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FORMULATION, OPTIMIZATION AND EVALUATION OF GASTRO-RETENTIVE FLOATING TABLETS OF TERBINAFINE BY QUALITY BY DESIGN (QBD) APPROACH.

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Abstract

The objective of the present study was to develop a sustained release floating tablet of Terbinafine hydrochloride (Hcl) for once- a -day dosing using the quality by design (QBD) approach. Gastro-retentive dosage forms enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal tract and improve the bioavailability of medications those are characterized by a narrow absorption window.hpmck100m and Carbopol 71gf polymer were used as biodegrable polymer. Central composite design was choosen as statistical design tool for analysis study and to optimize formulation variables like per drug release percentage, hardness. The formula that was found to be most efficient was chosen and characterize Prepared tablets of Terbinafine were evaluated tablet hardness, uniformity of weight, friability, uniformity of content, in vitro buoyancy test, swelling index, in vitro dissolution study and stability study. All the compositions were resulted in adequate Pharmacopoeia limits. Compatibility studies was execution during FTIR shown that there was absence of probable chemical interaction between pure drug and excipients. Optimized formulation had drug release 95.36, hardness 7, swelling index weight variation 530 ±0.210, friability 0.510, total floating more 12 hrs.as result, Terbinafine floating tablets might be used to improve bioavailability of narrow therapeutic index

Keywords: Terbinafine; Gastro-retentive; Floating tablet; Total floating time.

INTRODUCTION [1,2,3,4,5,6].

The alteration of drug properties is a popular issue in pharmaceutical science research. Due to their poor solubility and permeability, many medications have issues such as low solubility and frequent dosing. Gastro-retentive tablets are one way to improve the physiochemical properties of a drug. The physicochemical content of the medicine is changed in a gastro-retentive drug delivery mechanism.

The oral route is increasingly being employed to administer therapeutic drugs due to its low cost and convenience of administration. As a result, patient compliance is extremely high. Drug administration at a predetermined, predictable, and controlled rate will be included in CRDDS (controlled release drug delivery systems). Controlled-release drug delivery systems provide several advantages, including maintaining an

optimal ideal therapeutic drug concentration in the blood for an extended amount of time while releasing drugs at predictable and repeatable rates. Minimizing dosing frequency, and enhancing patient compliance. In comparison to a traditional dosing form, a drug delivery system's primary purpose is to deliver a therapeutic amount of drug to the appropriate region in the body and then maintain the desired plasma drug concentration. The oral route of administration has several drawbacks, including a short stay in the GI system, unpredictability in gastric emptying, and drug degradation due to its highly reactive nature. Resulting in a minimum effective drug concentration in the stomach. Gastro retentive systems can reside in the stomach for several hours, effectively extending the drug's time in the stomach. Longer stomach retention boosts bioavailability, reduces drug waste, and improves the solubility of drugs that are less soluble in a high pH environment. Drug can also deliver upper GIT-Tract. Floating tablets provides the availability of novel drug products with novel therapeutic potential and significant patient benefit. Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. Terbinafine hydrochloride is a broad-spectrum antifungal activity against a wide variety of fungi [4-6]. It is an ally amine antifungal used in the treatment of jock itch and athletes foot. It is highly lipophilic in nature and tends to accumulate in skin and nails when applied topically and cause side effects like rash, irritation etc. Because of the size and porous polymeric structure of microsponges, they slowly release the active ingredient, thereby prevent excess build up in epidermis and dermis and reduce side effects. Terbinafine hydrochloride has Pharmacokinetic interactions with drugs that are substrates for CYP2D6 (e. g., tricyclic antidepressants, β-blockers, selective serotonin reuptake inhibitors [SSRIs], and monoamine oxidase [MAO] inhibitors). The objective of the present research work was to provide gastroretentive formulation that will provide once daily, sustained release dosage form of terbinafine.

2. Material and Methods [7,8,9,10,11,12,13,14].

2.1. Materials

Terbinafine HCl was obtained as a gift sample from Aarti Pharmaceutical Pvt.Ltd.. Hydroxypropyl methylcellulose (HPMC K100M and Carbopol 71 Gnf) was procured from Lobachemie. Sodium bicarbonate, citric acid, magnesium stearate, talc were purchased from Lobachemie. Other solvents and chemicals used in the research were of LR grade. All the studies were carried in distilled water.

Table 1: independent variables and respective levels used in the preparation of floating Terbinafine tablets

Levels of independent variables

Sr. no	Factor(independent varibles)	Levels			Optimized levels
		Minimal (-1)	Intermediate (0)	Higher (1)	
1	HPMCK100M	25	50	70	72.12
2	Carbopol71 GNF	25	50	25	25

2.2 Experimental method

Nine batches i.e.F1 to F9 of floating tablets of Terbinafine were prepared by varying hpmck100m and Carbopol 71GNF as per run obtained from experimental design while amount of drug and other excipients concentration was kept constant. The Terbinafine floating tablets was prepared by direct compression method as reported by For independent variables three levels such as + 1, 0, -1 were selected

Table 2. Composition of Different Formulation

		Factor 1	Factor 2
Std	Run	A:hpmck100m	B:carbopol 71Gnf
		mg	mg
3	1	25	25
5	2	25	50
7	3	25	75
8	4	50	25
4	5	50	50
9	6	50	75
1	7	75	25
2	8	75	50
6	9	75	75

Table 2.2: Composition of Different Formulation

		Factor 1	Factor 2	Response 1	Response 2
Std	Run	A:hpmck100m	B:carbopol 71Gnf	hardness	drug release
		mg	mg	kg/cm3	%
3	1	25	25	5.5	95.21
5	2	25	50	4	91.32
7	3	25	75	5.5	92.25
8	4	50	25	6.7	99.08
4	5	50	50	5.6	92.42
9	6	50	75	5.12	91.11
1	7	75	25	7.03	95.16
2	8	75	50	6.9	91.19
6	9	75	75	6.56	89.53

Composition of Tablet Formulation

INGRIDENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Terbinafine hcl	250mg	250 mg	250mg	250mg	250mg	250mg	250mg	250mg	250mg
HPMCK100M	25	25	25	50	50	50	75	75	75
Carbopol 71 GNF	25	50	75	25	50	75	25	50	75
Lactose	80	55	30	55	30	5	30	5	0
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
Citric acid	50	50	50	50	50	50	50	50	50
Pvpk30	15	15	15	15	15	15	15	15	15
Magnesium sterate	3	3	3	3	3	3	3	3	3
talc	2	2	2	2	2	2	2	2	2

Characterization of Prepared Floating Tablets ,14,15,16,17,18,19,20,21,22,23]

2.2.1. Tablet Hardness

The crushing strength Kg/cm2 of prepared tablets was determined for 10 tablets of each batch by using Monsanto tablet hardness tester. The average hardness and standard deviation was determined.

2.2.2. Uniformity of Weight

Twenty tablets were individually weighed and the average weight was calculated. From the average weight of the prepared tablets, the standard deviation was determined.

2.2.3. Friability

Twenty tablets were weighed and placed in the Electro lab friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again.

$\% F = \{1-(Wt/W)\} \times 100$

Where, % F = friability in percentage

W = Initial weight of tablet

Wt = weight of tablets after revolution

2.2.4. Uniformity of Content

Five randomly selected tablets were weighed and powdered. The powdered tablet equivalent to 20 mg drug in one tablet was taken and transferred in a 250ml flask containing 100ml of 0.1N HCl (pH 1.2). The flask was shaken on a flask shaker for 24 hours and was kept for 12 hours for the sedimentation of undissolved materials. The solution is filtered through Whatman filter paper. 10ml of this filtrate was taken and appropriate dilution was made. The samples were analyzed at 283 nm using UV visible spectrophotometer.

2.2.5. In vitro Buoyancy Test

The prepared tablets were subjected to in vitro buoyancy test by placing them in 250 ml beaker containing 200ml 0.1 N HCl (pH 1.2, temp. 37±0.5 oC). The time between introduction of the dosage form and its buoyancy in the medium and the floating durations of tablets was calculated for the determination of lag time and total buoyancy time by visual observation. The Time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT)

2.5.6. Swelling index

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule; breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of weight gain by the tablet. Each tablet from all formulations pre-weighed and allowed to equilibrate with 0.1N Hcl (pH-1.2) for 5hr, was then removed, blotted using tissue paper and weighed. The swelling index was then calculated using the formula:

Swelling index WU = (W1 – W0) x 100 W0

Where, Wt = Weight of tablet at time t, W0 = Initial weight of tablet

2.2.7. In vitro Dissolution Study

In Vitro dissolution study was carried out using USP II apparatus in 900 ml of 0.1 N HCl (pH 1.2) for 8 hours. The temperature of the dissolution medium was kept at 37± 0.5oC and the paddle was set at 50 rpm. 10 ml of sample solution was withdrawn at specified interval of time and filtered through Whatman filter paper. The absorbance of the withdrawn samples was measured at λmax 283 nm using UV visible spectrophotometer.

Mathematical treatment of in-vitro release data The quantitate dissolution/release tests is simpler when mathematical formulas that express the dissolution comes about as an element of a portion of the measurement frames attributes are utilized.

Results and discussion

Design expert 13 software and central composite design are used to do statistical analysis of the data received from the trial. After imposing precise restriction on drug release and hardness. The optimize formula was found. The resulting optimal formula was then produced

3.0 CHARACTERIZATION FLOATING TABLETS OF TERBINAFINE

3.1 Hardness of Floating Tablets

Hardness of tablet of F1 to F9 batches were determined by using Monsanto hardness tester.

The results found to be as shown in below table: able 9.10: Hardness for

Table 3.1: Hardness for Formulations F1 to F9

Formulation	Hardness
F1	5.5
F2	4
F3	5.5
F4	6.7
F5	5.6
F6	5.12
F7	7.03
F8	6.9
F9	6.56

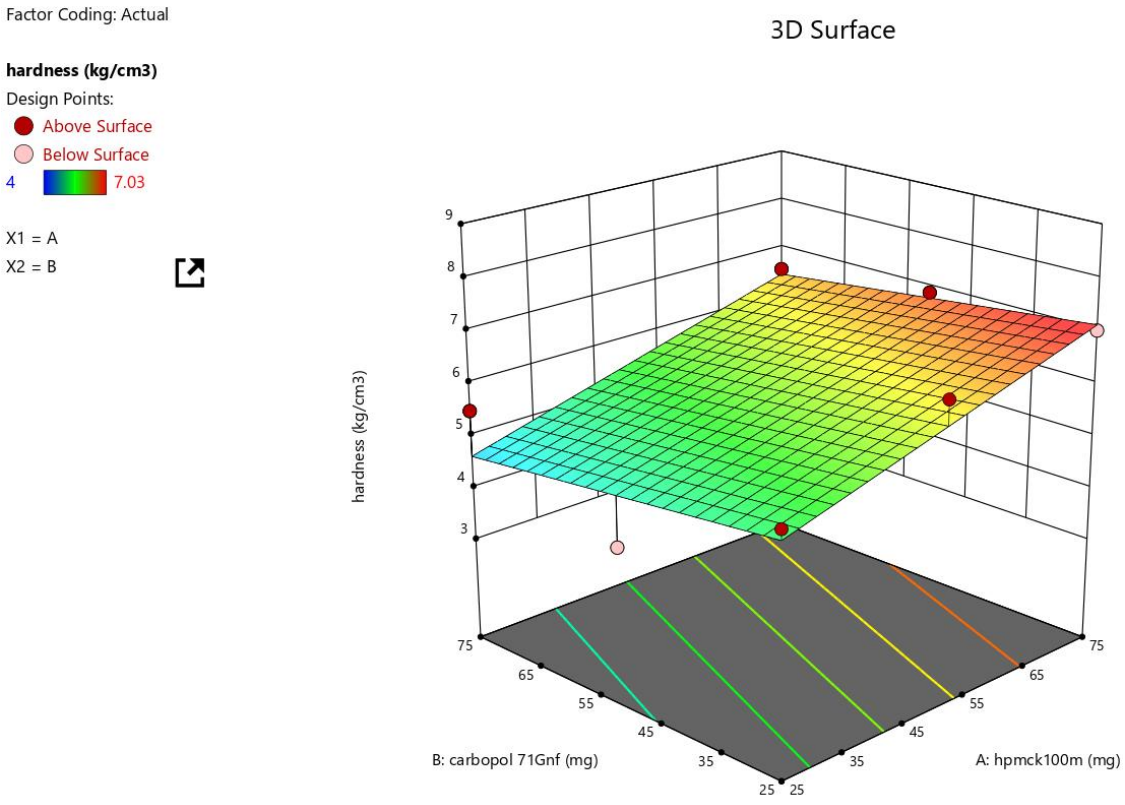


Fig 1.0 3D Surface graph of hardness

Equation Hardness = 0.9150 A + 5.88 + 0.9150 A – 0.3417 B

Discussion

The hardness of tablet was found to be in the range of 5.5 to 6.56kg/cm^2 i.e. they showed good mechanical strength .the hardness of all formulation were found in between 5.5-6.5kg/cm^2.

According to 3d spectra shows that when concentration of hpmck100m increases it will increases the hardness. Carbopol 71gnf concentration is not affect on hardness

DRUG RELEASE

Table no. 4.0-In-vitro drug release study of Formulation

Cumulative percentage drug release									
Time (hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	27.57±0.64	18.0.1±0.48	31.92±0.80	38.25±0.83	25.40±0.91	19.31±0.49	34.92±0.28	30.14±0.45	24.34±0.58
2	34.79±0.50	26.23±0.76	42.58±0.65	46.31±0.76	38.33±0.05	29.16±0.21	46.10±0.22	39.99±0.35	32.19±0.37
4	49.73±0.33	45.05±0.49	57.44±0.67	74.19±0.26	58.01±0.05	50.67±0.39	70.95±0.58	56.44±0.48	49.81±0.07
6	67.22±0.31	54.90±0.46	71.32±0.63	88.58±0.44	73.36±0.86	62.54±0.53	79.38±0.58	66.56±0.63	55.34±0.13
8	74.19±0.33	66.07±0.44	81.59±0.69	95.58±0.44	79.05±0.68	72.09±0.53	86.15±0.04	74.18±0.12	64.14±0.22
10	83.37±0.38	71.27±0.79	82.44±0.88	97.48±0.72	83.29±0.69	81.01±0.09	89.96±0.09	83.37±0.63	76.41±0.07
12	95.21±0.53	91.32±0.78	92.25±0.73	99.08±0.70	92.42±0.69	91.11±0.58	95.16±0.58	91.19±0.33	89.53±0.47

All value are expressed as mean ± (N=3)

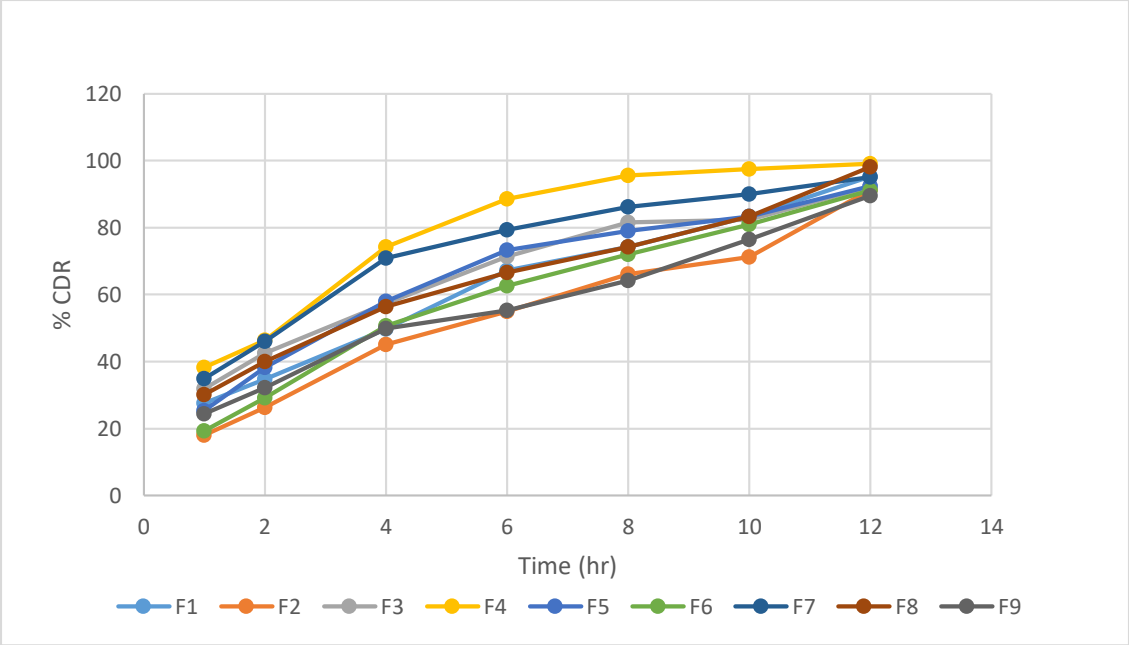


Fig no 2.0 -In-vitro drug release study of the formulation F1 To F 9

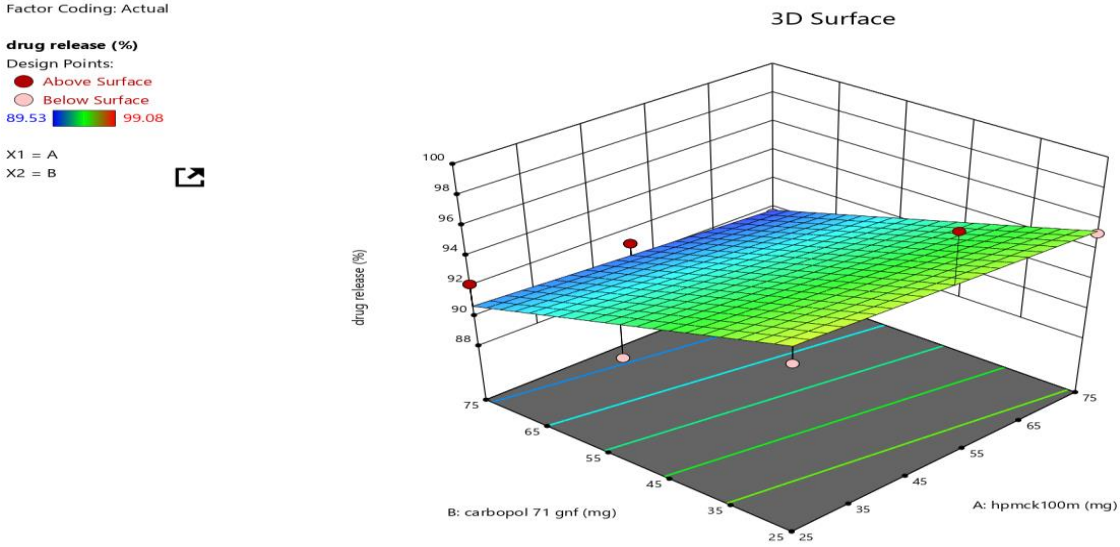


Fig 3.0 3D Surface graph of Drug Release

Equation Drug release = +99.51667-0.019333 hpmck100m-0.110400 carbopol 71gnf

From the fig F1 to F9 formulation were prepared from hpmck100m and Carbopol71G NF containing gas generating agent sodium bicarbonate and citric acid .release of f1 formulation was found to be after 12 hours 95.21±0.53. F2 was found to be 91.32±0.78. F3was found to be 92.25±0.73.F4 was found to be 99.08±0.70. F5 was found to be 92.42±0.69.F6 was found to be 91.11±0.58.F7 was found to be 95.16±0.58.F8 was found to be 91.19±0.33.F9 was found to be 89.53±0.47.

According to counter graph and 3d spectra surface graph show that when concentration Carbopol will increase drug release will be decreases. And concentration of hpmck100m is not affect on drug release

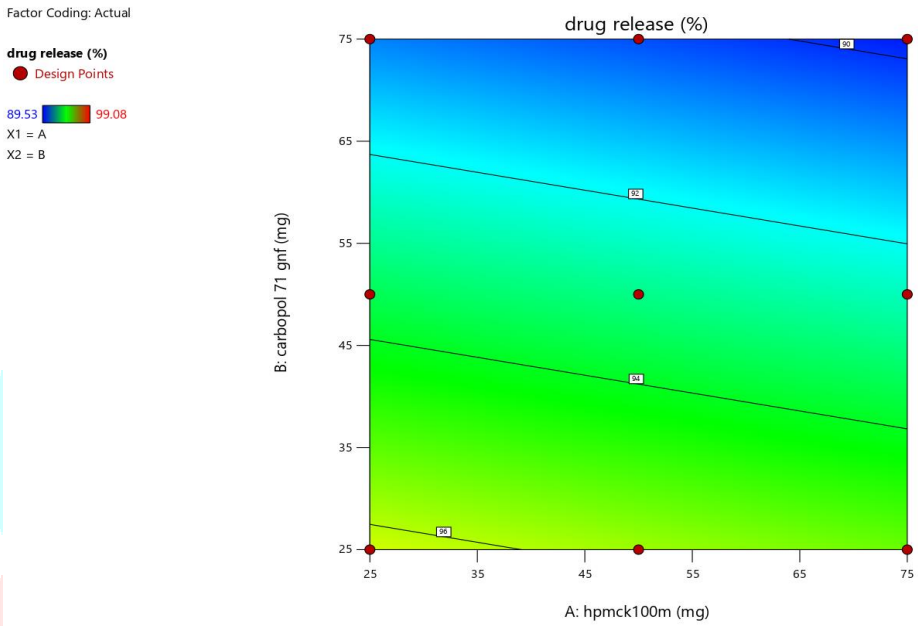


Fig no 4.0- contour plot of drug release

DISCUSSION

5.0 OPTIMIZATION OF BATCH:

The statistical analysis of all data obtained from experiment is done dy Design-Expert 13 software. And Central composite design. The optimum formula was generated after applying specific constraints on hardness and drug release. After which the obtained optimum formula was prepared and studied for further characterization such as friability, Wt variation, % swelling index, and floating time and lag time.

For the Design study two independent variables and two response variables. The Carbopol 71 gnf and Hpmck100M as a independent variables. Where Hardness (Y1), and Drug release (Y2) as response variables.

These responses were fitted individually to linear for hardness, l and Linear for Drug release using linear regression to obtain the model of choice with the highest adjusted and predicted r^2. Significance of difference was evaluated using one-way ANOVA at probability level of 0.05. The final equations for the responses related to different factors and interactions in terms of actual factors were obtained as shown in below:

Hardness = 0.9150 A + 5.88 + 0.9150 A – 0.3417 B

Drug release = +99.51667-0.019333 hpmck100m-0.110400 Carbopol 71gnf

ANOVA analysis: 1. ANOVA for Linear mode

Table no 5.1-ANOVA for Linear mode for hardness

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	5.72	2	2.86	7.62	0.0225	significant
A-hpmck100m	5.02	1	5.02	13.38	0.0106	
B-carbopol 71Gnf	0.7004	1	0.7004	1.87	0.2210	
Residual	2.25	6	0.3755			
Cor Total	7.98	8				

ANOVA for Linear model

Response 2: drug release

Table no 5.2.-ANOVA for Linear mode for hardness

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	47.11	2	23.55	6.42	0.0323	significant
A-hpmck100m	1.40	1	1.40	0.3821	0.5592	
B-carbopol 71 gnf	45.71	1	45.71	12.46	0.0124	
Residual	22.01	6	3.67			
Cor Total	69.12	8				

The Contour plot of each response and Overlay plot is mentioned as below

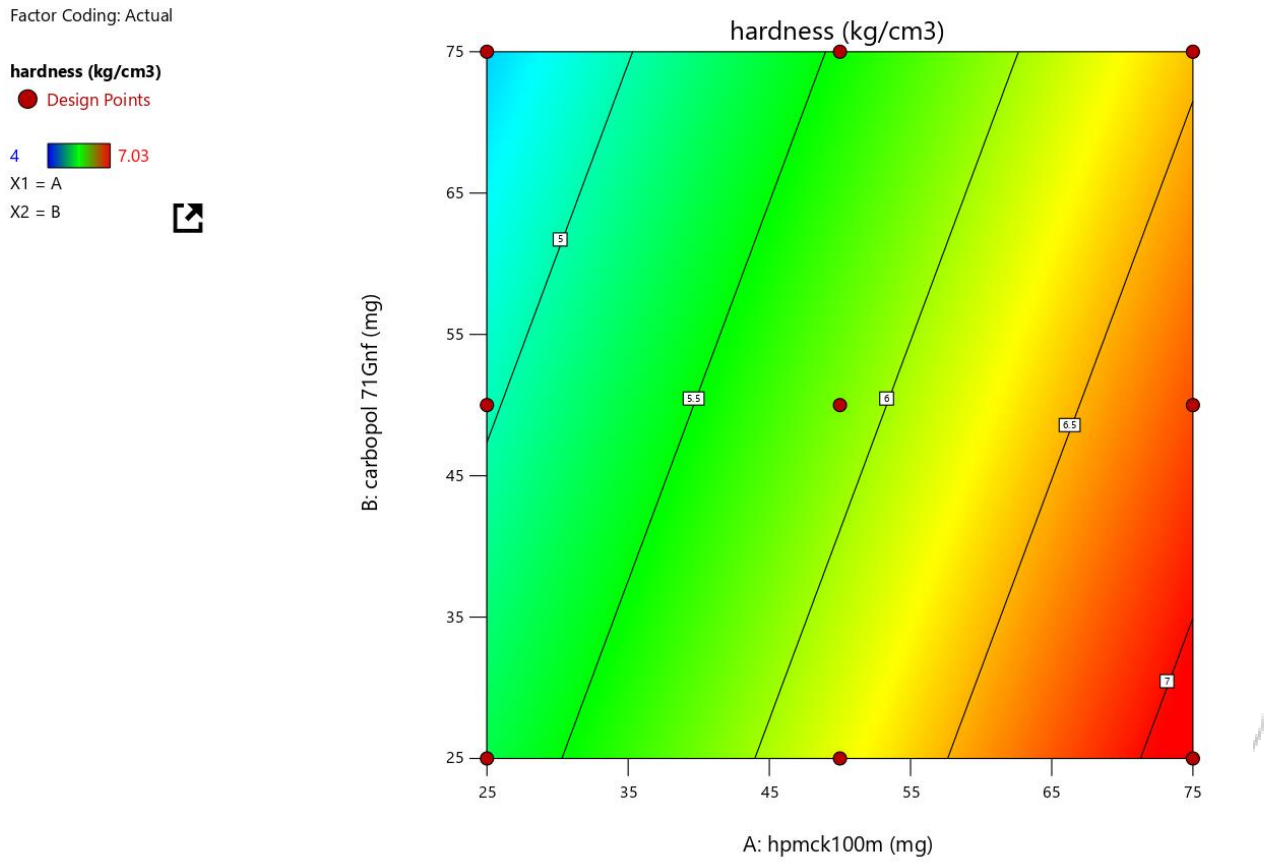


FIG NO 5.0 -Contour plot OF HARDNESS

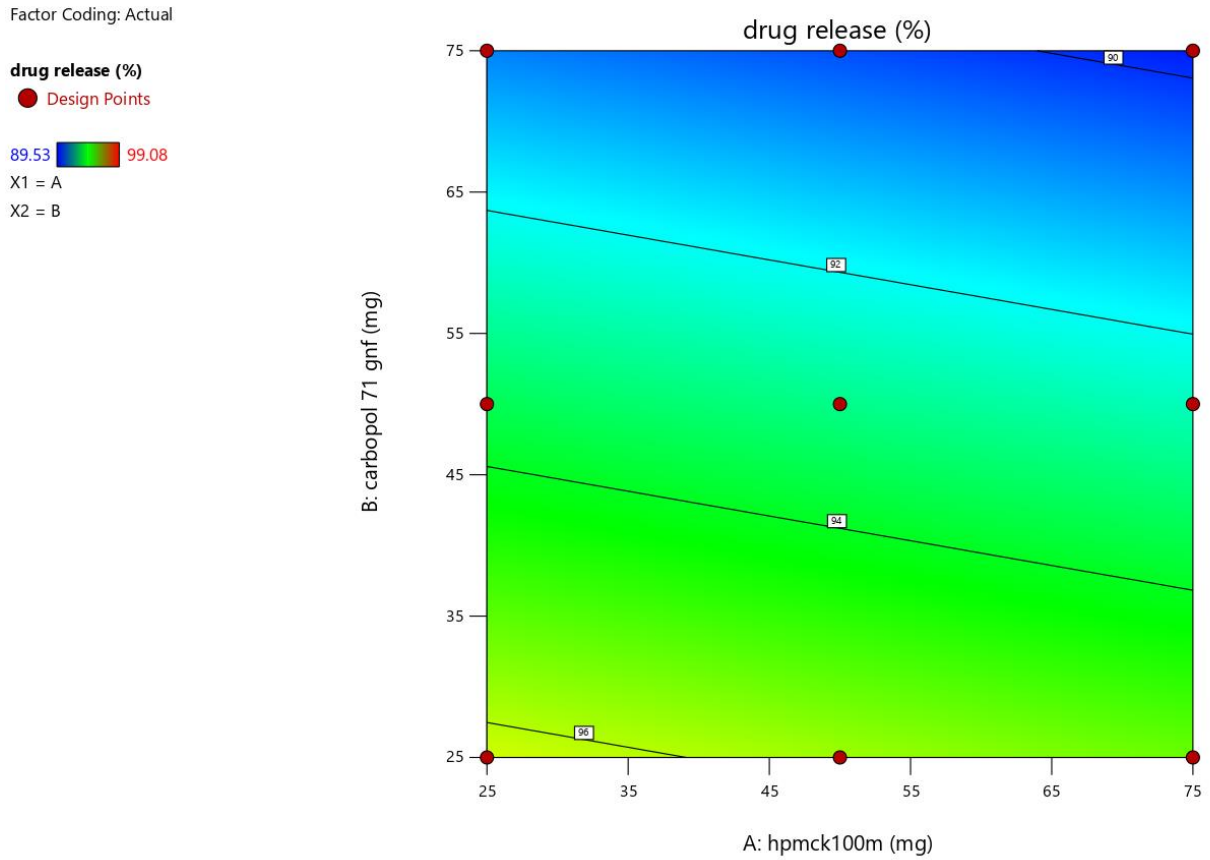


Fig no 6.0 Contour Plot OF Drug Release

Table no 5.3 –Composition of Optimized Batch F1

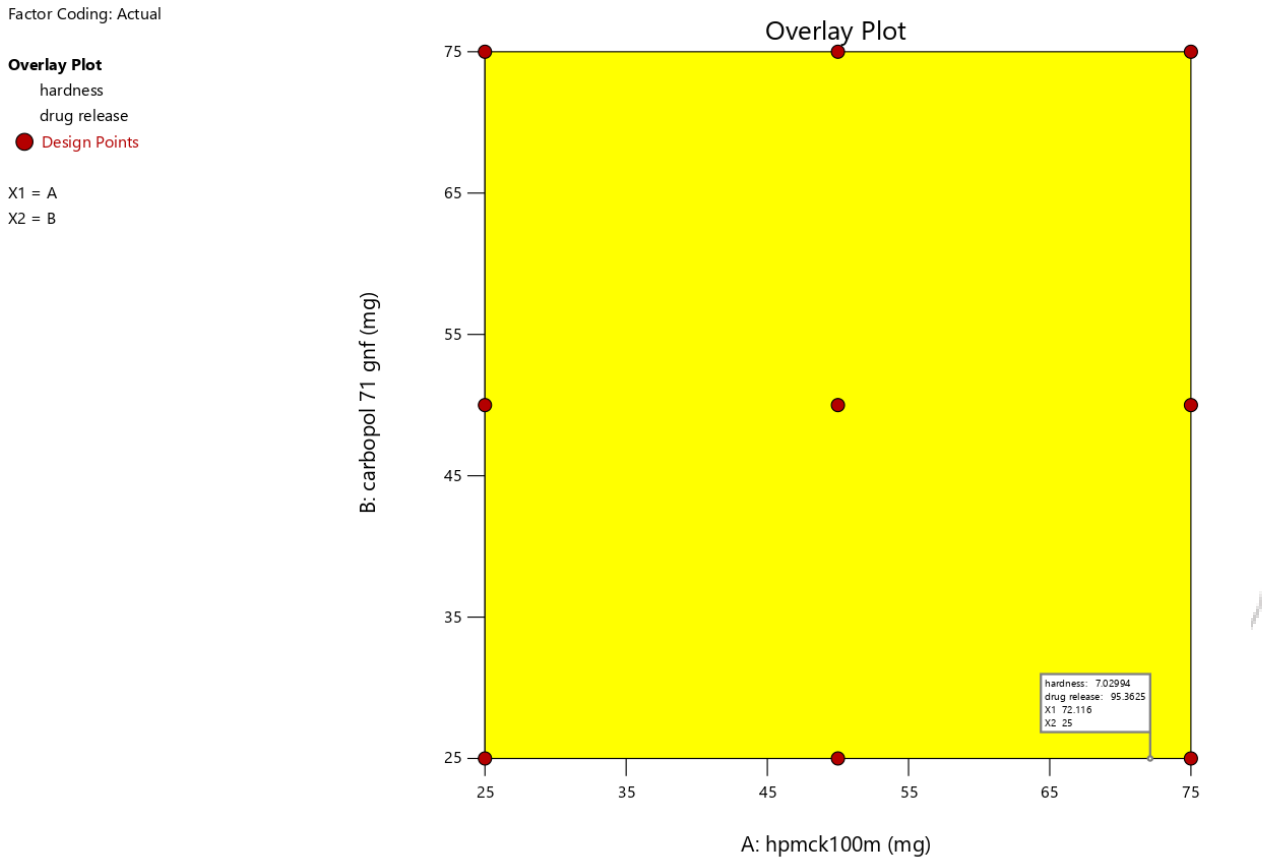


Fig No 7.0- Overlay Plot Of Drug Release and Hardness

From the study of results and graphs given by software the optimized batch was prepared and characterized.

The 59 solutions given by software out of which following formula was selected for further study.

Factor	Name	Level	Low Level	High Level	Std. Dev.	Coding
A	hpmck100m	72.12	25.00	75.00	0.0000	Actual
B	carbopol 71 gnf	25.00	25.00	75.00	0.0000	Actual

Table no 5.3 –Composition of Optimized Batch F1

Table no 5.4 Hardness and Drug Release of Optimized Batch F1

Solution 1 of 10 Response	Predicted Mean	Predicted Median	Observed	Std Dev	n	SE Pred	95% PI low	Data Mean	95% PI high
hardness	7.03	7.03		0.612797	1	0.727194	5.25062	7.2	8.80938
drug release	95.3624	95.3624		1.91534	1	2.27289	89.8009	93	100.924

	Intercept	A	B	AB	A^2	B^2
hardness	5.87889	**0.915**	-0.341667			
p-values		**0.0106**	0.2210			
drug release	93.03	-0.483333	**-2.76**			
p-values		0.5592	**0.0124**			

Table No 5.5: Granules Flow properties of optimized formulation

Batch / Parameters	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)	Flow
Optimized Batch	0.70	0.80	12.50	1.14	27.70	Good

***All values are mean ± SD (n=3)**

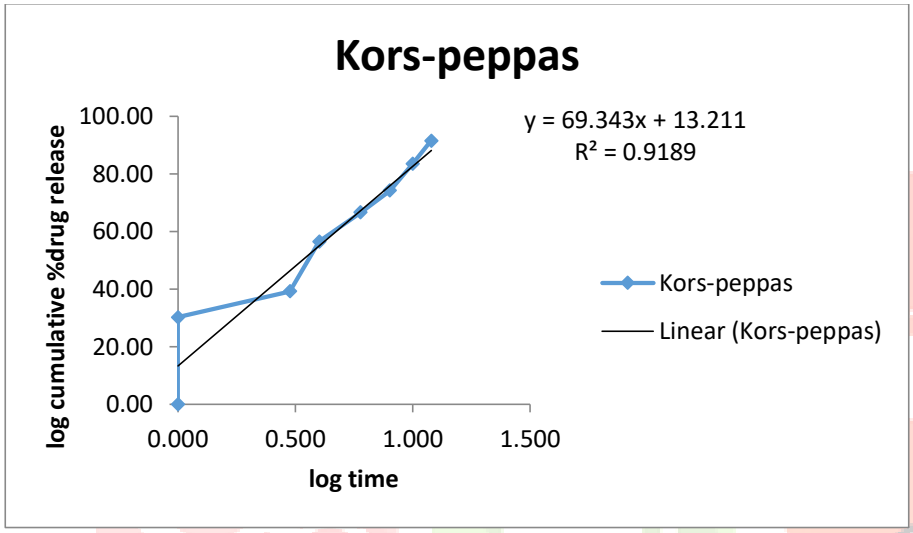
Table 5.6: Evaluation of optimized batch F1

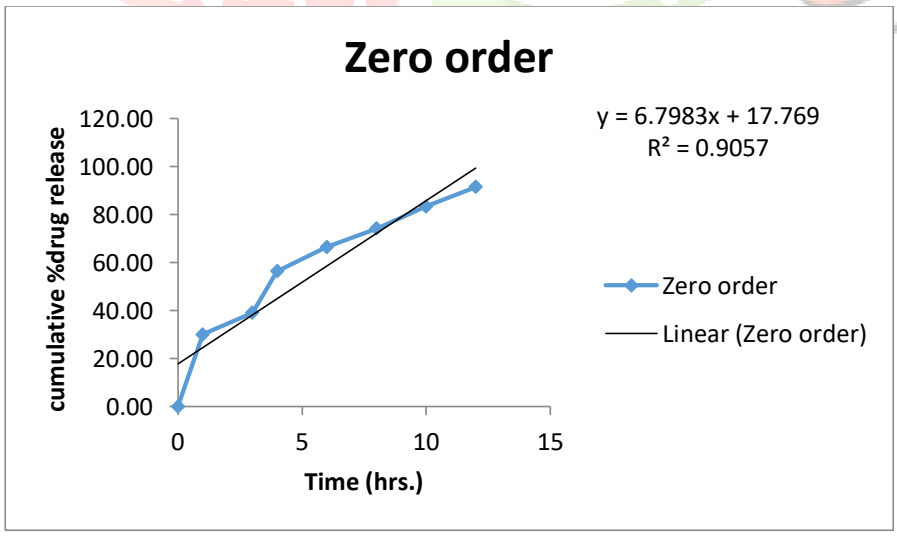
Parameters	Result of optimized batch
Physical appearance	White convex faced
Weight variation	530 ±0.210
Hardness	7
Friability	0.510
Drug contents	98.08
In vitro release	95.36
Floating lag time	69 sec
Total floating time	≥12
Buoyancy on disturbing	Float

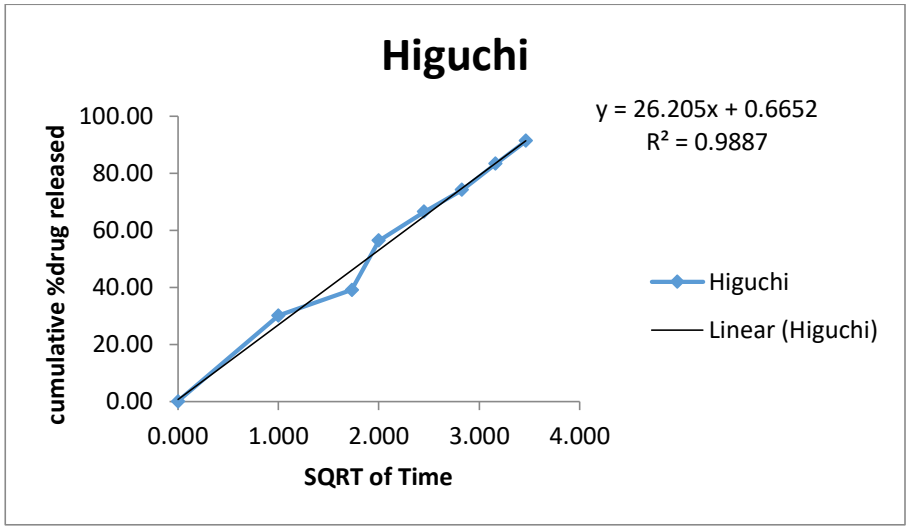
Kinetic Modeling of Drug Release of optimized batch

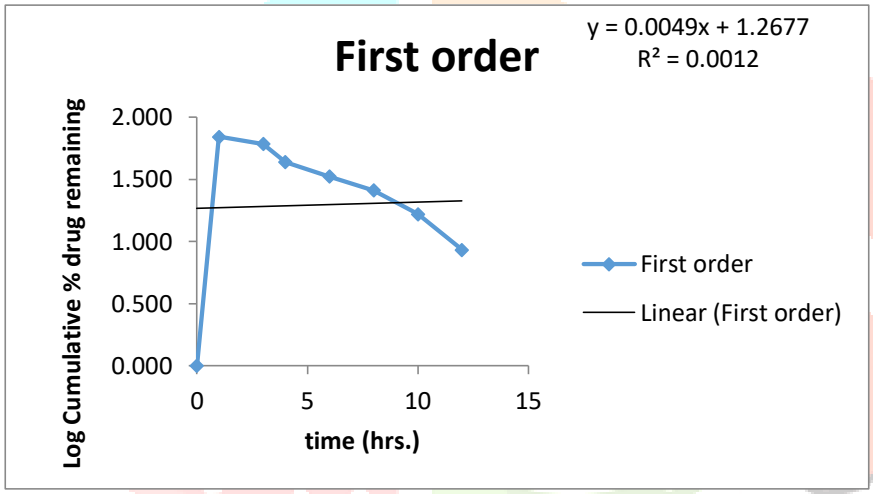
TABLE NO 5.17-Result of correlation for optimized batch

Formulation	**Correlation coefficient R^2**				
Order of release	ZERO Order	First order	Hixon matrix	Koremeyer peppas	
Optimized batch	0.9070	0.0012	0.9813	0.9189	






Higuchi
y = 26.205x + 0.6652
R² = 0.9887
cumulative %drug released
100.00
80.00
60.00
40.00
20.00
0.00
0.000
1.000
2.000
3.000
4.000
SQRT of Time
Higuchi
Linear (Higuchi)


First order
y = 0.0049x + 1.2677
R² = 0.0012
Log Cumulative % drug remaining
2.000
1.500
1.000
0.500
0.000
0
5
10
15
time (hrs.)
First order
Linear (First order)

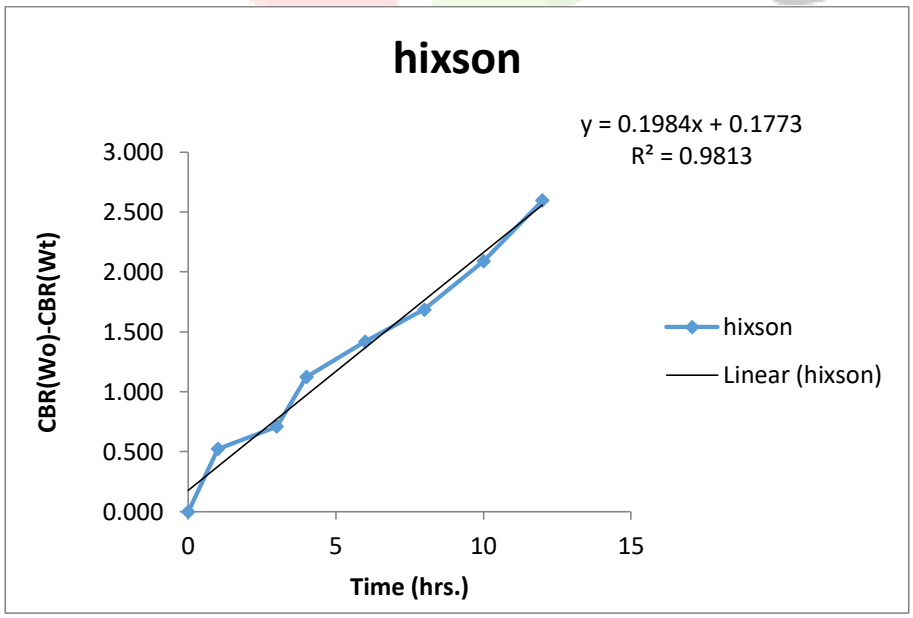

hixson
y = 0.1984x + 0.1773
R² = 0.9813
CBR(Wo)-CBR(Wt)
3.000
2.500
2.000
1.500
1.000
0.500
0.000
0
5
10
15
Time (hrs.)
hixson
Linear (hixson)

Fig no 9.11Drug release Kinetics Models for optimized batch F1

The dissolution profile of best optimized batch was fitted to zero order, first order ,higuchi,hixon-crowell,koresmeyer and peppas, to certain the kintic modeling of drug release by using PCP Disso version 2.08 software,and this model with the highest correlation coefficient was considered to be best model. The slope and R^2 are shown in table no and graph. Optimized formulation was best fitted heroxn with R^2 0.9813 Which is higher than 1 in experiment work, hence drug transport mechanism is super casell transport mechanism

Assessment by using developed analytical techniques such as,

A) IR spectra of Physical Mixture

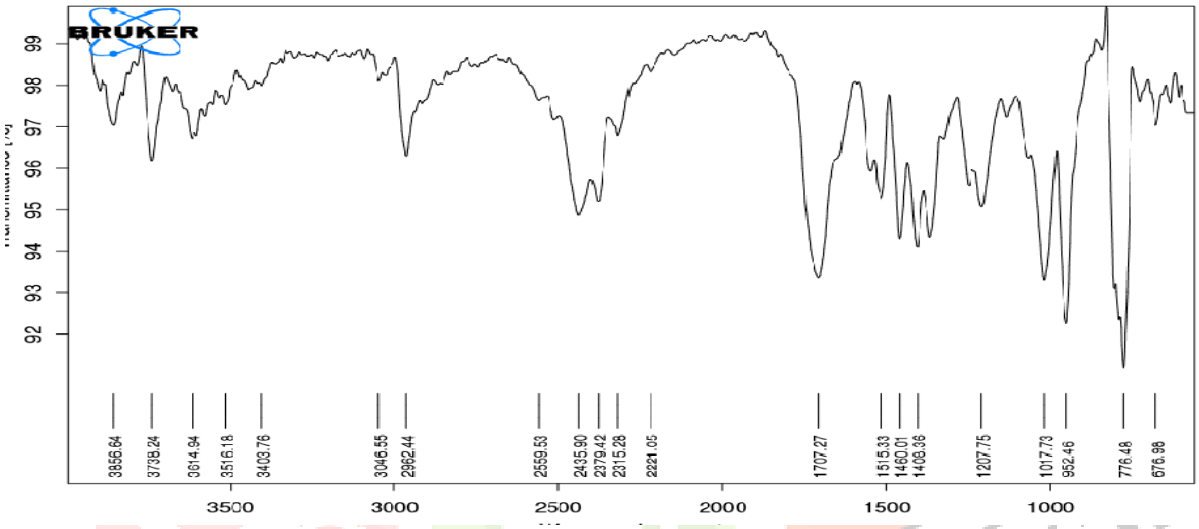


Fig 9.12 IR spectra of Physical Mixture

Table No 9.19- IR spectrum interpretation of Physical mixture

Functional Groups	Standard ranges Wave numbers -1 in cm	Observed ranges Wave numbers In cm-1
C=C	1620-1680	1645.87
N-C	1180-1380	1254.14
CH_3, C-H	2960-2850	2960.96
Aromatic C-H	3000-3100	3046.01
N-H	3300-3500	3046.01
COOH		
O-H	3600-3650	3614.94
C=O	1680-1760	1707.27

The characteristic functional groups of Carbopol 71gnf, HPMCK100M, and Terbinafine as mentioned above were observed in the same position in the physical mixture IR spectrum. Which indicated that there is no incompatibility between drug and other excipients.

Stability study of formulation

Table no 9.20 -Stability study of formulation

Parameters	**1 st month 25 ^{0}c/60 RH 5%**	**2 month 40 ^{0}c/60 RH 5 %**
Physical appearance	**White convex faced**	**White convex faced**
Weight variation	530 ±0.210	530±0.10
Hardness	h	7
Friability	0.510	0.510
Drug contents	98.08	95
Floating lag time	69	69
Total floating time	≥12	≥12
In vitro release	95.36	94.15
Buoyancy on disturbing	Float	Float

Conclusion

The study was undertaken to develop floating and sustained release tablets of Terbinafine using different polymer the matrix ER system release drug like Terbinafine Hcl throughout the G.I tract achieving peak drug release level within few hours followed by decreasing release rate over time

The QbD approach was used to study the effects of formulation parameters ranked as high risk in the initial risk assessment were include in the design experimentation concentration of HPMCK100M and Carbopol 71gNF. The effervescent based floating drug delivery was a promising approach to achieve vitro buoyancy by addition of gel forming polymer such as hpmck100m and Carbopol 71g NF and gas generating agent such as sodium bicarbonate and citric acid it was found that if concentration of polymer increases drug release rate decreases addition of gas generating agent drug release increase and tablet also float

Finally it can be conclude that Terbinafine tablet can be formulated by using polymer to achieve gastro retention and sustained release by direct compression technique.

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