Review Article

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Different ways to enhance the permeability, lipophilicity, and bioavailability of the antidiabetic drug, Metformin: Review Article

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Abstract

Metformin is a drug that needs improvement in its bioavailability and absorption. This can be acheived by using different drug delivery systems, making prodrugs, and changing the drug release environment. Drug delivery systems are used for various reasons, for example, targeted drug delivery, protecting the drugs from destruction by enzymes, and enhancing the drug's absorption, permeability, and bioavailability. According to the studies and surveys, the permeability, absorption, and bioavailability of metformin can be improved in many ways, like making prodrugs and using carriers. Prodrugs and lipid-based carriers like nanostructured lipid carriers and lipid-based polymers are the best methods that can help the medical system to reduce the dose of metformin usage in patients and reduce the side effects.

Keywords: Absorption, Bioavailability, Lipid-based drug delivery systems, Metformin, Polymers, Prodrugs.

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1. Introduction

Metformin is a hydrophilic drug with low absorption in the intestinal system (1). This causes high dosage requirement in the patients using it (the bioavailability of pure metformin is about 50%). Metformin was formulated as metformin hydrochloride to enhance its solubility and stability in all marketed drugs (in these products the rate of water solubility for drug is about 1:2.) (2). This drug has diverse usages, mainly it was discovered and marketed for the treatment of type 2 diabetes, but after its usage in patients, it was understood that it could be used for weight loss (3, 4), improving hypertension (5) and lipid metabolism (6) and treatment of liver lipids accumulation (7-9) (Figure 1). The researchers and development groups in many scientific centers and companies started to make better formulations for this drug with this vast range of therapy. It should be mentioned that one of the most important advantages of metformin is that it does not cause hypoglycemia (10). To get a better result from treatment with metformin, lipophilicity of metformin should be increased to reach a better absorbance in the intestinal system. After the dosage form enters the gastrointestinal system, the drug must be released and delivered to the target. This goal can be achieved by changing the molecular structure of metformin (11) (making prodrugs) or using carriers (12) like nanostructured lipid carriers (13), hydrogels (14) and liposomes (15). Using these sterategies, can increase metformin absorbance, and its blood concentration. Significantly, they can reduce the times and doses that the drug is taken and possibly its side effects. In this article, we tried to summarize

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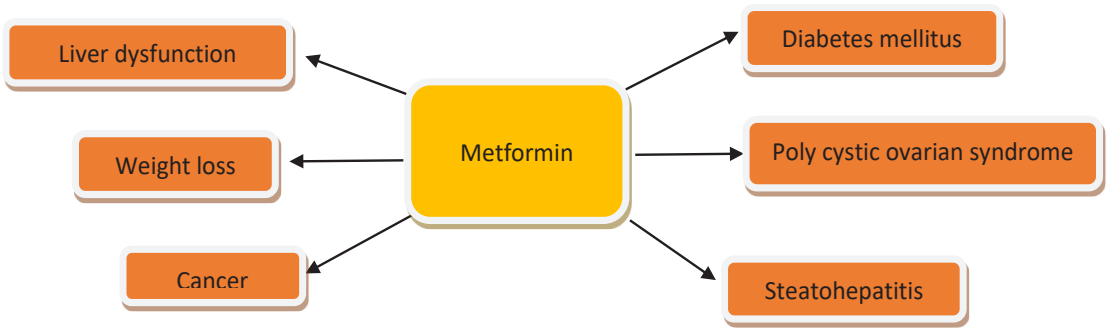

Figure 1. Most important clinical uses of metformin (8, 9).

the latest researches in the improvement of metformin bioavailability.

2. Metformin prodrugs

Making prodrugs reduces the drawbacks of many drugs (16, 17). Preparation/ synthesis of metformin prodrug has been studied before. For example, conjugating the base of sulfonamides to metformin increases its lipophilicity, absorbance bioavailability. The tests proved that more lipophilic sulfonamide causes more lipophilicity, absorbance, and bioavailability of metformin (the sulfonamides that were attached to metformin for making prodrugs were phenyl and cyclohexyl derivatives, and the effect of cyclohexyl on the biguanides bioavailability and absorbance was better and more acceptable than phenyl). Precisely these prodrugs showed better distribution coefficients than metformin itself. The cyclohexyl-metformin (CHMF) prodrug released the drug slowly and in a much longer time than phenyl-metformin at in vitro tests. But in in vivo tests it was not possible to compare the two drugs because the phenyl-metformin was forced out of the process (because it caused the death of rats because of thiophenol releasing). But in comparsion with CHMF and free metformin, it was turned out that therapeutic concentrations can be obtained with a much lower dose of Prodrug than pure medicine. The bioavailability of CHMF is about 20% more than metformin, and metformin was detectable in blood for about 300 hours (this time was between 25-30 h in pure metformin usage). In other comparisons between pure metformin and prodrugs, prodrugs could keep the drug concentration at the therapeutic level for a longer time. Both of these prodrugs were stable in buffer pH but they are not so stable and effective in acidic and oxidative environments. The phenyl based prodrug may be destroyed more easily in this situation (18). In another study in Finland, Kristiina M. Huttunen and her assistants examined three different structures of chain sulfonamide-metformin (ChSMet) prodrugs. This study showed increased metformin permeability because of increase in its lipophilicity in the prodrugs (it should be emphasized that higher permeability of metformin in combination with the most lipophilic sulfonamides is registries in this article like the previous one). This article has brought that not all of the ChSMet prodrugs are good candidates for *in vivo* tests. Only the sulfonamide with long alkyl chains (more than seven carbon) have shown acceptable results (11) in invasive tests in these researches. The mixture of metformin and sodium docusate, as a prodrug, showed more solubility in polyoxyl, medium-chain TG, glycerol, and propylene glycol monocaprylate, and type IIIA SEDDS, than market available and accessible metformin, and this can cause more permeability and bioavailability for this drug in the patients that should use it (19). Another important ancillary use of metformin is its usage in tumors because of this drug's antitumorigenic effect. A group of scientists in Egypt proved that if metformin was mixed with phospholipids and MET-phospholipid prodrug used as an antitumor drug, the effects of metformin was increased. For example, the lipophilicity of this prodrug is much more than pure metformin itself, and the antiproliferative effect of MET-phospholipid prodrug is more than MET (IC_{50} of the prodrug is lower

than the pure drug) for MiaPaCa-2 cells. Also, the effect of the prodrug for inhibition of hypoxia in cancer cells (Oxygen Consumption Rate) is about 20% better than the metformin itself (hypoxia in cancer cells causes resistance to radiotherapy and DNA radicals in cancer cells.). As another sign to prove this claim, the research team decided to measure the intracellular concentration of the prodrug and pure drug and the results were 158 and 75 µg/ml, respectively (20).

3. New carriers to deliver metformin

The carriers (Figure 2) are one of the best ways to improve drug delivery and bioavailability (21-24). They are the newly designed and particular dosages, nano and microcarriers, and polymeric drug delivery systems. Using water-in-oil microemulsions to improve the bioavailability of metformin in its oral administration showed that making microemulsions causes better permeability and bioavailability when metformin is administered to fast male rats. The concentration of the total used surfactants to make microemulsions should be less or equal to 35 percent of the mixture of the emulsion (ME35), because it was proved that higher concentrations of surfactants (45% (ME45)) cause a decrease in drugs, bioavailability in comparison with the above-mentioned concentration). It should be mentioned that metformin microemulsions have more absorption and bioavailability in each part of the intestinal region in comparison with the pure drug. To make these microemulsions, the research team selected Tween 80 and Cremopher EL as surfactants with the least dissolution of metformin, GMO (glycerol monooleate) as oil and ethanol as cosurfactant to have the best result (25). A test in India was done on tamarind seed polysaccharide (TSP) polymers containing metformin. Different structures of these polymers were used as carriers for this drug. The DEE% (drug encapsulation) for all of them was between 69-95%. *In vitro* analysis of these polymeric drugs showed that the metformin release was stable and well for up to 12 h after starting the releasing process. The best release was observed with the polymer combination of 700 mg pectin +175 mg TSP. More TSP and pectin causes decrease in drug release and the release process stability. At *in vivo* tests, the pure metformin caused a rapid reduction in blood glucose level, but after a few h, the blood glucose rate rose again. However, the blood glucose was decreased slower in patients used polymeric metformin, than in patients who used the free drug; however, it stayed at an appropriate level for many h (26). Microspheres were investigated in another test. They were made with double emulsion-solvent evaporation method. The composition of these microspheres consists of chitosan and eudragit (RL100 & RS100 forms). In this drug delivery system, the size of the microspheres is an essential factor that is precisely controlled by the EL and ES concentrations in the system (RL led to smaller microspheres and rapid drug releasing and RS led to larger and more stable structures which cause sustained drug release; increasing Chitosan concentration helps to sustain releasing of the drug). At *in vivo* tests, the results of this formulation was similarly to those of pectin-TPS polymers. It caused a more stable

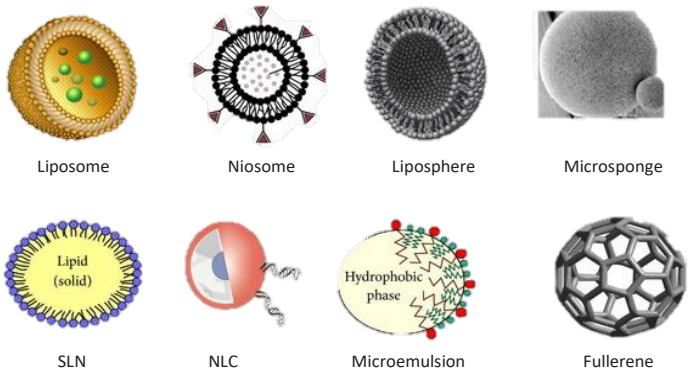

Figure 2. Drug carriers are used to design novel drug delivery systems (24).

blood glucose level than pure metformin. Also, the level of metformin in pure drug usage was raised and decreased quickly; however, it was raised slower than in administration of pure drug in microsphere-metformin formulas, and it remained at a therapeutic level longer than the usage of pure substance (27). Danish researchers found essential data in the research of chitosan-metformin discs. This study on TR146 cell line (as an alternative for buccal mucosa) showed that using chitosan as a carrier for metformin in buccal drug delivery can increase the permeation of the drug across the cell layer. The data obtained show that using chitosan discs loaded with metformin can be used for treatment of non-insulin dependent diabetic patients and ovarian ones in different daily dosages. The reason for using this cell line is because the chitosan discs are bioadhesive, so the cell line should have the ability of mucus secretion. For making chitosan discs, first chitosan and metformin was mixed in HCl and then dried with spray dry method; at the end the specific weight of this powder was pressed and disc was made (28). The last two articles can prove the role of chitosan in improving metformin delivery.

4. Miscellaneous methods

Other strategies to improve metformin dissolution rate are using surfactants and change in pH . It has been shown that the dissolution rate of metformin in buffers is better than in pure water, but using surfactants can enhance drug solubility in both water and buffers; for example the dissolution of metformin in acetate buffer is about 60% after 30 min but when SLS was added to the environment, this amount was increased up to 89%. This change is also seen for the dissolution of the drug in hydrochloric acid. It was examined and proved that the best dissolution rate for metformin can be observed in the pH range of 6.5-8. It should be noted that better solubility doesn't mean better drug absorption, and the absorption wasn't checked in that article (29). Another research in the United States of America, also proved the effect of buffers and pH on metformin dissolution. This research showed that the best pH for drug dissolution was between 6.8-7.5. The effect of NaCl on metformin dissolution was studied in this research too. A concentration of 250 mM of NaCl could make the drug 's solution better, and higher or lower than this concentration had adversed effects on metformin dissolution (30). It should be mentioned that both of these manuscripts had studied in *in vitro* environment. Only the dissolution rate and the effect of adding surfactants or changing the pH of the environment had been reported in those researches. Nothing about bioavailability, toxicity or any other factor regarding *in vivo* studieswas reported. Totally, it can be concluded that because the dissolution of the drug was changing drastically in both conditions, so the bioavailability should be changed, as well.

5. Conclusion

Metformin is a hydrophilic drug that has been used to treat hyperglycemia for many years. This drug can be used as a complementary medicine in some other diseases like cancers, ovarian diseaseases and etc. The hydrophilicity of this drug causes good disolution in water-based environments, but it causes low absorption and lower bioavailability in patients using it. The hydrophilicity of metformin occurs due to nitrogen and double bonds in its structure. Enhancing the absorption and bioavailability of metformin are the first targets of many of researches but it should be noted that the changes should be such that they do not interfere with the delivery of the drug. Many researches show that using carriers and different drug delivery systems can enhance bioavailability and absorption of metformin. For example prodrugs cause metformin more stability and better absorption, while carriers such as polymers can cause sustain releasing of the drug and decreasing the number of doses taken, each day, which can increase patient cooporation. It should be mentioned that some of metformin delivery processes which were discussed in this article could not determine whether that method was effective in absorption of the drug. Those processes could be excellent suggestions for *in vivo* experiments to discover their effect on drug uptake and metformin bioavailability.

Conflict of Interest

The authors have no conflict of interest.

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