INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN: 2320-2831

IJPAR |Vol.4 | Issue 4 | Oct- Dec -2015
Journal Home page: www.ijpar.com

Research article *Open Access*

Formulation and evaluation of oro-dispersible tablets of ivabradine by sublimation technique

Afreen Quereshi*, Salma Yasmeen, M.Suresh Babu.

Department of Pharmaceutics, Deccan School of Pharmacy, Hyderabad, Telangana 500001, India

Corresponding Author: Afreen Quereshi

E-mail: afreen_quereshi@yahoo.in

ABSTRACT

Recent developments in Oro-dispersible/disintegrating tablets have brought convenience in dosing to elderly and children who have trouble in swallowing tablets. The objective of the present study was to prepare the mouth disintegrating tablet of ivabradine. Tablets of drug were prepared by sublimation method or technique. In the formulation of ivabradine oro dispersible tablets, initially ivabradine fused with cross Carmellose sodium (optimized super disintegrate), is used as API and sublimating agent menthol were added to the formulation, results showed that 99% was released in 15min in formulation (F7), and 94% was released in 30min from the formulation containing super disintegrant Cross povidone (F8), and 95% was released in 30min from the formulation containing super disintegrant sodium starch glycolate (F9). In formulation F7, the super disintegrant CCS (15%) and sublimating agent menthol (10%) was added and 99% was released in 15min, which is the highest amongst all and hence this is finalized. All these tablets showed required hardness, limited friability and good disintegration time (with in IP and USP limits). All the formulations were evaluated for drug content and results are obtained. Amongst all formulations, formulation F7 and CCS as super disintegrant showed the least disintegration time and faster dissolution.

Key words: Ivabradine, Sublimation technique, Bioavailability, Super disintegrants.

DRUG DELIVERY SYSTEM[1]

Dosage forms are also referred to as "Drug Delivery Systems" or "Finished Drug Products". A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and site of release of drugs in the body. The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment. Oral route of drug administration is most appealing route for delivery of drugs for various dosage forms. The tablet is one of the most preferred dosage forms, because of its ease of administration, accurate dosing and stability as compared to oral liquid dosage forms.

TABLETS[2]

Tablets may be defined as the solid pharmaceutical dosage forms containing drug substances with or

without suitable diluents and prepared either by compression or moulding methods. They have been in wide spread use since the latter part of the 19th century and their popularity continues. The term compressed tablet is believed to have been first used by "JOHN WYETH". Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer and the patient.

SUBLIMATION TECHNIQUE/METHOD[4]

Sublimation is the process of transformation directly from the solid phase to the gaseous phase without passing through an intermediate liquid phase. Sublimation is an endothermic phase transition that occurs at temperatures and pressures below a substance's triple point in its phase diagram At normal pressures, most chemical compounds and elements possess three different states at different temperatures. In these cases, the transition from the solid to the gaseous state requires an intermediate liquid state. Note, however, that the pressure referred to here is the partial pressure of the substance, not the total (e.g., atmospheric) pressure of the entire system. So, all solids that possess an appreciable vapor pressure at a certain temperature usually can sublime in air (e.g., water ice just below 0°C).5 For some substances, such as carbon and arsenical, sublimation is much easier than evaporation from the melt, because the pressure of their triple point is very high, and it is difficult to obtain them as liquids. The key to rapid disintegration for mouth dissolving tablets3 is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fall to dissolve rapidly because of low porosity of the matrix. Hence to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. In studies conducted by Heinemann and Rothe, Knitsch et al., and Roser and Blair, inert solid ingredients that displayed high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethonium tetramine, naphthalene, phthalic anhydride, urea, and urethane were compressed along with other excipients into a tablet. The volatile material was then removed by sublimation, leaving behind a porous matrix. Solvents such as cyclohexane and benzene were also suggested for the generation of porosity in the matrix.6

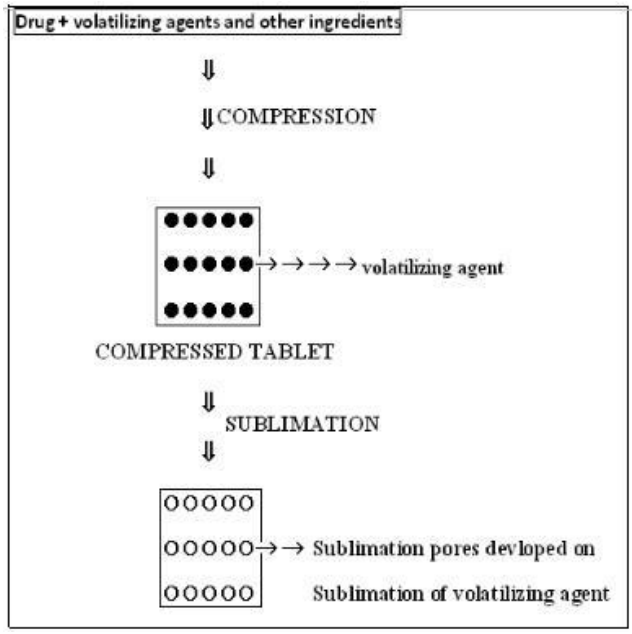


Figure: 1.10. Process of sublimation of volatilizing agent from Compressed Tablet

SCOPE'S FOR THE PRESENT WORK

- To formulate immediate release dosage form of ivabradine for the better and immediate treatment of angina.
- To overcome drawbacks and Side Effects, an attempt was made to design and evaluate Oro Dispersable tablets of ivabradine.
- To formulate and evaluate oro-dispersable tablets that should give maximum or immediate effect within a shorter period of time with long duration of action.
- To prepare such a tablets that can be easily administered to every age group population and to

that patients who cannot take tablets, capsules, and those who on different stages of diseases.7

PREPARATION OF TABLETS BY SUBLIMATION TECHNIQUE[8, 9, 10]

- Sublimation is the transition of a substance directly from the solid to the gas phase without passing through the intermediate liquid phase. Sublimation is an endothermic phase transition that occurs at temperatures and pressures below a substance's triple point in it phase diagram.
- Sublimation has also been used as generic term to describe phase changes between solid and gas that avoid the liquid state without specifying the direction of the transition.
- For some substances, such as carbon and arsenic, sublimation is much easier than evaporation from the melt, because the pressure of their triple point is very high, and it is difficult to obtain them as liquids.
- Sublimation requires additional energy and is an endothermic change. The enthalpy of sublimation (also called heat of sublimation) can be calculated as the enthalpy of fusion plus the enthalpy of vaporization.

DRUG - EXCIPIENT COMPATIBILITY STUDY

Fourier Transform infra-red (FTIR) spectroscopy

Infrared spectroscopy is a useful analytical technique utilized to check the chemical interaction between the drug and excipients used in the formulation.1-2 mg of solid fine powder of ivabadrine and 200-300 mg of dry powder of KBr (IR grade) were taken in a mortar and mixed well with the help of a spatula. Spectrum measurement was carried out using KBr disk method in the wavelength region of 4000-400cm-1 by FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with that of the pure drug to check any possible drug-excipient interaction.

FORMULATION OF IVABADRINE ORODISPERSIBLE TABLETS

Direct compression

- Lactose monohydrate, starch, cross Carmellose sodium/sodium starch glycolate/cross povidone were weighed and sifted through 40 mesh.
- To the above blend IVABRADINE was added.
- To the above blend add magnesium Stearate, talc and vanillin and menthol and mix or triturate well for 3-4min.
- The lubricated blend was compressed using 8mm round punches.
- Keep the compressed tablets in a Petri dish for 12 hrs for the sublimation of menthol and carry out the post formulation studies.

COMPOSITION OF FORMULATIONS

Table no: 3.3 a

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ivabradine	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Starch	7.5	7.5	7.5	5	5	5	5	5	5
Lactose monohydrate	111.75	111.75	111.75	111.75	111.75	111.75	111.75	111.75	111.75
Crosscarmellose sodium	7.5	10	10	12.5	12.5	12.5	15	--	--
Crosspovidone	--	--	--	--	--	--	--	7.5	--
Sodium starch glycolate	--	--	--	--	--	--	--	--	7.5
Mg. Stearate	3.75	3.75	3.75	2.5	2.5	2.5	2.5	2.5	2.5
Talc	3.75	3.75	3.75	2.5	2.5	2.5	2.5	2.5	2.5
Methanol	5	5	7.5	5	7.5	10	10	5	5
Vanillin	0.75	0.75	0.75	0.5	0.5	0.5	0.5	0.5	0.5
Total weight	**150mg**	**150mg**	**150mg**	**150mg**	**150mg**	**150mg**	**150mg**	**150mg**	**150mg**

POST COMPRESSION EVALUATION OF TABLETS[11, 12]

To design tablets and later monitor tablet production quality, quantitative evaluation and assessment of tablet chemical, physical and bioavailability properties must be made. The important parameters in the evaluation of tablets can be divided into physical and chemical parameters.

Physical appearance

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, colour, presence or absence of odour, taste, surface texture and consistency of any identification marks.

Hardness test

This is the force required to break a tablet in a diametric compression. Hardness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture.

Tablet size and Thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Callipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition thickness must be controlled to facilitate packaging.

Friability

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

%Friability = (W1-W2)/W1 X 100

Where, W1= weight o f tablets before test

W2 = weight of tablets after test

Weight variation of Tablets

It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits

Acceptance criteria for tablet weight variation

Table no: 3.7.a

Average weight of tablet(mg)	Maximum % difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

Twenty tablets were taken randomly and weighed accurately. The average weight was calculated by,

$$\text{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

Disintegration test

Disintegration time is considered to be one of the important criteria in selecting the best formulation. To achieve correlation between disintegration time in-vitro and in-vivo, several methods were proposed, developed and followed at their convenience. One tablet was placed into each tube and the assembly was suspended into the 1000ml beaker containing water maintained at 37±2oc and operated the apparatus for 15 minutes. The assembly was removed from the liquid and the tablets were observed. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated.

Estimation of drug content

From each batch of prepared tablets, ten tablets were collected randomly and powdered. 50 mg of powder, which was equivalent to 10 mg of drug, was accurately weighed and transferred to 100ml volumetric flask. Then the volume was made up with, PH-6.8 phosphate buffer and shaken or 10 min to ensure complete solubility of the drug. Then the solution was filtered. Same concentration of standard solution was prepared by dissolving 10 mg of standard drug in PH-6.8 phosphate buffer. For both the sample and standard solutions absorbance was measured at 277 nm in UV-Visible spectrophotometer.

Dissolution test

Dissolution

It is the amount of the solid substance that goes into the solution per unit time under standard conditions of the temperature and pressure

Method

Dissolution media was taken as 6.8pH phosphate buffer, 500ml was placed in the vessel and the USP apparatus – 2 (paddle) was assembled. The medium was allowed to equilibrate to temp of 37 + 0.5°C. Tablet was placed in the vessel; the apparatus was operated at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fluid was replaced. The samples were analyzed using U.V.

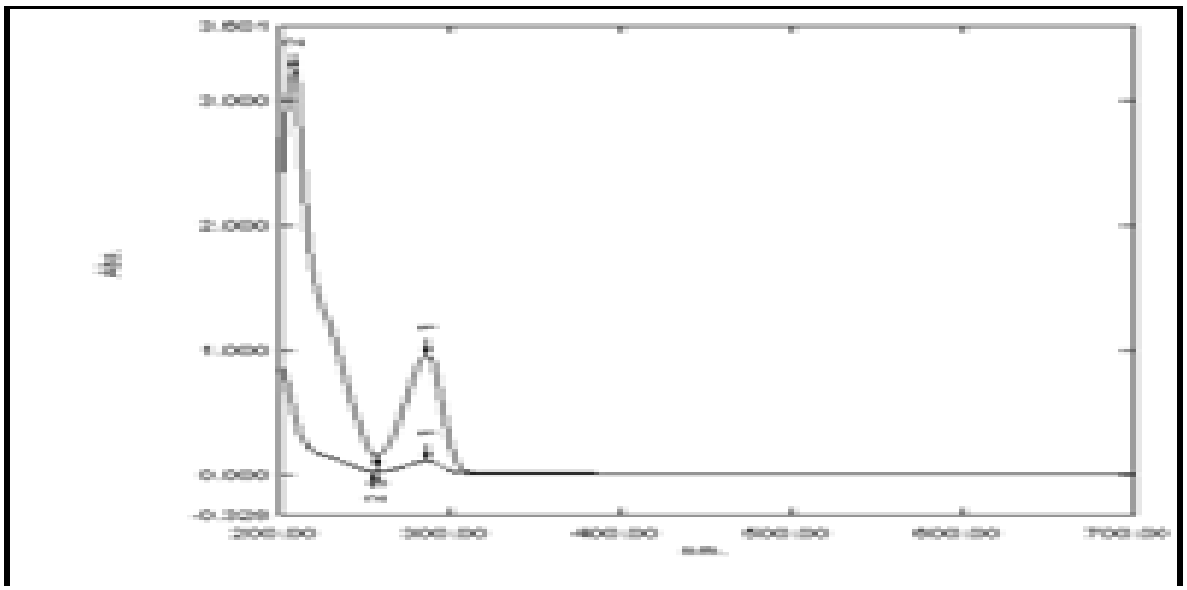
Dissolution parameters

Medium: 6.8pH phosphate buffer, 500ml.
Apparatus: USP Type 2 (paddle).
Rotation speed: 50 RPM
Temperature: 37±5oC.
Time: 2, 4, 6,8,10,12,15,30 min.

RESULTS AND DISCUSSION

Ivabradine Λ - Max Determination

The standard drug solution with water as well as with buffers of concentrations 10µg/ml and 50µg/ml was scanned in UV- Vis spectrophotometer over wavelength of 200nm-700nm in all the media. The experimentally determined λmax phosphate buffer pH 6.8 was found to be 286nm versus concentration of standard solutions was constructed.



Concentration (µg/ml)

Fig no: 4.1.a

Discussion

From the above graph, the maximum absorbance (λmax) peak was observed at 286 nm.

PREFORMULATION STUDIES

Description

These tests were performed as per the procedure and the results were illustrated in the following table:

Table showing the description of Ivabradine (API)

Table no: 4.2.a

Test	Description
Colour	A white to off white colour crystalline powder
Odour	Odourless

Result

The results were found as per specifications.

Solubility

It is soluble in water (100 mg/mL), methanol, and ethanol and slightly soluble in hexane.

Melting Point

This test is performed as per procedure and the result was illustrated in the following table.

Table showing the melting point of API's

Table no: 4.2.b

Material	Melting Point	Melting Point Range
Ivabradine	1900c	190-1920c

Result

The Result was found to be within limit.

ANALYTICAL METHODS

Calibration curve plot

Table no: 4.2.1.a

Sl.No	Concentration in µg/ml	Absorbance
1	0	0
2	1	0.165
3	2	0.325
4	3	0.471
5	4	0.627
6	5	0.789

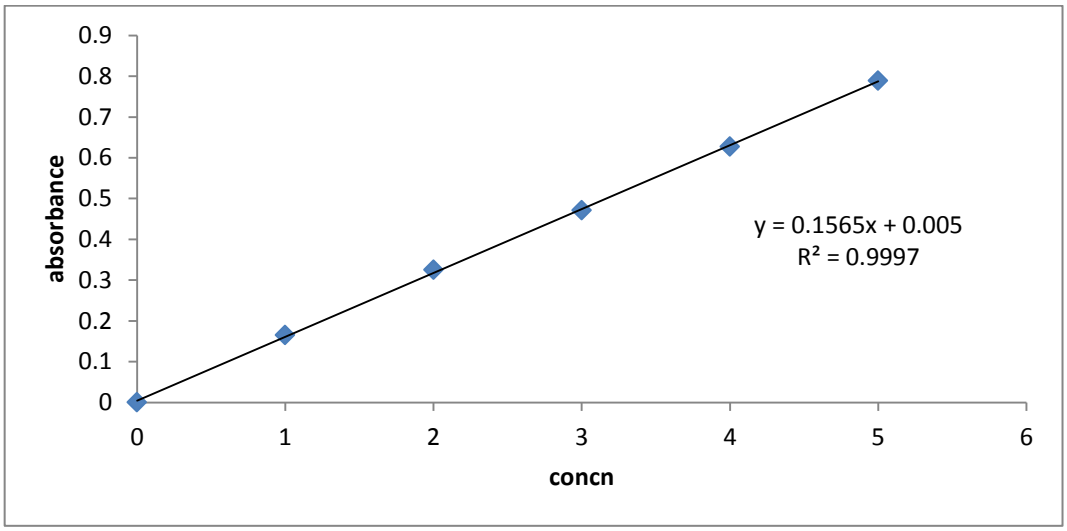


Fig no: 4.2.1.a

EVALUATION OF TABLET BLEND

Evaluation of tablet blend for formulations (F1 – F9)

Table no: 4.3.a

Formulation	Bulk Density(gm/cm3)	Tapped Density(gm/cm3)	Hausner ratio	Compressibility index (%)	Angle of repose(θ)
F1	0.464	0.574	1.23	19.1	29.47
F2	0.423	0.501	1.16	15.5	27.63
F3	0.456	0.542	1.22	15.8	25.54
F4	0.467	0.559	1.25	16.4	26.23
F5	0.485	0.593	1.10	18.2	27.21
F6	0.460	0.556	1.21	17.2	30.38
F7	0.478	0.575	1.24	16.8	28.46
F8	0.450	0.554	1.28	18.7	25.71
F9	0.442	0.537	1.27	17.6	31.82

Discussion

The flow properties of the formulations were found to be in limit and the optimized formula was in limit and has a fair flowing property. This had no effect during compression of tablet

COMPATIBILITY STUDIES

The peaks obtained in the spectra of each formulation correlates with the formulation components. Compatibility studies thus allow in systematic selection of excipients, for formulation development

FTIR for pure drug [ivabradine]

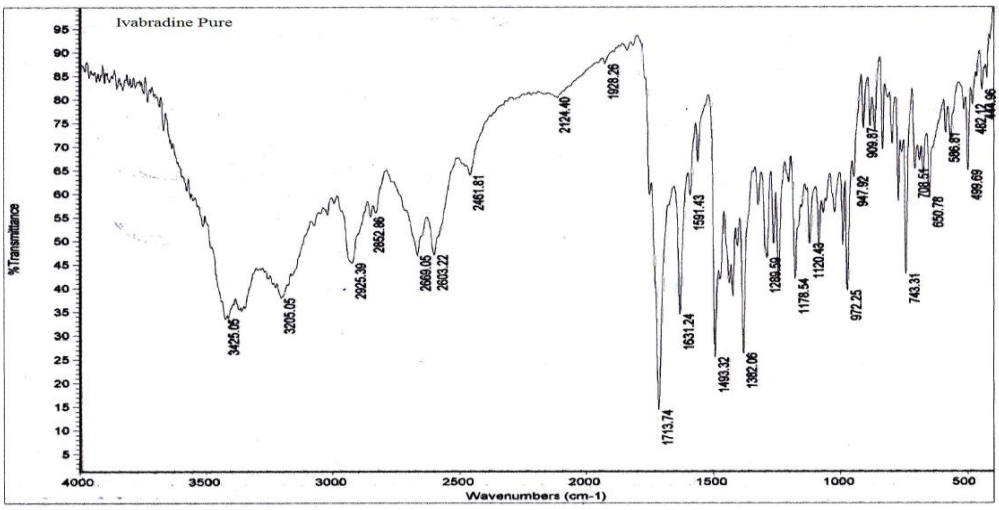


Fig no: 4.4.1.a

FTIR spectra of final drug ivabradine (ivabradine+excipients)

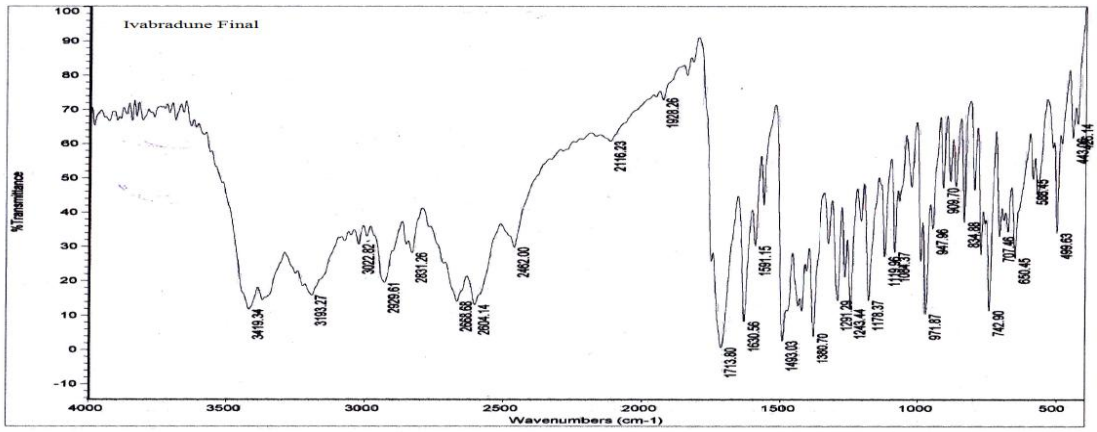


Fig no: 4.4.2.a

Discussion

FTIR studies revealed that there was no physico-chemical interaction between ivabradine and other excipients

EVALUATION OF TABLETS

Evaluation of porous Tablets for Formulations (F1 – F9)

Table no: 4.5.a

Formulation	Hardness (kg/cm2)	Weight (mg)	Thickness (mm)	Disintegration time (sec)	Drug content (%)	Friability [%]	Wetting time
F1	2.7	151	2.4	38sec	98.2	0.39	1min-4sec
F2	2.7	149	2.4	1min 14sec	98.72	0.58	20 sec
F3	2.9	152	2.6	47sec	98.4	0.69	25 sec
F4	2.8	153	2.5	1min	98	0.45	1min-4sec
F5	2.7	154	2.4	42sec	98.44	0.35	1min-21sec
F6	2.6	153	2.4	20sec	98.2	0.69	37sec
F7	2.4	150	2.4	16sec	100	0.30	12 sec
F8	2.9	153	2.5	28sec	98.4	0.66	40sec
F9	2.6	151	2.5	45sec	98.8	0.65	30sec

Discussion

From the above Table, it is observed that the thickness, hardness, weight variation and drug content of the porous tablets were in the passable range. The F1,F2,F3,F4,F5,F6,F8 and F9 formulations containing menthol as the subliming agent, CCS, CP, SSG as super disintegrating agent in the percentage of 5,7.5 and 10% each didn't show much effect on the Disintegration time.

RESULTS OF IN-VITRO RELEASE PROFILE

In-Vitro Release Profile of Ivabradine from formulations F1-F9

Table no: 4.6.a

Time (min)	Cumulative % drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	22	15	35	18	11	15	21	15	19
4	35	30	53	35	25	30	35	20	25
6	52	43	68	56	36	45	50	33	41
8	65	55	84	63	49	56	67	54	57
10	74	67	98	74	63	74	75	61	69
12	89	88	101	92	77	82	94	74	82
15	92	92	-	94	91	93	99	86	91
30	95	97	-	97	96	101	---	94	95

Discussion

ivabradine formulation 7 was optimised because the percentage drug release was found to be highest when compared to all the formulations.

Graph comparison between cumulative % drug release for formulations (F1- F9)

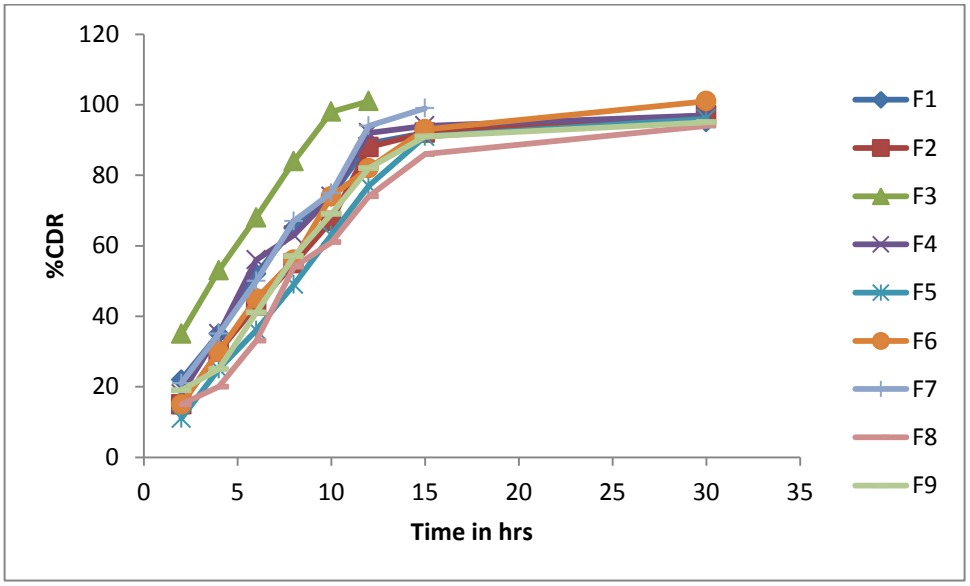


Fig No: 4.6. a

Result

The Excipient cross carmellose sodium showed the high percentage of drug release compared to cross povidone and SSG, which showed the good release as required for the oro-dispersable tablets; hence the CCS is optimized and used further for the tablet preparation.

KINETICS OF OPTIMIZED IVABRADINE FORMULATIONS

Table no: 4.7.a

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	3.288580247	-0.078138473	21.6686738	1.225451021
Intercept	28.21039095	1.989129198	0.606842566	0.584944839
Correlation	0.824134671	-0.894963371	0.93919156	0.877905309
R 2	0.679197956	0.800959435	0.882080786	0.770717732

FOR FORMULATION F7 THE HIGUCHI'S MODEL GRAPH OF KINETICS OBTAINED IS AS FOLLOWS

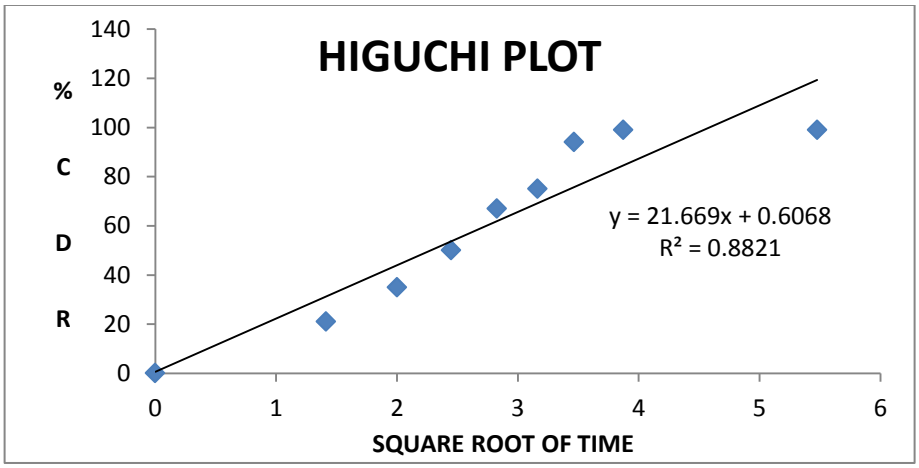


Fig no: 4.7.a

FOR FORMULATION F7 THE ZERO ORDER GRAPH OF KINETICS OBTAINED IS AS FOLLOWS

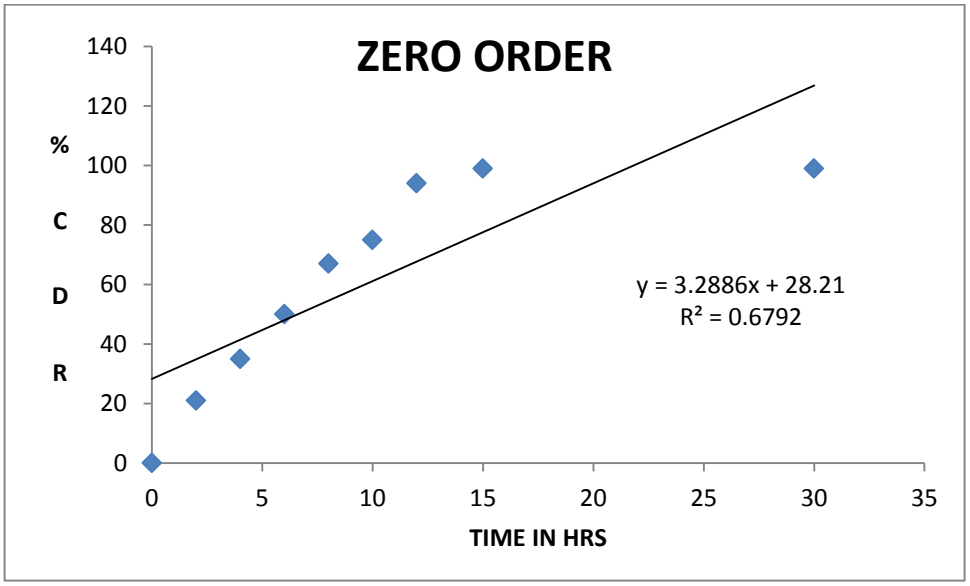


Fig no: 4.7.b

FOR FORMULATION F7 THE FIRST ORDER GRAPH OF KINETICS OBTAINED IS AS FOLLOWS

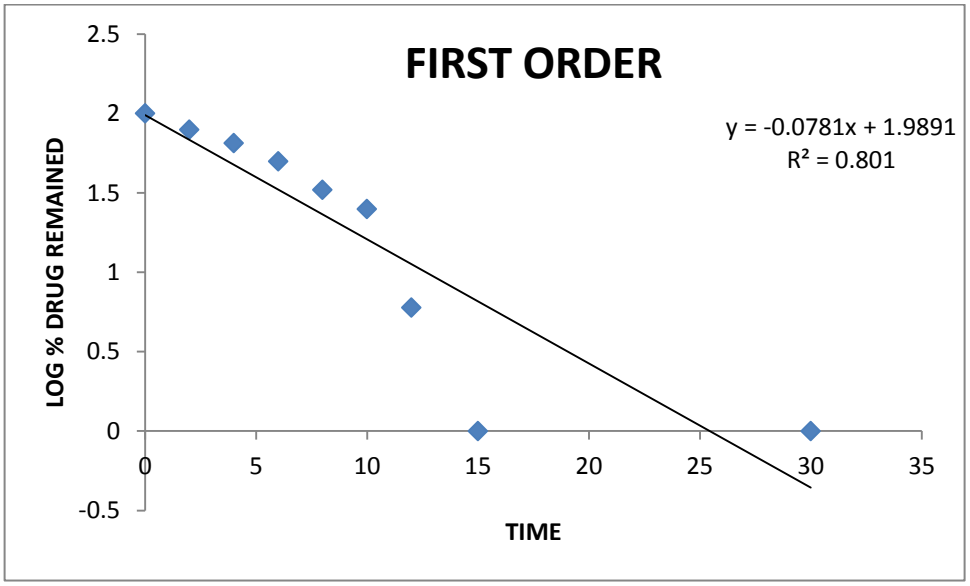


Fig no: 4.7.c

FOR FORMULATION F7 THE PEPPAS MODEL GRAPH OF KINETICS OBTAINED IS AS FOLLOWS

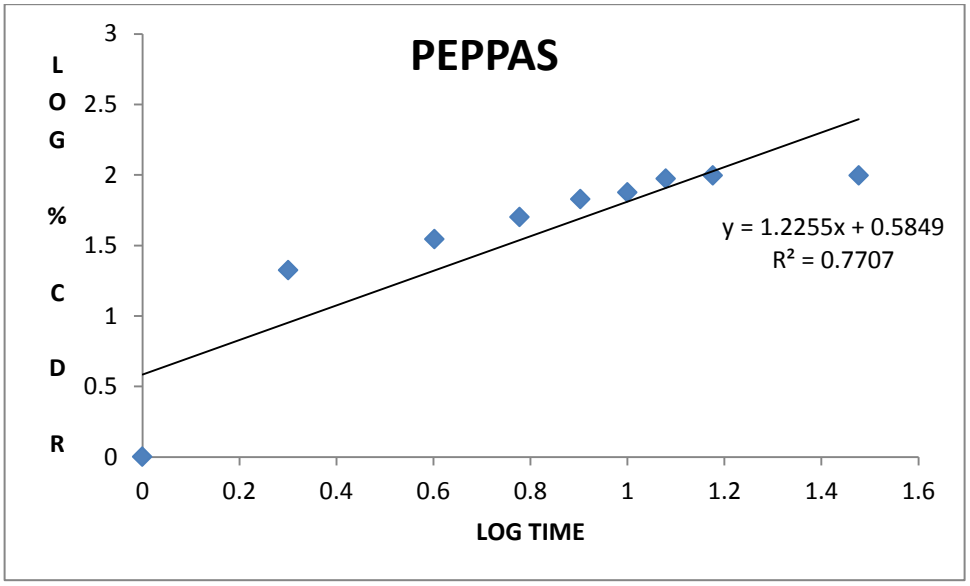


Fig no: 4.7.d

Discussion

From the above graphs of kinetics it is observed that formulation F7 it following first order release kinetics followed by Higuchi model.

STABILITY STUDIES

Optimized formulations were packed in HDPE (High density polyethylene) container with child resistant caps (CRC) and induction sealed. These bottles were charged for stability study at 400C &75% RH. Physical evaluation of Tablets for stability studies of optimized formulation

Table no: 4.8.a

Parameter 400C / 75%RH	Initial	after 10 days	after 30 days	after 60 days	after 90 days
Drug release in 24hrs	98.2	98.0	97.7	97.5	97.0

CONCLUSION

This dissertation work was done with an aim to design an Oro dispersible tablet dosage of Ivabadrine and evaluation of the tablets for various parameters including in vitro drug release studies.Ivabadrine tablets were formulated by using lactose monohydrate as filler, Crosscarmellose, sodium starch glycolate and crosspovidone as super disintegrates and magnesium stearate as lubricant and methanol as sublimating agent. The powdered blend were compressed into tablets and were analyzed for the parameters such as average weight, disintegration time, friability, thickness, weight variation, hardness and drug content.FT-IR Spectroscopic studies indicated that the drug is compatible with the polymer and co-excipients.The powdered blend has Good and fair flow properties and is suitable for direct compression. All the formulations showed uniformity in hardness, weight variation, thickness, friability and content uniformity was found to be within limits.Results of dissolution profiles of various formulations showed that formulation F7 showed 100% drug release at the end of 15 minutes which is much more than the other formulation. Thus due to fast release of drug within stipulated time F7 was chosen as best formulation. The formulation F7 and process can be easily scaled up and can be easily employed in large scale production because the process is simple, cost effective and precise and also yields reproducible good result that involves complex process for manufacturing the tablets. The Dissolution data were fitted into kinetic models like Zero-order, First order, Higuchi's model and Peppa's models. The correlation coefficient values (R2) indicate that the drug release was following first order release kinetics followed by Higuchi's model. The ivabradine tablets were subjected to stability studies at 40oC and 75% RH for 3 months and from the above results, it was found that there is no effect on the tablets and was found to be within the limits according to ICH guidelines. There was no significant change in % release of drug after 3 months indicating that the formulation is stable.From the above points, it is clear that, ivabradine is suitable drug to formulate into oral disintegrating tablet and may provide a better therapeutic profile than that of conventional dosage form.

FUTURE SCOPE

Further studies can be carried out on preclinical trials which provide a better option for patient's by decreasing angina pectoris. It can be easily employed in large scale and can yield good result and efficacy.

- The scope of the present study is that it can be further carried out for the in vivo study.

BIBLIOGRAPHY

[1]. Manoj AshokWagh, Techniques used in orally disintegrating drug delivery system, International Journal of Drug Delivery 2 (2010) 98-107.

[2]. Kibbe, A.H., ed. Handbook of Pharmaceutical Excipients. 3rd Edition ed. 2000, American Pharmaceutical Association & Pharmaceutical Press: Washington, DC & London, UK.

[3]. Hiestand, E.N., 2003. Mechanics and physical principles for powders and compacts, SSCI Inc., West Lafayette, In, USA.

[4]. United States Pharmacopeia, United States Pharmacopeia / National Formulary (USP25/NF20). 2002, Rockville, MD: United States Pharmacopeia Convention Inc.

[5]. Lesney, Mark S. (January 2001). "More than just the sugar in the pill". Today's Chemist at Work 10 (1): 30–36. ISSN 1532-4494. Archived from the original on August 13, 2013. Retrieved August 13, 2013.

[6]. Jump up "Micro-dosing equipment fills niche in R&D, clinical trial materials, 2009". Tablets & Capsules (CSC Publishing). March 2009. ISSN 1938-9159.

[7]. Jump up to:a b Mills, Simon (April 2007). "Excipients". Training Workshop on Pharmaceutical Development with focus on Paediatric Formulations. World Health Organization. Archived from the original on October 20, 2012.

[8]. Rudolf, J. S., Validation of solid dosage forms, 167-187

[9]. Madan, J., Prasad, V. and Mishra, P. R., Pharmaceutical validation, 524-548.

[10]. Chow S. Pharmaceutical Validation and Process Controls in Drug Development. Drug Inf J 1997; 31: 1195-201.
[11]. Nyol Sandeep, Immediate Drug Release Dosage Form: A Review, Journal of Drug Delivery & Therapeutics; 2013, 3(2), 155-161.
[12]. Kumar b sutradhar, Formulation And Evaluation Of Taste Masked Oral Dispersible Tablets Of Domperidone Using Sublimation Method, International Journal of Pharmacy and Pharmaceutical Sciences, ISSN- 0975-1491, Vol 4, Issue 2, 2012.