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FORMULATION AND EVALUATION OF LINEZOLID FILM COATED TABLETS

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ABSTRACT

The present investigation is undertaken with an aim to formulate and evaluate Film coated tablet of linezolid. The drug powders were subjected for preformulation studies. The Preformulation characteristics are within the Pharmacopoeial specifications. The drugs and excipients compatibility were carried out by FT-IR studies. The spectra showed that there was no interaction between them. The dissolution profile were carried out in Dissolution apparatus and then in UV spectrophotometer. For Linezolid-600 mg tablets, the main purpose of this study is to improve the hardness and dissolution profile of the core tablet and to minimize the defects occurs during coating of tablet. Optimization was done and it was found that dissolution release profile and hardness were found to be best and after coating, the tablet was found without any coating defect by non-aqueous coating i.e. IPA. Film coating of TiO_2 and IPA coating of 2 %w/w was done on Linezolid tablets as to avoid spores which occurs during the aqueous coating. Five formulations were prepared by the name of SAD01-SAD-05. For coating, two different types of coating material were used (aqueous coating and non-aqueous coating). The granules were evaluated for angle of repose, bulk density, compressibility index and drug content etc. The tablets were also subjected for thickness, hardness, friability and in vitro release studies. Evaluation parameters like weight variation, hardness, thickness, friability and disintegration test were performed. Results found that release profile of batch no. SAD-05 shows better hardness and dissolution profile of core tablet and good coating appearance after non-aqueous coating. This formulation is taken as an ideal or optimized formulation.

KEYWORDS: Linezolid; Preformulation; Film Coating; Hardness; Dissolution study etc.

INTRODUCTION

Oral drug delivery (OOD) is the most preferred and convenient route of drug administration due to high patient compliance, cost-effectiveness and ease of production.[1] It is the most common and advantageous route of administration, if it is compared to all other route of administration. Of all those medicaments that are administered orally, solid oral dosage form is the one which represents the preferred class of products. Solid oral dosage form such as pills, tablets, capsules, and powders are commonly used in today era.[2,3]

Tablets

According to the IP, tablet are solid flat or biconvex in shape which is manufactured by compressing a single medicament or a mixture of drug with or without excipient either by dry granulation, wet granulation process or by direct compression.[4] The compressed tablet is the most popular dosage form in today use. About two-thirds of all drugs currently prescribed are in solid form and many of these are compressed tablets.[5]

Advantages

1. Tablets are elegant in appearance and convenient to use.
2. The tablets dosage form is simple, economical in manufacturing, most stable and most convenient in packaging, shipping and for any transportation.
3. Tablets is formulated to contain maybe more than one therapeutic ingredients showing a combination thus reducing multiple tablets use.[6]
4. Provide protection of medicaments from environmental conditions like air, humidity and light.
5. Provide prolonged stability to medicaments.
6. It has Low manufacturing cost as compare to all other solid dosage form.
7. Administration of small quantity of drug in accurate amount.
8. Unpleasant order taste can be masked by sugar coating of tablet.
9. Easy to divide into halves and quarters whenever fraction dose is required as scored tablets are also manufactured.
10. Packaging and production is cheap and does not require more space for storage of tablet.[7]

Disadvantages

1. Its manufacturing involve several process thus at each step there is loss of ingredients of tablets.[6]
2. Drugs which are hygroscopic in nature are not suitable for compressed tablets.
3. Drugs those have low or poor water solubility, slow dissolution and high absorbance in GI tract is difficult to formulate.
4. The cost of production is increased because of coating material.
5. It is Difficult to formulate liquid or tiny droplets into tablet and swallowing of tablet is difficult for children and for the patients who are unconscious.[7]

Additives used in formulation of tablets

Excipients

Excipients are the additives which are chemically inert substances, non-toxic and inactive in nature and do not show any therapeutic action. It doesn't even interact with any active ingredient and other excipients. The good choice of excipients is necessary during the manufacturing process. If the excipients are not compatible with the API it shows some chemical reactions which may change the property of the drug.

Diluents

Diluents are the fillers which are used to produce the bulkiness and volume of the tablet when the tablet itself is not able to produce the appropriate quantity for the manufacturing of tablet. Diluents selection should be made carefully as physicochemical changes might render the product quality and may cause problems in the manufacturing process.

Binders

Binders are those binding agents which help to make the bond between the particles and help to increase the strength of the powder during compression. For the formation of granules. Binder is added in both dry and wet forms.

Disintegrants

Disintegrants are those excipients which are used for the breakdown of tablet when it comes in contact with water in the oral cavity or into the gastrointestinal tract. If the disintegrant is used in a proper amount the dissolution release profile will improve.

lubricatns

Lubricants are the agents used during manufacturing operation of tablet which is used to diminish the friction between die wall and tablet. It helps to prevent clinginess of the tablet to dies and punches by the use of lubricant, the tablet is easily ejected from the die cavity.

Glidants

Glidants are the additives which help to improve the flow of powder. a tablet machine with high speed requires smooth flow of powder to die cavity. For this, glidants are used which improve the flow property of granules from hopper to die cavity and the tablet can be easily ejected from the cavity. Glidants are used to diminish the friction between the particles during the manufacturing operation of the tablet.[8,9,10]

Coloring Agents

Approved drug and cosmetic dyes or mixture, water-soluble food or their corresponding lakes are used colouring agent. In tablet color is mainly serves as a mean of identification and for good appearance. Colouring agents also increase the stability of light-sensitive drugs during coating of tablet. Tablet color dye increases the aesthetic appearance of the tablet. Mostly food dyes are used during tablet coating whereas organic dyes that are synthetic dyes may interact with the human body may lead to health potential especially when it is taking in excessive amount.[11]

Types of Tablet

Tablets are classified into tow broad categories:

1. Compressed tablets &
2. Molded tablets

These two tablet types are further classifiable on purpose, use, and mode of administration as

1. Compressed tablets

a) Chewable tablets
b) Buccal or sub-lingual tablets
c) Lozenges
d) Effervescent tablets
e) Enteric coated tablets
f) Sustained release tablets
g) Vaginal tablets
h) Sugar-coated tablets
i) Film-coated tablets
j) Layered tablets
k) Implants
l) Soluble tablets.
m) Pressed coated tablets.

2. Molded tablets

a) Hypodermic tablets
b) Dispensing tablets

Manufacturing Process of Tablets

Granulation

Granulation is a process of collection of particles or the mixture of powder together to form bonds between them which are formed by compression and by using appropriate binding agents. In the process of granulation one or more powder form combines and the granules are formed. that will produce quality tablet within required tablet press speed range. If the process of granulation is uniform it improves granulation flow, compression parameters, the content of uniformity and increases productivity.[19] If granulation is proper according to the requirement, it will provide better hardness and variability, disintegration time as well as dissolution rate.[20]

The manufacturing of tablet is categorized into three different types of methods which are as follows:

1. Direct compression
2. Dry granulation
3. Wet granulation techniques

Direct Granulation/Compression

DRUG
↓
SIFTING & SIZING
↓
BLENDING
↓
COMPRESSION

Dry Granulation

DRUG
↓
SIFTING
↓
MIXING
↓
BLENDING
↓
SLUGGING (PRE-COMPRESSON)
↓
SIFTING AND SIZING
↓
SLUGGING
↓
MILLING
↓
COMPRESSION

Wet Granulation

Wet granulation is process in which binder is added to the mixture of blend powder and the components are massed to a predetermined end point at given mechanical speed.

The binder used during wet granulation may be aqueous or solvent based. Choice of binder is depend upon the properties of the powder. If only water is used for binding, it may form bonds between powder particles but after drying the water get dries, bonds will break and powder may fall apart from each other. in such cases, a binding agent is requires that should be stable enough after drying too.

Eg: Maize Starch, Agar, Gaur Gum etc.[19,26]

SIFTING
↓
BINDER PREPARATION (In kettle pan at 100 ^{0}C)
↓
GRANULATION (In RMG)
↓
DRYING (FBD)
↓
SIZING (In Multimill)
↓
BLENDING (In Blender)
↓
COMPRESSION[25]

Tablet Compression

Compression of the tablet is a critical step in the process of tablet manufacturing through which a tablet is formed. The tablet should be compressed according to their size and shape so it is necessary to set the required shape and size of punches. It is necessary to identify all the official and unofficial parameters during compression of the tablet which started in a sequence like weight variation of the tablet, hardness, thickness, disintegration time friability and dissolution release rate.[23]

Working Principle of Compression

The compression machine works on the principle of hydraulic pressure and pneumatic pressure. Hydraulic pressure play a key role in the formation of a tablet in which the upper punch and lower punch is compressed in the die cavity (hole) by which the tablet is formed. If the hydraulic pressure will be increased (maximum 4 ton) of the compression machine, the force will increase which affect the hardness of tablet. The tablet becomes too hard which may lead to the problem during disintegration time and dissolution time of tablet.

Tablet process divided into four main stages:

1. Filling
2. Metering
3. Compression
4. Ejection from die.[24]

Compressed Tablet Characteristics

1. **General appearance:** The general appearance of the tablet include overall appearance of the tablet like size, colour, surface, consistency for control of uniformity in tablet lot and for monitoring trouble free manufacturing.
2. **Tablet thickness:** Tablet thickness is determined by using verniercalliper which may be digital or manual. The tablet thickness is depend on the pressure applied on the compression machine. The standard limit of thickness varies in +_ 5%. Of the tablet thickness.
3. **Tablet hardness:** Hardness of the tablet is defines as the force required for breaking of tablet. Appropriate pressure is given during tablet compression as if the tablet become too hard it will not disintegrate at the given time and if tablet become too soft it will washout. The hardness of conventional tablet should be 2.5 to 5kg/cm^2 and for extended release tablet, the hardness should be between 5 to 7.5kg/cm^2.Various types of harness tester is used for the determination of hardness of tablet:

- Strong cobb hardness tester
- Pfizer hardness tester
- Schleuniger hardness tester.

1. **Tablet friability:** The friability of the tablet is determine to know the mechanical strength of the tablet during transportation but according to the scientific reason friability is determine to check its mechanical strength during coating of the tablet. The process is done for 4 minute i.e., 25 rotations per minute
2. **Weight variation:** The weight should be checked at every 30 minutes during compression of tablet. It is the most important parameter of the tablet manufacturing. For the tablets that contain more than 90% of the drug then weight variation test can be used as drug content uniformity of the tablet. Specified number of tablets is taken at random manner and average weight was determined. The average weight of tablets should not deviate from the maximum percentage deviation allowed.

According to the IP, the standard limit of the tablets should is categorized according to their weight.

Table 1.1: Weight Variation Limit of Tablet According to IP & BP.

Weight of tablet (mg)	Standard limit (%)
Less than 80 mg	Deviation upto 10%
80mg to 250mg	Deviation upto 7.5%
Above 250mg	Deviation upto 5%

1. **Content uniformity:** It is the intended amount of drug substance contained by every tablet with little variation among tablets within a batch. A fundamental quality attribute for all pharmaceutical preparation is the requirement for a constant dose of drug between individual tablets. Specified numbers of tablets are individually assayed for their content and requirements for content uniformity are met if the amount of active ingredient in each dosage unit lies within the range specified in the monograph.
2. **Disintegration:** The disintegration of tablet is define as the breaking up or disintegration of tablet at a given temperature and a given time in the liquid medium. This test is not applicable for sustained release tablets. Disintegration time of the following types of tablets are as follows:

- Uncoated tablet: NMT 15 minutes
- Film coated tablet: NMT 30 minutes
- Enteric coated tablet: 2 hours in 0.1N HCL, 1 hour in 6.8Ph Phosphate buffer.
- Sugar coated tablet: NMT 1 hour
- Dispersible tablet: NMT 3 minutes

Dissolution: Dissolution is defined as, how much time a tablet is taken to dissolve its active ingredient into the medium under specified condition as in vitro test.

Six tablets are taken and place one tablet into each tube of the basket, add the disc to each individual tube and operate the apparatus with using water by maintain its temperature at 35^0C to 39^0C.

The temperature of medium should be:

1. Basket type apparatus.
2. Paddle type apparatus.[26]

Common defects during compression of tablet

1. Sticking And Picking

Sticking and picking is the common defect during the manufacturing of the tablet. Sticking refers to the tablet material adhering to the die wall.

It occur when the powder is not completely dried or too much of binders are used during granulation which cause sticking of powder in the face of the punches picking occur when small amount of material is stick out or being remove off from the tablet surface by the punch faces. Mostly picking occur in embossed tablets.

2. Capping

Capping occur when upper and lower part (segment) of the tablet separate out horizontally from the main body of the tablet in **CAP** form. Capping occur due to improper binding of granules of tablets or by using too much lubricants.

3. Black Spots

Small spots occur by the oil used in compression machine. It is usually occur during the first 10 rounds of the machine or when the oil or Grease is used.

4. Chipping

Chipping occurs when the tablet started breaking up from the edge.

5. Binding

When the tablet is adhere, tear or seize in the die cavity the powder started to chock the cavity and a film is formed in the die due to which ejection of die is hinder.

6. Double Impression

Double impressing occurs mostly in the embossed tablets i.e, those punches have monographer other engraving on them.[27-33]

Tablet Coating

Tablet coating is perhaps one of the oldest Pharmaceutical process still in existence. Any introduction to tablet coating must be prefaced by an important question- "Why coat tablets???"-since many instances, the coating is being applied to a dosage form that already is functionally complete.[34]

Coating can be applied to several kinds of solid dosage forms like tablets, pellets, pills, drug crystals, etc.[35]

Tablet coating is a pharmaceutical technique of applying a thin polymer-based film to a tablet or a granule containing active pharmaceutical ingredients (APIs).

The amount of coating on the surface of a tablet is critical to the effectiveness of the oral dosage form.

Tablets are usually coated in horizontal rotating pans with the coating solution sprayed onto the free surface of the tablet bed.[36]

The coating can be specially formulated to regulate how fast the tablet dissolves and where the active drugs are to be absorbed into the body after ingestion.[37]

After making a tablet you must coat it. The coating can have several functions,[38] the most important of which is controlling the release profiles, produce an elegant product[36,39] to mask unpleasant taste and odor.[40,41,42] enhance stability against light and moisture.[40,43,44] Coating also provide identity to product and creating smooth covering to promote and improve swallow ability.[45,46,47]

There are three primary process involved in tablet coating:

i. Properties of tablet coating
ii. Coating process
a) Coating equipment
b) Parameters of the coating process
iii. Coating composition[48]

Properties of coating tablet

1. It also helps to control and increase the bioavailability of the drug and impart a functional purpose such as the modification of drug release profile.[44,49]
2. Improves product appearance and product identity.
3. Helps to mask the bitter taste and oral tablets.
4. Tablet coat also allow higher packaging speed by reducing friction as well as reducing dust generation from tablet.
5. Helps maintain the shape of the tablet.[47-49]

Coating equipment: The coating system consists of the:

a. Coating pan
b. Spraying system
c. Peristaltic pumps
d. Fans& Filters
e. Inlet and outlet heating pipes
f. Air handling unit
g. Dust collector
h. Controls[50]

Coating pan is consist of stainless steel 316 in the shape of drum with the cabinet which allow to control the air flow, air temperature and controlled solution application. Coating pans are used to for an aqueous or organic film around any type of pellets and tablets. RPM of the pan is variable. In this film coating is done by appropriate air handling system & spraying equipment.

Spraying system consists of spray gun, a peristaltic pump, silicon tube and air lines.

Spray gun used to distribute the coating solution uniformly through peristaltic pump which works in the principle of active diffusion. Spray gun is connected to peristaltic pump through silicon tube which is made up of food grade and is non-reactive with solution. Uniform solution distribution is depending on the RPM of peristaltic pump. If the solution is distributed properly then it may cause many coating defects like bridging, mottling, peeling, spores formation, twinning etc.

Some of the critical parameters which should be monitored during coating is given below

1. Spray rate
2. Inlet and exhaust temperature
3. Bed to gun distance
4. Atomized air pressure
5. RPM of coating pan and peristaltic pump
6. Bed temperature
7. Environmental condition of coating room

Advantages of Tablet Coating

1. Tablet coatings must be stable and strong enough to survive the handling of the tablet, must not make tablets stick together during the coating process, and must follow the fine contours of embossed characters or logos on tablets.
2. Coatings can also facilitate printing on tablets, if required. Coatings are necessary for tablets that have an unpleasant taste, and a smoother finish makes large tablets easier to swallow.

Disadvantages of Tablet Coating

1. Disadvantages of coating such as relatively high cost, long coating time and high bulk have led to the use of other coating materials.
2. This process is tedious and time-consuming and it requires the expertise of highly skilled technician.[55,56]

Preformulation studies
Description
Description of Linezolid

Sr. No.	Tests	Results
1.	Color	White
2.	Odor	Unpleasant
3.	Nature	Powder
4.	Taste	Bitter

DISCUSSION

The color, odor, nature and taste of the API were evaluated. It was found to be as per the monograph.

Melting Point

Melting point of linezolid was determined using open capillary method. The melting point was found out to be 324°C which is in range.

Solubility

Solubility of drug in different solvent.

Description term	Solubility
Freely soluble	0.1 M NaOH
Sparingly	Water & Mthanol
Slightly	0.1 mol/L HCL & ethanol

DISCUSSION

The results revealed that the drug was soluble in water, methanol and ethanol.

Drug - Excipient Compatibility Study

Sr. No.	Composition	Description		
		Initial Period	2nd Week	4th Week
1.	Linezolid + Magnesium stearate	White powder	NCC	NCC
2.	Linezolid + Starch	White to off white powder	NCC	NCC
3.	Linezolid + Microcrystalline Cellulose	White to off white powder	NCC	NCC
4.	Linezolid + Colloidal anhydrous silica	White powder	NCC	NCC
5.	Linezolid + Cross carmellose sodium	White powder	NCC	NCC
6.	Linezolid + Sodium Lauryl Sulphate	White powder	NCC	NCC

Note: NCC – No Characteristic Change

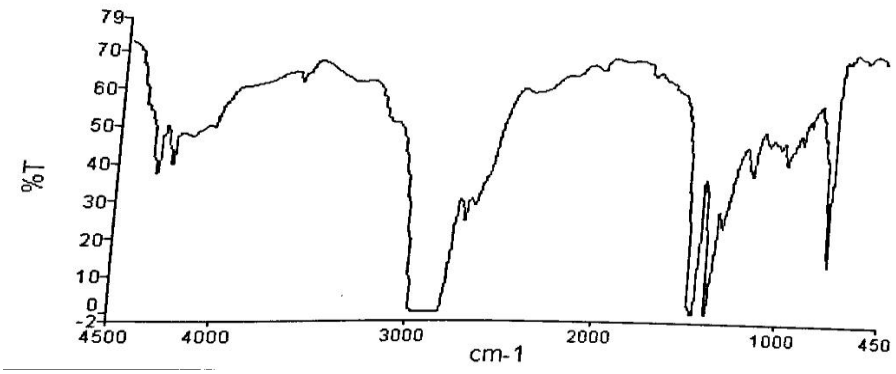
Discussion

From the drug excipients compatibility study, it was observed that there was no change between drug and excipients. Thus it was concluded that the excipients selected for the formulation were compatible with Linezolid.

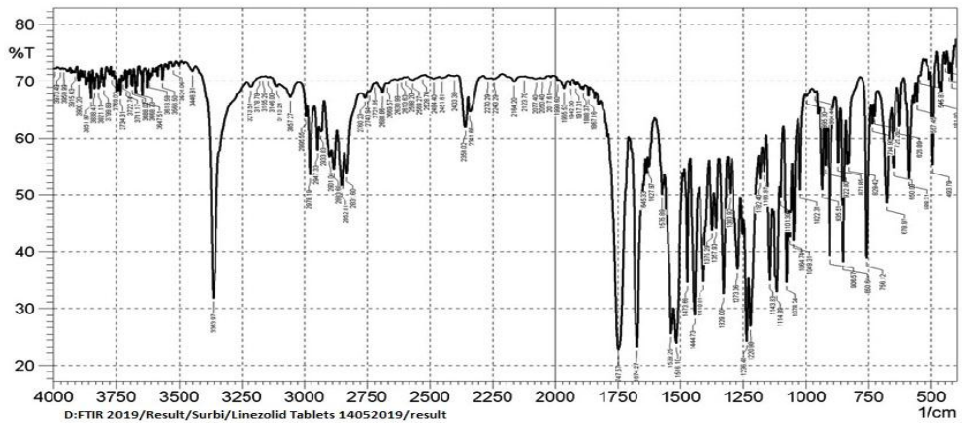
FTIR

Identification of drug purity through FTIR

Infrared spectra were taken by using KBr pellets technique using a Perkin Elmer IR (spectrum Two TM) spectrometer in the wavelength region of 4000-400 cm^{-1}. The procedure consisted of dispersing a sample (drug alone) in KBr & compressing into discs by applying a pressure of 5 tons for 5 minutes in a hydraulic pressure. The pellet was placed in the light path & the spectrum was obtained.



FTIR of pure drug (Linezolid) Reference standard IP 2018



FTIR spectra of Linezolid

Characteristic IR peaks of Linezolid

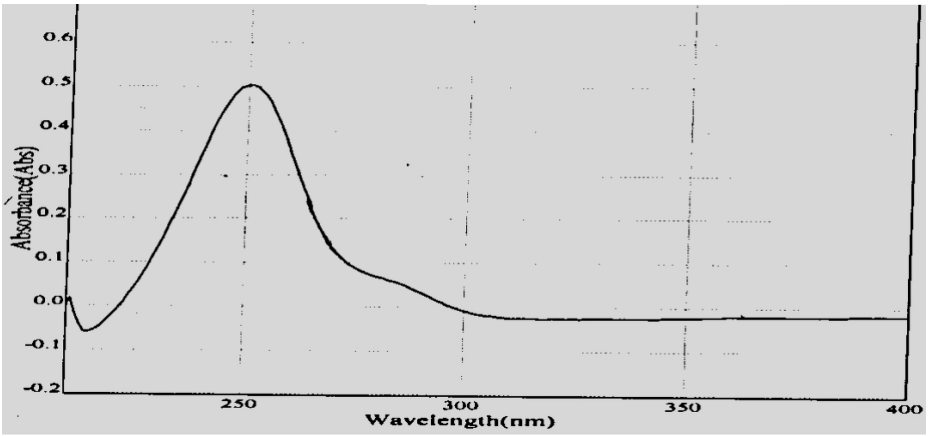
Sr. No.	Reference peaks (cm^{-1})	Obtained peaks (cm^{-1})	Functional group
1.	3100-3400	3363	N-H stretching
2.	2820-3000	2818	C-H stretching
3.	1760-1820	1335	C=O bending
4.	1550-1640	1452	N-H stretching

Preparation Of Standard Curve Of Linezolid

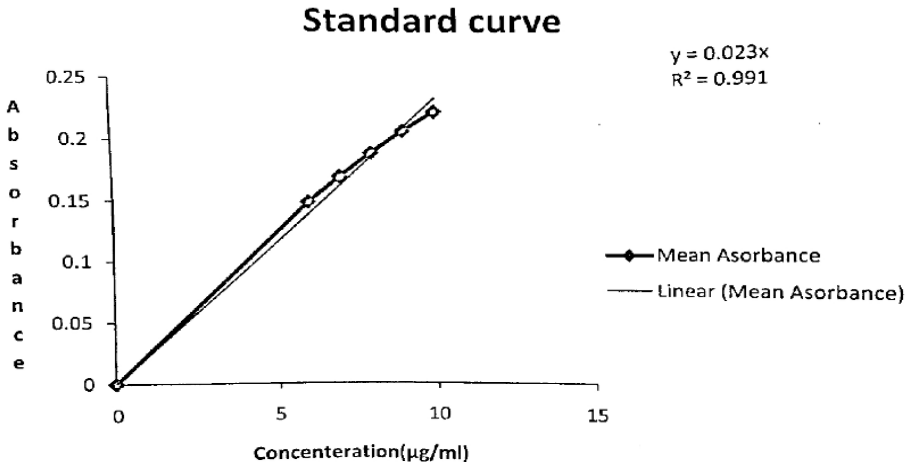
The standard curve of linezolid was prepared using methanol. The data of absorbance values for all the dilution in different solvent. The UV scan the standard solution between 200-400 nm with absorption maxima at 250 nm. The graph was plotted between concentration and absorbance taking points that seemed to be coincide within the linear line and it was found that it follows the beer's law in a concentration range of 7-9ug/ml in a methanol.

Drug absorbance data for standard graph in different media.

Concentration (µg/ml)	Mean absorbance (at λ_{max} 250 nm) In Methanol
0	0
1.0	0.048
2.0	0.055
3.0	0.078
4.0	0.101
5.0	0.133
6.0	0.150
7.0	0.172
8.0	0.191
9.0	0.207
10.0	0.224



Calibration curve at 250nm



Calibration graph of Linezolid in Methanol.

Line of equation: Y = Mx + C
Where, **Y** is absorbance
M is the slope
X is the concentration of linezolid in mcg/ml
y=0.0235+0.256

Beer's range: 0-10µg/ml
R2 value: 0.9917
λ_{max}: 250 nm

Evaluation of Precompression Parameters
Pre-compression Parameters of Linezolid Powder

Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility index (%)	Hausner's ratio
SAD-01	0.54	0.51	7.27±0.2	1.07±0.3
SAD-02	0.50	0.47	6.00±0.3	1.06±0.4
SAD-03	0.51	0.48	5.88±0.6	1.06±0.2
SAD-04	0.50	0.47	6.00±0.4	1.06±0.1
SAD-05	0.51	0.48	5.88±0.4	1.06±0.2

Bulk density of Linezolid Powder

FormulationCode	BulkDensity(g/ml)
SAD-01	0.54
SAD-02	0.50
SAD-03	0.51
SAD-04	0.50
SAD-05	0.51

Discussion
The bulk density of all formulations was measured by using bulk density apparatus. The bulk density was in the range of 0.50±0.2 to 0.55±0.1 g/ml.

Compressibility of Linezolid Powder

FormulationCode	Compressibility index (%)
SAD-01	7.27±0.2
SAD-02	6.00±0.3
SAD-03	5.88±0.6
SAD-04	6.00±0.4
SAD-05	5.88±0.4

Discussion
The compressibility index was in the range of 5.88±0.4 to 7.27±0.2 %. It proved that the flow behaviors and compressibility of the granules are good.

Tapped density of Linezolid Powder

FormulationCode	TappedDensity(g/ml)
SAD-01	0.51
SAD-02	0.47
SAD-03	0.48
SAD-04	0.47
SAD-05	0.48

Discussion
The tapped density of all formulations was measured by using tapped density apparatus. The tapped density was found in the range of 0.47±0.2 to 0.51±0.3 g/ml.

Hausner's ratio of Linezolid Powder

Formulation Code	Hausner's ratio
SAD-01	1.07±0.3
SAD-02	1.06±0.4
SAD-03	1.06±0.2
SAD-04	1.06±0.1
SAD-05	1.06±0.2

Discussion
The hausner's ratio lies in the range of 1.06±0.1 to 1.07±0.3. Hence the flow properties of all formulations were good.

Evaluation Of Post Compression Parameters
Evaluation of Linezolid-600 mg Uncoated Tablets.

Formulation Code	Thickness (mm)	Hardness (kg /cm^2)	Weight Variation (%)	Friability (%)	Assay (%)
SAD-01	5.90± 0.014	5.00	872±0.19	0.23	95.5
SAD-02	6.00± 0.010	3.20	868±1.20	0.57	103.16
SAD-03	5.90± 0.026	5.00	870±2.30	0.40	100.00
SAD-04	5.90 ± 0.022	2.50	879±0.40	0.86	101.35
SAD-05	5.93 ± 0.010	6.45	873±0.20	0.32	104.00

Discussion
General Appearance
The formulated tablets were evaluated for their organoleptic characters. The tablets were caplet in shape and white in color and having break line at one side. All the tablets showed elegance in appearance.

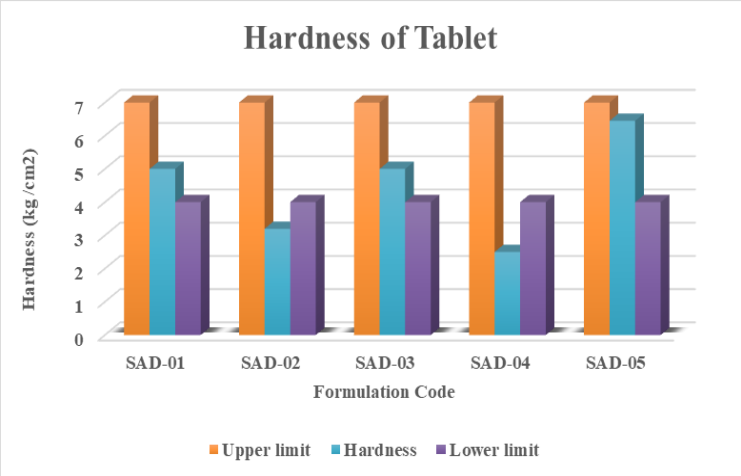
Thickness
Thickness of the tablets was found to be in the range of 5.90± 0.014 mm to 6.00± 0.010 mm. The results showed that the thickness of all formulated tablets was found to be uniform.

Hardness

The hardness of the tablets was measured by Monsanto hardness tester. The hardness of all the formulations was found to be in the range of 2.50 to 6.45 kg/cm^2. The hardness of formulation SAD-02 & SAD-04 were not under acceptance criteria.

Hardness of tablet of formulation SAD-01 to SAD-05

FORMULATION	HARDNESS (kg/cm^2)
SAD-01	5.00
SAD-02	3.20
SAD-03	5.00
SAD-04	2.50
SAD-05	6.45



Graphical representation for Hardness of linezolid tablet of all formulation (SAD-01 to SAD-05)

To improve the hardness of the tablet, procedure of granulation was changed for **5th trial**. Quantity of starch for paste and mixing were same as **SAD-04** but inlet and outlet temperature of FBD was increased (70 and 60^0 C respectively). Due to more heat of FBD, granules become harder as compared to other formulations which was determined by the end point method of drying.

Weight variation

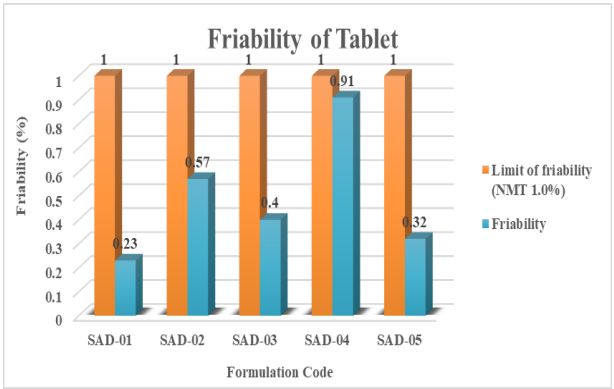
Twenty tablets of each formulation were selected for weight variation test. The accepted percentage deviation was ±5.0 % for 875 mg weight tablets. The results showed that weight variation was ranging from 868±1.20 to 879±0.40 mg. It was within the I.P. limit and all the tablets passed the weight variation test.

Friability test

Friability test was carried out by Roche friabilator. The maximum weight loss should be not more than 1%. The maximum and minimum friability values among 5 formulations were found to be in the range of 0.23 to 0.86% respectively. Hence the friability of formulation SAD-04 was passed but not uniform as compared to other formulations.

Data for Friability of tablet

Formulation Code	Friability (%)
SAD-01	0.23
SAD-02	0.57
SAD-03	0.40
SAD-04	0.91
SAD-05	0.32



Graphical representation for Friability of linezolid tablet of all formulation (SAD-01 to SAD-05)

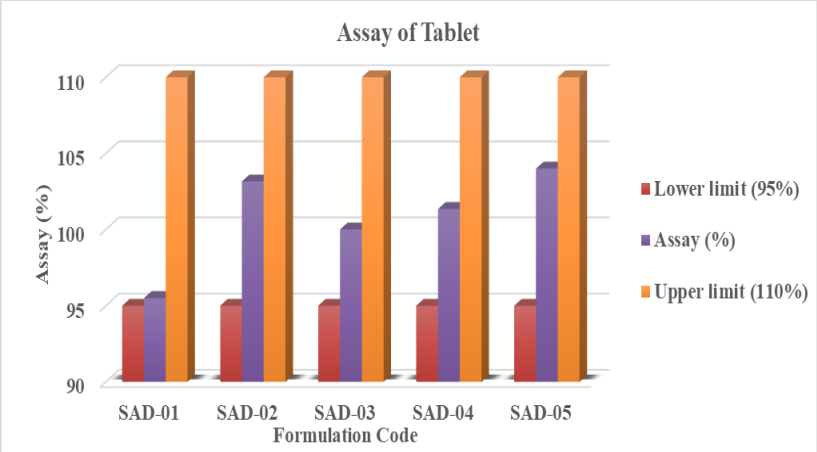
To improve the friability of tablets, formulation SAD-05 was prepared in which some internal parameters of FBD for drying and quantity of SLS during mixing in RMG and blending were changed.

Drug content

The assay of Linezolid-600 mg film coated tablets were found in the range between 95.5 and 104.000%. The acceptable limit of Linezolid-600 mg content as per I.P. is 90 to 110%. The results revealed that the assay of Linezolid-600 mg was within the acceptable limit.

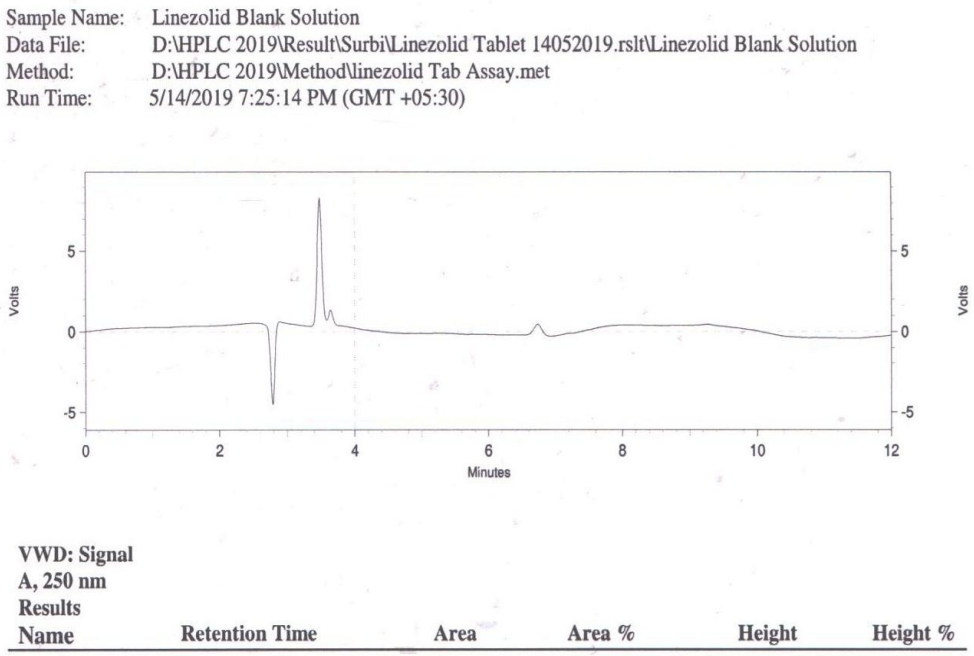
Data for Assay of Linezolid Tablet

FORMULATION	Assay (%)
SAD-01	95.5
SAD-02	103.16
SAD-03	100.00
SAD-04	101.35
SAD-05	104.00



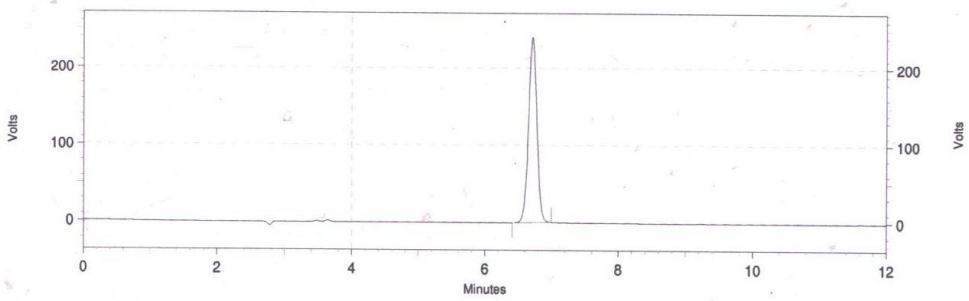
Graphical Representation for Assay (%) of Linezolid tablet

Graph Representation For Assay Of Linezolid Formulations (Sad-01-Sad-05)



Graphical Representation for Blank Solution

Sample Name: Linezolid Std
Data File: D:\HPLC 2019\Result\Surbi\Linezolid Tablet 14052019.rslt\Linezolid Std
Method: D:\HPLC 2019\Method\linezolid Tab Assay.met
Run Time: 5/14/2019 7:38:15 PM (GMT +05:30)



VWD: Signal A, 250 nm Results

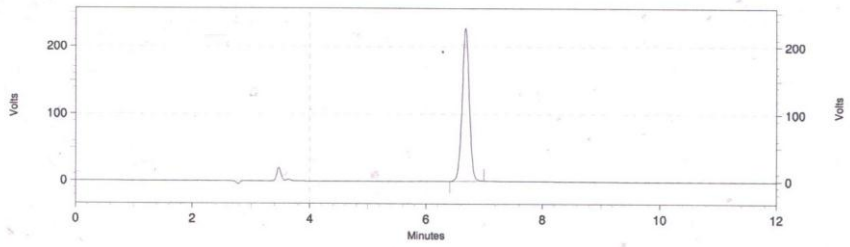
Name	Retention Time	Area	Area %	Height	Height %
	6.713	35759747	100.00	4040901	100.00
Totals		35759747	100.00	4040901	100.00

Graphical Representation for Standard Solution

Formulation SAD-01, during this formulation starch was used 3 % for paste formation and 2% was used for mixing whereas SLS was used 50-50% during mixing in RMG and for blending respectively.

After the granulation process, blend powder was proceed for compression of tablet in which all the in-process parameters were under acceptance criteriabut dissolution of the tablet was less i.e 95.50% according to the acceptable data.

Sample Name: Linezolid Tabs Test Solution (F-140519001)
Data File: D:\HPLC 2019\Result\Surbi\Linezolid Tablet 14052019.rslt\Linezolid Test Solution
Method: D:\HPLC 2019\Method\linezolid Tab Assay.met
Run Time: 5/14/2019 7:51:13 PM (GMT +05:30)



VWD: Signal A, 250 nm Results

Name	Retention Time	Area	Area %	Height	Height %
	6.683	33510765	100.00	3814560	100.00
Totals		33510765	100.00	3814560	100.00

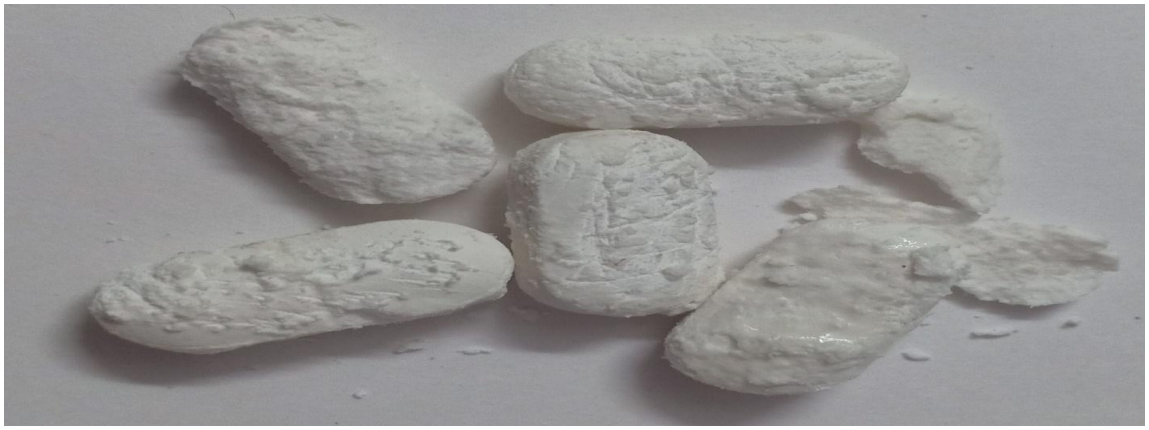
Assay of Formulation No 1 (Sad-01)

Then it was proceed for coating, in which the tablet was coated from aqueous based solvent that is water where many problems were occurred during water coating such spore formation, twinning of tablet.

Problem Occur During Coating Of Tablet From Aqueous Coating

Twinning of Tablet

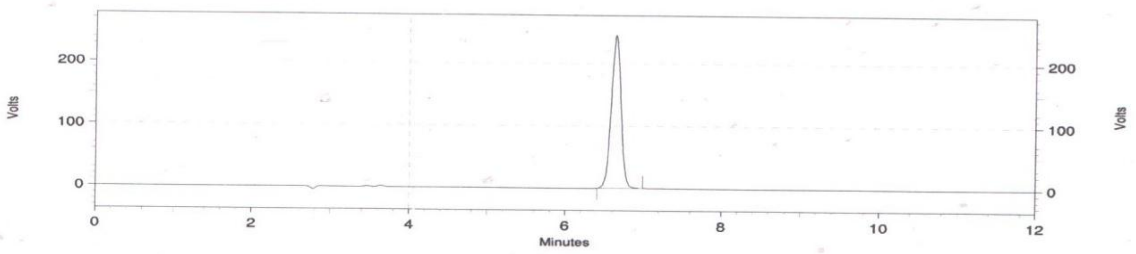
Spores formation of Tablet



Capping & Melting of Tablet

To improve the dissolution and coating of the tablet, formulation SAD-002 was formed in which percentage of starch were changed for paste formation as well as for mixing.

Sample Name: Linezolid Tabs Test Solution (F-140519003)
Data File: D:\HPLC 2019\Result\Surbi\Linezolid Tablet 14052019.rslt\Linezolid Test Solution
Method: D:\HPLC 2019\Method\linezolid Tab Assay.met
Run Time: 5/14/2019 8:17:09 PM (GMT +05:30)



VWD: Signal A, 250 nm
Results

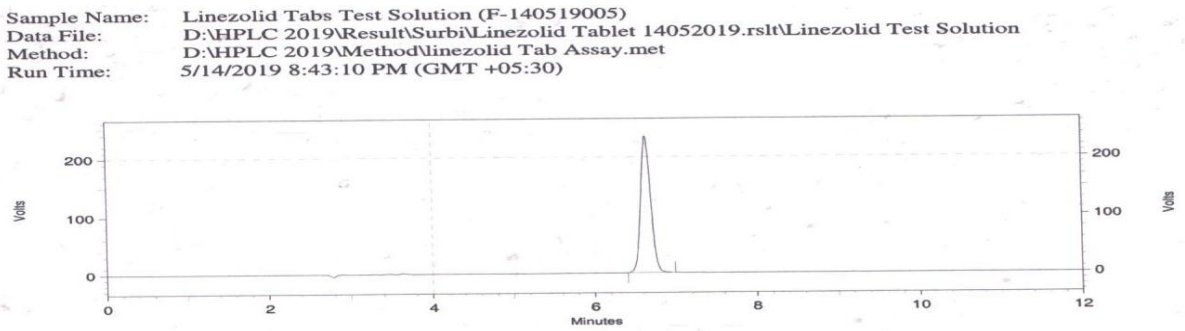
Name	Retention Time	Area	Area %	Height	Height %
	6.647	35846759	100.00	4124088	100.00
Totals		35846759	100.00	4124088	100.00

Assay of Formulation No 2 (Sad-02)

It was taken as 2% and 3% for paste formation and for mixing respectively. Due to these changes, the hardness of the tablet was reduces which was not under acceptance criteria during in-process control. Whenever hardness of tablet comes with in specification, the dissolution of the tablet was failed and vice versa.

3rdtrial was formulated **SAD-03**, to improve the hardness, dissolution release profile and coating of the tablet. Same procedure is used only the ratio of starch was changed where starch was used as 2.5% and 2.5% for paste and mixing respectively. After that the wet mass get dried and then was shifted through 20#.

The hardness of the tablet was passed & under acceptance criteria but due to large granules, dissolution of the core tablet was failed.



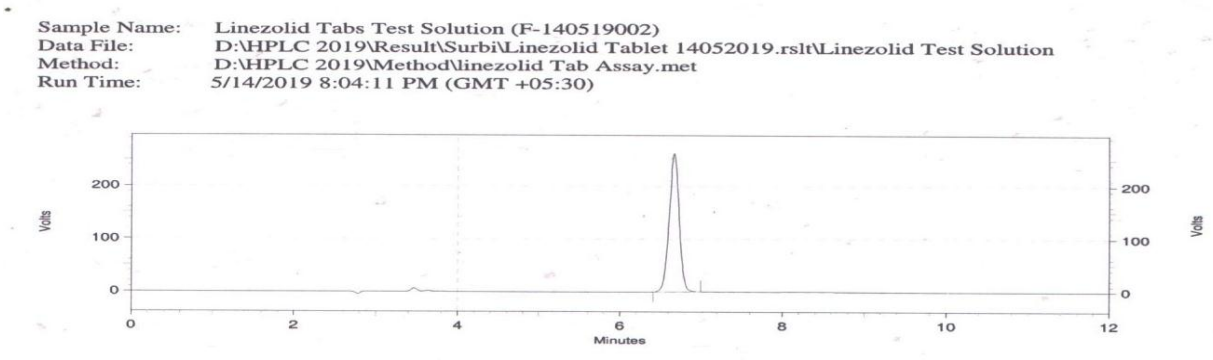
VWD: Signal A, 250 nm Results

Name	Retention Time	Area	Area %	Height	Height %
	6.647	34268308	100.00	3944407	100.00
Totals		34268308	100.00	3944407	100.00

Assay of Formulation No 3 (Sad-03)

So to improve the dissolution of the core tablet, the granules were passed through 14# mesh and some extra material were added by which the hardness and dissolution were passed but the final assay was decreased as according to other two last formulations.

Again to improve hardness and dissolution of the tablet without addition of extra granules, the coating solvent for the next trial **(4th formulation)** was changed. A new formulation was prepared SAD-004, in which the coating was done from non-aqueous solvent i.e IPA (Isopropyl Alcohol). During granulation process, starch was used in the ratio of 2% and 3% and SLS was used in the ratio of 70% and 30%.



VWD: Signal A, 250 nm Results

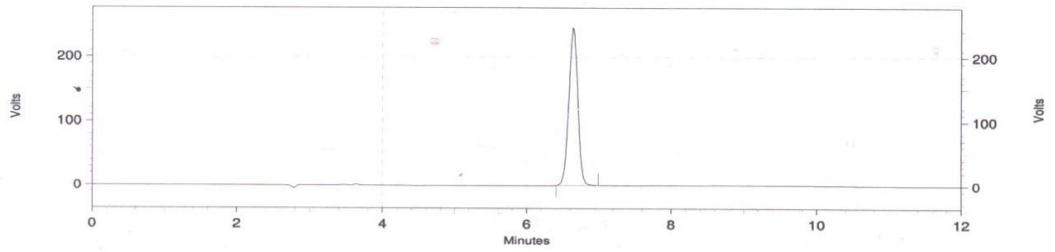
Name	Retention Time	Area	Area %	Height	Height %
	6.667	38448555	100.00	4400360	100.00
Totals		38448555	100.00	4400360	100.00

Assay of Formulation No 4 (SAD-04)

During granulation process, starch was used in the ratio of 2% and 3% and SLS was used in the ratio of 70% and 30% and some extra quantity of SLS was added to improve the dissolution release profile which lighten the weight of the powder and help to disintegrate the tablet easily. By addition of SLS, the dissolution of tablet was passed but it minimizes the hardness of the tablet.

To improve the hardness, dissolution & coating appearance, **5th trial SAD-05** was formed using same formulations, where starch was used in the ratio of 2% and 3% and SLS was used in the ratio of 20% and 80% for mixing & blending respectively. Temperature of FBD was changed according to other formulations (inlet and outlet temperature), which were taken as 70^0 C & 60^0 C respectively.

Sample Name: Linezolid Tabs Test Solution (F-140519004)
Data File: D:\HPLC 2019\Result\Surbi\Linezolid Tablet 14052019.rslt\Linezolid Test Solution
Method: D:\HPLC 2019\Method\linezolid Tab Assay.met
Run Time: 5/14/2019 8:30:09 PM (GMT +05:30)



VWD: Signal A, 250 nm
Results

Name	Retention Time	Area	Area %	Height	Height %
	6.643	35864436	100.00	4123475	100.00
Totals		35864436	100.00	4123475	100.00

Assay of Formulation No 5 (SAD-05)
SLS makes the powder weight lighten which is useful to disintegrate the tablet easily as well as help in fast dissolution and high temperature increase the hardness of tablet.

The core tablet passes all the in-process parameters including hardness, disintegration, friability and dissolution release profile. The hardness & assay was found to be 6.45 kg/cm^2 & 104.0% respectively which is under acceptance criteria and is better than other above four formulations. Then compressed tablet was proceed for coating of tablet where coating was done with non-aqueous solvent. Film coating from IPA was done successfully and no defect were found after coating of tablet in formulation SAD-05.

Formulation SAD-05 passes all the parameters during its formulation and was taken as ideal formulation.

SUMMARY AND CONCLUSION

In this research work, a novel effort is made to design a film coated tablet by wet granulation technique loaded with drug linezolid. The main purpose of formulating film coated tablet of linezolid by wet granulation was to improve its hardness, friability and to extend its dissolution release profile of core tablet. Another main aim was to formulate a film coated tablet without any coating defect which made possible by using IPA as a coating material. On the basis of thorough and regular study of review of literature and research work regarding Linezolid, no previous attempt have been made to formulate film coated tablet of linezolid by using IPA as a coating material. Therefore, a pioneer novel attempt has been made to formulate and evaluate linezolid film coated tablet.

Initially preformulation studies were carried out which include description, solubility, melting point and preparation of standard curve of the drug. The drug was found to be sparingly soluble in water and methanol and slightly soluble in ethanol, and the $\lambda_{max}$of drug was observed to observed to be 334nm in methanol.

The standard curve of the drug was prepared in methanol, phosphate buffer pH7.6, pH7.4 & pH5.5.

Linezolid tablet were prepared using wet granulation technique. All the formulated trials of tablet were evaluated for weight uniformity, hardness, friability, disintegration, thickness and in-vitro drug release study.

Thickness of the tablets was found to be in the range of 5.90± 0.014 mm to 6.00± 0.010 mm. The hardness of all the formulations was found to be in the range of 2.50 to 6.45 kg/cm^2.The results showed that weight variation was ranging from 868±1.20 to 879±0.40 mg.The maximum and minimum friability values among 5

formulations were found to be in the range of 0.23 to 0.86% respectively. The assay of Linezolid-600 mg film coated tablets were found in the range between 95.5 and 104.000%.

The thickness of the standard/ideal formulation were found to be5.93 ± 0.010. The hardness of the standard/ideal formulation were found to be 6.45kg/cm$^{2.}$ The weight variation of the standard/ideal formulation were found to be873±0.20%. The friability of the standard/ideal formulation were found to be 0.32%. The assay of the standard/ideal formulation were found to be 104.00%. From all above formulations **(SAD-01, SAD-02, SAD-03, SAD-04),** this formulation **(SAD-05)** were found to have best results.

Hence it can be concluded that more film coated linezolid by using IPA as a coating material can be prepared.

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