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Review Article

DESIGN AND DEVELOPMENT OF ORO-DISPERSIBLE FILM OF NICARDIPINE HYDROCHLORIDE

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ABSTRACT

Nicardipine is a antihypertensive drug, which undergoes extensive hepatic degradation (93%) and have poor bioavailability (35%). For overcoming this problem Oro-dispersible film of Nicardipine hydrochloride is formulated by employing Solvent casting technique with suitable film forming agent; beta cyclodextrin and Sodium Starch glycolate in a different proportion. The prepared film avoids extensive first pass metabolism and improvement in dissolution efficacy, disintegration time which results in improvement in bioavailability. The advantage of this formulation is such that in case of hypertension attack patient can take the drug without the usage of water.

Therefore the main objective of the present work is to develop Oro-dispersible films for Nicardipine hydrochloride to improve bioavailability, disintegration time, dissolution efficacy and patient compliance.

KEYWORDS: Solvent Casting Technique, Film forming agent, Sodium Starch Glycolate, Betacyclodextrine

INTRODUCTION

Antihypertensive drugs (ACE Inhibitors), which undergoes extensive hepatic degradation, which have poor bioavailability for overcoming this problem fast disintegrating film (FDF) of antihypertensive drugs can be formulated which avoids extensive first pass metabolism and improvement in dissolution efficacy, disintegration time which results in improvement in bioavailability. The advantage of this formulation is such that in case of hypertension attack patient can take the drug without the usage of water. Therefore the main objective of the present work is to develop fast disintegrating films (FDF) for antihypertensive drug to improve bioavailability, disintegration time, dissolution efficacy and increase patient compliance.

Despite of tremendous advancements in drug delivery, Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and, most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. The aforementioned advantages of drug administration via the oral cavity offer new possibilities in the administration of drugs to "problematical" subpopulations like children and the elderly. These patients have special drug administration requirements as they are often unable to swallow solid dosage forms (e.g. tablets, capsules). Poor taste can also lead to medication being refused or spat out. Furthermore, the pediatric subpopulation is a very heterogeneous group. Fast-dissolving solid drug dosage forms for application onto the oral cavity for the Pediatric population seem to be very appropriate, especially in preterm and term newborn infants.

Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking of water or chewing. More recently, fast-dissolving films which dissolve/disintegrate in the mouth within a few seconds without additional water and the need to swallow are gaining interest as an alternative to fast-dissolving tablets to definitely eliminate patients' fear of chocking and overcome patent impediments.

Nicardipine Hydrochloride is rapidly and completely absorbed from the gastrointestinal tract but is subject to saturable first pass hepatic metabolism. Bioavailability of about 35% has been reported after a 30 mg dose at steady state. The pharmacokinetics of Nicardipine Hydrochloride is non-linear due to the saturable first-pass hepatic metabolism and an increase in dose may produce a disproportionate increase in plasma concentration. There is also considerable interindividual variation in plasma drug concentrations. Nicardipine Hydrochloride is more than 95% bound to plasma proteins and extensively metabolised in the liver and is excreted in the

urine and faeces, mainly as inactive metabolites. The terminal plasma half-life is about 8.6 hrs, thus steady-state plasma concentrations are achieved after 2 to 3 days of dosing three times daily.

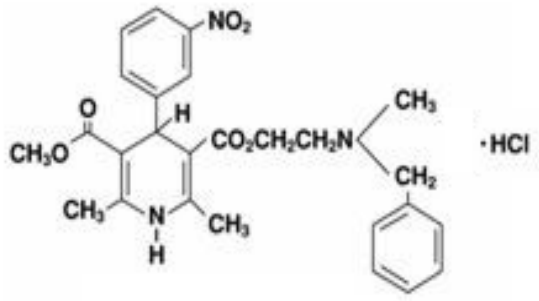

Fig. 1 Struture of Nicardipine Hydrochoride

METHOD

Pre-formulation studies2,3

It is one of the important prerequisites in development of any drug delivery system. Preformulation studies of the drug were performed, which included melting point determination, solubility and compatibility studies.

Identification of Nicardipine hydrochloride

Identification of Nicardipine hydrochloride was carried out by the following techniques:

a. UV spectroscopy

b. IR spectroscopy

c. Differential Scanning Colorimetry (DSC)

a. UV spectroscopy: Determination of λmax of Nicardipine Hydrochloride in methanol:

Standard stock solution of Nicardipine hydrochloride was prepared by dissolving accurately weighed 100 mg of Nicardipine hydrochloride in the little quantity of methanol in 100 ml volumetric flask. The volume was then made up mark by using methanol, so as to get the solution of 1000 µg/ml.

From the standard stock solution, 2 ml was diluted to 100 ml with modified phosphate buffer solution (pH 7.4). The resulting solution containing 20 µg/ml was scanned between 200 to 400 nm and λmax Nicardipine hydrochloride in methanol were observed.

b. Drug polymer interaction (FTIR) study

FTIR spectroscopy was performed on Fourier transformed infrared spectrophotometer (IR-Affinity-1, Shimadzu, Japan). The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr press and the spectra were scanned in the wave number range of 4000- 600 cm-1. FTIR study was carried on Nicardipine hydrochloride physical mixture and super disintegrants.

c. Differential scanning colorimetry (DSC)

The thermograms of pure Nicardipine hydrochloride the best formulation, and physical mixture of Nicardipine hydrochloride with physical mixture were obtained at a scanning rate of 10°C/min conducted over a temperature range of 25–350ºC respectively. The physical state of drug in tablet was analyzed by DSC (Mettler-Toledo star 822e system, Switzerland).

d. Determination of solubility3,4

The solubility of Nicardipine hydrochloride was determined according to the method adopted by krishniah. An excess amount of drug was taken and dissolved in a measured volume of distilled water in a glass vial to get a saturated solution. The solution was sonicate and kept at room temperature for the attainment of equilibrium. The concentration of Nicardipine hydrochloride in the filtrate were determined spectrophotometrically by measuring at 353 nm after 24 h.

The solubility of Nicardipine hydrochloride in chloroform, methanol, ethanol, n-butanol, distilled water and acetone were also performed.

e. Determination of melting point5

Melting point of the drug was determined by taking small amount of drug in a capillary tube closed at one end. The capillary tube was placed in a melting point apparatus and the temperature at which drug melts was recorded. This was performed thrice and average value was noted.

f. Determination of partition coefficient4

The known quantity of drugs was added into 5 ml of 1-octanol separately and it was mixed with 5 ml of water in a separating funnel. Then two phases were allowed to equilibrate at 37°C for 24 h with intermittent shaking. The concentration of the drug in the aqueous phase and organic phase was determined by UV spectroscopic method after necessary dilution. The apparent partition coefficient (Kp) was calculated as the ratio of drug concentration in each phase by the following formula;

$$Kp = \frac{Corg}{Caq}$$

Where, Corg is concentration of drug in organic phase and Caq is the concentration of drug in aqueous phase.

g. Drug polymer compatibility

Pure drug and polymers were subjected to FTIR studies alone and in combinations. 3 mg of pure drug / combination of drug - polymer were triturated with 97 mg of potassium bromide in a smooth mortar. The mixtures were placed in the sample holder and were analyzed by FTIR to study the interference of polymers with the drug.

Preparation of Oro-dispersible films of Nicardipine hydrochloride

Oral dispersible films of Nicardipine hydrochloride was prepared by solvent casting technique for the formulations shown

Table No.1: Composition of different formulations containing NC-HCL

Compositions	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Nicardipine hydrochloride (mg)	30	30	30	30	30	30	30	30	30
HPMC	1	3	5	7	9	11	13	15	17
PEG	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Mannitol	10	10	10	10	10	10	10	10	10
Tween-80	2	2	2	2	2	2	2	2	2
Citric acid	15	15	15	15	15	15	15	15	15
SSG	19	18	16	14	12	11	10	9	8
Betacyclodextrine	1	2	4	6	8	9	10	11	12
Water	qs	Qs	qs	Qs	qs	qs	qs	qs	qs

Evaluation of films of Nicardipine hydrochloride

a. Identification6-The films containing Nicardipine HCl subjected to InfraRed studies for identification and to study drug polymer compatibility. (IR 8400S, Shimadzu, Japan). The KBr disk method was used for preparation of samples and the spectra were recorded over the wave number 4000 to 400 cm-1.

b. Morphological properties7-Properties such as homogeneity, color, transparency and surface of the oral films were evaluated by visually inspection.

c. Uniformity of dosage units of the oral strips8-The content uniformity of dosage units of the oral film preparation was tested using UV spectroscopy. According to the USP standards, the contents of preparations should lie between the limits 98 to 101%. The results were expressed as mean of six determinations of each formulation and mean ± S.D calculated. The drug content was determined by using a standard calibration curve.

Preparation of standard calibration curve of Nicardipine hydrochloride in phosphate buffer solution (6.8 pH): 100 mg of Nicardipine hydrochloride was accurately weighed and dissolved in phosphate buffer 6.8 pH into a volumetric flask and the volume made upto 100ml with the same. 10 ml of this stock solution was taken and made up to 100 ml with phosphate buffer solution, which gives 100 mcg/ml concentrations (working standard). From this working standard, aliquots of 1.0, 3.0, 5.0, 7.0, 9.0 and 11.0 ml was pippeted into 50ml volumetric flask and the volume was made upto 50 ml with phosphate buffer 6.8 pH. The absorbance of the diluted solution was measured at 273 nm against reagent blank (phosphate buffer 6.8 pH) in triplicate and a standard plot was drawn using the mean data obtained. The correlation coefficient was calculated by linear regression analysis.

d. Film mass-The mass of films was determined by an analytical balance. This test was performed on six films of each formulation and mean ± S.D calculated.

e. Film thickness-Film thicknesses were determined using the Digimatic & Vernier Caliper. Each wafer was measured at five positions (central and the four corners) and the mean thickness was calculated. This test was performed on six films of each formulation and mean ± S.D calculated.

f. Folding endurance study9-It was measured manually for the prepared fast dissolving film (3 X 2 cm). A strip was repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. This test was performed on six films of each formulation and mean ± S.D calculated.

g. Surface pH study10-The surface pH of fast dissolving strip was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral strip was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. This study was performed on six films of each formulation and mean ± S.D calculated.

h. In vitro disintegration studies11-Disintegration time gives an indication about the disintegration characteristics and dissolution characteristics of the film. The film as per the dimensions (2x2 cm) required for dose delivery was placed on a stainless steel wire mesh placed in a petridish containing 10 ml phosphate buffer pH 6.8. Time required for the film to break was noted as in vitro disintegration time. This test was performed on six films of each formulation and mean ± S.D calculated.

i. Dissolution and drug release12-16-Dissolution test of Nicardipine HCl films was performed using (900 ml; phosphate buffer pH 6.8 with USP dissolution apparatus II (Labindia, Mumbai, India) at 50 rpm and 37±0.5°C temperature. The drug release was analyzed spectrophotometrically at λ max 273 nm using ultraviolet (UV) spectrophotometer (Shimadzu model) by using a calibration. One film was placed into each vessel and Test sample (5 mL) was withdrawn at particular time interval (10, 20, 30 and 40 Sec) and replaced with fresh dissolution media maintained at 37±0.5°C). This test was performed on six films of each formulation and mean ± S.D calculated.

RESULT AND DISCUSSION

PREFORMULATION STUDIES

The following preformulation studies were performed for Nicardipine Hydrochloride.

Table No. 2 Preformulation data of Nicardipine Hydrochloride

	Nicardipine Hydrochloride
λmax in methanol	352.90 nm
Melting Point	168.0- 170.1°C
Partition coefficient	3.47

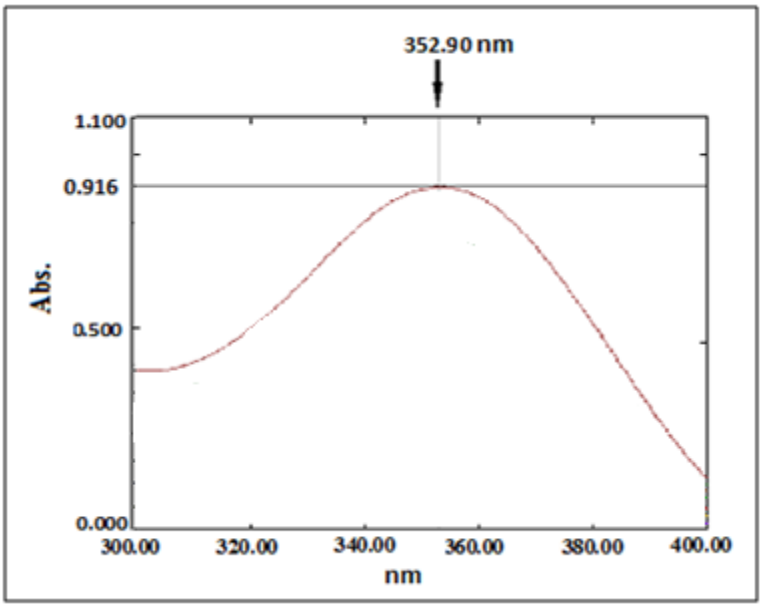

Fig 2 λmax of Nicardipine Hydrochloride in methanol

Solubility of Nicardipine Hydrochloride in other solvents

Nicardipine Hydrochloride is freely soluble in chloroform and methanol; sparingly soluble in ethanol; slightly soluble in n-butanol and acetone.

Calibration curve

Table 3 Absorbance data for the calibration curve of Nicardipine hydrochloride in pH 6.8 buffer

	Nicardipine	
Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.199
3	20	0.350
4	30	0.533
5	40	0.734
6	50	0.877

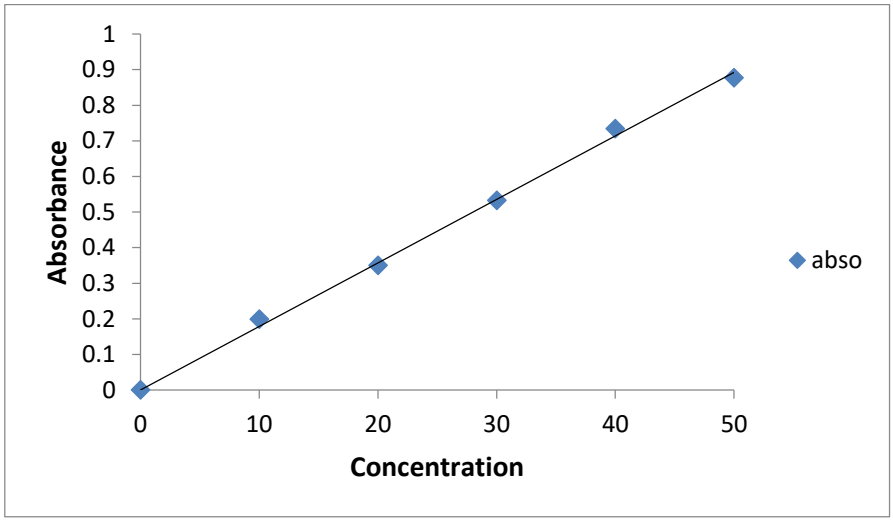

Fig 3 Standard calibration curve of nicardipine hydrochloride in pH6.8 buffer.

Differential scanning colorimetric study (DSC)

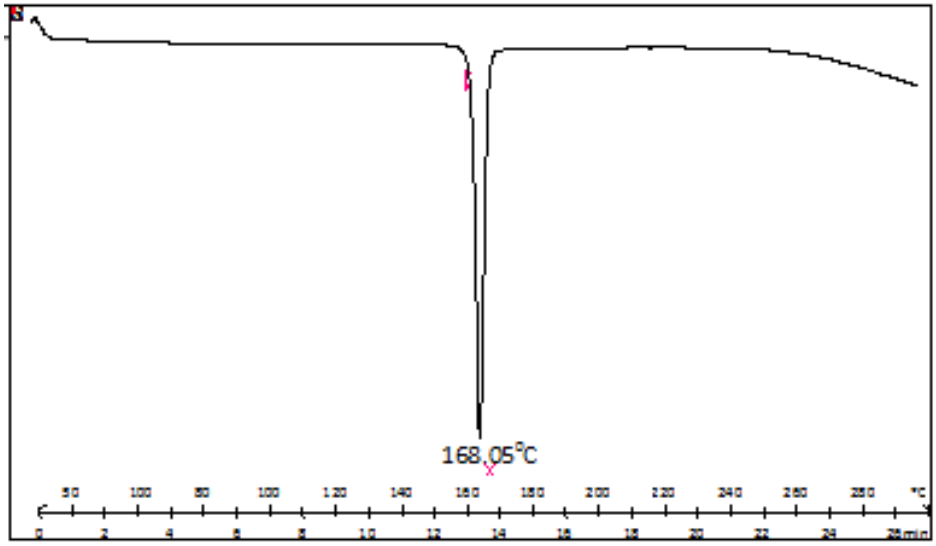

Fig 4 DSC of pure Nicardipine hydrochloride.

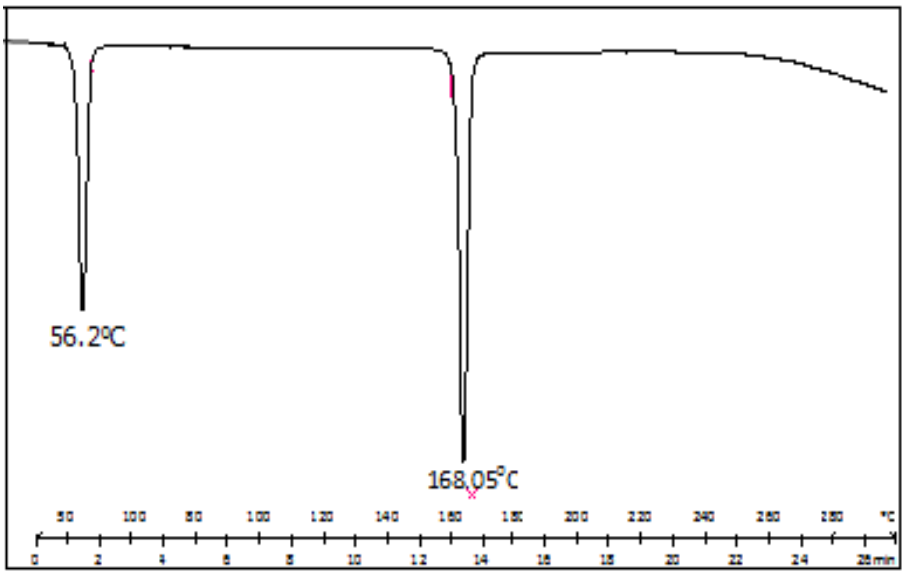

Fig 5 DSC of pure Nicardipine hydrochloride and HPMC.

Drug – Excipients compatibility studies

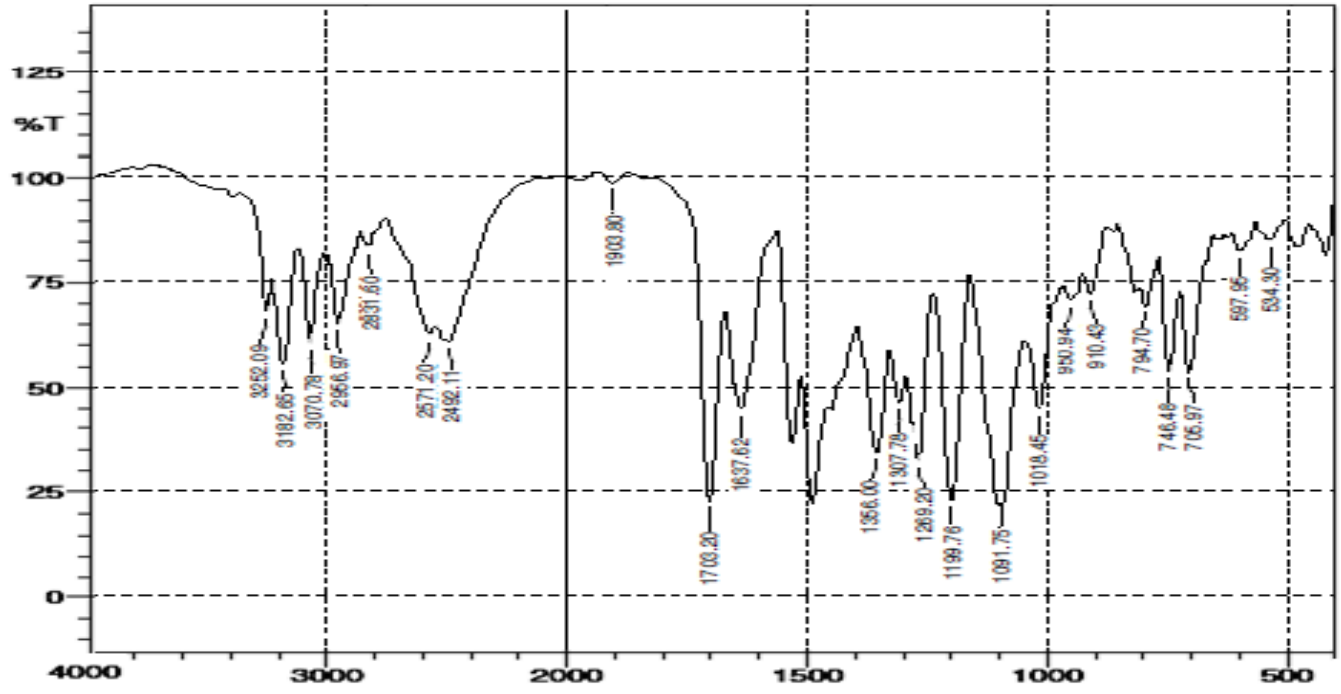

Fig 6. IR spectrum of Nicardipine Hydrochloride

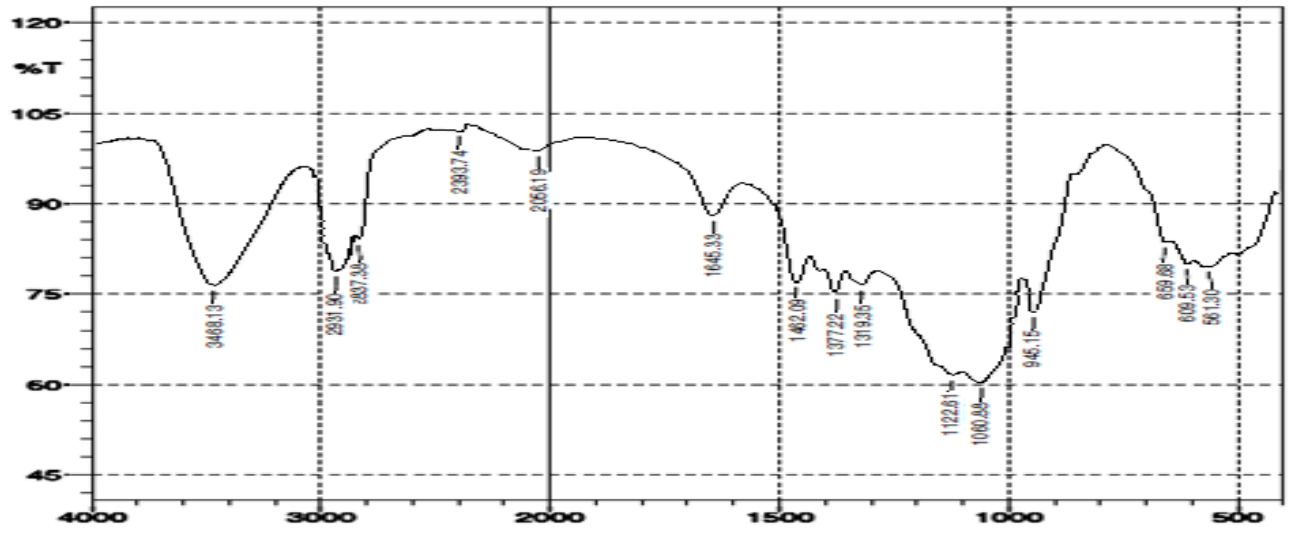

Fig 7 IR spectrum of HPMC

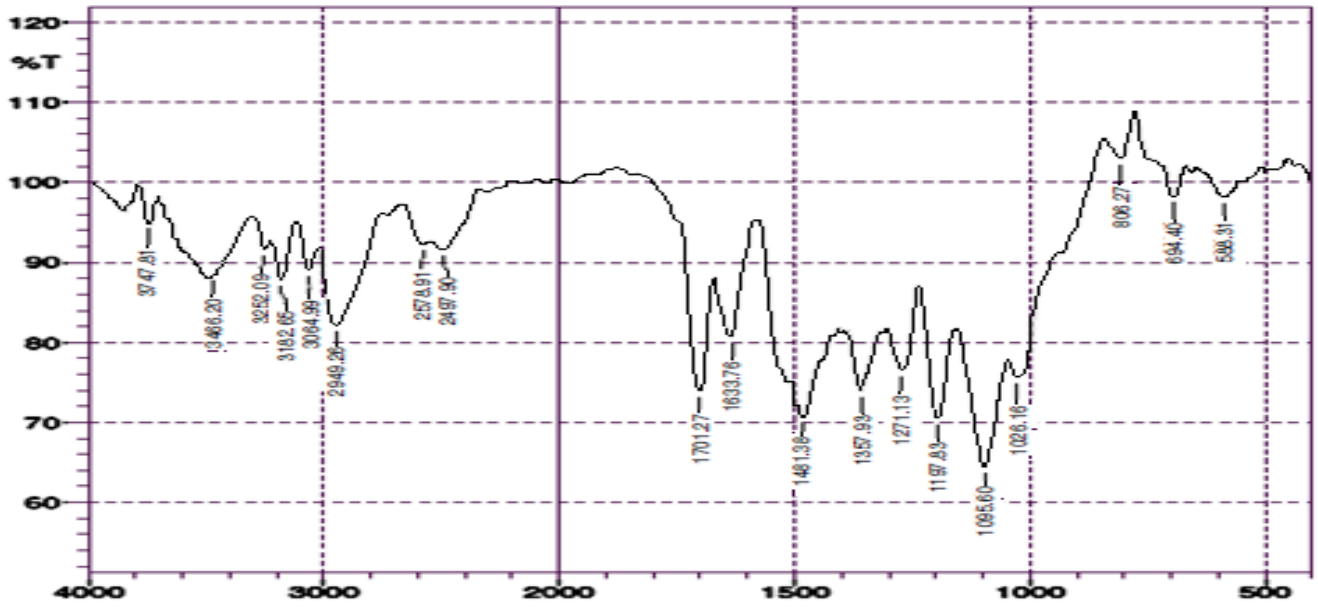

Fig 8 IR spectrum of physical mixture of Nicardipine hydrochloride and HPMC

FORMULATION STUDY

a. Physical characteristics

Characteristics such as homogecity, color, transparency and surface of the oral films were evaluated by visual inspection. All films were totally homogenous, absolutely transparent, colorless, both sides smooth.

Table No. 4 Evaluation of the Nicardipine hydrochloride Oro-dispersible Film

Formulation code	Uniformity of Dosage	Film Mass mg	Film Thickness mm	Surface pH	Folding Endurance
F-1	98.92±0.44	56.30±1.00	0.204±0.002	6.77±0.06	190.33±1.15
F-2	99.72±1.87	57.21±1.85	0.2±0.008	6.85±0.06	196.33±1.15
F-3	99.32±0.34	56.45±1.91	0.204±0.001	6.80±0.07	198.33±0.57
F-4	99.53±1.15	58.39±1.27	0.204±0.001	6.85±0.06	194.66±1.52
F-5	99.81±0.55	56.06±1.84	0.206±0.001	6.82±0.11	98.00±1.0
F-6	100.22±0.50	59.03±1.55	0.205±0.001	6.86±0.07	195.33±1.15
F-7	100.70±0.89	57.87±1.27	0.206±0.004	6.83±0.12	198.33±0.57
F-8	99.17±0.57	58.08±1.29	0.203±0.002	6.86±0.05	196.66±1.52
F-9	99.48±0.78	58.54±1.56	0.199±0.005	6.82±0.09	197.33±0.57

S.D*: Standard deviation of three determinations

g. In vitro disintegration studies

All the fast dissolving films of each formulation were found disintegrate in less than 30 sec. F7 formulation found to gave minimum disintegration time (20.23±0.75) as compared F1formulation (22.41±0.57).

h. In vitro Dissolution and release

In vitro dissolution and release studies of various formulations were performed using pH 6.8phosphate buffer as dissolution medium and measuring drug concentration spectrophotometrically at 273 nm by using a calibration. The in vitro drug release profile from the films of formulae F1 and F2 in phosphate buffer pH 6.8. After 20 seconds time interval more than 75% drug was released from films. Drug release rate was very good with films containing HPMC E6 as a polymer.

Table 5 In-vitro drug release data of orodispersible films of Nicardipine Hydrochloride

Sr. No.	Time (min.)	% Cumulative drug release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0

2	2	29.11	31.45	32.15	34.17	39.55	43.02	30.22	35.21	32.64
3	4	34.61	38.65	39.19	45.23	48.83	48.12	49.14	46.34	49.26
4	6	53.54	59.31	59.56	61.25	64.99	69.24	65.11	60.17	67.44
5	8	71.32	74.65	74.98	75.03	79.23	76.47	72.56	68.34	75.65
6	12	86.67	88.51	88.89	87.37	90.20	87.32	83.34	81.12	87.13
7	14	94.82	92.72	93.83	91.49	95.73	93.61	96.78	91.56	94.76

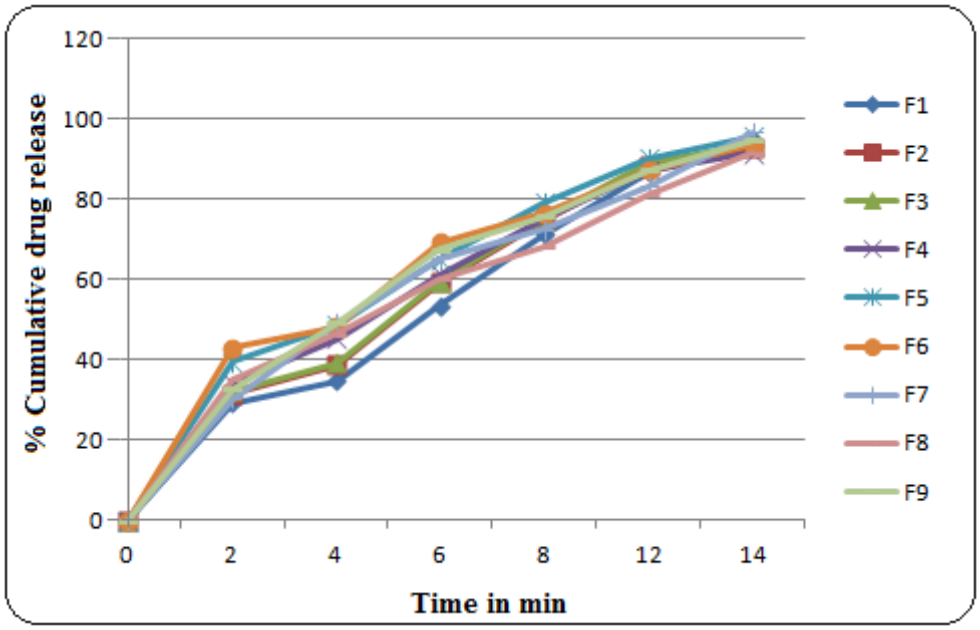

Fig 6.8 In-vitro drug release profile of Nicardipine hydrochloride

SUMMARY AND CONCLUSION:

Antihypertensive drugs (ACE Inhibitors), which undergoes extensive hepatic degradation, which have poor bioavailability for overcoming this problem fast disintegrating film (FDF) of antihypertensive drugs is formulated which avoids extensive first pass metabolism and improvement in dissolution efficacy, disintegration time which results in improvement in bioavailability. The advantage of this formulation is such that in case of hypertension attack patient can take the drug without the usage of water.

In the present study efforts were taken for preparation of fast dissolving film of drug Nicardipine HCl (Antihypertensive) formulation & consideration. Nicardipine are a antihypertensive drug, which undergoes

extensive hepatic degradation (93%), which have poor bioavailability (35%) for overcoming this problem orodispersible films of Nicardipine hydrochloride is formulated which avoids extensive first pass metabolism and improvement in dissolution efficacy, disintegration time which results in improvement in bioavailability.

Oral dispersible films of Nicardipine hydrochloride was prepared by solvent casting technique by using suitable combination of superdisintegrants and film forming polymer. The formulation F7 shows disintegration time less than 20 sec. and highest percentage drug release in 14 min of about 96.78%.

From the findings it can be concluded that:

This study shows that solubility and dissolution rate of Nicardipine Hydrochloride can be enhance considerably by formulating in it as Oro dispersible film with Sodium starch glycolate as a super disintegrant in combination with Betacyclodextrine in a ration of 1:1 by solvent casting technique.

Formulation containing SSG and Betacyclodextrine (1:1) shows improves disintegration rate than that of pure drug.

An attempt to develop Oro-dispersible film was achieved within view to improve bioavailability and enhancement of patient compliance.

Oro-dispersible film of Nicardipine Hydrochloride 30mg was prepared by using Solvent casting technique.

The IR study revealed that, polymers and excipients used were compatible with drug.

DSC data shows that no significant interaction between the drug and polymer.

Formulated film shows compliance for various physiochemical properties such as drug content, film mass, surface pH, folding endurance, disintegration time, and content uniformity.

In-vitro release studies shows that formulation F7 shows 96% drug release within 14min. in comparison to other formulation.

Formulation F7 were selected for stability study on the basis of their better & satisfactory evaluation study parameter mainly with the disintegration time and percentage drug release.

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