RESEARCH ARTICAL

Design Development and Characterization of Nicardipine Solid Lipid Nano-Particulars

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ABSTRACT

The present work was designed and characterized nicardipine solid lipid nano-particulars and formulated into capsule. The formulation was evaluated and stability also as per the specified limits. The nanoparticles were prepared by solid hydrophilic adsorbents. The obtained ratio of 1:1:1:2 of drugs, soy PC, DMPC, and labrasol shows the highest dissolved in water. The liquid form was converted into a solid product using an adsorbent like anhydrous lactose and aerosil 200. The above results indicated aerosil 200 containing which helped in enhanced dissolve state in water. The results indicated the formulation trial-6 %drug content -100.2, entrapment efficiency 84.13 ± 1.64, zeta potential measurement 0.789 ± 0.32, Drug release rate at 3rd hour 81.6% and relative bioavailability of optimized nanoparticle formulation (CNF-6) was significantly increased. As a result, the produced lipid-based formulation shown potential as a method for improving the transfer of lipophilic chemicals that are weakly water-soluble to the aqueous phase, hence improving oral bioavailability.

Keywords: Nicardipine, Soy PC, DMPC, Aerosil 200, Propylene Glycol, Tween-80.

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INTRODUCTION

The most common method of administration is still oral medication. Because it is convenient and avoids intravenous problems such catheter infection and thrombosis as well as hinders a good therapeutic outcome, oral administration does indeed improve patients' quality of life. Particularly, issues with low gastrointestinal solubility and chemical stability frequently lead to the less therapeutic effect.

Lipid-based Drug Delivery (LBDD)

offers a new approach to drug development can result in significant cost and time savings when it comes to getting a medicine to market.[1,2]

It is possible to physical mixes and liquids can produced (be included into capsules directly, or changed into as well as tablet form), depending on the excipient[3,4] (s) chosen and formulation methods. Evidence from the literature suggests that lipid-based effective in increasing the availability of compounds that are low-soluble.[5]

Super-saturating the GI tract's aqueous environment produces oil droplets with a large surface area and increased.

- Expanding membrane letting the tight connection open to let paracellular movement.
- A Solution of solid state is produced inside the carrier after particle size reduction to molecular size.

Advantages

- Increase the bioavailability of medications with limited water solubility or low membrane penetration capability by facilitating gastric absorption.
- Enhancement or modification of medication absorption and release,
- Preventing sensitive active compounds from deteriorating in the digestive system.
- Masking the unpleasant taste of medications taken orally.

However, these formulations have several drawbacks, such as component and/or excipient stability when the product is held at a lower temperature.

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Fate of Phospholipids[6,7]

One of the lipid systems with a unique amphiphilic quality is phospholipids. Depending on their unique qualities, they build a variety of formations in water. The hydrophobic tails are lined up against one another and the hydrophilic water-soluble medicines are arranged in lipid bilayers or micelles most of the time. Therefore, it must be remembered that the increased solubility of lipophilic medications from lipid-based systems would result from the It intraluminal processing before it is absorbed, rather than directly from the supplied lipid.

The co-lipases and lipases typically. About 25% of acyl chains are hydrolyzed by gastric lipases, preventing the GI system from degrading active components. Soybean/egg phosphatidylcholine, synthetic lecithin/ phosphatidylcholine, or hydrogenated phosphatidylcholine are only a few examples of phospholipids that might be employed in oral medication administration.[8-10]

MATERIALS AND METHODS

The nicardipine was free sample from Manus Aktteva Biopharma LLP. All the ingredients are as per Ip specifications.

Metholodogy[11]

Phase solubility studies of nicardipine

- *Solubility studies[12,13]*

The solubility studies for the drug were carried out using the rotary shaking method in the different solvents like purified water and different pH systems. These studies of excess drug till samples were filtered and required dilutions were made to the sample and was analyzed. The solubility was calculated using the formulas:

Q = Percent of drug dissolved (% w/v)
A =Standard Area
B = Test Area
C = Standard concentration (µg/mL)
Wt. = Total weight of drug added
V_1 = volume of test sample taken for dilution
V_2 = diluted volume of test sample
V_3 = volume of diluted sample (V_2) taken for dilution
V_4 = diluted volume of sample (V_3)
m = Amount/quantity (mg) of drug dissolved
S = Solubility (mg/mL)

- *HPLC analysis[14]*

The estimation of nicardipine done by HPLC method. The details of the method were given below.

- *Preparation of mobile phase*

The mobile liquid contains 64% 50 mM phosphate buffer that had been pH-modified to 3.0 using o-phosphoric acid and 36% acetonitrile. Every day, the mobile phase was produced, sonicated under decreased pressure to remove gas, and then filtered before use. In 2 liters of filtered water were treated with 13.6 g of monobasic potassium phosphate before the pH brought to 3.0 by adding diluted o-phosphoric acid. About 720 mL of acetonitrile were mixed with 1280 mL of this buffer. The aforementioned solution is sonicated for 30 minutes to degas it, after which it is filtered.

- *Preparation of standard solution (0.01 mg/mL):*

About 100 mL of a volumetric flask were filled to capacity with methanol after adding 50 mg of pure nicardipine API. Using mobile phase, the aforementioned solution was diluted to 50 mL and placed in an ultrasonic bath for 1-mL to produce a 10 ppm (0.01 mg/mL) solution. The necessary chromatographic conditions are listed in Table 10. Acetonitrile and filtered water were combined in the ratios of 90:10 and 10:90, respectively, to create two washing solvents.

- *Formulation development of nicardipine lipid-based nanoparticles[15,16]*

The TRIAL batch was formulated by using solid hydrophilic adsorbents. The drug was dissolved in the previously heated (at 60°C temperature) PEG. After that phospholips were dissolved in the drug solvent mixture consisting of soy PC, DMPC and Labrasol (1:1:1:2). Both the mixtures were mixed by using RMG and impeller mixer for 10 minutes at 100 rpm, then after in chopper mixer for 2 minutes at 500 rpm. The primary liquid lipid intermediate was obtained. The above liquid lipid formulation was converted into a solid product using an adsorbent. Two adsorbents were screened for the dissolution enhancement of the drug. Both anhydrous lactose and aerosil 200 used were of hydrophilic nature. The filtered solution was diluted and estimated using HPLC in 287 nm. Nanoparticles produced by the formulation had maximum EE and minimal particle size in the ratios of 1:1:1:2. The capsules are loaded with lipid-based nano nicardipine particles as shown in Figure 1 and Table 1.

Characterization of Nanoparticles

Particle size determination[17]

The particles were examined, the surface type revealed the crystalline structures of pure nicardipine. The sample nanoparticles were covered with adsorbent and had a spherical shape. It was discovered that the drug particles were completely entrapped within the lipid vesicles.

Solubility studies[18]

The enhanced drug's solubility, few other excipients like solvent, surfactant and co-surfactants were investigated, which were selected initially based on the drug's saturation solubility in the liquid excipient and temperature. If clear solution was observed, then again drug was added and the process was repeated. The point at which saturation was observed, addition of drug was stopped and the solubility. The solubility was analyzed using HPLC at 287 nm.

Total drug content (TDC)[19]

Of about 1-g of nicardipine nanoparticles were dissolved and pH-maintained with o-phosphoric acid and determined an amount of drug in the sample. The 720 mL of acetonitrile were mixed with 1280 mL of this buffer. The aforementioned solution is sonicated for 30 minutes to degas it; after which it is filtered.

Table: 1 Compiled formulation chart for nicardipine lipid based formulations[16]

Formulation No.		*Trial-1*	*TRIAL- 2*	*TRIAL- 3*	*TRIAL- 4*	*TRIAL- 5*	*TRIAL- 6*	*TRIAL- 7*	*TRIAL- 8*
Weights (mg)	Drug	60	60	60	60	60	60	60	60
	Soy PC	60	60	60	60	60	60	60	60
	DMPC	60	60	60	60	60	60	60	60
	Labrasol®	120	120	120	120	120	120	60	60
	Propylene glycol	-	-	-	500	-	350	150	150
	Tween-80	-	-	-	-	150	150	90	90
	Lactose	-	180	-	-	-	-	-	-
	Aerosil® 200	-	-	60	180	180	180	120	-
	Total wt.	300	480	360	980	630	980	600	480

** All the quantities are in mg only

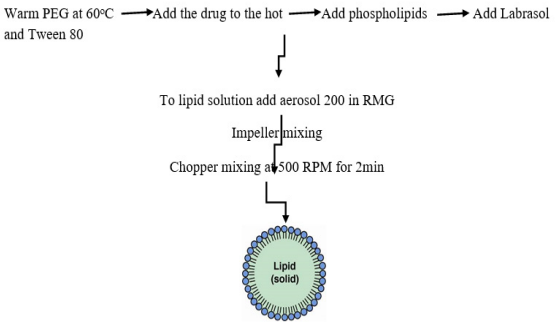

Figure 1: Flowchart for manufacturing of solid lipid-based Formulation[15]

Each individual nicardipine TRIAL- was examined using a photodiode array detector, and the absorption wavelength was found to be at 287 nm. Three duplicates of each experiment were carried out. As a control, a placebo formulation that was handled similarly to the sample was employed.

Drug Entrapment study[19]

The DE was calculated by measuring the drug present in the trial batches after centrifugation of about 30 minutes at 0°C at a high speed of 16000 rpm using Remi cooling centrifuge.

$$EE\% = \frac{\text{Actual drug loade}}{\text{Theoretical drug loading}} X100$$

Dissolution studies of nicardipine nanoparticles[20]

The dialysis bag model was used for in-vitro dissolving study of about 60 minutes. Nicardipine nanoparticles equivalent to 60 mg pure medication (Nicardipine) were employed in dissolving at 37 ± 0.5°C with 0.001 N HCl. The predetermined intervals aliquots of 5 mL were removed and maintained the sink condition., The samples were analysed using UV-spectrophotometer at 287 nm. Dissolution data was used to determine DE30%, T50, T90, and k-1 values.

Zeta potential measurement[21]

The Malvern Zetasizer ver. 6.12 was used to calculate the zeta value of the sample. The preparation was diluted with KCl (0.1 mM) and analysed.

Table 2: Weight variation limits as per USP[24]

Avg weight capsules	*Deviation(%)*	*Number of capsules*
Less than 300mg	± 10.0	Min 18 Max 20
More than 300mg	± 7.5	Min 18 Max 20

Table 3: Data for the nanoparticles size

Formulation No.	*Nanoparticles size values ± SD*
TRIAL- – 1	97.05 ± 0.49
TRIAL- – 2	94 ± 0.62
TRIAL- – 3	96 ± 0.78
TRIAL- – 4	93 ± 1.28
TRIAL- – 5	119 ± 0.41
TRIAL- – 6	90.56 ± 0.56
TRIAL- – 7	134 ± 0.67
TRIAL- – 8	128 ± 0.89

Scanning electron microscopy (SEM)[22]

The technique was used to study the crystalline structures of pure nicardipine. The adsorbent in the test sample of formulation was adsorbed. The presence of crystalline drug particle forms in the granulated formulation indicated that the particles were totally entrapped within the lipid vesicles.

Evaluation of Micromeritic Properties of the Granules

The various powdered derived properties were evaluated.

Evaluation of nanoparticles capsules

Various evaluation studies for capsules, were done. Those are weight variation, disintegrating time, and drug content (%) were performed.

Weight deviation test[23,24]

The %weight deviation was carried individually to each 20 capsule separately and calculated the variation in the weight as shown in Table 2.

Disintegration time[25]

The capsules disintegration time was estimated using the IP protocol.

Drug content

The powdered sample was transferred into a volumetric flask of 100 mL. First, 5 mL of 0.001 N HCl mixed and agitated about ten minutes. The volume increased to 100 mL using de mineralized water and determined at 287 nm.

Dissolution studies[26-28]

Nicardipine nanoparticles capsule *in-vitro* dissolving tests were carried out in 0.001 N HCl. The paddles were permitted to revolve at a pace of 100 revolutions per minute. The dissolving medium was held at 37+0.5 0C and samples were removed at 5 minutes. By maintain the constant sink conditions. The samples were analysed by HPLC at 287 nm.

Stability study[29]

The stability guidelines for the preparation Q1A(R2) were followed.

Table 4: Phase solubility study of nicardipine (Pure drug)

Solvent	*Volume (mL)*	*Pure drug at 25°C (mg/mL)*
pH-1.2 (0.1 N HCl)	20	0.092
pH-2.1(0.01 N HCl)	20	0.148
pH-3.0 (0.001 N HCl)	20	0.414
pH-4.5 (Acetate buffer)	20	0.179
pH-5.0 (phthalate buffer)	20	0.053
pH-6.8 (Phosphate buffer)	20	0.022
pH-7.4 (Phosphate buffer)	20	0.017
pH-8.0 (Phosphate buffer)	20	0.0089
Distilled water	20	0.229

Table 5: Solubility data for the effect of phospholipids on drug's solubility

Solvent	*Amount of drug (mg/mL)*	
	At 25°C	*At 37°C*
Cholesterol	0.0046	0.5451
Soy PC	0.2608	0.6270
EPC	0.0172	0.5157
DMPC	0.2914	0.6123
DPPG	0.1836	0.1012

RESULTS

Particle Size Determination

As shown in Table 3 and Figure 2

Phase Solubility Study

As shown in Table 4 and Figure 3, hence, it can be stated that nicardipine is poorly water-soluble drug. Solubility data showed that at low pH, solubility was less and with increasing pH, solubility increased up to 3.0 and again solubility 001 N HCl (pH-3.0) and least solubility in pH-8.0 buffer.

Screening of Phospholipids

Effect of phospholipids on drug's solubility:

As shown in Table 5, based on the above results, it can be considered that the phospholipids have the ability of enhancing the solubility of nicardipine. This might be due to the amphiphilic nature and bio compatibility of the phospholipids.

Effect of phospholipid on solubility:

As shown in Tables 6 and 7, the results showed an increase in the solubility with increasing concentrations of phospholipids. Hence, considering optimum quantities of phospholipids, the ratio comprising 1:1:1 of drug, Soy PC, DMPC respectively was selected and this ratio was extended further for formula development.

Table 6: Solubility studies for the effect of phospholipids concentrate ion on drug's solubility

S. No.	*Drug: Phospholipids*	*Drug: Soy PC: DMPC*	*Drug (mg)*	*Soy PC (mg)*	*DMPC (mg)*	*Volume (mL)*
1	1: 0.5	1: 0.25: 0.25	30	7.5	7.5	10
2	1: 1	1: 0.5: 0.5	30	15	15	10
3	1: 2	1: 1: 1	30	30	30	10
4	1: 4	1: 2: 2	30	60	60	10

Table 7: Solubility data for the effect of phospholipids concentration on drug's solubility

S.No.	*Drug:Phospholipids*	*Solubility (mg/mL)*
1	1: 0.5	0.6341
2	1: 1	0.7283
3	1: 2	0.9561
4	1: 4	1.1333

Table 8: Solubility data for the effect of excipients on drug's solubility

S.No.	*Drug (mg)*	*Soy PC (mg)*	*DMPC (mg)*	*Labrasol® (mg)*	*Ethanol (mg)*	*Tween-80 (mg)*	*Solubility (mg/mL)*
1	30	30	30	30	-	-	0.9950
2	30	30	30	60	-	-	1.1540
3	30	30	30	30	30	-	1.0054
4	30	30	30	30	60	-	0.8311
5	30	30	30	-	-	15	0.9953

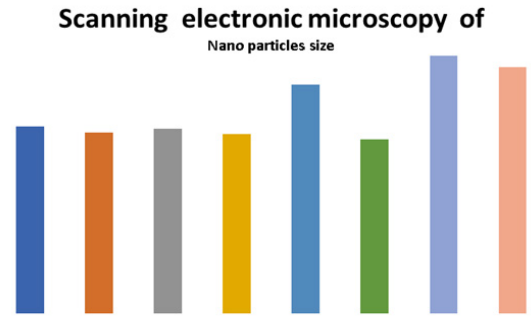

Figure 2: Scanning electronic microscopy of nanoparticles.

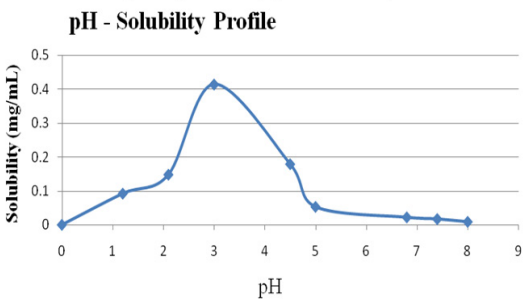

Figure 3: pH-Solubility profile of nicardipine

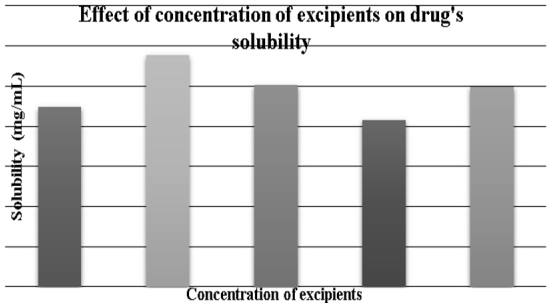

Figure 4: Effect of excipients concentration on drug's solubility

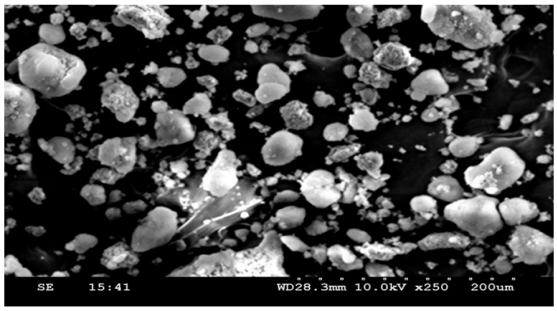

Figure 5: SEM image of granulated lipid formulation

Table 9: Data for the total drug content of the granules

Batch. No	*Drug Content (%)*
TRIAL- 1	97.1
TRIAL- 2	99.0
TRIAL- 3	98.7
TRIAL- 4	95.5
TRIAL- 5	98.8
TRIAL- 6	100.2
TRIAL- 7	99.9
TRIAL- 8	98.7

Table: 10 Data for the entrapment efficiency of the granules

Batch. No	*Entrapment efficiency (mg) ± SD*
TRIAL- 1	73.16 ± 1.54
TRIAL- 2	81.07 ± 0.83
TRIAL- 3	80.10 ± 1.58
TRIAL- 4	95.06. ± 1.14
TRIAL- 5	82.19 ± 2.0
TRIAL- 6	84.13 ± 1.64
TRIAL- 7	63.34 ± 1.87
TRIAL- 8	78.34 ± 1.68

Table 11: Compiled dissolution data of nicardipine lipid based formulations

Batch. No	*Cumulative %drug dissolved*					
	15 min	*30 minutes*	*45 minutes*	*60 minutes*	*2 hours*	*3 hours*
CARDENE 20 mg	7.7	13.4	17.7	24.3	30.6	33
API 60 mg	0.6	1.9	4.7	6.7	11	14.5
TRIAL-1	0.6	4.8	6.1	7.6	13.6	14.3
TRIAL-2	2.1	6.1	13.6	13.8	22.4	23.1
TRIAL-3	3.8	7.8	14	15.9	18.9	26.1
TRIAL-4	3.4	19.4	24.5	28.1	31.8	31
TRIAL-5	14.1	21.6	31.7	25.5	38.7	44.7
TRIAL-6	16.6	29.9	47.2	62	83	81.6
TRIAL-7	25.4	48.5	52.7	54.4	56.3	57.6
TRIAL-8	21	32.1	41.8	44.8	49.4	52.9

Solubility data for the effect of excipients on drug's solubility:

As shown in Table 8 Figure 4, the results showed enhanced solubility results with every excipient compared to the Labrasol and Tween 80.) Showed a greater solubility enhancement, for further studies in formulation

Total drug content (TDC)

As shown in Table 9

Entrapment efficiency.

As shown in Table 10

Dissolution studies of nicardipine nanoparticles

As shown in Table 11

Zeta potential measurement.

As shown in Table 12

SEM study.

As shown in Figure 5

Evaluation of micromeritic properties of the granules:

As shown in Table 13, from the data, the flow property exhibited convincing results. Hence, the granulated lipid formulations had good flow properties.

Evaluation of nicardipine nano-capsules:

As shown in Table 14

Table 12: Data for the zeta potential nanoparticles

Batch. No	*Zeta potential values ± SD*
TRIAL-1	0.652 ± 0.24
TRIAL- 2	0.714 ± 0.83
TRIAL- 3	0.619 ± 0.58
TRIAL- 4	0.653. ± 0.14
TRIAL- 5	0.698 ± 0.023
TRIAL- 6	0.789 ± 0.32
TRIAL- 7	0.563 ± 0.87
TRIAL- 8	0.543 ± 0.68

Table 13: Micromeritic properties of the granules

Batch. No	*Angle of repose (θ)*	*Bulk density (g/mL)*	*Tapped density (g/mL)*	*Compres sibility index (%)*	*Hausner's ratio*
TRIAL- 1	-	-	-	-	-
TRIAL- 2	25.1	0.454	0.555	18.19	1.22
TRIAL- 3	23.4	0.416	0.500	16.80	1.20
TRIAL- 4	34.7	0.405	0.555	27.02	1.37
TRIAL- 5	25.6	0.365	0.454	19.60	1.24
TRIAL- 6	30.8	0.384	0.500	23.20	1.30
TRIAL- 7	22.2	0.394	0.468	15.81	1.18
TRIAL- 8	12.4	0.412	0.567	12.18	1.11

Dissolution

As shown in Table 15 and Figure 6

Stability study:

As shown in Tables 16, 17 and Figure 7 The above results indicated the intermediate stability of the formulation. As the storage time period increased, there was a slight decrease in the release of decrease of around 4% at 25°C/60% RH and 6% at

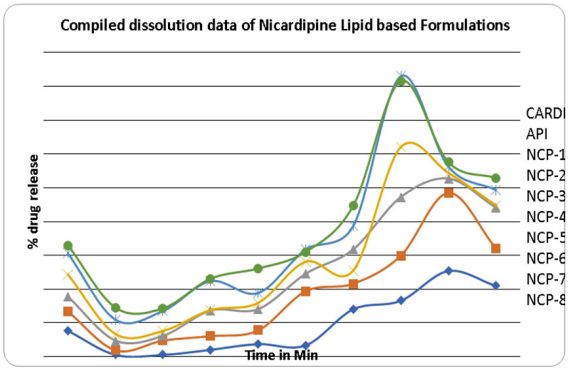

Figure 6: Effect of excipients concentration on drug's solubility

Table 14: Data for the evaluation of the capsule dosage form

Batch. No	*Weight variation (mg) ± SD*	*Disintegration Time*	*Drug Content (%)*
TRIAL- 1	150 ± 1.54	7 min 55 sec	97.1
TRIAL- 2	330 ± 0.83	8 min 33 sec	99.0
TRIAL- 3	180 ± 1.58	7 min 50 sec	98.7
TRIAL- 4	950 ± 1.14	8 min 40 sec	95.5
TRIAL- 5	860 ± 2.0	8 min 35 sec	98.8
TRIAL- 6	1040 ± 1.64	9 min 05 sec	100.2
TRIAL- 7	630 ± 1.87	8 min 30 sec	99.9
TRIAL- 8	510 ± 1.68	8 min 15 sec	98.7
CARDENE	245 ± 1.12	3 min 40 sec	98.3

Table 15: Compiled dissolution data of Nicardipine Lipid based Formulations

Batch. No	*Cumulative % Drug Dissolved*					
	15 min	*30 min*	*45 min*	*60 min*	*2 hr*	*3 hr*
CARDENE 20 mg	7.7	13.4	17.7	24.3	30.6	33
API 60 mg	0.6	1.9	4.7	6.7	11	14.5
TRIAL- 1	0.6	4.8	6.1	7.6	13.6	14.3
TRIAL- 2	2.1	6.1	13.6	13.8	22.4	23.1
TRIAL- 3	3.8	7.8	14	15.9	18.9	26.1
TRIAL- 4	3.4	19.4	24.5	28.1	31.8	31
TRIAL- 5	14.1	21.6	31.7	25.5	38.7	44.7
TRIAL- 6	16.6	29.9	47.2	62	83	81.6
TRIAL- 7	25.4	48.5	52.7	54.4	56.3	57.6
TRIAL- 8	21	32.1	41.8	44.8	49.4	52.9

Table 16: Stability results for CARDENE

Parameter	*25° C / 60 % RH*					*40° C / 75 % RH*			
	Initial	*15 days*	*30 days*	*45 days*	*60 days*	*15 days*	*30 days*	*45 days*	*60 days*
% Drug Content	101.5	101.1	101	99	100	101.5	98.9	99.5	99.23
15 min	79	81.84	83.79	83.05	81.34	86.47	83.55	81.34	85.26
30 min	87.4	90.40	89.94	87.01	90.18	91.65	89.20	86.02	88.72
45 min	90.1	91.94	92.67	93.64	94.14	93.90	92.91	90.48	93.17
60 min	97.6	98.83	96.88	95.90	97.12	96.39	95.17	95.16	95.90
Recovery	100.6	100.85	100.85	97.90	99.14	101.45	98.15	95.59	97.67

Table 17: Stability results for Nicardipine Lipid based formulation

Parameter	*25° C / 60 % RH*					*40° C / 75 % RH*			
	Initial	*15 days*	*30 days*	*45 days*	*60 days*	*15 days*	*30 days*	*45 days*	*60 days*
% Drug Content	101.0	101.2	100.5	99.78	99.19	102.0	99.87	98.9	98.7
15 min	76.8	72.70	81.17	75.25	76.10	74.68	78.07	76.95	70.18
30 min	83.9	84.88	83.76	81.78	83.75	79.51	82.61	81.40	81.78
45 min	93.7	90.84	90.85	88.30	87.18	89.99	90.57	90.0	89.72
60 min	99.0	99.06	97.09	95.69	94.56	97.94	95.12	95.12	92.29
Recovery	100.4	102.06	99.69	97.10	96.59	101.94	97.42	96.87	93.20

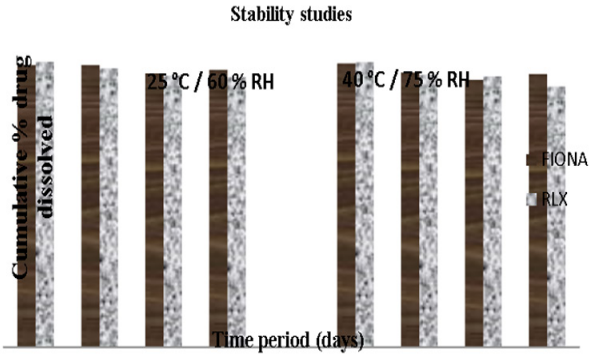

Figure 7: Comparative stability data

40°C/75% RH in the dissolution rate of the drug was observed in the formulation. While the marketed formulation showed good results at both temperature conditions.

The mass upon storage for extended periods. However, with polyvinyl alcohols potentially increased the stability of the formulation for longer period of time.[30,31]

CONCLUSION

Initially, solubility experiments spanning pH and water revealed that nicardipine was most soluble at pH-3.0 (0.001 N HCl). Nicardipine lipid in water. As a result of these findings, Soy PC, DMPC, and Labrasol® were chosen as lipid components. The produced formulations were assessed in a discriminating dissolving medium for the dissolution profile using the methods described above. In addition, the optimised formulation was tested by comparing it to the API and the commercial product (CARDENE). According to the evidence from *in-vitro* dissolution and solid-state characterisation, the carrier has a considerable influence on dissolving properties. As a result, the developed formulation showed a promising model for nano-capsule.

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