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NANOTECHNOLOGY IN DEVELOPMENT OF BCS CLASS II ANTI-HYPERGLYCEMIC AGENT

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NANOTECHNOLOGY IN DEVELOPMENT OF BCS CLASS II ANTI-HYPERGLYCEMIC AGENT

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ABSTRACT: Diabetes mellitus is a chronic metabolic disorder characterized by defects in insulin secretion and action, leading to severe complications if left uncontrolled. Glimepiride, a widely used sulfonylurea in the treatment of type 2 diabetes, falls under the Biopharmaceutical Classification System (BCS) class II, signifying its poor solubility and high permeability. This review explores the challenges associated with the solubility and bioavailability of BCS class II drugs, particularly glimepiride, and discusses nanocrystal technology as a promising approach to overcome these limitations. Nanocrystals enhance drug solubility and dissolution rates, thus improving bioavailability. The review delves into various techniques for the preparation of nanocrystals, including precipitation, milling, and high-pressure homogenization, and emphasizes the importance of characterization methods to ensure stability and efficacy. Factors influencing nanocrystal instability, such as aggregation and Ostwald ripening, are also addressed. The review concludes that nanocrystal formulations offer a significant advancement in the development of more effective and safer anti-diabetic therapies, with glimepiride serving as a prime example of the potential benefits of this approach.

KEYWORD: nanocrystal, BCS class II, Diabetes Mellitus, glimepiride, solubility, technology, stability.

INTRODUCTION

Today, the most important issue in drug discovery and development is the poor solubility of a drug. Therefore, various types of approaches have been established to overcome the problem of low aqueous solubility. These approaches are solved formation, co-solvent, compensation, and solid-state manipulation. Emulsion's surface-active agent and Micronisation. Nanocrystal is the conversion of microsystems to particles to nanosize particles in a logical step forward. Nanocrystals are crystalline nanoparticles with sizes ranging from 200 to 500 nm which are stabilized by surface stabilizer. (1,32)

Diabetes is a condition with a disturbance in the metabolism that leads to a high amount of sugar in the blood. Diabetes mellitus(DM) is a chronic lifelong endocrine and metabolic disorder, which occurs due to the defect in insulin secretion and insulin action. DM Is a widespread global health crisis, According to WHO the global cases of diabetes could reach 366 million by the year 2030. India has the use population of diabetes all over the world. According to the International Diabetes Federation (IDF) and WHO, So many people with diabetes in India will reach 75 million by the year 2025. The Ministry of Health and Family Welfare launched an ambitious initiative of its screening and placing 75 million people with hypertension or diabetes on standard care by 2025. This announcement was made at the G20 co-branded event "Accelerating the prevention and management of hypertension and diabetes" which was organized by the Union Health Ministry in collaboration with the WHO Country office in India to mark World Hypertension Day, 2023. (2)

Glimepiride is an oral antidiabetic drug, which is one of the third-generation sulfonylurea. It belongs to BCS class II(have low solubility), Due to which its absorption decreases which directly depends on the dissolution and aq. solubility. It reduces blood sugar levels by promoting the production of insulin from pancreatic beta cells and enhancing the activation of insulin receptors inside the cell through mechanisms outside the pancreas. The need for Glimepiride Nanocrystal is due to its over aq. solubility which is classified in BCS class II, leading to poor dissolution and limiting the drug absorption, Many approaches have been explored to increase the solubility of glimepiride.

DIABETES MELLITUS

DM is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or cells do not respond to the insulin that is produced(3,5)

This high blood sugar produces the classical symptoms.

- Polyurea (Frequent urination)
- Polydipsia (increased thirst)
- Polydipsia (increased hunger)

Type of diabetes mellitus

Table 1: Type 1, type 2, gestational diabetes (occur during pregnancy)(bastaki, et. al 2005)

Type 1	Type 2
It occurs when the body fails to produce insulin and the person is required to inject insulin to maintain the blood glucose level	It occurs when insulin resistance occurs a condition in which cells fail to maintain insulin properly
The destruction of beta cells in the pancreas	Moderate reduction in beta cells
It is less common	It is more common
Type 1 DM is also known as insulin-dependent diabetes mellitus (IDDM) or Juvenile diabetes.	Type 2 DM is also known as non-insulin dependent diabetes mellitus (NIDDM) or Adult onset diabetes
Treatment is the only insulin inject	Can be treated or maintained by orally active drugs or injection

Contributing Factors of DM

The contributing factors of Type 1 DM may be genetics, infection, environmental factors (eg. Toxins, diet, viruses), and stress. (Ozougwu et al., 2013)(4)

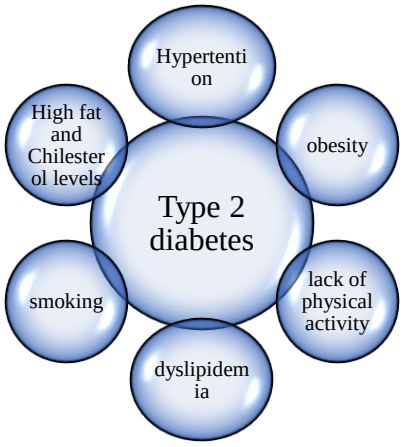

Figure 1: factors of type 2 DM

Table 2: Suggest blood sugar levels

Age(yrs.)	Mg/dl
Below 5yrs	80-200
5-11 yrs	70-180
≥12 years	70-150

Diabetes mellitus is diagnosed by

- fasting blood glucose exceeds 6.1 -7.0 mmol/L (110-126 mg/dl)
- Postprandial glucose > 200 mg/dl
- HbA $_{1c}$ > 6.5 gm%

Hormones of pancreas

It is an endocrine as well as exocrine gland, according to our review, the endocrine part of the pancreas is the main focus.

The hormones secreted from the pancreas are glucagon from Alpha cells, insulin from beta cells, and somatostatin from delta cells.

- Glucagon estimates the conversion of stored glycogen to glucose and stimulates glycogenesis, hyposecretion causes hypoglycemia.
- Insulin controls blood glucose levels by signaling the liver muscle and fat cells to take in glucose from the blood, hyposecretion causes diabetes mellitus
- Somatostatin surprises the release of insulin as well as glucagon.

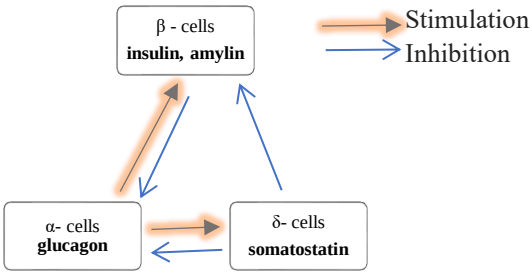

Figure 2: relation b/w glucagon, and somatostatin, insulin

Insulin

insulin was discovered by banking and best. It is composed of 51 amino acids in a molecule with two chain polypeptides. Chain A has 21 amino acids and chain B has 30 amino acids, both changes are joined by a disulfide bridge. The half-life of insulin is 4-6 minutes. The oral intake of insulin is not possible because it is degraded when comes in contact with the gastric juices and acid and due to its very short half-life. Therefore to control the high blood glucose level the oral anti-hyperglycemic

drug was developed and was used to control the high blood glucose level.

ORAL ANTI-HYPERGLYCEMIC DRUGS

Maintaining blood Levels within a regulated range is a critical factor in preventing severe diseases that are directly linked to diabetes Conventional oral hypoglycemic medicines can serve as a substitute for insulin injection Scientists are quickly developing new oral drugs to treat diabetes to meet the demand of patients. The drugs that exhibit high oral efficacy and efficiency lower the blood glucose level in individuals who are diagnosed with diabetes.

Oral anti-diabetic drugs (Tripathi. KD)

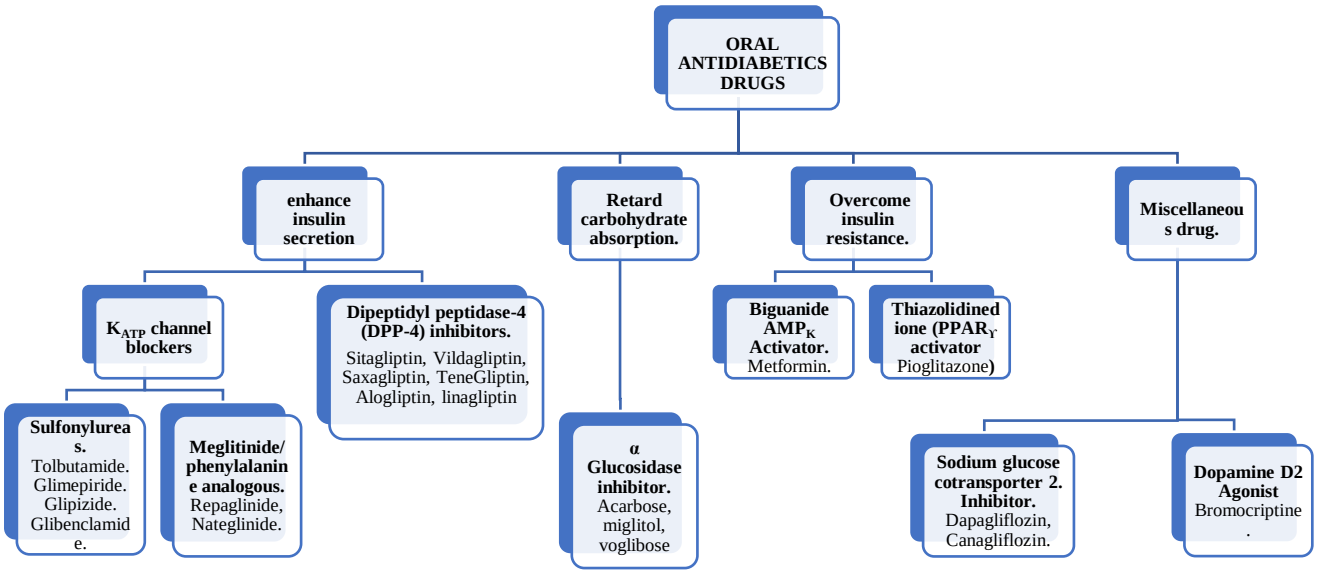

Figure 3: classification of oral anti-diabetic drugs

Sulfonylureas

Sulfonylureas are the first class of anti-diabetic drug that is generally used in the treatment of type diabetes mellitus they increase the insulin's creation by acting on beta cells of the pancreas by binding to sulfonylurea receptors which are present on beta cells in the plasma membrane which eventually closest the ATP sensitive quotation channel of cell membrane which was there is opening of voltage-gated calcium channel due to which there is an influx of calcium channel causes secretion of reformed insulin molecule(6,7,8,9).

MOA of Sulfonylureas

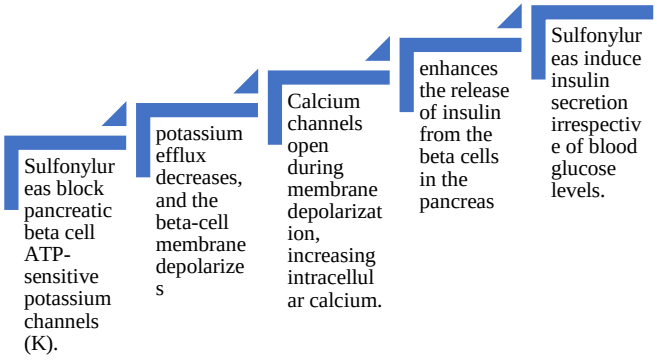

Figure 4: MOA of Sulfonylureas

Glimepiride(GM) is the third-generation sulphonylurea, one of the first-line drugs of choice for the management of (NIDDM). Glimepiride is only the drug that lowers the blood glucose level in healthy subjects as well as patients with diabetes mellitus type 2.(Mahalaxmi rt al., 2010)

Glimepiride belongs to the BCS biopharmaceutics classification system class II, with low solubility and high permeability. It is used for the prediction of in Vivo pharmacokinetics of oral immediate-

release products by classifying drugs into four classes.

GM is insoluble in water so its oral absorption is dissolution rate limited due to its poor solubility in GI fluid as a result of poor availability there are different techniques used to increase the solubility of a drug as solubility increases which eventually leads to an increase in bioavailability the major problem for faced by oral administration is bioavailability which can be increased by increasing the solubility of a drug. (5)

Table 3: BCS (Basanta Kumar Reddy & Karunakar, 2011)

Class	*Solubility*	*Permeability*	*Examples*
I	High	High	Metoprolol
II	Low	High	Glimepiride
III	High	Low	Cimetidine
IV	Low	Low	Hydrochlorothiazide

Pharmaceutical research focus on improving the bioavailability of drugs includes:

- Enhancement of solubility of poorly water-soluble drug
- Enhancement of dissolution of poorly water-soluble truck

Solubility

Solubility is defined as a maximum quantity of solid dissolved in a particular quantity of solvent at a particular temperature. Poor solubility means dissolution which eventually leads to poor bioavailability. (Patel et al., 2012)

Processes involved in the solubility of a compound

- Separation of the solute molecule which provides space for the solvent molecules
- Breakdown of an intermolecular ionic bond of the solute molecule
- Then at last interaction of solute and solvent molecule occurs.

Table 4: Define solubility as: (Kadam et al., 2013)

Solubility	Parts of solvent required for one part of the solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Practically insoluble	>10,000

Techniques used to increase solubility

There are different techniques that are used to increase solubility which are as follows (Savjani et al., 2012)

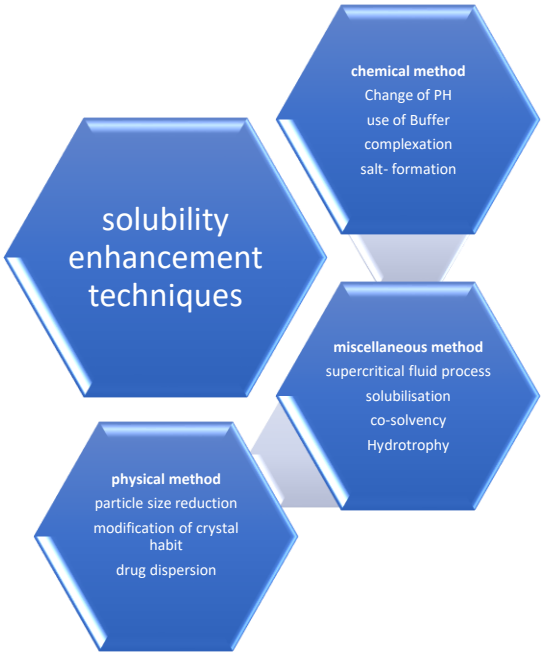

Figure 5: Solubility enhancement techniques

TECHNOLOGY

Nanocrystal

Nanocrystalline technology offers on novel solution for enhancing the solubility and effectiveness of typically insoluble medication. They are characterized by their diameter in the nanometer range from 1-1000 nanometers. (13)

The transformation of a drug microcrystal into a drug nanoparticle can result in either a crystalline or an amorphous output particularly when precipitation is used, depending on the production technology In the strictest output, It is not appropriate to refer to a drug nanoparticle with an undefined shape as a nanocrystal. However, it is common to use the term nanocrystals in the amorphous state.

Drug NCs have a drug composition of 100 percent, Nanoparticles, which do not include a carrier substance. Typically achieving stability of a dispersed particle The utilization of surfactant or polymeric stabilizers is essential. This dispersion medium might consist of water aqueous solution or nonaqueous solution such as liquid polyethylene glycol or oils.(13)

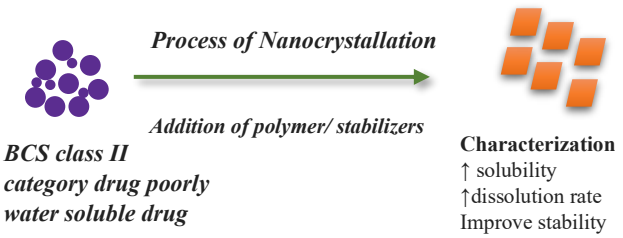

Figure 6: The process of nano crystallization of BCS II drugs that improve their physiochemical properties

Ideal Properties of nanocrystals

- Particle size below 1 µm
- 100% drug no carriers
- Generally needed to be stabilized by surface active agent
- Crystalline or amorphous structure (amorphous state offers more advantages)
- Increase in saturation solubility
- Increase in dissolution velocity
- Biocompatibility
- Bioadhesive properties
- High surface area

Techniques

The technique to produce drug nanocrystals can be divided into two basic approaches Bottom-up and top-down technology Nanocrystals are created through the reduction of particle size using top-down technology and the growth of particles in the nanometer size range, using bottom-up technology and the combination of these two approaches. (15)

- Precipitation method(bottom-up methods)
- Dispersion methods (top-down techniques)
- Combination methods

Bottom-up techniques

In this technology, the drug is dissolved in the solvent, and then the drug is dissolved in the solvent mixture, in a nonsolvent due to which precipitation of crystals takes place. (Sinha et al., 2013)(16,17,18)

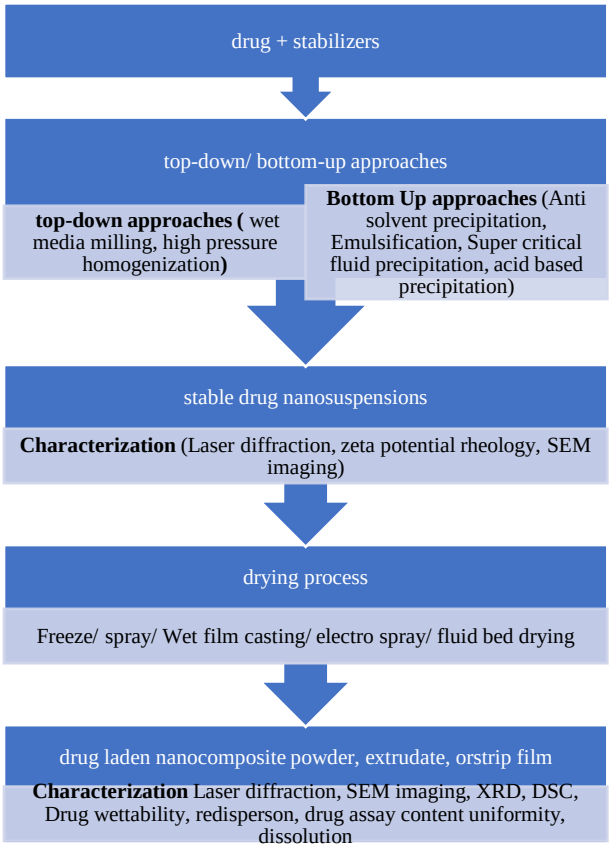

Figure 7: Preparation techniques of nanocrystals and their characterization

Solvent anti-solvent method

In this, the drug is dissolved in the solvent And then the drug solution is mixed with the miscible anti-solvent in the presence of a surfactant Dear rapid addition of drug solution in the anti-solvent leads to sudden supersaturation and formation of crystalline and amorphous drugs occur.(Mansour Mansouri, 2011)(19)

Supercritical fluid process

The use of supercritical fluid, which is noncondensable, The dense fluid having pressure and temperature greater than critical pressure and critical temperature The process allows the micronization of drug particles to submicron level. (20)

Emulsification solvent evaporation technique

The truck solution is prepared by the multiplication process. Then add this solution to that solvent(nonsolvent) For the drug evaporate the solvent When the solvent is evaporated the precipitates/ crystals of the drug form, the growth of crystals can be controlled by using high shear force using a high-speed stirrer.

Lipid emulsion method

That drug is dissolved in an organic solvent, then emulsified in the aqueous solution using a suitable surfactant The organic solvent was evaporated under reduced pressure and evaporation of the organic solvent leads to the formation of precipitates in the aqueous phase.

Top-down technology

The reduction in drug particles occurred due to sheer and collision forces generated mechanically which leads to the fragmentation of crystalline species. This technique is opposed to bottom-up technology in this technology The disintegration approach is followed which is the conversion of large size particles to nano size particles.(21,22,23)

High-pressure homogenization

This method is widely used in the preparation of Nano Crystal or nano suspension of a poorly soluble drug In this process the three steps are followed which are as:-

Step 1 Drug + stabilizer solution → formation of pre-suspension

Step 2 Homogeneous the tree suspension in a high-pressure homogenizer for the purpose of pre-milling

Step 3 At last almost a nice the above mixture was at high pressure homogenizer for 10 to 25 cycles until the desired size was obtained. (24)

Media milling techniques

The nanoparticles were prepared by high-pressure milling. The milling chamber is filled with drug, milling media, water, and the stabilizer solution, and the chamber is at a very high shear rate, under controlled temperature, for 2 to 7 days. (25)

CHARACTERIZATION OF NANOCRYSTALS

Table 5: Established validation techniques for characterization of nanocrystals

Characterization parameter	Examples of analytical method
Structure and morphology	Light microscopy, scanning electron microscopy, transmission electron microscopy, field emission scan Electron microscopy, atomic force microscopy.
Particle size and particle size distribution	Photon correlation spectroscopy, laser diffraction, microscopic methods
Surface charge	Zeta potential
Solid-state analysis crystallinity	Powder X-ray diffraction, differential scanning calorimetry

(26)

Factors that are responsible for the instability of nanocrystals

Particles of smaller sizes exhibit higher surface energy. Consequently, the size of the particles will increase to minimize the surface energy when stored. These phenomena influence the particle size, such as aggregation, sedimentation, and Ostwald ripening. (27)

Aggregation: a process in which larger particles grow at the cost of smaller particles in a dispersed system. This is observable during the preparation and storage of nanocrystal suspensions. Aggregation leads to an increase in particle size as a result decrease in solubility and dissolution.(Berre et al., citation1998).

Ostwald ripening: (crystal growth), is a phenomenon where crystals of different sizes develop as a result of variations in solubility.

Sedimentation: it is the process by which particles in a liquid settle down and accumulate at the bottom due to gravity. It is a common instability,

the settling velocity can be calculated using Stokes' law:

$$v=2r2(\rho 1-\rho 2)g/9\eta,$$

v: settling velocity,
r: radius of the particle,
ρ1 and **ρ2** are the densities of the particle and the medium respectively,
η: viscosity of the dispersion medium,
g: gravitational acceleration. (29)

Factors related to drugs

- Drug polymorphism
- Hydrophobicity of the drug
- In therapy of the drug and its cohesive energy

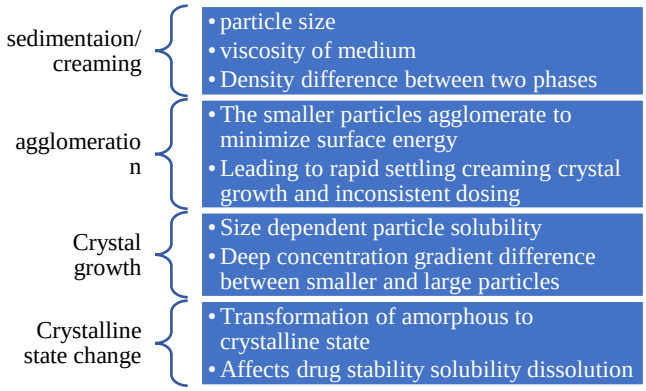

Figure 8: factors affecting stability of nanocrystal

Advantages of Nanocrystals

- Possibility of using several administration methods to deliver a medicine like overall intravenous intramuscular pulmonary ocular and dermal.
- The ability to create medicine in a variety of pharmaceutical doses like tablets, capsules, suspension, ointments, etc
- Greater solubility than typical particles
- Quicker dissolving than the traditional particles
- Potential for drug targeting
- It causes less tissue irritation and toxicity
- Possibility of procuring hybrid nanocrystals for both medical and diagnostic use
- Enhance bioavailability, Solubility, dissolution rate its stability.

Disadvantages of Nano Crystal

- Stability issue
- Accurate and uniform dosing is impossible to obtain.
- Complex production.
- Scalability.
- Potential toxicity.

Application of nanocrystals (30,31)

Table 6: drug delivery, its remarks, & limitations

DRUG DELIVERY.	REMARKS.	LIMITATIONS.
ORAL DRUG DELIVERY.	• Facilitates. adhesion. in the intestinal wall. • Improve the oral bioavailability. • Reduce gastric irritation. • Reduce. Local Prolonged. Concentrations.	During tablet manufacture, nanocrystals can merge with larger crystals when subjected to compression pressure, as they make contact with the excipient mixture.
PARENTERAL DRUG DELIVERY.	• Fast onset of action and reduce its dose. • Getting out of the reticuloendothelial system • Decrease rate of. Removal from systemic circulation.	Behavior. Of nanocrystal. By an injection. It's not been fully predictable.
OPHTHALMIC. DRUG DELIVERY.	Noninvasive route of administration, local toxicity. may occur.	
TARGETED DRUG DELIVERY.	Minimize phagocytosis. Predominant accumulation of drugs. In Target site.	

Conclusion

Diabetes mellitus is a chronic lifelong endocrine and metabolic disorder, which occurs due to defects in insulin secretion and insulin action. If diabetes is uncontrolled, then it leads to several diabetic complications like neuropathy and various cardiovascular complications. It can be treated with various anti-diabetic drugs but most of the drugs are having a problem related to poor solubility and dissolution. So to avoid this problem new and effective formulations were developed to increase the solubility of Anti-diabetic drugs by making them as nanocrystals/nanoparticles. As a sample for review glimepiride was selected as a BCS class II oral antidiabetic drug.

Drug Nano-formulation Technology has opened a new direction for product development and reformation, which was previously not available. The nano-formulation not only provides the opportunity to overcome the limitation of existing formulations but also provides new characteristics to the already marketed drug products to make them safer and more effective, the new manufacturing methods, and analytical techniques available for the characterization of several products for the marketing approval. This review provides information regarding the preparation of nano-formulation of glimepiride to improve its solubility and dissolution rate.

LIST OF ABBREVIATIONS

DM = Diabetes mellitus
WHO = World Health Organisation
IDF = International Diabetes Federation
BCS = biopharmaceutics classification system
GM = Glimepiride
IDDM = insulin-dependent diabetes mellitus
NIDDM = non-insulin dependent diabetes mellitus
yrs. = years
DPP-4 = Dipeptidyl peptidase-4 inhibitors
NCs = nanocrystals
µm = microgram
nm = nanometer
SEM = Scanning electron microscopy
DSC = Differential Scanning Calorimetry
XRD =X- ray Powder Diffraction
GI = gastrointestinal

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