 doi:10.20944/preprints202201.0456.v1

Do the polymeric nanoparticles really enhance the bioavailability of oral drugs? A quantitative answer using meta-analysis

Rania M. Hathout[1*]

[1] Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt.

[*]Correspondence: Rania M. Hathout, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, African Union Organization St.,11566 Cairo, Egypt.

Tel: +2 (0) 100 5252919

+ 2 02 22912685

Fax: +2 02 24011507

E-mail: r_hathout@yahoo.com; rania.hathout@pharma.asu.edu.eg

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 January 2022 doi:10.20944/preprints202201.0456.v1

Abstract

The oral route remains one of the most popular and important routes of administration that warrants the development of advanced drug delivery systems such as the polymeric nanoparticles capable of enhancing the absorption and bioavailability of the used drugs. In this work, systematic reviewing through several databases followed by a meta-analysis study were utilized in order to navigate the published studies and reach literature-based evidence about the capability of polymeric nanoparticulate systems of augmenting the absorption and the bioavailability of the orally administered drugs. The pharmacokinetic parameter; area under the curve (AUC) was utilized as the "effect" of the meta-analysis study. The meta-analysis study demonstrated the significant increase AUC as compared to the conventional formulations. Furthermore, comparing the synthetic polymeric nanoparticles versus the naturally-based counterparts, as subgroups of the meta-analysis, revealed no significant differences.

Keywords: oral; drugs; nanoparticles; systematic; meta-analysis

1. Introduction

The oral route remains the most common route of drug administration and one of the most convenient to the patients due to its non-invasiveness and ease of administration [1]. It is also preferred in the pharmaceutical industry due to the feasibility of its mass production [2]. Several attempts have been used in order to enhance the bioavailability of the orally admninistered drugs and increase their absorption. Encapsulating the drugs in different lipid and polymeric nanoparticles (NP) is an example of these attempts [3,4]. Moreover, the delivery of drugs in a controlled manner is currently a topic of great importance for both the industry and academia due to its huge benefits in healthcare [5]. Recently, the use of lipid-based nano-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 January 2022 doi:10.20944/preprints202201.0456.v1

carriers has proven superiority over the conventional formulations in augmenting the bioavailability of oral drugs using a quantitative meta-analysis study [6]. The close affinity of those carriers to the lipidic nature of the intestinal cell membranes may have contributed to this outcome. Consequently, a logical question arises, whether the use of polymeric nanoparticles increases the bioavailability of the aforementioned drugs or not bearing in mind its different nature and more rigid matrices. From the pharmaceutical point of view, the polymeric nanoparticles are of special interest as they are more stable than the other lipidic nanocarriers such as the liposomes and impart a more protective effects on their interior cargo [7,8]. Furthermore, they are coined by their facile modulation regarding the size, hydrophobicity and surface grafting and conjugation [9-12]. Accordingly, the same informatics tools; systematic reviewing and meta-analysis are utilized in this study to answer this question.

Systematic reviewing deals with the synthesis of empirical evidence from pre-specified eligibility criteria in order to address a specific research question. It is considered a qualitative informatics tool. On the other hand, meta-analysis is a quantitative synthesis tool [13]. Meta-analysis is an advanced statistical method that integrates data extracted from multiple studies originating from different sources. It increases the accuracy and precision of studies outcomes and predictions and is considered one of the informatics tools and a means of exploiting the available literature in answering scientific questions [14]. Nevertheless, meta-analyses play fundamental roles in evidence-based healthcare-related topics. Compared to other types of study designs (such as cohort studies, randomized controlled trials, cross-sectional studies, case-control studies, case series and case reports), the meta-analysis comes in at the top of the ‘levels of evidence’ pyramid [15,16]. Meta-analysis studies enjoy many advantages. It is considered an objective approach where it increases the statistical power by pooling the samples together. Moreover, this type of analysis increases the confidence about the conclusions and is an economic and affordable type of analysis that

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 January 2022 doi:10.20944/preprints202201.0456.v1

exploits the available online literature and databases[17-19]. The data gathering and its eligibility being sometimes highly challenging is the only drawback of the method.

Nowadays, the meta-analysis is being implemented in the drug delivery fields as it can be used to compare any new formulation or delivery system with a conventional one. It poses an important tool for the pharmaceutical industry decision-making [6,14,20,21].

To this end, the aim of the current study was to provide a quantitative proof extracted from the existing literature on the increase of bioavailability of drugs loaded in polymeric nanoparticles compared to their conventional formulations. The significance of the aformentioned approach in bioavailability enhancement was assessed. Moreover, another covariate factor was evaluated; namely; the type of the used polymer; synthetic such as PLGA (Poly-lactic-co-glycolic acid), PCL (Poly-Ɛ-caprolactone), Ethyl cellulose, Eudragit® E100, PVP and solupulus versus natural such as chitosan and the proteins e.g. gelatin, casein and zein.

2. Methodology

2.1. Data mining

A computer-based data search and gathering was performed using databases such as: Medline®, Embase® and on a search engine ; Google Scholar®.

The following were the English keywords used in the search: oral, polymer, nanoparticles, drug, synthetic and natural. The process of data mining of the literature according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses: http://www.prisma-statement.org/) guidelines is illustrated in the form of a flow diagram in **Figure 1**.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 January 2022 doi:10.20944/preprints202201.0456.v1

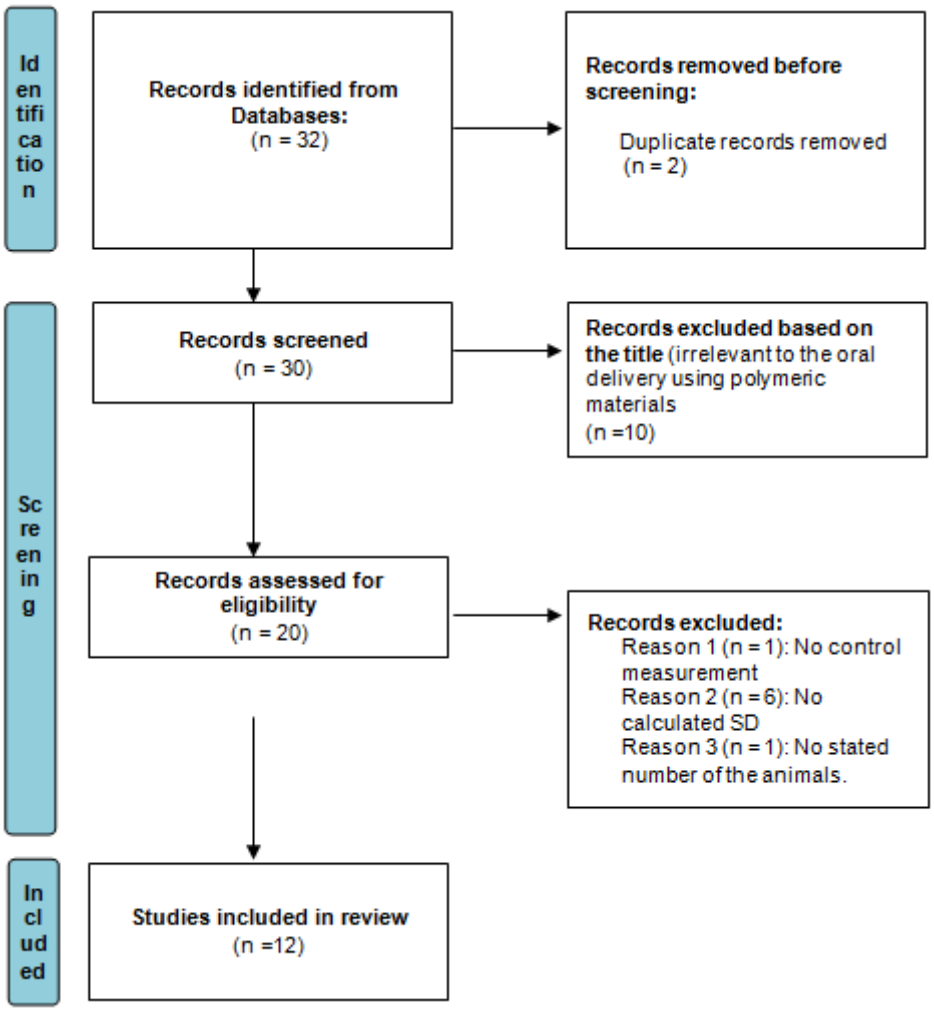

Fig. 1. The process of data mining conducted in the current study according to PRISMA guidelines.

2.2. Inclusion data and its criteria

The meta-analysis relied on obtaining the pharmacokinetic parameter, namely the area under the curve (AUC). The investigated articles were considered eligible for assessment if they comprise the methodology, an original data and the discussion related to the drugs loaded in polymeric nanoparticles (NP) that are utilized for oral delivery. All initially eligible articles were further screened in detail by analyzing the abstract and full text. All the articles should contain original data (research articles). The mean area under the curve (AUC) curve together with its standard deviation should have been reported. The control group comprising

 doi:10.20944/preprints202201.0456.v1

the investigated drug in the study delivered in a conventional formulation should have been stated. The following data were collected from articles fulfilling the inclusion criteria: the investigated drug, the name of the author and year of publication, the number of the used animals for each of the polymeric nanoparticles group and the conventional formulation group, the type of the used animal and the type of the polymer (synthetic versus natural). AUC was used as an indicative of the bioavailability of the drug-loaded polymeric nanoparticles compared to the control (conventional formulation of the drug). Table 1 shows the different elements of the conducted meta-analysis study.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 January 2022 doi:10.20944/preprints202201.0456.v1

Table 1. Summary of the Meta-Analysis of the Published Studies investigating the bioavailability of different orally loaded drugs in polymeric nano-particulate systems compared to conventional delivery systems as controls.

No.	Drug	Year of study	Grp A number of animals	Grp A Drug in NP Mean AUC (ng.h/ml)	Grp A AUC SD	Grp B number of animals	Grp B drug in conventional formulation Mean AUC (ng.h/ml)	Grp B AUC SD	SMD	Lower C.I.	Upper C.I.	Type of nano carriers*	Type of used animals	Reference
1	Celexocib, Morgen et al.	2012	6	2031	1250	6	698	414	1.321	0.072	2.570	Ethyl cellulose NPs[a]	Dogs	22
2	Quercetin, Dian et al.	2014	3	107840	54000	3	37680	16800	1.400	-0.386	3.185	Solupulus PMs[a]	Dogs	23
3	Triptolide, Liu et al.	2020	5	28000	9000	5	6500	700	3.041	1.221	4.860	Casein Nanoparticles[b]	Rats	24
4	Ibuprofen, Hedaya et al.	2021	5	207000	37900	5	114300	35900	2.267	0.678	3.856	PVP NPs[a]	Rabbits	25
5	Resveratrol, Penalva et al.	2015	6	5170	2610	6	280	130	2.442	0.947	3.937	Zein NPs[b]	Rats	26
6	CUR, Xie et al.	2011	5	34433	5533	5	6117	350	6.520	3.405	9.635	PLGA NPs[a]	Rats	27
7	Resveratrol, Hasija et al.	2021	6	3057	128	6	750	1	23.519	14.042	32.996	Eudragit® E100[a]	Rats	28
8	Ibrutinib, Alshetaili et al.	2019	3	2292	263	3	545	48	7.374	2.905	11.842	PLGA NPs[a]	Rats	29
9	daidzein, Ma et al.	2012	3	16900	6930	3	1910	810	2.424	0.317	4.532	PLGA NPs[a]	Rats	30
10	Capsaicin, Peng et al.	2015	5	13849	186	5	2324	113	67.604	37.950	97.258	MPEG-PCL NPs[a]	Rats	31
11	DOX, Feng et al.	2013	5	2101	404	5	574	255	4.080	1.904	6.256	Chitosan[b]	Rats	32
12	DOX, Feng et al.	2013	5	3720	584	5	574	255	6.302	3.275	9.330	CS/CMC[a]	Rats	32

* Types of the polymers used were designated as subgroup “a” for synthetic and subgroup “b” for natural.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 January 2022 doi:10.20944/preprints202201.0456.v1

3.3. Meta Analysis

The Meta analysis was conducted in order to prove the augmenting effect of loading orally administered drugs in polymeric nanoparticles on the bioavailabilty as demonstrated by the pharmacokinetic parameter; the area under the curve (AUC) which represents the "effect" of the study. Meta-analysis integrates the results originating from different studies and processes them into an overall conclusion. Hence, the "heterogeneity" should be considered.

The effect size (AUC) and the study sample size (number of the used animals) were fed into the OpenMetaAnalyst software (http://www.cebm.brown.edu/openMeta/) in order to meta-analyze the investigated studies and provide the distinguishing diagrams of this type of analyses; the Forest plots.

Since the studies in the current Meta-analysis were variable according to the number of the used animals (sample size) therefore they do not meet the only allowable underlying assumption of a fixed effects model that the sole source of variability comes from the sampling error. Accordingly, the overall effect size was estimated using a random-effects model and utilizing the Der Simonian-Laird method rather than the fixed effect model. A random effects model takes into account the variability between studies such as the year of the study, the authors, the drugs used and their doses, the conditions of performing the different studies, the type of the used animals, the origin of the polymeric material, the measurements method and the sample size and was therefore claimed adequate for the purpose of this Meta-analysis. Heterogeneity was assessed using two parameters; the Q statistic and the I^2 index. The Q statistic gives an indication of the presence or absence of heterogeneity among a set of studies related to the aforementioned variables while the I^2 index gives an indication of the degree of heterogeneity. The mean percent increase and a 95% confidence interval (CI) was calculated and represented in the Forest plot. Significance

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 January 2022 doi:10.20944/preprints202201.0456.v1

was employed by the P-value. The sensitivity and consistency of the study was evaluated using a leave-one-out Meta analysis.

The effect size was calculated as follows:

$$Effect\ size = \frac{AUC}{N} \qquad \text{Equation (1)}$$

where N is the sample size (number of animals)

The standard mean difference (SMD) was calculated :

$$SMD = \frac{Mean_a - Mean_b}{S_{pooled}} \qquad \text{Equation (2)}$$

where S_{pooled} is $\sqrt{\frac{(n_a-1)S_a^2 + (n_b-1)S_b^2}{n_a + n_b - 2}}$ Equation (3)

where n_a is the number of animals that received the polymeric nanoparticulate formulation, n_b is the number of animals that received the conventional drug formulation as a control, S_a is the standard deviation of the polymeric nanoparticulate formulation mean effect while S_b is the standard deviation of the drug conventional formulation mean effect.

Every study weight was calculated as follows:

$$Study\ weight\ (w) = \frac{1}{SE^2} \qquad \text{Equation (4)}$$

where SE is the standard error of each study

As an optimization step, studies of the odd highest and lowest weights were excluded and the meta-analysis was re-conducted.

Q is the amount of observed heterogeneity as compared to the amount of expected heterogeneity due to chance while I^2 index is the quantitative degree of heterogeneity and is calculated as follows: $I^2 = 100 \times \frac{Q-df}{Q}$ where df is the degrees of freedom taken as the number of studies – 1.

Furthermore, the mined studies were divided into subgroups as follows:

(a) Synthetic polymeric material

(b) Natural polymeric material.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 January 2022 doi:10.20944/preprints202201.0456.v1

3. Results and Discussion

Table 1 summarizes the results of the conducted meta-analysis after calculating the standardized mean difference (SMD) of each study and its corresponding lower and upper confidence intervals (C.I.s). The significance of all the included studies was confirmed with C.I.s always lying on one side of the zero as a cut-off (i.e. Either both positive or both negative) as demonstrated by the generated Forest plot from the used software (Figure 2) and with the diamond symbol representing the overall mean not touching the line of no effect (the zero line) [20,33].

The overall SMD estimate was extremely significant at a P-value < 0.001 and possessing a pooled estimate of 4.048 and C.I. (2.458, 5.638) [34]. Presence of both of the upper and the lower confidence interval values above zero confirms the significance of the results [35] and the presence of a real effect of the used polymeric nanoparticulate systems on the bioavailability of the investigated drugs as revealed by area under curve (AUC) pharmacokinetic parameter.

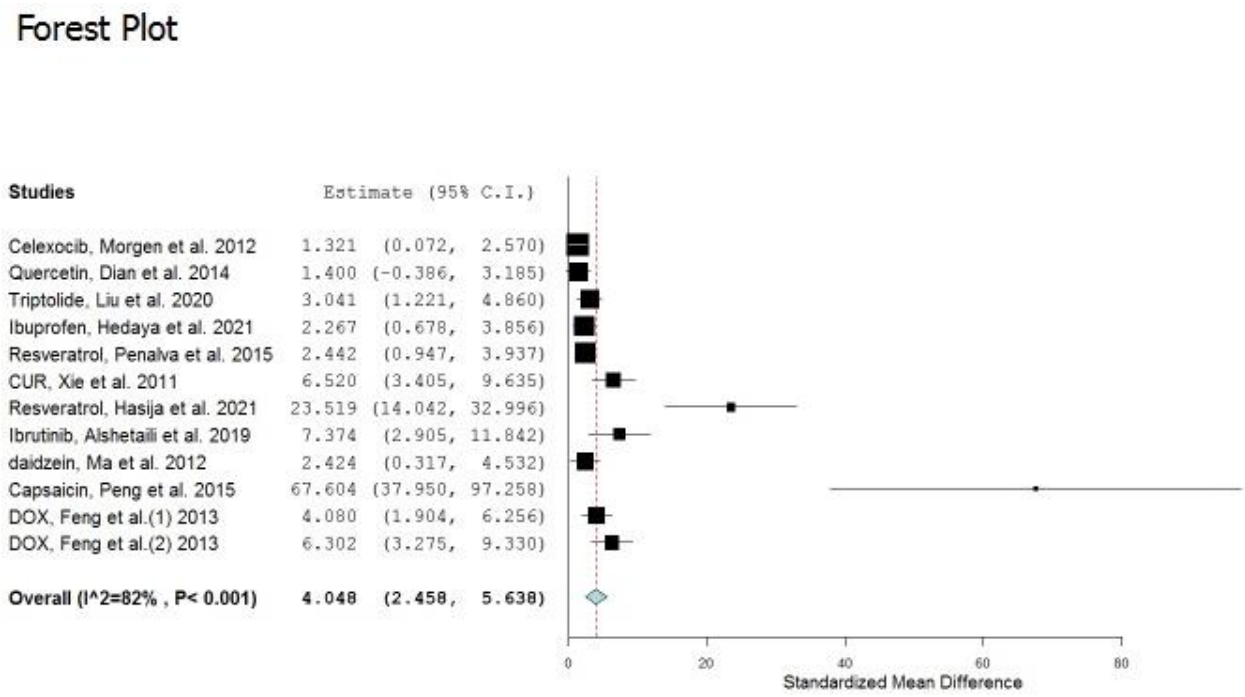

Figure 2. Forest plot of the meta-analyzed studies.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 January 2022 doi:10.20944/preprints202201.0456.v1

Validating the results using the leave-one-out meta-analysis (By omitting one study at a time and re-perforimg the analysis) revealed the high sensitivity and accuracy of the outcomes as the pooled estimate ranged from 3.802 to 4.500 for all of the carried analyses [36].

The polymeric nanoparticulate systems are usually absorbed by the gastrointestinal mucosal cells through different transport mechanisms. These include their non-specific intake and their uptake by the enterocytes and the M cells by trancytosis [9]. M cells are specialized epithelial cells of the mucosa-associated lymphoid tissues [37]. They possess a high trancytotic capacity where the uptake of nanoparticles have been proven to occur through adsorptive endocytosis through clathrin coated pits and vesicles, fluid phase endocytosis and phagocytosis [38]. Interaction of the polymers with mucin and thereby increasing the residence time of the nanoparticles and increasing the contact time for absorption could also be another reason [39].

The heterogeneity of the meta-analysis was relatively high with a quantitative degree of heterogeneity (I^2) scoring 82 %. The sources of heterogeneity are the different years of study, animals used, number of the used animals, used drugs, dosages, types of measurements, climates and breeding conditions and the different labs and operators [40].

The variability in the kind of the used animals and their number and the type of drugs and their dosages, in particular, has the most profound reflection on the weight of each study. Therefore, in an attempt to optimize the study regarding heterogeneity, the studies possessing the highest and lowest weights were excluded [41]; Morgen et al. 2012, Hasija et al. 2021 and Peng et al. 2015 (Table 2).

Table 2. Weights of the investigated studies.

study names	weights
Celexocib, Morgen et al.	11.365%
Quercetin, Dian et al.	10.590%
Triptolide, Liu et al.	10.535%
Ibuprofen, Hedaya et al.	10.893%
Resveratrol, Penalva et al.	11.031%

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 January 2022 doi:10.20944/preprints202201.0456.v1

CUR, Xie et al.	8.320%
Resveratrol, Hasija et al.	2.288%
Ibrutinib, Alshetaili et al.	6.219%
daidzein, Ma et al.	10.062%
Capsaicin, Peng et al.	0.281%
DOX, Feng et al.(1)	9.946%
DOX, Feng et al.(2)	8.469%

Accordingly, the overall pooled estimate changed to 3.404 (2.302, 4.506) and the heterogeneity significantly dropped to 58 % (Figure 3).

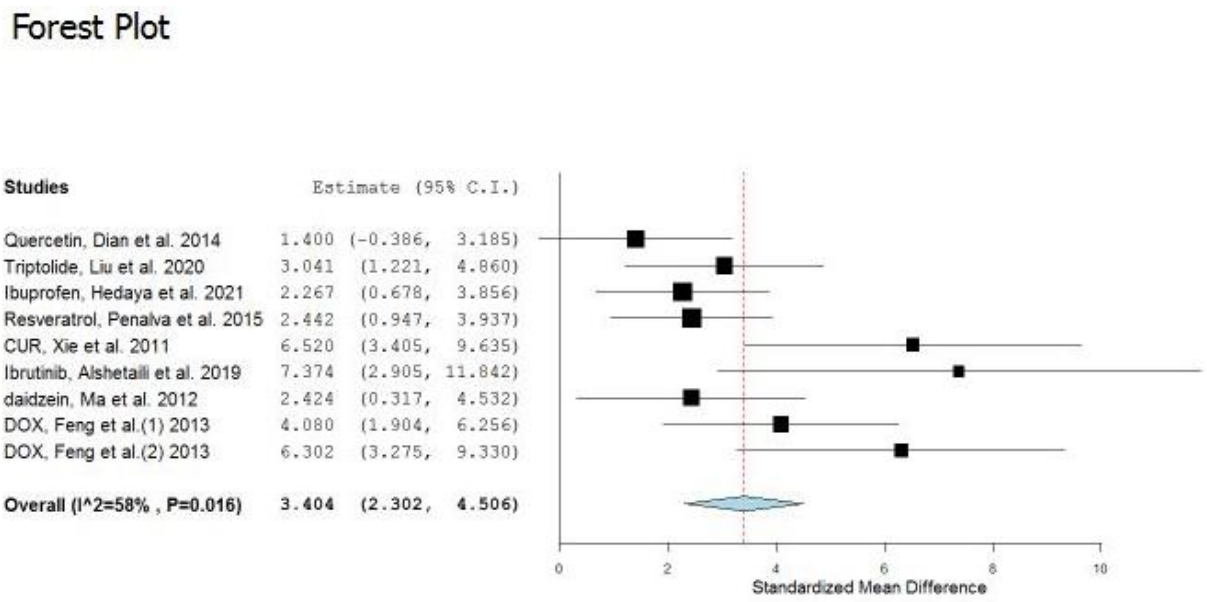

Figure 3. Forest plot of the optimized meta-analysis.

Going further, the investigated studies were divided into two new sub-groups according to the nature of the material that was used to fabricate the polymeric nanoparticulate system; subgroup 1: Synthetic Polymeric nanoparticles and was encoded (a) and subgroup 2: Natural Polymeric nanoparticles and was encoded (b). A sub-group meta-analysis was adopted where the sub-group (a) scored a pooled estimate of 3.356 with C.I.s (1.525, 5.186) while the other sub-group (b) scored a pooled estimate of 3.577 with C.I.s (2.191, 4.962). The overlapping

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 January 2022 doi:10.20944/preprints202201.0456.v1

confidence intervals indicate a non-significant difference between the two sub-groups [42]. This finding would therefore boost the formulators to focus on the safety and the toxicological profile of the polymeric material rather than its biological origin that may mistakenly imply better penetrability.

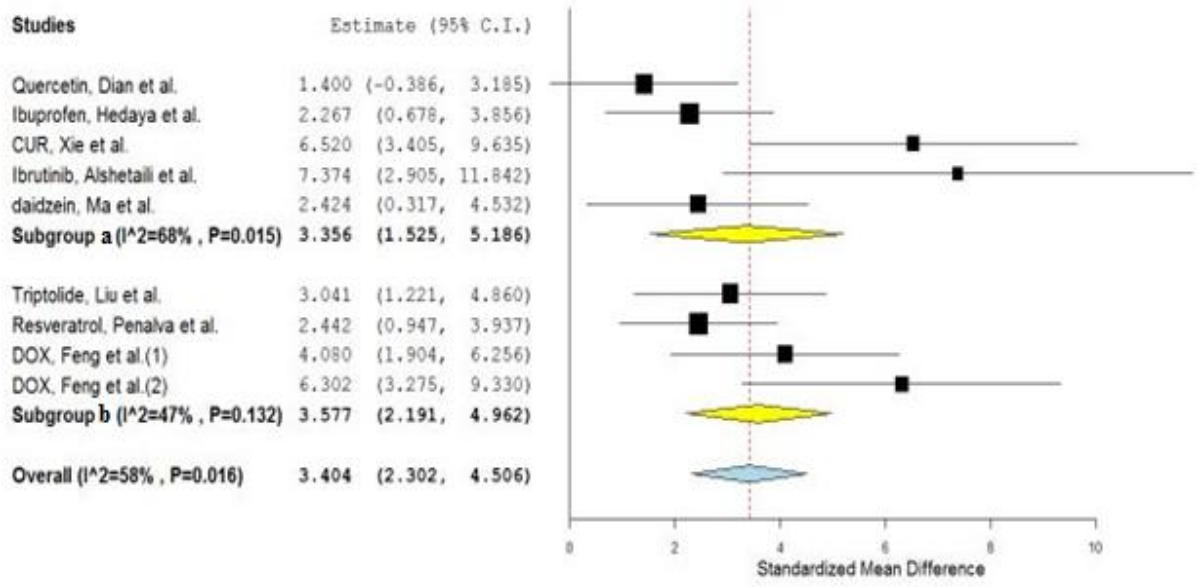

Fig.4. Forest Plot of the investigated sub-groups: (a) Synthetic Polymeric nanoparticles versus (b) Natural Polymeric nanoparticles.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 January 2022 doi:10.20944/preprints202201.0456.v1

4. Conclusion

This study has proven by a quantitative statistical synthetic tool; meta-analysis, the superiority of polymeric nanoparticles in augmenting the bioavailability of orally administered drugs over the conventional formulations. It has also revealed that the nature of the used polymeric (synthetic versus natural) material did not significantly affect the bioavailability. This outcome would direct the formulators and the drug delivery scientists to mainly conduct their comparison studies based on the toxicological profiles of the polymeric materials rather than the penetration efficacy of the intestinal mucosal (excluding the cases of surface-conjugation of certain ligands targeting special receptors).

Author Contributions: R.M.H. was responsible for conceptualization, methodology, analysis, validation, investigation, resources, data curation, writing—original draft preparation, writing—review and editing, visualization and interpretations of this manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hua, S. Advances in Oral Drug Delivery for Regional Targeting in the Gastrointestinal Tract - Influence of Physiological, Pathophysiological and Pharmaceutical Factors. *Frontiers in pharmacology* **2020,** *11*.
2. Homayun, B.; Lin, X.; Choi, H. J. Challenges and Recent Progress in Oral Drug Delivery Systems for Biopharmaceuticals. *Pharmaceutics* **2019,** *11* (3), 129.
3. Parodi, A.; Buzaeva, P.; Nigovora, D.; Baldin, A.; Kostyushev, D.; Chulanov, V.; Savvateeva, L. V.; Zamyatnin, A. A., Jr. Nanomedicine for increasing the oral bioavailability of cancer treatments. *J Nanobiotechnology* **2021,** *19* (1), 354.

4. Mohammed, M. A.; Syeda, J. T. M.; Wasan, K. M.; Wasan, E. K. An Overview of Chitosan Nanoparticles and Its Application in Non-Parenteral Drug Delivery. *Pharmaceutics* **2017,** *9* (4), 53.

5. Shah, S. A.; Firlak, M.; Berrow, S. R.; Halcovitch, N. R.; Baldock, S. J.; Yousafzai, B. M.; Hathout, R. M.; Hardy, J. G. Electrochemically Enhanced Drug Delivery Using Polypyrrole Films. **2018,** *11* (7).

6. Nasser, N.; Hathout, R. M.; bd-Allah, H.; Sammour, O. A. Enhancement of oral bioavailability of drugs using lipid-based carriers: a meta-analysis study. *null* **2020,** *46* (12), 2105-2110.

7. Hathout, R. M.; Omran, M. K. Gelatin-based particulate systems in ocular drug delivery. *Pharmaceutical Development and Technology* **2016,** *21* (3), 379-386.

8. Safwat, S.; Ishak, R. A.; Hathout, R. M.; Mortada, N. D. Statins anticancer targeted delivery systems: re-purposing an old molecule. *J Pharm Pharmacol* **2017,** *69* (6), 613-624.

9. des Rieux, A.; Fievez, V.; Garinot, M.; Schneider, Y. J.; Préat, V. Nanoparticles as potential oral delivery systems of proteins and vaccines: A mechanistic approach. *Journal of Controlled Release* **2006,** *116* (1), 1-27.

10. Hathout, R. M.; Metwally, A. A. Gelatin Nanoparticles. *Methods Mol Biol* **2019,** *2000*, 71-78.

11. Hathout, R. M.; Abdelhamid, S. G.; El-Housseiny, G. S.; Metwally, A. A. Comparing cefotaxime and ceftriaxone in combating meningitis through nose-to-brain delivery using bio/chemoinformatics tools. *Scientific Reports* **2020,** *10* (1), 21250.

12. Hathout, R. M.; Mahmoud, O. A.; Ali, D. S.; Mamdouh, M.; Metwally, A. A. Modeling Drugs-PLGA Nanoparticles Interactions Using Gaussian Processes: Pharmaceutics Informatics Approach. *Journal of Cluster Science* **2021**.

13. Kassem, D. H.; Kamal, M. M. Therapeutic efficacy of umbilical cord-derived stem cells for diabetes mellitus: a meta-analysis study. *Stem Cell Research & Therapy* **2020,** *11* (1), 484.

14. Elmeligy, S.; Hathout, R. M.; Khalifa, S. A. M.; El-Seedi, H. R.; Farag, M. A. Pharmaceutical manipulation of citrus flavonoids towards improvement of its bioavailability and stability. A mini review and a meta-analysis study. *Food Bioscience* **2021,** *44*, 101428.

15. Burns, P. B.; Rohrich, R. J.; Chung, K. C. The levels of evidence and their role in evidence-based medicine. *Plast. Reconstr. Surg.* **2011,** *128* (1), 305-310.

16. Fong, S. Y.; Brandl, M.; Bauer-Brandl, A. Phospholipid-based solid drug formulations for oral bioavailability enhancement: A meta-analysis. *Eur. J Pharm Sci* **2015,** *80*, 89-110.

17. Hathout, R. M.; Metwally, A. A. Towards better modeling of drug-loading in solid lipid nanoparticles: Molecular dynamics, docking experiments and Gaussian Processes machine learning. *Eur. J Pharm Biopharm.* **2016**.

18. Metwally, A. A.; Hathout, R. M. Computer-Assisted Drug Formulation Design: Novel Approach in Drug Delivery. *Mol. Pharm* **2015,** *12* (8), 2800-2810.

19. Metwally, A. A.; El-Ahmady, S. H.; Hathout, R. M. Selecting optimum protein nano-carriers for natural polyphenols using chemoinformatics tools. *Phytomedicine.* **2016,** *23* (14), 1764-1770.

20. Mills, E. J.; Bansback, N.; Ghement, I.; Thorlund, K.; Kelly, S.; Puhan, M. A.; Wright, J. Multiple treatment comparison meta-analyses: a step forward into complexity. *Clin. Epidemiol.* **2011,** *3*, 193-202.

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

22. Morgen, M.; Bloom, C.; Beyerinck, R.; Bello, A.; Song, W.; Wilkinson, K.; Steenwyk, R.; Shamblin, S. Polymeric Nanoparticles for Increased Oral Bioavailability and Rapid Absorption Using Celecoxib as a Model of a Low-Solubility, High-Permeability Drug. *Pharmaceutical Research* **2012,** *29* (2), 427-440.

23. Dian, L.; Yu, E.; Chen, X.; Wen, X.; Zhang, Z.; Qin, L.; Wang, Q.; Li, G.; Wu, C. Enhancing oral bioavailability of quercetin using novel soluplus polymeric micelles. *Nanoscale Research Letters* **2014,** *9* (1), 684.

24. Liu, C.; Jiang, T. t.; Yuan, Z. x.; Lu, Y. Self-Assembled Casein Nanoparticles Loading Triptolide for the Enhancement of Oral Bioavailability. *Natural Product Communications* **2020,** *15* (8), 1934578X20948352.

25. Hedaya, M.; Bandarkar, F.; Nada, A. In vitro and in vivo Evaluation of Ibuprofen Nanosuspensions for Enhanced Oral Bioavailability. *Medical Principles and Practice* **2021,** *30* (4), 361-368.

26. Penalva, R.; Esparza, I.; Larraneta, E.; Gonz+ílez-Navarro, C. J.; Gamazo, C.; Irache, J. M. Zein-Based Nanoparticles Improve the Oral Bioavailability of Resveratrol and Its Anti-inflammatory Effects in a Mouse Model of Endotoxic Shock. *J. Agric. Food Chem.* **2015,** *63* (23), 5603-5611.

27. Xie, X.; Tao, Q.; Zou, Y.; Zhang, F.; Guo, M.; Wang, Y.; Wang, H.; Zhou, Q.; Yu, S. PLGA Nanoparticles Improve the Oral Bioavailability of Curcumin in Rats: Characterizations and Mechanisms. *J. Agric. Food Chem.* **2011,** *59* (17), 9280-9289.

28. Hasija, R.; Chaurasia, S.; Gupta, S. Assessment of Polymeric Nanoparticles to Enhance Oral Bioavailability and Antioxidant Activity of Resveratrol. *Indian Journal of Pharmaceutical Sciences* **2021,** *83* (6), 1114-1128.

29. Alshetaili , S. A.; Mohammad, J.; Md, K.; Majid, A.; Iqbal , M.; Saad, M.; Alalaiwe , S. A.; Bader, B.; Alshehri , S.; Saleh, A. Enhanced Oral Bioavailability of Ibrutinib

Encapsulated Poly (Lactic-co- Glycolic Acid) Nanoparticles: Pharmacokinetic Evaluation in Rats. *Current Pharmaceutical Analysis* **2019,** *15* (6), 661-668.

30. Ma, Y.; Zhao, X.; Li, J.; Shen, Q. The comparison of different daidzein-PLGA nanoparticles in increasing its oral bioavailability. *Int J Nanomedicine* **2012,** *2012/02/02*, 559-570.

31. Peng, W.; Jiang, X. y.; Zhu, Y.; Omari-Siaw, E.; Deng, W. w.; Yu, J. n.; Xu, X. m.; Zhang, W. m. Oral delivery of capsaicin using MPEG-PCL nanoparticles. *Acta Pharmacologica Sinica* **2015,** *36* (1), 139-148.

32. Feng, C.; Wang, Z.; Jiang, C.; Kong, M.; Zhou, X.; Li, Y.; Cheng, X.; Chen, X. Chitosan/o-carboxymethyl chitosan nanoparticles for efficient and safe oral anticancer drug delivery: In vitro and in vivo evaluation. *International Journal of Pharmaceutics* **2013,** *457* (1), 158-167.

33. Rao, G.; Lopez-Jimenez, F.; Boyd, J.; DΓÇÖAmico, F.; Durant, N. H.; Hlatky, M. A.; Howard, G.; Kirley, K.; Masi, C.; Powell-Wiley, T. M.; Solomonides, A. E.; West, C. P.; Wessel, J. Methodological Standards for Meta-Analyses and Qualitative Systematic Reviews of Cardiac Prevention and Treatment Studies: A Scientific Statement From the American Heart Association. *Circulation* **2017,** *136* (10), e172-e194.

34. Greenland, S.; Senn, S. J.; Rothman, K. J.; Carlin, J. B.; Poole, C.; Goodman, S. N.; Altman, D. G. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol* **2016,** *2016/05/21* (4), 337-350.

35. Zlowodzki, M.; Poolman, R. W.; Kerkhoffs, G. M.; Tornetta, P.; Bhandari, M.; On behalf of the International Evidence-Based Orthopedic Surgery Working Group How to interpret a meta-analysis and judge its value as a guide for clinical practice. *Acta Orthopaedica* **2007,** *78* (5), 598-609.

36. Patsopoulos, N. A.; Evangelou, E.; Ioannidis, J. P. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. *International Journal of Epidemiology* **2008,** *37* (5), 1148-1157.

37. Corr, S. C.; Gahan, C. C. G. M.; Hill, C. M-cells: origin, morphology and role in mucosal immunity and microbial pathogenesis. *FEMS Immunology & Medical Microbiology* **2008,** *52* (1), 2-12.

38. Buda, A.; Sands, C.; Jepson, M. A. Use of fluorescence imaging to investigate the structure and function of intestinal M cells. *Advanced Drug Delivery Reviews* **2005,** *57* (1), 123-134.

39. Hathout, R. M.; El-Ahmady, S. H.; Metwally, A. A. Curcumin or bisdemethoxycurcumin for nose-to-brain treatment of Alzheimer disease? A bio/chemo-informatics case study. *Natural Product Research* **2018,** *32* (24), 2873-2881.

40. Fong, S. Y.; Brandl, M.; Bauer-Brandl, A. Phospholipid-based solid drug formulations for oral bioavailability enhancement: A meta-analysis. *Eur. J Pharm Sci* **2015,** *80*, 89-110.

41. Liberati, A.; Altman, D. G.; Tetzlaff, J.; Mulrow, C.; G+©tzsche, P. C.; Ioannidis, J. P. A.; Clarke, M.; Devereaux, P. J.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* **2009,** *2009/07/21* (7), e1000100.

42. Schäfer, T.; Schwarz, M. A. The Meaningfulness of Effect Sizes in Psychological Research: Differences Between Sub-Disciplines and the Impact of Potential Biases. *Frontiers in Psychology* **2019,** *10*.