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# Formulation Development and Evaluation of Oral Dispersible Tablet of Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium

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Oral dispersible tablet is solid unit dosage form. The objective of present investigation was to prepared oral dispersible tablet of Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium because it's active working patients who are busy or travelling, especially those who have no access to water. Such problems can be resolved by means of the oral dispersible tablet form which does not require water to aid swallowing. Oral dispersible tablet are put into the mouth, tablet disintegrates instantaneously releasing the drug which dissolves or disperses in the saliva. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Prepared tablets were evaluated for different properties like hardness, friability, disintegration time, Wetting time, time of dispersion and In-vitro dissolution study.

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*Keyword:* Oral Dispersible Tablet, Superdisintegrant, Dry Granulation Method

### 1. Introduction

Drug delivery systems (DDS) were a strategic tool for expanding markets/indication, extending product life cycles and generating opportunities. DDS has made a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Oral dispersible tablets (ODT) are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue. ODTs are solid dosage forms that disintegrate in the mouth in less than 60 seconds, and are thus swallowed without the need for water. Oral dispersible tablets (ODTs) have started gaining popularity and acceptance as new drug delivery systems, because they are easy to

administer & leads to better patient compliance especially in elderly & children<sup>[1]</sup>.

Pharmaceutical technologists have developed a novel oral dosage form known as Orodispersible Tablets (ODTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms<sup>[2]</sup>.

When such tablets are placed in oral cavity, saliva quickly penetrates into the pores to cause rapid tablet disintegration. The US Food and Drug Administration Center for Drug Evaluation and

Research (CDER) defines, in the 'Orange Book', an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue"<sup>[2]</sup>.

The oral route remains the trendy route for the administration of drugs because of accurate dosage, low cost of therapy, self-medication, non-invasive method, and ease of administration leading to high level of patient compliance. ODTs are designed to disintegrate rapidly on contact with saliva and enable oral administration without water or chewing, these formulations offer increased convenience and ease of administration with the potential to improve patient compliance, particularly in certain populations, where swallowing of conventional solid oral dosage forms presents difficulties. European Pharmacopoeia described ODTs as 'uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed' and as tablets which should disintegrate within 3 minutes<sup>[3]</sup>.

ODTs are also called as orodisperse, mouth dissolving, rapidly disintegrating, fast melt, and quick dissolve system. ODTs improve drug dissolution as well as onset of clinical effect and the pregastric absorption of drugs, which avoids first pass hepatic metabolism to reduce the dose than those observed from conventional dosage forms and finally, increase the bioavailability of drugs. ODTs release drugs in the mouth for absorption through local or mucosal tissues and through pregastric (e.g., oral cavity, pharynx, and esophagus), gastric (i.e., stomach), and postgastric (e.g., small and large intestines) segments of the gastrointestinal tract (GIT).<sup>[3]</sup>

Again, ODTs allow the luxury of much more accurate dosing the primary alternate, oral liquids. ODTs with good taste and flavour increase the acceptability of bitter drugs by various groups of population<sup>[3]</sup>.

### 1.1 Need To Formulate Oral dispersible Tablets<sup>[2]</sup>

- ✓ Paediatric patients who are unable to swallow easily because their central nervous system

and internal muscles are not developed completely.

- ✓ Travelling patients suffering from motion sickness and diarrhea that do not have easy access to water.
- ✓ Especially for Patients with persistent nausea for a long period of time are unable to swallow.
- ✓ Mentally challenged patients, bedridden patients and psychiatric patient.

## 2. Material and method

### 2.1 Material

Levocetirizine Dihydrochloride, Crosscarmellose sodium, Crospovidone, Aspartame, Magnesium Stearate, D-Mannitol were Gift sample obtain from ZED pharmaceuticals Pvt. Ltd, Karnal, Paracetamol, Microcrystalline Cellulose (M.C.C), Sodium Starch Glycolate (S.S.G) was Gift sample obtain from Theramax Laboratories, Ambala, india. Montelukast Sodium was Gift sample obtain from Ranbaxy pharmaceuticals, India.

### 2.2 Preparation of Powder Blend for Compression

#### 2.2.1 Preparation of Granules

**Step 1:** All the in-active excipients and drug were passed through mesh no. 45 individually. Then dried at 50°C for 4-5 min. So to assure that all the drug and excipients have to be used is dry in order to develop an optimized formulation through Dry Granulation Technique.

**Step 2:** All the three drugs i.e. Levocetirizine dihydrochloride, Paracetamol and Montelukast Sodium along with Microcrystalline Cellulose (P101) were taken and mixed thoroughly. Then by using large mm die and punch the slugs of API + MCC p101 was formed and crushed in pestle and mortar to form granular material. Now to get fine granules the granular material passed through sieve no. 18. Finally the required size of granules was obtained.

**Step 3:** In this step, the fine granules which were obtained again slugged using large mm die and punch because the desired hardness of tablets could not be achieved. So again it was slugged

and grind in pestle and mortar and finally sieve through mesh no 18.

**Step 4:** In final step the excipients which were left first passed through sieve no. 18 and thoroughly mixed with granular material. Then this blend was further analyzed for its flow properties

### 2.2.2 Evaluation of powder blend <sup>[4]</sup>

#### a. Bulk Density

Apparent bulk density ( $\rho_b$ ) will determined by pouring the blend into a graduated cylinder. The bulk volume ( $V_b$ ) and weight of powder ( $M$ ) was determined. The bulk density will calculated using the formula:

$$\rho_b = M/V_b$$

#### b. Tapped Density

The measuring cylinder containing known mass of blend will tapped for a fixed time. The minimum volume ( $V_t$ ) occupied in the cylinder and weight ( $M$ ) of the blend will measured. The tapped density ( $\rho_t$ ) will calculated using the following formula:

$$\rho_t = M/V_t$$

#### c. Carr's Compressibility Index

The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by % compressibility which is calculated using the formula:

$$C = (\rho_t - \rho_b) / \rho_t * 100$$

Where:

$\rho_t$ - Tapped density

$\rho_b$ - Untapped bulk density

#### d. Hausner's Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following Formula

$$\text{Hausner ration} = \rho_t/\rho_d$$

Where:

$\rho_t$  is tapped density

$\rho_d$  is bulk density.

#### e. Angle of Repose

Angle of repose will determine using funnel method. The blend will pour through funnel that can be raised vertically until a maximum cone height ( $h$ ) was obtained. Radius of the heap ( $r$ ) will measure and angle of repose is calculated using the formula:

$$\theta = \tan^{-1} h/r$$

Where,

$\theta$  is the angle of repose

$h$  is height of pile

$r$  is radius of the base of pile

### 2.3 Evaluation of Oral Dispersible Tablet: [2]-[5]-[6]

#### 2.3.1 Hardness:

A significant strength of ODT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of hardness for the ODT is usually kept in a lower range to facilitate early disintegration in the mouth. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

#### 2.3.2 Friability test:

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator was employed for finding the friability of the tablets. 20 tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 4 minutes. The tablets were dedusted and weighed again. The percentage of weight loss was calculated again. The percentage of weight loss was calculated using the formula

$$\% \text{ Friability} = [(W_1 - W_2)100]/W_1$$

Where,

$W_1$ = Weight of tablet before test

$W_2$  = Weight of tablet after test

#### 2.3.3 Thickness

The thickness is measured by placing tablet between two arms of the Vernier calipers. Tablets were taken and their thickness was measured.

**Table 1:** Evaluation of Powder Blends of Drugs\* and Excipient (Batch A1 to A9)

Parameters	Batch A1	Batch A2	Batch A3	Batch A4	Batch A5	Batch A6	Batch A7	Batch A8	Batch A9
<b>Bulk density</b>	0.692±1.3	0.701±1.4	0.710±1.4	0.662±1.2	0.713±1.5	0.697±1.3	0.777±1.8	0.723±1.6	0.747±1.6
<b>Tapped Density (TD)</b>	0.857±1.2	0.877±1.3	0.839±1.1	0.813±1.0	0.856±1.2	0.872±1.3	0.919±1.5	0.913±1.5	0.955±1.7
<b>Angle of repose</b>	29.2°±1.1	27.3°±1.4	26.2°±1.6	28.5°±1.3	28.1°±1.3	25.2°±1.6	24.9°±1.7	25.4°±1.6	24.3°±1.8
<b>Carr's Compressibility index</b>	19.25	20.06	14.37	16.57	16.70	20.06	19.68	19.41	20.78
<b>Hausner Ratio</b>	1.23	1.24	1.17	1.20	1.25	1.33	1.25	1.26	1.30

Drugs\*- Levocetirizine dihydrochloride, Paracetamol and Montelukast sodium

**Table 2:** Composition (In %) of oral dispersible tablet (Batch A1 to A9)

Ingredients	Batch A1 (%)	Batch A2 (%)	Batch A3 (%)	Batch A4 (%)	Batch A5 (%)	Batch A6 (%)	Batch A7 (%)	Batch A8 (%)	Batch A9 (%)
<b>Levocetirizine dihydrochloride</b>	1	1	1	1	1	1	1	1	1
<b>Paracetamol</b>	65	65	65	65	65	65	65	65	65
<b>Montelukast Sodium</b>	2	2	2	2	2	2	2	2	2
<b>MCC P101</b>	20	20	20	20	20	20	20	20	20
<b>Primogel</b>	4	5	6	-	-	-	-	-	-
<b>Primellose</b>	-	-	-	4	5	6	-	-	-
<b>Crospovidone</b>	-	-	-	-	-	-	4	5	6
<b>Aspartame</b>	1	1	1	1	1	1	1	1	1
<b>Magnesium Stearate</b>	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
<b>D-Mannitol</b>	5.5	4.5	3.5	5.5	4.5	3.5	5.5	4.5	3.5

NOTE-Total weight of tablet 500mg

**Table 3:** Evaluation of Oral Dispersible Tablet's of Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium (Batch A1 to A9)

Parameters	Batch A1	Batch A2	Batch A3	Batch A4	Batch A5	Batch A6	Batch A7	Batch A8	Batch A9
<b>Hardness (KN)</b>	6±1.1	6±1.0	6.1±1.2	6.2±1.3	6±1.0	6.1±1.1	6±1.2	6±1.0	6.2±1.1
<b>Thickness</b>	2.8	2.7	2.7	2.7	2.8	2.7	2.6	2.7	2.7
<b>Friability (%)</b>	0.91	0.92	0.90	0.93	0.94	0.92	0.90	0.92	0.93
<b>Weight Variation</b>	509±10.8	501±1.2	500±1.0	504±1.3	505±1.4	500±1.1	503±1.2	503±1.2	504±1.3
<b>Disintegration Time (Sec)</b>	42	38	32	45	39	33	44	38	34
<b>Wetting Time Time(Sec)</b>	14	20	9	10	17	18	19	12	15
<b>Test for Dispersible</b>	No Residue	No Residue	No Residue	No Residue	No Residue	No Residue	No Residue	No Residue	No Residue

**Table 4:** Plotted values of Time vs. Cumulative % Drug release (Batch A1 to A9)

Cumulative % Drug Release									
Time (min.)	Batch A1	Batch A2	Batch A3	Batch A4	Batch A5	Batch A6	Batch A7	Batch A8	Batch A9
<b>0</b>	0	0	0	0	0	0	0	0	0
<b>5</b>	12.69 ±0.2	12.26 ±0.3	15.69 ±0.5	10.69±0.6	10.11±0.3	11.69±0.4	10.21±0.8	11.23±0.7	10.80 ±0.6
<b>10</b>	42.12 ±1.2	47.67±1.4	47.95 ±0.8	45.03±0.4	41.78±0.5	49.78±0.9	42.03±0.4	44.12±0.6	43.53 ±0.9
<b>15</b>	57.38 ±1.4	52.50±1.6	58.21 ±1.1	50.21±1.8	54.38±0.8	58.55±1.6	55.62±1.3	51.96±1.3	55.62 ±1.1
<b>20</b>	65.65 ±1.5	62.04±1.7	72.81 ±1.3	63.81±1.9	62.98±1.1	62.73±1.8	62.56±1.6	66.14±1.5	67.31 ±1.3
<b>25</b>	77.08 ±1.6	68.11±2.1	79.07±1.6	72.90±2.1	68.90±1.3	74.33±2.1	73.16±1.8	74.33±1.6	70.74 ±1.6
<b>30</b>	86.51 ±0.7	74.65±2.2	89.16±2.1	79.16±2.3	77.33±1.5	81.83±2.4	85.25±1.9	83.00±1.8	81.25 ±1.9

### 2.3.4 Weight Variation

Weight variation test is done by weighing 20 tablets individually, by using Shimdzu balance. Calculating the average weight and comparing the individual tablet weight to the average weight.

### 2.3.5 Dissolution test:

The development of dissolution methods for ODT is comparable to approach taken for conventional tablets and is practically identical when ODT does not utilize taste masking.

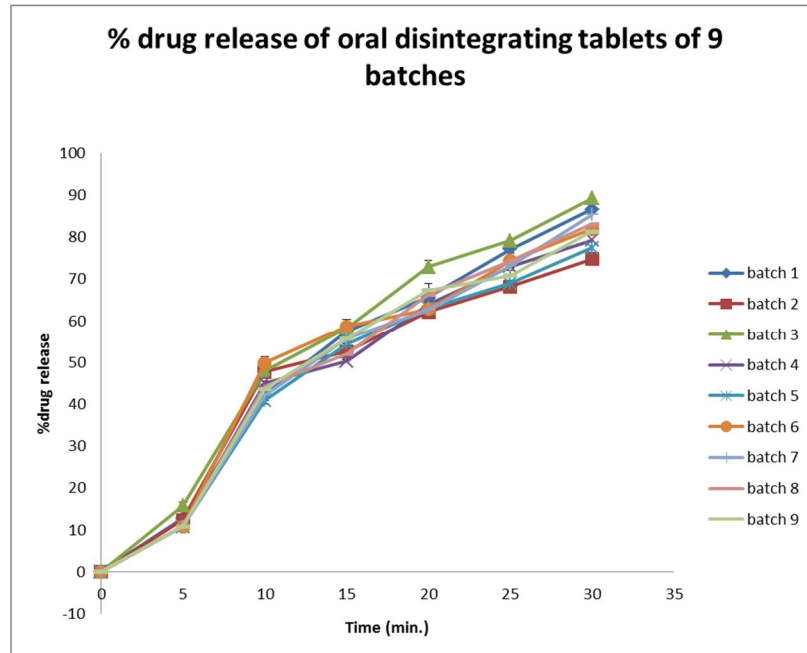


Figure 1: In-vitro drug release of batch A1 to A9

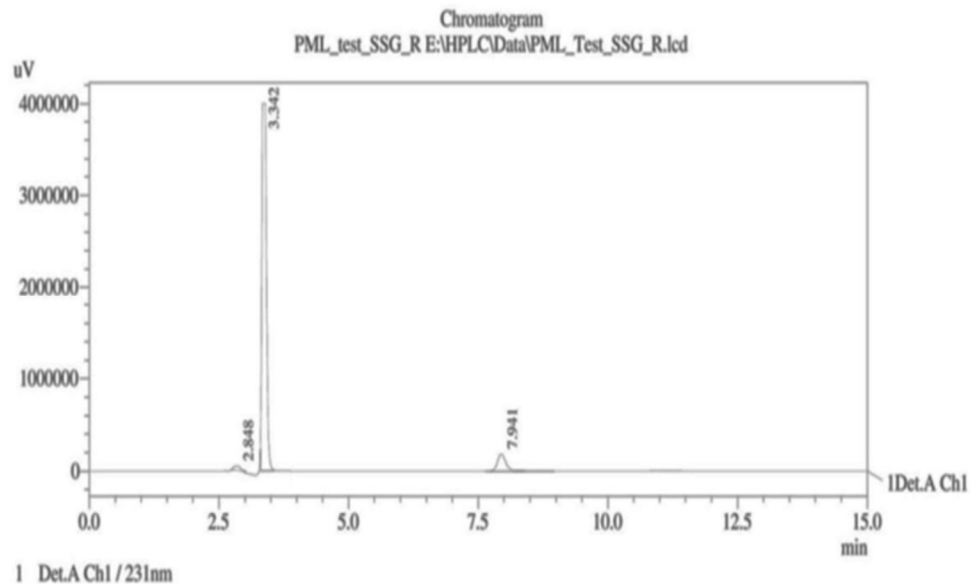


Figure 2: Simultaneous estimation plot of Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium in the prepared formulations

Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1 N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of ODT in the same way as their ordinary tablet counterparts.

Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for dissolution test of ODT tablets, where a paddle speed of 50 rpm is commonly used.



### 2.3.6 In Vivo Disintegration test:

The time for disintegration of ODTs is generally <1min and actual disintegration time that patient can experience ranges from 5 to 30s. The standard procedure are that the test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at 37°C} 2°C was used as a disintegration media and the time in second is taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

### 2.3.7 Wetting time

Five circular tissue paper of 10 cm diameter wear place in petri dish with 10 cm diameter. 10 millilitre of water containing eosin, a water soluble dye was added to petri dish. A tablet was carefully place in tissue paper. Time required for water to reach the upper surface of tablet was noted as a wetting time.

### 2.3.8 Test for dispersion

Two tablets were placed in 100 ml of water and stirred gently until it was completely dispersible and smooth dispersion was obtained. The dispersible liquid was passed through sieve no.22. No residue should remain over the sieve.

## 2.4 Simultaneous estimation of Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium in the prepared formulations by HPLC method

High performance liquid chromatography is used for separation can be carried out using column RP-HPLC C18 column 4.6 x 250 mm; 5 micron; 100 Å using UV detector lamp D2 and  $\lambda_{max}$  will be observed at 231 nm. The optimized mobile phase is consisted of Phosphate buffer pH 6.8: Acetonitrile (60:40) adjusted at pH 6.8 by using ammonia of HPLC grade. The retention times were observed at 2.848, 3.342 and 7.941 min for Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium, with flow rate 1 ml/min. respectively. The proposed method provided linear responses within the concentration 1-10 µg/ml, 25-75 µg/ml and 2-20 µg/ml. Correlation coefficients ( $r$ ) of the regression equations were

greater than 0.999 in all cases. All the process has been carried under ambient temperature. The proposed methods successfully applied for the determination of investigated drugs in tablets.

## 2.5 Determination of $\lambda_{max}$ . For HPLC analysis of Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium by UV Spectrophotometric analysis

- Three separate solutions of Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium were prepared in methanol separately at concentration of 10 µg/ml for each solution.
- The three samples were scanned using a UV spectrophotometer at wavelength range of 200-400 nm.
- The curves obtained for the three different drugs were overlapped on each other and the isobestic point was determined and was used as the  $\lambda_{max}$  for simultaneous estimation of Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium drugs by HPLC method.

### 2.5.1 Preparation of standard stock and working solution

- Mixed standard stock solution containing the three drugs Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium with concentration of 3000 µg/ml in methanol for paracetamol, 2000 µg/ml for montelukast sodium and 1000 µg/ml for Levocetirizine dihydrochloride were prepared in methanol.
- This mixture was used as standard stock solution.
- The working standards solutions were prepared by diluting the above standard stock solution in mobile phase so as to obtain the following concentration ranges for the drugs.

### 2.5.2 Further Concentrations were prepared

- Paracetamol- 25-75 µg/ml in mobile phase.
- Montelukast sodium- 2-20 µg/ml in mobile phase.
- Levocetirizine dihydrochloride- 1-10 µg/ml in mobile phase.
- These working standards were either freshly prepared or stored at 2-8°C for later use.

**Table 5:** Final Simultaneous Estimation Concentration Prepared

Sample Name	Levocetirizine Dihydrochloride (µg/ml)	Paracetamol (µg/ml)	Montelukast Sodium (µg/ml)
WS1	1	25	2
WS2	5	50	10
WS3	10	75	20

### 2.5.3 Standard calibration curves for the 3 drugs using HPLC method

- Working standard solutions prepared as per the above mentioned description were injected into the HPLC system at the above mentioned chromatographic conditions.
- Linear calibration curve were generated using least square linear regression analysis by plotting the peak area against concentration of each drug. Three standards calibration curves for Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium were plotted separately.

### 2.6 Simultaneous estimation of Levocetirizine Dihydrochloride (5 mg), Paracetamol (325 mg) and Montelukast Sodium (10 mg) in the prepared formulations by HPLC method

Ten tablets of Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium were weighed and powdered. An accurate weight of the powder equivalent to 5 mg of levocetirizine dihydrochloride and 325 mg of paracetamol and

10 mg of montelukast sodium was transferred into a 25 ml volumetric flask containing 15 ml methanol, sonicated for 30 min and diluted up to 25 ml with methanol. This solution was filtered through a 0.45 µm membrane filter. For HPLC, Suitable dilutions were made using mobile phase to prepare final tablet solution containing 10 µg/ml, 520 µg/ml and 20 µg/ml for Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium. Tablet solutions thus prepared were filtered then analyzed as mentioned under the construction of calibration graphs in the above section.

### 3. Summary

The aim of present investigation was to formulate, evaluate and optimize process of oral dispersible tablet of levocetirizine dihydrochloride, paracetamol and montelukast sodium. levocetirizine dihydrochloride is Anti-histaminic Drug, paracetamol is Anti-pyretic and Analgesic drug and montelukast sodium is Anti-asthmatic Drug. This oral dispersible tablet dissolved in pH 6.8 in saliva. Development of oral dispersible tablet dosage form can be advantageous, that can provide quickly disintegrate in saliva and increase efficacy of the dosage form.

In dissolution profile batch A3 is give a good % release of drug with superdisintegration (primogel). In Simultaneous estimation curve show that three drugs (Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium) release in tablet simultaneous. So, finally obtained batch A3 which is suitable for our experiment.

### 4. Conclusion

Oral dispersible tablet of Levocetirizine Dihydrochloride, Paracetamol and Montelukast Sodium were prepared by dry granulation method using primogel superdisintegrant. tablets disintegration oral cavity and acceptance friability and hardness. In vitro drug releasing from the tablets shows the significantly improved the drug dissolution. Hence it could be conclude that the superdisintegrant based oral dispersible tablet of Levocetirizine Dihydrochloride,



Paracetamol and Montelukast Sodium would be quite effective in emesis, providing quick onset of action without need of water for administration.

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