Drug Delivery System Using Biodegradable Nanoparticles Carrier

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Abstract
Recently, many biochemists have identified that chitosan is not rejected by the body and that it can improve the effective and safe delivery of drugs and vaccines with its absorptive power. Also, it has been known that chitosan is suitable for controlled drug release thanks to its advantages of biodegradability and bio-compatibility. As the interest into the extension of human life and personal health has been increased, the pharmaceutical and medical worlds have been making efforts to develop more sustained and effective drug release property in a body. This study investigated the individual drug characteristics and drug release behavior by manufacturing the chitosan patch using insulin, a drug used for treating diabetes, at a low temperature, and further tried to find the optimal condition by adding the skin activating agent to the chitosan patch using NOD (Non Obese Diabetic) mice. According to the analysis using the chitosan-insulin drug and the skin-activating agent, a dramatic decrease in the blood glucose level was achieved. An experiment was performed in vivo by utilizing chitosan nanoparticles as a biopolymer to control the drug delivery rate at an optimal concentration, pH and temperature. It was also observed that the experiment of the drug delivery by nanoparticles containing insulin could effectively lower the blood glucose of the mouse.

Keywords: Drug delivery system, Nanoparticles, Chitosan, Biopolymer

1. Introduction
As one of the most important and essential researches to develop convenient and effective drugs in the medical industry, more focus has been paid on the non-injection or parenteral drug. The study on drug release in the medical industry can be said to be one the most effective ways to stand up against side effects including: a) angioma due to an intramuscular and intravenous injection, b) allergies and mental stresses that are originated from other kinds of immune disorders on the skin, c) drug dissolution induced from the oral administration. The meaning of the drug release study is linked directly with the dignity of human beings in terms of reducing the pain of drug delivery. This study is valuable as a noble delivery method of the drug. This study has been increasingly applied to various fields including the inhibitor of partial nerves for local anesthesia, medical supplies for kids, and substitutes for the existing drug. Unlike the existing direct medication sought only after the treatments, a recent trend of drug manufacturing is toward longer lasting effects with less pain and less quantity. This field has been considered as one of the most prospective fields of the medical industry, and thus has been enormously invested in to develop the complex drug delivery system that releases multi-functional, compound and compact drugs. As the effect of a medicine appears in proportion to the drug concentration in the blood, it is necessary to control the curve of the blood concentration with
various pharmaceutical technologies. Hence, it is essential that the behavior of the drug in a body should be controlled by various technologies to perform the stable and effective medication on the selective area [1-3]. Throughout the world, the United States and Japan have set spurs to the development of the drug delivery system over the last 20 years thanks to their bio-technologies and genetic technologies. Considering the rapid growth in the patents application of the drug forms, the Korean pharmaceutical industry is also displaying interest in the development of new drugs through the new types of drug forms. Presently, several success stories have been announced and they have already started manufacturing and marketing the treatments of arthritis using the new technologies. An ideal drug delivery system can be achieved by materials that have no chemical changes and that satisfy the conditions of biodegradability and bio-compatibility of the nanoparticles carrier, the biodegradable speed of the carrier and the delivery speed of the drug [4, 5]. Another reason that the drug delivery system has come into the spotlight is because of shorter development periods and lower costs compared to the development of a new drug [6-8]. As the effect of a general medicine appears in proportion to the drug concentration in the blood, it is necessary to control the curve of the blood concentration with various pharmaceutical technologies. Especially, it is essential to maximize the drug delivery on the target areas using special technologies rather than controlling the drug concentration in the blood, in which an anti-cancer medicine and a genetic material are expected to generate severe side effects when delivered to the normal tissue. Therefore, it is also necessary to control the drug behavior in a body in order to effectively perform a stable treatment on the desired areas [9, 10]. This kind of drug form, which is designed for optimal treatments, is called the Drug Delivery System (DDS). The development of the drug forms originated because the necessities of new types of drug forms are on the rise based on the biotechnology, which is considered to be a breakthrough when development of materials with new chemical structures are at the height of their prosperity [11, 12]. Drugs are administered through injection, mouth, transdermal, and a mucous membrane, but the drug delivery system is invented to improve the way of drug administration. The drug delivery system raised a question in the existing pharmaceutical medication methodology (the drug forms and application methods), and moves toward the goal of optimization of drug therapy by handling the medical supplies as "the science of medication methodology", not only as "materials". In other words, it is designed so that the desired amount of drug can reach the desired area with the desired concentration. For example, when an antiphlogistic agent is administrated through the mouth for the treatment of arthritis, the drug will work upon the joint but will give rise to side effects on the other areas. Against this backdrop, the drug delivery system intends to design the drug forms to reduce this side effect and to maximize the remedial result [13-16]. Drugs are processed in the form that can display the most convenient and efficient medical action, and then are administered in a body through various ways. The administered drug is released from its form, and is absorbed into blood, which is then delivered to each organ through the bloodstream and finally is eliminated through metabolism and urination. All drugs will work upon the desired area (receptor) in a body while they will give rise to side effects on the other areas [17-22]. When the characteristic length of a high molecular substance is controlled in the size of a nanometer, several functions are displayed, which cannot be seen in the ordinary material. The material designed to have a stable structure in the size of a nanometer can lead the newly-advanced materials in the field of life science and environmental industry on its own or as a composite material mixed with other materials, as well as replacing the existing high-functional materials. As nanoparticles containing insulin are available in wide application using the chitosan that attracts public attention as the last biomass, they can be widely applied to the industry as well as to academic research [23-27]. Chitosan or poly (D-glucosamine) is the polymer consisting of chitin that is partially deacetylated. Chitosan can be easily made from chitin, a natural polymer, which is derived from the cuticles of insect species or Crustaceans such as crabs and shrimp. Chitin exists in nature with the largest amount but cellulose. Chitosan has various useful characteristics including high chemical resistance, big thermal stability, affinity with dyes and metal ions, and bio-compatibility. Over the last 20 years, these kinds of characteristics have been widely applied to chemical engineering, biomedicine, waste water treatment, the collection and recycling of metal, functional membranes, and the controlling of metal ions in a body [28-33]. As chitosan dissolves in an acidic solution, has reactive amino suitable for chemical changes, and is harmless to people, the functional polymer made from chitosan can be an excellent ion exchange resin or an absorbent. Hence,
it can be widely applied to medical supplies, as a remover of agrichemicals and heavy metals, waste water treatments, etc. [34, 35]. As chitosan nanoparticles manufactured in the present study have a low production cost, bio-compatibility and low toxicity, research on this subject has been widely conducted [36-38].

The present study investigated the release characteristics in vitro and in vivo after manufacturing penicillin and insulin using chitosan at a low temperature. Each process is optimized with its temperature, pH, time, etc. for making the optimal drugs. Then, their release characteristics in accordance with the drug concentration are investigated. The drug is processed in the form that can be easily applied and that can display its optimal medical action. Then, it is administered in a body through various routes. The administered drug is released from its form, and is absorbed into blood, which is then delivered to each organ through the bloodstream and finally is eliminated through metabolism and urination. All the drugs will work upon the desired area (receptor) in a body while they will give rise to side effects on the other areas [19]. The present study investigated its release effect in a body using insulin that contains chitosan. In addition, it also investigated its release characteristics in vitro and in vivo after manufacturing using chitosan, a biodegradable polymer, at a low temperature. Each process is optimized with its temperature, pH, time, etc. for making the optimal drugs. Then, their release characteristics in accordance with the drug concentration are investigated. People who have diabetes suffer from pain and financial loss, for insulin is administered through an injection. However, this pain can be relieved when the drug is administered through a mucous membrane in the nose using the chitosan nanoparticles. This study confirmed that drug delivery system using the biodegradable nanoparticles carrier are effective in drug release and can lower the blood glucose level..

2. Experimental

2.1 Reagent and Device

NOD (Non Obese Diabetic) mice in their 3rd, 5th and 7th weeks were bought from Korea Taconic Co., Ltd. for the experiment (Fig. 1). Norvolin-R was bought from Korea Green Cross Corporation, while glycerol, chitosan and acetic acid were bought from Sigma-Aldrich that won recognition for its degree of purity. Chitosan was gained from chitin after being deacetylated (95% of deacetylation), which was bought from Aldrich. Its molecular weight for the experiment was about 30,000-50,000 and 100,000-120,000.

2.2 In vitro and In vivo Experiments using the Chitosan Patch

2.0g of chitosan, 30ml of distilled water and 1ml of acetic acid are put into the 50ml sterilized vial and they are stirred regularly. Then, it is stabilized at 40 °C for three days. Next, it is blended with penicillin-G and insulin, respectively for their suitable concentration and stabilized at 4°C for a week. For the in vitro experiment using the chitosan patch, the stabilized chitosan drug is put into a container of stainless steel with 13㎠ of surface area and a size of 5㎠. Then, its surface is fixed with a sterile dressing of the same size. The fixed drug is neutralized in the solution that is set at pH 8 using NaOH, and then is soaked in the distilled water until just before the experiment. After that, it is put into 1l of phosphate buffer solution (KHCO₃: 9g/l, K₂HPO₄: 1.4g/l, KH₂PO₄: 1.1g, pH 7.4) and then is kept at 37°C by the constant temperature system. If the buffer solution reaches over pH 7.4 during the experiment, set it at 7.4 with the HCI 0.1M. Next, the chitosan drug is put into this buffer solution, and the supernatant should be stirred at the speed of 100rpm. The reagent is sampled three times at the interval of 1, 2, 4, 8, 12 and 24 hours. The values are averaged and their concentration is measured at 290_ which is the inflection point of 290_ with U.V

![Fig. 1](image_url) NOD mice for in vivo experiment.
For the in vivo experiment using the chitosan patch, its effect is analyzed after adding the skin activating agent. First of all, put each chitosan with different molecular weight (M, W: 50,000, 120,000; hereinafter called C1 and C2) into the sterilized vial together with distilled water and acetic acid. Then, it is stabilized at 40°C for three days. When the skin activating agent (glycerol, DMSO, DMF) is added, the same amount of distilled water is reduced for making the initial chitosan solution, while the rest of the process remains the same. Each insulin concentration of 10 IU and 20 IU is blended with the prearranged chitosan solution. Then, exactly 1 ml of manufactured drug is put into the container (2.5 cm in diameter, 0.25 cm in height) using a syringe, which is soaked in 0.1 M of NaOH solution for 10 seconds. Then, it is put into the small amount of distilled water of 4°C and is kept refrigerated. Drugs are apt to decompose, so prepare it within one hour prior to the experiment. The arranged drug is wrapped hard around the abdominal region of the mouse with sanitary tape, so that it is well fixed to observe the difference of the drug release. The blood glucose level is analyzed using SURE STEP Plus (see Fig. 2), which is a blood glucose test meter manufactured by LifeScan, Inc., USA. The test strips for the experiment are code 9, also from LifeScan, Inc. The insulin concentration is analyzed using the HPLC system of Waters Corporation. Particle size and zeta potential are analyzed using Zeta-plus from Brookheaven Instruments Corporation, while the formation of nanoparticles are confirmed using AFM from PSIA Corp. (see Fig. 3). The insulin concentration is measured using C-18 as a separate column and is analyzed using HPLC (HP-5420) from Waters Corporation, USA (see Fig. 4).

2.3 Manufacturing the Chitosan Nanoparticles Containing Insulin

For the in vivo experiment using the chitosan nanoparticles, these nanoparticles are manufactured by putting regular sized chitosan into the sterilized vial together with other materials including insulin, distilled water and acetic acid, which is then blended and is kept refrigerated for three days for stabilization. Then, it is completely dissolved in the Tripoly-
phosphate solution and is stabilized at room temperature. Next, it is reacted by adding glycerin for about 10 minutes, and its pH is measured. After that, it is centrifuged for 15 minutes. The centrifuged solution is frittered with a micro pipette. Then, the nanoparticles are confirmed with the Particle size analyzer, Zeta potential and Atomic Force Microscopy (AFM). After measuring the blood glucose level once from the arranged blood of a mouse, nano-chitosan solution is administered to the mucous membrane of a NOD mouse using a micro pipette. The number of administration varies: once, five times and seven times. For a chitosan solution containing 100 $\mu\ell$/ml of insulin, 0.3g (1%) of chitosan is put into the sterilized vial, which is evenly soaked with 1.2ml of insulin using a micro pipette and then is kept refrigerated for over four hours. Next, it is blended with 28.35ml of distilled water and then is combined with 0.15ml of acetic acid, which is completely dissolved using the glass rod and Voltex Mixer before being kept refrigerated. 0.09g of Tripolyphosphate (hereinafter called TPP) solution is completely dissolved in 29.19ml of distilled water and is kept refrigerated. With these two solutions, first put 25ml of chitosan solution into a new vial (50ml) and 10ml of TPP solution is added using the micro pipette, which are completely blended for five minutes. Five minutes later, 100 $\mu\ell$ of glycerin is added and stirred for 10 minutes, which is put into two micro tubes (1.7ml) up to 0.9ml respectively. This tube is centrifuged with a centrifugal separator set at 15,000rpm for 15 minutes. Then, the supernatant is separated from the centrifuged solution and is analyzed with the HPLC system. The analyses are performed twelve times at the beginning and then after 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, and 7 days. The reagents containing chitosan nanoparticles are composed of the insulin concentration ($\mu\ell$/ml) of 100, 75 and 30 respectively, and the composition of each reagent is as follows (see Table 1):

| Insulin Concentration ($\mu\ell$/ml) | 100 | 75 | 50 | 30 |
|-----------------------------------|-----|----|----|----|
| Chitosan (g)                      | 0.3 | 0.3 | 0.3 | 0.3 |
| Distilled Water (ml)              | 28.35 | 28.65 | 28.95 | 29.19 |
| Insulin (ml)                      | 1.2 | 0.9 | 0.6 | 0.36 |
| Acetic Acid (ml)                  | 0.15 | 0.15 | 0.15 | 0.15 |

3. Results and Discussion

Fig. 5 shows the drug release concentration at Penicillin-G 0.1, 0.3, 0.5, and 0.7 % in vitro. The value shows a relatively slow increase, in other words, a relatively stable increase. The value is more stable when its concentration is higher. Also, it is identified that transformation occurs when mixing chitosan and penicillin at over 30°C. This should be considered when mixing these two materials. Through this experiment, it is observed that chitosan allows the drug release to be stabilized. Therefore, it is estimated that chitosan and its derivatives are quite useful when conducting drug release experiments.

Fig. 6 shows the blood glucose level in NOD mice in accordance with three different hypodermic injections. For NOD mice in the control group, the blood glucose level does not fall below 200 mg/dl. The hypodermic injection was administered by 2 IU/Mouse (0.057 IU/g) and 5 IU/Mouse (0.143 IU/g) based on the 35g of NOD mice. For the hypodermic injection on 5 IU/Mouse, the lowest blood glucose level (40 mg/dl) is observed after four hours of ad-
administration, which is not a desirable value compared to that of the normal mouse. It is 2IU hypodermic injection that has similar effect with the blood glucose level (110-120 mg/dl) of a normal mouse. This value is the suitable blood glucose level that should be gained from the drug patch.

**Fig. 7** displays the effects of transdermal insulin delivery by a chitosan patch (Chsn1 = MW; 50,000, Chsn2 = MW; 120,000) on the blood glucose level. As shown in the **Fig. 7** chitosan 1 is more effective in its insulin delivery than chitosan 2.

As **Fig. 8** shows, the effects of DMSO molecular weight on the blood glucose level of NOD-mouse are investigated in order to find the most suitable DMSO concentration. As **Fig. 11** shows, the higher the DMSO concentration is, the higher the blood glucose level becomes. It is estimated that when the DMSO concentration reaches over a certain level, drug delivery is difficult due to the increase of skin reaction. The result found that DMSO2 (0.85 mg/ml), showing the most suitable blood glucose level of 135 mg/dl, is the optimal concentration of the skin activating agent. Unlike the hypodermic injection, this is because the drug is administered every three hours and then is given one hour of restoration period before re-administering the drug. Compared to drug administration through a hypodermic injection, drug administration through an insulin patch achieves 8% of drug delivery on the aspect of insulin, and maintains a reasonably low blood glucose level.

**Fig. 9** shows the blood glucose level change of a mouse at dietary state in vivo depending on the chitosan nanoparticles that contain various insulin concentrations (10 IU, 7.5 IU, and 5.0 IU). As shown in **Fig. 9**, when the insulin concentration is increased, the blood glucose level is decreased. The variation of the three curves is significant because the intake of each mouse varies among the several elements to change the blood glucose level (i.e. food intake, activities and the level of stress).

**Fig. 10** is an experiment to find the insulin transportation by nanoparticles. The mice are left eight hours without food, and then their blood glucose level change is observed for 24 hours. In this experiment, the insulin concentration of the nanoparticles is relatively lower than the prescribed diet because if a mouse is administrated with the same amount of insulin during hunger, it may go into shock. As shown
in Fig. 10, the blood glucose level is lowered in the order of 7.5 IU, 5.0 IU, and 3.0 IU, and unlike the prescribed diet, their blood glucose level is stabilized four hours later, which is an ideal result.

![Graph showing blood glucose level change](image)

**Fig. 10** Nanoparticles effect on blood glucose level change of mouse at abstention state **in vivo**.

4. Conclusions

During the **in vitro** experiment, it was found that chitosan can release the drug at a constant level, and that it is pertinent to apply chitosan and its derivatives for drug release experiments. Also, the mixture of chitosan and penicillin is transformed when made at over 30°C, which should be considered before mixing these two materials.

During the **in vivo** experiment using the chitosan-insulin patch, the author found that it can release the drug at a relatively constant level, and that chitosan is effective for drug release experiments. In addition, the author observed that a high molecular chitosan raises the efficiency as a drug release carrier more than a low molecular chitosan, and that the amount of drug release may be controlled depending on the condition. Chitosan containing insulin releases less drug when stored at a low temperature, and the insulin drug is decomposed over time. It is estimated that DMSO may cause stress accompanied by stigmas. Against this backdrop, the author conducted DMSO experiments with different concentrations. The result found that as the DMSO concentration is increased, the skin reacts against the drug due to skin irritation.

Based on the above experiments, the author summarizes the results as follows:

1. Capital Chitosan manufactured with over 95% degree of purity performs a relatively stable drug release during **in vitro** and **in vivo** experiments, and that it is reasonable to apply the chitosan derivatives for the drug release experiments.

2. With the chitosan patches, the blood glucose level is lowered the best when the skin activating agent, DMSO, is added.

3. It is possible to manufacture nanoparticles of 100-200 nm with the biodegradable high molecular weight chitosan, and the manufactured nanoparticles are highly efficient as a drug release carrier.

4. For insulin absorption through a mucous membrane, only a small amount of chitosan nanoparticles can maintain the stable blood glucose level of 100-120 mg/dl.

5. It is estimated that insulin absorption is increased through the chitosan nanoparticles because the nanoparticles can expand the connection of the epithelial cells loosely.

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Acknowledgement
This research was supported by the Kyungwon University TIC Research Fund in 2005.

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