Section A-Research paper

Comparative Meta-analysis of Free and Nano-Formulated Drugs Available for Systemic Circulation

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Abstract:

Oral administration is the most beneficial choice for drug delivery since it ensures improved patient compliance. However, the primary obstacles to efficient oral drug delivery are medicines' low metabolic/enzymatic stability and their difficulties dissolving in water. Among other methods, nanotechnology-based drug delivery systems can solve problems with oral medicine administration. Nanotechnology-based drug delivery systems allow the administration of antihypertensive drugs with improved therapeutic impact and bioavailability. In order to combine data on the improvement of oral bioavailability area under curve (AUC) by nanotechnology from several investigations, meta-analysis was used in this study. 21 studies from different countries were considered. Bioavailability was 95% CI [1.05–3.02], based on the total improvement potential of nano-formulations based on a drug delivery system. This study divided the vast and current data used to illustrate how nanotechnology improves bioavailability into five categories - solid lipid nanoparticles and nanoparticles made of polymers. Additionally, the findings of the meta-analysis showed that many treatments had a high relative bioavailability.

Keywords: Nanoparticles, Oral Bioavailability, Area Under Curve (AUC), Nanotechnology, Solid lipid nanoparticles, polymeric nanoparticles

Introduction:

The chemical, biological, and physical properties of nanoscale materials differ significantly from those of larger materials (Love et al., 2005). In order to uncover potential uses for the nanotechnology sector, researchers have focused a lot on the importance of this property of nanoparticulate materials. The fact that nanotechnology has the potential to significantly boost both the efficacy of treatments and the effectiveness of pharmaceuticals that may be administered in several ways makes the application of this technology in the pharmaceutical industry a significant benefit (Parveen et al., 2017). One of the most intriguing applications of nanotechnology is its potential to enhance the delivery of biological systems. Compounds or particles with a nanoscale that can increase drug bioavailability are employed for drug delivery (Patra et al., 2018). Nanorobots are used to carry out molecular targeting since they have been nano-engineered to boost bioavailability in certain bodily regions and over time. Since oral dose forms promote patient compliance, are easy to administer, and are more affordable than other dosage forms, they are the most extensively used and well-liked pharmaceutical delivery method (Shahiwala, 2011). Around 70% of all prescriptions are written for oral administration; depending on patient need, these drugs are frequently provided in liquid or solid form. It has been shown that drugs taken orally do not instantly create a therapeutic impact in systemic circulation compared to medications delivered by parenteral administration. This is applicable when using drugs that are supplied orally with those that are administered topically. Once they have passed through the digestive system and are ready to enter the body, they must first be absorbed into the circulation system (Mushtaque et al., 2020). Compared to the parenteral method of drug administration, the oral route of medication administration results in, at best, delayed onset of the medication's effects, and, at worst, it may completely exclude some therapies that cannot enter the circulation. This is because of the reason stated in the previous sentence (Scioli Montoto et al., 2020). It is crucial to understand how the medicine interacts with the physiological components of the gastrointestinal system, how much of the Drug is absorbed into the bloodstream, and how much of an effect it has. It is crucial to comprehend how these interactions function if the Drug can exhibit its full effects and is absorbed into the bloodstream naturally (Wasan et al., 2008). After oral medications reach the liver, they must travel through the intestinal wall and the portal circulation. These two locations frequently serve as first-pass metabolic sites. As a consequence of this, many drugs may be digested before reaching the appropriate plasma concentrations. Drugs with a low rate of water

solubility, a slow rate of absorption, and oral dose forms have the highest rate of low bioavailability (Tiwari et al., 2009). A lack of time for absorption in the gastrointestinal tract is the root cause of low bioavailability. Inadequate medication absorption may occur if it cannot dissolve completely or does not adequately manage to permeate the epithelium (Soundararajan, 2016). As a direct result, bioavailability may be poor and very variable. Numerous variables, such as gastrointestinal surgery, physical activity, age, gender, genetic genotype, infections, stress, and chemical reactions, impact a drug's bioavailability. Some of these factors include, during hydrolysis, the active component is hydrolyzed by digestive enzymes or a stomach acid compound is created, other medications are absorbed, and the Drug is digested within the lumen microflora. It is conjugated in the intestine (Al Jbour, 2022). Because it guarantees that patients will take their medication as prescribed, oral administration is the most effective way of drug delivery. The difficulty of pharmaceuticals dissolving in water and the absence of adequate enzyme activity in medications must be understood as a major cause of many difficulties associated with administering medications through the mouth (Khan et al., 2015). In pharmaceutical treatment, several strategies may be used to handle hydrophobic compounds. In the not-too-distant future, nanotechnology may prove to be one of the most successful means of delivering pharmaceuticals, in addition to the many other systems, for the purpose of resolving the issues involved with taking drugs by mouth. Antihypertensive medications can be delivered with more therapeutic effectiveness and bioavailability than can be achieved via the use of any other approach presently on the drug delivery systems based on nanotechnology (Baishya et al., 2021). In order to keep track of the progress of research on improving oral drug absorption and bioavailability using nanotechnology, it is necessary to conduct a thorough review of the studies accumulated in this field of research. This will allow monitoring of the current research progress (Fasinu et al., 2011). In addition, it is essential to determine whether or not nanotechnology can be utilized to improve the biodistribution of pharmaceuticals taken orally and what potential they have in this regard. In addition, we wish to establish a connection between the findings of the many research that have been connected, locate additional intriguing connections, and analyze other targets of disagreement that may emerge over time as a result of the large number of studies that have been completed (Dudhipala & Janga, 2017). According to the previous report, several research studies evaluated nanotechnology as a strategy for increasing the oral bioavailability of a substance. Oral bioavailability can be increased by using nanotechnology. The pharmacokinetic parameters of these studies were examined using

meta-analysis, a statistical approach developed particularly for this class. Meta-analysis is one of the most frequent ways to determine whether or not healthcare treatments are efficient (Hu et al., 2010). Previous research has demonstrated that a wide range of pharmacological formulations can increase their oral bioavailability by applying nanotechnology. The purpose of this research is to provide quantitative answers to queries such as "How realistic is the use of nanotechnology in the process of boosting bioavailability?" and "Which specific application of nanotechnology is the most successful?" in addition to "Which type of nanotechnology appears to be the most potential therapeutic candidate?" based on the material that has been previously reviewed.

Material and Methods:

PRISMA 2020 (Preferred Reporting Information Standards for Meta-Analysis Research). Guidelines for Contents for Systemic Reviews and Meta-Analysis Based on specified aims and qualifying restrictions, we systematically evaluated relevant papers up to July 2023 in PubMed, Science Direct, and Web of Science. There were sentences and words taken from literature. We included all the references to previous literature in both national and international research on the general effects of oral bioavailability caused by nanotechnology. New nanoparticle technology improves oral bioavailability strategies in the clinical setup.

Literature search

A meta-analysis of recent literature that identified nanotechnology as a potential strategy for enhancing oral bioavailability was produced due to our thorough and methodical search of recent literature pertinent to the questions above over the past few years (1990 to 2023). The results of this study and the information help those researchers planning on implementing nanotechnology to improve poor oral bioavailability by using nanotechnology.

Inclusion criteria

Finding relevant research on the connection between bioavailability through the oral route and nanotechnology required an analysis of the titles and abstracts of the numerous papers. Only research articles were included. Only the English language will be taken into consideration; other languages will not be taken into account. For research publications to be considered for examination during the screening phase, they must comply with certain standards.

1. Only primary studies that describe unique research on the oral bioavailability of nano-formulated medicines should be included in the analysis (nano-formulation).
2. Oral administration of nano-formulated medications should be the subject of research studies included in this meta-analysis.
3. Include only research that was done on human subjects. Experiments conducted on animals or in vitro should not be used because it is not mimic the oral bioavailability in humans.
4. All trials that are included should administer medications that have been nano-formulated.
5. The oral bioavailability of the nano-formulated medication must be quantified in studies. The area under the plasma concentration-time curve (AUC) or the maximum plasma concentration (Cmax) are two examples, and other pertinent pharmacokinetic metrics may be included.
6. Pharmacokinetic (PK) characteristics, such as AUC, are relevant to oral bioavailability.
7. Nanotechnology has enhanced the solubility, permeability, and oral bioavailability of drugs.
8. Medicine administered in a non-Nano formulated (conventional) form as a control group in trials that have one is a viable option. Evaluating the advantages of nano-formulation on bioavailability depend heavily on comparisons with traditional formulations.
9. To assure data reliability and validity. Pharmacokinetic study quality evaluation tools or research design, sample size, and methodology can be used.
10. Based on the available resources and the scope of the meta-analysis, consider research published in various languages. However, research released in widely acknowledged languages (such as English) is frequently chosen.
11. Including the studies is to ensure that the analysis is based on the most recent relevant information.
12. The text or table should make it obvious what the PK parameters are.

The analysis should have included studies already completed or not published in English or another language. Studies that did not discuss nanotechnology, nanomedicine, nano-formulation, nanomaterials, oral bioavailability enhancement, or those needing original data (i.e., research publications) were eliminated.

Extraction of data

During the assessment process, publications that did not match the inclusion requirements were removed. When the titles were not sufficiently descriptive, the abstracts were qualified. Data extraction and analysis were done after removing any duplicates from full-text publications. A Microsoft Excel spreadsheet (Redmond, WA, USA) was used to tabulate the data from the included studies (Samii et al., 2009).The bioavailability of oral nanoparticles, AUC, weight percentages, sample sizes tables, combining techniques, sample dimensions, testing procedures/standards, conditioning, mean (SD), SEM analysis, and outcomes were all examined.

Statistical analysis

Nanotechnology oral bioavailability was examined using the REVMAN 5.4 program (Cochrane Handbook for Systematic Reviews). Review Manager was used to generate a fixed effect model. The funnel plot was not feasible because there were only countable studies for each nanoparticle percentage included in the meta-analysis.

Meta-analysis

In this study, we evaluated the medication's highest possible plasma concentration vs. its area under the curve and its highest possible plasma concentration over time (Cmax vs. AUC/ Tmax). The meta-analysis data have shown that the oral bioavailability of prescribed drugs using nanotechnology compared to a generic drug absorption rate between the control and model. In order to get a general conclusion, meta-analysis integrated the results of numerous separate studies, which is another technique to measure heterogeneity. As a result, this study assessed the overall impact of nano-formulation on oral bioavailability compared to free form using meta-analysis. A forest plot was generated, and we analyzed it in the open-source REVMAN 5.4 software program. In the primary literature search, we identified and screened 374 scientific papers**(Fig 1)** using multiple databases (Pubmed, Scopus, Web of Science, and Science Direct). The study was omitted from 63 repetitions, 161 titles with inappropriate information, and 14 papers not published in English. A total of 136 papers were thoroughly assessed for their abstracts; 39 were found to be related to the review subjects.

Overall, we consider 22 to 35 papers related to oral bioavailability, out of which 21 articles were found to meet the requirements for inclusion criteria, and the remaining 26 from the overall article collections were either excluded from the data analysis.

Results and Discussion:

Treatment in Group A uses various nanoconjugates, such as solid lipid and polymeric nanoparticles. There was an improvement in the bioavailability of drugs investigated in all studies, except Gary et al. 1995; Agueros et al. 2010; Rebeca Penalva et al. 2014; Nayab Khalid et al. 2018, as a result of the significant increase in AUC, which in turn resulted in a significantly higher level of bioavailability in comparison to their control groups (free drug suspensions). **Table 1** shows the findings of a meta-analysis that summarizes the bioavailability of the medications under investigation, as shown by the area under the curve (AUC).

In support of this, there was a positive confidence interval for all the studies, with the exception of the research by Gary et al. 1995; Agueros et al. 2010; Rebeca Penalva et al. 2014; Nayab Khalid et al. 2018. **Table 2** provides the characterization of bio-conjugated nanoparticles, including particle size, PDI, zeta potential, and Drug encapsulated efficiency.

Further, table 2 shows the detail of solid lipid nanoparticles (SLNs); glyceryl monostearate-solid lipid nanoparticles (GMS-SLNs); Compritol 888 ATO-solid lipid nanoparticles (CP SLNs); Lipid Insulin-loaded SLNs (LP-INS-SLNs).

The forest plot shows the overall finding of the Meta-Analysis **(Fig 2).** Overall, the findings of this study were very significant ($p< 0.0001$), with a pooled estimate of 2.03 and positive confidence intervals for both the lower and upper confidence ranges, which were 1.05 and 3.02, respectively. Even though there is some heterogeneity in the meta-analysis study, it is important to note that the I2 score indicated heterogeneity. It is likely that heterogeneity is a result of a variety of factors, including differences in time periods, treatments (different subgroups of nanoparticles investigated), preparation techniques, experimental designs, sample sizes (number of animals involved), and variations in the animals used for research.

The creation of separate lipid-based nanocarriers that were further distinguished based on the vesicle size, zeta potential, and molar mass of the nanocarriers involved various production techniques.

These findings support previous findings that certain nano-formulations made possible by nanotechnology can increase the bioavailability of medications taken orally. **(Fig 3)**Explain how the two sets of data compared to establish the groups are connected and how some results indicate that they are not connected. A funnel plot is utilized to find any potential publishing bias or result in heterogeneity. It frequently shows patterns, connections, or changes in huge datasets. In a heat map, each cell is colored according to the variable values, and the rows and columns indicate the variables. The normal distribution of sample data is indicated by plot points that follow a straight diagonal line. Departures from the line indicate an abnormality.

This research's findings confirm the use of nanotechnology to improve oral bioavailability, as described in a study by Lian Dong et al., Michael et al., and Bader et al. Several nano-formulation platforms have demonstrated improved oral bioavailability of various medications for various purposes. Aside from being the best nano-formulation, SLN is also the most commonly used nano-drug delivery system. Its widespread usage is due to several reasons, including its good biocompatibility, capacity to transport both lipophilic and hydrophilic medicines, ability to release medications at a targeted rate, improved stability, and higher drug content. Aside from affordability and scalability, there are also easy validation criteria for regulatory approval. The different types of nanoparticles were included in the present study, such as Poly anhydride nanoparticles, polymeric nanoparticles, PLGA nanoparticles, and Solid lipid nanoparticles. A meta-analysis was conducted on all of the groups. Most of the treatments were within the SLNs subgroups, which are much more cost-effective because the lipids employed in manufacture are less expensive than those utilized to produce polymeric nanoparticles. Other advantages include better medication stability and decreased drug toxicity (Porter et al., 2007).

Medications can be dissolved and distributed orally by using polymer-based nanoparticles as nanocarriers, thereby increasing drug bioavailability through oral consumption. Following Binkhathlan et al., "PEO-b-PCL micelles have the potential of acting as effective solubilizers and can be used as a good substitute for the commercially available excipients used in oral preparations of medicines like CyA that are not very soluble." A significant advantage of polymer-based nanoparticles is their biocompatibility. This product has been designed to minimize adverse reactions, be effective due to its small size and potent targeting, and be simple to prepare. Polymeric nanoparticles as drug carriers have several advantages, including the capacity to shield pharmaceuticals and other

substances from the environment, boost bioavailability, and improve therapeutic index. Generally, meta-analysis studies are conducted with sample sizes bigger than one (n=2) because sample sizes vary from study to study, and factors such as sample size and study type are taken into account. Nevertheless, the number of papers included in the meta-analysis will always limit the ability to derive an accurate result.

Conclusion:

In this current study, 39 relevant "evidence" studies were selected, considered using certain eligibility criteria, and assessed for enhancing oral bioavailability. 18 of the selected publications are particularly noteworthy since this study focused more on literature and findings worldwide. As a result, the 21 studies gathered were examined for oral bioavailability increase by nanotechnology. For this study, the nanotechnology used to improve bioavailability was divided into two categories: solid lipid nanoparticles and polymeric nanoparticles. The findings of this study can help medication developers improve the efficacy of orally delivered pharmaceuticals, particularly antineoplastic agents. In the comparison that was carried out between the control and model groups (Oral bioavailability) that had been outlined before, some of the research indicated statistically significant differences; however, after doing the analysis, we discovered that the majority of the studies provided non-significant results. The best-performing nano-formulation was SLN. In addition, the meta-analysis revealed minimal differences between nanoparticles and free drug suspension. Despite this, the majority of the treatments had a significant relative bioavailability.

Disclosure statement

No potential conflict of interest was reported by the authors.

Data availability statement

All data generated or analysed during this study are included in this submitted article. The raw data shall be made available upon request to the corresponding author.

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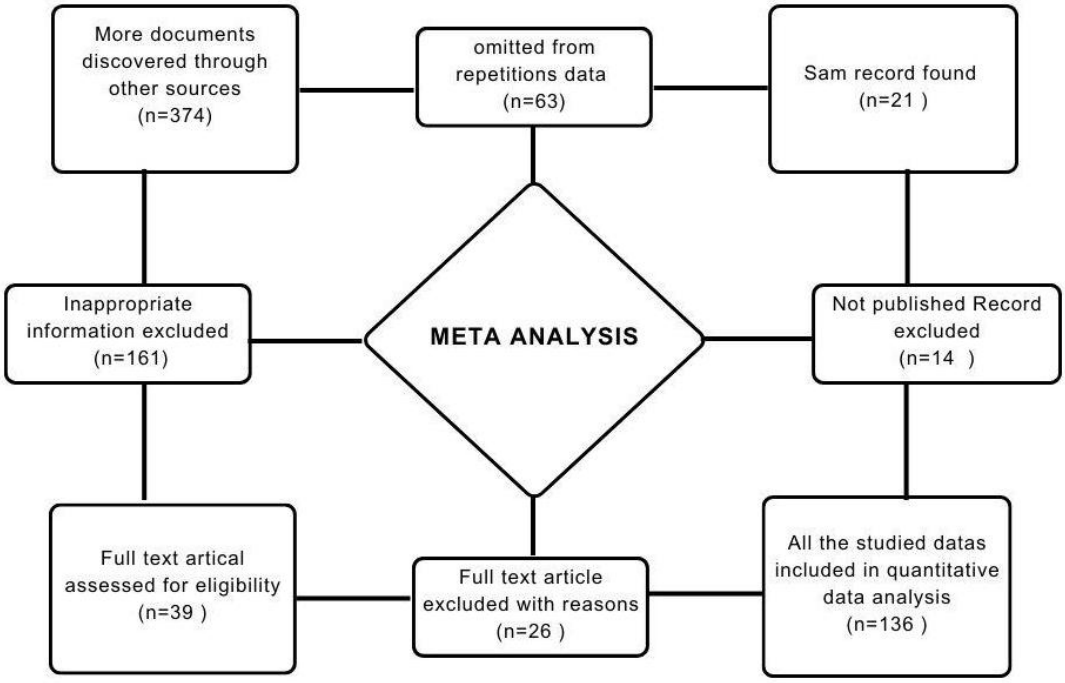
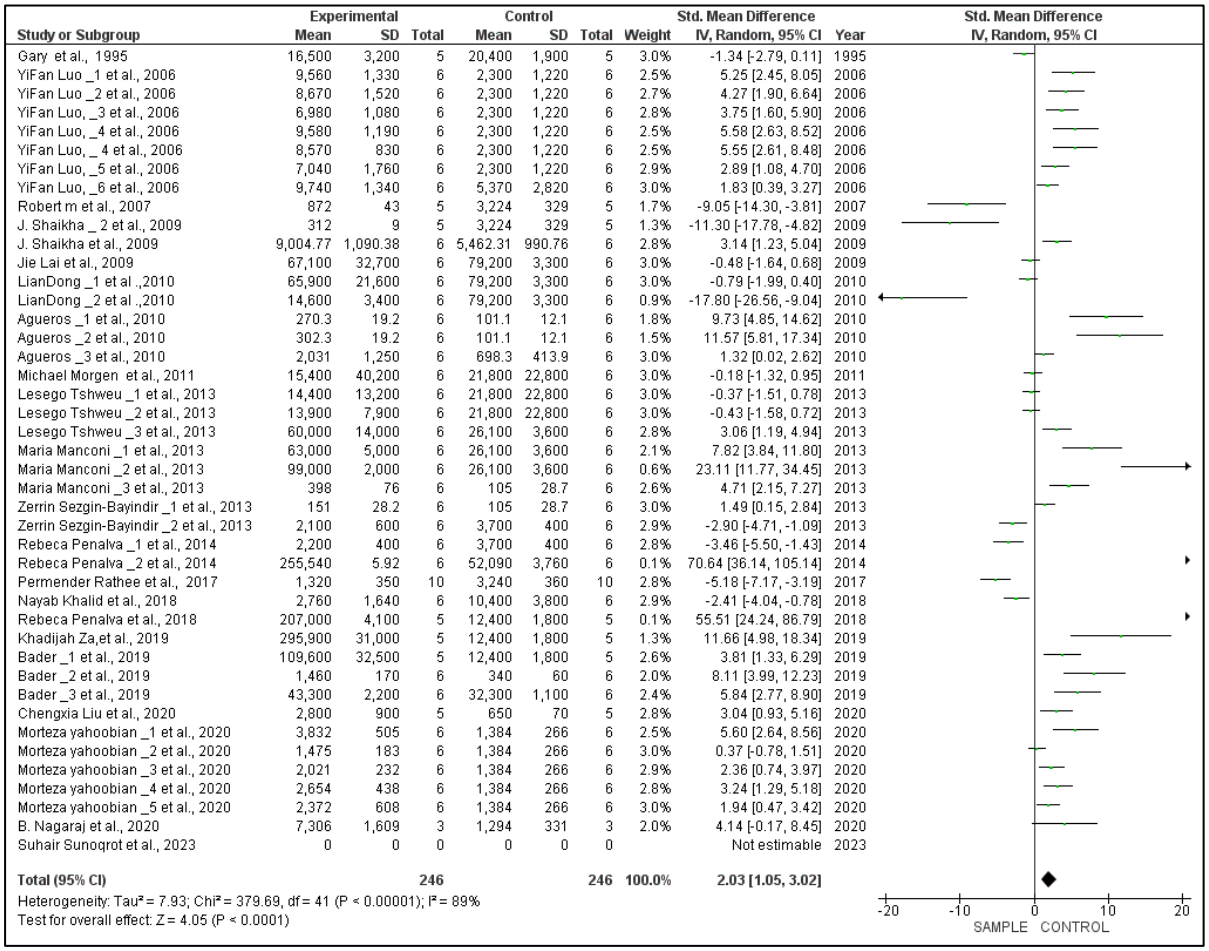


Figure 1 : Data screening flowchart for meta-analysis



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Gary et al., 1995	16,500	3,200	5	20,400	1,900	5	3.0%	-1.34 [-2.79, 0.11]	1995
YiFan Luo _1 et al., 2006	9,560	1,330	6	2,300	1,220	6	2.5%	5.25 [2.45, 8.05]	2006
YiFan Luo _2 et al., 2006	8,670	1,520	6	2,300	1,220	6	2.7%	4.27 [1.90, 6.64]	2006
YiFan Luo, _3 et al., 2006	6,980	1,080	6	2,300	1,220	6	2.8%	3.75 [1.60, 5.90]	2006
YiFan Luo, _4 et al., 2006	9,580	1,190	6	2,300	1,220	6	2.5%	5.58 [2.63, 8.52]	2006
YiFan Luo, _ 4 et al., 2006	8,570	830	6	2,300	1,220	6	2.5%	5.55 [2.61, 8.48]	2006
YiFan Luo, _5 et al., 2006	7,040	1,760	6	2,300	1,220	6	2.9%	2.89 [1.08, 4.70]	2006
YiFan Luo, _6 et al., 2006	9,740	1,340	6	5,370	2,820	6	3.0%	1.83 [0.39, 3.27]	2006
Robert m et al., 2007	872	43	5	3,224	329	5	1.7%	-9.05 [-14.30, -3.81]	2007
J. Shaikha _ 2 et al., 2009	312	9	5	3,224	329	5	1.3%	-11.30 [-17.78, -4.82]	2009
J. Shaikha et al., 2009	9,004.77	1,090.38	6	5,462.31	990.76	6	2.8%	3.14 [1.23, 5.04]	2009
Jie Lai et al., 2009	67,100	32,700	6	79,200	3,300	6	3.0%	-0.48 [-1.64, 0.68]	2009
LianDong _1 et al .,2010	65,900	21,600	6	79,200	3,300	6	3.0%	-0.79 [-1.99, 0.40]	2010
LianDong _2 et al .,2010	14,600	3,400	6	79,200	3,300	6	0.9%	-17.80 [-26.56, -9.04]	2010
Agueros _1 et al., 2010	270.3	19.2	6	101.1	12.1	6	1.8%	9.73 [4.85, 14.62]	2010
Agueros _2 et al., 2010	302.3	19.2	6	101.1	12.1	6	1.5%	11.57 [5.81, 17.34]	2010
Agueros _3 et al., 2010	2,031	1,250	6	698.3	413.9	6	3.0%	1.32 [0.02, 2.62]	2010
Michael Morgen et al., 2011	15,400	40,200	6	21,800	22,800	6	3.0%	-0.18 [-1.32, 0.95]	2011
Lesego Tshweu _1 et al., 2013	14,400	13,200	6	21,800	22,800	6	3.0%	-0.37 [-1.51, 0.78]	2013
Lesego Tshweu _2 et al., 2013	13,900	7,900	6	21,800	22,800	6	3.0%	-0.43 [-1.58, 0.72]	2013
Lesego Tshweu _3 et al., 2013	60,000	14,000	6	26,100	3,600	6	2.8%	3.06 [1.19, 4.94]	2013
Maria Manconi _1 et al., 2013	63,000	5,000	6	26,100	3,600	6	2.1%	7.82 [3.84, 11.80]	2013
Maria Manconi _2 et al., 2013	99,000	2,000	6	26,100	3,600	6	0.6%	23.11 [11.77, 34.45]	2013
Maria Manconi _3 et al., 2013	398	76	6	105	28.7	6	2.6%	4.71 [2.15, 7.27]	2013
Zerrin Sezgin-Bayindir _1 et al., 2013	151	28.2	6	105	28.7	6	3.0%	1.49 [0.15, 2.84]	2013
Zerrin Sezgin-Bayindir _2 et al., 2013	2,100	600	6	3,700	400	6	2.9%	-2.90 [-4.71, -1.09]	2013
Rebeca Penalva _1 et al., 2014	2,200	400	6	3,700	400	6	2.8%	-3.46 [-5.50, -1.43]	2014
Rebeca Penalva _2 et al., 2014	255,540	5.92	6	52,090	3,760	6	0.1%	70.64 [36.14, 105.14]	2014
Permender Rathee et al., 2017	1,320	350	10	3,240	360	10	2.8%	-5.18 [-7.17, -3.19]	2017
Nayab Khalid et al., 2018	2,760	1,640	6	10,400	3,800	6	2.9%	-2.41 [-4.04, -0.78]	2018
Rebeca Penalva et al., 2018	207,000	4,100	5	12,400	1,800	5	0.1%	55.51 [24.24, 86.79]	2018
Khadijah Za,et al., 2019	295,900	31,000	5	12,400	1,800	5	1.3%	11.66 [4.98, 18.34]	2019
Bader _1 et al., 2019	109,600	32,500	5	12,400	1,800	5	2.6%	3.81 [1.33, 6.29]	2019
Bader _2 et al., 2019	1,460	170	6	340	60	6	2.0%	8.11 [3.99, 12.23]	2019
Bader _3 et al., 2019	43,300	2,200	6	32,300	1,100	6	2.4%	5.84 [2.77, 8.90]	2019
Chengxia Liu et al., 2020	2,800	900	5	650	70	5	2.8%	3.04 [0.93, 5.16]	2020
Morteza yahoobian _1 et al., 2020	3,832	505	6	1,384	266	6	2.5%	5.60 [2.64, 8.56]	2020
Morteza yahoobian _2 et al., 2020	1,475	183	6	1,384	266	6	3.0%	0.37 [-0.78, 1.51]	2020
Morteza yahoobian _3 et al., 2020	2,021	232	6	1,384	266	6	2.9%	2.36 [0.74, 3.97]	2020
Morteza yahoobian _4 et al., 2020	2,654	438	6	1,384	266	6	2.8%	3.24 [1.29, 5.18]	2020
Morteza yahoobian _5 et al., 2020	2,372	608	6	1,384	266	6	3.0%	1.94 [0.47, 3.42]	2020
B. Nagaraj et al., 2020	7,306	1,609	3	1,294	331	3	2.0%	4.14 [-0.17, 8.45]	2020
Suhair Sunoqrot et al., 2023	0	0	0	0	0	0		Not estimable	2023
Total (95% CI)			**246**			**246**	**100.0%**	**2.03 [1.05, 3.02]**	

Heterogeneity: Tau² = 7.93; Chi² = 379.69, df = 41 (P < 0.00001); I² = 89%
Test for overall effect: Z = 4.05 (P < 0.0001)

Std. Mean Difference IV, Random, 95% CI

-20 -10 0 10 20

SAMPLE CONTROL

Figure 2: The example of continuous outcome measure: oral bioavailability of nano formulated drugs assessed with SMD differences. Tau, the estimated SMD of effects across the studies (Tau^2 shows the two groups) Ch^{i2} value result for heterogeneity of Random model.If no significant heterogeneity is found, we may have more faith in the pooled estimate because the majority or all of the independent studies provide the same conclusion.

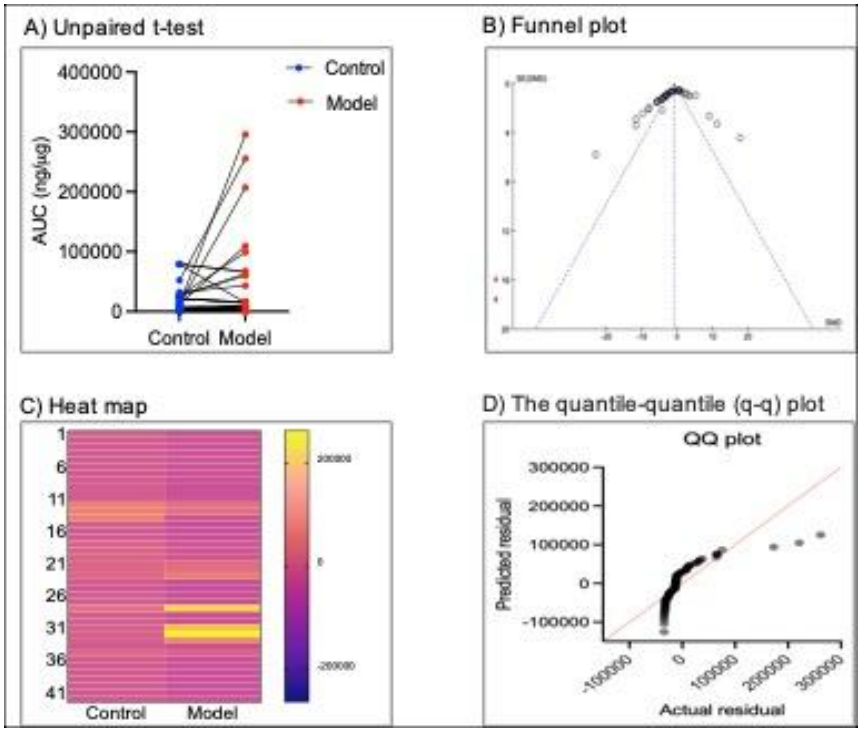


Figure 3:

(A) The comparison between the control and model groups was made using an unpaired t-test. The t-test result based on the difference in the sum of the total values is statistically significant.(B) Funnel plot using data from 21 studies on the AUC of nano-formulation drugs following oral bioavailability.funnel plot using total values to describe the difference is significant.(C) Heat map shows how samples interact with the particular range activity on this study. The colour change indicates that some studies have given significant results.(D) The quantile-quantile plot approach reveals the distributional fit of the sample data to a theoretical distribution, which is evaluated graphically using a Q-Q plot. A straight line implies similarity, whereas deviations imply variations in

the distribution's properties. Researchers may use it to evaluate the normalcy assumption and spot deviations from the predicted distribution.

Table 1: Shows the findings of a meta-analysis that summarizes the bioavailability of the medications under investigation as shown by the area under the curve (AUC).

Author and year	AUC sample ($ng.h,mL^{-1}$)		No. of sample(n)	Control AUC ($ng.h,mL^{-1}$)		No. of sample(n)
	mean	SD		mean	SD	
Gary et al 1995	16500	3200	5	20400	1900	5
YiFan Luo, et al 2006	9560	1330	6	2300	1220	6
YiFan Luo, et al 2006	8670	1520	6	2300	1220	6
YiFan Luo, et al 2006	6980	1080	6	2300	1220	6
YiFan Luo, et al 2006	9580	1190	6	2300	1220	6
YiFan Luo, et al 2006	8570	830	6	2300	1220	6
YiFan Luo, et al 2006	7040	1760	6	2300	1220	6
Robert m et al., 2007	5370	2820	6	9740	1340	6
J. Shaikha et al., 2009	872	43	5	3224	329	5
J. Shaikha et al., 2009	312	9	5	3224	329	5
Jie Lai et al 2009	9004.77	1090.38	6	5462.31	990.76	6
LianDong et al 2010	270.3	19.2	6	101.1	12.1	6
LianDong et al 2010	302.3	19.2	6	101.1	12.1	6

Agueros et al 2010	67100	32700	6	79200	3300	6
Agueros et al 2010	65900	21600	6	79200	3300	6
Agueros et al 2010	14600	3400	6	79200	3300	6
Michael Morgen 2011	2031	1250	6	698.3	413.9	6
Lesego Tshweu et al., 2013	15400	40200	6	21800	22800	6
Lesego Tshweu et al., 2013	14400	13200	6	21800	22800	6
Lesego Tshweu et al., 2013	13900	7900	6	21800	22800	6
Maria Manconi et al., 2013	60000	14000	6	26100	3600	6
Maria Manconi et al., 2013	63000	5000	6	26100	3600	6
Maria Manconi et al., 2013	99000	2000	6	26100	3600	6
Zerrin Sezgin-Bayindir et al., 2013	398	76	6	105	28.7	6
Zerrin Sezgin-Bayindir et al., 2013	151	28.2	6	105	28.7	6
Rebeca Penalva et al 2014	2100	600	6	3700	400	6
Rebeca Penalva et al 2014	2200	400	6	3700	400	6
Permender Rathee et al 2017	255540	5.92	6	52090	3760	6
Rebeca Penalva et al 2018	2760	1640	6	10400	3800	6
Nayab Khalid et al 2018	1320	350	10	3240	360	10
Khadijah Zai, et al 2019	1460	170	6	340	60	6
Bader et al 2019	207000	4100	5	12400	1800	5

Bader et al 2019	295900	31000	5	12400	1800	5
Bader et al 2019	109600	32500	5	12400	1800	5
B. Nagaraj et al 2020	43300	2200	6	32300	1100	6
Chengxia Liu et al 2020	2800	900	5	650	70	5
Morteza yahoobian et al., 2020	3832	505	6	1384	266	6
Morteza yahoobian et al., 2020	1475	183	6	1384	266	6
Morteza yahoobian et al., 2020	2021	232	6	1384	266	6
Morteza yahoobian et al., 2020	2654	438	6	1384	266	6
Morteza yahoobian et al., 2020	2372	608	6	1384	266	6
Suhair Sunoqrot et al., 2023	7306	1609	3	1294	331	3

Table 2: Characterization of the drug's loaded with nanoparticles.

Nano conjugate type	Particle size	PDI	Zeta Potential	Drug EE%
GMS-SLNs	127.3±8.1	-	−24.1±0.9	93.7±0.47
CP-SLNs	138.5±10.1	-	−27.9±1.4	95.5±0.51
SLN A	70.3 ± 7.8		−33.8 ± 0.9	97.2 ± 0.3
SLN B	100.2 ± 9.3		−29.7 ± 0.6	96.9 ± 0.4
SLN C	148.6 ± 11.8		−26.3 ± 1	98.1 ± 0.6
SLN D	77.8 ± 9.		29.6 ± 1.1	98.3 ± 0.4
SLN E	113.4 ± 8.5		−26.7 ± 0.7	98.2 ± 0.5
SLN F	167.6 ± 5.8		−22.4 ± 0.5	98.7 ± 0.3
PTX–CD NP	298±6		−39.3± 5.2	28.1
PTX–HPCD NP	307±7		−42.1± 1.4	97.4
PTX–NHCD NP	310±6		−34.5± 3.9	61.6
Nanocrystalline danazol	-	-	-	-
Celecoxib: ethyl cellulose: casein nanoparticles	100-150	-	-	-
nisoldipine-piperine nanoparticles	131.69	-	-	88.78

Folic acid loaded in casein nanoparticles,	144 ± 3	0.13 ± 0.01	13.6 ± 0.2	25 ± 5
Famotidine-SLN	151± 26	-	-	82 ± 4
Insulin-loaded SLNs	618.5±8.4	0.734	−17.0±1.53,	59.03±4.1
LP-INS-SLNs	745.3±12.6	0.227	−23.7±2.13	67.42±3.1
DP-INS-SLNs	973.0±15.3	0.710	−20.9±1.63	59.97±5.3
Zotepine loaded lipid nanoparticles	104.3 ± 2.4	0.17 ± 0.01	− 30.5 ± 2.5	98.4 ± 2.8
CyA-loaded cubic nanoparticles	136.4 ± 5.8	0.291		91.45 ± 1.4
TP-Cas	128.7 ± 11.5	0.49 ± 0.04,	−23.9 ± 1.5	72.9
MR-np nano particle PLGA and MR, nano particle	205±42 266±101	0.33±0.04 0.28±0.13	-15±1.4 -0.9±1.7	82±8 57±8
PL-N CP4-N CPI-N	133±6 134±3 320±6	0.294±0.006 0.470±0.040 0.510±0.041	-65.6±1.2 -81.1±2.2 -73.1±0.8	
Curcumin loading on nano particle	253±2	0.29±0.01	-4.3±0.3	3.9±0.1
Liposomes CH coated Liposomes GP/CH micro complexes	166±7 4061±1500 4730±1600	0.12	-22±1 56±1 11±1	10±3 15±5 25±4