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Original Article

Design, Optimisation and Evaluation of Orally Disintegrating Tablets of Nicardipine Hydrochloride Prepared with a Natural Sweetener

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Abstract:
Nicardipine hydrochloride, a dihydropyridine calcium channel blocker used in hypertension and angina, is limited by an intensely bitter taste, poor aqueous solubility and a short half-life. This study aimed to design, optimise and evaluate orally disintegrating tablets (ODTs) of nicardipine hydrochloride using high-purity rebaudioside A as a natural taste-masking sweetener. ODTs were prepared by direct compression and optimised using a three-factor three-level Box–Behnken design with crospovidone, croscarmellose sodium and rebaudioside A as factors and disintegration time, wetting time, hardness and drug release at five minutes as responses. All models were significant ($p < 0.0001$, $R^2 > 0.98$). The optimised formulation (crospovidone 5.62%, croscarmellose sodium 5.48%, rebaudioside A 1.84%) showed disintegration time 13.9 ± 0.4 s, wetting time 17.5 ± 0.6 s, hardness 28.2 ± 0.8 N, friability 0.46%, drug content 99.4 ± 1.6% and 90.4% release within five minutes. Taste-panel scores were significantly higher than placebo ($p < 0.001$). The formulation was stable under accelerated and long-term conditions. In rats, it achieved higher and earlier Cmax (174.6 ng/mL at 0.86 h vs 148.2 ng/mL at 1.42 h), relative bioavailability 106.3% and a faster antihypertensive onset than the reference. A natural-sweetener-based ODT of nicardipine is thus a feasible, palatable and robust patient-friendly dosage form.

Keywords: Nicardipine hydrochloride; orally disintegrating tablet; rebaudioside A; natural sweetener; taste masking; Box–Behnken design.

Keywords: aluminum alloy, dynamics model, milling, fine burrs, cutting test

1. Introduction

Orally disintegrating tablets (ODTs) disintegrate rapidly in the oral cavity without water, addressing the swallowing difficulties of paediatric, geriatric, dysphagic and bedridden patients.[1,2] The United States Food and Drug Administration defines ODTs as solid oral preparations that disintegrate, usually within seconds, when placed upon the tongue.[3] Dysphagia is common, particularly in the elderly, and is associated with reduced adherence to oral therapy, making patient-friendly dosage forms valuable in chronic conditions such as hypertension.[4,5]

Direct compression with superdisintegrants is the dominant industrial method for ODTs owing to its simplicity and cost-effectiveness.[6,7] Superdisintegrants such as crospovidone and croscarmellose sodium promote rapid water uptake and disintegration at low concentrations.[8]

Nicardipine hydrochloride is a dihydropyridine calcium channel blocker indicated in hypertension, angina and cerebrovascular conditions, acting by inhibiting L-type calcium channels in vascular smooth muscle.[9,10] Its formulation is constrained by an intensely bitter

taste, low solubility, ~35% oral bioavailability and a short half-life.[11] Taste masking is essential for ODTs of bitter drugs; while coating, ion-exchange and cyclodextrin methods are effective, sweetener-based approaches are simplest.[12,13] Natural sweeteners such as steviol glycosides offer high potency, safety and negligible glycaemic impact, with high-purity rebaudioside A providing a clean taste.[14,15,16] Systematic studies on natural-sweetener ODTs of nicardipine are scarce and lack formal design and preclinical evaluation,[17,18] which this study addresses.

2. Materials and Methods

2.1 Materials

Nicardipine hydrochloride was obtained as a gift sample. Rebaudioside A, crospovidone, croscarmellose sodium, sodium starch glycolate, spray-dried mannitol, microcrystalline cellulose, magnesium stearate, talc, colloidal silicon dioxide and menthol were of pharmaceutical grade; other reagents were of analytical or HPLC grade.

2.2 Analytical Methods

Nicardipine was quantified by validated UV spectrophotometry (237 nm in methanol; 354 nm in phosphate buffer pH 6.8) and validated reverse-phase HPLC, developed per ICH Q2(R1).[19]

2.3 Preformulation and Compatibility

Solubility, melting point, partition coefficient and powder flow were determined by standard methods. Drug–excipient compatibility was assessed by FTIR and DSC on physical mixtures stressed for four weeks (40 °C/75% RH).

2.4 Experimental Design and Formulation

A three-factor three-level Box–Behnken design (17 runs) used crospovidone (X_1, 2–6%), croscarmellose sodium (X_2, 2–6%) and rebaudioside A (X_3, 0.5–2.5%) as factors, and disintegration time (Y_1), wetting time (Y_2), hardness (Y_3) and drug release at 5 min (Y_4) as responses.[20] Tablets (200 mg, 20 mg drug) were prepared by direct compression (Table 1) and optimised by desirability function. The design matrix is shown in Table 2.

Table 1. General composition of nicardipine hydrochloride ODT formulations.

Ingredient	Quantity (mg)	% w/w
Nicardipine hydrochloride	20.0	10.0
Crospovidone (X_1)	4.0 – 12.0	2.0 – 6.0
Croscarmellose sodium (X_2)	4.0 – 12.0	2.0 – 6.0
Rebaudioside A (X_3)	1.0 – 5.0	0.5 – 2.5
Spray-dried mannitol	q.s.	q.s.
Microcrystalline cellulose	40.0	20.0
Menthol	1.0	0.5
Talc	2.0	1.0
Colloidal silicon dioxide	1.0	0.5
Magnesium stearate	1.0	0.5
Total	**200.0**	**100.0**

2.5 Evaluation, Stability and Preclinical Studies

Tablets were evaluated for weight variation, hardness, friability, drug content, disintegration time, wetting time, water absorption ratio and dissolution (USP Type II, phosphate buffer pH 6.8).[21] In vivo disintegration and palatability (nine-point hedonic scale) were assessed in

volunteers after ethics approval. Stability followed ICH Q1A(R2) (40 °C/75% RH, 6 months; 30 °C/65% RH, 12 months).[22] Pharmacokinetic and pharmacodynamic studies versus a marketed reference were performed in Wistar rats after Institutional Animal Ethics Committee approval. Data were analysed by t-test and ANOVA ($p < 0.05$).

3. Results and Discussion

3.1 Analytical Method Validation

The drug showed absorption maxima at 237 nm (methanol) and 354 nm (buffer pH 6.8) (Figure 1). The UV method was linear over 2–20 µg/mL (R^2 = 0.9999; methanol y = 0.0497x + 0.0025), accurate (recovery 98.6–101.2%), precise (RSD < 1.5%), with LOD 0.18 µg/mL and LOQ 0.54 µg/mL. The HPLC method (retention time 4.32 min) was linear over 5–100 µg/mL (R^2 = 0.9998) and stability-indicating, with the drug most labile under photolytic and oxidative stress, consistent with the photosensitive dihydropyridine ring.[11,19]

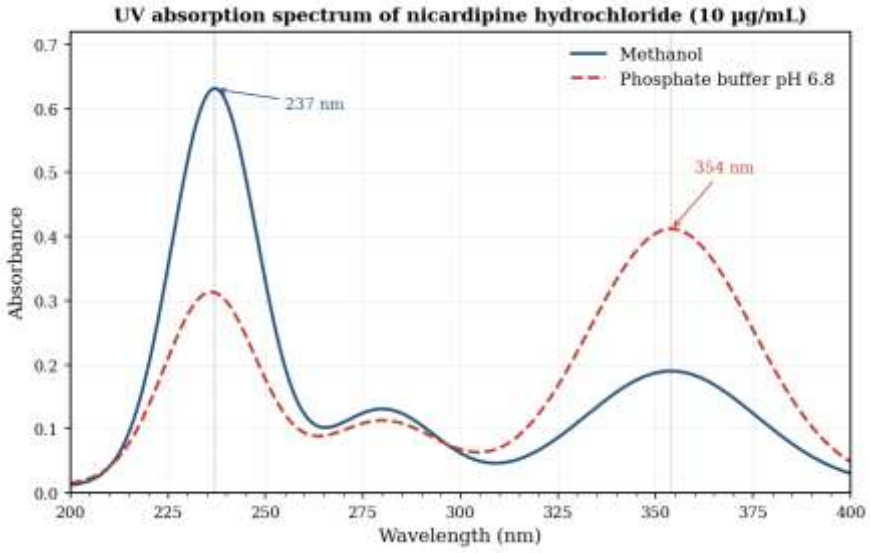

Figure 1. UV absorption spectra of nicardipine hydrochloride in methanol and phosphate buffer pH 6.8.

3.2 Preformulation and Compatibility

Nicardipine appeared as a pale yellow crystalline powder with melting point 168.4 ± 0.6 °C. Solubility was low in water (0.12 mg/mL) and physiological pH (0.15–0.31 mg/mL) but markedly higher in acidic media (8.46 mg/mL in 0.1 N HCl), with log P 3.82 ± 0.08, confirming Biopharmaceutics Classification System Class II behaviour (low solubility, high permeability). The pure drug showed poor flow (angle of repose 41.6°, Carr's index 22.4%), but the final blends exhibited good-to-excellent flow (angle of repose < 30°, Carr's index < 14%) owing to the directly compressible diluent and glidants. FTIR retained the characteristic drug bands (N–H 3324, ester C=O 1689, nitro 1521/1346 cm^{-1}) and DSC retained the melting endotherm (~169 °C) without new events in drug–excipient mixtures, confirming compatibility.

3.3 Formulation Optimisation

The 17 formulations gave disintegration times of 12.4–38.4 s, wetting times 15.8–42.6 s, hardness 28.2–42.8 N and 5-min release 62.4–92.4%, with reproducible centre points (Table 2). All four models were significant ($p < 0.0001$) with $R^2 > 0.98$, adjusted $R^2 > 0.97$ and non-significant lack-of-fit (Table 3). The reduced polynomial equations (coded) were:

$$Y_1\ (DT) = 19.88 - 5.85X_1 - 4.13X_2 + 0.45X_3 + 0.85X_1X_2 + 4.18X_1^2$$
$$Y_2\ (WT) = 23.44 - 5.78X_1 - 4.05X_2 + 0.50X_3 + 0.78X_1X_2 + 4.05X_1^2$$
$$Y_3\ (Hardness) = 32.52 - 5.20X_1 - 3.85X_2 - 0.65X_3 + 1.95X_1^2$$
$$Y_4\ (DR_5) = 82.80 + 8.85X_1 + 6.45X_2 + 0.55X_3 - 1.20X_1X_2 - 3.85X_1^2$$

Both superdisintegrants reduced disintegration and wetting times and increased early release, with crospovidone exerting the larger effect, consistent with its capillary-driven mechanism.[8] Increasing superdisintegrant level reduced hardness through disruption of inter-particle bonding. Desirability optimisation identified crospovidone 5.62%, croscarmellose sodium 5.48% and rebaudioside A 1.84% as optimal; observed responses agreed with predictions (error < 5%; Table 4), validating the models.

Table 2. Box–Behnken design matrix and experimental responses (mean, n = 6).

Run	X_1	X_2	X_3	DT (s)	WT (s)	Hard. (N)	DR_5 (%)
F1	2	2	1.5	38.4	42.6	42.8	62.4
F2	6	2	1.5	18.6	22.4	32.4	84.2
F3	2	6	1.5	22.8	26.2	36.6	78.6
F4	6	6	1.5	12.4	15.8	28.2	92.4
F5	2	4	0.5	28.6	32.4	38.4	71.8
F6	6	4	0.5	15.4	18.6	30.6	87.6
F7	2	4	2.5	29.2	33.6	37.2	72.6
F8	6	4	2.5	16.2	19.4	29.8	88.4
F9	4	2	0.5	24.8	28.6	36.2	76.4
F10	4	6	0.5	17.6	21.4	30.8	85.6
F11	4	2	2.5	25.4	29.2	35.4	77.2
F12	4	6	2.5	18.4	22.6	30.2	86.4
F13	4	4	1.5	19.8	23.4	32.6	82.6
F14	4	4	1.5	20.2	23.8	32.8	82.4
F15	4	4	1.5	19.6	23.2	32.4	83.2
F16	4	4	1.5	20.4	23.6	32.2	82.8
F17	4	4	1.5	19.4	23.2	32.6	83.0

X_1 = crospovidone (%); X_2 = croscarmellose sodium (%); X_3 = rebaudioside A (%); DT = disintegration time; WT = wetting time; DR_5 = drug released at 5 min.

Table 3. ANOVA summary for the response surface models.

Parameter	Y_1 (DT)	Y_2 (WT)	Y_3 (Hard.)	Y_4 (DR_5)
Model F-value	142.6	128.4	96.2	154.8
p-value	<0.0001	<0.0001	<0.0001	<0.0001
R^2	0.9942	0.9928	0.9876	0.9948
Adjusted R^2	0.9868	0.9836	0.9783	0.9881
Predicted R^2	0.9482	0.9396	0.9214	0.9544

Parameter	Y_1 (DT)	Y_2 (WT)	Y_3 (Hard.)	Y_4 (DR_5)
Adequate precision	38.4	36.2	28.4	42.6
Lack of fit (p)	0.43	0.51	0.38	0.62

Table 4. Predicted versus observed responses for the optimised formulation.

Response	Predicted	Observed (n=3)	Error (%)
Disintegration time (s)	13.6	13.9 ± 0.4	+2.21
Wetting time (s)	16.8	17.5 ± 0.6	+4.17
Hardness (N)	28.6	28.2 ± 0.8	−1.40
Drug release at 5 min (%)	91.2	90.4 ± 1.2	−0.88

3.4 Evaluation of the Optimised Formulation

The optimised tablets were pale yellow, smooth and defect-free (thickness 3.42 ± 0.04 mm, diameter 8.01 ± 0.02 mm). All pharmacopoeial parameters complied with specification (Table 5): mean weight 199.6 ± 2.4 mg, hardness 28.2 ± 0.8 N, friability 0.46%, drug content 99.4 ± 1.6% (RSD 1.61%). In vitro disintegration was 13.9 ± 0.4 s with wetting time 17.5 ± 0.6 s and water absorption ratio 82.6 ± 3.2%; in vivo disintegration in volunteers was 16.4 ± 1.8 s, demonstrating clinical relevance of the in vitro test.

Table 5. Evaluation parameters of the optimised formulation.

Parameter	Observed	Specification
Mean weight (mg)	199.6 ± 2.4	200 ± 7.5%
Hardness (N)	28.2 ± 0.8	25 – 50
Friability (%)	0.46	≤ 1.0
Drug content (%)	99.4 ± 1.6	85 – 115
Content uniformity (% RSD)	1.61	≤ 6.0
In vitro disintegration time (s)	13.9 ± 0.4	≤ 30
Wetting time (s)	17.5 ± 0.6	—
Water absorption ratio (%)	82.6 ± 3.2	—
In vivo disintegration time (s)	16.4 ± 1.8	—

The optimised formulation released 90.4% of the drug within 5 min versus 72.4% for the conventional reference, with complete release by 15 min (Figure 2). The dissolution profiles were dissimilar (f_2 = 38.4), reflecting the substantially faster early release of the ODT. This is attributable to rapid disintegration into a fine, high-surface-area suspension and addresses the dissolution-limited absorption of this Class II drug, potentially supporting a faster onset of action.

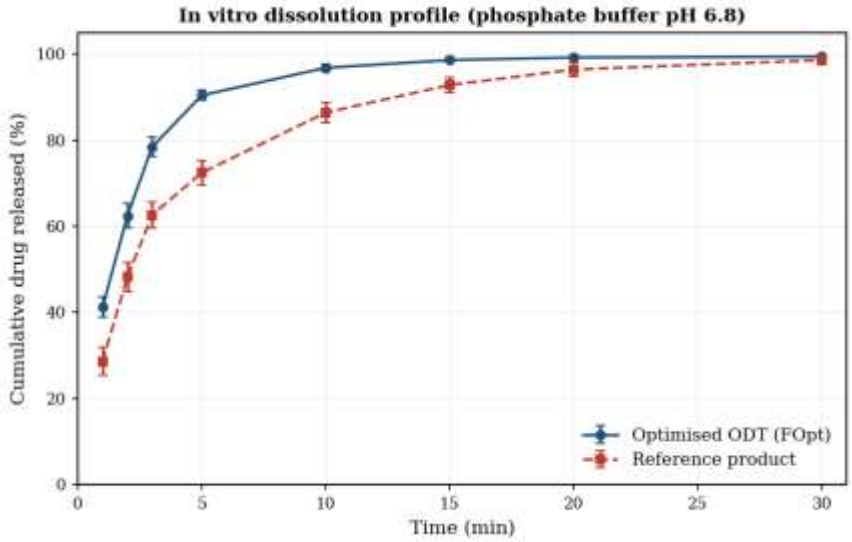

Figure 2. In vitro dissolution profiles of the optimised ODT and the reference product.

3.6 Stability studies

Under both accelerated and long-term conditions, the optimised formulation remained within specification (Table 6). Over 6 months of accelerated storage, hardness rose modestly (28.2→30.4 N), disintegration time increased (13.9→16.8 s, still <30 s), drug content remained high (99.4→97.8%), 5-min release stayed above 80% (90.4→86.8%) and total impurities remained low (0.18→0.46%, well below 1.0%). Long-term data showed smaller changes, with drug content above 98% and impurities below 0.4% at 12 months, supporting an inferred shelf life of at least 24 months.

Table 6. Stability data of the optimised formulation.

Parameter	Initial	Accel. 6 mo (40/75)	LT 6 mo (30/65)	LT 12 mo (30/65)
Hardness (N)	28.2	30.4	28.6	29.2
Friability (%)	0.46	0.58	0.48	0.50
Disintegration time (s)	13.9	16.8	14.6	15.4
Drug content (%)	99.4	97.8	99.0	98.2
Drug release 5 min (%)	90.4	86.8	89.4	87.8
Total impurities (%)	0.18	0.46	0.26	0.38

4. Conclusion

Orally disintegrating tablets of nicardipine hydrochloride were successfully designed, optimised and evaluated using rebaudioside A as a natural taste-masking sweetener. The Box–Behnken-optimised formulation showed rapid disintegration, complete early release, excellent palatability, satisfactory stability and a favourable preclinical profile featuring rapid onset of action without loss of bioavailability. A simple, natural-sweetener-based ODT is thus a feasible, palatable and robust patient-friendly dosage form for nicardipine, with particular relevance to elderly and dysphagic hypertensive patients. Clinical evaluation in the target population is warranted.

Declarations

Conflict of interest: The authors declare no conflict of interest.

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Ethics approval: The human taste-panel and animal studies were approved by the Institutional Ethics Committee and the Institutional Animal Ethics Committee respectively.

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