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Design and Characterization of Fast Dissolving Films of Cilnidipine Solid Dispersions

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ABSTRACT

The major problem in formulation of oral films of cilnidipine is that it belongs to BCS Class II moiety. Pharmacologically Cilnidipine is a dihydropyridine (DHP) type of calcium channel antagonist. Unlike other calcium channel antagonists, Cilnidipine blocks the influx of Ca^{2+} ions into both vascular smooth muscle at the level of L-type Ca^{2+} channels and neuronal cells at the level of N-type Ca^{2+} channels. Cilnidipine was absorbed over 2 hours and its bioavailability is 64-90%. Hence there is a need to increase the solubility and oral bioavailability of cilnidipine by formulating it in to solid dispersions and incorporating the same in to the formulation of fast dissolving films which gives fast onset of action. Nine formulations (FC 1 - FC 9) of cilnidipine films were prepared and evaluated for their physical characteristics such as thickness, weight variation, folding endurance, drug content uniformity and gave satisfactory results. The compatibility of the drug in the formulation was confirmed by FTIR and DSC studies. The formulations were subjected to disintegration, *in vitro* drug release studies and formulation FC 6 was found to be best formulation which contain HPMC, PVP as film forming polymers along with cilnidipine solid dispersion with poly ethylene glycol at weight ratio of 1:4 showed excellent film forming characteristics such as disintegration time of 49.3 sec and percentage drug release 97.92 within 8 minutes.

Keywords: Cilnidipine, Solid dispersions, Fast dissolving film, Solvent casting method, HPMC and PVP.

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INTRODUCTION

Recently fast dissolving drug delivery system have started gaining popularity and acceptance as new drug delivery systems which aim to enhance safety and efficacy of a drug moiety by formulating into a convenient dosage form for administration and to achieve better patient compliance. They undergo rapid disintegration in the salivary fluids of the oral cavity in less than a minute, where they release the drug¹. Most of the drug is swallowed orally with the saliva and the absorption of drug takes place in the gastro-intestinal tract. The fast dissolving dosage forms are referred by various names by researchers like quick disintegrating, orally disintegrating, rapidly disintegrating, mouth dissolve or melt in mouth dosage forms². Cilnidipine is calcium channel antagonist, which is used in the treatment of Hypertension. Cilnidipine belongs to class II drug in BCS classification the major problems with its low solubility in biological fluids, which results into poor bioavailability after oral administration and late onset of action. In order to enhance the solubility of cilnidipine and subsequently dissolution and absorption. Solid dispersions of cilnidipine were prepared by melting technique at different drug carrier (PEG 400) weight ratios and were evaluated³. The optimized formulation of solid dispersions, Cilnidipine : PEG 400 (1:4) was selected and used in the preparation of cilnidipine films by solvent casting method, which offers superiority over other.

Advantages of cilnidipine fast dissolving film include ^{4,5}

- Patient of increases Hypertension not capable to swallow large quantities of water.
- In case of high blood pressure quick onset of action required because uncontrolled high blood pressure create Strokes, Heart attack, Kidney Problem.
- Hypertension markedly reduces functional ability and extremely restlessness in such cases rapid onset of action required.
- No Marketed cilnidipine film available in India.
- Specially intended to geriatric patients who have problem of swallowing.

MATERIALS AND METHOD

Cilnidipine from swapnroop chemicals, Hydroxypropyl methyl cellulose (HPMC E15), polyvinyl pyrrolidone (PVP), poly ethylene glycol 400 (PEG 400) from yarrow chemicals. All other chemicals used were of analytical grade.

METHODOLOGY

Standard Curve of Cilnidipine

Cilnidipine is a yellow fine powder which was practically insoluble in water. Though several methods are reported for its estimation, the UV spectrophotometric method was employed in the

study. Cilnidipine shows maximum absorbance at 240 nm in simulated saliva pH 6.8. Based on this information, a standard graph was constructed (Figure No.1).

FTIR Studies

FT-IR spectra of pure cilnidipine, and combination with PEG 400, HPMC E15, PVP K30 were shown in the (Figure No.2-6). Pure cilnidipine showed principal absorption peaks at 1698.02 cm^{-1} (C=O stretching), 1617.98 cm^{-1} (C=C aromatic stretching), 1484.92 cm^{-1} (C-H aromatic bending), 2997.12 cm^{-1} (C-H stretching), 3224.40 cm^{-1} (-NH₂ stretching), 1303.4 cm^{-1} (-OCH₃ stretching) and 3288.04 cm^{-1} (-OH stretching). Same peaks of C=O, C=C, C-H, -NH₂ and -OCH₃ bonds were present as that of pure drug without much shifting in the spectra of cilnidipine along with the polymers. This suggested no chemical interaction between the drug and polymers.

Preparation of cilnidipine solid dispersion

Cilnidipine and PEG 400 are mixed using mortar and pestle. PEG 400 as carrier in different proportions 1:1, 1:2, 1:3 and 1:4 (drug:carrier) as shown in (Table No.2). To accomplish a homogenous dispersion the mixture is heated at or above the melting point of all the components with constant stirring. It is then cooled to acquire a congealed mass. It is crushed and sieved.

Characterization of cilnidipine solid dispersion

1. Percentage Practical Yield

Percentage practical yield is calculated to know about percent yield, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation (Figure No.7).

$$\text{Percentage of practical yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

2. Drug content

10 mg of solid dispersions were weighed accurately and dissolved in 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 240 nm by UV spectrophotometer. Each sample analyzed in triplicate (Figure No.8). Actual drug content was calculated for all batches using the equation as follows.

$$\text{Percentage of drug content} = \frac{\text{Observed value}}{\text{Actual value}} \times 100$$

3. *In vitro* drug release studies

The release profile of an entrapped drug predicts how a delivery system might function and gives valuable insight into its *in vivo* behaviour. *In vitro* release profile for each solid dispersion as well as pure drug was performed using USP type 2 dissolution apparatus. Sample equivalent to 5 mg of cilnidipine was added to 900ml of phosphate buffer of pH 6.8 at $37\pm 0.5^{\circ}\text{C}$ and stirred at 75 rpm (Table no.3). Aliquot of 5 ml was withdrawn at time intervals of 15, 30, 45 and 60 min. The withdrawn volume was replenished with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the samples was measured at λ max 240 nm after suitable dilution if necessary, using appropriate blank. Results of *in vitro* drug release studies obtained from absorbance data were shown graphically as cumulative percentage drug released versus time.

PREPARATION OF FAST DISSOLVING FILMS

Cilnidipine (CLN) therapeutic dose was 5mg, the optimized CLN:PVP solid dispersion (1:4 ratio) with equivalent weight 60 mg of cilnidipine was dissolved in the polymeric solution, after complete dissolution of the solid dispersion, propylene glycol (plasticizer) was added and stirred to form a homogeneous solution. Finally Vanillin and Sodium saccharin are added and stirred to form a homogeneous mixture. The solution was casted in a mould 6×8 cm (length and width). Then kept in hot air oven at 60°C for 24 hours. The film thus formed was cut into size of 2×2 cm square strips. The prepared square thin film strips were stored in desiccators for further studies. The detailed compositions of the cilnidipine oral films are given in table No 4.

Evaluation of fast dissolving films

a) Physical appearance and surface texture of films:

This parameter was checked simply with visual inspection of films and evaluation of texture by feel or touch.

b) Weight uniformity of films:

Three films of the size 2×2 cm were weighed individually using digital balance and the average weights were calculated.

c) Thickness of films:

Thickness of the films was measured using screw gauge with a least count of 0.01mm at different spots of the films. The thickness was measured at three different spots of the films and average was taken.

d) Folding endurance of patches:

The flexibility of films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the films was determined by repeatedly folding a small strip of the

films (approximately 2x2 cm) at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance.

e) Drug-polymer interaction study of films:

There is always a possibility of drug-excipients interaction in any formulation due to their intimate contact. The technique employed in this study to know drug- excipients interactions is IR spectroscopy. IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. Infra-red spectra of pure drug cilnidipine and formulations were scanned by using FTIR and DSC, by a thin film method.

f) Drug content uniformity of films:

The films were tested for drug content uniformity by UV Spectrophotometric method. Films of 2×2 cm size were cut from three different places from the casted films. Each film was placed in 100 mL volumetric flask and dissolved in simulated saliva pH 6.8 and 2 mL is taken and diluted with water up to 10 mL. The absorbance of the solution was measured at λ max 240 nm using UV/ visible spectrophotometer (Shimadzu). The percentage drug content was determined.

g) In vitro drug release:

The release rate of cilnidipine fast dissolving oral films was determined by using USP dissolution testing apparatus II at 50 RPM. The film with 2×2 cm was placed in the 500 mL of 6.8 pH simulated saliva as dissolution medium, and temperature was maintained at 37°C. From this dissolution medium, 5 mL of the sample solution was withdrawn at different time intervals. The samples were filtered through Whitman filter paper and absorbance was determined 240 nm using double beam UV- Visible spectrophotometer.

h) Permeation study:

The prepared fast dissolving oral films are placed in the diffusion cell on the upper membrane of the (donor compartment) and the receptor compartment contain a simulated saliva (20 ml) it can be contact with the dialysis membrane upper side of the donor compartment contain a film attach the film of length and width (2×2) cm it contain 5 mg of drug. And the receptor compartment it contain a simulated saliva and magnetic bead and this diffusion compartment placed in the magnetic stirrer the drug permeation start through the dialysis membrane and enter in to the receptor compartment the drug to be enter in the receptor compartment and this solution taken 2 ml every 5 minutes up to 45 minutes and maintain the sink condition by replace the 2ml of simulated saliva in to the receptor compartment and this every interval taken samples analyzed by (Shimadzu) Uv-visible spectrophotometer.

i) Stability studies:

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors. To assess the drug and formulation stability, stability studies were done as per ICH guidelines. The formulated fast dissolving oral films were wrapped in aluminium foil and stored at $45 \pm 0.5^\circ\text{C}$ for period of twelve weeks. After the period of three month films were tested for appearance, drug content and in vitro drug release.

RESULTS AND DISCUSSION

Among the four formulations of solid dispersions i.e. F1, F2, F3 and F4, the optimized formulation was F4 which shows maximum drug content and percentage drug release compared to other formulations (Figure No.8 and 9). These optimized cilnidipine: Poly ethylene glycol 400 solid dispersions (CLN: PEG 400) at weight ratio of 1:4 prepared by melting method was selected for this study. It was proposed to formulate and develop the fast dissolving films of above solid dispersions to evaluate the efficacy of PEG 400 solid dispersions in the FDF formulation. The formulated FDFs were appeared to be clear, homogeneous, some are transparent and some are partially transparent. They were found be physically flexible and dry. The folding endurance was measured manually, by folding the FDF repeatedly at a point till it broke. The breaking time was considered as the end point. Folding endurance was found to be highest for FC 7 and lowest for FC 6. It was found that the folding endurance of the FDF was affected with increase of carrier concentration. The folding endurance values of the FDF were found to be optimum and therefore, the FDFs exhibited the good physical and mechanical properties. The folding endurance of films was found to be in the range of 321 to 364 (Table No.5). As all the formulations contain different amount of polymers, the thickness was gradually increased with the amount of polymers. All the film formulations were found to have thickness in the range of 0.14 to 0.23 mm and were observed within the limits.

Weight variation

The randomly selected film strips about 2×2 cm areas were cut at different places from the casted film and weight was measured. Weight of film strip units varies from 43.36 to 55.33 mg. The results indicated that selected carriers used in method of solid dispersion preparation, proportion of carrier used have reduced the variation and improved the uniformity of the distribution in casted films (Table No.5).

It was observed that in vitro dissolving/disintegration time varies from 35 to 50 sec for all the formulations (Table No.5). *In vitro* disintegration time of FDFs was affected by polymers viz. HPMC E15, PVP and PVA. This is due to polymer's high water absorption and retention capacities.

Drug content

The prepared film formulations were studied for their drug content. The drug was dispersed in the range of 84 % to 98 %. Suggesting that drug was uniformly dispersed in all films.

In vitro dissolution studies

The *in-vitro* drug release profiles of the formulations in SSF pH 6.8 show differences depending on their composition. The rate of drug release from the HPMC E15 films was significantly lower than the films containing PVP K30 along with the HPMC E15 (Figure No.10 and 11). This is due to the swelling of the high viscosity HPMC E15 upon contact with the dissolution medium, resulting in the formation of a thick matrix gel. The formulation FC6 films containing combination of HPMC E15 and PVP K30 as hydrophilic polymers shows high percentage of drug release (97.92%) within 8 minutes compared to that of films containing HPMC E15 alone and PVA along with HPMC E15 as a polymers.

Table 1: Calibration curve of cilnidipine

Sl. No	Concentration (µg/mL)	Absorbance at 240 nm
1	2	0.1823
2	4	0.2816
3	6	0.3781
4	8	0.4887
5	10	0.5879
6	12	0.6684
7	14	0.7522
8	16	0.8725

Table 2: Formulation plan of cilnidipine solid dispersions

S.No	Formulation	Drug: Polymer
1	F1	1:1
2	F2	1:2
3	F3	1:3
4	F4	1:4

Table 3: *In-vitro* drug release data of solid dispersions

Sl.no	Time (min)	% Cumulative drug release				
		Pure drug	F1 (1:1)	F2 (1:2)	F3 (1:3)	F4 (1:4)
1	15	17.13	25.20	38.78	48.64	59.35
2	30	42.8	41.67	51.67	62.65	72.57
3	45	49.9	45.38	62.35	73.24	81.26
4	60	49.89	52.48	74.23	82.34	93.64

Table 4: Formulation details of cilnidipine fast dissolving oral film

Formulation	Polymer and its composition (mg)				Plasticizer (mL)	Sodium saccharin (mg)	Vanillin (mg)	D. water (mL)
	CLN:PEG 400	HPMC E15	PVP K30	PVA				

FC 1	300	300	---	---	0.1	2	2	10
FC 2	300	400	---	---	0.1	2	2	10
FC 3	300	500	---	---	0.1	2	2	10
FC 4	300	200	100	---	0.1	2	2	10
FC 5	300	200	200	---	0.1	2	2	10
FC 6	300	300	200	---	0.1	2	2	10
FC 7	300	200	---	100	0.1	2	2	10
FC 8	300	200	---	200	0.1	2	2	10
FC 9	300	300	---	200	0.1	2	2	10

Table 5: Evaluation data for fast dissolving films

S.No	Formulation code	Weight Variation(mg)	Thickness (mm)	Folding endurance	%Drug content	Disintegration time
1	F1	48.00±1.80	0.14±0.020	344.00±1.52	85±0.24	36.0±1.15
2	F2	56.33±1.25	0.20±0.020	346.66±1.52	84±0.15	42.0±1.15
3	F3	64.33±2.36	0.27±0.062	351.00±1.03	86±0.26	46.0±1.00
4	F4	46.40±1.15	0.15±0.025	312.33±1.15	94±0.12	35.0±1.00
5	F5	54.03±1.05	0.21±0.010	320.60±1.15	96±0.17	38.6±0.57
6	F6	63.36±1.48	0.25±0.017	353.00±1.52	98±0.22	49.3±1.15
7	F7	43.20±0.81	0.18±0.015	310.66±1.15	91±0.18	35.0±1.00
8	F8	58.06±1.05	0.21±0.016	317.66±2.51	90±0.34	48.6±1.15
9	F9	65.00±1.80	0.23±0.015	321.66±2.31	91±0.25	50.6±1.15

Table.6: *In-vitro* release data of various cilnidipine fast dissolving oral films

Time (min)	% Cumulative drug release				
	F1	F2	F3	F4	F5
2	22.00±0.02	40.00±0.25	50.00±0.16	54.00±0.24	52.00±0.14
4	22.22±0.12	40.40±0.27	50.50±0.28	60.54±0.23	64.52±0.16
6	23.44±0.13	60.8±0.15	61.00±0.18	66.14±0.21	82.16±0.25
8	39.67±0.25	71.40±0.21	76.60±0.14	71.79±0.16	91.97±0.24
10	61.06±0.17	77.10±0.19	83.35±0.21	78.49±0.22	95.87±0.14
12	61.66±0.19	77.85±0.26	85.66±0.16	85.25±0.19	-
14	71.26±0.14	83.60±0.22	-	88.07±0.24	-
16	72.95±0.23	-	-	93.91±0.11	-
18	83.65±0.25	-	-	-	-
20	-	-	-	-	-

Time (min)	% Cumulative drug release			
	F6	F7	F8	F9
2	42.00±0.24	40.92±0.11	40.48±0.17	41.80±0.15
4	65.42±0.22	48.77±0.23	50.96±0.14	50.98±0.21
6	86.07±0.12	55.81±0.15	55.82±0.26	58.04±0.15
8	97.92±0.18	62.47±0.13	62.92±0.24	65.16±0.23
10	-	68.74±0.14	70.08±0.19	74.54±0.22
12	-	78.15±0.19	75.10±0.23	81.80±0.25
14	-	87.64±0.23	83.24±0.24	84.72±0.16
16	-	89.29±0.22	88.37±0.23	86.78±0.18
18	-	-	-	89.29±0.17
20	-	-	-	-

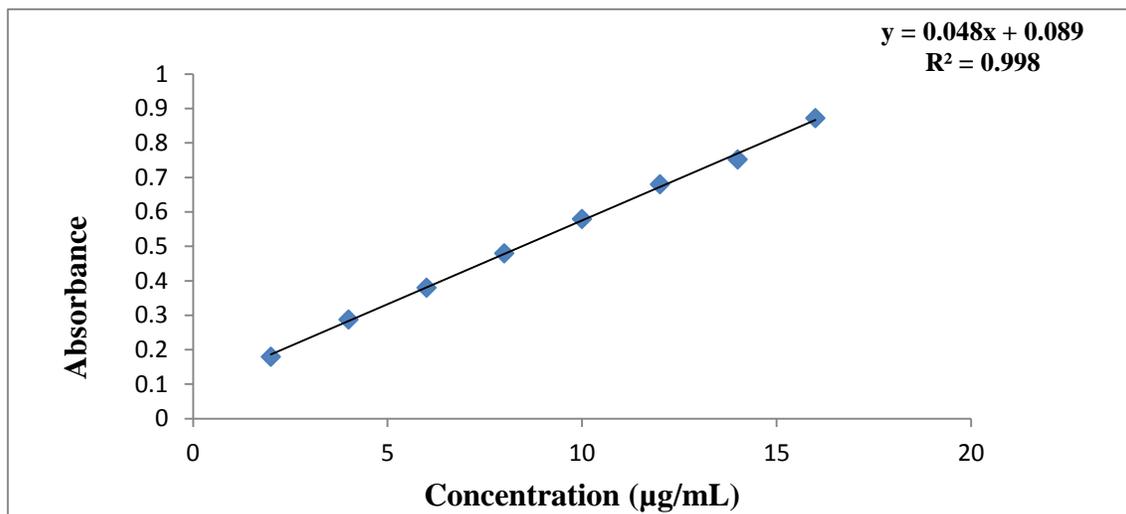


Figure 1: Standard plot of cilnidipine in simulated saliva

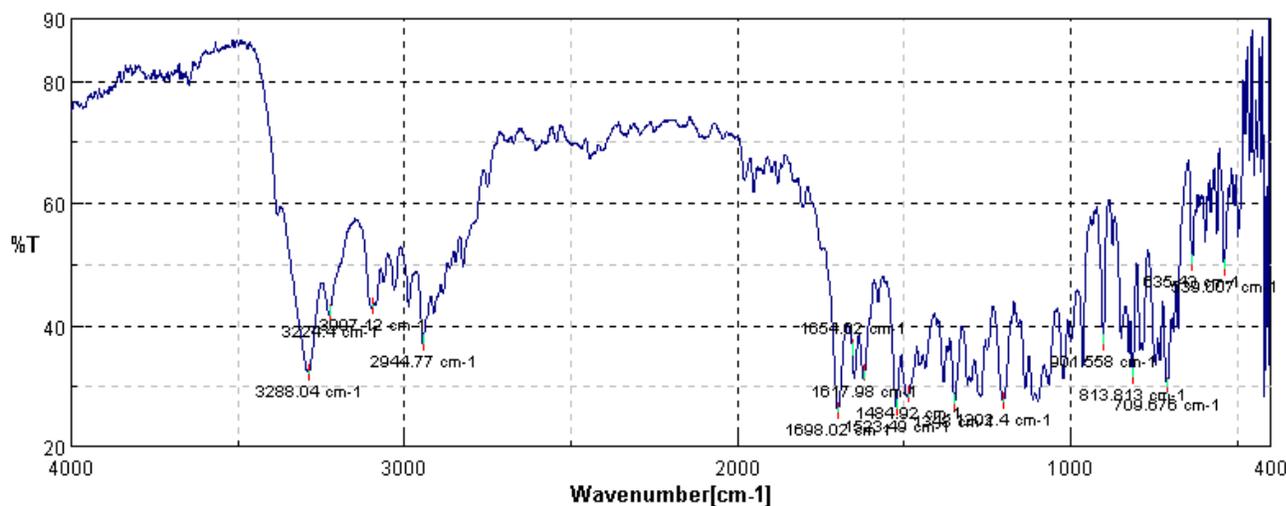


Figure 2: FTIR Spectrum of pure drug (Cilnidipine)

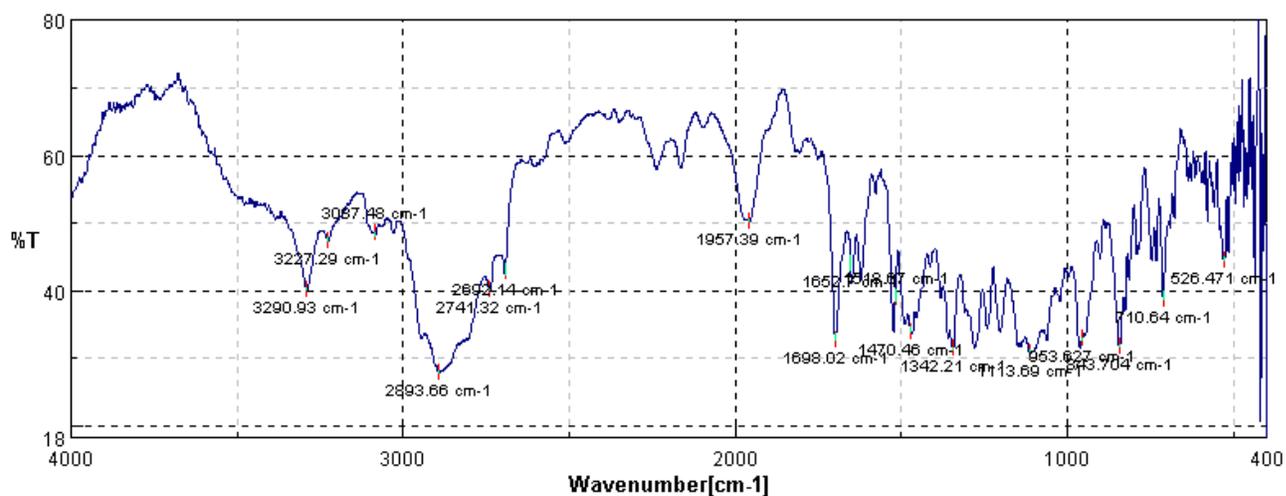


Figure 3: FTIR Spectrum of Cilnidipine + PEG 400

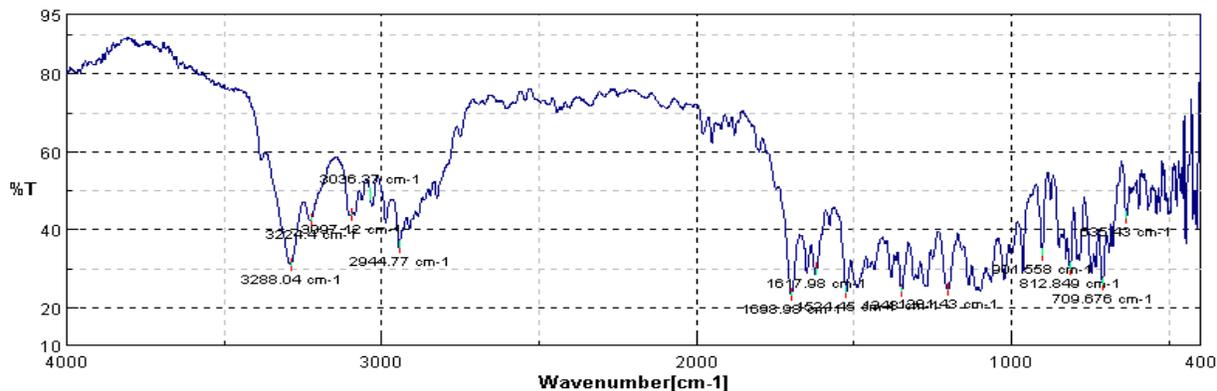


Figure : 4: FTIR Spectrum of Cilnidipine + HPMC

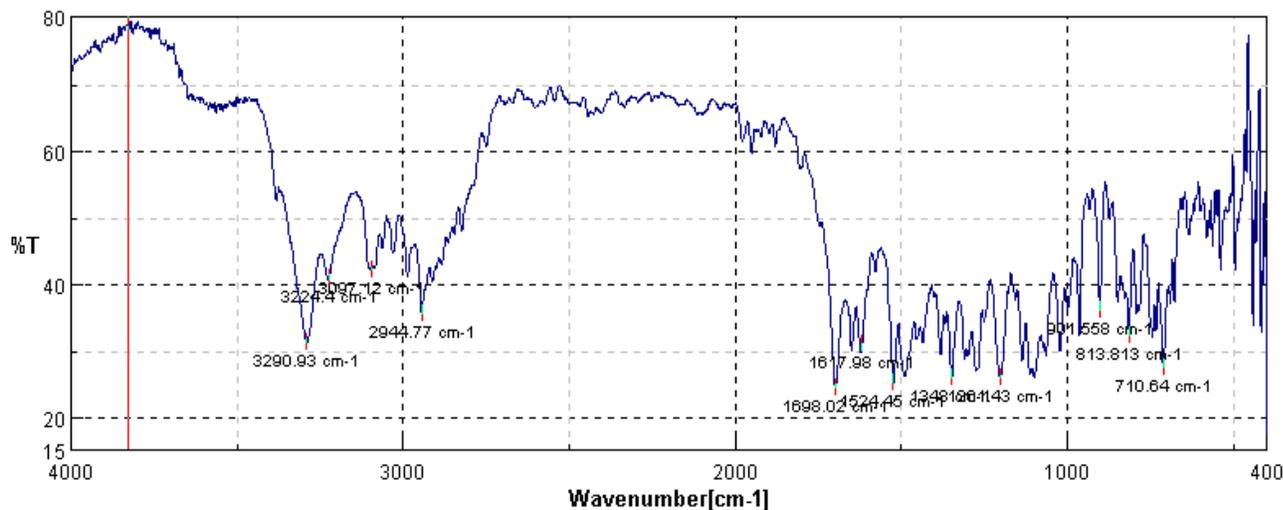


Figure 5: FTIR Spectrum of Cilnidipine + PVP

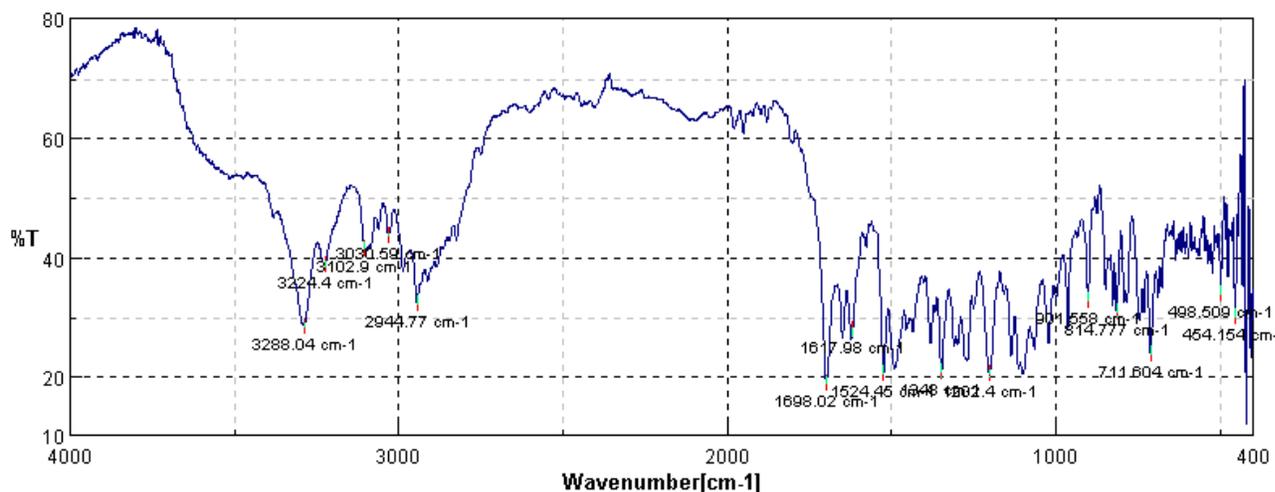


Figure 6: FTIR Spectrum of Cilnidipine + HPMC + PVP (FC6)

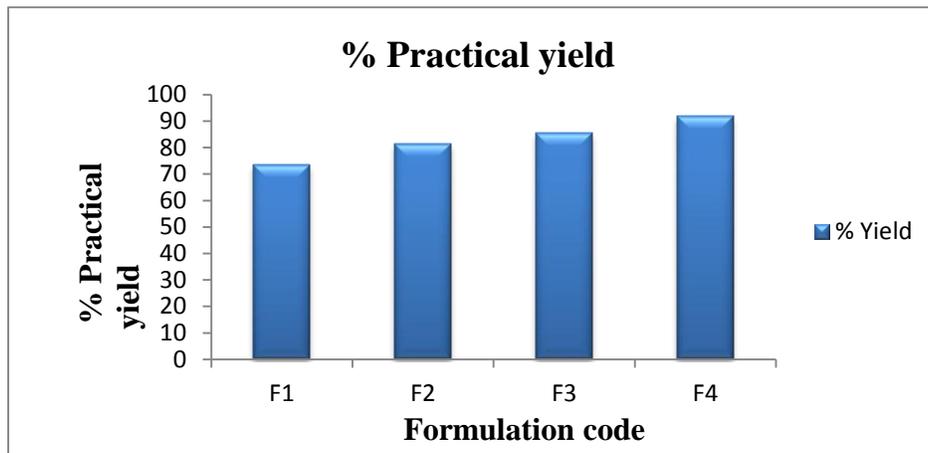


Figure 7: % Practical yield of solid dispersions

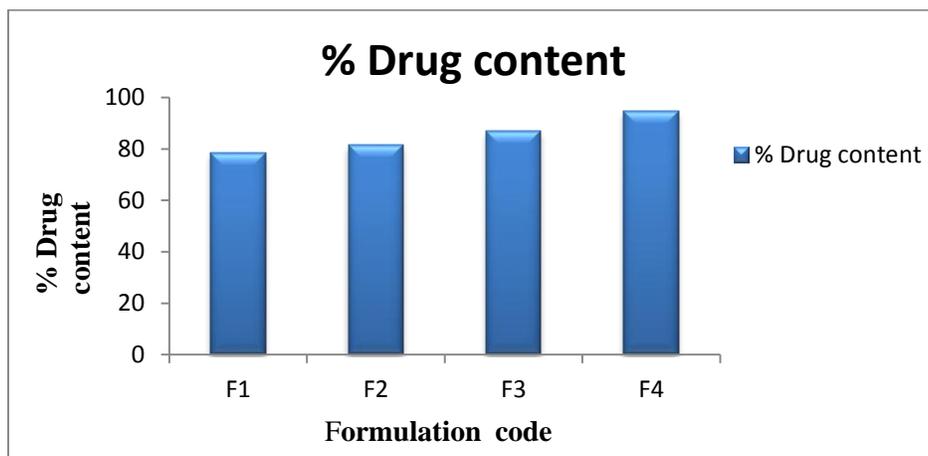


Figure 8: % Drug content of solid dispersions

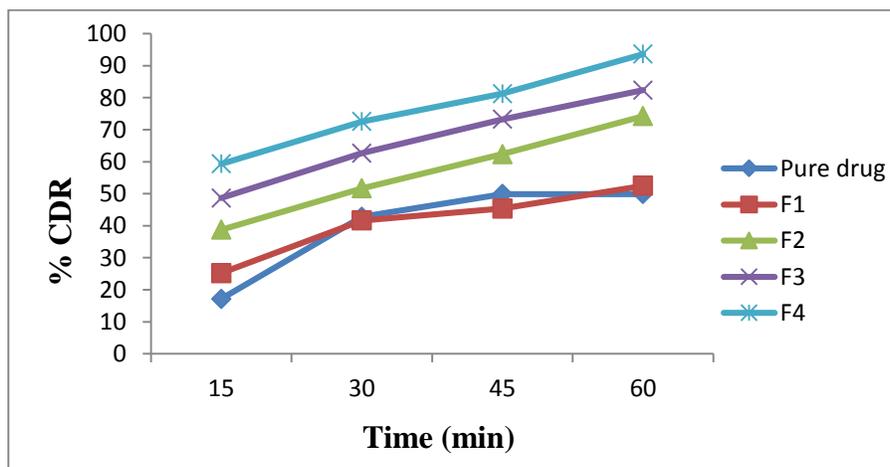


Figure 9: *In-vitro* drug release profile of solid dispersions of cilnidipine

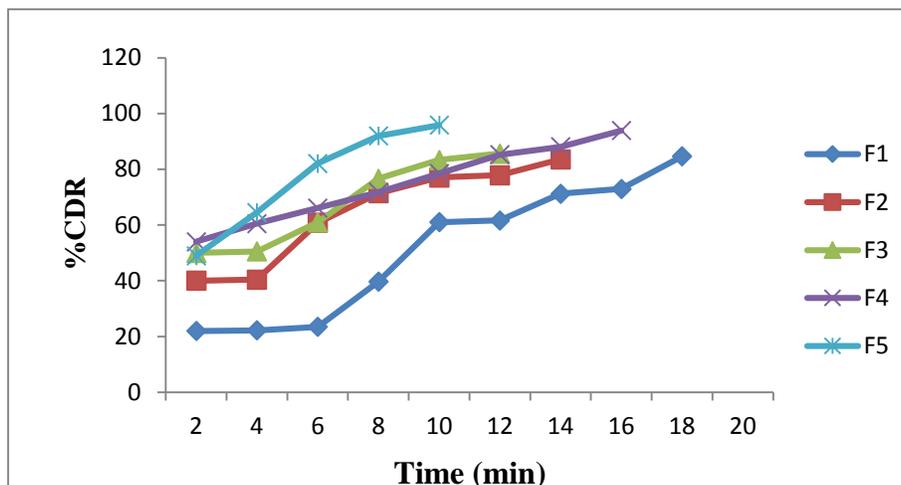


Figure 10: *In vitro* drug release profile of formulations F1-F5

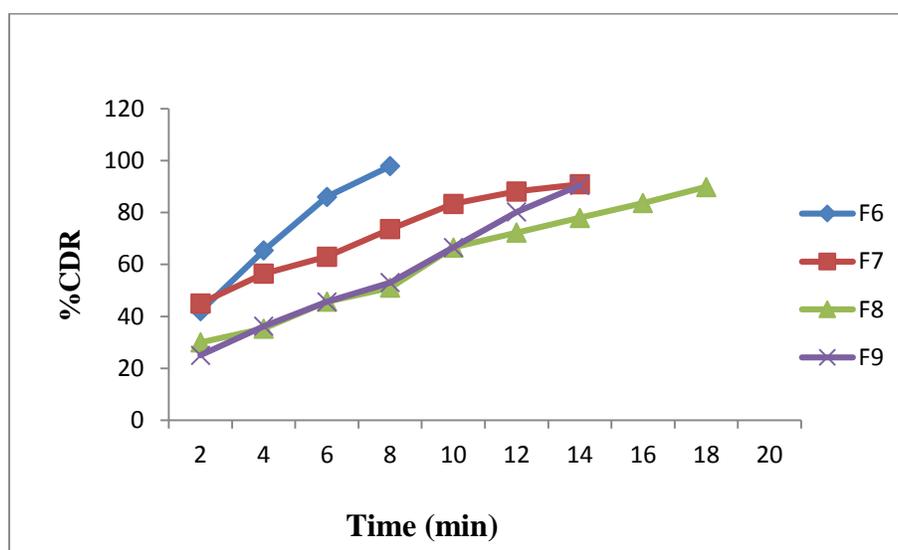


Figure 11: *In vitro* drug release profile of formulations F6-F9

CONCLUSION

Fast dissolving oral films or melt in mouth films constitute an innovative dosage form and are having great importance during the emergency cases such as hypertension, allergic reactions and asthmatic attacks whenever immediate onset of action was desired. In the present study, cilnidipine solubility was enhanced by the solid dispersion technique using carrier like PEG 400 and the optimized F4 formulation was incorporated in to the fast dissolving film. Among all the formulations cilnidipine oral fast dissolving films containing combination of HPMC and PVP K30 as hydrophilic polymers shows high percentage of drug release within 8 minutes compared to that of films containing HPMC alone as a polymer, combination of HPMC E15 and PVA. Present study reveals that fast dissolving films can be a potential novel drug delivery system for geriatric, pediatric and also for general population.

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REFERENCES

1. Bhupender B, Sarita J, Manideep K. Orally Fast Dissolving Films Innovation in Formulation and Technology, International Journal of Pharmaceutical Science Review and Research,9(2), 2011, 50-57.
2. Kunte S, Tan dale P, Fast dissolving strips a novel approach for the delivery of verapamil, J.Pharm Bioallied Sci, 2(4), 2010, 325-328.
3. Yamashita K. Establishment of new preparation method for solid dispersion formulation of Tacrolimus. Int J Pharm 2003;267:79-91.
4. Kaza R, Yalaravathi PR, Ravoru N. Design and Characterization of Fast Dissolving Films of Valsartan. Turk J Pharm Sci 2014; 11(2):175-84.
5. Debjit B, Jaykar B, Sampathkumar K. Design and Characterization of Fast Dissolving Tablet of Telmisartan, International Journal of Pharma Recent Research, 1(1), 2012, 31-40.

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