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Formulation and physico-technical evaluation of a fixed dose combination of amlodipine and spironolactone in the management of hypertension

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Abstract

A fixed dose combination (FDC) product is the resulting product of a combination of more than one active pharmaceutical ingredients from different classes combined into a single dosage form. A total of 3 batches of amlodipine (ADB) and spironolactone (SPRN) have been formulated employing various excipients at different concentrations. Pre-compression studies such as angle of repose, bulk and tapped density, and post- compression evaluation such as: weight variation, hardness, friability. *In-vitro* release study were similarly evaluated using standard procedures. All the evaluation parameters such as weight variation, hardness, friability and *in-vitro* release study were within the official acceptable limits. The release of ADB was 58 % (2 % binder), 55.58 % (4 % binder) and 55.78 % (6 % binder) after 10 min and gradually increased to 100 % drug release before 30 min of study; while release of SPRN was 48.64 % (2 % binder), 52.83 % (4 % binder) and 33.32 % (6 % binder) after initial 10 min and achieved 100 % release after 20 min of study. The FDC formulation of ADB/SPRN into an oral solid dosage form (tablet) was successful. The results of the physicochemical properties evaluated show a promising novel formulation for possible fixed dose combination of these molecules in the management of hypertension.

Keywords: Fixed Dose Combination; Amlodipine; Spironolactone; Excipients

1. Introduction

Hypertension also known as High Blood Pressure (HBP) is defined by Westerweel et al [1] as systolic blood pressure (SBP) and diastolic blood pressures (DBP) greater than 140 and 90 mmHg, respectively. It can also be defined as the persistent elevation of arterial blood pressures either systolic or diastolic blood pressure ≥ 140 and 90 mmHg, respectively [2]. High blood pressure (HBP) can have primary (idiopathic) or secondary causes [3] and is estimated to affect about one billion people globally, with a projection to reach 1.56 billion by 2025 [4]. It is a major risk factor for many cardiovascular diseases which are responsible for about 17 million mortality worldwide [5].

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Syme [6] opined that hypertension is a worldwide epidemic with an estimated 1.39 billion affected adults globally. Cardiovascular diseases are responsible for about 17 million deaths worldwide; this mortality rate is attributed to complications from high blood pressure. Mortality rate due to high blood pressure and disability adjusted life years (DALYs) is estimated to be 7.5 million and 57 million respectively in Nigeria [5]. Hypertension is more prevalent in older individuals and presumably affects more than half of individuals within the age range of 60-69 years and about three-fourth of individuals that are >70 years old in USA.

Several classes of therapeutic agents are currently in clinical use for the management of hypertension. Drugs in classes such as Angiotensin-Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs), Calcium Channel Blockers (CCBs), Beta-Blockers (BBs), and Diuretics are currently in use in clinical settings. These agents generally exert their pharmacological activities by modifying the following: vascular tone, cardiac performance or renal sodium excretion, with resultant effects on blood volume [7].

The World Health Organization recommends the following blood pressure (BP) targets: < 140/90 mmHg for patients with hypertension only, < 130/80 mmHg for patients with hypertension and other non-vascular health conditions and < 130/80 mmHg for patients with hypertension and co morbidities [8]. Hypertension management is based on two main interventions: non-pharmacological and pharmacological interventions, depending on the classification of BP levels [9]. Education, advice on lifestyle activities, and exercise are first line non-pharmacological management of people with hypertension. Patients should be counseled on weight reduction, minimal salt intake, and reduced alcohol consumption to within recommended limits, as each of these factors are known to contribute to elevated BP [10].

The pharmacological approach involves taking some drug as prescribed by the physician, and the goal is lowering the BPs to below the 140/90 mmHg threshold [7]. The classes of drugs most commonly used includes diuretics, β blockers, Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Blockers (ARBs), Calcium Channel Blockers (CCBs), $\alpha -$ adrenoceptor blockers, combined α and β blockers, direct vasodilators, and some centrally acting drugs such as $\alpha 2$ -adrenoceptor agonists [1].

Unfortunately, the management of this disease using mono-therapies does not often achieve the desired goal. However, in some cases, polypharmacy is being adopted or fairly enough two drug combination is used. The selectivity of the combination will be based on the mechanism of action and the likely associated side effects. To some extent, drugs are selected from two classes that their action could be potentiation or synergism. The choice of these agents largely depends on the type and duration of the diseases. At some point, age and sex are also a factor in the selection of drugs.

However, polypharmacy has some challenges, apart from the likely side effects or unwanted effects of the drugs, patient compliance is also a major factor. To many patients, taking a single tablet daily is highly preferred to multiple doses and at different times. This non-compliance to medication for hypertension has resulted in complications and often led to deaths. To avoid this issue of non-compliance to dosage and failure due to multiple doses of drugs, the pharmaceutical formulators or formulation scientists are in a race to get a good fixed dose of two or more medications as one entity to enhance the compliance of hypertensive patients.

In this case, many formulation ratios are exploited, some are already in the market and some are still under investigations [11]. The idea behind the fixed dose is to forestall drug resistance and loss of promising molecule to non-compliance leading to therapeutics failure [12].

Fixed-dose combination products (FDCs) also known as “Fixed Ratio Combinations” are medicines which contain two or more active pharmaceutical ingredients in fixed proportions in the same formulation [12, 13] . FDCs should be used in hypertensive patients who are not properly controlled on mono-therapy or require combination therapy initially [14]. FDCs help health providers to effectively manage patient therapeutic outcomes from the perspective of long-term care, allowing them to use combinations of active ingredients that are effective over time and can improve patient safety as seen for instance with FDCs for cardiovascular diseases [15]. Moreover, they lead to cost savings and improved collaboration between healthcare providers and patients, with the added benefit of increased savings through the availability of generic fixed-dose combinations [15].

Commercially, there is the availability of good number of FDCs for the treatment of hypertension, mainly combining diuretics with other classes of antihypertensives. Hydrochlorothiazide and Spironolactone are both diuretics but while hydrochlorothiazide is a thiazide diuretic, Spironolactone is a Potassium-sparing diuretic with the superior property of not eliminating potassium from the body. However, while Hydrochlorothiazide has widely been formulated as FDC with other classes of antihypertensives, there has not been any information on the combination of Spironolactone as FDC formulation with other antihypertensives.

This research aims to formulate a fixed dose combination of Amlodipine and Spironolactone which can serve as a ready alternative to the commercially available Amlodipine/hydrochlorothiazide FDC.

2. Materials and methods

2.1. Materials

Amlodipine besylate powder was received as a gift from JUHEL Pharmaceuticals Enugu, Spironolactone powder was procured from MEDISCA INC TX, 75063 USA, Microcrystalline cellulose, calcium hydrogen phosphate, sodium starch glycolate and magnesium stearate were supplied by a vendor and identified before use.

2.2. Methods

2.2.1. Wet granulation

The method used for wet granulation was previously outlined by Osonwa et al [16]. Granules of Amlodipine (3 g) and spironolactone (15 g) were made by wet granulation with sodium starch glycolate (as disintegrant) and microcrystalline cellulose (binder) at concentrations of 2, 4 and 6 %. The granules were dried, sieved through a 0.8 mm screen, and stored at room temperature conditions in airtight plastic containers before compression into tablets.

2.2.2. Evaluation of the prepared amlodipine/spironolactone granules

Granule properties such as Carr's compressibility index, angle of repose, Hausner ratio, flow rate, and percentage fine were determined by standard methods and recorded.

The volume of 5 g of the granules from each batch was obtained before and after tapping. The volume before tapping was used to determine the bulk density while the tapped volume was used to calculate the tap density mathematically.

$$Bulk\ Density\ = \frac{weight\ of\ granules\ (grams)}{bulk\ volume\ (milliliters)} \ldots\ldots. Eqn.1$$

$$Tapped\ Density\ = \frac{weight\ of\ granules\ (grams)}{tapped\ volume\ \ (milliliters)} \ldots\ldots\ldots. Eqn.2$$

Other evaluations such as flow rate, Angle of repose, Hausner quotient are calculated as state below:

$$Flow\ rate\ = \frac{weight\ of\ granules\ (grams)}{time\ of\ flow\ (seconds)} \ldots\ldots\ldots\ Eqn.3$$

$$Angle\ of\ repose\ (Tan\ \theta) = \frac{Height\ of\ cone\ (cm)}{radius\ of\ cone\ (cm)} \ldots\ldots\ldots Eqn.4$$

$$Percentage\ fine\ = \frac{Weight\ of\ fine}{Total\ weight\ of\ granules\ (fine + coarse)} X\ 100 \ldots Eqn.5$$

$$Hausner\ quotient\ = \frac{Tapped\ Density}{Bulk\ Density} \ldots\ldots\ldots\ Eqn.6$$

$$Carr's\ Compressibility\ Index\ = \frac{Tapped\ Density\ -\ Bulk\ Density}{Tapped\ density} X\ 100 \ldots\ldots\ Eqn.7$$

2.2.3. Tableting of the Pharmaceutical Active Ingredients (API)

As described by Osonwa et al [16] , the granules were mixed with the lubricant; magnesium stearate (1 %w/w). The blend was tableted using a 10-station rotary tablet press (Proton multiple punch rotary press, India) set at 933 (N/m2). The die-volume was set to obtain 250 mg tablets of the FDCs. The compositions are shown in Table 1.

Table 1 Composition of the Amlodipine/spironolactone fixed dose combination tablets

Batch	Amlodipine (mg)	Spironolactone (mg)	Micro crystalline cellulose	Calcium hydrogen phosphate (mg)	Sodium Starch Glycolate (12.2 %)	Magnesium stearate (1 %)
A	10	50	2 % (5 mg)	152	30.5 mg	2.5 mg
B	10	50	4 % (10 mg)	147	30.5 mg	2.5 mg
C	10	50	6 % (15 mg)	142	30.5 mg	2.5 mg

2.3. Physicochemical evaluation of the prepared fixed dose tablet

2.3.1. Weight variation test

Twenty (20) tablets were randomly selected from each batch and weighed individually to check for weight variation. The weight was compared to the USP provided limits for the average weight of uncoated compressed tablets [14].

2.3.2. Friability test

Twenty (20) tablets were randomly selected, weighed and placed in the Roche friabilator and exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After 4 minutes of 100 revolutions, the tablets were weighed, and the final weight was compared with the initial weight.

$$Friability = \frac{Initial\ weight - final\ weight}{Initial\ weight} X\ 100 \ldots\ldots Eqn. 8$$

2.3.3. Hardness test

Ten (10) tablets were randomly selected and placed into the tablet holder of the Monsanto Hardness Tester (COSLAB). The amount of pressure required to crush the tablets were recorded and the mean ± S.D of all 10 tablets was calculated [15].

2.3.4. Disintegration test

One tablet is placed in each tube of the disintegration unit of the apparatus (Erweka disintegration apparatus) with distilled water as the disintegration medium maintained at 37 ± 2 ^{o}c, through the upward and downward movement in the medium, the time taken for each tablet to completely break up to particles that pass through the wire mesh was recorded. The mean of the determinations was calculated [15].

2.3.5. Dissolution test

Drug release studies of all the batches were carried out using tablet dissolution test apparatus at 75 rpm.

For spironolactone

A 900 ml volume of 0.1 N HCl was used as the dissolution medium with temperature maintained at 37±2 °C in all experiments. A 5 ml sample was withdrawn at intervals for times 5, 10, 20, 30 45 and 60 minutes respectively and replaced with fresh medium to maintain sink conditions. Samples withdrawn were analyzed at 242 nm for percentage drug release using Shimadzu UV-Visible spectrophotometer.

For Amlodipine

A 500 ml volume of 0.01 N HCl was used as the dissolution medium with temperature maintained at 37±2 °C in all experiments. 5 ml of sample was withdrawn at intervals for times 5, 10, 15, 20 and 30 minutes respectively and replaced with fresh medium to maintain sink conditions. Samples withdrawn were analyzed at 239 nm for percentage drug release using Shimadzu UV-Visible spectrophotometer.

The concentrations were then calculated using the constant K obtained from Beer's calibration: A = K*C.

Where: A = Absorbance, C= Concentration K= constant

3. Results

3.1. Granule Characteristics

Bulk and tapped density of the different batches of the formulation were measured and the results are presented in Table 2.

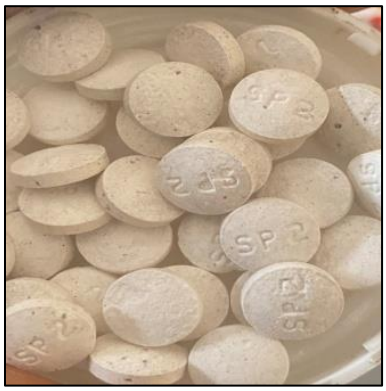
Table 2 Pre-compression parameters for the various parameters

Batches	Tapped volume (ml)	Bulk volume (ml)	Bulk density (g/ml)	Tapped density (g/ml)
A	10.50	11.00	0.454	0.476
B	11.00	11.90	0.420	0.454
C	10.00	11.00	0.454	0.500

Table 3 Granule properties

Batches	Flow rate(g/sec)	Angle of repose (°)	Percentage fine (%)	Haunser ratio	Carr's index (%)
A	0.65	24.53	14.39	1.048	4.6
B	1.16	24.62	13.92	1.080	7.4
C	1.29	29.05	10.30	1.101	9.2

3.2. Evaluation of tablet properties



ABD: Amlodipine, SPRN: Spironolactone

Figure 1 A presentation of the prepared 250mg ABD/SPRN tablets

Table 4 Friability, Hardness, Weight variation and Disintegration time of ABD/SPRN tablets

Batches	Friability (%) n=20	Hardness (kg/cm^2) n=10	Weight variation (mg) n=20	Disintegration time (sec) n=6
A	0.84 ± 2.3	8.32 ± 0.77	253.6 ± 9.43	248 ± 6.9
B	0.66 ± 2.0	9.04 ± 0.62	247.3 ± 9.48	281 ± 6.5
C	0.52 ± 1.2	9.34 ± 2.19	248.8 ± 9.61	373 ± 4.7

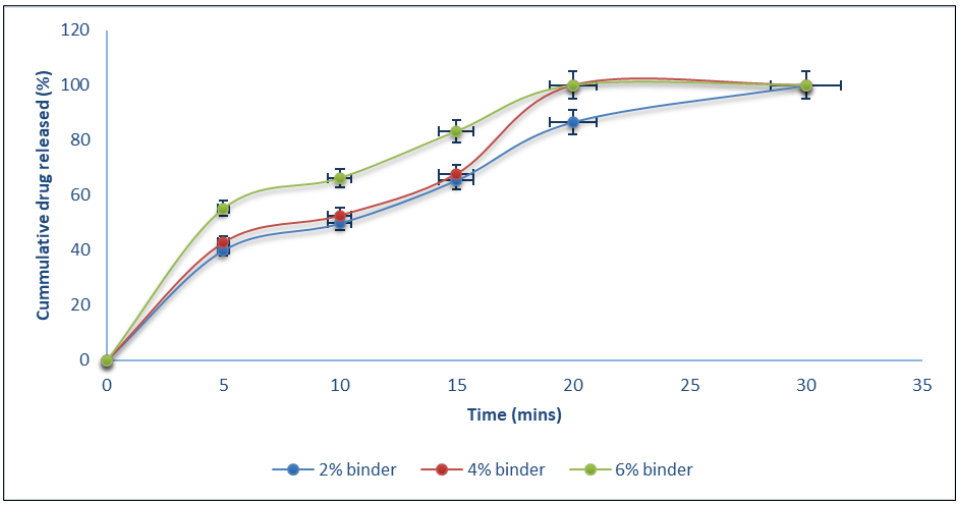


Figure 2 Drug release profile of Amlodipine in batches containing 2%, 4% and 6% binder.

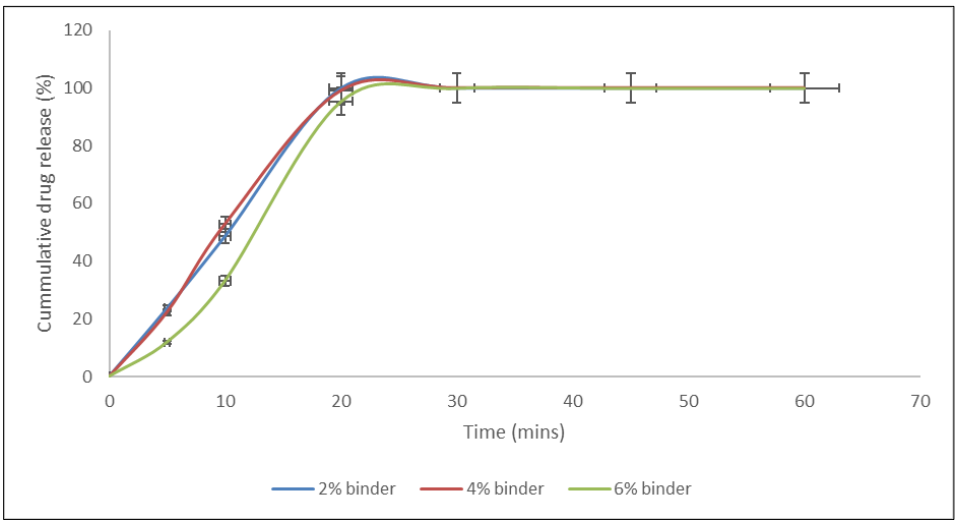


Figure 3 Drug release profile of Spironolactone in batches containing 2 %, 4 % and 6 % binder

4. Discussion

Tapped and bulk densities are not only required to determine powder compressibility but also the overall tableting process. The tapped and bulk densities of all the formulations are close to each other indicating good flow and compression properties.

The results of the granules properties such as angle of repose, flow rate, Hausner quotient, Carr's compressibility index, percentage fine, are shown in Table 3. Granules with excellent flow properties have their values of the angle of repose, Hausner ratio and Carr's index as < 30 °C, 1.00 – 1.11 and <10 % respectively [16].

The angle of repose is the angle formed by the horizontal base of the bench surface and the edge of a cone-like pile of granules [17]. The angle of repose also indicates the cohesiveness of the granular material, referring to the Carr's classification of flowability [18]. The correlation has been established between angle of repose and flow properties. When the angle of repose is less than 30 degrees, the flow is said to be excellent; on the other hand, if the angle of repose is more than 56 degrees, the flow is considered to be poor [16]. From the results, it was observed that the granules prepared with 2 %, 4 % and 6 % binder had their values of angle of repose to be 24.53˚, 24.62˚ and 29.05˚ respectively which indicates excellent flow properties.

Granules prepared with 2 % concentration of the binder showed lower flow rate of 0.65 g/sec as compared to that of 4 % and 6 % concentrations which had higher flow rate value of 1.16 and 1.29 g/sec respectively.

Carr's compressibility index is a measure of powder bridge strength and stability, and the Hausner ratio (HR) is a measure of the interparticulate friction. The relationship among compressibility ratio, Hausner ratio and powder flowability has been established. The lesser the degree of compression, the greater the flowability of the powder. When the compressibility ratio is from <10 %, the powder flowability is excellent. If the powder flowability is from 11 % to 15 % it shows good powder flowability, when the ratio is from 16 % to 20 %, the powder flowability is fair, 21 % to 35 % indicates poor flowability [19]. A HR of <1.11 is considered excellent flow while a HR >1.60 is considered 'very very poor' flow. The Hausner ratio (HR) and Carr's compressibility index (CI %) were also calculated based on the equations presented in Equations 3 and 4. From the results, it was observed that the HR and CI % of 3 batches of granules showed excellent powder flowability with values 1.048, 1.080, 1.101 and 4.6, 7.4 and 9.2 respectively.

According to Osonwa et al [15], the purpose of hardness test which is also known as crushing strength is to measure the ability of tablets to withstand stress or pressure during packaging, handling, transportation and storage with no permanent deformation. For the hardness test for a tablet to be satisfactory, the minimal crushing strength should be greater than or equal to 4 kgf [16]. Tablet hardness affects bioavailability of the API because a tablet that is too hard will take a long time to disintegrate and will be excreted unmetabolized. Table 4 shows that the hardness test values of all the batches are within acceptable range. At 2 %, 4 % and 6 % concentration, mean hardness value of the tablets prepared was 8.32, 9.04 and 9.34 kg/cm^2 respectively which shows that all the tablets passed the test. The hardness value increased with increase in the concentration of the binder. Difference in hardness could be as a result of type and concentration of binder, disintegrant, lubricant and compressional force.

Friability testing evaluates the ability of uncoated and compressed tablets to withstand physical stress upon exposure to attrition and mechanical shock, it is designed to evaluate the ability of the tablet to withstand abrasion during packaging, handling and shipping processes and the friability is closely related to tablet hardness [20]. As stated by Osonwa [16], a maximum weight loss of not more than 1 % is generally considered acceptable. Friability test could fail as a result of punches in poor condition or internal factors like the moisture content of tablet. From the results shown in table 4, tablets with concentration of binder 2 %, 4 % and 6 % passed the test as the percentage loss was 0.84 %, 0.66 % and 0.52 % respectively which is within the acceptable value of <1 %. The percentage loss decreased as the concentration of binder increased.

According to the official standards, tablets between 80mg and 250mg must meet a weight uniformity requirement: the weight of more than 2 tablets cannot differ by more than 7.5 % from the average weight of 20 tablets [21]. The total weight of the tablets of ADB/SPRN is 250 mg; from the results, all the tablets randomly selected from the 2 % formulation had the percentage deviation of ±7.5 %, which means that the tablets have uniform weight, so the tablets passed the test. This may indicate uniformity of tablet production; this uniformity may be caused by the usage of good weighing balance. The tablets in batch B (4 %) had the average weight of 247.3 mg which is under the category of 80 mg to 250 mg, 1 tablet had the weight of 267 mg and deviation% of 7.906 % which above the limit of ±7.5 % not exceeding the minimum of 18 tablets. The tablets in batch C had average weight of 248.8 mg which is under the category of 80 mg to 250 mg, all the tablets have the deviation of ±7.5 %, which means that all the tablets from batch C have uniform weight and passed the test. This also indicates uniformity in tablet production.

The disintegration of tablets is an important parameter to ensure uniformity. It is aimed at confirming if the oral solid dosage form disintegrated completely within the recommended time period when placed in a liquid medium under investigational conditions. All the tablets in the 3 batches disintegrated within 600 sec as seen in Table 4. Batch A with 2 % binder had the quickest disintegration time of 248 sec. The formulator should note that the operator recording the results, medium used and the temperature of the medium can have a considerable effect on disintegration time. Other factors such as: the diluents used, the nature of the drug, the binders, the type and amount of lubricant, the type and amount of disintegrating agent, as well as the method of incorporation for all of these additives involved with a tablet's formula and method of manufacture can affect its disintegration [22].

In this study, the various formulations showed a drug release of amlodipine greater than 50 % within 10 minutes as seen in Figure 2 which gradually increased to 100% drug release after 20 min with the exception of batch A (2 % binder) which had percentage drug release of 86.66 % at 20 min. However, all the batches recorded 100 % drug release before 30 min. On the other hand, the release of Spironolactone was above 95 % after 20 min for all the batches.

5. Conclusion

The FDC formulation of ADB/SPRN into an oral solid dosage form (tablet) was successful. Both the pre and post compression evaluation parameters show promising results and are within the official acceptable limits.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors wish to declare the absence of any conflicts of interest before, during and after this research work.

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