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Development of a dispersible paediatric pyrazinamide tablet : A model compounding formulary in resource limited primary healthcare settings.

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Background

Tuberculosis (TB) is a global and public health issue. TB burden is high in developing countries like Nigeria.

Paediatric TB patient population is high and therapy is challenged because commonly tablet formulations are presented as adult doses which necessitates breakages or splitting into either halves, one-thirds or quarters as equivalent paediatric doses. However, this often results in dose inaccuracies (sub-optimal and overdosing).

The End TB-Strategy of WHO targets a substantial reduction in paediatric TB by 2035.

Proactive measures such as the development of paediatric solid dosage formulations are needed to attain this set goal.

Compounding of cost-effective pharmaceuticals is an essential component in primary healthcare.

Aim

To develop using pyrazinamide as a model drug, a compounding formulary for dispersible anti-tubercular paediatric tablet formulations in resource limited healthcare settings.

Methods

Five different powder formulation batches which contained pyrazinamide (API), mannitol (diluent) and different concentrations (0.5-5 % w/w) of sodium carboxylmethyl cellulose (superdisintegrant) were subjected to wet granulation using polyvinyl pyrrolidone (PVP) as the binder. Granules were appropriately dried and subjected to direct compression.

Pre and post compression evaluations respectively for granules and tablet batches in accordance with established methods and protocols as indicated hereafter were undertaken.

Granules were evaluated for micrometric(bulk and tapped densities) and flow properties (angle of repose, hausner's ratio, carr's /compressibilty index and flow rate) .

The dispersed tablets were evaluated for uniformity of weight, hardness, diameter, friability, disintegration , water absorption ratio and wetting time.

Results were analysed statistically using analysis of variance(ANOVA). Level of significance set @ $p < 0.05$

Table 1. Composition of Dispersible Pyrazinamide Tablet Formulation

Formulation Ingredients	Formulation Ingredients of the Different Batches of Pyrazinamide Dispersible Tablets (%/w/w)				
	F1	F2	F3	F4	F5
Pyrazinamide	50	50	50	50	50
Mannitol	43	42	40	39.5	38.5
Sodium Carboxymethylcellulose	0.5	1.5	3.5	4.0	5.0
Polyvinyl pyrrolidone	6.0	6.0	6.0	6.0	6.0
Magnesium stearate	0.5	0.5	0.5	0.5	0.5
Total Tablet weight	100	100	100	100	100

Results

Table 2. Micromeritics Properties of Dispersible Pyrazinamide Granulation Batches

Granule Batch Code	Angle of Repose	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Flow rate
F1	22.27 ±1.1	0.635 ±0.01	0.793 ±0.02	19.9 ±0.35	1.25 ±0.01	28 ±1.1
F2	18.78 ±1.0	0.656 ±0.01	0.766 ±0.01	14.3±0.41	1.16 ±0.01	30 ±1.1
F3	17.24±1.0	0.807 ±0.02	0.811±0.03	9.43 ±0.5	1.10 ±0.02	43 ± 1.2
F4	10.30±0.82	0.749 ±0.01	0.817 ±0.04	8.3 ±0.32	1.09 ±0.01	68 ±1.1
F5	14.03 ±1.1	0.689 ±0.01	0.739 ±0.02	6.5 ± 0.41	1.06 ±0.01	85±1.1

More Results

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Table 3. Physical Properties of Dispersible Pyrazinamide Tablet

Tablet Batch Code	Uniformity of Weight (mg)	Hardness Kg/cm^3	Friability (%)	Thickness(mm)	Diameter (mm)	Disintegration Time (sec)
F1	0.152±0.001	4.0±0.1	0.440±0.01	6.056± 0.02	6.042±0.02	210± 1.3
F2	0.151±0.001	4.1±0.1	0.490±0.01	6.053±0.02	6.041±0.01	195± 1.5
F3	0.153±0.002	3.9±0.2	0.540±0.01	6.051±0.03	6.032±0.01	89± 1.2
F4	0.152±0.001	4.2±0.1	0.450±0.02	6.048±0.02	6.028±0.01	80± 1.3
F5	0.150±0.001	4.2±0.1	0.480±0.03	6.047±0.02	6.025±0.01	65± 1.0

Key. F1-F5 Formulation codes for Pyrazinamide Dispersible Tablet

Conclusions

Increasing concentration of the superdisintegrant (sodium carboxyl methyl cellulose) resulted in a corresponding faster disintegration time .An optimized formulation of a paediatric oral dispersible tablet of pyrazinamide that can be applied as a primary healthcare compounding model in a resource limited has been developed.

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