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Preparation and Evaluation of Extemporaneously Compounded Aspirin Capsules from Crushed Aspirin Tablets

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Authors' contributions

This work was carried out in collaboration between all authors. Author IMA managed the literature searches, designed the study, wrote the protocol, managed the analyses of the study, and wrote the first draft of the manuscript. Author LSA performed the experiments, managed the literature searches, managed the analyses of the study, and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Extemporaneous preparations of medications might bring about technical and clinical consequences due to formulation failures. Therefore, all such prepared formulas should undergo valid and reliable procedures supported by solid data. Otherwise, patients can experience significant risk due to microbial contamination or physical or chemical changes during the preparation process. Thus, effective extemporaneous preparation relies on correct calculations to avoid extra and serious harm. Therefore, because 50-mg aspirin capsules are not available in Saudi Arabia, this study aimed to formulate 50-mg capsules from available 100-mg aspirin tablets.
Methodology: Quality control tests of the preparations were carried out at the time of preparation and after one month of storage at 25 °C and at 40 °C and 75% relative humidity. All tests were carried out according to the British and United States pharmacopeia monograph of aspirin.
Results: The drug content assay and uniformity test indicated that the aspirin capsules were within the pharmacopeial limits. The disintegration time for all aspirin capsules was within the pharmacopeial limits of 30 minutes. The aspirin release profile showed that approximately 90% of the aspirin dissolved after 10 minutes.

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Conclusion: The results indicated that the extemporaneous preparation of ASA capsules complied with the quality control tests for freshly prepared capsules and after one month of storage at room temperature and at 40 °C and 75% relative humidity. The dissolution profile of these capsules indicates immediate and high release of ASA, which is essential to ensure the required absorption. This study is of great importance for patients who need to take this dose of ASA. Pharmacists can prepare good-quality capsules with the desired ASA content using a 100-mg ASA tablet as a source of the active ingredient.

Keywords: Aspirin; extemporaneous; quality control; capsules.

1. INTRODUCTION

Tablet splitting is an important and widely spread practice in the field of pharmacy. Patients usually split tablets for various reasons, such as to be provided with the desired dose when the product is not available in the required strength, starting therapy with the lowest possible dose to reduce the incidence of the side effects of certain drugs, reducing medication costs, and making the swallowing of large tablets easier. Nevertheless, some problems may arise due to this practice; the most important problem reported in this regard is poor weight and content uniformity of the obtained halves [1]. So, when obtaining equal tablet halves is difficult, or when the desired dose is to be calculated according to the body surface area or according to renal and liver functions, and this dose cannot be obtained even by splitting tablets into two equal halves, pharmacists can crush licensed tablets and reformulate them into capsules to provide patients with equal drug doses. This practice is known as the extemporaneous preparation of capsules [2]. While all alternatives should be considered before this option is chosen, some patients may need distinct clinical treatments that have no corresponding licensed product or recommended alternative. However, because extemporaneous preparation of medications might cause technical and clinical consequences due to formulation failures, all such formulations should be prepared through a valid and reliable procedure that is supported by solid data. Otherwise, immunocompromised patients might be exposed to significant risk due to microbial contamination or physical or chemical changes during the preparation process. Thus, effective extemporaneous preparation relies totally on correct calculations to avoid extra and serious harm; however, the more complicated the calculations demanded, the higher the risk of failure [2], [3].

Aspirin (acetylsalicylic acid, ASA) is a cyclooxygenase enzyme inhibitor 1 (COX-1) that modifies the enzymatic activity of cyclooxygenase-2 (COX-2). Unlike other nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen and naproxen), which bind reversibly to this enzyme, the binding of ASA is irreversible. It also irreversibly prevents thromboxane A2 adsorption on platelets, thus preventing platelet aggregation. Researchers hypothesize that due to the blockage of the COX pathway, arachidonic acids are transferred to the lipoxygenase pathway. The production of anti-inflammatory lipoxins is the result of a modification of prostaglandin endoperoxide synthase (PTGS2), also called COX-2, which results in the making of lipoxin fats, most of which are anti-inflammatory. These compounds are aspirin-catalyzed lipoxin, aspirin-induced solvents, and aspirin-stimulated merizin. ASA can be given orally or intravenously (IV) and is available in various dosages. Available dosage forms of ASA include tablet (325 mg, 500 mg), delayed-release tablet (81 mg, 325 mg, 500 mg, 650 mg), chewable (81 mg), suppository (60 mg, 120 mg, 200 mg, 300 mg, 600 mg), and IV (250 mg, 500 mg) [4].

Low-dose ASA (LDA) has been used widely for the prevention of cardiovascular and cerebrovascular diseases. In the prevention of ischemic stroke, a wide range of ASA dosages (30 to 1300 mg per day) was investigated. The results of pharmaceutical experiments indicate a lower risk of stroke and death compared to a placebo in patients with a history of strokes. However, both high and low daily doses of 325 mg and 50 to 166 mg, respectively, of an ASA routine would likewise prevent vascular events; however, higher doses are more likely to trigger episodes of bleeding and side effects. Moreover, taking 200 mg of ASA a day increased deadly or life-threatening gastrointestinal bleeding and total bleeding. Research has also shown that 50 mg/day of ASA are effective for both men and women with a history of stroke or transient ischemic attacks [5], [6]. Moreover, the results of pharmaceutical studies have confirmed that

continuous treatments with LDA can reduce the probability of developing such cancers as colorectal, esophageal, breast, lung, prostate, liver, and skin. Also, it was demonstrated that the administration of LDA before the 11th week of gestation in women might reduce the risk of preterm delivery [6], [7].

The aim of this research was to formulate and evaluate extemporaneous preparation of ASA capsules from crushed ASA tablets to ensure a high-quality product and evaluate the stability of capsules stored at 25 °C and 40 °C and 75% relative humidity, respectively, for one month.

2. MATERIALS AND METHODS

2.1 Materials

ASA was purchased from Winlab (Leicestershire, UK), and aspirin tablets (100 mg, Bayer, Leverkusen, Germany) were purchased from local pharmacies; lactose powder and sodium acetate were purchased from Avonchem Ltd (Cheshire, UK); hard gelatin capsules (size 00) were purchased from Capsuline (USA), and all reagents used were of analytical grade: sodium hydroxide (Qualikems Fine Chem Pt Ltd, Vadodara, India), sulfuric acid and hydrochloric acid 37% (BDH, GPR, England), and glacial acetic (BDH, GPR, England).

2.2 Methods

2.2.1 Extemporaneous preparation of ASA capsules from crushed ASA tablets

The ASA 50-mg capsules were prepared starting with 100-mg tablets of ASA. The tablets were crushed using a mortar and pestle. The powdered tablets were passed through a no. 20 mesh. The resultant powder was diluted with lactose. The mixture was filled manually into hard gelatin capsules (Fig. 1).

2.2.2 Official quality control tests for capsules

2.2.2.1 Drug content

This test was performed following the titrimetric assay described in the ASA monograph of the British Pharmacopoeia (BP) [8]. A quantity of powder equivalent to 0.5 g ASA from capsules (ten capsules) was transferred to an Erlenmeyer flask with 30 ml of 0.5 M sodium hydroxide. The mixture was then boiled for 10 minutes, after which three drops of phenol red indicator were added. The excess alkali was then back titrated with 0.5 M hydrochloric acid. The same procedure was performed without ASA (blank). The difference between the two titrations represents the amount of sodium hydroxide consumed to change ASA to sodium acetate and salicylic acid. Each ml of 0.5 M sodium hydroxide is equivalent to 45.04 mg of ASA. The percentage of ASA was calculated according to the following equation:

% of the drug = (end point of Blank (ml) − end point of experiment (ml) × *F* × *f)* / (initial weight) × 100 (1)

where *F* = equivalent factor and *f* = standardization factor of titrant.

2.2.2.2 Uniformity-of-mass test

For hard capsules according to BP, a batch of 20 capsules was selected randomly. Each capsule was weighed individually (JS1603-C/FACT Balance, Mettler Toledo, Switzerland), taking care to preserve the identity of each capsule. The contents of each capsule were removed. The emptied shells were weighed individually and the net weight of contents of each capsule determined by subtracting the weight of the shell from the respective gross weight. The average weight (W) was then calculated according to equation 2 [8].

Fig. 1. Schematic diagram of extemporaneous preparation and quality control process of the prepared capsules

According to BP, not more than 2 capsules' individual mass weight could deviate from the W by more than the percentage deviation shown in Table 1, and none deviates by more than double that percentage [8].

Table 1. Acceptance criteria for uniformity of weight according to BP [8]

W (mg)	Percentage Deviation
Less than 300 mg	±10
300 mg or more	±7.5

Calculation of the maximum acceptance value (MaxAV) and the minimum acceptance value (MinAV) was carried out according to the following equations:

W = (total weight of the capsules' contents) / 20 (2)

MaxAV (at percentage deviation) = W+ {((percentage deviation) / 100) × W} (3)

MinAV (at percentage deviation) = W− {((percentage deviation) / 100) × W} (4)

MaxAV (at double percentage deviation) = W + {((double percentage deviation) / 100) × W} (5)

MinAV (at double percentage deviation) = W − {((double percentage deviation) / 100) × W} (6)

2.2.2.3 Disintegration test

The disintegration behavior of the capsules was determined using a disintegration apparatus (ZT 320 Series, ERWEKA, Heusenstamm, Germany). A batch of six capsules was selected randomly. One capsule was placed in each tube of the disintegrator basket rack, which was then positioned in 600 ml of water 37 ºC ± 0.5 ºC such that the capsule rose to no less than 2.5 cm below the surface of the liquid and descended to not closer than 2.5 cm to the bottom of the beaker. A standard motor-driven device was used to move the basket assembly containing the capsules up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. Perforated plastic disks were placed on top of the capsules. The capsules met the criteria of the test if they disintegrated and all particles passed through the 10-mesh screen in 30 min. If any residue remained, it needed to have a soft mass with no palpably firm core [8].

2.2.2.4 Dissolution test

The dissolution test was carried out using a dissolution apparatus (basket apparatus; Pharma Test, DT 70, Hainburg, Germany) and 0.05 M acetate buffer pH 4.5 as the dissolution medium. A batch of six capsules was selected randomly. One capsule was placed in each basket of the apparatus using 500 ml of the medium at 37 °C ± 0.5 °C. The basket was rotated at 100 rpm. A 5 ml sample was withdrawn at intervals of 5, 10, 15, 20, and 30 min. This volume was immediately replaced with a fresh preheated dissolution medium to maintain the sink condition and constant volume throughout the experiment. The samples were filtered, and the absorbance was measured at 265 nm using a UV-visible spectrophotometer (Libra S22 UV/Vis. Biochrom Ltd., Cambridge, England), where the dissolution medium was used as a blank. The capsules met the criteria of the test if not less than 80% of the labeled amount of ASA was dissolved in 30 minutes. Also, the dissolution profile of the ASA capsules was generated from the graph of the percentage of ASA released versus time [8].

2.2.3 Stability study

The capsules were put into jars that were sealed with a cap. Samples were taken for initial analysis (month 0), and the remaining samples were divided and stored under two different conditions: half were stored at room temperature and half at 40 ˚C and 75% relative humidity. Both were analyzed after one month. The concentrations of ASA were all expressed as a percentage of the initial concentration. Stability was defined as a concentration in the range of 90% to 110% of the initial concentration and dissolution not less than 80% (Q) of the labeled amount of ASA within 30 minutes [3], [9]–[11].

3. RESULTS AND DISCUSSION

3.1 Extemporaneous Preparation of ASA Capsules from Crushed ASA Tablets

The extemporaneous preparation of asa capsules with the desired strength by crushing of existing commercial ASA tablets would be a valid alternative to achieve the desired strength if the obtained capsules could pass such pharmacopeial requirements for immediate-release oral solid dosage forms as drug content, weight uniformity, disintegration time, and dissolution profile. Accordingly, the purpose of this study was to prepare ASA 50-mg capsules

starting from a commercially available product of ASA tablets. Then, the properties of the obtained capsules were evaluated with regard to drug content, mass uniformity, disintegration time, and dissolution behavior according to the pharmacopeial monograph of ASA to ensure high quality of the obtained capsules.

3.2 Official Quality Control Tests for Capsules

3.2.1 Drug content

Content uniformity is an important characteristic to assure repeatability of dosages and thus the preparation of a safe and effective therapeutic formulation. Crushing tablets is a critical step in the formation of a powder mixture. The grinding technique can affect the resulting homogeneity of the powder mixture. Also, one must consider that the particles may become segregated if they need to be stored before the doses are dispensed. Therefore, professional skills are key factors in preparing extemporaneous medicines of good quality.

The results of the assay (Table 2) have shown that the capsules under study meet the official requirement of the assay according to the BP (95%–105%).

Table 2. Drug content of ASA capsules

Time (month)	Storage condition	% Drug content
0	Room temperature	99.088 ±1 %
1	Room temperature	99.088±1.5 %
1	40˚C/ RH 75%	103.59±1 %

**RH: relative humidity.*

3.2.2 Uniformity-of-mass test

The tested capsules had an average content weight of more than 300 mg/capsule; thus, the maximum acceptable weight variation was ±7.5% [7]. Table 3 shows maximum and minimum acceptance values at percentage of deviation allowed and at double the percentage of deviation allowed. According to the results presented in Table 4, all tested capsules complied with the BP requirements of the uniformity-of-mass test.

3.2.3 Disintegration test

The disintegration process of a solid dosage form is an important step toward its bioavailability [1]. The disintegration time for all ASA capsules was within the USP/BP 30-minute limits, as reported in Table 5.

3.2.4 Dissolution test

The results reported in Table 6 show that the percentage of ASA dissolved after 30 minutes was within the accepted BP limits for immediate-release oral dosage forms [7]; it was also higher than 100% at the end of the study period of one month at room temperature and at 40˚C and relative humidity 75%. Moreover, the ASA dissolution profile showed that more than 90% of ASA was dissolved after 10 minutes, as presented in Fig. 2.

The results of this study demonstrated that the extemporaneous preparation of ASA capsules was of good quality, since they passed the pharmacopeial tests for immediate-release solid dosage forms. Furthermore, when maintained at 40 ºC and 75% relative humidity, the capsules were stable for at least one month. The capsules demonstrated a disintegration time that was within the limits prescribed by the pharmacopeia so as not to impair the dissolution of the drug, which is an essential step for drug absorption. Since the dissolution of the drug from oral solid dosage forms is a necessary criterion for drug bioavailability, the dissolution test was carried out. The dissolution tests can provide an overview of the amount of drug available for absorption after oral administration. The release of ASA from the capsules was more than 90% after 30 minutes, which indicates that an appropriate amount of ASA was available for absorption. In practice, extemporaneous preparation is a multidisciplinary process where decisions are made in cooperation with physicians, pharmacists, and nurses. The decisions in different steps of the preparation process have to be made by using professional pharmaceutical skills because there are no comprehensive standards. In fact, drug manufacturers should provide their package inserts with directions on how to transform their commercial tablets into capsules as well as scientific information on the expiration date of the obtained capsules. This will lead to greater dosing accuracy. Furthermore, it may also promote the marketing of such tablets since pharmacists should use only tablets accompanied by scientific information needed for extemporaneous preparation in their package insert.

Table 3. Maximum and minimum acceptance value at percentage deviation allowed

Time (month)	Storage condition	W (mg)	MaxAV at percentage deviation (mg)	MinAV at percentage deviation (mg)	MaxAV at double percentage deviation (mg)	MinAV at double percentage deviation (mg)
0	Room temperature	484	520.3	447.7	556.6	411.4
1	Room temperature	470	505.25	434.75	540.5	399.5
1	40˚C/RH 75%	467	502.03	431.98	537.05	396.95

Table 4. Uniformity-of-mass test of ASA capsules

	Content weight (mg)		
Storage condition	**Freshly prepared**	**Room temperature One month**	**40 ˚C / RH 75% One month**
Capsule number			
Cap 1	473	457.2	498
Cap 2	496	493.9	474.7
Cap 3	467	456.4	472.5
Cap 4	502	502.6	471.3
Cap 5	491	445.1	497.5
Cap 6	487	447.6	477.1
Cap 7	476	456.2	460
Cap 8	489	474.3	465
Cap 9	482	489	460.9
Cap 10	479	475.4	442.6
Cap 11	497	463.6	469.1
Cap 12	481	472.3	441.2
Cap 13	471	457.4	438.5
Cap 14	48	452	443.5
Cap 15	482	452.7	466.4
Cap 16	485	455.8	468.4
Cap 17	459	486.3	450.6
Cap 18	487	477.7	495.3
Cap 19	500	484.6	498.7
Cap 20	497	491.4	456.2
***W* (mg)**	**484**	**470**	**467**

Table 5. Disintegration test results of ASA capsules

Time (month)	Storage condition	Disintegration time (min)
0	Freshly prepared	11
1	Room temperature	15
1	40˚C / RH 75%	20

Table 6. Dissolution test results of ASA capsules

Time (month)	Storage condition	% Dissolved after 30 min					
		Cap 1	Cap 2	Cap 3	Cap 4	Cap 5	Cap 6
0	Room temperature	114.8	129.3	114.8	117.5	131.9	135.9
1	Room temperature	116.9	108.8	108.1	110.8	110.2	114.2
1	40˚C/ RH 75%	89.9	113.5	114.2	116.9	106.8	105.4

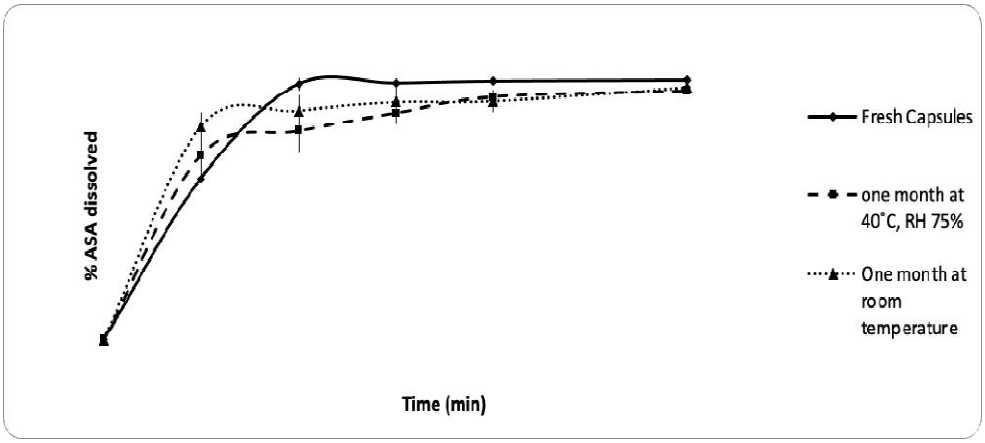

Fig. 2. Dissolution profile of ASA capsules

4. CONCLUSION

The results indicated that the extemporaneous preparation of ASA capsules complied with the quality control tests applied for freshly prepared capsules and after one month of storage at room temperature and at 40 °C and 75% relative humidity. The dissolution profile of these capsules indicates immediate and high release of ASA, which is essential to ensure the required absorption. This study is of great importance for patients who need to take this dose of ASA. Pharmacists can prepare good-quality capsules with the desired ASA content using a 100-mg ASA tablet as a source of active ingredient.

DISCLAIMER

The products used for this research are commonly and predominantly used in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we intend to use these products not as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company; rather, it was funded by the personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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