THE IMPACT OF DISSOLUTION MEDIA ON THE SIMILARITY OF RELEASE PROFILES OF TRIMETAZIDINE DIHYDROCHLORIDE FROM IMMEDIATE RELEASE TABLETS

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Abstract

The paper presents the impact of the composition of the dissolution media (water, hydrochloric acid pH=1.2 and phosphate buffer pH=6.8) on the *in vitro* release profiles of four immediate release formulations containing 20 mg trimetazidine dihydrochloride. The results suggest that, for quality control purposes, the most discriminatory test conditions are provided by the acidic media.

Rezumat

Lucrarea prezintă impactul compoziţiei mediului de dizolvare (apă, acid clorhidric pH=1,2 şi tampon fosfat pH=6,8) asupra profilelor de cedare *in vitro* pentru patru formulări conţinând 20 mg trimetazidină diclorhidrat. Rezultatele sugerează că mediul acid generează condiţiile cele mai discriminatorii.

Keywords: dissolution, trimetazidine dihydrochloride, similarity, immediate release.

Introduction

The *in vitro* drug release methodology has proved to be a highly important tool for the quality control of drugs and drug products that need to undergo a dissolution step prior to the absorption process. The solubility profile is a key parameter needed for accurate development of the *in vitro* testing methodology [1]. If not mentioned in a compendial monograph, one should first consider the intended use of the dissolution test, in either scale-up post-approval changes (SUPAC) [2] or biorelevant evaluation for the formulation including a specific active pharmaceutical ingredient (API). For

low solubility drugs, aqueous media can include several types of surfactants, in order to increase the fraction dissolved during a time interval acceptable for a quality control test [3]. The quantity of tensioactive agent needs to be selected in order to assure the discriminatory power. Non-physiological pH values are also reported, especially for chemical structures with acidic properties. The official adoption of the Biopharmaceutical Classification System (BCS) [4] offers the opportunity to approach the biowaiver procedures for abbreviated registration of drug products. If a very rapid dissolution is reported for the immediate release formulation of highly soluble, highly permeable API (BCS class I), then it can be assumed that, although the initial pharmaceutical vehicle was a solid dosage form, the content leaving the gastric environment will behave mainly as a solution. Consequently, the permeability is the main factor influencing the absorption profile, provided that no excipient is susceptible to induce a particular interaction. Paradoxically, while the research of both industry and academia have been focused mainly on the development of accurate *in vitro* drug release methodology in case of either dissolution-rate limited or solubility-limited profiles, it is not clear how should one approach a high solubility drug. Nevertheless, in this particular case it is not clear to what extent the currently available protocols can be considered as biorelevant, considering that to the best of our knowledge, the final goal, *in vitro* - *in vivo* correlations, are difficult to achieve.

The current paper presents the evaluation of four immediate release oral solid dosage forms containing a high solubility drug, trimetazidine dihydrochloride, in various dissolution media. The *in vitro* experimental protocol aimed to identify the testing conditions able to accurately reflect the existing differences in terms of qualitative and quantitative composition.

Materials and Methods

Four immediate release formulations containing 20 mg trimetazidine dihydrochloride were included in the study (further identified as R for reference and T1, T2, T3 for the generic products). The qualitative composition is presented in table I.

The dissolution tests were performed on a Hanson SR8 Plus equipment, Hanson Research Inc, USA, using the paddle apparatus at 75 rotations per minute. The *in vitro* release media consisted of 900 mL solution of either water, hydrochloric acid (pH=1.2, 0.1N) or phosphate buffer (pH=6.8, 50 mM), degassed by filtration under vacuum. Samples of 5.0 mL were collected and filtered using immersed canula filters (10 μm

pore size) at 5, 10, 15, 20, 30, 45 and 60 minutes after the debut of the test. The dissolution media was replaced after sampling procedure. Each test was performed on six units.

Table I

The composition of the evaluated oral solid dosage forms

Formulation / Excipient	R	T1	T2	T3
Microcrystalline cellulose		√		√
Magnesium stearate	√	√	√	√
Corn starch	√		√	
Mannitol	√	√	√	√
Polyvidone	√	√	√	
Talcum	√		√	
Anhydrous colloidal silicon oxide		√	√	√
Stearic acid		√		
Hydrogenated cotton seed oil			√	
Coating film (proprietary name)	Not specified*	Opadry® II HP 85F24190 Pink	Opadry® 85 F 25247 Red	Sepifilm® 5341 Red
Batch no.	**872763**	**01110852**	**1030010457**	**09100847**

***** - glycerol, hypromellose, macrogol 6000. magnesium stearate, Sunset Yellow FCF, Cochineal Red A, titanium dioxide.

The amounts of trimetazidine dihydrochloride dissolved were determined using a spectrophotometric method [5,6] at 230 nm, by interpolation on the calibration curves generated in the corresponding media (using a double fascicle, Jasco V-530 model spectrophotometer).

The reagents and analytical standards were purchased from Sigma Aldrich. The purified water was generated by a SGW Ultraclear UV PlusTM system.

The dissolution profiles were compared using compendial, model independent procedures (by calculating the difference and similarity factors, f_1 and f_2):

$$f_1 = \frac{\sum_{i=1}^{n} |\mu_{ri} - \mu_{ti}|}{\sum_{i=1}^{n} \mu_{Ri}} x100$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{\sum_{i=1}^{n} (\mu_{ri} - \mu_{ti})^2}{n} \right]^{-1/2} * 100 \right\}$$

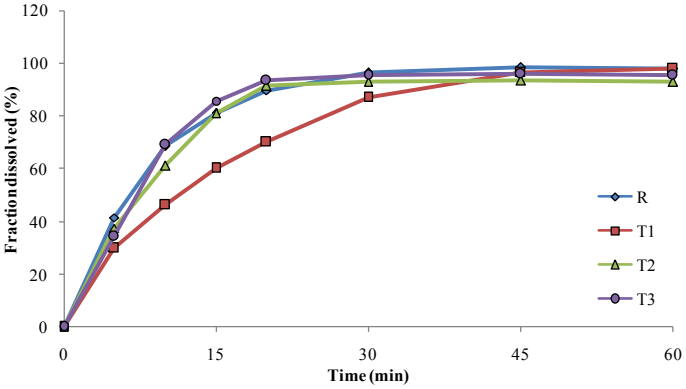
where n is the number of sampling points,
μ_{ri} = the mean fraction dissolved at the time point t_i for the reference formulation,
μ_{ti} = the mean fraction dissolved at the time point t_i for the tested formulation.

The similarity was concluded if the value of f_1 was between 0 and 15, while f_2 value had to be higher than 50 (corresponding to a average difference lower than 10%, for all the sampling probes).

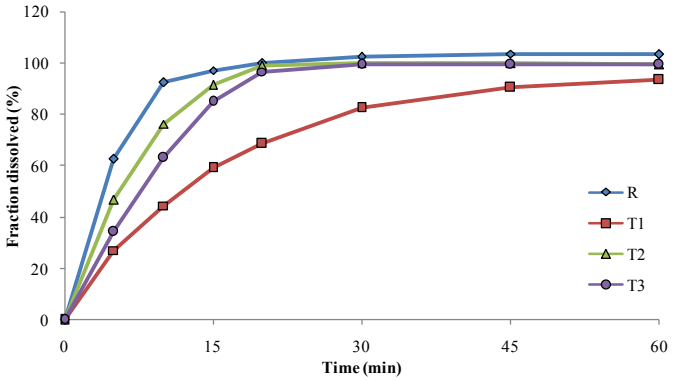
Results and Discussion

The *in vitro* profiles indicated, almost independent to the media composition, a very rapid release of trimetazidine. Complete dissolution was recorded at the end of the 60 minutes time interval, underlining the high solubility characteristics. A lower rate is reported for T1 drug product (Figure 1). The reference product presented the highest values of the fraction dissolved. The most discriminatory conditions seemed to be provided by the acidic conditions (approximately 35% difference between R and T1, 5 minutes after initiation of dissolution tests). After 20 minutes, the profiles become almost superposables, except for T1. The calculation of similarity factors confirms the above mentioned particularities of the release profiles (Table II).

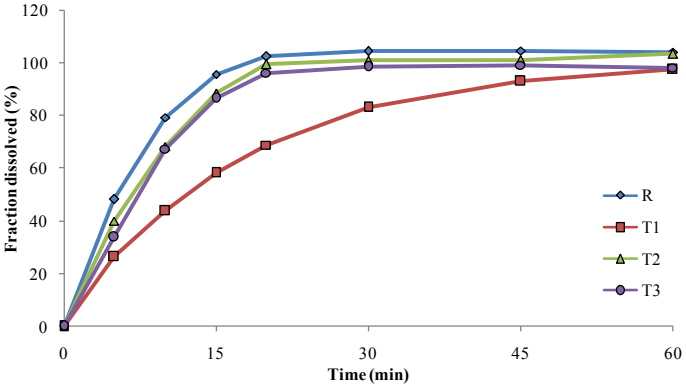
It is to be mentioned here previously conducted bioequivalence studies demonstrated equivalent pharmacokinetic profiles for R and T1, although non-similar dissolution profiles were obtained in all three media. In the same time, the reported maximum concentration was approximately 2.23% higher for R, while the difference in the area under curve after single oral administration was somewhat higher (5.15%). Therefore, it is reasonable to assume that, although the release rate is rapid in the gastric media and almost complete dissolution occurs at this level, this can lead to different peak and total exposure parameters. In this context, one should also consider the rapid absorption with a time of maximum concentration of 1.8 hours [7-9].



a) dissolution media: water, 900 mL



b) dissolution media: hydrochloric acid pH=1.2, 900 mL



c) dissolution media: phosphate buffer 50 mM pH=6.8, 900 mL

Figure 1

In vitro dissolution profiles for trimetazidine dihydrochloride from immediate release oral solid dosage forms, in different dissolution media

Table II

Pair-wise procedures for comparison of the *in vitro* release profiles

a) difference factor, f_1.

f_1		Water				pH=1.2				pH=6.8			
		R	**T1**	**T2**	**T3**	**R**	**T1**	**T2**	**T3**	**R**	**T1**	**T2**	**T3**
Water	**R**	0	14.98	4.63	3.83	**15.34**	**18.82**	6.86	5.1	11.36	**17.94**	5.6	4.25
	T1		0	**16.15**	**18.03**	**35.67**	4.51	**25.7**	**18.4**	**30.99**	3.47	**23.46**	**18.96**
	T2			0	4.59	**20.18**	**15.53**	11.35	5.99	**16.04**	**16.08**	9.36	6.70
	T3				0	**16.15**	**18.25**	7.61	3.83	12.14	**18.03**	6.01	2.69
pH=1.2	**R**					0	**29.62**	7.35	12.73	5.34	**28.85**	9.05	12.32
	T1						0	**31.64**	**23.99**	**37.18**	2.25	**29.28**	**24.57**
	T2							0	5.81	4.21	**23.21**	3.97	5.37
	T3								0	10.64	**18.47**	4.27	1.61
pH=6.8	**R**									0	**26.31**	5.76	9.19
	T1										0	**27.89**	**23.23**
	T2											0	3.64
	T3												0

b) similarity factor, f_2.

f_2		Water				pH=1.2				pH=6.8			
		R	**T1**	**T2**	**T3**	**R**	**T1**	**T2**	**T3**	**R**	**T1**	**T2**	**T3**
Water	**R**	100	**42.7**	68.52	71.73	**43.32**	**40.02**	60.36	66.97	51.69	**39.89**	63.91	68.36
	T1		100	**45.15**	**40.95**	**28.46**	72.65	**34.92**	**41.18**	**32.08**	78.52	**37.52**	**40.06**
	T2			100	69.87	**38.71**	**43.08**	52.64	66.04	**45.87**	**42.54**	56.92	64.66
	T3				100	**41.88**	**39.01**	59.68	72.31	51.23	**38.72**	64.61	80.30
pH=1.2	**R**					100	**26.96**	53.33	**40.75**	57.45	**26.88**	**45.73**	**42.11**
	T1						100	**33.04**	**38.68**	**30.21**	84.05	**35.2**	**37.82**
	T2							100	57.91	71.46	**32.93**	68.56	60.98
	T3								100	51.67	**38.75**	71.55	84.7
pH=6.8	**R**									100	**30.25**	61.44	53.53
	T1										100	**35.32**	**37.78**
	T2											100	72.68
	T3												100

All the evaluated immediate release formulations were film coated tablets. The *in vitro* release profile were fitted with the solution of a Weibull model. The results indicated a lag-time of approximately 2 minutes, with a low variability between the tested drug products and not correlated with the similarity conclusion for the dissolution patterns (Figure 2).

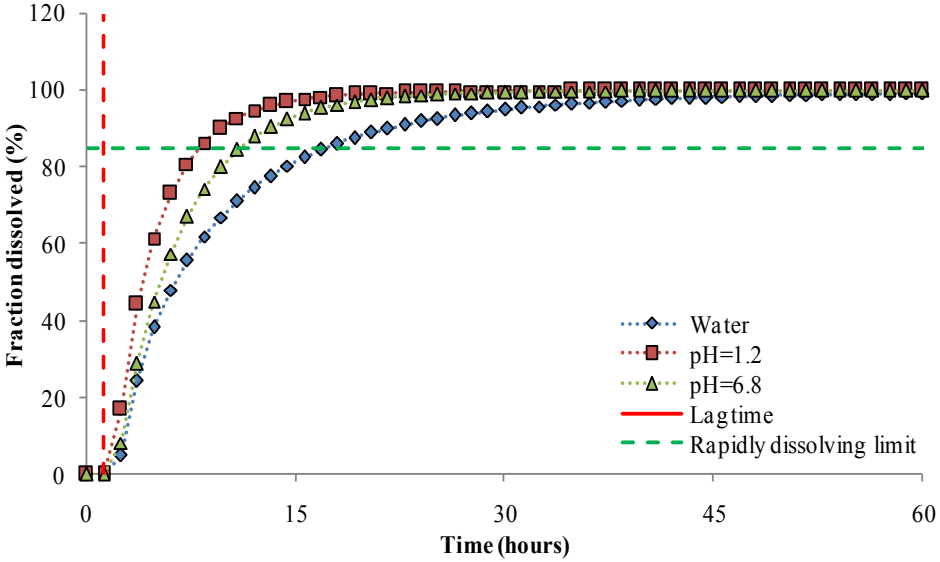


Figure 2
Estimated dissolution profiles for the reference product in various media (Weibull model)

We considered that trimetazidine hydrochloride could be a good candidate for biowaiver procedures, the BCS class I profile being associated with an adequate safety profile. Preliminary results currently under evaluation indicate that, although acidic conditions represent the most adequate selection for quality control purposes, better *in vitro – in vivo* correlations are generated by using water as dissolution media. Therefore, demonstration of similarity of the *in vitro* release in all the three media recommended by the regulatory guidance [2] must be assessed.

Conclusions

In vitro dissolution tests using three different media were performed on various immediate release oral solid dosage forms of trimetazidine hydrochloride. The *in vitro* profiles indicated a very rapid release of trimetazidine, almost independent on media composition. The most

discriminatory conditions seem to be provided by the acidic conditions, which can be considered as optimal for adequate quality control.

Acknowledgements

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