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An Overview on Solid Dispersion Techniques Implemented For Dissolution Enhancement of Glimepiride

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ABSTRACT

Drugs belonging to BCS class II, low solubility and high permeability; undergo dissolution-rate limited gastrointestinal absorption. Glimepiride is one of the famous drugs belonging to BCS class II. Its poor aqueous solubility usually causes poor dissolution and unpredicted bioavailability. Hence, formulation techniques that accelerate drug dissolution can guarantee a parallel improvement in bioavailability. Now a days different techniques are available to enhance the solubility of drug like co-solvent, solid dispersion, chemical modification of drug, liquisolid technique etc. One of the favorable strategy to improve the solubility and hence bioavailability of poorly water soluble drugs is theformulation of solid dispersion. The solid dispersion may be prepared by solvent evaporation method, melting method, melt solvent method, kneading method, co-grinding method, co-precipitation method, modified solvent evaporation method, spray drying, gel entrapment techniqueand co-precipitation with supercritical fluid. This review article comprises of the research materialized in the field of solubility and dissolution enhancement of glimepiride.

Keywords: Biopharmaceutical classification system, Diabetes, Glimepiride, Solubility, Solid dispersion.

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INTRODUCTION

The use of oral antidiabetic drugs for the treatment of Type 2 diabetes is increasing rapidly. Glimepiride is an antidiabetic drug belongs to second generation sulphonylurea drug. It lowers the blood glucose level in patients with Type 2 diabetes (non-insulin dependent diabetes mellitus) by stimulating the release of insulin from the pancreatic β-cells. In this way it exerts a long-term effect of reducing the blood glucose levels. In addition, extra pancreatic effects may also play a role in the activity of glimepiride. It has low risk of hypoglycemia because of preservation of physiological suppression of insulin secretion in response to low blood glucose levels[1]. It is completely (100%) absorbed following oral administration. It has rapid onset of action, 24 hr duration of effect with a half life of 5 hr and once a day dosing. A single daily dose of 1 mg has been shown to be effective, and the recommended maximal daily dose is 8 mg. It is completely metabolized by the liver to inactive products. The glimepiride belongs to Biopharmaceutical Classification System (BCS) class II having low solubility and high permeability. The drug shows low pH dependent solubility. It is practically insoluble in water, slightly soluble in methylene chloride (Dichloromethane) and very slightly soluble in methanol. It is soluble in DMSO (>10 mg/ml) and in ethanol (<1 mg/ml). In acidic and neutral aqueous media, glimepiride exhibits very poor solubility at 37^{o}C (<0.004 mg/ml). In media pH>7, solubility of drug is slightly increased to 0.02 mg/ml. The melting point of glimepiride is 207°C[2].

SOLUBILITY AND DISSOLUTION RATE ENHANCEMENT OF GLIMEPIRIDE

It is well known that drug efficacy can be severely limited by poor aqueous solubility that leads to low dissolution rate and thus results in low absorption in the gastrointestinal tract after oral administration. The ability to increase aqueous solubility is thus a valuable aid to increase the efficacy for certain drugs.

Vidyadhara S. et al, **2012** prepared solid dispersions of glimepiride with sodium starch glycolate (SSG) in different ratios by physical mixing, solvent evaporation and kneading method to enhance the solubility and dissolution of the drug. Among the three methods employed solvent evaporation and kneading methods were found to be suitable for improving the dissolution rate of glimepiride. Some of the dispersions prepared by the solvent evaporation method and kneading method were formulated into tablets with diluents such as lactose, Dicalcium phosphate (DCP) andMicro Crystalline Cellulose (MCC). All the tablet preparations containing diluents were found to release the drug in the order of DCP >MCC >Lactose. The dissolution rate of such tablet formulations were found to release the drug at a faster rate than that of tablets prepared with drug alone[3].

Kiran T et al, **2009** described solubility enhancement of glimepiride by using different polymers by solvent evaporation method using drug to carrier ratio at 1:9 and 1:19 and tablets were formulated by wet granulation method. The polymers used were Crospovidone, Croscarmellose, Sodium starch glycolate, Pre gelatin starch, Avicel PH101 and Potato starch. The improvement in dissolution was marginal for Avicel PH 101 and potato starch. At 1:19 ratio, carriers like pregelatinized starch, sodium starch glycolate and croscarmellose increased the dissolution efficiency of glimepiride by factor of 1.5-2.5, while the dissolution efficiency was increased by a factor of 3.5 when crospovidone was used as carrier. Crospovidone has shown highest dissolution profile at all ratios when compared to other carriers[4].

Chaudhari DM et al,**2012** formulated solid dispersion of glimepiride with water soluble polymer PVP K30 by the solvent evaporation method, and then formulated solid dispersion (SDs) tablets of the best formulation of SDs. Five different drug: carrier ratios (1:1, 1:2, 1:3, 1:4, and 1:5) were used. This activated system prepared with PVP K30 as carrier was able to remarkably increase the dissolution profile and solubility of the poorly soluble glimepiride as compared to other solid dispersion techniques[5].

Veerendra SR et al, **2011** prepared solid dispersion of glimepiride by modified solvent method using the carriers Poly Ethylene Glycol (PEG) 6000 and Poly Vinyl Pyrrolidine (PVP) K25. Three factors i.e. amount of drug and carriers (PEG 6000 and PVP K25) were studied at two levels (+1 and –1) and eight batches of solid dispersion were formulated using factorial design. All the batches were subjected to Differential Scanning Calorimetry (DSC), FTIR and *in vitro* release studies. The batch having concentration of drug 1mg, PEG 6000 10mg and PVP K25 as 2.5 mg showed maximum *in vitro* dissolution after 30 min[6].

Wagh TV et al, **2012** prepared solid dispersions by the kneading technique using polymers poloxamer 188 and poloxamer 407 in drug: polymer ratio 1:1, 1:2, 1:3, 1:4, 1:5, and 1:6.poloxamer ration 1:1, 1:2, 1:3, 1:4, 1:5, and 1:6**.** Solid dispersions of poloxamer 188 with glimepiride showed an enhancement in dissolution profile as compared to physical mixtures as well as solid dispersion with poloxamer 407 and whole in-vitro studies proved that glimepiride : poloxamer 188 in 1:5 ratio showed best results among all formulations and tablets prepared by that ratio also showed better dissolution[7].

Al-Saidan MS et al,2014 prepared solid dispersions by the solvent evaporation method using different proportions of water soluble inert carriers such as PEG-4000, Hydroxyl propyl cellulose (HPC) or lactose in the ratio of 1:9. Physical mixtures of glimepiride and PEG-4000, HPC or lactose were also prepared in the same ratio of 1:9. *In vitro* drug release of the solid dispersions

was studied in USP XXIII dissolutionapparatus (apparatus 2, 50 rpm) using 900 ml of phosphate buffer pH 7.4 at 37±0.5°C. The dissolution rate of glimepiride was increased by 3 to 4 fold withPEG 4000 or lactose[8].

Nagpal M et al, **2012** showed that solid dispersions prepared byusing modified gum karaya as carrier by solvent evaporation method have enhanced solubility than pure drug. Solid dispersions were prepared in four batches [SD1 (1:1), SD4 (1:4), SD9 (1:9), and SD14 (1:14)] and the four batches of physical mixture (PM1, PM4, PM9, and PM14) were prepared. Both type of batches were characterized by DSC, FTIR spectroscopy, powder X-Ray diffraction (X-RD) and scanning electron microscopy (SEM) studies and the maximum enhanced solubility was observed in SD4.[9]

Gill B et al, **2010** prepared solid dispersion by melt fusion method using poloxamer 188 as polymer to increase the solubility of glimepiride and then formulating SDs tablets of the best formulation of SDs. Tabletformulations were prepared by direct compression technique using super disintegrantcroscarmellose sodium in different concentrations. The best dissolution profile and dissolution efficiency was shown by SD containing drug: polymer ratio 1:4 and tablet formulation containing 5% croscarmellose sodium[10].

Sreenivasa RK et al, **2012** prepared and characterized inclusion complexes of glimepiride with β-CD and Hydroxypropyl-β-cyclodextrin (HP-β-CD) in different molar ratios (1:1M and 1:2M) to enhance its solubility and dissolution through complexation. These inclusion complexes were prepared by three different methods viz. physical mixing, kneading and co-precipitation method and characterized by using FT-IR, and DSC. The greatest enhancement in solubility and fastest dissolution was observed in inclusion complex prepared with HP-β-CD by kneading method i.e. 97.41% release in 60 min[11].

Prabhakar S et al, **2012** formulated and characterized inclusion complexes of glimepiride with cyclodextrin and HP-β-CD in 1:1 ratio. The inclusion complexes were prepared by three different methods viz. physical, kneading and co-precipitation method and their fast dissolving tablets were formulated by direct compression technique using super disintegrants like croscarmellose sodium, crospovidone and sodium starch glycolate. The inclusion complex tablets prepared with HP-β-CD by kneading method showed higher dissolution rate than marketed glimepiride tablet[12].

Kenichiro K et al, **2011** formulated solid preparation which contains an insulin sensitizer and glimepiride, an insulin secretogogue and dissolution is enhanced by using surfactants like sodium lauryl sulpahte (SLS), polysorbate 80, polyethylene polyoxy propylene glycol and polyoxyethylene hydrogenated castor oil by using solvent evaporation method. The solid preparation comprises a part containing coated particles in which the particles containing an

insulin sensitizer are coated with lactose or a sugar alcohol and a part containing an active ingredient other than an insulin sensitizer[13].

Milha J et al, **2013** prepared solid dispersion of glimepiride by using surface active agent having different drug surfactant ration. The ration of drug surfactant were from 20:1 - 1:10, preferably from 1:10 – 5:1, more preferably from 1:8 – 2:1, even more preferably from 1:4 – 1:1and the most preferably was 2:1 - 1:1. The method used for preparation of solid dispersion was solvent evaporation. The surfactant was obtained by reacting castor oil or hydrogenated castor oil with ethylene oxide, preferably hydrogenated castor oil[14].

Makar RR et al, **2013** presented a comparative study between carriers and techniques for the preparation of solid mixtures with glimepiride. Different methods such as physical mixtures (PM), co-ground mixtures (CGM), solid dispersions and other techniques based on solid dispersion were used to enhance solubility of glimepiride. The polymers used in these methods were sodium lauryl sulphate, sodium carboxymethyl cellulose (Na CMC), pregelatinized starch (PreGelSt), Crosscarmellose sodium (Ac-Di-Sol), crospovidone and gelucire 44/14 and 50/13.These mixtures were tested for drug content and dissolution and characterized by DSC, FTIR and XRPD. The dissolution data was collected by using dissolution apparatus for physical and co-ground mixtures, solid dispersions and their adsorbates, triple solid dispersions and their adsorbates, microwave generated or treated solid dispersions and the results revealed that enhancing effect mostly reached maximum with ternary solid dispersion adsorbats which were formed by the melting method using Gelucire 50/13 as surfactant, at drug to carrier to surfactant ratio 1:5:15[15].

Mehta Abhinav et al, 2009 investigated the dissolution and bioavailability behavior of glimepiride by forming solid dispersion with solvent evaporation method. The polymers used in this research were PEG 6000 and lactose(Sigma). The physicochemical interaction between the drug and carrier and its effect on dissolution behavior was identified by FTIR Spectroscopy, DSC and XRD. The solid dispersion tablets were formulated and characterized for their various physicochemical properties such as weight variation, % friability, disintegration and *in vitro* dissolution profiles and compared with commercial product. There was significant improvement in the dissolution of glimepiride in solid dispersion products (>85% in 5 minutes) [16].

Different methods and polymers that are used in the formulation of solid dispersion of glimepiride are given in **table1**.

Table 1: Different techniques employed for solid dispersion of Glimepiride

S. No.	Author, Year	Method of preparation	Polymer	Ref

1	Vidyadhara S. et al, 2011	Physical mixing, Solvent evaporation and Kneading method	Sodium starch Glycolate	3
2	Kiran T. et al, 2009	Solvent evaporation method	Crospovidone, Croscarmellose, Sodium starch 69 lycolate, Pre-gelatin starch, Avicel PH101 and Potato starch	4
3	Chaudhari D. Mayur et al, 2012	Solvent evaporation method	PVP K30	5
4	Rajpurohita S. et al, 2011	Modified solvent method	PEG 6000 and PVP K25	6
5	Wagh T.V. et al, 2012	Kneading technique	Poloxamer 188	7
6	Al-Saidan M.S. et al, 2014	Solvent evaporation method	PEG 4000, HPC or lactose	8
7	Nagpal M. et al, 2012	Solvent evaporation method	Gum karaya	9
8	GillBhawandeep et al, 2010	Fusion method	Poloxamer 188	10
9	SreenivasaRao K. et al, 2012	Physical mixing, Solvent evaporation and Kneading method	β-CD and HP-β-CD	11
10	ShirsePrabhakar, et al, 2012	Physical, Kneading and Co-precipitation method	β-CD and HP-β-CD	12
11	KenichiroKiyoshima et al, 2011	Solvent evaporation method	SLS, Polysorbate 80, Polyethylene polyoxy propylene glycol and Polyoxyethylene hydrogenated castor oil	13
12	MilhaJaklic et al, 2013	Solvent evaporation method	Polyoxyethylene hydrogenated castor oil	14
13	Makar R. Rana et al, 2013	Modified solvent evaporation method and Melting method	Sodium lauryl sulpahte (SLS), Na CMC, Pregelatinized Starch, Crosscarmellose sodium, Crospovidone XL and Gelucire 44/14 and 50/13	15
14	Mehta Abhinav et al, 2009	Solvent evaporation method	PEG 6000, Lactose	16

CONCLUSION

For poorly water soluble drugs dissolution is a rate-limiting step in absorption. By improving solubility of a drug its dissolution rate can be enhanced. There is a great requirement to develop such a formulation which release drug to the required extent so that it can produce rapid and desired effect. As glimepiride is a BCS class II drug it has low solubility but high permeability. Various methods were employed to enhance the solubility of the glimepiride. Solid dispersion is a technique which enhances the solubility by using different polymers. Several polymers and combination may also be used to improve the solubility and dissolution rate enhancement of the glimepiride.

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