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Taste Masked Tablets of Linezolid

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ABSTRACT

This research work aimed to develop a taste-masked tablet that disintegrates easily. Effect of different parameters such as swelling time, resin activation, drug resin ratio as well as stirring time was optimized by taste and percentage drug loading. Formulated DRC (Drug Resin Complex) was characterized by infrared spectroscopy, thermal analysis, and X-ray diffraction pattern. Tablets were formulated by wet granulation using PVP K-30 as the binding agent. Alginic acid NF and Crospovidone were evaluated as super disintegrants. The optimized disintegration time was found to be 55 seconds. Tablets formulated with Alginic acid showed slightly higher disintegration time when compared to the tablets made using Cross povidone as super disintegrant. Among superdisintegrant, crospovidone was found suitable with drug-resin complex to get the low disintegration time, wetting time, and friability of tablets.

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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 the development of numerous formulation techniques. In the recent era, oral administration of bitter drugs with an acceptable degree of palatability becomes a key issue for health care 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 the molecule with taste receptor cells, which reside in specific structures known, as TASTE BUDS.

Among all routes of administration, the oral route is the most important and preferable route of administration for solid dosage forms[1]. Tablets are the most common solid dosage form, administered orally, but many patients especially children, mentally ill patients, and geriatrics have a problem swallowing the tablets[2,3].

While the introduction of competing stimuli is part of the masking system, specific flavors and sweetness profiles are essential to complete the experience and produce a pleasant taste for the consumer [4-6]. Linezolid is an antibacterial compound developed by a team at Pharmacia and Upjohn Company[7]. 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 an activity that compares favorably with vancomycin for most clinically relevant pathogens. Linezolid is a 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 a need to develop a taste-masked formulation of Linezolid.

EXPERIMENTAL STUDIES:

Linezolid was procured as a gift sample from Symet labs, Hyderbad, Alginic acid was obtained from DMV International, Crospovidone from FMC Biopolymer, and Sodium Starch Glycolate from Rama production company. Ltd. Other chemicals were gifted by chemical companies.

Formulation of a drug resin complex

Formulation of DRC was made by the batch process; 100 mg of resin Tulsion-335 was placed in a beaker containing 25 mL of deionized water and allowed to swell for a definite period. Accurately weighed amount of Linezolid (per 1: 5 and 1: 7.55 drug resin ratio) was added and stirred for the desired period. The temperature of the water was warmed at 40 ± 3°C for about 10 minutes to solubilize the drug. Then the temperature of the solution was brought to room temperature. After attaining room temperature, the mixture was filtered and the residue was washed with deionized water. The filtrate was analyzed by a U.V. spectrophotometer for the unbound drug and percentage drug loading was calculated.

Optimization of drug resin ratio and stirring time

Separate batches of the drug-resin complex were prepared by altering the ratio of drug and resin as 1 :2.5, 1:5 and 1 : 7.5. The resin was soaked into 25 mL of deionized water contained in a beaker for 30 min and then the drug was added and stirred for different periods like 30, 60, 120, and 240 min. The complexation in the batch process was performed and percentage drug loading and taste were determined.

Optimization of temperature and pH on complex formation:

Temperature Optimization Study:

About 50 mg of drug with 400 mg of resin, slurred in 30 mL of deionized water in a beaker, was heated at a different temperature like at 40°C, 50^0C, and 80°C using temperature-controlled magnetic stirring for about 30 min. The volume of the filtrate was made up to 50 mL with aqueous washing of DRC. The amount of bound drug was estimated by UV at 255 nm from the unbound drug infiltrate. The stirring time for about 20 minutes was employed during this study.

pH Optimization Study:

About 50 mg of drug with 400 mg of resin, slurred in 30 mL of deionized water in a beaker, and then pH was adjusted to of different pH values like 2, 3, 4, 5, 6, and 8) solution prepared from a standard solution of HCl and NaOH in a 100 mL beaker. The drug loading efficiency was estimated. The stirring time for about 20 minutes was employed during this study.

Characterization of DRC

The sample was prepared in KBr disks, and FTIR spectra were recorded over wave number 4000- 400 cm-1. All three spectra [Pure drug, Resin, and drug resin complex] were completely analyzed.

The powder X-Ray diffraction pattern of Linezolid, Tulsion 335, and drug resin complex was measured in X-ray diffractometer.

To understand the compatibility between the drug and resin, pure drug, resin, and drug resin complex was submitted to the DSC test parameter.

Evaluation of Granules

Angle of Repose

The angle of repose of granules will be determined by the funnel method. The accurately weighed granules will be taken in a funnel. The height of the funnel will be adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules will be allowed to flow through the funnel freely on to the surface. The diameter of the the powder cone will be measured and angle of repose was calculated using the following equation[8]:

$$\tan\theta = h/r$$

where h and r are the height and radius of the powder cone.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) will be determined. A quantity of 2g of powder from each formula, previously lightly shaken to break any ag- glomerates formed, will be introducedintoa10-mL measuring cylinder. After the initial volume is observed, the cylinder will be allowed to fall under its own weight on to a a hard surface from the height of 2.5 cmat2-second intervals. The tapping will be continued until no further change in volume is noted. LBD and TBD were calculated using the following formula[8]:

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index[9]:

$$\text{Carr's index}(\%)=[(TBD–LBD)\times 100]/TBD$$

Formulation of tablets

Direct compression technique was employed to formulate the tablets which were complexed with resin. A corresponding amount of complex was taken to get 5 mg of Linezolid. Free-flowing lactose was used as diluents, PVP K 30 as a binding agent, granular Mannitol was used as a soothing agent, talc as an anti-adherent, and magnesium stearate as a lubricant. A mixed fruit flavor was added as a flavoring agent. Ingredients like lactose and mannitol accurately weighed and passed through 80 # sieve were mixed with resin complex. Then granulated using PVP K-30 as a binding agent. The granules were then dried at 80°C for about 4 hours. The dried granules were then sifted through # 30 and then mixed with the remaining ingredients. The above powder blend was compressed using a rotary tablet machine using 13 mm concave punches. The details are captured in table 4.

Evaluation of Tablets

Thickness:

The thickness of the tablets will is determined using a thickness gauge (Mitutoyo, New Delhi, India). Five tablets from each batch will be used, and average values will be calculated.

Weight Variation Test

To study weight variation, 20 tablets of each formulation will be weighed using an electronic balance (DenverAPX-100, Arvada, Colorado), and the test will be performed according to the official method[10].

Disintegration Time

Disintegration time for tablets was determined using disintegration apparatus with Water (900 ml at 37±1 °C) as the disintegrating medium.

Drug content

Five tablets were weighed individually, and the drug will be extracted in water. 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.

Taste characterization

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

In-vitro release study from drug resin complex and Tablet

To understand the drug release pattern from the tablets, drug release profile study was carried out in 900 mL of HCl buffer pH 1.2 using USP dissolution apparatus type II. The rotation speed of paddles was fixed at 50 rpm. The sample was taken from the medium and drug content was determined by taking absorbance in U.V. spectrophotometer.

FTIR OF LINEZOLID

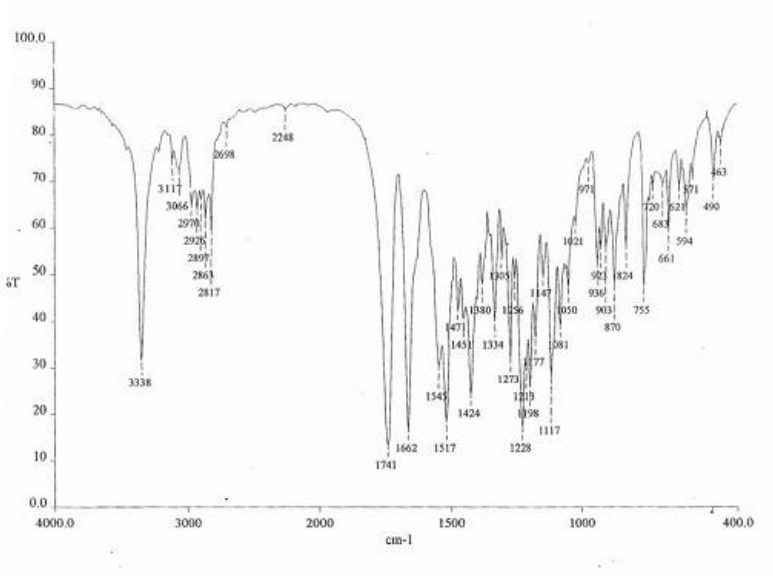

Fig.No.1: FTIR spectroscopy of pure drug, Linezolid

FTIR OF TULSION 335

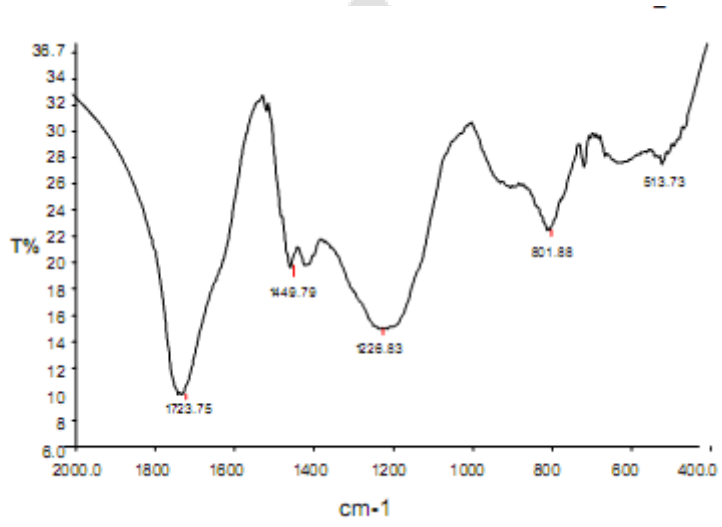

Fig. No. 2: FTIR spectroscopy of Resin Tulsion 335 [Resin]

FTIR of Mixture

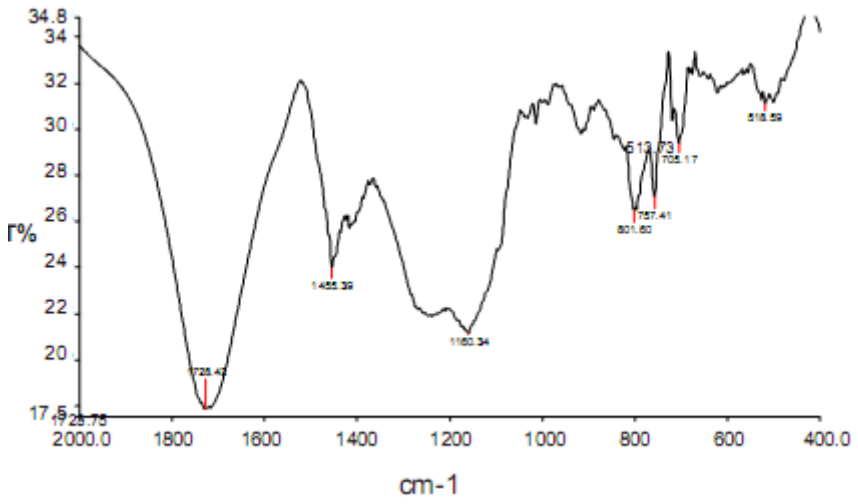

Fig. No. 3: FTIR spectroscopy of Mixture Pure Drug + Resin Tulsion 335 [Resin]

XRD OF LINEZOLID

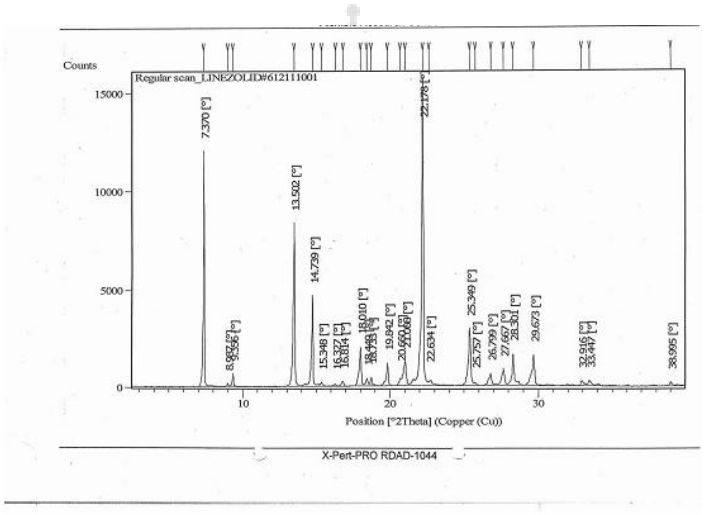

Fig. No.4: XRD of pure drug, Linezolid

XRD OF TULSION 335

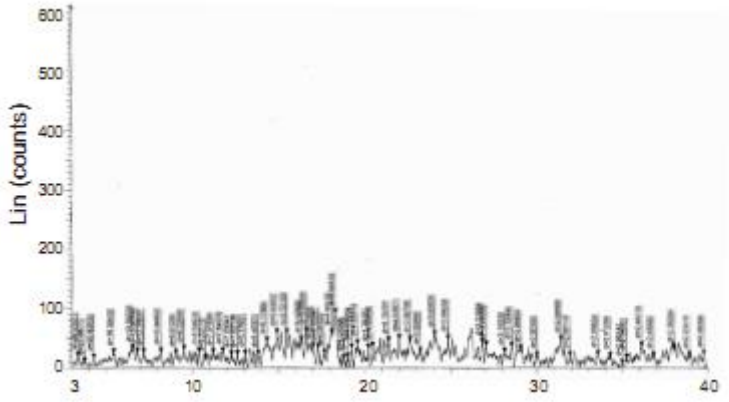

Fig. No.5: XRD of pure Resin, Tulsion 335

XRD of MIXTURE

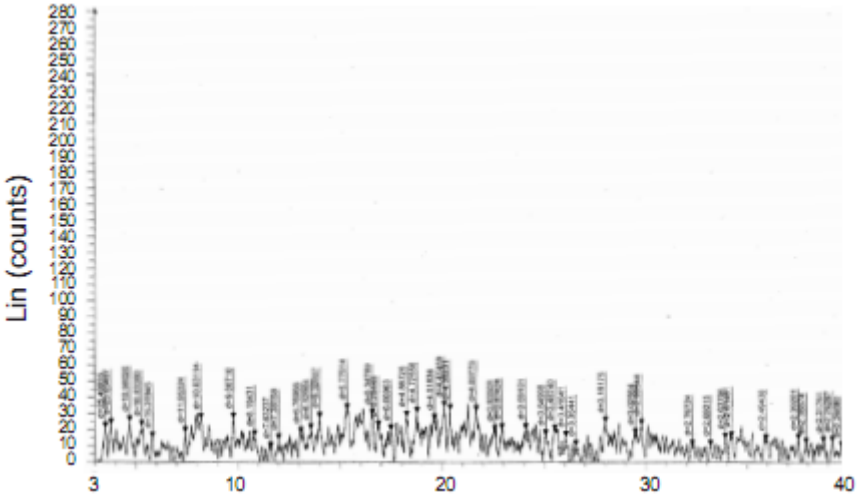

Fig. No. 6: XRD of Mixture Pure Drug + Resin Tulsion 335 [Resin]

DSC OF LINEZOLID

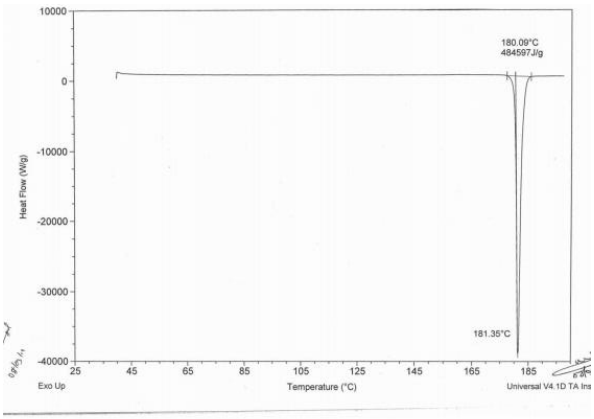

Fig.No. 7: DSC of pure drug, Linezolid

DSC OF TULSION 335

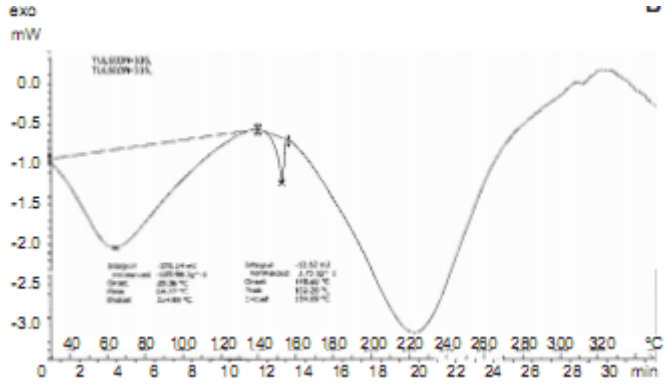

Fig. No.8: DSC of Resin, TULSION 335

DSC OF DRC MIXTURE

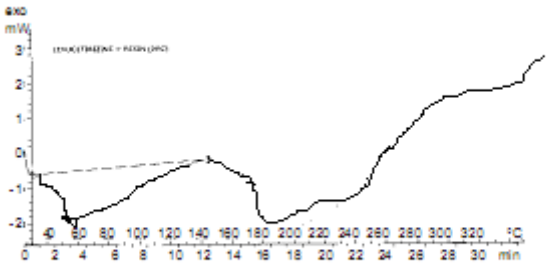

Fig. No. 9: DSC of Mixture, Pure drug + Resin, TULSION 335

RESULTS AND DISCUSSION:

Optimization of swelling and drug: resin ratio was done by taking inactivated resin in batches F1 to F6. In the F1 batch, the drug resin ratio was made kept constant at 1:2.5 and stirring time was also kept constant as 30 minutes. The taste was found to be slightly masked but % drug loading was observed 27.25% ± 1.04% for 30 min. had the stirring time been increased, the increased drug loading improvement wouldn't have been observed as the loading was found only 27.25%.

However, in the F2 drug: resin ratio increases to 1:5, stirring time was remain constant at 30 min and the taste was found to be better-masked percentage drug loading was found to be 39.68% ± 1.16%,

However, in the batches from F3 to F6, drug : resin ratio was increased to 1:7.5, swelling time remain constant at 30 min and stirring time varied for 30, 60, 120 and 240 min respectively and percentage drug loading was found 51.82% ± 1.57%, 59.41% ± 1.23%, 67.27% ± 0.61%and 82.32% ± 1.85% wt/wt. respectively and the taste was found better masked when compared to F2 batch.

The highest taste masking and percentage drug loading was achieved with drug resin ratio 1:7.5 and when stirring time was maximum upto 240 min. The details are captured in table 1. The percentage drug loading was also determined with acid-treated resin, alkali-treated and resin treated with both acid and alkali was found to be 71.40% ± 1.32%, 58.80% ± 0.32% and 38.69% ± 0.62%. wt/wt respectively. The details are captured in table 2.

It is generally assumed that the complexation process in between drug and resin depends on the pKa value of drug and resin; from the experimentation, the results indicated that an increase in pH from 3 to 6 increased the % of drug loading. A maximum drug loading of 95.32% wt/wt was found at pH 5. As pH increases above 5, the percentage of drug loading decreases. This could be for the fact that the pH of the solution affects both solubility and degree of ionization of drug and resin. Drug loading is low at lower pH due to -COO- groups of resin and compete with drug for binding. The details are captured in table 3.

Note: Drug: Resin followed is 1.75 and stirring time followed is 200 minutes.

Infrared spectra of, Linezolid, Tulsion-335and DRC were shown in Figures 1, 2, and 3 respectively. From the FTIR spectroscopy, it was concluded that the Linezolid is crystalline while Tulsion 335 is amorphous. X-ray pattern diffraction (XRD) of Linezolid, Tulsion-335, and DRC are shown in Figures 4, 5, and 6 respectively. Several sharp peaks in XRD spectra of pure drug represent the crystalline nature whereas a diffused peak in XRD spectra of Tulsion-335 represents the amorphous nature of the resin. But on the other hand, the XRD pattern of DRC shows the disappearance of characteristic peaks of the drug and also found to be broadened, and based on these findings, it can be confirmed that the drug resin complex is formed.

DSC images Linezolid, Tulsion-335and DRC were shown in Figures 7, 8, and 9 respectively, from the DSC curves, the thermal behavior of Pure Drug Linezolid shows peak endotherm at 179.15°C corresponding to loss of water of crystallization and melting of pure drug. Thermal behavior of Resin (Tulsion 335) shows peak endotherm at 152.28°C while thermal behavior

of Drug Resin Complex shows peak endotherm at 58.29°C the reduction of height and sharpness of endotherm is due to loading of drug in resin. That showed, there was no interaction was observed between drug and complex. It concludes that resin was not affecting the character of the drug due to the complexation process and indicates the amorphous nature of DRC.

The granules prepared were subjected to various physical parameters and met the required flow properties. The content of the granules was found satisfactory. The details are captured in table 5. The tablets were prepared by taking the drug: resin of 1.7.5 ratio which was stirred for the time of 240 minutes. Among the different ratios employed, drug: resin of 1.75 stirred for 240 minutes was found better taste-masked. Hence, selected for making the tablets. The thickness of the tablets was ranged from 3.09 ± 0.02 to 3.31 ± 0.06 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 96.89 to 99.56. 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 0.62 ± 0.05 to 0.75 ± 0.06%, respectively. The details are captured in table 6. The taste masking of the formulated tables.

The dissolution profile studies of all six formulations are shown in Table 7 and Fig 1. More than 50% of the action was released from all the six tablets at the end 5 minutes whereas about 98% of drug release was seen at the end of 15 minutes.

The initial dissolution profile at 5 minutes of formulation TF1 to TF3 is better than Tf4 to TF6. However, the release profiles at the end of 15 minutes of all formulation codes were comparable. The details are captured in table 6. A graphical representation of dissolution behavior is presented in figure 10.

Table 1: Drug:Resin ratio and Stirring time

Formulation Code	Drug : Resin Ratio	Swelling Time (min)	Stirring Time (min)	% Drug Loaded
F1	1:2.5	30 Min	30 Min	27.25%
F2	1:5	30 Min	30 Min	39.68%
F3	1:7.5	30 Min	30 Min	51.82%
F4	1:7.5	30 Min	60 Min	59.41%
F5	1:7.5	30 Min	120 Min	67.27%
F6	1:7.5	30 Min	240 Min	82.32%

Taste: Slight masking of bitterness was observed with F1 whereas better-masked taste was observed with F2 code and Codes F3 to F6 were found better masked when compared to F2 code.

Table 2: Impact of Resin activation

Formulation Code	Resin Activation	Drug : Resin Ratio	Swelling Time (min)	Stirring Time (min)	% Drug Loaded
F7	Acid	1:7.5	30 Min	200 Min	71.40%
F8	Alkali	1:7.5	30 Min	200 Min	58.80%
F9	Acid-Alkali	1:7.5	30 Min	200 Min	38.69%

Table 3: Impact of pH on % Drug loading

pH	% Drug Loading
2	68.36%
3	79.85%
4	84.52%
5	95.32%
6	91.36%
7	87.52%

Table 4: Formulation details of tablets with other ingredients

Ingredients	Formulation Codes					
	MT1	MT2	MT3	MT4	MT5	MT6
Drug:Resin	40	40	40	40	40	40
PVP K-30	6	6	6	6	6	6
Lactose [free flowing]	30	30	30	30	30	30
Alginic acid NF [cross linked]	--	--	--	7.5	10	12.5
Cross Povidone	7.5	10	12.5	--	--	--
Mannitol [DC grade]	35	35	35	35	35	35
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
Talc	2.5	2.5	2.5	2.5	2.5	2.5

Note: Drug: Resin is taken in such quantity that Linezolid is equivalent to 5 mg.

Table 5: Powder evaluation* Physical and chemical evaluation of wet granulation

Sl. No.	Formulation Code	Angle of Repose	Bulk Density [g/mL]	Tapped Density [g/mL]	Comp. Index [%]	Drug Content [%]
1	MT1	21.15	0.528	0.625	18.85	99.75
2	MT2	20.33	0.512	0.658	17.85	98.85
3	MT3	21.82	0.495	0.658	17.85	97.36
4	MT4	21.82	0.523	0.634	16.01	97.56
5	MT5	20.82	0.547	0.688	17.85	98.56
6	MT6	19.86	0.511	0.621	17.85	99.58

Table 6: Tablets Evaluation:

Sl. No.	Formulation Code	Thickness* (mm)	Friability‡ (%)	Hardness‡ (kg/cm2)	Disintegration time	Drug Content* (%)	Weight Variation
1	TF1	3.12 ± 0.01	0.65 ± 0.02	4.2 ± 0.20	55 sec	98.65	Passes
2	TF2	3.31 ± 0.06	0.71 ± 0.05	4.0 ± 0.14	50 sec	97.56	Passes
3	TF3	3.09 ± 0.02	0.75 ± 0.06	4.0 ± 0.23	50 sec	96.58	Passes
4	TF4	3.11 ± 0.03	0.66 ± 0.03	4.1 ± 0.25	80 sec	99.56	Passes
5	TF5	3.11 ± 0.04	0.62 ± 0.05	4.1 ± 0.16	75 sec	98.23	Passes
6	TF6	3.11 ± 0.03	0.63 ± 0.04	4.2 ± 0.16	70 sec	97.56	Passes

* All values are expressed as mean ± SE, n = 5. † All values are expressed as mean ± SE, n = 20. ‡ All values are expressed as mean ± SE, n = 6.

Dissolution Profile

Table 7: The in vitro release profiles of Taste Masked Linezolid Tablet Formulation

Sl. No.	Formulation Code	% Drug Release Observed	
		0 to 5 Mins	6 to 15 Hrs
1	TF1	69	98
2	TF2	68	99
3	TF3	66	99
4	TF4	55	98
5	TF5	55	99
6	TF6	58	98

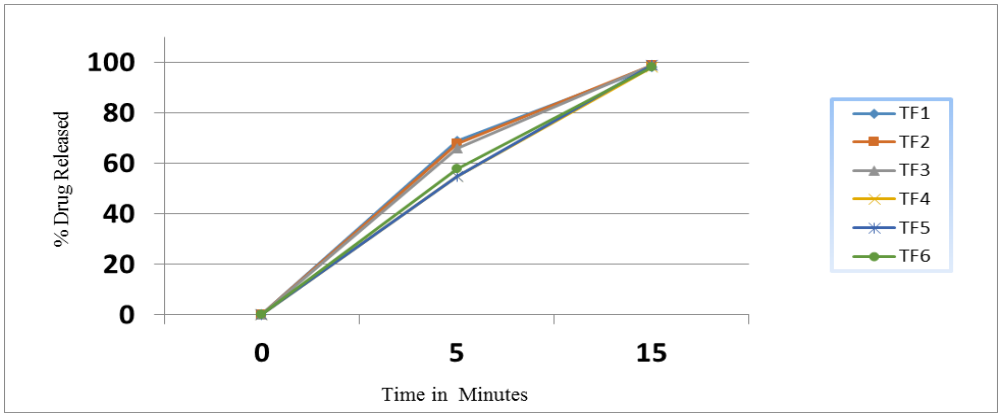

Fig. No. 10: Graphical representation of *in-vitro* dissolution pattern of taste-masked Linezolid Tablets.

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