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Original Research Article

Studies and Evaluation of Compressed Microspheres

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This work was aimed at the use of dissolution testing and similarity factor to assess the level of damage taken by active drug microspheres during compression in tablet dosage form. To achieve that, combinations of suitable excipients were used to protect drug microspheres during compression. The excipients were used in the form of powders, granules or placebo pellets prepared by extrusion-spheronization technology. The excipients were evaluated alone, in combinations and post-compression into compacts. Preliminary experiments included assessing density, hardness, friability and disintegration of all the selected excipients. Based on such experiments it was found that the flowability of combination of powders was more acceptable than individual excipients. Two combinations of microcrystalline -starch and microcrystalline cellulose -calcium carbonate granules were selected to be compressed with pellets of the active pharmaceutical ingredient ketoprofen. In all the combinations used there was a significant amount of damage to drug pellets. The kinetics of drug release appears to follow the zero-order rate, which remained unchanged even when a significant degree of damage to pellets occurs. It was found that a high level of excipients is required in order to prepare microspheres as a rapid disintegrating tablet.

Key Massages: degree of damage to microspheres under compression, direct compression, ketoprofen, dissolution testing and similarity function.

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1. Introduction

It is recognized that a multi-unit controlled release dosage form represents a preferable alternative to a single-unit system for oral administration [1]. However, it is not easy in practice to present a low potency drug in the form a multiparticulate delivery system. This is due mainly to patient compliance problems associated with the large size of the hard gelatin shell required for such dosage form. The compaction of pellets is usually of special interest in the pharmaceutical industry [2-4]. Hard gelatin capsules are a very elegant dosage form, but have the disadvantages of higher production cost, lower production rate and tampering potential, when compared to compressed tablets [5].

Compression of timed-release microspheres/microcapsules into tablets is an alternate to encapsulation in hard gelatin capsules (HGC). The design of such dosage form should reduce some of the disadvantages of HGC, namely; tampering potential with contents and higher cost associated with filling process. The new dosage form should be designed to disintegrate rapidly in the stomach, and upon disintegration should release its contents of, preferably, undamaged pellets. This work is aimed at developing rapidly disintegrating tablets, which upon disintegration release pellets which sustained little or no damage during compression. Such approach will be achieved by using combinations of well-known excipients in granular form rather than powder form. In addition, several formulation variables will be evaluated. The model drug used is ketoprofen; a drug that is commercially marketed as an immediate and sustained release dosage forms. The more common sustained-release dosage form is available as a HGC containing microspheres.

2. Materials & Methods

2.1. Materials

Ketofan® capsules 200 S-R (Al-Amriah pharm, Egypt), Microcrystalline cellulose {(MCC), Avicel PH101 (FMC, Belgium)}, Lactose, Calcium carbonate ($CaCO_3$), Starch, coloring pigment (methyl orange) and Ethanol.

2.2. Methods

A. Wet granulation

Equal mixes of excipients comprising MCC, starch, $CaCO_3$, or lactose in addition to a coloring pigment were mixed in a Turbula mixer for 5 min. then different volumes of either water (40%) or ethanol (50%) as a wetting solvent were added while mixing in a mortar until wet masses were formed. The wet masses were then fed to an oscillating granulator equipped with sieve size 1 mm, and the produced granules were then dried at 45° C.

B. Extrusion-Spheronization

Equal mixes of excipients were mixed, wetted with water, placed in an extruder

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(Caleva 25, UK), and spheronized at 1000 rpm in a Caleva spheronizer (250, UK) for 5 min. The produced pellets were then dried and separated into fractions by sieving analysis.

C. Direct Compression

Weights of 400 mg of powders, granules or pellets were compressed using hand operated IR press with a flat-face 12 mm punch and die set (Carver, USA).

D. Saturation Solubility of Ketoprofen

The solubility of ketoprofen after 24 hrs was measured in purified water, 0.1 N HCl and in phosphate buffer of 6.8. An excess of the drug ketoprofen was placed in 100 ml flasks, filled with medium and placed in a shaker water bath maintained at 37°C for 48 hrs. Samples were withdrawn after specific time intervals (0, 1, 6, 24 & 48 hrs), filtered, diluted and measured spectrophotometrically at 260 nm, after which the saturation concentration was determined.

E. Evaluation of Powders, Granules & Pellets

i. Flowability and Density of Granules and Pellets

The dry powders, and produced granules and pellets were evaluated for their flowability using tapping density method followed by estimation of Hausner's ratio, Carr's index, and angle of repose determination. Also, true density measurement using solvent displacement method was conducted (using ethanol as a non-solvent). The apparent true density is determined by using the following equation [6]:

$$Y = \frac{W3 - W1}{\delta ethanol} - \frac{W4 - W1 - 2}{\delta ethanol}$$

Where **Y** is the volume of solvent displaced by 2.00 gm of powder, δ_{ethanol} is the calculated true density of ethanol, $\mathbf{W_1}$ is the weight of dry and clean pycnometer, $\mathbf{W_2}$ is the weight of pycnometer filled with water, $\mathbf{W_3}$ weight of pycnometer filled with ethanol, $\mathbf{W_4}$ is the weight of pycnometer filled with the powder and ethanol. Then, the apparent true density of the selected powder is estimated by the formula:

$$\delta material = \frac{2}{Y}\left(g / cm^3\right)$$

ii. *Direct Compression of Microspheres*

Ketoprofen microspheres were emptied from their gelatin shell and mixed with a combination of excipients granules comprising MCC+$CaCO_3$ and MCC+starch. The percentage of active drug particles in tablets was at two levels, 40 and 30%. The compression force used was 2 tons for 15 seconds. The tablets were evaluated for their mechanical properties and release profiles at least 24 hours following preparation.

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F. Evaluation of Produced Tablets

The produced tablets were evaluated for the following properties:

i. The hardness was measuredusing a hardness tester (Pharma test PTB, Germany) followed by mathematical estimation of tensile strength (T_S) by using the following formula:

$$Ts = \frac{2F}{\pi dh}\left(kg/cm^2\right)$$

Where **F** is the force required for breaking the compact in kg, **d** is the tablet diameter in cm, and **h** is the tablet thickness in cm.

ii. The friability was estimated using a friability tester (Pharma test PTFE, Germany). In this method 5 tablets were subjected to this test for 4 min followed by calculation of percentage friability (F%) as follows:

$$\%F = \frac{W0 - W1}{W0} \times 100$$

Where **%F** is the percentage of friability, $W_0$is the original weight before performing the experiment; W_1 is the weight after performing the experiment.

iii. The disintegration time was measured using a disintegration tester (Erweka ZT3, Germany) employing 0.1 N HCl as the disintegration medium.

iv. Dissolution testing was carried out using the basket method (for pellets) and the paddle method (for tablets) and employing an Erweka dissolution tester (Erweka, Germany). The dissolution medium was 1000 ml of distilled water and the rotation speed of basket (for capsule) or paddle (for tablets) was 100 rpm. 5 ml samples were withdrawn at specific time intervals, filtered, diluted and measured spectrophotometrically at 260 nm (Analytic Specord 40ST, Germany).

The degree of damage to drug pellets was assessed by comparing the kinetics of drug release prior to and after compression (zero-order, first order and Higuchi's matrix models) and the use of the *similarity factor* (f_2):

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

Where R_t and T_t are the percent dissolved at each time point for reference (R) and (T) products. An f_2 value between 50-100 suggests that the two dissolution profiles are similar and the mean dissolution profiles are assumed to differ by no more than 15% at any time point [7].

G. Statistical Analysis

i. Modeling of Dissolution Profiles

The data obtained from dissolution testing was subjected to release kinetics, using the following equations [1]:

$$C_t = a + Kt \quad \text{for } \textbf{zero order}$$

$$\log c = \log a - \frac{Kt}{2.303} \quad \text{for } \textbf{1st order}$$

$$C_t = a + K\sqrt{t} \quad \text{for } \textbf{matrix model}$$

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ii. Analysis of Variance (ANOVA)

The comparisons between more than two-sample means were performed using two-way ANOVA test [8]. This was accomplished with the use of Microsoft Excel 2007 software.

3. Results

3.1 Apparent Density Measurement

The density of the materials used in this study was determined by solvent displacement method (Table 1), and the results indicate that those materials have similar densities except for calcium carbonate. This may imply that possible problems of segregation between the mixes of excipients may be minimal because of the similar densities [9].

Table1. The apparent true density of the different excipients used as determined by solvent displacement method.

Material	A	L	S	C
True density (g/cm^3)	1.59	1.54	1.49	2.74

N.B. A=microcrystalline cellulose; L=lactose; S=starch; C=calcium carbonate.

3.2 Flowability measurement

The effect of the type of granulating liquid on the flowability of prepared granules is summarized in Table 2. The results indicate that the flowability according to the tested parameters was acceptable for all the selected materials. In some of the combinations, the type of solvent used will have significant effect on the flowability of granules, and ethanol appears to be a better granulating liquid than water in this regard.

Table 2. Summary of the Flowability parameters of granules prepared with either water or ethanol as a granulating liquid.

Property	A+L	A+C	A+S
a. Water as a granulating solvent			
Hausner's ratio	0.7	0.6	0.8
Carr's index	40%	61.2 %	31.5 %
Angle of Repose	31.6	33.7	35.1
b. Ethanol as a granulating solvent			
Hausner's ratio	0.7	0.8	0.7
Carr's index	40%	28%	40%
Angle of Repose	36.0	33.7	39.2

N.B. A=microcrystalline cellulose; L=lactose; S=starch; C=calcium carbonate

3.3. Tablet properties

The effect of granules type on the compression and mechanical properties of tablets is presented in Table 3. It can be seen that the mechanical strength varies according to each combination of excipients used. A welcome finding was that the friability of all produced tablets was always below the 1% limit. Disintegration also was very rapid with a maximum value of not more than one minute was observed. These results also indicated that the selected wetting solvent for granulation would also affect the mechanical properties of any prepared tablets. It should be noted

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that pellets produced by extrusion-spheronization were found to resist compression into tablet form at the used compression force. Much higher force was needed to convert these pellets into tablets. This was an indication of the greater hardness these pellets possess.

Table 3. Summary of the mechanical properties of tablets prepared with different mixes of granules moistened with water or alcohol.

	Excipients Combination		
	A+L	**A+C**	**A+S**
a. Water as a granulating solvent			
Ts (kg/cm^2)	18.4	30.7	27
Friability (%)	0.15%	0.0	0.07
Disintegration time (sec)	23.0	8.0	23.0
b. Ethanol as a granulating solvent			
Ts (kg/cm^2)	25.51	25.4	23.4
Friability (%)	0.0%	0.36	0.083
Disintegration time (sec)	11.4	18.0	34.8

N.B. A=microcrystalline cellulose; L=lactose; S=starch; C=calcium carbonate**.**

3.4 Ketoprofen Solubility

Based on solubility determination at 37°C, it was found that the solubility of ketoprofen in 0.1 N HCl, purified water and in phosphate buffer of 6.8 was 17, 186, and 927 mg/100 ml, respectively. As a result, it was postulated that the evaluation of release rate of compressed pellets at the buffered pH 6.8 will not demonstrate clearly the level of damage to microspheres because of the high solubility of ketoprofen at this pH. Also, the use of acidic pH 1.2 where solubility of ketoprofen is lowest will not reveal the change in dissolution rate as a result of compression. Hence, it was decide that studies on the release rate of ketoprofen will be evaluated in purified water where the solubility of ketoprofen was in the middle of the solubility range obtained rather than the acidic or buffer media.

3.5 Compression of Ketoprofen Microspheres

A. At 60 % Excipient Level

The two combinations of MCC + starch and MCC + $CaCO_3$ granules (60%) were selected to be compressed with active ketoprofen pellets (40%). Mechanical properties of the compressed microspheres were acceptable with hardness and friability values similar to the compressed excipients. The dissolution profiles in purified water for these tablets are shown in Figure 1.

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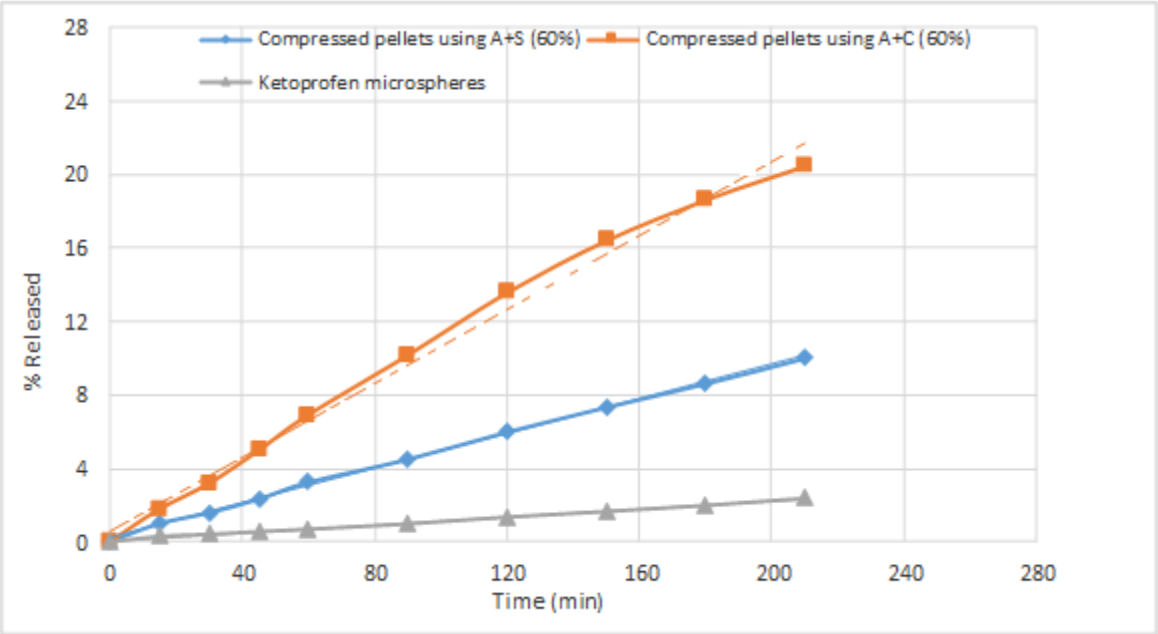

Figure 1. Dissolution rate of ketoprofen from pellets compressed with the aid of 60% excipient granules in purified water. Dotted line is the trend-line of the rate. A=microcrystalline cellulose; S=starch; C=calcium carbonate. The results are the mean of 6 experiments. Error bars were not included because of the very small range.

Based on statistical analysis using ANOVA and similarity function (f_2) a significant degree of damage occurred to the active drug pellets during compression. The ANOVA test revealed that there is a significant difference between the dissolution profiles obtained, while f_2 function, as compared to the uncompressed pellets, was always below the level of 50. The degree of damage was lower when MCC + starch combination was used. It is possible that when calcium carbonate was used, and because of its higher density, an added pressure was generated against the active drug molecules during compression from within the matrix which could result in higher degree of damage to the active drug molecules. These results collectively show that the need for higher level of excipients will be necessary in order to prepare pellets in the form of tablets with the optimum requirement.

B. At 70 % Excipient Level

In these formulations, the ratio of excipients increased to 70% using the same excipients. A summary to the mechanical properties is given in Table 4. The two combinations of MCC + starch and MCC + CaCO3 granules (70%) were selected to be compressed with active ketoprofen pellets (30%). The dissolution profiles in purified water from these tablets are shown in Figure 2. The statistical analysis using ANOVA of the dissolution profiles obtained revealed a highly significant difference between the three formulations, which indicate the incidence of high degree of

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damage to the pellets during compression. While based on similarity function as compared to the control, it was found that the combination of MCC + starch provided an acceptable limit of protection with acceptable f_2 value above 50.

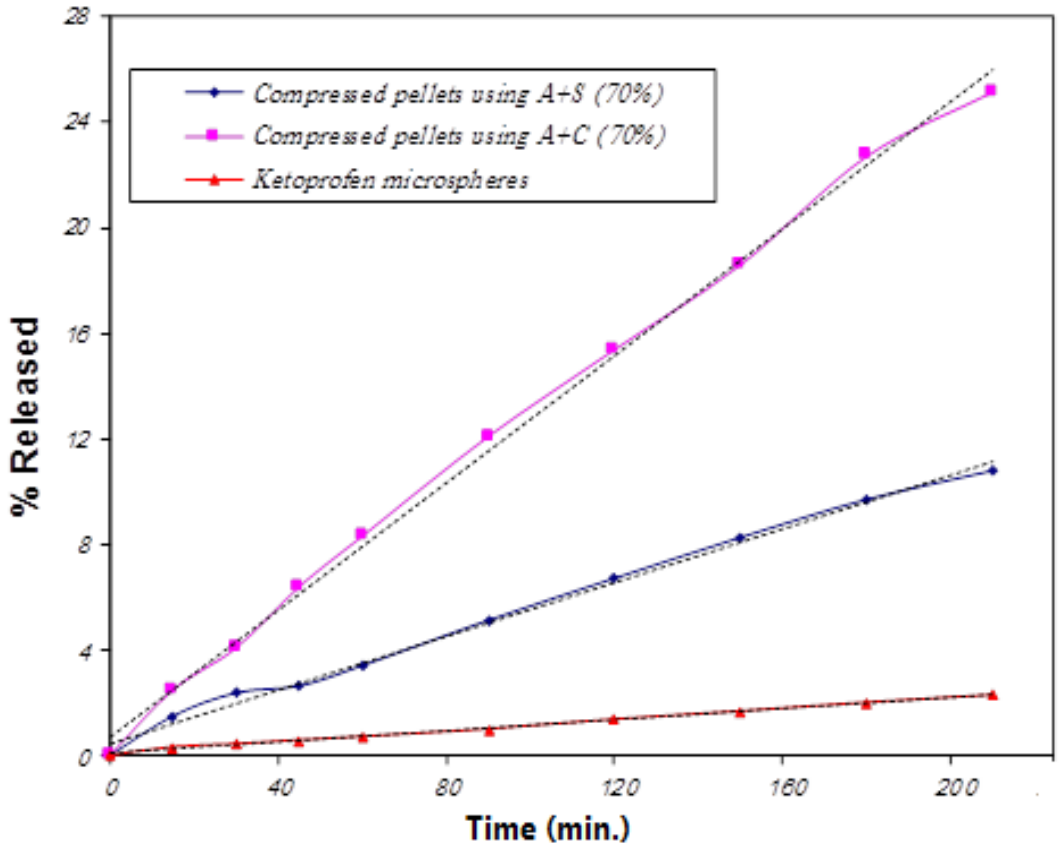

Figure 2. Dissolution rate of ketoprofen from pellets compressed with the aid of 70% excipient granules in purified water. Dotted line is the trend-line of the rate. A = microcrystalline cellulose; S=starch; C=calcium carbonate. The results are the mean of 6 experiments. Error bars were not included because of the very small range

C. Kinetics of Drug Release

When the dissolution profiles of either the compressed or uncompressed microspheres were fitted to the different models to simulate drug release kinetics, it was interesting to observe that drug release profiles were always best described using the zero-order model. And such observation remained even when the pellets sustained the damage during compression. The low solubility of the drug in water may play a role in such finding. Table 4 summarizes both the R^2 values and f_2 scores for all the preparations.

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Table 4. Summary of mechanical properties, disintegration times, regression analysis and similarity factor for compressed microspheres with different levels of granules.

Preparation	F (%)	Ts (kg/cm^2)	D (sec)	R^2	f_2
Ketofan® 200 S-R capsule	NA	NA	300	0.9971	100
Tablet with 60% A+S	0.20	20.12	23	0.9962	46.9
Tablet with 60% A+C	0.40	12.56	45	0.9908	45.2
Tablet with 70% A+S	0.13	23.13	27	0.9978	61.6
Tablet with 70% A+C	0.55	14.04	51	0.9954	41.0

N.B. F%=Friability; Ts=Tensile strength; D=Disintegration time; R^2=Correlation coefficient for zero order kinetics; f_2=Similarity factor. A=microcrystalline cellulose; L=lactose; S=starch; C=calcium carbonate.

4. Discussion

Preliminary results on the individual excipients used in this work revealed that materials used possess similar densities, which are indicative of minimal problems of segregation, except in the case of calcium carbonate, which was found to exhibit a higher density than other tested materials. This observation was expected because calcium carbonate is a material classically used in spheronization technology to increase the density of produced microspheres [10, 11]. As was predicted, the flowability of granules was better than the individual powders alone. Also, slight differences in flowability was observed between granules prepared with two different type of solvents which was attributed to the strength of binding bridges between excipients molecules as formed by the wetting liquid [12]. First attempts of tabletting were performed on excipient granules without the inclusion of ketoprofen microspheres. All the used combinations produced tablets of acceptable mechanical strength and disintegration. In addition, the type of solvent used in preparing the granules was found to affect the physical properties of the produced tablets. When ketoprofen was included at various levels with excipient granules during compression it was found that the drug microspheres sustained a high degree of damage during compression. And that a high amount of excipients will be necessary to protect and partially coat drug microspheres during the compression stage to minimize the degree of damage. The combination of excipients will also serve to optimize the disintegration time of the produced tablets to make it comparable to that of capsules [2].

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5. Conclusions

The result of this work solidifies the notion that no single excipient is sufficient to provide complete protection to microspheres/microcapsules, and more than one excipient is required to obtain such protection. It was possible to formulate commercial drug microspheres, currently marketed as hard gelatin capsules, as a tablet dosage form. However, a high amount of excipients was required to achieve such a design.

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الملخص باللغة العربية

دراسات تقييمية لعمليات تحويل الكبسولات المصغرة الى اقراص

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يهدف هذا العمل الى استعمال "اختبارات التحلل" و"معامل التشابه" لتقييم مستوى الضرر الذى تتعرض له "الكبسولات المصغرة" عند تشكيلها على هيئة اقراص. ولحماية هذا الشكل الدوائى فأن استعمال مجموعة مناسبة من المواد المضافة ضرورة حتمية. مثل هذه المواد المضافة استعملت على هيئة مسحوق، حبيبات او كريات مصغرة تم تصنيعها بتقنية "التكوير بالبثق". التجارب الاولية شملت قياس الكثافة، الصلابة، التفتت، والهشاشة سواء على المواد المضافة وحدها او على شكل الاقراص منها. وبناء عليه تم اختيار مواد الميكروسيلولوز البلورى مع النشا او كربونات الكالسيوم ليتم ضغطها مع كريات تحتوى عل عقار "الكيتوبروفين". وتبين بعد عمليات التقييم ان هناك قدر من الضرر حدث لهذه الحبيبات ولكن ميكانيكية خروج الدواء منها لم تتغير. وتم التوصل فى النهاية ومع استعمال نسبة كبيرة من المواد المضافة تحويل هذه الحبيبات الى اقراص مع نسبة ضئيلة ومقبولة من الضرر.

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