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Convolution approach to estimate the in vivo behavior of ibuprofen soft gelatin capsules from in vitro release data of USP Apparatus 4

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Abstract

Hypothetical plasma concentration-time profiles of ibuprofen gelatin soft capsules were calculated using data from the USP apparatus IV (flow-through cell method). Four ibuprofen formulations (reference and generic products at 400 and 600 mg) were tested with laminar flow at 16 ml/min in pH 6.8 phosphate buffer. Samples were withdrawn at 10, 20, 30, 45, and 60 minutes, and dissolved drug levels were measured using UV derivative spectrophotometric analysis. Dissolution curves were compared by calculating model-dependent and model-independent parameters, employing Student's t-test for statistical analysis (significance set at $p < 0.05$). The dissolution data were fitted to various mathematical models to explain ibuprofen's in vitro dissolution. Hypothetical plasma concentration-time profiles were also calculated using published pharmacokinetic data from in vivo studies combined with a convolution approach. Validation of results was assessed using prediction error (PE) data for two key pharmacokinetic parameters: peak plasma concentration (Cmax) and area under the curve from zero to infinity (AUC0-inf), with validity determined by a PE of ≤ 10%. Similar dissolution profiles were identified for the 400 mg formulations (f2 similarity factor), while dissimilarities were noted in other comparisons ($f2 < 50$, $p < 0.05$). The Weibull function best described the dissolution rate of the tested formulations. For the 400 mg reference product, PE values for Cmax and AUC0-inf were < 10%. A discriminatory dissolution method is essential for the 600 mg products, and further in vivo testing is necessary to corroborate the findings.

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INTRODUCTION

Ibuprofen is an anti-inflammatory compound that belongs to non-steroidal anti-inflammatory drugs. Solid dosage forms containing ibuprofen are available to the population as tablets and soft gelatin capsules. By its low solubility and high permeability ibuprofen is a Biopharmaceutical Classification System (BCS) Class II drug [1]. For this class of drugs in vitro release data can be used to simulate the in vivo behavior and a meaningful in vitro/in vivo correlation (IVIVC) can be estimated. On the other hand, a biowaiver monograph for ibuprofen tablets has been reported [2] however, no biowaiver monograph

for ibuprofen soft gelatin capsules is available. About, the pharmacopeial dissolution quality control test for ibuprofen tablets is defined in the USP [3]. The paddle apparatus (USP apparatus II) at 50 rpm with 900 ml of pH 7.2 phosphate buffer is suggested. At 60 min not less than 80% of the labelled amount should be dissolved. For ibuprofen soft gelatin capsules no pharmacopeial dissolution test is available.

The USP apparatus IV is a different dissolution apparatus to basket (USP apparatus I) and paddle method, and it has some advantages. Sink conditions can be obtained due to pumping of the dissolution medium through the dissolution cell where the solid formulation is placed and the ease of changing the dissolution medium (pH) over a test [4]. Some authors have found that dissolution information generated with the USP apparatus IV better reflect the in vivo behavior of poorly soluble drugs [5][6].

An important objective of the pharmaceutical product development is to gain better understanding of the in vitro and in vivo drug performances. Through the successful development and application of an IVIVC, the in vivo drug behavior can be simulated from its in vitro performance with a convolution methodology [7]. Some advantages of this procedure are: 1. An in vivo study with pharmacokinetic parameters such as volume of distribution (Vd), bioavailability factor (F), and elimination rate constant (Ke) is not necessary because data are reported in the scientific literature and 2. Calculations are carried out with a simple spreadsheet software (MS Excel) [8].

The objective of this research was to simulate the in vivo performance of ibuprofen from soft gelatin capsules. In vitro release data generated with the flow-through cell method, available information of ibuprofen bioequivalence studies, and a convolution methodology were considered. This information could be used for the design of better ibuprofen oral solid dosage forms.

MATERIAL AND METHODS

Formulations and Chemicals

Ibuprofen reference soft gelatin capsules (coded as R drug product) (Actron 400 and 600 mg, Bayer de México S.A. de C.V., Mexico City, Mexico) and two multisource drug products with same doses (coded as G formulation) were used. The reference formulation was Actron brand [9]. HCl, methanol and phosphate salts were supplied by J.T.Baker-Mexico (Xalostoc, Mexico). Ibuprofen standard compound was supplied by Sigma-Aldrich Co. (St. Louis MO, USA).

Ibuprofen determination

The spectrophotometric determination of ibuprofen in a mixture of ibuprofen + caffeine was developed by our research group [10]. It is important pointing that, soft gelatin capsules of the present work have only ibuprofen as active pharmaceutical ingredient and a UV derivative methodology has been used to eliminate interference of excipients. Briefly, a double beam UV/Vis spectrophotometer (PerkinElmer Lambda 35, Waltham MA, USA) was used. The operating conditions were second-derivative mode (D^2) with scan speed of 240 nm/min, slit width 2.0 nm and sampling interval 1.0 nm. Five pH 6.8 phosphate buffer standard solutions of ibuprofen (10-50 µg/ml) and one solution of caffeine (15 µg/ml) were prepared. Then, zero-order spectra of all solutions from 200 to 350 nm using 1-cm quartz cells were recorded and stored. To determine ibuprofen (235.5 nm), the zero-order spectra were transformed in D^2 spectra and a zero-crossing method was used.

Dissolution Profiles

Dissolution curves were obtained with an USP Apparatus IV, 22.6 mm cells (internal diameter), laminar flow, and flow rate of 16 ml/min (Sotax CE6, Sotax AG, Switzerland). As dissolution medium pH 6.8 phosphate buffer (37.0±0.5 °C) was used. Samples were withdrawn at 10-, 20-, 30-, 45-, and 60-min with the support of fiberglass filters (n=12). To quantify ibuprofen, the zero-order spectra were recorded and stored. Finally, the D^2 UV spectra of ibuprofen and standard solutions of known concentration were considered.

Data Analysis

The f_2 similarity factor, dissolution efficiency (DE), mean dissolution time (MDT), and time to release 50% of dose ($t_{50\%}$) were calculated and statistically compared (Student's t-test). If f_2=50-100 similar profiles were considered [11]. If $p<0.05$ significant differences were found. Data of f_2, DE and MDT were calculated [12] while with sigmoidal model inSigmaplot program (Version 11.0) $t_{50\%}$ values

were estimated. Sigmoidal model is described by Eq. 1.

$$y = \frac{ax^b}{c^b + x^b} \qquad \text{Eq. (1)}$$

Prediction of plasma concentrations

Ibuprofen plasma concentration-time profiles were computed with the Inverse Release Function methodology [13]. This procedure is used to adjust the time scale of the dissolution curve to enable a meaningful IVIVC. Once the new time scale is estimated, hypothetical drug levels were calculated with a convolution approach [14]. This calculation considers published ibuprofen pharmacokinetic information such as volume of distribution (V_d), bioavailability factor (F), and elimination rate constant (k_e) [2][15]. After in vivo behavior was estimated peak plasma concentration (C_{max}) and area under the concentration-time curve from zero time to infinity ($AUC_{0\text{-}inf}$) were calculated [16]. To evaluate the predictability of the convolution calculation ibuprofen published information of two bioequivalence studies (400 mg tablets) [17] and (600 mg coated tablets) was used [18]. The predictability was evaluated by the computation of prediction error (%PE) for C_{max} and $AUC_{0\text{-}inf}$ according to Eq. 2 (a %PE less than 10% is expected) [8][19].

$$(\%PE) = \frac{(\text{observed value} - \text{predicted value})}{\text{observed value}} \times 100$$

Eq. (2)

RESULTS AND DISCUSSION

Spectrophotometric determination

The D^2 spectra of five standard solutions of ibuprofen and one solution of caffeine are shown in **Figure 1**. Using a zero-crossing point method the best determination of ibuprofen was at 235.5 nm. With derivative spectroscopy no interference of excipients was found.

Analytical determinations of mixtures by UV derivative spectroscopy have been reported for several years [20][21]. This methodology allows simultaneous determination of each compound in the mixture without mutual interference. The identification and quantification of drugs by derivative spectroscopy has been reported similar to a chromatographic analysis [22]. The direct UV determination of ibuprofen from soft gelatin capsules has an interference generated by excipients (some of them dyers) and/or gelatin making an accurate quantification of the drug difficult (data not presented). In this work, the UV derivative method for determination of ibuprofen from soft gelatin capsules [10] was successfully applied.

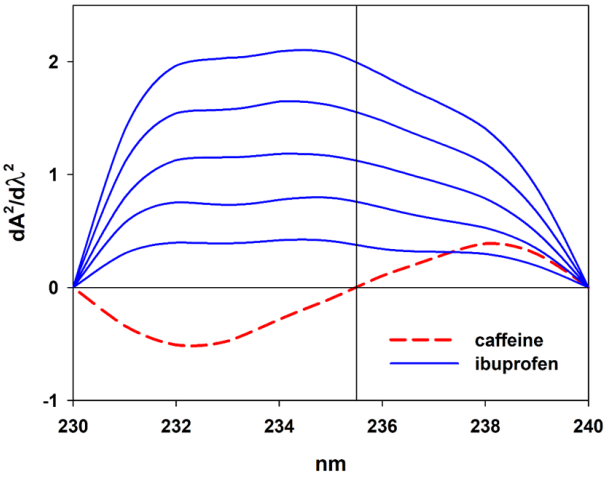

Figure 1 Second-derivative (D2) of standard solutions of ibuprofen and caffeine. Vertical straight line shows the zero-crossing point used to quantify ibuprofen (235.5 nm)

Dissolution Curves

Dissolution curves of ibuprofen soft gelatin capsules are depicted in **Figure 2**. A best dissolution behavior was found with 400 mg drug products as at 60 min the complete dose was dissolved while with 600 mg drug products, at same time, less than 80% of dose was quantified. Dissolution parameters are shown in **Table 1**. For 400 mg formulations and considering f_2 and Q_{60} values similar dissolution profiles were found while with the rest of the comparisons opposite results were found.

Results of fitting in vitro release data of used formulations are shown in **Table 2**. To explain the dissolution performance of ibuprofen from soft gelatin capsules the Weibull function was the best option. The adjustment of in vitro release information to Weibull function emphasizes the S-shape of dissolution curves [23]. In order to calculate a dissolution rate parameter that best reflects the release performance of ibuprofen soft gelatin capsules, the $t_{50\%}$ data were calculated with the sigmoidal equation.

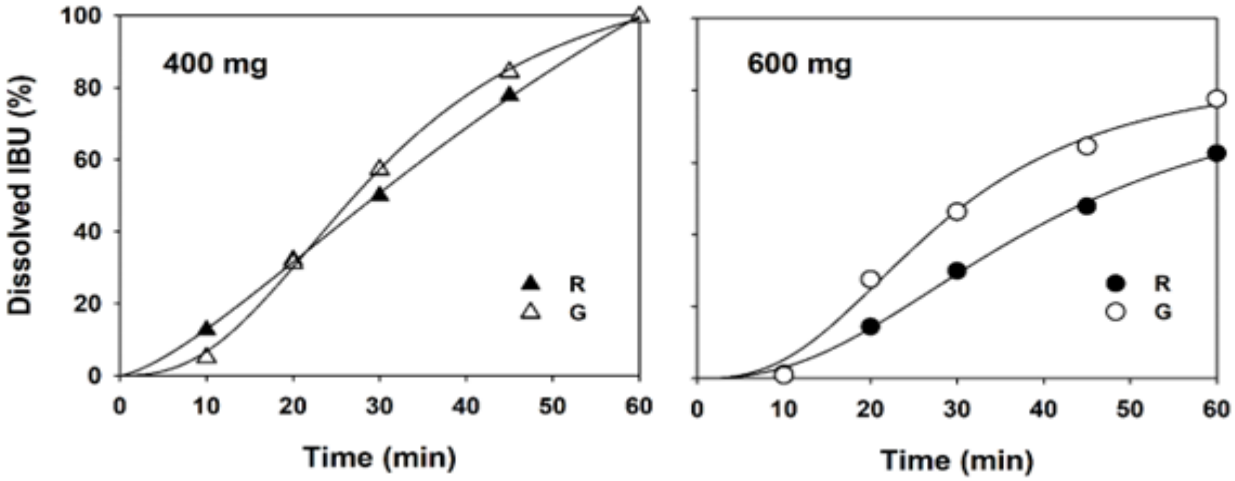

Figure 2 Dissolution profiles of ibuprofen soft gelatin capsules of reference formulation (R) and a generic drug product (G). Mean, n=12

Table 1 Dissolution parameters of ibuprofen soft gelatin capsules

Dose (mg)	Code	f_2	Q_{60} (%)	DE (%)	MDT (min)	$t_{50\%}$ (min)
400	R	-	99.65±1.00	49.72±0.38	30.05±0.26	29.53±0.30
	G	64.14	99.63±0.59	51.46±0.69*	29.00±0.42*	23.69±0.86*
600	R	-	62.50±0.54	28.59±0.18	32.53±0.30	45.96±0.30
	G	44.95	77.63±0.45*	40.19±0.30*	28.93±0.26*	31.96±0.40*

R: reference formulation; G: generic formulation; f_2: similarity factor; Q_{60}: dissolved ibuprofen at last sampling time; DE: dissolution efficiency; MDT: mean dissolution time; $t_{50\%}$: time to dissolve 50% of dose; *p<0.05

Table 2 Adjustment of dissolution data to several mathematical models

Dose (mg)	Code	Parameter	Korsmeyer-Peppas	Makoid - Banakar	Peppas-Sahlin	Logistic	Weibull
400	R	$R^2_{adjusted}$	0.9926	0.9972	0.9970	0.9436	0.9979
		AIC	18.03	8.34	11.63	30.34	5.99
	G	$R^2_{adjusted}$	0.9370	0.9869	0.9789	0.9800	0.9896
		AIC	31.89	22.92	25.62	24.99	17.91
600	R	$R^2_{adjusted}$	0.9766	0.9934	0.9952	0.9935	0.9985
		AIC	23.90	16.13	12.23	16.08	2.39
	G	$R^2_{adjusted}$	0.9192	0.9674	0.9939	0.9803	0.9995
		AIC	30.97	26.10	13.64	23.55	3.51

R: reference formulation; G: generic formulation; AIC: Akaike information criterion

Estimation of In Vivo Plasma Levels

As an example, hypothetical plasma concentration-time profile of ibuprofen from 400 mg reference formulation was depicted in **Figure 3**. As a comparison, ibuprofen observed plasma levels previously reported from an in vivo study (tablets, 400 mg) [17] are also shown in same plot. The used convolution methodology was able to generate plasma concentrations similar to those reported in scientific literature. To confirm this procedure, data of PE for C_{max} and $AUC_{0\text{-}inf}$ are shown in **Table 3**. Only for 400 mg reference formulation PE values were found within the established criteria. As these values were <10%, the convolution methodology

was validated. [19]. The USP Apparatus IV with laminar flow at 16 ml/min and pH 6.8 phosphate buffer were adequate settings to evaluate the dissolution performance of 400 mg generic formulations. At these settings, the reference formulation was able to give a hypothetical in vivo behavior similar to that found in a bioequivalence study. Some authors have stated that appropriate in vitro release settings based on in vivo behavior could be more confidently adapted for a routine and in-process quality control studies [24].

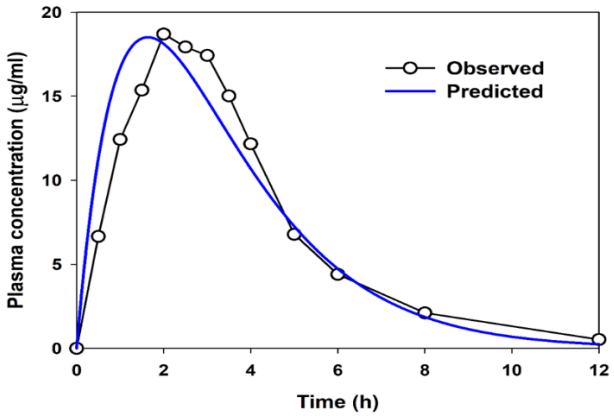

Figure 3 Plasma concentration-time profiles of ibuprofen. To predict plasma concentrations dissolution data of 400 mg reference formulation were used. Observed data reported from Villalva-Rojas et al.,

Table 3 Values of prediction errors (%) for main pharmacokinetic parameters

Dose (mg)	Code	C_{max}	$AUC_{0\text{-}inf}$
400	R	-2.27	0.43
	G	-6.28	-12.04
600	R	49.68	40.34
	G	43.82	21.25

Our results agree with previous reports where verapamil-HCl and acetaminophen studies in USP apparatus IV, showed an in vivo performance like those reported in a bioavailability study [25][[26]. The flow-through cell method can be used to propose a discriminative dissolution method able to differentiate the quality of pharmaceutical drug products and avoid therapeutic failures. Excipients and manufacture process are critical elements to have formulations that allow adequate in vitro release, especially those drugs with solubility problems as BCS Class II. Some authors have described a better absorption rate on USP apparatus IV for cilostazol and diclofenac sodium, both drugs with solubility problems [5][27]. For ibuprofen, a highest IVIVC with in vivo pharmacokinetic data of immediate-release formulations was found with USP apparatus IV (tablets, 200 mg). The in vitro release settings were turbulent flow at 8 ml/min and pH 7.2 buffer as dissolution medium. However, no drug product showed PE values less than 10% on both pharmacokinetic parameters [6].

CONCLUSION

The best conditions to estimate the in vivo behavior of 400 mg reference formulation were the flow-through cell method, laminar flow at 16 ml/min, and pH 6.8 buffer. At these settings, significant differences in DE, MDT and $t_{50\%}$ were able to reflect the difference in the hypothetical in vivo behavior proposed for generic drug product. It is necessary to find a discriminatory dissolution method that allows differentiating the quality of 600 mg formulations. To corroborate the obtained results, it is important to test the in vivo behavior of the used ibuprofen soft gelatin capsules.

Ethical Approval

This research was conducted in accordance with guidelines established by the Institutional Animal Ethic Committee (IAEC). Approval number: was obtained from the IAEC prior to the commencement of the study. All procedures involving animals were carried out with care and consideration for their welfare, in compliance with ethical standards and regulations. No ethical approval was necessary for this study.

Author Contribution

All authors made substantial contributions to the conception, design, acquisition, analysis, or interpretation of data for the work. They were involved in drafting the manuscript or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring its accuracy and integrity.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. Eur J Pharm Biopharm, 58(2):265-278, 2004.

[2] Potthast H, Dressman JB, Junginger HE, Midha KK, Oeser H, Shah VP, Vogelpoel H, Barends DM. Biowaiver monographs for immediate release solid oral dosage forms: ibuprofen. J Pharm Sci, 94(10):2121-2131, 2005.

[3] United States Pharmacopeia and national formulary USP43-NF38; The United States pharmacopeial convention. Rockville, MD: Inc; 2021

[4] D'Arcy DM, Liu B, Bradley G, Healy AM, Corrigan OI. Hydrodynamic and species transfer simulations in the USP 4 dissolution apparatus: considerations for dissolution in a low velocity pulsing flow. Pharm Res, 27(2):246-58, 2010.

[5] Jinno J, Kamada N, Miyake M, Yamada K, Mukai T, Odomi M, Toguchi H, Liversidge GG, Higaki K, Kimura T. In vitro-in vivo correlation for wet-milled tablet of poorly water-soluble cilostazol. J Control Release, 130(1):29-37, 2008.

[6] Abdelfattah F, Taha N, Abdou A, Mursi N, Emara L. Prediction of in vivo performance of ibuprofen immediate-release products using different dissolution models. J App Pharm Sci, 12(8):193-201, 2022.

[7] Lu Y, Kim S, Park K. In vitro-in vivo correlation: perspectives on model development. Int J Pharm, 418(1):142-148, 2011.

[8] Rastogi V, Yadav P, Lal N, Rastogi P, Singh BK, Verma N, Verma A. Mathematical prediction of pharmacokinetic parameters-an in-vitro approach for investigating pharmaceutical products for IVIVC. Future J Pharm Sci, 4(2):175-184, 2018.

[9] Cofepris, 2024. Listado actualizado de medicamentos de referencia 2024/01. Mexico. Accessed on: 30 Jun 2024.

[10] Medina-López JR, Soto-Juha JA, Contreras-Jiménez JM. Rapid and simple determination of ibuprofen and caffeine in fixed-dose combination formulations: application to dissolution studies. Int J Appl Pharm, 13(3):242-246, 2021.

[11] Moore JW, Flanner HH. Mathematical comparison of dissolution profiles. Pharmaceut Technol, 20(6):64-74, 1996.

[12] Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C, Xie S. DDSolver: an add-in program for modeling and comparison of drug dissolution profiles. AAPS J, 12(3):263-271, 2010.

[13] Cardot JM, Lukas JC, Muniz P. Time scaling for in vitro-in vivo correlation: the inverse release function (IRF) approach. AAPS J, 20(6):95, 2018.

[14] Qureshi SA. In vitro–in vivo correlation (IVIVC) and determining drug concentrations in blood from dissolution testing – a simple and practical approach. Open Drug Deliv J, 4:38-47, 2010.

[15] Poveda Andrés JL, García Robles AA, Pérez Huertas P. Farmacología del ibuprofeno intravenoso. Rev Soc Esp Dolor, 23(Supl. I):3-12, 2016.

[16] Zhang Y, Huo M, Zhou J, Xie S. PKSolver: an add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. Comput Methods Programs Biomed, 99(3):306-314, 2010.

[17] Villalva-Rojas O, Grande-Ortíz M, Ortiz J, Isasi J, Yantas D, Fiestas V. Estudio de bioequivalencia del ibuprofeno 400 mg tabletas. Rev Peru Med Exp Salud Publica, 24(4):356-362, 2007.

[18] Benvenuti C, Cancellieri V, Gambaro V, Marozzi E, Scaroni C. Pharmacokinetics of two new oral formulations of ibuprofen. Int J Clin Pharmacol Ther Toxicol, 24(6):308-312, 1986.

[19] FDA 1997. Guidance for Industry: extended release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations. U.S. Department of Health and Human Services. Center for Drug Evaluation and

Research (CDER). Accessed on: 30 Jun 2024.
[20] Sánchez F, Bosch C. Recent development in derivative ultraviolet/visible absorption spectrophotometry: 2004-2008. Anal Chim Acta, 635(1):22-44, 2009.
[21] Bosch C, Sánchez F. Recent applications in derivative ultraviolet/visible absorption spectrophotometry: 2009-2011. Microchem J, 106:1-16, 2013.
[22] Medina JR, García CA, Hurtado M, Domínguez-Ramírez AM. Simultaneous determination of ketoprofen and acetaminophen in fixed-dose combination formulations by first-order derivative spectroscopy: application to dissolution studies. Int J Pharm Pharm Sci, 8(2):244-248, 2016.
[23] Ilango KB, Kavimani S. A systematic review of mathematical models of pharmaceutical dosage forms. Int J Curr Pharm Rev Res, 6(1):59-70, 2015.
[24] Emami, J. Comparative in vitro and in vivo evaluation of three tablet formulations of amiodarone in healthy subjects. DARU, 18(3):193-199, 2010.
[25] Medina-López JR, Lugo-Ortíz L, Contreras-Jiménez JM, Hurtado M, Helmy SA. Dissolution performance of verapamil-HCl tablets using USP Apparatus 2 and 4: prediction of in vivo plasma profiles. Dissolut Technol, 30(4):230-237, 2023.
[26] Medina-López JR, Leyva-Hernández JM, Hernández-Osornio JJ, Ruiz-Segura JC. Simulated acetaminophen plasma profiles from fixed-dose combination formulations: studies using the flow-through cell dissolution method. Int J Res Pharm Sci, 15(2):33-41, 2024.
[27] Jantratid E, De Maio V, Ronda E, Mattavelli V, Vertzoni M, Dressman JB. Application of biorelevant dissolution tests to the prediction of in vivo performance of diclofenac sodium from an oral modified-release pellet dosage form. Eur J Pharm Sci, 37(3-4):434-441, 2009..