

## FORMULATION AND IN VITRO EVALUATION OF MOUTH DISSOLVING TABLETS OF LEVOSULPIRIDE

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### ABSTRACT

**Objective:** The objective of this study was to formulate and optimize a mouth dissolving formulation of levosulpiride. **Method:** Levosulpiride mouth dissolving tablet having D2-dopamine receptor antagonistic activity were made by direct compression using microcrystalline cellulose, mannitol, povidone and a disintegrant sodium starch glycolate. Thus, formulating levosulpiride into amouth dissolving dosage form would provide fast relief. **Results:** The tablets were evaluated for weight variation, drug content, content uniformity, hardness, friability, *in-vitro* disintegration time and *in-vitro* drug release. The results show that the presence of a superdisintegrant and mannitol is desirable for orodispersion. **Conclusion:** Formulations satisfied the limits of orodispersion with a dispersion time of less than 60 sec, optimized drug released within 30 min and the formulations followed first order linear kinetics. So, it is feasible to formulate mouth dissolving tablets of levosulpiride with acceptable disintegration time, rapid drug release and good hardness as an alternative to conventional tablet.

**Key words:** Levosulpiride, mouth dissolving, oral tablets

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### INTRODUCTION

Levosulpiride is the levo enantiomer of sulpiride. It is a substituted benzamide which is meant to be used for several indications: depression, psychosis, somatoform disorders, emesis and dyspepsia. It is physically present as a white crystalline powder with the chemical structure as follows:

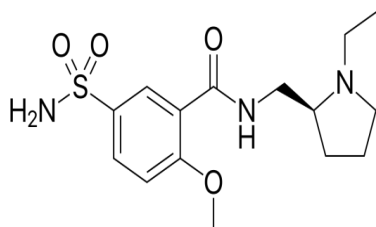


Figure 1: Chemical structure of levosulpiride.

Fast disintegrating tablets are solid unit dosage forms that are placed in mouth and allowed to disperse/dissolve in the saliva without the need of water and provide a quick onset of action. Some drugs are absorbed from mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [1].

The oral route of administration has gained wide acceptance because of ease of administration, self-medication and pain avoidance. Many elderly persons are reported to have difficulties in taking liquid orals such as solutions and suspensions due to hand tremors. On the contrary solid oral dosage forms like tablets or capsules may not be patient compliance in people with dysphagia. Nearly 35% of the general population, especially the elderly patients and children suffer from Dysphagia or difficulty in swallowing, which results in high incidence of noncompliance and ineffective therapy. Swallowing problems are also very common in young individuals because of their poorly developed muscular and nervous systems [2, 3]. To overcome these problems, formulators have considerably dedicated their effort to develop a novel type of tablet dosage form for oral administration, i.e., fast dissolving tablets [4].

### MATERIAL AND METHOD

#### Ingredients/Chemicals

Levosulpiride (active ingredient), Microcrystalline cellulose, Povidone, Sodium starch glycolate, Mannitol, Magnesium stearate, Avicel 200. Important ingredients that are used in the formulation of fast-disintegrating tablets should allow quick release of

the drug, resulting in faster dissolution. This includes both the active and inactive ingredients.

Excipients balance the properties of the actives in fast-disintegrating tablets. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives [5, 6]. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy [7].

### **Pre-compression Studies**

#### *Bulk Density*

Bulk density is described because the mass of a powder divided via the bulk volume. The majority density of a powder relies upon primarily on particle length distribution particle shape, and the tendency of the particles to stick to one another [8].

Bulk density was determined (bulk density apparatus, Konark instruments, India) by taking the dried granules in a measuring cylinder and measures the volume and weights of the total granules.

$$\text{Bulk Density} = \text{Total Weight} / \text{Total Bulk Volume}$$

#### *Tapped Density*

Tapped density was determined (bulk density apparatus, Konark instruments, India) by taking the dried granules in a measuring cylinder and measures the volume of granules after 100 tapping and weight of the total granules [8].

$$\text{Tapped Density} = \text{Total Weight} / \text{Total Tapped Volume}$$

#### *Compressibility Index*

Compressibility index was determined by placing the dried granules in a measuring cylinder and the volume ( $V_0$ ) was noticed before tapping, after 100 tappings again volume ( $V$ ) was noticed.

$$\text{Compressibility index} = (1 - V_0/V) * 100$$

Where,  $V_0$  = volume of powder/granules before tapping,  $V$  = volume of powder/granules after 100 tappings.

#### *Angle of Repose*

Angle of repose is defined as the maximum angle viable between the surface of a pile of the powder and horizontal aircraft. The frictional pressure in a unfastened powder or granules can be measured by using angle of repose [9].

Angle of repose was determined by measuring the height, radius of the heap of the powder bed. A cut system funnel was fixed to a stand and the bottom of the funnel was fixed at a height of 5 cm from the plane. Powder bed were placed in funnel and allowed to flow freely and measure the height and radius of the heap of powder bed. These studies were carried out before and after incorporating lubricants/glidants.

$$\text{Tan } \phi = h/r$$

Where  $h$  = height of heap of granules

$R$  = radius of heap of granules

#### *Hausner's Ratio*

Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. Hausner's ratio is calculated by the formula:

$$H = \text{Bulk Density} / \text{Tapped Density}$$

Where,  $H$  = Hausner's ratio [10]

#### *Drug Excipient Compatibility Studies*

The drug polymer and polymer-polymer interaction were studied by the FTIR spectrometer using Fourier transform infrared (FTIR) spectra were recorded on a Jasco FTIR-6100 spectrometer using KBr discs with a  $2 \text{ cm}^{-1}$  resolution in the range of  $4000\text{--}400 \text{ cm}^{-1}$ .

### **Preparation of Fast Dissolving Levosulpiride Tablets**

1. Before the compression of tablets, the mixture blends of all the formulation were subjected for pre-compression parameter like Bulk density, Tapped density, Angle of Repose, percentage compressibility and Hausner's ratio.
2. Levosulpiride fast dissolving tablets were prepared by direct compression method.
3. All the ingredients were passed through 60-mesh sieve separately and collected.
4. The drug and Avicel 200 were mixed in small portion of both at each time and blended to get a uniform mixture and kept aside.
5. Then the ingredients were weighed and mixed in geometrical order and the tablets were compressed using flat face 9 mm size punch to get a tablets of 200 mg weight using single punch tablet compression machine.

### **Post-compression Tests**

#### *Hardness Test*

The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted.

#### *Friability Test*

10 tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. [9]

The tablets were taken out, dedusted and reweighed. The percentage friability of the tablets was using the following formula:

$$F = \frac{\text{Initial weight} - \text{Final Weight} \times 100}{\text{Initial weight}}$$

% Friability of tablets less than 1% is considered acceptable

#### *Weight Variation Test*

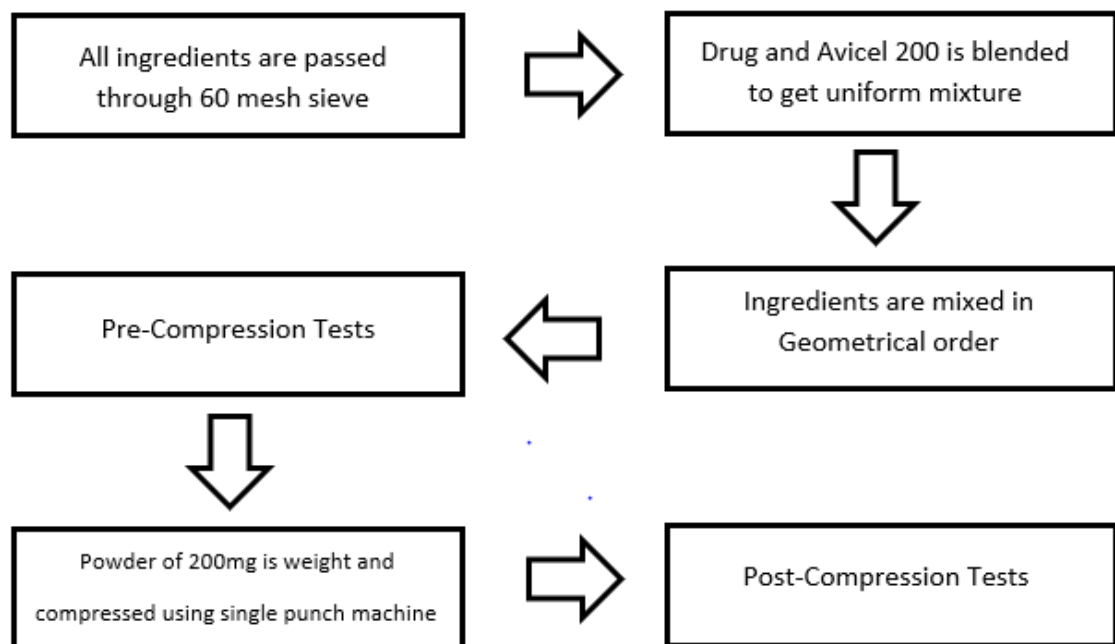
Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation.

#### Percentage Deviation in Weight Variation

In all the formulations the tablet weight was more than 130mg and less than 324 mg, hence 7.5% maximum difference allowed.

#### In-vitro Disintegration Time

Time Tablet was put into 100 ml distilled water at  $37 \pm 20C$ . Time required for complete dispersion of a tablet was measured with the help of digital tablet disintegration test apparatus.



**Figure 2:** Flow diagram showing steps of tablet preparation.

#### Content Uniformity Tests

Accurately weighed quantity (25mg) of Levosulpiride working standard taken in 100 ml volumetric flask. Dissolved and diluted up to the mark with 0.1N NaOH solution and stirred well to completely dissolve the powder. Next is the sonication and filtering of the solution and the absorbance measured at 214nm wavelength using 0.1N NaOH as blank. 20 tablets weighed from each formulation are triturated in mortar using a pestle. An accurately weighed powder equivalent to 25mg of Levosulpiride in 100ml volumetric flask is taken. This is dissolved and diluted up to the mark with 0.1N NaOH solution. It is stirred well to completely dissolve the powder before being filtered, diluted and sonicated. The absorbance is measured at 214 nm wavelength using 0.1N NaOH as blank.

#### In-vitro Drug Release

In vitro drug release studies were carried out using USP type II apparatus at 50 rpm. Phosphate buffer (900 ml) at pH 6.41 (corresponding to salivary pH) was used as the dissolution medium. The temperature of the dissolution medium was maintained at  $37 \pm 0.5^{\circ}C$ . An aliquot (5 ml) of dissolution medium

was withdrawn at specific time intervals, filtered and suitably diluted prior to spectrophotometric analysis. Absorption of the solution was measured by UV spectroscopy at 214 nm.

#### RESULTS AND DISCUSSION

##### Pre-Compression Studies

The pre-compression studies of powder were done and different parameters were observed like bulk density (0.75 g/ml), tapped density (0.937 g/ml), angle of repose, Carr's index (20%) and angle of repose ( $26.77^{\circ}$ ). This was further confirmed by Hausner's ratio (1.249).

The tablets obtained were of uniform weight with a range of 149-152 mg which was in acceptable range as described in specifications ( $\pm 7.5\%$ ) thus indicating consistency in preparation of tablets and minimal batch to batch variations.

##### Post-Compression Tests

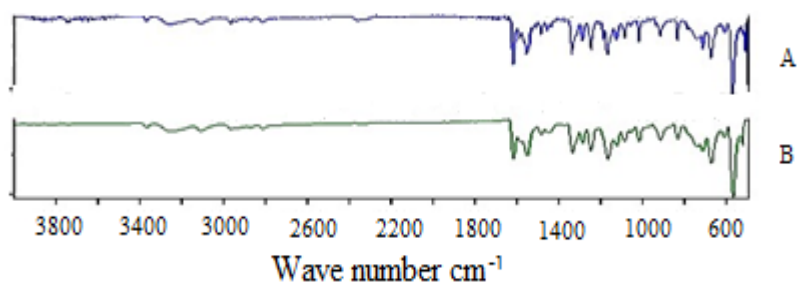
The tablets were evaluated for post-compression tests. The drug content in each tablet was in normal limits. The weight variation, thickness, hardness and friability were determined and the results were in normal ranges. Mouth dissolving tablets of levosulpiride were prepared by direct compression

method using sodium starch glycolate used as super disintegrant and microcrystalline cellulose as diluent along with directly compressible mannitol, which serves as a sweetening agent and helps in masking taste of the drug.

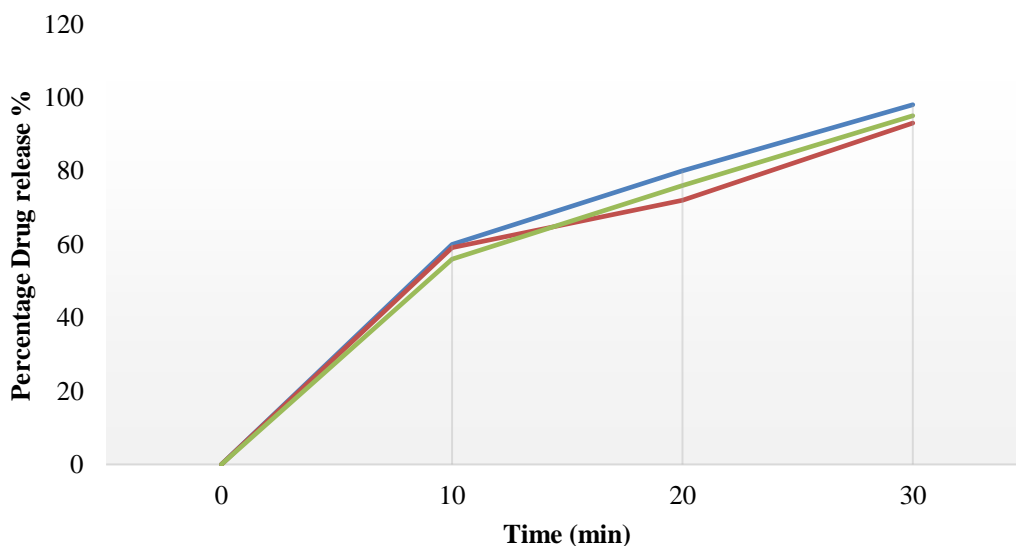
Drug content was found to be in the range of 97% to 98%, which is within acceptable limits. Hardness of the tablets was found to be 4.15 to 4.20 kg/cm<sup>2</sup> and did not show any significant difference among various formulations. Friability below 1% was an indication of good mechanical resistance of the tablets. Formulation complied with the dispersion time requirement of ≤ 60 sec for mouth dissolving tablets [10, 11]. Formulation showed the optimized drug released within 30 min and the formulation followed first order linear kinetics.

**Table 1:** Evaluation of mouth dissolving tablets of levosulpiride.

<i>Parameters/Formulation</i>	F-1	F-2	F-3
Weight per tablet (mg)	150	150	150
Weight variation (mg)	152	151	152
Thickness (mm)	3.65	3.6	3.64
Hardness (kg/cm <sup>2</sup> )	4.2	4.16	4.15
Friability (%)	0.15	0.16	0.15
Disintegration time (s)	54	52	55
Assay content (%)	97.68	97.93	97.02



**Figure 3:** FTIR spectra of levosulpiride (A) and mouth dissolving tablet (B).



**Figure 4:** In-vitro release profile of mouth dissolving levosulpiride tablets.

## CONCLUSION

Formulation showed disintegration times that were less than 60 seconds, as well as good physicochemical properties. Drug release rates of the

mouth dissolving /fast dissolving tablets were much higher than that of the conventional tablets. The results indicate mouth dissolving tablets exhibits

good in vitro disintegration as well as improved drug release rate and follow the first order release pattern. Thus the present study demonstrated potentials for

rapid absorption, improved bioavailability, effective therapy and patient compliance.

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