Review Article

Formulation Strategies for Enhancement of Solubility and Dissolution Rate and limitation for oral bioavailability of Repaglinide: A Review

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ABSTRACT

Diabetes mellitus is a disorder of glucose metabolism that results from an absolute or relative lack of insulin and it shows complication in the body. Thus, Diabetes has considered being a dangerous incurable disease in the world. The International Diabetes Federation is recently reported in 2015, that India was a country with the largest numbers of people with diabetes cases of 69.1 million. Therefore pharmaceutical industries take this challenge to resolve this issue by the discovery of new molecules with new approaches for the effective treatment of diabetes-like Glipizide, Repaglinide (RPGD), Pioglitazone, Glibenclamide etc. RPGD (2-ethoxy-4-[[3-methyl-1-[2-(1-piperidyl) phenyl] -butyl] carbamoylmethyl] benzoic acid) is a potent second generation oral hypoglycemic agent broadly used to treat type 2 diabetes mellitus, which acts on the beta cell to induced insulin secretion and reduce blood glucose concentration. As this drug belongs to BCS class-II its dissolution rate is low in the gastrointestinal fluids and its high permeability. Hence, there is need to improve solubility and dissolution rate of poorly water-soluble drugs leads to enhanced oral bioavailability. The dissolution rate of the orally administered poorly water-soluble drug is a long lasting problem of pharmaceutical industries. As the low dissolution rate of RPGD leads to poor bioavailability, this acts as a barrier for the development of therapeutic applications of poorly water soluble drug. This review fulfills the requirement of those researchers who work on solubility, dissolution enhancement for RPGD and poorly water soluble drugs i.e. BCS class-II drugs.

Key words: Repaglinide, Pharmacokinetic, Solubility, Dissolution, Bioavailability, Limitations, and Approaches.

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INTRODUCTION

Diabetes mellitus, commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period.[1] Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications. like diabetic ketoacidosis, nonketotic hyperosmolar coma, or death. Serious long-term complications include heart disease, stroke, chronic kidney failure, foot ulcers, and damage to the eyes.[2] Thus, Diabetes has considered being a dangerous incurable disease in the world.[3] On world Diabetes day 14 Nov. 2015, International diabetes federation provides the latest figures, information and projections on the current and future magnitude of the diabetes epidemic. In 2015 diabetes caused 5 million deaths; every six seconds a person dies from diabetes, more than 542,000 children live with type I & II diabetes and more than 20.9 million live births were affected by diabetes during pregnancy. Approximately 415 million adults have diabetes; by 2040 this will rise to 642 million. The proportion of people with type 2 diabetes is increasing in most countries.[4] The several drugs were discovered in past and currently used in the treatment of both types of diabetes disease conditions[5] viz. Glimepiride, Glimepiride-Pioglitazone, Glimepiride-Rosiglitazone,

Gliclazide, Glipizide-Metformin, Glyburide, Glyburide-Metformin, Repaglinide (RPGD), Nateglinide, Acarbose and Sulfonylureas plus Metformin. But these drugs have its own limitation like poorly solubility and dissolution rate leads to poor bioavailability of these formulations.[6] Therefore, literature revealed that several conventional and novel approaches were applied to enhanced solubility and dissolution rate of poorly soluble drugs.[7]

RPGD is a non –Sulphonylurea oral hypoglycemic agent used in the management of type -2 diabetes mellitus [8], Chemically it is (2-ethoxy-4-[[3-methyl-1-[2-(1-piperidyl) phenyl] -butyl] carbamoylmethyl] benzoic acid) is a potent second generation oral hypoglycemic agent broadly used to treat type 2 diabetes mellitus.[9] It belongs to BCS class-II drug owing to low solubility leads to only (60%) bioavailability upon oral administration[10]. It is reported that poor solubility in gastrointestinal fluids gives rise variations in its dissolution rate owing to incomplete bioavailability.[11] RPGD structure belongs to meglitinide class,[12] specifically developed to control the meal-related glucose fluctuations in patients, which acts on the beta cell to induced insulin secretion and reduce blood glucose concentration.[13]

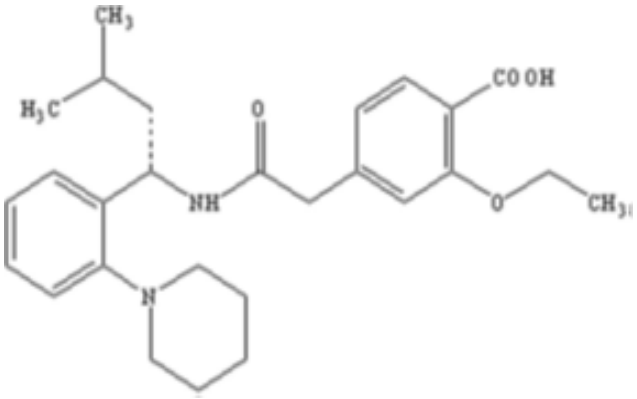

Figure 1:Chemical structure of RPGD.14 (Reproduced from : Zhu, Z.; Yang, T.; Zhao, Y.; Gao, N.; Leng, D.; Ding, P., A simple method to improve the dissolution of repaglinide and exploration of its mechanism. asian journal of pharmaceutical sciences 2014, 9 (4), 218-225.)

Physicochemical properties

RPGD registered on chemical abstracts service with registry no. [135062-02-1]. It is a solid, white, odorless, crystalline state of powder with molecular formula $C_{27}H_{36}N_4O_4$ having molecular weight 452.60 gm/mol and represent a melting point between 126 and 128 °C. It exists in two structural isomers: R and S. R-isomer is biologically more active than the S-isomer. it is poorly soluble in water, soluble in DMSO at ~34 mg/ml and in methanol.[15]

Pharmacokinetic characteristics

In pharmacokinetic characteristics includes absorption, distribution, metabolism, clearance, elimination and subsequent *in-vitro* and *in-vivo* studies clarified bioavailability of a drug.

Absorption

RPGD was rapidly absorbed after oral administration and its reaches into systemic circulation, peak plasma drug levels (Cmax) after 0.5 h with mean time to maximal serum concentration (Tmax) was 0.8 h due to inadequate solubility and dissolution rate in the gastrointestinal fluid owing to poor bioavailabilityn[16] It is rapidly eliminated from the bloodstream with a half-life of approximately 1 h. The mean absolute bioavailability is 56%. When given with food, the mean Tmax was not changed, but the mean Cmax and AUC (area under the time/plasma concentration curve) were decreased 20% and 12.4%, respectively.

Distribution and Clearance

When an intravenous infusion administration of RPGD (2 mg), body clearance over 15 min was 33 L/h (543 ml/min) and a total blood clearance of 876 ml/min based on a blood**:** plasma concentration ratio of 0.6 [16]. A total liver blood flow and blood clearance fraction was reported 1500 ml/min and 58% respectively, which indicates an intermediate, but close to high, extraction ratio for RPGD. Therefore clearance primarily depends on liver blood flow and secondarily on protein binding, liver enzyme activity. The apparent volume of distribution in the elimination phase at steady state was 24.4 L and 28.9 L, respectively.[18]

Metabolism

It is clinically proven that RPGD was completely metabolized and does not responsible their metabolites for hypoglycemic effect. It inhibits monoclonal antibodies against CYP3A4 and CYP2C8, which converts into its two primary metabolites namely M4 (resulting from hydroxylation on the piperidine ring system) and M1 (an aromatic amine) in HLM. M4 and M1 were varied from approximately 160–880 pmol min-1 mg- 1 protein and from 100–1110 pmol min-1 mg-1 protein respectively. [17,18]

Elimination

The plasma elimination half-life of RPGD was found approximately one hour and rapidly eliminated within 4 - 6 hours from the blood. RPGD metabolites M4 and M1 were excreted primarily through the bile. The less than 8% and 1% of the administered dose appears in the urine and recovered in feces respectively [19].

Pharmacodynamic properties

Mechanism of action

RPGD is a short-acting oral secretagogue, which reduced blood glucose levels intensely thought-provoking the release of insulin from the pancreas. In brief, RPGD target protein different from other secretagogues on closes ATP-dependent potassium channels in the β-cell membrane owing to depolarizes the β-cell and leads to an opening of the calcium channels. This results to stimulate insulin secretion from the β-cell due to increased calcium influx.[20]

Pharmacodynamic effects

The insulinotropic response to a meal was found within 30 min after an oral administration of RPGD dose in type 2 diabetic patients. This resulted in a blood glucose reduced throughout the meal period. The elevated insulin levels did not persist beyond the time of the meal challenge.[21]

Clinical efficacy and safety

The clinical study of RPGD in type 2 diabetic patients was reported that, dosed in relation to main meals (prepandial dosing depending on doses (0.5 to 4 mg), time at 15 min and 30 min within and before the meal respectively and compared to sulfonylurea-treated patients. The clinical study was reported as a safe and dose-dependent decrease in blood glucose level.[19]

The solubility challenge

Poor solubility is a technological challenge of active pharmaceutical ingredients owing to poor bioavailability[22] A number of new, possibly, beneficial chemical entities do not reach the market just because of their poor oral bioavailability due to inadequate solubility and dissolution rate represent BCS class-II drugs.[23] The rate-limiting step in the absorption process for such drugs is dissolution rate in the gastrointestinal fluid.[24] It has been proven fact that solubility, dissolution and gastrointestinal permeability are the most important parameters which control rate and extent of drug absorption and its bioavailability.[25] Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development.[26] Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations.[27] Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility.[28] The improvement of drug solubility thereby its oral bio-availability remains one of the most challenging aspects of drug development process especially for the oral-drug delivery system.[27] There are numerous approaches available and reported in the literature to enhance the solubility of poorly water-soluble drugs viz. solid dispersions,[24,29] high surface area carriers,[30] inclusion complexes,[31] lipid-based formulations,[32] co-grinding methods[33] etc. The techniques are chosen on the basis of certain aspects such as properties of the drug under consideration, nature of excipients to be selected, and nature of intended dosage form.[34] To enhanced solubility and dissolution rate of poorly water-soluble drugs is a great challenge to the pharmaceutical industry due to technologies and approaches used has its own limitations. Therefore, its need to develop simple, cost-effective method that would not only improve the dissolution rate of a poorly water-soluble drug but also be suitable for industrial production.

Approaches for solubility and dissolution rate enhancement

Literature revealed generally three approaches were used to increased solubility and dissolution rate of poorly water-soluble drugs and it can be categorized into physical, chemical modifications and recently, a few formulation approaches have been developed to improve its dissolution and oral absorption as follows.[35]

Physical approach

Solid dispersion prepared by different techniques like microwave induced, thermal infrared, binary and tertiary mixtures, microspheres, Ultra-rapid freezing process.

Chemical approach

Inclusion complex, co-amorphous systems.

Formulations approach

Self-emulsifying drug delivery systems, liquisolid tablets,

Nanotechnology base approach

Nanocrystal, polymeric nanoparticles, nano self-emulsifying drug delivery systems, solid lipid nanoparticles.

Solid dispersion techniques

The solid dispersion is a well known technique reported for solubility and dissolution rate enhancement of poorly water soluble drugs.[36] In solid dispersion, an active agent is dispersed in an inert excipients carrier, including systems in which the drug may exist as a molecular dispersion in which there is not a discernable second phase.[37] With respect to the complete drug-excipients composite, solid dispersions can be relatively large solid masses such as pellets, tablets, films or strands; or they can exist as free flowing powders consisting of micro or

nano-sized primary particles or aggregates.[38] The bulk state of solid dispersion composition depends largely on the mode of processing.[39] To achieve the faster dissolution rate of the poorly water-soluble drug, the drug is dispersed at a molecular level in a rapidly water-soluble inert carrier to form a solid dispersion. Successful dispersion of the drug in the carrier, at a molecular level, leads to a formation of a homogenous phase of the solid dispersion.[40] When such a product comes in contact with gastric fluid then the water-soluble carrier rapidly dissolves leading to an immediate release of the drug at the desired molecular level to cause dissolution with consequent improvement of bioavailability.[41] Solid dispersion were prepared by solvent evaporation methods using different hydrophilic polymers with polyvinyl pyrrolidone[10] as a carrier viz. hydroxyl propyl methyl cellulose,[42] polyethylene glycol 6000 with mannitol and urea,[43] polyethylene glycol 6000 with poloxamer 188 and crospovidone[44], polyethylene glycol 4000, HPMC[45] and ethyl cellulose,[46] Lutrol F127, Gelucire 44/14[47] and Zawar *et al*. was prepared and compared solid dispersion by kneading, solvent evaporation, conventional fusion and microwave induced fusion methods using poloxamer 188.[24]

Co amorphous

Co-amorphous systems gained a lot of interests due to their ability to overcomes limitations associated with solid dispersions.[48] It composed of drugs and the small amount of excipients which interact with each other and formed useful inclusion complex, which improves solubility, dissolution rate and stability of poorly water soluble drug. Co-amorphous inclusion complex was prepared with saccharin and meglumine leads to enhanced solubility and dissolution rate of RPGD.[13,14,49]

Liquisolid tablets

The liquisolid technique is a novel concept, where a liquid may be transformed into a free-flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. Liquisolid systems are acceptably flowing and compressible powdered forms of liquid medications.[50,51] The liquisolid compact formula of repaglinide containing well-known carrier as microcrystalline cellulose (Avicel PH101) and calcium silicate as a coating material was prepared and also reported enhanced bioavailability and biological activity in rabbits using glucose tolerance test with commercially available tablets.[52 53]

Inclusion Complex

The prepared inclusion complex is known for their ability to molecularly encapsulate a wide variety of drugs into their hydrophobic cavity without the formation of any covalent bonds.[54] β -cyclodextrin (β -CD) especially hydroxypropyl β-cyclodextrin (HP-β-CD) is widely used in the pharmaceutical field owing to their high aqueous solubility and ability to stabilize drug molecules.[44] HP-β-CD is a cyclic oligosaccharide containing seven D-(+)-glucopyranose units, with an average of one hydroxypropyl group per unit. The circular arrangement of the glucose units produces a torus-shaped molecule and CH_2 group and ether linkages of the molecule face the hollow interior of the configuration results in a non-polar cavity and a polar exterior.[45] This complexation isolates the aromatic portion of the molecule from the water thereby increasing its aqueous solubility[43]. Many techniques are used to prepared CD complexes, like co-precipitation, co-evaporation, slurry complexation, paste complexation, damp mixing, heating method, extrusion and dry mixing.[46] RPGD- β-CD inclusion complex was prepared by using spray drying.[10] solvent evaporation and kneading method[55] and RPGD-HP β–CD inclusion complex prepared by co-evaporated method[56] & kneading method[10,47]and freeze-drying method.[57] The RPGD inclusion complex of β-CD and HP β–CD was prepared for floating multi-particulate system owing to the sustained release of drug.[58]

Self-emulsifying drug delivery

A self-emulsifying drug delivery system (SEDDS) is a drug delivery system that uses a microemulsion and nanoemulsion (globule size in nm & mm) achieved by chemical rather than mechanical means.[59] The intrinsic property of the drug formulation, rather than by special mixing and handling.[60] Self-emulsifying systems comprise a defined mixture of lipid excipients, including simple oils, nonionic surfactants and co-surfactants.[61] Self-systems act as carriers for drugs by forming fine emulsions, or micro-emulsions, under gentle stirring, when diluted in water or physiological media with physiological motion.[62] Drug molecules are either dissolved or suspended in the SELF system, which maintains the drug in very fine dispersion droplets inside the intestinal lumen, providing optimal conditions for absorption. Self-emulsifying lipid formulations were used to improved the bioavailability of poorly water soluble drugs.[63] Self-emulsifying RPGD delivery systems were prepared using olive oil-Tween 80-PEG 400[64] and sesame oil-labrasol-translucol.[65] Self-nano emulsifying drug delivery system was prepared with neusillin US2 using Olive oil, Miglyol, Cremophore RH 40, Capryol 90 and Labrasol for enhancement of dissolution rate of RPGD.[66,67] Liquid fill technology is employed to prepare fast release capsule of an anti-diabetic drug using a hydrophilic surfactants or polymers like Tween, Poloxamer, PEG and Gelucire.[68]

Ultra-rapid freezing process

Ultra-rapid freezing process or techniques have been developed to enhanced the dissolution rate of the poorly water-soluble drug by creating nanostructured amorphous particles using a cryogenic substrate with a thermal conductivity between 10 and 20 W/m degrees K.[69] In this process, poorly water soluble drug was dissolved in a water-miscible organic solvent and mixed with previously prepared water soluble excipient in a co-solvent system.[70] Resulting organic/aqueous co-solvent systems was frozen on the cryogenic substrate maintained at –45°C and prepare amorphous powder under lyophilization process. The ultra-rapid freezing process was reported for enhancement of solubility and stability of RPGD using sodium dodecyl sulfate, diethanolamine, tromethamine and water/t-butanol as surfactants, alkalizing agents and co-solvent system respectively.[71]

Nanotechnology approach

Nanotechnology can simply be defined as the technology at the scale of one-billionth of a meter.[72] Nanotechnologies have numerous applications in the fields of biotechnology and nanomedicine due to novel drug developments using nanomaterials, nanotechnology has the potential to breathe new life into both suboptimally performing marketed drugs and also many of that pre-clinically promising candidate that owing to poor water-solubility.[73,74] The general method used for fabricating these systems can be categorized as bottom-up and top-down.[75] The top-down approach often uses traditional microfabrication methods, in which externally controlled tools are used to cut, mill, and shape materials into the desired shape and order.[76] Bottom-up approaches, in contrast, include methods in which new phases of submicron-sized entities are formed due to the phase separation from supersaturated homogenous mother phase.[77] The processes that form nanostructure—due to the self-assembling properties of molecules resulting from the change in the surrounding environs (solvent systems or processing temperature)—are also categorized as bottom-up approaches.[78] The nanotechnology-based approach generally consists of nano-nization strategies for the poorly soluble drug; nano-nization of hydrophobic drugs generally involves the production of drug nanocrystals through either chemical precipitation or disintegration.[79]

Nano-suspension

A pharmaceutical nano-suspension is biphasic systems consists of drug nanocrystals, stabilizing agents such as surfactants and/or polymeric stabilizers, and a liquid dispersion medium used for either oral, topical, parenteral and pulmonary administration.[8,80] Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs.[81] The particle size distribution of the solid particles in nano-suspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm.[82] There are various methods for preparation of nano-suspension includes media milling, high-pressure homogenization.[83,84]

Nanocrystal

A nanocrystal is a crystalline material with dimensions measured in nanometers; a Nanoparticle with a structure that is mainly crystalline.[85] The nanocrystallization is defined as a way of diminishing drug particles to the size range of 1-1000 nm.[86,87] The nature of nanocrystals either partially or completely amorphous depends on the methods used for the preparation of drug nanocrystals.[88,89] The nanocrystals of RPGD was prepared using high-pressure homogenization owing to increase surface area to improve solubility as well as dissolution rate.[90-93]

Micellar/surfactant systems

Micellar solubilization is a widely used alternative for the dissolution of poorly soluble drugs.[94] Micellar solubilization i.e., using surfactant is one of the oldest and robust techniques of solubilization. With an advent of nonionic surfactants, with low critical micellar concentration, compatibility with the biological system and high solubilizing power.[79,95,96] These surfactants, in an aqueous medium, aggregate themselves to form micelles that can be defined as a two-region system, an inner nonpolar region of hydrocarbon part and exterior capsular region of polyoxyethylene chains.[97,98] RPGD micellar concentration was prepared with various types of surfactants like an anionic, cationic and non-ionic used to enhanced solubility and dissolution rate.[99-101]

Polymeric Nanoparticles

The convenient method for nanomaterial drug delivery is the use of polymeric nanoparticles because mostly they are biodegradable and biocompatible.[102] They also illustrate a good potential for surface modification via chemical transformations, provide excellent pharmacokinetic control, and are suitable for the entrapment and delivery of a wide range of therapeutic agents.[103] The polymeric nanoparticles were prepared by using various polymers viz. gelatins, chitosan, poly(lactic-co-glycolic acid) copolymer, polylactic acid, polyglycolic acid, poly (alkyl cyanoacrylate), poly (methyl methacrylate), and poly (butyl) cyanoacrylate.[104,105] In addition to this, polymer-based coatings may be improving their biodistribution properties. The polymeric coating is considered to reduce immunogenicity, and limit the phagocytosis of

nanoparticles by the reticuloendothelial system, resulting in increased blood levels of the drug in organs such as the brain, intestines, and kidneys.[106,107] The US Food and Drug Administration (FDA) has approved biodegradable polymeric nanoparticles, such as PLA and PLGA, for human use108. The polymeric nanoparticles of RPGD was prepared by using polymers for controlled drug delivery systems like chitosan,[109] ethyl cellulose,[110,111] Pluronic-F68,[112] PLA and PCL,[113] PLGA,[114,115] Eudragit ® RSPO,[116] PVA[116] and ammonium methacrylate copolymer.[117]

Solid lipid nanoparticles

Solid lipid nanoparticles are solid, submicronic particulate carriers with a size ranging from 1 to 1000 nm and consisting of physiological and biodegradable/biocompatible lipids, suitable for the incorporation of lipophilic and hydrophilic drugs within the lipid matrix in considerable amounts. Generally, lipids that can be employed as a matrix for SLN are highly purified triglycerides, complex glyceride mixtures or even waxes, However, recently, SLN based on the mixture of solid lipid and liquid lipids (so-called nanostructured lipid carriers or NLCs).[118,119] Rawat MK *et al*, was prepared repaglinide-loaded binary solid lipid nanoparticles after oral administration *in-vivo* and cytotoxicity evaluation in rats.[112,120,121]

CONCLUSION

Repaglinide is an effective anti-diabetic drug but due to their poor solubility problem, there is the need to develop a unique formulation for their fast therapeutic action. The simplified and relevant techniques are presented in present review to increase the solubility and subsequent bioavailability of poorly water soluble drugs. The selection of polymer is based on their biocompatibility and biodegradable nature which increases their performance as used in drug delivery systems. In future, there is a need to develop industrially feasible formulation strategies and nanotechnology-based controlled release formulations, where the dose and quantity of drug will be reduced which helps to minimize the toxicity and other side effects related to dosage forms. This review fulfills the requirement of those researchers who work on solubility, dissolution enhancement for RPGD and poorly water soluble drugs i.e. BCS class-II drugs.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

RPGD: Repaglinide; BCS: Biopharmaceutical classification system; DMSO: Dimethyl sulfoxide; HP-β-CD: Hydroxypropyl β-cyclodextrin; SMEDDS: Self Micro Emulsifying Drug Delivery Systems; PLA: Poly(lactic acid); PCL: Polycaprolactone; PLGA: Poly(Lactide-co-Glycolide); PVA: Polyvinyl alcohol; SLN: Solid lipid nanoparticle; NLCs: Nanostructures lipid carries.

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