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DEVELOPMENT AND CHARACTERIZATION OF ORAL FAST DISSOLVING FILM CONTAINING NANOSUSPENSION OF CILNIDIPINE

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ABSTRACT

This study was carried out to formulate and characterize oral fast dissolving film containing nanosuspension of Cilnidipine. Initially Cilnidipine nanosuspension was prepared by high pressure homogenization (HPH) and optimized for effect of No. of cycle and Stabilizer. Nanosuspension was optimized by two factor-three level full factorial design using Design expert 10.0.0. Two independent Variables, The HPH pressure and Concentration of Tween 80 were selected based on preliminary screening. The dependent variable measured as a response were particle size D(90), particle size D(50) and Zeta potential. The Optimized nanosuspension was further transformed in fast dissolving film by solvent casting method utilizing HPMC E15, Hydroxy ethyl Cellulose (HEC), PVP K-30 and HPMC E5 as a film forming polymers. The effect of plasticizers (PEG 400, Glycerol and Triethylcitrate) and their concentration were tested for physicomechanical properties of casted films. The optimized formulation selected from overlay plot containing HPMC E15 and Triethylcitrate showed greater drug dissolution (more than 85% within 30min). The stability study of optimized formulation for 3 month showed no appreciable change in drug content and *in vitro* drug release.

KEYWORDS: Fast dissolving oral film, Nanosuspension, Solvent casting, Experimental design.

INTRODUCTION

Cilnidipine is a Novel and Unique dihydropyridine calcium antagonist that possesses a slow onset, long lasting vasodilating effect.[1] Although one of the reasons for slow onset may due to its poorly water soluble characterization[2]

Nanosuspension is distinctive approach to overcome poor bioavailability that is related with the delivery of hydrophobic drugs.[3] Nanosuspensions are the part of nanotechnology which contains submicron colloidal dispersion of Active ingredient particles in a liquid phase by surfactant. Nanosuspensions can be prepared by using Wet milling, High pressure homogenizer (HPH), emulsion solvent evaporation, melt emulsification method and super critical fluid techniques. Nanosuspension formation via high pressure homogenization is assumed to be due to Cavitation principle.[4] The dissolution rate may be improved due to particle size reduction to nanosize and ultimately increased surface area. Nanosuspension can be transform into different solid dosage form to improve the handiness to patient.

In the literature, different manufacturing methods described thoroughly for fast dissolving film i.e solvent Casting, Hot melt extrusion, Semisolid casting and rolling method.[5] Oral fast dissolving film is one of the easy ways of producing fast release dosage forms through solvent casting methods using film forming polymer, plasticizer and other excipients.[6]

In present study nanosuspension loaded in fast dissolving film for faster release and better in vitro dissolution was studied. Nanosuspensions were optimized by varying HPH pressure and concentration of stabilizer. Nanosuspension characterization carried out for Particle size and Zetapotential. Further Nanosuspension loaded in fast dissolving film by solvent casting method. Then fast dissolving film were characterized and evaluated for Surface pH, folding endurance, thickness, Drug content, FTIR and *in vitro* release studies.

MATERIALS AND METHODS

Materials

Cilnidipine was provided from Pure Chem Pvt. Ltd., Ankleshwar, India. Different grade of hydroxypropylmethylcellulose (HPMC), Hydroxy ethyl cellulose (HEC), PVP K30 were supplied by Yarrow Chem. Products, Mumbai, India. Polyethyleneglycol (PEG 400),

propylene glycol, triethaycitrate, glycerin were procured from Finar Chemicals Ltd, Ahmedabad, India. All other materials used were of pharmaceutical or analytical grade.

Drug Excipients Compatibility Study

In compatibility studies the formulation scientist identifies the physical, chemical and mechanical properties of drug substance, in order to develop stable, safe and effective dosage forms. During the studies, possible interaction with various ingredients proposed for use in final dosage form was also considered in the present study. Fourier transform infrared spectroscopy (FTIR) was conducted using a FTIR spectrophotometer (FTIR-1700, Shimadzu, Japan) and the spectrums were recorded in the wavelength region of 4000-400cm^{-1}.

Preparation of Nanosuspension Containing Oral Dissolving Film (ODF)

Cilnidipine nanosuspension was prepared using high pressure homogenizer. In 500ml glass beaker accurately weighed quantity of the Stabilizer was dissolved in 100ml water and 2000 mg of accurately weighed quantity of drug was dispersed in it. Pre-treatment was given by high speed homogenizer to reduce Cilnidipine particle sizes to the micrometer range. The dispersion was sonicated by bath sonicator for 10min to reduce foam and filter. Finally coarse suspension was then treated by high pressure homogenizer to get nanosuspension.

Preparation of the film was done by solvent casting method. The weighed quantity of polymer was dissolved in the minimum quantity of distilled water and stirred to ensure the complete mixing of polymer. Then drug suspension was dissolved in that polymer solution with stirring. After that the sweetening agent was added to the solution and stirred properly. Finally calculated quantity of plasticizer was added to the above mixture and kept for sonication (if required) till the solution became clear and free of bubbles. After sonication this solution was poured on the glass plate lubricated with light liquid paraffin. The glass plate was kept in controlled temperature oven at 40℃ for 6 hours for drying of the film. After the drying of film, it was peeled and cut in to 1cm × 1cm (1cm^2) sizes and stored in aluminum foil. These films were further subjected to various studies.

Preliminary Screening

The suspension pretreatment parameters were optimized to avoid the blockage of the passage in HPH. The pre-treatment was selected based on the foam formation and blockage in high pressure homogenizer at different stirring time of high speed homogenizer. The effect of the number of cycles on the mean particle sizes and polydispersity of Cilnidipine suspensions at a

fixed operating pressure of 1000 bar was studied. Various Stabilizers like Poloxamer 188, Tween 80 and Lutrol 400 were tried for the formulation of the nanosuspension based on the literature and availability. The Composition is shown in table 1.

Table 1: Composition of Batches for Stabilizer screening

Ingredients	Batch -A	Batch -B	Batch -C
Cilnidipine (mg/ml)	20	20	20
Tween 80 (%)	2	-	-
Poloxamer 188 (%)	-	2	-
Lutrol 400 (%)	-	-	2
Distilled Water q.s (ml)	100	100	100

For the selection of polymer type, preliminary batches were formulated using PEG 400 as plasticizer at 10%W/W and sucralose as sweetener as per the composition shown in table 2.

Table 2: Composition of Batches for Polymers Screening

Quantity for 19.62 cm^2 in mg				
Ingredients	OP1	OP2	OP3	OP4
Cilnidipine Nanosuspension (ml)	5	5	5	5
HPMC E15	200	-	-	-
HEC	-	200	-	-
PVP K-30	-	-	200	-
HPMC E5	-	-	-	200
PEG 400 (10%w/w of polymer)	20	20	20	20
Sucralose	10	10	10	10
Distilled Water (ml)	5	5	5	5

Once the polymer and it's quantity was finalized, the type of plasticizer was screened. Three plasticizers were screened for the selection at the same concentration (10 %W/W). The batches were shown in table 3.

Table 3: Composition of Batches for Plasticizers Screening

Quantity for 19.62 cm^2 in mg			
Ingredients	P1	P2	P3
Cilnidipine nanosuspension (ml)	5	5	5
HPMC E15	200	200	200
PEG – 400* (10% w/w of polymer)	20		
Triethylcitrate (10% w/w of polymer)		20	
Glycerol (10% w/w of polymer)			20
Sucralose	10	10	10
Distilled water (ml)	5	5	5

Optimization of Fast Dissolving Film Containing Cilnidipine Nanosuspension Using 3^2 Full Factorial Design

From the results of preliminary screening studies the optimization was carried out using design of expert (DOE) approach. To study the effect of 2 independent variables i.e. HPH pressure and Concentration of Tween 80 on responses 3^2full factorial design was used. In this design particle size D(90), particle size D(50) and Zeta potential were selected as response variables. Where as in study of fast dissolving film the concentration of HPMC E15 and the Triethylcitrate were two independent variables and dependent variables measured were Dissolution at 15min, Dissolution at 30min. The equations relating independent variables and responses were obtained by subjecting the results to statistical evaluation. Design – Expert 10.0.0 was used to perform multiple linear regressions to determine the control factors that significantly affect the responses.

Polynomial equation for 3^2 full factorial design: $Y = ß_0 + ß_1X_1 + ß_2X_2 + ß_{11}X_{11} + ß_{22}X_{22} + ß_{12}X_1X_2$ was used. In this equation Y is the dependent variable, $ß_0$ is the arithmetic mean response of the nine runs, $ß_1$ to $ß_{12}$ are the coefficients for factors.

The terms of full model having non-significant p value ($p > 0.05$) have negligible contribution and they were neglected.

The detailed layout of factorial batches for Cilnidipine nanosuspension and Fast dissolving film is shown in table 4 and Table 5, respectively.

Table 4: Detailed Layout of Different Factorial Batches of nanosuspension

Ingredients	**Formulation Code**								
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
Cilnidipine (mg/ml)	20	20	20	20	20	20	20	20	20
Tween 80 (%)	1	1	1	2	2	2	3	3	3
Water QS (ml)	100	100	100	100	100	100	100	100	100
HPH pressure (Bar)	800	1000	1200	800	1000	1200	800	1000	1200

Independent Variable	**Coded Value**			**Actual Value**		
HPH pressure(bar)	-1	0	+1	800	1000	1200
Concentration of Tween 80 (%)	-1	0	+1	1	2	3

Table 5: Detailed Layout of Different Factorial Batches of fast dissolving film

Ingredients	Formulation Code								
	NF_1	NF_2	NF_3	NF_4	NF_5	NF_6	NF_7	NF_8	NF_9
Cilnidipine nanosuspension (ml)	5	5	5	5	5	5	5	5	5
HPMC – 15 (mg)	100	100	100	200	200	200	300	300	300
Triethycitrate (% of Polymer)	10%	15%	20%	10%	15%	20%	10%	15%	20%
Sucralose (mg)	10	10	10	10	10	10	10	10	10
Distilled water q.s (ml)	5	5	5	5	5	5	5	5	5

Independent Variable	Coded Value			Actual Value		
HPMC E15 (mg)	-1	0	+1	100	200	300
Triethycitrate (%)	-1	0	+1	10	15	20

Evaluation of Oral Dissolving Films

The prepared films were evaluated for thickness, folding endurance, surface pH, assay, *in vitro* disintegration and dissolution studies. A thickness of the film was measured by using micrometer screw gauge .Film was measured at three positions i.e. central and the two corners and the mean thickness was calculated.[7] Folding endurance of the film was measured by folding the film at the same point until the film breaks. The number of folds before the film breaks is the folding endurance of the film.[8] The surface pH of oral dissolving film was determined in order to investigate the possibility of any side effect in vivo. Film was slightly wetted with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film.[9] The assay was determined by HPLC analysis. [10] The *in vitro* disintegration time is the time at which the film starts to break. The disintegration time was measured in a beaker containing 20ml phosphate buffer pH 6.8.The time film starts to break was measured as disintegration time of film.[11] For in vitro dissolution studies, each film was placed with the help of forceps in a 900ml of phosphate buffer pH 6.8 at 75 RPM using USP type-2 apparatus. The temperature of the dissolution media was maintained at 37±0.5°C. During the study, 5ml of aliquots were withdrawn at 5,10,15,30 and 60min and were replaced by fresh buffer.[12] The amount of Cilnidipine released in the media was determined by a HPLC. Stability study was conducted at accelerated condition of 75 ±5% relative humidity and 40± 2ºC temperature in the stability chamber for 3 months. After 1,2 and 3 month films were evaluated for the drug content, and physical appearance as well as change *in vitro* drug release pattern.

RESULT AND DISCUSSION

Drug Excipients Compatibility Study

FTIR spectrums of Cilnidipine and Cilnidipine in combination with excipients are shown in fig. 1 and fig. 2 respectively. It was observed that there were no changes in main peaks in the FTIR spectra of a mixture of Cilnidipine and excipients. The FTIR study demonstrate that no physical or chemical interactions of CIlnidipine with polymeric system.

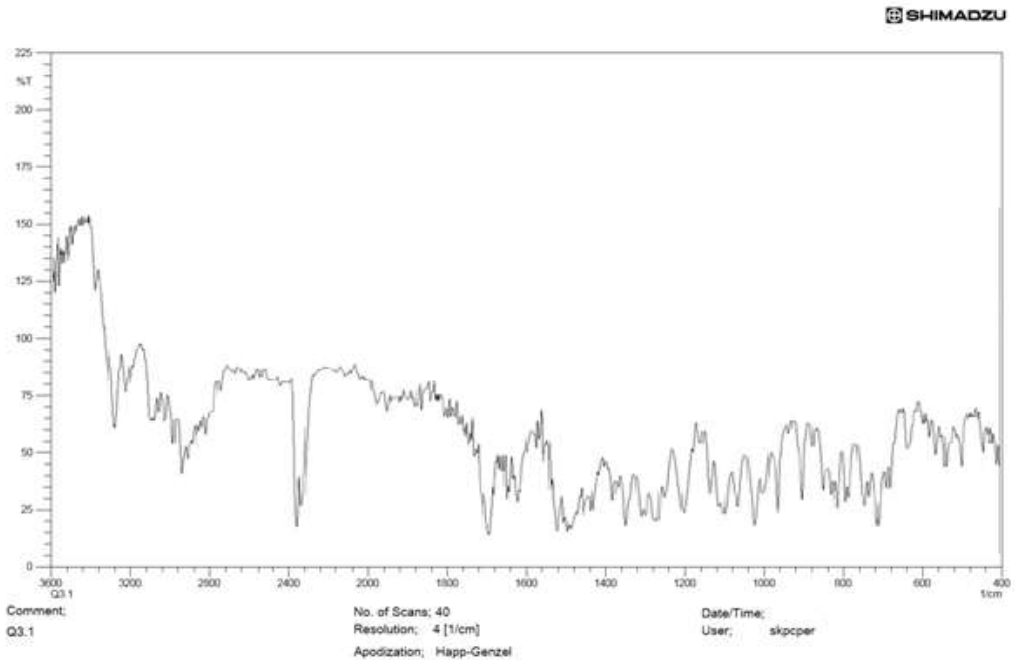


Fig.1: FT-IR Spectra of Cilnidipine

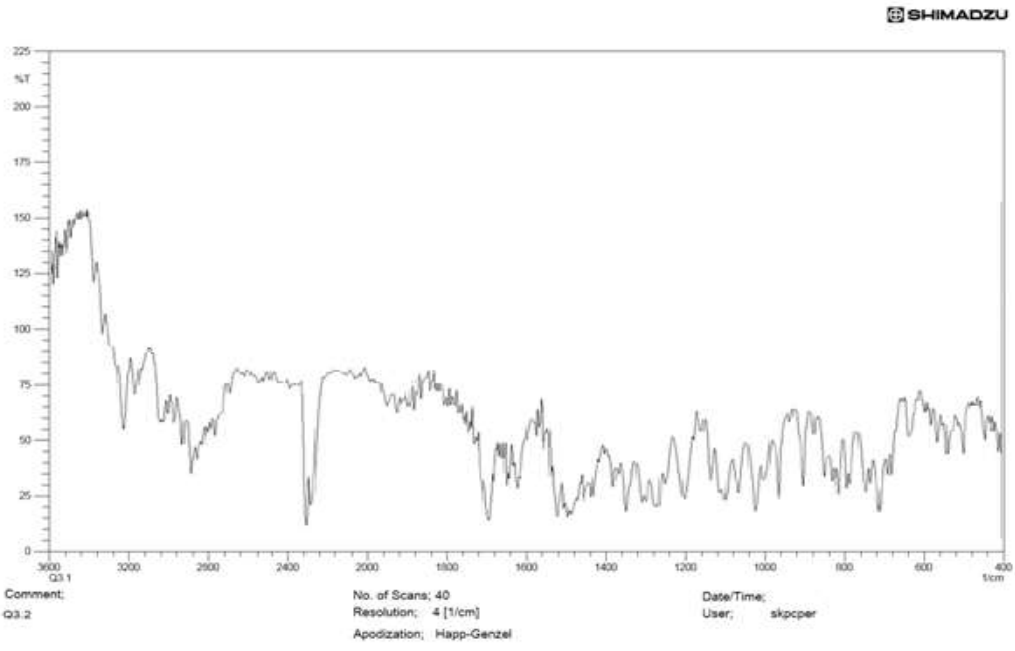


Fig. 2: FT-IR Spectra of Drug and Excipients Mixture

Analytical Method

HPLC measurements were carried out using Enable C18 column (150mm X 4.6mm, 5µm). The isocratic mobile phase was pumped through the column at a flow rate of 1.0 ml/min with the sample injection volume was 20µl. The photodiode array detector was set to a wavelength of 242nm for the detection. The linearity of the detector response to different concentrations of Cilnidipine was studied in the range of 5–30µg/mL The calibration curve is shown in Fig 3 and data of calibration curve is shown in fig. 4.

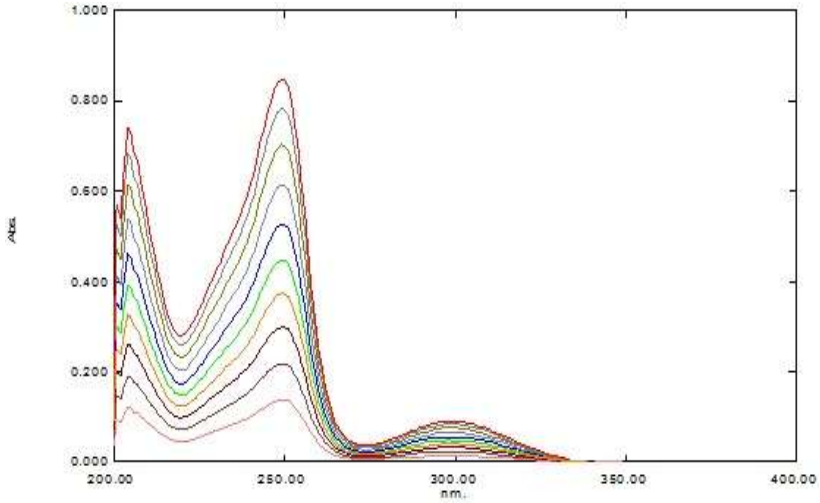


Fig. 3: Overlay Spectrum of Different Solutions

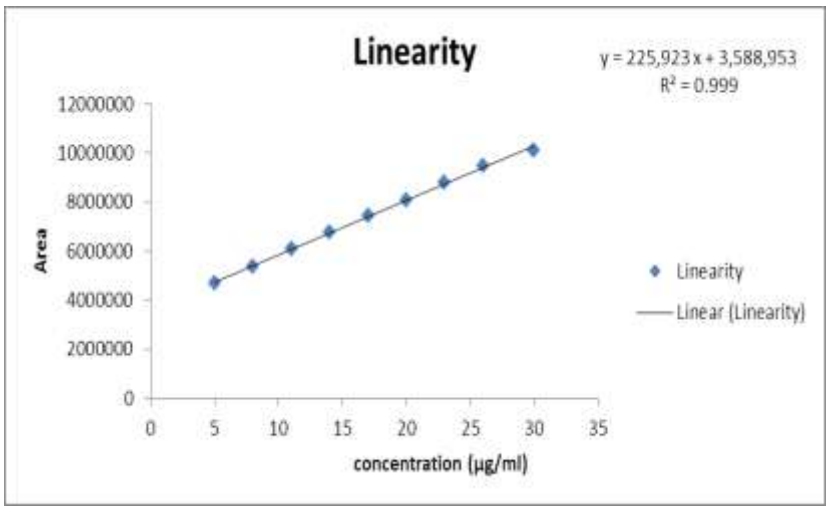


Fig 4: Calibration Curve of Cilnidipine

Preliminary Screening

Pretreatment was carried out using minimum RPM of High speed homogenizer i.e 11000 RPM and solution was homoginized for 1min, 2min, 3min. Solution pretreated for 1min shows blockage in High Pressure homogenizer whereas solution pretreted at 2 and 3min did

not blocked HPH. Higher Foam formation was observed as the stirring time increases. As from 2 and 3 min gives good results, 2min selected as minimum time. The mean particle sizes of Cilnidipine crystals in water and 2% Tween 80 solution (w/w) exhibited around 50% reduction after seven cycles. Reduction rate decreased with the following cycles and got a steady value (~180nm) after 9 cycles. After that point, increasing the number of cycles did not change the particle size. The polydispersity of samples reached a value of 0.25 for samples after around 9 cycles, but between cycles it showed fluctuations, which could indicate a slightly reversible formation of aggregates that were disaggregated in the subsequent cycles.

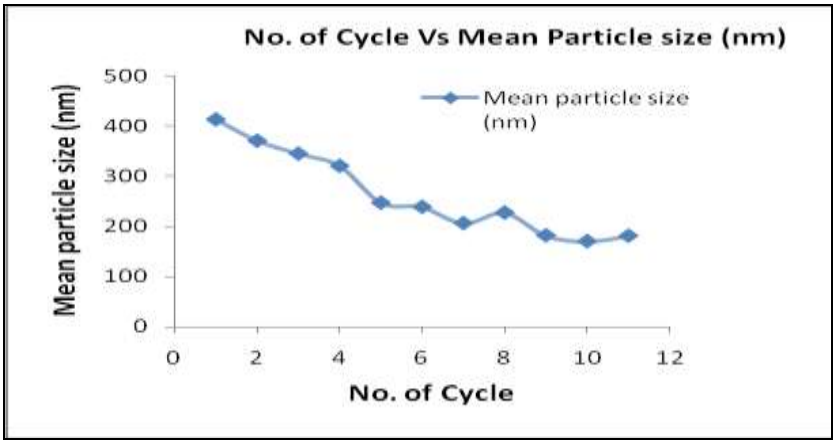


Fig. 5: Effect of No. of Cycle on Mean Particle Size

As a surfactant, Tween 80 provides particle wetting and it would adsorb onto the surface and decrease the interfacial tension between water and Cilnidipine particles, which would facilitate the dispersion of particles. This suggest that with Tween 80 got minimum particle size and zeta potential near to zero so tween 80 was selected for further studies. The results of Batches are as per table 6.

Table 6: Results of Stabilizer Screening

Batch code	D(90)(nm)	D(50)(nm)	Zeta potential	Polydispersity index
Batch-A	236	136	-9.22	0.155
Batch-B	429	249	-14.5	0.228
Batch-C	358	181	-11.1	0.237

Various preliminary trials were carried out to choose a suitable polymer-plasticizer system, capable of producing films of desirable physicomechanical property. Preliminary batches were prepared using different polymers. Among the film batches OP1-OP4, batch OP1 and OP4 containing HPMC E15 and HPMC E5 had given moderate tensile strength, smooth

surface texture, good transparency. As during film preparation it was observed that HPMC E5 takes more time to form clear solution in water as compare to HPMC E15. So that HPMC E15 (Batch OP1) was optimized polymer. Plasticizers were screened and evaluated based on Physical parameter, Tensile strength and Folding endurance. Results showed in Table 7, that batch P1 (PEG-400) good film observed but breaks when folded. In batch P2 (TEC) Very good film observed and batch P3(Glycerol) Good film observed but not much clear. Based on the above trials Triethylcitrate was used as plasticizer for further studies. As a result an attempt was made to prepare films using combination of HPMC E 15 and Triethylcitrate for the further studies, using DOE approach.

Table 7: Results of Plasticizer Screening

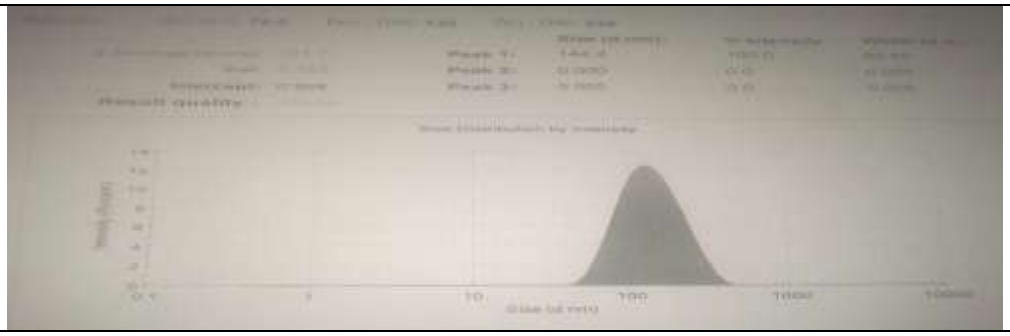
Batch No.	Tensile Strength (Kg/cm2)	Folding Endurance	Surface texture	Transparency
P1	0.200	85	Smooth	Medium
P2	0.150	150	Smooth	Good
P3	0.195	235	Smooth	Medium

Evaluation of factorial batches F1 to F9 – Cilnidipine Nanosuspension

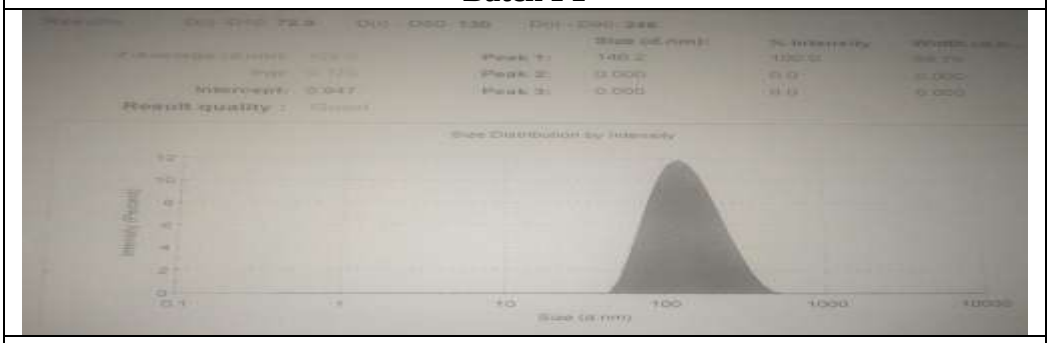
The factorial batches prepared for optimization of nanosuspension of Cilnidipine were evaluated and summary of results are as per Table 7.

Table 7: Evaluation Parameters of Factorial Batches of Cilnidipine Nanosuspension

Batch No.	Particle Size D(90) (nm)	Particle Size D(50) (nm)	Zeta Potential (V)	Polydispersity Index
F1	236	132	-14.7	0.153
F2	246	130	-13.9	0.176
F3	236	134	-14	0.157
F4	280	149	-15	0.165
F5	248	140	-18.5	0.180
F6	398	193	-15.6	0.240
F7	475	199	-18.9	0.252
F8	377	194	-36.2	0.246
F9	396	197	-61.6	0.266



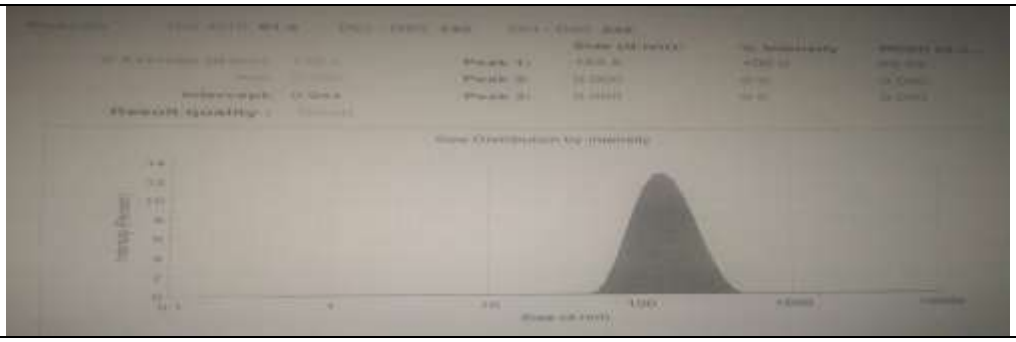
Batch F1



Batch F2

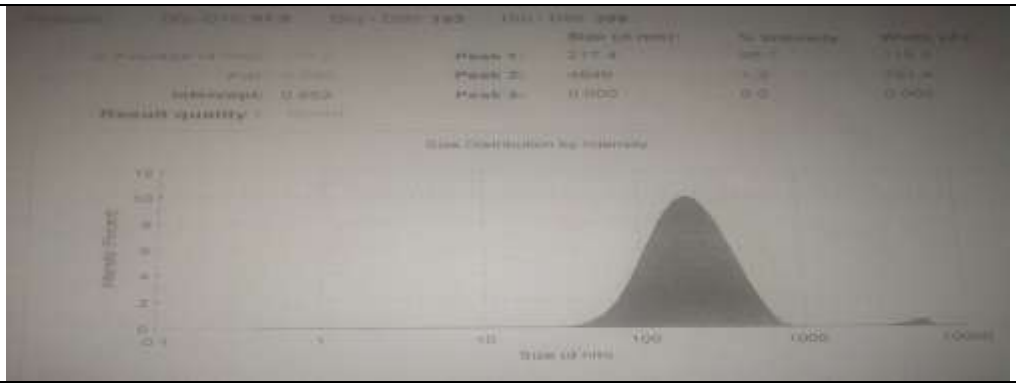
Batch F3

Batch F4

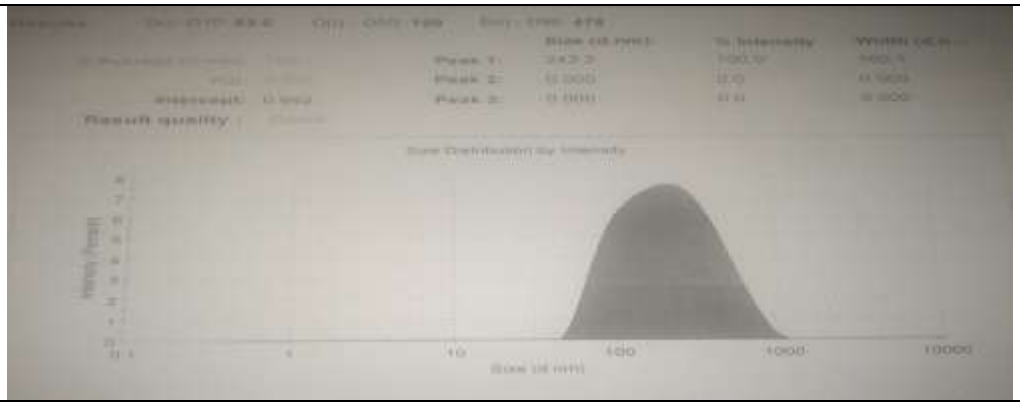


Batch F5

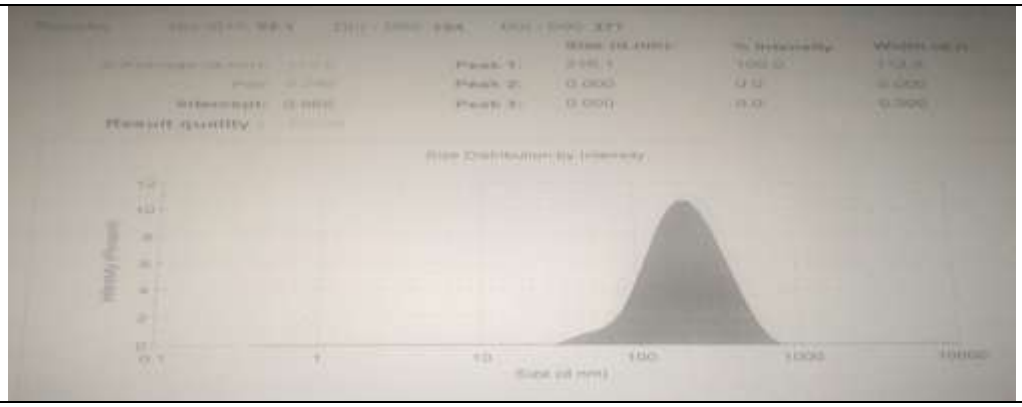
Fig 6: Particle Size Analysis by Zeta Sizer of Batch F1 to F5



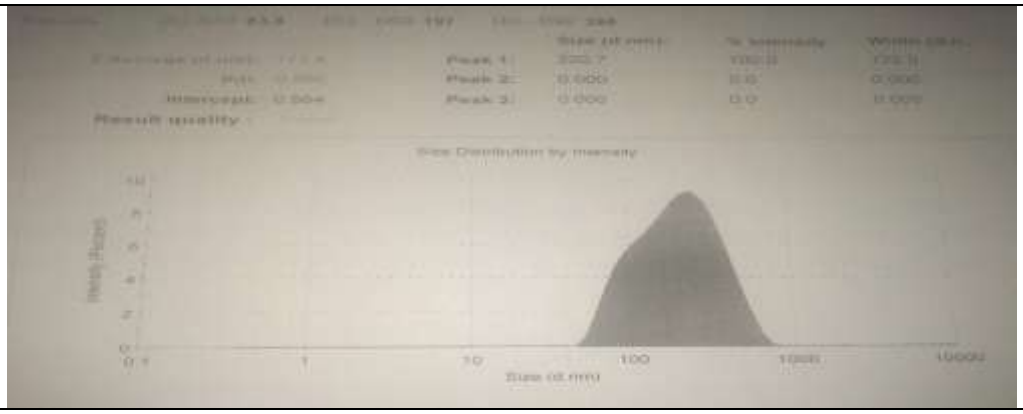
Batch F6



Batch F7



Batch F8



Batch F9

Fig 7: Particle Size Analysis by Zeta Sizer of Batch F6 to F9

For Verification of model check point batch was prepared with HPH pressure of 800 Bar and Conc. of Tween 80 of 1.11%. The Batch was used as Optimized batch based on results for further study i.e Film Preparation.

Table 8: Check Point Batch Evaluation

predicted Values			Practical Values		
Particle Size D(90) (nm)	**Particle Size D (50) (nm)**	**Zeta Potential (V)**	**Particle Size D(90) (nm)**	**Particle Size D(50) (nm)**	**Zeta Potential (V)**
236	123	-14.7	243	146	-14.5

Evaluation of factorial batches NF1 to NF9 – Cilnidipine Nanosuspension containing Film

The factorial batches prepared for optimization of nanosuspension of Cilnidipine were evaluated and summary of results are discussed. Thickness was found in the range of 0.02 to 0.07mm, the uneven surface of the plate could be the reason for variable thickness of the films. Folding endurance gives an signal of brittleness of the film and found from 157 to more than 300 times. From the results it can be conclude that concentration of plasticizer is directly proportional to folding endurance of film. Surface pH of all the films prepared was found in the range of 6.84 to 7.04 pH. Thus films may have less potential to irritate the oral mucosa. Content uniformity of formulations NF1 to NF9 showed better drug content of above 98% which indicates the uniformity of film. No significant difference in the drug content among the films indicated good content uniformity. *In vitro* disintegration time for fast dissolving film was ranges from 1.02min to 3.31min. A result showed as the polymer concentration increases which leads to increase in disintegration time. In Vitro Dissolution Study in phosphate buffer pH 6.8 was conducted as per method described earlier. The data for *in vitro* release are shown in table 9 and are compared in figure 8.

Table 9: *In Vitro* Drug Release Study

Time (min)	%Release								
	NF1	**NF2**	**NF3**	**NF4**	**NF5**	**NF6**	**NF7**	**NF8**	**NF9**
5	35	28	17	40	31	18	25	20	22
10	60	63	59	58	64	50	40	48	39
15	85	80	76	79	82	71	68	65	62
30	96	95	90	89	94	85	88	87	78
60	97	99	96	97	97	95	94	98	85

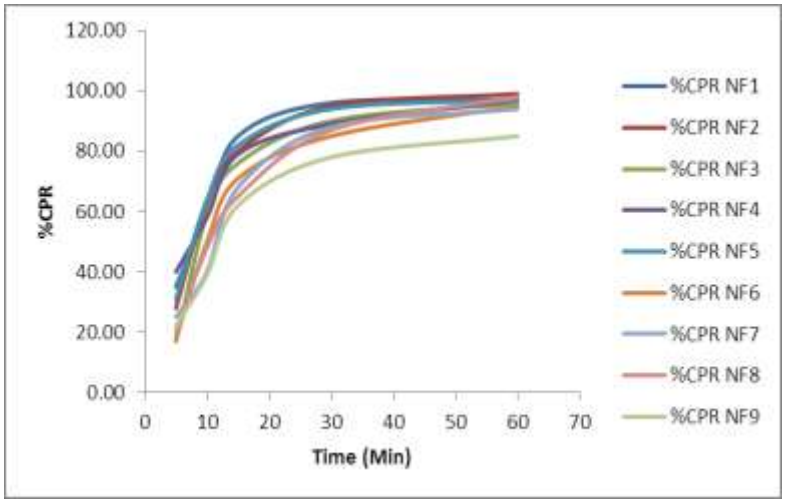


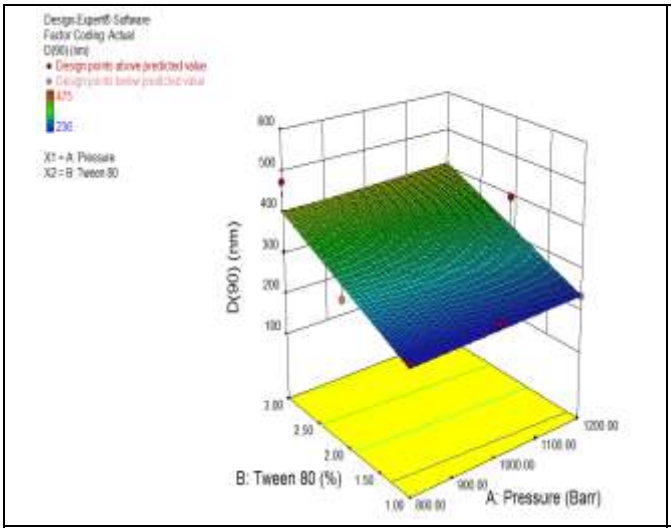
Fig 8: Drug Release Comparison of Batches NF1-NF9

Statistical Analysis of Factorial Design Batches

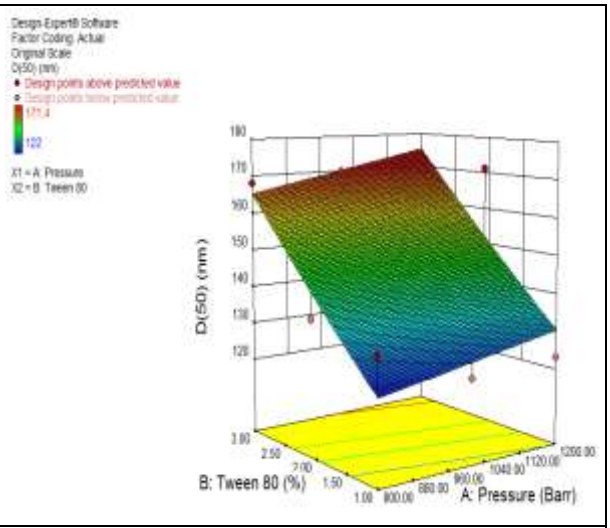
The summary of regression analysis and ANOVA for all the independent variable and response is shown in table 10. The 3D surface plot are shown in respective fig 9.

Table 10: Summary Output of Regression Analysis and ANOVA

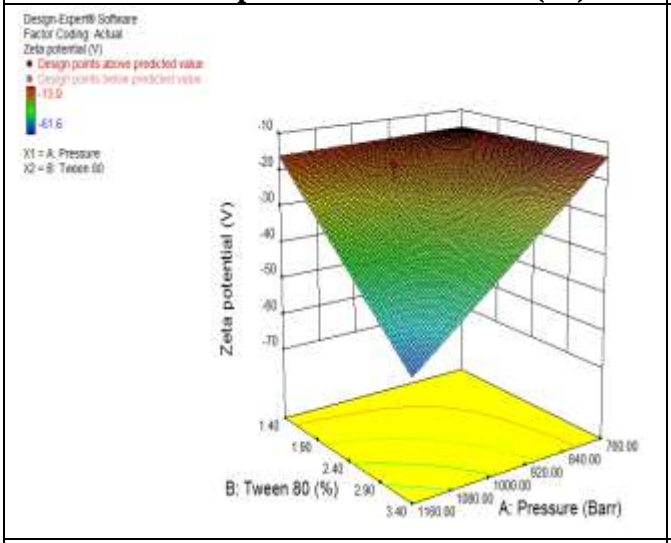
Response	P-Value	Final Equation (actual factor)
Particle Size D(90) (nm)	0.0255	D(90)=111.27 + (0.03250 * Pressure) + (88.33* Tween 80)
Particle Size D(50) (nm)	0.0064	D(50)= 9.33790+(0.0000976 * Pressure)+(0.91028 * Tween80)
Zeta Potential of nanosuspension(V)	0.0252	Zeta potential=-71.45556+ (0.073000 * Pressure) + (41.90 * Tween 80 – (0.054250* Pressure * Tween 80)
Release at 15min	0.0035	Release at 15 min = 101.06 – 0.077 * HPMC E15 – 0.766 *TEC
Release at 30min	0.0106	Release at 30 min = 108.44 – 0.047 * HPMC E15 – 0.667 *TEC



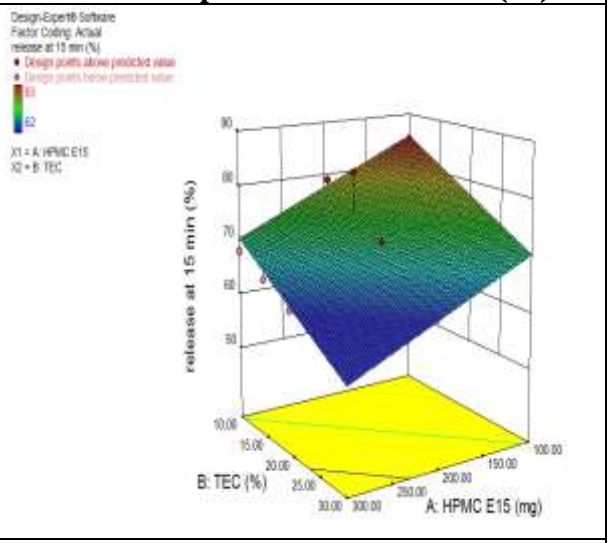
3D surface plot of Particle Size D(90)



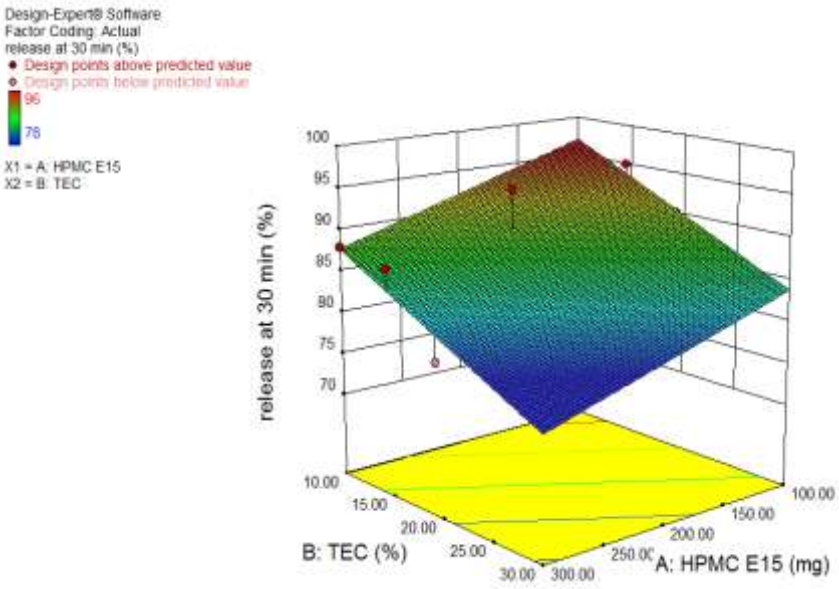
3D surface plot of Particle Size D(50)



3D surface plot of Zeta Potential



3D surface plot of Release at 15 min



3D surface plot of Release at 30 min

Fig 9: 3D Surface Plot of Responses

Verification of Model by Check Point Batch

Check point batch was selected from the overlay plot of responses. The amount of HPMC E 15 with 139.85 mg and TEC with 10% was selected from overlay plot and according to that predicted responses were given in the table 11. All the values of responses were within the upper and lower predicted interval. Hence, this model is valid and optimized batch can be selected from the overlay plot of this model.

Table 11: Predicted Response and Actual Response of Check Point Batch

predicted Values		Practical Values	
Release at 15 mins	**Release at 30 mins**	**Release at 15 mins**	**Release at 30 mins**
75.00 %	89.00 %	77.00 %	90.00 %

Stability Study of Optimized Batch

After three month of accelerated stability study (40ºC ± 2ºC and 75% RH ± 5%) of optimized batch i.e. Check point batch, Assay and dissolution test were performed. The results are shown in table 12. Results were shown no more drastically change in In-vitro drug release profile.

Table 12: Evaluation of Optimized Batch

Dissolution					Assay			
Time (min)	**Initial**	**1 Month**	**2 Month**	**3 Month**	**Initial**	**1 Month**	**2 Month**	**3 Month**
0	0	0	0	0	99.87	99.76	99.86	99.01
5	29	30.12	28.98	29.07				
10	46	48.20	47.2	45.98				
15	77.25	75.78	75.54	74.22				
30	90.10	94.68	90.87	91.43				
60	98.65	99.49	98.98	97.45				

CONCLUSION

A Design of Experiment approach was used to demonstrate the effect of HPH pressure and Concentration of stabilizer in case of Cilnidipine nanosuspension where as Concentration of polymer & concentration of Plasticizer in case of fast dissolving film. The quality of film was affected by type and concentration of polymer and plasticizer. The development of oral film drug delivery of Cilnidipine nanosuspension in to fast dissolving film is one of the alternative route to provide handiness to nanosuspension. The results of present study indicated that high pressure homogenization could be used as a alternative to other methods for Cilnidipine nanosuspension and can be transform in fast dissolving film to provide immediate release.

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