Available online on 15.11.2021 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Article

Systematic Review on the Effectiveness of Strategies for Increasing Insulin Bioavailability in Oral Route Delivery Systems Based on Manufacturing Techniques and Materials Used

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Article Info:

Article History:

Received 19 September 2021
Reviewed 20 October 2021
Accepted 24 October 2021
Published 15 November 2021

Cite this article as:

Krisna AP, Ningrum HW, Fimannuha TL, Puspita OE, Systematic Review on the Effectiveness of Strategies for Increasing Insulin Bioavailability in Oral Route Delivery Systems Based on Manufacturing Techniques and Materials Used, Journal of Drug Delivery and Therapeutics. 2021; 11(6):194-208

DOI: http://dx.doi.org/10.22270/jddt.v11i6.5132

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Abstract

Diabetes is a metabolic disease characterized by hyperglycemia due to impaired insulin secretion, insulin action, or both. All patients with type 1 diabetes and many type 2 diabetes require insulin therapy to achieve reasonable glycemic control. During this time, insulin is given through the subcutaneous injection route because it can be destroyed by gastric acid when given orally. Until now, many studies have developed oral insulin therapy using various delivery system strategies. This systematic literature review aims to answer several questions about the effect of technique and material on increasing oral insulin bioavailability and the best technique and type of material that can produce the best oral insulin bioavailability. We searched for published articles regarding the development of oral route insulin. Bioavailability parameters were assessed based on plasma insulin levels for relative bioavailability values and/or plasma glucose levels for pharmacological bioavailability values. Conclusion: The manufacturing technique in the delivery system affects insulin stability in maintaining its conformation to provide a therapeutic effect. The type of substance affects insulin bioavailability through its properties in paving the way for insulin across various barriers in the digestive tract. To date, the best results in the development of oral insulin have obtained oral insulin bioavailability of 73.10% achieved by mesoporous silica nanoparticles (MSN) delivery system with layer-by-layer technique coated with [poly (methacrylic acid-co-vinyl triethoxylsilane)] (PMV)].

Keywords: bioavailability, diabetes, insulin, nanoparticles, oral delivery system.

INTRODUCTION

Diabetes is a non-communicable disease characterized by hyperglycemia due to impaired insulin secretion, insulin action, or both. Chronic hyperglycemia in diabetes can lead to failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels [1]. Globally, people with diabetes in 2019 are estimated at 9.3% (463 million people), increasing to 10.2% (578 million) in 2030 and 10.9% (700 million) in 2045 [2]. Meanwhile, in Indonesia, based on Basic Health Research data, people with diabetes increased from 6.9% in 2013 to 8.5% in 2018, so the estimated number of sufferers in Indonesia reaches more than 16 million people (Kemenkes RI, 2018)[2(a)]. All patients with type 1 diabetes and many patients with type 2 diabetes require insulin therapy to achieve reasonable glycemic control [3].

Insulin is the most effective way to lower blood glucose, allowing the body to maintain glucose within a normal range [4]. Insulin is given by subcutaneous injection because it can be destroyed by stomach acid if given orally [3]. However, daily insulin injections are considered ineffective because they cause pain at the injection site, are inconvenient, uncomfortable, and lead to low patient compliance [5]. Therefore, many researchers have developed insulin administration via a convenient, non-invasive route such as the oral route. It is recognized as the most convenient and commonly used method of drug administration due to its ease of administration, high patient compliance, cost-effectiveness, minimum sterility constraints, and flexible dosage form design. However, low bioavailability is a significant challenge in designing oral dosage forms [6].

The bioavailability of a drug is the portion of the administered dose that reaches the systemic circulation [7]. Oral bioavailability is influenced by several factors such as water solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms [6]. A drug must reach the desired drug concentration in the systemic circulation [8]. Insulin has low oral bioavailability due to the degradation of proteolytic enzymes and lack of intrinsic permeability through the intestinal epithelium [9].

Several strategies have been carried out to develop insulin delivery systems via the oral route. Several reviews of

articles related to the development of the oral route of insulin have also been carried out. A review of articles conducted by Singh et al. (2019) reported that oral route insulin bioavailability could be increased through encapsulation to insulin [10]. In addition, Wong et al. (2021) reviewed articles on the characteristics of oral insulin preparation techniques and found that insulin bioavailability can be increased through various insulin preparation techniques used [11]. However, there has been no review of articles that analyze the best materials and techniques in the manufacture of insulin that can increase the bioavailability of oral insulin, so this is the background of this study. This study conducted a Systematic Literature Review to determine whether the manufacturing technique and material used to develop oral route insulin therapy can affect insulin bioavailability. The review results are expected to provide information about the best techniques and types of ingredients in increasing the bioavailability of oral insulin. In the future, the results of this study can be helpful to facilitate the development of oral insulin with the best results and quality. To achieve the research objectives, the results of this Systematic Literature Review must be able to answer the following research questions (RQ):

1. Can the manufacturing technique and the type of material used in the delivery system affect the bioavailability of oral insulin?
2. What are the best manufacturing techniques and types of ingredients to increase the bioavailability of oral insulin?

To answer the formulation of these questions requires relevant research results. Therefore, in this Systematic Literature Review, limitations are given to the criteria of the article, namely:

1. Inclusion Criteria (IC 1): Articles published in 2015-2021.
2. Inclusion Criteria (IC 2): The article on insulin research using the oral route is the original article.
3. Inclusion Criteria (IC 3): Articles written in English or Indonesian.
4. Inclusion Criteria (IC 4): Article on the results of an oral insulin study with parameters for measuring bioavailability (insulin levels in plasma and glucose levels in plasma) using in vivo research method.
5. Inclusion Criteria (IC 5): Insulin is formulated in the form of a nanomedicine delivery system (liposome, solid lipid nanoparticle, polymeric nanoparticle, inorganic nanoparticle, insulin emulsion, nanogels).

Thus, not all articles are used to answer this question. Articles that do not meet the data inclusion criteria or articles that contain data on insulin but have the following criteria will not be used to answer research questions. However, it is possible to use it as supporting data only. The article exclusion criteria are as follows:

1. Exclusion Criteria (EC 1): The article does not have copyright.

METHODS

The study was conducted based on the Systematic Literature Review method used by Rowley & Slack (2004) and based on the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) protocol [12,13] **(Figure 1)**. The research was carried out in 5 stages, namely (a) scanning documents, (b) making documentation, (c) arranging Literature Review, (d) writing Literature Review, and (e) compiling a bibliography. Scanning documents is done by identifying keywords and articles that must be included in the Systematic Literature Review. Documentation is made by listing the references from which the articles were downloaded. Structuring the Literature Review is done by identifying the main themes and then sorting them to select articles. Writing literature according to the themes identified in the previous step was performed. The bibliography is compiled by including all sources referenced in the preparation of the Systematic Literature Review.

a. Keyword Identification

The article search begins with determining the combination of keywords that match the formulation of research questions to scan documents on a digital database. The combination of keywords used is insulin AND bioavailability AND “oral administration” OR “oral delivery system” AND liposome OR “solid lipid nanoparticle” OR “polymeric nanoparticle” OR “inorganic nanoparticle” OR “insulin emulsion” OR nanogels.

b. Article Search

Based on article searches that have been carried out through three digital databases, 1000 articles were obtained from Google Scholar, seven articles from Pubmed, and 800 articles from Crossref. The total number of articles obtained is 1807 article titles. The first stage is metadata or combining articles that have been obtained from the three sources in .xlsx format. The next step is initial screening, sorting the early stages of articles with the same title and publisher (duplicate screening). Duplicated articles from 1807 articles are 97 articles. The total number of the article after the duplication was removed was 1710 articles. Based on the screening results through the title and abstract of the article against the suitability of the inclusion and exclusion criteria, it was found that the number of articles that met the inclusion criteria was 77 articles. The results of the article assessment using the Checklist for Quasi-Experimental Studies (Non-Randomized Experimental Studies) from the Joanna Briggs Institute obtained articles that meet the assessment or are eligible are 76 articles.

c. Article Profile Description

A description of the article profile was carried out on the selected articles, including article title, author's name, year of publication, publisher, citation per year, manufacturing technique, type of delivery system, formula content, test method, bioavailability test parameters, as well as the resulting bioavailability to be extracted and stored in a format. .xlsx. **Figure 2** shows the trend of article publication from year to year.

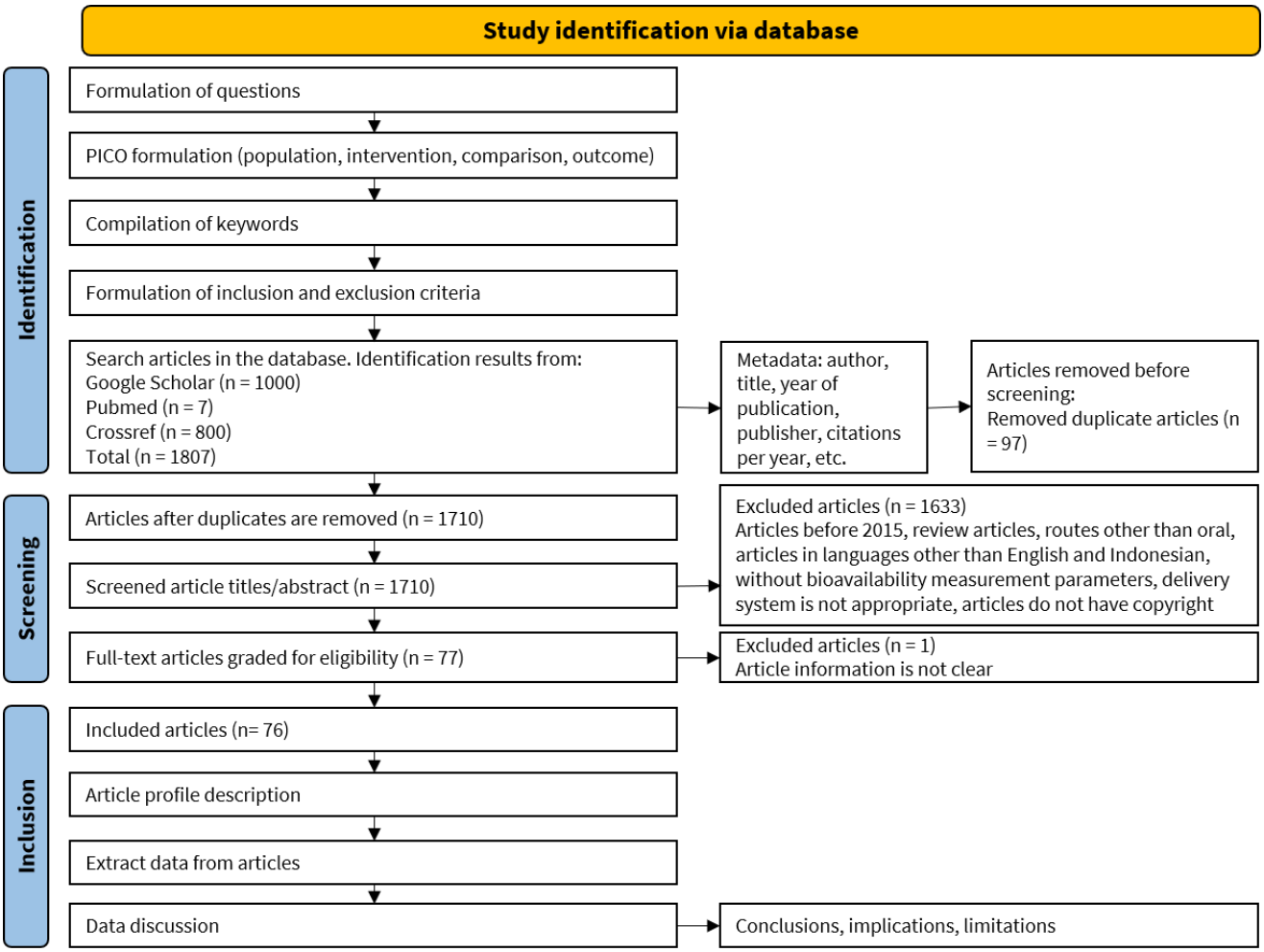

Figure 1: Systematic Literature Review Process

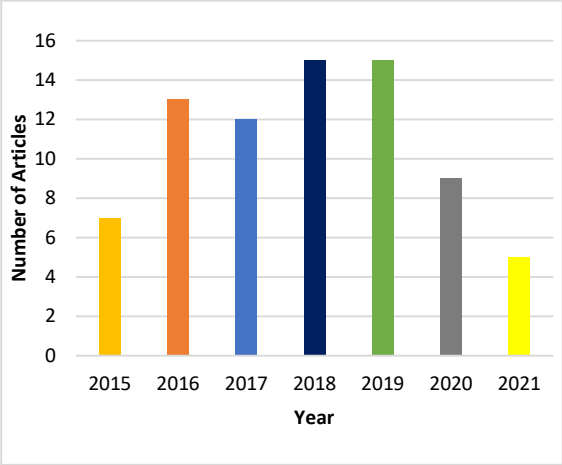

Figure 2: Trend of the Number of Articles Each Year in the 2015-2021 Range

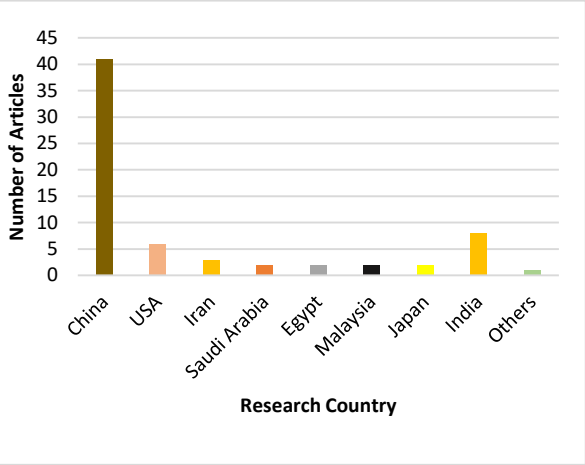

Figure 3: Country Profile of Research Site

The types of delivery systems used vary, including polymeric nanoparticles and lipid nanoparticles. Each country's contribution to the publication of research on the development of oral insulin is shown in **Figure 3**. Countries were determined based on the authors' affiliation—the country with the highest number of studies in China, followed by India in the second position.

All articles have been published in journals with Impact Factors showing that the journal is of high quality and contributes to the research field. Citation analysis is also used to determine the relevance between articles and how many articles are quoted. The citation of an article also shows that the article is of high quality. **Table 1** shows the ranking of articles based on citation analysis.

Table 1: Articles by Number of Citations

Rank	Author	Year	Citation per Year	Rank	Author	Year	Citation per Year	Rank	Author	Year	Citation per Year
1	He et al (20)	2017	33,5	27	Malathi et al (21)	2015	8,83	53	Wu et al (22)	2019	3,5
2	Liu et al (23)	2016	33,2	28	Wu et al (24)	2017	8,75	54	Alsulays et al (25)	2019	3,5
3	Wang et al (26)	2019	32	29	Ji et al (27)	2019	8,5	55	Agrawal et al (28)	2015	3,5
4	Fan et al (29)	2018	30	30	Omid et al (30)	2017	8	56	Zhang et al (31)	2017	3,25
5	Mumuni et al (32)	2020	25	31	Ukai et al (33)	2020	8	57	Fang et al (34)	2018	3
6	Han et al (14)	2020	21	32	Zhang et al (35)	2015	7,83	58	Sun et al (36)	2019	3
7	Li et al (37)	2017	19,5	33	Liu et al (38)	2016	6,6	59	Sahoo et al (39)	2019	3
8	Sheng et al (40)	2016	19,4	34	Sun et al (41)	2015	6,33	60	Alfaro et al (42)	2020	3
9	Sheng et al (43)	2015	19,17	35	Guha et al (19)	2016	6,2	61	Wang et al (44)	2018	2,67
10	Wu et al (45)	2018	19	36	Yazdi et al (46)	2020	6	62	Hu et al (47)	2019	2,5
11	Liu et al (48)	2019	18	37	Liu et al (49)	2019	6	63	Boushra et al (50)	2019	2,5
12	Shan et al (51)	2016	17,2	38	Ji et al (52)	2017	5,75	64	Xie et al (53)	2018	2,33
13	Tian et al (54)	2018	16	39	Guo et al (55)	2016	5,4	65	Zhang et al (56)	2021	2
14	Alibolandi et al (57)	2016	15,4	40	Kim et al (58)	2018	5,33	66	Zhang et al (59)	2018	1,67
15	Verma et al (60)	2015	15	41	Fukuoka et al (61)	2018	5,33	67	Yan et al (62)	2019	1,5
16	Wang et al (63)	2017	15	42	Chen et al (64)	2019	5	68	Bahman et al (65)	2020	1
17	Shrestha et al (66)	2016	15	43	Zhou et al (67)	2020	5	69	Winarti et al (68)	2018	0,67
18	Liu et al (18)	2016	14	44	Sun et al (69)	2016	4,5	70	Zhang et al (70)	2021	0
19	Zeng et al (71)	2018	11	45	He et al (72)	2015	4,5	71	Ansari et al (73)	2016	0
20	Niu et al (74)	2017	11	46	Boushra et al (75)	2016	4,4	72	Koland et al (76)	2021	0
21	Deng et al (77)	2017	10	47	Singh et al (78)	2018	4,33	73	Heade et al (79)	2021	0
22	Chen et al (80)	2017	10	48	Agrawal et al (81)	2017	4,25	74	Kaur et al (82)	2021	0
23	Zhu et al (83)	2016	10	49	Urimi et al (84)	2019	4	75	Wang et al (85)	2020	0
24	Xu et al (86)	2017	9,25	50	El-Leithy et al (87)	2019	4	76	Elkhatib et al (88)	2021	0
25	Chen et al (17)	2019	9	51	Elsayed et al (89)	2018	4				
26	Zheng et al (90)	2018	9	52	Jaafar & Hamid (15)	2019	3,5				

RESULTS AND DISCUSSIONS

The complete summary results of the 76 selected articles can be seen in **Supplementary File 1**. Selected articles are classified based on the research questions that will be answered in this study, namely (1) the effect of the technique on increasing oral insulin bioavailability (RQ1), (2) the best manufacturing technique in increasing the bioavailability of oral insulin (RQ2), (3) the effect of the type of substance on increasing the bioavailability of oral insulin (RQ3), and (4) the best type of substance in increasing the bioavailability of oral insulin (RQ4).

a. Oral Insulin Development Challenges

Insulin is a high-molecular-weight protein that is highly hydrophilic, so it cannot cross the digestive tract properly due to many barriers. In order to work orally, insulin must pass through three main physiological barriers, namely 1) insulin must be able to withstand a very acidic gastric pH (pH = 1-3) and proteolytic enzymes that can degrade/denature insulin; 2) insulin must be able to penetrate the mucous layer that protects the intestinal epithelial surface, and 3) insulin must be able to pass through the intestinal epithelial cell layer to enter the systemic circulation [14]. Therefore, insulin delivery systems must be designed effectively to protect insulin from obstacles in the digestive tract, biocompatible to maintain the conformational integrity of insulin to remain pharmacologically active, and able to load more insulin in the accurate concentrations that it can control insulin levels for optimal blood glucose [15].

b. Effect of Technique on Increasing Oral Insulin Bioavailability

The manufacturing technique is a factor that plays a role in efforts to increase the bioavailability of oral insulin. The manufacturing technique must pay attention to the physicochemical properties of insulin in order to maintain insulin stability until the end. Based on the review results, the technique used to manufacture an oral insulin delivery system can be seen in **Table 2**. The most widely used technique is double emulsion solvent evaporation, which is 18.42%. The hydrophilicity and hydrophobicity of the active substance are very important to determine the manufacturing technique used in the delivery system. The double emulsion technique [water in oil in water (w/o/w)], also known as emulsion, is a complex system in which the dispersed phase droplets consist of small dispersed phases. This technique is widely used to encapsulate proteins because it can protect against degradation due to acidic gastric pH and proteolytic enzymes in the small intestine. In addition, this technique can help drugs achieve sustained release, are biocompatible and biodegradable, and can encapsulate two types of hydrophilic and hydrophobic drugs separately and simultaneously. However, this technique has several disadvantages, including the need for high shear stresses and high-pressure homogenization so that the protein tends to denature and form aggregates due to the high shear force and the significant interface exposure between the aqueous and the organic phase. In addition, the resulting particles are relatively heterogeneous, the particle size is sensitive to various parameters of the manufacturing process, and this technique has not had excellent encapsulation efficiency [16]. Like the research that has been done by Chen et al. (2019) resulted in an oral insulin bioavailability of 7.51%, which is still relatively low [17].

c. Effect of Type of Substance on Increasing Oral Insulin Bioavailability

Several ingredients have been reported to increase oral insulin bioavailability, which can be seen in **Table 2**. Chitosan is the most widely used material in oral insulin delivery systems because it has nontoxic and biocompatible properties, can mediate the opening of tight junctions between epithelial cells reversibly, and can increase permeability via the paracellular pathway. The opening of tight junctions by chitosan is caused by the interaction between chitosan and integrin receptors on the cell membrane, which causes the conformation of integrin receptors which can then damage the tight junction area. The use of chitosan can also prevent nanoparticles from complicated intracellular transport and prevent the enzymatic degradation of insulin in lysosomes [18]. Research conducted by Jafar & Hamid (2019) showed that the use of chitosan polymer could increase the bioavailability of oral insulin by 40.23% [15].

d. The Best Techniques and Types of Materials in Increasing Oral Insulin Bioavailability

Based on the results of systematic studies that have been carried out, there are the best techniques and materials based on bioavailability parameters that can be recommended in the development of oral insulin routes. These findings are based on research by Guha et al. (2016) using a mesoporous silica nanoparticles (MSN) delivery system with a layer-by-layer technique coated with a polymer [poly (methacrylic acid-co-vinyl triethoxylsilane)] (PMV). PMV was obtained from the synthesis of methacrylic acid (MAA) and vinyl triethoxylsilane (VTES). PMV polymers are sensitive to pH values so that their release can be targeted in the intestine with the prolonged-release for 6 hours. PMV can protect insulin from the degradation of proteolytic enzymes and gastric acid environment. Encapsulation of insulin with PMV can help insulin cross the intestinal mucosa through paracellular and transcellular transport, then quickly absorbed by intestinal epithelial cells and directly reach the systemic circulation. The layer-by-layer technique is reported to produce a large nanoparticle surface area of 304.3921 m2/g and an adsorption pore width with a smaller dimension of 64.7844 nm to increase insulin absorption to obtain a significantly increased bioavailability of 73.10% [19].

Table 2: Comprehensive Summary of Oral Insulin Development Articles

No.	Author	Year	Publisher	Journal and Impact Factor	Method	Delivery System	Formulation	Test Method	BA Parameters	Theme Classification
1	Ji et al	2019	Elsevier	Journal of Controlled Release (7,633)	Antisolvent coprecipitation	nanocompocite	Carboxymethylated short-chain amylose; zein; chitosan.	in vivo	plasma insulin level	RQ3, RQ4
2	Kim et al	2018	ACS Publications	Molecular Pharmaceutics (4,44)	N/A	liposome	Chondroitin sulfate-g-taurocholic acid (CST).	in vivo	plasma insulin level	RQ3, RQ4
3	Yazdi et al	2020	Elsevier	Colloids and Surfaces B: Biointerfaces (5,268)	thin film hydration	liposome	PEG, folic acid, hydrogenated soya phosphatidylcholine (HSPC).	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
4	Wang et al	2018	Taylor & Francis	Pharmaceutical Development and Technology (2,347)	emulsion polymerization	nanogel	Hydroxyethyl methacrylate (HEMA).	in vivo	plasma insulin level, plasma glucose level	RQ1, RQ2, RQ3, RQ4
5	Agrawal et al	2017	ACS Publications	Molecular Pharmaceutics (4,44)	hydrotope	nanoparticle	lesitin, pluronic f-127	in vivo	plasma glucose level	RQ1, RQ2, RQ3, RQ4
6	Wang et al	2019	Wiley Online Library	Advanced Healthcare Materials (7,367)	thin film hydration	liposome	EPC, cholesterol, DOTAP	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
7	Singh et al	2018	Future Medicine	Nanomedicine (London) (4,727)	N/A	nanoparticle	Pluronic F-127, GMO, propylene glycol.	in vivo	plasma insulin level, plasma glucose level	RQ3. RQ4
8	Jaafar & Hamid	2019	Ingenta Connect	Current Drug Delivery (1,582)	polyelectrolyte complexation and ionotropic gelation	nanoparticle	Alginate, calcium chloride (CaCl2), Pluronic-68, dextran sulfate, chitosan	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
9	Zhang et al	2020	Royal Society of Chemistry	Nanoscale (6,895)	thin film rehydration	nanoliposome	Hydrogenated soybean phosphatidylcholine (HSPC), and 1,2-dipalmitoyl-sn-glycero-3-phosphoglycerol, sodium salt (DPPG)	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
10	Deng et al	2017	Elsevier	Nanomedicine Nanotechnology Biology Medicine (6,458)	ionic cross-linking/in situ reduction	nanoparticle	Chitosan, Reduced L-glutathione (GSH), sodium selenite (Na2SeO3).	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
11	Wu et al	2019	Elsevier	Journal of Pharmaceutical Sciences (3,534)	reversed-phase evaporation	liposome	Chitosan, deoxycholic acid.	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
12	Liu et al	2016	Dove Medical Press Limited	International Journal of Nanomedicine (6,400)	modified solvent-injection	nanoparticle	Lecithin, chitosan.	in vivo	glucose insulin level (pharmacological bioavailability)	RQ1, RQ2, RQ3, RQ4

No.	Author	Year	Publisher	Journal and Impact Factor	Method	Delivery System	Formulation	Test Method	BA Parameters	Theme Classification
13	Alibolandi et al	2016	Elsevier	Journal of Controlled Release (7,633)	modified direct hydration	polymersome	Dextran-PLGA.	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
14	Ji et al	2017	ACS Publications	Journal of Agricultural and Food Chemistry (4,192)	N/A	nanocomposite	short chain glucan (SGC), proanthocyanidins (PAC).	in vivo	glucose insulin level	RQ3, RQ4
15	Han et al	2020	Nature	Nature Nanotechnology (33,407)	N/A	micelles	polimer betaine zwitterionic (polycarboxybetaine, PCB) terkonjugasi menjadi 1,2 distearoyl-sn-glycero-3-phosphoethanolamine (DSPE)	in vivo	plasma insulin level	RQ3, RQ4
16	Chen et al	2017	Springer	AAPS PharmSciTech (3,246)	ionotropic gelation	nanoparticle	Chitosan, eudragit S100, transcriptional peptide (tat)	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
17	Urimi et al	2019	Springer	AAPS PharmSciTech (3,246)	ionotropic gelation	nanoparticle	Chitosan solution (1 mg/mL), PSS (poly(sodium 4-styrenesulfonate)), PGA (γ-polyglutamic acid)]	in vivo	glucose insulin level	RQ1, RQ2, RQ3, RQ4
18	Chen et al	2019	Taylor & Francis	Journal of Microencapsulation (5,82)	double-emulsion (water-in-oil-in-water) solvent evaporation	nanoparticle	Chitosan, alginate, mPEG-b-PLGA.	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
19	Alsulays et al	2019	Dove Medical Press Limited	International Journal of Nanomedicine (6,400)	double emulsification	Solid lipid nanoparticle	L-penetratin, D-penetratin.	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
20	Xie et al	2018	Future Medicine	Nanomedicine (London) (4,727)	N/A	polymersome	Pluronic p85, PLGA.	in vivo	plasma insulin level	RQ3, RQ4
21	Sheng et al	2015	ACS Publications	ACS Applied Materials & Interfaces (8,758)	double emulsion solvent evaporation	nanoparticle	N-trymethyl chitosan, PLGA.	in vivo	glucose insulin level	RQ1, RQ2, RQ3, RQ4
22	El-Leithy et al	2019	Elsevier	International Journal of Pharmaceutics (5,875)	ionic gelation	nanoparticle	chitosan, tripolyphosphate (TPP).	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
23	Zeng et al	2018	Wiley Online Library	Advanced Healthcare Materials (7,367)	N/A	nanoparticle	DDAB (dimethyldioctadecylammonium bromide).	in vivo	plasma insulin level	RQ3, RQ4
24	Verma et al	2015	Elsevier	Acta Biomaterialia (8,947)	microemulsion	nanoparticle	vitamin B12, chitosan.	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
25	Tian et al	2018	Wiley Online Library	Advanced Healthcare Materials	two-step flash nanocomple	nanoparticle	Hyaluronic acid, thiolated hyaluronic acid.	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4

No.	Author	Year	Publisher	Journal and Impact Factor	Method	Delivery System	Formulation	Test Method	BA Parameters	Theme Classification
				(7,367)	xation					
26	Malathi et al	2015	Dove Medical Press Limited	International Journal of Nanomedicine (6,400)	emulsion-solvent evaporation	nanoparticle	d-α-tocopherol poly(ethylene glycol) 1000 succinate (TPGS), PLGA, PEG.	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
27	Wang et al	2017	Elsevier	Carbohydrate Polymers (9.381)	N/A	nanoparticle	Deacetylated chitosan, Carboxymethyl chitosan	in vivo	plasma insulin level	RQ3, RQ4
28	Sun et al	2016	MDPI	International Journal of Molecular Sciences (5.923)	emulsion solvent diffusion	nanoparticle	Sodium deoxycholate, PLGA, Hydroxypropyl methyl cellulose phthalate (HP55).	in vivo	glucose insulin level	RQ1, RQ2, RQ3, RQ4
29	Liu et al	2016	Elsevier	Journal of Controlled Release (9,776)	Ionotropic gelation and polyelectrolyte complex	nanoparticle	TMC, sodium tripolyphosphate (TPP), Chitosan.	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
30	Fang et al	2018	Elsevier	Journal of Pharmaceutical Sciences (3.534)	spontaneous emulsion solvent diffusion	nanoparticle	hidroksipropil metilselulosa ftalat (HPMCP), PVA.	in vivo	glucose insulin level	RQ1, RQ2, RQ3, RQ4
31	Chen et al	2019	Elsevier	International Journal of Pharmaceutics (5,875)	N/A	nanoparticle	Chitosan /alginate, Cp1-11	in vivo	plasma insulin level	RQ3, RQ4
32	Zheng et al	2018	ACS Publications	ACS Applied Materials & Interfaces (8,758)	One step nanoprecipitation	nanoparticle	EGP peptide, PLGA	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
33	He et al	2017	Elsevier	Biomaterials (12.479)	Flash nanocomplexation	nanoparticle	Chitosan, tripolifosfat (TPP)	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
34	Li et al	2017	Elsevier	Materials Science and Engineering: C (7.328)	N/A	nanoparticle	Chitosan modified by L-valin	in vivo	plasma insulin level	RQ3. RQ4
35	Bahman et al	2020	MDPI	Pharmaceutics (6.321)	N/A	micelles	Poly(styrene-co-maleic acid)	in vivo	glucose insulin level	RQ3, RQ4
36	Hu et al	2019	NCBI	International Journal of Nanomedicine (6,400)	anhydrous co-solvent lyophilization	nanoemulsi	Phospolipid (Oleic Acid (OA), Ethyl Oleate (EO), Isopropyl Myristate (IPM)).	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
37	Fan et al	2018	Elsevier	Biomaterials (12.479)	N/A	nanoparticle	Deoxycholic acid, chloroquine (CQ), PGA.	in vivo	plasma insulin level	RQ3, RQ4
38	Sun et al	2018	ACS Publications	Biomacromolecules (6.988)	N/A	nanoparticle	Chitosan, eudragit S100, transcriptional peptide (tat)	in vivo	plasma insulin level, glucose insulin level	RQ3, RQ4
39	Shrestha et al	2016	Wiley Online Library	Advanced Functional Materials (18.808)	N/A	nanoparticle	Chitosan	in vivo	plasma insulin level	RQ3, RQ4
40	Fukuoka et al	2018	The Pharmaceutical Society of	Biological and Pharmaceutical Bulletin (2.233)	N/A	nanoparticle	Oligoarginin, CPP R6	in vivo	plasma insulin level, glucose insulin level	RQ3, RQ4

No.	Author	Year	Publisher	Journal and Impact Factor	Method	Delivery System	Formulation	Test Method	BA Parameters	Theme Classification
			Japan							
41	Zhang et al	2017	ACS Publications	Biomacromolecules (6.988)	W/O/W solvent evaporation	nanoparticle	PLGA, Chitosan.	in vivo	glucose insulin level	RQ3, RQ4
42	Wu et al	2018	ACS Publications	ACS Applied Materials & Interfaces (8,758)	self-assembly nanoprecipitation	nanoparticle	PLGA, oktaarginin.	in vivo	plasma insulin level	RQ3, RQ4
43	Wu et al	2017	Elsevier	Journal of Controlled Release (9,776)	self-assembly nanoprecipitation	nanoparticle	Butyrate	in vivo	plasma insulin level	RQ3, RQ4
44	He et al	2015	Elsevier	International Journal of Pharmaceutics (5,875)	combination of double emulsion and solvent-evaporation and a thermal-sensitive hydrogel	solid lipid nanoparticle	Vitamin B12	in vivo	glucose insulin level	RQ1, RQ2, RQ3, RQ4
45	Sahoo et al	2019	Elsevier	Materials Today Communications (3.383)	N/A	particle	Chitosan	in vivo	plasma insulin level	RQ3, RQ4
46	Shan et al	2016	ACS Publications	ACS Applied Materials & Interfaces (8,758)	self-assembly nanoprecipitation	nanoparticle	PVA	in vivo	plasma insulin level	RQ3, RQ4
47	Sheng et al	2016	Elsevier	Journal of Controlled Release (9,776)	N/A	nanoparticle	PLGA, Chitosan.	in vivo	plasma insulin level	RQ3, RQ4
48	Elsayed et al	2018	MDPI	Marine Drugs (5.118)	N/A	nanoparticle	Chitosan, oleic acid.	in vivo	plasma insulin level	RQ3, RQ4
49	Mumuni et al	2020	Elsevier	Carbohydrate Polymers (9.381)	Self-gelation	nanoparticle	Chitosan, aqueous soluble snail mucin	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
50	Yan et al	2019	Springer	AAPS PharmSciTech (3,246)	N/A	nanoparticle	Chitosan	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
51	Boushra et al	2016	Elsevier	International Journal of Pharmaceutics (5,875)	emulsification solvent-evaporation technique to form double emulsion (w/o/w)	solid lipid nanoparticle	propilen glikol (PG), polietilen glikol (PEG) 400, PEG 600.	in vivo	glucose insulin level	RQ1, RQ2, RQ3, RQ4
52	Niu et al	2017	Elsevier	Journal of Controlled Release (9,776)	modified solvent displacement	nanocapsule	Polyarginine	in vivo	glucose insulin level	RQ1, RQ2, RQ3, RQ4
53	Omid et al	2017	Elsevier	International Journal of Pharmaceutics (5,875)	N/A	nanoparticle	Chitosan, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC).	in vivo	plasma insulin level	RQ3, RQ4

No.	Author	Year	Publisher	Journal and Impact Factor	Method	Delivery System	Formulation	Test Method	BA Parameters	Theme Classification
54	Zhang et al	2021	ACS Publications	ACS Applied Materials & Interfaces (8,758)	N/A	silica nanoparticle	Cetyltrimethylammonium bromide, Tetraethyl silicate, 1,3,5-trimethylbenzene, Nhydroxysuccinimide.	in vivo	glucose insulin level	RQ3, RQ4
55	Zhou et al	2020	Springer	Journal of Nanobiotechnology (10.435)	N/A	nanoparticle	Sodium alginate (ALG)	in vivo	glucose insulin level	RQ3, RQ4
56	Winarti et al	2018	Indonesian Journal of Pharmacy	Indonesian Journal of Pharmacy (0,56)	N/A	self-nanoemulsifying drug delivery system (SNEDDS)	miglyol 812N, tween 80, propylene glycol.	in vivo	plasma insulin level	RQ3, RQ4
57	Liu et al	2019	Elsevier	International Journal of Pharmaceutics (5,875)	N/A	nanocomplex	Chitosan	in vivo	glucose insulin level	RQ1, RQ2, RQ3, RQ4
58	Zhang et al	2018	Royal Society of Chemistry	Journal of Materials Chemistry B (6.331)	N/A	nanoparticle	PGLA, alginate, chitosan.	in vivo	glucose insulin level	RQ3, RQ4
59	Guo et al	2016	Taylor & Francis	Drug Delivery (3.095)	emulsion-solvent evaporation	nanoparticle	PLGA; Stearyl-Tat (Ste-Tat); N,N,N-trimethyl-N-dodecyl chitosan.	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
60	Liu et al	2019	Elsevier	International Journal of Pharmaceutics (5,875)	N/A	self-emulsifying drug delivery systems (SEDDSs)	Monoacyl phosphatidylcholine (MAPC), Labrasol (LAB).	in vivo	glucose insulin level	RQ1, RQ2, RQ3, RQ4
61	Ansari et al	2016	Taylor & Francis	Drug Delivery (3.095)	double emulsion solvent evaporation (w/o/w) technique	solid lipid nanoparticles	Dynasan 14, Soya lecithin, polyvinyl alcohol (PVA), PLGA, eudragit	in vivo	plasma insulin level	RQ3, RQ4
62	Sun et al	2015	Dove Medical Press Limited	International Journal of Nanomedicine (6,400)	emulsion solvent diffusion	nanoparticle	Poly- vinyl alcohol, PLGA, Eudragit® FS 30D	in vivo	plasma insulin level	RQ3, RQ4
63	Alfaro et al	2020	Elsevier	Journal of Drug Delivery Science and Technology (3,981)	N/A	self-nanoemulsifying	Lauroglycol FCC, surfactant (Cremophor EL) and co-surfactant (Labrafil M1944CS)	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
64	Koland et al	2021	IJPER	Indian Journal of Pharmaceutical Education and Research (0.425)	modified solvent emulsification-evaporation	solid lipid nanoparticle	glyceryl behenate, glyceryl monostearate, sodium alginate	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
65	Heade et al	2021	MDPI	Pharmaceutics (6.321)	N/A	nanoparticle	BiPro WPI (97%)	in vivo	plasma insulin level	RQ3, RQ4
6	Agraw	20	Royal Society of	RSC Advances	N/A	nanoparticl	chitosan, poly(sodium 4-styrenesulfonate)	in	plasma	RQ3, RQ4

No.	Author	Year	Publisher	Journal and Impact Factor	Method	Delivery System	Formulation	Test Method	BA Parameters	Theme Classification
6	al et al	15	Chemistry	(3.361)		e	(PSS)	vivo	insulin level	
67	Xu et al	2017	Elsevier	Materials Science and Engineering C (7.328)	N/A	liposome	PLGA, asam folat, kitosan, PVA	in vivo	plasma insulin level	RQ3, RQ4
68	Zhu et al	2016	Taylor & Francis	Drug Delivery (3.095)	N/A	nanoparticle	PLGA, cell-penetrating peptides (R8, Tat, penetratin), PVA	in vivo	plasma insulin level	RQ3, RQ4
69	Liu et al	2016	Taylor & Francis	Drug Delivery (3.095)	N/A	nanoparticle	PLGA–mPEG copolymers, Chitosan	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
70	Kaur et al	2021	Elsevier	International Journal of Biological Macromolecules (6.953)	N/A	emulsion	piperin, albumin	in vivo	plasma insulin level	RQ3, RQ4
71	Zhang et al	2015	Elsevier	Indian Journal of Pharmaceutical Education and Research (0.425)	N/A	nanoparticle	PGA-g-DA, DMSO, Trimethyl Chitosan TMC/TMC-CSK, tripolyphosphate (TPP), magnesium sulphate (MgSO4)	in vivo	glucose insulin level	RQ1, RQ2, RQ3, RQ4
72	Wang et al	2020	Springer	Journal of Nanobiotechnology (10.435)	N/A	lipid nanoparticles	Soya phosphatidyl choline (LIPOID E80)	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
73	Guha et al	2016	Taylor & Francis	Drug Delivery (3.095)	layer-by-layer	mesoporous silica nanoparticles	Tetra ethoxy silane (TEOS), 1, 3, 5 tri methyl benzene (TMB), Pluronic P123, Azodiisobutyronitrile, PMV [poly (methacrylic acidco-vinyl triethoxylsilane)]	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
74	Ukai et al	2020	MDPI	Pharmaceutics (6.321)	N/A	self-emulsifying	caprylic acid (≥90%), capric acid (≤3.0%), lauric acid (≤3.0%), myristic acid (≤3.0%), palmitic acid (≤1.0%)	in vivo	glucose insulin level	RQ1, RQ2, RQ3, RQ4
75	Boushra et al	2019	Elsevier	Journal of Drug Delivery Science and Technology (3,981)	emulsification solvent-evaporation	Solid lipid nanoparticles	PLGA, PEG	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4
76	Elkhatib et al	2021	Pharmaceutical Society of Japan	Biological and Pharmaceutical Bulletin (2.233)	ionotropic pregelation	Nanoparticle	sodium alginate, chitosan, dextran sulphate, calcium chloride dehydrate	in vivo	plasma insulin level	RQ1, RQ2, RQ3, RQ4

CONCLUSION

Oral insulin faces various challenges in the gastrointestinal tract, such as insulin degradation by proteolytic enzymes at acidic gastric pH to lack of insulin permeability in intestinal epithelial cells. Various manufacturing techniques must be adapted to the physicochemical properties of insulin to maintain insulin stability so that it can provide an optimal therapeutic effect. The materials used in the manufacture of nanocarriers are very influential in increasing the bioavailability of oral insulin due to their effect in paving the way for insulin across various barriers in the digestive tract. Until now, from various studies of oral insulin that have been developed, it has succeeded in obtaining oral insulin bioavailability of 73.10% achieved by using a mesoporous silica nanoparticles (MSN) delivery system with a layer-by-layer technique coated with a polymer [poly (methacrylic acid-co-vinyl triethoxylsilane)] (PMV)].

SUGGESTIONS

Based on the results of this systematic review, it can then be used as a basis for the development of new oral insulin formulas for bioavailability testing through in vivo studies. Future studies are expected to overcome the three main barriers to oral insulin while having a greater insulin loading capacity to achieve higher bioavailability.

ACKNOWLEDGEMENT

The author would like to thank the Ministry of Education and Culture of the Republic of Indonesia for the funds provided in the 2021 Student Creativity Program activities and Brawijaya University for the facilities provided.

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