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The Suitability of Disintegrating Force Kinetics for Studying the Effect of Manufacturing Parameters on Spironolactone Tablet Properties

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Gina Massimo[1], Patrizia Santi[1], Gaia Colombo[1], Sara Nicoli[1], Franca Zani[1], Paolo Colombo[1], and Ruggero Bettini[1]

[1]Department of Pharmacy, University of Parma, Italy

ABSTRACT

The aim of this paper was to study the effect of the granulate properties and tablet compression force on disintegrating force behavior in order to investigate the capability of the disintegrating force to characterize tablets that have the same composition but were manufactured in different conditions. Several tablets containing spironolactone in the external or internal granulated mixture of calcium carbonate and maize starch differing in particle size distribution, were prepared at 3 compression levels. The force developed by tablets during water uptake and disintegration was measured and plotted versus time. The curves obtained were analyzed by the Weibull equation in order to calculate the parameters characterizing the tablet disintegration kinetics. The disintegrating force time parameter, the maximum force developed, and the area under the curve were determined. In general, the reduction of time parameter value and/or the increase in maximum force developed corresponded to an acceleration in tablet disintegration. In addition, the area under the force curve increased in stronger tablets, monitoring in a sensitive way the tablet structural changes introduced by compression force. The results showed that the disintegrating force measurement can detect small changes in the structure of the tablet that cannot be discriminated by pharmacopoeia tests. The effect of manufacturing, in particular compression force, on tablet properties was quantified by the parameters of disintegrating force kinetics.

KEYWORDS: disintegrating force, spironolactone, tablet, granulation, compression force

Corresponding Author: Gina Massimo, Department of Pharmacy, University of Parma, Parco Area delle Scienze, 43100 Parma, Italy. Phone: +39 0521 905084; Fax: +39 0521 905085; Email: gina.massimo@unipr.it.

INTRODUCTION

In tablets, disintegration behavior can strongly affect dissolution rate. Disintegration time has been shown to depend on type and percentage of drug and additives and on tablet manufacturing.[1-3] The swelling of disintegrant particles remains the only demonstrated mechanism of tablet disintegration.[4,5] In fact, the water taken up by disintegrant particles generates a force inside the tablet. We have measured the disintegrating force in tablets by means of an apparatus[6] able to detect the force during water uptake. The development rate of the force within the tablet and the consequent breaking of particle-particle links were related to water uptake kinetics. In this regard, disintegrating force kinetics could illustrate the effects of constituents and manufacturing procedures on tablet properties.

In a previous paper,[7] we presented a new technique, based on the force generated by disintegrant swelling and dissipated by tablet disintegration, for analyzing the propensity of a tablet to disintegrate. Using this experimental technique, we studied the effect of different disintegrant agents. The aim of the current paper was to study to the effect of granulate properties and tablet compression force on the disintegrating force behavior, in order to investigate the capability of the disintegrating force to characterize tablets having the same composition but manufactured in different conditions. The final goal was to verify the usefulness of the disintegrating force kinetics in the pharmaceutical development studies of conventional release tablets.

Spironolactone (SPL) was chosen as a model drug since its gastrointestinal absorption strongly depends on particle size and formulation.[8,9] Several SPL tablets were prepared at different compression forces using a granulation of calcium carbonate and maize starch as diluent. The mixtures for compression contained SPL in the external or internal granulated phase. Tablets were checked for the pharmacopoeia requirements, that is, crushing strength, friability, disintegration time, and dissolution rate. Then the force developed by tablets

during water uptake and disintegration was measured and plotted versus time. The curves were analyzed by the Weibull equation in order to obtain parameters characterizing the tablet disintegration kinetics. These parameters were discussed in relation to the disintegration time and dissolution rate of the tablets.

MATERIALS AND METHODS

Materials used in this study were calcium carbonate European Pharmacopoeia 4 (PhEur4) (Faravelli SpA, Milan, Italy), maize starch PhEur 4 (Lisapharma SpA, Erba, CO, Italy), povidone PhEur4 (ACEF SpA, Milan, Italy), SPL USP 25 (particle size, microscope: 90% < 10 μm; Dipharma SpA, Milan, Italy), croscarmellose sodium PhEur 4 (Ac-di-Sol, FMC, Philadelphia, PA), and magnesium stearate PhEur 4 grade (Fluka, Milano, Italy).

Granulate Preparation and Controls

Six hundred grams of maize starch and 1400 g of calcium carbonate were mixed in a high-shear mixer bowl (Roto Junior, Zanchetta, Lucca, Italy) for 5 minutes with the impeller rotating at 250 rpm and the chopper at 1000 rpm. Under continuous mixing, 600 mL of polyvinylpyrrolidone water solution (10% wt/vol) was sprayed on the powder at 40 mL per minute. Then the wet mass was granulated through a 1-mm net of an oscillating granulator (Erweka, Type AR 400, Hensenstamen, Germany). The granules were dried in a ventilated air oven (Celsius 2000, Memmert, Schwabach, Germany) at 40°C until 3% (wt/wt) residual humidity was reached. This granulate was coded DC whole. Part of it was sieved collecting 2 fractions, the first between 850 and 425 μm (code: DC ≥ 425) and the second between 425 and 38 μm (code: DC < 425). In this way, 3 granulates with the same composition but different particle size could be used in mixtures having SPL in the external phase.

A granulate of SPL with the same excipients was prepared as well. In this case, the drug introduced in the internal phase was kneaded with the excipients (code: WET SPL).

All the granulates were tested for loss of weight by Infra Red-drying balance (Sauter-Vismara, Berlin, Germany), bulk density (PhEur 4, 2002), and particle size distribution by sieving (Endecotts Sieves, London, UK). Carr's index, the geometric mean diameter, and the geometric SD were calculated.

Tablet Preparation and Controls

Three tableting mixtures containing the drug in external phase were prepared by mixing 266.6 g of each DC granulate with 31 g of SPL, 9.3 g of Ac-di-Sol, and 3.1 g of magnesium stearate in a Turbula mixer (Bachofen, Basel, Switzerland) for 30 minutes. Mixing time was checked and found to be appropriate for SPL mixture uniformity. The mixture prepared from DC whole granulate was coded SPL I, the mixture from DC ≥ 425 granulate was coded SPL II, and the mixture from DC < 425 granulate was coded SPL III.

The tableting mixture containing the drug in the internal phase was prepared by mixing for 10 minutes 297.6 g of WET SPL granulate with 9.3 g of Ac-di-Sol and 3.1 g of magnesium stearate. This mixture was coded SPL IV.

Three batches of tablets were prepared with each mixture, using a reciprocating instrumented tableting machine (EKO Korsh, Berlin, Germany) equipped with flat cylindrical 11.3-mm punches, at 3 different compression force levels (ie, 10, 20, 30 kN). Each tablet batch was identified with the mixture code followed by the Arabic numeral denoting the compression force used.

The reference weight of the tablets was 500 mg. The tablets were tested for crushing strength (Monsanto tablet tester, Optolab, Modena, Italy) and friability (PhEur 4, 2002). The disintegration time and dissolution rate were performed in 0.1N hydrochloric acid with 0.1% of sodium lauryl sulfate at 37°C, that is, the dissolution medium given in USP 25 Spironolactone Tablets/Official Monograph. The dissolution rate curves were analyzed using the Weibull equation in order to calculate the time parameter of the curve, that is, the time when 63.2% of the drug had dissolved.

A custom-made apparatus capable of measuring tablet disintegrating force during water uptake was used.[6] Briefly, the tablet was placed in the measuring head of the apparatus between 2 porous glass disks and kept in close contact with a loading cell by applying a preload of 10 N. Then the measuring head was immersed in the dissolution medium at 37°C. Values of disintegrating force developed were recorded every second. The curves of disintegrating force versus time were analyzed using the Weibull function.[10] The curve parameters were calculated using Kaleida Graph 3.02, Synergy Software, Reading, PA, running on a Macintosh Powerbook G4, Apple, Cuppertino, CA.

Table 1. Size and Packing Characteristics of Granulates Used for Spironolactone Tablets

	Geometric Mean Diameter ± Geometric SD (μm)	Carr's Index, mean ± SD
DC whole granulate	360 ± 3.3	16.3 ± 1
DC ≥ 425 μm granulate	647 ± 2.3	9.8 ± 1.5
DC < 425 μm granulate	102 ± 1.9	25 ± 0.6
Wet granulate	227 ± 2.6	20 ± 0.7

RESULTS AND DISCUSSION

Granulate and Tablet Properties

To study the effect of manufacturing variables on tablet properties, tablets having the same composition were prepared in different conditions. A granulated mixture of calcium carbonate and starch was used as diluent for SPL tablets in order to have a base that could easily disintegrate in an hydrochloric acid medium. The tablet mixtures differed as to particle size distribution and the presence of SPL in the external or internal granulated phase. The mean particle size and Carr's index of granulates are reported in **Table 1**. It can be seen that the DC < 425 μm granulate presented the least favorable packing/flow (Carr's index), because its particles had the lowest mean size value. As a consequence, the tablets containing this granulate were manufactured at low compression speed, in order to guarantee an accurate filling of the machine die. Using the mixtures containing SPL in external phase, tablets were prepared at the above-mentioned 3 different compression force levels. The same tableting procedure was adopted with the granulated mixture containing SPL in the internal phase. All the tablets, checked for weight and thickness, were tested for crushing strength, friability, disintegration time, and dissolution rate. The results obtained are reported in **Table 2**.

No significant relationship between particle size of granulates and mechanical properties of the tablets was found. However, for each mixture the relationship between compression force and crushing strength or friability was highly significant. For example, tablet strength increased linearly within the applied pressure (crushing strength = 6.4 + 4.3 x compression force; R = 0.96). The tablets prepared at the lowest compression level exhibited a rather low mechanical resistance. In particular, for these tablets (except SPL I 10) the values of friability exceeded the limit of 1% required for acceptable tablets. As generally expected, an increase of compression force up to 20 kN led to improved tablet resistance, resulting in mechanically stronger SPL tablets.

The biopharmaceutical properties of SPL tablets—that is, disintegration time and dissolution rate—behave differently in relation to granulate particle size and compression force. As for disintegration time, 2 groups of tablets could be identified (see **Table 2**). One group consisted of the tablets prepared with larger granulates (mixtures SPL I and SPL II). The second group contained the smaller-granulate mixtures (SPL III and SPL IV). In the case of larger granulates, tablet disintegration time evidently increased by increasing compression force. In the case of tablets prepared with smaller granulates, slight if any dependence on compression force was observed. Moreover, in this second group of tablets, disintegration times were shorter than in the case of SPL I and SPL II tablets.

In the case of these formulations, compression force did not affect the SPL tablet dissolution rate. However, as seen for the disintegration time, the dissolution time of SPL tablets was shorter when the size of granulated diluents was reduced (SPL III) and, furthermore, when SPL was employed in the internal phase (SPL IV).

In summary, there was no univocal dependence of biopharmaceutical properties on the manufacturing variables. Despite the changes performed in the manufacturing, the tablets were not critically different, probably because in all cases short disintegration time and quite fast dissolution rate were observed. Nevertheless, the fastest dissolution rates always corresponded to the lowest disintegration times.

Disintegrating Force Development During Tablet Disintegration

In the experimental conditions adopted, the concomitant swelling and disintegration of the tablet determined the disintegrating force. In fact, the swelling of disintegrant particles generated force while the tablet

Table 2. Mechanical and Biopharmaceutical Properties and Disintegrating Force Curve Parameters of the Prepared Tablets (mean ± SEM; n = 6)*

	Hardness (N)	Friability (%)	Disintegration Time (s)	Mean Dissolution Time (s)	DFT (s)	F_{max} (N)	AUC (N x s)
SPL I							
10	55 ± 0.3	0.8	354 ± 5	626 ± 22	65 ± 2	15.2 ± 0.4	1524 ± 136
20	89 ± 0.3	0.4	449 ± 12	628 ± 14	81 ± 2	16.8 ± 0.3	2405 ± 288
30	134 ± 0.1	0.1	513 ± 11	616 ± 4	127 ± 2	18.5 ± 0.4	3682 ± 323
SPL II							
10	41 ± 0.1	1.1	175 ± 3	748 ± 6	62 ± 2	15.8 ± 0.35	1493 ± 193
20	84 ± 0.2	0.7	283 ± 11	626 ± 78	77 ± 2	16.5 ± 0.44	2129 ± 184
30	120 ± 0.1	0.3	345 ± 13	841 ± 33	121 ± 3	18.4 ± 0.21	3360 ± 212
SPL III							
10	54 ± 0.3	1.96	55 ± 2	267 ± 48	49 ± 1	22.4 ± 0.3	1393 ±109
20	116 ± 0.2	0.9	61 ± 4	214 ± 58	74 ± 4	21.3 ± 0.6	2233 ± 118
30	> 147	0.58	78 ± 4	227 ± 55	94 ± 1	20.8 ± 0.4	2802 ± 171
SPL IV							
10	39 ± 0.1	1.4	72 ± 1.3	167 ± 14	33 ± *2*	25.5 ± 2.1	963 ± 79
20	88 ± 0.2	0.6	57 ± 0.7	136 ± 16	50 ± 1	30.5 ± 1.8	2132 ± 146
30	127 ± 0.1	0.6	60 ± 1.8	184 ± 15	85 ± 3	28.9 ± 0.4	3559 ± 123

*DFT indicates disintegrating force time; F_{max}, maximum force developed; AUC: area under the curve of force development versus time; SPL, spironolactone.

disintegration dissipated force. The tablet disintegrating force was measured versus time, and results are illustrated in **Figure 1**. The curves are the mean of 6 determinations, and the experimental points are reproduced without error bars for the sake of clarity. The variability of the measurements can be appreciated from the curve parameters reported in **Table 2**.

In the apparatus for the force measurement, the tablet was clamped between 2 porous glass disks. To keep the tablet firmly in contact with the force transducer, a preload of approximately 10 N was applied. Therefore, the disintegrating force curve started from the preload value. Then, as the water penetrated the tablet, the force generated by disintegrant swelling was graphically represented by a curve rising up to a peak after which the curve decreased because of tablet disintegration. The force value returned to zero when contact between tablet and transducer was lost. At this point, the tablet was fully disintegrated.

Different shapes characterized the disintegrating force curves obtained with the tablets prepared. Some curves showed a sudden increase in force to a sharp peak value, followed by a rapid decrease to zero; others showed lower peak values and a broader shape owing to a slow return of the force to zero. The broadening of curve shape was particularly evident with tablets prepared at higher compression force (compare A, B, and C in **Figure 1**).

To transform the curve into parameters characterizing the different tablets, the disintegrating force curves were analyzed using the Weibull equation.[10,11] Three main parameters were calculated and related to the manufacturing conditions and properties of the tablets (**Table 2**). The first parameter was the overall time parameter of force development.[7] The time course of the disintegrating force development was dependent on the time it took the tablet to disintegrate in the test conditions. This disintegrating force time (DFT) parameter value corresponds to 63.2% of the force developed and is an evaluation of the rate of the process. We observed that the DFT values increased with the compression force (**Figure 2**). Since the increase in compression force led to stronger and less porous tablets, the rate of disintegrating force development slowed down. In fact, the DFT increased with tablet mechanical resistance.

For SPL I, SPL II, and SPL III tablets, a correlation between DFT values and disintegration times measured with the pharmacopoeia apparatus was observed. In fact, both disintegration time and DFT increased with the compression force applied for tablet preparation.

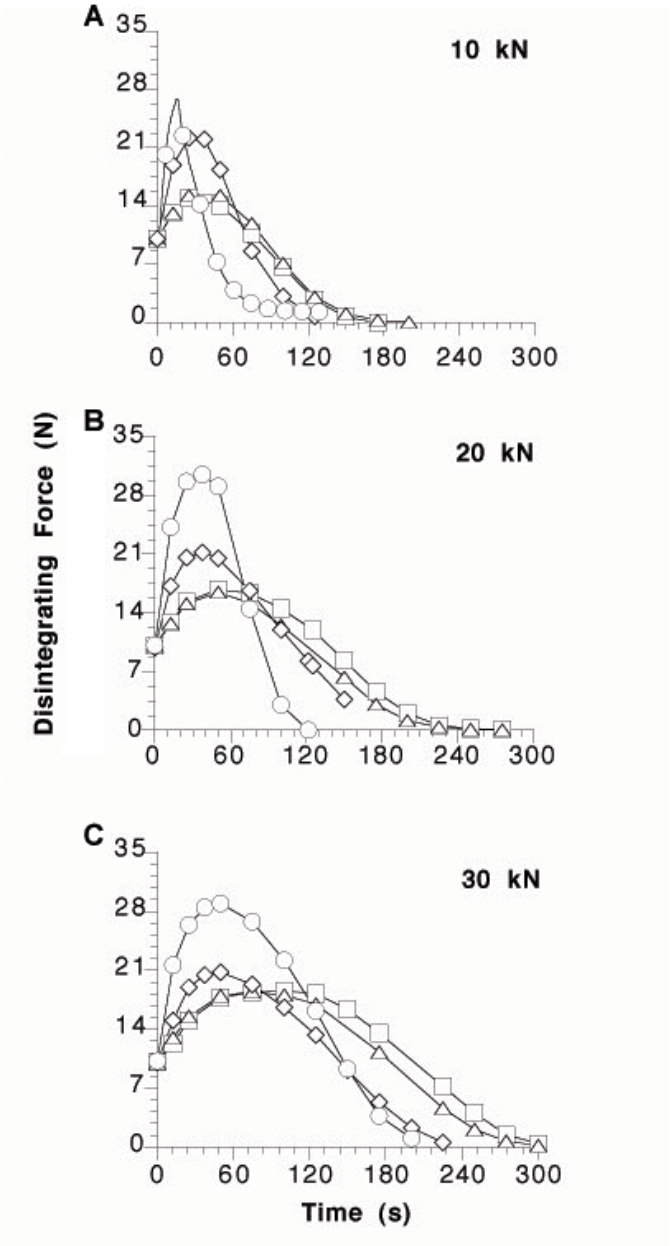

Figure 1. Disintegrating force versus time curves measured on the SPL tablets prepared at 3 different compression forces: SPL I (❑), SPL II (Δ), SPL III (◇), SPL IV (○).

This was not observed for SPL IV tablets since disintegration time was not influenced by compression force.

A relationship between DFT and dissolution rate was not found, because dissolution rate was not dependent on compression force. A similar behavior of dissolution rate has been already observed for SPL tablets and attributed to the dissolution medium's containing a surface-active agent.[8] In our case, because of the tablet composition and dissolution medium, the dissolution rate was quite fast, and therefore the differences between tablets were not evident. However, the particle size of granulates affected the DFT value in much the same way as it had affected the biopharmaceutical properties. In fact, 2 groups of tablets characterized by close granule size could be identified. Groups SPL III and SPL IV, exhibiting the quickest dissolution and disintegration values, showed the shortest DFT values. In addition, the fastest disintegrating force development at each compression force level was exhibited by the preparation SPL IV, in which the SPL was in the internal phase.

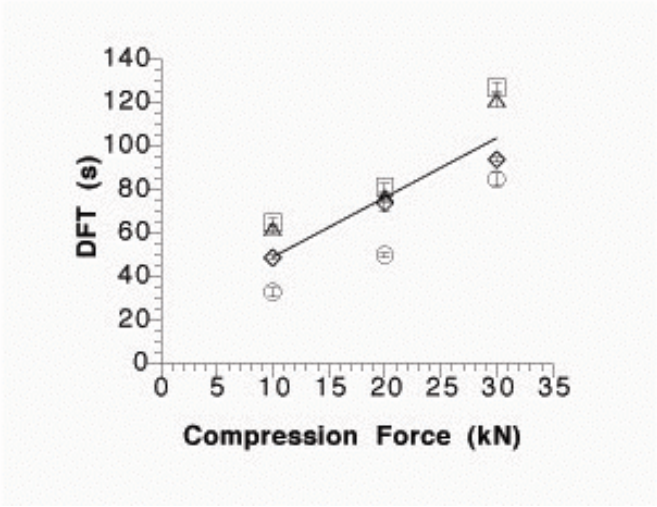

Figure 2. Relationship between compression force and DFT parameter of SPL tablets: SPL I (❑), SPL II (Δ), SPL III (◇), SPL IV (○).

The second parameter of the disintegrating force curve was the maximum force developed (F_{max}), that is, the value of the peak of the force curve. The meaning of this parameter is also linked to the rate of force development. The water entering the tablet can develop a quick and intense force as a result of penetration rate and disintegrant swelling. However, a tablet showing a high water penetration rate and intense disintegrant swelling is generally a tablet that quickly disintegrates. Therefore, the peak value of the disintegrating force is reduced by fast disintegration of the tablet, which quickly dissipates the force generated. In fact, we noticed that quickly disintegrating tablets showed a sharp peak force. There was an inverse relationship between F_{max} and disintegration time, and the tablets showing higher F_{max} values exhibited shorter disintegration times.

The third parameter of disintegrating force curves was the area under the curve of force development versus time (AUC). This parameter measures the exposure of the tablet to the disintegrating force. To have a tablet that releases quickly, the disintegrating force must be as high as possible and the time of development short. When the force persisted for a long time in the tablet, owing to slow water uptake and/or to slow disintegration rate (force dissipation), a high AUC value was measured. This occurred, for instance, when the tablet became more resistant because of compression force increase. In fact, there was a good linear correlation between the compression force used for tablet preparation and the AUC value of these tablets: as the compression force increased, the AUC value also increased (**Figure 3**). Nevertheless, for the assessment of the biopharmaceutical quality of the tablet, the AUC value has to be combined with a rate parameter.

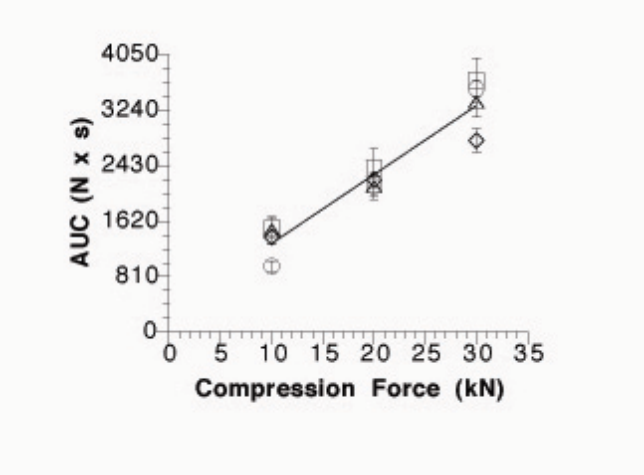

Figure 3. Relationship between the compression force and AUC of SPL tablets: SPL I (❑), SPL II (△), SPL III (◇), SPL IV (○) (regression line: y = 298.8 + 100.4x, $R = 0.96$).

In conclusion, in SPL conventional release tablets manufactured by different granulate techniques (internal or external SPL), an improvement in drug dissolution was registered by the inclusion of SPL in the internal phase during excipient granulation and with the reduction of granulate particle size. With the studied formulations the increase of compression force did not affect the dissolution performance of SPL tablets. However, in all the cases, the SPL tablets complied with USP 25 requirements (no less than 75% of the SPL is dissolved in 60 minutes). This was attributed to the granulated diluents (calcium carbonate and starch) used for tablet preparation that were dissolving and/or disintegrating in hydrochloric acid 0.1N solution.

On the contrary, the disintegrating force behavior clearly characterized the tablets, since it could describe small changes in tablet structure. All the modifications introduced in the tablet by the preparation technique were quantified by the parameters of the disintegrating force versus time curve. The force curves promptly changed shape, reflecting the manufacturing variations, in particular the effect of compression force. When the compression force or granulation changes were not reflected by the disintegration time or dissolution rate, the disintegrating force parameters discriminated among the different tablets.

In general, the reduction of the time parameter value (DFT) and/or the increase in F_{max} developed corresponded to an acceleration in tablet disintegration. In addition, the AUC increased in stronger tablets, monitoring in a sensitive way the structural changes of the tablet introduced by compression force.

Therefore, the disintegrating force curve is able to illustrate the rate of water penetration and its effect on tablet disintegration. The propensity of the tablet to disintegrate and to release the drug can be described by the combination of rate and extent parameters of the disintegration force kinetics. The disintegrating force parameters could be used as sensitive tools for pharmaceutical development of conventional or fast-release tablets and for comparing the pharmaceutical equivalence of essentially similar preparations.

REFERENCES

1. Caramella C, Ferrari F, Bonferoni MC, Ronchi M. Disintegrants in solid dosage forms. Drug Dev Ind Pharm. 1990;16:2561-2577.

2. Ferrari F, Bertoni M, Bonferoni MC, et al. Influence of porosity and formula solubility of disintegrant efficiency in tablet. STP Pharma Sciences. 1995;5:116-121.

3. Vadas EB, Down GRB, Miller RA. Effect of compressional force on tablets containing cellulosic disintegrators, I: dimensionless disintegration values. J Pharm Sci. 1984;73:781-783.

4. Caramella C, Colombo P, Conte U, Gazzaniga A, La Manna A. The role of swelling in the disintegration process. International Journal of Pharmaceutical Technology & Product Manufacture 1984;5:1-5.

5. Colombo P, Conte U, Caramella C, Geddo M, La Manna A. Disintegrating force as a new formulation parameter. J Pharm Sci. 1984;73:701-705.

6. Catellani PL, Predella P, Bellotti A, Colombo P. Tablet water uptake and disintegration force measurements. Int J Pharm. 1989;51:63-66.

7. Massimo G, Catellani PL, Santi P, et al. Disintegration propensity of tablets evaluated by means of disintegrating force kinetics. Pharm Dev Technol. 2000;5:163-169.

8. Badwan AA, Nabulsi LN, Saleh MR, Arafat TA. Leveling off the effect of particle size on dissolution in spironolactone tablets. Congr Int Technol Pharm 5th. 1989;5:418-426.

9. ElShabouri MH. Nanoparticles for improving the dissolution and oral bioavailability of spironolactone, a poorly-soluble drug. STP Pharma Sciences. 2002;12:97-101.

10. Langenbucher L. Parametric representation of dissolution-rate curves by the RRSBW distribution. Die Pharmazeutische Industie. 1976;38:472-477.

11. Rodriguez F, Arama E, Maghi M, Paulin T, Ruffiac R. Application of the Weibull function to the study of in vivo/in vitro correlation. J Pharm Belg. 1990;45(3):173-183.