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Research Article

Formulation and Characterization of Sublingual Tablets Containing Nicardipine Hydrochloride

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Abstract

Nicardipine hydrochloride is a Calcium channel blocker. It is used in the treatment of Angina having low bioavailability about 10 - 40% orally is attributed to the hepatic first pass metabolism. The purpose of present research was to formulate sublingual tablets of Nicardipine hydrochloride. For Preparation of sublingual tablets disintegration time was set by carrying out *ex-vivo* permeation study of drug- β-Cyclodextrin. The Sub-lingual tablets were prepared using Sodium starch glycolate, Croscarmellose sodium, Crospovidone as super disintegrating agent and microcrystalline cellulose, PVP K 30 as a binder by direct compressible technique and evaluated for various parameter. Stability study of optimized formulation was performed as per ICH guideline. The *in-vitro* disintegration time of the optimized formulation (F4) was 41 seconds and showed 99.45% drug release within 8 minutes. Formulation containing 4% Crospovidone and 2% PVP K 30 (Batch F4) show highest disintegration and *ex-vivo* permeation was 96.81% within 14 minutes. Optimized formulation was stable for 10 days during stability study as per ICH guideline.

Keywords: Nicardipine Hydrochloride; β-Cyclodextrin; PVP K 30; Crospovidone; *Ex-vivo* Permeation Study; *In-vitro* Disintegration Time

Introduction

In pharmaceutical industry invention of new medicines, and the improvement of existing drugs constitute trigger the growth of industry, formulating a new dosage foam leads to patient acceptance. Despite of that conventional dosage foam shows high patient compliance due to ease of administration and non-invasive route of administration. Angina pectoris, the primary symptom of ischemic heart disease, is caused by transient episodes of myocardial ischemia that are due to an imbalance in the myocardial oxygen supply-demand relationship. The name denotes chest pain caused by accumulation of metabolites resulting from myocardial ischemia [1]. Sublingual drug delivery offers rapid absorption of drugs which are diffuse into the blood through tissues under the tongue [2]. In case of Anginal attack sublingual delivery offers patient compliance ease of administration of accurate dose which provides sudden symptomatic relief. Nicardipine hydrochloride is a Ca2+ channel blocker used to treat angina. it is belonging to BCS class-II having 10 - 40% bioavailability on oral administration [3]. Poor solubility of a drug is a major challenge for formulation scientist which can be solved by different technological approaches during the pharmaceutical product development work. By formulating complex of drug with cyclodextrin mask bitter taste of drug and also leads to improve solubility of drug [4]. Hence in the present study an attempt is made to formulate and evaluate sublingual tablet of nicardipine hydrochloride for improve bioavailability of drug.

Material and Method

Nicardipine hydrochloride was obtained as a gift sample from Cadila Pharmaceuticals (Baroda), β- Cyclodextrin was obtained as a gift sample from Sunrise Remedies Pvt. Ltd, Avicel, PVP K 30, Mannitol, Talc, Magnesium stearate was obtained as a gift sample from S D Fine Chem Limited, Aspartame was obtained as a gift sample from Elite chemio, Crospovidone was obtained as a gift sample from ASES Chemical Woks. All other ingredient used are analytical grade.

Preparation of Nicardipine hydrochloride Inclusion complex

Solid dispersion were prepared by using different ratio of drug with complexation agent by different method which are mention in table 1.

Drug carrier complex	Carrier	Method
F1(1:0.5)	β-cyclodextrin	Physical mixture
F2(1:1)	β-cyclodextrin	Physical mixture
F3(1:2)	β-cyclodextrin	Physical mixture
F4(1:3)	β-cyclodextrin	Physical mixture
0F5(1:4)	β-cyclodextrin	Physical mixture
F6(1:0.5)	β-cyclodextrin	Kneading method
F7(1:1)	β-cyclodextrin	Kneading method
F8(1:2)	β-cyclodextrin	Kneading method
F9(1:3)	β-cyclodextrin	Kneading method
F10(1:4)	β-cyclodextrin	Kneading method
F11(1:0.5)	β-cyclodextrin	Solvent evaporation
F12(1:1)	β-cyclodextrin	Solvent evaporation
F13(1:2)	β-cyclodextrin	Solvent evaporation
F13(1:3)	β-cyclodextrin	Solvent evaporation
F14(1:4)	β-cyclodextrin	Solvent evaporation
F15(1:1)	Poloxamer 188	Physical mixture
F16(1:2)	Poloxamer 188	Physical mixture
F17(1:3)	Poloxamer 188	Physical mixture

Table 1: Nicardipine hydrochloride inclusion complex.

Preparation of sublingual tablet of Nicardipine hydrochloride

Direct compression method: Weighed solid dispersion complex which was prepared by Physical mixing method. Then require quantity of each ingredient was taken for each specified formulation and all the ingredients are co -grind in a mortar -pestle until

to get uniform mixture then passed through mesh 60#. The powder blend was evaluated for flow properties. Finally magnesium stearate and talc was added and mixed for 5 minutes. The mixed blend of drug and excipients was compressed using Double Rotary Tablet Compression Machine (Rimek 10 station minipress) Karnavati Engineering Pvt. Ltd., Ahmedabad, India to produce tablets.

Preparation of calibration curve of Nicardipine hydrochloride: The calibration curves for estimation of Nicardipine hydrochloride were prepared in phosphate buffer pH 6.8 buffer containing 1% SLS. The stock solution obtained was 10 µg/ml solutions. Aliquots 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 ml stock solution were pipetted to 10 ml with 6.8 pH phosphate buffer gave the concentration of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 µg/ml. The absorbance was measured at 239 nm in UV spectrophotometry against reagent blank 6.8 pH phosphate buffer.

Evaluation of nicardipine hydrochloride sublingual tablet

Evaluation of solid dispersion for solubility study

Phase Solubility studies [5,6]: Excess amounts of Nicardipine hydrochloride and Nicardipine hydrochloride – β-cyclodextrin complex were suspended in distilled water in tightly closed screw-cap vials, equilibrated in a magnetic stirrer at room temperature for 24 hours, then filtered using a 0.45-mm Millipore filter and assayed spectrophotometrically (Shimadzu 2450, Japan) at predetermined λ_{max}. Three determinations were carried out to calculate the saturated solubility of Nicardipine hydrochloride.

Stoichiometry determination by the continuous variation method (Job's plot) [7]: Stoichiometry of inclusion was determined by the method developed by Job. Equimolar solutions of NCH and β-CD were mixed to a standard volume varying the molar ratio but keeping the total concentration of the species constant. The complex formed for each reaction mixture has been allowed to stand for 24 hours. The absorbance at 239 nm was measured for all solutions and ΔA = A - Ao, the difference in absorbance in the presence and in the absence of CDs, was plotted against r;

r = [Drug]/ [Drug]+[CD]

[CD] = Conc. of β-CD

Preformulation Study

Organoleptic properties

The colour, odour and taste of the drug are characterized and recorded using descriptive terminology.

Angle of repose [8]

Flow property is characterized in terms of angle of repose; the drug is poured gently through the walls of funnel, which is fixed at a position such that its lower tip is at a height (h) of exactly 2 cm above a hard surface. The drug is poured till the time when the upper tip of the pile surface is touched to the lower tip of the funnel. Angle of re-pose is calculated using formula.

Angle of repose (degree)	Type of flow
< 20	Excellent
20 - 30	Good
30 - 34	Passable*
> 40	Very poor
*Can be improved by a glidant, e.g. 0.2% aerosol	

Table 2: Interpretation of Angle of repose for powder flow Angle of repose as an indication of flow properties.
Where, m: Bulk mass (gm); vf: Final volume after Tapping

Carr's Index (% Compressibility) [8]

It is one of the most important parameter to characterize compressibility of powder and granules. It is simple index that can be determined on small quantities of powders and granules. Carr's index is calculated using formula,

Carr's index = [(Tapped density-Bulk density) / Tapped density] * 100

Carr's index (%)	Compressibility
5 - 15	Excellent
12 - 16	Good
18 - 21	Fair to passable*
23 - 35	Poor*
33 - 38	Very poor
> 40	Extremely poor
*Can be improved by a glidant, e.g. 0.2% aerosol	

Table 3: Interpretation of Carr's index for powder flow.

The pure drug and physical mixture were then separately mixed with IR grade KBr. This mixture was then scanned over a wave number range of 4000 to 400 cm^{-1}.

DSC study [9]

Samples was been placed in pierced aluminium pans and hold for 1 minute at 500°C and then heated gradually at 100C min^{-1} from 500°C to 2500°C. The onsets of melting points were calculated by the instrument.

FTIR spectrophotometric study for compatibility [9]

The infrared spectrum of the native drug Nicardipine hydrochloride was recorded on a Fourier transform infrared spectrophotometer in the range of 4000 - 400 cm^{-1} and 1 cm^{-1} resolution. Infrared spectra of Nicardipine hydrochloride and excipients mixture were recorded using KBr mixing method on FTIR instrument (FTIR- 8400S, Shimadzu, Kyoto, Japan).

Differential scanning calorimeter (DSC) study [9]

Differential Scanning Calorimeter study was carried out using Shimadzu DSC- 60 (Shimadzu, Kyoto, Japan) instrument. DSC ther-

mogram of pure drug of and mixture of Nicardipine hydrochloride and polymer was taken. DSC aluminium cells were used as sample holder and blank DSC aluminium cell was used as reference. 2 - 3 mg sample was used for analysis. Thermograms were recorded over the range of 60ºC - 260°C at a constant rate of 10ºC per minute under nitrogen purge at 20 ml/min.

X-ray diffraction study (XRD) [9]

The diffraction pattern of pure NCH and final optimized batch F4 tablet was evaluated by using an X-ray powder diffractometer to assess the polymorphic state. Each diffractogram was recorded from 3 to 1500 (2θ) at a scanning speed of 30/min and using Si (Li) PSD detector.

Result and Discussion

Preformulation Studies

Identification of Nicardipine hydrochloride

Drug: Nicardipine hydrochloride

Colour: Pale Yellow

FTIR Spectra of Nicardipine hydrochloride

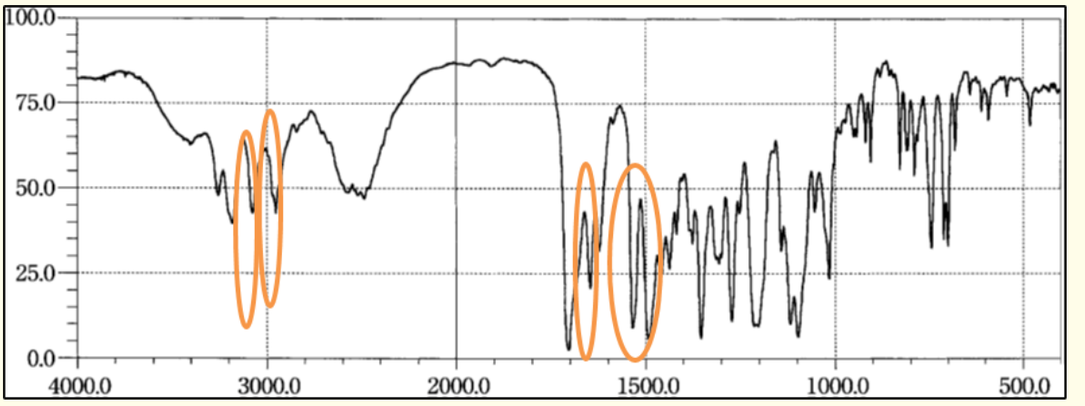

Figure 1: FTIR spectra of Nicardipine hydrochloride [10].

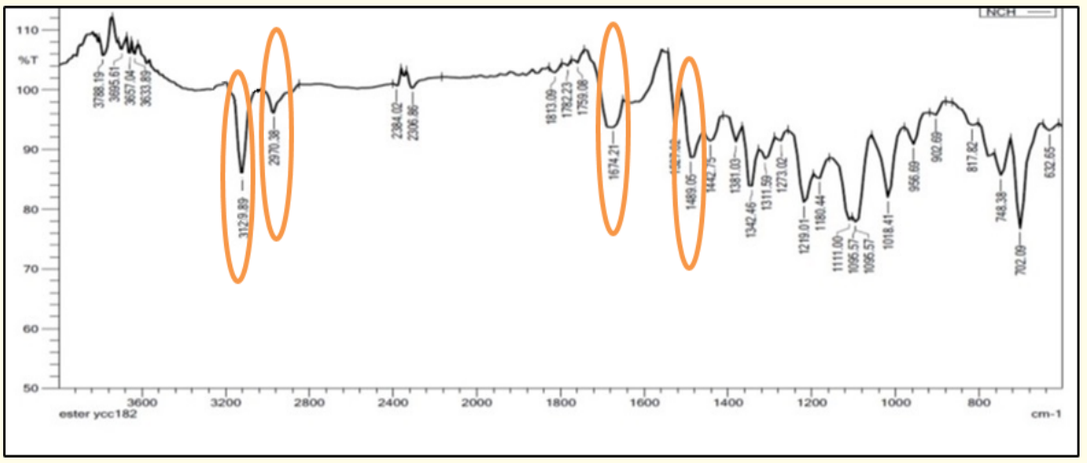

Figure 2: FTIR spectra of Nicardipine hydrochloride.

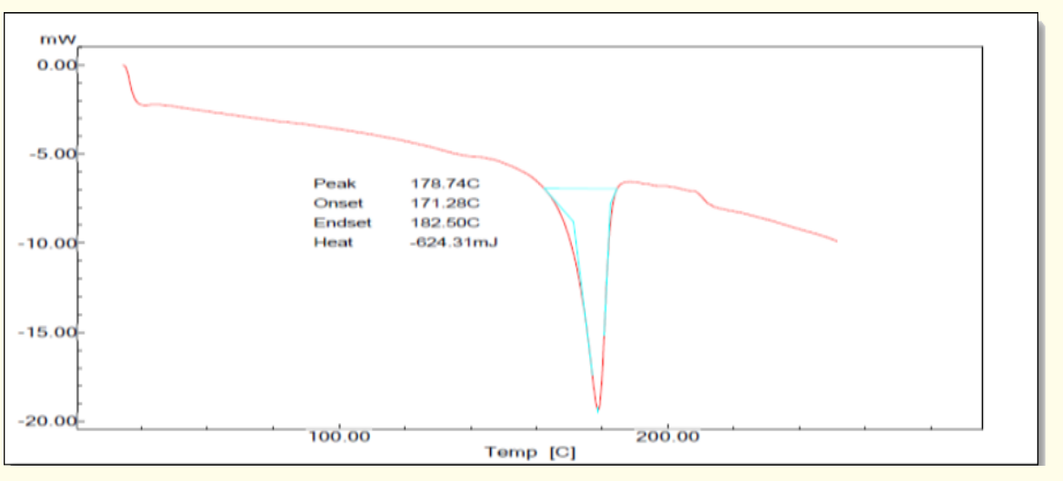

Figure 3: DSC of Nicardipine hydrochloride.

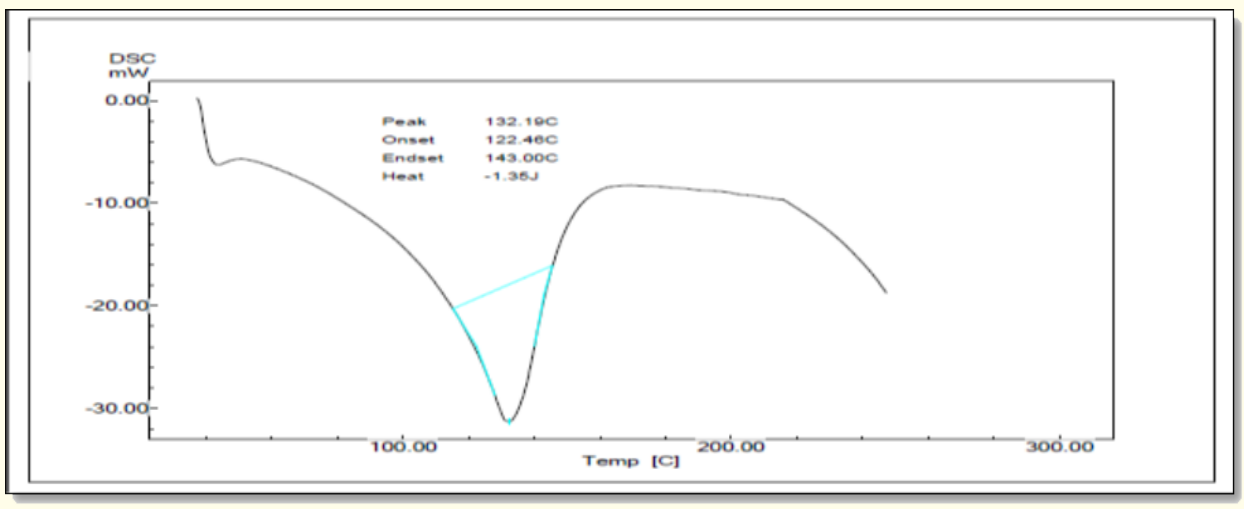

Figure 4: DSC of Drug+β-CD.

Determination of UV absorption maximum

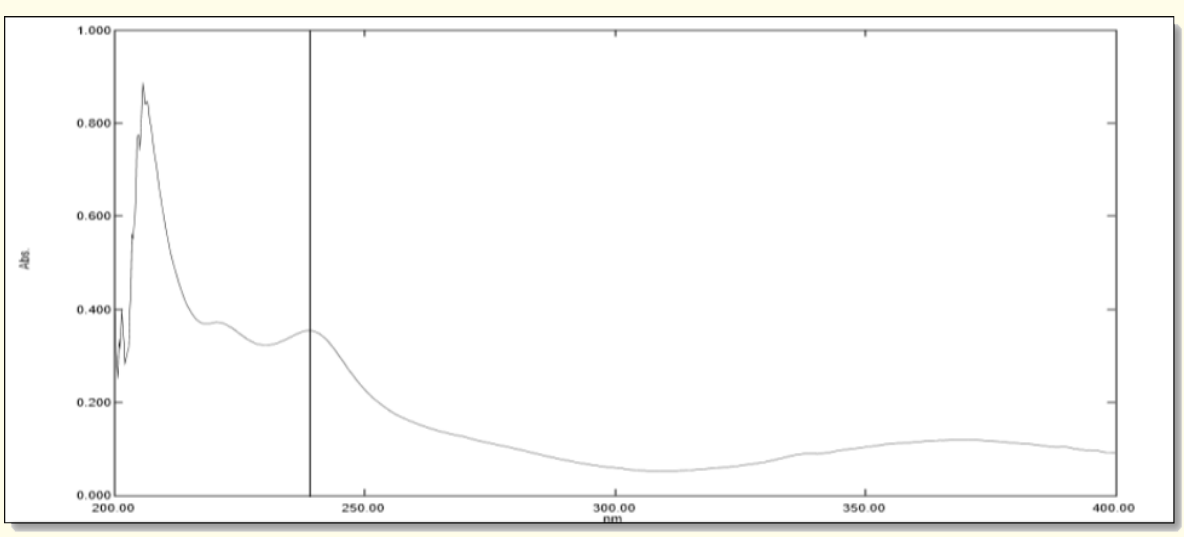

Figure 5: Standard curve of Nicardipine Hydrochloride in phosphate buffer pH-6.8 containing 1% SLS.

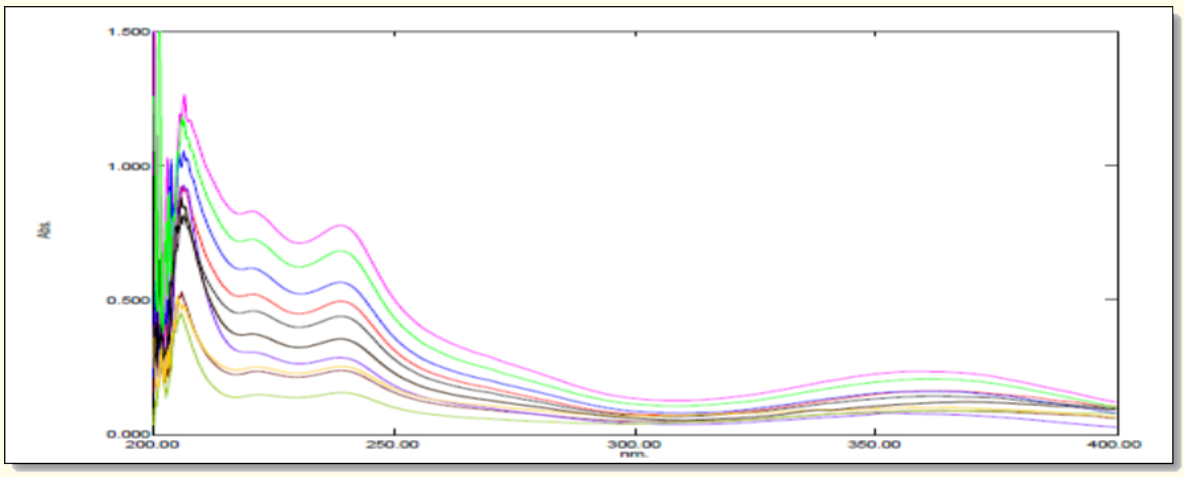

Figure 6: U.V Scan of Nicardipine hydrochloride in Phosphate buffer pH 6.8 containing 1% SLS
Nicardipine hydrochloride β-CD Interaction study.

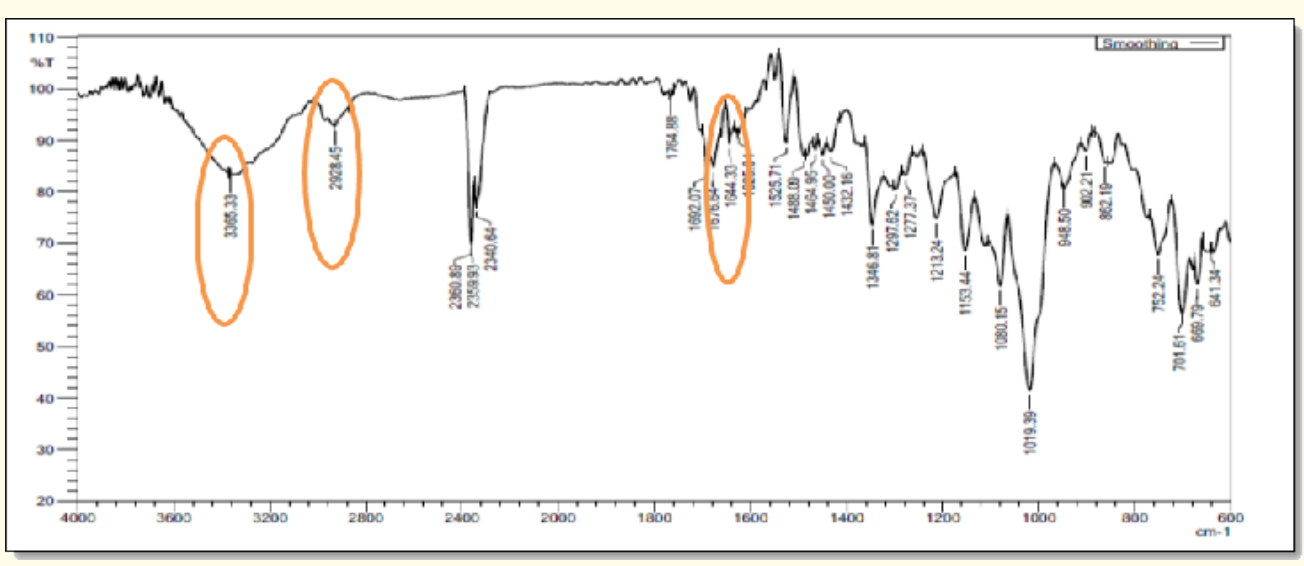

Figure 7: Nicardipine hydrochloride β-CD Interaction.

Concentration (µg/ml)		Average absorbance		Mean Absorbance
A1		A2		A3
0	0	0	0	0
4	0.154	0.158	0.146	0.15 ± 0.012
8	0.285	0.278	0.282	0.28 ± 0.013
12	0.438	0.453	0.446	0.44 ± 0.007
16	0.575	0.564	0.572	0.57 ± 0.006
20	0.723	0.728	0.726	0.72 ± 0.003
24	0.852	0.856	0.86	0.85 ± 0.01

Table 4: U.V Scan of Nicardipine hydrochloride in Phosphate buffer pH 6.8 containing 1% SLS.

Functional Group	Wave number Pure drug (cm^{-1})	Wave number Drug+Excipients (cm^{-1})
C-N stretching	1342.46	1346.81
N-H stretching	3129.89	3365.33
C-0 stretching	1273.	1149.57
C=O stretching	1759.08	1764.88
Aromatic C-C	1674.80	1676.64
C-H stretching	2970.38	2928.45
N=O stretching	1527.62 and 1489.06	1525.04 and 1488.09

Table 5: Nicardipine hydrochloride β-CD Interaction data.

FTIR spectra of pure Nicardipine hydrochloride showed characteristic peaks of its functional group as per table 5. Mixture of Nicardipine hydrochloride with β-CD negligible change in peaks and their for we conclude that there is no interaction be-tween Nicardipine hydrochloride and β-CD.

Selection of solubility enhancing agent and method

Phase solubility study of Nicardipine hydrochloride was conducted and the result of phase solubility study is given in table 6.

Here β-cyclodextrin was selected as solubility enhancing agent and physical mixture as solid dispersion method, because drug: β-cyclodextrin (1:1) complex gave higher solubility of Nicardipine hydrochloride.

Result of phase solubility

Drug carrier complex	Carrier	Method	Solubility (µg/ml)
F1(1:0.5)	β-cyclodextrin	Physical mixture	18
F2(1:1)	β-cyclodextrin	Physical mixture	60
F3(1:2)	β-cyclodextrin	Physical mixture	23.6
F4(1:3)	β-cyclodextrin	Physical mixture	26.3
F5(1:4)	β-cyclodextrin	Physical mixture	30.25
F6(1:0.5)	β-cyclodextrin	Kneading method	12.8
F7(1:1)	β-cyclodextrin	Kneading method	4.6
F8(1:2)	β-cyclodextrin	Kneading method	12.8
F9(1:3)	β-cyclodextrin	Kneading method	12.8
F10(1:4)	β-cyclodextrin	Kneading method	12.8
F11(1:0.5)	β-cyclodextrin	Solvent evaporation	10.29
F12(1:1)	β-cyclodextrin	Solvent evaporation	6.36
F13(1:2)	β-cyclodextrin	Solvent evaporation	11.2
F13(1:3)	β-cyclodextrin	Solvent evaporation	4.07
F14(1:1)	Poloxamer 188	Physical mixture	2.3
F15(1:2)	Poloxamer 188	Physical mixture	1.5
F16(1:3)	Poloxamer 188	Physical mixture	1.02

Table 6: Phase solubility.

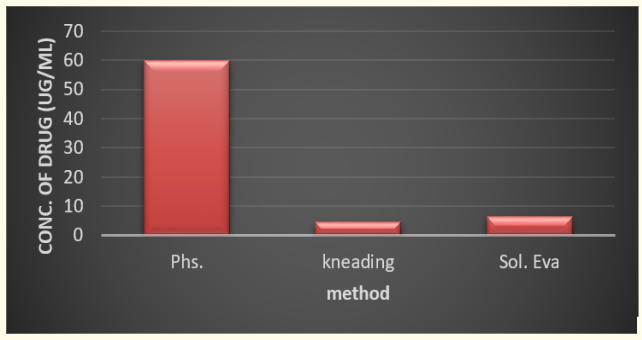

Figure 8: Selection of Method of Preparation of Inclusion Complex.

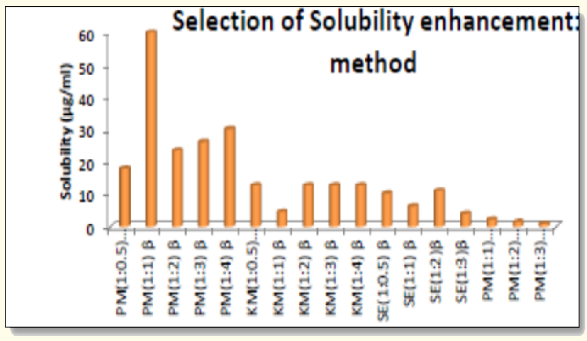

Figure 9: Selection of Solubility Enhancement Method.

Selection of method of preparation of inclusion complex

For sublingual tablet it required quick dissolution from dosage form, for this higher solubility of drug was necessary and this can achieve by enhancing the solubility of drug at its higher level. Here F12 (1:6) batch was selected because, there was higher solubility observed in this batch.

Phase Solubility

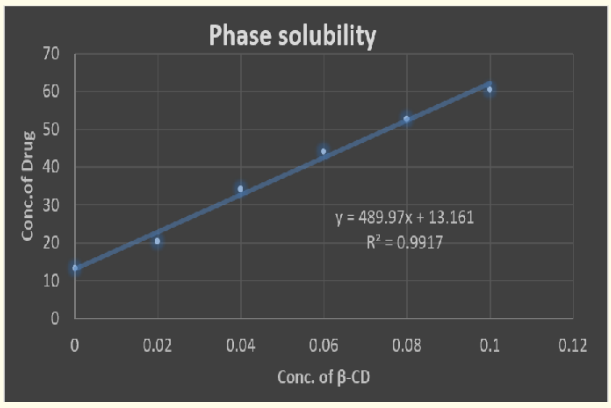

Figure 10: Phase Solubility.

Preformulation Study

Physical properties of Solid dispersion

Description	Amorphous
Colour	Yellowish white
Odour	Odourless
Taste	Slightly bitter
Bulk density (gm/ml)	0.37
Tapped density (gm/ml)	0.5
Angle of repose (°)	33.53
Carr's index	26
Hausner's ratio	1.35

Table 7: Physical properties of Solid dispersion.

Evaluation of powder blend ready for compression

Powder blend	Angle of repose	Bulk Density (gm/ml)	Tapped density (gm/ml)	Carr's index(%)	Hausner ratio (%)
P1	26.55	0.388 ± 0.05	0.428	11.56	1.148
P2	27.53	0.392 ± 0.06	0.432	11.60	1.152
P3	27.33	0.389 ± 0.03	0.436	11.63	1.163
P4	27.89	0.393 ± 0.03	0.438	11.69	1.183
P5	28.48	0.389 ± 0.05	0.435	11.73	1.185
P6	28.56	0.394 ± 0.04	0.390	11.79	1.186
P7	28.60	0.396 ± 0.03	0.393	11.83	1.191
P8	28.75	0.395 ± 0.04	0.395	11.86	1.194
P9	28.78	0.398 ± 0.04	0.399	11.92	1.198

Table 8: Evaluation of powder blend.

Angle of repose of all formulation varied from 26.56 to 28.45. Angle of repose less < 30 indicates good flow property. Compressibility index vary from 11.56% to 11.92%. Compressibility index 12 to 16% indicates good compressibility and Hausne's ratio varies from 1.11 to 1.17. Hausner's ratio less than 1.25 indicate good flow.

Evaluation of sublingual tablets of formulation

All formulations were evaluated for Hardness, Thickness, Weight variation, Friability, Disintegration time and % CPR Results were shown in table 9.

Formula	Hardness (kg/cm^2)	Thickness of tablets (mm)	Weight variation	Friability
P1	2.7 ± 0.03	2.94	99.8 ± 0.23	0.89
P2	2.9 ± 0.04	1.94	99.9 ± 0.07	0.82
P3	3.0 ± 0.03	1.95	99.6 ± 0.25	0.73
P4	3.2 ± 0.05	1.95	99.7 ± 0.26	0.69
P5	3.4 ± 0.04	1.95	99.5 ± 0.32	0.57
P6	3.3 ± 0.03	1.95	98.8 ± 0.73	0.56
P7	3.3 ± 0.04	1.94	98.6 ± 0.86	0.52
P8	3.5 ± 0.05	1.94	99.6 ± 0.30	0.47
P9	3.5 ± 0.04	1.94	99.8 ± 0.16	0.32

Table 9: Evaluation of sublingual tablets.

Evaluation of sublingual tablets of formulation P1-P9

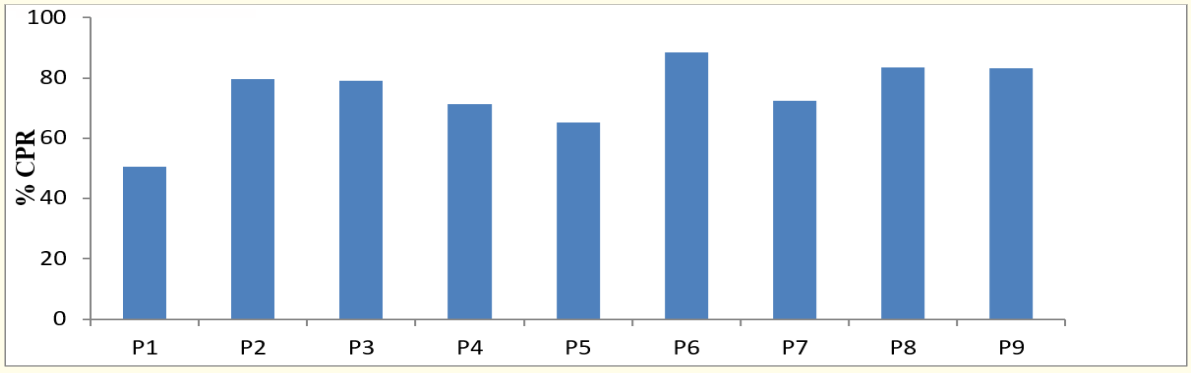

Table 11: Evaluation of sublingual tablets of formulation P1-P9.

Concentration of superdisintegrants and binder has important effect on disintegration time and drug release. Sodium starch glycolate, Croscarmellose sodium and Crospovidone are act as a super disintegrants. Microcrystalline cellulose and PVP K 30 are act as binders. Binder is selected on basis of lower disintegration time with acceptable hardness and friability. From the trial batches it was observed that concentration of MCC PH 102 and PVP K 30 has important effect on Disintegration time. Formulation P1, P2, P3 Contain only MCC pH-102 have higher disintegration time and low dissolution rate. PVP K 30 is a hydrophilic polymer with increase in conc. of PVP K 30 it will increase the Disintegration time and drug release. Here, from flux study I need to prepare sublingual tablet having disintegration time 40 sec. so, Batch P2, P6 taken into consideration. The higher drug release was found in Batch P6, P8, P9. But Disintegration time of batch P8 and P9 was high and therefore to decrease the disintegration time concentration of PVP K 30 needs to be decreased. So, concentration of PVP K 30 was reduced and concentration of MCC PH 102 was increased proportionally. When tablets containing adequate conc. of super disintegrants and binders come in contact with water, it allows rapidly disintegrate the tablets leading to rapidly drug release of tablets rather than other formulation containing different conc. of superdisintegrants and binders. The amount of drug release from formulations de-pended on super disintegrants and binders and its concentration. The *in-vitro* drug re-lease was higher with formulation P6 (containing 4% Crospovidone and 3% PVP K 30) which was about 82.33% at 6 minutes. Thus, Crospovidone and PVP K 30 was selected for further optimization using factorial design.

Pre formulation screening of 3^2 full factorial batches

Batch	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (IC)	Hauser's ratio (HR)	Angle of repose (°)
F1	0.386	0.434	12.54	1.187	23.49
F2	0.387	0.427	12.50	1.125	22.47
F3	0.393	0.415	11.60	1.027	22.25
F4	0.385	0.437	12.50	1.890	23.45
F5	0.386	0.425	12.55	1.155	22.45
F6	0.390	0.413	11.58	1.015	22.23
F7	0.388	0.433	12.56	1.186	23.41
F8	0.391	0.425	11.59	1.186	22.70
F9	0.391	0.415	11.05	1.025	22.15

Table 10: Pre compression evaluation of Sublingual tablet of Formulation F1-F9.

Batch code	Disintegration time (Sec)	Wetting time (Sec)	Water absorption ratio
F1	55 ± 3	48 ± 6	64.9
F2	67 ± 5	54 ± 3	64.25
F3	92 ± 3	85 ± 2	65.38
F4	41 ± 2	34 ± 3	74.75
F5	49 ± 6	37 ± 3	59.28
F6	70 ± 5	62 ± 4	76.28
F7	20 ± 2	16 ± 2	88.78
F8	24 ± 3	18 ± 3	80.37
F9	26 ± 2	21 ± 2	88.23

Table 11: Evaluation of Sublingual tablet of Formulation F1-F9.

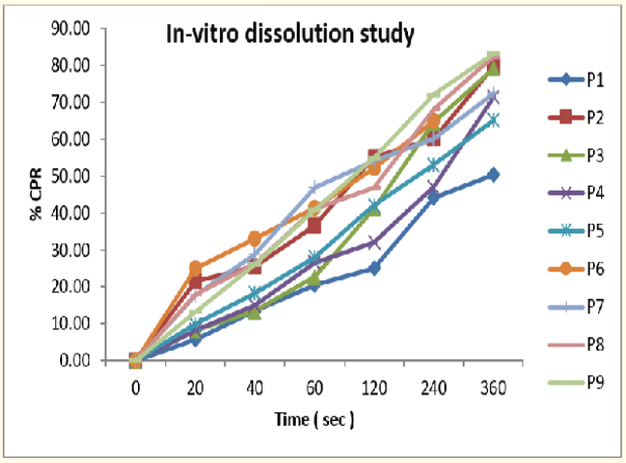

Figure 12: *In vitro* Dissolution study of Formulation F1-F9.

Above figure 12 indicates that all the batches showed 85% of drug release within 8 minutes whereas batch F1, F4, F7 showed 95% drug release within 8 minutes. Fast dissolution of the drug from the formulations can be explained as follow: As the concentration of Crospovidone increased, disintegration time of tablet increased.

In vitro Diffusion study of optimise Batch

Time	%CPR
0	0
40	10.16
2	23.33
4	43.52
6	53.51
8	61.30
10	73.02
12	86.76
14	96.81

Table 12: *In vitro* Diffusion study of optimise Batch.

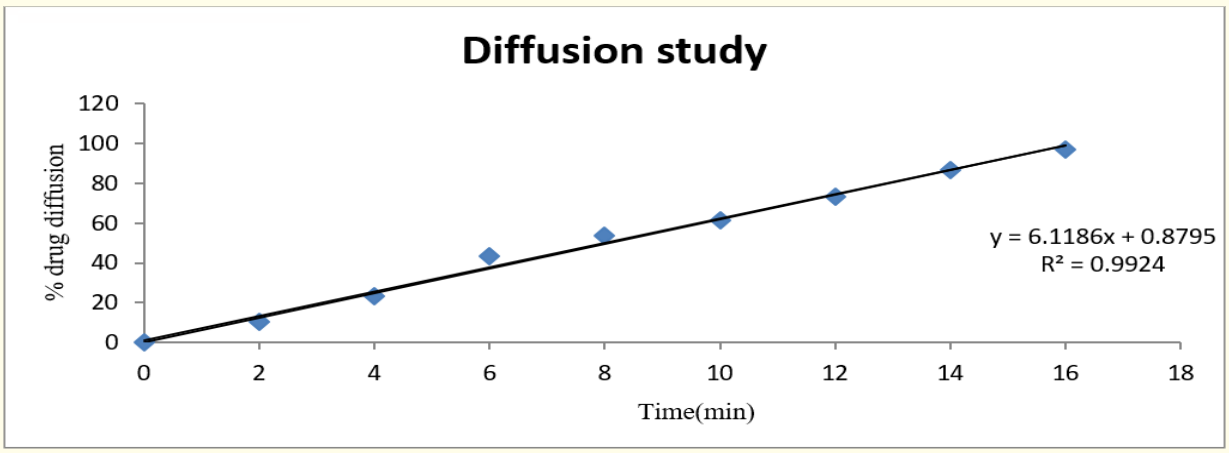

Table 13: *In vitro* Diffusion study.

Stability Studies of Optimized Batch

The stability study was performed in accordance to ICH guideline. Stability study was performed to see the effect of temperature and humidity on tablets during the storage time. The tablets were checked periodically (0 and 10 days) for various parameters such as Physical appearance, hardness, Friability, Disintegration time, wetting time, drug content and *in-vitro* dissolution study before and after stability study. The results obtained are shown in table 13 and 14.

Parameters	Before	After 10 days
Hardness	3.4 kg/cm^2	3.4 kg/cm^2
Friability (%)	0.8	0.79
Disintegration time (sec)	41sec	40 sec
Wetting time (sec)	34	34
Drug content (%)	99.40	98.86

Table 13: Result of stability data of optimized formulation subjected for stability studies (40 0Cand 75% RH).

Time (min)	% CPR (before)	%CPR (after)
0	0	0
40	21.56	20.33
60	34.25	33.02
120	40.03	38.67
240	49.40	45.83
360	60.98	60.61
480	99.45	98.10

Table 14: Comparison of drug release profile of optimized batch subjected for stability study (400C and 75% RH).

Conclusion

From the study on sublingual tablet of Nicardipine hydrochloride, following points can be concluded: Nicardipine hydrochloride is a antianginal anti-hypertensive drug used in treatment of emergency condition of angina. The concept of preparing sublingual tablets containing Nicardipine hydrochloride offers a suitable and practical approach in serving the desired objective of management of Angina. The result of FTIR and DSC showed that there was no interaction between drug and selected excipients used. Nicardipine hydrochloride have least solubility, the solubility of drug can be enhanced by preparing inclusion complex using various complexation agent like β-cyclodextrin, Poloxamer 188 and Poloxamer 407. Amongst this solubility of drug was improve by using (1:1) molar ratio of Drug: β- cyclodextrin. Bioavailability of drug may be enhanced by avoiding hepatic first pass metabolism. Bitter taste of Nicardipine hydrochloride was also be masked by using various taste masking agent. By *ex-vivo* permeation study Flux was found out to set disintegration time of sublingual tablet which was 40 sec. For the preparation of sublingual tablet various superdisintegrants used like Sodium starch glycolate, Croscarmellose sodium and Crospovidone were screened to achieve faster disintegration and acceptable hardness, MCC PH102 and PVP K 30 as binder, Mannitol as filler, Aspartame is used as sweetening agent to mask the bitter taste of drug eliciting a better patient compliance and patient acceptance, Magnesium stearate as lubricant and talc as glidant.

From the preliminary studies, it was concluded that Crospovidone as a superdisintegrant and PVP K30 as a binder gave superior results in terms of low disintegrating time (41 seconds) and high % CPR (82.33%) as compared to sodium starch glycolate,

Croscarmellose. Thus Crospovidone and PVP K 30 were selected as independent variable at three levels in 3^2 factorial design and disintegrating time and % CPR were selected as the dependent factors. Sublingual tablets of batch F4 have 4% Crospovidone and 2% PVP K 30 gave optimum *in vitro* drug release in 40 SEC OF disintegration time considered to be the best among all other nine batches of tablets. Thus, sublingual tablets of Batch F4 were selected as an optimum batch by using desirability function. The results of comparison of predicted response and obtained response were found in good agreement and evaluated for further parameters like stability study. The result of stability study of the most satisfactory formulations showed that there was no significant change in hardness, disintegration time, wetting time, drug content, and *in-vitro* dissolution profile when stored at 400C and 75% RH for a period of 10 days. In conclusion, sublingual tablet Nicardipine hydrochloride was formulated by direct compression technique, using 4% w/w of Crospovidone as superdisintegrant and 2% w/w of PVP K 30 as binder which showed acceptable disintegrating time and *in-vitro* dissolution profile. The proposed 3^2 full factorial, design helped in achieving a stable, optimized formulation with less time and efforts.

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