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Formulation and Evaluation of Linezolid Microspheres: An Approach for Taste Masking Through Mouth Disintegrating Tablets

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ABSTRACT

Aim of this research work was to develop taste masked tablet that disintegrates easily through microspheres forms of Linezolid using Eudragit and to prepare mouth disintegrating tablets of the formulated microspheres using sodium starch glycolate and Sodium caramellose as superdisintegrant. Taste masking Eudragit E100 microspheres were prepared by solvent evaporation technique with an entrapment efficiency ranging from 78 to 85 %. DSC revealed no interaction between the drug and polymer. Microspheres prepared at a drug/polymer ratio of 1:2 and 1:5 revealed sufficient flow properties and better taste masking as compared to other ratios. Drug loaded microspheres were formulated as mouth disintegrating tablets using various additives. The dissolution behavior of Linezolid release was about 97.25 % within 180 minutes. The results obtained from the study suggested the use of Eudragit polymer for preparing Linezolid loaded microspheres with an aim to mask the bitter taste of the drug and furthermore mouth disintegrating tablets could be formulated using Sodium starch glycollate and sodium cross caramellose as superdisintegrant. The tablets were evaluated for evaluated for parametric tests thickness, hardness, tensile strength and friability, wetting time, water absorption ratio, moisture uptake studies, disintegration time and *in vitro* release studies.

INTRODUCTION

In earlier days, it was believed that the drugs having bitter taste are more efficient as well as more curable. This concept has been reversed with development of numerous formulation techniques. In recent era oral administration of bitter drugs with an acceptable degree of palatability becomes key issue for the healthcare providers, especially for pediatric and geriatric patients. Palatability is the combination of sensory perceptions including taste and smell and to a lesser extent texture, appearance and temperature of the products. Taste transduction involves the interaction of molecule with taste receptor cells, which reside in specific structures known, as taste buds.

Taste is detected when the soluble substances react with taste receptors and the perception of taste is transmitted to the brain via ninth cranial nerve. Various techniques to eliminate bitter taste of drugs include use of flavours[1], polymeric coatings[2], complexation with ion exchange resins[3], complexation with cyclodextrins[4], microencapsulation[5], chemical modifications etc. Microencapsulation is a process in which very thin coatings are applied around particles (solid/liquid). Therefore a microsphere is a small sphere having uniform coating around it, which provides it many useful properties like taste masking, controlled release etc. There diameter usually falls in a range of 1 μm to 1000 μm. Microspheres can be prepared by variety of methods including air suspension, coacervation phase separation, spray drying and congealing, pan coating, solvent evaporation and multiorifice centrifugation techniques[6]. Micro particulated entrapment of bitter drugs in the matrix of pH sensitive reverse enteric coated polymer, without compromising dissolution and bioavailability of drugs, were prepared by different methods has been reported in US Patent 20050136114[7]. Eudragit E100 is a polymethacrylate with pH dependent solubility, specifically used for taste masking. It is soluble in gastric fluid up to pH 5.0 and is swellable and permeable above pH 5.0[8]. So when the microencapsulated drug is consumed, it does not interact with taste receptors as it is insoluble in mouth. The moment the microencapsulated drug reaches the stomach the acidic pH conditions favour dissolution and thus the drug is released. Thus microencapsulation is a useful technique for masking the unpleasant taste. The most convenient method for preparation of microspheres is solvent evaporation technique. This technique is easier to perform in laboratory conditions[9]. Linezolid is an antibacterial compound developed by a team at Pharmacia and Upjohn

Company[10]. It is used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics. A member of the oxazolidinone class of antibiotics, linezolid is highly effective for the treatment of serious Gram-positive infections and has activity that compares favorably with vancomycin for most clinically relevant pathogens. Linezolid is new line antibiotic used to treat infections caused by Gram-positive bacteria that are resistant to several other antibiotics, the drug is highly bitter and there is need to develop a taste masked formulation of Lineolid.

MATERIALS AND METHODS

Experimental

Linezolid was procured as gift sample from Symet labs, Hyderabad, Sodium caramellose from FMC Biopolymer and Sodium Starch Glycolate from Rama Production Company. Ltd. Magnesium sterate was procured from Canton Labs, Mumbai. Hydrochloric acid and n-Hexane were obtained from Loba Chemie, Mumbai, India. Eudragit E-100 was obtained as gift sample from Panacea Biotec, Lalru, India. All other chemicals and reagents were of analytical grade and were used as such. Other chemicals were gifted by chemical companies.

Preparation of Microspheres

Microspheres were formulated using solvent evaporation method. Eudragit E100 was dissolved in mixture of organic solvent, ethanol (8): dichloromethane (2) on a magnetic stirrer to obtain uniform mixing. Magnesium stearate (5% w/v) was added which served as droplet stabilizer followed by addition of Linezolid with continuous stirring. The drug-polymer ratio was taken as 1:2 and 1:5. The polymer drug solution was added drop wise into a mixture of light liquid paraffin and n-Hexane containing Span 80 (2% w/v) maintained at 40 ºC. After complete evaporation of the solvent the microspheres were allowed to settle, supernatant was decanted and the microspheres were recovered by filtration through a Whatman filter paper followed by washing thoroughly with n-Hexane. The microspheres were dried at room temperature in a desiccators and stored in desiccators till further use.

Preparation of tablets

Microspheres equivalent to 5 mg Linezolid were taken for each tablet composition. Free flowing lactose was used as a directly compressible diluent. Granular Mannitol was used as

soothing agent, talc as an antiadherent and magnesium stearate as a lubricant. Mixed fruit flavor was added as flavoring agent. Ingredients like lactose and mannitol accurately weighed and passed through # 30 sieve were mixed with microspheres. The granules were then mixed with remaining ingredients. The above powder blend was compressed using rotary tablet machine using 11 mm concave punches. The prime parameters for selection of batches of microspheres for tableting were based on particle size, entrapment efficiency, flow characters and taste masking evaluation.

Evaluation of microspheres

Entrapment efficiency

The entrapment efficiency was calculated by the formula

$$EE = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Entrapment efficiency was calculated by digesting outer layer of 20 mg microspheres in 10 ml Chloroform and then 100 ml 0.1 N HCl was added. The suspension was then warmed for a few minutes, filtered & 1 ml of filtrate was made up to 10 ml with 0.1 N HCl. The solution was analysed using UV spectrophotometer at 271 nm to determine amount of linezolid entrapped in microspheres.

Evaluation of flow properties of microspheres

The prepared microspheres were evaluated for flow properties including bulk density, tapped density, angle of repose, Carr's compressibility index and Hausner ratio.

Particle size evaluation

Size distribution and average particle size of microspheres was calculated with optical microscopy. Optical microscope was fitted with eyepiece micrometer which was then calibrated with a stage micrometer. Size of about 100 microspheres was calculated from each batch and then the average size was calculated.

Compatibility Study

Chemical interaction between the drug and the polymeric material, if any, during the preparation of the microspheres was studied by Differential Scanning Calorimetry (DSC).

Taste characterization of microspheres

Taste evaluation was done by a panel of six volunteer using time intensity method. One tablet was in mouth for 10 sec, bitterness level was recorded, written consent was prepared volunteer as per protocol prepared.

Evaluation of Tablets

Thickness

The thickness of the tablets was determined using a thickness gauge.

Weight Variation Test

To study weight variation, 20 tablets of each formulation was weighed using an electronic balance, and the test was performed according to the official method.

Drug Content

Five tablets were weighed individually. The drug content was determined as described above.

Hardness and Friability

For each formulation, the hardness and friability of tablets was determined using the Monsanto hardness tester and the Friabilator respectively.

***In vitro* dissolution Studies**

In vitro drug release of the prepared batches was determined using eight stage USP dissolution apparatus II. The dissolution test was performed using 900 ml of 0.1 N HCl buffer at 37 ± 0.5 ºC. The speed of rotation of paddle was set at 50 rpm. At a predetermined time interval, 5 ml samples were withdrawn, filtered through Whatman filter paper, amply diluted and analysed using UV-Visible spectrophotometer.

RESULTS AND DISCUSSION

The percentage drug loading was also determined with both the ratios of Eudragit. The drug entrapment was found better with 1:5 ratio with about 85 % entrapment. The details are captured in Table 1.

The granules prepared were subjected for various physical parameters and met required flow properties. The content of the granules were found satisfactory. The details are captured in Table 2.

The prepared microspheres were subjected to taste evaluation test in male volunteers according to set protocol. The microspheres having drug to polymer ratio 1:5 were found better masked when compared to the microspheres made of ratio 1:2 to most of the volunteers.

In order to check chemical interaction between drug and polymer, thermal analysis was carried out by using Differential Scanning Calorimetry. DSC thermograms of Linezolod, Eudragit E100 and microsphere showed that there were no changes in the endotherms. The drug exhibited a sharp melting endotherm. The details are captured in Figure 1.

Size distribution and average particle size of microspheres was calculated with optical microscopy. Higher the stirring speed, reduction in average particle size of microspheres was observed. The mean diameter of the prepared batches of microspheres (M3-M4) was found to be 270.52 µm and 232.23 µm respectively. Particle size distribution of microspheres is represented by various histograms. The details are captured in Figure 2 and 3.

Mouth dissolving tablets of Linezolid microspheres were prepared using direct compression technique. Linezolid microsphere having 1:5 ratio having stirred at both RPM was taken to prepare the tablets. Criteria for selection of microspheres included were particle size, flow properties, encapsulation efficiency and taste masking ability. The details are captured in Table 3.

All the batches of mouth disintegrating tablets were formulated under similar conditions to avoid processing variables. The thickness of the tablets was ranged from 3.38 ± 0.08 to 3.48 ± 0.01 mm. The average percentage deviation of 20 tablets of each formula was less than ±5%. Drug content was found to be uniform among different batches of the tablets and ranged from 96.58 to 99.69. The hardness and percentage friability of the tablets of all batches ranged from 4.0 ± 0.14 to 4.2 ± 0.20 kg/cm^2 and 0.68 ± 0.02 to 0.79 ± 0.02 % respectively. The disintegration time of tablets were found between 20 to 30 seconds. The details are captured in Table 4. The

taste masking of the formulated tables was better as already taste masked granules were taken for further tablets making.

The dissolution profile studies of all six formulations are shown in Table 5 and Figure 4. More than 50 % of the active drug was released from all the six tablets at the end 30 minutes whereas about 90 % of drug release was seen at the end of 60 minutes.

CONCLUSION

The purpose of the present study was to develop taste masked microspheres of Linezolid using Eudragit E100 employing solvent evaporation technique as method of preparation of microspheres. The formulated microspheres were incorporated into tablet dosage form using super disintegrants by direct compression technique. In conclusion eudragit polymer was able to give the better taste masking potential for the highly bitter drug candidate like Linezolid.

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TABLE

Table No. 1. Microsphere evaluation parameters

Formulation Code	Drug: Eudragit	Stirring Speed	Entrapment Efficiency
M1	1:2	400 rpm	78.12 ± 0.93
M2	1:2	800 rpm	76.56 ± 1.23
M3	1:5	400 rpm	86.52 ± 2.25
M4	1:5	800 rpm	85.97± 1.09

Table No. 2: Powder evaluation: Physical and chemical evaluation powder granules

Sl. No.	Formulation Code	Angle of Repose	Bulk Density [g/mL]	Tapped Density [g/mL]	Comp. Index [%]	Drug Content [%]
1	TM1	24.15	0.318	0.488	21.85	98.75
2	TM2	23.33	0.306	0.468	20.36	97.85
3	TM3	24.82	0.312	0.478	20.71	99.36
4	TM4	25.25	0.309	0.474	21.08	98.56
5	TM5	26.25	0.315	0.464	21.58	97.56
6	TM6	25.94	0.311	0.471	20.85	98.23

Table No. 3: Formulation details of tablets with other ingredients

Ingredients	Formulation Codes					
	MT1	MT2	MT3	MT4	MT5	MT6
Drug:Resin	30	30	30	30	30	30
Lactose [free flowing]	65	65	65	65	65	65
Sodium starch glycollate	--	--	--	7.5	10	12.5
Crosscaramellose sodium	7.5	10	12.5	--	--	--
Mannitol [DC grade]	45	45	45	45	45	45
Aspartame	5	5	5	5	5	5
Mixed fruit flavor	2	2	2	2	2	2
Magnesium Sterate	1.5	1.5	1.5	1.5	1.5	1.5
Colloidal Silicone Dioxide	1.5	1.5	1.5	1.5	1.5	1.5
Talc	2	2	2	2	2	2

Note: Microsphere is taken in such quantity that Linezolid equivalent to 5 mg

MT1, MT2 & MT3 are from 1:2 [Drug:Resin] stirred with 800 RPM [M2, refer Table 3]

MT4, MT5 & MT6 are from 1:5 [Drug:Resin] stirred with 800 RPM [M4, refer Table 3]

Table No. 4. Evaluation of prepared tablets

Sl. No.	Formulation Code	Thickness* (mm)	Friability‡ (%)	Hardness‡ (kg/cm2)	Disintegration time	Drug Content* (%)	Weight Variation
1	MT1	3.48 ± 0.01	0.68 ± 0.02	4.2 ± 0.20	28 seconds	98.65	Passes
2	MT2	3.39 ± 0.06	0.71 ± 0.05	4.0 ± 0.14	30 seconds	97.56	Passes
3	MT3	3.41 ± 0.02	0.78 ± 0.06	4.0 ± 0.23	30 seconds	96.58	Passes
4	MT4	3.39 ± 0.03	0.69 ± 0.03	4.1 ± 0.25	24 seconds	99.69	Passes
5	MT5	3.38 ± 0.08	0.79 ± 0.02	4.1 ± 0.35	22 seconds	97.56	Passes
6	MT6	3.46 ± 0.12	0.68 ± 0.09	4.1 ± 0.32	20 seconds	98.36	Passes

Table No. 5. Dissolution profile of Linezolid taste masked tablets

Sl. No.	Formulation Code	% Drug Release Observed				
		15 Min	30 Min	45 Min	60 Min	90 Min
1	TF1	40	60	88	96	99
2	TF2	45	62	87	97	99
3	TF3	43	65	85	95	98
4	TF4	38	57	77	89	98
5	TF5	41	55	80	86	97
6	TF6	40	58	75	87	98

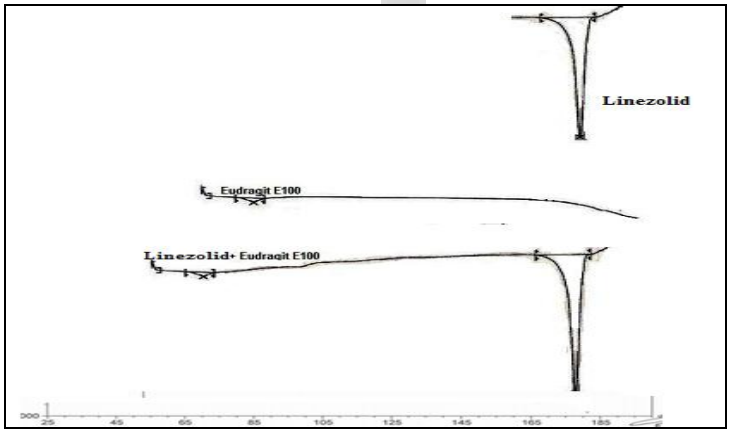

Figure No. 1. DSC Thermograms of Linezolid, Eudragit E100 and microspheres

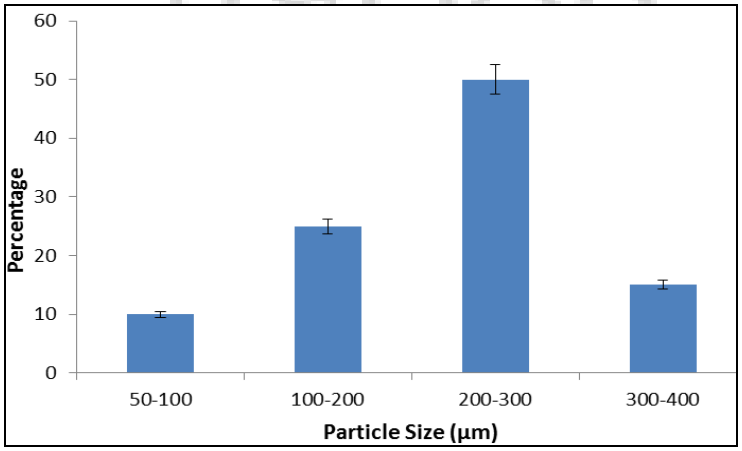

Figure No. 2. Histogram of particle size distribution of prepared microspheres at 400 rpm

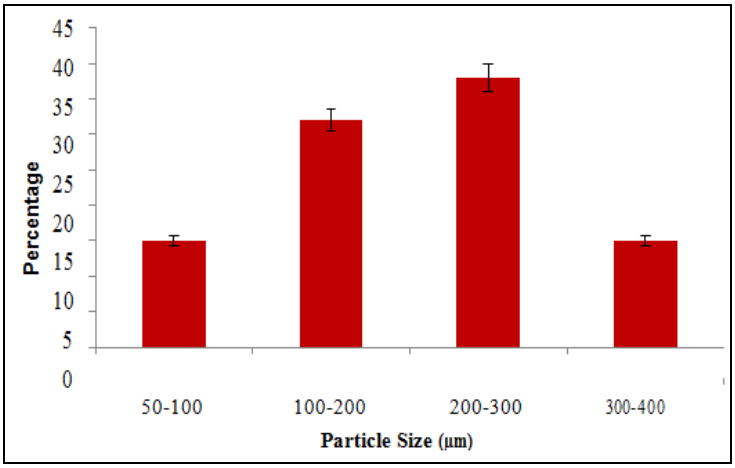

Figure No. 3. Histogram of particle size distribution of prepared microspheres at 800 rpm

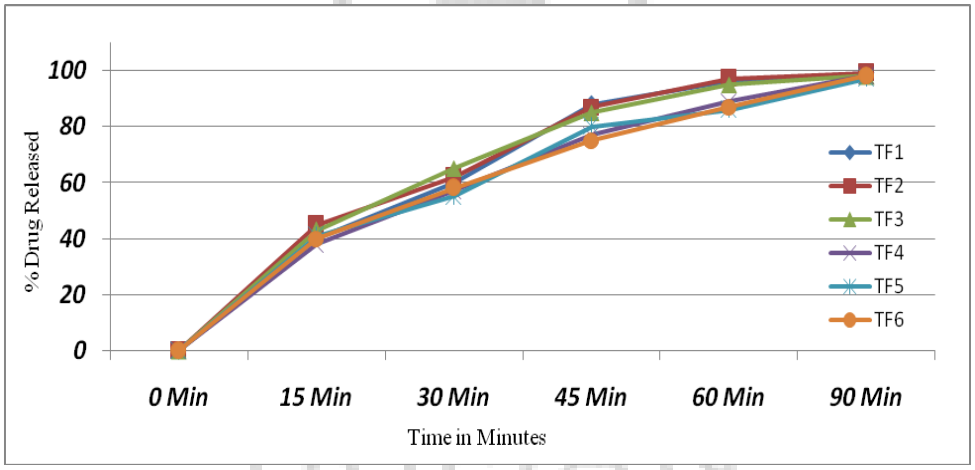

Figure No. 4. Graphical representation of invitro dissolution pattern of taste masked Linezolid Tablets