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Bioavailability enhancement of alendronate by novel drug delivery systems: A systematic review and meta-analysis

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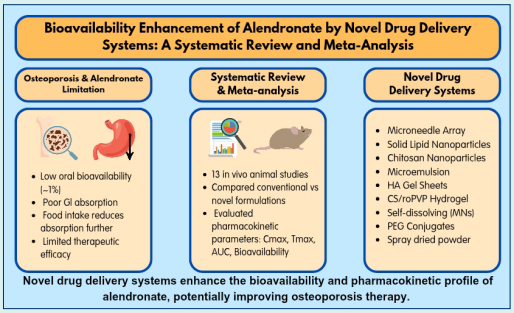
Abstract

Introduction: Osteoporosis is characterized by reduced bone mineral density and an increased risk of fractures, resulting in substantial healthcare costs and higher mortality. Bisphosphonates, such as alendronate, effectively treat osteoporosis by inhibiting bone resorption; however, their limited oral bioavailability restricts therapeutic efficacy. This study aims to evaluate different strategies developed to enhance the oral bioavailability of alendronate.



Methods: A comprehensive literature search was performed across multiple databases without language or publication date restrictions, using a predefined search strategy. Two independent reviewers screened and selected eligible studies according to predetermined inclusion and exclusion criteria. The inclusion criteria comprised in vivo animal studies investigating the pharmacokinetics of alendronate formulations, focusing on bioavailability. Studies lacking essential pharmacokinetic data were excluded. Extracted data included pharmacokinetic parameters such as C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and bioavailability, along with study characteristics, drug properties, animal details, and formulation specifics. Discrepancies in data extraction were resolved through discussion and consensus between reviewers.

Results: Meta-analyses revealed significant differences in $AUC_{0-\infty}$ and bioavailability between novel drug delivery systems (NDDS) and the pure drug ($P<0.05$), while no significant differences were observed in C_{max} and T_{max} ($P>0.05$).

Conclusion: The drug delivery systems evaluated in this review demonstrated a marked influence on pharmacokinetic parameters and enhancement of bioavailability. These findings suggest that the use of NDDS may improve the bioavailability and therapeutic effectiveness of alendronate.

Introduction

Osteoporosis is a well-recognized systemic skeletal disorder characterized by reduced bone mineral density and deterioration of bone microarchitecture, leading to an elevated risk of fractures.[1]

Osteoporotic fractures are strongly associated with increased healthcare costs, physical disability, diminished quality of life, and higher mortality rates.[2] Consequently, osteoporosis substantially increases fracture risk.[1]

Currently, osteoporosis remains one of the leading causes of morbidity and mortality among the elderly population worldwide.[1] In the United States, approximately 1.5 million individuals experience fractures attributable to osteoporosis each year, and many fail to achieve full recovery. The direct healthcare costs of osteoporotic fractures were estimated at $13.3 billion in 1994, while the indirect costs related to reduced quality of life are considerably higher. Timely and appropriate treatment for individuals at high risk of osteoporosis can therefore minimize its detrimental consequences.[3]

Several drugs are used for the treatment of osteoporosis. Among them, bisphosphonates have emerged as effective

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therapeutic choices for the prevention and treatment of various forms of osteoporosis. Since, these medications exhibit specific efficacy in promoting bone health and demonstrate a rapid response, they offer protection against spine and hip fractures in individuals with osteoporosis, meeting our expectations from them. Despite the availability of anabolic agents, bisphosphonates maintain their significance as important treatment options.[4]

The primary mechanism of bisphosphonates is their strong ability to inhibit the activity of osteoclasts. By reducing bone resorption and restoring the balance between resorption and formation, bisphosphonates promote bone strength and density.[5] These drugs could be administered either orally or intravenously, allowing flexibility in drug delivery. Alendronate, which is also known as alendronic acid or 4-amino-1-hydroxybutylidene bisphosphonate, has been shown to be effective when taken orally for treating and preventing osteoporosis caused by menopause, corticosteroids, and glucocorticoids. However, when taken orally, alendronate has a limited bioavailability ranging from approximately 0.9% to 1.8%. Additionally, food intake significantly reduces its absorption in the gastrointestinal system.[6]

The main challenge in using alendronate is its low oral bioavailability. Only 0.6% of the alendronate is absorbed when taken 2 hours before a meal or after an overnight fasting.[7] This problem significantly limits its clinical application.[8]

One of the challenges of low oral bioavailability arising from the poor solubility of drugs in aqueous media presents a significant obstacle in the development of novel pharmaceutical products.[9] Enhancing drug bioavailability can be accomplished through various strategies, including the selection of appropriate drug delivery systems, formulation adjustments, dosage optimization, identification and management of factors hindering bioavailability, and monitoring drug levels in the bloodstream following dosage modifications. It is important to note that a drug can only exert the expected effect when it reaches an adequate concentration at the target site within the patient's body. Improving the bioavailability can result in an increased drug concentrations at the desired site and prolonged duration of action leads to a more effective disease treatment.[10]

Given these challenges, developing alternative formulations of alendronate that enhance treatment efficacy and improve patients' quality of life is crucial.[11] Various formulation strategies have been investigated to enhance the oral bioavailability of alendronate. One promising approach involves the use of nanosized drug carriers such as polymeric nanoparticles, liposomes, and micelles.[12]

Given the substantial research devoted to formulating designs to improve alendronate bioavailability, this study aims to conduct a comprehensive systematic review to evaluate and compare various strategies for enhancing its oral bioavailability.

Methods

Protocol

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with code CRD420261381460.

Literature search and screening

Two independent reviewers conducted a comprehensive literature search across Medline/PubMed, Scopus, Embase, and the Cochrane Library, without restrictions on language or publication date through 2024. The following search query was applied in PubMed:

(alendronate[Title/Abstract]) AND ((bioavailability[MeSH Terms]) OR (bioavailability[Title/Abstract]) OR (bioavailabilit*[Title/Abstract]) OR (bioavailabilities[Title/Abstract]) OR (solubilit*[Title/Abstract]) OR (absorption[Title/Abstract])).

The same search strategy was adapted for the other databases. A detailed description of search strategies used in each database is provided in Table 1.

Two independent reviewers screened the titles and abstracts of retrieved articles based on predefined criteria. Full-text assessments were performed to identify eligible studies. Any disagreements were resolved through discussion with a third reviewer. The final set of studies was reviewed collectively by the entire research team to reach consensus on any uncertain points.

In conducting this review, the primary research question was defined, a search strategy was developed, inclusion criteria were established, and study selection and data extraction were performed in accordance with

Table 1. Search strategy and number of records retrieved from each database

Database	Search query	Number of retrieved records
PubMed	(alendronate[Title/Abstract]) AND ((bioavailability[MeSH Terms]) OR (bioavailability[Title/Abstract]) OR (bioavailabilit*[Title/Abstract]) OR (Bioavailabilities[Title/Abstract]) OR (Solubilit*[title/abstract]) OR (absorption[title/abstract]))	190
Scopus	(TITLE-ABS-KEY ((alendronate)) AND TITLE-ABS-KEY ((bioavailability) OR (bioavailability) OR (bioavailabilit*) OR (bioavailabilities) OR (solubilit*) OR (absorption)))	422
Embase	('alendronate'/exp OR alendronate) AND ('bioavailability'/exp OR bioavailability OR bioavailabilit* OR bioavailabilities OR solubilit*)	566
Cochrane Library	(alendronate) in Title Abstract Keyword AND (bioavailability) OR (Bioavailabilities) OR (Solubility) OR (absorption) in Title Abstract Keyword - (Word variations have been searched)	37

the methodological framework described in SYRCLE's Risk of Bias Tool for Animal Studies.[14]

Eligibility criteria

Inclusion criteria

In vivo studies conducted on animals, regardless of species, were included. All eligible studies were required to investigate the pharmacokinetics of alendronate formulations in animals; studies that did not meet this requirement were excluded. No restrictions were applied regarding language or publication date. Additional inclusion criteria, consistent with the PICO (Population, Intervention, Comparison, Outcomes) framework, were as follows:

- Population: Animal studies
- Intervention: Administration of alendronate in conventional form or through novel drug delivery systems (NDDS)
- Comparison: Pharmacokinetic parameters
- Outcome: Studies assessing at least one primary pharmacokinetic parameter, including AUC, T_{max}, or $_{Cmax}$

Only studies that fulfilled all the above criteria were included in the review.

Exclusion criteria

The following studies were excluded: those lacking full-text availability, duplicates, and studies without relevant pharmacokinetic parameters. Studies without a control group for comparison, as well as human or in vitro studies, were also excluded. Non-original articles, including reviews, commentaries, letters to the editor, opinions, editorials, and notes, were removed.

Data extraction

A standardized data extraction sheet was designed, and two independent reviewers extracted the following parameters: maximum plasma concentration (C_{max}, μg/mL), time to reach maximum concentration (T_{max}, h), area under the concentration–time curve extrapolated to infinity ($AUC_{0-\infty}$, μg·h/mL), and bioavailability (%). All parameters were converted to uniform units.

Additional information extracted from each included study comprised the first author's name, country, year of publication, drug name, drug category, preparation method, particle size (nm), zeta potential (mV), route of administration, dosage (mg/kg), animal species, mean age (weeks), body weight (g), and number of animals per group. Data extraction was conducted independently by two reviewers, and any discrepancies were resolved through discussion until consensus was reached.

Quality assessment and of risk of bias

Cochrane protocols were employed for designing risk of bias assessment. We classified the elements as Yes (low risk of bias), No (high risk of bias), or Unclear. Quality of studies was then determined according to overall results of risk of bias assessments.

Data synthesis and meta-analyses

Statistical analyses were performed using *Stata* version 11.2 (StataCorp, College Station, TX). A P value < 0.05 was considered statistically significant. Heterogeneity was assessed using Higgins' I^2 statistic, which ranges from 0 to 100%. When substantial heterogeneity was observed ($I^2 > 75\%$), a random-effects model was applied; for low heterogeneity ($I^2 < 25\%$), a fixed-effects model was used to calculate summary estimates and their corresponding 95% confidence intervals (CIs).[15,16]

To identify potential sources of heterogeneity, subgroup analyses were conducted based on categorical confounders such as the route of administration (oral, transdermal). Meta-regression was also performed to assess the influence of quantitative confounders, particularly drug dose. The standardized mean difference (SMD) was used as the outcome measure to compare NDDS with conventional formulations across pharmacokinetic parameters. Mean and standard deviation (SD) values were extracted from each study. The pooled SMD and corresponding 95% CI were estimated using either Cohen's or Hedges' approach.

Results

Study selection

The study selection process is illustrated in Fig. 1. A total of 1,205 records were retrieved from Embase, PubMed, Cochrane Library, and Scopus up to 2024. After removing 111 duplicates, title and abstract screening were conducted. Studies that did not meet the inclusion criteria or were irrelevant to the topic were excluded, leaving 206 articles for full-text evaluation. Ultimately, 13 studies were included in the meta-analysis.[7,11,17,18]

Seven studies investigated transdermal delivery,[11,19-24] four examined oral formulations,[7,18,25,26] and two evaluated inhalation systems.[17,27] Four studies utilized microemulsion or microneedle arrays to enhance bioavailability.[19,20,24,26] Three studies focused on solid lipid nanoparticles (SLN) and chitosan (CS) nanoparticles.[7,23,27] Additionally, three investigations employed carriers such as CS/PVP hydrogel, chitosan conjugated with polyethylene glycol, and HA gel sheet.[11,18,25] One study used a spray-dried powder formulation.[17] All included studies reported bioavailability percentages, eleven provided $AUC_{0-\infty}$ values, and twelve reported either C_{max} or T_{max} for the final formulation. A summary of extracted data is provided in Table 2.

Risk of bias and quality assessment

The methodological quality of included studies is shown in Table 3. According to this methodology, eight studies showed good, two fair, and three had poor quality.

Meta analysis results

The meta-analysis compared bioavailability, T_{max}, AUC, and C_{max} between conventional formulations and NDDS. Differences among administration routes—oral, transdermal, and inhalation—were examined. Subgroup analyses assessed variations in bioavailability, AUC, C_{max}, and T_{max}, while dose was evaluated as a potential

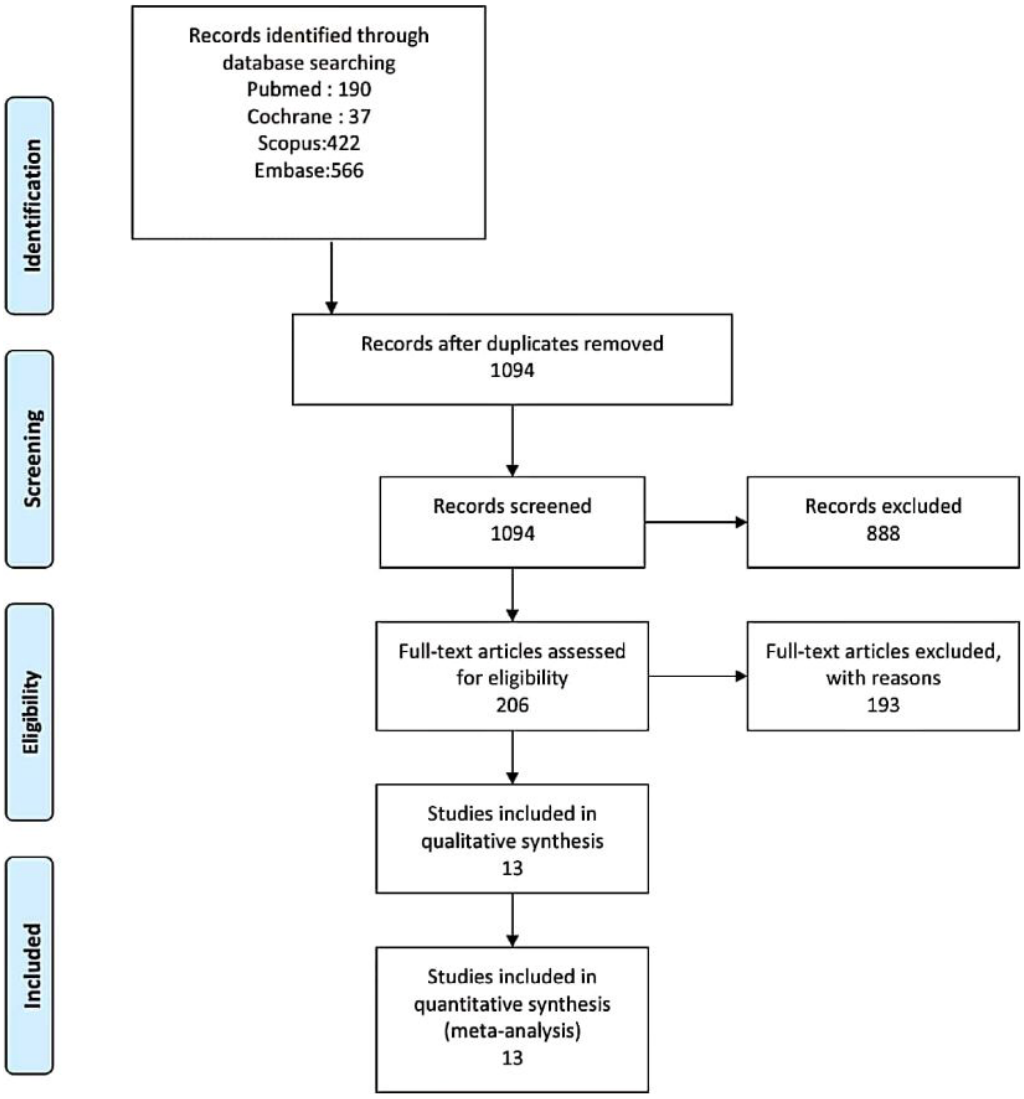

Fig. 1. Flow chart of study selection process.

confounder affecting AUC and C_{max}.

Maximum concentration in plasma between conventional formulations and NDDS (C_{max})

No significant difference was observed between conventional formulations and NDDS in terms of C_{max} (SMD = 1.04; 95% *CI*: −1.96 to 4.03; $P = 0.498$; $I^2 = 88.4\%$). The test for residual heterogeneity was significant (Q-test, $P < 0.0001$).

In the subgroup analysis based on the route of administration, neither oral (SMD = 3.06; 95% CI: −2.74 to 8.86; $P = 0.302$; $I^2 = 89.9\%$; $P = 0.000$) nor transdermal (SMD = −0.82; 95% CI: −3.27 to 1.63; $P = 0.512$; $I^2 = 75.1\%$; $P = 0.018$) formulations showed significant differences (Fig. 2).

Maximum concentration in plasma in NDDS (C_{max})

the pooled effect of NDDS was statistically significant (SMD = 0.20; 95% CI: 0.11 to 0.30; $P < 0.001$; $I^2 = 99.4\%$). In subgroup analyses by administration route, both oral formulations (SMD = 0.21; 95% CI: 0.03 to 0.38; $P = 0.021$; $I^2 = 99.7\%$) and transdermal formulations (SMD = 0.18; 95% CI: 0.12 to 0.25; $P < 0.001$; $I^2 = 92.3\%$) demonstrated significant differences. The covariate, drug dose, did not significantly influence the results ($P = 0.066$) (Fig. 3).

Bioavailability

The comparison of bioavailability between NDDS and conventional formulations revealed statistically significant differences (SMD = 4.52; 95% CI: 2.42 to 6.62; $P < 0.001$; $I^2 = 94.5\%$). The test for residual heterogeneity was also significant (Q-test, $P < 0.0001$). In addition, bioavailability was significantly higher in NDDS compared with conventional formulations (SMD = 1.77; 95% CI: 0.56 to 2.98; $P = 0.004$; $I^2 = 0.0\%$; $P = 0.858$) (Fig. 4).

Time to C_{max} (T_{max})

The effect of NDDS on T_{max} was statistically significant (SMD = 1.96; 95% CI: 0.04 to 3.96; $P = 0.05$; $I^2 = 99.4\%$). The test for residual heterogeneity was significant (Q-test, $P < 0.0001$). However, meta-analysis comparing conventional and NDDS demonstrated no significant difference in T_{max} (SMD = 3.8; 95% CI: −6.13 to 13.74; $P = 0.453$; $I^2 = 94.3\%$; Q-test, $P < 0.0001$). (Fig. 5).

Area under the concentration-time curve from zero to time in NDDS formulations ($AUC_{0-\infty}$)

Overall, NDDS significantly increased the $AUC_{0-\infty}$ (SMD = 2.19; 95% CI: 0.92 to 3.47; $P = 0.001$; $I^2 = 100\%$; Q-test, $P < 0.0001$). Subgroup analysis based on the route

Table 2. Main characteristics and pharmacokinetic parameters of final accepted studies

No.	1	2	3	4	5	6	7	8	9	10	11	12	13
General													
First author	Boche	Li	Zameer	Kusamori	Hosny	Naito	Chia-Yu Su	Boche	Katsumi	Katsumi	Meng and Hu	Katsumi	Cruz l
Country	India	china	India	Japan	Saudi Arabia	Japan	Taiwan	India	Japan	Japan	china	Japan	Brazil
Year	2020	2020	2020	2010	2016	2019	2018	2018	2017	2011	2011	2012	2011
Preparation method	Microemulsion	chitosan nano particle	Chitosan nano particle	Transdermal patch	solid lipid nano particle	HA gel sheet	CS / roPVP hydrogel	Microemulsion	self-dissolving (MNs)	conjugated whit polyethylene glycol	Microemulsion	Micro needle array	spray dried powder
Particle size (nm)	93.21 ± 5.95	250	135.75 ± 5.80	-	99 ± 4	-	-	93.21 ± 5.95	-	-	30.6	-	-
range particle size	< 100	100-300	100-300	-	< 100	-	-	< 100	-	-	-	-	-
Zeta potential (mV)	-	28	23.8 ± 3.69	-	-	-	-	− 41.0 ± 3.6	-	-	8.5	-	-
Animal species	Wistar Rats (male)	S.D rats (male)	Swiss albino mice	Wistar rats (male)	albino rabbits (male)	Male Wistar rats and male and female Sprague Dawley rats	New Zealand white rabbits	Wistar rats (female)	Wistar rats (male)	Male Wistar rats and male Sprague Dawley rats	male beagle dogs	male Wistar rats and female SD	male Wister rats
Mean age (wk)	-	-	6-8	8	-	-	-	-	8	8 - 7	-	8-7	
Mean weight	-	-	25-30 g	230-250 g	2-2.5 kg	250–270g, 180-200g	4-5 kg	-	220-250 g	230-250g, 200-220g	10-12.5 kg	220-250, 200-220g	280-350 mg
Novel drug delivery systems													
Dose (mg/kg)	30	10	0.0352	14.4	1	2.5	3.88	30	1.5	0.	6.22	0.8	2
Route of administration	Transdermal	Transdermal	inhalation	Transdermal	oral	Transdermal	oral	Transdermal	Transdermal	oral	oral	Transdermal	inhalation
n	3	-	6	-	6	-	3	6	3	-	6	-	24
C max(µg/ml) (mean ± SD)	0.132 ± 0.02162	0.16	0.3855	0.0833 ± 0.021	0.01654 ± 0.00312	0.053 ± 0.01	0.10483 ± 0.01732	0.132 ± 0.02162	0.37 ± 0.08	2.82	0.502 ± 0.0532	0.236 ± 0.108	-
T max(h) (mean ± SD)	3	24	2	3	4.5 ± 0.52	12 ± 6	0.83 ± 0.29	3	0.25	0.44	0.563 ± 0.125	0.28 ± 0.11	-
t 1/2 β (h) (mean ± SD)	-	-	20.484	-	-	-	15.5 ± 1.47	-	-	-	1.860.327	-	-
AUC 0-infinity µg.h/ml (mean ± SD)	-	0.098	378.258	0.109	3.7815 ± 0.2964	0.833 ± 0.1083	2.51891 ± 0.2723	1.7985 ± 0.23098	0.136	5.9796	0.682 ± 0.0187	0.926 ± 0.138	-
AUC 0-t (µg.h/ml) (mean ± SD)	1.7985 ± 0.20398	-	-	-	2.173 ± 0.2164	-	-	-	-	-	0.676 ± 0.112	-	-
Kel (h1) (mean ± SD)	-	-	0.00057	-	0.203 ± 0.06	-	0.04 ± 0.01	-	-	-	-	-	-
bioavailability% (mean ± SD)	3.58 ± 1.21	7.4	2	8.3	5.18	20 ± 2.6	2.1	3.58 ± 1.21	96	44	1.974	90 ± 14	6.23 ± 0.83
relative bioavailability	1.935	6.167	-	4.882	7.4	-	3	2	11.566	48.889	2.82	47.368	3.5
Pure drug													
Dose (mg/kg)	30	30	0.0352	50	1	1	3.88	30	50	0.6	6.22	30	2
n	3	-	6	-	6	-	3	6	3	-	6	-	-
Route of administration	oral	Transdermal	inhalation	oral	oral	IV	oral	oral	oral	-	oral	Oral	Oral
C max(µg/ml) (mean ± SD)	0.285 ± 0.08941	90	1.0564	0.5 ± 0.25	0.00492 ± 0.00102	-	0.18805 ± 0.02651	0.285 ± 0.08941	0.22 ± 0.04	-	0.152 ± 0.0273	0.407 ± 0.12	-
T max(h) (mean ± SD)	1	15	0.25	1	0.75 ± 0.13	-	0.5	1	1	-	0.75 ± 0.204	0.92 ± 0.36	-
t 1/2 β (h) (mean ± SD)	-	-	1.089	-	-	-	8.15 ± 1.89	-	-	-	1.75 ± 0.267	-	-
AUC 0-infinity µg./ml. h (mean ± SD)	-	0.905	101.242	1.104	0.5114 ± 0.03821	1.75 ± 0.2	0.73299 ± 0.14472	0.93112 ± 0.27115	0.3916	-	0.319 ± 0.0467	0.747 ± 0.324	-
AUC 0-t (µg.h/ml) (mean ± SD)	0.9311 ± 0.27115	-	-	-	0.2916 ± 0.02814	-	-	-	-	-	0.303 ± 0.0451	-	-
Kel (h1) (mean ± SD)	-	-	0.01138	-	0.638 ± 0.17	-	0.09 ± 0.02	-	-	-	-	-	-
bioavailability% (mean ± SD)	1.85 ± 0.21	1.2	-	1.7	0.7	-	0.7	1.85 ± 0.21	8.3	0.9	0.7	1.9 ± 0.8	1.7

Note: The pharmacokinetics parameters include maximum concentration in plasma (C_{max} (µg/ml)), time to C_{max} (T_{max} (h)), half-life (t ½ (h)), the area under the concentration-time curve from zero to time t (AUC_{0-t} (µg.h/ml)), the area under the concentration-time curve from zero to infinitive ($AUC_{0-\infty}$ (µg.h/ml)).

Table 3. Risk of bias evaluation and overall quality assessment of the included studies

Author	Was the allocation sequence adequately generated and applied?	Were the groups similar at baseline or were they adjusted for confounders in the analysis?	Was the allocation to the different groups adequately concealed during?	Were the animals randomly housed during the experiment?	Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	Were Animals selected at random for outcome assessment?	Was the outcome assessor blinded?	Were incomplete outcome data adequately addressed?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could result in high risk of bias?	Quality
Mithila Boche	+	+	-	؟	-	+	+	؟	+	+	Medium
Baofeng Li	؟	؟	؟	+	-	؟	+	-	؟	-	Low
Saima Zameer	+	+	+	+	+	+	+	+	+	+	High
Yanhai Xi	+	+	+	+	؟	+	+	؟	+	+	High
Kosuke Kusamori	+	+	+	+	؟	+	+	؟	+	+	High
Khaled Mohamed Hosny	+	+	+	+	+	؟	+	؟	+	+	High
Tammam Alama	+	+	+	؟	؟	+	+	؟	+	+	High
Yuka Nakaya	؟	؟	؟	؟	؟	؟	؟	-	؟	-	Low
Chihiro Naito	+	+	؟	؟	-	+	+	؟	+	+	Medium
Chia-Yu Su	+	+	؟	؟	+	+	+	؟	+	+	High
Mithila Boche	+	+	؟	؟	+	+	+	؟	+	+	High
Hidemasa Katsumi	+	+	+	+	؟	+	+	؟	+	+	High
Chengyun Yan	+	+	؟	؟	؟	؟	+	-	؟	-	Low

of administration revealed a significant increase for oral formulations (SMD = 2.32; 95% CI: 0.83 to 3.82; $P = 0.002$; $I^2 = 100\%$; $P < 0.0001$) (Fig. 6).

Area under the concentration-time curve from zero to time t ($AUC_{0-\infty}$) conventional formulations and NDDS

NDDS produced a significant increase in $AUC_0-\infty$ compared with conventional formulations (SMD = 7.79; 95% CI: 2.93 to 12.65; $P = 0.002$; $I^2 = 76.7\%$; $P = 0.005$). Subgroup analysis by route of administration indicated that oral delivery systems markedly affected $AUC_{0-\infty}$ (SMD = 9.82; 95% CI: 5.96 to 13.67; $P < 0.001$; $I^2 = 20.7\%$; $P = 0.283$) (Fig. 7).

Sensitivity analysis

Sensitivity analysis demonstrated that sequential exclusion of individual studies did not alter the overall results of pharmacokinetic parameters. Funnel plots, along with Egger's and Begg's regression tests, indicated no evidence of publication bias for bioavailability (P for Begg's = 0.317), $AUC_{0-\infty}$ (P for Begg's = 0.174), T_{max} (P for Begg's = 0.317), and C_{max} (P for Egger's = 0.228; P for Begg's = 0.091).

Discussion

The oral bioavailability of alendronate is limited to approximately 0.9%–1.8% and is further reduced in the presence of food.[6] Alendronate is classified as a Biopharmaceutics Classification System (BCS) Class III compound, indicating high solubility but low membrane permeability. Consequently, inadequate intestinal permeation represents a major factor contributing to its poor oral bioavailability.[28]

In this systematic review, alternative formulations developed to enhance the bioavailability of alendronate were compared with conventional formulations. In addition to bioavailability, other pharmacokinetic parameters—C_{max} (μg/mL), T_{max} (h), $AUC_{0-\infty}$ (μg·h/mL), and bioavailability (%)—were evaluated to determine whether NDDS influence the pharmacokinetic behavior of alendronate. Overall, the novel formulations demonstrated significant increases in bioavailability and $AUC_0-\infty$, whereas no significant differences were observed between conventional and NDDS formulations in C_{max} and $T_{max.}$[7,11,17-21,23-27]

C_{max}

The maximum plasma concentration (C_{max}) is traditionally used as a metric for the absorption rate, despite the fact that there are several concerns.[29] The rate and extent of drug absorption are typically characterized by C_{max} and $AUC_{0-\infty}$, respectively.[30] C_{max} represents the peak plasma concentration of a drug and serves as an indicator of the absorption rate.[31] The results of this analysis showed that NDDS administered via oral and transdermal routes significantly increased $C_{max.}$[7,11,18-21,23-25] For instance, Katsumi et al developed self-dissolving microneedle (MNs) arrays in which alendronate was localized at the tip of micron-scale needles using a dip-coating technique [ALN(TIP)–MN]. Following transdermal application of ALN(TIP)–MN in

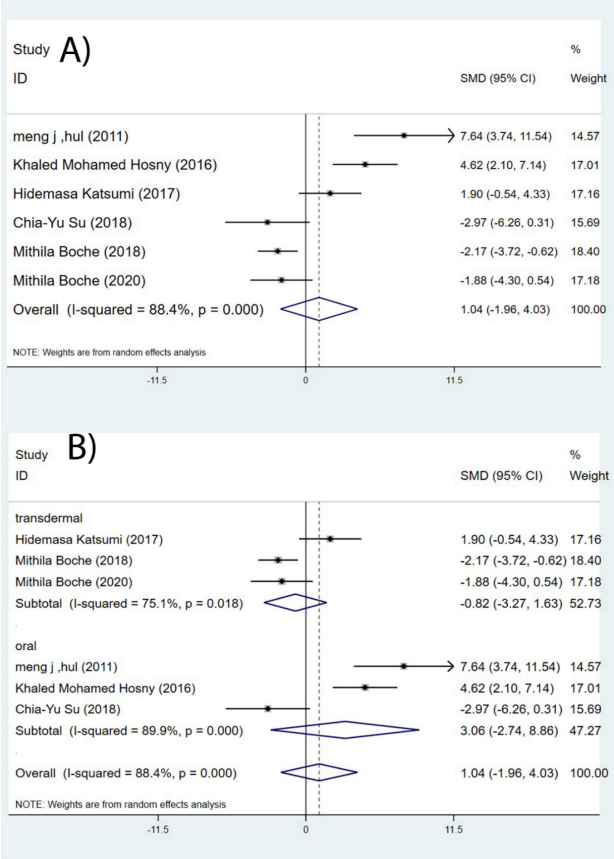

Fig. 2. Forest plots obtained after meta-analyses of C_{max} (A) Analysis between conventional and novel drug delivery systems; (B) Sub group analysis between conventional and novel drug delivery systems.

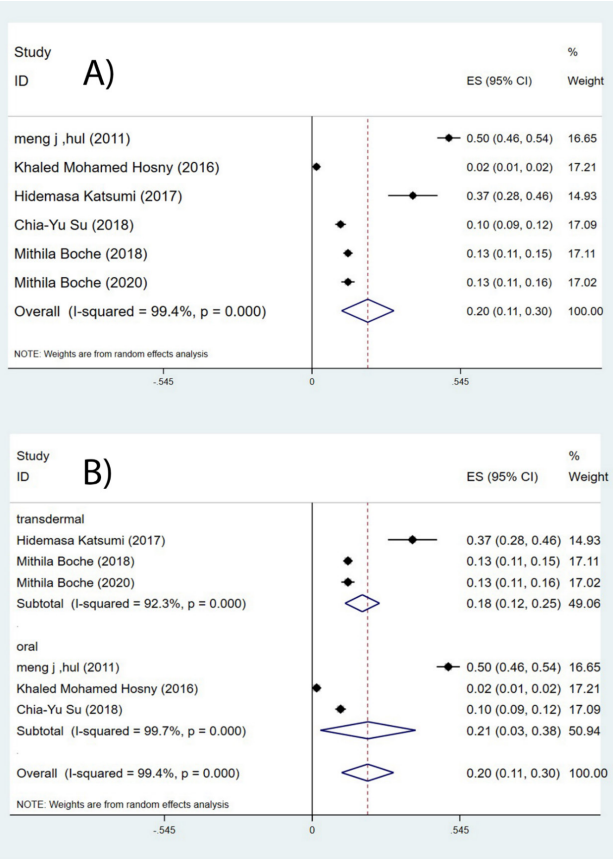

Fig. 3. Forest plots obtained after meta-analyses of C_{max} (A) Analysis between novel drug delivery systems; (B) Sub group analysis between novel drug delivery systems.

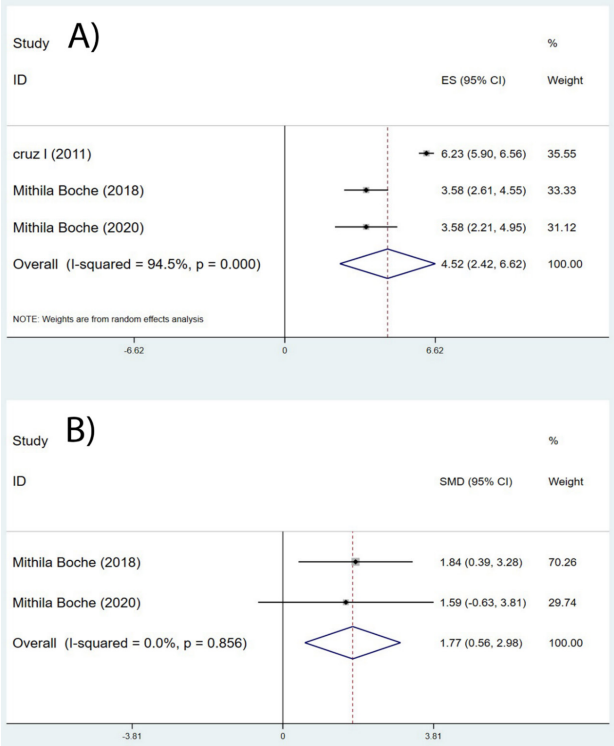

Fig. 4. Forest plots obtained after meta-analyses of bioavailability A) Analysis between novel drug delivery systems; B) Analysis between conventional and novel drug delivery systems.

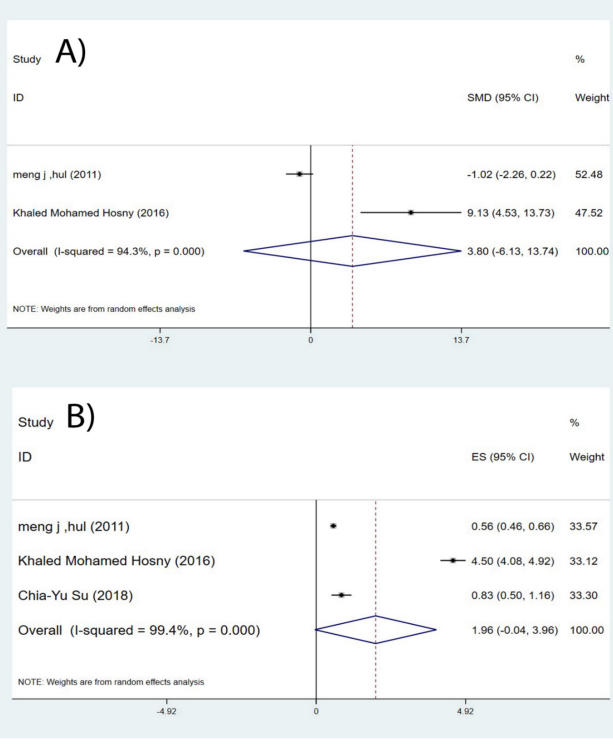

Fig. 5. Forest plots obtained after meta analyses of T_{max} (A) Analysis between conventional and novel drug delivery systems; B) Analysis between novel drug delivery systems.

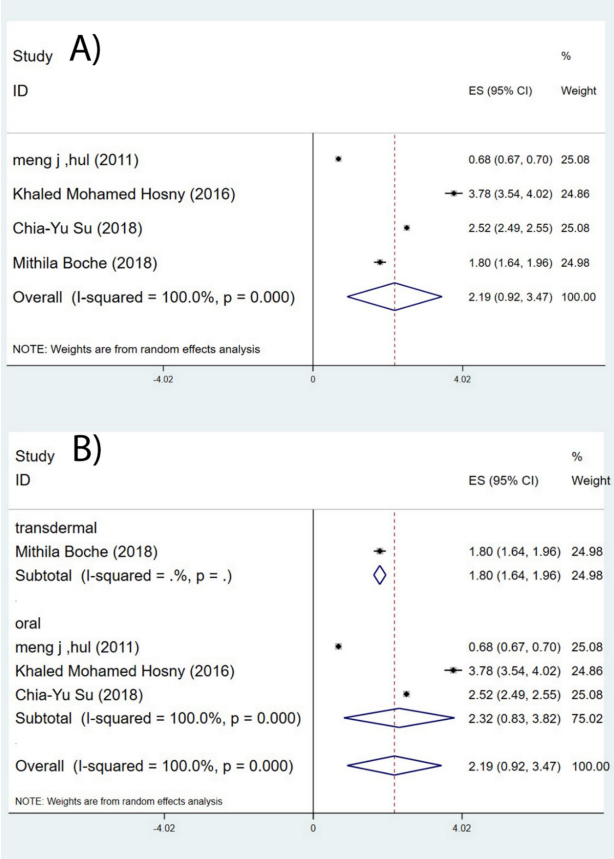

Fig. 6. Forest plots obtained after meta-analyses of AUC (A) Analysis between novel drug delivery systems; (B) Sub group analysis between conventional and novel drug delivery systems.

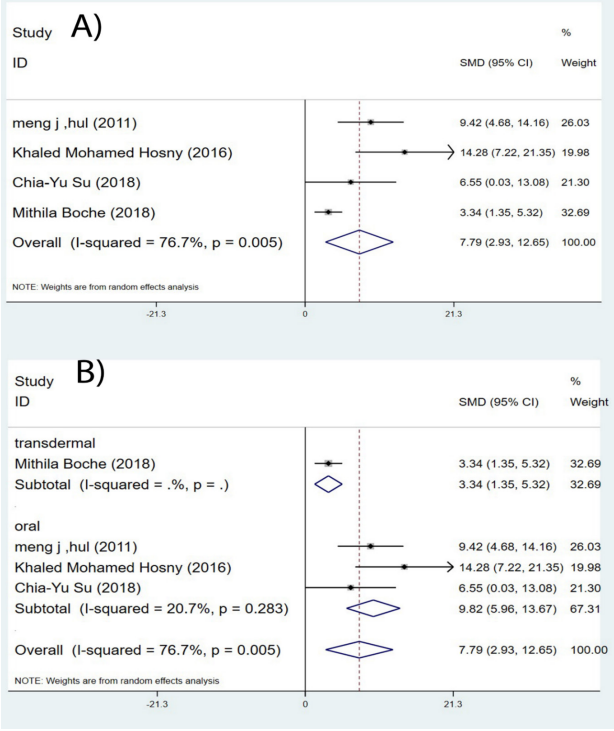

Fig. 7. Forest plots obtained after meta-analyses of AUC (A) Analysis between conventional and novel drug delivery systems; (B) Sub group analysis between novel drug delivery systems.

mice, plasma concentrations of alendronate rose rapidly, achieving a bioavailability of approximately 96%.[20]

Bioavailability

The results demonstrated that novel formulations significantly enhanced the bioavailability of alendronate compared with the pure drug, highlighting the superiority of the NDDS approach.[7,11,17-21,23-27] Bioavailability is a key pharmacokinetic determinant that directly influences therapeutic efficacy.[10] Hosny et al reported that encapsulation of alendronate in SLN enhanced bioavailability by more than sevenfold, an improvement attributed to the nanoscale size (~100 nm), which facilitates adhesion to and uptake by intestinal epithelial cells.[7]

Techniques used to enhance alendronate bioavailability in the studies reviewed included microemulsion, chitosan nanoparticles, transdermal patches, SLN, hyaluronic acid (HA) gel sheets, chitosan/polyvinylpyrrolidone (CS/PVP) hydrogels, polyethylene glycol–conjugated MNs, microneedle arrays, and spray-dried powders.[7,11,17-21,23-27] For example, Boche et al demonstrated that *w/o* microemulsion formulations achieved higher bioavailability than oral alendronate solution.[24] Similarly, in rats, transdermal administration of alendronate-loaded microemulsion yielded a twofold increase in bioavailability compared with oral delivery.[19] Li et al developed an alendronate–chitosan nanoformulation that produced sixfold higher bioavailability than a patch containing unmodified alendronate. [23] The methodologies employed to enhance the bioavailability of Alendronate, as reported in the studies included in this review, are as follows: Microemulsion, chitosan nanoparticle, transdermal patch, solid lipid nanoparticle, HA gel sheet, CS / roPVP hydrogel, self-dissolving MNs-conjugated with polyethylene glycol, Microneedle array, spray dried powder.

$AUC_{0-\infty}$

The $AUC_{0-\infty}$ represents the total systemic exposure to a drug and reflects the overall extent of absorption.[10,31] Pharmacokinetic comparisons frequently rely on $AUC_{0-\infty}$ and C_{max} to quantify absorption and exposure.[32] In this study, NDDS administered via oral and transdermal routes significantly increased $AUC_{0-\infty}$ compared with conventional formulations, supporting the enhanced absorption achieved by innovative delivery platforms. Boche et al reported that transdermal administration of alendronate microemulsion at 30 mg/kg yielded significantly higher $AUC_{0-\infty}$ values than oral solution at the same dose ($P < 0.05$). Even at a lower dose (25 mg/kg), transdermal microemulsion achieved a higher $AUC_{0-\infty}$ than oral solution, although the difference was not statistically significant.[24]

Increased AUC_{0-t} indicates an improved rate and extent of drug absorption. The present findings demonstrate that NDDS significantly enhances the bioavailability of pharmaceutical compounds.[33] Subgroup analyses further revealed that nanoparticles within the 100–300 nm size range produced a marked increase in AUC_{0-t}. This increase can be attributed to their larger surface area, which

facilitates faster dissolution, greater membrane permeation, and consequently enhanced absorption.

Although zeta potential does not directly affect drug absorption, it influences the stability and dispersion of nanocarriers. A higher absolute zeta potential reduces particle aggregation, promotes uniform particle distribution, and strengthens the interaction between drug-loaded nanoparticles and biological membranes. Therefore, formulations with higher absolute zeta potential values typically exhibit improved bioavailability along with elevated C_{max} and $AUC_{0-\infty}$.[34,35]

The findings of this study indicate that microneedle-based delivery of alendronate achieved higher absorption and bioavailability compared with SLNs. MNs, as a minimally invasive route, avoid first-pass metabolism and bypass the gastrointestinal tract, resulting in improved patient compliance and superior therapeutic outcomes. In addition, MNs offer potential for commercial translation due to their simplicity and cost-effectiveness. Thus, formulating alendronate into microneedle patches represents a promising strategy for osteoporosis therapy, providing enhanced efficacy through a more patient-friendly administration route.[36-38]

Although this study presents encouraging preclinical results, further clinical research is needed to assess the safety, efficacy, and patient adherence of these novel delivery systems. Such studies will confirm these findings and establish their clinical applicability. Translating preclinical data to humans involves several challenges, including formulation scale-up, excipient selection, and safety evaluations. Nonetheless, employing biocompatible and biodegradable excipients at early stages of formulation development enhances safety in both animals and humans, reduces toxicity potential, and facilitates smoother translation to clinical settings.

T_{max}

An increase in T_{max} indicates slower entry of the drug into systemic circulation, leading to prolonged exposure. Sustained-release formulations typically exhibit higher T_{max} values; however, factors such as gastric emptying rate, absorption site, and formulation excipients may also influence T_{max}. Therefore, T_{max} should be interpreted alongside $Cmax$ and $AUC_0-\infty$ to characterize sustained-release pharmacokinetic behavior.[39,40]

Limitations of current systematic review

The primary limitation encountered in this systematic review was the scarcity of studies evaluating additional pharmacokinetic parameters that could clarify the mechanisms underlying bioavailability enhancement. Parameters such as the elimination rate constant (*kel*, h^{-1}), mean residence time (*MRT*), and the elimination phase constant (β_1) were seldom reported. Including these parameters in future meta-analyses would provide a deeper mechanistic understanding of how *NDDS* influence both the absorption and elimination phases of alendronate pharmacokinetics.

Another limitation was the incomplete data in several studies. Despite attempts to contact corresponding authors, some missing information could not be obtained, which posed additional challenges during data synthesis.

Although the authors acknowledge these limitations, this systematic review offers valuable insight into the potential of *NDDS* to enhance the bioavailability of alendronate and to alter its pharmacokinetic characteristics. However, substantial heterogeneity was observed among the included studies, as reflected by I^2 values exceeding 75%. Consequently, the pooled estimates should be interpreted with caution, and the findings may not be broadly generalizable.

Conclusion

The drug delivery systems mentioned in this study, demonstrated a significant impact on pharmacokinetic parameters and enhancement of bioavailability. It seems that the utilization of novel drug delivery systems may enhance the efficacy of alendronate by improving the bioavailability. Among the investigated methods to increase the bioavailability of alendronate microneedle array technology has significantly enhanced the transdermal absorption of alendronate, achieving a bioavailability of around 96%, far exceeding previous delivery methods.[21]

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Competing Interests

The authors declare no conflict of interest.

Ethical Approval

Not applicable.

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