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Formulation Development and Evaluation of taste masked orally disintegrating tablets of Perindopril Erbumine by direct Compression method

Ratnaparkhi Mukesh P.*, Jagadale Sachin K., Patil Pradeep S. and Dhiwar Suresh B
Marathwada Mitra Mandal's College of Pharmacy, Thergaon (Kalewadi), Pune-4110 33 India

Abstract

The aim of the current study is to develop and evaluate patient friendly taste masked oro-dispersible tablets of Perindopril Erbumine. Perindopril is an antihypertensive drug and is used in the management of hypertensive urgency. The bitter taste of the drug and the fact that it being a pro-drug needs to be converted to active metabolite after being absorbed emphasizes on the need for improvement in patient compliance and improvement in disintegration time in order to enhance the onset of action. Taste masking is done by using polymethacrylate co-polymer by mass extrusion technique. The preliminary batches were prepared by using different superdisintegrants like Ac-Di-Sol, Primogel, Tulsion-335 and Tulsion-339. From the preliminary study it was found that orodispersible tablets containing Ac-Di-Sol showed better disintegration time and it was considered for further studies. A 3^2 full factorial design was applied to optimize the formulations, nine batches were prepared and evaluated. It was observed from the evaluations that the batch A_2 showed the best disintegration time and also completes drug release within five minutes. Hence it was concluded that orally disintegrating tablets of Perindopril Erbumine can be successfully formulated using Ac-Di-Sol.

*Corresponding author, Mailing address:
Mukesh P Ratnaparkhi
Marathwada Mitra Mandal's College of Pharmacy,
Thergaon (Kalewadi),
Pune-4110 33 India
Email ID: mukeshparkhi@yahoo.co.in

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Perindopril Erbumine, Taste masking, Ac-Di-Sol, Avicel PH101, 3^2 full factorial design.

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Introduction

Although various novel and advanced drug delivery systems have been introduced for therapeutic use, the popularity of oral dosage forms, particularly

tablets have not been eclipsed, because tablets still have numerous advantages, besides others an economical production. However, one important drawback of tablets as a dosage form is the need to swallow. Dysphasia or general difficulties in swallowing of tablets may be a problem for geriatric, paediatric, or travelling patients, if the latter do not have access to water. Dysphasia is also pertinent with the number of medical conditions including strokes, Parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders including cerebral palsy hence resulting in higher incidence of non-compliance and ineffective therapy. Thus, the orally disintegrating drug delivery system (DDS) is fast dissolving / dispersing, and dissolves in the patient's mouth within a matter of seconds without need of water or chewing. It may therefore be the best solution for patient suffering from dysphasia.

Perindopril ter-butyl amine belongs to a group called Angiotensin Converting Enzyme (ACE) inhibitors [1]. Inhibition of ACE results in decreased plasma Angiotensin II, leading to decreased vasoconstriction, increased plasma rennin activity and decreased aldosterone secretion. The overall effect of this is a drop in blood pressure and a decrease in the workload of the heart. Perindopril tert-butyl amine is a pro-drug that is hydrolyzed by esterases to the active metabolite Perindoprilat. Perindopril is rapidly absorbed, reaching peak plasma concentration about 1 hour after a single oral dose. Perindoprilat reaches peak plasma concentrations in 2 to 6 hours. The bioavailability of Perindopril is about 70%. The presence of food does not affect the rate and extent of absorption of Perindopril; however, food reduces the conversion of Perindopril to Perindoprilat. [2, 3]

Therefore, the purpose of the present study was to develop a fast disintegrating tablet of Perindopril Erbumine by direct compression and to mask the bitter taste of Perindopril. Such tablet should disintegrate rapidly in the saliva without need of water and release the drug instantly for immediate therapeutic effect, and be of acceptable taste.

Material and method:-

Perindopril Erbumine was generously gifted by Hetero drugs Pvt Ltd, Eudragit E100 was gifted by Evonick (Mumbai). Primogel, Ac-Di-Sol and Avicel (PH101) were procured from Maple Biotech Pvt Ltd, Tulsion 335 and Tulsion 339 were obtained from Thermax India Pvt Ltd. Manitol was obtained from Oswal chemicals. All other chemicals used were of analytical grade.

Preformulation Studies

Solubility Studies The solubility determination of Perindopril Erbumine was carried out in different solvents including distilled water and ethanol**.**

Identification of Pure Drug Identification of pure drug was carried out using FTIR spectroscopy.

Melting Point Determination Melting point was determined using capillary method.

Determination of λmax

Preparation of Stock Solution

An accurately weighed 10 mg of Perindopril Erbumine was transferred in a 100ml volumetric flask. To the flask 0.1 N HCl was added in small proportion so as to dissolve Perindopril Erbumine. The volume was made up to 100ml with 0.1 N HCl to get a concentration of 100µg/ml

Determination of λmax

20µg/ml solution of Perindopril Erbumine was prepared in diluent. The resulting solution was scanned in UV-Vis spectrophotometer from 400-200nm to determine the λmax. The λmax of Perindopril Erbumine was found to be 215 nm.

Preparation of Calibration Curve for Perindopril Erbumine

Aliquots (0.2-2.0ml) from standard stock solution were pipetted out in series of ten 10 ml volumetric flask and the volume was made up with 0.1 N HCl.

The absorbance was measured in triplicate at 215 nm against blank.

Determination of Taste Threshold Value of Bitterness for Perindopril Erbumine [4-6]

The minimum concentration among a range of dilutions of a substance at which the volunteer just starts feeling the bitter taste is known as taste threshold concentration. The threshold bitterness concentration of Perindopril Erbumine was determined by a panel of 12 healthy human volunteers from whome the written consent were taken. The design of the experiment is shown in table 1 .Different concentrations of the drug sample ranging from 10µg/ml to 150 µg/ml were prepared in phosphate buffer pH6.8. The volunteers were administered with 10 ml of the test samples one at a time with an interval of ten minutes. The volunteers were told to keep the test solution in mouth for 30 seconds and later spit it out. The taste observed by the volunteers for each test sample was recorded. It was observed that 9 out of 12 volunteers felt bitterness after 30 seconds at concentration of 120µg/ml and three volunteers observed the bitter taste at 110µg/ml. therefore the concentration of 110µg/ml was considered as the taste threshold concentration of Perindopril Erbumine.

Table No. 1 Determination of Taste Threshold Value Of Bitterness Of Perindopril Erbumine.

Sr no	Concentration µg/ml	0	1	2	3	4
1	10					
2	50					
3	100		12			
4	110			3		
5	120			9		
6	130				12	
7	140				12	
8	150					12

0=sweet, 1= acceptable, 2=slightly bitter, 3= bitter, 4=intensely bitter.

6.2.2. Preparation of the Taste Masked Granules [7-9]

Physical mixtures of Perindopril Erbumine Eudragit® E 100 were prepared in various ratios from 1:1 to 1:7. The recommended solvent for Eudragit® E 100 is ethanol and water respectively. A gel containing Perindopril erbumine and Eudragit® E 100 was prepared by the following method. Perindopril Erbumine was mixed with different amount of powdered Eudragit E100 then 10% ethanol was added to this mixture in a glass beaker and gel was prepared using a mechanical stirrer. The gel was manually extrudated through a syringe. The ethanol was evaporated, by keeping the extrudates overnight at room temperature. The solidified gel in the shape of strings was crushed and sieved through a sieve sized 255 µm to make the granules.

6.2.3. In-Vitro Taste Evaluation[9-12]

The in-vitro taste evaluation was carried out to determine the drug release from the taste masked granules at the salivary pH. It was determined by placing Perindopril Erbumine Eudragit E100 complex equivalent to 4 mg of Perindopril Erbumine in 10 ml of phosphate buffer and shaken for 30 seconds. The amount of drug released was then analysed at 215nm. The results of analysis are shown in Table 2.

Table No. 2 Uv Method For Determination Of The Ratio For Drug Eudragit Complex For Taste Masking.

Taste threshold value	Absorbance noted	Drugeudragit complex	% drug released in relation to taste threshold value
		1:1	234.35%
		1:2	121.80%
		1:3	84.71%
100µg/ml	1.243	1:4	64.11%
		1:5	55.51%
		1:6	49.39%
		1:7	33.18%

6.2.4. Compatibility Studies

The prepared granules were subjected to thermal analysis, FTIR, X-Ray diffraction (XRD) studies.

6.2.4.1. Thermal Analysis

Differential scanning calorimetry (DSC) was performed using a Mettler TA 823 apparatus. The drug, the polymer, and the drug-polymer complex were subjected to the DSC study. Samples were heated at a scanning rate of 20 K/min from 40°C to 300°C under nitrogen.

6.2.4.2. Fourier Transform Infrared Spectroscopy (FTIR)

The drug, polymer and drug polymer complex were subjected to IR spectroscopy to check the drug polymer Interaction using FT-IR (SHIMADZU 8400 S) and the KBr disk method.

6.2.4.3. X-Ray Diffraction (XRD) Studies

X-Ray Diffraction analysis was carried out to evaluate the degree of crystallinity. The pure Perindopril Erbumine, pure Eudragit® E 100, and the Perindopril-Erbumine: Eudragit® E 100 complex (1:3) was subjected to powder XRD at 2θ angles between 5° and 50° in increments of 0.4°.

6.3. Preparation of Preliminary Batches of Orodispersible Tablets of Perindopril Erbumine

For the preliminary batches, Drug-Eudragit complex, Mannitol, Avicel (PH101), Superdisintegrants, Talc and Magnesium sterate were used. Mannitol was used as filler and also to impart cooling sensation in mouth. Avicel (PH101) was used as a filler binder because of its binding property. The concentration of Superdisintegrants such as Ac-Di-Sol, Primojel®, Tulsion® 335 and Tulsion® 339 was between 2–5%. A control formulation was made without a disintegrant. All ingredients were passed through mesh 250 µm. The ingredients were mixed according to Table 3. Magnesium stearate and talc were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio[13,14]. The Blend was compressed on 8 mm (diameter) flat punches on a 'Rimek mini press 16 station rotary compression machine. Each tablet weighing 200 mg corresponding to 4 mg of Perindopril Erbumine were obtained.

The tablets were evaluated for weight variation, thickness, friability, hardness and in-vitro disintegration time. In-vitro dissolution time was not evaluated for preliminary batches as improvement in disintegration time was of prime importance for this study.

Table No.3 Formulation of preliminary batches of fast disintegrating tablets of Perindopril erbumine.

Ingredients	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)	F_7 (mg)	F_8 (mg)	F_9 (mg)	F_{10} (mg)	F_{11} (mg)	F_{12} (mg)
Drug: Polymer complex	12	12	12	12	12	12	12	12	12	12	12	12
Mannitol	129	127	124	129	127	124	129	127	124	129	127	124
Avicel	50	50	50	50	50	50	50	50	50	50	50	50
Ac-di-sol	5	7	10									
Primogel				5	7	10						
Tulsion335							5	7	10			
Tulsion339										5	7	10
Mag- stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

Full Factorial Design [15-18]

A 3^2 randomized full factorial design was adopted to optimize the variables. In this design 2 factors were

evaluated, each at 3 levels, and experiment al trials were performed at all 9 possible combinations. Layout of full factorial design is shown in Table 4. The amounts of binder, Avicel PH101(X_1) and the amount of Ac-Di-Sol (X_2) were selected as independent variables precompression parameters were evaluated. The batches were formulated according to the formula given in table 5.The optimized batches were evaluated for content uniformity, disintegration time, wetting time, water absorption ratio and % drug release in 5 minutes (Q_{T5}).

Table No. 4 Layout of factorial design.

Batch code	X_1	X_2
A_1	-1	-1
A_2	-1	0
A_3	-1	1
A_4	0	-1
A_5	0	0
A_6	0	1
A_7	1	-1
A_8	1	0
A_9	1	1

Coded Values	Amount of Binder (Avicel PH101) X_1	Amount of Superdisintegrant (Ac-Di-Sol) X_2
-1	30mg	5mg
0	50mg	7mg
1	70mg	10mg

Table No. 5 Formulation of optimized batches of orodispersible tablets of Perindopril Erbumine.

Ingredients	A_1 (mg)	A_2 (mg)	A_3 (mg)	A_4 (mg)	A_5 (mg)	A_6 (mg)	A_7 (mg)	A_8 (mg)	A_9 (mg)	Control
Drug: Polymer complex	12	12	12	12	12	12	12	12	12	12
Mannitol	149	147	144	129	127	124	109	107	104	134
Avicel (PH101)	30	30	30	50	50	50	70	70	70	50
Ac-di-sol	5	7	10	5	7	10	5	7	10	
Mag- stearate	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200	200	200	200

Precompression Parameters

1. Angle of Repose *(θ)*

Angle of repose is defined as the maximum angle possible between the surface of a pile of the Powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

$\tan \theta = h / r$

$\theta = \tan^{-1} (h/r)$

Where, θ is the angle of repose

h is height of pile

r is radius of the base of pile

2. Bulk Density

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

LBD = Weight of the powder --------- (a)

Volume of the packing

TBD = Weight of the powder ---------- (b)

Tapped volume of packing

Carr's Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's Index (%) = TBD – LBD/TBD x 100 ----- (c)

Hausners Ratio

It is determined by comparing tapped density to the bulk density by using following equation

Hausners ratio= tapped density / bulk deksity.

The results of the powder flow properties determination are summarised in table no 17

Evaluation of Tablet Properties

Uniformity of Weight [19]

The test was performed according to specifications given in the Ph. Eur., 2004 on 20 tablets. The maximum acceptable limit is ±7.5% deviation of an individual mass from average mass.

Measurement of Tablet Friability [20]

Tablet friability was measured using the Roche Friabilator according to Ph. Eur, on ten tablets each. The friability was determined as the mass loss in percent according to Eq

$F= W_A-W_B/W_A .100$

Where f—Friability, WA—Initial weight (g), WB—Final weight (g). Tablets of friabilities under 1% are acceptable .

Measurement of Tablet hardness

The crushing strength of tablets was measured by a Monsanto Hardness Tester

Uniformity of Drug Content

The test is mandatory for tablets with 10mg or less weight of active ingredient[21].Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and powder equivalent to 4 mg of Perindopril was accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of 0.1N HCL. The flasks were shaken to mix the contents thoroughly. The volume was made up to the mark with 0.1 N HCL and filtered. One ml of the filtrate was suitably diluted and Perindopril content was estimated at 215.0 nm using a double beam UV-visible spectrophotometer.

Wetting Time [22]

A piece of tissue paper was folded twice and placed in small petri dish containing 6 ml of phosphate buffer (pH 6.8) the tablet was placed on it and the time required for complete wetting of tablet was recorded.

Water Absorption Ratio [23]

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was put on the paper and was allowed for complete wetting. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation

$R= (W_A-W_B) /W_B *100$

Where, W_B—Weight of tablet before water absorption, W_A— Weight of tablet after water absorption.

In-Vitro Disintegration Time

In Vitro Disintegration Time (DT) Using Petri Dish Method

The in- vitro disintegration time of the orally disintegrating tablets was determined following the procedure described by Gohel et al (2004)[24]. 10 mL of water at 37 ^oC was placed in a petri dish of 10 cm diameter. The tablet was then carefully positioned in the center of the petri dish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in replicates of three tablet (n=3) and mean were recorded.

In Vitro Dissolution Study

Perindopril erbumine tablet test conditions for the dissolution rate studies were used according USP specifications using USP 24, type II apparatus. The dissolution medium was 900 ml of 0.1N HCl. The temperature of the dissolution medium and the rate of agitation were maintained at 37±0.5°C and 50 rpm, respectively. Aliquots of 5.0 ml of the dissolution medium were withdrawn at specific time intervals and the volume replaced by fresh dissolution medium, pre-warmed to 37±0.5°C. The drug concentration was determined spectrophotometrically at 215 nm using UV spectrophotometer (shimadzu 1800).

6.5. Statistical Analysis of Data

Development Of Polynomial Equation From the data of in vitro drug release and wetting time of factorial formulation A_1 to A_9 polynomial equation for in-vitro drug release and wetting time was

derived using design expert 8.0 software. The polynomial equation for 3^2 factorial designs is

$Y= b_0+ b_1X_{1+} b_2 X_2 + b_{12} X_1X_2 +b_{11}X_1^2+ b_{22}X_2^2$

Where Y is the dependent variable, b_0 is the arithmetic mean response of nine batches and $b_1$is the estimated coefficient for factor X_1. The main effects X_1 and X_2 represent the average result of changing one factor at a time from its low value to high value. The interaction terms $X_1 X_2$ shows how response changes when two factors are simultaneously changed. The polynomial terms X_1^2 and X_2^2 are included to investigate non linearity.

Result and Discussion

Preformulation Studies

Solubility Studies

The solubility of Perindopril Erbumine was determined using distilled water and ethanol. It was observed that the drug is freely soluble in water and ethanol.

Identification of Pure Drug

FT-IR spectroscopy was used to determine the functional group present in the pure drug sample. The characteristic peaks were observed at 2928cm^{-1} corresponding to N-H stretching, 1730cm^{-1}, corresponding to C=O stretching, 1645cm^{-1} corresponding to C=O stretching and 1568 cm^{-1} corresponding to C=C stretching. The Ir Spectra of Perindopril Erbumine is shown in the following Figure No 1.

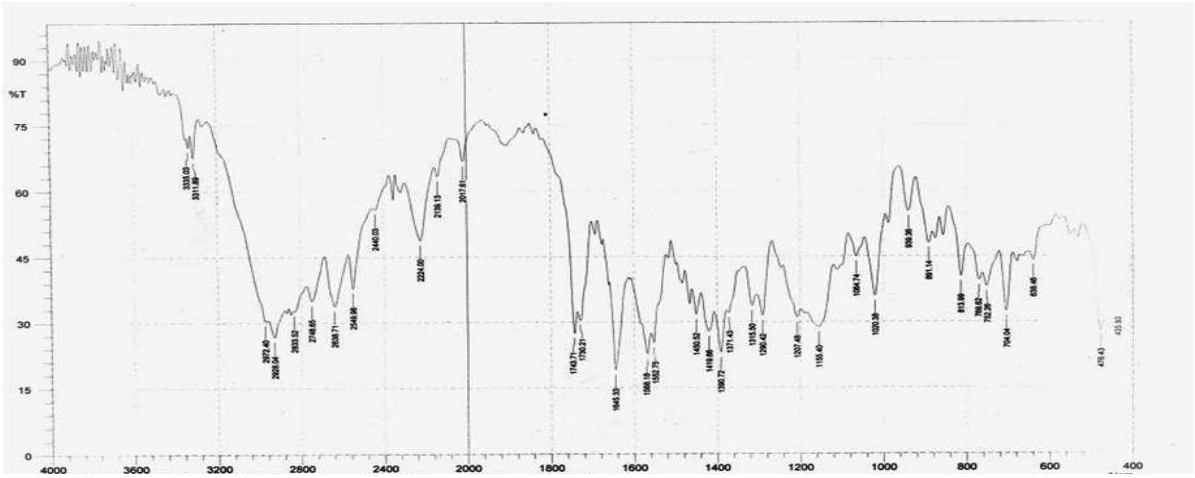


Figure No. 1 Ir Spectra of Perindopril Erbumine

Melting Point Determination Melting point of Perindopril Erbumine was determined by capillary method, the melting point of Perindopril erbumine was found to be in the range of 154-156^{o}C.

Standard Calibration Curve of Perindopril Erbumine

The λmax was found to be at 215 nm, so the standard calibration curve of Perindopril Erbumine was developed at this wavelength. The calibration curve showed linearity between 2-10 µg/ml concentration ranges. The standard calibration curve of Perindopril Erbumine was determined in 0.1 N HCl by plotting absorbance against concentration at 215 nm the r^2 value was found to be 0.998. The calibration curve is presented in figure No. 2.

Determination of Taste Threshold Value of Bitterness of Perindopril Erbumine

The minimum concentration among a range of dilutions to a substance at which the volunteers just start feeling the bitter taste is known as taste threshold concentration. Taste threshold bitterness concentration of Perindopril Erbumine was determined by panel of 12 volunteers and was found to be 110µg/ml.

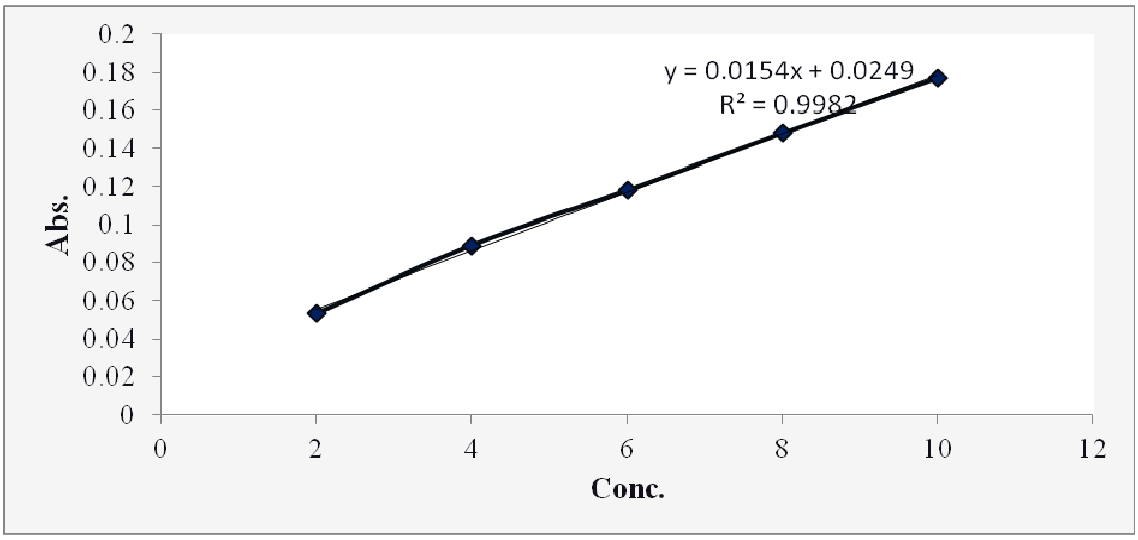


Figure No. 2 Calibration curve of Perindopril Erbumine at 215nm using 0.1 N HCL

Determination of Taste Threshold Value of Bitterness of Perindopril Erbumine

The minimum concentration among a range of dilutions to a substance at which the volunteers just start feeling the bitter taste is known as taste threshold concentration. Taste threshold bitterness concentration of Perindopril Erbumine was determined by panel of 12 volunteers and was found to be 110µg/ml.

Taste Masking Of Perindopril Erbumine By Eudragit E100

In order to mask the bitter taste of Perindopril Erbumine taste masked granules of Perindopril Erbumine Eudragit E100 (1:1to1:7) were prepared by mass extrusion technique. A simplified dissolution test was performed to determine the degree of taste masking of bitter taste of Perindopril Erbumine by Eudragit E100. It was found that the amount of Perindopril Erbumine dissolved from the drug polymer complex within 30 seconds decreased with increased concentration of Eudragit E100. The drug polymer complex that yielded drug release values just below the taste threshold concentration was considered optimum and was used for taste masking.

7.2.3 In-Vitro Evaluation of Taste Masked Granules

It was observed that the Perindopril Erbumine complexed with Eudragit E100 in proportion of 1:3 showed D_{30s} values below 100µg/ml. thus it was concluded that EudragitE100 in proportion to 1:3 was optimum with respect to masking bitter taste of Perindopril Erbumine.

Drug Polymer Compatibility Studies

The prepared granules were subjected to thermal analysis, FTIR, X-Ray diffraction (XRD) studies.

Thermal Analysis

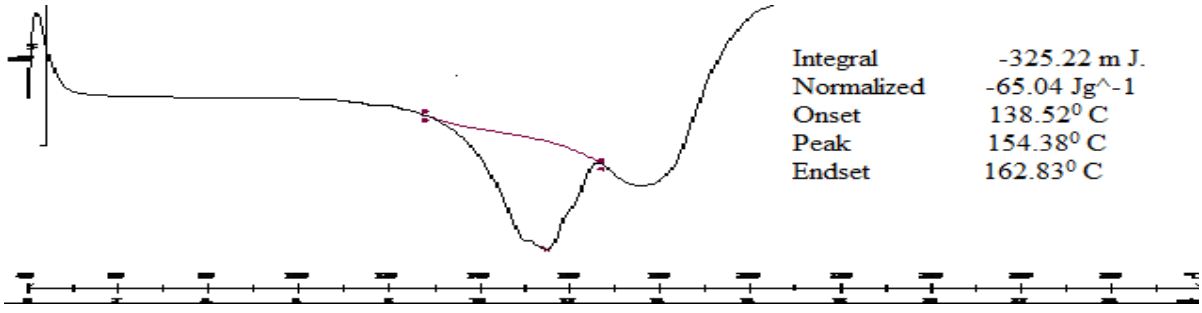


Figure No. 3 DSC Thermogram of Perindopril Erbumine

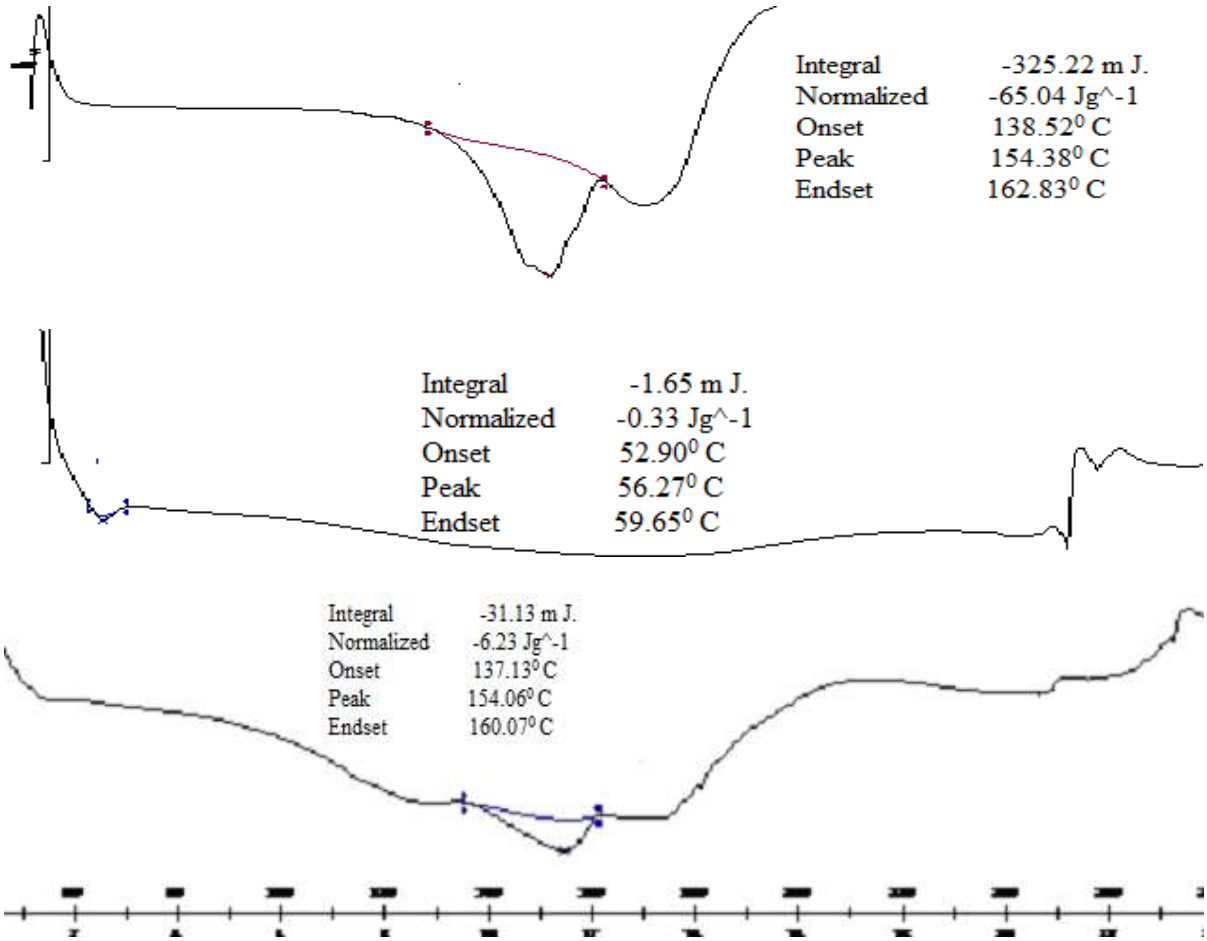
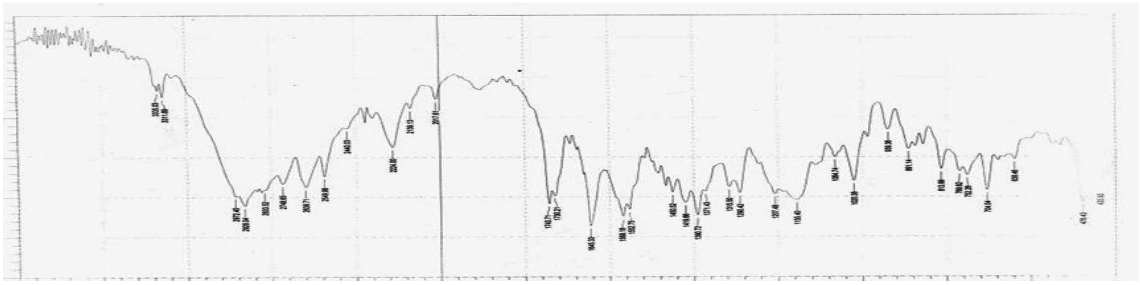


Figure No. 4 DSC Thermogram of Perindopril Erbumine, Eudragit E100 and Perindopril Erbumine :Eudragit E100 complex

The DSC thermograms of Perindopril Erbumine, Eudragit E100 and Perindopril Erbumine: Eudragit E100 complex are shown in figure No. 3 and 4 respectively.The DSC thermogram of Perindopril Erbumine shows endothermic peak at 154.38ºc the thermogram of Perindopril Erbumine complex exhibits a peak at 154.06ºc which indicates that there is very slight drug polymer interaction.Perindopril erbumine, Eudragit E 100 and Perindopril erbumine: Eudragit E100 complex were also analysed using FTIR to check the changes in the IR spectra that might occur due to the slight drug polymer interaction as observed during the DSC studies.

7.2.4.2 FT-IR analysis



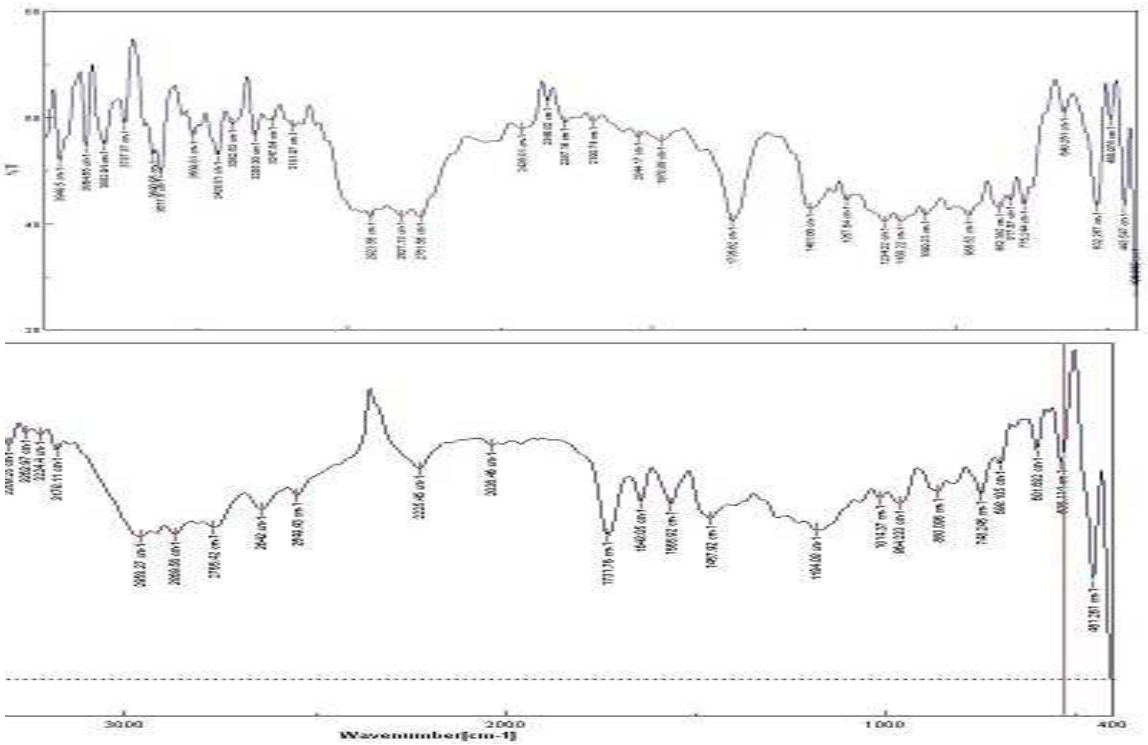


Figure No. 5 IR spectra of Perindopril Erbumine, Eudragit E100 and Perindopril Erbumine Eudragit E100 complex

The IR spectra of Perindopril erbumine, Eudragit E100 and perindopril erbumine Eudragit E100 complex are shown in above figure No.5. The spectrum of pure Perindopril Erbumine showed characteristic peaks at 2928cm^{-1}, 1730cm^{-1}, 1645cm^{-1}and 1568cm^{-1}. The spectra of Perindopril Erbumine: Eudragit E100 complex showed the characteristic bands of both Perindopril Erbumine and Eudragit E100 with the exception of peak at 2928cm^{-1}, in this case the peak at 2928cm^{-1} for pure drug was shifted to 2958cm^{-1}. This indicates the presence of very slight drug polymer interaction which is acceptable as a new complex is being formed.

The XRD diffraction pattern of Perindopril Erbumine shows sharp peak indicating that the drug is of crystalline nature while that of Eudragit E100 shows blunt peaks indicating its amorphous nature. When crystalline Perindopril Erbumine forms complex with amorphous Eudragit E100 the sharp peak of Perindopril Erbumine disappear. This indicates that the drug forms an apparent amorphous state. The change in crystallinity may be the reason for improved dissolution rate of Perindopril Erbumine when complexed with Eudragit E100. The XRD patterns of Perindopril Erbumine, Eudragit E100 and Perindopril Erbumine: Eudragit E100 complex are shown in figure No. 6 and 7 respectively

7.2.4.3 X –Ray Diffraction Studies

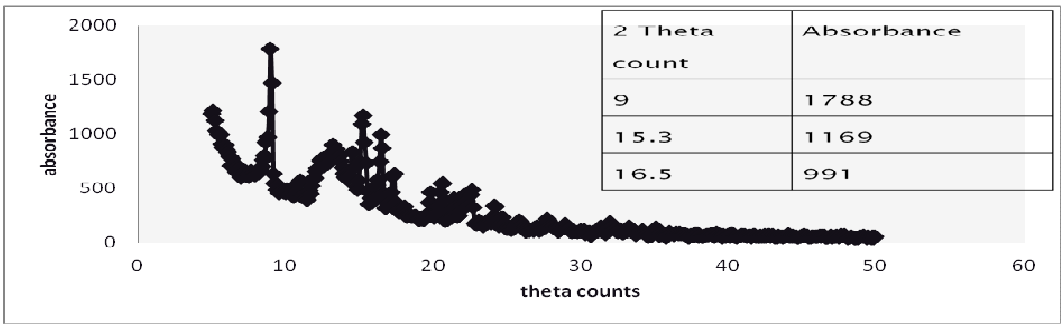


Figure No. 6 XRD analysis of Perindopril Erbumine

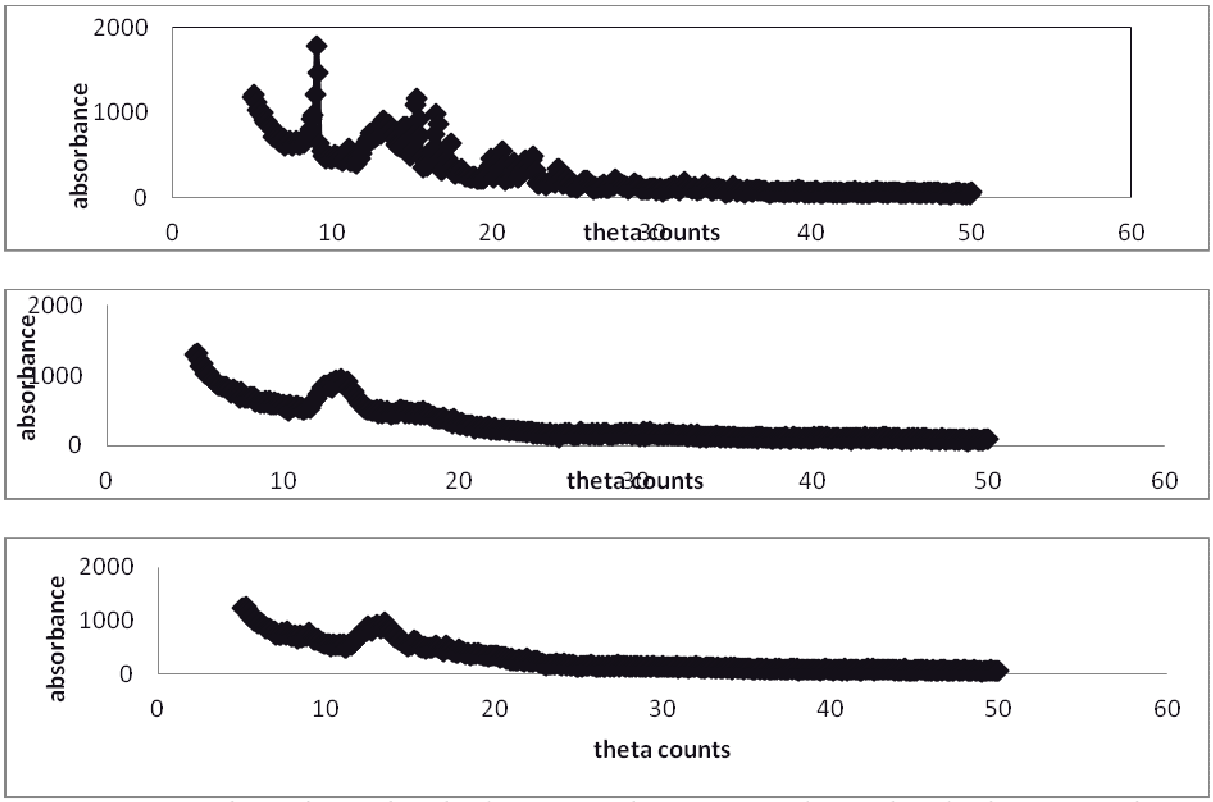


Figure No. 7 XRD analysis of Perindopril Erbumine, Eudragit E100 and Perindopril Erbumine: Eudragit E100 complex

Evaluation Of Precompression Characteristics of Preliminary Batches The preliminary batches were evaluated for precompression parameters such as angle of repose, Bulk density,Tap density, Carr's Index and Hausner's ratio. The result of evaluation is summarised in following table.

Table No. 6 1 Evaluation Of Powder Characteristics Of Preliminary Batches.

Sr.no	Formulation	Angle of repose	Bulk density	Tap density	Carr's index	Hausner's ratio
1	F_1	23.19	0.55	0.64	14.22	1.16
2	F_2	24.10	0.53	0.60	11.66	1.13
3	F_3	24.77	0.50	0.58	13.79	1.16
4	F_4	25.27	0.51	0.58	12.06	1.13
5	F_5	25.97	0.53	0.61	13.11	1.15
6	F_6	26.56	0.51	0.60	15.00	1.17
7	F_7	29.19	0.50	0.59	15.25	1.18
8	F_8	29.74	0.50	0.60	16.66	1.20
9	F_9	29.93	0.52	0.62	16.12	1.19
10	F_{10}	27.82	0.51	0.61	16.39	1.19
11	F_{11}	27.89	0.52	0.62	16.12	1.19
12	F_{12}	29.05	0.51	0.63	19.04	1.23

The powder flow properties were analysed. It was observed that all formulations showed good flow properties with Carr's index ranging from 11.66 to 19.04 and Hausner's ratio below 1.25 which indicated good compressibility and flowability.

Evaluation of Post Compression Parameters of Preliminary Batches of Perindopril Erbumine Orodispersible Tablets The preliminary batches were evaluated for the post compression characteristics such as uniformity of weight, friability, hardness and In-Vitro Disintegration. The results of the evaluation are given in the following table.

Table No. 7 Evaluation Of Preliminary Batches of Fast Disintegrating Tablets of Perindopril Erbumine.

Sr. no	Formulation	Uniformity of weight	Friability %	Hardness Kg/cm^2	In-vitro disintegration time (Sec)
1	F_1	Passes	0.40	3.4	71±0.47
2	F_2	Passes	0.55	3.5	63±0.81
3	F_3	Passes	0.46	3.5	95±0.94
4	F_4	Passes	0.35	4.0	82±1.24
5	F_5	Passes	0.60	3.8	78±0.94
6	F_6	Passes	0.55	3.5	152±1.24
7	F_7	Passes	0.60	3.0	116±1.24
8	F_8	Passes	0.35	3.6	100±1.24
9	F_9	Passes	0.20	4.2	166±1.24
10	F_{10}	Passes	0.55	3.4	123±0.47
11	F_{11}	Passes	0.36	3.6	84±0.94
12	F_{12}	Passes	0.31	3.8	174±1.24
13	Control	Passes	0.40	3.8	137±1.24

Orally disintegrating tablets were prepared by direct compression method. A total of twelve formulations and a control formulation (without superdisintegrant) were prepared using different superdisintegrants described above. All the formulations passed weight variation test. The hardness of all the tablets containing superdisintegrants was found in the range of 3.0-4.2Kg/cm^2. The hardness of control batch was found to be 3.8 Kg/cm^2. Friability was found to be below 1% which was an indication of good resistance of tablets.

In-vitro disintegration time

Various reports have suggested the unsuitability of conventional disintegrating test apparatus when used for testing the disintegration time of orally disintegrating tablets. This is because of extreme operating conditions in the disintegration test apparatus which fail to provide significant discrimination among the orally disintegrating tablets. Furthermore the conventional disintegration test apparatus employs a relatively huge volume of test solution as compared to the volume of saliva present in human buccal cavity. Therefore the results obtained from conventional disintegration test apparatus do not reflect the actual disintegration time; hence in order to get a better response different method of testing the disintegration time was employed. The disintegration time was measured using a petri plate method as described above. It was found that tablets containing 2.5%, 3.75% and 5% of Ac-Di-Sol, 2.5% and 3.75% of Primogel, Tulsion-335 and Tulsion 339 showed disintegration time less than that of controlled tablet. However it was observed that tablets containing 5% of Primogel, Tulsion-335 and Tulsion -339 required more time to disintegrate than the controlled tablet.

The basic principal that governs the action of superdisintegrant Primogel is its extensive swelling which was found to increase with the increasing concentration of Primogel above 3.75% as the contact of water with Primogel led to formation of viscous plug. Due to increased viscosity with increased concentration of Primogel it was observed that further uptake may be retarded and the tablets break into large particles instead of disintegrating into smaller particles. This might be the reason for increased disintegration time with increased amount of Primogel. Tulsion -335 and Tulsion-339 are swellable ion exchangers. Tulsion -335 is generally used as taste masking agent but owing to it s swelling ability it was considered for the study to check its disintegrating efficiency as a superdisintegrant. It was observed that tablets containing Tulsion-335 and Tulsion-339 showed comparatively larger disintegration time compared to Ac-Di-Sol and Primogel. Furthermore it was also observed that increased concentration of Tulsion -335 as well as Tulsion-339 above 3.75% caused a longer disintegration time than controlled tablets. This slow disintegration time may be due to the fact that these superdisintegrants have highly crosslinked structures as compared to other superdisintegrants which resulted into longer disintegration time.

It was observed that tablets containing 2.5%, 3.75% and 5% of Ac-Di-Sol showed lesser disintegration

time when compared with the other superdisintegrants at the same concentration levels. Ac-Di-Sol swells to a larger extent when it comes in contact with water. The fibrous nature of Ac-Di-Sol allows intraparticulate as well as extraparticulate wicking of water at lower concentrations. Ac-Di-Sol is prepared by cross linking of sodium carboxymethyl cellulose, which greatly reduces its water solubility while permitting the material to swell and absorb water several times its mass without losing its fibrous structure. However it was observed that there was a prolongation is disintegration time with concentration of 5%. The reason behind this increased disintegration time may be because of increased viscosity and adhesiveness at higher concentration. As the disintegration time of all batches of tablets containing Ac-Di-Sol showed good disintegration time, it was considered as promising candidate for further studies.

Characterization of Powder Flow Properties of Optimized Batches The precompression parameters of the optimized batches were analysed and the result of evaluation parameters are summarized in following table.

Table No. 8 Evaluation of precompression parameters of optimization batches.

Sr.no	Formulation	Angle of repose	Bulk density	Tap density	Carr's index	Hausner's ratio
1	A_1	25.27	0.50	0.58	13.79	1.16
2	A2	25.94	0.52	0.58	10.34	1.11
3	A_3	25.27	0.58	0.62	10.77	1.07
4	A_4	23.19	0.55	0.64	14.22	1.16
5	A_5	24.10	0.53	0.60	11.66	1.13
6	A_6	24.77	0.50	0.58	13.79	1.16
7	A_7	27.82	0.50	0.60	16.66	1.20
8	A_8	27.25	0.52	0.62	16.8	1.20
9	A_9	27.89	0.50	0.62	19.35	1.24

The powder flow properties of the optimized batches were also studied and from the observations it was concluded that the optimized batches showed good powder flow properties with good compressibility.

7.4.2. Evaluation of Post Compression Parameters of Optimized Batches The optimized batches were evaluated for uniformity of weight, % friability, In-Vitro wetting time, Water absorption ratio, In-Vitro disintegration time and In-Vitro % drug release. The results of evaluation are shown in the following table

Table No. 9 Evaluation of Post Compression Parameters of Optimized Batches.

Batches	Uniformity of weight	Hardness Kg/cm²	% Friability	Wetting time (sec)	Water absorption ratio %	In-Vitro disintegration time (sec)	In-Vitro % drug release $Q_{T\,5}$
A_1	Passes	3.4	0.40	85±2	62.23±0.04	77±1.52	100.90±1.8
A_2	Passes	3.4	0.55	63±2	102.84±0.75	50±2	101.29±0.7
A_3	Passes	3.5	0.46	79±1.73	77.60±1.10	70±1.7	100.4±1.4
A_4	Passes	3.6	0.35	89±1.52	68.8±0.73	71±0.47	100.3±1.8
A_5	Passes	3.5	0.31	73±0.57	98.32±1.03	63±0.81	99.35±0.70
A_6	Passes	3.8	0.36	109±2	63.40±1.17	95±0.94	100.63±0.65
A_7	Passes	4.2	0.25	99±1.73	60.78±0.75	89±2	90.82±3.03
A_8	Passes	4.0	0.25	84±2	63.83±0.59	74±1.52	92.89±1.19
A_9	Passes	4.2	0.35	116±1.5	57.14±0.97	97±1.15	88.90±2.4
Control	Passes	3.8	0.40	143±0.7	51.75±0.24	137±1.24	72.32±2.19

Figure No. 8 Disintegration Time Using Petri Plate Method

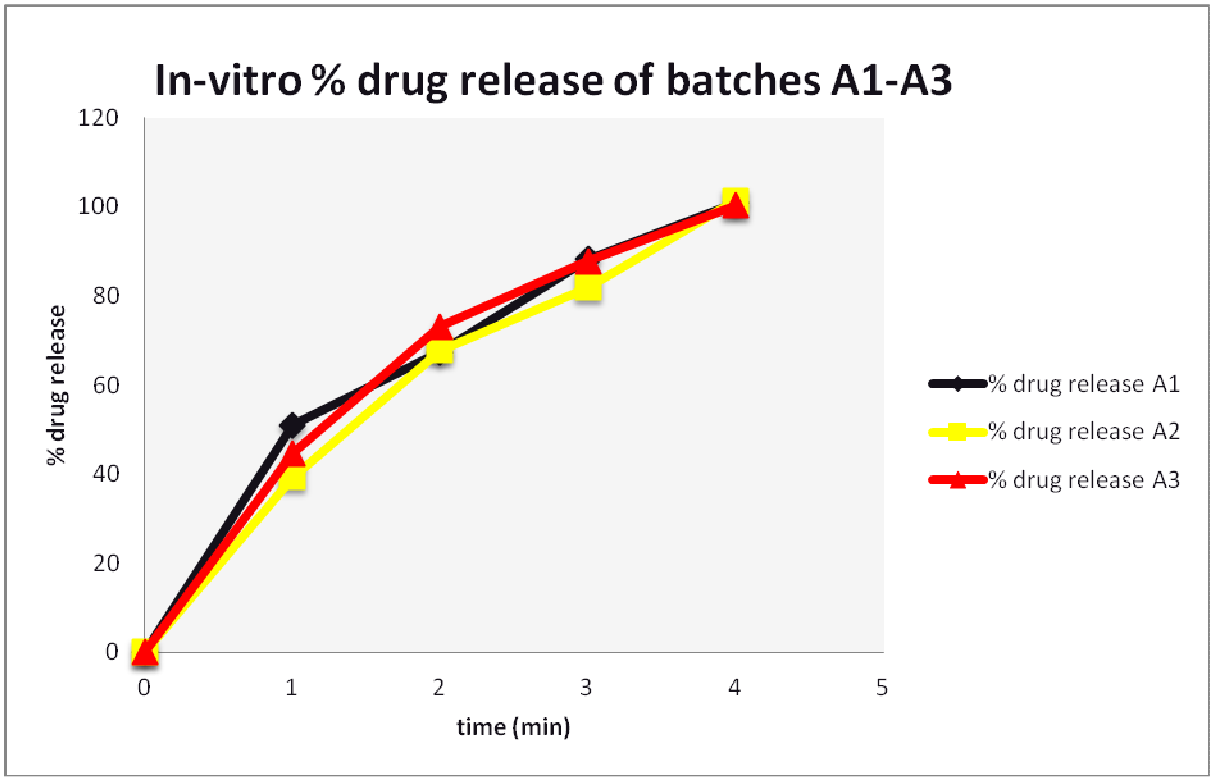


Figure No. 9 In-Vitro % drug release of batches A_1 to A_3

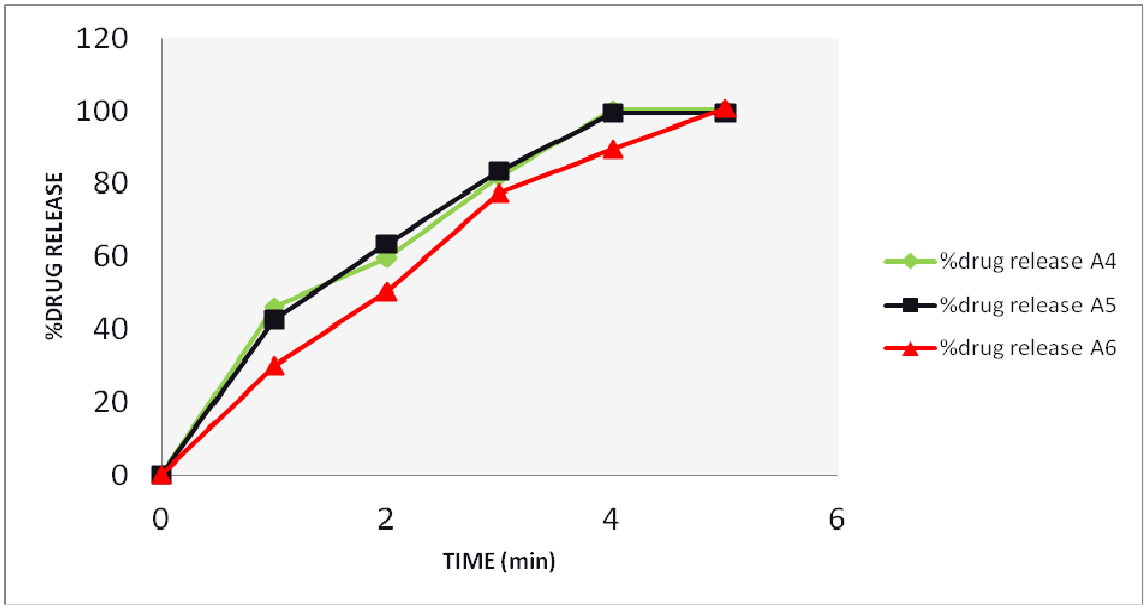


Figure No. 10 In-Vitro % drug release of batches A_4-A_6

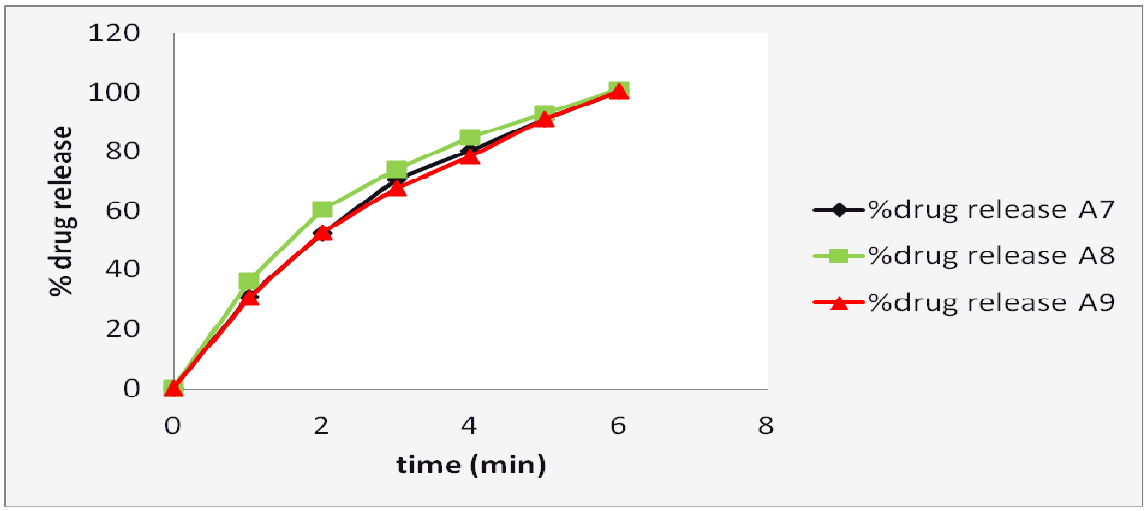


Figure No. 111 In-Vitro % drug release of batches A_7-A_9

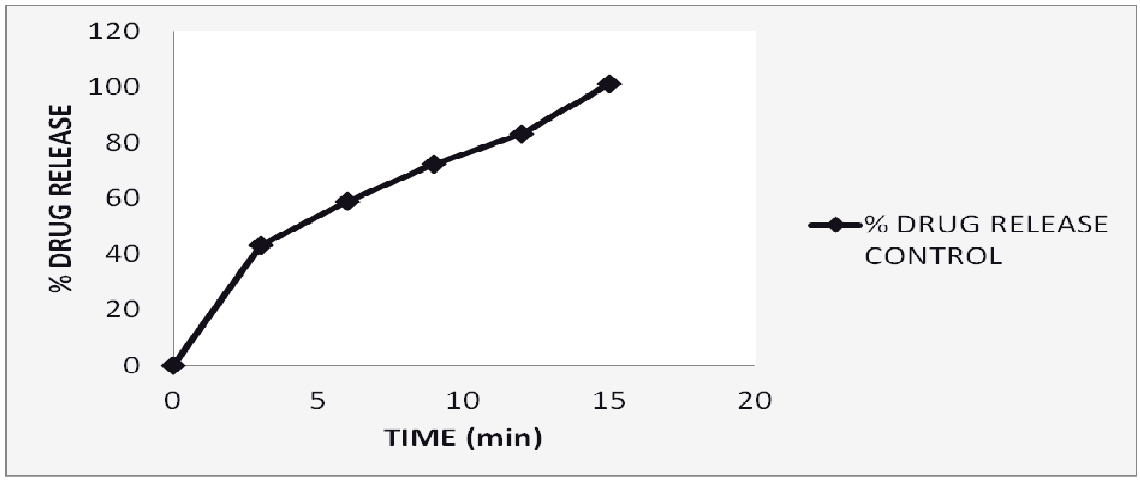


Figure No. 12 In-Vitro % drug release of control batch

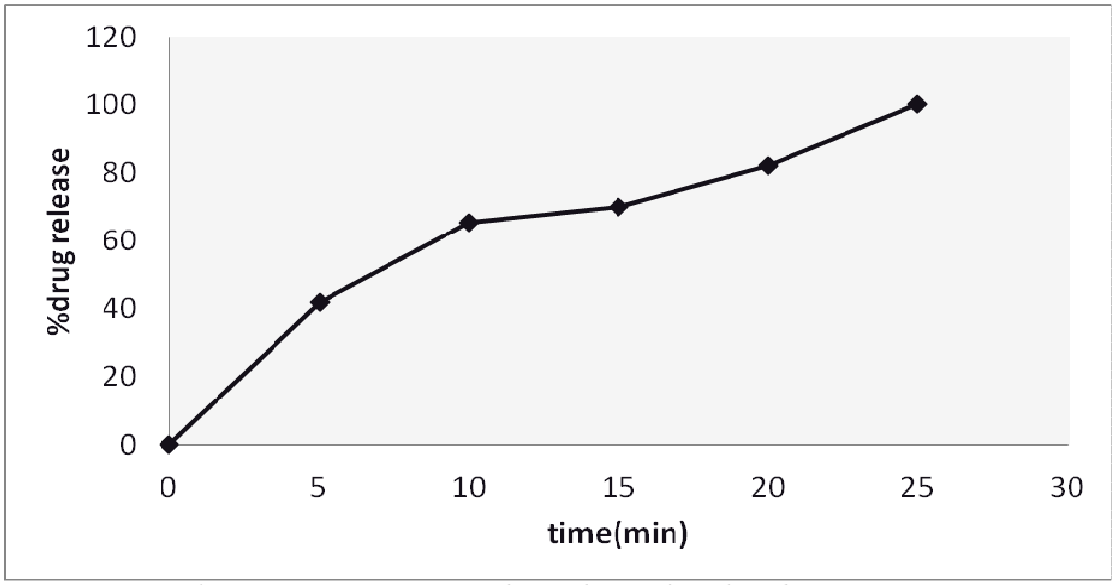


Figure No. 13 In-Vitro % drug release of marketed preparation

Orally disintegrating tablets were prepared by direct compression method. A total of nine optimized formulations were prepared using three different levels of concentration of Avicel PH101 and Ac-Di-Sol described above. All the formulations passed weight variation test and uniformity of content test. The hardness of all the tablets was found in the range of 3.4-4.2Kg/cm². Friability was found to be below 1% which was an indication of good resistance of tablets. It was found that with increase in concentration of Avicel PH101the hardness of tablets increased. Smaller particle size of Avicel PH101 and strong hydrogen bonding between hydroxyl groups due to presence of large number of free hydroxyl groups and thus interaction force at contact points between particles may be a reason for the increased hardness.

Wetting Time

Wetting time was determined for all the nine optimized formulations including the controlled batch it was observed that all formulations showed less wetting time as compared to control batch. It was also observed that the batch A_2 showed the wetting time of 63±2 seconds which was less as compared to other batches. It was also observed that the batches containing 3.75% of Ac-Di-Sol showed better wetting time as compared to tablets containing 2.5% and 5% of Ac-Di-Sol.

Water Absorption Ratio

Water absorption being one of the important steps in disintegration process it was evaluated. It was observed that with increase in water absorption ration the disintegration of tablets was faster as compared to the tablets with low water absorption ratio. It was observed that the tablets containing 3.75% of Ac-Di-Sol and 15% of Avicel PH101 showed highest water absorption ratio of 102.84± 0.752 which was the highest among all other batches.

In Vitro Disintegration Time

In-vitro disintegration test was carried out using the method described above. It was observed that the disintegration time of all optimized batches was less as compared to the controlled batch. It was also observed that the disintegration time of batch A_2 was the least (50±2 seconds). Thus it was concluded that with lesser concentration of Avicel PH101 upto 15% and 3.75% of Ac-Di-Sol tablets with good wetting time, water absorption ratio and lesser disintegration time were obtained figure No. 8 shows the disintegration of optimized batch A_2.

In-Vitro Dissolution Studies

The drug release of all optimized batches was found to be better than the controlled batch and marketed

tablet. The control batch showed 100% drug release within 15 minutes where-as marketed immediate release tablet of Perindopril Erbumine (Conpae 4) showed 100% drug release within 25 minutes. It was observed that as the concentration of Avicel PH101 increased the drug release was retarded and the formulations containing very high percentage of Avicel Ph101 showed 100% drug release above 5 minutes whereas the batches containing lesser concentration of Avicel PH101 showed maximum drug release within 5 minutes .The graphs showing drug release are given in figure No.9, 10, 11, 12 and 13 respectively.

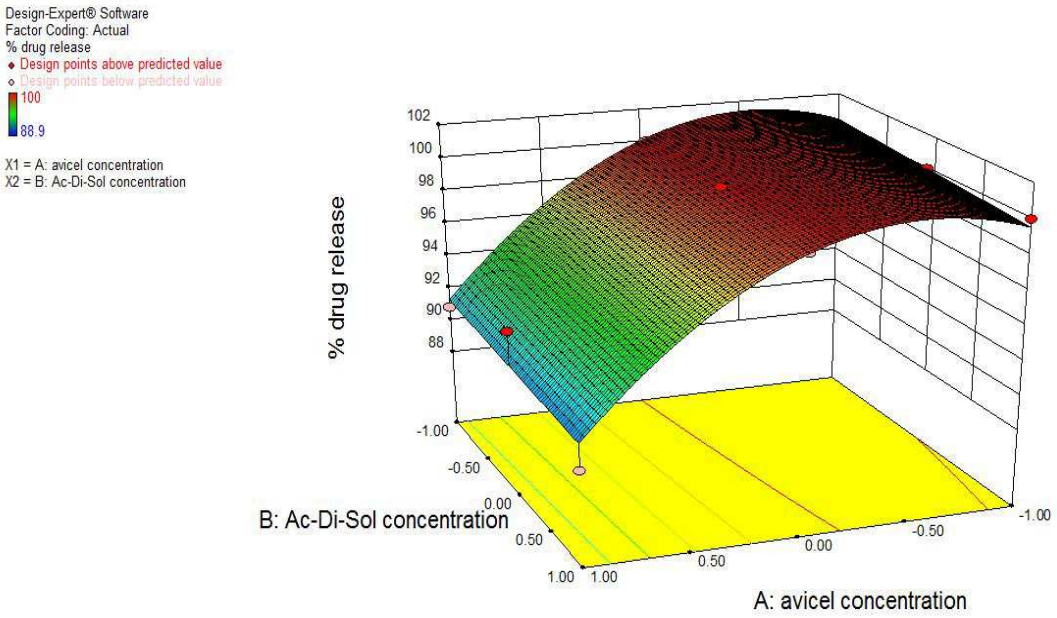


Figure No. 14 3-D Surface plot for In-Vitro % drug release

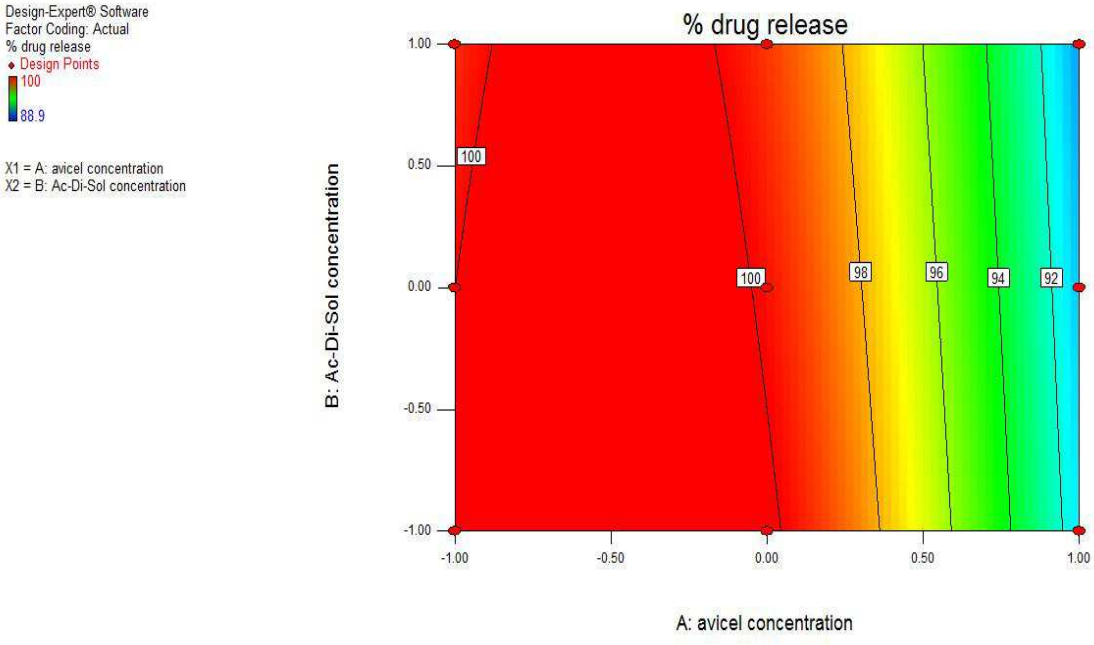


Figure No.15 Contour plot for In-Vitro % drug release

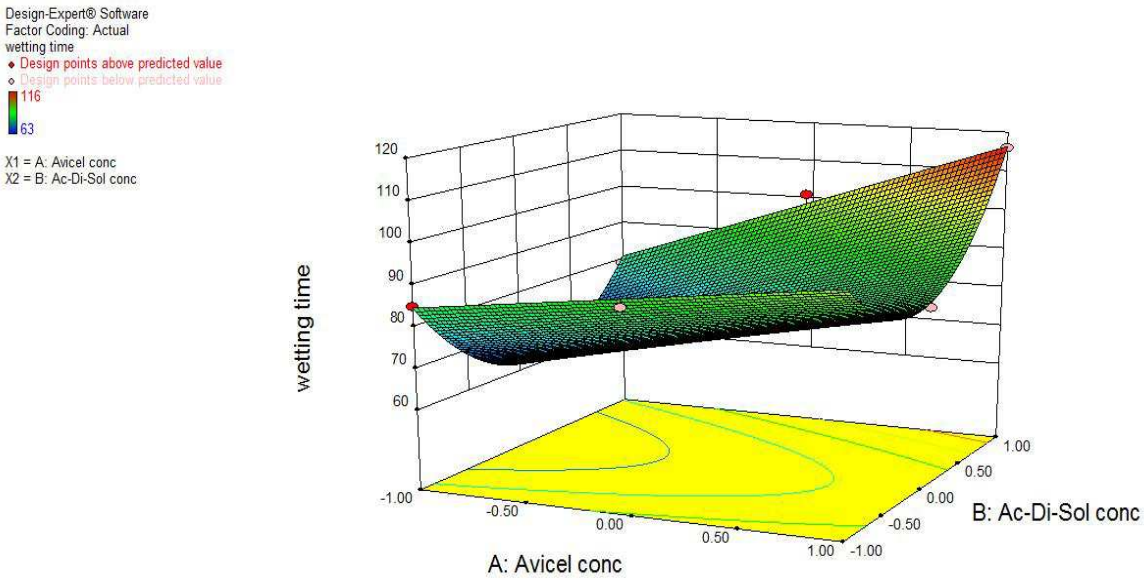


Figure No. 15 3-D Surface plot for In-vitro wetting time

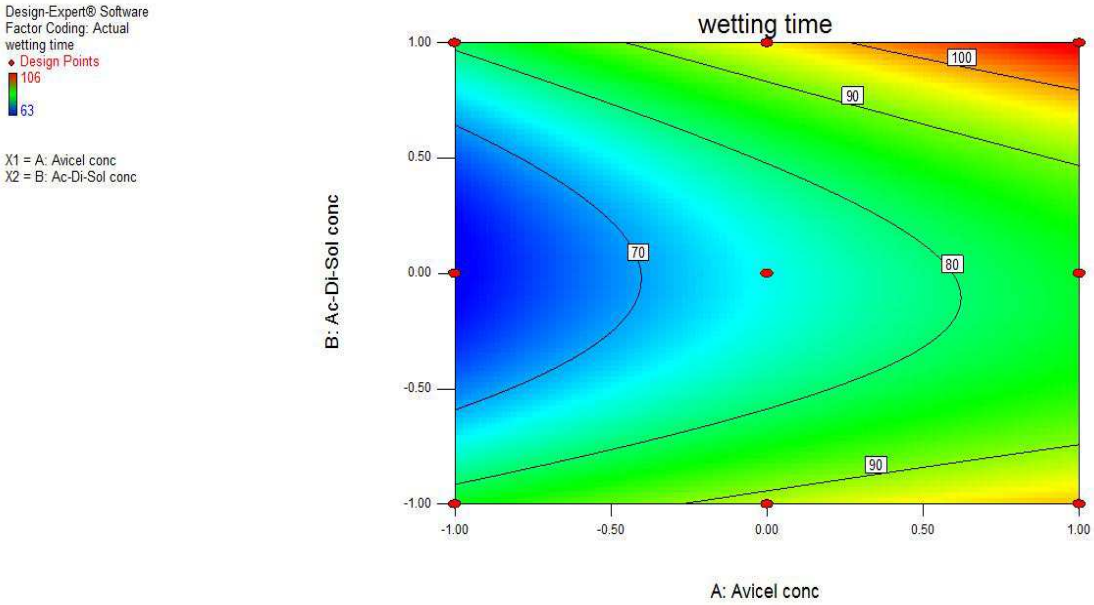


Figure No. 16 Contour plot for In-Vitro wetting time

Development of Polynomial Equation

The % drug release within 5 minutes for the nine batches A_1 to A_9 showed wide variation from 88.90 to 100% drug release, thus the data clearly indicated that the % drug release in 5 minutes is strongly dependent on selected independent variables. The 3-D surface plot and Contour Plot for % In-Vitro drug release are shown in figure No.s 14 and 15 respectively. It ws observed that with increase in concentration of Avicel PH101 and Ac-Di-Sol the drug release within 5 minutes decreased

ANOVA showed that the F value of 26.98 implies significant model. There is only 1.07% chance that the 'model F-value' this large could occur due to noise. Values of prob>F less than 0.0500 indicate model terms are significant. In this case the model terms X_1 andX_1^2 are found to be significant. The R^2

value of 0.8752 indicates that the model is in reasonable agreement with the adjusted R^2 value.

The final equation relating to the response % drug release in 5 minutes (Q_{T5}) is given as follows

Coded factors

% drug release (Q_{T5})=100.53- 4.56* X_1 -0.43*X_2 – 0.48*X_1X_2 – 4.35*X_1^2-1.12*X_2^2

Actual factors % drug release (Q_{T5})=100.53-4.56* avicel PH101concentration- 0.43*Ac-Di-Sol concentration -0.48*avicel PH101*Ac-Di-Sol concentration -4.35* avicel PH101 concentration^2 - 1.12* Ac-Di-Sol concentration^2

It was found that the significance level of coefficient b_{12} and b_{22} were found to be P=0.4521 and 0.2507 respectively, hence they were omitted from the full model to generate a reduced model. The final equation for the reduced model was found to be.

Coded factors

% drug release (Q_{T5}) = 99.78-4.56* X_1 -0.43*X_2-4.35*X_1^2

Actual factors

% drug release (Q_{T5}) = 99.78-4.56* avicel PH101concentration- 0.43*Ac-Di-Sol concentration-4.35* avicel PH101 concentration^2.

The negative signs of coefficients X_1 andX_2 indicate that as the concentration of binder (Avicel PH101) and superdisintegrant (Ac-Di-Sol) increases the in-vitro drug release decreases. It can also be observed that with increase in the concentrations of Avicel PH101and Ac-Di-Sol the disintegration time increased.

The In-Vitro wetting time for the nine batches A_1 to A_9 showed wide variation from 63 to 116 seconds, thus the data clearly indicated that the wetting time is strongly dependent on selected independent variables. The 3-Dsurface plot and the Contour plot for In-Vitro wetting time is shown in figure No. 16 and 17 respectively. It was observed that with increasing the concentration of Avicel PH101 and Ac-Di-Sol the In-Vitro wetting time increased.

ANOVA showed that the F value of 57.17 implies significant model. There is only 0.36% chance that the 'model F-value' this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B, AB, B2 are significant model terms.

The "Pred R-Squared" of 0.8740 is in reasonable agreement with the "Adj R-Squared" of 0.9723.

The final equation relating to the response In-Vitro wetting time is as follows

Final Equation in Terms of Coded Factors.

Wetting time =+73.33+12.0 * X_1+3.83 * X_2+5.75 * X_1 * X_2+0.000 * X_1^2+21.50 * X_2^2

Final Equation in Terms of Actual Factors.

Wetting time =+73.33333+12.0 * Avicel conc+3.83333 * Ac-Di-Sol conc+5.75 * Avicel conc * Ac-Di-Sol conc-0.000 * Avicel conc^2+21.50 * Ac-Di-Sol conc^2.

The positive signs of coefficients X_1 and X_2 indicate that as the concentration of binder (Avicel PH101) and superdisintegrant (Ac-Di-Sol) increases the in-vitro wetting time increases.

It can also be observed that with increase in the concentrations of Avicel PH101and Ac-Di-Sol the disintegration time increased.

Validity of the above equation was verified by designing 5 check point formulations (B_1 to B_5) and determining the in-vitro % drug release (Q_{T5}) and in-vitro wetting time.

The In-Vitro drug release (Q_{T5}) and In-Vitro wetting time predicted from the equation derived and those observed from the experimental results are summarized in table 10

The observed values were in close agreement with the predicted values. This proved the validity of the model.

Table No. 20. Summary of Observed and Predicted Values of Checkpoint Batches.

Sr. No	Batches	X_1	X_2	Predicted values % drug release	Observed values % drug release	STD Dev	Predicted values wetting time	Observed values wetting time	STD Dev
1	B_1	0.00	-1.00	99.870	100.058	0.133	91	89	1.141
2	B_2	-0.89	0.31	100.66	100.39	0.193	67	66	0.707
3	B_3	-0.77	-0.17	100.85	100.42	0.306	76	75	0.306
4	B_4	0.03	-0.28	100.02	100.014	0.003	84	85	0.707
5	B_5	-0.01	-0.45	100.12	100.30	0.132	71	69	1.141

Conclusion

From the evaluations we found that Taste masked orodispersible tablet of Perindopril erbumine containing 15% Avicel PH101 and 3.75% Ac-Di-Sol gave the best disintegration time and also complete drug release within 5 minutes, it was thus concluded that Eudragit E100 can successfully mask the bitter taste of Perindopril Erbumine in the ratio of 1:3 and orally disintegrating tablets of Perindopril can thus be formed successfully by direct compression method.

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