Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense)*
Lat. Am. J. Pharm. **29** (1): 111-6 (2010)

Original Article

Received: May 11, 2009
Accepted: August 26, 2009

Technological Development of Hard Capsules of Sertraline Hydrochloride

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SUMMARY. **Fast release capsules, containing sertraline hydrochloride, pregelatinized maize starch and microcrystalline cellulose were formulated. For this purpose, different technological assays were elaborated being the formulation 2 selected as the better technological variant. Dry powders were filled into hard gelatin capsules. From this formulation were derived capsules with satisfactory technological properties. The quantification of sertraline through HPLC UV detection method was validated for accuracy, precision, linearity and selectivity. The method was linear over the concentration range 0.5 to 0.75 mg/mL and was shown to be highly reproducible. It could be used, without any interference of capsule excipients, for determination of sertraline from solid dosage form. Hard capsules showed an adequate stability during 24 months demonstrating the feasibility from the process of production of this formulation. Parameters, *f1* and *f2*, were used to confirm similarity of dissolution, in deaerated distilled water, of test formulation and capsules of Prosertin as reference product.**

INTRODUCTION

Depression, a common mental disorder, is a chronic or recurrent illness that affects both economic and social functions of patients and can eventually lead to suicidal behaviour. The selective serotonin reuptake inhibitors (SSRIs) are the most widespread class of second-generation antidepressant drugs and are in fact becoming the drugs of first choice for the treatment of depression. SSRIs block the reuptake of serotonin at central synapses selectively and powerfully. SSRIs have a therapeutic efficacy similar to that of traditional, tricyclic antidepressants, but have a much more favourable side- and toxic-effect profile; furthermore, the former are also very useful in the treatment of depression-related disorders, such as anxiety, panic and obsessive-compulsive disorders. The members of this class are fluoxetine, citalopram, paroxetine, sertraline and fluvoxamine [1,2].

Several methods for analytical determination of sertraline in biological samples or in pharmaceutical formulations have been developed [3]. The majority of these methods are based on high performance liquid chromatography (HPLC) [4-6]. The literature indicates others methods such as ultraviolet and visible spectrophotometry [7] and thin layer chromatography [8]. Recently, a liquid chromatographic/tandem mass spectrometric was reported [9]. However, it is not included in any pharmacopoeia.

To get an optimal therapeutic action, an active pharmaceutical substance should be delivered to its site of action in an effective concentration. To allow reliable prediction of the therapeutic effect, the performance of the pharmaceutical preparation should be characterized by *in vivo* and/or *in vitro* studies. Approval of multisource formulations using comparative in vitro dissolution studies should be based on generation of comparative dissolution profiles rather than a single point dissolution test.

When comparing the multisource products, dissolution profiles can be compared using the similarity factors [10]. Moore & Flanner [11] have proposed a similarity factor, *f2*, for comparison of dissolution profiles that has been adopted in SUPAC IR guidelines [12].

The aim of the present study was the technological development of fast release hard gelatin capsules formulation of sertraline hydrochloride and comparison with two reference products using similarity factors, *f1* and *f2*. Furthermore, to validate HPLC UV detection analytical method to quantify sertraline in hard capsules, and evaluates the stability, during 24 months, of the proposed formulation.

KEY WORDS: hard gelatin capsule, sertraline, stability, validation of analytical methods

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MATERIALS AND METHODS

Materials

The following reagents were used: sertraline hydrochloride (Zydus Cadila, India), pregelatinized maize starch (Roquette, Italia), microcrystalline cellulose (MCC pH-250, Blanver, Brazil), maize starch (Roquette, Italia), lactose (Borculo, Holland), sodium lauryl sulphate (Basf, Alemania), magnesium stearate (Otto Barlocher GmbH, Germany) and colloidal silicon dioxide (Aerosil, Blanver, Brazil). As reference products, capsules of Prosertin, Mexico (Lot 4484) and tablets of Cipla, India (Lot-DA4262) were employed. All other chemical and solvents were of analytical reagent grade.

Preparation of sertraline hydrochloride fast release hard capsules

The composition of the evaluated formulations is listed in Table 1, where amounts of sodium lauryl sulphate, magnesium stearate and aerosil used were constants. Three batches of fast release hard gelatin capsules of sertraline (Formulation 2) were filled with dry powders using a semi-automatic machine Doot Bonapace (Italy). Each capsule of 250 mg (size No. 2) contained 50 mg of sertraline clorhydrate.

Components	Formulations (% w/w)		
	F_1	F_2	F_3
Sertraline clorhydrate	22.39	22.39	22.39
Pregelatinized maize starch	-	16.85	16.85
Lactose	59.46	-	59.46
Maize starch	16.85	-	-
Microcrystalline cellulose	-	59.46	-

Table 1. Composition of evaluated dry powders formulations.

Evaluation of dry powders

The mean particle size and the size distribution of powders were measured by applying a shaking sieve with a set of sieves consisting of sieves with 250, 80, 63, 45, 32 µm apertures.

The flow rate was determined according to the fixed-funnel method [13]. Each reported value is the average of three determinations.

For the determination of bulk and tap densities, an appropriate amount of the sample was poured in a 100 mL tared graduated cylinder.

The volume was then read directly from the cylinder and used to calculate the bulk density (D_b) according to the mass/volume ratio. For tap density (D_t) the cylinder was tapped 1000 times using a tap density analyzer (Erweka SVM1, Germany). The Carr index (C) was measured and calculated from equation [**1**] [14].

$$C = \frac{D_t - D_b}{D_t} \cdot 100 \qquad [\mathbf{1}]$$

Evaluation of sertraline hydrochloride capsules (Formulation 2)

The disintegration time, in minutes, was determined by using a disintegrator Pharma Test (Germany) apparatus. Deionized water at 37 ± 1 °C was used as immersion medium. All measurements were made in triplicate.

The percentage of drug dissolved was measured using paddle method with stirring speed of 50 rpm, in 900 mL deaerated distilled water at 37 ± 0.5 °C, dissolution time was 45 min using a dissolution tester (Pharma Test, WS3C, Germany). Six capsules of each batch were evaluated. Dissolution profile was made taking samples at 5, 10, 15, 20, 30 and 45 min of 1 mL each one and the same volume of fresh dissolution medium was returned to the vessel. The method was carried out in the quality control laboratory of the Cuban enterprise.

The amounts of drug released from capsules and assay were analyzed using a HPLC KNAUER (Germany). The chromatographic determinations of sertraline by proposed HPLC UV detection method (275 nm) employed C18 100A Luna (15 cm x 4.6 mm, 5 µm particle size) column (USA) and a mobile phase compound for sodium heptanesulfonate (0.20%), sodium phosphate dibasic (0.04%) and water (99.75%). It was pumped at a flow rate of 1.0 mL/min with an injection volume of 20 µL. The column was thermostated at an ambient temperature.

Validation and stability studies

The drug concentration was determined by using proposed chromatographic method. Linearity and interval was evaluated with solutions containing 0.25; 0.4; 0.5; 0.6 and 0.75 mg/mL of sertraline hydrochloride which correspond with 50%, 80%, 100%, 120% and 150%, respectively, analyzed by triplicate. The calibration curve obtained was analyzed through linear regression, in which the correlation coefficients, equation, t Student were calculated. The calibration curve for HPLC analysis was constructed by plotting the peak area of drug against the drug concentration [15].

Accuracy of the chromatographic assay was verified by means of the recovery test [16]. The precision was verified by evaluating repeatability and intermediate precision. Intraday variability of the assay method was determined by repeated analysis of three quality control samples at low (80%), medium (100%) and high (120%) concentrations on the same day (n = 3).

Intermediate precision of the method was tested on both the between day and between analysts. Inter-day variability of the assay method was determined by repeated analysis of control samples at 100% concentration on two different days (n = 3). Similarly, inter-analysts variability was determined by repeated analysis of control samples at 100% concentration on two different analysts (n = 3). The variation coefficient of the results, the parameters t Student and Fisher were calculated.

The selectivity of the method was determined by assessing the influence of the excipients of formulation. The chromatographic determinations were carried out on mixes of the excipients of test preparation, without sertraline, test solid formulation and standard solution of sertraline 0.5 mg/mL.

For the robustness study, different analytical columns, C18 100A Luna (250 x 4.6 mm) 5 µm particle (USA) and Nucleosil C18 (250 X 4.6 mm) 5 µm particle size (Germany), were employed. The variation in the flow-rate was also studied.

Batches of Sertraline capsules were exposed at 30 °C ± 2 °C / 70 % RH ± 5 % for 24 months. The disintegration time, the percentage of drug dissolved and assay of capsules were determined at initial, 6, 12 and 24 months.

Similarity and dissimilarity factors

The similarity factors *f1* and *f2*, were performed to compare the drug percent dissolved between the test formulation and reference products. For dissolution profile to be considered similar, the value of *f1* should be lower than 15 and the value of *f2* should be between 50 and 100 [12,17].

RESULTS AND DISCUSSION

The experimental results of evaluated dry powders are given in Table 2. From those results, it can be seen that amount of MCC pH-250 has more influence on the flow rate and size particle of the powders. It was supposed that as high particle size of MCC pH-250, generates good flowability of powders. The inclusion of MCC decreased both densities values in formulation 2. Particle size and the free spaces among particle increased, then volume for the same mass augment too. However, densities values of F_1 y F_3 are high as a result of percent of small particle (> 70%) of dry powders. Independent of composition of formulations, distribution of particle size showed a normal behaviour ($D_{max} < D_{critic} = 0.486$).

Carr's Index showed similar behaviour with bulk and tap densities; it is caused by Carr's mathematical definition. Direct measured of granulates flowabilty (flow rate) are not in concordance with indirect measured. Many studies suggest the results of flow properties depend upon the manner in which the test is formed [18]. Results can also vary due to differences in the way of the samples are handled prior to measurement [19]. For these reasons, is recommended, for practical purposes, to use direct methods to evaluate fluidity.

The formulation having the highest flow rate ($Fr \geq 7$ g/cm²s) and acceptable size particle, Formulation 2, was considered the best and further batches were prepared keeping % pregelatinized maize starch and MCC pH-250, as direct compressible diluents, according to its composition. Therefore, the formulation 2 was selected as the better technological variant.

Capsules properties of the hard gelatin capsules containing 50 mg sertraline hydrochloride are given in Table 3. The three batches fulfill all the constraints for the rapidly disintegrating capsule. The disintegration time (t < 30 min), the percentages of dissolved drug higher than 80% and values of assay from between 90 % and 110 % are within acceptable limits.

Analytical validation is one of the basic elements in quality systems. The validation of an analytical method affords a greater degree of reliability to the data obtained. The resulting findings are directly proportional to the quality of the processes designed to obtain such data [20].

Property	Formulations		
	F1	F2	F3
Particle size (µm)	82.22 ± 0.02 $D_{máx}$ = 0.176	147.04 ± 0.12 $D_{máx}$ = 0.134	97.87 ± 0.10 $D_{máx}$ = 0.172
Flow rate (g/cm²s)	5.78 ± 0.20	12.63 ± 0.01	4.56 ± 0.06
Bulk density (g/cm³)	0.62 ± 0.01	0.49 ± 0.11	0.59 ± 0.02
Tap density (g/cm³)	0.90 ± 0.10	0.68 ± 0.01	0.85 ± 0.05
Carr's Index (%)	31.1 ± 0.01	27.9 ± 0.25	30.6 ± 0.04

Table 2. Properties of dry powders (mean ± DS). $D_{máx}$: from Kolmogorov-Smirnovn test ($D_{máx} < D_{critic} = 0.486$).

Parameters		Time (months)			
		Initial	6	12	24
Disintegration (n = 6) (t < 30 min)	B*1	11.0 ± 1.1	13.0 ± 1.1	12.0 ± 1.1	14.0 ± 1.1
	B2	13.0 ± 1.1	15.0 ± 1.1	14.0 ± 1.1	16.0 ± 1.1
	B3	11.0 ± 1.1	12.0 ± 1.1	13.0 ± 1.1	15.0 ± 1.1
Dissolution (n = 6) (Q ≥ 80% in 45 min)	B1	95.8 ± 1.5	92.4 ± 1.9	92.7 ± 2.5	94.3 ± 1.5
	B2	95.9 ± 2.5	94.7 ± 2.5	92.5 ± 0.7	91.8 ± 1.8
	B3	95.1 ± 3.3	93.4 ± 1.7	93.6 ± 1.7	92.5 ± 0.7
Assay (n = 20) (90.0 – 110.0 %)	B1	101.4 ± 1.1	100.9 ± 0.5	98.1 ± 0.8	97.9 ± 0.5
	B2	101.3 ± 1.1	100.3 ± 0.6	97.2 ± 0.5	97.8 ± 1.0
	B3	101.6 ± 1.3	101.7 ± 0.6	97.3 ± 0.5	96.1 ± 0.3

Table 3. Results of test capsule formulation (mean ± DS). B*: batch.

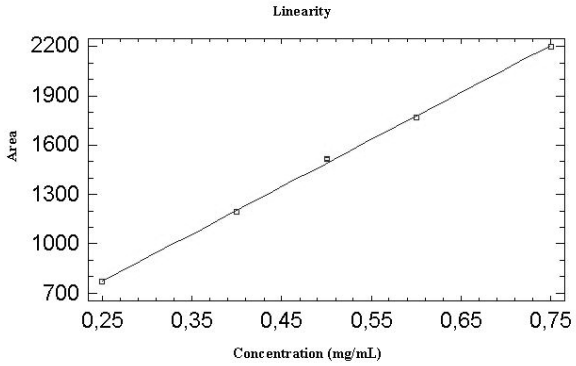

Figure 1. Calibration curve of sertraline hydrochloride (n = 3).

The calibration curve (Fig. 1) was obtained through the peak area of different concentrations of sertraline and showed that, within the interval of 0.5 to 0.75 mg/mL, the method is lineal and presents a correlation coefficient (r) of 0.9996, as described in Table 4. Linearity determines the region of the response or quantification curve, in which a direct relationship between the signal given by the instrument and the concentration of the product analyzed exists [15].

Inter-day and inter-analysts precision and accuracy of method were assessed by analyzing of samples at 100% concentration (0.5 mg/mL), and results are given in Table 4. The high percentage of recovered sertraline shows that the method can be considered as being exact. This is to mean that the values obtained in its determination are close to true values. Recovery percentage values from between 98% and 102% are considered as being acceptable [15].

The repeatability of the sertraline concentration values from low, medium and high concentrations, indicate that the method is precise (CV ≤ 2%). The results for intermediate precision were also satisfactory. This analysis was complemented with a Fisher's F and Student t tests. The consistency found in all of these results confirms the precision of the method.

According to the described conditions, the proposed method has not the interferences with the excipients used in the capsule formulation. Typical chromatograms of sertraline standard, excipients of capsule formulation without sertraline and hard capsule formulation with sertraline are shown in Figure 2.

In robustness study, different analytical columns, as mentioned in experimental section, were successfully used with no significant variations in the chromatography results. Variation in flow-rate resulted in the change in retention times, prolonging the chromatogram time. A low flow-rate (0.6 mL/min) sertraline standard and sample of sertraline capsule formulation retention times (9.083 min and 9.017 min, respectively) were more prolonged (Fig. 3) from those to 1.0 mL/min as flow-rate (Fig. 2). Nevertheless, no single parameter, extended to specific limits, resulted in a dramatic adverse effect on the system suitability.

Consequently, the proposed method is sufficiently accurate and precise in order to be applied to pharmaceutical dosage forms. The proposed method could be used to quality control and stability study of selected formulation of sertraline.

With regard to the stability of the hard gelatin capsule selected formulation (Formulation 2), the values obtained are found in Table 3. The utility of this method was verified by means of replicate estimations from the test capsules through 24 months. Disintegration time's values of less than 30 min, the percentages of dissolved drug higher than 80% during two years and the values of assay from between 90% and 110% are considered as being acceptable.

Parameter	Results	Limits
Linearity	Y = 2856.51X + 61.08 r = 0.9996 r^2 = 0.9993 $t_{exp} < t_{tab}(\alpha=0.05, n=13)$ t_{exp} = 0.31 < 2.16 CV_f = 0.0272%	Y= bx + a r ≥ 0.99 r^2 ≥ 0.98 Non-significative intercept $t_{exp} < t_{tab}$ t_{tab} = 2.16 CV_f < 5%
Accuracy	Y= 1.0032X - 0.2719 r = 0.9999 r^2 = 0.9998 b = 1.0032	Y= bx + a r ≥ 0.99 r^2 ≥ 0.98 b≅1
	R_{total} = 99.80% CV_{total} = 0.50%	R_{total} = 98-102% CV_{total} ≤ 2.0 %
	t_{exp} = 0.98 < 2.571	Student t test $t_{exp} < t_{tab}$ (2.571)
Repeatability	$CV_{80\%}$ = 1.58% $CV_{100\%}$ = 0.89% $CV_{120\%}$ = 0.31%	CV ≤ 2.0 %
Intermediate precision	CV = 0.89%	CV_{total} ≤ 2.0 %
	F_{exp} = 0.1334, t_{exp} = 0.6423	Fisher (F) and Student (t) between analysts F_{tab} = 5.05 , t tab = 2.23
	F_{exp} = 0.4505, t_{exp} = 0.0753	Fisher (F) and Student (t) between days F_{tab} = 5.05 , t_{tab} = 2.23

Table 4. Analytical data summary obtained by the HPLC UV method.

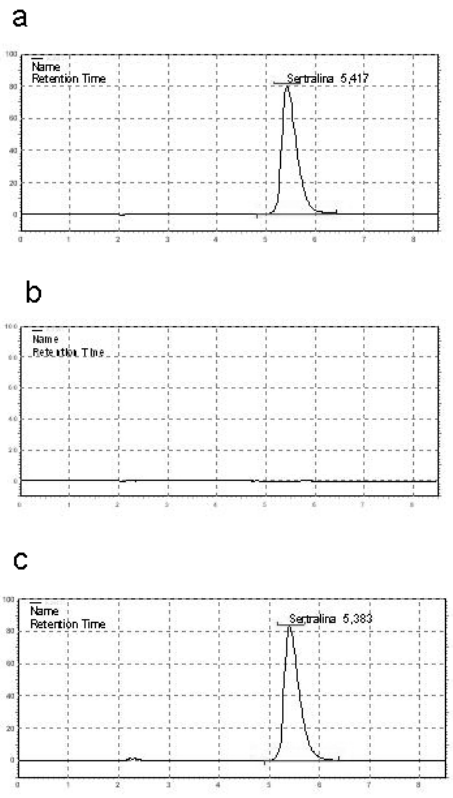

Figure 2. Chromatograms of (**a**) sertraline standard (0.5 mg/mL), (**b**) excipients of capsule formulation without sertraline and (**c**) hard capsule formulation with sertraline (0.5 mg/mL).

The dissolution data (Table 5) of test formulation in deaerated distilled water was compared with the dissolution data of reference products, using *f1* and *f2* parameters. The values of *f1* and *f2* (Table 5) indicate that the release profile of test solid dosage form is comparable with and in a good agreement with Prosertin, reference product. Whereas for Cipla (tablet, 50 mg), the value of *f2* was 37.54, indicated the dissimilarity between release profiles of both products is high.

The formulation 2 was selected as the better technological variant. From this formulation were obtained capsules with satisfactory technological properties. The chromatographic assay was a selective, linearity, precise and reproducible method for the separation and determination of sertraline in pharmaceutical capsules, from the rest of excipients used to prepare the solid dosage form.

Application of the suggested method was successfully applied to the determination of sertraline in capsule formulation during the stability study. Hard capsules showed an adequate stability during 24 months demonstrating the feasibility from the process of production of this formulation. Similarity and dissimilarity factors, *f1* and *f2*, confirmed similarity of dissolution, in deaerated distilled water, of test formulation and capsules of Prosertin as reference product.

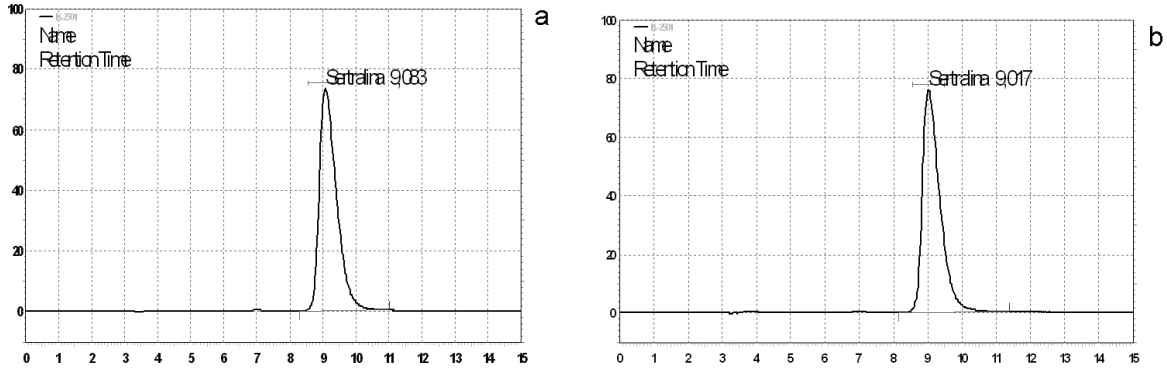

Figure 3. Chromatograms of (**a**) sertraline standard (0.5 mg/mL) and (**b**) hard capsule formulation with sertraline (0.5 mg/mL) at 0.6 mL/min as flow-rate.

Time (min)	Percent of drug dissolved		
	Test formulation	Prosertin (capsule, 50 mg)	Cipla (tablet, 50 mg)
10	22.8	33.7	58.9
15	68.8	72.2	81.7
20	75.3	72.4	83.5
25	78.4	73.5	84.4
30	84.3	85.4	85.9
f1 (f1< 15)	*2.327*		*2.209*
f2 (50 < f2 <100)	*61.790*		*37.547*

Table 5. Percent of drug dissolved from sertraline formulations in deaerated distilled water and similarity factors.

REFERENCES

1. Mourilhe, P. & P.E. Stokes (1998) *Drugs Safety* **18**: 57-82.
2. Vetulani, J. & I. Nalepa (2000) *Eur. J. Pharmacol.* **405**: 351-63.
3. Espinosa Bosch, M., A.J. Ruiz Sánchez, F. Sánchez Rojas & C. Bosch Ojeda (2008) *J. Pharm. Biomed. Anal.* **48**: 1290-302.
4. Lucca, A., G. Gentilini, S. Lopez-Silva & A. Soldarini (2000) *Ther. Drug Monit.* **22**: 271-6.
5. Frahnert, C., M.L. Rao & K. Grasmäder (2003) *J. Chromatogr. B.* **794**: 35-47.
6. Wille, S.M.R., K.E. Maudens, C.H. van Peteghem & W.E.E. Lambert (2005) *J. Chromatogr. A.* **1098**: 19-29.
7. Önal, A., S.E. Kepekci¸ S.M. Cetin & S. Erturk (2006) *J. AOAC Int.* **89**: 966-71.
8. Gondová, T., D. Halamová & K. ?pacayová (2008) *J. Liq. Chromatogr. Relat. Technol.* **31**: 2429-41.
9. Chen, X., X. Duan, X. Dai & D. Zhong (2006) *Rapid Commun. Mass Spectrom.* **20**: 2483-9.
10. World Health Organization (2005) *Multisource (generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability.* QAS/04.093.
11. Moore, J.W. & H.H. Flanne (1996) *Pharm. Techn.* **20**: 64-74.
12. Pillay, V. & R. Fassihi (1997) *J. Control Rel.* **55**: 45-55.
13. Iraizoz, A., O. Bilbao & M.A. Barrios (1990) *"Tabletas",* en *"Conferencias de Tecnología Farmacéutica II".* Facultad de Farmacia y Alimentos. Departamento de Tecnología y Control de Medicamentos. Universidad de La Habana, ENPES, Ciudad Habana, pp. 170-81.
14. Staniforth, J.N. (1988) *"Powder flow",* in *"Pharmaceutics – the science of dosage form design"* (M.E. Aulton, ed.), Churchill Livingstone, London, pp. 600-15.
15. Food and Drug Administration (2001) *Guidance for industry analytical procedures and methods validation chemistry, manufacturing and controls documentation.* U.S. Department of Health and Human Services. Centre for Drug Evaluation and Research.
16. United States Pharmacopeia USP 28 (2005) *Validation of compendial methods.* The United States Pharmacopeial Convention, Inc., Mack printing, Electronic version.
17. Food and Drug Administration (1997) *Guidance for industry: Dissolution testing of immediate release solid dosage forms.* U.S. Department of Health and Human Services. Centre for Drug Evaluation and Research.
18. Sch?ssele, A. & A. Bauer-Brandl (2003) *Int. J. Pharm.* **257**: 301-4.
19. Antikainen, O. (2003) *"New methods to evaluate applicability of powders and granules for tablet compression",* University of Helsinki, Faculty of Science, Finland. ISBN 952-10-1061-4, págs. 3-4.
20. Shap, J. (2000) *"Quality in manufacture of medicines and other healthcare products",* in: *"Part 5: Quality control"*, London: Pharmaceutical Press, pp. 283-358.