Advances in Bioresearch
Adv. Biores., Vol 14 (6) November 2023: 493-503

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.14.6.493503

Advances in Bioresearch

REVIEW ARTICLE

Microparticle Drug Delivery: A Review of The System and Its Wide Range of Therapeutic Applications in Diabetes

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ABSTRACT
Modern society gives great thought to the microparticulate drug delivery system (MDDS) because of its potential to solve the issues that have plagued conventional medicine for so long. Round particles with sizes between 10 and 1000 nm in diameter are called microparticles (MPs). MPs have the ability to encapsulate both soluble and insoluble substances. In clinical trials, MDDS were shown to be superior to conventional drug delivery methods in enhancing drug bioavailability, stability, targeting, and release control. By decreasing medication toxicity and dosing frequency, MPs also provide comfort, ease of administration, and enhanced patient compliance. This article discussed the production process, drug delivery, and potential therapeutic applications of MDDS. Drug release control via gastroretention, enhanced drug dissolution, reduced side effects, targeted drug delivery, mucosal drug delivery, natural products loaded with MPs, improved insulin stability, administration routes, andsustained drug release discussed in detail as therapeutic applications of antidiabetic drug-loaded MPs. The present scenario and potential future developments in creating MPs loaded with antidiabetic medicines also examined.
Keywords: *MDDS, Stability, Drug release, Microspheres*

Received 24.05.2023 Revised 01.09.2023 Accepted 20.12.2023

How to cite this article:
Satish K S, Gyan S, Prateek P, Dilip K C. Microparticle Drug Delivery: A Review of The System and Its Wide Range of Therapeutic Applications in Diabetes.. Adv. Biores., Vol 12 (6) November 2023: 493-503.

INTRODUCTION

Powders ranging in size from 10 nm to 1 mm in diameter are known as microparticles (MPs) [1]. They are made from many materials, including minerals, polymers, and inorganic compounds. Magnetic particles (MPs), lipid vesicles (liposomes, niosomes), microgranules, micropellets, microcapsules, microsponges, microemulsions, and microemulsions are only a few of the many structural forms that MPs may take [2]. Polymeric MPs, formed from either natural biodegradable or synthetic polymers, are by far the most popular kind of MP. They may take the form of either MPs or microspheres, the former of which is the more frequent. Polymers, copolymer, and the active medicinal component form the MPs' matrix (API). Microspheres, on the other hand, have a core made of a solid or liquid immediate by a coat made of a different substance [3, 4].

Polymers are the primary component of polymeric MPs, giving them their structure and influencing their qualities greatly. Polymers should ideally be inexpensive, biocompatible, biodegradable, inert, and stable. Various MPs from both natural and synthetic polymer sources are prepared. The many classes of polymers are shown in Figure2 [5].

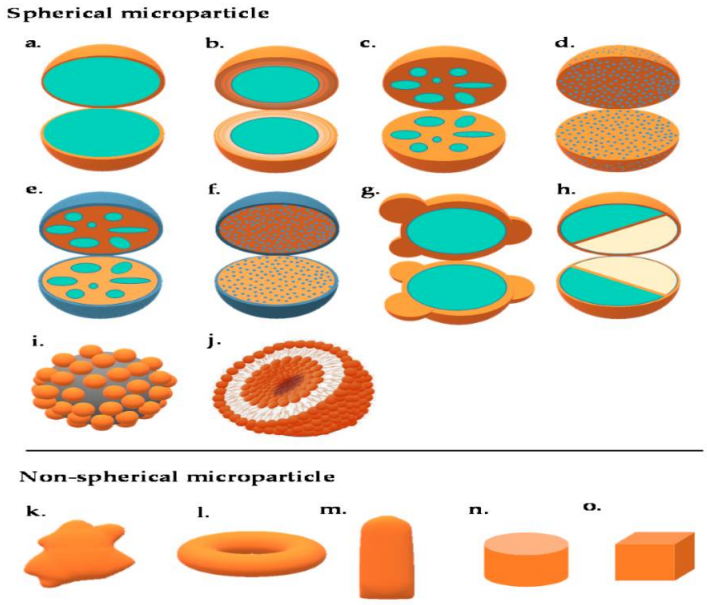

Figure 1: Spherical and non-spherical microparticulate [3, 4]

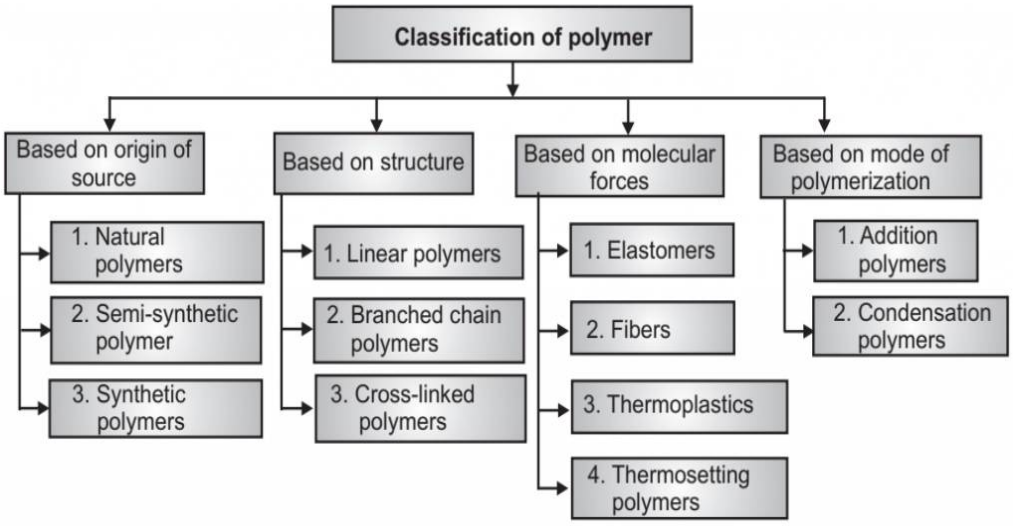

Figure 2:The classes of polymers [5]

MPs' medication release rates are tunable because of their polymer composition. High entrapment efficiency, achieved by loading medicines at larger concentrations into the MPs, may be tuned with respect to polymer type [6, 7].

Researchers also found that the drug loading capacity is inversely proportional to particle size, meaning that smaller particles have a lower drug loading capacity and larger particles have a higher drug loading capacity [8].

The MPs' surface morphology often results from the particles' chemical composition and the production process. Multiple techniques, including scanning electron microscopy, are capable of detecting it. Surface morphology has an impact on the qualities of MP, including wettability and adhesiveness [9]. It has been found that an increase in surface asperities and roughness enhances the wettability of MPs. However, particle adhesion was shown to be negatively influenced by surface roughness. The adhesion qualities of the MPs degrade as the surface roughness rises because the pull-off force is greatly decreased [10].

The electric charge of particles is another important factor that must be taken into account during MPs production and characterisation. When analysing a colloidal system, the zeta potential is often used to calculate the surface charge. Itmay use it find out how stable the colloidal dispersion of microparticles is over both the short and long term11. Negative or positive, a high zeta potential indicates that the repulsive interactions between particles in the colloidal system are strong enough to keep the system from becoming electrically unstable. Systems with low zeta potentials are more likely to coagulate or flocculate, which may reduce physical stability12.

The many practical advantages of the technology behind the microparticulate drug delivery system (MDDS) have garnered a lot of attention. MDDS provide several benefits over traditional dosage forms, including the following: regulated and sustained drug release pattern; reduced drug dose and toxicity; increased drug bioavailability; and improved solubility of poorly soluble medicines due to their relatively large surface area13. Patients are more likely to take their medication as prescribed when it is coated to shield it from the in vitro/in vivo environment, directed to a particular biological site of action, masked from an unpleasant taste or smell, and administered less often14. However, MDDS has to be risk-free for effective clinical applications, execute therapeutic activities, offer convenient administration routes, and be conveniently made. Low repeatability, high material and production costs, and the potential environmental hazards posed by the degradation of various MDDS components and excipients all hampered the development of these drugs15. A large number of unique microparticulate products are undergoing clinical testing at the present time, while others have already been released to the public. Commercially available goods containing MPs are shown as examples in Table 116.

Table 1: Commercially available goods containing MPs

Product	Company	Polymer	Active ingredient	Duration of action	Indication
Sandostatin LAR	Novartis	PLGA-glucose	Octreotide	30 days	Acromegaly
Arestin	OraPharma	PLGA	Minocycline	14 days	Periodontal disease
Bydureon	Amylin	PLGA	Exenatidde	7 days	Type 2 diabetes
Decapeptyl SR	Ipsen	PLGA	Triptorelin	30-90 days	Prostate cancer
Somatulin PR	Ipsen	PLGA	Lanreotode	30 days	Acromegaly
Risperdal Consta	Janssen	PLGA	Resperidone	14 days	Schizophrenia
Lupron Depot	Leuprolide	PLGA	Leuprolide	30-120 days	Prostate cancer

Over the last several decades, diabetes mellitus (DM) has risen to prominence as a serious health issue across the world. Diabetes mellitus is a leading cause of cardiovascular disease and renal illness, and it is currently the fifth leading cause of mortality worldwide [17].

Type 2 diabetes (DM) is a metabolic condition characterised by incorrect lipid, carbohydrate, and protein metabolism and manifested as persistent hyperglycemia. The two most frequent types of diabetes are type 1 and type 2. Type 1 diabetes is caused mostly by an absolute lack of insulin18. Type 2 DM, on the other hand, results from insulin resistance, impaired insulin secretion, and elevated glucose production. Therefore, insulin is an effective treatment for both forms of diabetes. On the other hand, hypoglycemic medications may be utilised to control type 2 DM [19].

The substantial side effects of these drugs-including hypoglycemia, gastrointestinal nausea, irritation, injection fear, and diarrhoea, among others-have prevented a full cure of DM from being achieved despite the flood of antidiabetic treatments entering the pharmaceutical market20. Adherence to therapy and patient compliance will suffer as a consequence of these medications. Consequently, it may be therapeutically advantageous to create a reliable, non-invasive drug delivery system that also has controlled-release [21,22].

Microparticulate formulations have shown promise in the literature for a number of reasons, including the capacity to improve pharmacokinetics and bioavailability, maintain a constant blood concentration of the drug, and improve dissolution and release23. Surface-modified and mucoadhesive MPs have showed advantages in a protective action against enzymatic degradation and enhancing peptide stability, in addition to targeted medicine delivery and stomach retention [24, 25].

According to published works, drug delivery has advanced at a breakneck rate, and many different drug delivery methods have emerged as frontrunners in the last decade26. To that purpose, this review provides a comprehensive overview of MDDS, with a special emphasis on their therapeutic potential as efficient carriers for antidiabetic medicines, and serves to show the worldwide trend of research in this field [27].

Fabrication method of Microparticulate

The Use of a Single Emulsifier

MPs based on natural polymers like proteins and polysaccharides may be produced using this technique. The polymer is first dispersed in an aqueous medium, then in an oily, non-aqueous solvent28. Heat or chemical crosslinkers like glutaraldehyde are then used to create a crosslinked dispersion. Bio-

performance, drug loading, drug release, particle size, and surface morphology are all positively affected by the kind of surfactant used to create the MPs [29, 30].

Double emulsion technique

The formulation of a water-in-oil-in-water (w/o/w) or an oil-in-water-in-oil (o/w/o) double emulsion is part of the double emulsion method. MPs may be made using either natural or synthetic polymers31. Figure 3 depicts a double emulsion w/o/w, which is preferable for medicines, peptides, proteins, and vaccines that dissolve in water. For instance, by using the double emulsion technique, a luteinizing hormone-releasing hormone (LHRH) agonist was able to be encapsulated inside the MPs [32].

Spray drying technique

An organic solvent that is also volatile is used to dissolve the polymer and the medication, and then the mixture is homogenised at high speed (Figure 3). The resultant dispersion is then sprayed into a heated air stream, at which point the solvent instantly evaporates, leaving behind the MPs [33].

Solvent extraction

To carry out solvent extraction or evaporation, the medication and polymer are first dissolved in an appropriate organic solvent. To make an emulsion, the substance is first stirred together, and then added to a solution of surfactant in water. Finally, the MPs are recovered following solvent evaporation (Figure 3). Directly incorporating the medication into the MPs and decreasing the hardening time are the key benefits of this approach [34].

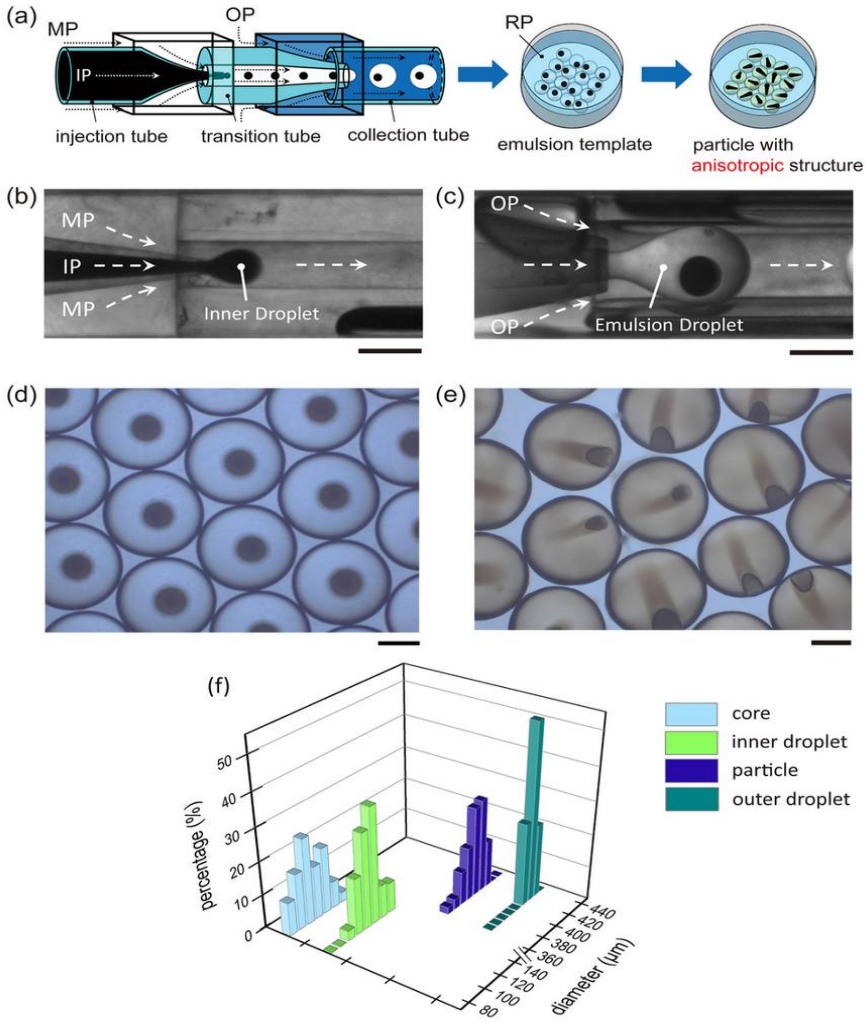

Figure 3: Methods of Fabricating MDDS

Phase separation coacervation technique

This method is mostly used to ready the reservoir systems for encapsulating hydrophilic medicines like peptides and proteins. The formation of a coacervate, which is rich in polymers, is the key premise behind

this method. The coacervate is then separated into a supernatant and a polymer-rich phase using a third component. Phase separation may also be accomplished with the addition of salt, a non-solvent, or an incompatible polymer35.

Drug release from MDDS: influencing factors

Drug content

The concentration of the drug in the MP has an effect on the rate of drug release; a higher concentration results in a faster release rate36.

Molecular weight of polymer

Erosion rates are directly related to polymer molecular weight, which is inversely related to the amount of material released. Because of this, the rate at which a medicine is released slows down as its molecular weight rises37. The polymer breaks down into soluble monomers and oligomers, allowing the drug to diffuse out of the pores into the water. Consequently, progress toward these nanoscale products is quicker since the polymers have a smaller molecular weight38.

Copolymer concentration

The release rate of a medicine from a copolymer depends on the co-monomer ratio; using a more quickly degrading monomer in the polymer results in a faster release rate39. A higher release rate may be achieved by using smaller and more soluble monomers during the polymer erosion process. However, the copolymer composition may be affected by differences in the polymer's phase behaviour or the thermodynamics of the encapsulating active component40.

Types of excipients

Excipients serve a number of important purposes in the formulation, including affecting the drug's release through different mechanisms and the efficacy of the encapsulation. Through the addition of polyvinyl alcohol (PVA), Yang et al. enhanced the encapsulation and size distribution homogeneity of bovine serum albumin (BSA) in MPs. When the concentration of PVA was raised, the MPs became more porous and the BSA release was modulated41.

Nature of the polymer

The pace at which MPs are released is highly dependent on the kind of polymer employed in their composition and the functional groups that impact polymer breakdown. Surface eroding polymers and bulk eroding polymers are the two main classes of polymers42. Polymer degradation and drug burst (in which half the drug is released in the first hour of the run, followed by a regulated release) are the results of fast water absorption into the MP matrix for bulk-eroding polymers like PLGA43. Meanwhile, surface-eroding polymers like polyanhydrides are constructed from hydrophobic monomers connected by pliable bonds. It is hydrolytically degradable at the polymer/water interface, where it exhibits resistance to water penetration and hydrolysis produces oligomers and monomers. As the polymer breaks down, the medication is released at the surface44.

MPs size

The drug's loading capacity into the MPs and the MPs' subsequent release profile are both affected by the MPs' size. Dispersion of drug particles and their rate of discharge both improve with decreasing particle size because of the larger ratio of surface area to volume. The MPs' tiny size, on the other hand, allows more water to penetrate them and leads to their disintegration, resulting in an instant burst release of their content rather than a slow, steady drip45.

Environmental pH

Studies on a smaller scale have demonstrated that the degree to which cross-linked hydrophilic polymers expand and become hydrated is strongly influenced by the medium's pH. Polymers with acidic or basic functional groups expand differently depending on whether or not the surrounding medium has a pH value closer to their respective pKa or pKb values46. Example: the anionic polymer has negative charges on its surface due to the ionisation of acidic functional groups, hence may connect with the medium's other positive charges, which are opposite in sign47. The erosion of polymers may also be influenced by the pH of their surroundings. Accordingly, the pH-sensitive polymer responsible for regulating the MPs' drug-release profile is modified by the swelling and/or breakdown48.

The concentration of hydrogen ions in the medium also affects the extent to which the functional groups on the polymer's surface and the mucous membrane's surface are ionised. Thus, MPs, especially mucoadhesive polymers, are able to control the duration and intensity of their interaction with the absorption site49. Positively charged polymers, such chitosan, were shown to have superior mucosal adhesion qualities versus anionic polymers, which meant improved conditions for medication release and absorption. How it's administered Several formulation approaches, including oral, transdermal, vaginal, ophthalmic, and pulmonary for drug inhalation, are employed in the production of MDDS for various routes of administration50The mechanism and kinetics of drug release from microparticulate carriers is

determined by a variety of physiological factors unique to each route of administration, including the structure of tissues, the pH of the medium, the existence of permeability barriers, and the presence of metabolic enzymes51.

An anti-diabetic microparticle-based therapy

Water-insoluble and water-soluble pharmaceuticals have both been effectively encapsulated using MDDS since its invention. To improve therapeutic effectiveness, gastroretentive drug release, medicinal chemical targeting, insulin stability, side effects, drug dissolution, and patient compliance, MDDS incorporates insulin and other anti-diabetic drugs 52.

Drug retention in the stomach with controlled release

Extending the amount of time, a medicine is kept in the stomach is a common strategy for increasing its bioavailability. Several gastroretentive drug delivery methods, including as floating and mucoadhesive MPs, loaded with antidiabetics have been presented and assessed. For the MPs to float in the stomach fluid, their bulk density must be lower than that of the fluid itself53.

Hollow MPs are another method, which allow the formula to float in the stomach without influencing the pace at which the stomach empties. By dispersing throughout the stomach's contents, MPs speed up the drug's release, allowing for a longer gastric residence period and better plasma concentration control. Moreover, the unique benefits of floating MPs lessen the need for dosing as often, as well as the risk of mucosal adhesion and dose dumping54.

Enhanced drug dissolution Several variables determine how well a drug is absorbed after being taken orally; two of them are water solubility and dissolution rate55. Researchers have shown that MPs increase the solubility and dissolution rate of lipophilic hypoglycemic medications, and hence they are suggested for this purpose. Because of its poor oral bioavailability in ordinary glibenclamide tablets, MPs was developed to increase the drug's solubility in water.

The integration of pioglitazone into hydrophilic MPs also enhanced the drug's solubility and bioavailability. The MPs were made using the spray-drying method from two water-soluble ingredients, cyclodextrinandpoloxamer 407. In comparison to the standard, pure pioglitazone, the drug release rate was dramatically boosted by the spray-dried particles56.

Reducing side effects

The potential for harmful reactions to medications is a major problem that has to be solved before effective treatments can be created. Polymeric MPs are used as one kind of modified drug delivery technology to improve the security and efficacy of pharmaceuticals57.

Localized medication delivery to treat illness

Magnetic microparticles

The magnetic MPs were used to target the medicine delivery to the affected area. This allowed the freely circulating medicine to be directed to the receptor site and kept there at therapeutic concentration for a predetermined amount of time58. To do this, nano/micromagnets were incorporated into polymeric MPs (such chitosan and dextran) and the MPs were immobilised in a magnetic field. Proteins, peptides, and chemotherapeutic drugs were delivered to tumours, including liver tumours, via therapeutic magnetic MPs, while diagnostic magnetic MPs were used to image liver metastases 59. Several reports in the scientific literature describe the use of magnetic particle carriers to deliver anti-diabetic drugs to a specific disease site. Prior research exposed ethynyl vinyl acetate MPs to an oscillating magnetic field to see how polymer composition affected insulin release. Mice were given insulin-magnetite-PLGA MPs orally while in a magnetic field. With blood glucose levels down by 43.8%, it's clear that the magnetic microspheres are an effective oral insulin therapy60.

Stabilizing insulin for better use

Due to its instability in the stomach, insulin can only be given through the parenteral route. To increase the stability and bioavailability of oral insulin, many methods have been presented to date61, 62.

MPs stuffed with natural products

Traditional herbal medicine practitioners utilise the plant *Gongronemalatifolium* to treat a wide range of illnesses, including diabetes. In the solid-lipid MPs, the plant extract was loaded with a retention efficiency of 68% [63].

Catechin is a naturally occurring chemical with anti-diabetic properties. Its utility is limited by its poor oral bioavailability. Encapsulating catechin in Eudragit RS100 MPs, however, greatly increased its absorption and decreased blood glucose levels in diabetic rats [64].

The active element berberine may be found in many different plants. Some examples are European barberry, goldenseal, Oregon grape, and tree turmeric. Its potential as a non-synthetic alternative to existing antidiabetic medications has garnered a lot of attention in recent years. However, its limited oral bioavailability prevents it from progressing to other clinical therapies. Scientists have been working on

ways to improve the oral hypoglycemic effect of berberine by incorporating a berberine-phospholipid complex into the phytosomes delivery mechanism. Anti-diabetic medicines and antioxidants containing bioflavonoids, such rosmarinic acid, were formerly in use. Rosmarinic acid crosslinked MPs had a greater inhibitory impact on -glycosidase than the free molecule, with less cytotoxicity and antioxidant activity to boot [65].

Prolonged medication effect

Several approaches, including matrix sustained-release tablets, orodispersible tablets, and depots, were explored for the development of extended-release formulations of antidiabetic medicines [66]. However, MDDS had paid a lot of attention to this submission. Drug release was slowed, dosage was reduced, bioavailability was increased, and safety was improved with the use of biodegradable polymeric MPs. Biodegradable MPs may be made from either naturally occurring polymers like starch or manufactured polymers like polylactic acid. Once they come into touch with the mucous membrane's aqueous environment, biodegradable polymeric MPs expand and assume a gel-like shape [67]. The drug's release rate and effectiveness are both affected by the kind and amount of polymer used. The key challenges in the creation of biodegradable polymeric MPs are improving drug loading efficiency and controlling drug release [68].

Synthetic polymers

Due to their safety and biocompatibility, MPs were employed as drug delivery vehicles in clinical studies. On the other hand, they do have certain negatives, such as a tendency to travel away from the injection site, which may raise the risk of embolism and, as a result, organ damage [69].

Also, mucoadhesive microspheres of rosiglitazone maleate were created for sustained release of the medication. The mucoadhesive microsphere has a strong tendency to remain attached to the mucosal tissue for up to 12 hours. Metformin hydrochloride sustained-release polylactic acid microparticles (MPs) were shown to be an effective therapy for diabetes in a separate investigation. The drug bioavailability was increased and the problem of swallowing oral tablets was eliminated thanks to the MPs, making them a viable alternative to traditional oral medication delivery methods [70].

Mucosal administration of anti-diabetic medications

Bioadhesion is the attachment of a medicine to a membrane utilising water-soluble polymers, while adhesion explains the sticking process. Mucoadhesive microparticles (MPs) may be produced by either coating the MPs with a mucoadhesive polymer or integrating a mucoadhesive polymer-based matrix into the formulation. Both methods result in the same mucoadhesive microparticles [71]. These MPs' several benefits over more traditional formulations include increased drug penetration and bioavailability, longer residence duration at the application location, and controlled drug release. The ocular, rectal, oral, buccal, vaginal, and nasal mucous membranes are all potential delivery sites for mucoadhesive MPs [72].

However, the physicochemical features of the polymeric formulation and the kind of mucosal tissue being targeted are both critical in determining a dosage form's mucoadhesive performance [73]. These mucoadhesive substances are typically high molecular weight polymers that engage with the mucus layer of the mucosa epithelium by means of hydrogen bonding, ionic contacts, hydrophobic interactions, or van der Waals interactions [74].

Modes of administration

Treatments for people with DM have been suggested using a variety of antidiabetic drug delivery strategies. The researchers realised that different patients would respond better to different administration methods for the antidiabetic medicines loaded MPs, therefore they designed the MPs accordingly [75]. The pulmonary route of administration, for instance, has been employed for many decades to administer medications for systemic and local submissions to treat a wide range of respiratory system illnesses. Research on inhaled antidiabetic drug-loaded MPs has been a major focus in the pharmaceutical sector in recent years [76].

It is generally recognised that the amount of time a medicine spends at the site of absorption is a major element in determining the drug's bioavailability. To do this, mucoadhesive polymers were used [77]. Previously, pulmonary insulin administration in diabetic rats was accomplished using N-trimethyl chitosan MPs modified with permeability enhancers. When compared with subcutaneous injection, chitosan-based MPs were shown to be both pharmacologically effective and comparably bioavailable. Analysis of lung tissue from a histologically preserved rat provided conclusive evidence that the formulation was risk-free [78].

The use of multilayered surface-modified MDDS for oral insulin administration has been proposed. Ferric ions and dextran sulphate were alternately deposited on the microspheres' surfaces to create the MPs. Deposition of 10 bilayers of insulin produced a hypoglycemic effect that persisted for 12 hours. The

polymer, production technique, and administration route for several polymeric MPs loaded with antidiabetic medicines [79,80].

Current status and anticipated developments

As a result of vast differences in drug loading, particle properties, and manufacturing methods, there are still many obstacles to overcome despite the worldwide progress in creating new microparticulate delivery methods for diabetes drugs are now being development. Therefore, the market offers only a limited selection of medications based on antidiabetic MPs. Bydureon®, for instance, is a subcutaneously administered sustained-release injection of exenatide, a glucagon-like peptide-1 receptor agonist. Microspheres technology is used to create this depot by AstraZeneca U.K. Limited; the medication particles are encapsulated inside PLGA-based microspheres. Patients with type 2 diabetes may get relief from their condition by using this medicine.

Additionally, relevant patents published on Google Patent.com were analysed to represent the current state and potential advances in this subject.

CONCLUSION

The advantages of MDDS over more conventional pharmaceutical dose forms include better effectiveness, lower toxicity, and more convenient administration. Producing MPs may be accomplished using a wide variety of processes, including as spray drying, solvent extraction, single and double emulsion, and the technique of phase separation coacervation. The content of the medication as well as its physical state, as well as the nature, molecular weight, and concentration of the polymer, as well as the kind of excipients that are used, are the primary factors that determine the drug release profile from MPs. Although diabetes is a worldwide problem, scientists are always exploring new approaches to medicine delivery and disease management in an effort to improve the effectiveness and safety of existing treatments. Anti-diabetes medications loaded onto MPs were developed for their distinct benefits in drug delivery, including localised drug delivery, enhanced drug dissolution, controlled drug release, decreased drug toxicity, and increased bioavailability and stability. Currently, there is a rising amount of curiosity in the potential of MDDS for the treatment of diabetes, particularly when applied to non-oral delivery. The MPs may be strategically put and employed, especially in cell sorting, diagnostics, biological products, and genetics, *via* the integration of many approaches.

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