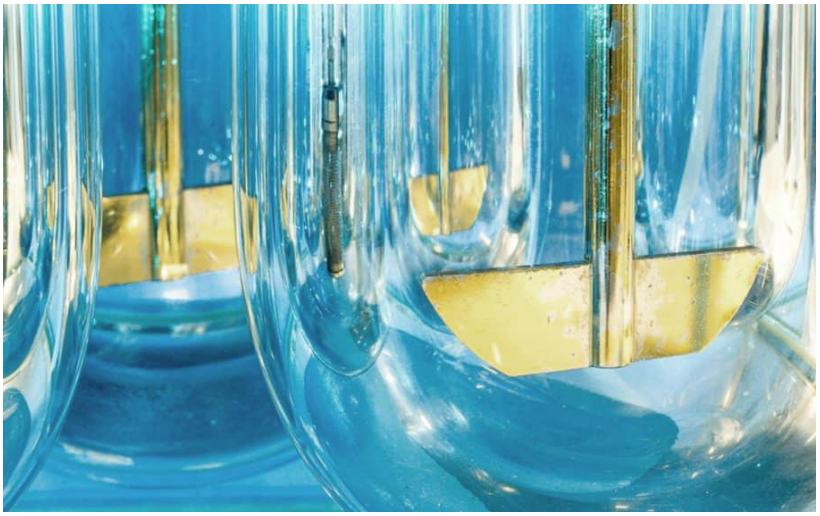
TÉCNICO LISBOA

Extended Abstract

Dissolution Profile comparison of *In Vitro* Immediate Release Solid Oral Dosage Forms



Safa Adel A. Al-Karam

Supervisor(s): MSc. Iva Vinhas

Prof. Dr. José Monteiro Cardoso de Menezes

Examination Committee

Chairperson: Prof. Dr. Miguel Angelo Joaquim Rodrigues
Supervisor(s): MSc. Iva Vinhas
Member of the Committee: Prof. Dr. Joana Marques Marto

November 2021

1. Background

Solid dosage forms given orally (tablets and capsules) form a large fraction of pharmaceutical products. These formulations are engineered to release the active pharmaceutical ingredient (API) through the patient's gastrointestinal (GI) tract in a specified delivery form. Our understanding of the *in vivo* mechanism of API release and absorption is a key objective for streamlining and enhancing the development of orally administered pharmaceutical products. Drug release testing is an *in vitro* pharmaceutical laboratory achievement test that assesses the efficiency of a drug's delivery from its dosage form. Dissolution profiles are employed throughout the development of the drug to comprehend the impact of both formulation composition and process parameters on the *in vitro* API delivery. Dissolution testing also has an important role within the context of risk- based science and development, validation, evaluation of post-approval formulation changes in drug quality, bioequivalence assessment, and as a surrogate for *in vivo* drug release.

For manufacturing, *in vitro* dissolution routinely served as a quality control (QC) release test to secure batch-to-batch consistency and/or quality of fabrication.

2. Purpose

The aim of this thesis is to establish a comparative study into the dissolution profiles for baclofen 10 mg and 25 mg tablets manufactured at Labatec Pharma S.A Switzerland and Labatec farmacêutica S.A Portugal, under different dissolution media.

3. Scope

The scope of this media is to demonstrate the comparability of dissolution profiles due to change of manufacturing site. the study was performed on different pH media of 3 batches of baclofen tablets fabricated at Labatec farmacêutica versus three commercial batches held recently as reference batches, elaborated by Labatec pharma.

4. Participants

Transferring Unit: Labatec Pharma S.A

Receiving Unit: Labatec Farmacêutica S.A

5. Abbreviations

QC- Quality Control

RSD- Relative Standard Deviation

API- Active Pharmaceutical Ingredient

WS- Working Standard

6. Introduction

In order to achieve a similarity among test and reference batches, an *in vitro* dissolution profile comparison was done using an independent model through similarity and difference factors calculations expressed in the equations 6.1 and 6.2 below:

$$f1 = \left[\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right] \times 10 \qquad \textit{Equation 6.1}$$

$$f2 = 50 \times log\left[\frac{1}{\sqrt{1+\frac{\sum_{t=1}^{t=n}[R(t)-T(t)]^2}{n}}}\right] \qquad \textit{Equation 6.2}$$

Where;

n= number of time points,

Rt= dissolution value of the reference batch at time t (%),

Tt= dissolution value of the test batch at time t (%).

The difference factor calculates the percent difference (%) between the two curves at each time point and is a measurement of the relative error between the two curves. The similarity factor is a logarithmic reciprocal square root transformation of the sum of square error and is a measurement of similarity percent between the two curves.

The calculations were done accordingly with the guidelines applicable within the ranges stated in the table.

Table 1- Recommended range values of *f1* and *f2* for dissolution profiles comparison.

f1 (Difference factor)	≤ 15
f2 (Similarity factor)	≥ 50
RSD (Relative Standard Deviation)	≤ 20% (at the first time points – 5 min,10 min)
	≤ 10% (for the remaining time points)

Note: if the dissolution at 15 minutes is equal or higher to 85% in different media, the dissolution profiles are considered identical. Therefore, a comparison with the similarity factor f_2 is not mandatory.

The dissolution profiles were performed for twelve units from each batch, at the following pH media:

1. HCl 0.1N.
2. Acetate buffer pH 4.5.
3. Phosphate buffer pH 6.8.

Since the dissolution media for batch release is 0.1N HCl, the water media is not a requirement for the comparative study.

7. Product Specification

Complying with the listed product specification:

Table 2 Product Specification.

Physical and Chemical tests	Release specification
Dissolution	≥ 80% (Q) the nominal dosage of the tablets (15min)

8. Procedure

Sampling time points were collected automatically and filtered by glass filters GF/D to characterize the dissolution profile of Baclofen tablets.

Dissolution and UV conditions are described in table 3 and 4.

8.1 Dissolution conditions:

Table 3- Dissolution conditions for Baclofen 10 mg and 25 mg.

Apparatus **Equipment**	**Apparatus type II (paddle elements)** **Sotax AT Xtend**		
Dissolution media	HCl 0.1N	Acetate buffer pH 4.5	Phosphate buffer pH 6.8
Dissolution media volume	900 mL	900 mL	900 mL
Temperature	37± 0.5 °C	37± 0.5 °C	37± 0.5 °C
Rotational speed (rpm)	50 rpm	50 rpm	50 rpm
Sample volume (mL)	1.2 mL	1.2 mL	1.2 mL
Sampling time-points (min)	5,10,15,20,25 and 30		

Table 4- HPLC equipment and chromatographic conditions

HPLC waters	EQC-049
Detector	UV, 220 nm
Column	Waters BEH C18, 1.7 µm, 2.1 x 50 mm
Mobile phase	Buffer pH 5.0/ Methanol (80/20) (v/v)
Column Temperature	30°C
Autosampler Temperature	20°C
Flow rate	0.3 ml/min
Injection volume	0.5 µL
Retention time	= 1.3 min
Run time	=2 min
System Suitability	For Baclofen reference solution: - RSD for 6 injections ≤ 2.0% - Symmetry factor ≤ 1.5 - Theoretical plate count ≥ 5000

8.2 Samples and reference substances:

Table 5 - samples used in the dissolution profile study

Manufacturer	Batches
Labatec Pharma S.A.	3827 3828 3830 3751 3843 3861
Labatec Farmacêutica S.A.	200347 200348 200349 200350 200531 200532

Table 6- Reference substance used during the dissolution profile study

Reference substance	Baclofen WS	Baclofen USP
Batch	200235	J1H297
Potency	99.6%	99.4%

8.3 Reagents:

Table 7- Reagents used during the dissolution profiles

Reagents	Brand
Ammonium Acetate	VMR
Potassium dihydrogen phosphate	VMR
Sodium Hydroxide	VMR
Sodium acetate trihydrate	Merck
Acetonitrile	Carlo Erba
Glacial Acetic Acid	Carlo Erba
Hydrochloride Acid 37%	Carlo Erba
Methanol	Carlo Erba

8.4 Dissolution Media preparation:

8.4.1 HCl 0.1N pH 1.2

Dilute 50 mL of 1 M hydrochloride acid 37% into a 6000 mL flask with purified water.

8.4.2 Acetate Buffer pH 4.5

Dissolve 2.99 g of sodium acetate trihydrate in purified water. Add 14 mL of 2M acetic acid and dilute to 1000 mL volumetric flask with purified water.

Acetic Acid 2M*:* Dilute 11.6 ml of glacial acetic acid into a 100 mL volumetric flask with purified water. Allow the solution to stabilize at room temperature. Complete the volume with purified water.

8.4.3 Phosphate Buffer pH 6.8

Mix 250 mL of 0.2M potassium monobasic phosphate and 112 mL of 0.2M sodium hydroxide solution. Complete the volume to 1000 mL volumetric flask with purified water.

Monobasic potassium phosphate 0.2M: Dissolve 27.22 g of potassium dihydrogen phosphate in purified water. Complete the volume into 1000 mL volumetric flask.

NaOH 0.2M*:* Dissolve 8.00 g of sodium hydroxide in purified water. Complete the volume into 1000 mL volumetric flask with purified water, after the solution stabilizes at room temperature.

Note: All dissolution media were prepared with filtered purified water and pre heated before use.

9. Results:

The tables and the figures below show the results obtained for the release profiling of the test and commercial batches, in different dissolution media.

- Throughout this section, the reference batches (manufactured by the swiss site) are going to be highlighted in blue for easier distinction.

9.1 Dissolution media: HCl 0.1N

Table 8- Average values of dissolved % API of Baclofen 10 mg per pH 1.2

HCl 0.1 N Medium						
Batches	**% API Dissolved for each sampling time point (min)**					
	5	10	15	20	25	30
3827	97.3	100.2	101.0	101.4	102.0	102.4
3828	97.4	99.0	100.0	101.8	101.0	101.3
3830	98.5	100.4	100.6	101.5	101.5	102.0
200347	94.3	95.7	96.5	96.7	97.8	98.0
200348	92.9	94.8	96.5	96.5	97.3	97.4
200531	95.4	97.7	98.3	98.9	99.4	99.6
Mean CH	97.7	99.8	100.6	101.6	101.5	101.9
% RSD CH	0.7	0.8	0.5	0.2	0.5	0.5
Mean PT	94.2	96.1	97.1	97.4	98.2	98.3
% RSD PT	1.4	1.5	1.1	1.4	1.1	1.2

Table 9- Average values of Dissolved % API of Baclofen 25 mg per pH 1.2.

HCl 0.1 N Media						
Batches	**% API Dissolved for each sampling time point (min)**					
	5	10	15	20	25	30
3751	87.8	92.0	93.6	95.0	95.8	96.7
3843	89.7	92.8	94.5	95.7	96.7	97.2
3861	90.1	93.7	95.6	97.1	98.3	98.8
200349	92.6	95.3	96.8	97.6	98.1	98.3
200350	87.6	90.3	91.7	92.7	93.4	93.9
200532	87.6	91.5	92.9	94.1	95.1	95.6
Mean CH	89.2	92.8	94.6	95.9	96.9	97.6
% RSD CH	1.4	0.9	1.0	1.1	1.3	1.1
Mean PT	89.3	92.3	93.8	94.8	95.5	96.0
% RSD PT	3.2	2.8	2.8	2.7	2.5	2.3

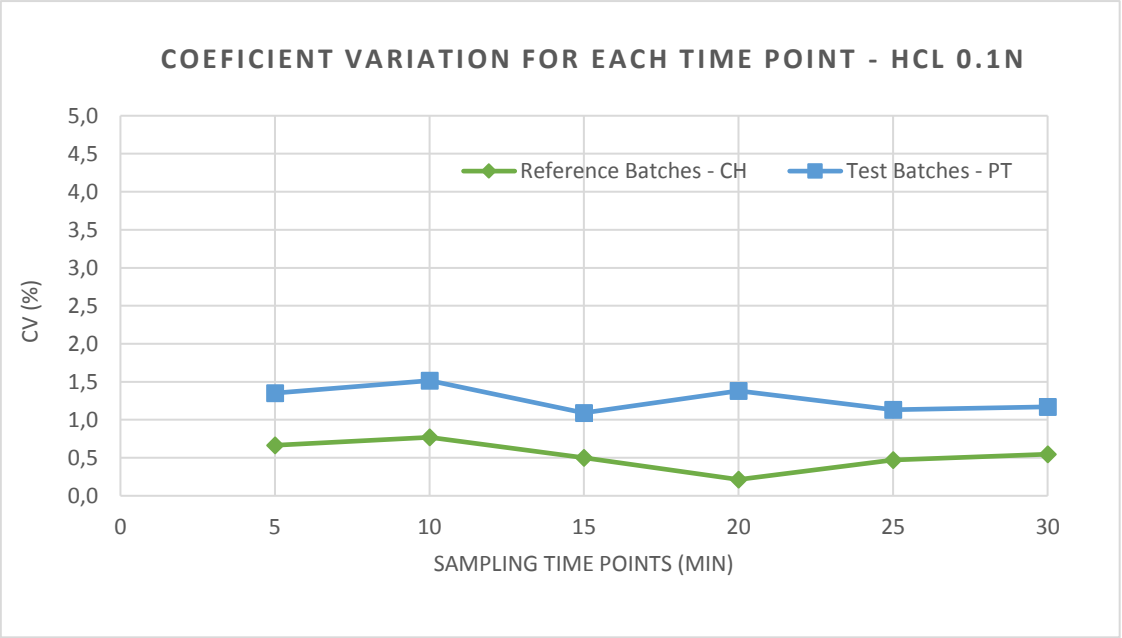


Figure 1 Relative Standard deviation for 10 mg at each time point - HCl 0.1N media.

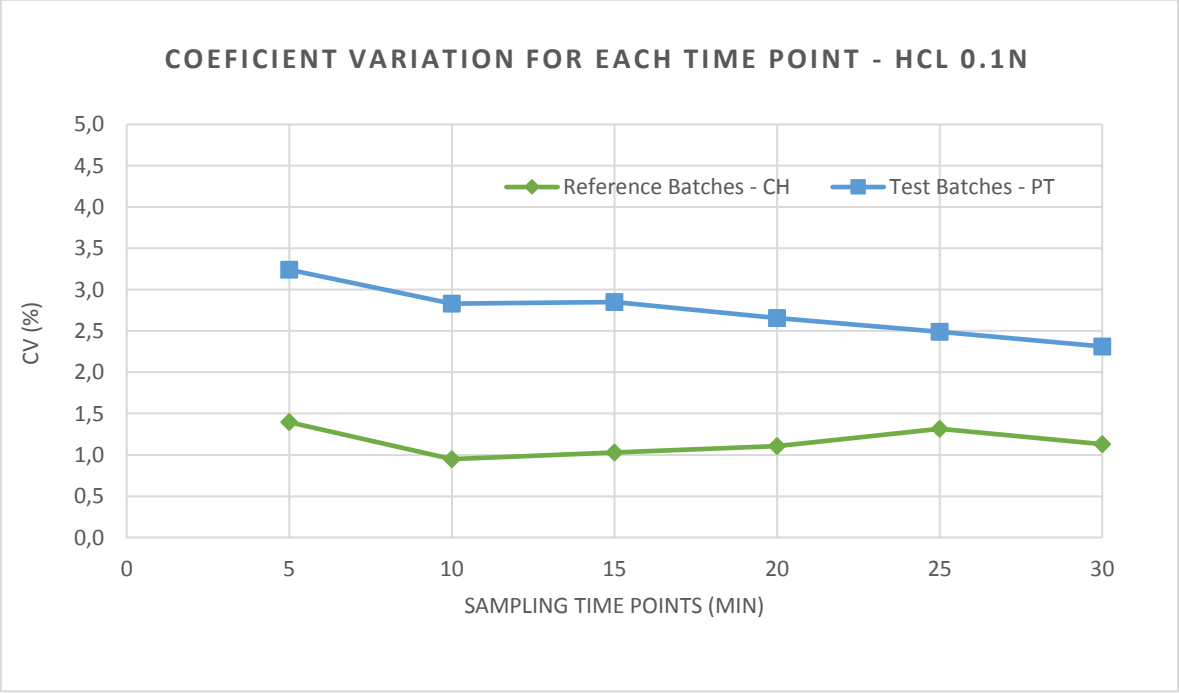


Figure 2 Relative Standard deviation for 25 mg at each time point - HCl 0.1N media.

9.2 Dissolution media: Acetate Buffer pH 4.5

Table 10- Average values of dissolved % API of Baclofen 10 mg at pH 4.5.

Acetate Buffer pH 4.5 Media						
Batches	**% API Dissolved for each sampling time point (min)**					
	5	10	15	20	25	30
3827	91.7	95.8	98.0	98.8	100.2	100.6
3828	89.5	94.2	96.1	97.5	98.4	99.5
3830	88.1	92.7	94.7	96.1	97.2	98.2
200347	87.4	93.1	95.1	96.9	97.6	98.1
200348	87.3	91.3	93.0	94.2	94.9	94.5
200531	88.3	92.5	94.0	95.3	95.9	98.6
Mean CH	89.8	94.2	96.3	97.5	98.6	99.5
% RSD CH	2.0	1.7	1.7	1.4	1.5	1.2
Mean PT	87.7	92.3	94.1	95.5	96.1	97.1
% RSD PT	0.6	1.0	1.1	1.4	1.4	2.3

Table 11 -Average values of dissolved % of Baclofen 25 mg at pH 4.5.

Acetate Buffer pH 4.5 Media						
Batches	**% API Dissolved for each sampling time point (min)**					
	5	10	15	20	25	30
3751	79.9	85.5	88.5	90.4	92.0	93.7
3843	78.8	84.6	87.0	88.5	90.0	91.1
3861	83.0	87.6	89.9	91.7	93.3	94.4
200349	87.4	91.8	94.0	95.4	96.6	97.7
200350	82.6	86.8	89.1	90.7	91.8	92.9
200532	83.2	86.9	88.9	90.5	91.6	92.6
Mean CH	80.6	85.9	88.5	90.2	91.8	93.1
% RSD CH	2.7	1.8	1.6	1.8	1.8	1.9
Mean PT	84.4	88.5	90.6	92.2	93.3	94.4
% RSD PT	3.1	3.2	3.2	3.0	3.1	3.0

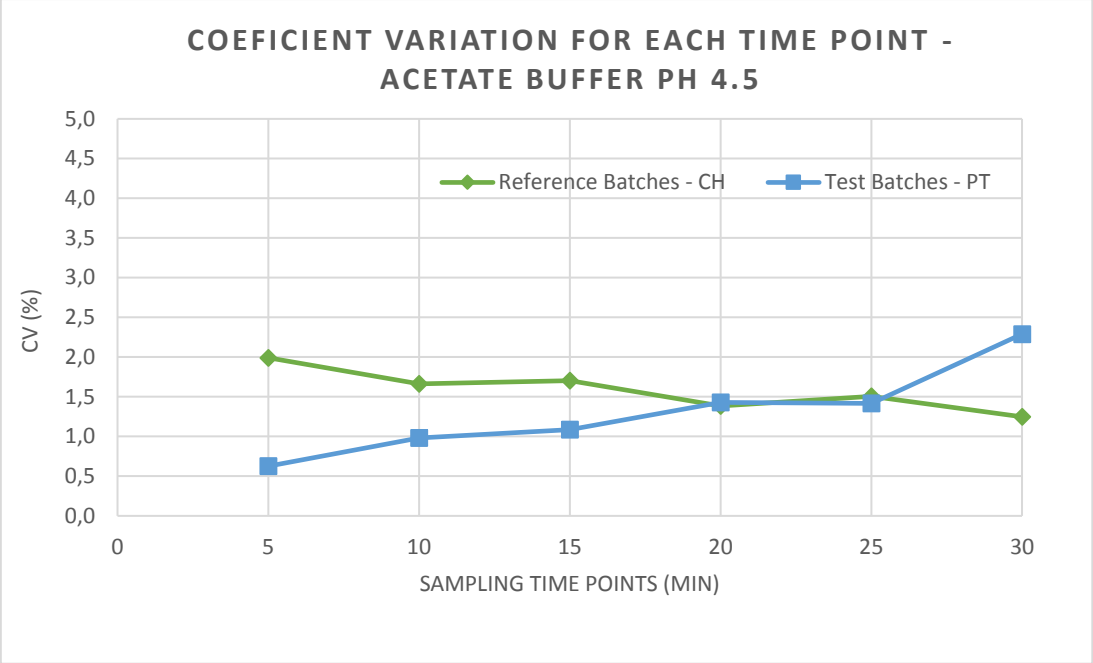


Figure 3 Relative Standard deviation for 10 mg at each time point – Acetate buffer media.

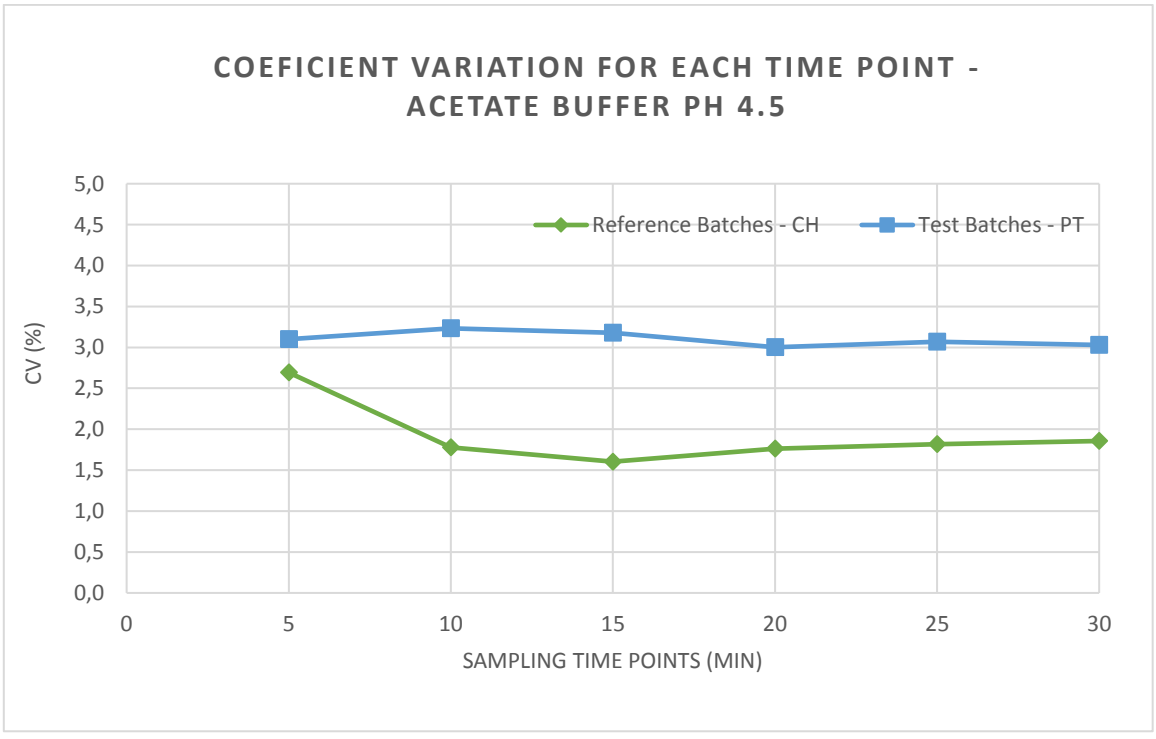


Figure 4 Relative Standard deviation for 25 mg at each time point – Acetate buffer media.

9.3 Dissolution media: Phosphate Buffer pH 6.8

Table 12- Average values of dissolved % API of Baclofen 10 mg at pH 6.8.

Phosphate Buffer pH 6.8 Media						
Batches	**% API Dissolved for each sampling time point (min)**					
	5	**10**	**15**	**20**	**25**	**30**
3827	84.5	91.8	94.6	95.7	96.7	97.5
3828	81.8	91.4	95.2	96.9	97.8	98.7
3830	86.8	94.2	98.5	97.8	98.8	98.5
200347	73.1	87.4	91.6	94.0	95.6	96.2
200348	77.5	86.8	89.6	91.3	92.0	92.8
200531	76.9	86.1	91.6	93.9	95.0	96.0
Mean CH	84.4	92.5	96.1	96.8	97.8	98.2
% RSD CH	3.0	1.6	2.2	1.1	1.1	0.6
Mean PT	75.9	86.8	90.9	93.1	94.2	95.0
% RSD PT	3.1	0.8	1.3	1.7	2.0	2.0

Table 13- Average values of Dissolved % API of Baclofen 25 mg at pH 6.8.

Phosphate Buffer pH 6.8 Medium						
Batches	**% API Dissolved for each sampling time point (min)**					
	5	10	15	20	25	30
3751	81.2	86.5	89.0	90.7	91.9	92.8
3843	83.5	88.1	90.2	91.5	92.9	94.5
3861	83.4	88.1	90.1	91.7	92.7	93.6
200349	82.9	86.5	88.7	90.1	91.0	92.1
200350	83.0	87.3	88.6	89.9	91.6	92.6
200532	80.8	84.9	86.8	88.4	89.4	90.5
Mean CH	82.7	87.6	89.8	91.3	92.5	93.6
% RSD CH	1.6	1.1	0.8	0.6	0.6	0.9
Mean PT	82.2	86.2	88.0	89.5	90.7	91.7
% RSD PT	1.5	1.4	1.2	1.1	1.2	1.2

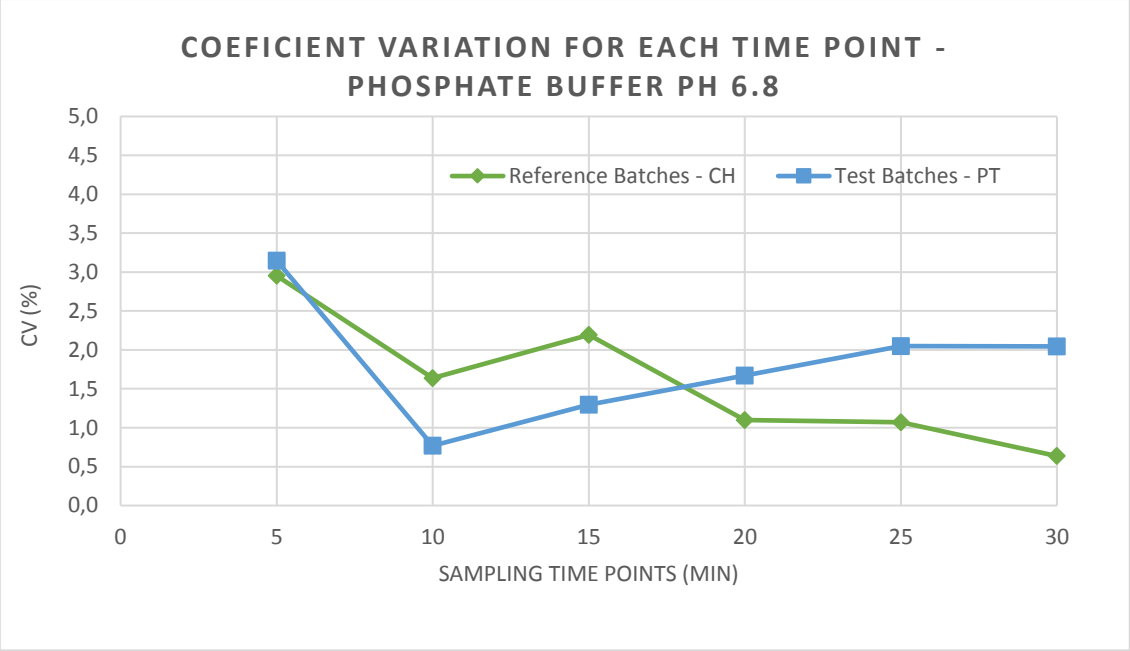


Figure 5 Relative Standard deviation for 10 mg at each time point – phosphate buffer media.

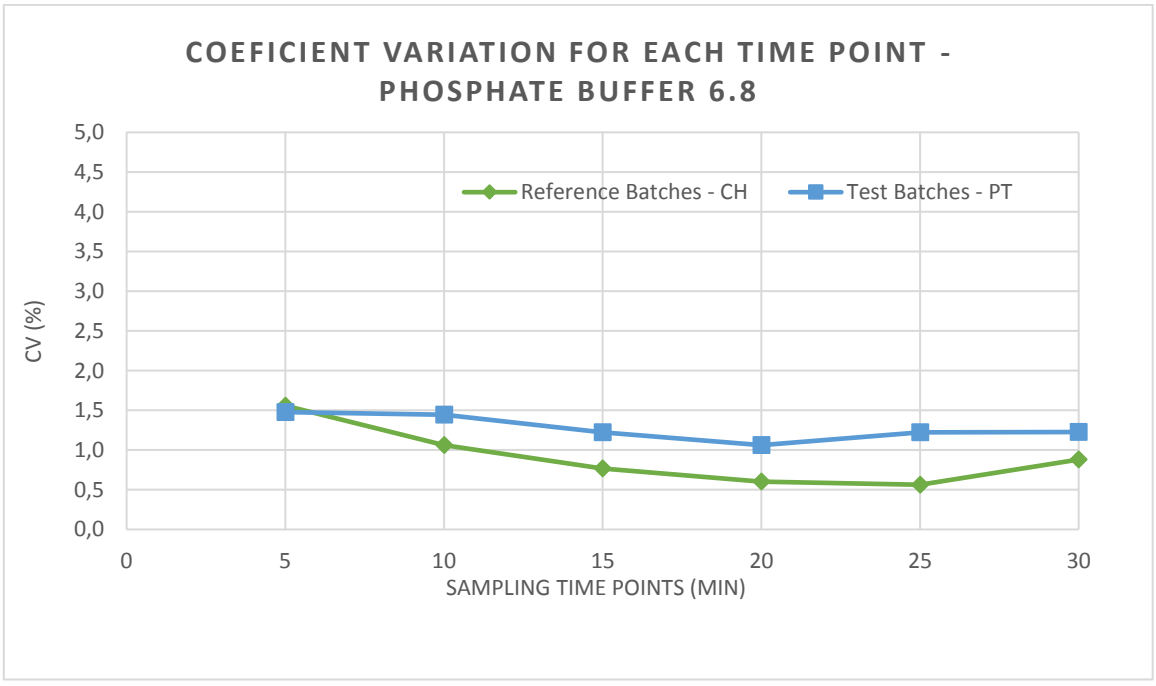


Figure 6 Relative Standard deviation for 25 mg at each time point – phosphate buffer media.

- **<u>Comparison of formulation 10 mg in different media</u>**

By comparing the performance of test and commercial batches presented in figure 1, it is notable that the % of baclofen API released over the selected different media at 15 minutes is higher than 85%, as well as:

1. HCl 0.1N is the dissolution media with highest % of API dissolved over time.
2. Phosphate buffer is the lowest % of API dissolved.

Therefore, a conclusion of similarity among batches of dosage 10 mg is achieved at different dissolution media.

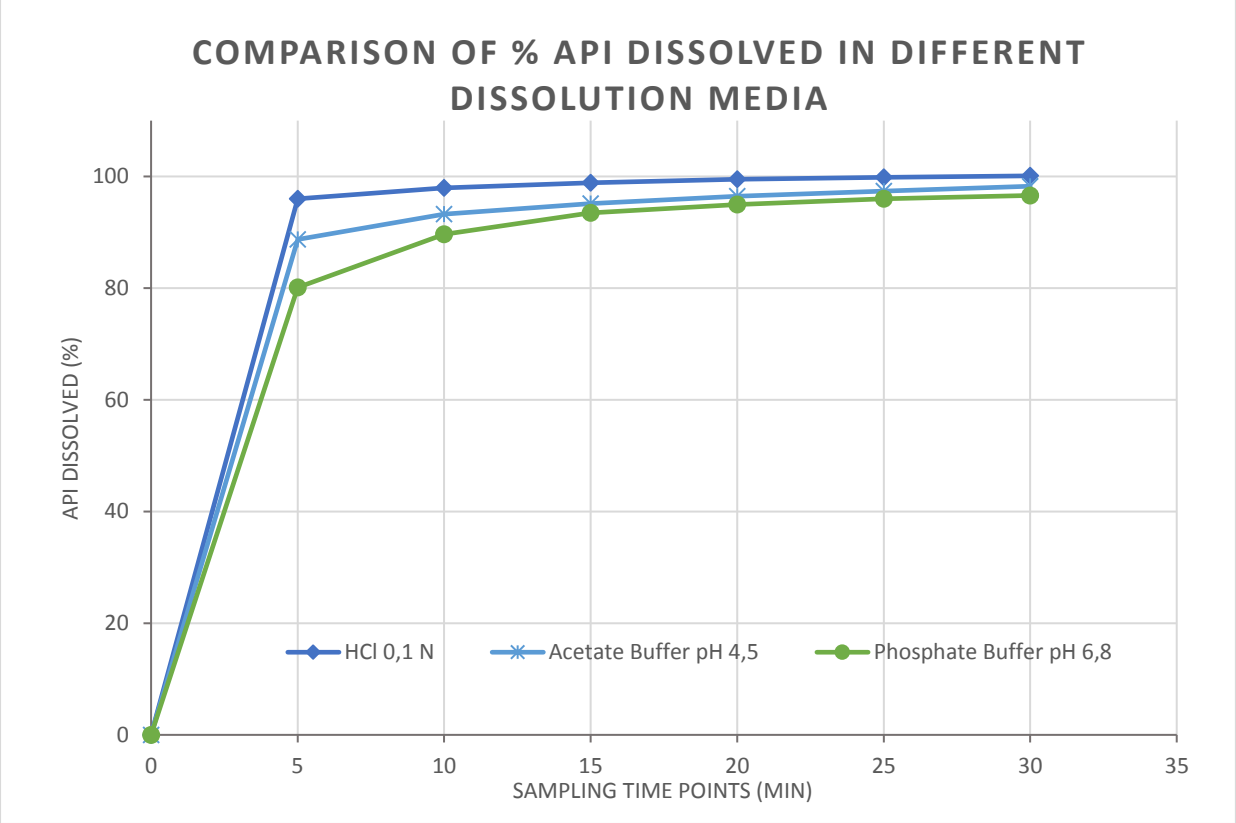


Figure 7 -Profile release comparison of Baclofen 10 mg dissolved API in different dissolution media over time.

- **Comparison of formulation 25 mg in different media**

Regarding the indicated dosage, further comparability was made between all the batches over different media, assuring that the acid media is the most appropriate with highest % API released over time, as shown in Figure 2.

In addition, the % API released from baclofen 25 mg at 15 minutes for all of the batches under analysis is over 85%, a fact which allowed the conclusion of similarities between them ensuring identical profiles.

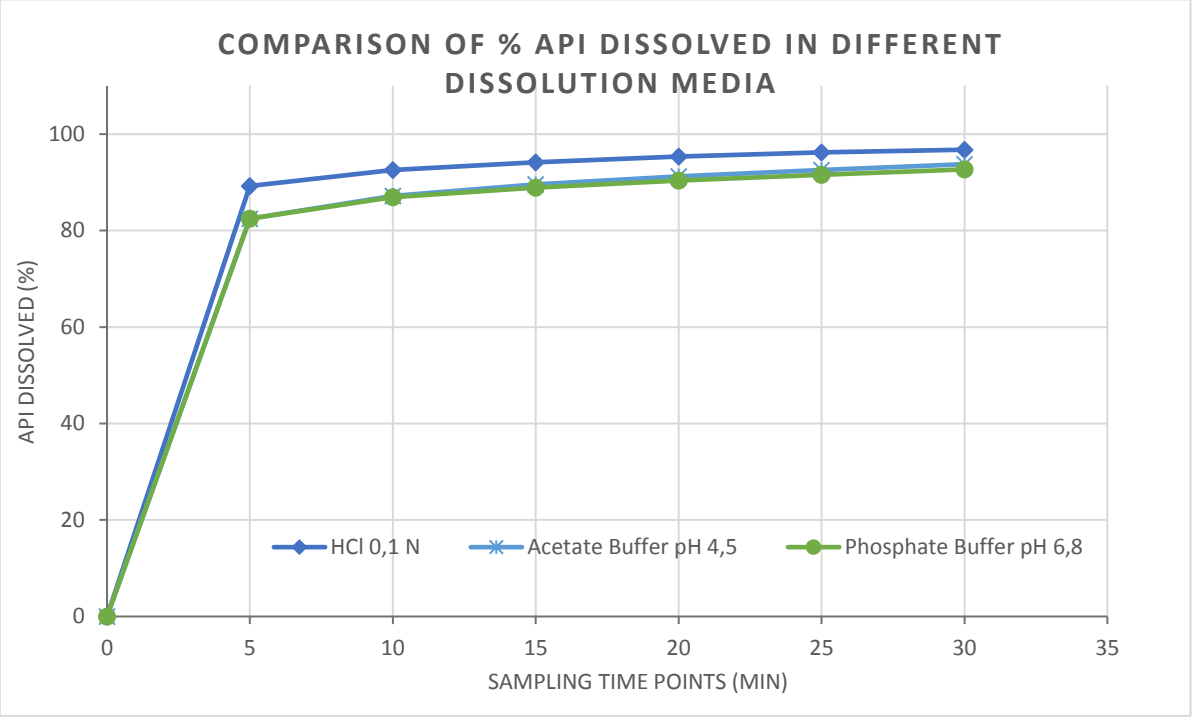


Figure 8 Profile release comparison of Baclofen 25 mg dissolved in different dissolution media.

10. Conclusions

By comparing the commercial batches manufactured in Labatec Pharma S.A with test batches manufactured in Labatec farmacêutica S.A, the following points can be concluded:

- The batches of baclofen tablets containing the intended dosage can achieve a full release characteristic (Q≥ 80%) within 15 minutes in different dissolution media.

- The dissolution profiles of all test and reference batches achieved an average of released values varying among 90%-101% of API, at 15 minutes time point.

- Regardless the pH of the used media, the same trend of release profile was showed for all dissolution media.
  HCl 0.1N being the ideal dissolution media with highest percent released in comparison with the remaining medias.

- A low relative standard deviation was observed across medias with less than 5% at each time point when comparing the average of the commercial with test batches fulfilling the criteria specified in accordance with the guidelines

- An independent model approach was used for the comparison of dissolution profiles at several media, through the calculation of similarity and difference factors that ensured equivalence among pre and post batches in all media.

Considering the points listed above and once the release profiling proved similarity between batches, the dissolution comparative study can be considered successfully implemented at Labatec farmacêutica site.

11. References

- Dissolution testing of immediate release solid oral dosage forms, Guidance for industry, food and drug administration (FDA), 1997.
- Guideline on the investigation of bioequivalence, European medicines Agency, 20 January 2010, CPMP/EWP/QWP/1401/98 Rev.1/Corr.
- Realization of dissolution profiles internal procedure.