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Original scientific paper

Non-compendial *vs* compendial analytical tests - a powerful tool for predicting *in vitro* similarity of highly viscous oral suspension

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Abstract

In vitro dissolution profiles are increasingly used to evaluate drug release characteristics of pharmaceutical products. The dissolution methods is expected to be an appropriate tool for checking consistency of the pharmaceutical attributes by discriminating similarities and dissimilarities between different drug formulations. Expansion in development of novel "special" dosage forms, due to the manner in which these dosage forms release the active pharmaceutical ingredient, usually requires applying non-compendial dissolution strategy that differs from the traditional compendial recommendations.

For demonstrating sameness in the dissolution profile, *in vitro* drug release comparison between test and reference product of highly viscous oral suspension by applying non-compendial peak vessel against conventional hemispheric vessel was demonstrated in this study.

All reference batches exhibited high variability in dissolution data when using hemispheric vessel due to forming mound compact mass at the bottom of the vessel. Different strategies for samples manipulation, before and during dissolution period, were performed in order to eliminate additional variabilities. Modifications of conventional USP 2 apparatus such as using peak vessel provided with more reproducible and reliable result for distinguishing *in vitro* similarities between different formulations of oral suspensions.

Misinterpretation of dissolution data can lead to negative impact on product development. Taking time to observe and evaluate what is happening to the product in the vessel during dissolution is of curtail consideration for proper selection of the dissolution strategy.

Keywords: oral suspensions; in-vitro release; hydrodynamic variability; USP apparatus 2/ Paddle apparatus; peak vessel

Introduction

Pharmaceutical oral suspensions are liquid preparations consisting of solid particles, usually medicinal agent, dispersed through liquid phase in which the particles are not soluble (Brown et al., 2011). The external phase is an aqueous, organic, or oily lipid phase in which the insoluble internal phase is uniformly dispersed (Brown et al., 2011).

Depending of the route of administration, oral administration remains the preferred route with the

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highest degree of patient compliance and is the most user-friendly form of drug delivery with majority of 84% of the most-sold pharmaceutical products in the European market and US (Fotaki and Vertzoni, 2010). After oral administration of the product, the extent of desired pharmacological effect depends of the amount of absorption of the active pharmaceutical ingredient (API) in gastrointestinal tract (GIT). Determination of the dissolution rate of drug product which is prerequisite for bioequivalence since the drug must dissolve before it can be absorbed is of special analytical challenge.

Dissolution test plays essential part in the product development and could be adopted as the surrogate basis for the decision as to whether two pharmaceutical products are same in terms of bioequivalence. *In vitro* drug release is used to assure product sameness by profile comparison between two products or pre-change and post change products using appropriate *in vitro* test. Also, a specific value of *in vitro* dissolution is recognized in the application of batch-to-batch quality control tests reflecting the levels of change in composition, site of manufacturing, scale of manufacturing and process and equipment changes providing better product understanding (Siewert et al, 2003).

As modern pharmaceutical development gains in recent years, complex formulation became more and more prevalent in the pharmaceutical industry. Due to its "special" design formulation which in turns lead to different physicochemical and release behavior, different apparatus, procedures and technics for *in vitro* determination are employed on case by case basis. Recent paper reviews classified high viscosity suspension as "special dosage form". As a result of high quantity of viscosity and sedimentation building agents in the matrix, several steps should be considered while performing drug release study of highly viscose suspension for oral use (Brown et al., 2011). In order to prevent variability in the dissolution data: homogeneity of samples by applying proper sample preparation (mixing acceleration, frequency, time, course of shaking); employing procedure for sample introduction; treatment of samples (filtration and filter compatibility and stability of samples in appropriate media), selecting of proper dissolution conditions (apparatus, agitation rates).

According to the Food and Drug Administration (FDA) Dissolution Database, USP apparatus 2 is the most common apparatus for determination of the rate of drug release from oral dosage forms. It is recommended for approximately 70% of the dissolution methods and it's considered as apparatus of first choice for predicting *in vitro* similarity for oral suspensions (Shohin et al., 2016). Lower agitation rates of 25-50 rpm are usually recommended for this dosage form (Siewert et al., 2003). In some cases, when high viscosity persists, in order to prevent sedimentation and accumulation at the bottom of the vessel, higher rates may be applied. However, not in all cases apparatus 2 is the best apparatus to use for testing suspension (Parker and Gray, 2006). Recent findings refer to its high variability when producing dissolution data which simultaneously leads to misinterpretation and possible wrong outcomes (Quershi and Shabnam, 2001). Investigations have indicated on existing of "dead zone" at the bottom of the vessel underneath the dissolution paddle due to very low mixing hydrodynamics (Liu and Vivilecchia, 2005). Additionally, this leads to "cone formation", effect which mainly confined to dosage forms that are formulated with high amount of insoluble excipients that form compact mass in which the active ingredient is trapped and leads to non-reproducible results. For eliminating these variabilities, usually operating with higher rotation of the paddle, displacing of the formation can be achieved but, in that case, the discriminatory power of the method will be compromised.

Literature surveys reveal several approaches for bridging the USP 2 variability by changing the geometry of the vessel thus changing the hydrodynamics in the environment referring to solid dosages forms only (Collins and Nair, 1998, Legace et al., 2004; Liu and Vivilecchia, 2005; Quershi, 2006). Far from our knowledge, until now there are no published studies for using non-compendial peak vessel in evaluating dissolution drug release from oral suspension as dosage forms.

Therefore, the aim of this study is to challenge the dissolution behavior of different formulation of highly viscose suspension by modifying the general recommended dissolution conditions and use non-compendial approach for performing the dissolution test. The analysis focus on the impact of sample preparation and sample introduction technique as well as the effect of the vessel geometry (peak vessel) in providing more sensitive thus more accurate and reproducible results.

Material and methods

Samples used for in vitro study

Laboratory test batches (test product) for orally administered suspension with API BCS **(**Biopharmaceutical Classification System**)** class II were manufactured in the Research and Development department in Alkaloid AD, Skopje, North Macedonia. All together twenty formulations were made and coded randomly from A1 to A20, but only two were selected (Table 1), as they resulted in forming satisfactory suspensions and showing relevant results.

Commercially available batches (reference products) of the same dosage form and dosage strength were purchased from two different markets, German and Ireland. The samples were checked for their expiry dates before purchasing. The suspensions were randomly coded as listed in Table 1.

Table 1. List of samples used for in vitro dissolution study

Batch code	Viscosity (cP)	Exp. date	Country of origin	Status
A-16	~ 800	NA	Macedonia	Test product
A-18	~ 1300	NA	Macedonia	Test product
B-IR	~ 1400	04.2017	Ireland	Reference product
C-IR	~ 1400	05.2017	Ireland	Reference product
B-DE	~ 1400	10.2018	Germany	Reference product

All used materials were of analytical grade, Saccharum album/sucrose/ (Studen-Agrana, Bosnia and Hercegovina), Kolliphor SLS Fine/Sodium lauryl sulphate/(SLS) (BASF, Germany), Aqua purificata (System for production of Purified Water WERNER, Alkaloid).

Aliquot of 5 mL suspension containing 200 mg of API, which reflects typical dose of the product, were transferred in the dissolution media. For applying the suspension in the dissolution vessel, 5 mL dose syringe, 10 mL plastic syringe and 10 mL plastic syringe attached with cannula (Bent Cannula W/LUER 4.75 in form Agilent) were used. Sample introduction was performed by applying the samples above and in the dissolution media, on non-rotating paddle and during rotation of the paddles. Due to the high viscosity of the samples, transfer of the aliquots was performed by weighing. The syringes were weighed before and after adding the product and the weight difference was related to product density.

All suspension containers prior withdrawing of the appropriate dose of suspension and transferring in the dissolution vessel were vigorously mixed for 5 minutes. Quantitation of assay content, for evaluating homogeneity of the withdrawn aliquot, was performed on high performance liquid chromatography (HPLC).

API solubility

The solubility of API was determined in four different solvents, such as: phosphate buffer (pH 6.8 and pH 7.2), acetate buffer (pH 4.5) and hydrochloric acid buffer (pH 1.2). An amount of API equivalent to the highest individual dose that can be administered was added in 250 mL of each medium. After stirring for 1 hours, drug solubility in each medium was determined.

Dissolution conditions

Dissolution of the test and reference products was carried out on Agilent 708- DS standard compendial configuration. 1000 mL round bottom (hemispheric) vessels and non-compendial 1000 mL peak vessels (protruded bottom) from Agilent were used.

Dissolution media 900 mL pH 1.2 (hydrochloric acid), pH 4.5 (acetate buffer), pH 6.8 (phosphate buffer) and pH 7.2 (phosphate buffer) were prepared as described in the European Pharmacopoeia (Ph Eur., 5.17.1). All dissolution media were degassed prior introducing in the apparatus and used at a temperature of 37±0.5 °C.

A minimum of 6 vessels were sampled for each analysis. 5 mL aliquots of suspension containing 200 mg of API were introduced in each vessel.

Paddle speed conditions at 50, 60, 65, 75, 85, 100 rpm were evaluated for choosing the best agitation rate. Samples were taken at predetermined intervals of 5, 10, 15, 20, 30, 45 and 60 minutes. Aliquots of 10 mL were withdrawn at each time point through bent cannula with stopper at which end 35-micron ultra-high molecular weight polyethylene (UHMW PE) full flow filters were placed to ensure that no large undissolved particles are withdrawn. Due to the high quantity of viscosity building agents in the suspension matrix which could result with clogging the system while quantitation, samples were again filtered through 0.20 μm regenerated cellulose (RC) membrane syringe filters.

All filters were purchased from Agilent Technologies (USA).

Sample solution in concentration of 0.2222 mg/mL in pH 4.5 and pH 1.2 were evaluated in time interval of 7 h after the end of the dissolution period due to instability, while samples prepared in pH 7.2 and 6.8 were more stable and evaluation was performed in time interval of 48 h.

Reagents

Analytical grade methanol (CH_3OH), sodium hydroxide (NaOH), hydrochloric acid (HCl), 85% o-phosphoric acid (H_3PO_4), sodium acetate (CH_3COONa), sodium chloride (NaCl), glacial acid (CH_3COOH) and potassium dihydrogen phosphate (KH_2PO_4), acetonitrile (CH_3OH) were purchased from Merck (Darmstadt, Germany).

Water was purified by a Werner water purification system, obtained in-house at Alkaloid AD Skopje, Skopje, R. North Macedonia.

Quantitation methodology

Quantitation of collected samples was performed on Agilent Technologies 1290 Infinity Liquid Chromatographic System (Agilent Technologies, USA) equipped with a Quaternary Pump VL, a column compartment, auto sampler and photo-diode array detector. Instrument control, data acquisition and processing were done by using OpenLab Chemstation chromatography software (version A.02.02/1.3.4). The separation was performed on Zorbax XDB C18 (Agilent Technologies, USA), 150 x 3.0 mm, 5 μm using solution of o-H_3PO_4 and CH_3OH as a mobile phase in ratio 30:70 (*v/v*). The column temperature was 35 ºC. Flow rate was 1.5 mL/min. Injection volume was 5 μL. UV detection was performed at 221 nm.

Results and discussion

Choosing the right media and dissolution conditions, for providing relevant results, depends on the required release characteristics of the intended product, solubility and stability of the analyte in the test medium (Brown et al. 2004). Pharmacokinetic properties of the API indicate small intestines as site of absorption of the drug where pH of the environment exhibits pH 6.5-7.5. From the results presented in Table 2 it can be concluded that API is highly soluble in pH 7.2 and pH 6.8 thus showing sink conditions when 5 mL individual dose of the oral suspension (equivalent to 200 mg of API) is applied in 900 mL of these buffer media. This is not the case in pH 4.5 and pH 1.2 were solubility is respectively decreasing, which is to be expected since the API is week acid with pKa value around 4, those showing no satisfactory sink conditions. The stability of sample solution prepared in concentration of 0.22 mg/mL, indicated buffer pH 7.2 as most appropriate media with satisfactory data for more than 2 days stability. Taking into consideration all above elaborated, media pH 7.2 was chosen as most appropriate medium for initial screening of the dissolution behavior of the suspension for establishing *in vitro* release strategy.

Table 2. API solubility in four different buffer media

Medium	Solubility (mg/mL)
Buffer pH 1.2	0.029
Buffer pH 4.5	0.086
Buffer pH 6.8	2.60
Buffer pH 7.2	4.35

Sample introduction

Vigorously mixing the suspension container for 5 min before withdrawing samples, assured accurate and reproducible quantity of API between 98% and 101% assay with every 5 mL withdrawn aliquots of suspension.

Starting dissolution conditions were set as per recommendations for oral suspension with agitation of 50 rpm (Siewert et al., 2003), in hemispheric vessel, with media replacement during sampling intervals and by applying the suspension samples on non-rotating paddles. Initially the dissolution study was performed by evaluating the dissolution behavior of the reference product. Applying the suspension above the media provided with unsatisfactory data which were visually apparent even with higher agitation of 75 rpm (Table 3). This could be result of the media surface tension which enables the suspension sample to fall down in the vessel and let it partially float on the top of the media (Fig. 1a). When pulling down the shaft of the dissolution apparatus, these floating particles would adhere on the paddles and therefore poor mixing of the suspension occurred (Fig. 1b, Table 3). By transferring the suspension in the media at the side or at the bottom of the vessel, no floating or sticking remains were evident. Nevertheless, lower dissolution rate for 60 minutes (below 85%) were observed when using 5 mL dose syringe for sample introduction, at stirring speed of 75 rpm. Improvements of the released rate in period of 45 minutes (above 90%) were observed when using 10 mL plastic syringe as transferring device.

However, variability in the results persists to occur as evident by the high values of relative standard deviation (RSD). In addition to this, when visually observed, the reference product tends to form compact mound mass at the bottom of the vessel, with no consistent behavior during the dissolution period (Fig. 2).

In one set of six individual portion of reference suspension, some would remain adhered to the vessel bottom while other tend to show displacement more rapidly which correlates directly with the dissolution results (lower and higher released % respectively).

As suggested for some viscous suspension (Brown et al., 2011) although not typical for this dosage forms, higher agitation speeds of 100 rpm were applied in order to prevent accumulation of the suspension. The use of higher agitation speed had no positive impact in decreasing the variability of the dissolution data (Table 3).

Further investigation required modification of the compendial conditions, by applying the suspension in the apparatus 2 while paddles were rotating, in attempt to prevent sticking of the suspension at the bottom of the vessel. It was assumed that this occurrence happens due to non-existing hydrodynamic motion in the media prior starting the dissolution paddles, which allows the high viscosity and suspending agents to settle and adhere to the bottom. Application of the suspension on rotating paddles required prolonged duration of dissolution test as a compensation of the time needed to administer six portions of suspension individually, in order to retain correct sampling intervals. Additionally, to prevent

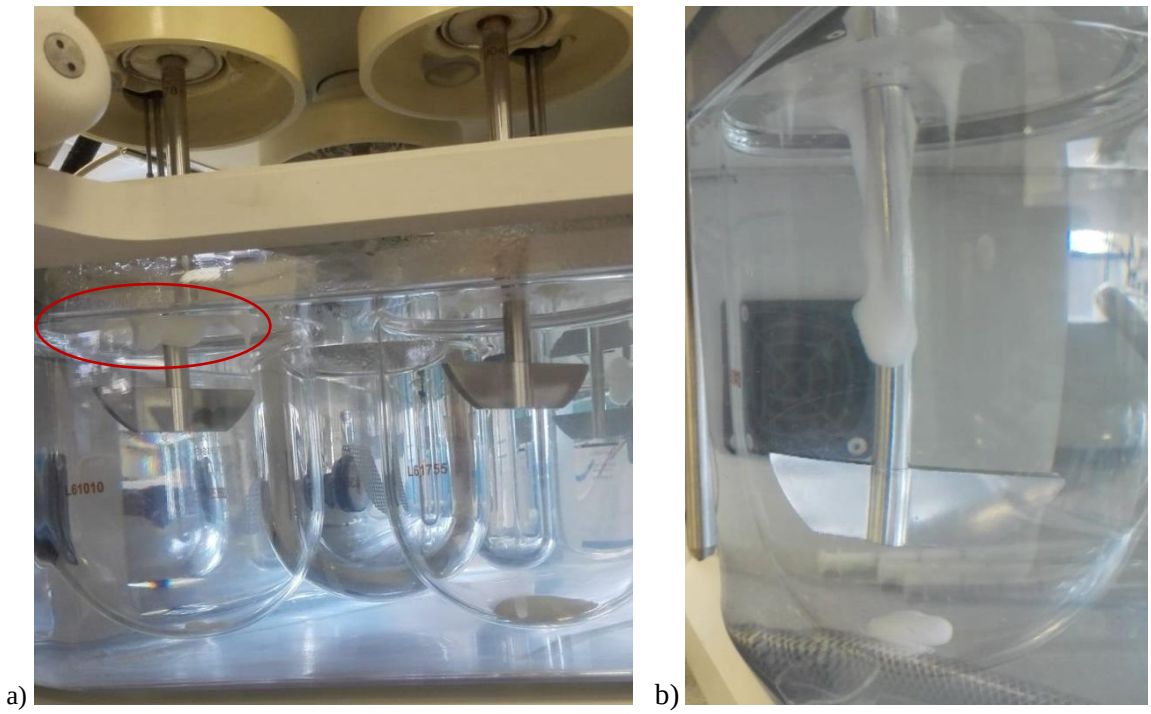


Fig. 1. Dissolution behavior of reference suspension when applied above the medium - particles of suspension floating on the surface of the medium (a), suspension adhering on the paddle (b).

disturbance of the hydrodynamic, the withdrawn volumes during sampling period were not replaced with fresh dissolution media as the sink conditions in pH 7.2 remain preserved (Table 4).

No significant difference was observed with 75 rpm agitation speed as for the compact mass persists to occur in the vessels. Significant difference with acceptable variability was detected only on very high mixing speed of 100 rpm when applying the suspension with 10ml plastic syringe attached to cannula during rotation of the paddles. There was more than twofold increase of the dissolution rate providing sharper profile than 75 rpm (Table 4, Fig. 4a & 4b). The compact mass was quickly displaced which reflected with approximately 100% drug released evident at the end of 10 minutes compared to 45 minutes with 75 rpm.

Regardless to low reproducibility between samples of the reference batches, this was not the case with the suspensions of the test product - no significant variability between individual suspensions samples in hemispheric vessel were demonstrated (Fig. 5b). This observation was related with no compact accumulation of the test product under the rotating paddle and eventually due to different formulation design (Fig. 3).

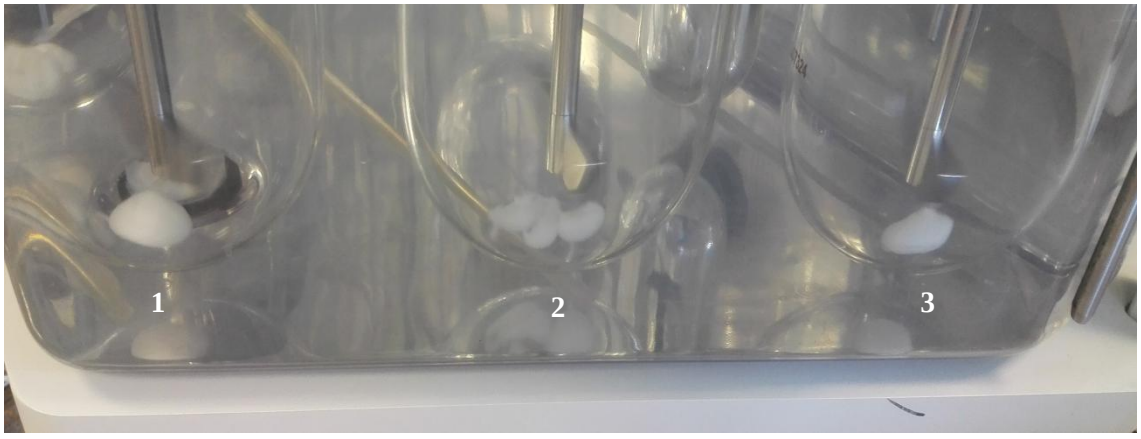
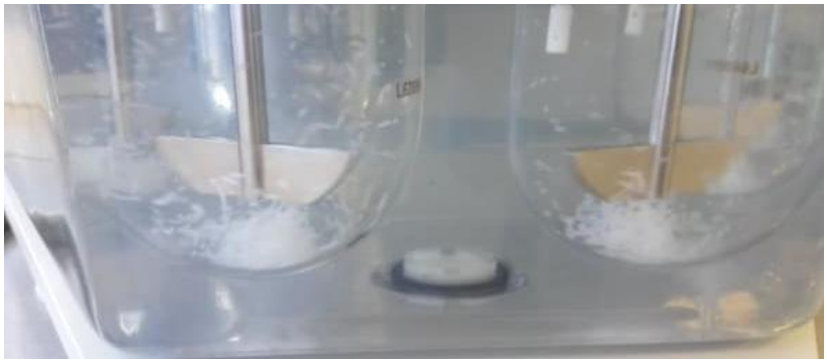


Fig. 2. Dissolution behavior of reference product during sampling intervals in hemispheric vessel, (1, 3- adhered mound; 2 - displaced mound).

a)



b)

Fig. 3. Dissolution behavior of test product in hemispheric vessel applied on rotating paddles, observed at the beginning (a) and at middle of dissolution period (b).

Effects of different geometry of dissolution vessel

Even though with 100 rpm no accumulation of the suspension from the reference product was accomplished, yet the produced results should be considered with high suspicion. It is well known that higher agitation rates compromises the ability of the method to discriminate whether similarity or dissimilarity between products occurs due to formulation or manufacturing attributes or due to experimental conditions (Quershi, 2006). From the results presented in Fig. 4, all dissolution profiles reveal great similarity with no significant difference between reference (B-IR and C-IR) and test products (A16 and A18). All four batches exhibit dissolution rate above 85% for period of 15 minutes.

Lower agitation rates of 75 rpm in hemispheric vessel point out difference in the dissolution profile of test and reference batches. The percentage of drug released differed significantly during the initial 10 minutes (Fig. 5a). Around 45% were released form all reference batches and test batch A16, compared to 95 % released form A18. As dissolution proceeded, there appeared to be no difference in the release profiles indicating similarity between reference products and A16 test batch.

However, when applying non-compendial peak vessel at the same agitation speed of 75 rpm, the difference in dissolution behavior became more distinctive and totally different from the previously presented. As seen in Fig. 5c, all commercial batches reviled similar dissolution profile with test batch A18, approximately 100% released drug within 10 minutes compared to 55% released from the test batch A16. In addition, the dense compact formation, which occurs with the reference products, was immediately eliminated appearing with great reproducibility in the dissolution data. The variability ranged from 0.4-6% in peak vessel compared to 5-24% relative standard deviation (RSD) in hemispheric vessel (Fig. 5b & 5d). The presence of a protrusion at the bottom of the vessel pronounced existing of better mixing environment underneath the paddle resulting with less variability in the dissolution (released) data.

Optimisation of agitation speed and in vitro evaluation

In attempt to challenge the robustness of the dissolution condition, deliberate manipulation of the hydrodynamic effects in peak vessel were performed by applying lower agitation rate to a point of desired discrimination of the reproducibility of the reference drug product (Liu and Vivilecchia, 2005).

From the results presented in Fig. 6b, at 50 rpm significant variability occurs during whole dissolution period with RSD ranging 10 - 45%, displaying extensive

Table 3. In vitro drug release of reference product when applied with compendial conditions on USP 2 in pH 7.2 buffer

	75 rpm/ non-rotating paddles/ **with** media replacement							**100 rpm/ non-rotating** paddles/ **with** media replacement							device for transfer	position of application in the dissolution vessel
(n=6)	5 min	10 min	15 min	20 min	30 min	45 min	60 min	5 min	10 min	15 min	20 min	30 min	45 min	60 min		
mean (%)	18.6	28.7	36.0	41.8	51.2	71.3	80.0								5 mL dose syringe	above the medium
RSD (%)	19.4	18.2	17.7	14.1	10.7	25.0	17.4				/					
mean (%)	16.8	23.9	31.9	38.1	46.8	59.3	70.8	28.5	54.6	80.0	84.4	96.5	95.9	/	5 mL dose syringe	in the medium at the side of the vessel
RSD (%)	20.3	10.4	5.5	5.4	5.1	3.7	3.3	17.6	17.3	18.0	20.0	2.2	3.5	/		
mean (%)	35.2	55.0	71.0	78.1	84.1	89.6	93.2								10ml plastic syringe	in the medium at the side of the vessel
RSD (%)	16.5	19.0	26.3	21.3	16.9	9.7	4.6				/					
mean (%)	21.5	28.8	35.5	42.1	60.0	85.8	102.3								10ml plastic syringe attached with cannula	at the bottom of the vessel
RSD (%)	30.3	25.3	19.6	13.3	13.3	14.9	1.1				/					

Table 4. In vitro drug release of reference product when applied with non-compendial conditions on USP 2 in pH 7.2 buffer

	75 rpm/ rotating paddles/ **without** media replacement							**100 rpm/ rotating** paddles/ **without** media replacement							device for transfer	position of application in the dissolution vessel
(n=6)	5 min	10 min	15 min	20 min	30 min	45 min	60 min	5 min	10 min	15 min	20 min	30 min	45 min	60 min		
mean (%)	13.7	26.8	35.2	42.8	65.0	83.1	/								5 mL dose syringe	in the medium at the side of the vessel
RSD (%)	25.5	19.7	13.4	11.3	25.7	22.2	/				/					
mean (%)	31.1	47.1	60.8	75.9	90.7	98.3	100.2	73.14	101.01	101.73	101.74	101.71	/	/	10ml plastic syringe attached with cannula	in the medium at the side of the vessel
RSD (%)	9.9	18.6	21.0	20.1	15.7	9.0	4.8	5.91	1.23	0.23	0.16	0.16	/	/		
mean (%)	16.4	28.4	34.6	41.7	63.5	92.5	101.0								10ml plastic syringe attached with cannula	at the bottom of the vessel
RSD (%)	18.2	16.0	13.1	11.7	24.2	14.6	1.0				/					

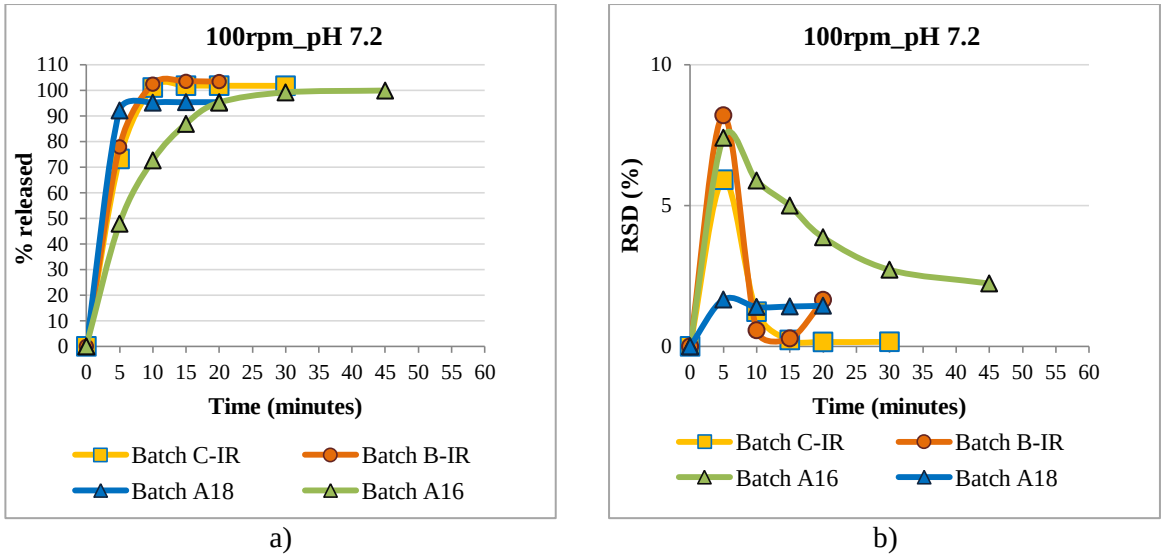


Fig. 4. *In vitro* release profile of reference products B-IR, C-IR, and test products A16, A18 performed on 100 rpm in pH 7.2 hemispheric vessel/application on rotating paddles/without media replacement (a - % released in relation of time; b - RSD (%) in relation of time).

mounding. Average released percent was less than 80% for a period of 45 minutes which excludes 50 rpm as relevant operating speed. Nevertheless, operating speed of 60 and 65 rpm provided relevant dissolution results of about 95% release within 10 minutes and satisfactory variability of less than 10% RSD during dissolution test. Based on visual observation and robustness evaluation of hydrodynamic sensitivity, the dissolution procedure of 65 rpm reflects more rugged and reliable dissolution profile of the reference product than 75 rpm. Therefore, the rotational speed of 65 rpm was chosen for performing *in vitro* release testing.

Table 5. f2 similarity factor in pH 7.2, pH 6.8, pH 4.5 and pH 1.2 performed in peak vessels between test product (A18) and reference product (B-DE), on 65rpm/ application on rotating paddles/ without media replacement

	A18 (peak v.)			
(n=12)	pH 7.2	pH 6.8	pH 4.5	pH 1.2
B-DE (peak v.)	NA*	NA*	73	80

*NA-not applicable (According to the Guideline on the investigation of bioequivalence, Doc. Ref. CPMP/EWP/QWP/1401/98 Rev. 1, where more than 85.0% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation)

Analyzing the graphics presented in Fig. 7a, when operated on modified USP 2 apparatus with peak vessel, on 65 rpm agitation speed, without media replacement during sampling period and by applying the suspension samples in the media during rotation of the paddles, similarity of test batch A18 and apparent dissimilarity of test batch A16 in comparison to reference batches (B-DE, B-IR) in pH 7.2 can be deduced. In analogy to previous conclusion, consistency of the dissolution behavior was verified by performing the dissolution study in pH 1.2, pH 4.5 and pH 6.8 as recommended for simulating physiological environment. The performed analysis, in relation to reference batch B-DE, excluded test batch A16 as formulation with similar *in vitro* behavior and affirmed sameness in the released rate with test batch A18 (Fig. 7b, 7c, 7d).

Additionally to close up the *in vitro* outcome between different formulations (generic A18 *vs* brand formulation batch B-DE), model independent approach of f2 similarity was applied by performing the dissolution test on additional 6 doses (total of 12 individual doses of the products) in above mentioned different media (Table 5). In pH 7.2 and pH 6.8 both products release more than 85% of the drug within 15 minutes, which according to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) the profiles are accepted as similar without further mathematical evaluation. High values for f_2 above 70 in pH 4.5 and pH 1.2, indicates very similar drug release behavior between test and reference batch which in terms of similarity they exhibit *in vitro* equivalency. As expected, the chosen dissolution strategy reflected minimal variability in comparison to compendial hemispheric vessel providing more reliable results for differentiation of dissolution profiles as a reflection of formulation change.

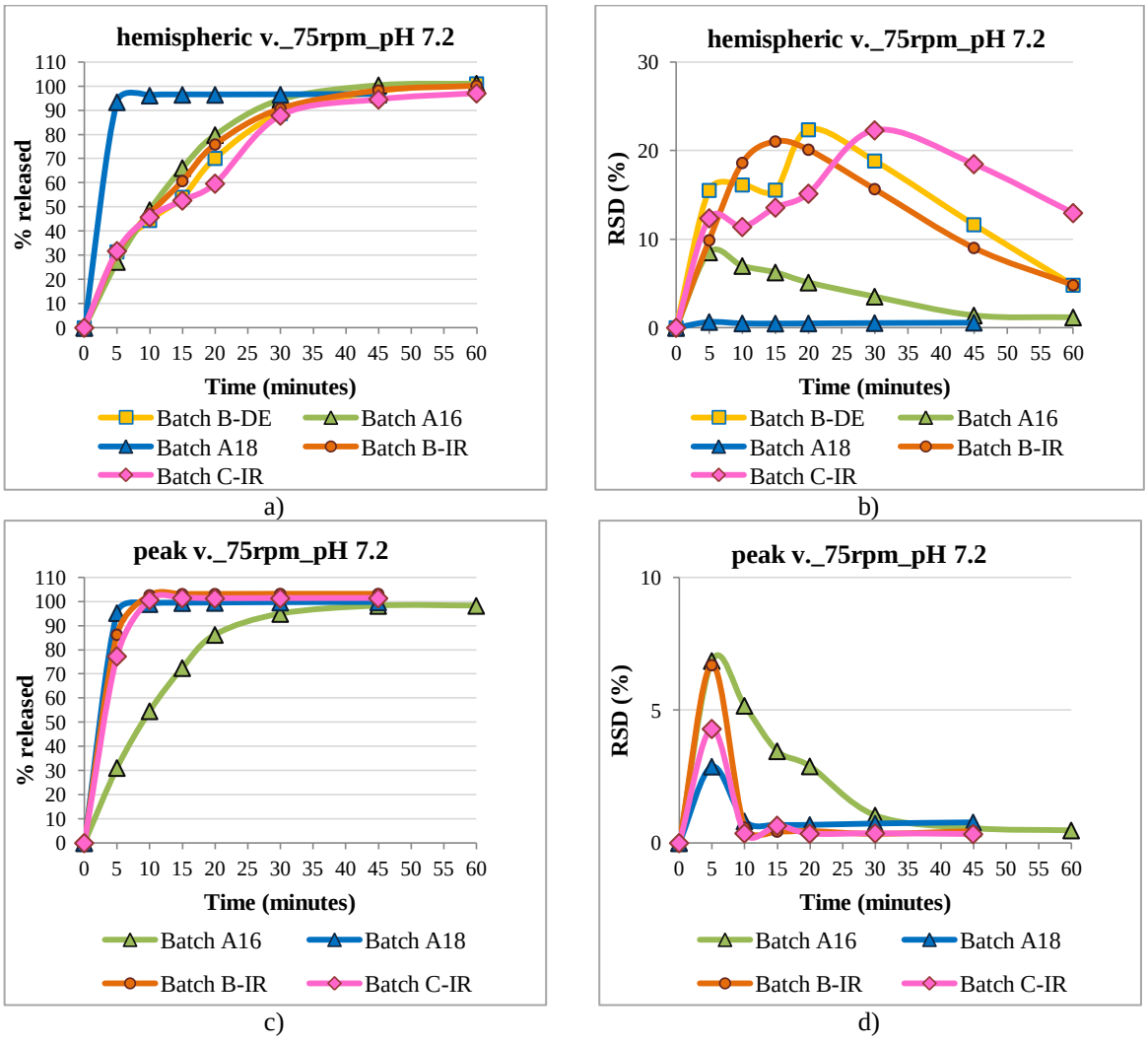


Fig. 5. *In vitro* release profile of reference products B-IR, C-IR, B-DE and test products A16, A18 performed on 75 rpm in pH 7.2 hemispheric vessel (a - % released in relation of time; b – RSD (%) in relation of time) and peak vessel (c - % released in relation of time; d – RSD (%) in relation of time) application on rotating paddles/without media replacement.

Conclusions

Understanding the physicochemical properties of the drug product is crucial for determining the most effective methodology for predicting *in vitro* similarity between two products. Suspensions with high viscosity require more work before a method can be recommended due to its complexity and data variability. For highly viscose suspension, special attention should be paid on sample homogeneity prior introducing in the vessel and using standardized sample introduction procedure to ensure accurate and repeatable results.

As presented in this investigation, traditional compendial apparatus 2, although recommended as first choice for dissolution methodology for oral suspension, is often not the best approach for some highly viscose oral suspension due to its complex matrix composition. Taking in consideration that when applying higher agitation rates of 100 rpm, as recommended for preventing mounding at the bottom of the vessel, the discriminative power of the method will be decreased therefore unable to distinct more realistic dissolution behavior between different formulations which could result with misinterpretation of the dissolution data. The presented non-compendial strategy: replacing hemispheric with peak vessels; introducing suspension sample in vessel during rotating paddles; no replacement of the withdrawn aliquots of samples with equal volume of fresh media during multipoint dissolution testing, provides better hydrodynamics by removing the mounding and preventing adhesion of the suspension in the round bottom vessel.

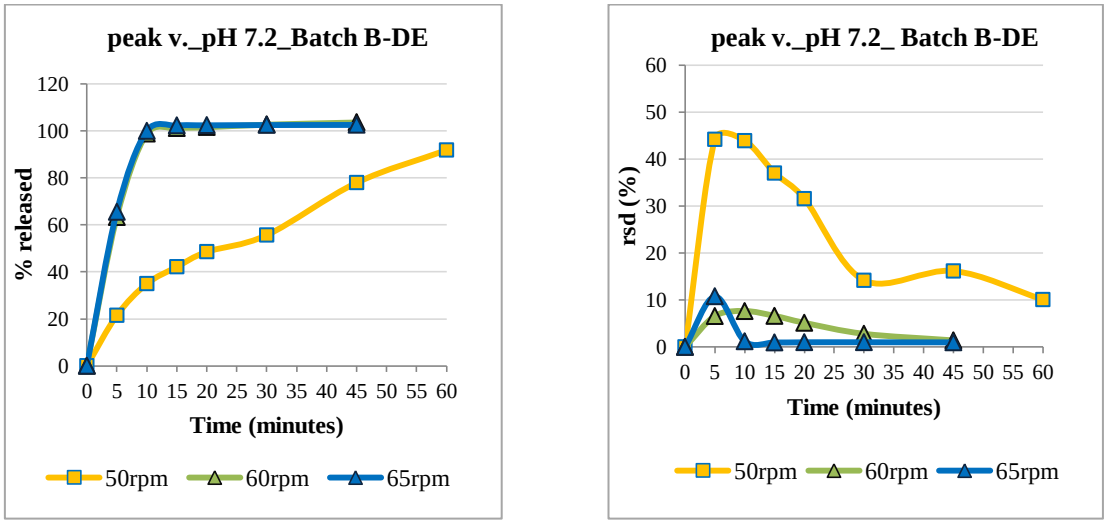


Fig. 6. *In vitro* release profile of reference products B-IR, B-DE performed on 50, 60, 65 rpm in peak vessel in pH 7.2/application on rotating paddles/without media replacement (a, c - % released in relation of time; b, d - rsd (%) in relation of time).

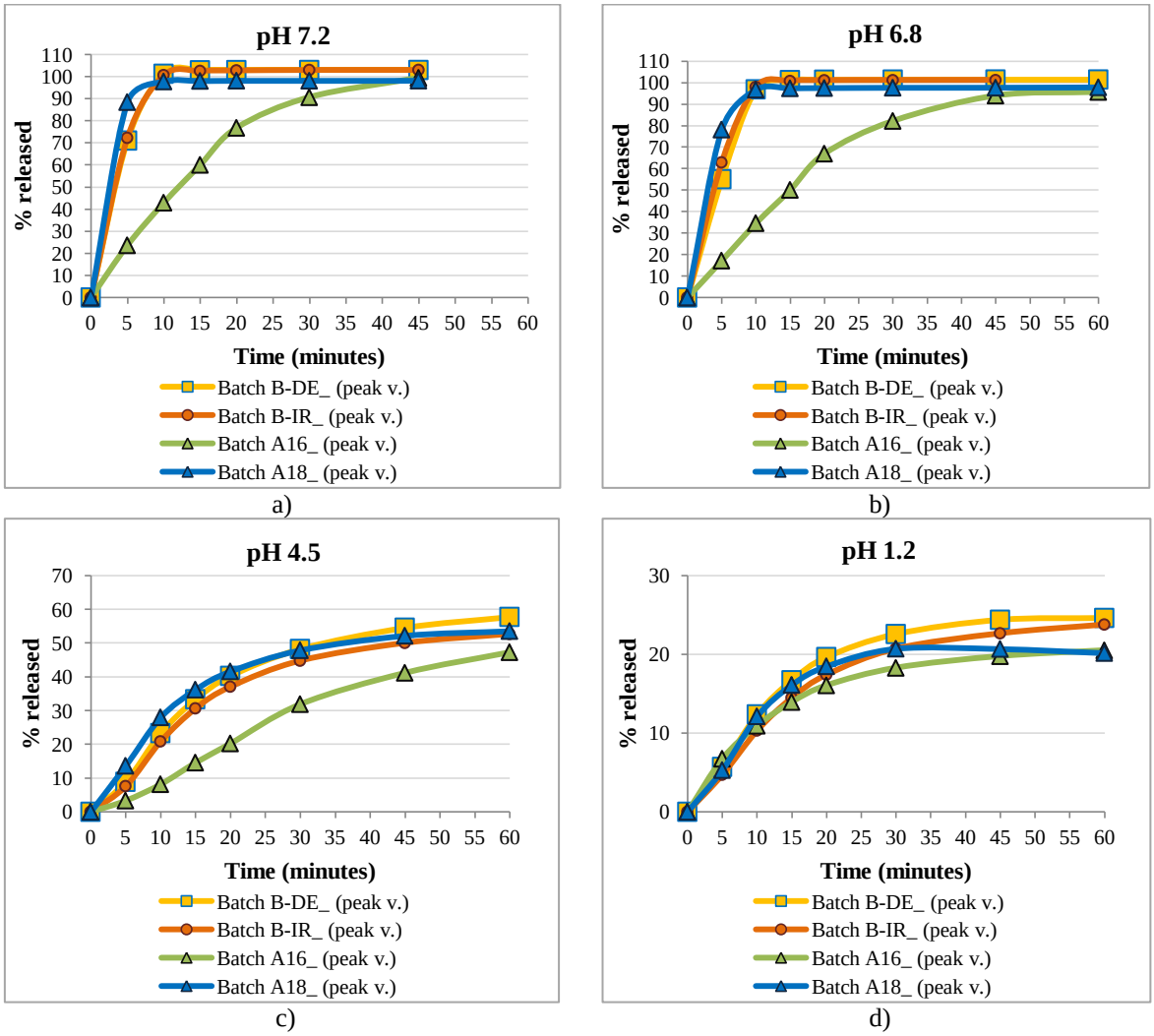


Fig. 7. *In vitro* release profile of test (A16, A18) and reference products (B-DE, B-IR), performed on 65 rpm peak vessel in pH 7.2 (a), pH 6.8 (b), pH 4.5 (c) and pH 1.2 (d), application on rotating paddles/without media replacement.

Using this non-compendial test helped overcoming the above-mentioned disadvantages of apparatus 2 thereby more discriminative technique with relevant reproducible data for predicting *in vitro* equivalency between different drug products (formulation) was provided.

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Резиме

Некомпендијали vs компендијални аналитички тестови – моќна алатка за предвидување на *in vitro* сличност помеѓу орални суспензии со голема вискозност

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Клучни зборови: орални суспензии, *in vitro* ослободување, хидродинамична варијабилност, USP апарат 2/ Апарат со примена на весла, *peak* чаши

In vitro тестовите за испитување степен на растворливост покажуваат значителен пораст на искористување при евалуација и карактеризација на фармацевтските производи. Очекувањата од методот за дисолуција се во насока на соодветна проверка на конзистентноста на фармацевтските атрибути преку дискриминирање на сличности и различности помеѓу различни дозажни формулации. Зголемениот развој на „специјални" дозажни форми, во однос на начинот на ослободување на активната супстанција, изискуваат примена на некомпендијални стратегии за растворливост кои што се разликуваат од традиционалните фармакопејски препораки.

За демонстрирање на сличност во профилот на ослободување помеѓу генерички и оригинаторски високо вискозни суспензии за орална употреба, во овој труд е прикажана компаративна *in vitro* студија на растворливост со употреба на некомпендијални чаши со испакнато дно наспрема фармакопејски хемисферни чаши.

При употреба на хемисферни чаши, поради формирање на компактна маса на дното од чашите, сите евалуирани оригинаторски серии покажаа значителна варијабилност во резултатите. Со цел намалување варијабилност во добиените резултати, различни стратегии на манипулација со примерокот, пред и за време на изведба на тестот за растворливост, беа применети. Употребата на чаши со испакнато дно, резултираше со голема репродуцибилност, а со тоа и поголема сигурност во проценката на *in vitro* сличност помеѓу различни формулации на орални суспензии.

Несоодветна интерпретација на резултатите од тестот на растворливост може да доведе до негативно влијание врз целокупниот исход од развојот на фармацевтскиот препарат. За таа цел значително важна е визуелната обсервација и проценка на однесувањето на препаратот за време на тестот за растворливост при донесување одлука за правилен избор на стратегија за изведување на тест на растворливост.