Table 1. Metformin solubolity, permeability, bioavailability and, effection enhancing methods.				
Type of enhancing method	Enhacer / Carrier / etc.	*invitro*/ *in vivo*	Results	Ref
Prodrug	Cyclohexyl & Phenyl	*In vitro* and *in vivo*	- The prodrugs were made by attaching cyclohexyl and phenyl to metformin molecules. - *In vitro* solution was made with human and rat plasma; in this solution, the phenyl-metformin had a more acceptable behavior. - Both of prodrugs are stable in buffer PH and vulnerable in acidic one. - Phenyl-Met is more destroyable in acidic PH than cyclohexyl-Met. - In in vivo tests on rats, the phenyl-based prodrugs caused rats' death because of thiophenol released as a by-product. - Cyclohexyl-metformin prodrugs in comparison with pure metformin behave better because of patients' need for a lower dose, longer time concentration stability, and more bioavailability.	(18)
Prodrug	Chain sulfonamides and sodium docusate	*in vitro*	- Adding chain sulfonamides to metformin causes increasing in its lipophilicity and permeability. - Sulfonamide chains with more than seven carbons can be selected as good and effective chains for metformin prodrugs. - Sodium docusate helps more and more prodrugs for their solubility and permeability and followed by them causes increasing in metformin bioavailability.	(19)

Prodrug	Phospholipids	*in vitro*	- Using phospholipids causes increasing in lipophilicity and permeability of the drug. - Antiproliferative effect of these prodrugs is more than pure metformin and in lower concentration can inhibit the tumoral (MiaPaCa-2 cells) cells (lower IC50 concentration.). - Hypoxia in the cancer cells which are received metformin prodrug were occurs 20% lower than pure metformin receivers. - Metformin intr acellular concentration is about twice more in prodrug receivers (150 vs. 75 µg/ml).	(20)
Carriers	Microemulsions	*in vivo*	- Microemulsions were create by using glycerol monooleate as oil and Tween 80 and cremopher as surfactants and ethanol as co surfactant. - The best concentrations of surfactants in system is about 35% because each percent more than this can cause decreasing in metformin bioavailability. - Loading metformin in these water-in-oil microemulsions causes increasing in both bioavailability and permeability in oral usage of drug. - Improving in drug behavior is visible in all of gastro intestinal parts. - In vivo tests were done on male rats which are fast when they received the medicine.	(25)
Carriers	Tamarind seed polysaccharide(TSP) polymers	*in vitro* & *in vivo*	- DEE% (drug encapsulation) was about 69-95% for these polymers. - Loading metformin in TSPs causes stable and long-term releasing in in vitro tests. - The most stable release and concentration for in vitro releasing tests was obtained in 700mg pectin + 175 mg TSP (as carrier) formulation. - At in vivo tests it was showed that polymer + metformin can keep blood glucose low and therapeutic for much longer time than pure metformin but it is important that pure drug starts its effect and decreasing blood glucose so fast and so rapid.	(26)

Carriers	Microspheres	*in vitro* & *in vivo*	- Microspheres which were used in this article were made with chitosan and eudragit (RS100 & RL100) as materials and with double emulsion-solvent evaporation method. - Changing the amount of each raw material can affect the size and speed of drug release in such a way that more Chitosan refers to smaller particles and rapid drug releasing while the other does exactly the opposite. - In double forms of eudragit the RS is better for sustain releasing. - At in vivo tests the drug concentration in blood increases slower than pure drug but stays in therapeutic range more and more than pure substance.	(27)
Carriers	Chitosan discs	*in vitro*	- For making chitosan discs first the 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 - TR146 cell line was selected for its suitability for simulation of buccal drug delivery. - Chitosan as a carrier for metformin can increase the buccal delivery of this drug. - This delivery system is suitable for non-insulin dependent diabetic and ovarian patients.	(28)
Miscellaneous methods	SLS & NaCl	*In vitro*	- Adding SLS help to metformin dissolution in environment (water or buffer environment). - Metformin solubility in buffer PH can be enhance by adding surfactants in solution. - The best PH for drug solubility in this method is 6.5-8; solubility ≠ absorption. - The better dissolution in environment does not necessarily mean optimal absorption from the environment. - Adding 250 mM of NaCl to metformin solution causes enhancing the drug dissolution. - Lower or upper than 250mM of salt can cause unwanted and inappropriate response for drug dissolution.	(29, 30)