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Microcapsules: An emerging tool for Delivery of Antidiabetic Drugs

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ABSTRACT: Microcapsule is a drug polymeric matrix of capsular shape, centrally containing drug as core surrounded by polymeric coat of approximate size of 1 to 1000 µm. The microcapsules offers several benefits of releasing drug in controlled manner, masking the unpleasant taste and odor of drug(s), enhances the stability of drugs by protecting from the gastric environment and enhances patient compliances. The methods of enveloping of drug either liquid droplets or fine solid particles by polymer are called microencapsulation. Microencapsulation methods are divided into two basic groups, namely chemical and physical. The most frequently used methods are solvent evaporation, polymerization coacervation and ionic gelation techniques. Mostly antidiabetic drugs need for microencapsulation as they involves with problems, which can be overtaken from advantages of Microcapsules. This review includes basic concept of microcapsules, microencapsulation techniques, and characterization of microcapsules with special references to microencapsulation of antidiabetic drug. The review also emphasizes the modern trends of microcapsules.

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INTRODUCTIONS:

The controlled release drug delivery system, releases the active drug or medicament at a predetermined rate targeting the drug to specific site over a prolonged period of time. Microencapsulation provides a promising drug delivery system since it provides unlimited combinations of core and shell materials, targeting to the specific areas of gastrointestinal tract. Microencapsulation is the process of enclosing a substance inside a miniature called capsule [1,2].

Microcapsules:

Microcapsule is a small sphere with a uniform wall around it, containing the drug or drugs as core surrounded by polymeric coat. Some materials like lipids and polymers, such as alginate, may be used as a mixture to trap the material of interest inside. Most microcapsules have pores with diameters between a few micrometers and a few millimeters. The coating materials generally used for coating are Ethyl cellulose, polyvinyl alcohol, Gelatin and Sodium alginate. The technique of microencapsulation depends on the physical and chemical properties of the material to be encapsulated [1,2].

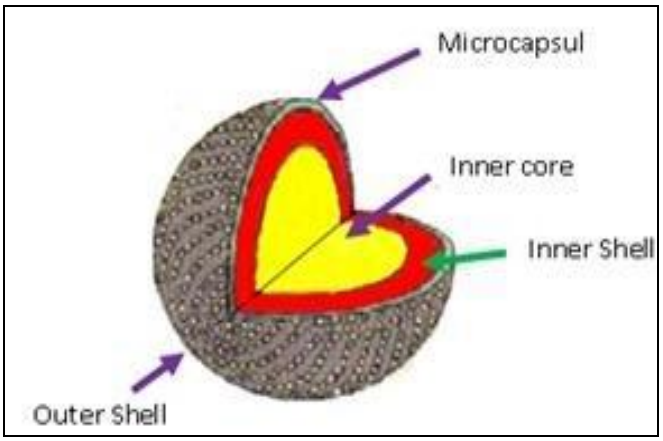

Fig 1. Structure of microcapsule.

Development of microcapsules:

Core material:

The core material is defined as the specific material to be coated whether it can be a solid or liquid. The solid core can be the active ingredient, stabilizers, diluents, excipients, release rate retardants whereas liquid core include the dissolved materials [3].

Coating material:

Coating materials are defined as a layer of substance covered over the core for production of the drug. The coating material should possess properties such are; it should have controlled release under specific conditions, soluble in aqueous media/solvent; it should possess sufficient properties such as flexibility, strength, impermeability, stability and optical properties; it should be chemically compatible with the core and non-reactive and it should be capable of forming a film [3].

Advantages of Microcapsules:

The Microcapsules possesses various advantages like Food products have increased nutritional and health benefits; Microencapsulated ingredients do not interfere with other ingredients; The microencapsulated ingredients can be added at any time at the processing and remains unaltered; Self-life may be increased; Sensory properties remain unaltered; Consumers are unable to taste the added capsules and Wider range of specific products for consumers to choose from [3,4].

Disadvantages of Microcapsules:

Due to foreign ingredients in foods, consumers with allergies may not be aware. More skills and knowledge is required to use the advanced and complex technology. Production cost is more. Self-life of hygroscopic drugs is reduced. Difficult to achieve continuous and uniform film. Possible cross-reaction that may occur between the core and wall material selected [4].

Drug Criteria for Microcapsule formulation:

The drug should have short biological half life. The drug should be therapeutically used for chronic diseases. The drug should have appropriate solubility characteristics. The drug must be compatible with wide varieties of polymers and excipients [4].

Polymers in Microcapsule preparation [5,6]:

Natural Polymers: Proteins (Albumins, Gelatin and Collagen) and *Carbohydrates* (Agarose, Chitosan and Starch).

Chemically modified carbohydrates: Poly-starch and Poly-dextrin.

Synthetic Polymers: Biodegradable (Lactides, Glycolides and co-polymers) and Non-biodegradable (Poly methyl methacrylate (PMMA) and Epoxy polymers).

Depending upon solubility: Water soluble resins (Gelatin, Gum Arabic. Hydroxy ethyl cellulose and Poly vinyl alcohol), Water insoluble resins (Poly ethylene, Nylon, Cellulose nitrates, Silicones and Ethyl cellulose), Waxes and Lipids (Paraffin, Bees wax, Stearic acid, Glyceryl stearate, Carnauba and Stearyl alcohol) and Enteric resins (Shellac, Zein and Cellulose acetate phthalate).

Microencapsulation:

Microencapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules, of many useful properties. In general, it is used to incorporate food ingredients, enzymes, cells or other materials on a micro metric scale. The

microcapsule size range from 1 μ to 7 mm. All the 3 states i.e. solid, liquid and gases may be encapsulated which may affect the size and shape of capsules [6,7].

Reasons for Microencapsulation [7,8]:

- It is mainly used to increase the stability, and sustained/prolonged release of the product.
- Controlling the release rate of the drug from the microcapsules.
- This technique was widely used for masking taste and odour of many drugs and to improve patient compliance.
- For converting liquid drugs into a free flowing powder.
- To reduce the toxicity and GI irritation and many major side effects of the drugs.
- Alteration in site of absorption can be achieved by microencapsulation.

Objectives of Microencapsulation:

It ensures label claim, which met by microencapsulating. Microcapsules protect drugs from external environment like moisture, acids, ingredient interactions, heat, and exposure to oxygen. Microcapsules alter or modify drug release pattern line sustained or control release form. Alternatively decreases frequency of dosing of drug. It mask unpleasant flavors or taste of drug(s). Thus it increases patient compliance. Microcapsule enhances stability of drug. Microcapsule reduces drug loss, thus increases economy of formulation. Microcapsule prevents chemical incompatibilities between drugs. Microcapsule enhances therapeutic effectiveness of drug(s). Encapsulated offers ease of handling of drug(s) as they make the drug(s) free flowing. Microcapsule increases bioavailability of drug(s) [9,10].

METHODOLOGY FOR MANUFACTURING MICROCAPSULES:

The different techniques used for Preparation of Microcapsules are Physical Methods, Chemical Methods and Physicochemical Methods [8-12].

Physical Methods:

Air suspension coating:

In this method the core material which is a solid is dispersed into supporting air stream and these suspended particles are drug coated with polymers in volatile solvent release leaving a very thin layer/film of a polymer on core. The process is repeated for several times until required parameters such as coating thickness are achieved. The air stream which supports particles also helps to dry the particles. The rate of drying is directly proportional to the temperature of air stream. The coating chamber is arranged such that particles move upwards through coating zone, then disperses into moving air and back to the base of coating chamber making repeated passes until desired thickness is achieved.

Process variables to be considered during formulation are_concentration of coating material, properties of core material (Solubility, Melting point, Surface area, Density and Volatility of core material) and air properties (Temperature of air stream and amount of air stream required to fluidize).

Coacervation process:

In this process, the core material is dispersed in the solution of coating material such that the Core material doesn't dissolve/react in solvent. Coacervation occurs when there is a change of pH value of the dispersion which is done either by adding sulphuric acid, HCl, organic acids as a result it decreases the solubility of the dispersed phase (shell material) and proceeds to form precipitate from the solution. The shell material forms a continuous coating around core and shell cools down to harden and forms a microcapsule. The hardening agents such as formaldehyde may be added to the process. The suspension was the dried in spray drier / fluidized bed dryer.

Centrifugal extrusion process:

This process is suitable only for liquid/slurries. In this process the encapsulation occurs using a rotating extrusion head which contains concentric nozzles. The jet of core liquid is surrounded by sheath of solution. As the jet moves through the air breaks owing into droplets of core each coated with wall solution. While the droplets are in fluidized/flight molten wall is hardened/solvent may be evaporated from wall solution. Since, the droplets are within ±10 % mean diameter, they settle as a narrow ring around the spray nozzle. So, capsule can be hardened after formation by holding them in a ring shaped hardening bath. This process is suitable for forming particles of 400 to 2000 μm.

Pan coating:

It is the one of the oldest method used in pharmaceutical industry. In this method, the particles are tumbled in a

pan while the coating material is applied slowly. The solution is applied from the atomized spray to the core materials; hot air is passed to remove coating solvent. Particles > 600µm in size are essentially effective for pan coating.

Spray drying and congealing method:
This method is suitable for labile drugs because of less contact time in dryer and it is economical. In this process active material is dissolved/suspended in polymer solution and trapped in the dried particle. Both the methods are similar in process of dispersion of core and coating substance but there is a difference in rate of solidification of coating. In spray drying, there is a rapid evaporation of solvent in which coating material is dissolved whereas in case of spray congealing solidifying occurs by thermal congealing/introducing a non-solvent. Removal of non-solvent is by sorption, extraction and evaporation.

Chemical methods:

Solvent evaporation method:
This method is widely used for water soluble and water insoluble materials to produce solid and liquid core materials. A variety of film forming agents or polymers can be used. In this method, the coating material (polymer) is dissolved in a volatile solvent which is immiscible with the liquid vehicle phase. A core material (drug) which is to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core coating material mixture or dispersion is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The solvent is evaporated either by continuous agitation or by application of external heat supply.

Interfacial Polymerisation:
In this method, the reactants join at the internal phase and react rapidly. The reaction involves an acid chloride and a compound containing an active hydrogen atom such as amine or alcohol, polyesters, polyuria. As a result, thin flexible walls are rapidly formed at the interface; the acid formed is neutralized by the base formed during the reaction.

Interfacial cross linking:
In this method, the monomer containing active hydrogen is replaced by a polymer such as protein. As a result, reaction occurs at the interface of emulsion, the acid chloride reacts with various functional groups of protein which leads to formation of a membrane. This method was developed to avoid the use of toxic diamines.

In-situ polymerisation:
This method involves direct polymerization of a single monomer is carried out on the particle surface. The coating thickness ranges from 0.2 to 75µm.

Matrix polymerisation:
In this method, a core material is embedded in a polymeric matrix during formation of particles. This method is similar to that of spray drying, in which particle is formed by evaporation of the solvent from matrix material.

Physico-chemical Methods:

Coacervation phase separation:
It includes 3 steps; i. Formation of 3 immiscible phases (core material, coating material phase, liquid phase), ii. Deposition of polymer on core material and iii. Rigidization of coating material.

Inotropic gelation method:
This method is based on the ability of polyelectrolyte to crosslink in the presence of counter ions to form hydro-gels. Inotropic gelation is produced when units of uric acid of the chains in the polymer alginate, crosslink with multivalent cations. These may include calcium, zinc, iron and aluminium. This method includes Microencapsulation was carried out using the Buchi-based microencapsulating system developed in laboratory. Using the polymer, sodium alginate (SA), empty (control, SA) and loaded (test, PB-SA) microcapsules were prepared at a constant ratio (1:30). Complete characterizations of microcapsules, in terms of morphology, thermal profiles, dispersity, and spectral studies, were carried out in triplicate. PB-SA microcapsules displayed uniform and homogeneous characteristics with an average diameter of 1 mm. The microcapsules exhibited pseudo plastic-thixotropic characteristics and showed no chemical interactions between the ingredients. These data were further supported by differential scanning calorimetric analysis and Fourier transform infrared spectral studies, suggesting microcapsule stability. The new PB-SA microcapsules have good structural properties.

MECHANISM OF DRUG RELEASE FROM MICROCAPSULES [11-13]:

Diffusion controlled monolithic system:

It is the most common mechanism of drug release from core material in which the dissolution fluid penetrates the shell then the core comes into contact with dissolution fluid and leaks through interstitial channels or pores. The drug release depends upon; The rate of drug dissolution in dissolution fluid and Rate of penetration of dissolution fluid to the microcapsules and rate at which the dissolved drug escapes from the microcapsules. The rate kinetics of drug release follows higuchi equation;

$Q=[D/J\ (2A- € CS)CSt\ ]^{½}$ ….(1)

Where, Q is the amount of drug release per unit area of exposed surface in time t. J is the Tortuosity of the capillary system in the wall. D is the Diffusion co-efficient of solute in solution. A is the total amount of drug per unit volume. € is the Porosity of the wall of microcapsules. CS is the Solubility of the drug in permeating dissolution fluid.

Dissolution:

The rate of drug release depends upon the dissolution rate of polymer coat, when coat is soluble in dissolution fluid. It also depends upon the solubility in the dissolution fluid and thickness of coat material. The release of the drug occurs by dissolution of the coat or by melting the wall of the capsule.

Degradation controlled monolithic system:

The drug is dissolved in matrix and is distributed throughout the core. The drug is attached to the matrix and is released on degradation of the matrix. The diffusion of the drug is slow when compared to degradation of the matrix.

Erosion:

The release of the drug by erosion mechanism occurs due to pH or enzymatic hydrolysis of the coat. The drug release from microcapsules has become complex. The physicochemical properties of core material like solubility, diffusibility, partition co-efficient and for coating materials like thickness, porosity.

CHARACTERIZATION [12-16]:

Microcapsule size study by Sieve analysis:

Separation of the microspheres into various size fractions can be determined by using a mechanical sieve shaker. The size of microcapsule can also be determined by light and optical microscopy.

Shape and Surface Morphology study:

The surface morphologies of microcapsule are examined by Light Microscopy, Optical Microscopy, Scanning Electron Microscope (SEM), Transmission Electron Microscopy (TEM), Freez Fracture Microscopy and Atomic Force Microscopy (AFM).

Polymer solubility in the solvents:

Solution turbidity is a strong indication of solvent power. The cloud point can be used for the determination of the solubility of the polymer in different organic solvent.

Viscosity of the polymer solutions:

The absolute viscosity, kinematic viscosity, and the intrinsic viscosity of the polymer solutions in different solvents can be measured by a U - tube viscometer and digital Brookfield viscometer.

Density determination:

The density of the microcapsules can be measured by using a multi volume pychnometer.

Encapsulation efficiency (EE):

The encapsulation efficiency or entrapment efficiency of the microcapsules can be determined by analysing drug content using UV-Visible spectrophotometer. The encapsulation efficiency can be calculated by using following equations;

$EE\ (\%) = [PDC/\ TDC]\times 100$ …..(2)

Where, PDC and TDC is practical and theoretical drug content.

Angle of contact:

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The angle of contact is measured at the solid/air/water interface. The advancing angle of contact are measured by placing a droplet in a circular cell mounted above objective of microscope.

Flow properties of microcapsules:

The flow properties of microcapsule can be determine by calculating bulk, tapped densities, Compressibility index, Hausner's ratio and angle of repose.

***In vitro* drug release study:**

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production. The in vitro drug release from microcapsule is studied by using dissolution apparatus of USP or BP grade.

***In vivo* studies:**

The drug release pattern of drug from microcapsule in biological system is studied by using various animal models like dog, rabbit, monkey etc., using sophisticated analytical techniques.

Stability studies:

To determine self life and expiry date of microcapsules dosage form, the stability study is carried out as per ICH guidelines at different storage conditions.

DIABETES:

Diabetes can strike anyone, from any walk of life. And it does in numbers that are dramatically increasing. In the last decade, the cases of people living with diabetes jumped almost 50 percent to more than 30 million Americans. Worldwide, it afflicts more than 422 million people. Diabetes is a leading cause of blindness, kidney failure, amputations, heart failure and stroke. Living with diabetes places an emotional, physical and financial burden on the entire family [17,18].

Diabetes Mellitus (**DM**):

It commonly referred to as diabetes, is a group of metabolic disorders in which there are blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications. Acute complications can include diabetic keto-acidosis, hyper-osmolar hyperglycemic state, or death. Serious long-term complications include cardiovascular disease, stroke, chronic kidney disease foot ulcers, and damage to the eyes [17,18].

Its specialty is **e**ndocrinology. It's major symptoms are frequent urination and increased hunger. DM includes major complications are; Diabetic ketoacidosis, hyperosmolar coma Diabetes is due to either the pancreas not producing enough insulin or the cells of insulin produced. There are three main types of diabetes mellitus foot ulcers. The diagnostic method for detection is high blood sugar. It could be treated by healthy diet and physical exercise. It can be treated by using medicines like Insulin, metformin, Glibenclamide, Gliclazide, Glipizide, Glimepiride etc. Type 1: Diabetes mellitus results from the pancreas's failure to produce enough insulin. This "insulin-dependent diabetes mellitus "cause is unknown (IDDM). Type 2: DM begins with insulin resistance a condition in which a cell fail to respond to insulin properly [17,18].

This form was previously referred to as "noninsulin dependent Diabetes mellitus" (NIDDM)or "adult-onset diabetes". The most common cause is excessive bodyweight and insufficient exercise. Gestational diabetes is the third main form, and occurs when pregnant women without a previous history of diabetes develop high blood sugar levels. Prevention and treatment involve maintaining a healthy diet, regular physical exercise, a normal body weight, and avoiding use of tobacco. Control of blood pressure and maintaining proper foot care are important for people with the disease.

Type 1 DM must be managed with insulin injections. Type 2 DM may be treated with medications with or without insulin. Insulin and some oral medications can cause low blood sugar. Weight loss surgery in those with obesity is sometimes an effective measure in those with type 2 DM. Gestational diabetes usually resolves after the birth of the baby as of 2015, an estimated 415 million people had diabetes worldwide, with type 2 DM making up about 90% of the cases. This represents 8.3% of the adult population, with equal rates in both women and men. As of 2014, trends suggested the rate would continue to rise. Diabetes at least doubles a person's risk of early death. From 2012 to 2015, approximately 1.5 to 5.0 million deaths each year resulted from diabetes. From 2012 to 2015, approximately 1.5 to 5.0 million deaths each year resulted from diabetes. The global economic cost of diabetes in 2014 was estimated to be US$ 612 billion [17,18].

Overview of the most significant symptoms of Diabetes:

The classic symptoms of untreated diabetes are weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger). Symptoms may develop rapidly (weeks or months) in type 1 DM, while they usually develop much more slowly and may be subtle or absent in type 2 DM.

Several other signs and symptoms can mark the onset of diabetes although they are not specific to the disease. In addition to the known ones above, they include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes [17,18].

ANTIDIABETIC DRUGS:

Antidiabetic drugs are all pharmacological agents that have been approved for hypoglycaemic treatment in type 2 diabetes mellitus (DM). If lifestyle modifications (weight loss, dietary modification, and exercise) do not sufficiently reduce A1C levels (target level: -7%), pharmacological treatment with anti-diabetic drugs should be initiated. These drugs may be classified according to their mechanism of action as insulin tropic or non-insulin tropic. They are available as monotherapy or combination therapies, with the latter involving two (or, less commonly, three) antidiabetic drugs and/or insulin. The exact treatment algorithms are reviewed in the treatment section of diabetes mellitus. The drug of choice for all type 2 diabetic patients is metformin. This drug has beneficial effects on glucose metabolism and promotes weight loss or at least weight stabilization. In addition, numerous studies have demonstrated that metformin can reduce mortality and the risk of complications. If metformin is contraindicated, not tolerated, or does not sufficiently control blood glucose levels, another class of antidiabetic drug may be administered. Most antidiabetic drugs are not recommended or should be used with caution in patients with moderate or severe renal failure or other significant co-morbidities. Oral antidiabetic drugs are not recommended during pregnancy or breastfeeding [18].

APPLICATIONS OF MICROCAPSULES [18-20]:

Microencapsulation has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat. A great degree of protection can be provided by microencapsulation. For ex: Vitamin A, K has been shown to be protected from moisture and oxygen. In the field of agriculture microencapsulation has been used to decrease potential danger of handling toxic/noxious substances. Toxicity occurred due to handling of fumigants, herbicides, insectides and pesticides which has been decreased by the use of microencapsulation techniques. To reduce gastric irritation.

In Food Industry:

In conventional drug delivery system, the ingredients react and slowly degrade and lose activity or become hazardous by oxidation reactions and limits bioavailability. Hence microencapsulation can overcome all these challenges by providing texture, colour, blending, odour and masking taste, appealing aroma release. By microencapsulation liquids are converted to solid powder at low cost and stabilize the shelf life of active ingredients.

In Vaccine Delivery:

Microcapsules have been used as carriers as they stabilize and modulate the antigen release. The drug reduces the multiple dosing, increasing patients' convenience. For Ex: LUCRIN depot which contains lyophilized polymer made from lactic acid. The core contains leuprolide acetate which is analog of gonadotropin releasing hormone for the treatment of prostate cancer, breast cancer and endometriosis (Thies and Bissey, 1983). Novel drug delivery system has potential applications in controlled/sustained delivery of the drugs. Microencapsulation has proven to be potential for the replacement of therapeutic agents, gene therapy, for treatment of AIDS, tumors, diabetes.

MARKETED PRODUCTS OF MICROCAPSULES (ANTIDIABETIC DRUGS):

The various marketed commercialized microcapsules of different drugs is given in Table 1 [21,22].

RECENT ADVANCES IN MICROCAPSULE MANUFACTURING TECHNOLOGY:

Polymeric carriers being essentially multi-disciplinary are commonly utilized in microparticle fabrication and they can be of an erodible or a non-erodible type. Recently, numbers of publications and patents have been published. An injectable slow-release partial opioid agonist or opioid antagonist in poly (D, L-lactide) microcapsules with a small amount of residual ethyl acetate was provided by Scientist also being developed. The research also developed a method for preparing enteric polymeric microparticles containing a proteinaceous antigen in a single or double emulsification process in which the enteric polymer acts as a stabilizer for the microparticles which are formed in the process.

A method of encapsulating DNA retaining its ability to induce expression of its coding sequence in a

microparticle for oral administration prepared using the w/o/w emulsion and using biodegradable polymers under reduced shear is also being produced.

Encapsulation of nucleotides and growth hormone using simple or double emulsification methods was achieved by Researcher.

The surface modified microparticles are the advanced microcapsules, which possess a novel protein shell, and a surface coating. The protein shell might consist of cross-linked albumin or other proteins with functional moieties for cross-linking, while the surface coating comprises polyethylene glycol, a second protein or an antibody.

Microparticles are prepared via emulsification followed by protein agglomeration and cross-linking. The surface coating may be covalently-bonded to the cross-linked protein shell or it may be electrostatically adsorbed to the cross-linked protein shell. The surface of the microparticles can be altered to vary the *in vivo* pharmacokinetics and bio-distribution [22,23].

PATENTS OF MICROCAPSULES:

The patent details of microcapsules of various drugs are given in Table 2 [24,25].

Table 1. The various marketed commercialized microcapsules of different drugs.

Drug	Commercial Name	Company	Technology
Risperidon	RISPERIDAL® CONSTA®	Janssen/ Alkemes	(o/w) Double Emulsion
Naltrexone	Vivitrol®	Alkemes	(o/w) Double Emulsion
Leuprolide	Leupron Depot® Trenantone® EnantoneGyn Enantone Depor®	TAPE Takeda Takeda Takeda Takeda	Double Emulsion (w/o/w)
Octreotide	Sandostatin® LAR	Novartis	Phase separation
Somatropin	Neutropin® Depot	Genentech Alkemes	Cryogenic spray drying
Mino-cycline	Arestin®	Ora-pharma	NA
Bromo-criptine	Trelstar™ depot	Pfizer	Phase separation
Busereline	suprecur®MP	Sanofi-Aventis	NA
Triptoreline	Parlodel LAR™ DecapeptylSR	Novartis Ferring	Spray drying
Lanreotide	Somatuline ®LR	Ipsen-Beafour	Phase separation

Table 2. Patent details of microcapsules of various drugs.

Publication	Publication date	Title
US6613354B2	2003/09/02	Proton pump inhibitor & NSAID
US6056977A	2000/05/02	Once-a-day controlled release Sulfonylurea formulation.
US20060-153916A1	2006/07/13	Novel dosage form.
US2002015-6133A1	2002/10/24	Oral administration form of Tramadol & Diclofenac.
US6756056B2	2004/06/29	Carbidopa-Livodopa.
US6558701B2	2003/05/06	Multilayer tablet of Tramadol & Diclofenac.
US200601-65797A1	2007/07/27	GIT disorder
US6099862A	2000/08/08	Oral dosage form for the controlled release of a Biguanides & Sulfonylurea

CONCLUSION:

Microcapsules are a promising carrier for delivery of antidiabetic drugs as it offers several significances to both Pharmacokinetic, Pharmacodynamic and as well as Biopharmaceutical profile of drugs. Despite of numerous advantages of Microcapsules, still several challenges are there, which have to overcome by designing advanced Microcapsules by using novel bioadhesive biodegradable polymers. The next generation of Pharmaceutical market is going to be marketed with various microcapsule drug formulations with affordable cost.

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