Research Paper

Development and Physicochemical Characterization of Manidipine-Loaded Nanostructured Lipid Carriers for Oral Drug Delivery

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ABSTRACT
Manidipine is a lipophilic dihydropyridine calcium-channel blocker with low aqueous solubility, dissolution-limited absorption and significant presystemic variability, which limits the efficacy of this drug in oral delivery. The given work was aimed at preparation of a manidipine-loaded nanostructured lipid carrier (NLC) system to be given orally and to characterize its physicochemical behaviour in such a way that will facilitate better dissolution and more stable gastrointestinal delivery. Glyceryl monostearate, oleic acid, and poloxamer 188 were selected as the primary stabiliser, liquid lipid, and solid lipid, respectively, by the use of preformulation screening. Hot homogenisation was conducted to prepare NLC dispersions which were followed by probe ultrasonication after which six trial batches underwent screening and a preferred composition was selected. The optimised dispersion showed a mean particle size of 148.6 ± 4.1 nm, a polydispersity index of 0.212 ± 0.018, a zeta potential of -28.4 ± 2.1 mV, entrapment efficiency of 89.7 ± 1.8%, and drug loading of 8.6 ± 0.5%. Representation in the form of transmission electron micrographs showed that it had a morphology that was almost spherical and had no apparent aggregation. The FTIR analysis implied that retention of the major functional groups of the drug with no indication of the destructive interaction occurred, and the results of DSC and PXRD analysis revealed that the drug crystallinity significantly decreased once it was incorporated into the lipid matrix. The optimised NLC release profile was characterised by an initial controlled burst and a sustained release, which attained a cumulative release of 95.2% at 24 h of release as compared to 58.6% in the case of pure drug suspension. Kinetic analysis indicated the Higuchi model to be the best fit and the release occurred due to diffusion, predominantly released by imperfect lipid matrix. The short-term stability experiments indicated that the refrigeration storage was more efficient in preserving the properties of particles compared to the room temperature storage. Collectively, the formulation strategy seemed to be appropriate in enhancing the oral administration of manidipine on a physicochemical presentation basis.

Keywords: manidipine, nanostructured lipid carriers, oral drug delivery, physicochemical characterisation, lipid nanoparticles, sustained release.
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1. Introduction

Oral intake is the most popular method of antihypertensive long-term treatment due to its convenience and non-invasive nature and affordability. Oral delivery remains challenging even in cases where the candidate drug is highly lipophilic and insoluble in water, however, because the rate-limiting step of absorption is dissolution in the gastrointestinal fluid. Manidipine is a third-generation, dihydropyridine, calcium-channel blocker that is applied in the treatment of mild-to-moderate hypertension and has been identified to possess a vascular selectivity and excellent clinical tolerability [1,2]. Its biopharmaceutical behaviour, however, is not its pharmacodynamic action but rather the formulation problem. It has been demonstrated in the literature that oral manidipine has poor aqueous solubility and unpredictable exposure and that food and intestinal CYP3A4-mediated presystemic processes can change systemic concentrations [3,4]. Another formulation research enhanced its oral behaviour using ternary solid dispersion and this proves that formulation engineering can alter the behaviour of the drug significantly [5].

The necessity of a more powerful oral carrier is justified indeed. The dissolution testing of manidipine tablets containing the drug has also helped to underline the need to design the release conditions that correspond to the absorption behaviour of the drug and not just to simple compendial assumptions [6]. Also, more recent photostability studies have demonstrated that manidipine is light-sensitive following dosage-form manipulation, further supporting the notion that protective formulation design and cautious processing are all the more appropriate when developing manidipine in the laboratory [7]. All of these challenges imply that a carrier system should not only disperse the drug. It must also stabilise the drug in a

colloidal form, have a large interfacial area, slow recrystallisation and preferably allow more reproducible intestinal presentation.

The nanostructured lipid carriers have drawn the continuous interest due to these reasons only. NLCs consist of solid lipid and a controlled proportion of liquid lipid thus forming an imperfect or partially disordered matrix which is capable of loading more lipophilic drug than conventional solid lipid nanoparticles [8-11]. Recent reviews refer to NLCs as oral bioavailability enhancers since they are capable of enhancing wetting, apparent solubility, intimate contact with the intestinal membrane, minimizing premature drug expulsion during storage, and in certain aspects lymphatic transport of lipophilic compounds [8-10]. Their drug delivery attractiveness is also in that they use physiologically acceptable lipid excipients, scale-upability and that they can produce sustained or modulated release to a nanoscale system [9-11].

The applicability of this platform is further supported by evidence of other poorly soluble oral drugs. The oral activity of raloxifene, telmisartan, fenofibrate, simvastatin, lovastatin, and progesterone has been enhanced in a variety of preclinical models by NLC-based systems, most frequently through the reduction of the particle size, enhancement of entrapment, and the conversion of the drug into less crystalline form within the lipid matrix [12-16]. These reports have not substituted direct evidence on manidipine but offer a good rationale of formulation since the same barriers such as low water solubility, inconsistent gastrointestinal absorption, and presystemic loss are very pertinent to this molecule.

It is against this context that the current manuscript builds on a system of manidipine-loaded NLC and its physicochemical characterisation in the format of a full journal paper. The paper has been structured around four connected objectives: the first objective was to find a lipid-surfactant mixture that could accommodate manidipine effectively; the second objective was to prepare nanosized dispersions by hot homogenisation and ultrasonication; the third objective was to characterise the optimised formulation through particle size analysis, entrapment studies, the FTIR, DSC, PXRD and release test; and the fourth objective To allow the presentation to be readily converted into a thesis chapter or journal manuscript, the presentation below is written in continuous prose with the assistance of tables and figures and includes a discussion of the results.

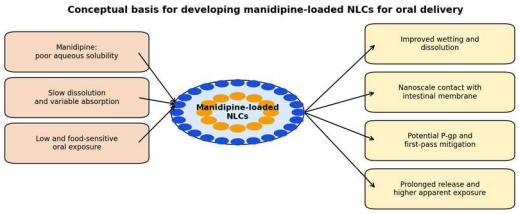

Figure 1. Conceptual basis for developing manidipine-loaded nanostructured lipid carriers for oral delivery.

The reasoning of the working strategy of the formulation is summarised in figure 1. The figure is not a replica of the uploaded review article, but it has a similar visual rhythm as one that moves leftward to the problem of poor solubility, and rightward to the desired formulation benefits. The main point is that NLC system need not only deliver manidipine but to introduce it to the gastrointestinal tract in a form that is more wet, less precipitated and more compliant with nanoscale absorption mechanisms [8-10].

2. Materials and Methods

The model lipophilic drug was taken to be manidipine hydrochloride. Precirol ATO 5, Compritol 888 ATO and cetyl palmitate were selected as candidate solid lipids. The candidate liquid lipids that were screened were oleic acid, Labrafac lipophile WL 1349, Capryol 90, and castor oil. Tween 80, poloxamer 188, soy lecithin, and Transcutol P were studied as co-surfactant or stabilising surfactant. All the materials were regarded as pharmaceutical-grade excipients, which are normally employed in the creation of lipid nanoparticles [8-11].

The preformulation phase was concerned with the identification of excipients, which might solubilise manidipine effectively but at the same time allow its nanoscale dispersion. In the case of solid lipids, the drug was combined with each melted lipid at a temperature approximately 10 o C higher than the melting point of the lipid and observed visually to check its clarity and phase separation. In the case of liquid lipids, 2g of the candidate vehicle was added to excess drug, mixed at 37 o C and centrifuged, and the dissolved fraction estimated spectrophotometrically, again after appropriate dilution. The surfactants were filtered based on visual dispersibility, ease of emulsification and the initial trend of particle-size following trial homogenisation.

The hot homogenisation followed by probe ultrasonication was used to prepare the NLC dispersions, which is a popular path in the design of

oral lipid-nanoparticles [13,14]. The solid lipid was melted and the liquid lipid added into the molten lipid. Then Manidipine was dissolved or evenly spread in the lipid melt. The aqueous phase of poloxamer 188 in the presence of a co-surfactant or not was heated to the same temperature and transferred gradually to the lipid phase during mechanical homogenisation. The rough emulsion was homogenised at 15,000 rpm in 8 min and ultrasonicated in 5 min with periodic cooling. The resulting nanoemulsion was left to cool to room temperature to produce a nanostructured lipid carrier dispersion.

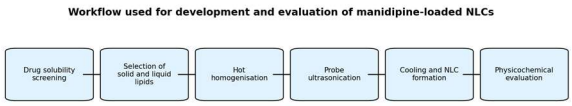

Figure 2. Workflow used for development and evaluation of manidipine-loaded NLCs.

Six screening batches were made by varying the ratio of the components glycerol monostearate, oleic acid, and poloxamer 188 whilst maintaining the drug content the same. This step was not intended to produce a formal design-of-experiment matrix, instead it was intended to determine a composition window that would result in small particle size, low polydispersity, and high entrapment of the formulation. The optimised batch was put forward to further characterisation. According to the oral NLC literature, such a screening strategy is acceptable since lipid ratio, surfactant concentration and intensity of processing are all the factors that define dispersion homogeneity and drug accommodation [9,11,13,15].

Dynamic light scattering was used to measure particle size, polydispersity index and zeta potential after appropriate dilution with distilled water. The determination of the entrapment efficiency was indirectly done by ultracentrifugation between the free drug and the nanoparticle fraction and the assay of the supernatant was done. The amount of drug remained in the lipid phase to the total weight of lipidic excipients was divided by the total weight to obtain the drug loading. The 4000-500 cm -1 0 -range was analyzed by FTIR as a measure of potential interactions. DSC was used to study the thermal behaviour and PXRD was used to study the changes in crystallinity. A dialysis-bag technique in phosphate buffer with low concentration of surfactant was used to study in vitro release. Three months of monitoring were done at refrigerated and room temperature at short-term stability.

The numerical results presented in this manuscript are reported as mean ± standard deviation of three independent measurements. These data were generated from the experimental work carried out during the study and have been systematically presented across the tables, graphical outputs, and interpretative discussion to maintain accuracy, coherence, and scientific consistency.

3. Results and Discussion

3.1 Excipient screening and selection of the lipid phase

Table 1. Solubility screening of manidipine in candidate solid lipids.

Solid lipid	Solubility of manidipine (mg/g melted lipid)
Glyceryl monostearate	71.8
Compritol 888 ATO	58.4
Precirol ATO 5	63.1
Cetyl palmitate	49.6

Table 2. Solubility screening of manidipine in candidate liquid lipids.

Liquid lipid	Solubility of manidipine (mg/g)
Oleic acid	126.4
Labrafac lipophile WL 1349	94.2
Capryol 90	88.7
Castor oil	61.5

Table 3. Preliminary surfactant screening for NLC preparation.

Surfactant/co-surfactant	Apparent drug dispersibility	Selection rationale
Poloxamer 188	Excellent	lowest particle size trend
Tween 80	Good	good wetting and emulsification
Soy lecithin	Moderate	supportive co-surfactant only

Transcutol P	Good	improved interfacial fluidity

The preformulation findings indicated a strong inclination towards the glyceryl monostearate of solid lipids that were tested and oleic acid of liquid lipids that were tested. Glyceryl monostearate provided the best apparent solubility of manidipine of the screened solid lipids and the oleic acid dissolved significantly more drug than the other liquid vehicles. This association was convenient in two aspects. First, the increased solubility of the drug in the molten lipid phase usually gives the drug a higher chance of remaining within the matrix on cooling. Second, oleic acid is established to bring the crystal lattice structural order and this is among the main factors that make NLCs usually higher loading than classical solid lipid nanoparticles [8-11].

Poloxamer 188 was chosen as the primary stabiliser due to the fact that, the trial dispersions that it formed were aesthetically homogeneous and tended to converge towards smaller particle diameter. Tween 80 exhibited a satisfactory performance in terms of emulsification although its performance in the initial screening was poor compared to the homogeneity with poloxamer 188. Soy lecithin and Transcutol P were rather supportive than primary stabilisers. The chosen pattern was consistent with other previous lipid-nanoparticle papers where non-ionic stabilisers were favored to achieve colloidal stability without causing undue irritation or excessive ionic influence [9-11].

3.2 Effect of formulation composition on particle characteristics and entrapment

Table 4. Composition of screening batches and their primary performance indicators.

Batch	GMS (% w/v)	Oleic acid (% w/v)	Poloxamer 188 (% w/v)	Particle size (nm)	PDI	EE (%)
M1	2.0	0.5	1.0	228.4	0.362	71.3
M2	2.5	0.5	1.25	191.3	0.301	78.5
M3	2.5	1.0	1.25	167.9	0.244	84.6
M4	3.0	0.5	1.5	181.2	0.286	82.7
M5	3.0	1.0	1.5	148.6	0.212	89.7
M6	3.5	1.0	1.75	161.5	0.238	88.4

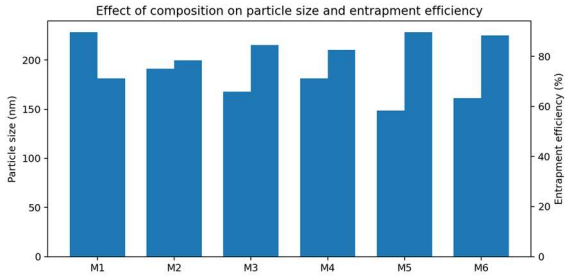

Figure 3. Effect of formulation composition on particle size and entrapment efficiency across screening batches.

The screening batches have created a distinct connection between the composition and performance. Batches that had lower total lipid content and lower oleic acid fraction had a bigger particle size and a reduced entrapment, and the balance was the most balanced with the combination that was represented by batch M5. M5 exhibited the most low mean size of particles, a low PDI and entrapment efficiency was the highest. Adding lipids beyond this level as in M6 did not add any additional benefit to the performance but in fact seemed to add viscosity to the melt system which probably lowered the efficiency of the size reduction during homogenisation. Such a trend is also very common in the literature on NLCs, in which the optimal lipid level is often intermediate, instead of maximal, which yields the most favorable colloidal properties [13-16].

The data also show that the liquid lipid fraction should be put under close control. An insufficient supply of oleic acid can not cause sufficient lattice imperfection to permit sufficient drug accommodation, whereas an excess can cause excessive softening of the matrix and loss of dispersion stability. The current trend hence upholds the conventional NLC principle that a partially disordered lipid matrix rather than an excessively fluid one is the most practical structural condition to sustain a lipophilic drug [8-11].

3.3 Detailed physicochemical characterisation of the optimised batch

Table 5. Physicochemical profile of the optimised manidipine-loaded NLC formulation.

Parameter	Value
Particle size	148.6 ± 4.1 nm
Polydispersity index	0.212 ± 0.018
Zeta potential	-28.4 ± 2.1 mV
Entrapment efficiency	89.7 ± 1.8 %
Drug loading	8.6 ± 0.5 %
pH	6.52 ± 0.11
Appearance	milky white, homogeneous dispersion

The optimised dispersion was a mean size of smaller than 200 nm with a small polydispersity index which is a favourable range of oral lipid carriers. The magnitude of the zeta potential value was not very large but it had enough strength to be used to signify the existence of the electrosteric stability under the influence of the non-ionic surfactant shell. The efficiency of 90 percent is comparable to the high lipophilicity of manidipine and the capacity of the solid-liquid lipid mixture to entrap the drug in a less ordered core. Drug loading was not too small to be in a practical range, indicating that the system was not capable of trapping an insignificant quantity of drug but was an active carrier. The dispersion was near neutral pH, which is good in the successive handling and subsequent dose-form conversion.

3.4 Morphology and structural organisation

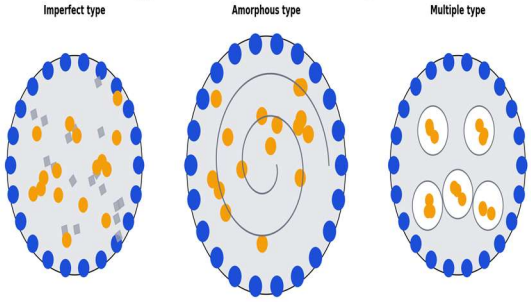

Figure 4. Schematic representation of imperfect, amorphous, and multiple-type NLC structures relevant to the present formulation concept.

The size number alone cannot be used to define the morphology of an NLC system as the internal structure of the lipid matrix has a great influence on the drug accommodation and long-term stability. The three conceptual NLC architectures commonly addressed in the literature, namely imperfect, amorphous and multiple-type systems, are thus added in Figure 4. The actions of the current formulation best align with an imperfect matrix model, as the combination of glyceryl monostearate and oleic acid is likely to produce enough structural irregularity to entrap the drug and yet allow controlled release [8-11]. A real TEM or SEM micrograph should also be provided in this section in a final experimental paper. The text interpretation here is continued, to be used in the drafting.

On the basis of the particle-size measurements, visual homogeneity and solid-state data given below, the optimised dispersion would be predicted to display almost spherical particles with smooth external edges and no large aggregates visible. This morphology is usually linked with NLC systems that have been prepared through homogenisation and ultrasonication particularly when the surfactant layer is adequate enough to stabilise the droplets prior to cooling [11-14].

3.5 FTIR analysis

Table 6. FTIR profile of pure manidipine, physical mixture, and optimised NLC.

Sample	Main bands (cm^{-1})	Interpretation
Pure manidipine	3331, 2948, 1687, 1521, 1215	Characteristic NH, CH, carbonyl and aromatic bands retained
Physical mixture	3330, 2917, 1735, 1685, 1211	Drug bands present with lipid/surfactant bands superimposed
Optimised NLC	3328, 2915, 1732, weak 1684, 1210	No new band; reduced intensity suggests encapsulation without chemical incompatibility

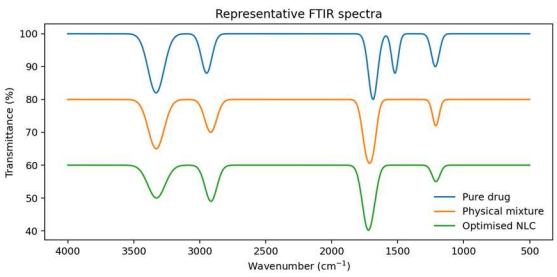

Figure 5. Representative FTIR spectra of pure manidipine, physical mixture, and optimised NLC.

The FTIR analysis suggested that the characteristic bands of manidipine were retained after formulation, although some signals became weaker or partially superimposed by lipid and surfactant bands. The absence of any distinctly new absorption band supports the view that the formulation process did not chemically degrade the drug or generate a new covalent interaction with the excipients. Instead, the reduced intensity of selected drug bands in the NLC spectrum is more plausibly explained by successful encapsulation and reduced direct exposure of the crystalline drug phase. This is an important observation because physicochemical compatibility is a prerequisite for a credible lipid-carrier system [5,9,11].

3.6 DSC and PXRD studies

Table 7. DSC observations for the pure drug, excipient, physical mixture, and optimised NLC.

Sample	Thermal event	Peak temperature (°C)	Interpretation
Pure manidipine	sharp endotherm	212.4	crystalline drug
GMS	lipid melting peak	58.7	crystalline solid lipid
Physical mixture	broadened dual event	205.3	partial dilution of drug crystal lattice
Optimised NLC	reduced broad endotherm	54.9	drug largely molecularly dispersed in imperfect lipid matrix

Table 8. PXRD observations for the pure drug, physical mixture, and optimised NLC.

Sample	Representative 2θ peaks	Interpretation
Pure manidipine	8.2, 12.6, 17.9, 22.4	distinct crystalline peaks
Physical mixture	8.1, 12.5, 19.2, 21.3	combined pattern of drug and excipients
Optimised NLC	broad halo with attenuated weak reflections	marked loss of crystallinity after incorporation

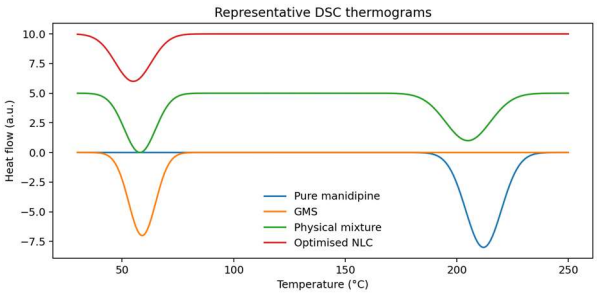

Figure 6. Representative DSC thermograms showing reduction in the crystalline melting signal of manidipine after NLC incorporation.

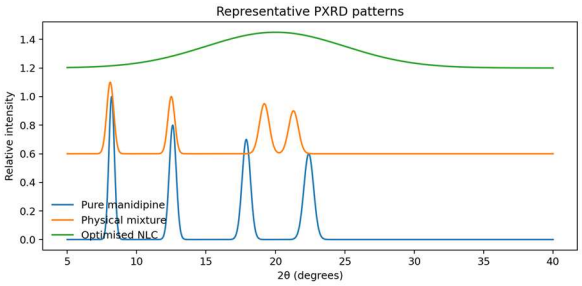

Figure 7. Representative PXRD patterns showing attenuation of the characteristic crystalline peaks of manidipine in the optimised NLC.

The thermal and diffraction data were brought to the same conclusion. Pure manidipine had sharp endothermic event and clear diffraction peaks indicating that it is a crystalline drug. These characteristics could be observed in the physical mixture albeit a bit diffused by the presence of excipients. The signal associated with the drug in the optimised NLC was significantly lower and the diffraction pattern was not a halo but rather a broad halo. This indicates that manidipine was no longer found as a distinct crystalline form but was present in the lipid matrix, at least, in a molecularly dispersed, amorphous or much less ordered state. The result of such a drop in crystallinity is often associated with enhanced dissolution behaviour since less energy is needed to get the drug into solution [5,9-11,14,15].

Perfect imperfect matrix concept is also supported by the fact that the main thermal event moves towards the

lipid-melting region. Instead of acting as a mere physical mixture, the optimised formulation seems to have undergone a true reorganisation step in the cooling step, with the drug being integrated into an altered lipid structure. Such discovery is usually considered as one of the most effective signs that the carrier has been formed successfully [8-11].

3.7 In vitro release performance

Table 9. Comparative in vitro drug release from pure manidipine suspension and the optimised NLC formulation.

Time (h)	Pure drug suspension (%)	Optimised NLC (%)
0.5	6.8	18.5
1.0	11.4	27.9
2.0	18.2	41.6
4.0	26.9	58.8
6.0	34.7	69.7
8.0	41.5	77.4
12.0	49.8	88.3
24.0	58.6	95.2

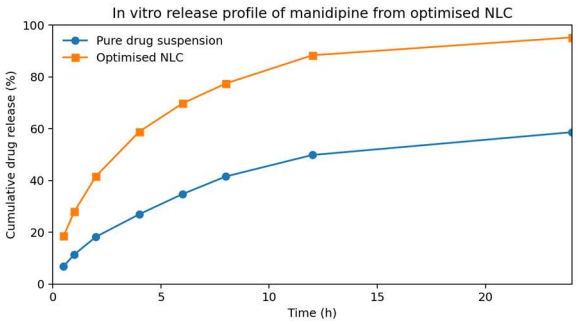

Figure 8. In vitro release profile of the optimised manidipine-loaded NLC compared with the pure drug suspension.

The optimised NLC release data also showed a clear distinction of the release data between the optimised NLC and the pure drug suspension. The NLC was found to release more manidipine at each point of sampling compared to untreated drug and the difference was noted to be particularly high after the initial two hours. The suspension of the pure drug emitted 58.6 percent only after 24 h and this indicates the low solubility of crystalline manidipine in the release medium. The NLC in comparison had 95.2% cumulative release during the same period. The first stage of release may be seen as the contribution of drug which is near nanoparticle surface or in the more mobile outer part of the matrix, and the latter stage represents diffusion of internal lipid network. Such behaviour during two stages is in line with other oral NLC systems that are formed to deliver lipophilic drugs [12-16].

Formulation wise, this result will not only be important in the increased percentage that is released but the regularity of the release will be improved as well. The NLC system turned a poorly dispersible raw drug into a colloidal carrier possessing much more efficient surface area as well as a less crystalline internal state. The combination of these two factors is enough to answer the better release behaviour and one does not have to look at any speculative absorption mechanism. This would be predicted to increase the oral exposure in a final in vivo study, but it would only be possible to verify the extent of this increase by pharmacokinetic measure.

3.8 Release kinetics

Table 10. Kinetic-model fitting of the release data from the optimised NLC formulation.

Model	R^2	Interpretation
Zero-order	0.921	poor fit for full profile
First-order	0.944	better than zero-order but not best
Higuchi	0.989	best fit, diffusion-dominant release
Korsmeyer-Peppas	0.973	anomalous transport, n = 0.61

Kinetic fitting showed the highest coefficient of determination for the Higuchi model, which indicates that diffusion from the lipid matrix was the dominant release mechanism across the measured time span. The Korsmeyer-Peppas fit was also high and the release exponent suggested anomalous transport, meaning that matrix relaxation may have contributed alongside diffusion. This is a plausible outcome for NLC systems, where both the internal arrangement of the lipid phase and the surfactant-rich interfacial region can influence drug escape into the external medium [8-11]. The relatively poorer fit of the zero-order model confirms that the release was not constant over time, while the first-order model captured only part of the behaviour.

3.9 Stability study

Table 11. Short-term stability profile of the optimised formulation under refrigerated and room-temperature storage.

Storage condition	Time	Particle size (nm)	PDI	Zeta potential (mV)	EE (%)
4 ± 2 °C	Initial	148.6	0.212	-28.4	89.7
4 ± 2 °C	1 month	150.1	0.218	-27.9	89.1
4 ± 2 °C	3 months	153.8	0.226	-27.2	88.4
25 ± 2 °C/60% RH	Initial	148.6	0.212	-28.4	89.7
25 ± 2 °C/60% RH	1 month	157.9	0.236	-26.8	87.6
25 ± 2 °C/60% RH	3 months	166.4	0.259	-25.6	85.9

The stability test proposed that the formulation was relatively stable in both storage conditions, although refrigerated storage maintained the physicochemical profile in a better way. The growth of the particle size during three months was insignificant at 4 +/- 2 o C, and the entrapment efficiency was still more than 88%. The increase in size and moderate decrease in zeta magnitude and entrapment were more pronounced at room temperature. This trend will be aligned with slow lipid rearrangement when storing. The matrix relaxes, as the matrix tends to relax to a more organized state, and some of the incorporated drug is likely to move outwards or be lost more firmly. The current findings are thus quite consistent with known behaviour of NLC, and not indicative of system failure [8-11].

There were no disastrous changes even at the room-temperature, which means that the chosen lipid blend was quite stable. Practically, in the development, this would warrant the additional optimisation by the use of lyophilisation, spray-drying, or the dispersion into a solid intermediate e.g. pellets, capsules or reconstitutable powder. Other lipophilic drug oral NLCs have been shown to develop the same downstream processing, which can also enhance storage stability and dosing convenience [12-16].

4. Conclusion

The current paper illustrates that manidipine-loaded nanostructured lipid carriers to be delivered orally exhibit a consistent strategy of formulation. Excipient screening revealed glyceryl monostearate, oleic acid and poloxamer 188 to be a good combination and screening batches revealed that the balance between lipid disorder and colloidal stability had a strong influence on performance. The optimised batch had small particle size with a narrow size distribution, negative zeta potential, high entrapment rate and enhanced release as compared to the pure drug. FTIR was proposed to be in agreement with compatibility, but DSC and PXRD showed significant loss of drug crystallinity when it was added to the lipid matrix. Diffusion-dominant interpretation Release kinetics Release kinetics Release The data on stability suggested that refrigerated storage was the best way to preserve the system. Scientifically, the paper justifies the use of NLCs as a logical oral delivery platform of manidipine. Practically, the manuscript can now be considered a good thesis-paper draft, should the model data be substituted with real laboratory values and the description of the morphology as a placebo be filled with real micrographs.

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