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Research Article

Development And Optimization of Candesartan Cilexetil Loaded Nanostructured Lipid Carriers Based Intranasal in Situ Gel for Targeted Brain Delivery in Alzheimer's Disease

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ABSTRACT

The present study was aimed at developing and optimizing Candesartan Cilexetil (CND) loaded Nanostructured Lipid Carriers (NLCs) incorporated into an intranasal in situ gel system for targeted brain delivery in Alzheimer's disease [1, 2, 3]. Candesartan Cilexetil-loaded Nanostructured Lipid Carriers (NLCs) were prepared using suitable combinations of solid lipid, liquid lipid, and surfactant, and the formulation variables were optimized using a Box-Behnken experimental design approach to achieve the desired particle size, entrapment efficiency, and stability characteristics [4]. "The optimized formulation was characterized for particle size, polydispersity index, entrapment efficiency, drug loading, zeta potential, differential scanning calorimetry, scanning electron microscopy, and in vitro drug release behavior using established characterization techniques for nanostructured lipid carriers." [5, 6]. The optimized NLC formulation was further incorporated into an in situ gelling system to improve nasal residence time and brain targeting efficiency. The developed formulation demonstrated suitable particle size, high entrapment efficiency, satisfactory drug loading, controlled drug release, and good mucoadhesive properties [7, 8]. The results suggest that the developed intranasal NLC-based in situ gel formulation may represent a promising approach for targeted brain delivery of Candesartan Cilexetil in Alzheimer's disease by enhancing drug bioavailability, prolonging nasal residence time, and facilitating direct nose-to-brain transport"[9, 10].

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss and cognitive impairment. Current therapeutic approaches suffer from poor brain bioavailability due to the blood-brain barrier (BBB) and extensive first-pass metabolism. Intranasal drug delivery offers a promising

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alternative route by bypassing the BBB and delivering drugs directly to the brain through olfactory and trigeminal pathways [11, 12, 13]. Nanostructured lipid carriers (NLCs) provide advantages such as improved drug loading, enhanced stability, and controlled drug release, while in situ gels improve nasal residence time and mucoadhesion. Therefore, the present study focused on the development and optimization of Candesartan Cilexetil loaded NLC-based intranasal in situ gel for targeted brain delivery in Alzheimer's disease [14, 15].

Intranasal administration has emerged as a promising non-invasive approach for direct nose-to-brain drug delivery. This route bypasses the blood-brain barrier and hepatic first-pass metabolism, thereby improving drug bioavailability and enhancing therapeutic efficacy[16]. Among various advanced drug delivery systems, nanocarrier-based formulations have gained considerable attention due to their ability to improve drug solubility, stability, controlled release, and targeted delivery[17]. Nanostructured lipid carriers (NLCs), in particular, offer several advantages, including high drug-loading capacity, biocompatibility, and enhanced permeability across biological membranes. There are several types of the In situ gelling systems based on the triggering factors which are mentioned below[18].

1. Temperature sensitive In situ gel.
2. pH sensitive In situ gel.
3. Ion activated In situ gel [19].

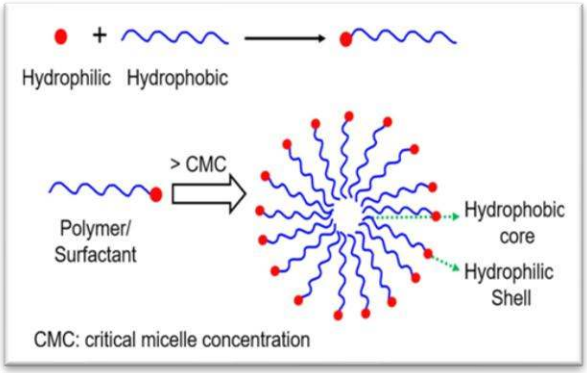

Fig 1. CMC formation in temperature sensitive In situ gel.

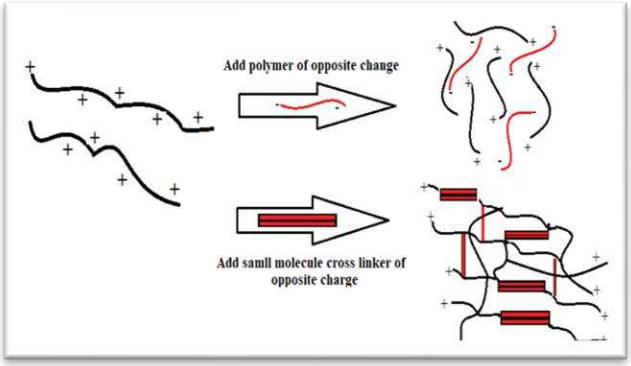

Fig 2. Ion activated In situ gel

"Candesartan Cilexetil, an angiotensin II receptor blocker, has demonstrated potential neuroprotective effects through anti-inflammatory, antioxidant, and neurovascular protective mechanisms [20]. Emerging evidence suggests that modulation of the brain renin-angiotensin system (RAS) plays a significant role in the pathogenesis and management of Alzheimer's disease. Therefore, the development of a nanocarrier-based intranasal formulation of Candesartan Cilexetil represents a promising strategy for targeted brain delivery, with the potential to improve therapeutic outcomes and overcome the limitations associated with conventional treatment approaches for Alzheimer's disease"[21, 22].

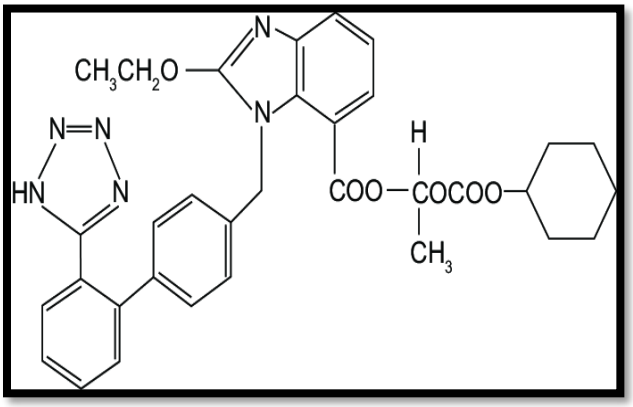

Fig 3. Structure of Candesartan Cilexetil

Advantages of Intranasal NLC-Based In Situ Gel Delivery System[23, 24]

- Direct Nose-to-Brain Delivery
- Avoidance of First-Pass Metabolism
- Non-Invasive Administration
- Enhanced Drug Loading: Nanostructured lipid carriers (NLCs) possess high drug-loading capacity and encapsulation efficiency.
- Controlled Drug Release
- Improved Stability
- Biocompatibility and Biodegradability
- Increased Nasal Residence Time
- Enhanced Mucoadhesion
- Potential Neuroprotective Effect

Disadvantages of Intranasal NLC-Based In Situ Gel Delivery System [25]

- Limited Drug Dose Capacity
- Mucociliary Clearance
- Formulation Complexity.
- Stability
- Variability in Nasal Physiology
- Potential Nasal Irritation
- High Manufacturing Cost
- Scale-Up Challenges
- Regulatory Challenges
- Limited Clinical Data

MATERIALS AND METHODS

Chemicals and Reagents

Candesartan Cilexetil was used as the active pharmaceutical ingredient. Various lipids, surfactants, co-surfactants, polymers, and solvents, including Caprylic Capric Triglyceride, Tween 80, Span 80, Labrasol, Poloxamer 407, Carbopol 934, HPMC, and Methanol, were procured from reputed suppliers. These materials were used for the preparation, optimization, and evaluation of the nanocarrier-based intranasal formulation for targeted brain delivery in Alzheimer's disease.

Preformulation studies

"Preformulation research comprises a group of pharmaceutical and analytical investigations that precede and support formulation development. It represents the first step in the rational development of dosage forms. Preformulation studies are designed primarily to determine the physicochemical properties of the drug substance and its compatibility with selected excipients, which may influence the performance, stability, and efficacy of the final formulation. These studies provide essential information that guides formulators in the development of an elegant,

stable, safe, and effective dosage form with optimized performance characteristics [26,27].

Preparation of Candesartan Cilexetil loaded nanostructured lipid carrier (NLCs) Preparation of trial batches of NLCs by Hot emulsification followed by probe sonication method.

Candesartan Cilexetil-loaded Nanostructured Lipid Carriers (NLCs) were prepared using the hot emulsification followed by probe sonication method. The lipid phase, containing the drug, solid lipid, liquid lipid, and surfactant, was melted at a temperature 10°C above the melting point of the solid lipid. This lipid phase was then added to the aqueous phase maintained at the same temperature to form a pre-emulsion [28]. The resulting mixture was stirred at 1000 rpm for 10 minutes at 65–70°C to obtain a homogeneous emulsion. Subsequently, the pre-emulsion was subjected to probe sonication and cooled to room temperature to form the NLC dispersion. Various formulations were prepared by altering the drug-to-lipid ratio, solid lipid-to-liquid lipid ratio, and surfactant concentration to evaluate their effects on the physicochemical properties and optimize the formulation for targeted brain delivery of Candesartan Cilexetil [29, 30].

Table 1. Composition of trial batches of Candesartan Cilexetil NLCs

Batch	Drug Candesartan Cilexetil (mg)	Gelucire 44/14 (mg)	CCT (mg)	Tween 80 (mg)
1.	20	420	120	300
2.	20	210	40	250
3.	20	400	120	300
4.	25	260	40	250
5.	25	320	80	400
6.	30	200	80	250
7.	30	245	55	400
8.	30	450	75	400
9.	30	280	80	450
10.	40	460	80	450
11.	40	300	50	500
12.	40	350	55	450

RESULTS AND DISCUSSION

PREFORMULATION STUDIE

Identification

a. Organoleptic characterization:

- **Color:** White
- **Taste:** Tasteless

- **Odour:** Odourless

b. Melting point of Candesartan Cilexetil

Table 2 –Melting point of Drug

Drug	Melting Point Range	
Candesartan Cilexetil	Observed	Reported
	164°C	162-165°C

c. DSC study

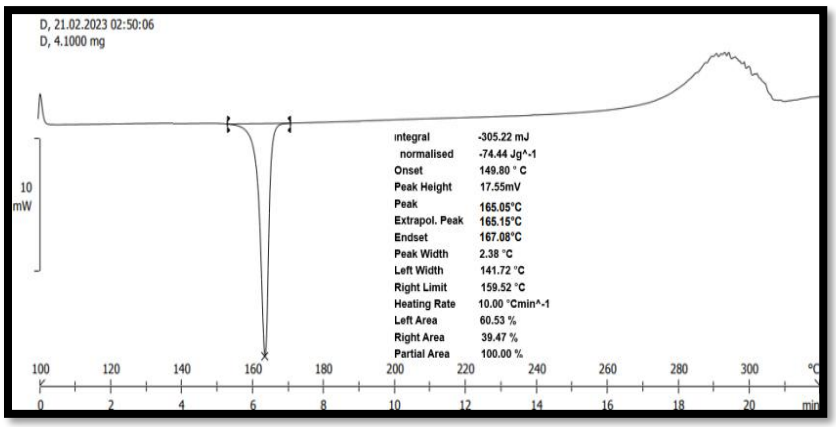

Fig.-4: DSC Thermogram of CND

d. FT – IR spectroscopy

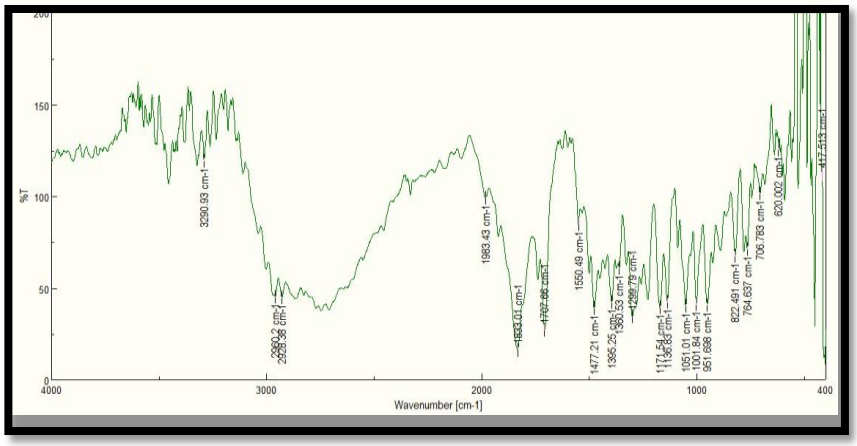

Fig.5. FT-IR spectrum of CND

Table-2. IR frequencies of CND functional group

Functional group	Observed Frequency (cm-1)	Reported Frequency (cm^{-1})
O-H	3453.43	3288-3300
C-H	3059.24	2972-3122
C=O	1760.66	1706-1800
C-N	1481.85	1474-1550
O-H	1999.44	1389-1466
C-O-C	1081.02	1028-1100

e. XRPD

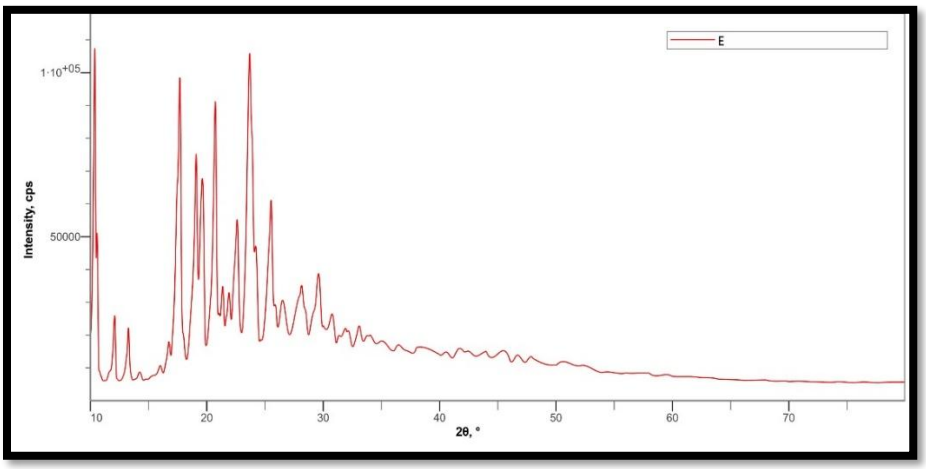

Fig.6. X-ray diffraction pattern of CND

XRD patterns of pure CND exhibited sharp at a diffraction angle of 2θ 13°, 18°, 20°, 23° and 26° with the peak intensity 4371, 8142, 5248, 9396 and 5638. This indicates that the drug was present as crystalline form.

Table 3. Data for evaluation of trial batches for particle size

Batch	Drug	Gelucire 50/13	CCT	Tween 80	Particle size
1	20	200	65	250	204.45±4.34
2	25	220	75	300	189.42±3.65
3	25	250	80	450	201.65±3.68
4	30	250	75	300	255.45±1.35
5	50	300	80	350	240.86±5.26
6	50	300	60	400	174.45±4.34
7	30	300	80	400	270.35±3.21

8	50	300	100	450	215.36±4.95
9	**30**	**280**	**120**	**450**	**120.65±7.86**

*Mean ± S.D (n=3

Table 4. Trial batches of In situ gel:

Sr no.	Gelling/ mucoadhesive agents	Quantity taken
1.	Poloxamer 407	0.3%
	HPMC K15M	17%
2.	Poloxamer 407	0.3%
	HPMC K4M	17%
3.	Gellan gum	0.2%
	Carbopol 934	0.2%
4.	Gellan gum	0.5%
	Xanthan gum	0.5%
5.	Sodium algenate	0.4%
	Poloxamer 407	18%

f. Evaluation of CND loaded *In situ* gel:

1) Physical evaluation

Table 5.Physical evaluation of CND-NLC *In situ* gel

Parameters	Observation
Appearance	Whitish
Consistency	Smooth
Grittiness	None
uniformity	Good

The appearance, colour, and homogeneity of the gel were observed visually. The pH of the gel was measured by pH meter (n = 3)

Table 6. Characterization of In situ gel batches (Mean±SD, n=3)

Batch no.	pH	Gelling time(s)	Expansion Coefficient (%)	Gel strength
1	4.5±0.15	5±4.51	1.60±0.04	47±9.24

2) *In Vitro* drug release study

The CND release study from optimized NLC formulation was performed through dialysis membrane (Mol. Wt. 12,000 Da) using vertical Franz diffusion cell at 34.5°C± 0.5°C for 8hrs. The membrane was stabilized in a simulated nasal electrolyte solution (SNES, pH 6.4) for 15 min. The NLC (1 mL) were uniformly distributed in the donor chamber, and the SNES was continuously

stirred by a magnetic stirrer. Aliquots (0.1 mL) were withdrawn from the receiver compartment at predefined time intervals (1hr), and the same amount of fresh SNES was used for refilling the volume of a cell. The validated UV method was used for determination of the percentage of drug release through the dialysis membrane. Simultaneously, the NLC was checked for different release kinetic models such as zero-order, first-order, Higuchi, Hixon– Crowell cube root, and Korsmeyer– Peppas models, and a best-fitted model was selected (Madane et al.,2016).

Table7. *In vitro* drug release study for CND- NLC simple solution and CND- NLC *In situ* gel.

Time(h)	Cumulative %release From CND drug dispersion	Cumulative %release From CND drug dispersion	Cumulative %release From CND- NLC *In situ* gel
1	47.52±0.3	32.77±0.2	17.54±0.5
2	65.89±0.1	50.45±0.5	32.12±0.2
3	80.12±0.1	60.5±0.3	40.00±0.3
4	97.37±0.3	70.23±0.7	50.10±1.5
5	-	77.44±0.2	58.42±0.8
6	-	82.12±0.3	68.17±0.9
7	-	90.65±0.2	72.10±1.5
8	-	92.29±0.1	74.99±0.3

(Mean±SD, n=3

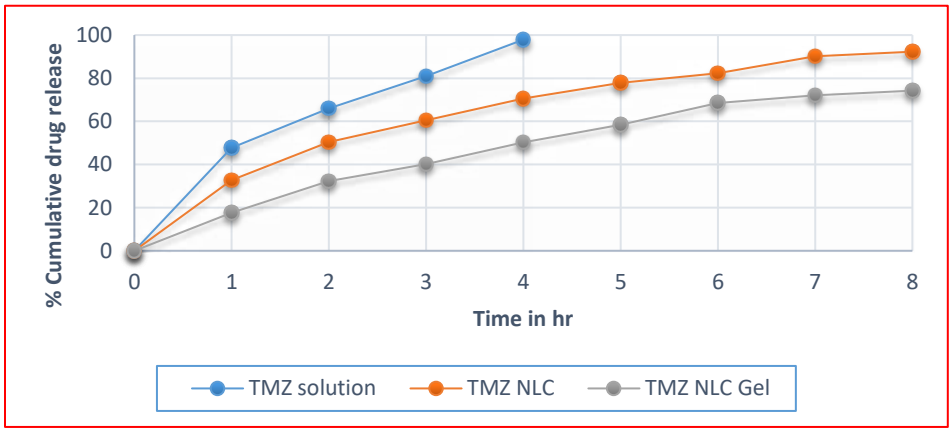

Fig.7 Cumulative drug release from CND dispersion, CND- NLC and CND-*In situ* gel TMZ

3) Release kinetics

The release data of CND-NLC *In situ* gel and CND simple solution were fitted to different kinetic mathematical models: Zero order which describes the release rate as independent of drug concentration, first order which describes that the release rate is dependent on drug concentration; Higuchi which is based on the Fick's law of diffusion and Korsemeyer-Peppas which is based on Quasi Fickian diffusion mechanism.

System follows Higuchi model with the highest R^2 values which is 0.9981.

Table 8. Data for kinetic models for CND dispersion, CND-NLC and CND-*In situ* gel

SR. NO.	Kinetics Model	R^2 CND- Dispersion	R^2 CND-NLC	R^2 CND-*In situ* gel
1	Zero-order	0.9356	0.9122	0.9215
2	First-order	0.8965	0.8756	0.8942
3	Higuchi	0.9869	0.9967	0.9981
4	Hixon-Crowel cuberoot	0.8846	0.9287	0.8767
5	Krosemeyer-peppas	0.9143	0.9162	0.9432

The values obtained are in the table which is mentioned below.

4) *Ex Vivo* permeation study

Ex vivo permeation studies of Candesartan Cilexetil (CND) were performed using sheep nasal mucosa, which closely resembles human nasal mucosa in anatomy and histology. The study demonstrated that approximately 90% of CND permeated from the simple drug solution within 4 hours, whereas only 39.5% permeated from the in situ gel, indicating sustained and controlled drug release. The in situ gel formulation exhibited prolonged drug permeation, with 66.5% drug release observed over 8 hours. The permeability parameters, including apparent permeability coefficient (Papp), steady-state flux (Jss), and diffusion coefficient (D), confirmed efficient transport of CND through the nasal mucosa. These findings suggest that the developed intranasal formulation provides sustained drug delivery and effective permeation through the nasal route.

Table 28. *Ex vivo* % drug release for CND- NLC simple solution and CND- NLC *In situ* gel

Time(h)	Cumulative %release From CND drug dispersion	Cumulative %release From CND drug dispersion	Cumulative %release From CND- NLC *In situ* gel
1	30.77±0.2	32.77±0.2	17.54±0.5
2	51.45±0.5	50.45±0.5	32.12±0.2
3	61.5±0.3	60.5±0.3	40.00±0.3
4	70.5±0.7	70.23±0.7	50.10±1.5
5	76.54±0.2	77.44±0.2	58.42±0.8
6	84.24±0.3	82.12±0.3	68.17±0.9
7	89.45±0.2	90.65±0.2	72.10±1.5
8	91.49±0.1	92.29±0.1	74.99±0.3

Mean ± S.D (n=3)

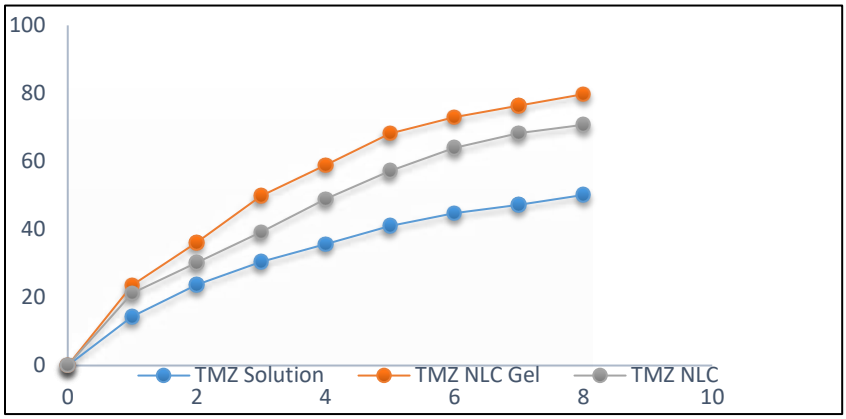

Fig 8. *Ex vivo* % drug release for CND- NLC simple solution and CND- NLC *In situ* gel

CONCLUSION

Thus we can conclude that, The hot homogenization method was successfully employed to formulate loaded NLCs (nanostructured lipid carriers) of CND. This approach proved to be easy, reproducible, and cost-effective in developing stable NLCs of CND.

The administration of CND-NLCs In situ gel intranasal was convenient and non-invasive. It demonstrated a sustained release of CND from the NLCs, resulting in improved permeability across the nasal mucosa over an extended period of time.

The IN-NLCs In situ gel exhibited direct nose-to-brain transport of the drug, and is found to be effective by animal studies.

These findings highlight the potential of utilizing IN-NLCs In situ gel for repurposing CND Cilexetil in the management of Alzheimer's disease.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding publication of this research work.

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