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The Effectiveness Study of Drug Delivery System with Chitosan Nanoparticle Carrier on Various Routes of Administration: A Review

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Abstract:
Background*: Drug delivery system was a controlled drug release technology engineering with a specific purpose. There were drug delivery systems that use carriers. The use of carriers such as chitosan nanoparticles in drug delivery systems can improve drug delivery objectives. This review aims to provide information on the effectiveness of drug delivery with chitosan nanoparticles as a carrier on various routes of administration.*
Materials and Methods*: Data collection from this review was carried out by searching scientific journals through electronic databases.*
Results*: The results of the review showed that the use of chitosan nanoparticles as a carrier in improving drug delivery showed good effectiveness on oral, intranasal, and sublingual route. Chitosan in nano size makes it possible to increase drug absorption to the cellular level because it is mucoadhesive, cationic thereby increasing membrane permeability. In addition, chitosan nanoparticles are able to protect drugs from biological or chemical degradation. These are the main keys to the success of chitosan nanoparticles in increasing drug delivery to target organs.*
Conclusion: *The drug delivery system based on chitosan nanoparticles has a great opportunity to be further developed in the future for various routes of administration.*
Key Word*: Drug Delivery System, Nanoparticle, Drug Carrier, Chitosan*

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I. Introduction

Drug delivery system was a controlled drug release technology engineering[1]. The drug delivery system aims to deliver drugs directly to the center of the disease under various conditions[2], protect drugs from degradation which will ultimately increase drug concentrations in target tissues[3], make treatment effective, and minimize side effects. A controlled drug delivery system can be pursued in several ways, one of which is the addition of a carrier in the delivery system[4].

Drug delivery systems with carriers designed to target delivery to specific cells[1], tissues or genes are in increasing demand[5]. Drug delivery with an appropriate carrier is able to improve the properties of drug compounds such as increasing drug solubility, preventing drug decomposition[6], increasing drug bioavailability and reducing side effects[5]. Carrier materials derived from polymers have been widely used as targeted drug delivery because of their good potency[7]. One of the polymer compounds that is widely used is chitosan[3], because in addition to its abundant availability, chitosan also offers many advantages when developed as a drug carrier[1].

Chitosan is a naturally occurring polycationic linear polysaccharide derived from the deacetylation of chitin[7]. Chitin is a structural element in the exoskeleton of insects, crustaceans especially shrimp and crabs[8], fungal cell walls, and the second most abundant natural polysaccharide after cellulose[9]. Chitosan is known as a versatile biomaterial because chitosan is polycationic in acidic conditions, mucoadhesive[10], permeability enhancer[1], non-toxic (non-immunogenic & non-carcinogenic), biodegradable and biocompatible[6]. In addition, chitosan can form a gel as a matrix, has good stability when made in the form of nanoparticles[10]. These advantages make chitosan has a great opportunity to be used as a drug carrier[5].

Nanoparticles are described as particles having a size of only 1-100 nm[11]. Nano-shaped particles offer unique physicochemical properties such as ultra small size[12], large surface area or mass ratio and increased chemical reactivity[2]. This advantage can be utilized for controlled drug delivery so that it can interact at the subcellular level in body tissues[13]. Researchers have developed a drug delivery system with nanoparticles of chitosan nanoparticles[14], because it offers many advantages in drug delivery[15].

Chitosan nanoparticle carriers in drug delivery systems can be applied in various routes of administration including intranasal, oral, and sublingual. This review aims to present information on the

effectiveness of chitosan nanoparticles as drug carriers on various routes of administration. The results of the study are expected to be a reference for researchers to further develop the use of chitosan nanoparticles as a good and efficient drug carrier.

II. Material And Methods

This article uses the primary literature review derived from original articles published in indexed scientific journals Google Scholar, Springerlink, Elsevier, Pubmed and NCBI based on keywords including nanoparticles, chitosan, drug delivery. The literature obtained was screened based on review criteria that focused on one topic related to the effectiveness of drug delivery systems using chitosan nanoparticle carriers. A total of 58 articles were obtained, 10 of them as main refences.

III. Result

The results of the review article (Table no 1) show that chitosan nanoparticles (CN) can be applied in several routes of administration including intranasal, oral, and sublingual as well as studies on their effectiveness studies.

Table no 1: Study of the effectiveness of chitosan nanoparticles as drug carriers on various routes of administration.

Ref. no.	Drug Loaded in CN	Route of administration	Effectiveness
16	Olanzapine (OZ)	Intranasal (i.n.)	OZ loaded in CN has higher Cmax when compared to single OZ solution.
17	Theophylline (TPL) loaded in CN thiolate (CNTO)	Intranasal (i.n.)	TPL loaded in CNTO was able to reduce lung inflammation and reduce epithelial cell damage which was greater when compared to single TPL.
18	Midazolam (MDZ)	Intranasal (i.n.)	Cmax in the brain and %DTE and %DTP of MDZ loaded in CN were significantly higher when compared to single i.n. or i.v. MDZ solutions.
19	Rivastigmine (RHT)	Intranasal (i.n.)	Cmax in the brain as well as %DTE and %DTP of RHT loaded in CN were significantly higher when compared to i.n. RHT and i.v. RHT solutions.
20	Rutin	Intranasal (i.n.)	Cmax in brain as well as %DTE and %DTP of rutin loaded in CN were significantly greater when compared with i.n and i.v. rutin solutions.
21	Tapentadol HCl (TAP)	Intranasal (i.n.)	Cmax and brain transit time of TAP loaded in CN were 5 times greater and 4 times longer, respectively, when compared to TAP solutions administered via the i.n route.
22	Tenofovir disoproxil fumarate (TDF)	Oral	%TDF, Cmax and transit time of TDF loaded in CN were significantly higher when compared to single TDF.
23	Clopidogrel (CPD) loaded in CN Diacetate (CNDA) and CN Triacetate (CNTA). Doxorubicin (DSB) loaded in CN Triacetate (CNTA).	Oral	CPD loaded in CNTA and CNDA increased delivery and accumulation in MCF-7 cells by 2.1 and 1.8-fold and in Caco-II cells by 3.1 and 3.3-fold, respectively compared to single CPD. Cmax and DSB transit time in blood from DSBs loaded in CNTA were each 3 times greater and lasted longer, i.e. approximately 24 hours, when compared to single DSBs which only lasted about 6 hours.
24	Gemcitabine (GCB) loaded in CN Trimethyl (CNTM) peptide conjugate CSKSSDYQC (CSK)	Oral	GCB loaded in CSK-CNTM conjugate showed drug delivery to the Caco-2/HT29-MTX-E12 cell layer which was 2.3 times greater than that of GCB solution.
25	Ketorolac (KC)	Spray sublingual	The bioavailability of KC loaded in CN was increased by 40% and Cmax was greater when compared to KC solution.

Cmax : Maximum concentration ; %DTE : Drug targeting efficiency ; %DTP : Direct transport percentage

IV. Discussion

Nature provides several kinds of polymers that can be used as drug carriers such as albumin (BSA)[26], cellulose[27], gelatin[28], starch[15], sodium alginate[29], natural rubber[30], chitosan and others. Of course, the various types of natural polymers have their respective advantages. Chitosan is the compound most widely developed by researchers to be used as a drug carrier[10]. Chitosan offers many advantages such as being cationic, non-toxic, low allergenicity, mucoadhesive[1], biocompatible, biodegradable and as a permeability enhancer[8]. In addition, chitosan has good stability when formed in nanoparticle size[15]. Decreasing the particle size of chitosan will increase the surface area[2], increase the dissolution rate, increase bioavailability[13], accelerate the desired effect, allow continuous release and reduce the possibility of side effects[17].

Drug delivery systems with chitosan nanoparticles have several drug release mechanisms that occur from chitosan nanoparticles such as polymer swelling, diffusion of adsorbed drugs and erosion or degradation[3]. The diffusion mechanism occurs when the drug in the matrix diffuses from the polymer matrix to the surrounding medium or target organ in a controlled manner. Controlled release occurs because in the polymer matrix there are polymer chains that function as a diffusion rate limiting membrane for drug release. Furthermore, the polymer swelling mechanism begins with the dissolution of the polymer in water or biological media around the target organ and then the polymer chain will be released and followed by the release of the

drug in the polymer matrix region which will affect the rate of drug absorption at that site. The erosion or degradation mechanism occurs due to polymer degradation which causes physical erosion after the polymer chain bonds are broken followed by drug release. Polymer degradation may occur due to the influence of the pH of the surrounding medium, water absorption by the polymer and or the presence of enzymes[10].

The use of chitosan nanoparticles (CN) as a drug carrier is becoming increasingly widespread[10] due to the good ability of CN as a drug carrier so that the use of CN continues to be developed[12]. Currently the ability of drug delivery with CN carriers (Table 1) is not only for one route of administration[3], but can be used for several routes of administration such as oral[22], intranasal both targeted delivery to the brain[18] or systemic[21], sublingual[25] and others.

The effectiveness study of chitosan nanoparticles on the intranasal route

Drug delivery by the intranasal (i.n) route is a non-invasive drug delivery technique that can reach the respiratory system, brain and systemic circulation[10]. The intranasal route is usually intended for topical applications such as for the treatment of nasal congestion or allergic rhinitis. However, with the development of pharmaceutical technology, the intranasal route can be applied for drug delivery to the systemic circulation or targeted to the brain[18]. The intranasal route continues to be developed because this route offers many advantages such as a thin nasal mucosa, able to avoid first-pass metabolism, does not require special equipment such as the intravenous route so as to improve patient compliance[3].

Systemic Effect

The intranasal route can improve drug delivery because it does not pass through intestinal or hepatic metabolism and the large absorption surface area makes it possible to increase systemic effects, especially when used in serious and life-threatening conditions[18]. However, the intranasal route has disadvantages such as limited nasal cavity capacity[3], mucociliary clearance of the drug and is not suitable for drugs with poor water solubility[10]. This weakness can be overcome by using mucoadhesive carrier systems such as nanoparticle-based chitosan polymers[1,6].

Olanzapine (OZ) is an atypical antipsychotic used to treat schizophrenia. OZ tends to undergo first-pass metabolism so that the bioavailability of OZ in the blood is low. Bioavailability and OZ protection can be increased by using chitosan nanoparticles as a carrier. Research conducted by Baltzley et al has tested the ability of CN to increase systemic absorption of OZ. The test showed that the OZ loaded in CN had a higher C_{max} than the single OZ solution. The C_{max} of OZ loaded in CN was 197.0 ng/mL ± 75.19 ng/mL with a half-life ($t_{1/2}$) of 109.00 ± 20.20 minutes, while the C_{max} achieved by the OZ solution was 84.04 ng /mL ± 44.38 ng/mL, with $t_{1/2}$ for 160.53 ± 51.96 min. This shows that the absorption of OZ loaded in CN can increase significantly due to the high mucoadhesive properties of CN and its ability to increase membrane permeability[16].

Theophylline (TPL) is one of the drugs used for the treatment of asthma and has been used worldwide. However, the use of theophylline is reported to often cause side effects such as headaches and cardiac arrhythmias, so its use is limited. Therefore, a formulation was needed to minimize side effects and still increase the delivery and therapeutic effect of TPL. For example, a study conducted by Lee et al who has tested the effectiveness of TPL loaded in chitosan thiolate (CNTO) nanoparticles in reducing the number of eosinophils in bronchoalveolar lavage (BAL) fluid in mice induced with ovalbumin allergy (OVA) which is able to increase the number of eosinophils, and anti-inflammatory test of TPL. This study demonstrated that TPL loaded in CNTO significantly suppressed eosinophil secretion and enhanced the anti-inflammatory effect of TPL when compared to single TPL. The results of these data indicate that TCN with enhanced mucoadhesive can increase the absorption of theophylline and also increase its anti-inflammatory effect and reduce side effects because it can provide protection against lung inflammation caused by OVA induction[17].

Targeted to the Brain

Currently, targeted drug delivery to the brain is still a problem for drugs that are specifically intended to have an effect on the brain[18], because of the blood brain barrier so that not all drugs are able to enter the brain[19]. However, with increasing knowledge regarding the blood brain barrier, there are opportunities to develop drug formulations so that they can improve drug delivery to the brain[10]. There are 3 main pathways of drug delivery to the brain from the nasal mucosa, namely (1) lymphatic pathways, (2) direct pathways from the nasal mucosal epithelium to the brain via the olfactory nerve, (3) systemic absorption pathways into the blood circulation which then reach the brain by crossing blood brain barrier[20]. A strategy to improve drug delivery to the brain is to use a delivery system that can target drugs to the brain[31]. Such as using a chitosan polymer carrier which has cationic properties, good mucoadhesive and can increase membrane permeability so that it can open junctions between cells which will then increase their delivery[1,8,10].

Midazolam (MDZ) is a benzodiazepine anti-epileptic drug that has been widely used. Most anti-epileptic drugs have poor water solubility which limits absorption and results in suboptimal therapeutic efficacy.

Therefore, a drug carrier such as chitosan nanoparticles is needed which is expected to be able to overcome the limitations of MDZ and increase the delivery and therapeutic effect of MDZ. Such as the study conducted by N. Shrestha et al that evaluated the effectiveness of CN in increasing MDZ drug delivery to the brain. The study showed the MDZ C_{max} in the brain of MDZ (in) loaded in CN was 423.41 ng/mL ± 10.23 ng/mL, which was significantly greater than the C_{max} achieved by a single MDZ solution (i.n.) and MDZ (iv) which were 211.67 ng/mL ± 12.82 ng/mL and 245.44 ng/mL ± 12.83 ng/mL, respectively. Similar results were shown in %DTE and %DTP which represent the amount of drug that is directly transported to the brain via the olfactory pathway. %DTE and %DTP of i.n. MDZ were loaded with CN of 270.707 and 63.09, while %DTE and %DTP of single i.n. MDZ solution were 191.373 and 49.13, respectively. These results indicate that CN as a drug carrier can increase membrane permeability, protect drugs from biological or chemical degradation and the mucoadhesive nature of CN can prolong transit time in the nasal cavity so as to reduce mucociliary clearance[18].

Rivastigmine (RHT) is an inhibitor of the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) which is 4–17 times more specific for inhibiting AChE in the brain. However, the oral route of RHT has limitations, namely low water solubility, requiring large multiple doses, which may cause severe side effects. Therefore, Fazil et al investigated the effectiveness of delivering RHT to the brain with CN carriers by the intranasal route. The results of this study showed that the Cmax of RHT in the brain of the intravenous RHT group loaded in CN was significantly higher, namely 966 ng/mL ± 20.66 ng/mL with a time to reach the maximum concentration (tmax) of 60 minutes, when compared with Intranasal RHT and intravenous RHT solutions that obtained Cmax were 508.66 ng/mL ± 22.50 ng/mL with a tmax of 60 minutes and 387 ng/mL ± 29.51 ng/mL with a tmax of 30 minutes. In addition, the %DTE and %DTP in the intranasal RHT group contained in the CN had a %DTE of 355 ± 13.52 and %DTP of 71.80 ± 6.71, which were significantly greater when compared to the intranasal RHT solution group. These results indicate that CN carriers are able to deliver RHT from the nose to the brain directly across the blood-brain barrier and enhance its delivery[19].

Rutin has an antioxidant effect that can be used for the treatment of cerebral ischemia. However, limitations such as low water solubility, chemical and enzymatic degradation in the digestive tract and low bioavailability cause the therapeutic effect of rutin to be less than optimal, so that drug carriers are needed to minimize the limitations of rutin. Like the study conducted by Ahmad et al who evaluated the effectiveness of routine delivery to the brain via the intranasal route using CN as a carrier. The study showed an increase in permeation of >80% within 24 hours produced by rutin loaded in CN, while the permeation obtained by a pure rutin solution was only 19.01%. Then the routine C_{max} in the brain achieved by the intranasal routine group loaded in CN was 1449.3 ng/mL ± 3.7 ng/mL with %DTE and %DTP being 1443.48 ± 39.39 and 93.00± 5.69, respectively. The result is significantly greater when compared to the pure rutin solution which has a C_{max} in the brain of 206.2 ng/mL ± 11.3 ng/mL with %DTE and %DTP respectively 433.33 ± 5.98 and 29.48 ± 1.05. The increased permeation, delivery and bioavailability of intranasal rutin loaded in CN is due to the interaction between the positively charged amino groups of chitosan and the negatively charged parts of the cell membrane, thereby increasing membrane permeability and opening tight junctions between cells in the mucosal epithelium[20] (Ahmad et al. al., 2016).

Tapentadol hydrochloride (TAP) is an analgesic with a dual mechanism of action combining μ-opioid receptor agonism with noradrenaline reuptake inhibition, so TAP can be used to treat acute, chronic, and neuropathic pain. However, TAP tends to undergo first-pass metabolism so that the bioavailability of TAP is low. Thus, TAP requires a carrier that can protect against first-pass metabolism and increase its bioavailability. Like the study conducted by Javia & Thakkar which evaluated the effectiveness of delivering TAP to the brain via the intranasal route using a CN carrier. The study showed that the C_{max} and TAP transit time in the brain achieved by intranasal TAP loaded in CN were 5 times and 4 times greater when compared to the intranasal TAP solution. The %DTE and %DTP results achieved by intranasal TAP loaded in CN were 3.21 ± 0.6 and 68.85 ± 0.49%, respectively, these results were significantly greater when compared to the intranasal TAP solution which showed that TAP loaded in CN has better brain targeting efficiency. The use of low doses of intranasal TAP loaded in CN is able to produce C_{max} and increased brain transit time, thus enabling increased therapeutic effects over a longer period of time with minimized side effects[21].

The effectiveness study of chitosan nanoparticles on the oral route

Administration of drugs through the oral route is currently the most widely used route, even most of the drug administration is via the oral route[23]. The oral route is the most convenient route for drug administration and provides convenience in administering the drug because it does not require special equipment or special treatment from health workers[3]. However, there are still some obstacles to the oral route of drug administration, such as the presence of enzymes, variations in pH especially in the stomach which has a very acidic pH, first-pass effect on the liver and the presence of intestinal obstructions[10]. However, of course, there are many ways that can be taken in order to minimize the problems that exist in the oral route[22], one way is by using a natural

polymer carrier such as chitosan made of nanoparticles, because the chitosan carrier has good mucoadhesive properties[1], easily biodegradable and low toxicity[8], and its nano-sized form has a large surface area and increases the effect of chitosan which will ultimately improve drug delivery[10].

Tenofovir disoproxil fumarate (TDF) is a nucleoside reverse transcriptase inhibitor/NRTI widely used for the treatment of HIV-AIDS. However, pure TDF is reported to have only 25% oral bioavailability in humans, so the proper formulation is needed for the use of TDF to obtain an optimal therapeutic effect. The study conducted by Shailender et al demonstrated the effectiveness of CN in increasing the bioavailability of oral TDF. The study showed that %DTP in intestinal mucosa from TDF loaded in CN obtained a significantly higher concentration of 91.3 ± 1.8%, when compared to single TDF which had %DTP 6.6 ± 0.3%. C_{max} and mean residence time (MRT) of TDF loaded in CN have a significant increase compared to single TDF. The increase in oral absorption of TDF is due to its mucoadhesive properties and metabolic protection by CN which provides protection against TDF so that more TDF is available for absorption[22] .

Gemcitabine (GCB) is a nucleoside analog that has therapeutic effect as an anticancer that can be used for the treatment of breast, pancreatic, and bladder cancer. GCB administered intravenously tends to reach peak plasma concentrations above the maximum tolerable concentration/MTC and rapid elimination of the drug in plasma occurs. Chen et al conducted a study evaluating the effectiveness of GCB contained in CNTM-CSK in enhancing the absorption, bioavailability, and anticancer effects of GCB after oral administration. The test results show that GCB loaded in CNTM-CSK at a concentration of 500 g/ml has a 2-fold greater absorption and the ability to conduct delivery across the Caco-2/HT29-MTX-E12 cell layer is 2.3 times greater than the GCB solution. The C_{max} achieved by GCB loaded in CNTM-CSK was 1056.0 ng/mL ± 143.6 ng/mL with an absolute oral bioavailability of 60.1%, while gemcitabine solution obtained a C_{max} of 577.1 ng/mL ± 98.2 ng/mL with absolute oral bioavailability of 9.9%. Then GCB loaded in CNTM-CSK was able to reduce tumor size which was significantly larger 5.13-fold and 3.03-fold when compared to the control group without treatment and the gemcitabine solution group[24].

Doxorubicin (DSB) is a drug that has a therapeutic effect as an anticancer and clopidogrel (CDP) is an antiplatelet drug. Both drugs have been shown to have pharmacological effects as expected, but in pure state DSB and CDP have limitations on bioavailability after oral administration, so that a good formulation is needed to increase the availability of DSB and CDP in the body. Therefore Khdair et al conducted a study evaluating the effectiveness of CPD drugs loaded in CNTA and CNDA in increasing cellular drug delivery to cancer cells MCF-7 cells and Caco-II cells and their ability to penetrate the defenses of cancer cells in the form of P-glycoprotein (P-glycoprotein). P-gp) which is able to prevent the accumulation of anticancer drugs. The results of the study showed that CPD loaded in CNTA and CNDA could enhance drug delivery to MCF-7 tumor cells and Caco-II cells significantly increasing cell uptake and cellular accumulation compared to single CPD. The increase in accumulation produced by CPD loaded in CNTA and CNDA was 2.1 and 1.8-fold in MCF-7 cells and 3.1 and 3.3-fold in Caco-II cells compared with single CPD. Then in another test by Khdair et al that evaluated the bioavailability of DSB loaded in CNTA carried out in vivo. The results showed that DSBs contained in CNTA obtained relatively longer bioavailability of DSBs that lasted ± 24 hours, when compared to single DSBs which only lasted ± 6 hours. Then the C_{max} achieved by the DSB contained in the CNTA is 3 times when compared to a single DSB. These results can be obtained because CNTA and CNDA are able to increase significant cellular accumulation in intestinal cells (Caco-II), maintain drug release and are able to suppress P-gp secretion mechanisms. The ability of CPD & DSB to penetrate intestinal cells as an intact system increases thereby increasing peak plasma concentrations and oral bioavailability[23].

The effectiveness study of chitosan nanoparticles on the sublingual route

Administration of drugs through the sublingual route is one of the most desirable drug delivery routes because it can provide rapid pharmacological effects so that the sublingual route is the preferred route for drug administration in serious situations that require rapid pharmacological effects[25], or for patients who have difficulty swallowing such as the elderly, children and patients with other conditions[32]. The advantages of the sublingual route include the onset of action of the drug relatively quickly compared to the oral route because it passes through the first metabolism in the liver and also the drug is protected from degradation due to pH and digestive enzymes, then it can be used for low-dose drugs[33]. However, there are also drawbacks to the sublingual route, such as being unsuitable for prolonged administration and unsuitable for compounds that have low solubility[3,32]. Thus, it is necessary to use a good delivery system such as using a chitosan carrier made of nanoparticles. Chitosan nanoparticles are mucoadhesive[1], are able to increase membrane permeability and are able to increase the prolonged release of drug compounds so as to minimize deficiencies that may arise[8].

Ketorolac (KC) is a non-steroidal anti-inflammatory drug / NSAID that has strong analgesic activity that can be used for the treatment of migraine headaches and postoperative pain. The use of ketorolac by the oral route can cause side effects in the digestive tract and is rapidly metabolized. Therefore, Baltzley et al conducted a study to evaluate the effectiveness of KC loaded in CN after administration by the sublingual route. The

results of this study showed that the bioavailability of KC loaded in CN by the sublingual route increased by 40% when compared to the concentration of sublingual KC solution. The C_{max} achieved by KC was loaded in CN of 1205 ± 9 ng/ml with a half-life of 20 minutes earlier than that of KC solution which reached C_{max} of 755 ± 89 ng/ml with t1/2 42 minutes. Then KC loaded in CN showed absorption of sublingual KC loaded in CN relatively faster than sublingual KC solution and sublingual KC tablets. In addition, KC loaded in CN shows a prolonged release in the body ± 200 minutes, where the time is relatively longer when compared to intravenous and oral route administration which allows the use of sublingual route of KC to reduce the need for dose frequency which will ultimately reduce side effects, especially in digestive tract. This is due to the good mucoadhesive properties offered by CN so that it can increase mucosal absorption and increase membrane permeability[25].

V. Conclusion

The use of chitosan nanoparticles as a carrier in improving drug delivery shows good effectiveness. The main key to the success of chitosan nanoparticles in increasing drug delivery to drug targets is based on the very small size of chitosan nanoparticles that can increase absorption to the cellular level, as well as because of their mucoadhesive, cationic properties, increasing membrane permeability and protection ability from biological or chemical degradation. . Thus, drug delivery systems based on chitosan nanoparticles have a great opportunity to be further developed in the future. However, it is recommended that further clinical studies be conducted to evaluate the benefits and toxicity of chitosan nanoparticle carriers.

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