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Review Article

Pharmaceutical Perspectives on Direct Compression: Formulation and Evaluation of Antidiabetic Tablets

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A B S T R A C T

Diabetes Mellitus is one of the chronic diseases that require lifetime treatment through drug therapy. Oral solid dosage forms such as tablets still form a bulk of the drug market due to the convenience, stability, and efficiency associated with them. There are various techniques used in tablet formulation. However, direct compression remains one of the most promising methods used for the production of antidiabetic drugs owing to its simplicity and cost-effectiveness as well as fewer processes involved in it. This paper aims at exploring some of the aspects of the direct compression of pharmaceutical products with special emphasis on antidiabetic drugs' formulations. The classification of drugs as well as the biopharmaceutical aspects of antidiabetic drugs (such as solubility and permeability according to Biopharmaceutics Classification System) is explained.Besides, powder blending, manufacturing of antidiabetic tablets, powder blend evaluation and evaluation of finished tablets as well as their quality attributes are discussed in detail. Other topics covered include recent developments in direct compression, such as use of co-processed excipients, nanotechnology and AI-based optimization. the current regulatory guidance and Quality by Design approach are emphasized.

Keywords: Diabetes Mellitus, Direct Compression, Antidiabetic Tablets, Excipients, Preformulation Studies

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INTRODUCTION

Diabetes mellitus is defined as a condition marked by high blood sugar levels caused by deficiencies in either insulin production or utilization and has become a serious global health problem due to the rising cases and related complications such as cardiovascular problems, nerve damage, kidney damage, and eye damage. Successful management of diabetes involves consistent drug treatment alongside lifestyle changes which necessitate the role of medication compliance in therapy. From that perspective, oral solid preparations especially tablets have gained considerable significance in the treatment of this condition since they are convenient, stable, accurately deliver the dose, and economical in comparison to liquid preparations or parenteral methods. Antidiabetic treatments benefit from the use of tablets greatly due to their accurate dosage, easy delivery method in case of chronic illnesses, and increased compliance rates which have been observed mostly in elderly people who constitute a substantial percentage of patients diagnosed with diabetes. Additionally, the versatility of the tablet form allows preparation of immediate and modified release formulations for better treatment outcomes. Efficient methods of production like direct compression make it easier to manufacture antidiabetic tablets.(1,2,3)

The tablet dosage form is among the most favored methods of treatment for chronic ailments such as Diabetes Mellitus because of its many merits. These include easy administration, precise dosing, mobility, and shelf life. Chronic treatment involves long-term drug intake by patients, and tablets increase patient adherence to treatment because of their convenience and ease of dosing, particularly for extended release tablets or once daily formulations. Tablets are relatively inexpensive to produce and distribute, thus affordable to a large number of patients. They are also

flexible regarding formulation; they can be designed to provide different drug release mechanisms and combinations that make it easier to treat complex illnesses such as diabetes. Direct compression technology is among the easiest and efficient ways of tablet production, whereby tablets are made from a mixture of active compounds and other additives using compression without the need for granulation(4,5). The process also reduces the number of processes, safeguards the drug from any undue heat and moisture, and is highly suitable for the production of drugs that may be susceptible to such factors. Moreover, the process is cost-effective and efficient and, when fine-tuned, results in high-strength and rapidly dissolvable tablets, which makes the process perfect for producing antidiabetic tablets.(6,7,8)

This literature review attempts to cover all possible pharmaceutical aspects regarding the application of direct compression as a highly efficient approach in manufacturing antidiabetic tablets for managing Diabetes Mellitus. The scope of the present study covers not only the basic theoretical background concerning direct compression, choice of excipients and their action, but also a number of pre-formulation issues that are crucial for ensuring a successful outcome. Another important aspect to be covered involves formulation and processing considerations needed for producing high-quality tablets in terms of flowability, mechanical strength, disintegration and dissolution rate. In addition, this review will highlight some of the problems associated with antidiabetic drugs, such as the need for dose uniformity, low flow properties of active substance and stability issues, along with new trends in this area, namely development of co-processed excipients and new formulations.

Overview of Antidiabetic Drugs

Classification

Classification of antidiabetic agents depends on the mechanism of action and targets in the treatment of diabetes mellitus. These medications are targeted at regulating blood sugar levels through insulin release promotion, insulin resistance reduction, inhibition of glucose absorption and glucose elimination. One of the most common groups includes biguanides like metformin which regulate glucose output from the liver, increase insulin sensitivity, and have no hypoglycemic effect. Sulfonylureas like glibenclamide and glipizide increase insulin secretion by pancreatic β-cells and thus have a hypoglycemic effect. DPP-4 inhibitors like sitagliptin increase incretin hormone activity by glucose dependence and therefore stimulate insulin secretion and decrease glucagon output. SGLT2 inhibitors include dapagliflozin and canagliflozin and regulate blood glucose levels by facilitating renal glucose elimination, which additionally leads to weight loss and cardio protective effects. Thiazolidinediones like pioglitazone increase insulin sensitivity, while alpha-glucosidase inhibitors delay carbohydrate absorption. Novel antidiabetic medications include GLP-1 receptor agonists among others. The classification of these drugs is essential for proper selection of drug candidates and formulation approaches especially in cases where tablet formulation with direct compression technique is applied.(3-5)

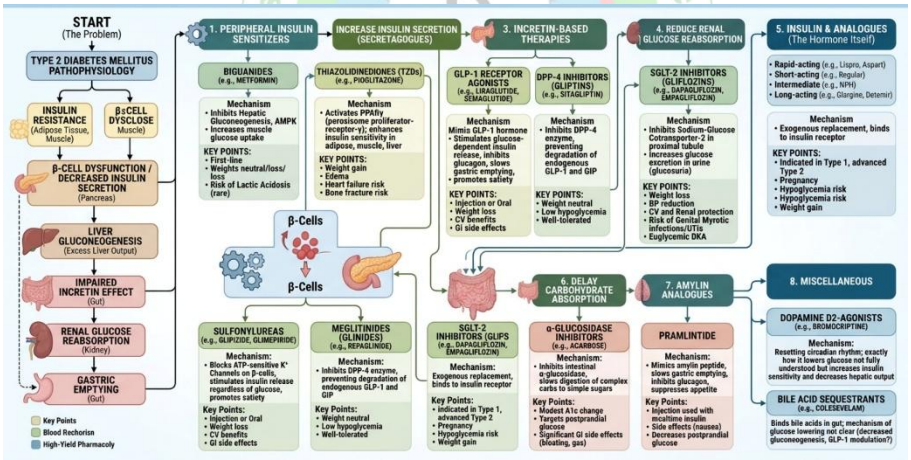

Figure 1: Classification of Antidiabetic Drugs Based on Mechanism of Action

Biopharmaceutical Properties

It is evident that the properties associated with biopharmaceutics of antidiabetic drugs will influence the effectiveness of absorption and the bioavailability of the drug. The solubility property of a drug will affect its ease of dissolution in gastrointestinal fluid; drugs that are not very soluble in water tend to have difficulty in being absorbed, making the process of drug development very hard especially in cases like direct compression where there will be need to improve the dissolution properties of the drug. The classification of drug based on its solubility and intestinal permeability into one of the four classes under the Biopharmaceutics Classification System is very helpful in formulation strategies since drugs classified in Class 1 (those with high solubility and high permeability) are very good candidates for tablet formulation. Drugs that fall within Class II and Class IV may need either the improvement in solubility or permeability respectively. It is also important to take into account the stability of antidiabetic drugs because most of these drugs are unstable especially when exposed to light, heat, and humidity.(29,30)

Direct Compression Technique

Direct compression is one of the methods used in the manufacture of tablets, where an even mixture of the active pharmaceutical ingredient with the excipients is directly pressed into tablets without going through any granulation process. In this case, the powder that is used should have sufficient compressibility and flow properties. The powder mixture is compacted to form the required tablets using

tableting machines. As compared to other processes like wet or dry granulation, direct compression is more convenient since it does not require any intermediate steps. The advantage of direct compression is that the heat-sensitive and moisture-sensitive drug substance can be stabilized during its preparation.(9,10)

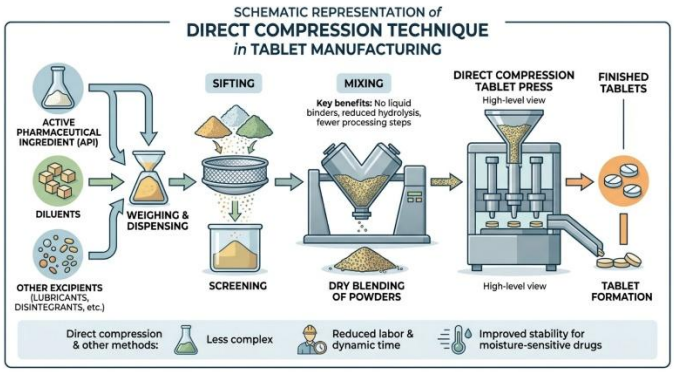

Figure 2: Direct Compression Technique in Tablet Manufacturing

Advantages of Direct Compression

There are various advantages associated with direct compression technology, especially in the manufacture of antidiabetic drugs used for treatment of Diabetes Mellitus. Firstly, it is economical since it does not require many processing procedures such as granulation, drying, and milling that will increase labor costs, energy use, and machine utilization. Secondly, it is an easy method since few processing stages are involved; thus, the chances of contamination and variation are reduced significantly, and therefore, the quality of the resulting product is enhanced. Thirdly, it is suitable for the production of heat- and moisture-sensitive drugs because it does not require any wet granulation or drying procedure, thus avoiding deterioration of heat and moisture-sensitive substances.(10,12)

Limitations of Direct Compression

Although the technique offers several benefits, some of the drawbacks of this process might affect the efficacy of the tablet produced, especially those that have been developed to treat diseases such as Diabetes Mellitus. The first disadvantage involves the need for powder formulations with adequate flowability and compressibility, which unfortunately many of the active ingredients in medicines do not have, and thus require the addition of proper excipient. Poor flowability leads to poor die-filling and weight variation while compressibility determines the mechanical strength of the product.(11) Secondly, direct compression can be subject to the problem of segregation. As mentioned above, this occurs due to differences in density, particle size or even shape of the drug substance and excipient, which leads to a non-homogeneous distribution of the active ingredient in the tablet. This is especially important in cases where low dose antidiabetic drugs are involved.(41)

Excipients Used in Direct Compression

Excipients are very important in the effectiveness of direct compression technology, especially the preparation of antidiabetic drugs tablets for the treatment of Diabetes Mellitus. As direct compression technology depends on the utilization of powders that have good flow properties and compressibility, the choice of excipients is vital in making sure uniform mixture, good compressibility, and proper characteristics of tablets. Some of the most commonly used excipients in this process are the diluents or fillers like microcrystalline cellulose and lactose, which help increase the bulk volume and enhance compressibility. The other commonly used excipients in direct compression are binders like pregelatinized starch, which increases the hardness of the tablet, and superdisintegrants like crospovidone and sodium starch glycolate, which ensure disintegration and dissolution of the drug.On the other hand, lubricants, such as magnesium stearate, decrease the friction when the tablets are compressed and ejected from the die cavity, while glidants such as talc increase powder flowability.(8,15,16)

Fillers/Diluents

Diluents are important additives that play an integral part in direct compression formulations where the quantity of API in the drug is low, which is common for drugs that have been formulated for treating Diabetes Mellitus. Diluents make the dosage larger by providing the necessary weight to ensure consistency of dosage and ease of manipulation during the manufacturing process. Of the various diluents available, microcrystalline cellulose (MCC) is considered one of the best due to its high compressibility, good flow and capacity of forming tough tablets even under relatively low compression forces, which makes them very suitable for direct compression. It has some disintegration capability too, thus making its use all the more convenient. Other examples of diluents that are extensively used include lactose, owing to its good flowability, pleasant taste and wide applicability for a variety of drugs. Variants of lactose, such as spray-dried lactose, are especially designed for use in direct compression formulations owing to their flowability and compressibility.(17,18)

Binders

Binders are additives that increase cohesion among the components in the blend, which ensures that the particles stick to each other during the compaction process to create tablets that have sufficient mechanical strength. Regarding antidiabetic drugs for treating patients with Diabetes Mellitus in the form of direct compression, it is extremely important to select an effective binder that will not only give the right amount of binding ability but also ensure adequate flow and disintegration. Pregelatinized starch is among the most

popular binders utilized in direct compression because apart from being a binder, it is also considered to be a good disintegrating agent. Pregelatinized starch is produced by partially hydrolyzing and dehydrating starch.This additive increases the hardness and structure of tablets while remaining capable of absorbing water quickly, making pregelatinized starch especially useful for immediate-release tablets.(18,19)

Disintegrants

Disintegrants are very important excipients in making tablets as they help in breaking up tablets into small pieces when they come into contact with gastro-intestinal fluid, which leads to faster dissolution and absorption. For instance, in the development of antidiabetic tablets that are meant to treat Diabetes Mellitus, fast and effective disintegration will help them act on time as expected. Examples of superdisintegrants that can be incorporated in tablets made using direct compression method include crospovidone and sodium starch glycolate because of their extensive swelling property and high rate of water uptake. Crospovidone acts via wicking action to promote disintegration within short time but does not form gel whereas sodium starch glycolate expands a lot on coming into contact with water hence causes the tablet to fragment fast. Other examples include croscarmellose sodium that utilizes both wicking and swelling action to promote fast disintegration and Low-substituted hydroxypropyl cellulose (L-HPC) that exhibits excellent disintegration efficiency. Natural disintegrators that can be used include starch, alginic acid, and guar gum.(37,39)

Lubricants & Glidants

These two types of excipients have a critical role in the direct compression method since they facilitate the manufacturing process while ensuring that there is proper formation of tablets. In the formulation of antidiabetic tablets for the management of diabetes mellitus, these two types of excipients have an important role to play in ensuring that there are no processing problems, especially those associated with sticking, friction, and flow. For instance, lubricants such as magnesium stearate are included in the formulation to prevent friction between the material used to make the tablets and the walls of the dies in order to prevent sticking. However, excessive use of magnesium stearate could affect the hardness of the tablet and even dissolution, which means that its levels should be optimized.(38)

Preformulation Studies

Preformulation study is an integral part of the process of tablet formulation; it provides valuable information regarding the physicochemical properties of the drug and drug-excipient interaction, particularly in direct compression formulations applied for the treatment of Diabetes Mellitus. One of the important aspects of preformulation studies is the drug-excipient compatibility testing, which guarantees that there will be no negative chemical or physical reaction occurring during the drug formulation process, and this will not result in instability of the formulation. FTIR technique allows us to analyze the possibility of any chemical interaction based on the changes in functional groups; DSC, on the other hand, allows for evaluating thermal properties of the substance and determining potential compatibility issues via melting point and enthalpy measurement.(2,28,34)

Other factors to consider in preformulation are those involving flow properties of the powder mixture because they affect the feasibility of the direct compression method. Factors like the angle of repose give an idea of powder flowability with smaller angles being indicative of greater flowability. In turn, bulk density and tapped density give information about powder packing. The two factors mentioned are measured alongside others like Carr's Index and Hausner ratio in order to evaluate compressibility and flow characteristics. Failure to optimize flow properties may cause problems such as weight variation and uneven distribution.(14,26,35)

Formulation Considerations

Antidiabetic tablets formulated via the technique of direct compression will need to be made using excipients whose function is to help improve their flowability and compressibility. It is essential to identify suitable excipients based on the physicochemical characteristics of the active ingredients. For example, microcrystalline cellulose can be added to help increase compressibility, whereas spray-dried lactose will improve the flow of the ingredients. Disintegrants such as crospovidone and croscarmellose sodium can also be added to the formulation to guarantee that the resulting tablets will disintegrate very quickly. Ensuring dose uniformity can be rather difficult because low-dose drugs like glimepiride can produce variations in dose due to even minor differences during the blending process of the drug formulation. The techniques employed to achieve uniformity of dosage include the use of geometric dilution as well as suitable diluents. Moisture sensitivity is another problem that can arise when formulating antidiabetic drugs like metformin because some of the active drugs and excipients may easily get damaged by moisture. Taste masking will be necessary even for some antidiabetic medications such as metformin hydrochloride due to their bitter flavor.(11,15)

Formulation factor optimization is another issue that should be considered because it allows manufacturing high-quality tablets. In this respect, the application of DOE technique is quite popular since this approach helps evaluate the effects of several formulation and process factors simultaneously without engaging in empirical experiments. One can take advantage of the concept of factorial design to study the impact of varying concentrations of superdisintegrants and binders on tablet hardness and disintegration time. Meanwhile, the method of response surface methodology (RSM) can be employed to optimize compression pressure, the concentration of lubricants, and the ratio of excipients in order to enhance the dissolution rate and mechanical strength of tablets. If the substance in question is insoluble (e.g., glibenclamide), the formulation will consist of solubilizers and co-processed excipients that increase the dissolution rate of the active pharmaceutical ingredient.(47,48)

Manufacturing Process (Direct Compression)

Tablet manufacturing using direct compression requires adherence to precisely defined procedure(s) intended to produce drug tablets consistently with respect to the quality and efficiency of each dose unit manufactured. For example, this process is often used to formulate antidiabetic medications that help manage diabetes mellitus. The initial

step in the tablet manufacturing process is the mixing together of active ingredient(s), and other excipients including filler(s), binder(s), and disintegration aid(s), into a homogeneous blend before compression can occur. Mixing is essential in producing an acceptable final product because it ensures a uniform mix, especially when working with very low doses. After the blended ingredients have been thoroughly mixed together and resulted in a homogeneous powder mass, lubricant(s), such as magnesium stearate, and glidant(s), such as talc, are added to the blend to decrease interparticle friction between the individual powder particles and to improve the flow and minimize the tendency for them to become adherent to each other during compaction into tablets.(40,42)

Tablets are produced in tablet machines through a compression process. This process is the final stage that occurs when the lubricated mixture of ingredients is pressed into a tablet shape. In order to produce acceptable tablets from this process, various parameters must be optimized during the compression process. For example, the amount of compression force applied to the tablets will impact the tablet's hardness, thickness, and friability. If the compression force is excessive, the resulting Tablet will be too hard, leading to slow breakdown of the Tablet after ingestion. Conversely, if insufficient compression force is applied to the Tablet, the resulting tablet will be very weak and will fail due to breakage. Likewise, the speed at which the compression occurs will also impact the tablet's final properties. When the compression is performed at an extremely fast rate, it may lead to the possibility of not filling the die adequately or the capping problem of the Tablet. Other process variables (e.g., dwell time, punch design, etc.) will also play an important role in creating acceptable tablets(41).

Evaluation methods

The evaluation of the powder blend has a key importance in the direct compression process, maintaining consistent tablets manufactured using diabetic formulations. Another important characteristic of the powder mixture is its flowability, as this determines the ability of the powder to flow freely into the die cavity.Angle of repose, Carr's Index, and Hausner Ratio can be used to determine the flowability of the powder. High flowability ensures that there will be uniform filling of the dies, which in turn reduces variations in tablet weight. Compressibility is the other significant factor, which indicates the capability of the powder to reduce in volume due to pressure, forming a solid tablet. Particle size and shape, as well as the nature of the excipients present in the powder, affect its compressibility. Finally, uniformity is necessary for effective tablet formation, particularly for low dose medications.(31,32)

Table 1: Evaluation Parameters of Powder Blend with Pharmacopoeial Limits

Category	Parameter	Method	Acceptable Limits (IP/USP/BP)
Powder Blend	Angle of Repose	Funnel method	≤ 30° (Good flow)
	Bulk Density	Graduated cylinder	— (Used for calculations)
	Tapped Density	Tapping method	—
	Carr's Index	Calculated	≤ 15% (Good), 16–25% (Fair)
	Hausner Ratio	Calculated	≤ 1.25 (Good flow)
	Flowability	Visual/Flow rate	Good to excellent flow required

There are several tests used in assessing the quality of compressed tablets as per the standard set by pharmacopoeia to ensure their performance in the management of DM. Weight variation tests are conducted to ensure the uniformity in tablet weight; hardness tests are done to check the mechanical strength necessary to withstand handling. Thickness of the tablet is checked to determine its size; friability tests are carried out to assess the ability of a tablet to withstand wear and tear during transportation. The mechanical strength of a tablet is determined through hardness and friability tests, hence showing its ability to withstand any form of pressure. Disintegration tests are done to assess how long it takes for a tablet to disintegrate into fine particles. Dissolution tests are conducted to test the time taken to dissolve and the degree of drug release from the tablets. The drug release process can be determined by using one of the models of release kinetics such as zero order, first order, Higuchi and Korsmeyer-Peppas. Content uniformity tests determine the amount of active ingredient in each tablet.(40)

Table 2: Evaluation Parameters of Tablets with Pharmacopoeial Limits

Tablets	Parameter	Method	Pharmacopoeial Limits
Physical Tests	Weight Variation	Weighing 20 tablets	±5% (>250 mg), ±7.5% (80–250 mg), ±10% (<80 mg)
	Hardness	Monsanto/Pfizer tester	4–8 kg/cm² (typical)
	Thickness	Vernier caliper	±5% variation
	Friability	Roche friabilator	≤ 1% weight loss
Mechanical Strength	Crushing strength	Hardness tester	Adequate to withstand handling
Disintegration	Disintegration Test	IP/USP apparatus	≤ 15 min (uncoated tablets)
Dissolution	Dissolution Study	USP Apparatus I/II	≥ 80% drug release in 30–45 min*
Content Uniformity	Assay	HPLC/UV method	85–115% of label claim

Recent Advances

The recent development in the direct compression process technique has been very effective in improving the quality and performance of the antidiabetic tablets that are used to treat Diabetes Mellitus. Amongst other advances, the most important is the incorporation of the use of co-processed excipients which involves using a combination of two or more excipients to offer better function than those used in ordinary physical mixtures. These include the use of microcrystalline cellulose in combination with lactose and crospovidone which make the tablets more flowable and thus ideal for use in direct compression. There have also been great improvements in the formulations, and this has led to the success in applying direct compression on poorly soluble compounds like glibenclamide and pioglitazone.(36,43)

Moreover, the application of nanotechnology has opened up new possibilities for enhancing the potential of direct compression through the use of nanoparticles of drug molecules or nanoparticulate delivery systems that increase solubility, dissolution rates, and effectiveness. For instance, nanosuspension and nanoparticulate carriers of antidiabetic medicines may be used for direct compression into tablets, offering improved absorption and efficacy. The area of artificial intelligence and machine learning in formulation science is yet another emerging frontier in formulation science. Here, the technology uses predictive models to determine the right excipient and optimize the physical characteristics of the tablets economically, with little experimentation. Machine learning algorithms allow massive data to be processed for predictive modeling of formulations, resulting in major breakthroughs in formulation science.(46,45)

Regulatory Considerations

The regulatory matters play a very important role in ensuring that the safety, efficacy, and quality of antidiabetic tablets prepared using the direct compression technique in treating the disorder named Diabetes Mellitus are ensured. It is essential to abide by the guidelines that have been stipulated by the International Conference for Harmonisation throughout the whole process of development of the drugs. The ICH guidelines like Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality System) serve to facilitate this purpose.(19-21)

In addition to the ICH guidelines, another requirement for quality control and assessment is adherence to the guidelines established by the pharmacopoeia, including Indian Pharmacopoeia (IP), US Pharmacopeia (USP), and British Pharmacopoeia (BP).(22-28). Within these guidelines, there are detailed procedures and acceptable ranges for weight variation, dissolution, disintegration, and content uniformity tests. Another approach that has gained attention recently in pharmaceutical formulation development is Quality by Design (QbD). It involves designing formulations based on the critical quality attributes (CQAs), critical material attributes (CMAs), and critical process parameters (CPPs), which affect the performance of formulations.(25,48)

Challenges and Future Perspectives

However, despite the numerous advantages of direct compression technology, there are certain difficulties that need to be overcome before being able to use the process of manufacturing antidiabetic pills as an effective way of treating Diabetes Mellitus. The first difficulty arises when trying to upscale the process since the laboratory formulations of pills may fail due to the inability to manufacture pills on a greater scale. The machinery, different compression pressures, and difficulties with powder blending could lead to inconsistent tablets that are excessively soft or hard, or dissolve unequally. Also, assuring good flowability and avoiding powder segregation become crucial when manufacturing tablets in a large quantity. The problem of stability needs to be mentioned separately because of its importance to antidiabetic drugs that tend to be environmentally sensitive.(49)

In the future, the development of antidiabetic tablets will be more geared towards the concept of personalized medicines where the drug will be developed according to the particular need of the individual. With technological advancements in the formulation of drugs, tablets can now be formulated according to the particular dosage required by the patients. Another method that can be used is the use of digital technologies to formulate personalized drugs for the patients with diabetes. The future of antidiabetic tablets does not only focus on addressing existing challenges but also uses modern methods of developing the drug.(50)

CONCLUSION

Overall, direct compression has proven to be a very effective and popular technique in formulating antidiabetic tablets that can effectively manage diabetes mellitus in the long term. Its benefits include simplicity, economy, fewer production stages, and compatibility with heat- and moisture-sensitive drugs. Nonetheless, there is the need for proper assessment of several key elements when using direct compression, such as flowability, compressibility, compatibility of the drug with the excipient, and dose homogeneity, particularly for small doses. The choice of the excipient and proper preformulation study is crucial. Moreover, technologies like co-processing of excipients, nanoparticle-based drug delivery systems, and the use of artificial intelligence for optimizing formulation have contributed immensely to widening the application spectrum of DC technology towards difficult drugs such as poorly soluble antidiabetic drugs. Regulations such as ICH guidelines and QbD approach contribute greatly to the development of effective and reliable formulations. Although there are several challenges in terms of scalability, stability, and processing of highly potent or poor flow drugs, further advances will help in improving the potential of DC technology in the future. Everything considered, the application of DC technology to the creation of potent antidiabetic pills is highly promising.

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