FORMULATION OF ITRACONAZOLE NANOSUSPENSION FOR IMPROVING DISSOLUTION

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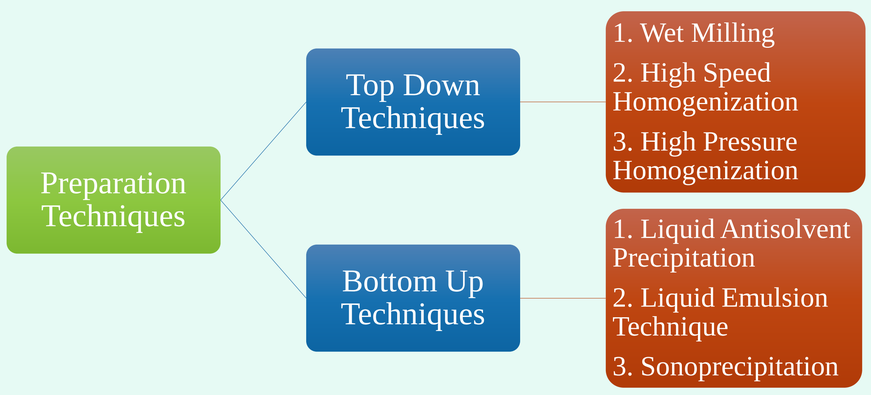
Introduction

Oral administration is the most favorable route of drug delivery. BCS class-II drugs are major challenge to modern drug delivery system, because of their poor water solubility which leads to low bioavailability. Itraconazole (ITN), shows 45% bioavailability, this strongly indicates need to improve dissolution. Nanosuspension is one such approach which has revealed its potential to tackle problems associated with the delivery of poorly soluble drugs, and are unique because of their simplicity with respect to manufacturing and scalability.

Properties of Nanosuspension

- Usually less than one micron with the average particle size ranging 200- 600nm
- Drug is maintained in the required crystalline form with reduced particle size leads to the increased dissolution rate and enhances the bioavailability
- Increase in insolubility
- Increase in apparent saturated solubility Cs, and Surface area.
- Increase in dissolution velocity
- Increase adhesiveness



Process Flow

Screening of Excipients

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Selection of excipients based on Drug – excipient compatibility study

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Process selection for preparation of Nanosuspension

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Optimization of the formulation

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In-vitro Analysis

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Stability studies

Trial 1: High Speed Homogenization (IKA)

	ITN01	ITN02	ITN03	ITN04
Batch size	100 ml	100 ml	100 ml	100 ml
Ingredients	g/100ml	g/100ml	g/100ml	g/100ml
ITN	1	1	1	1
Propylene Glycol	1	1	1	1
SLS	-	2	-	-
Poloxamer 407	2	-	-	4
PVP-K30	-	-	-	-
HPMC E5	-	-	2	-
Water	Q.S.	Q.S.	Q.S.	Q.S.

Results : Size achieved was higher than 800 nm. HPMC E5 gave higher viscosity of the solution. In ITN04 foam was formed due to high amount of poloxamer 407.

Trial 2: High Pressure Homogenization (HPH)

	ITN05	ITN06	ITN07	ITN08
Batch Size	25 ml	25 ml	25 ml	25 ml
Ingredients	g/100ml	g/100ml	g/100ml	g/100ml
ITN	1	1	1	1
Propylene Glycol	1	1	1	1
Poloxamer 407	2	3	2	
Poloxamer 188	-	-	-	-
PVP-K30	-	-	-	-
HPMC E5	-	-	-	2
Water	Q.S.	Q.S.	Q.S.	Q.S.

Results: Particle size with ITN05, ITN06, ITN07 and ITN08 was 500 nm, 400 nm, 400 nm and 380 nm respectively. But in case of ITN06 required pressure and No of HPH cycles were higher.

Trial 3: Combination of High Speed and High Pressure Homogenization

	ITN09	ITN10	ITN11	ITN12
Batch Size	100 ml	100 ml	100 ml	100 ml
Ingredients	g/100ml	g/100ml	g/100ml	g/100ml
ITN	1	1	1	1
Propylene Glycol	0.5	1	0.5	1
SLS	1	-	-	1
Poloxamer 407	2	2	-	2.5
Poloxamer 188	-	-	2	-
PVP-K30	-	-	1	-
HPMC E5	-	2	-	-
Water	Q.S.	Q.S.	Q.S.	Q.S.

Results: Particle size with ITN09, ITN10, ITN11 and ITN12 was 450 nm, 380 nm, 450 nm and 400 nm respectively. ITN11 gave sticky powder like final product

Trial 4: NanoEdge™ (Combination of Precipitation + High Pressure Homogenization)

	ITN13	ITN14	ITN15	ITN16
Batch Size	100 ml	100 ml	100 ml	100 ml
Ingredients	g/100ml	g/100ml	g/100ml	g/100ml
ITN	1	1	1	1
N-Methyl Pyrolidone	5	5	5	5
SLS	1	-	-	1
Poloxamer 407	2	-	3	-
PVP-K30	-	2	1	-
HPMC E5	-	2	-	3
Water	Q.S.	Q.S.	Q.S.	Q.S.

Results: Particle size with ITN13, ITN14, ITN15 and ITN16 was 420 nm, 450 nm, 400 nm and 320 nm respectively. In ITN15 little amount of foam was formed.

Batch Selection Criteria

- Particle size should be ≤ 450 nm
- PDI should be ≤ 0.3
- % Assay should be ≥ 98%

Hence, based on the results obtained and taking batch selection criteria in to the consideration, Batches ITN06, ITN07, ITN08, ITN10, ITN12, ITN15 and ITN16 were further taken for spray drying.

Optimized Parameters for Spray Drying

Parameters	Optimum value
Solvent	Purified water
Inlet temperature	75° C ± 5° C
Outlet temperature	50° C ± 5° C
Pump speed	3 ml/Min
Atomization pressure	0.8 to 1 kg/cm^2

Results of Selected Batches (Before Spray drying)

	ITN06	ITN07	ITN08	ITN10	ITN12	ITN15	ITN16
Z-Average	401.2	380.5	363.6	432.2	378.1	380.5	320.8
PDI	0.193	0.186	0.150	0.113	0.444	0.186	0.127
Assay (%)	101.2	99.3	100.6	101.3	99.5	99.4	100.9

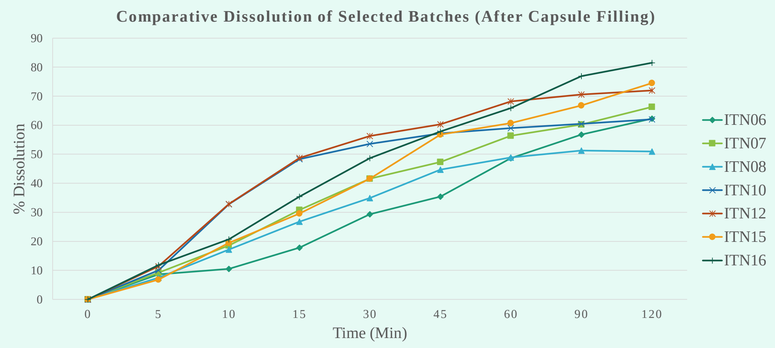
Results of Selected Batches (After Spray drying)

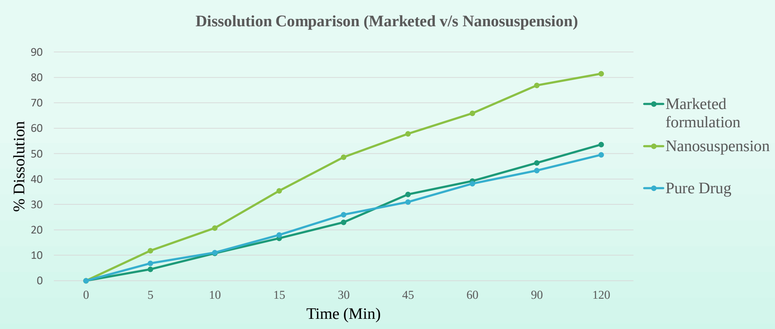
	ITN06	ITN07	ITN08	ITN10	ITN12	ITN15	ITN16
Z-Average	460	411	409.6	478.1	401.6	431.2	355.2
PDI	0.175	0.148	0.154	0.288	0.182	0.08	0.277
Assay (%)	99.7	99.3	100.1	101.3	98.5	100.2	99.9

Optimized Capsule formulation

Components	Quantity
Mannitol	‘’ mg
Microcrystalline cellulose pH112	‘’ mg
Drug ITN	100 mg drug ITN eq. of spray dried powder
Hydoxypropylmethyl cellulose E5 (Solubility enhancer)	50 mg
Talc (Glidant)	‘’ mg
Magnesium Stearate (Lubricant)	‘’ mg

‘’mg - confidential





Conclusion

- Amongst all the techniques, NANOEDGE™ was found most suitable for nanosuspensions formulation.
- Further optimized formulation of ITN Nanosuspension was proven stable in stability studies (40 °C/75 % RH).
- Formulating a nanosuspension of Drug, increased the dissolution and can improve the Bioavailability as well.
- Nanosuspensions represent a promising alternative to current delivery systems and the developed nanosuspension of ITN exhibits huge potential for improving bioavailability.

References

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