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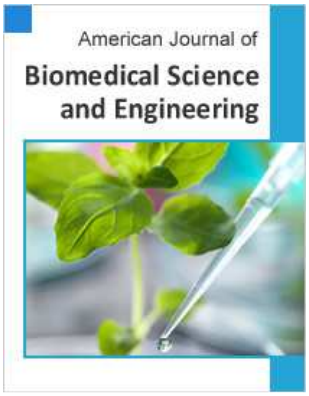

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Application of a Multicomponent *Lentinus tuber regium* Based Co-Processed Excipient (*fizlent*) as a Novel Directly Compressible Filler-Binder-Superdisintegrant in Ibuprofen Tablet Formulation

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Abstract
Ibuprofen has poor water solubility. Its direct compressibility into tablet is difficult due to poor flowability and compactibility. The suitability of a novel multicomponent *Lentinus tuber regium* based co-processed excipient (*fizlent)* as a directly compressible (DC) filler-binder and superdisintegrant in ibuprofen tablet was investigated. Ibuprofen (76.92% w/w) blended with *fizlent* (22.58% w/w) and lubricated with 0.50% w/w magnesium stearate was compressed at 8 tons in Erweka table top single punch tablet press fitted with 8.50 mm biconvex punch and die. Tablet weights, total drug content, crushing strength, friability and disintegration time were determined using the British Pharmacopoeia methods. The basket method in Erweka dissolution apparatus at 50 rpm was used for dissolution study in 900 ml phosphate buffer (pH 7.2) at 37 ± 1 °C for 60 min. The absorbance of samples withdrawn at 5 min intervals were spectrophometrically determined at wavelength of 221nm. Glossy, intact, off-white, round and convex shaped tablets obtained disintegrated within 30.17 ± 1.94s. Other tablet properties complied within pharmacopoeia limit. The application of *fizlent* as filler-binder in DC of ibuprofen tablet solved problem of its poor compactability and flowability. The ability of the tablet to break down completely in 30.17 ± 1.94 s shows that *fizlent* has a superdisintegrant property. This aided the early release and dissolution of ibuprofen, hence its ability to achieve $T_{50,}$ T_{80} in less than 5 min and T_{90} in 12.50 min. Furthermore, the onset of action and attainment of peak plasma concentration of ibuprofen will not be prolonged, thus, resolving the issues with poor water solubility noted for ibuprofen.

1. Introduction

The oral route of drug administration is very common for systemic effects. Tablet or capsule is the most widely used dosage form because of convenience in the ease of administration, accuracy of dosing and patient compliance (1, 2). Tablets are unit solid dosage forms meant for oral use and are manufactured from blend of powders containing the active pharmaceutical ingredient (API) and other additives to be compressed into a tablet which could be prepared by either wet granulation, dry granulation or direct compression. Each of these techniques has its advantages and disadvantages. The

invention of direct compression (DC) technology increased the production of tablets all over the world due to its advantages over the dry granulation and wet granulation techniques. This method involves simple combination of API with other ingredients and directly compacting of the resultant mixture. Direct compression (DC) is gaining popularity since compared to current APIs, the emerging new molecules are usually sensitive to moisture, oxidation and heat, making wet granulation less attractive (3). DC presents few stability issues, involves few excipients and require less multi-functional excipients. Compacts made by DC disintegrate into primary particles, rather than granules, and hence, can provide faster API release (4). The DC technique in comparison with other tablet manufacturing methods is simple and requires few unit operations and utilizes much less energy, making the process more economical (5). It is highly influenced by the material characteristics, such as flowability, compressibility and dilution potential, since ≈ 70% of commercial formulations contain excipients at higher fractions than APIs. Thus, an ideal DC excipient enables one to prepare compacts with APIs even at levels lower than 50% excipient (6). It is not suitable for poorly flowing powdered drugs since they may agglomerate or segregate during manufacture (7). In addition, problems, such as weight variation and content uniformity might occur because most filler-binders commercially available have limited dilution potential (5).The main driving force behind DC technique is the use of direct compression vehicle (DCV). By using DCVs, the flow properties of the drugs with poor flow can be improved and hence can be manufactured by direct compression technique. In order to apply DC technique in the manufacture of tablet, parameters such as compressibility and flowability are to be maintained at optimal range. In general, a good conventional tablet must have enough hardness to withstand various stages of stress and must disintegrate and dissolve within pharmacopeia acceptable time limit. For the tablet to have enough hardness, the excipients housing the API should have enough compaction properties. Also, effective flow of powders is required in each step of tablet preparation. Poor flow may result in difficulties for the compression mix to flow from hopper to the die cavity which may cause inconsistency in tablet weight as well as content of API. The processing steps in wet granulation increases flowability of granules but in the case of DC a direct compressible grade excipient is very necessary for better flow. Proper flow can be attained by using glidants at levels of 0.1 - 0.2% w/w. Also if the flow exceeds the optimum range, it may result in segregation of tablet ingredients which may also lead to content uniformity problems (8).Currently, about 80% of all tablets are manufactured by wet granulation even though this technique involves a great number of processing steps, the addition and removal of water and stability problems for thermolabile as well as hydro-degradable drugs. Furthermore, the equipment used, material handling and energy consumption are also problems to consider. Therefore, the most recent trend is to use the direct compression technique (9).

However, only a few excipients can be directly compressed into tablets, owing to their poor physical properties such as compactibility, flowability and compressibility (10). In order to determine the suitability of an excipient for DC its functional properties must be assessed. The most important functional property is compactibility, which is related to the deformation mechanism that occurs when a pressure is applied to bind particles together to form a compact. For example, brittle-deforming materials fragment during compaction, easing the formation of a large bonding area. On the other hand, ductile materials show plastic deformation and deform by dislocation of the crystals along slip-planes, forming hard compacts (11). In addition to powder compactability and flowability, dilution potential is other crucial property in a DC excipient. The dilution potential is defined as the minimum amount of excipient needed in the blend with an active ingredient to form tablets of adequate compactibility and friability (<1%). The dilution potential varies with the API and allows the researcher to select the right combination of API and excipient in a formulation. For this reason, the selection of appropriate excipients with a low dilution potential has generated great interest among formulation scientists (12). Excipients with improved functionality which can meet up with the above challenges can be obtained by developing new chemical entities, new grades of existing materials or their combinations (13). In the last three decades, a new grade of existing excipients has been developed (14, 15). New grades of existing excipients can be achieved by modifying fundamental properties, leading to improved derived functional properties (16, 17). Fundamental characteristics, such as morphology, particle size, shape, surface area, porosity and density, all determine excipient functional properties, such as flowability, compressibility, compactibility, dilution potential, disintegration and lubrication potential (13).

The above challenges have opened doors for introduction of new excipients into the market. However, few excipients are made available due to relatively high cost involved in excipient development, including the toxicological tests. With the increasing number of new drug moieties having varying physicochemical, pharmacokinetic, permeation and stability properties, there is a growing interest among formulators to search for new excipients that have minimal scale-up problems, low manufacturing costs, and little environmental impact (18). Other factors driving the search for new excipients are the growing popularity of the DC process and demands for an ideal filler-binder that can replace two or more excipients avoiding the need for multiple excipients such as disintegrant, lubricant, glidant, etc. Such new excipients are also expected to meet the demand for the increasing speed capabilities of modern tablet presses which require excipients to maintain good compressibility and low weight variation even at short dwell times. They are also to address the shortcomings of existing excipients, such as loss

of compaction upon wet granulation, high moisture sensitivity and poor die filling as a result of agglomeration.

Considering these deficiencies, a multicomponent *Lentinus tuber regium* based co-processed filler-binder designated as *fizlent* was developed and its physico-technical properties has been evaluated. It was compressible, flowable and had good dilution potential for some drugs that were tested. In addition, it was recorded to have high swelling index and hydration capacity (19). Its introduction as a DCV will hopefully provide a novel pharmaceutical excipient with filler-binder and superdisintegrant potentials. This will add to the choice of excipients suitable for the tableting of some thermolabile and hydro-degradable drugs. It will also give room for few unit operations that utilizes much less energy, making the process more economical.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAIDs) which also has analgesic and antipyretic activities. It has been a non-prescription drug since 1984. The drug is practically very slightly soluble in water and has poor flow and compaction characteristics owing to its needle-like (acicular) crystalline structure and viscoelastic properties, respectively. It is readily absorbed from the gastrointestinal tract and has an onset of action of approximately 30 to 60 min with a duration of action of 6-8 hrs. (20-24). Ibuprofen is a core medicine in WHO's "Essential Drugs List" that serves as a list of minimum medical needs for a basic health care system (25).

This study was designed to produce ibuprofen tablet by direct compression technology using *fizlent* as filler-binder and disintegrant. Its flowability will be assessed by examining the uniformity of weight of the tablet produced while the compactability will be evaluated through the tablet mechanical properties such as crushing strength, friability and possibly, crushing strength-friability ratio (CSFR). The superdisintegrant property will be evaluated through the disintegration time and the dissolution profiles for the release of drug content. It is expected that the technical problem of poor flow and compaction characteristic of ibuprofen will be solved by compressing it with *fizlent.* Ibuprofen has onset of action of 30-60 min (23, 24). The possibility of very fast release of ibuprofen from *fizlent* as anticipated through its predictable superdisintegrant action makes it very useful as analgesic, anti-inflammatory and anti-pyretic since its onset of action and time of attaining peak plasma concentration may not be delayed.

2. Materials and Methods

2.1. Materials

All reagents were used as received and includes hypo® (sodium hypochlorite solution) (Multipro, Nigeria), ethanol (Fischer Scientific, UK), n-hexane (Sigma-Aldrich, USA), citric acid, tartaric acid (Loba Chemie, India), magnesium stearate (BDH, England), ibuprofen (Boai Nky, China), potassium dihydrogen orthophosphate, sodium carbonate, sodium hydrogen carbonate (Surechem, England). *Lentinus tuber-regium* tubers were purchased from *Ahia-ohuru* market, Aba, Nigeria.

2.2. Methods

2.2.1. Formulation of Multicomponent *Lentinus tuber regium* Based Co-processed Excipient (*fizlent*)

The directly compressible excipient used for this study was prepared as described by Ugoeze and Nkoro (19).

2.2.2. Formulation of Ibuprofen Tablets Using *fizlent*

Tablets, each containing 200 mg of ibuprofen were prepared as shown in Table 1. Weighed portion of *fizlent* was blended with exact amount of ibuprofen. The mixture was lubricated with magnesium stearate and compressed on single punch tablet press (Erweka, EP-1, Germany) at compression pressure of 8 tons.

2.2.3. Evaluation of Tablets

The British Pharmacopeia methods were used to evaluate the ibuprofen tablets (26). Tablet uniformity of weight was evaluated by individually weighing twenty randomly selected tablets on analytical electronic balance (Ohaus, China). The diametrical crushing strength of ten tablets was determined with digital hardness tester (Erweka TBH 100, Germany). The friability of ten tablets was determined in tablet friabilator (Erweka TAR 220, Germany) set at 25 rpm for 4 min. The disintegration time of 6 tablets was determined using a tablet disintegration apparatus (Erweka, ZT 122, Germany) in 900 ml of 0.1 N hydrochloric acid maintained at 37 ± 1 °C.

Table 1. *Formula for ibuprofen directly compressible tablet using fizlent.*

Ingredient	Amount	
	% w/w	mg
Ibuprofen	76.92	200.00
Fizlent	22.58	58.70
Magnesium stearate	0.5	1.30

2.2.4. Dissolution Test

The release rate of ibuprofen from the tablet was conducted with the basket method in a dissolution apparatus (Erweka DT-600, Germany) in 900 ml of phosphate buffer (pH 7.2) maintained at 37 ± 1 ^{o}C. The basket speed was set at 50 rpm and the procedure lasted for 60 min. A 10 ml sample was withdrawn at intervals of 5 min and replaced with the same volume of phosphate buffer. The absorbance of the respective filtered and ten-fold diluted samples were spectrophotometrically determined at wavelength of 221 nm (Jenway, 6405).

3. Results and Discussion

3.1. Tablet Properties

The results obtained from the evaluation of tablet properties are presented in Table 2. Wholesome, glossy, off -

white, round and convex shaped tablets were obtained. Deviation of the mean tablet weight was less than 5%. The British Pharmacopeia, 2012 specifies that tablets weighing 250 mg or more should not deviate by more than 5% (26). Tablets with acceptable crushing strength were obtained. A tablet breaking force of 4 kg is usually considered to be the minimum for satisfactory uncoated tablets (27). Oral tablets normally have a crushing strength of 4-10 kg. However, hypodermic and chewable tablets are usually softer (about 3 kg) and some sustained release tablets are harder (about 10-20 kg). Tablet crushing strength has been associated with other tablet properties such as density and porosity. Crushing strength generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression (28). Values obtained for tablet friability were slightly above 1%. For uncoated tablets, friability should not exceed 1% especially for tablets produced by wet granulation, but tablets produced by direct compression can give friability above1 % (29). Another measure of the mechanical strength of pharmaceutical tablets is the crushing strength-friability ratio (CSFR). The crushing strength provides a measure of tablet strength while friability is a measure of tablet weakness. Studies have shown that the higher the CSFR, the stronger the tablet (28, 30). The value of CSFR obtained is fairly good since tablets were prepared by direct compression technique. Considering disintegration time, for most uncoated tablets, the British Pharmacopeia specifies 15 min (although it varies for some uncoated tablets) while for coated tablets, up to 2 hrs. may be required. Thus, the tablet disintegration test is limited to manufacturing control of batch-to-batch variations in individual products and is not most of the time a measure of bioavailability (31). Nevertheless, it is used to provide a simple and useful means for monitoring and controlling the quality of tablets. Complete disintegration of the tablets formulated with *fizlent* occurred in 30.17 ± 1.94 s with mild effervescence mechanism. Literature reveals that *fizlent* applied in this study as filler-binder have high swelling index as well as hydration capacity (19). This may be the reason for its superdisintegrant action obtained in less than 1 min. For ibuprofen immediate release tablet, the United States Pharmacopeia specifies that not less than 80 % of the labelled amount is dissolved in 60 min (32). The dissolution profile for ibuprofen tablet compressed directly with *fizlent* shows that 88.54 % of ibuprofen was released in 5 min. Maximum release of 95.17 % occurred in 20 min (Fig. 1). The major technical problems associated with ibuprofen powder, especially in its application in DC method of tablet production are poor flowability, compaction and water solubility (21-24). The values of tablet uniformity of weight, crushing strength and friability obtained in this study comply with the British Pharmacopeia specifications. This showed that the application of *fizlent* as filler-binder in the direct compression of ibuprofen tablet facilitated in overcoming these major technical hitches of poor compactability and flowability. The ability of the tablet to break down completely in 30.17 ± 1.94 s shows that *fizlent* have a superdisintegrant property. This aided in the early release and dissolution of the API, hence its ability to achieve $T_{50,}$ T_{80} in less than 5 min and T_{90} in 12.50 min. With ibuprofen having onset of action of 30-60 min (23, 24), the very early release from its tablet as facilitated with *fizlent* ensures that its onset of action and attainment of peak plasma concentration will not be prolonged. This shows that the problem of poor water solubility noted for ibuprofen could be resolved by compressing it directly with *fizlent.*

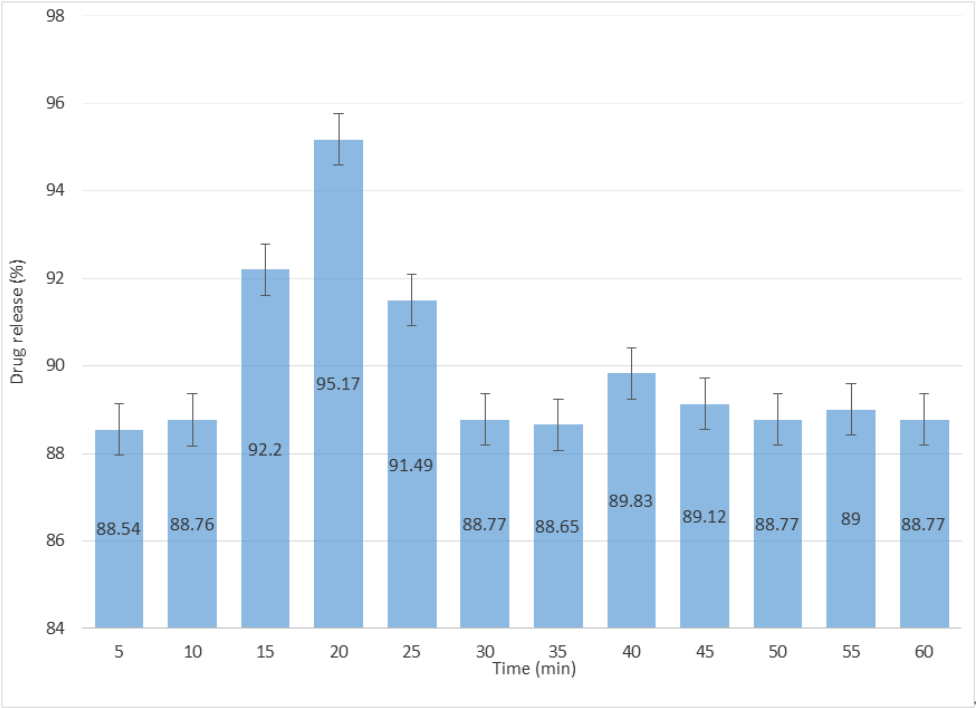

Fig. 1. *Bar chart showing the release of ibuprofen from the tablet prepared by direct compression using Fizlent.*

Table 2. *Tablet properties.*

Parameter	Value
Weight uniformity (mg)	253.55 ± 1.10
Total drug content (mg)	198.95±0.34
Crushing strength (kgf)	4.54 ± 0.84
Friability (%)	1.25 ± 0.96
CSFR	3.63 ± 0.75
Disintegration time (s)	30.17 ± 1.94

3.2. Conclusion

The results obtained in this study showed that the innovative multicomponent *Lentinus tuber regium* based co-processed excipient, *fizlent* may be applicable as directly compressible filler-binder for very fast release of ibuprofen. Its ability to function as filler-binder and superdisintegrant makes it to have added economic advantage over several commercially available DC powders. Moreover, considering that the major bulk of *fizlent* is an edible agricultural product makes it of more economic interest. The large scale cultivation of *Lentinus tuber regium* is feasible having been successfully cultivated in the laboratory (33, 34). The authors suggest the need for further application of *fizlent* as filler-binder using the direct compression method with several other analgesic and other drugs especially where very fast immediate drug release is necessary.

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