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Apparent Solubility and Dissolution Profile at Non-Sink Conditions as Quality Improvement Tools

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1. Introduction

The excipients used during manufacturing as well as the quality of the pharmaceutical product development and preparation are of great importance to dosage form performance. A continuous know-how improvement of both formulation and production process parameters with respect to drug release profiles is a basic aspect of the quality framework for pharmaceutical products. Drug release/dissolution studies from solid dosage forms can be considered among as the most investigated topics in pharmaceutical research (De Castro et al., 2006; Macheras & Iliadis, 2006; Siepmann & Siepmann, 2008). Such a background becomes of paramount relevance in the case of insoluble or poorly soluble drugs, where dissolution represents the most critical factor affecting the rate of systemic absorption, especially in the presence of polymorphism (Snider et al., 2004). Moreover, apart from representing an important element in development and quality control in drug research, dissolution test is proposed to be a surrogate for drug bioavailability evaluation. In fact, *in vivo-in vitro* relationship represents a useful tool to answer the question about the interchangeability of generic and branded products by revealing differences in dissolution kinetics (Dressmann & Reppas, 2010; Hlinak et al., 2006). In order to increase predictability of these results, several attempts to make *in vitro* test conditions closer to the physiological ones have been made, for example by adjusting pH or by adding surfactants. However, the so-called "sink conditions" (based on bulk drug solubility i.e. in a system where the solute is present for more than 15% of its maximum solubility have been studied), obtained by using

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a high concentration of a surfactant in the dissolution medium, may not be a proper approach in developing a bio-relevant dissolution method for a poorly water-soluble drugs (Sirisuth et al. 2002; Tang et al., 2001; Jamzad & Fassihi, 2006). "Non-sink conditions" represented a very discriminating dissolution conditions, acting as a sort of magnifier lens for an in-depth evaluation of the dissolution phenomenology, and dissolution tests under non-sink conditions can be a predictive tool during formulation development as well as for batch-to-batch quality control (Siewert et al., 2003).

2. Dissolution testing in pharmacopeia

The methods of i*n vitro* dissolution testing can be traced to two general categories: "stirrer beaker method" and "flow through procedure".

From a regulatory standpoint, the legally-binding documents to carry out the dissolution tests are reported in the 7th edition of European Pharmacopoeia (EP), the 34 United States Pharmacopoeia (USP), and the 15th edition of Japanese Pharmacopoeia (JP). The World Health Organization (WHO) provides in the 4th edition of International Pharmacopoeia (IntPh) a more global coverage of issues and strives towards harmonisation among world pharmacopoeia guidance and source material.

The various texts are comparable to the general notions, but differ in the apparatuses described: EP with "Dissolution test for solid dosage forms" (Council of Europe, 2011) and USP with "Dissolution" (United States Convention, 2011a) show four apparatuses: 1 (for Basket method); 2 (for paddle method), 3 (Reciprocating cylinder) and 4 (Flow-through cell), the latter being lacking in the JP "Dissolution test" (Society of Japanese Pharmacopoeia, 2007) monograph. On the other hand, in the IntPh "Dissolution test for solid oral dosage forms" section (World Health Organization, 2011), only the first two devices are indicated. In Table 1, the relation between the dimensions for the first three devices is shown: all the measures are equivalent, and any differences can be noticed only by IntPh, mainly in terms of the significant digits.

Even the choice of the dissolution medium is almost completely overlapped between EP and USP, with a variety of buffers at various pH (e.g. phosphate, acetate, TRIS). Besides, the JP refers to the monographs of specific formulations, but ranging over various possibilities, from pure water to the various buffers. On the other hand, the IntPh indicates eight different points for different pHs of the dissolution media, including simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF); worthy of note is the pH differences of the latter: 7.5 for IntPh *vs.* 6.8 for both EP and USP.

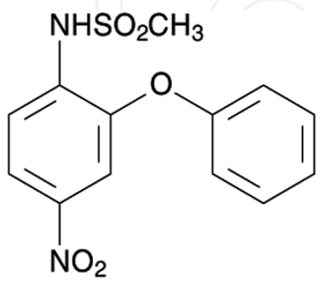
Moreover, in the latest edition of the EP, as well as in the USP section "The dissolution procedure: development and validation" (United States Convention, 2011b), a chapter entitled "Recommendations on methods for dosage forms testing" (Council of Europe, 2010a) is given, suggesting the use of sink-condition. Sink conditions normally occur in a volume of dissolution medium that is at least 5-10 times the saturation volume, usually by adding surfactants. However, such an approach may be inappropriate in developing a bio-relevant dissolution method for a poorly water-soluble drug (Sirisuth et al. 2002; Tang et al., 2001; Jamzad & Fassihi, 2006).

Item	EP 7th	USP 34	JP 15th	IntPh 3rd
Vessel				
Height	160-210	160-210	160-210	168±8
Internal diameter	98-106	98-106	98-106	102±4
Basket				
Shaft Diameter	6.4±0.1 or 9.75±0.35	6.3-6.5 or 9.4-10.1	6.3-6.5 or 9.4-10.1	6.4±0.1 or 9.75±0.35
Screen				
Wire thickness	0.22-0.31	0.25-0.31	0.25-0.31	0.254
Openings	0.36-0.44	0.36-0.44	0.36-0.44	0.381
Height of screen	27.0±1	27.0±1.0	27.0±1	27.0±1
Total height of basket	37±3	37.0±3.0	37±3	36.8±3
Internal diam. of basket	20.2±1	20.2±1.0	20.2±1	20.2±1
External diam. of basket	22.2±1	22.2±1.0	22.2±1	22.2±1
External diam. of ring	25.0±3	25.0±3.0	25.0±3	25.4±3
Vent hole diameter	2.0±0.5	2.0±0.5	2.0±0.5	2
Height of coupling disk	5.1±0.5	5.1±0.5	5.1±0.5	5.1±0.5
Position of the stirring device				
Distance from the bottom	25±2	25±2	25±2	25±2
Distance between shaft axis and vertical axis of the vessel	≤2	≤2	≤2	≤2
Stirring characteristics	Smoothly without significant wobble	Smoothly without significant wobble	Smoothly without significant wobble	Ensure there is no significant wobble on any rotating shaft
Paddle				
Shaft Diameter	9.4-10.1	9.4-10.1	9.4-10.1	9.75±0.35
Blade				
Upper chord	74.5±0.5	74.0-75.0	74.0-75.0	74.5±0.35
Lower chord	42	42.0	42.0	42.0±1
Height	19.0±0.5	19.0±0.5	19.0±0.5	19.0±1
Radius (disk)	41.5	41.5	41.5	41.5
Radius (upper corners)	1.2±0.2	1.2±0.2	1.2±0.2	-
Thickness	4.0±1.0	4.0±1.0	4.0±1.0	4.0±1
Position of the stirring device				
Distance from the bottom	25±2	25±2	25±2	25±2
Distance between shaft axis and vertical axis of the vessel	≤2	≤2	≤2	≤2
Stirring characteristics	Smoothly without significant wobble	Smoothly without significant wobble	Smoothly without significant wobble	Ensure there is no significant wobble on any rotating shaft

Table 1. Dissolution Apparatuses. Dimensions (mm) of the vessel, basket and paddle.

3. Nimesulide

Nimesulide (NIM) is a non-steroidal anti-inflammatory drug, selective COX-2 inhibitor with analgesic and antipyretic properties (Martindale, 2009). IUPAC nomenclature is N-(4-Nitro-2-phenoxyphenyl)methanesulfonamide, with empirical formula $C_{13}H_{12}N_2O_5S$ (MW=308.31) and CAS number 51803-78-2 (Scheme 1). NIM monograph is present only in the EP (Council of Europe, 2010b).



Scheme 1. Chemical structure of NIM

Its approved indications are the treatment of acute pain, the symptomatic treatment of osteoarthritis and primary dysmenorrhoea in adolescents and adults above 12 years old.

NIM was discovered in 1971 in the U.S. by George G.I. Moore at Riker Laboratories (later acquired by 3M Co.), but in 1980 NIM was licensed by Helsinn Healthcare SA (Switzerland) who proceeded to invest in extensive investigations on the drug (Rainsford, 2006). It was launched in Italy for the first time as Aulin® in 1985 (Consalvo et al., 2010) and is currently available in more than 50 countries worldwide, among others France, Portugal, Greece, Switzerland, Belgium, Mexico and Brazil. NIM has never been filed for Food and Drug Administration (FDA) evaluation in the United States, where it is not marketed (Traversa et al., 2003)

After the expiry of patent protection, a number of other companies have started production and marketing of NIM products.

Controversy regarding NIM toxicity persists due to the fact that clinical series reports and epidemiological trials continue to involve NIM in severe liver damage during the post-marketing studies (Bessone, 2010). Briefly, on August 1, 2003 the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Agency (EMA) reported that the benefit/risk profile of NIM containing medicinal products (e.g. Aulin, Mesulide, Nimed and associated product names) for systemic and topical use is favourable and that Marketing Authorisations should be maintained/granted. The CPMP recommended to restrict the use of NIM to the indications of treatment of acute pain, symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea for the systemic formulations and symptomatic relief of pain associated with sprains and acute tendinitis for the topical formulation (EMEA, 2003).

The Irish Medicines Board (IMB) announced the suspension of NIM from the Irish market and reported it to the EU Committee for Human Medicinal Products (CHMP) for a review of its benefit/risk profile. The decision is due to the reporting of six cases of potentially related liver failures to the IMB by the National Liver Transplant Unit, St Vincent Hospital.

These cases occurred in the period from 1999 to 2006 (IMB, 2007). On December 3, 2007 Ireland's RTÉ aired an investigative programme highlighting the deadly side effects of NIM and how it has been linked to over 300 cases of liver disease throughout Europe.

On September 21, 2007 the EMA released a press release on their review on the liver-related safety of NIM. The EMA has concluded that the benefits of these medicines outweigh their risks, but that there is a need to limit the duration of use to ensure that the risk of patients developing liver problems is kept to a minimum. Therefore the EMA has limited the use of systemic formulations (tablets, solutions, suppositories) of NIM-containing medicinal products to 15 days because of reports of severe hepatic adverse reactions (EMA, 2007; Li et al., 2009).

Singapore Health Science Authority (HSA) suspended NIM containing drugs in June 2007 (Singapore News, 2007; HSA, 2007). Several reports have been made of adverse drug reactions in India (Khan & Rahman, 2004a, 2004b; Rahman & Khan, 2004). On Feb 12, 2011, Express India reported that the Union Ministry of Health and Family Welfare had finally decided to ban the pediatric use of the analgesic, NIM suspension. From 2011 onwards, it has been totally banned in India.

NIM chemico-physical properties could be summarised as: i) weak acid properties (pKa reported ranging between 5.9 and 6.56 (Singh et al., 1999; Singh et al., 2001; Dellis et al., 2007); ii) values of octanol-water partition coefficient (log P) of 2.38 (Singh et al., 2001); iii) practically insoluble in water (10 µg/mL) (Piel et al. 1997); iv) according to the Biopharmaceutical Classification System, BCS, (FDA, 2000), NIM can be classified as a class II drug (low solubility and high permeability), therefore, the drug dissolution may be a rate-limiting step in the drug adsorption process.

Previous studies were carried out for both in vitro (Butler et al., 2000; Rădulescu et al., 2010) and in vivo comparisons among NIM-containing tablets (Hutt et al. 2001; Ilic et al. 2009). However, in the former only a small number of commercial preparations were investigated under sink-condition by means of abnormal surfactant concentration (Butler et al. 2000), and the release rate seems to be critically influenced not by pH value or the concentration of endogenous surfactant, but by the combination of the two characteristics of the *in vitro* dissolution media (Rădulescu et al., 2010), while in the latter no *in vitro* and *in vivo* correlation (IVIVC) was investigated. Moreover, since due to different crystallization processes, crystallographic modification has been recently reported (Kapoor et al. 1998; Di Martino et al. 2007; Moneghini et al. 2007), even though only a single crystal structure has been identified (Dupont et al., 1995). Thus, information on the influence of the different nature and/or amount of excipients as well as of the adopted technological parameters on the *in vitro* drug release characteristics are reputed of interest.

4. Materials and methods

4.1 Dosage form selection

Ten multisource IR NIM tablet formulations (RF for reference formulation, MSF for the multiple-source product formulation, and BF1-BF8 for non-branded bioequivalent formulations) were obtained from the Italian market. They all nominally contain 100 mg of the active ingredient, but greatly differ with respect to the excipient composition. Table 2 summarizes the qualitative excipient composition of the various NIM tablets.

Auxiliary Substances	RF	MSF	BF1	BF2	BF3	BF4	BF5	BF6	BF7	BF8
Hydroxypropyl cellulose	X	X	X	X	X			X		
Lactose	X		X	X	X	X	X	X	X*	X
Cellulose, microcrystalline	X	X	X	X	X	X	X	X†	X	X
Castor oil, hydrogenate	X	X	X	X	X					X
Magnesium stearate	X	X	X	X	X	X	X	X	X	X
Sodium docusate	X	X	X	X	X		X			
Sodium starch glycolate	X	X	X	X	X			X	X	X
Maize starch						X	X			
Sodium dodecyl sulphate						X	X		X	
Glyceryl behenate						X‡	X			
PEG§										X
Talc									X	

*explicitly reported as Lactose monohydrate; †reported as microgranular; ‡referred as Compritol 888; §no more info are reported

Table 2. Qualitative excipient composition of the various NIM tablets.

4.2 Tablet appearance

Each tablet was visually examined for shape and any evidence of physical differences such as weight, thickness and dimension was recorded.

4.3 Calibration curve

Calibration curve for NIM reference standard (RS) was obtained by measuring the UV absorption (Perkin Elmer L25 spectrophotometer, λ_{max}: 392.6 nm) in dissolution medium (Simulated Intestinal Fluid, SIF, pH 6.8) prepared according to EP (Council of Europe, 2010a) except for the absence of pancreatin, in conformity with the aim of this study. This pH value was selected because of the NIM negligible dissolution in acidic conditions. Due to the low aqueous NIM solubility, NIM stock solution was prepared by accurate weight of the substance and subsequent dissolution in 5 mL of ethanol, submitting to ultrasound in a sonicator bath for five minutes, and then diluted to a final volume of 100 mL with SIF, corresponding to 50 µg/mL of NIM. Calibration samples were prepared from three separately weighed stock solutions to obtain sample solutions containing scalar concentrations of NIM. Samples were stored at +4 °C until analysis. The linearity of the calibration curves was confirmed over the range 1-20 µg/mL.

4.4 Solubility studies

Apparent solubility (S_{app}) referring to the dynamic solubility (Mosharraf & Nystrom, 2003) of both NIM RS and NIM tablets were determined by stirring an excess amount of the samples in 250 mL of SIF, on a multistirrer thermostatted at 37 ± 0.5 °C for a suitable time in order to achieve equilibrium (max 72 hours). Twenty tablets of the same commercial product were weighed and powdered (particle size ≤ 150 µm, by sieving). An amount corresponding to one-fourth of a tablet (equivalent to 25 mg of NIM) was weighed and suspended in 250 mL dissolution medium. In such a way the ratio among active agent, excipients and volume agrees with dissolution studies conditions (see below). The samples were filtered with a 0.45 µm

nylon membrane filter (Whatman, Maidstone, UK) and the absorbance of the filtrate was measured by UV. Temperature (37 ± 0.5 °C) was carefully maintained constant during all the operations and the amount of drug dissolved was calculated using the calibration curve (see above). All solubility determinations were performed in triplicate.

4.5 Dissolution studies

For tablet dissolution tests, apparatus I (rotating basket method) (Council of Europe, 2011) was used employing 1000 mL of SIF at a temperature of 37 ± 0.5 °C and a rotational speed of 100 rpm. Sample solution (5 mL) was withdrawn at appropriated time intervals (5, 10, 15, 30, 45 and 60 min) and the drawn volume was replaced with the same amount of blank dissolution medium from a separate vessel, also held at a temperature of 37 ± 0.5 °C. The samples were filtered with a 0.45 µm nylon membrane filter (Whatman, Maidstone, UK) and the absorbance of the filtrate was measured by UV. The amount of NIM was calculated through the calibration curve. All the dissolution tests were conducted on twelve tablets for each formulation.

4.6 Mathematical dissolution models

The data obtained from dissolution studies were analyzed using various mathematical models (Table 3), as reported in DDSolver. It is a specialized, freely available software program developed by Zhang *et al.* with the main objective to provide a tool for facilitating the parameter calculations in dissolution data analysis using nonlinear optimization model-dependent approaches (Zhang et al., 2010). In the present chapter, the selection of the models for fitting dissolution data has been based on their theoretical applicability.

Dissolution model	Equation[a]
First-order[b,c]	$F = F_{\max} \cdot (1 - e^{-k_1 \cdot t})$
Higuchi[d]	$F = k_H \cdot t^{0.5}$
Korsmeyer-Peppas[e]	$F = k_{KP} \cdot t^n$
Hixson-Crowell[f]	$F = 100 \cdot [1 - (1 - k_{HC} \cdot t)^3]$
Hopfenberg[g]	$F = 100 \cdot [1 - (1 - k_{HB} \cdot t)^n]$
Baker-Lonsdale[h]	$\frac{3}{2}\left[1 - \left(1 - \frac{F}{100}\right)^{\frac{2}{3}}\right] - \frac{F}{100} = k_{BL} \cdot t$
Makoid-Banakar[i]	$F = k_{MB} \cdot t^n \cdot e^{-k \cdot t}$
Peppas-Sahlin 1[l]	$F = k_1 \cdot t^m + k_2 \cdot t^{2m}$
Peppas-Sahlin 2[m]	$F = k_1 \cdot t^{0.5} + k_2 \cdot t$
Quadratic[n]	$F = 100 \cdot (k_1 \cdot t^2 + k_2 \cdot t)$
Weibull 1[o,p]	$F = 100 \cdot \left[1 - e^{-\frac{(t - T_i)^\beta}{\alpha}}\right]$

Weibull 2[o]	$F = 100 \cdot \left[1 - e^{-\frac{t^{\beta}}{\alpha}}\right]$
Weibull 3[c,o]	$F = F_{\max} \cdot \left[1 - e^{-\frac{t^{\beta}}{\alpha}}\right]$
Weibull 4[c,o,p]	$F = F_{\max} \cdot \left[1 - e^{-\frac{(t-T_i)^{\beta}}{\alpha}}\right]$
Logistic 1[q]	$F = 100 \cdot \frac{e^{\alpha} + \beta \cdot \log(t)}{1 + e^{\alpha} + \beta \cdot \log(t)}$
Logistic 2[c,q]	$F = F_{\max} \cdot \frac{e^{\alpha} + \beta \cdot \log(t)}{1 + e^{\alpha} + \beta \cdot \log(t)}$
Logistic 3[c,r]	$F = F_{\max} \cdot \frac{1}{1 + e^{-k \cdot (t-\gamma)}}$
Gompertz 1[s]	$F = 100 \cdot e^{-\alpha \cdot e^{\beta \cdot \log(t)}}$
Gompertz 2[c,s]	$F = F_{\max} \cdot e^{-\alpha \cdot e^{\beta \cdot \log(t)}}$
Gompertz 3[c,t]	$F = F_{\max} \cdot e^{-e^{-k \cdot (t-\gamma)}}$
Gompertz 4[c,u]	$F = F_{\max} \cdot e^{-\beta \cdot e^{-k \cdot t}}$
Probit 1[v]	$F = 100 \cdot \Phi\left[\alpha + \beta \cdot \log(t)\right]$
Probit 2[c,v]	$F = F_{\max} \cdot \Phi\left[\alpha + \beta \cdot \log(t)\right]$

Table 3. Applied dissolution methods.

[a]In all models. F is the concentration (μg/mL) of the drug release in time t.
[b]k_1 is the first-order release constant.
[c]F_{max} is the maximum fraction of the drug released at infinite time
[d]k_H is the Higuchi release constant
[e]k_{KP} is the release constant incorporating structural and geometric characteristics of the drug-dosage form; n is the diffusional exponent indicating the drug-release mechanism
[f]k_{HC} is the release constant in Hixson–Crowell model
[g]k_{HB} is the combined constant in Hopfenberg model, $k_{HB}=k_0/(C_0 \times a_0)$, where k_0 is the erosion rate constant, C_0 is the initial concentration of drug in the matrix, and a_0 is the initial radius for a sphere or cylinder or the half thickness for a slab; n is 1, 2, and 3 for a slab, cylinder, and sphere, respectively
[h]k_{BL} is the combined constant in Baker–Lonsdale model, $k_{BL}=[3 \times D \times C_s/(r_0^2 \times C_0)]$, where D is the diffusion coefficient, C_s is the saturation solubility, r_0 is the initial radius for a sphere or cylinder or the half-thickness for a slab, and C_0 is the initial drug loading in the matrix
[i]k_{MB}, n, and k are empirical parameters in Makoid–Banakar model (k_{MB}, n, k>0)
[l]k_1 is the constant related to the Fickian kinetics; k_2 is the constant related to Case-II relaxation kinetics; m is the diffusional exponent for a device of any geometric shape which inhibits controlled release
[m]k_1 is the constant denoting the relative contribution of $t^{0.5}$-dependent drug diffusion to drug release; k_2 is the constant denoting the relative contribution of t-dependent polymer relaxation to drug release
[n]k_1 is the constant in Quadratic model denoting the relative contribution of t^2-dependent drug release; k_2

is the constant in Quadratic model denoting the relative contribution of t-dependent drug release
[o]α is the scale parameter which defines the time scale of the process; β is the shape parameter which characterizes the curve as either exponential (β=1; case 1), sigmoid, S-shaped, with upward curvature followed by a turning point (β>1; case 2), or parabolic, with a higher initial slope and after that consistent with the exponential (β<1; case 3)
[p]T_i is the location parameter which represents the lag time before the onset of the dissolution or release process and in most cases will be near zero
[q]α is the scale factor in Logistic 1 and 2 models; β is the shape factor in Logistic 1 and 2 models
[r]*k* is the shape factor in Logistic 3 model; γ is the time at which $F = F_{max}/2$
[s]α is the scale factor in Gompertz 1 and 2 models; β is the shape factor in Gompertz 1 and 2 models
[t]*k* is the shape factor in Gompertz 3 model; γ is the time at which $F = F_{max}/\exp(1) \approx 0.368 \times F_{max}$
[u]β is the scale factor in Gompertz 4 model; *k* is the shape factor in Gompertz 4 model
[v]Φ is the standard normal distribution; α is the scale factor in Probit model; β is the shape factor in Probit model

4.7 Statistical analysis

Results were expressed as the mean ± SD of at least six independent measurements. ANOVA one-way performing the Bonferroni post-test (Instat software, version 3.0 GraphPAD Software Inc., San Diego, CA) were used for the statistical analysis of the results. Significance was defined as a p value less than 0.05 (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

5. Results and discussion

Tablet weight and dimensions data obtained for the formulations studied are reported in Table 4.

PRODUCT	Weight (g ± SD)	Thickness (mm ± SD)	Diameter (mm ± SD)
RF	0.4022 ± 0.0032	0.59 ± 0.006	0.97 ± 0.02
MSF*	0.3995 ± 0.0037	0.58 ± 0.004	0.96 ± 0.01
BF1*	0.4018 ± 0.0033	0.57 ± 0.002	0.91 ± 0.01
BF2	0.4049 ± 0.0077	0.58 ± 0.005	0.96 ± 0.02
BF3	0.4017 ± 0.0130	0.57 ± 0.006	0.95 ± 0.03
BF4	0.4065 ± 0.0098	0.53 ± 0.002	1.02 ± 0.01
BF5	0.4061 ± 0.0073	0.58 ± 0.003	0.92 ± 0.02
BF6	0.7074 ± 0.0083	0.42 ± 0.003	1.33 ± 0.02
BF7†	0.7063 ± 0.0075	0.42 ± 0.001	1.32 ± 0.02
BF8	0.4044 ± 0.0068	0.46 ± 0.003	1.12 ± 0.03

* a fracture line appears along the tablets diameter; †visible lamination with different coloration along the thickness.

Table 4. Weight and shape size of tablets

In detail, all the tablets have the same shape and each tablet has a weight of about 400 mg, except BF6 and BF7 that are heavier reaching a weight of about 700 mg. As far as the visual inspection is concerned, BF1 and BF8 show a fracture line along the tablets diameter as well as a different appearance along thickness of BF7 tablets was observed, suggesting lamination due to compression steps (Carstensen et al., 1985).

From dissolution data analysis it is possible to note that, apart from BF8 representing the lower amount released (6.0 mg, corresponding to the 6% after 1 h), the % of release for the formulations was between 16.1% and 23.0% (Figure 1).

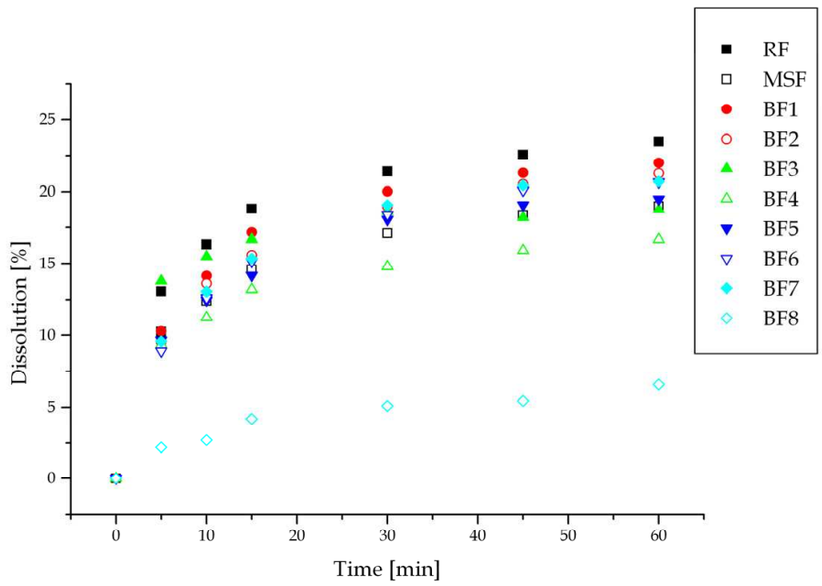


Fig. 1. Dissolution profiles of the various tablets at pH 6.8 (CV%<5).

Such differences, that our adopted experimental conditions in the absence of sink-conditions were able to blow up, were attributed to formulation differences and/or manufacturing procedures. For this reason, to better explain the dissolution profile, saturation concentrations obtained from solubility studies in the presence of the various auxiliary substances were also adopted. They are shown in Figure 2.

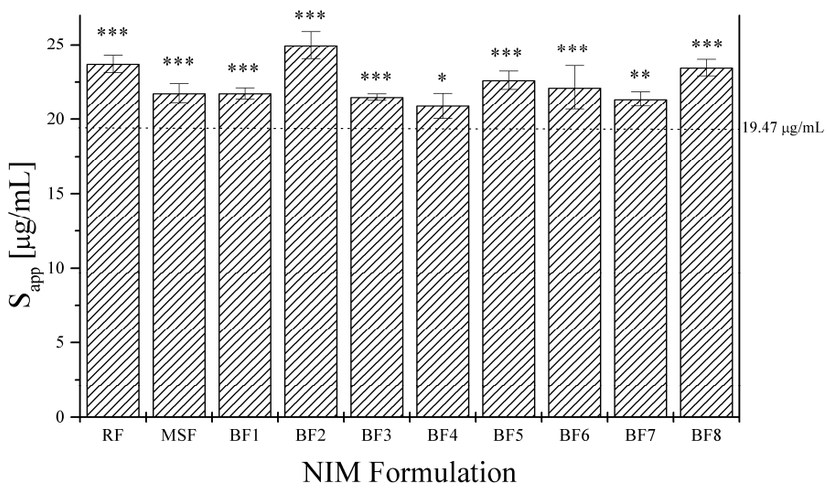


Fig. 2. Apparent solubility of NIM in the presence of tablet excipients (mean ± SD). The apparent solubility of NIM RS alone is indicated by the dotted line. Statistical significance with respect to NIM RS are also indicated.

NIM RS has the lowest S_{app} (19.47 µg/mL) while for BF2 an increment of S_{app} value near 30% (24.97 µg/mL) was obtained. With respect to NIM value, statistically significant increase in Sapp was obtained in all cases ($p < 0.001$, except than NIM vs. BF7 and NIM vs. BF4, for which $p < 0.01$ and $p < 0.05$ were observed, respectively).

These data suggested us to use S_{app} value of each formulation as normalization factor for each dissolution evaluation, instead of that of NIM solubility. Results are depicted in Figure 3, from which it appears that also in this case BF8 is not able to reach the 30% of dissolution.

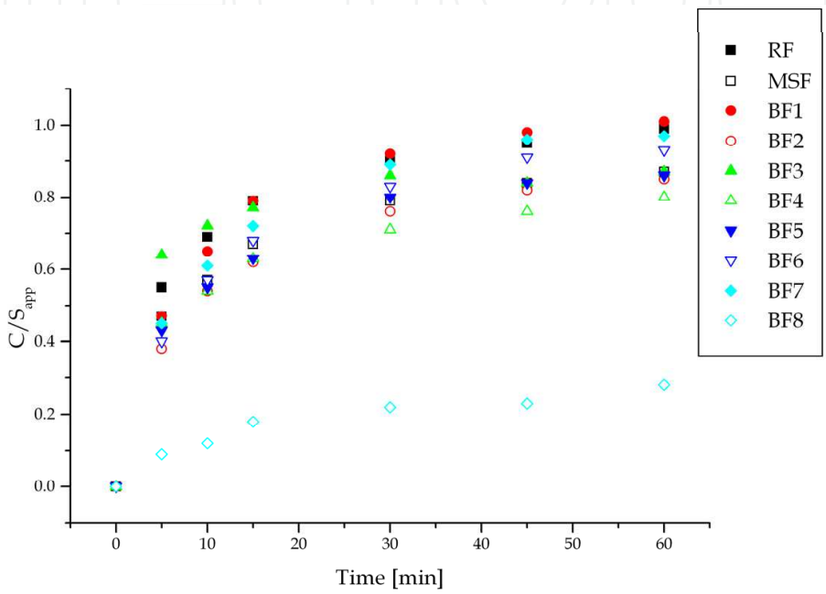


Fig. 3. Dissolution profiles of the various tablets at pH 6.8 as obtained with respect to apparent solubility (CV%<5).

As concerns BF4 its profile remains below all other curves. On the contrary, for BF1, after 1h is appreciable the achievement of 100%; such a result were not obtained by the other formulations, except than for RF.

The simplest model to represent a dissolution of a BCS II drug is a first-order model, with a dissolution rate proportional to the difference between the apparent solubility of drug and the drug concentration in the liquid phase. Such a model, along with others, has been applied with DDSolver Software and the obtained results are shown in Table 5.

The corresponding correlation coefficients, R^2, in most of the adopted equations gave results higher than 0.97, and in all these cases the worst result is obtained in the description of the dissolution of the BF8 formulation.

On the other hand, for Higuchi ($R^2<0.97$, except than for BF8), Baker-Lonsdale ($R^2<0.97$, except than for BF8), Quadratic ($R^2<0.90$), Logistic3 ($R^2<0.97$), Gompertz 3 and 4 ($R^2<0.95$) models, the mathematical description often did not appear to be entirely sufficient. Moreover, for both Hixson-Crowell and Hopfenberg models, the mathematical fitting cannot be considered acceptable ($R^2<0.61$).

Best-fit values	RF	MSF	BF1	BF2	BF3	BF4	BF5	BF6	BF7	BF8
Dissolution model										
First-order with F_{max}										
k_1	0.144	0.129	0.115	0.170	0.251	0.144	0.111	0.100	0.106	0.067
F_{max}	22.374	18.130	21.344	20.541	18.071	15.708	18.970	20.125	20.334	6.195
R^2	0.9855	0.9797	0.9942	0.9914	0.9860	0.9786	0.9846	0.9933	0.9921	0.9708
Higuchi										
k_H	3.626	2.925	3.376	3.218	3.113	2.573	2.989	3.115	3.176	0.881
R^2	0.9274	0.9427	0.9496	0.9597	0.8429	0.9315	0.9551	0.9647	0.9581	0.9854
Korsmeyer-Peppas										
k_{KP}	9.864	7.264	7.596	6.819	11.787	6.858	6.651	6.233	6.738	1.192
N	0.219	0.242	0.271	0.288	0.119	0.222	0.274	0.304	0.287	0.415
R^2	0.9931	0.9949	0.9839	0.9887	0.9939	0.9957	0.9902	0.9870	0.9863	0.9793
Hixson-Crowell										
k_{HC}	$1.96 \cdot 10^{-3}$	$1.53 \cdot 10^{-3}$	$1.80 \cdot 10^{-3}$	$1.71 \cdot 10^{-3}$	$1.60 \cdot 10^{-3}$	$1.32 \cdot 10^{-3}$	$1.58 \cdot 10^{-3}$	$1.66 \cdot 10^{-3}$	$1.69 \cdot 10^{-3}$	$4.45 \cdot 10^{-4}$
R^2	-0.0173	0.0746	0.1949	0.2647	-0.5867	-0.0293	0.2054	0.3204	0.2582	0.6021
Hopfenberg										
k_{HC}	$3.06 \cdot 10^{-5}$	$1.15 \cdot 10^{-5}$	$7.04 \cdot 10^{-5}$	$1.91 \cdot 10^{-5}$	$2.31 \cdot 10^{-5}$	$2.50 \cdot 10^{-5}$	$2.09 \cdot 10^{-5}$	$1.72 \cdot 10^{-5}$	$1.27 \cdot 10^{-5}$	$2.27 \cdot 10^{-5}$
n	204.251	418.380	811.300	284.294	218.499	165.644	237.060	304.395	418.635	59.470
R^2	0.0338	0.1126	0.2371	0.3025	-0.5351	0.0046	0.2417	0.3555	0.2961	0.6082
Baker-Lonsdale										
k_{BL}	$2.53 \cdot 10^{-4}$	$1.57 \cdot 10^{-4}$	$2.12 \cdot 10^{-4}$	$1.92 \cdot 10^{-4}$	$1.80 \cdot 10^{-4}$	$1.20 \cdot 10^{-4}$	$1.64 \cdot 10^{-4}$	$1.79 \cdot 10^{-4}$	$1.87 \cdot 10^{-4}$	$1.33 \cdot 10^{-5}$
R^2	0.7892	0.8286	0.8655	0.8919	0.5211	0.7882	0.8737	0.9084	0.8888	0.9673
Makoid-Banakar										
k_{MB}	7.743	5.831	5.020	4.754	9.821	5.794	4.758	4.134	4.410	0.984
n	0.350	0.360	0.491	0.478	0.221	0.313	0.451	0.520	0.511	0.513
k	0.006	0.005	0.009	0.008	0.004	0.004	0.007	0.009	0.009	0.004
R^2	0.9991	0.9994	0.9981	0.9989	0.9984	0.9986	0.9992	0.9993	1.0000	0.9811
Peppas-Sahlin 1										
k_1	8.128	6.052	5.287	4.935	10.950	6.091	4.873	4.302	4.572	0.995
k_2	-0.708	-0.478	-0.320	-0.288	-1.608	-0.548	-0.304	-0.225	-0.252	-0.033
m	0.418	0.426	0.528	0.523	0.310	0.381	0.506	0.555	0.550	0.547
R^2	0.9992	0.9994	0.9980	0.9990	0.9984	0.9987	0.9992	0.9992	1.0000	0.9813
Peppas-Sahlin 2										
k_1	6.639	5.075	5.671	5.209	6.605	4.605	4.948	4.908	5.168	1.087
k_2	-0.476	-0.344	-0.367	-0.318	-0.558	-0.325	-0.313	-0.287	-0.319	-0.033
R^2	0.9960	0.9973	0.9976	0.9988	0.9759	0.9931	0.9992	0.9981	0.9990	0.9809
Quadratic										
k_1	$-1.64 \cdot 10^{-4}$	$-1.26 \cdot 10^{-4}$	$-1.45 \cdot 10^{-4}$	$-1.33 \cdot 10^{-4}$	$-1.58 \cdot 10^{-4}$	$-1.13 \cdot 10^{-4}$	$-1.26 \cdot 10^{-4}$	$-1.27 \cdot 10^{-4}$	$-1.33 \cdot 10^{-4}$	$-2.78 \cdot 10^{-5}$
k_2	0.013	0.010	0.012	0.011	0.012	0.009	0.011	0.011	0.011	0.003
R^2	0.7173	0.7597	0.8227	0.8378	0.4934	0.7077	0.8284	0.8639	0.8539	0.9008
Weibull 1										
α	7.498	10.917	8.863	9.992	6.820	11.592	11.339	10.889	10.364	64.265
β	0.176	0.210	0.202	0.221	0.090	0.187	0.231	0.236	0.227	0.359
T_i	3.717	2.900	4.198	4.011	3.910	3.058	3.257	3.960	3.845	2.533
R^2	0.9987	0.9978	0.9967	0.9990	0.9967	0.9984	0.9952	0.9977	0.9957	0.9818
Weibull 2										
α	9.851	13.529	13.054	14.618	8.026	14.282	14.921	16.069	14.795	84.457
β	0.244	0.264	0.299	0.317	0.131	0.239	0.299	0.333	0.316	0.425
R^2	0.9937	0.9954	0.9851	0.9898	0.9940	0.9960	0.9910	0.9881	0.9874	0.9795
Weibull 3										
α	3.270	3.537	5.410	5.303	1.703	3.067	4.589	6.038	5.551	9.326
β	0.567	0.522	0.749	0.692	0.472	0.479	0.624	0.732	0.719	0.626
F_{max}	24.458	20.970	22.296	22.119	19.086	18.408	20.968	21.461	21.608	8.499
R^2	0.9996	0.9992	0.9994	0.9997	0.9981	0.9989	0.9982	0.9998	0.9995	0.9818

Weibull 4										
α	3.136	3.531	4.935	3.580	1.708	3.021	4.584	5.517	5.551	8.735
β	0.551	0.522	0.718	0.539	0.474	0.472	0.624	0.700	0.719	0.490
T_i	0.208	0.000	0.338	1.726	0.000	0.103	0.000	0.357	0.000	1.577
F_{max}	24.559	20.980	22.387	23.231	19.074	18.482	20.980	21.597	21.608	11.250
R^2	0.9996	0.9992	0.9994	0.9999	0.9981	0.9989	0.9982	0.9998	0.9995	0.9820
Logistic 1										
α	-2.261	-2.588	-2.563	-2.680	-2.026	-2.639	-2.696	-2.781	-2.693	-4.444
β	0.626	0.659	0.760	0.799	0.331	0.591	0.749	0.839	0.796	1.001
R^2	0.9942	0.9957	0.9861	0.9907	0.9942	0.9962	0.9916	0.9892	0.9884	0.9797
Logistic 2										
α	-1.342	-1.411	-2.006	-1.945	-0.497	-1.244	-1.709	-2.091	-1.968	-2.546
β	1.805	1.490	2.399	2.128	1.786	1.414	1.778	2.215	2.156	1.635
F_{max}	27.070	24.666	24.318	24.700	20.109	21.295	24.443	24.070	24.293	10.810
R^2	0.9996	0.9990	0.9993	0.9999	0.9978	0.9989	0.9976	0.9997	0.9988	0.9821
Logistic 3										
k	0.340	0.269	0.265	0.248	1.197	0.324	0.231	0.235	0.236	0.192
γ	5.271	6.083	6.837	7.154	3.923	5.324	7.072	7.637	7.358	10.074
F_{max}	21.639	17.707	20.766	19.927	17.549	15.229	18.552	19.506	19.803	5.775
R^2	0.9285	0.9190	0.9489	0.9423	0.9699	0.9179	0.9287	0.9480	0.9433	0.9344
Gompertz 1										
α	2.462	2.776	2.806	2.932	2.176	2.797	2.919	3.050	2.944	4.713
β	0.307	0.297	0.361	0.372	0.155	0.255	0.339	0.385	0.369	0.305
R^2	0.9959	0.9971	0.9898	0.9939	0.9946	0.9973	0.9939	0.9929	0.9918	0.9815
Gompertz 2										
α	1.903	1.936	2.913	2.708	1.119	1.761	2.284	2.912	2.714	3.479
β	1.223	0.864	1.615	1.353	1.455	0.857	1.041	1.374	1.351	0.628
F_{max}	29.151	29.053	26.049	27.274	20.482	24.445	28.420	26.859	26.975	19.954
R^2	0.9995	0.9988	0.9991	0.9999	0.9977	0.9989	0.9971	0.9995	0.9983	0.9823
Gompertz 3										
k	0.243	0.202	0.191	0.178	0.517	0.237	0.172	0.167	0.171	0.120
γ	3.569	3.899	4.530	4.731	2.523	3.537	4.515	5.058	4.804	7.011
F_{max}	21.88	17.800	20.905	20.082	17.685	15.369	18.650	19.657	19.930	5.907
R^2	0.9560	0.9467	0.9705	0.9651	0.9739	0.9466	0.9538	0.9688	0.9656	0.9492
Gompertz 4										
k	0.243	0.202	0.191	0.178	0.518	0.237	0.172	0.167	0.171	0.120
β	2.378	2.202	2.381	2.319	3.693	2.310	2.169	2.325	2.272	2.315
F_{max}	21.882	17.801	20.904	20.082	17.685	15.370	18.650	19.659	19.931	5.908
R^2	0.9560	0.9467	0.9705	0.9651	0.9739	0.9466	0.9538	0.9688	0.9656	0.9492
Probit 1										
α	-1.337	-1.502	-1.500	-1.560	-1.199	-1.521	-1.562	-1.612	-1.566	-2.318
β	0.356	0.361	0.427	0.444	0.185	0.318	0.412	0.464	0.442	0.452
R^2	0.9949	0.9964	0.9877	0.9922	0.9944	0.9968	0.9927	0.9909	0.9900	0.9808
Probit 2										
α	-0.830	-0.872	-1.256	-1.215	-0.279	-0.765	-1.065	-1.308	-1.234	-1.581
β	1.175	0.966	1.551	1.375	1.136	0.917	1.158	1.430	1.404	0.926
F_{max}	26.154	23.865	23.571	23.928	19.598	20.617	23.574	23.317	23.449	12.131
R^2	0.9996	0.9989	0.9993	0.9999	0.9978	0.9989	0.9975	0.9997	0.9988	0.9822

Table 5. Parameters and determination coefficients of various dissolution models.

Further investigation may be done by going to compare the S_{app} experimental data with those determined using some equations, which allows to calculate a value of F_{max} (Figure 4).

As it is possible to observe, no model is able to estimate properly the experimental S_{app} parameter of the various preparations, except than the Weibull functions. In detail, either under- or overestimations have been observed, with the model Gompertz 2 that provides a

value always greater than the others. As for BF8, the non-sink conditions allow to show a significant extension of time to reach the maximum value of the dynamic solubility.

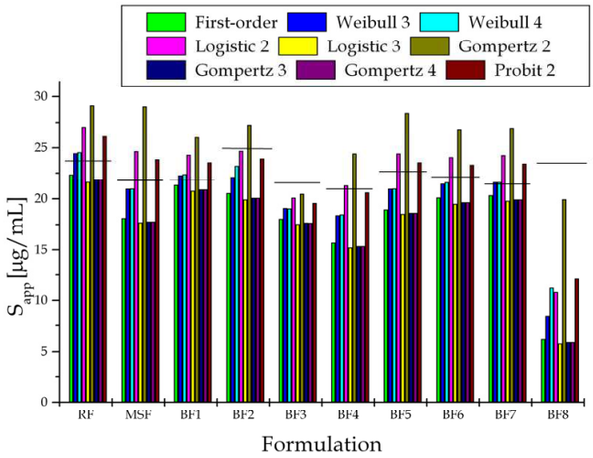


Fig. 4. Comparison of experimental S_{app} and calculated F_{max} derived from mathematical fitting.

6. Conclusion

A continuous know-how improvement of both formulation and manufacturing process parameters with respect to drug release modalities is a basic aspect of the quality framework for pharmaceutical products. Such features become of paramount relevance for generic manufacturers in the case of formulation of insoluble or poorly soluble drugs, where dissolution represents the most critical factor. In fact, both the excipients used as well as the manufacture parameters are of great importance to solid dosage form performance. The *in vivo* solubility behaviour is dependent on many factors and it cannot be fully obtained *in vitro.* Regardless the worth of "sink conditions" in the achievement of bio-relevant dissolution methods for poorly water-soluble drugs, an approach more suitable as developmental tool as well as for batch quality control in both pre-formulation and formulation stages is of great interest.

For such purposes, various commercial Immediate Release tablets containing a drug, namely NIM, differently banned, used and prescribed in the various European Countries have been chosen. NIM apparent solubilities and dissolution patterns as obtained in "non-sink conditions", i.e. in a system where the solute is present for more than 15% of its maximum solubility, have been studied. "Non-sink conditions" represented a very discriminating dissolution conditions, acting as a sort of magnifier lens for an in-depth evaluation of the dissolution phenomenology, useful since the preformulation stages.

Eventually, in such a situation of drug saturation during tablet dissolution the mathematical approaches far developed usually are not capable of describing the overall profile peculiarity.

For this reason, a more complex dissolution scheme based on the ash layer diffusion control by shrinking core model is under study.

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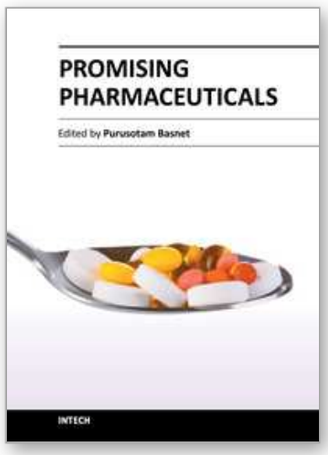

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From the dawn of civilization, humans have been dreaming of happy, healthy and long-life. Our life expectancy is twice longer than 100 years ago. We know more about the diseases. Therefore we have developed new drugs to fight against them. The demand for drugs was so high that we developed Pharma industries. Although Pharma industries took responsibility of producing the needed drugs and gave us a quality of life, misuse of drugs brought further complication. Therefore, discovery, production, distribution, and the phase of administration of patients' quality assurance has to be controlled with a technological procedure and tight regulations to make the system as effective as possible for the benefit of human health. Our book provides selected but vital information on the sources, tools, technologies and regulations regarding the current status of medicine development.

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