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FORMULATION DEVELOPMENT AND QUALITY PROFILING OF PARACETAMOL – IBUPROFEN COMBINATION TABLETS

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ABSTRACT: Opportunity is envisaged by some astute pharmaceuticals manufacturers to increase product portfolio and widen the spectrum of treatment of pains to cover analgesia, pyrexia and inflammation using one product. In this research work, paracetamol – ibuprofen combination tablet was designed and formulated, developed and profiled to address this anticipation thus satisfying the requirement of one product fits 3 health challenges. As a consequence of adoption of wet granulation method, granules of acceptable quality profiles were developed and processed and subsequently culminated in production of tablets that met all required critical quality attributes as defined in quality target product profile. Characterization of both granules and tablets showed results that reassured that the requirements of fitness for purpose were met and will lead to product quality and patient safety on the long run. Indeed, content uniformity of active ingredients in each tablet was engendered by equally uniform tablet weight to the extent that relative standard deviation was only 1.29% for uniformity of weight, 1.74% for ibuprofen content and 0.28% for paracetamol content. Brittle/friable index of 9.2 is high enough to assure that the tablets will withstand both normal and abnormal stresses during handling throughout life cycle as time-release capability of the tablets was evident in the result of disintegration time.

INTRODUCTION: In pharmaceutical dosage forms design especially tablets, cognizance must be taken of the critical implication of defective and suboptimal formulation. In fact, formulation experts are of the opinion that formulation as well as process variables in addition to other physicochemical metrics must be properly gauged in order for the product to deliver good performance [1-3].

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It is when all these variables are logically monitored that critical quality attributes such as safety and purity, potency and efficacy and hence fitness for purpose could be assured. Mustapha *et al* (2011) observed that proper articulation and implementation of rational formulation design especially when active ingredients are poorly water soluble remain the only panacea that could guarantee efficient time-release capabilities in the final product [4]. In effect, rational formulation design must take into consideration biological and chemical, physicochemical and physicomechanical properties of both active ingredients and excipients. It is also opined that manufacturing process must not in any way negatively impacts the quality attributes of the process output [5, 6].

It is highly recommended that the critical materials attributes (CMAs) as well as critical process parameters (CPPs) that will combine and interact to deliver efficient critical quality attributes (CQAs) to the final product be scientifically known and understood [7]. So also the risks inherent in each of the attributes must be assessed for the sources and extent of variations and impacts on the product brought forth and mitigated and or controlled.

Although wet granulation is an age long method in pharmaceutical processing, its relevance in present day pharmaceutical manufacturing is not in doubt. This is due primarily to its capability to deliver granules that are usable in various applications such as Tableting, encapsulation and dry powder suspension among others [4]. According to formulation experts, wet granulation ensures drug homogeneity and consolidation, reduces agglomeration and dust level, and improves wetability, flowability and tabletability of starting materials [4, 8].

Others opined that wet granulation improves powder flow rate and compressibility which are necessary if acceptable product would be made from materials with different physicochemical properties [4, 9]. Shaikh (2013) agreed that granulation process output such as granules and blends could be used to control and manipulate release rate of final product, improve yield and productivity, reduce down time and facilitate metering and or volumetric dispensing [10].

Paracetamol is an old first generation non-opioid analgesic and antipyretic drug [11], manufactured by more than 80% of local pharmaceutical manufacturers in Nigeria hence it is a "me-too" product with rock bottom price [12].

In recent time however, manufacturers that desire to carve a niche for themselves in the market place developed and manufactured paracetamol in combination with Ibuprofen – a non-steroidal anti-inflammatory drug (NSAID) which is also administered for the treatment of aches and pains arising from all shades of inflammation [11]. This effort increased the share and coverage of analgesic market by those manufacturers to some extent, in addition to improvement in patients' compliance arising from better efficacy noticed as engendered by analgesic, antipyretic and anti-inflammatory activities of the combination [13]. Other benefits derived from this venture by the manufacturers include expansion of product portfolio and extension of patent period, improved product differentiation and enrichment and enhancement of product life cycle management.

This research work was therefore positioned to develop Paracetamol – Ibuprofen combination tablets and evaluate its quality profiles such as weight uniformity and friability, hardness and disintegration time, and potency as measured by assay and recommended by formulation scientists [2, 14, 15]. All these response variables were assessed in line with official specifications in reference books [16, 17] and compared with pre-set quality target product profile (QTPP).

MATERIALS AND METHODS:

Materials: The formulation was designed to contain paracetamol (Tianjin Co., China) and ibuprofen (IOL chemicals, India) as active pharmaceutical ingredients. Other materials included microcrystalline cellulose (J. Rotten Maier and Sohnne, Germany) and sodium carboxyl methyl cellulose (Shadong Yulong, China) all as disintegrants, potassium sorbate (Globe chemicals, Germany) as preservative, maize starch (Royal Ingredients, Holland) as binder, silicon dioxide (Evonik Degussa, Germany) as anti-caking and anti-sticking agent, sodium lauryl sulfate (Vinamax organics Ltd., India) as surfactant and lubricant, and magnesium stearate (S Kant Healthcare, India) as lubricant. All materials were sourced courtesy Edo Pharmaceuticals Ltd, Benin City, Nigeria.

Methods: As contained in the formulation design, each of the materials was carefully weighed using UTE weighing balance (United Trade Electronic Co. Ltd, China) and counter checked for accuracy and completeness. Total quantities of paracetamol and ibuprofen, microcrystalline cellulose and sodium carboxyl methyl cellulose and potassium sorbate were added into mixing equipment (Hobert, England) and dry-mixed for 10 min at 30rpm. Maize starch was suspended in 100ml demineralised (DM) water to form slurry and while stirring, 400ml of boiling DM water was added to form paste which was allowed to cool below 60^{o}C. The starch paste was introduced to the powder blend in the mixer and kneaded for 5 min while

ensuring adequate wetness of the mass. Wet mass was carefully removed from the mixer and manually pressed through 3mm stainless sieve, spread and dried in a tray oven (Manesty-Mitchell, England) at temperature of 50^{o}C until moisture content was about 2.2% determined with a moisture analyser (Ohaus, China). Dried mass was removed from oven and pressed manually through 3mm stainless sieve to form granules which were transferred into mixer. Silicon dioxide, sodium lauryl sulfate and magnesium stearate were passed through 1mm stainless sieve and added into the granules in the mixer and blended for 5 min while observing homogeneity.

Micromeritic properties of the blended granules were evaluated using metrics such as flow rate, angle of repose, bulk and tapped densities, compressibility (Carr's) index and Hausner ratio following previously reported method [4]. However, 20g of granules was used in the evaluation and repeated in triplicate while dimensions of funnel used were base diameter of 8.8cm, efflux length of 6.2cm and orifice diameter is 4mm. Blended granules were fed into tablet press (Manesty, England) to which punches and dies have been fitted and granules compressed into tablets while monitoring quality attributes of the final tablets.

Evaluation of quality of tablets: During Tableting process, the quality target product profile (QTPP) as constituted in Table 2 was monitored to ensure they comply with pre-set specification limits.

Weight uniformity was checked with precision standard analytical balance (Ohaus Corporation, USA) using 20 tablets each of which was weighed individually and minimum, maximum, mean, standard deviation and relative standard deviation computed.

Hardness (crushing strength) of 10 tablets was evaluated singly with hardness tester (Type Monsanto) and recorded with its mean and standard deviation calculated.

Friability was checked using 10 tablets. The initial weight of 10 tablets was noted and then introduced into friabilator (Erweka, Germany) which was allowed to rotate 100 times (i.e. for 4 min at 25rpm).

The tablets were carefully removed, de-dusted and reweighed. The % friability was estimated from the difference in the weight of 10 tablets before and after the determination which was done in triplicate.

Disintegration time using 6 tablets was evaluated with disintegration apparatus (Manesty, England). A tablet is placed in each tube which was in turn kept in a thermostatically controlled chamber that contained water at temperature of 37±1^{o}C. The apparatus was switched on and the time it took each tablet to break down into particles smaller enough to pass through a pre-set mesh aperture was noted and analyzed.

The content of each of the active ingredients in the tablet (i.e. assay) was analyzed as followed. 20 tablets were accurately weighed individually and average weight computed. The tablets were crushed and powder equivalent to 0.300g of paracetamol was weighed into a 250ml flask and 10ml distilled water and 30ml dilute sulfuric acid solution added. It was boiled under reflux for one hour then cooled and the content diluted with distilled water to 100ml mark. To 20ml of resulting solution was added 40ml of distilled water, 40g of ice and 15ml dilute HCL solution. The content was titrated with 0.1M solution of Ammonium Cerium Sulfate until greenish yellow colour is observed. Blank titration was carried out with distilled water. Difference between the volume of test titration and blank titration is the actual volume required. Amount of paracetamol in the sample is calculated from equation 1 below and % potency estimated.

Amount of paracetamol (mg) =Actual volume of ammonium cerium sulfate used x 75.6 ----------1

For ibuprofen, powder equivalent to 0.450g of ibuprofen was taken and dissolved in 50ml of methanol in a 250ml conical flask. 0.4ml of phenolphthalein solution was added and titrated against 0.1M sodium hydroxide solution until colour changed to pink/ red. A blank titration was similarly carried out with methanol and the difference between the two volumes gave the actual amount used. Amount of ibuprofen in the sample is estimated using equation 2 and % potency computed.

Amount of ibuprofen (mg) = Actual volume of 0.1M NaOH used x 20.63 ---------- 2

RESULTS: The outcome of characterization of resultant granules was as contained in **Table 1** and observation was to the effects that the starting raw materials have responded to wet granulation process as shown by the values of the parameters.

Both quality targets as well as observed qualities were reported in **Table 2**. The values were indications of good performance of granulate during tablet compression process.

TABLE 1: MICROMERITICS OF PARACETAMOL – IBUPROFEN COMBINATION GRANULES

Micromeritic parameters	Observed outcome
Flow rate - g/s, (n=3, ±SD)	1.18 ± 0.0695
Angle of repose - (^{o}), (n=3, ±SD)	31.64 ± 2.11
Bulk density - g/ml, (n=3, ±SD)	0.5314 ± 0.0086
Tapped density - g/ml, (n=3, ±SD)	0.6266 ± 0.0046
Hausner ratio (n=3, ±SD)	1.179 ± 0.026
Carr's (compressibility) index – %, (n=3, ±SD)	15.18 ± 1.92

DISCUSSION: Given the physical characteristics of each of the starting raw materials in the formulation especially flow properties; it is not difficult to infer that the choice of wet granulation as a processing method has imparted good attributes on the granules as indicated in Table 1. With high flow rate of 1.18g/s and angle of repose of 31.64^o, uniform and rapid filling of dies cavities by granulates during tableting was ensured as shown by uniformity of tablets weight in Table 2 to the extent that the RSD is just 1.29% as against official maximum limit of 5%.

As key indices of flow, both bulk and tapped densities have shown that consolidation of granules during tablet compression did not pose any problems. With values of 0.5314g/ml for bulk and 0.6266g/ml for tapped densities respectively, Hausner ratio of 1.179 and Carr's index of 15.18% were estimated. These values are indications that tablets of uniform weight could be produced as free flow and compressibility of granules are engendered by such values as observed by other researchers [18, 19, 20]. The progressive increase in density from bulk to tapped and finally to tablet is an indication that the onset and attainment of granules consolidation especially during tablet compression were swift.

Results of tablet weight uniformity alluded to uniform die fill and rapid onset of consolidation as indicated in Table 2. The minimal weight variation of tablet (RSD of 1.29%) has culminated in optimal content uniformity of active ingredients in the tablets as indicated.

Hardness (crushing strength) which measures the compactness and strength of the tablets to withstand stress at any point during handling was high enough and uniformly distributed to ensure this. This was reflected in the value of friability of the tablets which was estimated and found to be lower than 1% maximum limit.

Both hardness and friability did show that the propensity of the tablets for capping, chipping and lamination was remote as brittle – friable index which was derived from ratio of hardness and friability being 9.2 is high enough to maintain the strength throughout the tablets life cycle as opined by other researchers [21].

Attainment of relatively high crushing strength and low friability has not in any way affected disintegration time negatively. With a value of 7.39±1.1 min, it is evident that time-disintegration of active ingredients components of tablets was not impaired and that tablets disintegrated fast enough to assure rapid dissolution.

The assay results showed the presence of active components to the tune of 99.6±0.28% for paracetamol and 101.75±1.77% for ibuprofen – this was an indication that processing has not imparted negatively on the active ingredients and thus ensuring quality of product and safety of patients.

TABLE 2: QUALITY OBJECTIVES OF THE FORMULATION AND JUSTIFICATION

Quality parameters	Quality targets	Justification	Observed qualities
Physical appearance	White, smooth tablets without objectionable smell.	Tablets with good aesthetics encourage patients' compliance.	White, smooth tablets without objectionable smell
Weight uniformity- g, (n=20, ±SD, %RSD)	Mean weight ± 5% with relative standard deviation (RSD) of not more than 6%. (Range: 0.5869g ± 5%)	Tablet weight uniformity is a critical quality attribute (CQA) as content uniformity of actives depended on it. For tablets of this size, official weight range is ±5%.	0.5782 ± 0.0074 (RSD is 1.29%)
Hardness (crushing strength) – Kp, (n=10, ±SD)	4 – 10	Stronger tablets withstand both normal and abnormal stresses thus keeping the tablets intact.	6.7 ± 1.337
Friability - % (n=3, ±SD)	Not more than 1%	Capping and chipping make tablet appearance rough. It is an official requirement.	0.727 ± 0.25
Disintegration time – min, (n=6, ±SD)	Not more than 15 min.	Only timely disintegrated tablet could provide time-release capability that will engender better dissolution and bioavailability hence a CQA.	7.39 ± 1.1
Assay (active content / tablet) - % (n=2, ±SD)	95 – 105% of labeled amount	Therapeutic efficacy is contingent upon accurate amount of active ingredient hence assay is a CQA and official requirement.	Paracetamol: 99.6±0.28% Ibuprofen: 101.75±1.77%

CONCLUSION: The choice of wet granulation method has enabled formulation and development of a combination tablet of paracetamol and ibuprofen with quality profiles that are acceptable in line with international quality standards as contained in reference books. The pre-set quality objectives were achieved much well than anticipated. This is evident when observed qualities are compared with the QTPP. Characterization and quality profiling at both granules and tablets stages elucidated potential quality attributes inherent in the formulation that could make it a better option than either paracetamol or ibuprofen tablet alone.

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