The effect of dissolution media, torque and flow speed on intrinsic dissolution rate of mebendazole, using Surface Dissolution Imaging (SDI)

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Leandro Giogetti[1], Eduardo José Barbosa[1], Rebeca Ruiz[2], John Comer[2], Karl Box[2], Robert Taylor[2], Jon Mole[3], Humberto Gomes Ferraz[1]

[1]Faculty of Pharmaceutical Sciences, University of São Paulo, Brazil [2]Sirius Analytical Ltd., Forest Row, East Sussex. UK [3]Sirius Analytical Inc., Beverly, MA. USA

Purpose

The aim of the study is to evaluate the effect of dissolution medium, torque and flow speed on intrinsic dissolution rate (IDR) of the antiparasitic low-soluble drug mebendazole .

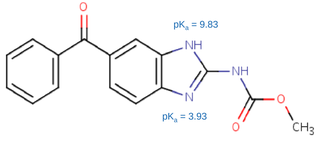

Fig. 1 – Molecular structure of mebendazole

Methods

The planning of tests was done by a fractional factorial design[1] (3^{3-1} assays), using dissolution medium, torque and flow speed as independent variables. IDR results were compared statistically using Statistica® software program.

Table 1 – Description of intrinsic dissolution assays of mebendazole, according to the proposed fractional factorial design

Assay	Torque (cN.m)	Dissolution Media	Flow (mL.min^{-1})
1	60	Phosphate buffer pH 6.8	0.5
2	60	Acetate buffer pH 4.5	1.5
3	60	HCl 0.1M	1
4	90	Phosphate buffer pH 6.8	1.5
5	90	Acetate buffer pH 4.5	1
6	90	HCl 0.1M	0.5
7	120	Phosphate buffer pH 6.8	1
8	120	Acetate buffer pH 4.5	0.5
9	120	HCl 0.1M	1.5

Dissolution experiments were conducted on Sirius SDI equipment. This system allows measurement and visualization of dissolution events on the surface of the drug by an ActiPix camera, that captures UV light absorbed by the dissolved drug inside a flow cell. Approximately 2 – 3 mg of mebendazole were analyzed in each of 10 min run, according to the proposed design. Drug pK_a was obtained by Fast-UV analysis on SiriusT3 equipment.

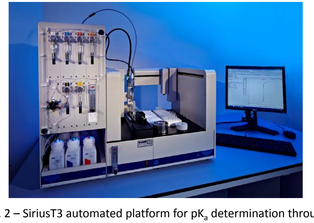

Fig. 2 – SiriusT3 automated platform for pK_a determination through Fast-UV analysis.

Fig. 3 – Above: Sirius SDI. Above right: Flow cell. Below right: press set with sample cups

Results and Discussion

All tests showed good linearity between time and mass released, providing reliable results. Also, intrinsic dissolution rate values are consistent with a Biopharmaceutical Classification System Class II drug[2], especially with phosphate buffer at pH 6.8 (IDR < 1.7 µg.s^{-1}.cm^{-2}). As expected, statistical analysis indicated that only the dissolution medium has a significant impact on the IDR of the drug as mebendazole is an ampholyte (pK_as= 3.93 basic, 9.83 acidic). Therefore, mebendazole was completely protonated in 0.1 M HCl, mostly neutral at pH 4.5 and 100% neutral at pH 6.8 (table 1). Mebendazole showed considerable mass release in the assays containing 0.1M HCl, regardless of torque or flow speed employed.

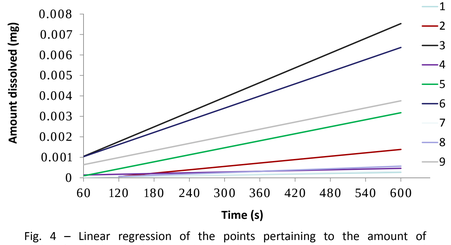

Fig. 4 – Linear regression of the points pertaining to the amount of mebendazole dissolved against time, in the intrinsic dissolution tests carried out according to Table 1.

Table 2 – IDR values for assays 1-9

Assay	IDR (µg.s^{-1}.cm^{-2})
1	0.83
2	6.01
3	25.48
4	1.13
5	10.73
6	18.58
7	1.06
8	2.01
9	10.97

Table 3 – Significance tests (ANOVA) for the factors studied. Result is significant for p < 0.05 (red)

Factor	Sum of squares	Degrees of freedom	Mean of Squares	F	p
Torque	67.36	2	33.68	10.89	0.08
Dissolution Media	474.17	2	237.09	76.69	0.01
Flow	69.92	2	34.96	11.31	0.08
Error	6.18	2	3.09		
Total SS	617.63	8			

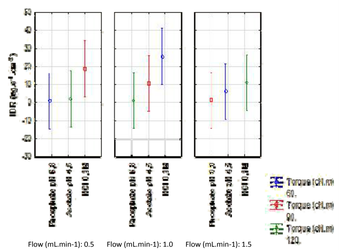

Fig. 5 – Mean values of mebendazole IDR (µg.s^{-1}.cm^{-2}). Error bars indicate the standard deviation of the media.

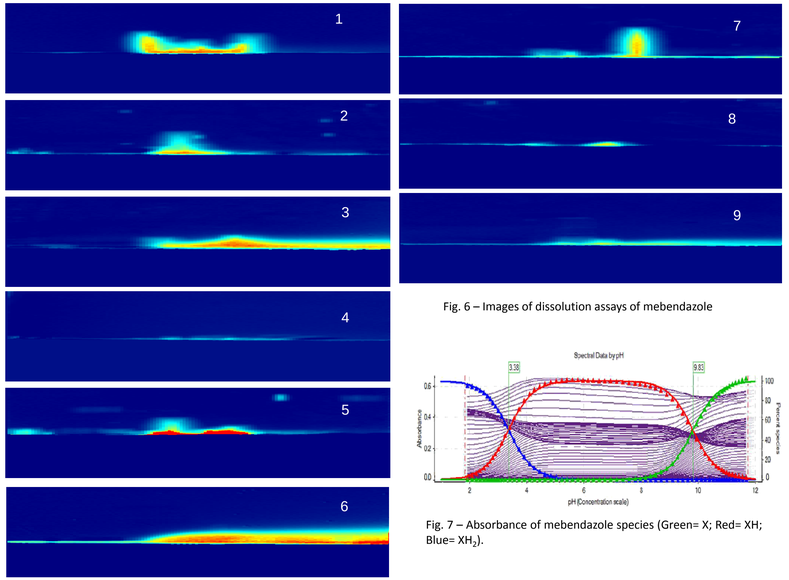

Fig. 6 – Images of dissolution assays of mebendazole

Fig. 7 – Absorbance of mebendazole species (Green= X; Red= XH; Blue= XH_2).

Conclusion

In this poster we showed that the dissolution medium had a considerable impact on the IDR of mebendazole, regardless of torque and flow speed employed. The Sirius SDI equipment provided an easy and low volume technique that was used to study the factors that impacted on the intrinsic dissolution of mebendazole.

References

[1] Issa et. al. Int. J. Pharm. Eng.1 (1), 17-29. 2013.
[2] Yu et. Al. Int. J. Pharm. 270 (1-2), 221-227. 2004.

For more information please contact:
Sirius Analytical, Forest Row Business Park, Station Road, Forest Row, East Sussex, RH18 5DW, UK
T +44 (0)1342 820720 **F** +44 (0)1342 820725 **E** sales@sirius-analytical.com