WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 6.647
Volume 7, Issue 1, 655-679 Research Article ISSN 2278 – 4357

FORMULATION, STATISTICAL OPTIMIZATION AND EVALUATION OF INCLUSION COMPLEXED FAST ORAL DISSOLVING FILMS OF CARVEDILOL

G. Swathi*[1], K. Brahma, B. Moulika Lakshmi, S. Sravani, P. Indira and Dr. P. Shailaja[2]

[1]Department of Pharmaceutical Technology, Andhra University, Visakhapatnam, 530003, India.

[2]Asst. Professor, Department of Pharmaceutical Technology.

Article Received on
27 Oct. 2017,

Revised on 17 Nov. 2017,
Accepted on 07 Dec. 2017,

DOI: 10.20959/wjpps20181-10697

***Corresponding Author**
G. Swathi
Department of Pharmaceutical Technology, Andhra University, Visakhapatnam, 530003, India.

ABSTRACT

Carvedilol is a β-blocker, belongs to BCS class II, with low oral bioavailability (25%), primarily used for the treatment of hypertension, and heart failure, after a heart attack to improve the chance of survival, prevents strokes kidney problems. The purpose of this research is to formulate carvedilol as oral dissolving films to provide an immediate release of drug and fast onset of action, thereby improving the bioavailability. The films are prepared by solvent casting method using polymers such as HPMC, PVA and PVP in different composition in addition with poly ethylene glycol-400 as plasticizer. The formulated films are assessed for their physicochemical parameters such as transparency, thickness, weight variation, folding endurance, surface pH, disintegration time, swelling studies and drug content uniformity, *in vitro* dissolution study. The optimized films were characterized for interaction studies by FT-IR. To increase the percentage of drug release at minimum duration, the drug with β cyclodextrin is prepared as inclusion complex by kneading method using 3^2 factorial design, the optimized inclusion complex mixture was incorporated into the films, and further optimized by the evaluation studies. The optimized non-inclusion complexed and inclusion complexed FDF formulations were evaluated for *Ex-vivo* drug release study using porcine oral mucosa and stability studies.

KEYWORDS: Carvedilol, Fast Dissolving Films, Solvent Casting, Kneading Method, Inclusion Complexation, Non-Inclusion Complexed FDFs.

1. INTRODUCTION

Carvedilol is classified as β-blocker, works by blocking the action of epinephrine, on the heart and blood vessels. Absolute bioavailability of the drug is 25% for an oral administration at 3.125 mg dose. The low oral bioavailability of carvedilol is mainly due to the most critical factors like first pass effect, low aqueous solubility and dissolution rate of the drug. Several approaches have been developed recently to overcome these factors, which includes salt formation, solid dispersion, inclusion complex, micro emulsion micronization etc. These methods results in reduction of particle size which in turn increases the surface area, wet ability and solubility. For an immediate release of this drug and to improve its bioavailability, a novel dosage form is developed by formulating strips containing inclusion complex of drug with β-CD. Mouth dissolving strips are recently developing for both immediate and controlled release drug delivery system out of which immediate release is of special importance due to its significant advantages. The strip made for immediate release dissolves or disperses in the mouth without need of drinking water or chewing. This type of formulation helps to improve the bioavailability of drugs and is mainly focused for the ease of administration especially for patients who are mentally ill and in coma state. The ability to mask the taste helps in administering these drugs to non-co-operative patients. The rapid disintegration or dissolution leading to quick effect is very important especially in the patients suffering from acute or chronic conditions like hypertension, myocardial infarction (heart attacks), heart failure, peripheral arterial disease and chronic kidney disease. The work here concentrates on developing fast dissolving strips by a solvent casting method using various polymers. Also the effect of kneading inclusion complexation of drug using β-cyclodextrin for incorporating into the strips was compared to understand the raise in bioavailability due to decreasing particle size and increasing the solubility of the drug.

1.1. Fast oral dissolving films

Oral films also called as oral wafers, oral thin films, and mouth dissolving films, mouth melting films and fast dissolving films. Novel drug delivery system in the recent years was developed to enhance safety and efficacy of drug molecules by designing a suitable dosage form for administration.[1] The oral route is the most acceptable and preferred route for drug delivery and also it has its own merits and demerits.[2] There is a need for development of dosage form with better therapeutic efficacy and fewer side effects. Various bio adhesive mucosal dosage forms include buccoadhesive tablets, gels, ointments, patches have been developed.[3] Recently, fast dissolving drug delivery systems has become one of the popular

and acceptable drug delivery systems, because of their ease of administration and better patient compliance. This novel drug delivery system can also be beneficial for the enhancement of bioavailability of drugs.[4] Fast oral dissolving films (FDFs) have attracted interest as an excellent dosage form, not only for oral care, but also for patients with aphasia or dysphasia.[5,6] They can be taken with ease at any time by the patient without requiring any water for swallowing.[7,8] The oral strip technology delivery system consists of very thin oral strips which are postage stamp-sized rectangular shape polymeric films[9], which is placed on the patients tongue or along the inside of the cheek. The hydration of the film by the saliva gets adhered on to the site of application. Then it disintegrates rapidly and dissolves to release the medication for absorption on to the oral mucosa as well as gastro intestinal tract producing faster onset of action.[10] These flexible films are suitable for oral, topical and enteral use where they can be applied to mucosal membrane areas of the mouth, rectum, vagina, nose and ear. The release of the active ingredients from the films can be controlled by selecting the polymer type, concentration and by adjusting the levels of different ingredients of the formulation. A dissolving strip comprises of,

- An inert base material soluble in saliva.
- A therapeutic active ingredient where it can be mixed with inert base material to form the dissolving strips.

This is taken orally where it is dissolved in to the oral cavity, releasing the therapeutic material in to the cavity and the duration ranges from 30 seconds to 10 minutes. The rapidly dissolving films were initially available in the market as breath fresheners and personal care products such as dental care strips and soap strips. The following properties of the thin film were observed when placed in the mouth

- Spontaneous disintegration when in contact with saliva
- Pleasant taste and
- Good feel in mouth.

1.2. Inclusion complexation technique[11]

In host-guest chemistry, an inclusion compound is a complex in which one chemical compound (the “host”) forms a cavity in which molecules of a second “guest” compound are located. The definition of inclusion compounds is very broad, extending to channels formed between molecules in a crystal lattice in which guest molecules can fit. If the spaces in the host lattice are enclosed on all sides so that the guest species is “trapped” as in a cage, the

compound is known as a clathrate. In molecular encapsulation, a guest molecule is actually trapped inside another molecule.

There are numerous approaches to enhance the solubility of poorly water soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected and nature of intended dosage form. Among these approaches salt formation, solubilisation, particle size reduction, solid dispersion and solvent deposition technique are most frequently used. But, there are practical limitations of these techniques.

Cyclodextrins (CDs) are belongs to the category of carbohydrates and are cyclic oligosaccharides discovered just over 100 years ago. They are called "Cellulosine", when first discovered by A.Villiers in 1891. F.Schardinger identified the three naturally occurring cyclodextrins α, β and γ. And these were referred to as "Schardinger Sugars". For 25 years, between 1911 and 1935, Pringsheim in Germany was the leading researcher in this area, demonstrated that CDs formed stable aqueous complexed with many other chemicals. CDs are produced form starch by means of enzymatic conversion. Over the last few years, an application of CDs is expanded into food, pharmaceutical, chemical, agricultural and environmental engineering fields. Due to specific structure and the orientation of the hydroxyl groups made the CDs capable of solubilize in aqueous medium and to encapsulate the lipophilic molecules into their interior cavity.

2. MATERIALS AND METHODS

2.1 Materials used

Carvedilol Gift sample from Hetero laboratory, β-CD (sisco research laboratories PVT Ltd), HPMC E-5 (central drug house PVT Ltd.), Poly vinyl alcohol (central drug house Pvt Ltd.), poly vinyl pyrrolidine (Otto Chemika-Biochemika- Reagents), PEG-400 (central drug house PVT Ltd.), tween-80 (qualigens fine chemicals), sucrose (Otto Chemika- Biochemika-Reagents), menthol (sisco research laboratories PVT Ltd), methanol (universal laboratories) these materials were used for preparation of FDF.

2.2. Phase Solubility Studies[12]

Phase solubility studies on pure drug with β-CD were performed by the method described by Higuchi and Connors. Excess amount of the drug is added to 15 mL of distilled water containing various concentrations of β-CD, both stoichiometric and molar mass ratios (1:1),

(1:2), (1:3) taken in a series of 25 mL stopped conical flask and the mixture was shaken for 72 hours at room temperature on a rotary flask shaker. After 72 hours of shaking to achieve equilibrium, 2mL aliquots are withdrawn at 1hr interval and filtered through 0.45µ membrane filter. The filtered samples are diluted suitably and assayed for the drug content by specific UV method at 240 nm against blank in same concentrations of β-CD in water so as to cancel any absorbance that may be exhibited by the β-CD molecules. Shaking is continued until the consecutive estimations are the same. The solubility experiments are conducted in triplicate.

2.3. Experimental Design[13]

A 3^2 factorial Design was used for the development and optimization of inclusion complexation of carvedilol, two factors were evaluated at 3 levels and experimental trials were conducted for the 13 combinations. One face centered value was repeated five times. The amount of β-cyclodextrin(X_1) and tween 80(X_2) used were selected as independent variables. Dissolution rate (Y) was selected as dependent variable to optimize the response data.

The polynomial equation given below was used to study the effect of variables on evaluation response (Y), where the coefficients in the equation (β_0, β_1, β_2 ,β_{12}) were related to the effects and interactions of the factors.

$Y=\beta_0+ \beta_1X_1+ \beta_2X_2+ \beta_{12} X_1X_2+ \beta_{11}X_1X_1+ \beta_{22}X_2X_2$

Where,

Y is the dependent variable

β_0 is the arithmetic mean response of the 13 runs

β_1 and β_2 are the estimated coefficients for the factors X_1 and X_2 respectively.

The main effect (X_1 and X_2) represents the average result of changing one factor at a time from its low to high value.

The interaction term (X_1X_2) shows how the response changes when two factors are changed simultaneously.

The polynomial terms (X_1X_1 and X_2X_2) are included to investigate nonlinearity.

Table. 1: Experimental range and levels of the independent variables in a 3^2 factorial design.

Run No.	Independent Variable level in coded form	
	X_1	X_2
1	-1	-1
2	0	-1
3	+1	-1
4	-1	0
5	0	0
6	+1	0
7	-1	+1
8	0	+1
9	+1	+1
10	0	0
11	0	0
12	0	0
13	0	0

Table. 2: Coded values for independent variables.

Coded values	Actual values	
	X_1 (Amount of β-CD in mg)	X_2 (Amount of tween 80 in mg)
-1	250	20
0	500	50
+1	750	80

2.3.1. Procedure for preparation of inclusion complex mixture by kneading method[14]

250 mg of drug and increasing concentrations of β-CD were triturated using 4 mL of 50% water-methanol for 45 minutes, dried in hot air oven at 50°C; dried powder was then sieved through sieve no. 80(315 µm).

2.4. Calculation of drug loaded in the film[14]

Diameter of petridish = 6.2 cm diameter

Radius of the petridish (r) = 3.1 cm radius πr^2 = 3.14 X 3.1 X 3.1 = 30.17 cm²

Now, Dose is 3.125 mg in 2 cm X 2 cm = 4 cm²

4cm² contain 3.125 mg drug.

So, 30.17 cm² contain = 23.57 mg drug.

2.5. Preparation of non-inclusion and inclusion complexed FDFs[14]

Table. 3: Formula for preparation of non-inclusion and inclusion complexed FDFs.

Ingredients	Non-inclusion complex mixture FDFs				Inclusion complex mixture FDF
	F1	F2	F3	F4	
Drug/ Drug equivalent complex mixture	23.57 mg	23.57 mg	23.57 mg	23.57 mg	50.23 mg
HPMC E5	500 mg	500 mg	500 mg	500 mg	500 mg
PVA	400 mg	500 mg	-	-	500 mg
PVP	-	-	400 mg	500 mg	-
PEG-400	0.177 mL	0.177 mL	0.177 mL	0.177 mL	0.177 mL
Sucrose	400 mg	400 mg	400 mg	400 mg	400 mg
Citric acid	200 mg	200 mg	200mg	200 mg	200 mg
Tween 80	20 mg	20 mg	20 mg	20 mg	
Menthol	20 mg	20 mg	20 mg	20 mg	20 mg
Water	10 mL	10 mL	10 mL	10 Ml	10 mL
Methanol	1 mL	1 mL	1 mL	1 mL	1 mL

Non-inclusion and Inclusion complexed FDFs were prepared by using solvent casting method

- ✓ HPMC is soaked for overnight in 5 mL of distilled water, stirred for 30 minutes
- ✓ 5 mL of distilled water was added to PVA and heated upto 80°C
- ✓ Then the polymeric solutions were mixed thoroughly
- ✓ Sucrose and citric acid were added to the polymeric solution and stirred for 15 minutes
- ✓ Drug / drug equivalent inclusion complexed powder mixture, tween 80, menthol were dissolved in 1mL of methanol and sonicated for 30 minutes
- ✓ Polymeric solution was added to the drug solution and PEG 400 was added, again stirred for 15minutes
- ✓ The resulting solution was poured into the petriplate and dried in hot air oven at 40°C.

2.6. Characterization

2.6.1. Preformulation studies

Drug-polymer compatibility studies FT-IR spectroscopy

Fourier transform infrared spectroscopy (FT-IR) is a simple technique for the detection of changes with excipients-drug mixture. Disappearance of an absorption peak or reduction of the peak intensity combined with the appearance of new peaks gives a clear evidence for interactions between drug and excipients. For the FT-IR studies of our samples the sample was grounded gently with anhydrous KBr and compressed to form pellet. The scanning range was 400-4000 cm^{-1}.

2.6.2. Evaluation of oral thin films

2.6.2.1. Physical appearance[14]

Physical appearance was checked by visual inspection.

2.6.2.2. Thickness[14]

The thickness of three randomly selected films from every batch was determined using a standard screw gauge and average values were reported.

2.6.2.3. Weight variation test[15]

The 4cm^2 film was cut at three different places in the cast film. The weight of each strip was taken and then the weight variation was observed.

2.6.2.4. Surface pH

The 4cm^2 film of each formulation was taken and was placed in a petri dish containing 2mL of water. After complete wetting of the film, the pH at the surface of the film was checked using the pH paper.

2.6.2.5. *In vitro* disintegration time[16]

In vitro disintegration time is determined visually in a petridish of 20mL distilled water with swirling for every 10 seconds. The disintegration time is the time when the film starts to break or disintegrates.

2.6.2.6. Folding endurance[13]

Folding endurance was determined by repeatedly folding the film (2 cm x 2 cm) ate the same place until it breaks at the place of folding. The number of times the film can be folded at the same place without breaking was the folding endurance value.

2.6.2.7. Swelling property[15]

Film swelling studies is conducted using simulated saliva solution. Each film sample is weighed and placed in a pre-weighed stainless steel wire mesh. The mesh containing film sample is submerged into 15 mL medium in a petridish. Increase in the weight of the film was determined at preset time interval until a constant weight was observed. The degree of swelling was calculated using parameters.

$$\text{Degree of swelling} = \frac{\text{Final weight } (w_t) - \text{Initial weight } (w_0)}{\text{Initial weight } (w_0)}$$

2.6.2.8. Drug content[15]

The film was dissolved in 100 mL of volumetric flask using pH 6.8 phosphate buffer and sonicated for 3 hours and then 1mL was taken and diluted to 10 mL with pH 6.8 phosphate buffer. The absorbance was measured at 240 nm using UV-spectrophotometer.

2.6.2.9. *In-vitro* dissolution studies [16]

The dissolution study of fast dissolving film was carried out in a beaker containing 30 mL of the simulated salivary fluid (pH 6.8) as a dissolution medium, maintained at 37±0.5^{0}C. Fast dissolving films equivalent to 3.125 mg of Carvedilol were used for dissolution studies. The medium was stirred at 50 rpm. Aliquot of 2 mL was withdrawn from dissolution medium at predetermined time intervals and the same amount was replaced with fresh medium. Samples were analysed using UV-spectroscopy at 240 nm.

2.6.2.9.1. *In-vitro* dissolution studies for marketed tablet (Cardivas 3.125 mg)

The dissolution test was carried out in USP type II apparatus, pH 1.2 HCl buffer as a dissolution medium, maintained at 37±0.5°C. 3.125 mg uncoated tablet was used for dissolution study. The medium was stirred at 75 rpm. Aliquots of 5 mL were withdrawn from dissolution medium at predetermined time intervals and the same amount was replaced with fresh medium. Samples were analysed using UV-spectroscopy at 240 nm.

2.6.2.10. Stability study[16]

Stability study was carried out as per ICH guidelines Q1A (R2). The optimized formulation was wrapped in aluminium pouch and was sealed. It was stored at accelerated (40^{0}C±2^{0}C / 75%RH±5%RH) condition for a period of two months. Films were evaluated for drug content using UV-spectroscopy.

2.6.2.11. *Ex-vivo* drug release study[16]

Ex-vivo permeation studies were carried out through porcine oral mucosa using modified Franz diffusion cell. The system consists of donor chamber, receptor chamber, jacket and sampling port. A Teflon coated mini magnetic bead was placed in the receiver compartment for agitating the contained vehicle at 50 rpm (i.e., rotations/minute of magnetic bead within diffusion cell). The receptor compartment was filled with vehicle, containing pH 6.8 phosphate buffer. Receptor fluid was sonicated to remove dissolved gases and equilibrated at 37°C before placing in the receptor compartment. Porcine oral mucosa was used as the model membrane. The mucosa was mounted between the donor and receptor compartments. The

receptor compartment was filled with 15 mL of pH 6.8 phosphate buffer and the hydrodynamics were maintained by stirring with a magnetic bead at 50 rpm. Optimized film of dimensions 2 × 2 cm loaded with 3.125 mg of drug, previously weighed was placed in intimate contact with the mucosal surface of the membrane that was previously moistened with a few drops of phosphate buffer. The donor compartment was filled with 1 mL of pH 6.8 phosphate buffer. Samples were withdrawn at suitable intervals of 5, 10, 15, 20, 25 and 30 minutes, replacing the same amount with the fresh medium.

3. RESULTS

3.1. Phase solubility studies

Table. 4: Results for phase solubility.

Ratio type	Concentration of β-CD (mM)	Concentration of carvedilol (mM)
	0	0.65
Weight		
1:1	25	1.51
1:2	50	2.89
1:3	75	3.92
Molecular mass		
1:1	64.48	1.51
1:2	128.96	2.23
1:3	193.44	3.62

K_c values for stoichiometric and molar mass ratios are $406M^{-1}$ and $267M^{-1}$.

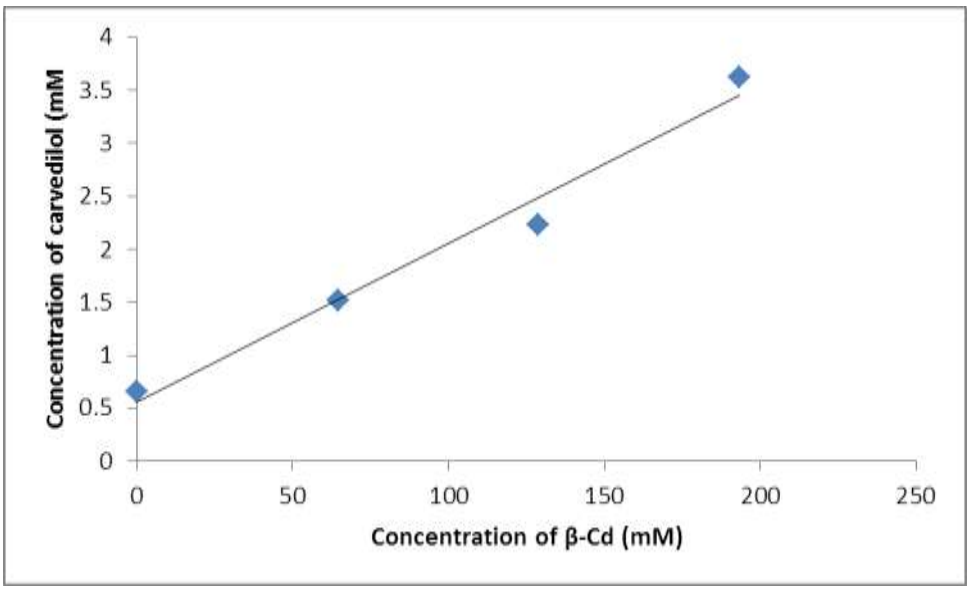

Figure. 1: Phase diagram for β-Cd and carvedilol (molar mass ratio).

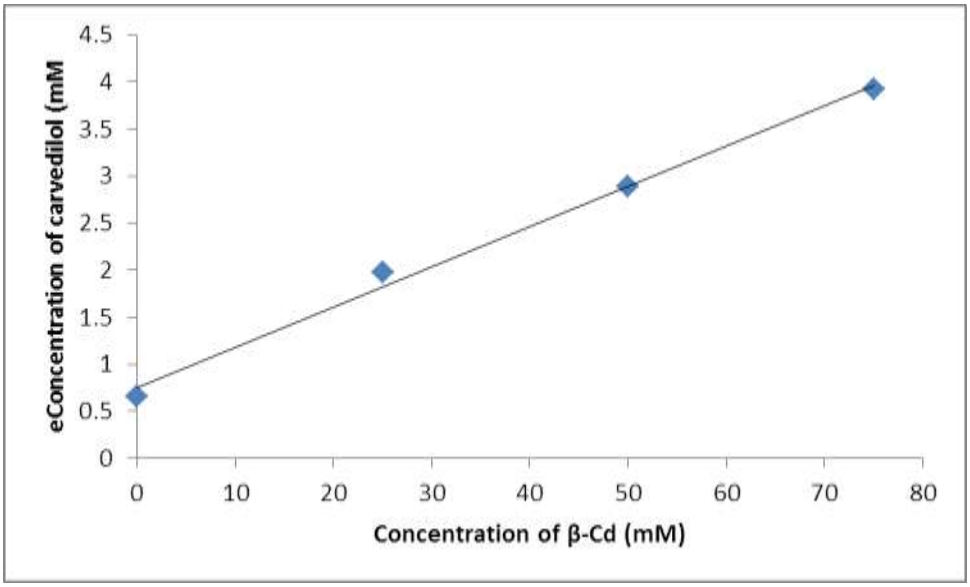

Figure. 2: Phase diagram for β-Cd and carvedilol (weight ratio).

3.2. Experimental design results of inclusion complex mixtures.

Table. 5: Drug release profiles of the inclusion complex mixtures (IP1-IP7).

Time (mins)	Formulation codes and respective drug release (%) of inclusion complexation mixtures						
	IP1	IP2	IP3	IP4	IP5	IP6	IP7
0	0	0	0	0	0	0	0
5	25.8±0.12 14	35.8±0.52 13	29.6±0.3 231	28.6±0.2 156	41.3±0.4 321	37.6±0.12 54	15.4±0.85 15
10	45.1±0.34 22	59.7±0.38 11	49.3±0.4 556	49.9±0.6 171	66.5±0.1 011	63.6±0.23 12	39.9±0.84 12
15	66.12±0.2 458	75.15±0.2 587	59.28±0. 9421	66.45±0. 5879	79.12±0. 9845	75.26±0.3 647	45.26±0.9 743
20	73.89± 0.5742	86.71± 0.2335	79.6± 0.3605	80.33± 0.1761	91.44± 0.2300	88.21± 0.4966	56.58± 0.5609

All values are expressed as mean±SD (n=3)

Table. 6: Drug release profiles of the inclusion complex mixtures (IP8-IP13).

Time (mins)	Formulation codes and respective drug release (%) of inclusion complexation mixtures					
	IP8	IP9	IP10	IP11	IP12	IP13
0	0	0	0	0	0	0
5	23.31±0.3444	17.1±0.5432	39.8±0.5413	39.1±0.1211	43.7±0.0223	45.9±0.0181
10	41.11±0.7317	38.4±0.1222	46.7±0.5245	61.1±0.6812	65.9±0.1233	69.3±0.2731
15	61.25±0.2145	51.28±0.9845	66.25±0.3647	78.24±0.5478	74.21±0.4785	77.25±0.4512
20	70.62±0.2042	67.36±0.3955	90.04±0.3269	90.44±0.4366	89.28±0.7540	91.67±0.6931

All values are expressed as mean±SD (n=3)

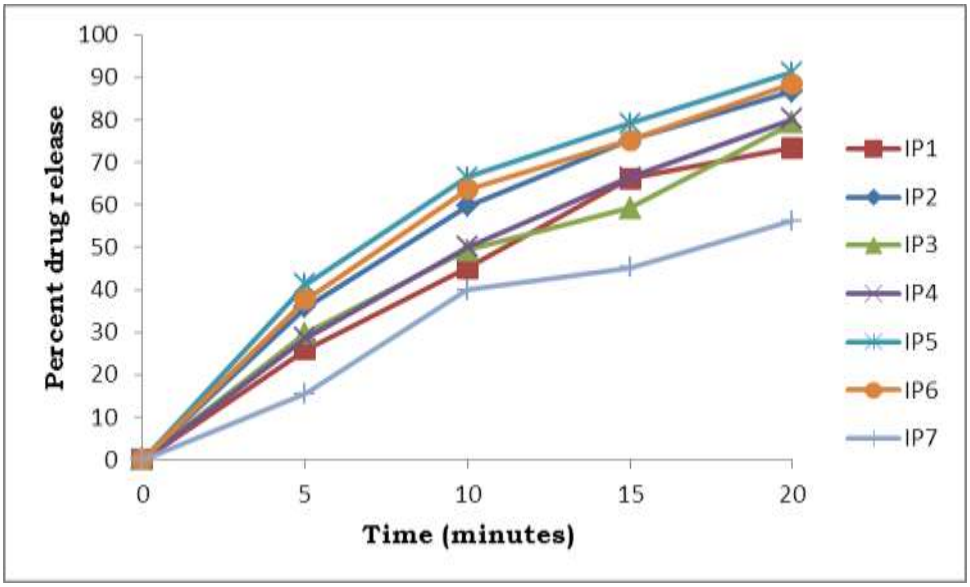

Figure. 3: Drug release (%) profiles for inclusion complex mixtures (IP1-IP7).

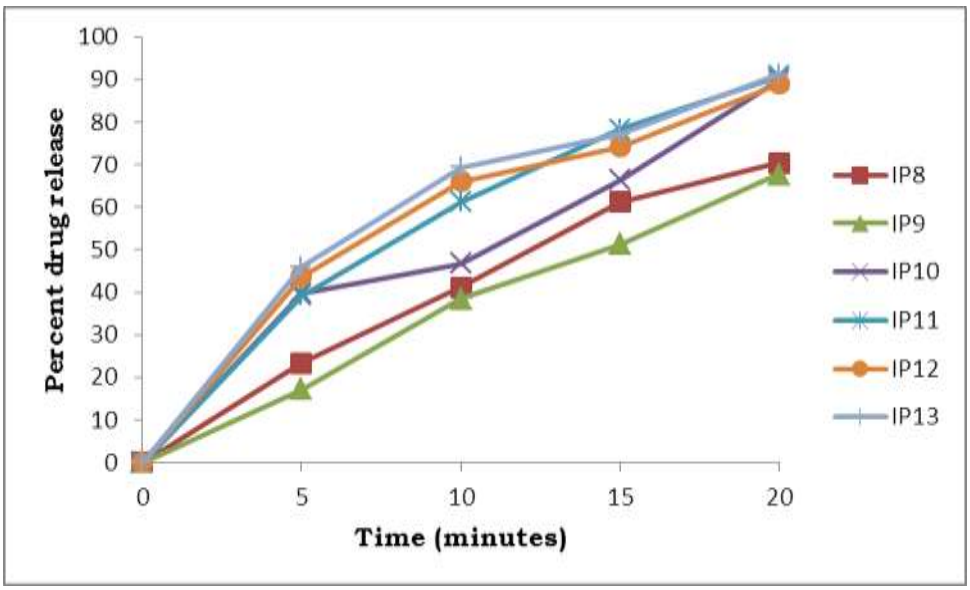

Figure. 4: Drug release (%) profiles for inclusion complex mixtures (IP8-IP13).

3.2.1. Design expert (7.0.7.1version) was used for ANOVA, multiple regression analysis (to obtain coefficient values in the equation), generate response surface plots and optimize the data. 5% level of significance was considered as significant

Table. 7: Summary of results of regression analysis for response Y.

Models	R^2	Adjusted R^2	Predicted R^2	SD	%CV	Remarks
Dissolution rate (%)						
Linear model	0.2996	0.1595	-0.4877	10.21	2215.40	-
Second order	0.3039	0.0719	-2.6728	10.73	5469.35	-
Quadratic model	0.9932	0.9876	0.5107	1.24	54.46	Suggested

Table. 8: ANOVA for the response of dissolution rate.

Source	Sum of squares	df	Mean square	F value	P value	Remark
Model	1478.37	5	295.67	192.16	<0.0001	Significant
X_1	98.98	1	98.98	64.33	<0.0001	Significant
X_2	347.17	1	347.17	225.62	<0.0001	Significant
$X_1 X_2$	6.43	1	6.43	4.18	0.0803	Significant
X_1^2	166.06	1	166.06	107.92	<0.0001	Significant
X_2^2	492.89	1	492.89	320.33	<0.0001	Significant
Lack of fit	6.84	3	2.28	2.32	0.2167	Not significant
Total	1489.14	12				

Table. 9: Fitted model and the coefficients of response of dissolution rate.

Term	Size		Range		VIF
	coefficient	SE	Low	High	
Intercept	90.99	0.52	89.77	92.21	-
A-β cyclodextrin	4.06	0.51	2.86	5.26	1.00
B-Tween 80	-7.61	0.51	-8.80	-6.41	1.00
AB	1.27	0.62	-0.20	2.73	1.00
A^2	-7.75	0.75	-9.52	-5.99	1.17
B^2	-13.36	0.75	-15.12	-11.59	1.17

✓ **Regression equations for dependent variables Y**

Fitting data to the model

$$Y = 90.99 – 40.6X_1 - 7.61X_2 + 1.27X_1X_2 - 7.75X_1^2 - 13.36X_2^2$$

Plots showing the effect of concentration of β-Cd and tween-80 on dissolution rate.

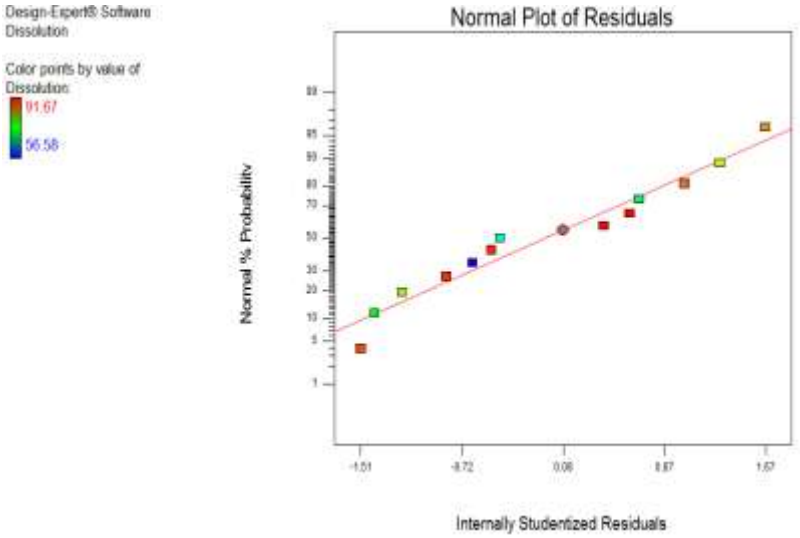

Figure. 5: Normal plot of residuals.

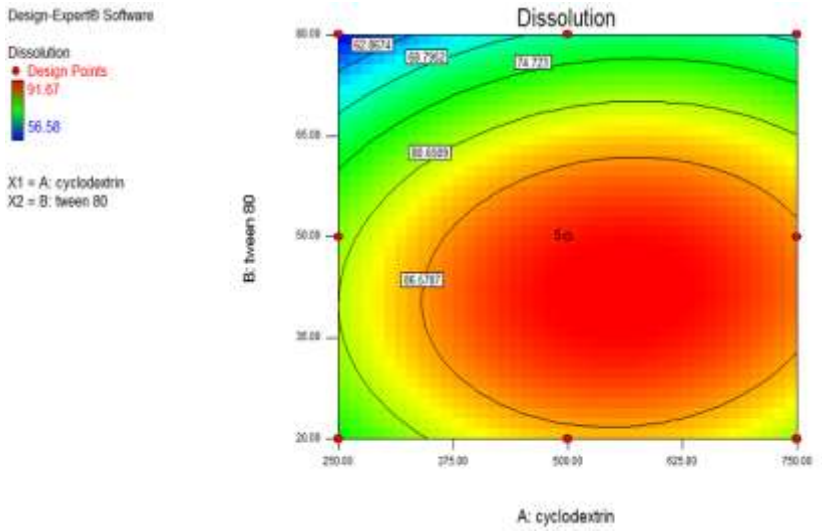

Figure. 6: Response surface plot.

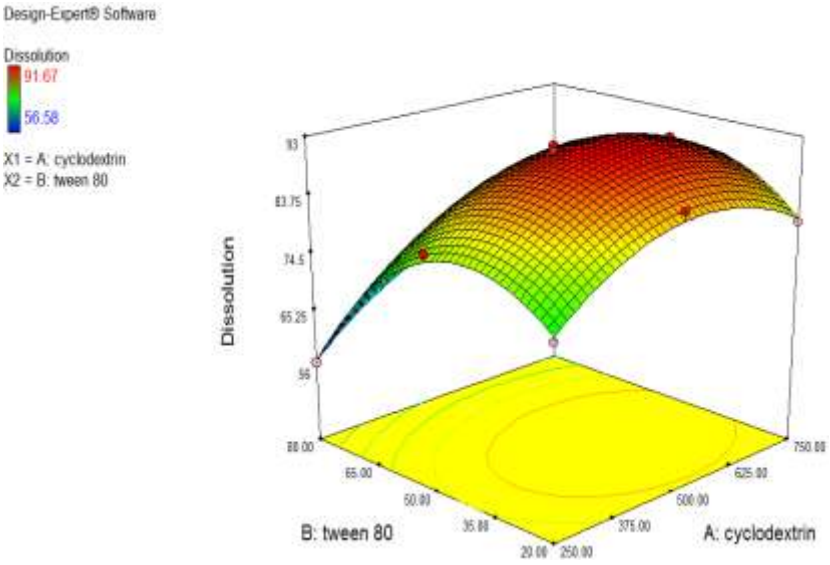

Figure. 7: Contour plot.

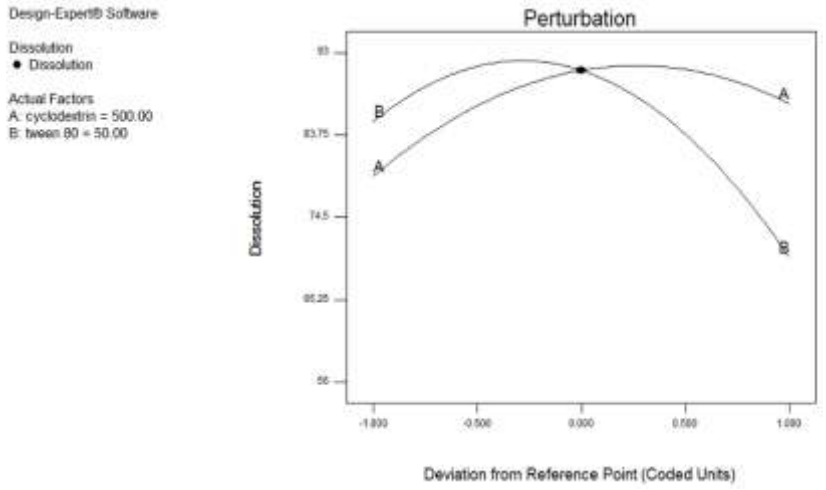

Figure. 8: Perturbation plot.

✓ **Overlay plots of optimized inclusion complex mixtures**

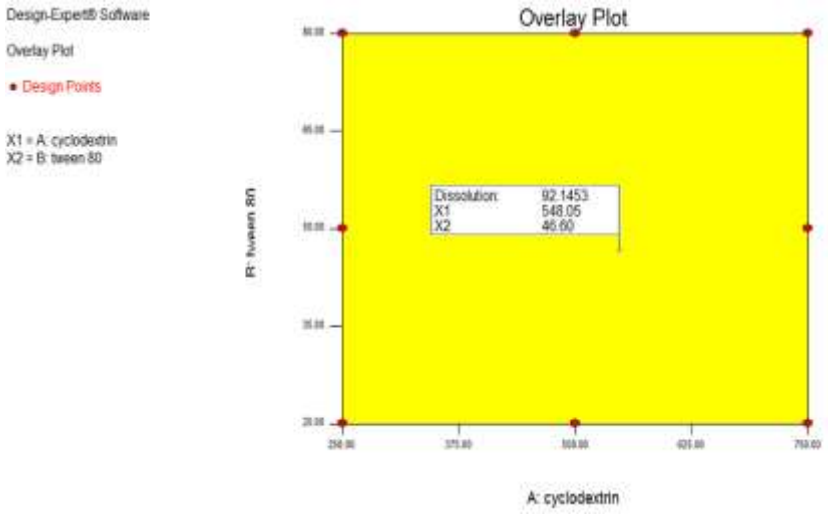

Figure. 9: Overlay plot of OIP1.

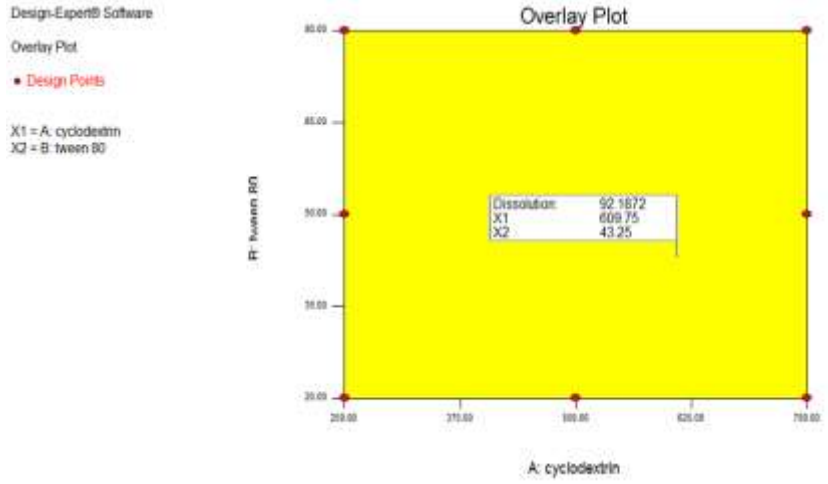

Figure. 10: Overlay plot of OIP2.

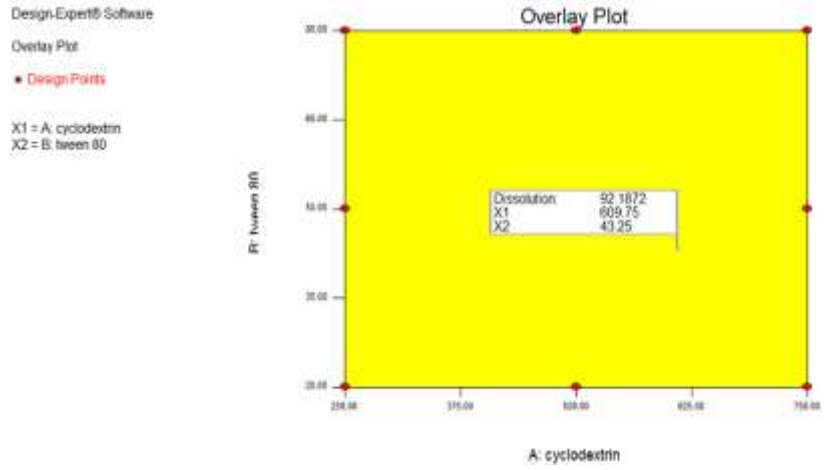

Figure. 11: Overlay plot of OIP3.

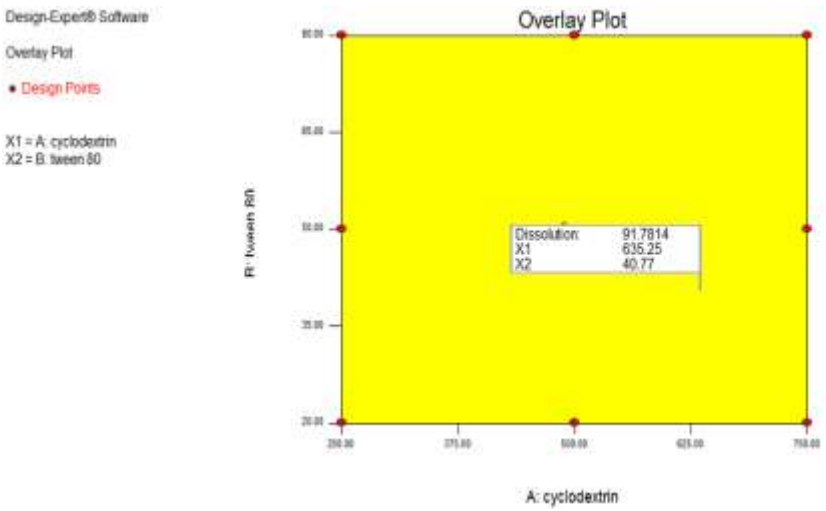

Figure. 12: Overlay plot of OIP4.

Table. 10: Drug release (%) profiles of optimized inclusion complex mixtures.

Time (mins)	OIP1	OIP2	OIP3	OIP4
0	0	0	0	0
5	85.55±0.2356	80.55±0.2471	87.12±0.2148	85.43±0.9874
10	89.92±0.4596	85.75±0.3214	90.15±0.3657	86.53±0.3648
15	92.75±0.1211	88.47±0.4112	94.75±0.2456	91.89±0.3419
20	98.01±0.2113	89.01±0.3244	99.88±0.3456	95.13±0.3287

All values are expressed as mean±SD (n=3).

Table. 11: Relative error for optimized formulations.

Formulation code	Predicted values	Experimental values	Relative error
OIP1	90.89	98.01±0.2113	-6.36
OIP2	92.14	89.01±0.3244	3.30
OIP3	90.22	99.88±0.3456	-8.344
OIP4	90.48	95.13±0.3287	-3.6491

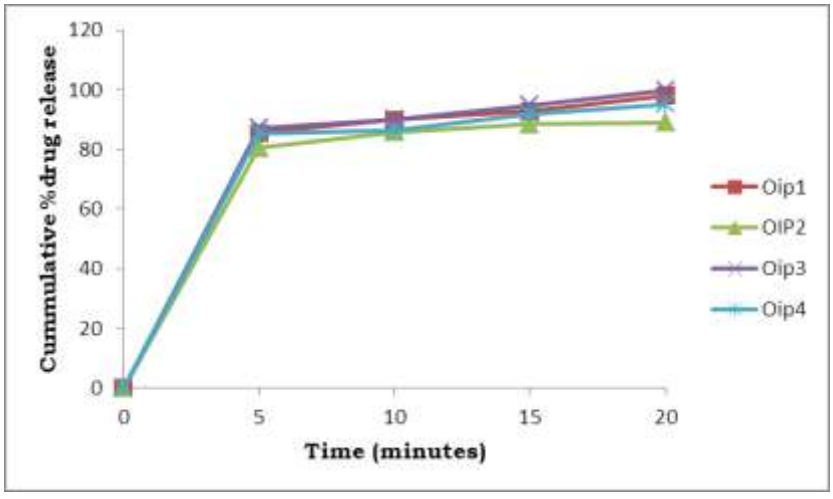

Figure. 13: Drug release (%) profiles for optimized inclusion complex mixtures.

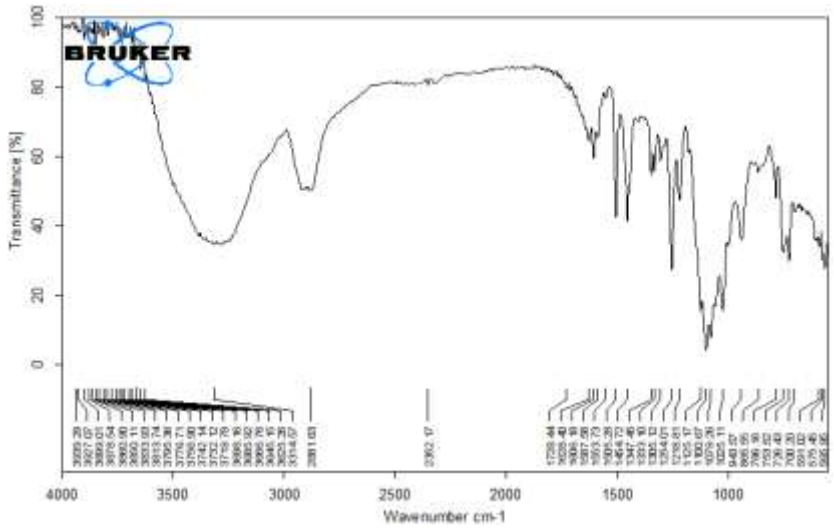

Figure. 14: FT-IR of optimized inclusion complex mixture.

3.3. Results for evaluation tests of non-inclusion and inclusion complexed FDFs

Parameters	Formulation code				
	Non-inclusion complexed FDFs				Inclusion complexed film
	F1	F2	F3	F4	
Physical appearance (Transparency)	Transparent	Transparent	Semi-transparent	Semi-transparent	Transparent
Thickness (kg/cm^2)	0.040±0.010	0.037±0.010	0.038±0.020	0.039±0.010	0.038±0.0545
Weight variation (g)	0.15±0.005	0.15±0.005	0.16±0.005	0.15±0.011	0.18±0.012
pH	6.8	6.8	6.8	6.8	6.8
Disintegration time (seconds)	24±0.05	18±0.15	90±0.40	110±0.40	20±0.412
Folding endurance (no. of folds)	500±0.012	650±0.258	250±0.674	300±0.257	600±0.874
Swelling property	2.423±0.119	2.368±0.139	1.928±0.632	1.845±0.514	1.883±0.066
Drug content (%)	91.44±0.982	92.99±0.5075	90.45±0.541	89.58±0.452	92.14±0.171

All values are expressed as mean±SD (n=3).

Table. 12: Drug release profiles for optimized non-inclusion complexed and inclusion complexed FDFs and marketed tablet.

Time (mins)	Drug release (%) profiles for F2, IC FDF and marketed tablet		
	F2	IC FDF	Marketed tablet
0	0	0	0
5	24.72±0.1256	91.25±0.1458	28.18±0.5412
10	38.97±0.2658	**98.24±0.2547**	34.32±0.3654
15	57.56±0.5124	-	37.86±0.9845
20	74.53±0.6254	-	44.13±0.8425
25	89.22±0.7895	-	-
30	**97.07±0258**	-	54.25±0.2148
45	-	-	56.81±0.2187
60	-	-	63.93±0.7452
75	-	-	68.98±0.2541
90	-	-	74.84±0.2185
105	-	-	79.34±0.3146
120	-	-	81.08±0.8452
135	-	-	84.86±0.8745
150	-	-	88.17±0.6452
165	-	-	90.14±0.8742
180	-	-	**98.77±0.6423**

All values are expressed as mean±SD (n=3)

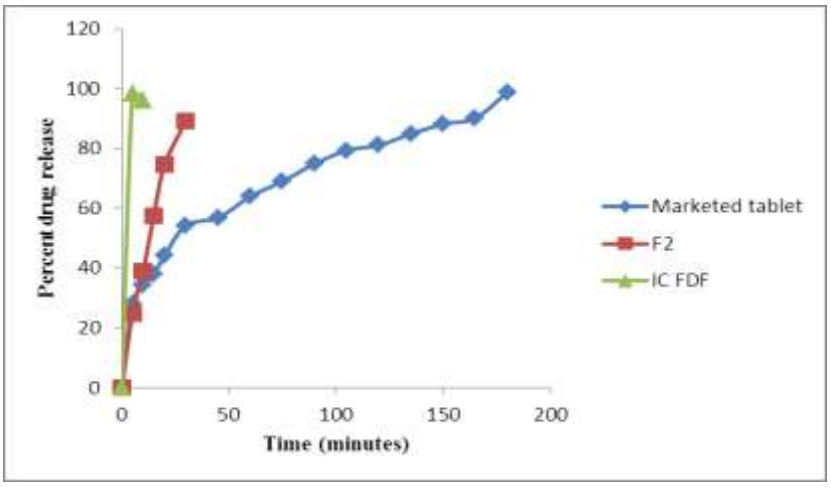

Figure. 15: Drug release graph for optimized non-inclusion complexed, inclusion complexed FDFs and marketed tablet.

3.4. FT-IR results

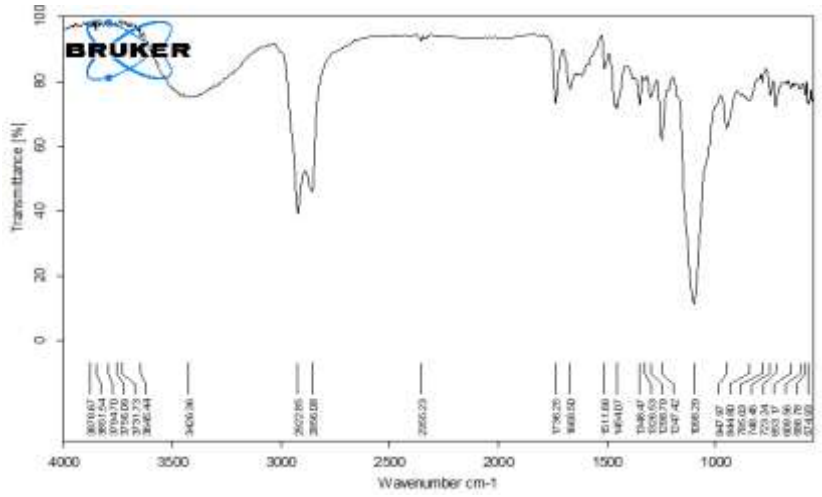

Figure. 16: FT-IR of drug (carvedilol).

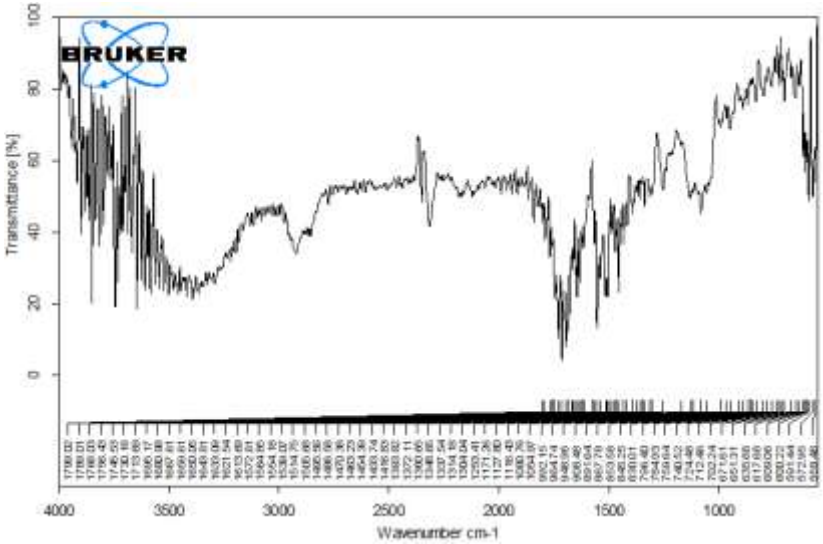

Figure. 17: FT-IR of optimized non-inclusion complexed FDF.

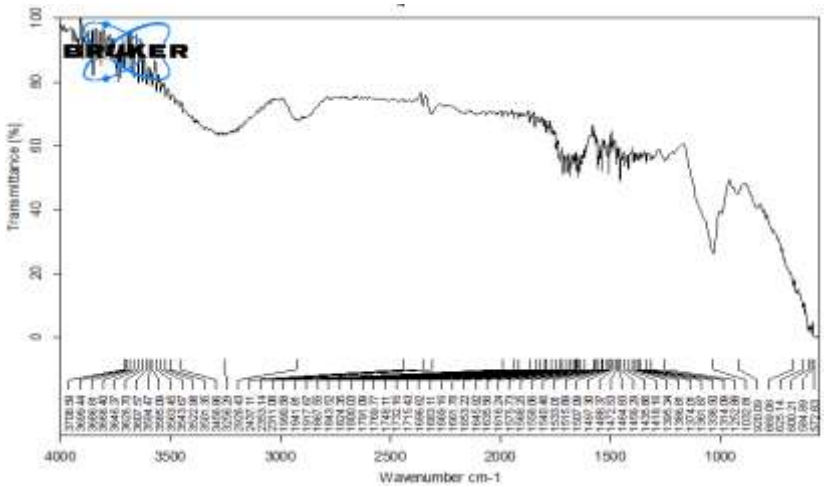

Figure 18: FT-IR of inclusion complexed FDF.

3.5. Stability studies for non-inclusion complex FDFs.

Table. 13: Drug content (%) profiles of non-inclusion complex FDFs upto 60 days.

Days	Drug content (%) profiles for optimized non-inclusion complex FDF and inclusion complexed FDF	
	F2	IC FDF
30	90.25±0.8452	91.56±0.4587
60	88.54±0.1247	90.67±0.2489

All values are expressed as mean±SD (n=3).

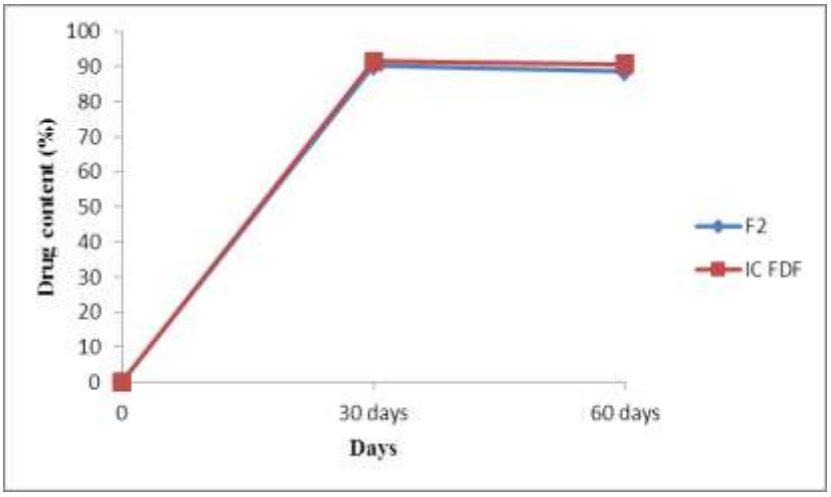

Figure 19: Stability study graph for non-inclusion complex FDFs (F1-F4)

3.6. *Ex vivo* drug release (%) profile for optimized non-inclusion complex and inclusion complexed FDFs.

Table. 14: *Ex vivo* drug release (%) profile for optimized non-inclusion complex and inclusion complexed FDFs.

Time (minutes)	Drug release (%) profiles for optimized non-inclusion complex and inclusion complexed FDFs	
	F2	IC FDF
0	0	0
5	23.2145	55.7218
10	35.2365	98.9918
15	59.2315	-
20	73.2696	-
25	86.2654	-
30	92.3187	-

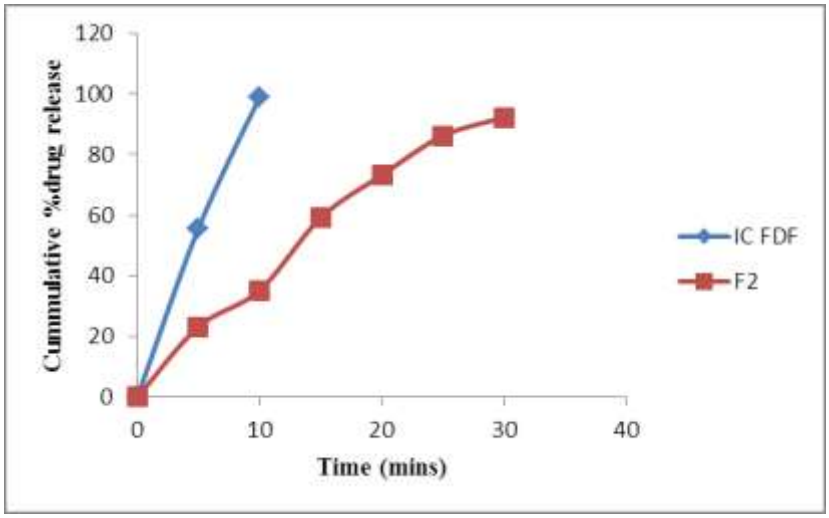

Figure. 20: *Ex vivo* drug release (%) profiles for optimized non-inclusion complex and inclusion complexed FDFs.

4. DISCUSSION

Infrared spectra for pure drug, excipients, physical mixture and all the FDFs of the drug were determined to find the compatibility of the drug in the mixture using FTIR-Spectrophotometer by disc method. The FTIR were performed and the spectra obtained are represented from **Fig 2 to Fig 8 and Fig 38, 39.** The data is represented in **Table 11.**

The FT-IR results showed that the prominent characteristic peaks of the drugs are maintained in the physical mixtures as well as in the final formulations which is an indication that there are no interactions affecting the activity of the drug. These excipients could be used for further study using these combinations.

Phase solubility study

The aqueous solubility of the drug was increased linearly with β-CD in both stoichiometric and molar mass ratios. The phase solubility diagrams for the complex formation between carvedilol and β-CD of both weight and molar mass ratios are shown in **Figures 11, 12** and the data was represented in **Table 14** respectively.

The phase solubility diagram can be classified as type A_L according to Higuchi and Connors. Because the straight line had a slope less than unity in each case, the increase in solubility was due to the formation of a 1:1 M complex in solution with the drug. The apparent stability constant (K_c) was calculated from the linear plot of the phase solubility diagram according to the equation.

K_c = Slope / S_0 (1- Slope)

Where S_0 = Solubility of the drug in absence of β-CD

K_c values in the range of 200-500M^{-1} indicated stronger interactions between the guest molecule (drug) and the host molecule (β-CD) and greater stability of the complex formed. Thus the value of stability constant indicated that the complexes formed between drug-β-CD are quite stable in all cases.

In the inclusion complex mixtures, we can observe the correlation between β-CD and tween-80 is proportional to each other, indicating the prominence of complexation in the drug release of drug molecules.

By using this data one response %Drug release were selected for statistical optimization and fitted to linear, interactive and quadratic models. The summary of statistics is presented in **Table 18.** The comparative R^2, adjusted R^2, predicted R^2, PRESS, S.D, F- values and P-values were determined using the Design Expert Software. A suitable polynomial model for describing the data was selected based on coefficient of determination R^2 and PRESS values. Responses follow quadratic model. Hence these models are selected for further optimization. These models show higher R^2 and F-values and lower PRESS and P-values.

The results of the response surface model fitting in the form of ANOVA are given in **Table 19** and **Table 20** for all formulations.

F-values for the response was found to be 192.16 for the inclusion complex mixtures which indicate that the models are significant. The values of prob>F (less than 0.05) for all the responses indicated the significance of the models.

The FT-IR results showed that the prominent characteristic peaks of the drugs are maintained in the physical mixtures as well as in the final formulations which is an indication that there are no interactions affecting the activity of the drug. These excipients could be used for further study using these combinations. FT-IR studies of drug and optimized final FDF formulation was determined and shown in figures 7, 8. The non-inclusion and inclusion complexed FDFs were prepared and evaluated, among them for non-inclusion complexed FDFs F2 transparency, thickness, folding endurance, weight variation, surface pH, swelling studies are transparent, 0.037±0.010, 0.15±0.005, 6.8, 0.2367 due to low polymer concentration. Disintegration time for F2 18±1.15 seconds is the lowest when compared to

other formulations due to low polymer concentration. F2 shows highest percent of drug release 97.07929±0.6548% within short duration of time (30 minutes). The IC FDF and marketed tablet shows the highest percentage of drug release (for IC FDF 98.24±0.2547 and 98.77±0.6423) marketed tablet) within 10 minutes and 180 minutes. *Ex vivo* studies shows highest percentage of drug release of 98.9918 % for IC FDF within 10 minutes. Stability studies for two months results that the optimized IC FDF and F2 dosage forms are stable.

5. CONCLUSION

Hypertension is a serious medical condition has become a major public health issue and its prevalence is rapidly increasing among the population. Since it requires immediate pharmacological action, anti-hypertensive agents are formulated into FDFs becoming an alternative to conventional dosage forms. FDFs recently have acquired great importance in the pharmaceutical field due to their unique properties such as needless of water for administration like the conventional tablets, disintegration, rapid onset of action and bypassing first pass metabolism of drug. These films provide an advantage to geriatric, bedridden, psychiatric patients. Carvedilol solubility and bioavailability are increased by using inclusion complexation with β-CD. Among non-inclusion complexed and inclusion complexed FDFs, IC FDF shows the highest percentage of drug release and less disintegration time. Inclusion complexation increased the solubility and bioavailability of the drug by reducing the particle size.

6. ACKNOWLEDGEMENT

I sincerely acknowledge my university for providing me all facilities in fulfilling my research work.

7. REFERENCES

1. Dhaneshwar Kumar, Lokesh Rathi, Avinash Tripathi, Yogesh P, Maddheshiya; A Review on oral mucosal drug delivery system; International journal of pharmaceutical sciences and research, 2010; 1(5): 50-56.
2. Nidhi P. Sapkal, Vaishali A. Kilor, Anwar S. Daud, Minal N. Bonde: Development of fast dissolving oral thin films of ambroxol hydrochloride: Effect of formulation. Variables; Journal of advanced pharmaceutical research, 2011; 2(2): 102-109.
3. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: an innovative drug delivery system and dosage form. International Journal of Chem Tech Research, 2010 Jan; 2(1): 576-583.

4. Mashru C, Sutariya V, Sankalia M, Parikh P. Development and evaluation of fast dissolving film of salbutamol sulphate. Drug Development and Industrial Pharmacy, 2005; 31(1): 25-34.
5. Nishimura M, Matsuura K, Tsukioka T, Yamashita H, Inagaki N, Sugiyama T, Itoh Y. In vitro and in vivo characteristics of prochlorperazine oral disintegrating film. International journal of pharmaceutics, Feb 23, 2009; 368(1): 98-102.
6. Sakuda Y, Ito A, Sasatsu M, Machida Y. Preparation and evaluation of medical carbon oral films. Chem. Pharm. Bull, 2010; 58: 454-457.
7. Seager H. Drug delivery products and the zydis fast dissolving dosage forms. Journal of Pharmacy and Pharmacology, 1998; 50(4): 375-382.
8. Kunte S and Tandale P, Fast dissolving strips: A novel approach for the delivery of verapamil. Journal of Pharmacy And Bioallied Sciences Oct-Dec, 2010; 2(4): 325-328.
9. Lakshmi PK, Sreekanth J, Sridharan A. Formulation development of fast releasing oral thin films of levocetrizine dihydrochloride with Eudragit® Epo and optimization through Taguchi orthogonal experimental design. Asian Journal of Pharmaceutics (AJP): 2014 Aug 23; 5(2).
10. Sandeep Saini A. Nanda J Dhari, Formulation, Development & Evaluation of oral fast dissolving anti-allergic film of levocetrizine dihydrochloride: Journal of Pharmaceutical Sciences And Research, 2011; 3(7): 1322-1325.
11. Jamakandi VG. Formulation and Evaluation of Immediate Release Tablet of Carvedilol using Liquisolid Compacts Technique for Solubility Enhancement. Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian Journal of Pharmaceutics. 2016 Sep 10; 10(03).
12. Mohana. M. Nair, Shajan. A, Leena Jacob. Formulation and evaluation of mouth dissolving film of a poorly soluble antihypertensive drug. International Journal of Pharmacy and Technology. 0.975-766X, 2016.
13. Muhammad Irfan, Sumeira Rabel, Quaratulain Bukhtar, Muhammad Imran Qadir, Farhat Jabeen, Ahmed Khan., Orally disintegrating films: A modern expansion in drug delivery system., Saudi pharmaceutical journal, 2016; 24: 537-546.
14. Dos Santos C, del Pilar Buera M, Mazzobre MF. Phase solubility studies of terpineol with β-cyclodextrins and stability of the freeze-dried inclusion complex. Procedia Food Science, 2011 Jan 1; 1: 355-362.
15. Chonkar AD, Rao JV, Managuli RS, Mutalik S, Dengale S, Jain P, Udupa N. Development of fast dissolving oral films containing lercandipine HCl nanoparticles in

semi crystalline polymeric matrix for enhanced dissolution and ex vivo permeation. European Journal of Pharmaceutics and Biopharmaceutics, 2016 Jun 30; 103: 179-191.

16. Chaudhary H, Gauri S, Rathee P, Kumar V. Development and optimization of fast dissolving oro-dispersible films of granisetron HCl using Box–Behnken statistical design. Bulletin of Faculty of Pharmacy, Cairo University, 2013 Dec 31; 51(2): 193-201.