Development of a stable nystatin oral suspension to overcome shortages of the commercial dosage form

TCH-009

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Background

Nystatin is often used in the treatment of cutaneous, vaginal, mucosal and esophageal Candida. It's widely employed in cancer and immunocompromised patients suffering from mucositis.
The lack of the industrial oral suspension from July 2011 to February 2012 caused difficulties in the provision of the medicine for these inpatients and outpatients types.

Purpose

With the aim to ensure a safe continuity of therapy, liquid formulations of nystatin 100,000 IU/ml were developed as oral suspensions, due to the insolubility of the drug in water. The suspensions obtained were studied to assess their chemical-physical stability to find the most suitable formulation.

Materials and Methods

The Suspending agents used to disperse nystatin were:
- carboxymethyl cellulose (**CMC**)
- **tragacanth gum**

The aqueous vehicles used were:
- **sucrose syrup**
- sorbitol syrup (for the treatment of diabetic or paediatric patients)

Flavour used was:
- raspberry flavour

Final pH :
- 7.0-7.8 range.

Stability studies *(over a 3-month period):*
- particle mean sizes
- viscosity
- Zeta potential
- active ingredient content (HPLC analysis)

Temperature:
- 25 C and 40 C

Time
- t= 0 day, 7 day
- t=15 day, 30 day
- t= 60 day, 90 day

Results

Stable suspensions of nystatin were obtained with mean sizes slightly greater than **1 µm**, with both suspending agents and vehicles.

	PARTICLE SIZES (nm)	P.I.*	pH	ZETA POTENTIAL (mV)
Commercial medicine	2196 256	0,218	7,3	-37,26 1,08
Nystatin suspension not homogenized	1980 210	0,428	7,7	-25,53 0,57
Nystatin suspension after homogenization	1131 46	0,305	7,7	-37,72 2,33

* **PI** =Polydispersion Index

CMC and **sucrose syrup**-containing suspension, however, **was more resistant against microbiological attack** and it was chosen as the most suitable preparation.

CONTENT OF NYSTATIN	*T 25°C*	*T 40 °C*
	% nys**	% nys**
0 day	100	100
30 day	84	84
60 day	84	83
90 day	83	82

** **nys** =nystatin

The content of nystatin in the suspension decreased by about **16% after the first month** and **then remained constant over time.**

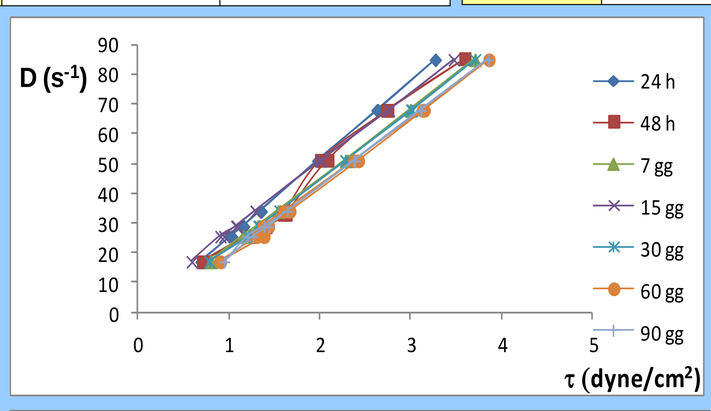
Stability studies

Particle sizes, Zeta potential and viscosity remained unchanged for at least 3 months at 25 and 40 C.

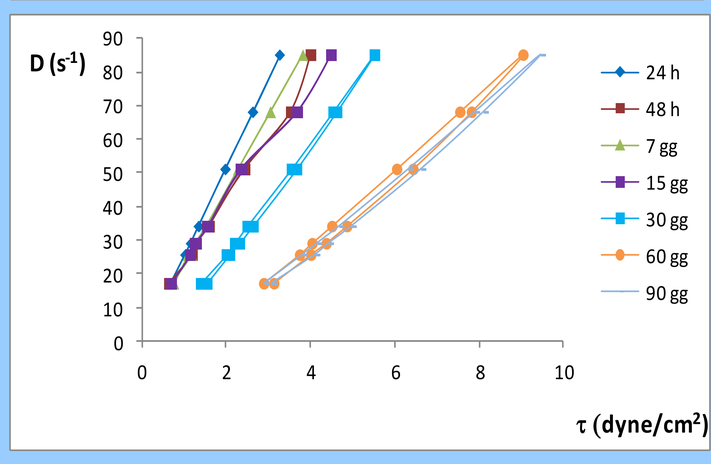
	T 25 C		*T 40 C*	
	PARTICLE SIZES (nm)	P.I.*	PARTICLE SIZES (nm)	P.I.*
0 day	1131 46	0,305	1131 46	0,305
30 day	903 57	0,215	1157 134	0,130
60 day	1205 91	0,005	1322 82	0,153
90 day	1199 114	0,010	1171 60	0,082

ZETA POTENTIAL (mV)	*T 25 °C*	*T 40 °C*
0 day	- 37,72 ± 2,33	/
30 day	- 32,77 ± 1,74	- 35,82 ± 4,97
60 day	-26,25 ± 3,32	-29,77 ± 1,32
90 day	-28,00 ± 1,60	-35,04 ± 1,45

pH	*T 25 °C*	*T 40 °C*
0 day	7,77	/
30 day	7,24	7,22
60 day	7,12	7,10
90 day	7,08	7,02



At 25 C: Newtonian behaviour



At 40 C: PSEUDOPLASTIC behaviour

Conclusions

The development of a stable nystatin suspension was crucial to ensure care continuity for patients with oral mucositis previously treated with the medication of industrial origin, whose temporary commercial lack offered new formulation challenges to the hospital pharmacists.

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