Ternary solid solutions, obtained by hot melt extrusion (hme) of itraconazole in a binary matrix

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INTRODUCTION

Achieving good drug dissolution and bioavailability has always been an issue for poorly soluble drugs. One approach to overcome the problem of poorly soluble drugs is to form a solid dispersion of an API within a hydrophilic excipient. The presence of intimate mixing between the drug and excipient, which can be achieved through HME technology, has demonstrated marked improvements in dissolution performance.[1] In addition, extruded formulations containing amorphous poorly water soluble drug have shown improved dissolution rates and as a result, bioavailability enhancement when compared to crystalline drug or the physical mix formulation. Optimum drug dissolution rate and stabilisation of amorphous drug against drug recrystallisation could be achieved with appropriate selection of excipients and processing conditions, for example extrusion temperature and screw speed.

EXPERIMENTAL METHODS

- Excipients selection was performed by measuring saturation solubility of itraconazole (ITZ) in a polymer solution. ITZ/excipient films were prepared by film/solvent casting, except for amorphous ITZ and ITZ/HPMC which were obtained by melting and rapid cooling of samples in liquid nitrogen. Phosphate buffer pH 6.8 was added to the film/samples and the solution was shaken for 72 h at 37°C. Samples were filtered prior to UV-Vis spectroscopy analysis.
- Solubilisation capacities of excipients at different ITZ content were investigated using Differential Scanning Calorimetry (DSC). Samples were prepared as ITZ/excipient films.
- Formulations were extruded at various feed compositions and temperatures using a twin-screw extruder. Extrudates were characterised using Powdered X-ray Diffractometer (PXRD) and DSC. The uniformity of the extrudates (i.e. initial, middle and end segments) was investigated using DSC, PXRD and High Performance Liquid Chromatography (HPLC).

RESULTS AND DISCUSSION

- The results of the solubility enhancement of ITZ in 14 excipients compared to the crystalline and amorphous ITZ solubility in phosphate buffer pH 6.8 are shown in Figure 1. Eudragit E100, Vitamin E TPGS, Soluplus and HPMC E5, showed the highest enhancement in saturated solubility and were selected for the extrusion study.
- Eudragit E100, Soluplus and Vitamin E TPGS were shown to form amorphous ITZ at 10%, 20% and 10% ITZ content, respectively (results not shown).
- Table 1 shows the results of extrudates processed at different extrusion temperatures and initial ITZ contents (%). Three formulations contained amorphous ITZ in the extrudate.
- ITZ recovery (%) after the extrusion was approximately 90% for ITZ/Eudragit/Vitamin E TPGS and ITZ/HPMC/Vitamin E TPGS extrudates and approximately 25% for ITZ/Soluplus/Vitamin E TPGS extrudate.
- Uniformity of these extrudates was verified from the similar Tg values and ITZ content (%) in all segments of the extrudates (Table 2).

Excipient 1	Extrusion temp. (C)	Initial ITZ content (%)	Results		
			Tg (C)	Tm (C)	Drug state
Eudragit E100	150	30	52.5	152.5	Crystal
	150	10	45.5	136.5	Crystal
	180	10	127.2±3.1	No	Amorphous
Soluplus	150	30	80.4±1.1	No	Amorphous
HPMC E5	180	30	25.5	153	Crystal
	180	10	121.0±1.6	34.0±0.5	Amorphous

Table 1: DSC and PXRD results of extrudates
[Excipient 1: Vit E TPGS and combination excipient (70/30)]

Extrudate	Tm/Tg (oC)	Actual drug content (%)
ITZ/Eud/Vit E TPGS (initial segment)	Tg = 130.66	9.3 ± 0.0
ITZ/Eud/Vit E TPGS (middle segment)	Tg = 124.75	9.1 ± 0.1
ITZ/Eud/Vit E TPGS (last segment)	Tg = 126.19	8.9 ± 0.1
ITZ/Soluplus/Vit E TPGS (initial segment)	Tg = 80.79	9.1 ± 0.0
ITZ/Soluplus/Vit E TPGS (middle segment)	Tg = 81.23	9.1 ± 0.1
ITZ/Soluplus/Vit E TPGS (end segment)	Tg = 79.10	9.0 ± 0.1
ITZ/HPMC/Vit E TPGS (initial segment)	Tm = 34.52[a], Tg = 121.28	24.0 ± 0.3
ITZ/HPMC/Vit E TPGS (middle segment)	Tm = 33.52[a], Tg = 122.43	24.7 ± 0.3
ITZ/HPMC/Vit E TPGS (end segment)	Tm = 34.08[a], Tg = 119.3	25.2 ± 0.1

Table 2: Melting point, glass transition temperature and drug content of extruded formulations

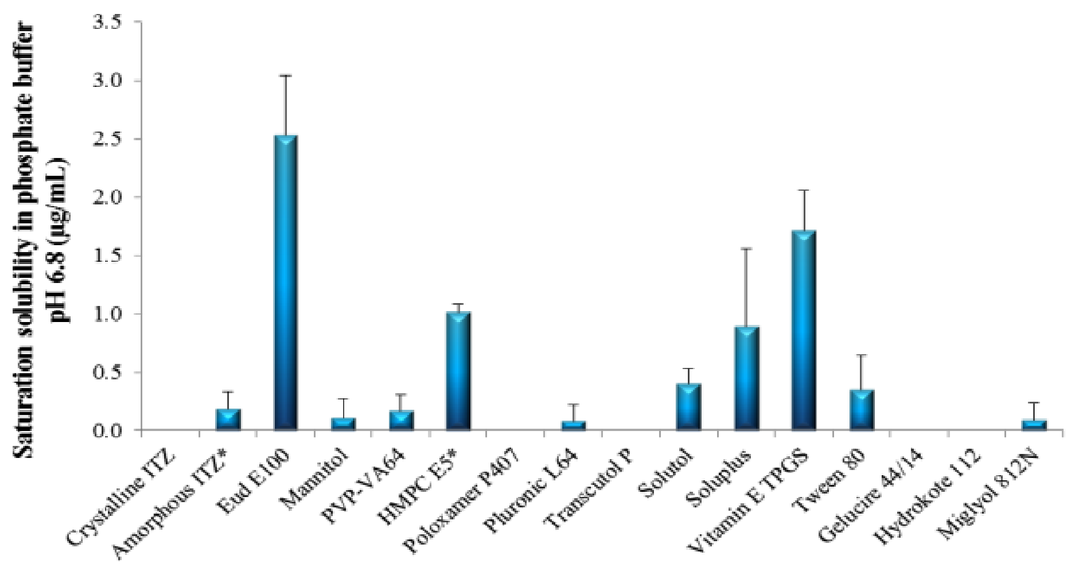

Figure 1. Saturation solubility of ITZ in excipient in phosphate buffer pH 6.8

CONCLUSIONS

Single-phase and binary-phase ITZ systems were obtained using HME. The miscibilities of ITZ with Eudragit/Vitamin E TPGS and Soluplus/Vitamin E TPGS enabled the stabilisation of amorphous ITZ against crystallisation following HME. Further studies are planned to evaluate the dissolution performance of the formulations prepared by HME.

REFERENCES

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