

# DIFFERENT ACTION OF METFORMIN WITH DIFFERENT ROUTES OF DELIVERY

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**Abstract:** This review defines novel and conventional developments in delivery of metformin via various routes of administration & dosage forms of metformin are available in single dosage or in combination. Many proposed evidence explained that metformin not plays a role in treatment of diabetes by decreasing blood sugar level yet also in the prevention of some other diseases like cardiovascular diseases, neurodisorders, and antiaging, anti-inflammatory and in treatment for polycystic ovary syndrome (PCOS). This review encapsulate the different routes of administration of metformin with different dosage form (formulations) & also discussed the novel approaches which are recently developed for improvement of bioavailability of these antihyperglycemic agent.

**Keywords:** metformin, various types of formulations, Polymer, antiaging effect, antitumour effect, neuro protective effect, cardioprotective effect, PCOS.

## HISTORY OF METFORMIN

In first line treatment of hyperglycemia the metformin (biguanide) preferred as first line drug as oral blood glucose decreasing agent known as antihyperglycemic drug belonging to the category of biguanide. The history of metformin is related to Galega officinalis (also called as goat's rue), the metformin is famous in Europe as a herbal traditional drug mainly prescribing for diabetic patients. In the 1940s re again search of metformin was occurred for treatment of malaria. Many clinical trial certified that metformin is used in the treatment of influenza and sometimes lowers blood glucose level. Many investigations regards other prospective signs have emerged, that is the antiaging, antiviral, cardio protective, neuroprotective effect and also in polycystic ovary syndrome (PCOS). Yi-Wei Wang, #1,\* Si-Jia He, #1,\*

## INTRODUCTION

In 1995 United States and in 1958 United Kingdom give approval to metformin for using in the treatment of type 2 diabetes mellitus with dosing range from 500 to 2,500 mg/day. According to the American Diabetes Association/European Association metformin is the first-line treatment for patients with type 2 diabetes mellitus. The reduction of glucose level from blood occurs via a different different mechanisms- reducing intestinal glucose absorption, promote peripheral glucose uptake, decreasing amount of insulin in plasma and also by promoting sensitivity of insulin, Yi-Wei Wang, #1,\* Si-Jia He, #1,\* In the various countries the metformin and other related drugs like phenformin was banned because of their adverse effect (lactic acidosis)

## PHARMACOKINETIC PROFILE OF METFORMIN

In biological fluid metformin can be defined in various mechanism, by utilizing high performance liquid chromatography, which permits pharmacokinetic examining in diabetic patients and in healthy volunteers. The use of different formulations slightly effect the disposition of Metformin & diabetes also effect disposition of this glucose lowering drug. The absolute oral bioavailability of metformin is 40 to 60%, and absorption occurs in gastrointestinal tract apparently complete within 6 hours of administration. The binding of metformin with plasma protein is negligible.

No conjugates of metformin have been noticed. Metformin is excreted by renal excretion and has a mean plasma excretion half-life after taking via oral route between 4.0 and 8.7 hours. The elimination of drug is increases in patients who suffers from renal impairment & other problems which relates with creatinine clearance. The metformin having a side effect which is known as Lactic acidosis, although in comparison to phenformin and buformin the rarer side effects of metformine because of changes in pharmacokinetic profile linking with biguanides and chemical structure. AndreJ. Scheen

## MECHANISM OF ACTION

The mechanism of action of metformin follows both activated protein kinase (AMP) and (AMPK) dependent and (AMPK) independent mechanism by decreasing mitochondrial respiration yet also perhaps by blocking of mitochondrial glycerophosphate dehydrogenase, and block a mechanism participating the lysosome. In the earlier 10 years, we have proceed from a normal picture, that this biguanide prevent glycaemia by effecting on the liver via AMPK animating, to a more typical images reflecting metformin's multiple mechanism of action. For understanding how metformin works on the target population of diabetes higher work is needed. Graham Rena, I D. Grahame Hardie,

## Summary of different formulations of metformin with different clinical uses :

Sr.No.	Type of delivery	Methodology	Name of Drug	Uses	Name of polymers	References
01.	Cargo-loaded mesoporous silica nanoparticles (MSNs)	Encapsulation	Citraconic anhydride (CAH)-metformin (MT)	Anticancer	Poly acrylic acid	Murugan C <sup>1</sup> , Venkatesan S <sup>1</sup> , Kannan S <sup>1</sup> .et all 2017 Nov 30
02.	Borneol W/O/W composite submicron emulsion	Encapsulation shear stirring method.	Metformin	In brain targeting	Tween 80	Zhang C <sup>4</sup> , Chen W <sup>1</sup> , Peng et all 2019
03.	Chitosan cross-linked alginate microparticles	Spray drying method	Metformin hydrochloride	Hypoglycemic activity	Chitosan , sodium alginate	Marta Szekalska 1, Katarzyna Sosnowska20 17 Jan
04.	liposomes	Coencapsulation	Epirubicin and metformin	Murine sarcoma	Hydrogenated soy phosphatidylcholine	Yang Q, Zhang T, et all 2014 Nov
05.	Niosomes	By the reverse phase evaporation technique	Metformin hydrochloride	Antidiabetic	Span 40	Hasan AA <sup>1</sup> , Madkor H, Wageh S et all2013 Apr
06.	Liposomes	Glycerolphosphate-chitosan microcomplexation	Metformin	Antidiabetic	Chitosan	Manconi M <sup>1</sup> , Nacher A et all 2013 Jun
07.	Liposome	Encapsulation	Metformin	Antidiabetic		Detaille D <sup>1</sup> , Guigas B et all 2002 Apr
08	Hydrogel-forming microneedles;	Crosslinking by esterification	Metformin HCl;	Enhancing transdermal delivery	poly (ethylene glycol)	Eman M Migdadi 1, Aron J Courtenay201 8 Sep
09.	Hydroxy Propyl Methyl Cellulose-Poly Vinyl Alcoholblend patches	Three cycle freeze-thaw technique.	Metormin HCl	Antidiabetic	Hydroxy Propyl Methyl Cellulose-Poly Vinyl Alcohol (HPMC-PVA)	Sharif Mohammad Shaheen2015 Sep
10.	Mucoadhesive beads	Ionic gelation	(TSP)-blended gellan gum (GG) mucoadhesive beads containing metformin HCl	Antidiabetic	Deacetylated gellan gum	Nayak AK <sup>1</sup> , Pal D <sup>2</sup> , Santra K et all 2014 Mar
11.	Floating Alginate Beads	By Incorporation	Metformin	aging effect, hypoglycemic activity	Hydroxypropyl methylcellulose (HPMC)	Ashutosh Nayak, Sunil K. Jain,*October 21, 2011
12.	Matrix pellets of hydroxy propyl methyl cellulose K200M and	Pelletization technique using an extruder-spheronizer.	Metformin hydrochloride	Antidiabetic	Hydroxy propyl methyl cellulose K200M and	.Ige PP <sup>1</sup> , Gattani SG

	microcrystalline cellulose				microcrystalline cellulose	2012 Mar
13.	Mucoadhesive polymer-coated pellets	Powder-layering technique using a centrifugal fluidizing (CF)-granulator.	Metformin hydrochloride	Antidiabetic	Hydroxymethylcellulose (HPMC), Carbopol, and 4) sodium carboxymethylcellulose (Na-CMC).	Piao J <sup>1</sup> , Lee JE et al 2009 Mar
14.	Bilayer tablets;	Solvent evaporation and cogrinding techniques.	Metformin hydrochloride	Antidiabetic	Eudragit RS 100 and RL 100 polyvinylpyrrolidone K30 (PVP K30) and polyethylene glycol 6000 (PEG 6000)	Tiwari R <sup>1</sup> , Gupta A, et al 2014 Mar-
15.	spray dried Bora rice microspheres.	Spray drying method.	Metformin hydrochloride	Antidiabetic	Sodium alginate	Sharma HK <sup>1</sup> , Mohapatra J et al 2013 Jan;
16..	Sodium alginate microspheres of metformin HCl:	Emulsion-cross linking method	Metformin hydrochloride and in combination with gellan	Antidiabetic	HPMC hydroxymethylcellulose	Balasubramanian J <sup>1</sup> , Rao VU2007 Jul
17.	Tamarind alginate beads.	Ionotropic-gelation technique	Metformin HCl	Antidiabetic	Sodium alginate	Nayak AK <sup>1</sup> , Pal D <sup>2</sup> , Santra K 2016 Jan
18.	Hydrogel beads	Blending in ferric chloride solution.	Metformin hydrochloride (MH)	Antidiabetic	Sodium carboxymethyl cellulose (NaCMC);	Swamy BY <sup>1</sup> , Yun YS et al 2015 Mar
19.	Jackfruit seed starch-alginate mucoadhesive beads of metformin HCl.	Ionotropic gelation using 3(2) factorial design	Metformin HCl	Antidiabetic	Sodium alginate	Nayak AK <sup>1</sup> , Pal D. et al 2013 Aug;
20.	Metformin-loaded alginate nanoparticles	Water-in-oil-in-water metformin nanoemulsion	Metformin	Antidiabetic	Sodium alginate	Kumar S <sup>1</sup> , Bhanjana G et al 2017 Feb
21.	metformin hydrochloride pellets.	Centrifugal granulation	Metformin hydrochloride (MH)	Antidiabetic	Microcrystalline cellulose	Hu LD <sup>1</sup> , Liu Y, et al 2006 Oct
22.	Bioadhesive metformin microparticles	Spray drying aqueous dispersions with different chitosan	Metformin hydrochloride and chitosan	Antidiabetic	Chitosan-	Sander C <sup>1</sup> , Madsen KD et al 2013 Nov;

23.	Water-in-oil microemulsions	Phase separation.	Metformin hydrochloride	Antidiabetic& increasing oral bioavailability	Span 80	Li Y <sup>1</sup> , Song J <sup>1</sup> , Tian N et al 2014 Oct
24.	Floating tablets of metformin based on psyllium	Conjugation	Metformin hydrochloride	Antidiabetic	HPMC K15M and carbopol 940	Rathnanand M <sup>1</sup> , Narkhede R et al 2013 Jun
25.	gastro-retentive matrix tablets	Wet granulation method	Metformin hydrochloride	Antidiabetic	Natural polymer, cellulose microcrystalline	Razavi M <sup>1</sup> , Karimian H et al 2015 Jun
26.	Emulsion	Co-encapsulation double emulsion method	Doxorubicin and Metformin	Antidiabetic	Poly(lactide-co-glycolide)-d- $\alpha$ -tocopheryl Polyethylene Glycol 1000	Samadi N <sup>2,3</sup> , Salehi R et al 2018 Apr
27.	liposomes	Thin-film hydration through various loading methods; passive loading, active loading, and drug-loaded lipid film. The drug-loaded film method exhibited encapsulation	Metformin hydrochloride	Breast cancer		Shukla SK <sup>1</sup> , Kulkarni NS et al 2019 Oct
28..	Metformin hydrochloride-loaded alginate-gelatin nanoparticles	Nano spray drying	Metformin hydrochloride	Antidiabetic (sustained release)	Sodium alginate	Shehata TM <sup>1,2</sup> , Ibrahim MM et al 2019 Oct
29.	Sterosome	coencapsulation	Metformin	Anticancer(lung cancer)	Poly ethylene glycol	Osama H <sup>1</sup> , et.all 2014 Nov
30.	PEGylated Liposomes	Coencapsulation of epirubicin (EPI) and metformin (MET)	(EPI)Epirubicin and metformin (MET)	Anticancer	Poly Ethylene Glycol	Yang Q, et.all 2017 Jul 5
31.	Envelope-type Nanoparticle	Conjugation & centrifugation	Metformin	Anticancer	Poly ethylene Glycol(2000)	Zhao Y <sup>1,2</sup> , Shik. Et all
32.	Polymeric nanoparticles	Nano encapsulation of MET into polymeric PLGA-PEG	Metformin;	Anticancer	Poly Lactic Glycolic Acid Poly Ethylene Glycol (PLGA-PEG)	FaramarziL 1975 Oct
33.	Metformin loaded O-carboxymethyl chitosan	Ionic-gelation method.	Metformin	Anticancer	O-Carboxy Methyl Cellulose	Snima KS <sup>1</sup> , et.all Apr 28, 2012
34.	Chitosan nanoparticles	Ionic gelation	Metformin	Pancreatic Cancer	Chitosan	Arafa K <sup>1</sup> , et.all 19, 2018
35.	Nanoparticle	Conjugation	Metformin	Anticancer	Polyethylenimine	Zhao Y <sup>1,2</sup> , et.all 2016 june

## CONCLUSION

In type 2 diabetes patients this antihyperglycemic drug (Metformin) is commonly prescribed drug for their treatment but this drug is also helpful in treatment of Cardiovascular diseases, cancer, PCOS, aging, neuroprotection, via different routes of administration with different delivery system like-dendrimer delivery, liposomal delivery nanocarrier pills, microneedles, hydrogels, mucoadhesive beads, microemulsion, pellets, hybrid Micelles, nanocubosomes, tablets etc. which are given below in formulation table,

Metformin having good safety profile with low cost & different formulations are available.

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