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Article

Dissolution test for oral suspension: an overview about use and importance

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This work aims to ascertain the comprehensiveness of dissolution tests for oral suspensions registered in Brazil and the USA. After consulting literature since 1994, a paucity of information about dissolution methods for suspensions was detected. It makes it difficult to establish the most appropriate test parameters. In January, 2019, there were 46 drugs registered in Anvisa (Brazil) as oral suspension, being 47 reference, 173 generic and 114 interchangeable similar (IS) medicines; while in the USA, 90 drugs were registered as oral suspension by FDA, 235 Abreviatted New Drug Application and 111 New Drug Application medicines. Out of 46 and 90, only six and 15 drugs as oral suspension had a pharmacopeial dissolution test, corresponding to 70 (20.9%) and 82 (23.7%) products in Brazil and the USA, respectively. Dissolution studies were found for 17 drugs as oral suspension in the non-compendial literature. Dissolution test conditions were established to few marketable oral suspension drugs, most of which are BCS class II or IV. Thus, investing in dissolution studies could subsidize the registration of these products by regulators, especially for generic and IS drugs, by comparing dissolution profiles, and predicting their *in vivo* behavior to avoid exposure of healthy individuals to clinical research.

Keywords: Dissolution. Suspension. Therapeutic equivalence. Regulatory.

INTRODUCTION

Dissolution profiles conducted in similar physiological conditions are useful tools to predict aspects related to the pharmacokinetics of the products, which could indicate bioequivalence between medicines. Furthermore, they are employed to optimize the development and ensure the quality of medicinal formulations (Brown *et al.*, 2011; Dressman *et al.*, 1998).

These studies make it possible to select a medicinal formulation with the most suitable and reproducible release profile. However, if appropriate conditions are not used, the prediction of which drugs and which dosage forms will exhibit the desired *in vivo* release profiles may be completely erroneous (Dressman *et al.*, 1998). The purpose of these studies is to evaluate the amount of drug released to a medium similar to body fluids from a pharmaceutical dosage form, under experimental conditions described in pharmacopeias or official guidelines, using specific device (Anvisa, 2010a; 2019a).

In many cases, the dissolution rate or time that the drug takes to dissolve in biological fluids from the dosage form represents the limiting step for *in vivo* absorption (Amidon *et al.*, 1995). Therefore, it is important to develop an *in vitro* dissolution test that can be correlated with drug release in physiological conditions. The development of *in vitro* tests seeks a reduction of the work in a pharmaceutical product process as well as in human clinical studies (Dressman *et al.*, 1998). The comparison of the dissolution profiles provides evidences to evaluate the need for clinical studies when test and reference medicines are confronted using buffered media (Anvisa, 2010a; FDA, 2014; Dressman *et al.*, 1998).

Brazilian Health Regulatory Agency - Anvisa, European Medicines Evaluation Agency - EMEA,

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and Food and Drug Administration - FDA require the dissolution profile comparison as a prior step to bioequivalence studies between the reference and generic candidate products, in solid oral dosage form to systemic action of immediate or modified release, and suppositories (Anvisa, 2010a; EMEA 2010; FDA, 2014). These regulatory agencies do so through resolution RDC 31/2010 (Anvisa, 2010a), guideline on the investigation of bioequivalence (EMEA, 2010) and guidance for industry bioavailability and bioequivalence studies submitted in New Drugs Applications - NDAs or Investigational New Drug Applications - INDs (FDA, 2014), respectively.

In Brazil, the dissolution profile comparison, prior to relative bioavailability and bioequivalence studies, occurs during the pharmaceutical equivalence studies of solid dosage forms (Anvisa, 2010a) and it must be carried out under specific conditions in case of biowaiver and post-registration change requests (Anvisa, 2011; 2016a).

Similar *in vitro* dissolution profiles are required to NDA and ANDA and their supplemental. Dissolution studies can be used to subsidize biowaivers in two conditions, due to postapproval changes and based on Biopharmaceutics Classification System – BCS. For NDA, this approach is applicable when there are changes in components, composition, and/or method of manufacture that occur in the marketed formulation that differentiate it from the clinical trial formulation. As long as the dosage forms exhibit either rapid or very rapid dissolution, a drug substance belongs to BCS class 1 or 3, and the formulations pre- and post-change are pharmaceutical equivalents. For ANDAs, the BCS-based biowaiver includes comparison to dissolution profiles between the proposed (generic medicine) and the reference drug products employing the dissolution apparatus (USP Apparatus 1 or 2) established for the reference listed drug product. BCS-based biowaivers may be applicable for pharmaceutical alternatives including other oral dosage forms, if appropriately justified (FDA, 2017).

For systemic action oral dosage forms, such as suspensions, the dissolution profile comparison is also required prior to the bioequivalence study between generic and reference products (FDA, 2014) . Suspensions are constituted by a heterogeneous system in which the dispersant or external phase is liquid (vehicle) and the dispersed or internal phase is constituted of insoluble finely divided solids (drug) in the liquid phase (Allen *et al.*, 2012; Brown *et al.,* 2011). This pharmaceutical preparation presents more rapid dissolution and consequently greater drug absorption speed compared to solid oral dosage forms, capacity of masking the unpleasant taste of some drugs and higher stability compared to solutions (Allen *et al.*, 2012). These advantages make it more suitable to children and the elderly with difficult swallowing and who need of dosage adjusting (Lajoinie *et al.*, 2015).

Although dissolution testing must include even special dosage forms that are not immediate release solid oral dosage forms and must also consider their different characteristics in relation to the others, usually there is not test standardization for such dosage forms. It is noted that the dissolution test principles for solid dosage forms also apply to the other pharmaceutical dosage forms and the correct selection of the apparatus, agitation rate, temperature control, volume and medium composition are essential. For oral suspension dosage form, the rotating paddle method using an aqueous medium is recommended for the drug release testing (Brown *et al.*, 2011).

Nevertheless, for this dosage form considering all administration routes, dissolution test represents only 2.5% of the FDA dissolution methods database (Shohin, *et al.,* 2016). The information is scarce, especially regarding the product preparation and insertion in the vessel, sample collection, and the system agitation influence, among other important factors to the method planning (Brown *et al.*, 2011; Shohin, *et al.,* 2016; USP, 2013; 2018).

In this context, this work presents a survey about studies and conditions for oral suspension dissolution test in the scientific non-compendial literature and pharmacopeias, as well as about the availability of oral suspension dissolution tests for pharmaceutical products registered by Anvisa in Brazil and by FDA in the USA. In this scenario a critical evaluation about the dissolution procedure of the suspension was performed considering the BCS and its requirements to maintain the *sink* condition.

MATERIAL AND METHODS

Data collection in pharmacopeias and non-compendial literature

Data collection about oral suspension with dissolution test was carried out in the British Pharmacopeia (BP, 2013; 2017), Brazilian Pharmacopeia (Farmacopeia, 1977; 2000; Anvisa, 2010b; 2016b; 2017; 2019b), International Pharmacopeia (WHO, 2018), Japanese Pharmacopeia (JP, 2016), United States Pharmacopeia (USP, 1994; 1995; 1996; 2006; 2008; 2009; 2011; 2013; 2018) monographs and in other scientific literature published over the last 23 years. 'Oral suspension' and 'dissolution test' or 'dissolution study' keywords were searched in Pubmed, ScienceDirect, Scopus, Periodicos Capes, SciELO and Web of Science databases.

The pharmaceutical product dosage form, composition and volume of the dissolution medium, apparatus, rotation speed, dissolution time, and if available, position of the sample insertion, amount inserted and removed from the sample, analysis method obtained in pharmacopeias and in previously mentioned databases were all compiled in spreadsheets in Microsoft Excel® version 2013.

Registered oral suspensions

Registered and commercially available oral suspensions in Brazil and the USA were searched in Anvisa (www.anvisa.gov.br) and FDA (www.fda.gov) homepages, respectively, in January 2019. The data were organized in order to consider the drugs available in each country (Brazil and USA) as oral suspension and their commercial availability as reference, generic and similar medicines in Brazil or as NDA and ANDA in the USA. The registration of the dissolution test conditions for oral suspensions were also searched on the pages of Anvisa and FDA.

Biopharmaceutical dissolution studies

Dissolution studies were approached in the BCS-based biowaiver context. For oral suspensions with dissolution test, the drugs were classified according to BCS (Amidon *et al.*, 1995) from literature data. The drug amount in the medium from the experimental conditions of oral suspension dissolution test was confronted with drug solubility data obtained from biopharmaceutical studies (FDA, 2017) available in the literature in order to observe the compliance of the no saturation condition in the dissolution test.

RESULTS AND DISCUSSION

Data collection in pharmacopeias and other scientific literature

The dissolution test allows us to quantify the active substance released from a pharmaceutical form when it is submitted to the experimental controlled conditions using specific dissolutors apparatus (Anvisa, 2019a; Friedel *et al.,* 2018; WHO, 2018). Initially, the test was applied to solid oral dosage forms, such as capsules and tablets, however, currently it also covers suspensions and other dosage forms (Brown *et al.,* 2011).

The test conditions are in the pharmaceutical product monographs, which are contained in official compendia (Limberg, Potthast, 2013). In general, these compendial dissolution standards are single-point dissolution tests, not profiles, which are performed at different sampling to determine the curve of the percentage of drug dissolved versus time (FDA*,* 1997).

Oral suspension monographs which mention the dissolution test were found in the United States Pharmacopeia (USP, 1995; 1996; 2006; 2008; 2009; 2011; 2013; 2018), Brazilian Pharmacopeia (Farmacopeia, 2000; Anvisa, 2017; 2019b) and British Pharmacopeia (BP, 2013; 2017) (Table I). In 1995, the United States Pharmacopeia 23th edition presented the first monograph with a dissolution test described for indomethacin oral suspension (USP, 1995). In the United States Pharmacopeia (USP, 1995; 1996; 2006; 2008; 2009; 2011; 2013; 2018) subsequent editions had an increase of the oral suspension monographs which mention the dissolution test from one in USP23, two in USP24, four in USP29, six in USP31, USP32, USP34, 12 in USP36 and then 15 in USP41 (Table I).

TABLE I – Oral suspension monographs with dissolution test described in United States (USP), British (BP) and Brazilian (BraP) pharmacopeias

Drugs	Dissolution test conditions	Pharmacopeia
Acetazolamide (suspension)	0.01M hydrochloric acid[a]; 0.9L[b]; paddle[c]; 50rpm[d]; one dose volume[f]	BP 2017, 2013
Allopurinol (suspension)	0.01M hydrochloric acid[a]; 0.9L[b]; paddle[c]; 75rpm[d]; one dose volume[f]	BP 2017, 2013
Azathioprine (suspension)	water[a]; 0.9L[b]; paddle[c]; 50rpm[d]; one dose volume[f]	BP 2017, 2013
Cefadroxil (for suspension)	water[a]; 0.9L[b]; paddle[c]; 25rpm[d]; 30min[e]; 5mL[f]; NS[g]; NS[h]; UV spectrophotometry at 263nm[i]	USP 2018, 2013
Cefdinir (for suspension)	0.05M phosphate buffer pH6.8[a]; 0.9L[b]; paddle[c]; 50rpm[d]; 30min[e]; 5mL[f]; UV spectrophotometry at 290nm[g], NS[h]; NS[i].	USP 2018, 2013
Cefuroxime axetil (for suspension)	0.07M phosphate buffer pH7.0[a]; 0.9L[b]; paddle[c]; 50rpm[d]; 30min[e]; 5mL[f]; NS[g]; NS[h]; UV spectrophotometry at 280nm[i].	USP 2018, 2013
	1.43% hydrogen ortophosphate and 0.42% sodium dihydrogen ortophosphate in water; pH 7.0 (adjust 20%v/v ortophosphoric acid or 1M sodium hydroxide)[a]; 0.9L[b]; paddle[c]; 50rpm[d]	BP 2017, 2013
Cephalexin (tablets for)	water[a], 0.9L[b], basket[c], 100rpm[d], 30min[e], UV 262nm[i]	USP 2018
Ciprofloxacin (for suspension)	sodium acetate in water (6.8g/L), pH4.5 (adjust glacial acetic acid) and polyoxyethylene lauryl ether (0.25g/L)[a]; 0.9L[b]; paddle[c]; 100rpm[d]; 30min[e]; 5mL[f]; bottom[g]; 10mL[h]; HPLC/UV[i] at 278nm.	USP, 2018
Doxycycline (for suspension)	0.01M hydrochloric acid[a]; 0.9L[b]; padlle[c]; 25rpm[d]; 10min[e]; equivalent to 25mg[f]; NS[g]; NS[h]; HPLC/UV[i] at 355nm.	USP 2018
Felbamate (suspension)	water[a]; 0.9L[b]; paddle[c]; 50rpm[d]; 15min[e]; 5mL[f]; NS[g]; NS[h]; HPLC/UV[i] at 210nm	USP 2018, 2013
Fluconazole (for suspension)	water[a]; 0.9L[b] (40mg/mL suspension) or 0.5L[b] (10mg/mL suspension); paddle[c]; 50rpm[e]; 30min[e]; equivalent to one dose[f]; NS[g]; 10mL[h]; HPLC/UV[i] 260nm	USP 2018
Ibuprofen (suspension)	pH7.2 phosphate buffer[a]; 0.9L[b]; paddle[c]; 50rpm[d]; 60min[e]; NS[f]; NS[g]; NS[h]; HPLC/UV[i] at 220nm	USP 2018, 2013, 2011, 2009, 2008, 2006, 1996; BraP 2019
Indomethacin (suspension)	0.01M phosphate buffer, pH7.2[a]; 0.9L[b]; paddle[c]; 50rpm[d]; 20min[e]; equivalent to 25mg[f]; surface[g]; NS[h]; UV spectrophotometry at 320nm[i].	USP 2018, 2013, 2011, 2009, 2008, 2006, 1996, 1995
Megestrol acetate (suspension)	0.5% sodium lauryl sulfate in water[a]; 0.9L[b]; paddle[c]; 25rpm[d]; 30min[e]; equivalent to 160mg[f]; surface[g]; NS[h]; UV spectrophotometry at 292 nm[i]	USP 2018, 2013, 2011, 2009, 2008, 2006
Meloxicam (suspension)	pH7.5 phosphate buffer[a]; 0.9L[b]; paddle[c]: 25rpm[d]; 15min[e]; equivalent to 7.5mg[f]; NS[g]; NS[h]; UV spectrophotometry at 362nm[i].	USP 2018, 2013, 2009, 2008
Mercaptopurine (suspension)	0.01M hydrochloric acid[a]; 0.9L[b]; paddle[c]; 50rpm[d]; one dose volume[f]	BP 2017, 2013

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TABLE I – Oral suspension monographs with dissolution test described in United States (USP), British (BP) and Brazilian (BraP) pharmacopeias

Drugs	Dissolution test conditions	Pharmacopeia
Mycophenolate mofetil (for suspension)	0.1M hydrochloric acid[a]; 0.9L[b](deaerated); paddle[c]; 40rpm[d]; 20min[e]; 1.2mL[f]; surface[g]; NS[h]; UV spectrophotometry at 304nm[i].	USP 2018, 2013, 2011
Nevirapine (suspension)	0.1M hydrochloric acid[a]; 0.9L[b]; paddle[c]; 25rpm[d]; 45min[e]; equivalent to 50mg[f]; 1cm below the meniscus[g]; 5mL[h]; HPLC/UV[i] at 214nm	USP 2018, 2013, 2011, 2009, 2008
Nitazoxanide (for suspension)	pH 7.5 phophate buffer with 6% cetrimonium bromide[a]; 0.9L[b] (bath at 25°C); padlle[c]; 100rpm[d]; 45min[e]; NS[f]; NS[g]; NS[h]; HPLC/UV[i] at 240nm.	BraP 2017, 2019
Oxcarbazepine (suspension)	1% sodium lauryl sulfate in water[a]; 0.89L[b]; paddle[c]; 75rpm[d]; 30min[e]; 10mL[f]; bottom[g]; NS[h]; HPLC/UV[i] at 310nm.	USP 2018, 2013
Phenytoin (suspension)	0.6% tris(hydroxymethyl)aminomethane and 1% sodium lauryl sulfate in water, pH 7.5 (adjust hydrochloric acid); 0.9L[b] (degassed); paddle[c]; 35rpm[d]; 60min[e]; 5mL[f]; bottom[g]; 4mL[h]; HPLC/UV[i] at 240nm.	USP 2018, 2013, 2011, 2009, 2008, 2006
	Borate buffer[a]; 0.9L[b]; paddle[c]; 50rpm[d]; 30min[e]; 5mL[f]; NS[g]; NS[h]; HPLC/UV[i] at 240nm.	BraP 2000
Pyrazinamide (suspension)	Water[a], 0.9L[b]; paddle[c]; 50rpm[d]; one dose volume[f]	BP 2017, 2013

a: dissolution media; b: media volume; c: apparatus; d: apparatus rotation speed; e: test time; f: sample mass/volume; g: insertion local in the vessel; h: removed sample volume; i: quantitation method; NS, not stated. (Amiodarone, bendroflumethiazide, clonazepam, dantrolene, hydrocortisone acetate, loperamide, omeprazole, spironolactone are not included because the British monographs do not describe specific conditions for dissolution test.

From British Pharmacopeia, only drugs as oral suspension with specific conditions for dissolution test were listed in Table I. Those whose volume of one dose must comply with the requirements for unlicensed medicinal products, oral suspensions (amiodarone, bendroflumethiazide, clonazepam, dantrolene, hydrocortisone acetate, loperamide) and those whose requirements do not apply (omeprazole, spironolactone) were not included. The dissolution conditions described in Table I refer to the most recent editions of the pharmacopeias studied in this work. There was also an increase of two monographs with dissolution test in British Pharmacopeia, from BP 2014 (clobazam included) to BP2018 (clobazam was withdrawn, with addition of loperamide, spironolactone, bendroflumethiazide). Although few, this increase in both USP and BP pharmacopeias indicates the importance of the development of these studies.

In Brazilian Pharmacopeia 4th edition, dissolution test was described only for phenytoin oral suspension (Farmacopeia, 2000), and no mention about dissolution test was found in oral suspension monographs in the Brazilian Pharmacopeia 5th edition (Anvisa, 2010b). The dissolution test was presented in the nitazoxanide powder for oral suspension monograph since the 2nd supplement of Brazilian Pharmacopeia (Anvisa, 2017) and also in the ibuprofen oral suspension monograph in the Brazilian Pharmacopeia 6th edition (Anvisa, 2019b).

Out of the 177, 63 and 20 oral suspension monographs in the United States Pharmacopeia (USP, 2018), British Pharmacopeia (BP, 2017) and Brazilian Pharmacopeia (Anvisa, 2010b; 2016b; 2017; 2019b), only 15 (8.5%), six (9.5%) and two (10%) presented the dissolution test, respectively, referring to 21 drugs in Table I. These data reinforce the need of studies for the development of dissolution tests for oral suspensions.

The number of oral suspension monographs in the United States Pharmacopeia (USP, 2018) is higher than in the other pharmacopeias, because it includes 77 (43.8%) compounded oral suspension monographs besides the 33 (18.7%) powder for oral suspension and 66 (37.5%) oral suspension monographs. None of USP compounded oral suspension monograph mentions the dissolution test, probably because these formulations are prepared for extemporaneous use (USP, 2018). If compounded oral suspensions are not considered, only 15% of the drugs have the dissolution test described in their USP monographs.

More than two decades since the publication of the first oral suspension monograph that exhibits the dissolution test, the dissolution test or dissolution studies have been reported in non-compendial scientific literature only for 17 drugs described as oral suspensions (Table II). Some of these suspensions are extemporaneous preparations or new formulations for suspension, thus non-marketable products. Out of these, oral suspension of three drugs (cefadroxil, cefuroxime axetil, ibuprofen) also have a dissolution test in their monographs (USP, 2018; BP, 2017; Anvisa, 2019b). All these studies dated from the last 13 years, between 2007 and 2019.

TABLE II – Dissolution studies for suspension by oral administration published in the scientific journals in the last 23 years

Drug (formulation)	Dissolution conditions	Reference (DOI)
Esomeprazole (sachet for suspension)	0.1M hydrochloric acida; NSb; paddlec; 100rpmd; 120mine; and then in pH 6.8 buffer in 150mine; NSf; NSg; NSh; HPLC/UVi at 302nm.	Bladh et al., 2007 (10.1016/j.clinthera.2007.03.014)
Cefadroxil (powder for suspension)	Deaerated distilled watera; 0.9Lb; paddlec; 50rpmd; 7.5,15,30,45,60mine; 5mLf; middleg; 10mLh; HPLC/UVi at 230nm.	Vidal et al., 2008 (10.14227/DT150308P29)
Nimesulide (suspension)	1% polysorbate 80 in pH 6.8 simulated enteric fluida; 1Lb; paddlec; 50rpmd; 180mine; equivalent to 100mgf; NSg; NSh; spectrophotometry UV–VIS at 396nm.	da Fonseca et al., 2009 (10.1208/s12249-009-9320-4)
Roxithromycin (tablet and powder for suspension)	(A) pH 1.2, (B) pH 4.5, (C) pH 6.8 buffersa; 1Lb; 15,30,45mine; (D) pH 1.2 buffera; 0.75Lb; 60mine; then addition 0.25Lb 0.2M Na3PO4 buffer plus 1mL 2M HCl to pH 6.8a; 75, 90,105mine. Paddlesc; 75rpmd; NSf; NSg; 10mLh; HPLC/UVi at 205nm.	Ostrowski et al., 2010 (10.2478/s11536-009-0113-7)
Clarithromycin (granules for suspension)	(A) 0.1M hydrochloric acida; 0.5Lb; 30,60,90,120minf with addition pH6.8 phosphate buffera; 0.5Lb; 10,20,30,45,60mine; (B) pH5 acetate buffera; 0.9Lb; 5,10,15,20,25,30,60,90,120, 150mine; (C) pH6.8 phosphate buffer; 0.9Lb; 5,10,15,20,25,30,60,90,120, 150,180minf; (D) pH2.2 sodium citrate buffera; 0.3Lb; 60mine; with addition 0.2Lb to pH5; 30,60,90,120mine; and addition of pH6.8 0.4Lb; 30,150,180,240,300,360mine. Paddlec; 50rpmd; mass equivalent to 5mLf; NSg; 5mLh; HPLC/UVi at 210nm.	Alkhalidi, et al., 2010 (10.3109/10837450903188493)
Cefuroxime axetil (for suspension, suspension)	0.07M phosphate buffer pH7 (3.7g monobasic sodium phosphate+5.7g anhydrous dibasic sodium phosphate) a; 0.9Lb; paddlec; 50rpmd; 30 mine; 5mLf; NSg; NSh; spectrophotometry UVi at 281nm.	Valizadeh et al., 2011 (10.5681/apb.2011.014)
Buclizine hydrochloride (suspension)	1.5% sodium lauryl sulfate in watera; 0.9Lb; paddlec; 25,50rpmd; 5,10,15,20,30,60,90, 120mine; NSf; NSg; 10mLh; HPLC/UVi at 230nm.	Kuminek et al., 2012 (10.1590/S0100-40422012000100036)

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TABLE II – Dissolution studies for suspension by oral administration published in the scientific journals in the last 23 years

Drug (formulation)	Dissolution conditions	Reference (DOI)
Ibuprofen (suspension)	pH 7.2, pH 6.8, pH4.5 phosphate buffers and 0.1M hydrochloric acida; 0.9Lb; paddlec; 25,50rpmd; 5,10,2 0,30,45,60,90,120,150,180mine; amount equivalent to 100mg/5mLg; NSh; spectrophotometry UVi at 221nm.	Rivera-Leyva et al., 2012 (10.4103/0250-474X.107062)
Albendazole (suspension)	0.1M hydrochloric acida, 0.9Lb; paddlec; 25,50rpmd; 2,5,10,20,30,60,90mine; 5mLf; middleg; 10mLh; spectrophotometry UVi at 310nm.	Vidal et al., 2013 (10.14227/DT200413P27)
Diclofenac potassium (suspension)	0.3% sodium lauryl sulfate in watera; 0.9Lb; paddlec; 50rpmd; 5,10,15,30,60mine; amount equivalent to 10mgf; NSg; NSh; HPLC/PDAi at 275 nm.	Rubim et al., 2014 (10.1590/ S1984-82502014000200022)
Spironolactone (pediatric suspension)	0.1% sodium lauryl sulfate in 0.1M hydrochloric acida; 1Lb; paddlec; 75rpmd; 1,2,3,4,5,6,7, 8,9,10,11,12,13,14,15,60mine; 5mLf; topg; NSh; spectrophotometry UVi at 242nm.	Bernal et al., 2014 (10.14227/DT210114P19)
Carvedilol (micro/nano suspension)	pH 1 and pH 6.8 buffer mediaa; 0.9Lb; paddlec; 100rpmd; 5,15,30,60 mine; equivalent to 25mgf NSf; NSg; 5mLh; spectrophotometry UVi at 242nm.	Liu et al., 2015 (10.2147/IJN.S8 7143)
Montelukast sodium (suspension)	0.5% sodium lauryl sulfate in watera; 0.9Lb; paddlec; 50rpmd; 5,10,15,30mine; 4mgf; NSg; 1mLh; HPLC/UVi at 238nm.	Kim et al., 2016 (10.1007/ s12272-015-0664-x)
Benzoyl metronidazole (suspension)	pH 1.2 simulated gastrintestinal fluid without enzymesa; 0.9Lb; paddlec; 50rpmd; 5,10,15,30, 45,60,90 mine; weight equivalent to 200mg/5mLf; NSg; 10mLh; HPLC/UVi at 235nm.	da Silva et al., 2016 (10.1208/ s12249-015-0407-9)
Rosuvastatin (suspension)	0.05M sodium citrate buffer pH 6.6a; 0.9Lb; paddlec; 50rpmd; 10,20,30,45mine; 5mLf; in paddleg; 10mLh; HPLC/UVi at 248nm.	Zaid et al., 2017 (10.2146/ ajhp16 0235)
Celecoxib (dry/nano suspensions)	0.1% polysorbate 80 in pH 1.2 gastric and in pH 6.8 intestinal fluidsa; 0.9Lb; paddlec; 50rpmd; 5,10,15,30,60,90,120mine; amount equivalent to 2.5mgf; NSg; 3mLh; HPLC/UVi at 250nm.	Kim et al., 2018 (10.3390/ pharma ceutics10030140)
Dasatinib (powder for suspension)	0.1M hydrochloric acid pH 1.2a; 0.05Lb; 20mine (stage 1); with addition fasted state simulated intestinal fluid (FaSSIF)a; 0.25Lb; paddlec; 75rpmd; 180mine (stage 2); NSf; NSg; NSh; NSi.	Vaidhyanathan et al., 2019 (10.1016/j.xphs.2018.11.005)

a: dissolution media; b: media volume; c: apparatus; d: apparatus rotation speed; e: times of aliquot withdrawal in dissolution studies; f: added sample; g: insertion local in the vessel; h: removed sample volume; i: method for drug quantitation method.

The most representative data in that period may be related to the biopharmaceutical evaluation processes to support the drug biopharmaceutical classification, or for pharmaceutical equivalence purposes (Mishra *et al*., 2010). The drug biopharmaceutical classification system created by Amidon and collaborators in 1995, has been applied as a biowaiver regulatory tool which consists in the replacement of bioequivalence studies *in vivo* by *in vitro* dissolution tests (Amidon *et al.,*1995; FDA, 2014, 2017; Friedel *et al*., 2018). Considerations to the pharmaceutical equivalence, dissolution test and other pharmacopeial requirements described in the product monograph are necessary to be fulfilled by test and reference medicines in order to prove their quality. Only products that have the same pharmaceutical form, route of administration and amount of drug can be pharmaceutical equivalents (Anvisa, 2010a).

From 2009 to the present, there have been a shortage of dissolution test for suspension in the literature (da Fonseca *et al.,* 2009). Thus, the need to develop and standardize the conditions to dissolution procedure for oral suspensions is evident, which is a challenge because it requires the definition of the best conditions for the test execution. These conditions comprise apparatus selection and its speed, composition and volume of the dissolution medium, the sample amount inserted into the vessel and how this insertion is fulfilled, the aliquot to be withdrawn from the vessel, the test total time and the collection times. Besides that, a method is necessary for drug quantification, in aliquots withdrawn from the vessels during the test in order to obtain the dissolution profiles (FDA, 2017; USP, 2018; Brown *et al*., 2011). The dissolution test conditions for oral suspensions found in the compendial and non-compendial scientific literature are summarized in Table I and Table II, respectively.

All oral suspension dissolution media have water as basis such as recommended in the literature (Brown *et al.,* 2011), with pH within physiological range from 1 (USA) or 1.2 (Brazil) to 6.8 according legislation (Anvisa, 2011; FDA, 2017; USP, 2018; Pharmacopeial, 2019). Among the media that aim to mimic the constitution of biological fluids, the most described in oral suspension monographs and in non-compendial literature are hydrochloric acid followed by pH 6.8 phosphate buffer, and less frequently, acetate (pH 4.5), citrate, borate and tris buffers. This reveals that in general at least one of the following media 0.1M hydrochloric acid or simulated gastric fluid without enzymes, or pH 4.5 buffer and pH 6.8 buffer or simulated intestinal fluid without enzymes indicated by regulatory agencies were employed (Anvisa, 2011; FDA, 2017). Some monographs and published studies have reported the use of water with or without additive (0.3%-1.5% sodium lauryl sulfate) as dissolution medium, which is advantageous to represent the basis of the physiological means, in addition to being easily obtained, inexpensive, causes less impact on the environment and mainly does not exert any corrosive action on the equipment (USP, 2018). However, its use as a dissolution medium is discouraged because its quality can vary depending on the source, its pH value can not be controlled, can vary from day to day and also changes during the course, depending on the active substance, excipients and the (re)absorption of carbon dioxide from air (USP, 2018; Pharmacopeial, 2019). In accordance with FIP guidelines for dissolution testing of solid oral products, despite the disadvantages of some details of pH and surface tension, the use of purified water is recommended when these variations do not influence dissolution characteristics, and when it is possible to obtain a discriminatory dissolution method (Aiache *et al*., 1997; Friedel *et al.,* 2018).

As well as for other pharmaceutical forms, many dissolution conditions employed for oral suspensions do not consider biorelevant conditions as shown in Table I and Table II. The non-biorelevant media are simple aqueous buffers typically used in quality control that can be used to reflect typical pH conditions in the stomach or small intestine. However, these media do not represent other key aspects of the composition of the gastrintestinal contents (e.g., osmolality, ionic strength, viscosity, surface tension) that can be relevant to drug release from the dosage form to be tested (Klein, 2010).

There is an agreement between the compendial (92%) and non-compendial (94%) literature for dissolution medium volume of at least 0.9L, that should be enough to ensure the solubility of the chemical substances in the media and maintain the *sink* condition, which corresponds to solvent volume 3, 5 or 10 times larger than the saturation point (USP, 2018; Phillips *et al*., 2012; Pharmacopeial, 2019). A volume up to 0.9L is recommended by the regulatory agency in Brazil (Anvisa, 2011), which is accepted in the USA when appropriately justified, since a volume up to 0.5L is established by FDA (FDA, 2017).

Excepting for nitazoxanide, whose bath is maintained at 25 ºC, whereas for all other oral suspensions the test temperature is set at 37ºC simulating human body temperature (Anvisa, 2019b). For regulatory purposes, the temperature variation is set in 1ºC in Brazil (Anvisa, 2011) and 0.5ºC in USA (FDA, 2017; Van Oudtshoorn *et al.,* 2018), the latter is similar to the compendials (Anvisa, 2019a; USP, 2018; Pharmacopeial, 2019).

Regulatory agencies of both countries recommend the use of basket (USP apparatus I) or paddle (USP apparatus II) in dissolution studies (Anvisa, 2011; FDA, 2017). All studies employed the paddle apparatus, which

is the most suitable and indicated for oral suspension dosage form, since it would be impractical to use the baskets that allow only the insertion of dry samples (Anvisa, 2019a; Brown *et al.*, 2011; Pharmacopeial, 2019; USP, 2018).

The paddle apparatus at 50 rotations per minute (rpm), recommended in FDA guide, was the most frequently used speed in pharmacopeical monographs (52.1%) and in published studies (70.5%) for oral suspension. The USA regulatory agency also suggested the speed of 75 rpm when appropriately justified (FDA, 2017). Other values described in these sources 25, 35, 40, 75 and 100 rpm were within the values indicated for this pharmaceutical dosage form, which are 25 to 100 rpm (Brown *et al*., 2011). For speed selection, it should be considered the oral suspension viscosity, where the less viscous products need lower rotational speeds compared to those of higher viscosity. For the latter, it is necessary to prevent sedimentation and accumulation at the bottom of the vessel and to facilitate the discriminative testing of different batches or formulations (Brown *et al*., 2011). The 100 rpm was cited in the ciprofloxacin and nitazoxanide oral suspension monographs, as in non-compendial literature for carvedilol microsuspension/nanosuspension and esomeprazole sachet for suspension. Furthermore, different rotational speeds up to 100 rpm were found in the literature, commonly for solid dosage forms, which require the drug disintegration process prior to dissolution. Regarding oral suspensions, which already have the disintegrated drug, requiring only the dissolution process, high-speed rotation can interfere in drug release in the dissolution medium, presenting illusory results or it may suggest that such oral suspensions have very high viscosity, requiring more powerful rotation.

The test duration described in the non-compendial literature (Table II) is longer compared to the pharmacopeial data (Table I). All compendial dissolution data presented only a single time of sample collection, however, in some cases two specification times can occur. The compendial time is usually based on the average time for gastric emptying, typically 30 minutes, and is used to characterize a pharmaceutical product or as a routine quality control. However, for modified (delayed) release oral suspensions, the test time is especially long, because two stages are required, an acid, at which no drug is released and another in an intestinal pH, where drug release occurs (Anvisa, 2019a; Pharmacopeial, 2019). On the other hand, most of the non-compendial data refer to dissolution profile studies with sample collection at different times, which is used in pharmaceutics development to define the best timepoint to verify the quality of the final product (Brown *et al.,* 2011; Friedel *et al.,* 2018; FDA, 1997). Both dissolution test and dissolution profile comparison are generally the basis of the biowaiver (Friedel *et al.,* 2018).

The sample amount to be inserted is referred as the volume equivalent to the drug mass contained in one dose, for instance, it is 25 mg for doxycycline (USP, 2018) or as the volume equivalent to one dose (BP, 2017; USP, 2018), which is usually mentioned as 5 mL in USP oral suspension monographs. Although there is no standardization, the volume of 5 mL is also the most cited in the literature, since it refers to a single dose. Almost half of the studies omit this information (Table II). The weight before the sample transfer to the dissolution vessel may be necessary to determine the dose inserted with accuracy in case of high-viscosity suspensions (Brown *et al.,* 2011). In general, the weighting of a syringe before and after the sample introduction into the dissolution vessel with the specific gravity of the formulation is used to determine the drug dissolved in the sampled volume, as employed in oral suspension studies of albendazole, benzoyl metronidazole, cefadroxil, diclofenac potassium, ibuprofen, nimesulide and spironolactone mentioned in Table II.

There is no standardization regarding the local of the sample insertion in the dissolution vessel. Only some USP pharmacopeial monographs indicate the bottom (ciprofloxacin, oxcarbazepine and phenytoin) or the surface (indomethacin, megestrol acetate and mycophenolate mofetil). In the non-compendial literature, oral suspension studies report the top (spironolactone) and the middle (albendazole and cefadroxil).

The aliquot volume withdrawn for analysis may vary from 4mL (phenytoin monograph) to 20mL (meloxicam monograph) in pharmacopeias, or from 1mL (montelukast sodium suspension) to 10mL (albendazole, benzoyl

metronidazole, buclizine hydrochloride cefadroxil, rosuvastatin, roxithromycin) in non-compendial literature. Besides that, there is little information in both compendial and non-compendial literature as to the point of the vessel in which the collection is to be carried out. This is probably due to pharmacopeial standardization of withdrawal of the sample from a zone midway between the surface of the dissolution medium and the top of the rotating basket or blade, not less than 1 cm from the vessel wall (Anvisa, 2019a; USP, 2018; Pharmacopeial, 2019).

The quantification of these drugs has been described by ultraviolet spectrophotometry or by high performance liquid chromatography methods (Anvisa 2010a; 2019b; FDA, 2014).

It reveals that dissolution studies for oral suspensions should be conducted in order to clarify aspects related to the product preparation, mass or volume to be introduced in the vessel, local in the vessel where sample insertion should occur and local sample collection (Brown *et al.*, 2011; Shohin, *et al.,* 2016; USP, 2013; 2018; Pharmacopeial, 2019).

Registered oral suspensions

By January 2019, in Brazil, there were records of 334 products from 46 drugs (isolated or in association) as suspension for oral administration among which 47 (14.1%) were reference, 173 (51.8%) generic and 114 (34.1%) interchangeable similar medicines, which are those that have been approved by Anvisa in pharmaceutical equivalence tests, relative bioavailability or biowaiver (Anvisa, 2019c; 2019d; 2019e; 2019f; 2014). These records take into account powder and tablets for oral suspension. Out of these products, 289, 44 and one consisted of one, two and three drugs respectively. The drugs and the respective number of oral suspension medicines available in Brazil are listed in Table III (the products of the same drug were not distinguished according to the commercially available doses). In addition, there were other 90 records of products as suspension for administration by intravenous (32), inhalation (27), ophthalmic (26), subcutaneous (2), otic (1), rectal (1) and infusion (1) routes.

TABLE III – Medicines registered as suspensions for oral administration in Brazil (Anvisa, 2019c, e, f)

Drug(s)	Reference	Generic	Interchangeable Similar	Dissolution Test Available
Acetaminophen	3	12	-	No
Albendazole	1	7	3	No
Alginate sodium; Bicarbonate sodium	1	-	-	No
Aluminum hydroxide; Magnesium hydroxide; Simethicone	2	-		No
Amoxicillin[1]	5	21	25	Table V
Amoxicillin; Clavulanate potassium[1]	5	11	13	Table V
Amoxicillin; Sulbactam[1]	-	-	1	No
Amphotericin B[1]	1	-	-	No
Ampicillin[1]	-	3	3	Table V
Azithromycin Dihydrate[1]	1	6	12	Table V
Benzoilmetronidazol	-	5	-	Table II
Carbamazepine	1	5	1	Table II

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TABLE III – Medicines registered as suspensions for oral administration in Brazil (Anvisa, 2019c, e, f)

Drug(s)	Reference	Generic	Interchangeable Similar	Dissolution Test Available
Cefaclor	-	4	-	No
Cefadroxil/Cefadroxil hemihydrate[1]	2	6	5	Table I, II, V
Cefuroxime axetil[a]	1	2	-	Table I, II, V
Cephalexin[1,2]	3	12	6	Table I, V
Clarithromycin[1]	2	1	2	Table II, V
Cloperastine fendizoate	1	-	-	No
Deferasirox[2]	-	1	-	Table V
Diclofenac acid	1	-	1	No
Diclofenac potassium	-	1	-	Table II
Diclofenac resinate	1	9	5	No
Domperidone	1	2	1	No
Erythromycin estolate	-	1	2	No
Fexofenadine hydrochloride	1	-	-	Table V
Fosamprenavir calcium	1	-	-	Table V
Ibuprofen	3	18	-	Table I, II, V
Lamotrigine[2]	-	2	-	No
Linezolid	-	1	-	Table V
Mebendazole	1	12	-	No
Metronidazole	-	-	3	No
Nimesulide	2	12	8	Table II
Nystatin	1	8	6	Table V
Nitazoxanide[1]	1	1	5	Table I, V
Oseltamivir phosphate[1]	1	-	-	Table V
Oxamniquina	1	-	-	No
Oxcarbazepine	1	2	2	Table I, V
Rifampicin[1]	1	-	1	No
Secnidazole[1]	-	3	-	No
Strontium ranelate[1]	1	1	-	No
Sulfamethoxazole; Trimethoprim	-	4	9	Table V
Sultamicillin[1]	1	-	-	No

1, powder for suspension; 2, tablet for suspension.

In the USA, in the same period, there were 346 marketable products registered as suspension for oral administration, including powder and tablet for suspension, of which 111 (32%) were reference (New Drug Application, NDA) and 235 (68%) generic medicines (Abbreviated New Drug Application, ANDA) from 90 drugs, isolated or in association. These data are shown in Table IV (FDA, 2019a). In addition, there still were 103 marketable products (79 NDA and 24 ANDA) registered as suspensions, however for administration by intramuscular (29), ophthalmic (27), inhalation (18), otic (9), topical (6), subcutaneous (5), intratracheal (3), intravenous (2), intravenous infusion (1), intraocular (1), intra-articular (1) and enteral (1) routes. Registered discontinued products have been disregarded. After searching in regulatory agencies websites about dissolution test for oral suspension, information was obtained only in FDA database (FDA, 2019b), whose data are presented in Table V.

TABLE IV – Medicines registered as suspensions for oral administration in USA (FDA, 2019a)

Drug(s)[Formulation]	**NDA**	**ANDA**	**Dissolution Test Available**
Acyclovir[1]	1	2	Table V
Amoxicillin[2]	-	25	Table V
Amoxicillin; clavulanate potassium[2]	2	16	Table V
Amphetamin[3]	2	-	No
Ampicillin/Ampicillin trihydrate[2]	-	2	Table V
Aprepitant[2]	1	-	Table V
Atovaquone[1]	1	5	No
Azithromycin[2]	3	14	Table V*
Barium sulfate[1]	9	-	No
Bosentan[4]	1	-	Table V
Carbamazepine[1]	1	2	Table V
Carbinoxamine maleate[3]	1	-	Table V
Cefaclor[2]	-	4	No
Cefadroxil/Cefadroxil hemihydrate[2]	-	8	Table I, II, III
Cefdinir[2]	-	10	Table I, V
Cefixime[2]	1	9	Table V
Cefpodoxime proxetil[2]	-	4	Table V
Cefprozil[2]	-	12	Table V
Cephalexin[2]	-	10	Table V
Chlorothiazide[1]	1	-	No
Chlorpheniramine maleate; Ibuprofen; Pseudoephedrine hydrochloride[1]	1	-	No
Chlorpheniramine polistirex; Codeine polistirex[3]	1	-	Table V
Chlorpheniramine polistirex; Hydrocodone polistirex[3]	-	2	Table V

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TABLE IV – Medicines registered as suspensions for oral administration in USA (FDA, 2019a)

Drug(s)[Formulation]	NDA	ANDA	Dissolution Test Available
Ciprofloxacin[2]	2	2	Table I, V*
Clarithromycin[2]	-	2	Table II, V*
Clobazam[1]	1	6	Table V
Clozapine[1]	1	-	Table V
Colesevelam hydrochloride[2]	2	2	No
Darunavir ethanolate[1]	1	-	Table V
Deferasirox[4]	3	3	Table V
Deflazacort[1]	1	-	No
Dextromethorphan polistirex[3]	1	2	Table V
Diazoxide[1]	1	-	No
Doxycycline[2]	1	2	Table I, V*
Doxycycline calcium[1]	1	-	No
Eltrombopag olamine[2]	2	-	Table V*
Esomeprazole magnesium[5]	5	-	Table V
Everolimus[4]	3	-	No
Famotidine[2]	1	4	Table V*
Felbamate[1]	1	2	Table I, V
Fexofenadine hydrochloride[1]	1	2	Table V
Fluconazole[2]	2	6	Table I, V*
Fosamprenavir calcium[1]	1	-	Table V
Griseofulvin, microsize[1]	-	4	Table V
Ibuprofen[1]	6	15	Table I, II, V
Ibuprofen; Pseudoephedrine hydrochloride[1]	2	1	Table V
Indomethacin[1]	1	-	Table I
Levetiracetam[4]	4	-	Table V
Linezolid[2]	1	1	Table V*
Loperamide hydrochloride[1]	1	1	Table V
Loratadine[1]	1	-	No
Megestrol acetate[1]	1	7	Table I
Mercaptopurine[1]	1	-	Table I
Methadone hydrochloride[4]	1	3	No
Methylphenidate hydrochloride[6]	1	1	Table V
Mycophenolate mofetil[1]	1	1	Table I*, V

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TABLE IV – Medicines registered as suspensions for oral administration in USA (FDA, 2019a)

Drug(s)[Formulation]	NDA	ANDA	Dissolution Test Available
Naproxen[1]	1	1	No
Nevirapine[1]	1	2	Table I, V
Nitazoxanide[2]	1	-	Table I, V*
Nitisinone[1]	1	-	Table V
Nitrofurantoin[1]	1	4	Table V
Nystatin[1]	-	8	Table V
Omeprazole magnesium[5]	2	-	Table V
Omeprazole; Sodium bicarbonate[2]	3	4	Table V
Oseltamivir phosphate[2]	1	4	Table V
Oxcarbazepine[1]	1	3	Table I, V
Pantoprazole sodium[5]	1	-	Table V
Paroxetine hydrochloride[1]	1	-	Table V
Perampanel[1]	1	-	Table V
Phenytoin[1]	1	4	Table I, V
Posaconazole[1]	1	-	Table V
Riluzole[1]	1	-	No
Rufinamide[1]	1	-	Table V
Sevelamer carbonate[2]	2	4	No
Sildenafil citrate[2]	1	-	Table V*
Simvastatin[1]	2	-	Table V
Sodium polystyrene sulfonate[1]	-	4	No
Sodium zirconium cyclosilicate[2]	2	-	No
Spironolactone[1]	1	-	Table II
Stiripentol[2]	2	-	No
Sucralfate[1]	1	-	Table V
Sulfamethoxazol; Trimethoprim[1]	1	3	Table V
Tacrolimus[2]	2	-	No

NDA, New Drug Application; ANDA, Abbreviated New Drug Application; 1, suspension; 2, for suspension; 3, suspension, extended release; 4, tablet for suspension; 5, for suspension, delayed release; 6, for suspension, extended release. *Product whose dissolution test refers to formulation not identical to that marketable registered with the FDA.

TABLE V – Dissolution tests registered for oral suspension products in FDA database (FDA, 2019b)

Drugs[(Formulation)]	Dissolution media	Volume (L)	Paddle (rpm)	Time (min[a], hour[b])
Acyclovir[1]	0.1M hydrochloric acid	0.9	50	10,20,30,45,60[a]
Amoxicillin[2] (Amox)	water (degassed)	0.9	50	5,10,15,20,30,45[a]
Amox/clavulanate potassium[1]	water (deaerated)	0.9	75	5,10,15,30[a]
Ampicillin[2] (trihydrate)	water (deaerated)	0.9	25	5,10,15,20[a]
Aprepitant[2]	1.2% polysorbate 80 in water	0.9	50	5,10,15,20[a]
Azithromycin[3]	pH 6.0 phosphate buffer	0.9	50	15,30,45,60,120,180[a]
Azithromycin[1]	pH 6.0 phosphate buffer	0.9	50	10,20,30,45[a]
Bosentan[4]	0.5% sodium lauryl sulfate in 0.1M hydrochloric acid, pH 1.1	0.9	75	5,10,15,20,30[a]
Carbamazepine[1]	water (deaerated)	0.9	50	10,20,30,45,60[a]
Carbinoxamine maleate[3]	0.4M phosphate buffer	0.895	50	0.5,1,2,3,4,6,8,12[b]
Cefadroxil[1]	water	0.9	25	5,10,15,30,45[a]
Cefdinir[1]	0.05M phosphate buffer, pH 6.8	0.9	50	10,20,30,45[a]
Cefixime[1]	0.05M phosphate buffer, pH 7.2	0.9	50	10,20,30,45[a]
Cefpodoxime proxetil[1]	0.04M glycine buffer, pH 3.0	0.9	50	10,20,30,45[a]
Cefprozil[2]	water	0.9	25	5,10,15,20,30[a]
Cefprozil monohydrate[1]	water	0.9	25	5,10,15,30[a]
Cephalexin[1]	water	0.9	25	5,10,20,30[a]
Chlorpheniramine polistirex/ Codeine polistirex[3]	0.1M hydrochloric acid (stage 1) pH 6.8 phosphate buffer (addition of 0.4L of 0.2M NaH_2P0_4 to pH 6.8)	0.5 0.9	50 50	1[b] 1,2,4,6,8,12[b]
Chlorpheniramine polistirex/ Hydrocodone polistirex[3]	Simulated gastric fluid	0.495	50	1,2,3,6,8,12,16,24[b]
Ciprofloxacin[1]	0.025% polyoxyethylene lauryl ether in 0.05M acetate buffer, pH 4.5	0.9	100	10,20,30,45[a]
Clarithromycin[1]	0.05M phosphate buffer, pH 6.8	0.9	50	10,20,30,45,60[a]
Clobazam[1]	0.1M hydrochloric acid (degassed)	0.9	75	5,10,15,20,25,30[a]
Clozapine[1]	pH 4.0 acetate buffer	0.9	50	5,10,15,20,30[a]
Darunavir ethanolate[1]	0.05% polysorbate 20 in 0.05M phosphate buffer, pH 6.8	0.9	75	5,10,15,20,30,45[a]
Deferasirox[4]	0.5% polysorbate 20 in phosphate buffer, pH 6.8	0.9	50	10,20,30,45[a]
Dextromethorphan polistirex[3]	0.1M hydrochloric acid	0.5	50	30,60,90,180[a]

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TABLE V – Dissolution tests registered for oral suspension products in FDA database (FDA, 2019b)

Drugs(Formulation)	Dissolution media	Volume (L)	Paddle (rpm)	Time (min[a], hour[b])
Doxycycline[1]	0.01M hydrochloric acid	0.9	25	5,10,15,20[a]
Eltrombopag olamine[1]	50 mM potassium phosphate in water, pH 6.8 with 0.2% polysorbate 80	0.75	50	4,8,12,15,20[a]
Erythromycin ethylsuccinate[1]	1% sodium lauryl sulfate in monobasic sodium phosphate buffer, pH 6.8	0.9	75	10,20,30,45,60 [a]
Esomeprazole magnesium[5]	0.1M hydrochloric acid (stage 1) pH 6.8 sodium phosphate buffer (stage 2)	0.3 1.0	100 100	120[a] 10,20,30,45,60[a]
Famotidine[1]	0.1M phosphate buffer, pH 4.5	0.9	25, 50	10,15,30,45[a]
Felbamate[1]	water (deaerated)	0.9	50	5,10,15,30[a]
Fexofenadine hydrochloride[1]	0.001M hydrochloric acid	0.9	50	10,20,30,45[a]
Fluconazole[1] (40mg/mL) (10mg/mL)	water (deaerated) water (deaerated)	0.9 0.5	50 50	10,20,30,45[a] 10,20,30,45[a]
Fosamprenavir calcium[1]	10mM hydrochloric acid	0.9	25	5,10,15,20[a]
Griseofulvin[1] (microsize or not)	0.54% sodium lauryl sulfate in water	1.0	25, 50	10,20,30,45[a]
Ibuprofen[6]	pH 7.2 phosphate buffer	0.9	50	5,10,15,20[a]
Ibuprofen/ pseudoephedrine hydrochloride[1]	0.05M phosphate buffer, pH 7.2	0.9	50	5,10,15,30[a]
Levetiracetam[4]	pH 6.8 phosphate buffer (degassed)	0.9	50	2.5,5,10,15,20[a]
Linezolid[1]	0.05M phosphate buffer, pH 6.8	0.9	50	10,20,30,45[a]
Loperamide hydrochloride[1]	0.01M hydrochloric acid	0.9	25	10,20,30,45,60,75,90[a]
Meloxicam[1]	pH 7.5 phosphate buffer	0.9	25	5,10,15,30[a]
Mercaptopurine[1]	0.1M hydrochloric acid	0.9	50	5,10,15,20,30[a]
Methylphenidate hydrochloride[7]	0.4M phosphate buffer, pH 4.5	0.9	75	0.25,0.5,1,2,3,4,6,8[b]
Mycophenolate mofetil[1]	0.1M hydrochloric acid	0.9	40	5,10,20,30[a]
Nevirapine[1]	0.1M hydrochloric acid	0.9	25	10,20,30,45,60[a]
Nitazoxanide[1]	6% hexadecyltrimethyl ammonium bromide in phosphate buffer, pH 7.5	0.9	100	10,20,30,45,60[a]
Nitisinone[1]	pH 1.2 hydrochloric acid buffer (degassed)	1.0	50	10,15,20,30,45[a]
Nitrofurantoin[1]	pH 7.2 phosphate buffer	0.9	50	15,30,60,120,180[a]
Nystatin[1]	0.1% and 0.2% sodium lauryl sulfate in water	0.9	25,50,75	5,10,20,30,45,60[a]

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TABLE V – Dissolution tests registered for oral suspension products in FDA database (FDA, 2019b)

Drugs[(Formulation)]	Dissolution media	Volume (L)	Paddle (rpm)	Time (min[a], hour[b])
Omeprazole sodium bicarbonate[2]	0.25 mM sodium phosphate buffer, pH 7.4	0.9	50	5,10,15,30[a]
Oseltamivir phosphate[1]	0.1M hydrochloric acid	0.9	25	5,10,15,20,30[a]
Oxcarbazepine[1]	1% sodium lauryl sulfate in water	0.9	75	10,20,30,45[a]
Pantoprazole sodium[8]	0.1M hydrochloric acid (stage 1) 0.05M tribasic sodium phosphate/TSP pH 6.8 (add 0.25L of 0.2mM TSP)	0.75 1.0	100 100	60,90,120[a] 10,20,30,45,60[a]
Paroxetine hydrochloride[1]	Simulated gastric fluid without enzyme	0.9	100	10,20,30,45[a]
Perampanel[1]	0.1M hydrochloric acid	0.89	50	5,10,15,20,30[a]
Posaconazole[1]	0.3% sodium lauryl sulfate	0.9	25	10,20,30,45[a]
Rufinamide	2.0% sodium lauryl sulfate in water	0.9	50	5,10 15,20,30[a]
Sildenafil citrate[1]	McIlvaine buffer, pH 5.0	0.5	50	5,10,15,20,30[a]
Simvastatin[1]	0.14% sodium lauryl sulfate in phosphate buffer, pH 7.0	0.9	50	10,15,20,30,45[a]
Sucralfate[1]	0.1M hydrochloric acid/0.067 M potassium chloride, pH 1.0	0.9	75	10,20,30,45[a]
Sulfamethoxazole/ trimethoprim[1]	1mL of 0.2M hydrochloric acid in water	0.9	50	10,20,30,45,60,90[a]
Voriconazole[1]	0.1M hydrochloric acid	0.9	50	10,20,30,45[a]

1: suspension; 2: for suspension; 3: suspension (extended release); 4: tablet for suspension; 5: for suspension (delayed release); 6: suspension/drop; 7: powder for suspension (extended release); 8: granules (delayed release) for oral suspension.

The number of commercially available drugs in the oral suspension dosage form in the USA (346) is slightly higher than in Brazil (334). Although the diversity of NDA is lower (0.48 times) compared to ANDA medicines in USA, it is still higher than the diversity of the reference compared to the other medicines in Brazil. The number of reference medicines in Brazil is 0.27 and 0.41 times lower than generic and interchangeable similar medicines, respectively. The number of NDA medicines (111) in the USA is 2.33-fold higher than the number of reference medicines (47) in Brazil. This result reveals that, despite the lower number of reference medicines in Brazil, for a particular reference medicine the population has a greater diversity supply of generic medicines by the pharmaceutical laboratories than in the USA. This situation corroborates to free competition and cost reduction to the consumers.

Out of the commercially available oral suspensions in Brazil, 248 (74.2%) products among reference (9.3%), generic (35.9%), interchangeable similar (29%) medicines have a dissolution test (Figure 1) described for its drug in the respective oral suspension monograph (USP, 2018; Anvisa, 2019b), in the non-compendial literature (Table II) or in regulatory agency database (FDA, 2019b). None of the Anvisa registered oral suspension has the dissolution test described in British Pharmacopeia monographs (BP, 2017).

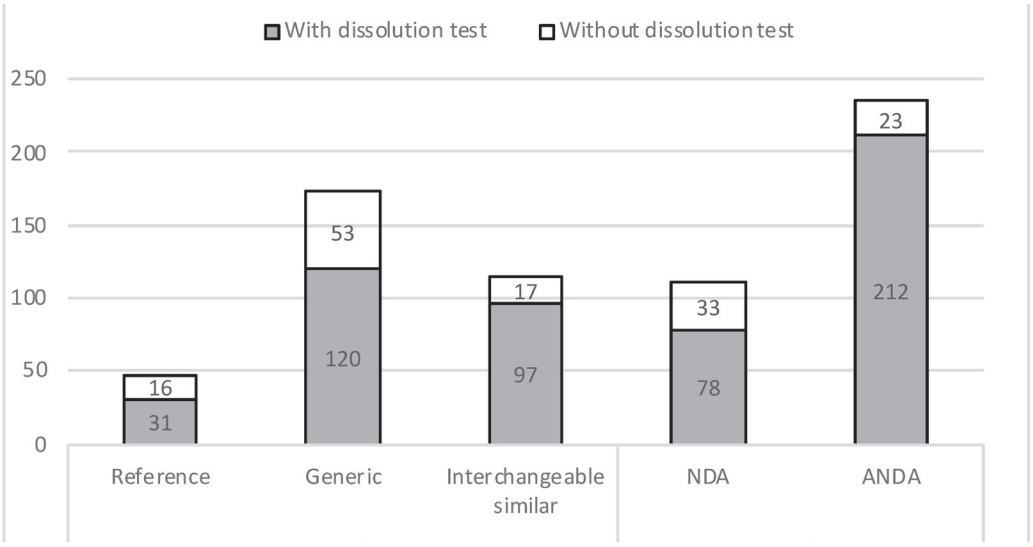

FIGURE 1 - Relationship between oral suspensions registered in Brazil and in the USA with or without a dissolution test described in FDA dissolution database, pharmacopeias and other literature.

In the USA, out of the oral suspensions registered, 290 (83.8%) between NDA (22.5%) and ANDA (61.3%) have dissolution tests described in pharmacopeial monographs (USP, 2018; BP, 2017; Anvisa, 2017), in non-compendial literature (Table II) or in FDA dissolution method database (FDA, 2019b).

Out of the 248 and 290 products that have dissolution test, only 28.2% (70 and 82) have such test in an official pharmacopeial monograph, corresponding to 20.9% and 23.7% of all oral suspensions marketed in Brazil and the USA, respectively.

Despite the increasing number of registered oral suspensions in Brazil (from 215 to 334) and in USA (from 219 to 346) since 2015, still only a few have the dissolution test described in a pharmacopeial monograph, whose methods have been developed and validated. In Brazil, it requires collaborative interlaboratory studies. Regarding the data described in the non-compendial literature (Table II), there is mention to the development and validation of the dissolution method only for the oral suspensions of benzoyl metronidazole, buclizine hydrochloride, diclofenac potassium, ibuprofen, nimesulide, spironolactone and rosuvastatin. For this latter, the authors only mentioned the validation.

FDA dissolution test data (Table V) must have been obtained from developed and validated methods since the regulatory agencies through their legislations and guidelines require so and, in its absence, the pharmaceutical industry must develop the dissolution study as a prior step of bioequivalence tests and present it to a regulatory agency when applying for registration (Anvisa, 2010a, FDA, 2017). The FDA's dissolution database for oral suspension refers to the USP monographs only to the phenytoin and megestrol acetate drugs (FDA, 2019b).

There are no records about dissolution test for oral suspension on Anvisa's website, however this regulatory agency, through its guidelines, establishes the use of the methods described in the Brazilian Pharmacopeia preferably, or in other official compendia such as USP and British Pharmacopeias (Anvisa, 2009), for quality control routine, pharmaceutical equivalence test and dissolution profile comparison with biowaiver purposes (Anvisa, 2010a; Anvisa, 2011).

In vitro dissolution test represents an important quality control tool for batches of a given product, and it is also a requirement to be fulfilled in the pharmaceutical equivalence tests. For quality, test conditions are described in pharmacopeial monographs (Limberg, Potthast, 2013; Friedel *et al.*, 2018). Moreover, dissolution testing is of high relevance in regulatory stability and biopharmaceutical studies. Since it is a means of predicting the *in vivo* behavior of the drug with respect to dissolution, it becomes a paramount tool to BCS-based biowaiver request (FDA, 2014, 2017; Friedel *et al.*, 2018).

From the foregoing, the scarcity of oral suspension monographs with dissolution test conditions impacts at least on the drug pharmaceutical development, quality control, stability, regulatory drug approval and postapproval process. Otherwise, the existence of official methods implies both in the credibility of the methods of analysis by the parties involved and in the savings of time and cost mainly by the applicant companies.

Biopharmaceutical dissolution studies

Dissolution studies for oral suspension in BCS-based biowaiver context

The BCS classification system is an objective, science-based approach with the purpose of identifying possible biowaivers to avoid unnecessary *in vivo* bioequivalence studies, replacing them by *in vitro* dissolution studies (Van Oudtshoorn *et al.,* 2018).

The BCS combines solubility, permeability and *in vitro* dissolution data, to predict the *in vivo* behavior of the drug (Amidon *et al*., 1995).

According to this system, the drug solubility is determined after the equilibrium between the solute and the medium. A drug is considered highly soluble, when its highest dose may dissolve up to 0.25L of medium at 37±1ºC in a pH range from 1 (FDA, 2017) or 1.2 (Anvisa, 2010a) to 6.8 that simulate physiological conditions (Amidon *et al*., 1995; Anvisa, 2010a; FDA, 2017). In Brazil, other pH ranges may be used with proper justification (Anvisa, 2010a).

The permeability can be obtained by experiments with cell cultures and intestinal perfusion studies in animals and humans. The dissolution studies for this case should also be done in biorelevant medium that simulate gastrointestinal conditions before and after meals and are essential for adequately predicting the *in vivo* behavior of the drug delivered by the medicines. With these results, the drugs can be classified into four classes: I, high solubility and high permeability; II, low solubility and high permeability; III, high solubility and low permeability and IV, low solubility and low permeability (Amidon *et al*., 1995; Klein, 2010).

Having established high solubility and high (class I) or low permeability (class III), the dissolution profiles of the test and reference products must demonstrate similarly rapid (85% release within 30 minutes) or very rapid (85% release within 15 minutes) dissolution in all three biorrelevant media to be elegible for a BCS-based biowaiver (Anvisa, 2010a; FDA, 2017; Van Oudtshoorn *et al.,* 2018).

Although BCS-based biowaivers are well established for solid oral dosage forms, it also may be applicable to other pharmaceutical dosage forms, if properly justified (FDA, 2017).

The BCS classification of the drugs in oral suspension dosage form with a dissolution test are in Table VI. In accordance with the literature data, most of these drugs belong unequivocally to BCS class II (26) or present a controversial BCS classification (25). Only five, eight and six drugs were unequivocally classified as BCS class I, III and IV, respectively.

TABLE VI – Biopharmaceutical classification (BCS) of the drugs available as oral suspension with a dissolution test described

BCS	Drug[(Reference)]	Reference [(DOI)]
I	Chlorpheniramine[20,43]	1 – Almukainzi *et al.,* 2015 (10.1208/s12249-014-0241-5)
	Hydrocodone[28]	2 – Alvarez *et al*., 2011 (10.1002/jps.22472)
	Oseltamivir[41,45]	3 – Bajaj *et al.,* 2012 (10.3109/03639045.2012.683440)
	Paroxetine hydrochloride[41]	4 – Bialer, Midha, 2010 (10.1111/j.1528-1167.2010.02573.x)
	Sildenafil citrate[20,41,43,47]	5 – Breda *et al.,* 2009 (10.1016/j.ijpharm.2008.12.026)

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TABLE VI – Biopharmaceutical classification (BCS) of the drugs available as oral suspension with a dissolution test described

BCS	Drug[(Reference)]	Reference [(DOI)]
II	Azithromycin[20,41,43] Bosentan[25,54] Carbamazepine[4,20,33,39,47,50,52,54] Carvedilol[41,43,47] Celecoxib[20,21] Clarithromycin[35,41] Clozapine[16,61] Darunavir ethanolate[12] Dasatinib[55] Deferasirox[18] Diclofenac potassium[11] Felbamate[4,20] Fosamprenavir calcium[8,54] Ibuprofen[2,20,33,38,43,46,47,50,52,14] Indomethacin[20,40] Loperamide HCl[56,59] Megestrol acetate[26,36] Meloxicam[8,9,41,43] Methylphenidate HCl[20] Mycophenolate mofetil[20,47,49] Nevirapine[20,33,51] Nimesulide[14] Phenytoin[33,38,43,50,52] Posaconazole[13,29] Rufinamide[4] Simvastatin[20,41,47,50]	6 – Campos *et al.,* 2007 (10.1055/s-0031-1296624) 7 – Charoo *et al.*, 2014 (10.1002/jps.2418) 8 – Chilukuri *et al.,* 2014(10.1093/chromsci/bmt110) 9 – Cho *et al.,* 2012 (10.1007/s40005-012-0020-9) 10 – Choonara *et al.*, 2014 (10.1208/s12249-014-0271-z) 11 – Chuasuwan *et al.*, 2009 (10.1002/jps.21525) 12 – Corrêa *et al.,* 2014 (10.1080/10408347.2013.826573) 13 – Cristofoletti *et al.,* 2016 (10.1016/j.xphs.2015.11.033) 14 – da Fonseca *et al.*, 2009 (10.1208/s12249-009-9320-4) 15 – da Silva *et al.*, 2015 (10.1208/s12249-015-0407-9) 16 – Dias *et al.*, 2014 (10.1007/s10973-014-4142-3) 17 – Douroumis, Fahr, 2007 (10.1016/j.colsurfb.2007.05.009) 18 – Durdunji *et al.*,2016 (10.1016/j.ejpb.2016.02.006) 19 – Fairstein *et al.,* 2013 (10.1208/s12248-013-9462-x) 20 – FDA, NICHD (bpca.nichd.nih.gov/collaborativeefforts/initiatives/documents/formulations_platform_report1.pdf) 21 – Fong *et al.,* 2015 (10.1016/j.ijpharm.2015.10.029) 22 – Fujioka *et al.*, 2007 (10.1016/j.jconrel.2007.03.002) 23 – Fujioka *et al.*, 2008 (10.1016/j.ijpharm.2007.10.008) 24 – Ghadi, Dand, 2017 (10.1016/j.jconrel.2017.01.014) 25 – Ghasemian *et al.,* 2016 (10.15171/apb.2016.029) 26 – Guk *et al.*, 2017 (10.1111/bcpt.12677) 27 – Helmy, Bedaiwy, 2016 (10.14227/DT230316P32) 28 – Hemmingsen *et. al.,* 2011 (10.3390/pharmaceutics3010073) 29 – Hens *et al.,* 2016 (10.1002/jps.24690) 30 – Israr *et al.,* 2014(10.1590/S1984-82502014000400030) 31 – Jha *et al.,* 2014 (10.1155/2014/452051)
III	Ampicillin[49] Cefadroxil[20] Cefprozil[20] Clavulanate potassium[20,54] Codeine[20,33,38,43,47] Esomeprazole magnesium[20,54] Pantoprazole sodium[6,20,54] Rosuvastatin[20,54]	32 – Kalvakuntla *et al.,* 2016 (10.15171/apb.2016.013) 33 – Kasim *et al.,* 2004 (10.1021/mp034006h) 34 – Khan *et al.,* 2010 (10.1208/s12249-010-9505-x) 35 – Kristin *et al.,* 2017 (10.1016/j.ejps.2017.02.003) 36 – Li *et al.,* 2015 (10.1007/s12272-015-0604-9) 37 – Liew *et al.,* 2014 (10.3109/03639045.2013.798805) 38 – Lindenberg *et al.*, 2004 (10.1016/j.ejpb.2004.03.001) 39 – Mishra *et al.*, 2010 (10.1691/ph.2010.9231)
IV	Acetazolamide[20,24,33,38] Aprepitant[24,32] Azathioprine[20,24,33,38,50] Benzoyl metronidazole[15,50] Cefdinir[20,41,53,54] Cefixime[20,47]	40 – Nokhodchi *et al.,* 2005 (sites.ualberta.ca/~csps/JPPS8(1)/ A.Nokhodchi/indomethacin.pdf) 41 – Ono *et al.,* 2016 (10.5599/admet.4.4.338) 42 – Pál *et al.,* 2013 (10.1016/j.ejps.2013.03.006) 43 – Papich, Martinez, 2015(10.1208/s12248-015-9743-7) 44 – Petrusevska *et al.,* 2015 (10.1002/jps.24350) 45 – Ploger *et al.,* 2018 (10.1016/j.xphs.2018.01.025)

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TABLE VI – Biopharmaceutical classification (BCS) of the drugs available as oral suspension with a dissolution test described

BCS	Drug[Reference]	Reference [DOI]
Two or more	Acyclovir: III[20,33,38,39,50], IV[20,41] Albendazole: II[33,38,50,52,57], IV[38] Allopurinol: I[20,54], II[41], III[20,38,54], IV[33,50] Amoxicillin: III[33,43,52], IV[47,50,52] Cefpodoxime proxetil: II[34,] IV[3] Cefuroxime axetil: II[30], IV[20,47,54] Cephalexin: III[37,52], IV[20,43,52] Ciprofloxacin: II[38], III[20,33,50,52],IV[5,38,43] Doxycycline: I[38,43], III[52], IV[33,43,50,52] Famotidine: III[20,41,31], IV[24,47] Fexofenadine HCl: I[20,41] III[9,20] Fluconazole: I[20,38], II[41], III[20,27,33,47,50] Griseofulvin: II[20,22,23,33,38,39,54], IV[20,33,54] Levetiracetam: I[43,44], III[20,47] Linezolid: I[27,43], IV[20,43,54] Mercaptopurine: II[58,60], IV[20] Montelukast sodium: I[20,41,54], II[1] Nitrofurantoin: II[38], IV[33,52] Nystatin: III[20,33,38], IV[38,42] Oxcarbazepine: II[4,17], IV[20,47] Pseudoephedrine HCl: I[41] IV[41] Pyrazinamide: I[38,20], III[33,20,47] Spironolactone: II[33,38,48], IV[38] Sulfamethoxazole: II[10,20,38], IV[20,33,50,52] Trimethoprim: II[38], IV[20,33,50,52]	46 – Potthast *et al*., 2005 (10.1002/jps.20444) 47 – Ramirez *et al.,* 2010 (10.1111/j.1365-2125.2010.03757.x) 48 – Resende *et al.,* 2016 (10.1590/s1984-82502016000400005) 49 – Rumondor *et al.,* 2016 (10.1016/j.xphs.2015.11.004) 50 – Santos *et al.,* 2014 (10.1590/S1984-82502011000100002) 51 – Sarkar *et al*., 2008 (10.4103/0250-474X.45401) 52 – Shawahna, 2016 (10.1208/s12248-016-9885-2) 53 – Thota *et al*., 2014 (IJPSN-3-20-14-KISHAN) 54 – Tiwari *et al.,* 2014 (10.7897/2277-4572.035187) 55 – Vaidhyanathan *et al*., 2019(10.1016/j.xphs.2018.11.005) 56 – Venkateswarlu *et al.,* 2016 (10.15171/apb.2016.050) 57 – Vidal *et al.,* 2014 (10.14227/DT210214P42) 58 – Wang *et al*., 2015 (10.1016/j.bmcl.2015.01.022) 59 – Widjojokusumo *et al.,* 2013 (10.1007/s11814-013-0115-7) 60 – Yang *et al*., 2016 (10.1248/cpb.c15-00949) 61 – Zeng *et al.,* 2013 (10.1208/s12249-013-9973-x)

Drugs not found: Buclizine, Carbinoxamine maleate, Ceftibuten, Clobazam, Dextromethorphan polistirex, Eltrombopag olamine, Erythromycin ethylsuccinate, Nitazoxanide, Nitisinone, Omeprazole magnesium, Perampanel, Roxithromycin, Sulfisoxazole acetyl. Sucralfate is locally acting drug.

Whereas biowaivers for oral suspension may be accepted in Brazil, and it could be considered in the USA according to the product-specific recommendation of the FDA (Van Oudtshoorn *et al.,* 2018), which means that only five and 16 of these drugs can be candidates for BCS-based biowaiver in Brazil and the USA, respectively. According to current legislation, BCS class I drugs are accepted for biowaiver in both countries, while BCS class III drugs only in the USA (Anvisa, 2011; FDA, 2017).

It is interesting to note that among the drugs cataloged on the International Federation of Pharmacists (FIP) list of candidates for BCS-based biowaiver, 39 are comercially available as oral suspension dosage form (FIP, 2018). Out of them, for omeprazole and erythromycin, no data of BCS classification was found in the literature. The major drugs are designated by FIP or in literature as BCS class II (amiodarone hydrochloride, azithromycin, carbamazepine, clarithromycin, clozapine, darunavir, dasatinib, ibuprofen, lamotrigine, loperamide, loratadine, nevirapine, rifampicin, simvastatin, tacrolimus), followed by BCS class IV (acetazolamide, azathioprine, cefixime, oxamniquine), BCS class I (methadone hydrochloride, oseltamivir) and BCS class III (acetaminophen). Moreover, the FIP monograph classification for ciprofloxacin is BCS class IV, fluconazole and levetiracetam as BCS class I and pyrazinamide as BCS class III; according to literature data (Table VI) ciprofloxacin and fluconazole are also designated as BCS class II and class III, levetiracetam as BCS class III and pyrazinamide as BCS class I.

Acyclovir and amoxicillin with clavulanic acid were classified in FIP monographs according to the strength of the dosage form in two (III and IV) and three (I, II and IV) BCS classes, respectively, which cover the literature data (Table VI). For the remaining drugs of the FIP list candidates for BCS-based biowaiver that are commercially available as oral suspension, there is controverse regarding BCS classification in the literature for allopurinol (class I, II, III and IV), linezolid (class I and IV), griseofulvin, mercaptopurine, nitrofurantoin, spironolactone, sulfamethoxazole and trimethropim (class II and IV).

Most of the commercially available oral suspensions contain drugs that present low aqueous solubilty and high (BCS class II) or low (BCS class IV) permeability. These data are consistent with the charactheristics of this pharmaceutical dosage form that is a dispersal system developed to vehicula stable sparingly water-soluble drugs (Allen *et al.*, 2012; Brown *et al.,* 2011). Low solubility drugs require a careful evaluation of the conditions of the dissolution test, with respect to maintenance of the *sink* conditions.

Conditions of non-saturation for oral suspensions

The *in vitro* dissolution should occur in conditions of non-saturation (*sink*), one in which the concentration of drug in solution is three to ten times the non-saturation concentration, and also corresponds to what happens *in vivo* (Rohrs, 2001).

However, for low solubility BCS class II and class IV drugs, for which dissolution is a limiting step in the absorption (Mishra *et al*., 2010), it becomes difficult to maintain *sink* conditions in aqueous media using *in vitro* models© proposition, which is a barrier in a dissolution test development. Due to the low solubility of the drug and the need not to saturate the dissolution medium, the use of surfactant (for instance, sodium lauryl sulfate) or enzyme is generally recommended for the pharmacopoeic dissolution tests employed in routine of quality control. However, it is noteworthy that the use of these additives is not recommended in biopharmaceutical studies aimed at classifying the drug according to the BCS or as a step prior to the registration of new drugs (generic or similar) compared to the reference. Besides the surfactant and enzyme addition, other ways to promote the increase of the drug solubility are the use of larger solvent volume, co-solvents, flow cell apparatus and dissolution test developed in biphasic systems (Phillips *et al*., 2012). Data of the *sink* conditions presented in Table VII were calculated according to equation 1 from pharmacological dose, dissolution and drug solubility data described in literature.

$$\frac{D}{S} = \text{dose (mg)} \Big/ \text{solubility } \left(\frac{\text{mg}}{\text{mL}}\right) \qquad \text{(Equation 1)}$$

TABLE VII – Dissolution test data for oral suspensions according pharmacopeias and non-compendial literature and the media volume calculated to achieve the *sink* conditions

Drug	Dissolution media	Drug solubility $mg.mL^{-1}$ (Ref.; DOI)	Oral suspension drug concentration ($mg.mL^{-1}$)	Drug concentration in 0.9L dissolution media ($mg.mL^{-1}$)	Pharmacological maximum single dose (mg)	Minimum mL for *sink* condition
Acetazolamide	0.01M hydrochloric acid	1.23 (Granero et al., 2008; 10.1002/jps.21282)	25	0.28	250	610[a]
Albendazole	0.1M hydrochloric acid	0.900 (Vidal et al., 2013; *)	40	0.22	400	667[b]
Azathioprine	water	0.130 (Newton et al.., 1982; doi. org/ 10.1016/0378-5173(82)90039-4)	10; 50[b]	0.011; 0.055	150	1,153[b]

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TABLE VII – Dissolution test data for oral suspensions according pharmacopeias and non-compendial literature and the media volume calculated to achieve the *sink* conditions

Drug	Dissolution media	Drug solubility mg.mL^{-1} (Ref.; DOI)	Oral suspension drug concentration (mg.mL^{-1})	Drug concentration in 0.9L dissolution media (mg.mL^{-1})	Pharmacological maximum single dose (mg)	Minimum mL for *sink* condition
Benzoyl metronidazole	pH1.2 simulated gastric fluid without enzymes	0.66 (da SILVA et al., 2016;*)	40	0.22	200	909[a]
Buclizine hydrochloride	water with 1.5% sodium lauryl sulfate	0.0825 (Kuminek et al., 2012; 10.1590/S0100-40422012000100036)	1	0.005	25	909[a]
Carvedilol	pH 1.2 buffer pH 6.8 buffer	0.832 0.0315 (Hamed et al., 2015; 10.1208/s12249-015-0365-2)	25	0.028	80	289[a] 7,619[a]
Cefadroxil	water	1.11(Drugbank;**)	50; 100	0.28; 0.56	1000	2,702[a]
Cefdinir	0.05M phosphate buffer pH6.8	0.48(Thota et al., 2014; IJPSN-3-20-14-KISHAN)	25; 50	0.14; 0.28	600	3,750[a]
Cephalexin	water	1.789(Drugbank, 2019;**)	25; 50	0.14; 0.28	1000	419[b]
Clarithromycin	pH 5 acetate buffer pH 6.8 phosphate buffer	14.42 0.57 (Morakul et al., 2014; 10.1016/ j.ejpb.2014.08.013)	25; 50	0.14; 0.28	500	104[a] 2,631[a]
Diclofenac potassium	water with 0.3% sodium lauryl sulfate	0.197 (Rubim et al.,2014;*)	1.8	0.011	50	761[a]
Felbamate	water	0.742 (Drugbank, 2006;**)	120	0.67	600	2,426[a]
Fluconazole	water	7.5 (Charoo et al.,2014; 10.1002/jps .24181)	10; 40	0.22[b]	800	320[a]
Ibuprofen	pH 7.2 phosphate buffer pH 6.8 phosphate buffer pH 4.5 phosphate buffer 0.1M hydrochloric acid	5.86 5.57 5.1 2.18(Rivera-Leyva et al., 2012;*)	20; 50; 100; 300 20 20 20	0.11; 0.28; 0.56; 1.67 0.89 0.89 0.89	800	768[b] 431[a] 470[a] 1,100[a]
Indomethacin	pH 7.2 phosphate buffer	0.7675 (Nokhodchi et al.,2005; (sites.ualberta.ca/~csps/JPPS8(1)/A. Nokhodchi/indomethacin.pdf)	5	0.11[a]	100	391[a]
Nevirapine	0.1M hydrochloric acid	4.32 (Sarkar et al., 2008; 10.4103/ 0250-474X.45401)	10	0.056	200	139[b]
Nimesulide	pH 6.8 simulated enteric fluid+ 1% polysorbate 80	0.1477 (da Fonseca et al, 2009;*)	10; 50	0.22	200	4,062[a]

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TABLE VII – Dissolution test data for oral suspensions according pharmacopeias and non-compendial literature and the media volume calculated to achieve the *sink* conditions

Drug	Dissolution media	Drug solubility $mg.mL^{-1}$ (Ref.; DOI)	Oral suspension drug concentration ($mg.mL^{-1}$)	Drug concentration in 0.9L dissolution media ($mg.mL^{-1}$)	Pharmacological maximum single dose (mg)	Minimum mL for *sink* condition
Pyrazinamide	water	20.3 (Becker et al., 2008; 10.1002/jps.21250)	10; 100	0.11	500	73.89[a]
Roxithromycin	pH 4.5 acetate buffer pH 6.8 phosphate buffer	0.00037 $74.8x10^{-6}$ (Liebenberg, 2011;***)	10	0.055	300	405,405[b] 2,005,347[b]

a: calculated from pharmacological maximum single dose, b: calculated from (greater, if more than one) drug mass indicated in dissolution test. *See Table II for DOI. **www.drugbank.ca. Allopurinol, buclizine, cefuroxime axetil, celecoxib, ciprofloxacin, dasatinib, doxycycline, esomeprazole, megestrol acetate, meloxicam, mercatopurine, montelukast sodium, mycophenolate mofetil, nitazoxanide, oxcarbazepine, phenytoin, rosuvastatin and spironolactone solubility's data were not found, thus their *sink* condition could not be calculated. ***https://patents.google.com/patent/WO2011128869A1/em

Regarding the pharmacological maximum single dose, as recommended in biopharmaceutical studies, of the drugs listed in Table VII, dissolution test media volume did not fulfill the condition of non-saturation in nine cases. Azathioprine, cefadroxil and felbamate in water; carvedilol, clarithromycin and cefdinir in pH 6.8 buffer; ibuprofen in 0.1M hydrochloric acid; indomethacin in pH 7.2 phosphate buffer; nimesulide in pH 6.8 simulated enteric fluid added of 1% polysorbate 80; and roxithromycin in pH 4.5 acetate and pH 6.8 phosphate buffers. For these drugs, a much greater dissolution medium volume was required than that supported in the dissolution vessel, whose maximum volume is usually 1L (Anvisa, 2019a; USP, 2018; Pharmacopeial, 2019).

However, it is possible that the *sink* condition had been reached in some of these cases, since the volume of medium needed to guarantee the *sink* condition was based on the biopharmaceutical criterion of the pharmacological maximum single dose, which was usually superior to that used in the studies. In other words, some studies employed lower doses than the pharmacological maximum single dose.

The dissolution of the benzoylmetronidazole and buclizine hydrochloride in the respective media is limitrofe. The acetazolamide, albendazole and pyrazinamide in 0.01M hydrochloric acid; nevirapine in 1M hydrochloric acid; cephalexin and fluconazole in water; diclofenac potassium in water with 0.3% sodium lauryl sulfate; carvedilol in pH 1.2 buffer; clarithromycin in pH 5 acetate buffer; ibuprofen and indomethacin in phosphate buffers require a small dissolution media amount to achieve the non-saturation condition. In these cases, the concentration of drug in solution can be three times the non-saturation concentration as shown in Table VII.

The vast majority of oral suspension drugs with dissolution test have differences in their solubility data between pharmacopeias, other official compendia and scientific literature or absence of complete information, presenting difficulties to recommend the non-saturation conditions.

The low solubility in aqueous media justifies the BCS class II and IV drugs to be manufactured as oral suspension instead of solution pharmaceutical dosage form. However, a production of oral suspension from high solubility BCS class I (chlorpheniramine, hydrocodone, oseltamivir, paroxetine hydrochloride, sildenafil citrate) and class III (ampicillin, cefadroxil, cefprozil, clavulanate potassium, codeine, esomeprazole magnesium, pantoprazole sodium, rosuvastatin) drugs would not be justified a priori. This situation requires

further clarification, as there can be a misunderstanding about the concept of oral suspensions.

Indeed, it is necessary to produce advances in the dissolution test development for oral suspension in order to contribute to biopharmaceutical studies to comply with regulatory requirements.

CONCLUSION

In this scenario, the issues about the evaluation of requests for registration of new medicines by regulatory agencies and the establishment of the tests and their parameters to be performed by the manufacturers in order to obtain the oral suspension registration should be considered. Based on the literature, the establishment of the dissolution profile conditions is essential to support the oral suspension registration by the regulatory agencies due to the test relevance in the oral suspensions' *in vivo* performance prediction. It is important that the solubility and permeability of the drug are clearly defined according to the BCS to understand its dissolution characteristic and to determine the exact drug non-saturation condition for the test. In the case of high solubility drugs, further studies are necessary in order to understand the factors that culminate in oral suspension formulation. Finally, developing oral suspension dissolution tests is still a challenge to researchers, since, besides all already mentioned, it depends on the excipient information in monographs, in official textbooks and literature, many variables still need to be set so that the test is actually indicative of the *in vivo* behavior of the carried drugs under the pharmaceutical oral suspension form.

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