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REVIEW ARTICLE

Enhanced oral bioavailability through nanotechnology in Saudi Arabia: A meta-analysis

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Abstract Oral administration represents the most suitable mean among different means of administering drugs because it ensures high compliance by patients. Nevertheless, the lacking aqueoussolubility, as well as, inadequate metabolic/enzymatic stability of medicines are leading obstacles to successful drug administration by oral route. Among different systems, drug administration systems based on nanotechnology have the potential to surmount the problems associated with oral drug administration. Drug delivery systems based on nanotechnology offer an alternative to deliver antihypertensive agents with enhanced therapeutic effect and bioavailability. In this study, meta-analysis was utilized in combining data relating to oral bioavailability (area under plasma concentration time curve, AUC) enhancement through nanotechnology from multiple studies. Twenty-one studies of the total 37articles included in this study were from the kingdom of Saudi Arabia and were included in a specific meta-analysis. From the analysis conducted, the overall enhancement power of the nanotechnology based formulations on drug bioavailability was found to be 7.94% (95 %CI [5.809, 10.064]). Haven utilized comprehensive and recent data of the confirmed the enhancement of bioavailability using nanotechnology which for this study was grouped into five: solid lipid nanoparticles; polymer based nanoparticles; SNEEDS/Nanoemulsion; liposomes/proliposomes and; nanostructured lipid carriers. Furthermore, the meta-analysis, provided evidence of insignificant differences between APG Bio-SNEDDS and its free drug suspension (Apeginin, APG), though with relative bioavailabiilty of 1.91. Notwithstanding most of the treatment showed a substantial relative bioavailability.

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Contents

1. Introduction

It is a common knowledge today that materials whose sizes are in the nanometer range have chemical, biological and physical properties from those which are not. This distinctive property of nanoparticlate materials has been studied widely for the possible use of nanotechnology in the field of media (Berardi and Bisharat, 2016). The utilization of nanotechnology for delivery of drugs is among the most promising as well as exciting application of this technology; nanotechnology mechanisms have the potentials to enhance the potency of drugs as well as efficiency of therapeutics given via various means of administration (Perrie, 2013). Nano technologies applied in delivery of drug consist of nano scale molecules or particles which are capable of improving the bioavailability of drugs. Molecular targeting is carried out through devices like nanorobots which are nano-engineered in order to maximize bioavailability both at definite areas in the body as well as over a period of time (Cavalcanti et al., 2008).

The most preferred and most frequently used route of administering drugs is the oral route: oral dosage types facilitate enhanced compliance of patients, are easy to receive and are less expensive than other dosage types. Over 70% of all drugs are given via oral route and they can either be in liquid forms (i.e. suspensions and solutions) or solid forms (i.e. capsules and tablets). It has been noted however, that ‘‘orally administered drugs, compared to those given via the parenteral route are not directly available in the systemic circulation to exert their therapeutic effect (McConnell and Basit, 2013; York, 2013). Instead, they must first transit through the gastro-intestinal (GI) tract and be absorbed before they reach the blood. Hence, the oral route for the delivery of drugs provides at best a delayed onset of action compared to the parenteral route or at worst it can be completely precluded for those drugs that cannot reach the blood”. The physical, biological and chemical relations of the medicine with the physiological parts of the GI tract determine whether or not as well as to what degree the drug can get to the blood circulation intact and carry out a complete effect.

According to Le, ‘‘orally administered drugs must pass through the intestinal wall and then the portal circulation to the liver; both are common sites of first-pass metabolism (metabolism that occurs before a drug reaches systemic circulation). Thus, many drugs may be metabolized before adequate plasma concentrations are reached. Low bioavailability is most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs” (Le, 2020).

Low bioavailability generally results from inadequate time for absorption in the GI. Time may not be sufficient at the absorption site if the drug does not readily dissolve or is not able to do through the epithelial covering (if it is highly polar and ionized, for instance). Bioavailability may be low and highly variable in such instances.

Previous gastrointestinal surgery (like bariatric surgery), physical activities, age, genetic phenotype, sex, disorders (like mal-absorption syndromes and alchlorhydria) and stress can also affect bioavailability of drugs.

Bioavailability can also be reduced by chemical reactions that decrease absorption. Such reactions include hydrolysis by digestive enzymes or gastric acid (for example, penicillin and chloramphenicol palmitate hydrolysis), formation of a complex (for instance, polyvalent metal ions and tetracycline), other drugs absorption (example, cholestynamine and digoxin), metabolism by microflora in the lumen and conjugation in the wall of the intestine (example, sulfuconjugationof isoproterenol).

Oral administration represents the most suitable means among different means of administering drugs because it ensures high compliance by patients. Nevertheless, the lacking aqueous solubility as well as inadequate metabolic/enzymatic stability of medicines are leading obstacles to successful drug administration by oral route. There are many ways to improve hydrophobic drugs related problems (Bernkop-Schnürch, 2013; Zhang et al., 2013). Among different systems, drug administration systems based on nanotechnology have the potential to surmount the problems associated with oral drug administration (Sharma et al., 2016). Drug delivery systems based on nanotechnology offer an alternative to deliver antihypertensive agents with enhanced therapeutic effect and bioavailability (Prisant et al., 1992).

With the purpose of monitoring the presentprogress on the research on oral bioavailability and nanotechnology and finding out the application/capabilities of nano-technological approaches in enhancing the bioavailability of orally administered drugs, it is necessary to carry out a thorough investigation and analysis of related studies (compiled) on nanotechnology enhancement of oral bioavailability. In addition, the objective is to identify general patterns presented among results of related study, other relationships of interest, and possible sources of disagreement that may be revealed in course of multiple studies. Meta-analysis, a statistical technique which is suitable for this courseof ‘‘combining the findings from independent studies most often used to assess the clinical effectiveness of healthcare interventions” (Fong et al., 2016), was utilizedto analyze quantitatively, the related pharmacokinetic parameters compiled from multiple studies on enhanced oral bioavailability through nanotechnology and presented in this review.

Nanotechnologyhas been effectivelyutilized by previous studies in varying pharmaceutical formulations for oral bioavailability enhancement (Fong et al., 2016; Nasser et al., 2020; Fong et al., 2015; Jain, 2010; Singh and Lillard, 2009; Guan et al., 2011; Safari and Zarnegar, 2014; Khadka et al., 2014; Hetal et al., 2010; Berardi, 2016; Price and Patel, 2020; Anwar et al., 2011; Ma et al., 2015; Ipar et al., 2019; Suri et al., 2007; Agrawal et al., 2014; Moher et al., 2009). The aim of the current review was to provide quantitative answers to the questions on "how promising nanotechnologyis for bioavailability enhancement?", "Whichtype of nanotechnology performs the best?" And "what are the most promising drug candidates from this review?" By performing a broad and systematic search of recent literature dating from the past 20 years (from 2000 to 2021) that reported nanotechnology for the enhancement of oral bioavailability of drugs and conducting a meta-analysis, the aforementioned questions have been dealt with and we foresee that the information in this study will be of importance to scientists who wish to implement nanotechnology in overcoming poor oral bioavailability.

2. Methods

2.1. Search strategy

This research followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guideline (Brakmane et al., 2012). Based on specified goals and eligibility criteria, we carried out a systematic literature search for all relevant studies up to July 2021 in Google Scholar (https://scholar.google.com), Pub Med (https://pubmed.ncbi.nlm.nih.gov), ResearchGate (https://www.researchgate.net) and Web of Science (http://www.webofknowledge.com) utililizing predefined keywords. Text words and phrase words were utilized. Also reference lists titles and full texts of studies on nanotechnology in oral bioavailability (Sharma et al., 2016; Nasser et al., 2020; Guan et al., 2011; Ma et al., 2015; Ipar et al., 2019; Suri et al., 2007; Agrawal et al., 2014; Moher et al., 2009; Xiaojun et al., 2007; Charoo et al., 2019; Arshad et al., 2021; Koo et al., 2005; Kumar, 2000; Higgins and Thompson, 2002; Yang et al., 2009; Gupta et al., 2020; Pandita et al., 2011; Li et al., 2012; Shah et al., 2006; Alsulays et al., 2019) in general and other related studies carried out in the kingdom of Saudi Arabia. Search terms used include: "biological availability"[MeSH Terms] OR bioavailability[Text Word]; "nanotechnology"[MeSH Terms] OR nanotechnology [Text Word], "enhance", "nanoparticles", "enhancement of oral bioavailability", and 'Enhanced Oral Bioavailability through Nanotechnology in Saudi Arabia'. The use of these terms ensured the inclusion of related studies pertaining to oral bioavailability and nanotechnology. To find out whether a study had fulfilled the eligibility requirements, one reviewer screen details and abstracts of all titles and manuscripts.

2.2. Inclusion and exclusion criteria

The title and abstracts of the various studies were screened so as to identify suitable studies on the association between oral bioavailability and nanotechnology. Preprints were excluded in the systematic review and meta-analysis, thus, only research articles published in peer-reviewed (refereed or scholarly) journals were searched.

Research papers considered eligible for assessment while screening, had to fulfill these criteria:

i. Nanotechnology related formulation (nanoformulation).
ii. Nanotechnology was used as enhancement of oral bioavailability of drugs and/or solubility and permeability of drug.
iii. The intended route of delivery of the studied nanomedicine nanostructured polymer (such as nanoparticles, dendrimers, micelles and drug conjugates) was oral.
iv. Presence of pharmacokinetic (PK) parameters (relating to oral bioavailability) such as AUC, Cmax, Tmax or $T_{1/2}$.
v. PK parameters should be clearly stated either in table or text.

Duplicated studies and those not printed in the English or Arabic language were excluded. After studies that did notcontain original data (i.e research paper) nor provide information on nanotechnology, nano medicine, nano formulation, nano materials, oral bioavailability and enhancement of oral bioavailability, were further screened out.

2.3. Data extraction

Duplicated studies were sorted out with the aid of Zotero 5.0.96.2 (http://www.zotero.org). The search results (literature) were screened and the eligible studies were selected after going through the titles, abstracts and full-texts.

2.4. Meta-analysis

Meta-analysis was carried out to reveal the overall enhancement of oralbioavailability of administered drugsthrough nanotechnology (experiment) as compared to actual drug suspension or solution (control). This is revealed by the pharmacokinetic parameters of the drugs, which are area under curve (AUC), maximum plasma concentration (Cmax), and time to reach maximum plasma concentration (Tmax). "Heterogeneity" was also measured as Meta-analysis brings togetherresult of different individual studies and presents a general conclusion (Yang et al., 2009). Hence, meta-analysis was carried out in this present study to assess the overall enhancement effect of oral bioavailability through nanotechnology across different publications.

The area under the curve (AUC) and the study sample size, mean and standard deviation (SD) were fed into an open source software funded by the Agency for Healthcare Research and Quality (AHRQ), OpenMetaAnalyst which is used for conducting meta-analysis and generate a forest plot. and to perform Meta analysis of the investigated studies and provide Forest plot.

A random effect model was utilized for this study as it takes into account the variability that exist between the studies. The "DerSimonian-Laird" was the random-effect method used. Also the heterogeneity was evaluated with the Q statistic, I^2 and τ^2 index. The Q statistic is the true statistical test for heterogeneity of the studies employed in this review and the degree of heterogeneity was indicated by I^2 index. The study

weights and forest plot (with mean ratio and confidence interval – 95 %CI estimates) wasconsideredin this study.

3. Result and discussion

3.1. Literature search

The search for relevant literatures pertaining to the context of this study gave 2,455 articles as seen in the *identification* phase of the PRISMA flow chart (Fig. 1). These were distributed across four database: *PubMed* (*n = 539*), *Web of Science* (n = 813) and *ResearchGate (n = 611)*. Removing the duplicate documents (n = 108), those removed for other reasons such as not been relevant to the main subject and those not written in either English or Arabic (n = 72) left 2,275 items to be screened as seen in the *screening* phase in Fig. 1. Afterwards the selection was carried out by going through the titles and abstracts of this study to where irrelevant articles especially does not drug related, or other fields of studies were excluded (n = 1684). The full texts of reports sought for retrieval (n = 591) were further screenedbased on the exclusion criteria on full-text article excluded (n = 128) in the Fig. 1. The remaining reports assessed for eligibility were 463. Of these reports, a total of426 studies were excluded as they were not eligible to be used in the meta analysis. Thus, a total of 37 (21 from*Saudi Arabia* and the remaining *16* from other places around the world) were included for this study. This is presented in the *included* phase of Fig. 1.

3.2. Saudi Arabia

Twenty-one studies of the total 37articlesincluded in this study were from the kingdom of Saudi Arabia and were included in a specific meta-analysis, "Meta Analysis results summarizing the oral bioavailability indicated by the area under curve (AUC) of the investigated drugs from Saudi Arabia" as described in Table 1 below.

Group (A) is the treatment. It comprises nano-formulated drug conjugates as represented in the Subgroups (1–5) asrepresented in the Table 1: (1) Solid Lipid Nanoparticles (SLNs) (2) Polymer Based Nanoparticles (Polymer nanoparticles, polymeric micelles and or dendrimers) (3) SNEEDS/Nanoemulsion (4) Liposomes/proliposomes(5) Nanostructured Lipid Carriers (NLC), Group (B) is the control which is the actual/free drug suspension of any drug formulation (see Figs. 2–6).

Given the presentation of the results in Table 1 above, all the studies except (Kazi et al., 2020) have established a significant increase in the AUC and accordingly the bioavailability of alldrugs investigated wasimproved as compared to their control (free drug suspensions) groups. This was confirmed as all the studies had positive confidence interval scoresexcept that carried out by Kazi et al and the conclusion drawn from a study by Mills *et al.* (Glasziou and Sanders, 2002).

On the whole, this study has proven to be extremely significant ($P < 0.001$) with a pooled estimate of 7.936 and positive confidence intervals of 5.809 and 10.064 for the lower and upper confidence intervals, respectively.

It is worthy of note that the degree of heterogeneity (I^2) of the Meta Analysis study was 91 %.The cause of the heterogeneity could be as a result of several reasons ranging from chronological differences, differences intreatments (different subgroup of nanoparticles) investigated, differences in the method of preparation and experimental design used, or differences in the sample size (the number of animals used), variation in the types and/or species of animals used (Hathout, 2019; Pathak and Raghuvanshi, 2015). Some method of preparation utilized were – antisolvent participation method (Fahmy et al., 2014) utilized in Furosemide nanosuspension; double emulsification techniques employed (Hosny, 2016) in formulating insulin-loaded nanoparticles (INS-SLNs) used in preparing L-and D- penetratin; synthesizing PEO-b-PCL copolymers to form micelles encapsulating Cy A; development of different lipid-based nano carriers which is further differentiated for vesicle size, zeta potential, morphological characterization using transmission electron microscope and others.

These results confirm previous proposition regarding the effectiveness of nanotechnology in enhancing the bioavailability of orally administered drugs (Tatham et al., 2015) through different nanoformulations (Pathak and Raghuvanshi, 2015; Tatham et al., 2015; Sinha et al., 2010; Ekambaram et al., 2012; Elshafeey et al., 2009; Sanna et al., 2010). The result of this study is an affirmation of the enhancement of oral bioavailability through nanotechnology as this consistent with a variety of nanoformulation platforms that have established that "better oral bioavailability of a range of drugs for different indications" as reported in the study of Tatham, Rannard & Owen (Sinha et al., 2010).

SLN is not only the nanoformulation that performed best but also the most used nanosystem. Its pronounced usage is largely due to its several advantages such as excellent biocompatibility; ability to carry both lipophilic and hydrophilic drugs; target drug release; enhanced stability of drugs; and better drug content. Others include affordability; scalability; and easy validity for regulatory approval.

SLN was the best performing nanoformulation. An instance is seen form the SlN formulation of the Penetratin [L-Penetratin INS-SLN] with a relative bioavailability of over 1,800% (18.17-fold).

Two different studies utilizing different nano formulations on Alendronate sodium (ALS) were observed. The two studies utilized SLN [Eudragit coated ALS-SLN] and nano-liposome [Euc-ALS nanoliposome, EuC-NLS] nanoformulation respectively. Euc-NLS showed a higher relative bioavailability (12.57 folds) than ALS-SLN having a relative bioavailability of 7.47-fold.

Coating the ALS-NLS with Eudragit (EuC-NLS), increased the zeta potential to positive 4.92 mV (from negative −21.45 mV). The increase zeta potential also resulted in greater stability of ALS.

ALS-SLN showed higher encapsulation efficiency (74.3%) than EuC-NLS (41.92%). However, the two nanoformulations of ALS could eliminate eosophagal inflammation and/or bleeding among osteoporotic patients, which is a major drawback in conventionally used tablets.

Fig. 7 represents the Forest plot of the Meta Analysis study depicting the results of all thestudies where the red line indicates the estimated pooled mean and the squared dots representthe SMD of each study together with the confidences intervals on both sides.

The weights of each study contributing in the overall pooled mean and the production of the Forest plot were also determined as shown in Table 4.

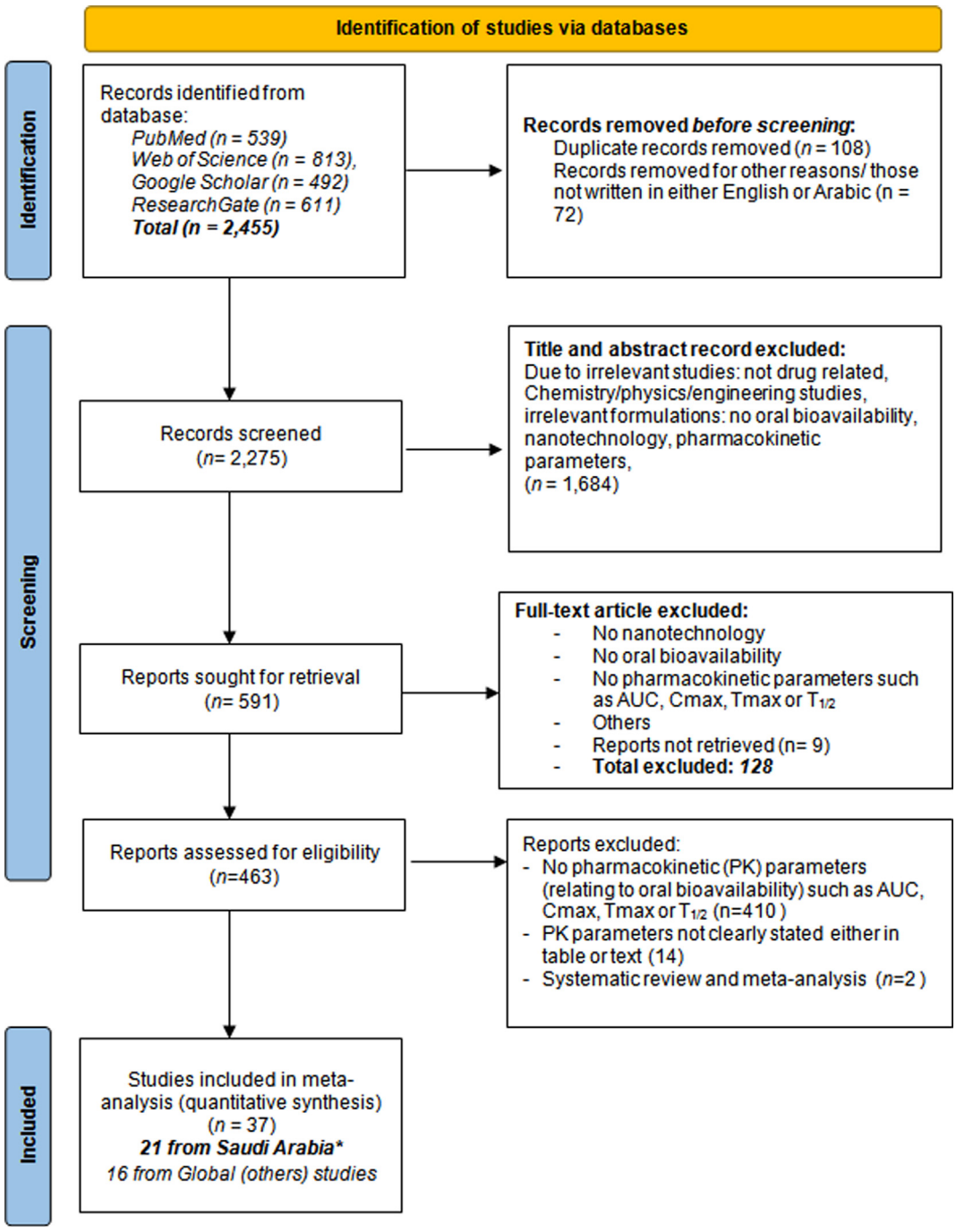

Fig. 1 PRISMA 2020 flow chart diagram for this review which included the record indentified from database, screened, and those (full text) included in the meta-analysis. Exclusion criteria which comprised title and abstract excluded, full text article excluded and report (of result) excluded were all indicated.

Going further, the investigated studies were sub-divided into five groups; solid lipid nanoparticles (1); polymer based nanoparticles (PbN) (2), SNEEDS/Nanoemulsion (3); liposomes/proliposomes (4) and; nanostructured lipid carriers (5).

All groups with the exception of group (5) were subject to meta-analysis as only studies within the ranges of two and above can be analysed using meta-analysis. The simple exclusion of group (5) was as a result of its sample size (n = 1) as only one study on nanostructured lipid carriers was included, thus disqualifies it from undergoing a meta-analysis as meta –analysis involves combination of several studies addressing the same outcome, and the result presented in the same measurement (Van Slooten et al., 2001).

These groups in Meta-Analysis revealed no significant differences between the two classes except that of group 4 (Liposome/proliposome), where the first (SLNs) scored an estimated mean of 6.748 associated with 3.880 and 9.616 as the lower and upper confidence intervals (CIs), respectively. The second

Table 1 Meta-Analysis results summarizing the bioavailability indicated by the area under curve (AUC) of the investigated drugs (Studies from Saudi Arabia, *n = 21*).

	Group A: Treatment			Group B: Control						Type of nanotechnology		Ref
	PK: AUC (ng.h.mL^{-1})			PK: AUC (ng.h. mL^{-1})						Sub-Grp	Type	
Study	No	Mean	SD	No	Mean	SD	SMD	Lower	Upper			Ref
Penetratin (Alsulays et al., 2019)	5	20,760	4100	5	12,400	1800	2.383	0.762	4.004	1	(L-penetratin-INS-SLNs)	41
Alendronate sodium (Fosamax®) (Hosny, 2016)	6	2173	216.4	6	291.6	28.14	11.251	6.610	15.892	1	Optimized Eudragit coated ALS-SLN formula	42
Miconazole marketed capsules (MN) (Aljaeid and Hosny, 2016)	6	231	20	6	94	11	7.832	4.501	11.164	1	MN-SLNs	43
carvedilol (CVD) (El-Say and Hosny, 2018)	6	844.21	101.32	6	551.73	69.12	3.112	1.429	4.794	1	CVD-SLNs dispersion	44
Sildenafil citrate marketed tablet Hosny and Aljaeid, 2014)	6	1638	35	6	1032	22	19.129	11.393	26.866	1	Sildenafil citrate SLNs	45
Cyclosporine A (CyA) Binkhathlan et al., 2018	5	18,760	360	5	16,170	250	7.544	4.013	11.075	2	methoxypoly(ethyleneoxide)-block-poly(ε-caprolactone) (PEO-b-PCL)	46
Doxorubicin (DOX) (Ahmad et al., 2018)	6	20577.90	256.34	6	2130.75	49.56	92.202	55.297	129.107	2	Polymeric Nanoparticles (PEGylated-DOX-PLGA-NPs)	47
Thymoquinone (TQ) (Kalam et al., 2017)	6	1,657,700	7960	6	511.04	5.31	271.679	162.981	380.377	3	TQ-SNEDDS	48
Vinpocetine (VPN) (Ahmed et al., 2019)	6	2388.568	10.32	6	1498.34	9.12	84.351	50.585	118.117	2	VPN-loaded TPGS-micelles-ISG	49
Alendronate sodium (ALS) (Hosny et al., 2013)	6	4280	304.5	6	340.6	31.23	16.795	9.981	23.608	4	(EuC-ALS nanoliposomes)	50
Fenofibrate. (Moshin *et al.*, 2016)	6	12414.46	86.28	6	7419.50	78.13	55.999	33.567	78.432	3	Fenofibrate-SNEDDS	51
ibrutinib (IBR) (Alshetaili et al., 2019)	3	2175.68	224.92	3	511.75	54.21	8.115	3.253	12.978	2	IBR PLGA Nanoparticles	52
Atazanavir (ATZ) (Khan et al., 2020)	3	705,670	64,180	3	468,300	52,930	3.926	2.702	5.150	5	ATZ-NLCs	53
Docosahexaenoic acid (DHA) (Alhakamy et al., 2020)	4	65,301	7504	4	19,609	583	7.457	3.549	11.365	3	DHA-SNEDDS	54
Domperidone (DOP) (Shazly et al., 2018)	6	205,430	30,610	6	78,400	70,190	2.165	0.740	3.590	1	DOP-SLNs	55
Atrovastin (At) (Shaker et al., 2021)	5	8759	0.407	5	2517	330	24.147	13.492	34.803	2	At-loaded ethylcellulose nanoparticle (At-NPs)	56
Apigenin (APG) (Kazi et al., 2020)	6	280.37	58.62	6	146.54	139.62	1.153	−0.069	2.375	3	APG Bio-SNEDDS	57
Delafloxacin(Anwer et al., 2020)	6	3717	1600	6	1618	301	1.682	0.366	2.999	4	Lipomer nanoparticle	58
Sertraline (SRT) (Rahman et al., 2019)	3	1125.67	38.34	3	181.19	32.68	21.155	9.079	33.230	1	SRT-SLNs	59
Furosemide microsuspension (Shariare et al., 2019)	5	4293.14	32.68	5	1610	27.13	80.646	45.280	116.012	3	Furosemide nanosuspension	60
Avanafil (AVA) (Fahmy et al., 2014)	6	7150.50	834.73	6	5130.24	717.42	2.395	0.912	3.878	3	AVA-SNEDDS	61

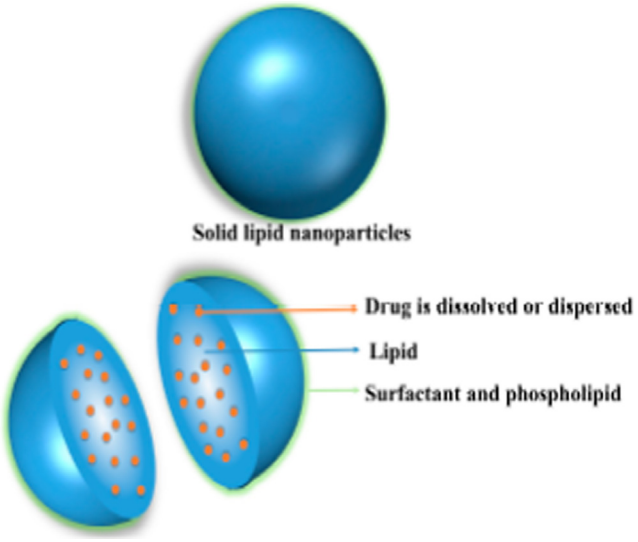

Fig. 2 General structure of solid lipid nanoparticle (SLN) loaded with drug (Mishra et al., 2018).

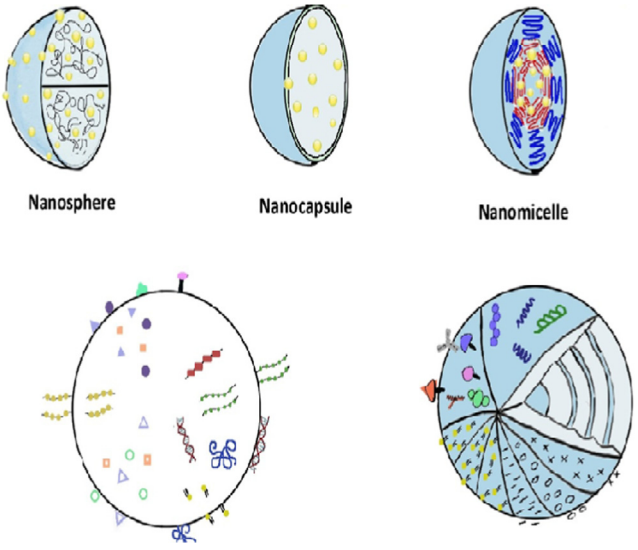

Fig. 3 Structure of polymeric nanoparticle (Massadeh et al., 2016).

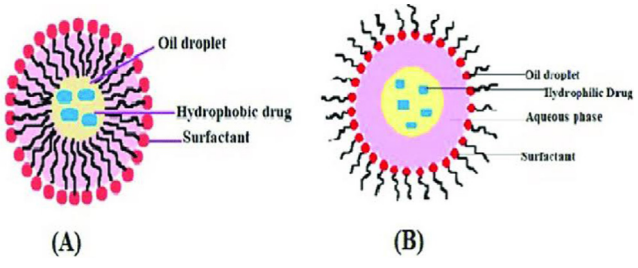

Fig. 4 Structure of SNEEDS/nanoemulsion loaded with drug. {A} O/W Nanoemulsion and {B} W/O Nanoemulsion (Halnor et al., 2018).

(PbN) group had a mean estimate of 27.127 with 13.833 and 40.422 upper and lower CIs, respectively. The third group (SNEEDS/Nanoemulsion) had a mean estimate of 9.283with 3.376 and 15.190 upper and lower CIs, respectively. While the fourth group had an estimated mean of 8.854 with −5.937 and 23.644 as its lower and upper CIs. The overlapping confidence interval of the first three groups (group1, 2 and 3) points outa lack of significant differences between them. Thus, a fact that signifies similar bioavailability performance for the three (of the five) groups investigated (insignificant AUC values though profiles may differ). Meta-analysis on group 4 (Liposome/proliposome) shows no significant difference between the treatments and indicate a dissimilar bioavailability effectexistent between them. This is contrary to the study carried out by Nasser *et al*. (Nasser et al., 2020) who reported that "…the lipid vesicular drug carriers (Liposome) are sought; being superior to their non-vesicular counterparts due to their high compatibility with the cell membranes and further due to their sustained effects balanceyet, the high penetration abilities of the surfactants and co-surfactants components of the SMEDDS and the microemulsions together with their confirmed uptake through the lymphatic system led to the overall obtained balance" (Van Slooten et al., 2001; Daraee et al., 2016; Hathout et al., 2010; Wang et al., 2014; Ali et al., 2013; El-Shabouri, 2002). The reason for the non-significant performance of Liposome/Proliposome could be largely as a result of the extremely small sample size (n = 2), as each of these treatment in the Liposome/Proliposome subgroup independently enhanced bioavailability as seen in Table 1 above.

Most of the treatmentswere within the SLNs subgroup which are much economical as the lipids used for production are cheaper that those used in the productions of polymeric nanoparticles (Shah et al., 2013). Other benefits include increased drug stability (Porter et al., 2007) as well as decreased drug toxicity (Yeh et al., 2014); high drug payload (Porter et al., 2007).

Polymer based nanoparticles act as nanocarriers for drug solubilization and oral delivery; and thus enhance oral bioavailability of drugs. Binkhathlan *et al*. had reported that "PEO-b-PCL micelles can act as effective solubilizing agent and serve as good alternative to commercially available excipients used in oral formulation of a poorly soluble drug i.e. CyA" (Ahmad et al., 2018). Other advantages of polymer based nanoparticles include its good biocompatibility (Peer et al., 2007), reduced adverse reactions (Yan et al., 2015), effective administration due to its minute size (Zhen et al., 2020), and powerful targeting alongside an easy method of preparation (Dian et al., 2014).

The pros of SNEEDS such as increased rate of extent of absorption, increased drug dissolution rate and nano sized particles are features that make SNEEDS to better enhance oral exposure of poorly lipophilic drug (Yamasaki et al., 2019; Pandita et al., 2014). In bid to enhance bioavailability of drugs, SNEEDS not only improves the solubility of the drugs but also increases the membrane permeability of the GI tract (Pandita et al., 2014; Tian et al., 2018).

It is worthy of note that the Meta Analysis studies as a rule work with any number of sample size greater than one ($n \leq 2$) taking into consideration the sample numbers in each study considered. However, the analysis is constantly limited with the number of related studies in the review.

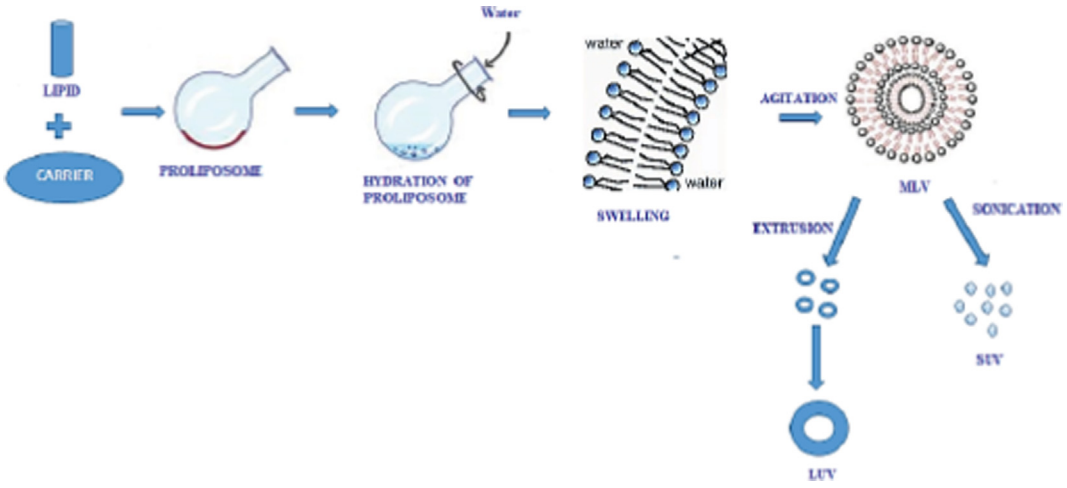

Fig. 5 Mechanism of formation of Liposomes from Proliposome (Singh et al., 2019).

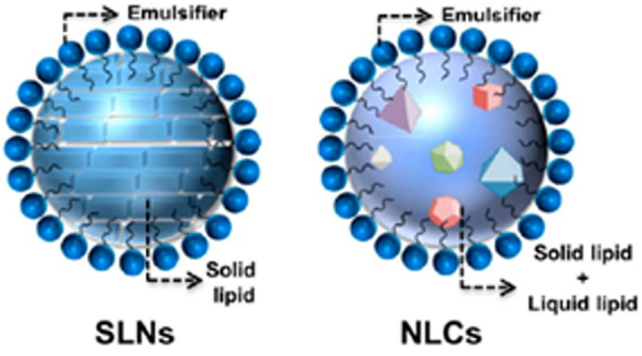

Fig. 6 A schematic illustration of nanostructured lipid carriers (NLC) and solid lipid nanoparticles (SLN) (Rahman et al., 2020).

3.3. Global studies including Saudi Arabia

A total of thirty-seven (37) studies were included in this study, and meta-analysis done on the data generated from them. The meta analysis result for the 37 studies which summarized the results on oral bioavailability indicated by the area under curve (AUC) of the investigated drugs were presented in Table 1 (APPENDIX III).

The result (presented Table 1 of the APPENDIX), revealed that all the studies except Dian et al (Yamasaki et al., 2019), Kazi *et al.* (Anwer et al., 2020), and El Shabouri (Pandita et al., 2014) established a significant increase in the AUC and accordingly the bioavailability of all drugs investigated was improved as compared to their control (free drug suspensions) groups. This was confirmed as all the studies had positive confidence interval

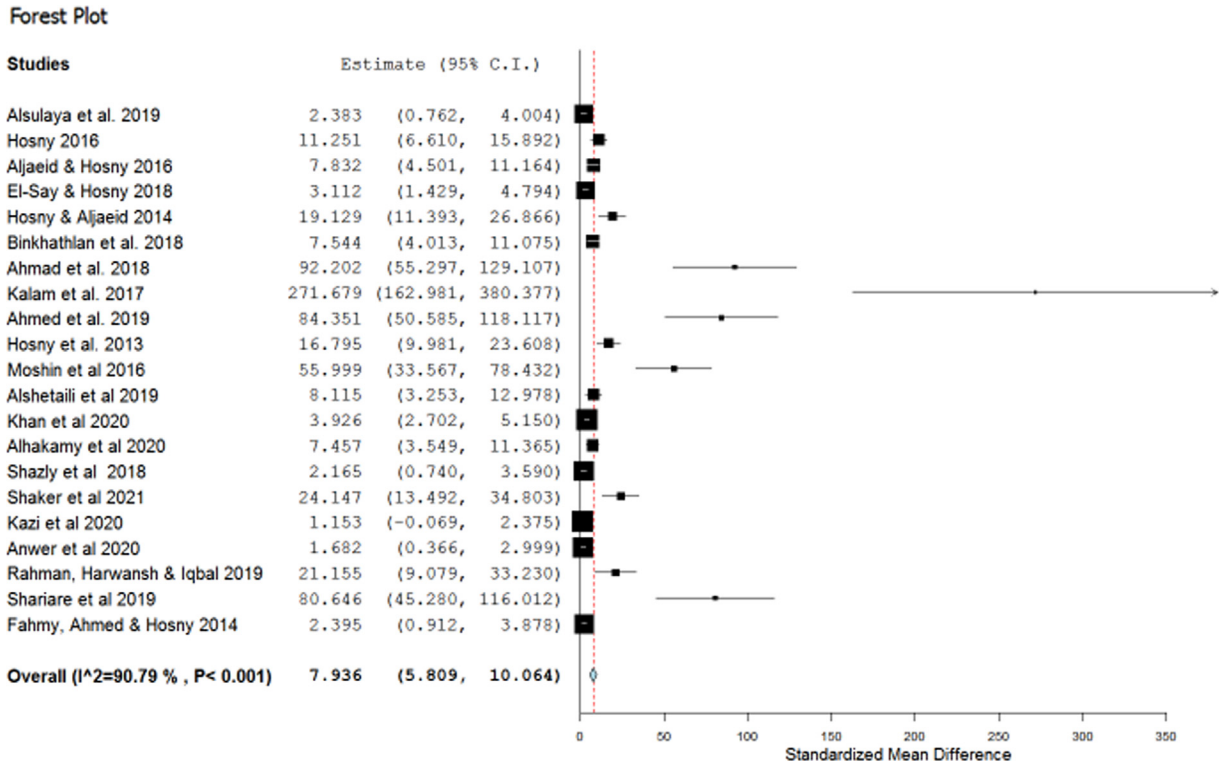

Fig. 7 The overall Forest plot of the published studies (n = 21) conducted in Saudi Arabia included in the Meta Analysis.

Table 2 Particle characterization of drug loaded with nano-particles.

Drug	Particle Size (nm)	Polydispersity index	Zeta potential (mV)	Encapsulation efficiency (%)	Drug Content (μg/mg)
Penetratin (Alsulays et al., 2019)	618.5 ± 8.4	0.734	−17.0 ± 1.53	59.03 ± 4.21	1.64 ± 0.05
Alendronate sodium (Fosamax®) (Hosny, 2016)	100	–	–	74.3	–
Miconazole marketed capsules (MN) (Aljaeid and Hosny, 2016)	23	–	−16	90.2	–
carvedilol (CVD) (El-Say and Hosny, 2018)	31.3	0.3	25.2 ± 1.33	95 ± 4.12	–
Sildenafil citrate marketed tablet (Hosny and Aljaeid, 2014)	28.51 ± 3.43	–	14.34 ± 3.56	95.34 ± 3.22	–
Cyclosporine A (CyA) Binkhathlan et al., 2018	83.8 ± 1.6	0.17 ± 0.09	–	73.77 ± 1.18	–
Doxorubicin (DOX) (Ahmad et al., 2018)	183.10 ± 7.41	0.132 ± 0.010	−13.10 ± 1.04	76.86 ± 3.51	42.69 ± 1.97
Thymoquinone (TQ) (Kalam et al., 2017)	54.25 ± 3.54	0.125	−18.88 ± 1.12	–	100
Vinpocetine (VPN) (Ahmed et al., 2019)	13 ± 2	0.484	−2.79 ± 0.35	100	–
Alendronate sodium (ALS) (Hosny et al., 2013)	110	–	4.92	41.92	–
Fenofibrate. (Moshin *et al*., 2016)	219.91 ± 10.11	0.266	–	–	–
ibrutinib (IBR) (Alshetaili et al., 2019)	–	–	–	–	–
Atazanavir (ATZ) (Khan et al., 2020)	227.6 ± 5.4	0.338 ± 0.021	−11.7 ± 0.47	71.09 ± 5.84	8.12 ± 2.7
Docosahexaenoic acid (DHA) (Alhakamy et al., 2020)	111.5 ± 4.2	0.269 ± 0.05	–23.53 ± 2.9	–	–
Domperidone (DOP) (Shazly et al., 2018)	201.4	0.071	−6.2	66.3	–
Atrovastin (At) (Shaker et al., 2021)	319 ± 14.5	0.53 ± 0.12	−15.9 ± 1.7	73.8 ± 4.2	69.7 ± 2.1
Apigenin (APG) (Kazi et al., 2020)	57.12 ± 11.45	0.419	−14.21 ± 3.12	–	100
Delafloxacin(Anwer et al., 2020)	368 ± 5.2	0.215 ± 0.015	19.2 ± 1.4	80.4 ± 3.1	1.7 ± 0.1
Sertraline (SRT) (Rahman et al., 2019)	108.5 ± 2.77	0.183 ± 0.004	36.5 ± 0.43	73.22 ± 2.18	0.71 ± 0.03
Furosemide microsuspension (Shariare et al., 2019)	129.0 ± 3.0	0.09 ± 0.01	20	–	–
Avanafil (AVA) (Fahmy et al., 2014)	95.0	12.22	–	–	

Table 3 Relative bioavailability of the study drugs.

Study names	Sub-Group	Nanosystem	Relative bioavailability
Penetratin (Alsulays et al., 2019)	1	SLN	18.17-fold
Alendronate sodium (Hosny, 2016)	1	SLN	7.47-fold
Miconazole (Aljaeid and Hosny, 2016)	1	SLN	2.46-fold
Carvedilol (El-Say and Hosny, 2018)	1	SLN	1.53-fold
Sildenafil citrate (Hosny and Aljaeid, 2014)	1	SLN	1.59-fold
Cyclosporine A (Binkhathlan et al., 2018)	2	Polymeric Nanoparticles	1.16-fold
Doxorubicin (Ahmad et al., 2018)	2	Polymeric Nanoparticles	9.66-fold
Thymoquinone (Kalam et al., 2017)	3	SNEEDS/Nanoemulsion	3.24-fold
Vinpocetine(Ahmed et al., 2019)	2	Polymeric Nanoparticles	1.91-fold
Alendronate sodium(Hosny et al., 2013)	4	Liposomes/proliposomes	12.57-fold
Fenofibrate. (Moshin *et al.,* 2016)	3	SNEEDS/Nanoemulsion	1.67-fold
Ibrutinib (Alshetaili et al., 2019)	2	Polymeric Nanoparticles	4.25-fold
Atazanavir (Khan et al., 2020)	5	NLC	2.36-fold
Docosahexaenoic acid (Alhakamy et al., 2020)	3	SNEEDS/Nanoemulsion	3.33-fold
Domperidone (Shazly et al., 2018)	1	SLN	2.62-fold
Atorvastatin (Shaker et al., 2021)	2	Polymeric Nanoparticles	3.48-fold
Apigenin (Kazi et al., 2020)	3	SNEEDS/Nanoemulsion	1.91-fold
Delafloxacin (Anwer et al., 2020)	4	Liposomes/proliposomes	2.30-fold
Sertraline (Rahman et al., 2019)	1	SLN	6.21-fold
Furosemide (Shariare et al., 2019)	3	SNEEDS/Nanoemulsion	2.67-fold
Avanafil (Fahmy et al., 2014)	3	SNEEDS/Nanoemulsion	1.39-fold

Table 4 The calculated weights of the studies included in the Meta Analysis (Studies from Saudi Arabi, $n = 21$).

Study names	Weights
Penetratin (Alsulays et al., 2019)	7.637%
esodium (Hosny, 2016)	5.790%
Miconazole (Aljaeid and Hosny, 2016)	6.682%
Carvedilol (El-Say and Hosny, 2018)	7.611%
Sildenafil citrate (Hosny and Aljaeid, 2014)	3.885%
Cyclosporine A (Binkhathlan et al., 2018)	6.550%
Doxorubicin (Ahmad et al., 2018)	0.319%
Thymoquinone (Kalam et al., 2017)	0.038%
Vinpocetine (Ahmed et al., 2019)	0.378%
Alendronate sodium (Hosny et al., 2013)	4.392%
Fenofibrate. (Moshin *et al*., 2016)	0.808%
Ibrutinib (Alshetaili et al., 2019)	5.638%
Atazanavir (Khan et al., 2020)	7.786%
Docosahexaenoic acid (Alhakamy et al., 2020)	6.294%
Domperidone (Shazly et al., 2018)	7.715%
Atrovastin (Shaker et al., 2021)	2.660%
Apigenin (Kazi et al., 2020)	7.787%
Delafloxacin (Anwer et al., 2020)	7.754%
Sertraline (Rahman et al., 2019)	2.235%
Furosemide (Shariare et al., 2019)	0.346%
Avanafil (Fahmy et al., 2014)	7.693%

scores except the aforementioned (Anwer et al., 2020; Yamasaki et al., 2019; Pandita et al., 2014).

Generally, the study (n = 37) has proven to be extremely significant ($P < 0.001$) having a pooled estimate of 6.715 and positive confidence intervals of 5.157 and 8.273 for the lower and upper confidence intervals, respectively (Table 2, APPENDIX III) (see Tables 3 and 4).

4. Conclusion

In the presentstudy, a total of 37obtainable 'proof-of-concept' studies were identified, included using certain eligibility criteria and analyzed for the oral bioavailability enhancement. 21 of the included studies where of vital importance as this study focused more on literatures and outcome from Saudi Arabia. In view of this the 21 studies obtained were analyzed oral bioavailability enhancement through nanotechnology in Saudi Arabia. Haven utilized comprehensive and recent data of the confirmed the enhancement of bioavailability using nanotechnology which for this study was grouped into five: solid lipid nanoparticles; polymer based nanoparticles; SNEEDS/Nanoemulsion; liposomes/proliposomes and; nanostructured lipid carriers. The result of this study can provide a better guide for drug formulators on enhancing the effectiveness of orally administered drugs especially the antineoplastic drugs. SLN was the best performing nanoformulation. An instance is seen form the SLN formulation of the Penetratin [L-Penetratin INS-SLN] with a relative bioavailability of over 1,800% (18.17-fold). Furthermore, the meta-analysis, provided evidence of insignificant differences between APG Bio-SNEDDS and its free drug suspension (Apeginin, APG), though with relative bioavailabiilty of 1.91. Notwithstanding most of the treatment showed a substantial relative bioavailability

Declaration of Competing Interest

The author declares that she have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Agrawal, U., Sharma, R., Gupta, M., Vyas, S.P., 2014. Is nanotechnology a boon for oral drug delivery? Drug Discovery Today 19 (10), 1530–1546.

Ahmad, N., Ahmad, R., Alam, M.A., Ahmad, F.J., 2018. Enhancement of oral bioavailability of doxorubicin through surface modified biodegradable polymeric nanoparticles. Chemistry Central J. 12 (1), 65. https://doi.org/10.1186/s13065-018-0434-1.

Ahmed, T.A., El-Say, K.M., Ahmed, O.A.A., Aljaeid, B.M., 2019. Superiority of TPGS-loaded micelles in the brain delivery of vinpocetine via administration of thermosensitive intranasal gel. Int J. Nanomed. 14, 5555–5567. https://doi.org/10.2147/IJN.S213086.

Alhakamy, N.A., Aldawsari, H.M., Hosny, K.M., Ahmad, J., Akhter, S., Kammoun, A.K., Alghaith, A.F., Asfour, H.Z., Al-Rabia, M. W., Md, S., 2020. Formulation design and pharmacokinetic evaluation of docosahexaenoic acid containing self-nanoemulsifying drug delivery system for oral administration. Nanomaterials and Nanotechnology. https://doi.org/10.1177/1847980420950988.

Ali, K.A., Mudassir, J., Mohtar, N., Darwis, Y., 2013. Advanced drug delivery to the lymphatic system: lipid-based nanoformulations. Int. J. Nanomed. 8, 2733–2744.

Aljaeid, B.M., Hosny, K.M., 2016. Miconazole-loaded solid lipid nanoparticles: formulation and evaluation of a novel formula with high bioavailability and antifungal activity. Int. J. Nanomed. 11, 441–447. https://doi.org/10.2147/IJN.S100625.

Alshetaili, A.S., Ansari, M.J., Anwer, M.K., Ganaie, M.A., Iqbal, M., Alshahrani, S.M., Alalaiwe, A.S., Alsulays, B.B., Alshehri, S., Sultan, A.S., 2019. Enhanced Oral Bioavailability of Ibrutinib Encapsulated Poly (Lactic-co-Glycolic Acid) Nanoparticles: Pharmacokinetic Evaluation in Rats. Current Pharmaceutical Analysis 15, 661–668. https://doi.org/10.2174/1573412915666190314124932.

Alsulays, B.B., Anwer, M.K., Soliman, G.A., Alshehri, S.M., Khafagy, E.S., 2019. Impact OfPenetratin Stereochemistry On The Oral Bioavailability Of Insulin-Loaded Solid Lipid Nanoparticles. Int. J. Nanomed. 14, 9127–9138. https://doi.org/10.2147/IJN.S225086.

Anwar, M., Warsi, M.H., Mallick, N., Akhter, S., Gahoi, S., Jain, G. K., Talegaonkar, S., Ahmad, F.J., Khar, R.K., 2011. Enhanced bioavailability of nano-sized chitosan–atorvastatin conjugate after oral administration to rats. Eur. J. Pharm. Sci. 44 (2011), 241–249.

Anwer, M.K., Iqbal, M., Muharram, M.M., Mohammad, M., Ezzeldin, E., Aldawsari, M.F., Alalaiwe, A., Imam, F., 2020. Development of Lipomer Nanoparticles for the Enhancement of Drug Release, Anti-microbial Activity and Bioavailability of Delafloxacin. Pharmaceutics 12 (3), 252. https://doi.org/10.3390/pharmaceutics12030252.

Rizwan Arshad, LubabaGulshad, Iahtisham-Ul- Haq, Muhammad Adil Farooq, Ammar Al-Farga, Rabia Siddique, Muhammad Faisal Manzoor, EmadKarrar, 2021. Nanotechnology: A novel tool to enhance the bioavailability of micronutrients. First published: 04 May 2021, 10.1002/fsn3.2311.

Berardi, A., Bisharat, L., 2016. Nanotechnology systems for oral drug delivery: challenges and opportunities. In: Salam Massadeh (Ed.), Nanotechnology in Drug Delivery. Chapter 3, One Central Press (UK), pp. 52-84.

Berardi, Alberto, Bisharat, Lorina, 2016. Nanotechnology systems for oral drug delivery: challenges and opportunities. In: Salam Massadeh (Ed.), Nanotechnology in Drug Delivery, Chapter: 3. Publisher: One Central Press, UK, pp. 52-84.

Bernkop-Schnürch, A., 2013. ''Nanocarrier systems for oral drug delivery: do we really need them?" European Journal of Pharmaceutical Sciences, 49(2), 272–277, 2013.

Binkhathlan, Z., Ali, R., Qamar, W., Lavasanifar, A., 2018. Pharmacokinetics of Orally Administered Poly(Ethylene Oxide)-block-Poly (ε-Caprolactone) Micelles of Cyclosporine A in Rats: Comparison with Neoral®. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societecanadienne des sciences pharmaceutiques, 21(1s), 192s–199s. 10.18433/jpps28987.

Brakmane, G., Winslet, M., Seifalian, A.M., 2012. Systematic review: the applications of nanotechnology in gastroenterology. Alimentary Pharmacol. Therapeutics 36 (3), 213–221. https://doi.org/10.1111/j.1365-2036.2012.05179.x.

Cavalcanti, A., Shirinzadeh, B., Freitas, R.A., Hogg, T., 2008. Nano robot architecture for medical target identification. Nanotechnology 19, 15.

Charoo, N.A., Rahman, Z., Khan, M.A., 2019. Nanoparticles for improvement in oral bioavailability. In: Grumezescu, A.M. (Ed.), Nanoarchitectonics in Biomedicine. William Andrew Publishing. Crossref Google Scholar, pp. 371–410.

Daraee, H., Etemadi, A., Kouhi, M., Alimirzalu, S., Akbarzadeh, A., 2016. Application of liposomes in medicine and drug delivery. Artif. Cells Nanomed. Biotechnol. 44 (1), 381–391.

Dian, L., Yu, E., Chen, X., Wen, X., Zhang, Z., Qin, L., Wu, C., 2014. Enhancing oral bioavailability of quercetin using novel soluplus polymeric micelles. Nanoscale Res. Lett. 9 (1), 684. https://doi.org/10.1186/1556-276x-9-684.

Ekambaram, P., Sathali, A.A.H., Priyanka, K., 2012. Solid lipid nanoparticles: a review. Sci. Rev. Chem. Commun. 2 (1), 80–102.

El-Say, K.M., Hosny, K.M., 2018. Optimization of carvedilol solid lipid nanoparticles: An approach to control the release and enhance the oral bioavailability on rabbits. PLoS ONE 13 (8), e0203405. https://doi.org/10.1371/journal.pone.0203405.

El-Shabouri, M.H., 2002. Positively charged nanoparticles for improving the oral bioavailability of cyclosporin-A. Int. J. Pharm. 249 (1–2), 101–108. https://doi.org/10.1016/s0378-5173(02)00461-1.

Elshafeey, A., Bendas, E., Mohamed, O., 2009. Intranasal microemulsion of sildenafil citrate: in vitro evaluation and in vivo pharmacokinetic study in rabbits. AAPS PharmSciTech. 10 (2), 361–367.

Fahmy, U.A., Ahmed, O.A., Hosny, K.M., 2014. Development and evaluation of avanafil self-nanoemulsifying drug delivery system with rapid onset of action and enhanced bioavailability. AAPS PharmSciTech 16 (1), 53–58. https://doi.org/10.1208/s12249-014-0199-3.

Fong, S.Y., Brandl, M., Bauer-Brandl, A., 2015. Phospholipid-based solid drug formulations for oral bioavailability enhancement: a meta-analysis. European journal of pharmaceutical science: Official Journal of the European Federation for Pharmaceutical Sciences 80, 89–110. https://doi.org/10.1016/j.ejps.2015.08.005.

Fong, S.Y.K., Bauer-Brandl, A., Brandl, M., 2016. Oral bioavailability enhancement through supersaturation: an update and meta-analysis, Expert Opinion on Drug Delivery, pp. 1-77. 10.1080/17425247.2016.1218465Epub 2016 Aug 11. PMID: 2748804.

Glasziou, P.P., Sanders, S.L., 2002. Investigating causes of heterogeneity in systematic reviews. Statistics in Medicine 21 (11), 1503–1511. https://doi.org/10.1002/sim.1183.

Guan, P., Lu, Y., Qi, J., Niu, M., Lian, R., Hu, F., Wu, W., 2011. Enhanced oral bioavailability of cyclosporine A by liposomes containing a bile salt. Int. J. Nanomed. 2011 (05/04), 965–974.

Gupta, T., Singh, J., Kaur, S., Sandhu, S., Singh, G., Kaur, I.P., 2020. Enhancing Bioavailability and Stability of Curcumin Using Solid Lipid Nanoparticles (CLEN): A Covenant for Its Effectiveness. Front. Bioeng. Biotechnol. 8, 879. https://doi.org/10.3389/fbioe.2020.00879.

Halnor, V.V., Pande, V.V., Borawake, D.D., Nagare, H.S., 2018. Nanoemulsion: A Novel Platform for Drug Delivery System. J. Mater. Sci. Nanotechol. 6 (1), 104.

Hathout, R.M., 2019. Particulate Systems in the Enhancement of the Antiglaucomatous Drug Pharmacodynamics: A Meta-Analysis Study. ACS Omega 4 (26), 21909–21913.

Hathout, R.M., Woodman, T.J., Mansour, S., Mortada, N.D., Geneidi, A.S., Guy, R.H., 2010. Microemulsion formulations for the transdermal delivery of testosterone. Eur. J. Pharm. Sci. 40 (3), 188–196.

Hetal, T., Bindesh, P., Sneha, T., 2010. A review on techniques for oral bioavailability enhancement of drugs. Int. J. Pharm. Sci. Rev. Res. 4 (3), 203–223.

Higgins, J.P.T., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine 21, 1539–1558. https://doi.org/10.1002/sim.1186.

Hosny, K.M., 2016. Alendronate Sodium as Enteric Coated Solid Lipid Nanoparticles; Preparation, Optimization, and In Vivo Evaluation to Enhance Its Oral Bioavailability. PloS one 11 (5), e0154926. https://doi.org/10.1371/journal.pone.0154926.

Hosny, K.M., Aljaeid, B.M., 2014. Sildenafil citrate as oral solid lipid nanoparticles: a novel formula with higher bioavailability and sustained action for treatment of erectile dysfunction. Expert Opinion Drug Delivery 11 (7), 1015–1022. https://doi.org/10.1517/17425247.2014.912212.

Hosny, K.M., Ahmed, O.A., Al-Abdali, R.T., 2013. Enteric-coated alendronate sodium nanoliposomes: a novel formula to overcome barriers for the treatment of osteoporosis. Expert Opinion Drug Deliv. 10 (6), 741–746. https://doi.org/10.1517/17425247.2013.799136.

Ipar, V.S., Dsouza, A., Devarajan, P.V., 2019. Enhancing Curcumin Oral Bioavailability Through Nanoformulations. Eur. J. Drug MetabPharmacokinet. 44 (4), 459–480. https://doi.org/10.1007/s13318-019-00545-z. PMID: 30771095.

Jain, Niharika, Jain, Dr. Ruchi, Thakur, N., Gupta, B.P., Jain, D.K., Banveer, J., Jain, Shreynahs, 2010. Nanotechnology: A safe and effective drug delivery system. Asian Journal of Pharmaceutical and Clinical Research. 3, 159-165.

Kalam, M.A., Raish, M., Ahmed, A., Alkharfy, K.M., Mohsin, K., Alshamsan, A., Al-Jenoobi, F.I., Al-Mohizea, A.M., Shakeel, F., 2017. Oral bioavailability enhancement and hepatoprotective effects of thymoquinone by self-nanoemulsifying drug delivery system. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Msc(2017), doi: 10.1016/j.msec.2017.03.088.

Kazi, M., Alhajri, A., Alshehri, S.M., Elzayat, E.M., Al Meanazel, O. T., Shakeel, F., Noman, O., Altamimi, M.A., Alanazi, F.K., 2020. Enhancing Oral Bioavailability of Apigenin Using a Bioactive Self-Nanoemulsifying Drug Delivery System (Bio-SNEDDS): In Vitro, In Vivo and Stability Evaluations. Pharmaceutics, 12(8), 749.10.3390/pharmaceutics12080749.

Khadka, P., Ro, J., Kim, H., Kim, I., Kim, J.T., Kim, H., Cho, J.M., Yun, G., Lee, J., 2014. Pharmaceutical particle technologies: an approach to improve drug solubility, dissolution and bioavailability. Asian J. Pharm. Sci. 9 (6), 304–316. https://doi.org/10.1016/j.ajps.2014.05.005.

Khan, S.A., Rehman, S., Nabi, B., Iqubal, A., Nehal, N., Fahmy, U. A., Kotta, S., Baboota, S., Md, S., Ali, J., 2020. Boosting the Brain Delivery of Atazanavir through Nanostructured Lipid Carrier-Based Approach for Mitigating NeuroAIDS. Pharmaceutics 12 (11), 1059. https://doi.org/10.3390/pharmaceutics12111059.

Koo, O.M., Rubinstein, I., Onyuksel, H., 2005. Role of nanotechnology in targeted drug delivery and imaging: A concise review. Nanomedicine: Nanotechnology Biology and Medicine 1, 193–212. https://doi.org/10.1016/j.nano.2005.06.004Crossref CAS PubMed Web of Science®Google Scholar.

Kumar, M.N.R., 2000. Nano and microparticles as controlled drug delivery devices. *Journal of Pharmacy and Pharmaceutical* Sciences, 3(2), 234– 258.PMID: 10994037. PubMed Web of Science®Google Scholar.

Le, J., 2020. Drug Bioavailability. Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, 2021

Merck Sharp &Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Li, C., Zhang, Y., Su, T., Feng, L., Long, Y., Chen, Z., 2012. Silica-Coated Flexible Liposomes as a Nanohybrid Delivery System for Enhanced Oral Bioavailability of Curcumin. Int. J. Nanomed. 7, 5995–6002. https://doi.org/10.2147/IJN.S38043.

Ma, Y., Li, H., Guan, S., 2015. Enhancement of the oral bioavailability of breviscapine by nanoemulsions drug delivery system. Drug Dev. Ind. Pharm. 41 (2), 177–182. https://doi.org/10.3109/03639045.2014.947510. Epub 2014 Aug 12 PMID: 25113432.

Massadeh, S., Al-Aamery, M., Bawazeer, S., AlAhmad, O., AlSubai, R., et al, 2016. Nano-materials for Gene Therapy: An Efficient Way in Overcoming Challenges of Gene Delivery. J. Biosens. Bioelectron. 7, 195. https://doi.org/10.4172/2155-6210.1000195.

McConnell, E.L., Basit, A.W., 2013. Modified-release oral drug delivery. In: Aulton, M.E., Taylor, K.M.(Eds.), Aulton's Pharmaceutics: The Design and Manufacture of Medicines, fourth ed., Churcill Livingstone, 2013, pp. 550–565.

Mishra, V., Bansal, K.K., Verma, A., Yadav, N., Thakur, S., Sudhakar, K., Rosenholm, J.M., 2018. Solid Lipid Nanoparticles: Emerging Colloidal Nano Drug Delivery Systems. Pharmaceutics 10 (191), 1–21. https://doi.org/10.3390/pharmaceutics10040191.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6, e1000097.

Nasser, N., Hathout, R.M., Abd-Allah, H., Sammour, O.A., 2020. Enhancement of oral bioavailability of drugs using lipid-based carriers: a meta-analysis study. Drug Dev. Ind. Pharm. 46 (12), 2105–2110. https://doi.org/10.1080/03639045.2020.1851245. Epub 2020 Nov 23 PMID: 33185482.

Pandita, D., Ahuja, A., Lather, V., Benjamin, B., Dutta, T., Velpandian, T., Khar, R.K., 2011. Development of Lipid-Based Nanoparticles for Enhancing the Oral Bioavailability of Paclitaxel. AAPS PharmSciTech 12 (2), 712–722. https://doi.org/10.1208/s12249-011-9636-8.

Pandita, D., Kumar, S., Poonia, N., Lather, V., 2014. Solid lipid nanoparticles enhance oral bioavailability of resveratrol, a natural polyphenol. Food Research International 62, 1165–1174. https://doi.org/10.1016/j.foodres.2014.05.059. ISSN 0963-9969.

Pathak, K., Raghuvanshi, S., 2015. Oral Bioavailability: Issues and Solutions via Nanoformulations. Clinical Pharmacokinetics 54 (4), 325–357. https://doi.org/10.1007/s40262-015-0242-x.

Peer, D., Karp, J.M., Hong, S., et al. 2007. Nanocarriers as an emerging platform for cancer therapy. Nat. Nanotechnol. 2, 751–760.

Perrie, Y., 2013. Pharmaceutical nanotechnology and nanomedicine. In: Aulton, M.E., Taylor, K.M. (Eds.), Aulton's Pharmaceutics: The Design and Manufacture of Medicines, Churcill Livingstone, 2013, pp. 777–796.

Porter, C.J., Trevaskis, N.L., Charman, W.N., 2007. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nat. Rev. Drug Discov. 6, 231–248.

Price, G., Patel, D.A., 2021. Drug Bioavailability. [Updated 2020 Oct 20]. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island (FL), 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557852/.

Prisant, L.M., Bottini, B., DiPiro, J.T., Carr, A.A., 1992. Novel drug-delivery systems for hypertension. Am. J. Med. 93 (2), 45S–55S.

Rahman, M.A., Harwansh, R.K., Iqbal, Z., 2019. Systematic Development of Sertraline Loaded Solid Lipid Nanoparticle (SLN) by Emulsification-Ultrasonication Method and Pharmacokinetic Study in Sprague-Dawley Rats. Pharmaceutical nanotechnology 7 (2), 162–176. https://doi.org/10.2174/2211738507666190327145628.

Rahman, H.S., Othman, H.H., Hammadi, N.I., Yeap, S.K., Amin, K. M., Abdul Samad, N., Alitheen, N.B., 2020. Novel Drug Delivery Systems for Loading of Natural Plant Extracts and Their Biomedical Applications. Int. J. Nanomed. 15, 2439–2483. https://doi.org/10.2147/IJN.S227805.

Safari, J., Zarnegar, Z., 2014. Advanced drug delivery systems: nanotechnology of health design—a review. Journal of Saudi Chemical Society, 18(2), 85–99.

Sanna, V., Caria, G., Mariani, A., 2010. Effect of lipid nanoparticles containing fatty alcohols having different chain length on the ex vivo skin permeability of econazole nitrate. Powder Technol. 201 (1), 32–36.

Shah, N.M., Parikh, J., Namdeo, A., Subramanian, N., Bhowmick, S., 2006. Preparation, Characterization and in Vivo Studies of Proliposomes Containing Cyclosporine A. J. Nanosci. Nanotechnol., 6, 2967–2973. http://dx.doi.org/10.1166/jnn.2006.403.

Shah, S.R., Parikh, R.H., Chavda, J.R., Sheth, N.R., 2013. Self-nanoemulsifying drug delivery system of glimepiride: design, development, and optimization. PDA J. Pharm. Sci. Technol. 67, 201–213.

Shaker, M.A., Elbadawy, H.M., Al Thagfan, S.S., Shaker, M.A., 2021. Enhancement of atorvastatin oral bioavailability via encapsulation in polymeric nanoparticles. International Journal of Pharmaceutics 592, 120077. https://doi.org/10.1016/j.ijpharm.2020.120077.

Shariare, M.H., Altamimi, M.A., Marzan, A.L., Tabassum, R., Jahan, B., Reza, H.M., Rahman, M., Ahsan, G.U., Kazi, M., 2019. In vitro dissolution and bioavailability study of furosemide nanosuspension prepared using design of experiment (DoE). Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society 27 (1), 96–105. https://doi.org/10.1016/j.jsps.2018.09.002.

Sharma, M., Sharma, R., Jain, D.K., 2016. Nanotechnology Based Approaches for Enhancing Oral Bioavailability of Poorly Water Soluble Antihypertensive Drugs. Scientifica 2016, 1–11. https://doi.org/10.1155/2016/8525679. Article ID 8525679.

Shazly, G.A., Alshehri, S., Ibrahim, M.A., Tawfeek, H.M., Razik, J. A., Hassan, Y.A., Shakeel, F., 2018. Development of Domperidone Solid Lipid Nanoparticles. In Vitro and In Vivo Characterization. AAPS PharmSciTech 19 (4), 1712–1719. https://doi.org/10.1208/s12249-018-0987-2.

Singh, N., Kushwaha, P., Ahmad, U., Abdullah, M., 2019. Prolipo-somes: An Approach for the Development of Stable Liposome. Ars Pharm. 60 (4), 231–240.

Singh, R., Lillard Jr., J.W., 2009. Nanoparticle-based targeted drug delivery. Exp. Mol. Pathol. 86 (3), 215–223.

Sinha, V.R., Srivastava, S., Goel, H., et al, 2010. Solid lipid nanoparticles (SLN'S)-trends and implications in drug targeting. Int. J. Adv. Pharm. Sci. 1 (3), 212–238.

Suri, S.S., Fenniri, H., Singh, B., 2007. Nanotechnology-based drug delivery systems. Journal of Occupational Medicine and Toxicology, vol. 2, article 16, 2007. doi: 10.1186/1745-6673-2-16. PMID: 18053152; PMCID: PMC2222591.

Tatham, L.M., Rannard, S.P., Owen, A., 2015. Nanoformulation strategies for the enhanced oral bioavailability of antiretroviral therapeutics. Therapeutic delivery 6 (4), 469–490. https://doi.org/10.4155/tde.15.4.

Tian, M., Song, R., Wang, T., Sun, M., Liu, Y., Chen, X., 2018. Inducing sustained release and improving oral bioavailability of curcumin via chitosan derivatives-coated liposomes, International Journal of Biological Macromolecules, 120 (Part A), 702-710. 10.1016/j.ijbiomac.2018.08.146.

Van Slooten, M.L., Boerman, O., Romoren, K., Kedar, E., Crommelin, D.J., Storm, G., 2001. Liposomes as sustained release system for human interferongamma: biopharmaceutical aspects. Biochim. Biophys. Acta 1530 (2–3), 134–145.

Wang, K., Qi, J., Weng, T., Tian, Z., Lu, Y., Hu, K., Yin, Z., Wu, W., 2014. Enhancement of oral bioavailability of cyclosporine A: comparison of various nanoscale drug-delivery systems. Int. J. Nanomed. 9, 4991–4999.

Xiaojun Yu, Chandra M. Valmikinathan, Amanda Rogers, Junping Wang, 2007. In: Kenneth E. Gonsalves, Craig R. Halberstadt, Cato T. Laurencin, Lakshmi S. Nair (Eds.), Nanotechnology and Drug

Delivery, First published: 11 April 2007 Biomedical Nanostructures. 10.1002/9780470185834.ch5.

Yamasaki, K., Taguchi, K., Nishi, K., Otagiri, M., Seo, H., 2019. Enhanced dissolution and oral bioavailability of praziquantel by emulsification with human serum albumin followed by spray drying. Eur. J. Pharm. Sci.: Off. J. Eur. Federation Pharm. Sci. 139, 105064. https://doi.org/10.1016/j.ejps.2019.105064.

Yan, H.M., Song, J., Zhang, Z.H., et al, 2015. Optimization and anticancer activity in vitro and in vivo of baohuoside I incorporated into mixed micelles based on lecithin and Solutol HS15. Drug Deliv. 8, 1–8.

Yang, L.i., Geng, Y., Li, H., Zhang, Y., You, J., Chang, Y., 2009. Enhancement the oral bioavailability of praziquantel by incorporation into solid lipid nanoparticles. Die Pharmazie. 64, 86–89. https://doi.org/10.1691/ph.2009.8140.

Yeh, J.C., Hsu, Y.T., Su, C.M., et al, 2014. Preparation and characterization of biocompatible and thermoresponsive micelles based on poly(N-isopropylacrylamide-co-N, N-dimethylacrylamide) grafted on polysuccinimide for drug delivery. J. Biomater. Appl. 29, 442–453.

York, P., 2013. Design of dosage forms. In: Aulton, M.E., Taylor, K. M.G. (Eds.), Aulton's Pharmaceutics: The Design and Manufacture of Medicines, fourth ed., Churcill Livingstone, 2013, pp. 7–19.

Zhang, L., Wang, S., Zhang, M., Sun, J., 2013. Nanocarriers for oral drug delivery. J. Drug Targeting 21 (6), 515–527.

Zhen, L., Wei, Q., Wang, Q., et al, 2020. Preparation and in vitro/in vivo evaluation of 6-gingerol TPGS/PEG-PCL polymeric micelles. Pharm. Dev. Technol. 25, 1–8.