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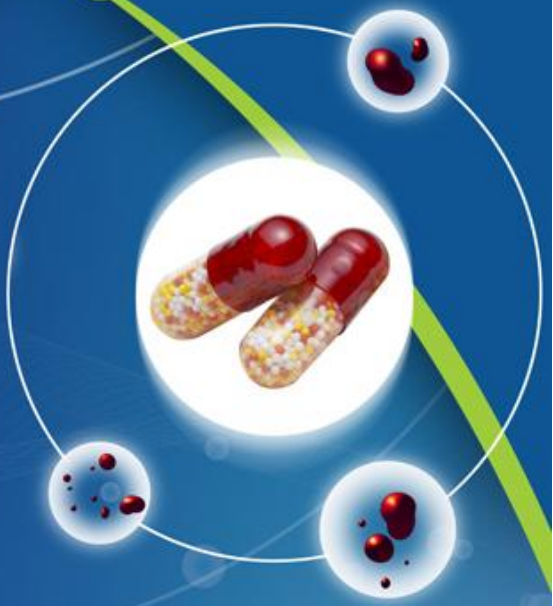

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Review Article

RECENT TRENDS IN NOVEL DRUG DELIVERY FOR TREATMENT OF TYPE I AND II DIABETES MELLITUS

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ABSTRACT

Around 200 million people worldwide are found to be affected by Diabetes mellitus (DM). DM is a metabolic disorder which occurs due to reduced insulin action and/or insulin secretion in the body. With the progression of disease, pathological changes like nephropathy, retinopathy and cardiovascular complications start occurring in the body. DM is mainly categorized into 2 types: type 1 DM and type 2 DM. Type 1 is generally treated through insulin replacement therapy. Type 2 DM is treated with oral hypoglycemics. Insulin administration is essential for type 1 patients while it is required at later stage by the patients of type 2. Current insulin delivery system is invasive approach. Several non-invasive approaches for insulin delivery are being pursued by pharmaceutical companies to reduce the pain, and hypoglycemic incidences associated with injections in order to improve patient compliance. Although the availability of new agents for treatment of type 2 DM, oral hypoglycemic are base of therapy, because they are relatively economical and well tolerated. A well designed controlled drug delivery system can overcome some of the inconvenience of conventional therapy and enhance the therapeutic efficacy of drug. These newer generations of drug delivery systems are advantageous over conventionally available drug delivery systems. This review article discusses the various non-invasive techniques for insulin administration and also highlights various novel drug delivery systems that have been investigated by different researchers for achieving sustained and controlled drug delivery of oral hypoglycemics and for overcoming the limitations related with conventional dosage forms of oral hypoglycemics.

Keywords:*Diabetes, Insulin, Oral hypoglycemics, Conventional therapy, Novel Drug Delivery Systems, Sustained release.*

INTRODUCTION

Diabetes (Diabetes mellitus) is categorized as a metabolic disorder. The food that we eat is converted into glucose by the process of metabolism. Glucose sugar is present in the blood, which is the fundamental source of fuel for the human body. After digestion of food, glucose goes into the bloodstream and our cells use this glucose for providing energy and growth of the body. Insulin, a hormone produced by beta cells of the pancreas, makes it possible for our cells take in the glucose.

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After eating, the pancreas automatically releases an adequate quantity of insulin to move the glucose present in our blood into the cells, and lowers the blood sugar level. Persons suffering with diabetes have hyperglycemia i.e. blood glucose level is elevated. This happens because our body, does not produce enough insulin, produces no insulin, or has cells that do not respond properly to the insulin produced. As a result, glucose level increases in the blood. Inadequate lowering of blood glucose level to normal level results in diabetes [1]. Normal people have fasting sugar level less than 110 mg/dl as set by the American Diabetes Association. This excess blood glucose eventually passes out of the body in urine. So, despite of the blood having plenty of glucose,

the cells don't get it for their essential energy and growth requirements [2].

Uncontrolled diabetes can lead in severe complications to practically every system of the body. Some of the serious complications of diabetes include blindness (due to diabetic retinopathy), end-stage renal disease (due to diabetic nephropathy), lower extremity amputations (resulting from diabetic neuropathy), decreased ability to fight infection and impotence or sexual dysfunction. Diabetes mellitus is a major risk factor for heart disease, stroke and peripheral vascular diseases [3].

Diabetes affects a large percentage of the population around the world and has assumed epidemic dimensions [4], [5]. The current estimate of the number of diabetic patients in the world is 171.2 million (2.8%)in the year 2000 and predicted to be 366.2 million (4.4%) by the year 2030 [6].

The percentage of type I diabetic patients in the total diabetic patients is 5-10%.This means that in the year 2000, there were about 12.8 million of types I diabetic patients depending on insulin administration. In addition, 7% of the remaining 158.4 million, i.e.11.1 million also require the administration of insulin making a total of 23.9 million insulin dependants [1], [2]

Types of diabetes

Type -1

Type 1 occurs due to beta–cell destruction leading to diminished production of insulin. It is usually characterized by the presence of anti–GAD, islet cell or insulin antibodies which identify the autoimmune processes that lead to beta cell destruction [1]

Type -2

Type 2 is the most common form of diabetes and is characterized by insulin resistance that may be the inability of insulin action of cells and or disorders of insulin secretions. But the reasons for the development of these abnormalities are idiosyncratic [1].

Management strategies for treatment of diabetes mellitus

1. Type 1 diabetes is undeviatingly treated with insulin and some diet control is required.
2. Type 2 diabetes is often linked with obesity. It is basically a disease of insulin resistance which is commonly treated with oral hypoglycemic agents. Though insulin is not required initially, but administration of insulin may be needed sometimes because of a decrease in the insulin secretion[7], [8].

INSULIN THERAPY

More than 60,000 insulin injections are taken by the patients throughout their life[9].

In type 1 diabetes, good glycemic control usually requires at least two or more often three or more daily insulin injections. Such invasive and rigorous technique urges the search for alternative more pleasant methods for administering insulin [10].

The conventional and most anticipated method for the insulin administration is by subcutaneous injections. The various problems associated with the subcutaneous method of insulin delivery:

- Local pain
- Inconvenience of multiple injections, especially for those requiring multiple dose injections of four times a day.
- Occasional hypoglycemia as a consequence of an overdose, itching, allergy, hyperinsulinemia and insulin lipodystrophy around the injection site.

Clinical trials data reveal that many patients cannot achieve long lasting glycemic control because of non-compliance [11].

Also, there have been reports of hypoglycemic episodes following multi dose injections of insulin [12].

To overcome the disadvantages of traditional method numerous new approaches have been developed to decrease the suffering of the diabetic patients, which includes the use of supersonic injector, infusion pump, sharp needles and pens. Some of these techniques reduced the pain encountered by the diabetic patients, but they offer incomplete convenience. New concepts are presently investigated to deliver insulin using oral, pulmonary, nasal, ocular and rectal routes, but the eventual goal would be to eradicate the need to deliver insulin exogenously and regaining the ability of patients to produce and use own insulin. The success of the route of administration is judged on the basis of its

ability to elicit effective and predictable lowering of blood glucose level and therefore minimizing the risk of diabetic complications. It is clear that several difficulties have to overcome with the use of formulation and application device's technology. The various explored routes and other techniques of insulin delivery are discussed as under.

ADVANCES IN INSULIN DELIVERY SYSTEM

Insulin syringes

Most common ways of insulin administration are via needle and syringe. Initially used insulin syringes were large and heavy with reusable glass plungers and barrels with a long, large bore needle. Currently available insulin syringes are derived from plastics which are light weighted, disposable and flexible in use of variety of microfine needles [13], [14]. These syringes offer patient compliance with increasing patient comfort[15].The suitable selection of an appropriate syringe depends on many factors, like the chemical composition of the material from which syringes are made, syringe capacity [16], ease with which air bubbles are removed, clarity of the markings on the syringe barrel and convenience of syringe disposal.

Drawbacks

- Heavy weight.
- Training and practice required to learn optimal syringe technique.
- In cases where patients mix different types of insulin preparations in one syringe to meet their individual needs process becomes cumbersome and complicated.
- In patients with less proficiency, this may result in inaccurate doses, compromising their glycemic control.

Insulin Pens

Insulin pen injectors are a suitable and discreet way of administering insulin. They often resemble fountain pen. The first insulin pen (NovoPen) was introduced by Novo Nordisk in 1987.Insulin Pensare novel devices in which the insulin container and the syringe are combined into a single modular unit. The amount of insulin to be injected can be decided by the presence of built-in dial. Insulin pens eliminate the inconvenience of carrying insulin and syringes.

There are two main types of pens:

- Reusable pens: They are durable, flexible to carry 3 to 5 day supply and eradicate the need of cartridge refrigeration.
- Prefilled device: They are of small size and light weight and are well accepted in a bedtime insulin regimen for type 2 patients [17]. They cause the least pain due to the finest and shortest disposable needle. Also, they are quick and easy to use.

Irrespective of the type, both pens can hold cartridges containing from 1.5 ml to 3 ml of U100/ml insulin. A study has shown that reusing insulin pen needles could help in reducing the economic burden of diabetes without leading to needle tip deformity and increased pain [18]. The needles for pens are available in varying lengths (from 8 mm to 12.7 mm) and varying gauges (from 29- to 31-gauge; the larger the gauge number, the smaller the diameter of the needle bore). The needles have a bevel on each end; one is intended to be inserted into the skin and the other is to pierce the septum of the insulin cartridge. The precision of insulin doses varies between different pens, but remains better than that obtained in studies where traditional syringes were used [19]. Many newer generation pens are able to deliver 60 U at a time for type 2 patients. Insulin pens have become very popular in some countries such as France, where over 50 percent of insulin-treated patients are using insulin pens [20].

Benefits

- Portability, speed, and ease of use in delivering basal or bolus insulin
- Pens offer convenience, accuracy, discretion, durability and ease of storage[21], [22]
- The devices can add lifestyle flexibility and may result in better glycemic control[23]
- May improve accuracy in patients with poor dexterity or neurological impairment and in those
  requiring smalldoses [24]
- May be associated with less discomfort [25]

- Studies show preference among patients of insulin pens versus the vial and syringe method of insulin delivery [26]
- Studies indicate wider acceptability in elderly and adolescent patients with respect to easier and faster injection and greater comfort
- May improve patient compliance during multiple injection regimen management

Drawbacks/cautions

- Not available for all insulin types
- Patient education is necessary in order to avoid operational errors, particularly when changing the cartridge in reusable pens.
- Cannot mix insulin types
- Air bubbles can reduce insulin flow rate
- Per-unit cost higher than for l0-mL vials

Insulin Jet Injectors

Jet injectors which were developed in the 1980s are substitute to needles and are designed in such a way that it can deliver a fine stream of insulin transcutaneous lyathigh speed and high pressure to penetrate the skin without a needle. These can deliver insulin without using a needle by the application of a large force on a fluid under considerable pressure through a very small opening. The dose is controlled by a dial-a-dose operation through a single component design in comparison to the conventional multicomponent syringe and vial method. They allow a dose range of two to 50 units of insulin and can deliver insulin in half-unit increments.

Benefits

- Insulin is absorbed rapidly and chances of subcutaneous infection are not there.
- Can be used for patients suffering from needle phobia and also for patients who suffer from severe lipomas [27].

Drawbacks

- Due to unfavorable size and the cost, routine use of it is limited.
- On repeated administration decreased amount of insulin is absorbed.
- Pain or bruising may occur at the site of administration. Difficulty in adjusting pressure.

Insulin pumps

Continuous subcutaneous insulin infusion (CSII) (developed in 1974) imitates the physiological functioning of daily insulin secretion [28]. Design of an insulin pump consists of 3 parts viz: insulin filled reservoir (e.g., Velosulin® BR), pump operated on small battery and a computer chip that permits the patient in controlling the insulin delivery. Continuous supply of insulin infusion is delivered by the pump around the clock. Infusion set delivers appropriate amounts of insulin into the body by the pump.

Technological advancements led to the development of newer pump designs that are much smaller in size (approximately the size of a pager, i.e., 5×7.5 cm) and are relatively easier to operate and can be carried conveniently in a shirt pocket. These may also accurately deliver microdoses (0.1 units) of insulin.

Benefits

- American Diabetes Association has recommended continuous SC insulin infusion as acceptable for intensive insulin management
- Tight control of plasma glucose levels can be achieved and overall quality of life is enhanced.
- Needle is inserted once every three to four days.
- When recommended procedures are followed pumps demonstrates efficacy alike to that of multiple daily insulin injections in achieving glycemic control [29]

Drawbacks/cautions

- Some people may feel discomfort in wearing pump all day long.
- Site of insertion must be changed every 3 days to prevent site infectionsand lipohypertrophy[25]
- Risk of ketoacidosis prevails on the blockage of the catheter so frequent glucose monitoring is needed [25]
- Expensive therapy as compared to traditional methods.

Special considerations

- Requires a motivated patient committed to improve glucose control and willing to accept responsibility for self-care
- May be especially beneficial for hospitalized patients with high pretreatment glycosylated hemoglobin values[29] and those with a history of long-term poor glycemic control [30]
- Patient education by a healthcare team is a crucial component of successful insulin pump therapy.

EMERGING DEVELOPMENT IN INSULIN THERAPY

Novel techniques for insulin delivery are being explored by various companies such as pills, patches, mouth sprays, inhalers. Inhalerhas been developed since long time and has already been approved for marketing. The products under development as an alternative to injection insulin delivery are depicted in the Table 1.

Table I: Summary of The Alternative Insulin Delivery Products Being Developed

Name	Nature of the product	Company	Stage in the development	Key findings
Exubera®	Inhaled insulin powder	Pfizer, Sanofi-Aventis and Nektar	FDA and EC approved (January, 2006)	As stated above
AERx® iDMS (insulin diabetes management system)	Inhaled insulin solution	Aradigm and Novo Nordisk (Novo Nordisk bought all the developing rights)	Phase III in progress	Glycemic control similar to such injection
Aerodose®	Inhaled insulin solution	Aerogen and Disetronic Medical Systems	Phase II completed	Dose response curve similar to that of subcutaneous injection
Technosphere insulin	Inhaled insulin powder	MannKind Corporation, Danbury, Connecticut	Phase III clinical and safety trials	Onset of action similar to that of iv insulin
HIIP (Device Name Air®) Human insulin inhalation powder	Inhaled insulin powder	Alkermes and Eli Lilly & Company	Clinical Trial-Phase III (for type 1 and 2)	Data not available
Rapid Mist/Oralin	Mouth spray for buccal delivery (Rapid Mist is device, Oralin is insulin)	Generex Biotechnology	Completed phase II in Canada and Europe. Undisclosed in U.S.A. Oral-lyn™ (identical product) has been approved for commercial marketing and sale by the Ecuadorian Ministry of Public Health for the treatment of both Type-1 and Type-2 diabetes	Reduced postprandial glucose vs placebo
EMISPHERE® oral insulin tablets	Tablet	Emisphere Technologies	Phase II completed	Hepatic glucose production similar to normal physiologic state
NIN-058 (No trade name yet)	Tablet	Nobex Corporation and GlaxoSmithKline	Phase II in progress	Data not available
IN-105	Tablet	Biocon	Phase I completed	Data not available
Patch (No trade name yet)	Basal insulin patch	Altea Development Corporation	Phase I	Data not available
U-strip ™ insulin delivery system	Insulin patch	Encapsulation Systems,Inc., Springfield, Pennsylvania	Clinical studies	Data unavailable

Inhaled insulin

Insulin inhalers are new technique of delivering pre-mealtime insulin and are much similar to asthma inhalers. It is quick-acting, dry powder insulin inhaled through the mouth and into the lungs using a portable handheld inhaler.

Benefits

- For mealtime bolus, no need of an injection.
- Can be given pre-mealtime.
- Glycemic control has been found to be equivalent to that of SC insulin (based on results of 24-week trials) [31], [32]
- May result in lower incidence of hypoglycemia than SC insulin(based on results of 24-week trials) [31], [32]

Drawbacks/cautions

- Frequency of cough is more in initial therapy [31], [32]
- Requirement of large doses since the dose actually reaching the bloodstream is less because in pulmonary delivery of insulin some loss of drug occurs within the inhaler or mouth during inhalation.
- Efficiency of inhaled insulin is lower than subcutaneous injection.
- Decline in FEV 1 and DLco [33]
- Spirometry assessment and monitoring required[33]
- These can only be used to deliver fast-acting insulin.

Contraindications

- Smoking must be stopped 6 months before starting therapy[33]
- Unstable or poorly controlled lung disease[33]
- Not recommended for patients with asthma, emphysema, chronic obstructive pulmonary disease and FEV 1 or DLco<70% of predicted value.

FEV 1 = forced expiratory volume in 1 second;

DLco = carbon monoxide-diffusing capacity.

Inhaled insulin can be used effectively in diabetes treatment, especially in the treatment of postprandial hyperglycemia [34].

Numerous companies are currently working on insulin inhalers. The products are categorized into two main groups: the dry powder formulations and solution, which are generally delivered through different patented inhaler systems.

Exubera®, the first US-FDA approved recombinant human insulin for inhalationcontaining rapid-acting insulin in powder form, has been studied extensively in patients with type 1 and type 2 diabetes mellitus [35].

The AERx Insulin Diabetes Management System (AERxIDMS) delivers a liquid form of human insulin. Preliminary data suggestthat patients converting from insulin injections to inhalation systems showed higher compliance to this therapy, which was shown by improvement in glycemic control.

Many other pulmonary insulin delivery systems which are under investigation includesProMaxx (Epic Therapeutic- Baxter Healthcare Corporation), AIR (Alkermes, Eli Lilly), Spiros (Dura Pharmaceuticals and Eli Lilly), and Technosphere™-insulin Med Tone inhaler (Pharmaceutical Discovery Corp.) [36].

Insulin shows growth-promoting properties so the possibility of long-term effects from the intra-alveolar deposition of insulin within the lung is a matter of concern to the clinicians. Pulmonary function tests have been carried out to study various parameters. The long-term safety of these products has not been yet established. Studies on the basal insulin for the prolonged pulmonary delivery need to be carried out as many companies are engaged in developing fast acting insulin for pulmonary delivery[37], [38].

i. ***Exubera***has been developed under the collaboration between Sanofi-Aventis and Pfizer, where they used a proprietary inhalation device and powdered insulin formulation developed by Nektar Therapeutics. It was approved by FDA and the European Commission (EC) in January 2006 for use in type 1 and type 2 diabetes patients above 18 years of age.

Exubera device is about 25 cm long, having a base containing packet of insulin powder and a clear chamber above which the insulin powder is turned into an aerosol cloud for inhalation. The dose of Exubera must be provided 10 minutes before a meal. The device can deliver insulin powder in approximately 3 and 9 insulin units. The compressed air traveling at the speed of sound creates a cloud of insulin

powder that the patient can breathe in slowly and deeply into their lungs, and from there it goes into the blood stream. Its onset of action is similar to that of rapid-acting insulin (range, 10-20 minutes), but its duration of action (~6 hours) is comparable to injected regular human insulin [33].

ii. *AERxiDMS*

Another breakthrough in the development of inhaled insulin was brought about by Novo Nordisk which has bought all the manufacturingand development rights for AERxiDMS from Aradigm Corporation after ending early phase III trial. The AERx insulin Diabetes Management System (AERxiDMS), is 17.5 by 10 by 3.75 cm, deposits insulin deep in the lungs by aerosolizing a fine mist of liquid insulin. It is an electromechanical device delivering insulin from solution at correct rate and depth of breathing. This device ensures consistent insulin administration by use of the 'active breathcontrol' system. Tight control of glucose may be achieved because of the dose increments like injectable insulin in steps equivalent to 1 unit.

iii. *Mouth sprays*

Mouth sprays differs from inhalers in that they deliver liquid insulin through an aerosolized spray for absorption in the oropharyngeal mucosainstead of lungs [39]. Generex Biotechnology has developed twodesigns of mouth spray (Rapid Mist/Oralin)[40], [41]. One type of design is rapid-acting and another type focuses on the basal rate of insulin.

ORAL INSULIN DELIVERY

Approaches for oral insulin

Most peptides are not bioavailable from GIT after oral administration. Therefore for the successful delivery of insulin orally involves overcoming the enzymatic and physical barriers and taking steps to conserve bioactivity during formulation processing. For developing oral protein delivery systems with high bioavailability, these approaches can be used:

1. Modification of physicochemical properties such as lipophilicity and enzyme susceptibility.
2. Addition of novel function to macromolecules.
3. Use of improved carrier systems.

Pills

The oral delivery of insulin is a major challenging task.Insulin if given orally, undergoes rapid degradation by the enzymes present in the stomach and becomes inactivated in intestine lumen by proteolytic enzymes.Due to high molecular weight of insulin, the permeability across intestine epithelium is poor[42],[43].Continuous research is being carried out to surmount such barriers. For example,complexation of insulin with cyclodextrins (CD) was done in order to improve its solubility and stability in the form of adry powder, which was then encapsulated into poly (D,L-lactic-co-glycolic acid) (PLGA) microspheres [44]. Otherexamples include insulin incorporation in delivery agent SNAC (sodium N-[8-(2-hydroxybenzoyl) amino] caprylate) [45], calcium phosphate-PEGinsulin-casein (CAPIC) particles were produced for oral delivery of insulin [46].
Insulin pills are under the process of development in which modification in insulin is done by attachment of special molecules that will help to prevent insulin breakdown or bypass the through thegastrointestinal lining, or both. NOBEX Corporation has developed an oral delivery technology that delivers insulin orally as an orally absorbed, bioactive conjugate. Unique in its approach, this technique is found to be safe, rapidly absorbed andduring trials in animal models, healthy human volunteers and patients of type 1 diabetesdose-dependent, glucose-lowering effects were observed [47]. Emisphere Technologies are also working on oral insulin delivery by which insulin would directly act on hepatic glucose production in the same way of normal physiological state.

Transdermal delivery of insulin

Transdermal system offers non-invasive methods for delivery of insulin that could

provide sustained physiological levels ofbasal insulin in a pain-free manner. Transdermal insulin patches are being developed that may deliver basal insulin rather than fast-actinginsulin bolus. Altea Development Corporation is working on developing one- or half-day patch. Another patch named U-Strip TM Insulin Delivery System is being developed and is undergoing US clinical trials [48]. This system uses ultrasonic and microelectronics, ultrasonic transmissions are pulsed through the patch that acts on drug contained within it.The device can be programmed to deliver particular amount of drug product in a regimen. The device facilitated a >7-fold increase in the noninvasive transdermaltransport of Humulin R insulin through human skin compared with passive transmission [49]. Another promising approach to transdermal drug delivery is use of *iontophoresis technique* which uses small electric current to enhance the transdermal delivery by electromigration and electro-osmosis [50].

Another recent technique under investigation is *Microneedles* for transdermal drug delivery which are painless as per the reports obtained till now [51].

Intranasal Delivery of Insulin

Extensive research has been carried out for delivery of insulin through nasal mucosa. Pharmacological studies were conducted on 8 healthy volunteers and acceptable duration of action (1.5-2 hours) was achieved in controlling postprandial hyperglycemia [52]. Experimental and preliminary clinical studies of intranasal products using a bioadhesive gel have demonstrated absorption and reduction of blood glucose [53]

OTHER APPROACHES

Islet Cell Transplantation

Technological advancements have led to the development of a latest technique called the Edmonton protocol in which surgery is carried out to transplant islet cells from a donor's pancreas into the type 1 diabetes recipient's liver. Insulin is secreted from the transplanted cells and immunosuppressive drugs are provided to the recipient that helps in avoiding transplant rejection. Though safety and long-term effectiveness of this processneed to be evaluated [54], [55].

Insulin Nanopump

The nanopump is a revolutionary conceptand works on the principal of microfluidic MEMS (Micro-Electro-Mechanical System) technology. Debiotech introduced unique miniaturized insulin-delivery pump. Thistiny device can be attached on a disposable skin patch to provide continuous insulin infusion, enabling substantial advancements in the availability, treatment efficiency and the quality of life of diabetes patients. The Nanopump is less than one fourth the size of existing insulin-pump devices and can be worn as a nearly invisible patch on the skin. Microfluidic technology also provides better control of the administered insulin doses, more closely mimicking the natural secretion of insulin from the pancreas, while detecting potential malfunctions of the pump to further protect patients. Since this is a disposable device, manufactured using high-volume semiconductor processing technologies, the MEMS-based Nanopump is also much more affordable.

Gene Therapy:

Ongoing research is being done on gene therapy for different aspects of diabetes.

- A gene named SHIP2 that regulates insulin has been recognized by scientists. Such discoveries make SHIP2 a potential gene therapy target for the treatment of type 2 diabetes aimed at improving the individual insulin regulation.
- As scientists identify specific genes whose absence or improper functioning are associated with specific conditions, more possibilities for gene therapy are offered for diabetes as well as all disease [1].

TREATMENT STRATEGIES FOR TYPE II DIABETES

Type II diabetes is increasing at an alarming rate and this increasing prevalence has

stimulated development of many new approaches to safely treat hyperglycemia .The ultimate goal of these therapies is to reduce and maintain glucose concentrations as close to normal for as long as possible and thereby prevent development of complications. Various oral hypoglycemic agents have been developed for this purpose. The following Table.2 [56] shows a list of oral hypoglycemic agents along with their properties.

TABLE II: List of Oral Hypoglycemic Agents

Drug class	Brand name	Generic name	Available stengths (mg)	Mechanism of action
Sulfonylureas	Diabeta	Glyburide	1.25, 2.5, 5	Stimulate pancreatic beta cells to increase first-phase insulin secretion. May cause hypoglycemia
	Micronase	Glyburide	1.25, 2.5, 5	
	Glynase	Glyburide (micronized)	1.5, 3.0, 4.4, 6.0	
	Glucotrol, Glucotrol XL	Glipizide	5,10	
	Amaryl	Glimiperide	1,2,4	
Meglitinides	Prandin	Repaglinide	0.5,1, 2	
	Starlix	Nateglinide	60, 120	
Biguanides	Glucophage	Metformin	500, 850, 1000	Decrease hepatic glucose output
	Glucophage XR	Metformin	500	
Thiazoledinediones	Actos	Pioglitazone	15, 30, 45	Decrease insulin resistance
	Avandia	Rosiglitazone	2, 4, 8	
Alpha glucosidase inhibitors	Precose	Acarbose	25, 50, 100	Delay glucose absorption
	Glyset	Miglitol	5, 50, 100	
Combinations	Glucovance	Glyburide/metformin	1.25/250, 2.5/500, 5.0/500	Decrease Hepatic glucose output Decrease insulin resistance Increase insulin secretion
	Avandamet	Rosiglitazone/metformin	1/500, 2/500, 4/500	
	Actos + mets	Pioglitazone/metformin	15/500, 15/850	
	Prandimet	Metformin /repaglinide	500/1, 500/2	
Dipeptidyl peptidase IV inhibitors	Januvia	Sitagliptin	25, 50, 100	
	Janumet	Sitagliptin/metformin	50/500, 50/1000	

NOVEL DRUG DELIVERY SYSTEM FOR MANAGEMENT OF TYPE II DIABETES MELLITUS

Scientific and technological evolution has led to expansion in the drug delivery system. The Novel drug delivery system is latest and innovative tactic to conventional drug delivery. NDDS modifies the drug and delivery system in such a way that the duration of action is increased, overcomes physiological problems of drugs and effectivity is increased. NDDS overcomes drawbacks and restrictions of traditional drug delivery. Drug distribution is controlled in NDDS either by drug incorporation in carriers or molecular modification of drug. Various novel drug delivery system have been developed such as Microspheres, niosomes, proniosomes, micro emulsions, nanoparticles, etc. Most of the novel techniques have been discussed below.

MICROSPHERES

Microspheres [57] are usually the free flowing powders made up of biodegradable polymers or proteins. They range in the particle size

generally less than 200µm. This is one of the major approachesto deliver therapeutically active substance in controlled fashion and also to target the drug at appropriate site of action.

The following Table 3 depicts a review on various oral hypoglycemic agents used for microsphere preparation.

Table III: Brief Review on Microspheres of Oral Hypoglycemic Agents

Drug	Polymer	Method used	Conclusion	Reference
Glipizide	Galactomannan, Tween 80	Emulsification- cross linking technique	Sustained glucose lowering effect obtained and significant improvement in diabetic condition.	[58]
	Eudragit RS 100 and RL 100	Solvent evaporation method.	Sustained drug release obtained.	[59]
	Ethyl cellulose and eudragit S 100	Emulsion solvent diffusion-evaporation technique	Dosing frequency decreased and more patient compliance.	[60]
Metformin HCl	Ethyl cellulose, Chitosan, Carbopol 934P, HPMC	Non-aqueous solvent evaporation method	Drug release was prolonged at gastrointestinal pH Improves bioavailibilty of drug and patient compliance.	[61]
	Sodium alginate, gellan	Emulsification- cross linking technique	Sustained drug release.	[62]
Repaglinide	Calcium silicate. Eudragit S	modified emulsion solvent diffusion technique	Bioavailibility enhanced.	[63]
	HPMCP, Ethyl cellulose, Eudragit RSPO	Quasi emulsion solvent diffusion technique	Drug release prolonged.	[64]
Rosiglitazone	Sodium carboxy methyl cellulose, Carbopol 934, sodium alginate.	Emulsification solvent evaporation method	Sustained delivery. Reduction in dosage frequency.	[65]
Pioglitazone HCl	Sodium alginate, HPMC K15M, calcium chloride.	Ionotropic gelation method	Reduction in dosing frequency and untoward effects decreased. Drug entrapment efficiency more.	[66]

Benefits of microspheres:

- Enhances the bioavailability
- Improves the patient compliance
- Delivers the drug to the target site specifically.
- Maintains the desired concentration at the site of interest without untoward effects.
- Protects the drug from external environment.
- The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles in vivo.
- In case of volatile materials, evaporation rate is reduced.
- Protects the GIT from irritant effects of the drug.
- Provides Controlled drug release.

Shortcomings:

- Removal once injected is difficult.
- Drug content may not be uniform.
- Unknown toxicity of beads.

Proniosomesare latest improvement in Novel drug delivery system as drug carrier which overcomes the limitations of liposomes and niosomes. These, hydrated by agitation in hot water for a short period of time, offer a versatile vesicle delivery.

The following Table 4 depicts a review on various oral hypoglycemic agents used for proniosme preparation.

Table IV: Brief Review on Proniosomes of Oral Hypoglycemic Agents

Drug	Polymer	Method of prepration	Conclusion	Reference
Metformin proniosomal gel	Span 60,span 40	Co-acervation phase seperation method	Prolonged drug delivery Reasonably good stability.	[68]
	Span 20, span 80, tween 40, tween 80	Slurry method	Improved oral bioavailibility	[69]
Gliclazide loaded maltodextrin based proniosomes	Span60, maltodextrin	Slurry method	1. Dosing frequency decreased to once a day. 2. enhanced oral bioavailability. 3. Increased penetration property & stability of gliclazideniosoms.	[70]

Niosomes

Niosomes[67] are non-ionic surfactant vesicles consisting of non-ionic surfactants with or without incorporation of cholesterol.

The following Table 5 depicts a review on various oral hypoglycemic agents used for niosome preparation.

Table V: Brief Review on Niosomesof Oral Hypoglycemic Agents

Drug	**Surfactants**	**Method of preparation**	**Conclusion**	**Reference**
Metformin	Span 20, Span 40, Span 60, Span 80, Tween 20,tween 60, Tween 80 and Brij 30	Thin Film Hydration Method	Sustained release dosage form, Reduction in dosing frequency, Better patient compliance.	[71]
Gliclazide	Span 60	lipid film hydration technique	Enhancement of oral bioavailability, drug release prolonged.	[72]
Insulin	Span 60, dicetyl phosphate	lipid layer hydration methods	Existence of insulin in body prolonged, increase in therapeutic value	[73]
	Brij 35, brij 52, brij 58, brij 72, brij 76, brij 92, brij 97	film hydration method.	Sustained release oral dosage form for delivery of peptides and proteins.	[74]

Benefits of niosomes

- Enhances the oral bioavailability and permeation of the drug.
- Reduction in drug toxicity because of their non-ionic nature of the surfactant.
- More physical and chemical stability as compared to liposomes.
- Osmotically stable.
- Used for targeted drug delivery of drugs.
- They are used for sustained as well as controlled drug delivery system.
- Handling, storage and transportation is easy.

Shortcomings

- Drug may not be entrapped completely.
- Sometimes vesicle may leak leading to loss of drug.

Nanoparticles

Nanoparticles [75] are solid colloidal submicron-sized matrix-like particles made of polymers or lipids. Nano-encapsulation of drugs involves formation of drug loaded nanoparticles with having diameters ranging from 1 to 1000 nm. Nanoparticles can be nanospheres or nanocapsules depending on technique of preparation.

The following Table 6 depicts a review on various oral hypoglycemic agents used for nanoparticle preparation.

Table VI: Brief Review on Nanoparticles of Oral Hypoglycemic Agents

Drug	Emulsifier and lipids	Method of preparation	Conclusion	Reference
Metformin	Eudragit®RSPO, PLGA	Nanoprecipitation method	Sustained release, reduction in dosing frequency, better patient compliance.	[76]
Glibenclamide	Cellulose Acetate, tween 80, span 80	Emulsion-solvent evaporation method	Sustained drug release. Reduction in dosing frequency.	[77]
	Eudragit L 100	Solvent displacement method	Reduced dosing frequency, decreased side effects, better patient compliance.	[78]
	Poly(lactic-co-glycolic) acid	Solvent evaporation method	Controlled drug delivery	[79]
Glipizide	polycaprolactone	Emulsification-solvent evaporation technique	Better patient compliance, reduced dose frequency	[80]
Repaglinide	Polymethyl methacrylate	Solvent evaporation method	Drug release prolonged and dosing frequency decreased.	[81]
	Ethyl cellulose	Solvent emulsion diffusion technique	Side effects associated with repeated dosing may be decreased because of sustained release dosage.	[82]
Pioglitazone	Piperine, Bovine serum albumin (BSA) Glutaraldehyde	Modified desolvation and coacervation method	Better control of diabetes. Drawbacks of weight gain and liver damage reduced on using pioglitazone with piperine	[83]
Insulin coated with HP55	Eudragit RS, PLGA	Multiple solvent evaporation method	Protection of insulin from acidic environment of stomach. Oral absorption of insulin increased.	[84]
Insulin	Thiolatedeudragit L100	Precipitation method	Improved absorption of insulin in the intestinal tract.	[85]
Exenatide	Pluronic F-68	Freeze drying	Sustained drug release.	[86]

Benefits

- Manipulation in Particle size and surface characteristics of nanoparticles can be done so as toto attaintargeting of drug following after parenteral administration.
- Release of drug can be controlled and particle degradation features can be varied by substituting various matrix constituents.
- Comparatively high drug loading and incorporation of drugs does not need chemical reactions. Thus activity of drug is preserved.
- Targeting to specific site can be accomplished by attachment of ligands.
- Adverse effects are decreased.
- More patient compliance.

Shortcomings

- Less size and more surface area lead to aggregation between particle-particle.
- Physical handling is pretty tough.

MICROEMULSION

Microemulsions[88] are the optically isotropic and thermodynamically stable liquid dispersions made by mixing surfactant and co-surfactant having the 100 – 1000 A (10 – 100 nm) diameter of droplets. The following Table 7 depicts a review on various oral hypoglycemic agents used for microemulsion preparation.

Table VII: Brief Review on Microemulsionsof Oral Hypoglycemic Agents

Drug	Surfactant and co-surfactant	Method of preparation	Conclusion	Reference
Insulin	Didoceyldimethylammonium bromide (DMAB), Propylene glycol (PG), Triacetin (TA)	low shear reverse micellar approach	10 times Enhancement of oral bioavailability of insulin	[88]
	Labrasol, glyceryloleate, isopropyl palmitate, propylene carbonate	Titration method	Bioavailibility increased.	[89]
Glipizide	Capmul MCM, Cremophor EL, Transcutol	water titration method	Bioavailability of poor water soluble compound glipizide increased	[90]

Benefits

- Thermodynamically stable system.
- Both hydrophilic and lipophilic drugs can be solubilized.
- Improved penetration across the biological membrane.
- Filtration sterilization can be used since the diameter of droplets is less than 0.22 mm.
- Therapeutic activity of drug is increased and in turn reduction of dose and less untoward effects.
- Simple method of preparation and energy requirement is negligible.

Shortcomings

- Nanodroplets can be stabilized by using huge concentration of surfactant and co-surfactant
- Drugs having high melting point suffers from restricted solubilizing capacity.
- Toxicity of surfactant need to be considered.
- Temperature and pH plays an important role in affecting stability of microemulsion
- Sometimes phase separation may occur.

CONCLUSION

The abovementioned review highlights different aspects related with the novel drug delivery system (NDDS) approaching a vital role to deliver a drug by different route to achieve better therapeutic action. The current advocacy of intensive insulin therapy regimens involving multiple daily subcutaneous injections places a heavy burden of compliance on patients and has prompted interest in developing various alternatives. Hence, studies into various means to administer insulin in a safe and effective manner should continue. Despite of certain drawbacks, NDDS still play an important role in the selective targeting and controlled delivery of various drugs. Researchers are implementing their efforts in improving the design of NDDS by making them stable in nature, so as to avoidcontents leaching, oxidation and uptake by natural defense mechanism. A wide range of potential is there if some flexibility in design is there and the

application of such modified techniques needed to be explored all over the world by encouraging the participation of researcher in the field of Novel drug delivery system.

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