

The Redesign of Amoxicillin Capsules as a Tablet Dosage form Using Direct Compression

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Abstract

Introduction: Solid dosage forms are the most commonly used dosage form for drug delivery, and tablets are more popular than capsules because of its lower production cost, minimal potential of content tampering, and the large number of designs of tablets for various applications. **Aims:** The aim of this work is to redesign amoxicillin hard gelatin capsules (HGCs), commonly filled into HGCs, into tablet dosage form by employing preformulation principles. **Materials and Methods:** Amoxicillin capsules were obtained from the local market for this purpose. Experiments included studies on flowability and effect of compression force, followed by addition of excipients, production of tablets by direct compression, and evaluation employing standard methods of friability, hardness, disintegration, dissolution, and simulation of release kinetics. **Results:** The flowability of powder was estimated using Carr's index, Hausner ratio, angle of repose, and bulk density. The flowability was found poor for amoxicillin alone or with starch but improved with talc. Compression force was found to be a significant factor on friability, hardness, and disintegration. The disintegration time was rapid in case of tablets containing starch compared to amoxicillin powder compressed alone. It was essential to include small amounts of disintegrant and a lubricant to optimize tablet properties. Dissolution rates for the prepared tablets were found to be acceptable, while some formulations showed a slow release profiles corresponding to their slow disintegration. Release kinetics was found to follow both the zero-order and matrix models. **Conclusion:** Amoxicillin capsules can be modified to a tablet dosage form with simple handling of preformulation properties.

Keywords: Capsules, direct compression, redesign, tablets

INTRODUCTION

Tablets are considered the most common solid dosage forms in contemporary use.^[1] Tablets offer several advantages that may include dose precision, less content variability, ease of swallowing, and relatively low production cost.^[2] When compared to hard gelatin capsules (HGC), the manufacturing process of tablets involves fewer steps. In addition, the cost of capsule shells adds to the total costs of the capsule. Furthermore, the tampering potential of capsules content which leads to the more rigorous restrictions on their packaging resulted in an added cost of production.^[2,3] Moreover, among the minor disadvantages of capsules, the possible "aging" of gelatin shells is due to improper storage conditions.^[4-6] Therefore, it is an ultimate goal to produce an equivalent cheaper tablet dosage form to replace, at least partially, the conventional used capsule. It is arguable that HGC provides better absorption of its active content because of the nature of its powdered content and the minimal/none

compression force used in its manufacturing resulting in the optimum/rapid absorption following solubility of its gelatin shell.^[1,2,7] However, tablets are/can be designed to provide rapid disintegration and dissolution as well.^[2,8] Hence, the aim of this work is to redesign the antibiotic amoxicillin, commonly marketed as an HGC,^[9] into a tablet dosage form using direct compression method. Furthermore, compatible excipients might be added in the redesign process to improve flowability, hardness, disintegration, or dissolution. All these properties are tested and evaluated carefully in this work.

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MATERIALS AND METHODS

The materials used in this work include amoxicillin trihydrate capsules (Bristol Labs, UK), starch (Riedel-de Haën, Germany), and talc (Agropharm Ltd., India).

Determination of preformulation parameters

As per the standard procedures, the preformulation studies included bulk density, tapped density, Hausner ratio, Carr's index, and the angle of repose and was performed on the HGC content and the selected excipients.

Angle of repose measurement

The static angle of repose " θ " was measured according to the fixed funnel and freestanding cone method. A funnel was clamped with its tip 2 cm above a graph paper placed on a flat horizontal surface. The powder (HGC content with or without excipients) was carefully poured through the funnel until the apex of the cone formed just reached the tip of the funnel. The mean diameter of the base of the powder cone was determined, and the tangent of the angle of repose was calculated using the following equation:

$$\tan \theta = \frac{2h}{d}$$

where " h " is the height of the heap of powder and " d " is the diameter of the base of the heap of powder. As a general guide, powders with angles of repose $>50^\circ$ have unsatisfactory flow properties, whereas powders with minimum angles close to 25° exhibit very good flow properties.^[8,10]

Bulk and tapped densities measurements

A 6.55-g quantity of each powder samples was placed in a 10-mL clean, dry measuring cylinder, and the volume " V_1 " occupied by each of the samples without tapping was determined. The volume was recorded every 10 taps and measurement continued until no further decrease in volume was observed " V_2 ." The bulk and tap densities were calculated as the ratio of weight to volume.^[8,10]

Hausner ratio determination

This was calculated as the ratio of tapped density to the bulk density of the samples, as determined by the following equation:

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{poured density}}$$

Values <1.25 indicate good flowability, whereas values >1.6 indicates poor flowability.^[8,10]

Carr's index estimation (% compressibility)

This was calculated using bulk and tap densities data when fitted into the following equation:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

The relationship between powder flowability and % compressibility is represented in Table 1.^[8]

Production of tablets

The weight of each capsule was measured, then the capsule emptied in a mortar, and the weight of the empty shell was recorded followed by estimation of the weight of the content. Then, a specific amount of starch was added and physically mixed with the aid of a pestle in a mortar. Samples of 500 mg of amoxicillin powder (with or without starch) were subjected to compression using hand-operated IR press with a flat-face 12-mm punch and die set (Carver, USA). The preliminary results were performed to establish the range of compression force which can be used to produce intact tablets without physical defects. At the beginning, experiments using compression force of 4 tons and a release time of 5 s produced tablets with problems of capping and lamination. When compression force was reduced to 2.5 tons with a release time of 1 s, almost 50% of the prepared tablets have capping problems. Intact tablets were successfully and reproducibly produced when the compression force was reduced to 1 ton with a release time of 1 s. The final formulations developed in this work are as described in Table 2.

Evaluation of the produced tablets

Evaluation tests were performed, and the quality of the prepared tablets was determined using the following tests:

Friability

The weight of 10 tablets was measured and placed in friability tester (Pharma Test PTFE, Germany) which is then operated for 100 revolutions for 4 min. The tablets are reweighed and the friability percentage was calculated. Conventional compressed tablets that lose $<1.0\%$ of their weight are generally considered acceptable.^[11] The friability was calculated using the following formula:

$$\text{Friability} = \frac{w^* - w}{w^*} \times 100$$

where (w^*) and (w) are the weights of the tablets pre and posttesting of tablets, respectively.

Table 1: Relationship between Carr's index and powder flowability^[8]

Carr's index range	Flow description
5-15	Excellent (free-flowing granules)
12-16	Good (free-flowing powdered granules)
18-21	Fair (powdered granules)
23-28	Poor (very fluid powders)
28-35	Poor (fluid cohesive powders)
35-38	Very poor (fluid cohesive powders)
>40	Extremely poor (cohesive powders)

Table 2: Composition of formulations developed in this work

	HGCC (%)	Talc (%)	Starch (%)
Formulation 1	100	0	0
Formulation 2	95	0	5
Formulation 3	95	2.5	2.5

HGCC: Hard gelatin capsule content

Hardness

The force required to fracture the tablet (in tons) was measured using a tablet hardness tester (Pharma Test PTB, Germany). The machine allows for the simultaneous measurement of hardness, thickness, and diameter.

Disintegration

The time that it takes a tablet to disintegrate into smaller particles in 900 ml of prewarmed purified water maintained at 37°C was measured using a disintegration tester (Pharma Test, GmbH, Germany). The mean of six tablets was measured, and the results were considered acceptable if disintegration takes place in <15-min.^[11,12]

Dissolution

The rate of drug release of amoxicillin in purified water was measured using an 8 Station Dissolution Tester (Erweka DT 600). The paddle method was used, agitation rate was 50 rpm, and the volume of dissolution medium was 900 ml maintained at 37°C. Five milliliter samples were taken at 15-min intervals, filtered, and measured spectrophotometrically (Analytic Specord 40 ST, Germany) at 272-nm. The result is considered acceptable if not <80% of the prepared amoxicillin tablet is released within 60 min.^[11] The mean of six tablets was recorded.

For the purpose of comparison between dissolution profiles, the similarity factor (f_2) was used as follows:

$$f_2 = 50 \log \left[\left(1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right)^{-0.5} \cdot 100 \right]$$

where R_t and T_t are the percentage dissolved at each time point for reference (R) and (T) products, respectively. An f_2 value in the range 50–100 suggests that the two dissolution profiles are similar and the mean dissolution profiles are assumed to differ by no. >15% at any time point.^[13,14] It should be noted that the dissolution of HGC was done on the content alone without the shell because it was found to interfere with the ultraviolet assay because of the presence of coloring dyes in their composition.

To postulate the mechanism of drug release, the dissolution profiles were fitted to the following orders: zero-order, first-order, and matrix (Higuchi) model according to the standard equations.^[14]

Statistical analysis

The comparisons between two-sample means were performed by Student's *t*-test, whereas >two-sample means were analyzed using a one-way ANOVA test.^[15] The two-way ANOVA was used to test the significance of dissolution profiles. This was accomplished with the use of Microsoft Excel 2007 software (Bristol Labs, UK).

RESULTS

Flowability of powders

Flowability studies were performed on amoxicillin powder alone, with starch, and with starch–talc mix. Improvement in flowability was observed after adding starch and talc.

The flowability parameters are summarized in Table 3. The optimum readings were obtained when starch–talc combination was incorporated to the amoxicillin powder (Angle of repose <25°, Hausner ratio <1.25, and Carr's index <21 which indicates fair flowability).

Tablets friability

Friability experiment was used not just in the measurement of loss of tablet mass upon testing but also to detect problems of capping and lamination.^[2] Tablets with mechanical problems will show high friability percentage.^[16] The friability % values for Formulations 1–3 are summarized in Table 4. The friability values of all the formulations were <1% and considered acceptable.^[11]

Tablets hardness

As shown in Table 4, the hardness values for Formulations 1 and 2 were similar at 111 and 112 N, respectively. On the other hand, the average hardness value for Formulation 3 was relatively lower at 74 N. This could be attributed to the presence of talc in the formulation which might result in reduced cohesion between ingredients.^[17]

Tablets disintegration

Large variability was observed during disintegration testing of the formulations. Compressed amoxicillin tablets, Formulation 1, disintegrated in 2 h which is considered a very long time and way above the required pharmacopeial limit for tablets/capsules and coated tablets.^[11,12] The disintegration time was much reduced to 40 min when the starch–talc combination was included Formulation 3. The optimum disintegration time of 3.5 min was achieved when 5% starch was added to Formulation 2.

Tablets dissolution

The amount of drug released from the dosage forms evaluated in this work in purified water is given in Figure 1. The drug content of samples was estimated using the linear equation $Y = 0.0019 + 0.0163 X$ derived from the standard curve. Dissolution rate from HGC and Formulation 2 released 100% of its content after the first 15 min, whereas Formulations 1 and 3 showed 60 and 70%, respectively, following 60 min of dissolution testing. The dissolution experiments were observed only for 1 h as per the USP requirement.^[11] It appears that Formulations 1 and 3 exhibited slow dissolution profiles.

The two-way ANOVA for the four sets of data revealed that both the type of formulation and time of sampling are significant factors, and the presence of a significant statistical

Table 3: Summary of flowability parameters according to the different indicators

	Angle of repose (°)	Poured density	Tapped density	Hausner ratio	Carr's index (%)
Amoxicillin powder	32.8	0.73	0.98	1.35	25.9
Amoxicillin + starch	35.5	0.57	0.91	1.59	37.4
Amoxicillin + starch + talc	25	0.65	0.81	1.24	19.8

Table 4: Summary of tablet properties according to the different tests performed

	Friability (%)	Disintegration time (min)	Hardness (n)	Total amount released after 1 h of dissolution (%)
Formulation 1	0.7	120±5.0	111±7	60
Formulation 2	0.8	3.5±0.2	112±6	100
Formulation 3	0.8	40±2.0	74±9	72

Data are±SD. SD: Standard deviation

Table 5: Correlation coefficient (R^2) for Formulations 1 and 3 according to the release kinetics models

	Zero order	First order	Matrix model
Formulation 1	0.9828	0.8491	0.8472
Formulation 3	0.8865	0.6127	0.9865

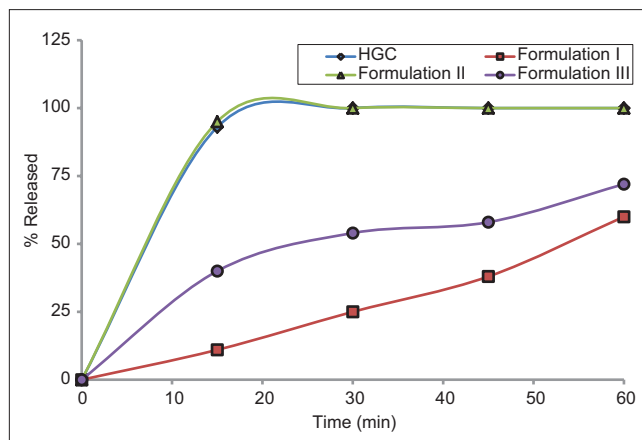
difference between the dissolution profiles ($P < 0.01$). The dissolution profiles for the HGC and Formulation 2 appears to be identical and the f_2 value was 98 in purified water, which implies that the tablet and capsule possess the same dissolution profile, while revealed different profiles for Formulations 1 and 3 when compared to HGC ($f_2 = 40$ and 48, respectively).

The release kinetics according to the proposed models is given in Table 5. It shows that the rate of drug release from Formulation 1 follows the zero-order model, whereas drug release from Formulation 3 follows the matrix (Higuchi) model.

DISCUSSION

Preliminary results showed that the content of evaluated amoxicillin capsules has poor flowability, which necessitates the inclusion of talc as antiadherent, lubricant, and glidant to improve flowability.^[1,18] It is essential for powders to be free-flowing to facilitate uniform tablets' production.^[8] The use of compression force above 5 tons resulted in the formation of tablets with defects such as capping and lamination. These problems are associated with the use of very high compression force.^[2,19] Consequently, the compression force was reduced to 1 ton in order to produce intact tablets without any obvious defects. In case of hidden defects in tablets, friability testing was used as a measure to detect such problems.^[2,20] When the content of HGC was compressed alone without any added excipients, it resulted in tablets with very long disintegration time of >2 h. As a result, starch was included as a disintegrant at 5% concentration. Even at 2.5% starch concentration, the produced tablets possess acceptable mechanical strength and disintegration time. Although it is commonly known that excipients are essential for the production of solid dosage forms, capsules, in particular, require less excipients than tablets.^[21] Depending on the filling technique used, capsule filling formulations may require the addition of fillers, lubricants, and possibly binders.^[1,21]

The hardness of the tablets was found to decrease dramatically upon the addition of talc, while almost unchanged and remained high after starch inclusion. This could be attributed to the

**Figure 1:** Dissolution rate for hard gelatin capsule and Formulations 1–3 in purified water

antiadherent effect of talc resulting in reduced binding between ingredients.^[22] However, the starch effect is the opposite of that of talc as it is well known that the strong binding properties of starch and its applications as a tablet binder are well documented.^[23,24] The disintegration time was reduced from 2 h to 2 min upon addition of starch. This dramatic change in disintegration time was an expected event as starch, and its derivatives are considered the most effective disintegrants in tablet dosage forms.^[23] An interesting finding was the long disintegration time of the directly compressed content of HGC, which is considered a prediction of a prolonged dissolution rate.^[25] The dissolution rate studies revealed that when amoxicillin HGC content was directly compressed, without any added excipients, showed slow release profiles and only 60% were released after 1 h of dissolution, whereas a 100% drug release was achieved in <30 min when starch was included in the formulation. When talc was included in the tablet design, 70% of amoxicillin was released after 1 h of testing. This alteration in the release profiles could be attributed to the talc action as a lubricant which involves the partial coating of other powders in the formula thus forming an impenetrable layer, thus reducing friction between particles, which in turn prolongs the diffusion path of dissolution medium resulting in the decreased dissolution of the drug.^[26] The slow dissolution rate for Formulation 1 was found to follow the zero-order kinetics which implies that the dissolution rate is independent on amoxicillin concentration in the formula.^[27] While for Formulation 3, the kinetics of drug release followed the matrix model. It appears that the minor addition of 5% of starch–talc combination was sufficient enough to alter the mechanism of drug release from the tablets.

CONCLUSION

Based on the results, amoxicillin HGC s can be formulated into tablets by direct compression method, and the resulted tablets exhibit acceptable organoleptic, physical properties, and mechanical strength, but the inclusion of a lubricant and a disintegrant is essential for the successful design of such tablets. The addition of excipients, even at a minor level, can also affect the kinetics of drug release as well.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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ملخص المقال باللغة العربية

إعادة تصميم كبسولات أموكسيسيلين كجرعة قرصية باستخدام الضغط المباشر

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مقدمة: إن أشكال الجرعات الصلبة هي أكثر أشكال الجرعة المستخدمة شيوعاً لتعاطي الأدوية، كما أن الأقراص أكثر شيوعاً من الكبسولات بسبب انخفاض تكلفة الإنتاج، والحد الأدنى من احتمال التلاعب بالمحتويات، كما توجد العديد من تصاميم الأقراص لمختلف التطبيقات.

الأهداف: الهدف من هذا العمل هو إعادة تصميم كبسولات الجيلاتين الصلبة للأموكسيسيلين، والتي يتم تعبئتها عادة في كبسولات جيلاتينية صلبة، إلى شكل جرعات أقراص بواسطة توظيف مبادئ ما قبل التشكيل.

المواد والطرق: تم الحصول على كبسولات أموكسيسيلين من السوق المحلية. وشملت التجارب دراسات على انسيابية التدفق (السيولة)، وتأثير قوة الضغط المستعملة لتحضر الأقراص، تليها إضافة السواغات، وإنتاج أقراص عن طريق الضغط المباشر، وتقييم الأقراص المحضرة باستخدام أساليب قياسية مثل الهشاشة، والصلابة، والتفكك، ودراسة حركية الإفراز.

النتائج: تم تقدير انسيابية تدفق مسحوق الأموكسيسيلين (السيولة) باستخدام مؤشر كار Carr's index ، ونسبة هاوزنر Hausner ratio ، وزاوية الاستراحة، والكثافة الظاهرية. وكانت السيولة ضعيفة للأموكسيسيلين وحده أو مع النشا ولكنها تحسنت مع إضافة التلك. ولقد وجد أن قوة الضغط عاملاً هاماً في تقنيت وصلابة وتفكك الأقراص. كان وقت التفكك سريعاً في حالة الأقراص المحتوية على النشا مقارنةً بمسحوق أموكسيسيلين وحده. كان من الضروري تضمين كميات صغيرة من مادة مفتتة ومادة مزلفة لتحسين خصائص الأقراص. وكانت سرعة الذوبان مقبولة للأقراص المحضرة، في حين أظهرت بعض الصيغ ملامح إفراز بطيئة نتيجة تفككها البطيء. وجد أن حركية الإفراز تتبع النموذج الصفري ونموذج المصفوفة.

الاستنتاج: من الممكن تعديل كبسولات أموكسيسيلين إلى جرعة في هيئة أقراص وذلك بمعالجة بسيطة في خصائص التشكيل.

الكلمات المفتاحية: كبسولات، ضغط مباشر، إعادة تصميم، أقراص.