1. INTRODUCTION

1.1 Diabetes mellitus (DM)

DM is a metabolic disease which is characterized by increased blood glucose level, either due to failure of insulin production by the β-cells of pancreas or due to insulin resistance (Shoback and David, 2011). DM is mainly classified into two types: type 1 DM (T1DM) and type 2 DM (T2DM). According to the International Diabetes Federation (IDF) report of 2017, about 425 million people were reported to be suffering from DM and among them 90% cases were of T2DM. By 2045, this number is expected to reach to 628.6 million. DM is spread throughout the world however; T2DM is more common than T1DM in developed countries. According to the IDF, the numbers of people suffering from DM in a year are reported to be more in India than in any other country in the world. India stands at second position, after China; in terms of total number of people (20-79 yrs) suffering from DM. India has a statistical figure of 72.9 million people suffering from DM. By 2045, the estimated number of people with DM in India will be 134.3 million, and that will take India to number one position (IDF, 2017). In a survey carried out in 2010, it was reported that more than 92 million Chinese adults were suffering from DM and another 150 million adults were diagnosed with early symptoms (Grens, 2012). About 3.8 million people were reported to be affected with DM in United Kingdom while in United States about 26 million people were reported to be diabetic (Diabetes: cases and costs predicted to rise, 2015; Kaur et al., 2016a; NHS, 2015).

1.1.1. Pathophysiology of DM

T2DM is a complex metabolic/cardiovascular disorder with multiple pathophysiological abnormalities. Patients having impaired glucose tolerance (IGT) are those who are near-maximally insulin resistant and have lost 80% of their β-cell function. Insulin resistance is generally manifested in liver and muscles. Insulin-resistance causes stress on pancreatic β-cells to augment insulin secretion. As long as β-cells are able to augment insulin secretion, glucose tolerance remains normal (Shoback and David, 2011).

According to DeFronzo, 2009, there are eight other pathophysiological abnormalities that contribute to development of glucose intolerance in T2DM individuals. These include
- β-cells: Diminished insulin production,
- Muscle: Defective insulin action
- Liver: Defective insulin action
- Adipocytes: Accelerated lipolysis
- Incretin deficiency/ resistance, α–cells: Increase glucagon level
- Kidney: Increased glucose reabsorption
- Brain - Insulin resistance and neurotransmitter β dysregulation (DeFronzo, 2009).

Due to the increased blood glucose level, symptoms like polyuria, polydipsia and polyphagia can be observed in patients suffering from DM. With the progression of disease, pathological changes like nephropathy, retinopathy and cardio-vascular complications start occurring in the body (Melmed et al., 2011).

1.1.2. Treatment strategies in DM

1.1.2.1. Conventional treatment strategies in DM

T1DM is generally managed and treated with insulin replacement therapy while T2DM is treated with both oral hypoglycaemics and insulin replacement therapy. The subcutaneous or intravenous administration of insulin makes its delivery painful. It also leads to development of lipid hypertrophy. Another limitation of insulin therapy is that it may cause hypoglycaemia (Melmed et al., 2011; Shoback and David, 2011). The most widely used oral hypoglycaemics are classified into sulfonylureas, Glucagon-like peptide-1 (GLP-1) gliptins, sodium/glucose cotransporter 2 (SGLT2) inhibitors, biguanides, α-glucosidase inhibitors, meglitinide analogues and thiazolidinediones. Drugs belonging to all these categories have associated side effects. GLP-1 analogues which are administered through subcutaneous route have shown clinical effectiveness in reducing glucose levels in clinical trials (Trujillo et al., 2015). The most common adverse effect seen with sulfonylureas is hypoglycaemia (most common with the use of chlorpropamide and glibenclamide) (Garber et al., 2015; Hackett and Thomas, 2007). The other side effects that have been reported include cholestatic jaundice and cardiovascular mortality. The reports, nevertheless, are not very significant. Meglitinides are reported to cause a range of side effects, most commonly hypoglycaemia, visual disturbances, abdominal pain, diarrhoea, constipation, nausea and vomiting. More rarely, hypersensitivity reactions as well as elevation of liver enzymes may also occur.
Thiazolidinediones like rosiglitazone and pioglitazone may cause oedema, particularly in patients with hypertension, and risks of other cardiovascular diseases. α-glucosidase inhibitors like acarbose cause abdominal discomfort associated with flatulence and diarrhea (Hackett and Thomas, 2007). Glitins and GLP-1 analogues can cause pancreatitis while SGLT2 inhibitors can lead to urinary tract infections (Garber et al., 2015). Hence, there is a need for safer and effective medicine for the treatment of DM, irrespective of the fact whether they belong to synthetic or natural/herbal origin.

1.1.2.2. Traditional treatment strategies in DM

Herbal drugs could be the best alternative to conventional synthetic drugs for management of DM. Various herbal drugs e.g. *Terminalia chebula*, *Momordica charantia*, *Tinospora cordifolia*, *Curcuma longa* etc. have been reported for their antidiabetic potential. *Momordica charantia* (MC) is one of such important plants widely known for its significance as antidiabetic drug in both Chinese and Ayurvedic literature. MC leaves have jagged edges that appear as if leaves are bitten leading to the name known as *Momordica, which means “to bite”* (Grover and Yadav, 2004; Raman and Lau, 1996). The plant is known by a number of vernacular names e.g. in South America, it is known as bitter gourd and bitter-melon; in India, as karela; in Jamaica, as “carilla or goo- fah”. The wild variety of the plant (MC) is grown in West Indies and there, it is known as cerasee (Jamaica) or sorossie (Dominician Republic) (Garg et al., 2017a; Kaur et al., 2016a; Raman and Lau, 1996).

1.1.2.3. Novel treatment strategies in DM

Antidiabetic drugs are either available in oral dosage form or in the form of injectables. As diabetes is a chronic disease requiring long term therapy, oral route is most suitable route due to its ease of administration and compliance. Most of the antidiabetic drugs which are available in oral dosage form are either tablets or capsules. These suffer from certain limitations in terms of side effects i.e. gastric irritation, diarrhea, loss of appetite and lactic acidosis in people with abnormal kidney or liver function (Oral Diabetes Medications Summary Chart, 2018).

There are a number of approaches that are reported to improve the dissolution rate limited bioavailability of poorly soluble drugs (Renuka et al., 2014). These approaches include increasing the surface area (Renuka et al., 2014), particle size
reduction (Romero et al., 1999), formulation in a dissolved state (Brittain, 2007), liquisolid compacts (Singh et al., 2012), preparation of inclusion complexes (Bond, 2009), solid dispersions (Cabri et al., 2007), use of pro drugs (Raw and Yu, 2004), and generation of metastable polymorphs (Bartolomei et al., 2007).

Insulin is generally delivered by subcutaneous route. Alternative to this painful route has been explored by a number of researchers. A number of novel drug delivery systems have been explored for oral, transdermal or pulmonary delivery of insulin. Similarly, other antidiabetic agents have been explored for other novel drug delivery systems (NDDS) as given in Table 1 (Battaglia et al., 2007; Cetin et al., 2013; Chen et al., 2011a; Furtado et al., 2008; Huang & Wang, 2006). However, none of these approaches has been found to be suitable to overcome the challenge related to enzymatic degradation of insulin in the GI tract (Garg et al., 2016a and 2017a).

A number of novel nano formulation strategies are being developed to overcome the problems related to oral absorption and bioavailability of these drugs. These novel formulations have been utilized not only for enhancing the solubility and bioavailability of these bio-actives but have also proved effective in enhancing their physical, chemical, biological and photo stability. These formulations offer an added advantage of controlling the release of drugs for a prolonged period of time and also of delivering them at the required site, thus preventing the exposure to non target sites (Ajazuddin and Saraf, 2010). Many phytoconstituents like curcumin (CRM), flavonoids, vitamin etc. have been reported to show enhanced therapeutic effect at lower doses when incorporated into novel delivery systems vis-a-vis that from their conventionally delivered counterparts (Garg et al., 2016a; Gosangari and Dyakonov, 2013; Joshi et al., 2013; Wahlang et al., 2012).

A number of lipid based novel nano delivery systems like liposomes, niosomes, transfersomes, ethosomes, phytosomes, nano emulsions, solid lipid nanoparticles, self-emulsifying delivery systems have been developed in recent years which provide enhanced solubility, bioavailability and stability (Table 1) (Kalepu et al., 2013).
Table 1
NDDS for antidibetic drugs

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drug</th>
<th>Formulation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Insulin</td>
<td>Microparticulate system via phase inversion nanoencapsulation</td>
<td>Furtado et al., 2008</td>
</tr>
<tr>
<td>2</td>
<td>Insulin</td>
<td>Implantable system</td>
<td>Chen et al., 2011a</td>
</tr>
<tr>
<td>3</td>
<td>Insulin</td>
<td>Microgel beads (nanofiber hydrogel)</td>
<td>Nishimura et al., 2012</td>
</tr>
<tr>
<td>4</td>
<td>Insulin</td>
<td>Solid lipid nanoparticles formed by solvent-in-water emulsion-diffusion technique</td>
<td>Battaglia et al., 2007</td>
</tr>
<tr>
<td>5</td>
<td>Insulin</td>
<td>Nanoparticles for transdermal delivery</td>
<td>Zhao et al., 2010a</td>
</tr>
<tr>
<td>6</td>
<td>Insulin</td>
<td>Nanoparticles of quaternized chitosan derivatives as carrier for colon delivery</td>
<td>Bayat et al., 2008</td>
</tr>
<tr>
<td>7</td>
<td>Insulin</td>
<td>Microcapsules of alginate/chitosan containing magnetic nanoparticles</td>
<td>Finotelli et al., 2010</td>
</tr>
<tr>
<td>8</td>
<td>Insulin</td>
<td>Liposomes for pulmonary delivery</td>
<td>Huang &amp; Wang, 2006</td>
</tr>
<tr>
<td>9</td>
<td>Insulin</td>
<td>Niosomes</td>
<td>Pardakhty et al., 2007</td>
</tr>
<tr>
<td>10</td>
<td>Metformin</td>
<td>Nanoparticle</td>
<td>Cetin et al., 2013</td>
</tr>
<tr>
<td>11</td>
<td>Glibenclamide</td>
<td>Amorphous nanoparticles</td>
<td>Yu et al., 2011</td>
</tr>
<tr>
<td>12</td>
<td>Glimepiride</td>
<td>Microparticulate system via spray congealing</td>
<td>Ilić et al, 2009</td>
</tr>
<tr>
<td>13</td>
<td>Exenatide</td>
<td>Microsphere</td>
<td>Liu et al., 2010</td>
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</table>

1.2. Self emulsifying drug delivery system (SEDDS)

1.2.1. Lipid based systems

Lipid based delivery systems have been able to dramatically alter the availability of poorly water soluble drugs. These systems also have commercial viability for oral, transdermal or parental formulations (Shrestha et al., 2014). Lipid based systems include emulsions, vesicular system and lipid particulate system.

Lipid based systems like emulsions or SEDDS have been reported to overcome such challenges for delivery of proteins and peptides through oral route.

1.2.2. Liquid SEDDS (L-SEDDS)

L-SEDDS were first reported by Poulton in 1982 (Pouton, 1982). These delivery systems offer advantages like improved solubility, increased bioavailability, increased absorption via lymphatic system, increased P-gp efflux. These are basically isotropic mixtures of bio-actives, lipids and emulsifiers, with or without co-solvents/co-emulsifiers (Singh et al., 2009a). The mechanism for delivery from these vehicles has been well explained by Rao and Shao 2008a. Delivering the protein loaded inside the oil droplets that are in nanometer range [i.e. nanoemulsion/ SNEDDS] may provide the effective absorption of the drug after oral administration (Rao and Shao, 2008a, 2008b). By using this approach, oral delivery of lipophilic and/or gastric labile drug candidates/enzymes such as, flurbiprofen (Kang et al.,
β-lactamase (Rao and Shao, 2008a, 2008b), lacidipine (Basalious et al., 2010), persimmon leaf extract (Li et al., 2011), CRM (Joshi et al., 2013), ubiquinone (Nazzal et al., 2002), darunavir (Inugala et al., 2015) etc., have been successfully achieved.

1.2.3. Solid SEDDS (S-SEDDS)

S-SEDDS as the name suggests are solid dosage forms which have the ability to self emulsify when come in contact with GI media (Cho et al., 2013). Development of SEDDS as solid dosage form is generally undertaken to overcome the limitations associated with the L-SEDDS. S-SEDDS have been developed to add the ease of administration, storage, convenience and stability to the SEDDS formulations (Tang et al., 2008a). S-SEDDS offer the advantages of low production cost, high stability, and convenience leading to high patient compliance. S-SEDDS carry the advantage of conventional solid dosage form along with properties of novel drug delivery system of SEDDS. To prepare S-SEDDS, L-SEDDS are converted into powder form and then formulated as different dosage forms like tablets, pellets etc. (Chen et al., 2011a; Tarate et al., 2014). S-SEDDS can be prepared by different methods like extrusion-spheronization, melt granulation, spray drying, lyophilization, adsorption on solid support (Chen et al., 2011a,b; Kang et al., 2012; Garg et al., 2016a; Lei et al., 2011; Onoue et al., 2012; Shanmugam et al., 2011a).

1.3. Drug profiles

1.3.1 Polypeptide K (PPK)

1.3.1.1 Traditional uses of Momordica charantia (MC) in treatment of DM

MC is well known for its use as traditional medicine in developing countries. The decoction from leaves of MC is used for treatment of DM, expulsion of intestinal gas, promotion of menstruation, treatment of measles, hepatitis and feverish conditions. The topical application of MC extracts is used for treating sores, wounds and infections (Grover and Yadav, 2004). Table 2 enlists various uses of MC in different countries.

Antidiabetic activity of MC has been proven by several animal and human studies (Akhtar, 1982; Ahmad et al., 1999; Baldwa et al., 1977; Efird et al., 2014; Grover and Gupta, 1990; John et al., 2003; Khanna et al., 1981; Leatherdale et al., 1981; Patel et al., 1968; Srivastava et al., 1993; Welihinda et al., 1982). MC has many constituents which act as antidiabetic and in dyslipidemia. There are different
mechanisms reported by which it treats DM like, via inhibiting gluconeogenesis, increasing uptake of glucose in muscles, increasing the number of GLUT 4 receptors expressed in intracellular vesicles in muscle and fat cells and increasing rate of phosphorylation of insulin receptor substrate (Chaturvedi, 2012).

### Table 2

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Traditional Use</th>
<th>Country</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Tumors, wounds, rheumatoid arthritis, malaria, vaginal discharge, inflammation, menstrual problems, DM, fevers, worms, to induce abortions, as an aphrodisiac, treatment of vaginitis, haemorrhoids, scabies, itchy rashes, eczema, leprosy and other skin problems</td>
<td>Brazil</td>
<td>Chaturvedi, 2012; Garg et al., 2017a; Grover and Yadav, 2004; Joseph and Jini, 2013; Kaur et al., 2016a</td>
</tr>
<tr>
<td>2</td>
<td>Entire plant is used for DM and dysentery and the root is a reputed aphrodisiac.</td>
<td>Mexico</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Leaf or aerial parts of the plant are used to treat measles, malaria, and all types of inflammation.</td>
<td>Peru</td>
<td>Jini, 2013; Kaur et al., 2016a</td>
</tr>
<tr>
<td>4</td>
<td>Leaf is commonly used for stomach pain, DM, fevers, colds, coughs, headaches, malaria, skin complaints, menstrual disorders, aches and pains, hypertension, infections, and as an aid in childbirth.</td>
<td>Nicaragua</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>As a folk medicine, mature fruits of MC are used in treatment of peptic ulcers.</td>
<td>Turkey</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Antidiabetic, abortifacient, contraceptive, antimalarial and laxative properties. MC is used for treatment of dysmenorrhoea, eczema, emmenagogue, galactagogue, gout, jaundice, kidney stones, leucorrhoea, leprosy, piles, pneumonia, scabies and rheumatism</td>
<td>India</td>
<td></td>
</tr>
</tbody>
</table>

Active constituents responsible for antidiabetic activity of MC have been reported. The two isolated peptides of MC that are responsible for antidiabetic activity are named as polypeptide-P (PPP) and polypeptide-K (PPK) (Garg et al., 2017; Kaur et al., 2016; Khanna, 2004).

#### 1.3.1.2 Polypeptide P (PPP)

PPP shows structural similarity to bovine insulin. Its structure is reported to be different from bovine insulin in respect of an extra amino acid, methionine. It is reported that when given by subcutaneous route, it reduces blood glucose levels in gerbils, langurs as well as humans (Joseph and Jini, 2013). It is reported to be stable at 4°C. The electrophoretic pattern also resembles that of bovine insulin (Baldwa et al., 1977; Kaur et al., 2016a; Khanna et al., 1981).
The effect of PPP has also been studied in human beings. A total of 19 human subjects, of both genders participated in the study. Among them, 11 were suffering from T1DM while 8 suffered from T2DM. PPP significantly reduced blood glucose levels in both type 1 and type 2 diabetic patients. Peak effect of PPP was observed between 4-8 h while for regular bovine insulin, it was observed at 2 h. The results of PPP were found to be similar to those of Neutral Protamine Hagedron insulin in term of action. However, no side effects were observed with PPP (Baldwa et al., 1977; Kaur et al., 2016a; Khanna et al., 1981).

It is pertinent to add here that despite very good antidiabetic activity as well as similarity with insulin, PPP has been unable to make its place in the pharmaceutical market. The major hurdle behind this appears to be its lack of stability and poor aqueous solubility. These limitations of PPP lead to evolution of PPK, which is more stable than PPP (Garg et al., 2017a; Kaur et al., 2016a).

PPK is a hypoglycaemic protein isolated from dried seeds from ripened fruits of MC of family Cucurbitaceae. The word k is used with this polypeptide because it is obtained from karela whose botanical name is *Momordica charantia* (Khanna, 2004, Khanna et al., 1981). PPK is a polypeptide having structural similarity with insulin (Fig 1) and reported potential in management of DM. Furthermore, PPK has been reported to inhibit α-glucosidase and α-amylase up to 79.18% and 35.58% level. Khanna et al., extracted PPP followed by PPK (Filho et.al., 2003; Kaur et al., 2016a;
Khanna et al., 1981; Khanna, 2004). It has been well reported for its antidiabetic activity and this is available in market in the form of sublingual tablets under brand name Diabegard™, in powder form under brand name Sugard™ and in Organic Spirullina Atta noodles (Polypeptide K, 2015; Kaur et al., 2016a; Lok et al., 2011).

Despite having unique antidiabetic property, oral delivery of PPK remains a challenge. The drug exhibits poor aqueous solubility which leads to dissolution rate limited bioavailability. The polypeptide is prone to enzymatic degradation in the GI tract (Garg et al., 2017a; Kaur et al., 2016a).

1.3.2. Curcumin (CRM)

CRM (1, 7-bis [4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione) (Fig 2) is a yellow colored compound isolated from Curcuma longa, family: Zingiberaceae. The solubility of CRM is poor in water which leads to poor dissolution and bioavailability (Modasiya and Patel, 2012). CRM contains different functional moieties which are bonded to two phenol rings. The α- and β-unsaturated diketone moiety in the chemical framework of CRM has a crucial role in the inhibition of nuclear factor-kB (NF-kB) and reactive oxygen species (ROS)-production (Nabavi et al., 2015). Commercial CRM contains approximately 77% diferuloylmethane, 17% demethoxycurcumin, and 6% bisdemethoxycurcumin (Jeenger et al., 2015).

![Diagram of Curcumin](image.png)
1.3.2.1 Traditional uses of CRM in treatment of DM

CRM has shown excellent potential to be used as antidiabetic, anticancer, anti-inflammatory, antioxidant and neuroprotective agent (Nabavi et al., 2015). It also plays important role in management of DM and its complications via modulating several cellular mechanisms (Zhang et al., 2013). CRM is supposed to be act via suppressing AGE formation is suggested to involve the suppression of AGE receptor (RAGE) expression through the activation of peroxisome proliferator-activated receptor gamma (PPARγ) activity and increase in glutathione synthesis (Meghana et al., 2007). Various uses of CRM are enlisted below (Nabavi et al., 2015).

- Antidiabetic
- Antiinflammatory
- Antioxidant
- Anticancer
- Immunomodulatory,
- Neuroprotective
- Diabetic vascular disease