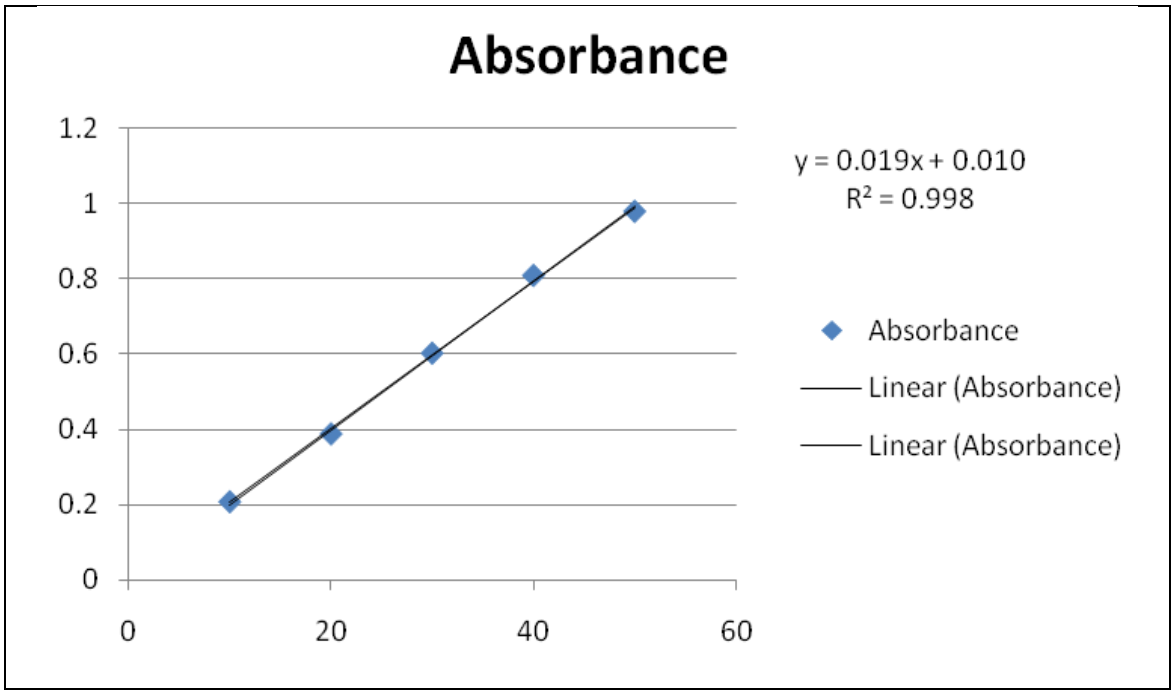

Figure No. 2 Calibration curve of Ivabradine

Table No. 10 Results of standard calibration curve

Drug	Solvent	Linearity range (mcg/ml)	Linear equation	Correlation coefficient (R^2)
Ivabradine	0.1N HCL	10-50	y=0.019x-0.010	0.998

FTIR Spectroscopy:

FTIR spectra of Ivabradine HCL.

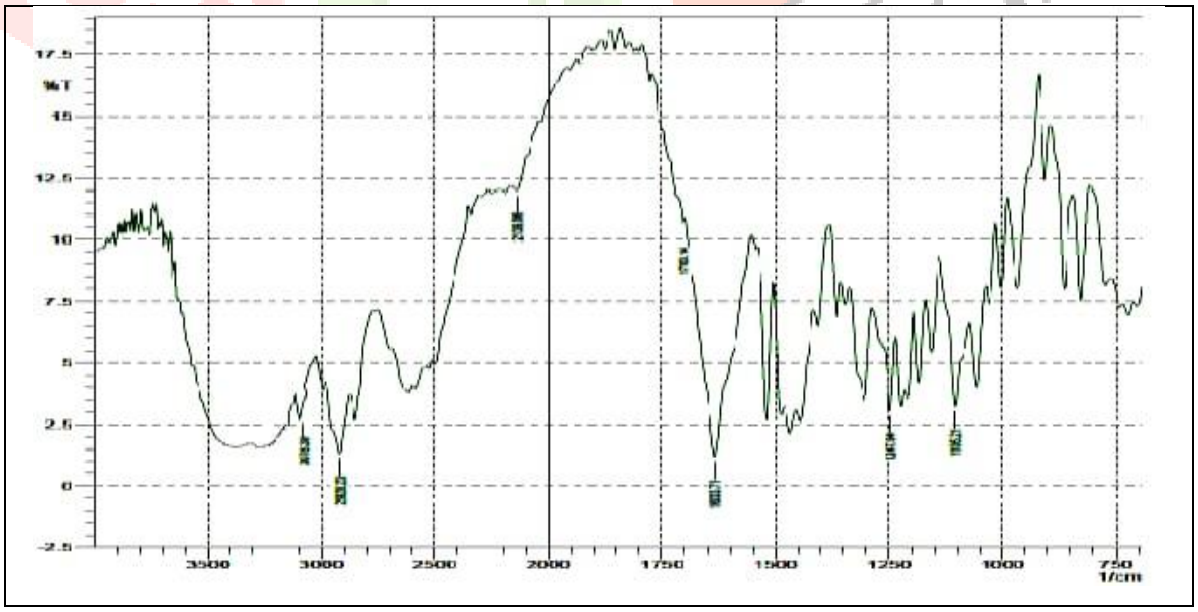

Figure No. 3 FTIR Spectra of Ivabradine

Conclusion:
From the above data of UV spectroscopy and FTIR spectroscopy the drug Ivabradine were confirmed as the all the values match with the reference values.

Evaluation of Pre-Compression granules

Table No. 11 Evaluation of Ivabradine granules

Formulations	Parameters				
	Angle of repose (degree)	BD (g/ml)	TD (g/ml)	HR	CI (%)
F1	23.13	0.25	0.48	1.17	11.68
F2	21.10	0.28	0.49	1.16	11.65
F3	25.15	0.36	0.51	1.14	11.64
F4	28.09	0.30	0.48	1.15	11.62
F5	24.14	0.26	0.50	1.14	11.66
F6	25.07	0.32	0.53	1.15	11.65
F7	26.14	0.38	0.54	1.14	11.65

The value of F7 formulation for bulk density and tapped density was found as 0.38 g/ml and 0.54 g/ml respectively. The Carr's Compressibility indices were observed 11.65 % and angle of repose were 26.14°. This indicates that F7 formulations have good flow property.
Hence no chances of any defects during compression of tablet compression problems.

Evaluation of compressed tablet

Table No. 12 Evaluation of compressed tablet

Evaluation Parameters	Batches						
	F1	F2	F3	F4	F5	F6	F7
Appearance	White to off white coloured, capsule shaped biconvex uncoated tablet with breakline on one side and plain on other side.						
Weight variation (mg)	96.0	94.2	110.1	105.3	106.5	104.3	101.0
Thickness (mm)	2.30	2.95	3.41	3.35	3.60	3.03	2.84
Hardness (kp)	30.1	25.6	24.8	26.2	35.2	24.9	27.6
% Friability	1.01	0.49	0.52	0.84	1.21	1.19	0.40
Disintegration Time (min/sec)	2 min 29 sec	1 min 21 sec	1 min 26 sec	2 min 19 sec	1 min 39 sec	2 min 5 sec	1 min 40 sec

Evaluation of Film coated tablet

Table No. 13 Evaluation of Film coated tablet

Evaluation Parameters	Batches						
	F1	F2	F3	F4	F5	F6	F7
Appearance	Salmon coloured, capsule shaped, biconvex, film coated tablet, with breakline on one side and plain on other side						
Weight variation (mg)	96.9	94.8	110.7	106.3	106.8	104.9	104.0
Thickness (mm)	2.37	3.15	3.90	3.75	3.98	3.85	2.84
Disintegration Time (Min)	4 min 29 sec	5 min 21 sec	8 min 26 sec	5 min 19 sec	3 min 39 sec	4 min 5 sec	3 min 45 sec

The observations of F7 formulations showed uniform thickness. F7 batch passed weight variation test and found to be within the range. Disintegration time of all the formulations i.e. F1 to F7 are within the limit. Friability was less than 1 % for F7 batch, indicates that surfaces are strong enough to withstand mechanical shock or attrition during storage, transportation and until they are consumed.

Dissolution Test:

Table No. 14 In-vitro drug release profile of Ivabradine Film Coated Tablet

Time (min.)	% Drug Release							
	F1	F2	F3	F4	F5	F6	F7	MKT
0	0	0	0	0	0	0	0	0
5	50.67	49.40	53.87	51.97	51.14	50.90	50.09	47.40
10	61.78	68.34	72.32	68.30	71.24	61.94	66.46	69.22
15	68.83	87.27	89.76	80.38	80.31	91.09	77.55	87.54
30	90.57	93.10	98.70	95.78	91.90	95.40	88.75	93.60
45	95.20	95.46	99.54	97.78	97.06	98.49	99.06	97.12

The trial batches dissolution test was performed by comparing with marketed formulation and the results are within the acceptance criteria.

Conclusion:

From the experimental work performed it is concluded that:

F7 is the optimized batch and shows all results within the acceptance criteria. The lubricant ratio between 1-5 % is excellent for the formulation.

Acknowledgement: The authors are thankful to Sandip institute of pharmaceutical science, mahiravni, Nashik for providing necessary facilities to carry out the research work.

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