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Formulation and Evaluation of Dry Syrup Containing Linezolid

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ABSTRACT

Taste is an important factor in the development of dosage form. The problem of bitter and obnoxious taste of drug in pediatric patient can create a bad psychological effect on mind. The purpose of this research was to mask the intensely bitter taste of Linezolid using ion exchange resin and to formulate the dry syrup of the taste masked drug. When suspension is swallowed the bitter taste of the drug may not be felt as ion exchange resin does not release the drug at salivary pH. When it comes in contact with acidic environment of stomach, the complex will be broken down releasing the drug which may then absorbed. Batch method was used for formation of drug resin complex. Various ion exchange resin like different grade of kyron and indion 214 were used for masking the bitter taste. Optimization of drug loading was carried out. Indion 214 was selected as a optimized resin with 84.47 % drug loading. Dry syrup was made using suspending agent like gellan gum, guar gum and CMC and evaluated for various parameters like colour, odour, taste, viscosity, sedimentation volume, redispersibility, % drug content, drug release. By evaluating all the parameter the batch formulation contained guar gum 3 % was the best one amongst all the other formulations.

Keywords: Ebola haemorrhagic fever, EBOV, WHO, NHP, EVD

INTRODUCTION

A number of patients, especially pediatric and geriatric, have difficulty in swallowing solid dosage forms hence liquid dosage forms are needed. Linezolid is slightly soluble in water hence formulation of a suspension will be most suitable but product may not be physically and chemically stable. In the present work, attention is paid to develop a reconstitutable suspension dosage form of linezolid and to study the stability and palatability of the same.[1]

Dry Syrups: [3,4,2] Dry Syrups are commercial dry mixtures that require the addition of water at the time of dispensing. A number of official and commercial preparations are available as dry powder mixtures or granules that are intended to be suspended in water or some other vehicle prior to oral administration. Most of the drugs prepared as a dry suspension for oral suspension are antibiotics. The dry mixture of oral suspension is prepared commercially to contain the drug, colorants, flavors, sweeteners, stabilizing agents, suspending agents and preserving agents that may be need to enhance the stability of the formulation.

Major application - pediatric therapy: taste masking[7]**:**

Oral Route of administration is the route of choice for administration of medicines in children. The only hurdle for dosage form designing for pediatric patients is the patient's acceptance of the dosage form. Pediatric Patients tend to become un-cooperative during the administration of oral medication; the most common reason being the taste of the oral formulation administered among the children. Most of the drugs administered as granules for oral suspension under pediatric therapy are Antibiotics, which when administered orally as any other dosage form have a bitter taste making it unpleasant for Children to consume the medication.

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MATERIALS AND METHODS

Table 1: List of materials

Sr. No	Materials used	Manufacturer
1	Linezolid	Zydus cadila pharmaceuticals
2	Indion 214	Ion exchange Pharmaceuticals
3	Gellan Gum	Chemdyes Corporation
4	Guar Gum	Leben pharma, Akola
5	Carboxy Methyl Cellulose	Colorcon Asia Pvt. Ltd.
6	Sodium Starch Glycollate	Maple Biotech Pvt. Ltd.,
7	Sodium Benzoate	Lesar Chemicals Ltd.
8	Sodium Citrate	Lesar Chemicals Ltd.
9	Sodium Lauryl Sulphate	Finar Chemicals Pvt. Ltd.
10	Potassium Bromide	Finar Chemicals Pvt. Ltd.
11	Aerosil	Finar Chemicals Pvt. Ltd.
12	Strawberry Flavor	Themis Medicare Ltd.
13	Quinoline yellow Colour	Themis Medicare Ltd.

Table 2: List of Batch code of formulation

Ingredients (%w/v)	Batch code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Linezolid + indion 214	3.86	3.86	3.86	3.86	3.86	3.86	3.86	3.86	3.86
Gellan gum	1	2	3	-	-	-	-	-	-
Guar gum	-	-	-	1	2	3	-	-	-
CMC	-	-	-	-	-	-	1	2	3
SSG	1	1	1	1	1	1	1	1	1
Sodium benzoate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sodium citrate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sucrose	23.13	23.13	23.13	23.13	23.13	23.13	23.13	23.13	23.13
SLS	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
KBr	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.006
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Flavor	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Qunoline yellow	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total (gm)	10gm	10gm	10gm	10gm	10gm	10gm	10gm	10gm	10gm
Reconstitute with water upto 30 ml									

EXPERIMENTAL METHOD[5,8,9]

PREPARATION OF DRY SYRUP OF LINEZOLID

- The dose of dry syrup was selected 100 mg/5 ml as syrup was meant to be prepared for pediatric patient. For pediatric patient the dose will be calculated on the basis of the weight of the patient. For Linezolid the pediatric dose is 8 mg/kg/day.
- So total 30 ml of dry syrup was prepared which contained total amount of 600 mg of Linezolid.
- Dry syrup of Linezolid (100 mg/5ml) was prepared using suspending agents, wetting agent, preservative, flocculating agent, superdisintegrant, buffer, anticaking agent, sweetener, flavours by granulation technique.
- All ingredients were passed through 200# before mixing.

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• The complex of drug and resin equivalent to 600 mg Linezolid was blended with the other ingredients by geometric mixing.
• The solid ingredients were blended and massed using water.
• Granulation was carried out by means of wet granulation using water as granulating fluid.
• The wet mass was formed into granules using 30 mesh sieve. The formed granules were dried in the oven and passed through 32 mesh after drying.
• 10 gm of final Linezolid dry syrup formulation were diluted upto 30 ml for final formulation.
• Dose of granulations: 1.66gm of the granulations diluted upto was 5ml equivalent to 100 mg of Linezolid.

EVALUATION PARAMETER OF DRY SYRUP

a) Colour, odour and appearance[6]

All the developed batches of syrup were evaluated for organoleptic properties such as colour, odour and appearance.

b) Drug content[11]

Dry syrup equivalent to 100 mg of linezolid was taken in 100 ml volumetric flask and dissolved in 10 ml methanol and volume was made up to 100 ml by adding sufficient 0.1 N HCl. The solution was analyzed at 243.6 nm to found out drug content

Bulk density:

The powder (2 gm) filled in measuring cylinder called as bulk volume of powder and measure mass of that powder. Bulk density is ratio of mass of powder to bulk volume of powder. It is a measure used to describe a packing of powder. The equation for determining bulk density is

ρb = m/ vb-

Where, ρb= Bulk density m = Mass of powder vb= Volume of powder

Tapped density:

The pre-weighed powder (2gm) was filled in measuring cylinder. Then it was tapped in bulk density test apparatus. After 50 taps the volume is measured and the tapped density was measured using following formula.

ρt = m/ vt-

Where, ρt= Tapped density m = Mass of powder vt= Tapped volume

ii. Carr's index (CI):[9,10]

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size distribution of the powder. Powders with compressibility values lesser than about 20%, has been found to exhibit good flow properties. Tapped (ρt) and Apparent (ρb) Bulk density measurements can be used to estimate the compressibility of a material.

Carr's index (%) = (ρt - ρb) / ρt * 100 --

Where, ρb= Bulk density ρt= Tapped density

RESULTS AND DISCUSSION[13,14]

Colour, odour and appearance

Table 3: Organoleptic properties of all formulations

Formulations	Colour	Odour	Appearance
F1	Quinoline	Strawberry	Granular
F2	Quinoline	Strawberry	Granular
F3	Quinoline	Strawberry	Granular
F4	Quinoline	Strawberry	Granular
F5	Quinoline	Strawberry	Granular
F6	Quinoline	Strawberry	Granular
F7	Quinoline	Strawberry	Granular
F8	Quinoline	Strawberry	Granular
F9	Quinoline	Strawberry	Granular

In all the formulation Quinoline yellow was used as a coloring agent and strawberry flavor was used. Dry suspension was formed by means of granulation technique. All the formulations from F1 to F9 were appeared as a granular.

b) Drug content

Table 4: % drug content of Linezolid dry syrup

Formulations	% drug content
F1	98.47 %
F2	101. 84 %
F3	99.36 %
F4	99.27 %
F5	100.67%
F6	99.54 %
F7	102.45 %
F8	98.46 %
F9	98. 62 %

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c) Flow properties of dry syrup[15]

Table 5: Micromeritics property of Dry syrup

Formulations	Bulk density	Tapped density	Hausner ratio	Carr's index	Angle of repose
F1	0.426	0.512	1.20	16.79	20.70
F2	0.486	0.571	1.17	14.88	21.27
F3	0.468	0.562	1.20	16.72	20.33
F4	0.482	0.556	1.15	13.30	21.46
F5	0.458	0.539	1.17	15.02	19.86
F6	0.477	0.562	1.17	15.12	19.37
F7	0.438	0.530	1.22	17.35	21.67
F8	0.470	0.563	1.19	16.51	22.27
F9	0.450	0.525	1.16	14.28	22.84

Micromeritics property of the dry syrup was carried out and it was found that all the batches of formulation were have all the parameter in the good to excellent range. As the dry syrup were in the form of granules they were free flowing having good flow property

VISCOSITY[12]

Table 6: Viscosity of different formulation of Linezolid dry syrup

Formulations	Viscosity (cps)
F1	347 cps
F2	451 cps
F3	566 cps
F4	1033 cps
F5	1296 cps
F6	1563 cps
F7	426 cps
F8	510 cps
F9	762 cps

Viscosity of the different formulations is shown in table 6. The guar gum had the highest viscosity than two other suspending agents. So it was concluded that the high sedimentation volume and the better redispersibility was because of high viscosity of the suspending agent guar gum.

As the viscosity of suspension was higher the particles or the solid contents present in the suspension will not sediment for a long time. So they will remain suspended in the suspension. Due to this effect the sedimentation volume of suspension was higher and the sedimentation rate was slow.

Redispersibility of higher viscous suspension is also better. This was because of that as the lowest sediments of particles occur it will easily redisperse again. So in present work it was shown that due to high viscosity of guar gum (3 %), its the sedimentation volume was highest and redispersibility was better than any other batch.

Sedimentation volume[10]

Table 7: Sedimentation volume of formulations

Formulations	Height of Sediment (cm) after								Sedimentation volume F= Hu/Ho
	3 min Ho	1 day	2 day	3 day	4 day	5 day	6 day	7 day	
F1	7.0	6.2	5.0	4.5	4.1	3.6	3.4	3.2	0.45
F2	7.0	6.3	5.2	4.6	4.2	3.7	3.6	3.6	0.51
F3	7.0	6.7	5.5	5.2	4.5	4.1	3.9	3.9	0.55
F4	7.0	6.7	6.4	6.6	6.2	6.1	6.0	5.9	0.84
F5	7.0	6.8	6.7	6.6	6.4	6.3	6.2	6.1	0.87
F6	7.0	7.0	7.0	6.8	6.8	6.5	6.4	6.4	0.91
F7	7.0	6.2	5.6	5.1	4.8	4.5	4.2	4.1	0.58
F8	7.0	6.5	5.9	5.4	5.1	4.6	4.4	4.4	0.62
F9	7.0	6.6	6.0	5.5	5.3	4.8	4.7	4.6	0.65

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The sedimentation volume was measured to check the physical stability of the reconstitutable suspension. The sedimentation volume can have values ranging from less than 1. The ultimate height of the solid phase after settling depends on the concentration of solid content. To obtain an acceptable suspension, the sedimentation volume (F) should be at least 0.9 for 1 hour but a longer period is preferred for our purpose.

The sedimentation volume in above formulations is shown in table 8. The results showed that for formulation batch F6 the sedimentation volume was 0.91 even after 7 days which is very nearer to the standard value of sedimentation volume 1. Means no sediment of the solid content occurred et the end of 7 days. This was due to the suspending agent Guar gum (3 %), as suspending agent is responsible for suspend the solid particles in suspension. From results it was proved that guar gum 3 % was the optimum concentration of suspending agent required to make a good quality Linezolid suspension. So the formulation of batch F6 was better than all other formulation as they all had sedimentation volume less than batch F6.

Redispersibility[11,8]

Table 8: Redispersibility of formulations

Formulations	Redispersibility (no. of strokes)
F1	13
F2	10
F3	8
F4	9
F5	7
F6	5
F7	13
F8	11
F9	9

Redispersibility is an important factor when one has to deal with suspension. As if there is no redispersion of suspension then it will lead to caking of solid content and if cracking occurs then there must be chance of non uniform dose of drug during medication because the drug will remain in the cake.

Redispersibility is measured by means of number of strokes. Means after maintaining the suspension in undisturbed condition for 7 days, at the end of 7th day how many strokes required to redisperse the suspension.

Table 8 shows the number of strokes required for different formulation. From the results it was concluded that the formulation batch F6 (guar gum 3 %) had the minimum number (5) of strokes as compared to all the other formulation. So results concluded that the formulation with guar gum (3 %) was easily redispersable this was because the sedimentation volume was also higher for the same formulation than any other formulation.

***In-vitro* drug release of oral taste masked suspension**

Table 9: *In vitro* drug release in 0.1 N HCl

Time (min)	% drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	94.23	95.76	93.99	96.79	96.86	94.24	96.24	95.74	94.19
10	95.34	96.29	95.57	97.89	97.59	96.33	97.46	97.69	96.69
15	96.87	97.59	96.49	99.29	99.55	97.86	99.48	99.55	99.48
30	98.64	99.59	97.87	99.55	99.87	99.69	99.82	99.76	99.77
45	99.09	99.87	99.79	99.88	99.92	99.84	99.98	99.91	99.89
60	99.85	99.94	99.87	99.98	99.98	99.89	99.98	99.91	99.98

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Table 9 shows the release of Linezolid in 0.1 N HCl. Results were shown that the drug (Linezolid) were release within 30 minutes. It means that the Linezolid-indion214 complex was broke down when it comes in contact with 0.1 N HCl. So it was given fast onset of action as the drug release was occurred within 30 min.

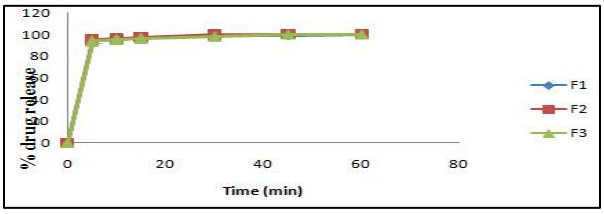

Figure 1: Drug release of all three concentration of gellan gum in 0.1 N HCl

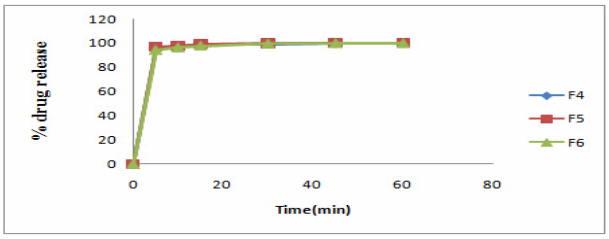

Figure 2: Drug release of all three concentration of Gaur Gum in 0.1 N HCL

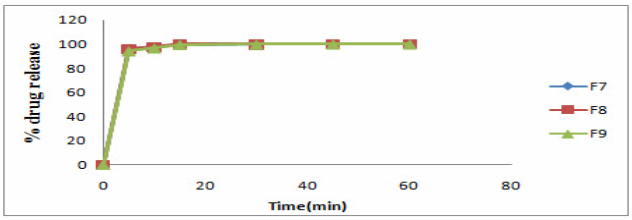

Figure 3: Drug release of all three conc of CMC in 0.1 N HCL

pH of reconstitutable suspension

Table 10: pH of reconstitutable suspension

Formulations	pH
F1	6.5
F2	6.3
F3	6.2
F4	6.6
F5	6.7
F6	6.4
F7	6.8
F8	6.7
F9	6.6

Accelerated stability study

Table 11: Accelerated stability study data for optimized batch

Evaluation Parameters	Initial	After 18 days
Colour	Quinoline Yellow	Quinoline
Odour	Strawberry	Strawberry
Sedimentation volume	6.4	6.2
Redispersibility	5	6
Drug content	98.53	97.98
% Drug release	98.88 %	97.59 %
pH	6.4	6.3

Accelerated stability study was carried out of optimized batch (F6) for 18 days. The two dependent variables were checked mainly named sedimentation volume and redispersibility. From results it was measured that there was little difference in both the parameter. The sedimentation volume was 6.2 in place of 6.4 which were before stability study and the redispersion strokes were 6 in place of 5. So it was concluded that the optimized batch was stable after 18 days.

CONCLUSION

The aim of this present investigation was to develop taste masked Linezolid pediatric dry syrup. Ion exchange resin technique was selected to mask the bitter taste of Linezolid as complexation with ion exchange resin is a simple and cost effective technique. Several ion exchange resins like kyron T-104, kyron T-134, kyron T-154, kyron T-314 and indion 214 were used to mask the taste. Complexation of Linezolid and resin was done by stirring them together for 6-8 hours on magnetic stirrer. Taste masked dry syrup of Linezolid was prepared using indion 214 as Linezolid had a maximum binding efficiency with indion 214 about 84. 47 %. So it was selected as a resin for final taste masked dry syrup. The resinate were evaluated for different parameters like taste evaluation, micromeritic properties and % drug content. It was concluded that the taste was completely masked and acceptable for pediatric patients. The taste masked syrup was prepared using three different

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suspending agents namely gellan gum, guar gum and CMC. The final formulation contained three different concentrations of each suspending agents. Then it was evaluated for different parameters like colour, odour, % drug content, flow properties, sedimentation volume, pH, redispersibility, viscosity and in- vitro drug release. From the results it was concluded that the formulation with suspending agent guar gum with 3 % concentration showed highest sedimentation volume and better redispersibility which were very important parameter when once have to deal with suspension. The other parameters were also showed better results for the same suspending agent. So it was selected as a optimized suspending agent amongst three. Even after studying the stability study of 18 days the results of parameters were matched with the initial once.

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