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# Formulation Development and Evaluation of Oseltamivir Fast Dissolving Tablets Using Super Disintegrants

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**Keywords:** Oseltamivir, Solutab, Explotab, Polyplasdone XL, Fast dissolving tablets

**ABSTRACT**

Novel drug delivery system and formulation research are oriented towards increasing safety and efficacy of existing drug molecule through novel concepts of drug delivery. The present study was carried out on Oseltamivir. Fast dissolving tablets were prepared by Super disintegrants. A total of 9 formulations were prepared and evaluated for various pre and post compression parameters like angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, weight variation, hardness, friability, thickness, wetting time, water absorption ratio, drug content, *in vitro* disintegration time, *in vitro* drug release. Among all formulations, F3 formulation was shown maximum drug release at 15 min. Hence, it was concluded as optimised formulation. FTIR studies showed good compatibility between drug and excipients.

## INTRODUCTION

The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients noncompliance particularly in case of paediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water.[1]

For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Oral dispersible tablets are not only indicated for people who have swallowing difficulties but also are ideal for active people.[2]

US FDA defined FDT tablets as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds when placed upon the tongue".[3]

Recently, European Pharmacopoeia used the term 'Fast dissolving tablet' as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing.

Orally disintegrating tablets are also called as mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapidmelts, porous tablets, quick dissolving tablet[4.]

The US Food and Drug Administration responded to this challenge with the 2008 publication of Guidance for Industry: Orally Disintegrating Tablets[5]. Three main points stand out in the final guidance:

- FDTs should have an *in vitro* disintegration time of approximately 30sec or less.
- Generally, FDT tablet weight should not exceed 500mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of FDT for both patients and regulators.
- The guidance serves to define the upper limits of the FDT category, but it does not supersede or replace the original regulatory definition mentioned. In other words, disintegration within a matter of seconds remains the target for FDT.

**Need To Develop Fdt[6]:**

The need for one of the non-invasive delivery system i.e., Fast disintegrating tablets persist due to patients' poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug usage, coupled with high cost of disease management.

**Mechanism of Action of FDT in Oral Mucosa:**

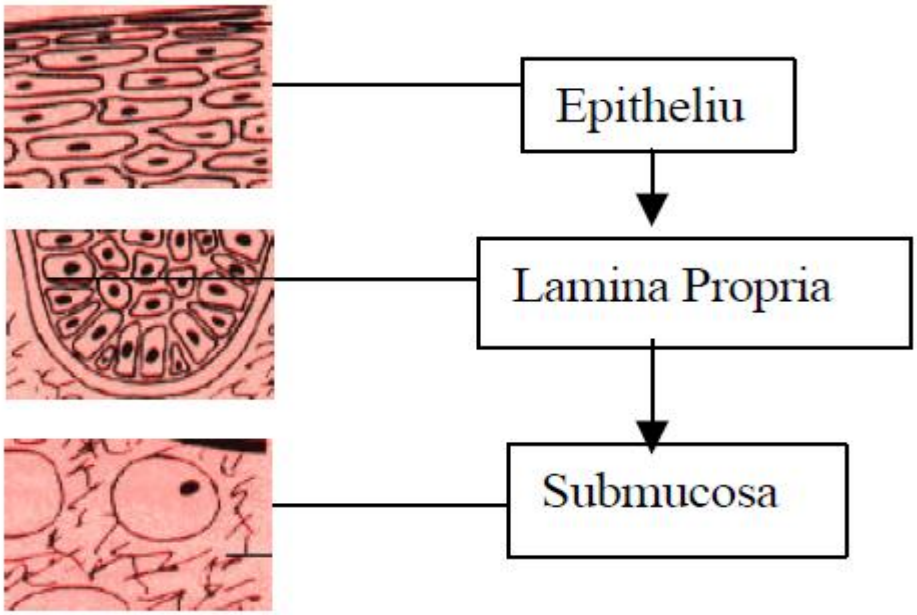


**Fig: 1. Different layers of oral mucosa [7]**

**Mechanism of Action**: The FDT is placed upon patient's tongue or any oromucosal tissue. It instantly gets wet by saliva due to presence of hydrophilic polymer and other excipients, then the tablet rapidly hydrates and dissolves to release the medication for oromucosal absorption.

**Advantages Of FDT[8-10]:**

Advantages of FDTs include:

- Ease of administration to geriatric, paediatric, mentally disabled, and bed-ridden patients, who have difficulty in swallowing the tablet.
- The FDTs do not need water for swallowing, unlike conventional dosage forms. This is very convenient for patients who are travelling or do not have immediate access to water, and thus, provide improved patient compliance.

- Bioavailability of drugs is enhanced due to absorption from mouth, pharynx, and oesophagus.
- Rapid onset of therapeutic action as tablet is disintegrated rapidly along with quick dissolution and absorption in oral cavity.

**Disadvantages of Fast Dissolving Tablets[11-13]**

1. Fast dissolving tablets are hygroscopic in nature so must be kept in dry place.
2. Sometimes, it possesses mouth feeling.
3. FDT require special packaging.

**Limitations To Fast Dissolving Tablets:**

- Drugs with relatively larger doses are difficult to formulate into FDTs e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500mg of the drug.
- Patients who concurrently take anticholinergic medications may not be the best candidates for FDTS

**Desired Characteristics And Challenges To Develop Fast Dissolving Tablets[14].**

Rapid Disintegration ,Palatability, Mechanical Strength, Hygroscopicity ,Amount Of Drug, Size Of The Tablet:

**Various Technologies Used In Formulation Of Fdt[15-20]:**

- The technologies that have been used by various researchers to prepare orally disintegrating dosage forms include: Patented and Non-patented technologies.

**Table 1. Patented and Non- patented technologies**

| Non –patented | Patented |
|---|---|
| Freeze drying<br>Spray drying<br>Molding<br>Phase transition process<br>Melt granulation<br>Sublimation<br>Mass extrusion<br>Cotton candy process<br>Direct compression<br>Nanonization<br>Effervescent method | Zydus technology<br>Orosolv technology<br>Durosolv technology<br>Wowtab technology<br>Fashtab technology<br>Oraquick technology<br>Lyoc technology<br>Quick –Dis technology<br>Nanocrystal technology<br>Frosta technology<br>Pharmaburst technology<br>Flash Dose technology<br>Ziplet/Advatab technology<br>QuickSolv technology |

**Criteria For Selection Of Drug To Develop FDT:**

FDT may have varying degrees of pregastric absorption of drugs and thus, the pharmacokinetic profiles of drugs will vary, therefore, the FDTs will not be bioequivalent to the conventional dosage forms.

The ideal characteristics of a drug to develop as an FDT include:

- No bitter taste.
- Small to moderate molecular weight.
- Good stability in water and saliva.
- Partially non-ionized at the oral cavities pH.

- Ability to permeate oral mucosal tissue.
- Dose should be low as possible.

Unsuitable drug characteristic for FDTs:

- Short half-life and frequent dosing.
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved.
- Required controlled or sustained release.

**Selection Of Super Disintegrants:**

Super disintegrants not only affect the rate of disintegration, but when used at higher concentrations they also affect mouth feel, tablet hardness and friability [21]. Hydrotropic agents are selected according to critical concentration of disintegrant. Below this concentration, tablet disintegration time is inversely proportional to the concentration of the Hydrotropic agent. Hence, various ideal characteristics of super disintegrants should be considered while selecting for a particular formulation.

- Produce rapid disintegration.
- Be compactable enough to produce less-friable tablets.
- Produce good mouth feel to the patient. Thus, small particle size is preferred to achieve patient's compliance
- Should have good flow properties to improve the flow ability of the total blend.

**Mechanism Of Super Disintegrants:**

There are major mechanisms for tablets disintegration as follows.

**Swelling:** Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

**Porosity And Capillary Action (Wicking):** Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipients and on tableting conditions.

For these types of disintegrants, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

**Due To disintegrating Particle/Particle Repulsive Forces:** Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

**Due To Deformation:** During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

**Because Of Heat Of Wetting (Air Expansion):** When disintegrants with exothermic properties get wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

**By Enzymatic Reaction:** Here, enzymes present in the body act as disintegrants. These enzymes destroy the binding action of binder and help in disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

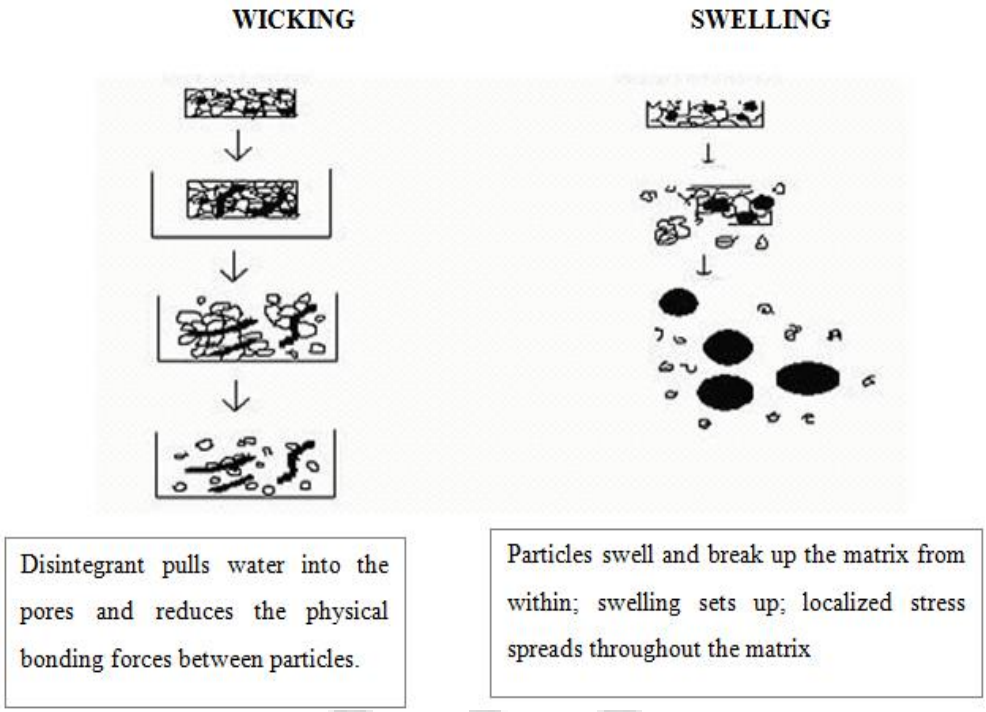


**Figure: 2 Disintegration of tablet by wicking and swelling**

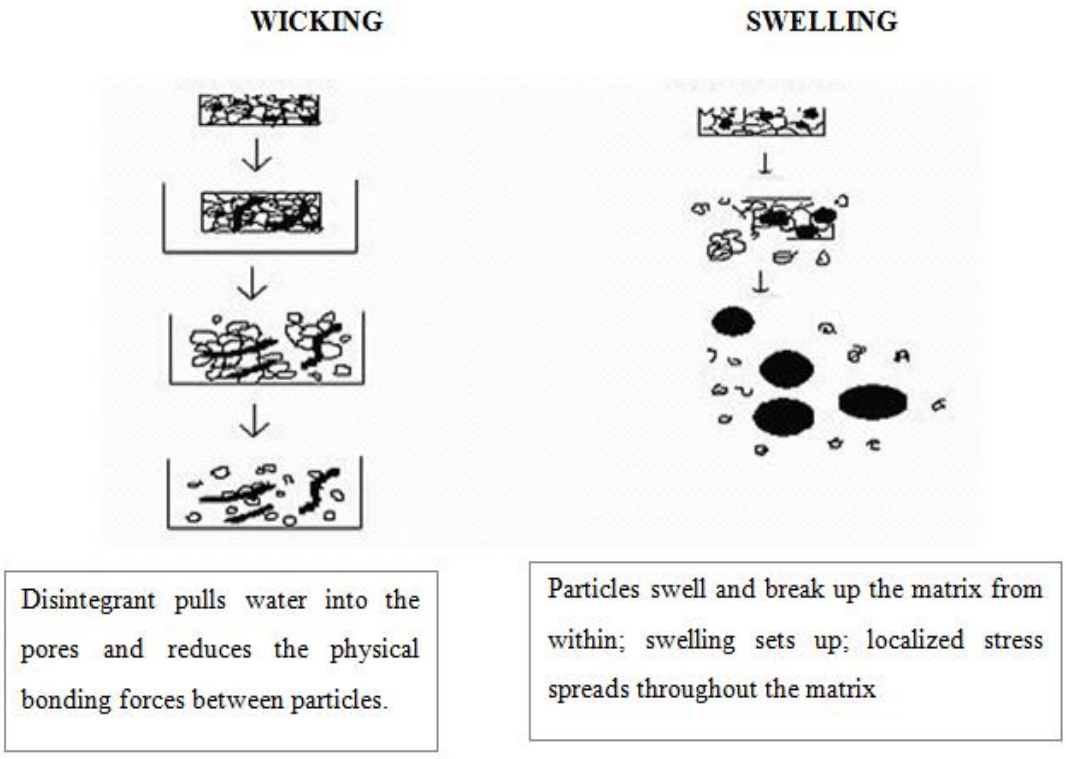


**Figure: 3 Disintegration of tablet by deformation and repulsion.**

## MARKETED PRODUCTS AVAILABLE AS FDT:

**Table.2. Commercially available Mouth disintegrating tablets**

| Brand name | Active ingredient | Company |
|---|---|---|
| Zomig ZMT and Rapimelt | Zolmitriptan | AstraZeneca |
| Alavert | Loratidine | Wyeth Consumer Healthcare |
| Cibalginadue FAST | Ibuprofen | Novartis Consumer Health |
| Hyoscyamine Sulfate FDT | Hyoscyamine Sulfate | ETHEX corporation |
| Nulev | Hyoscyamine Sulfate | Schwarz Pharma |
| Kemstro | Baclofen | Schwarz Pharma |
| Fluoxetine FDT | Fluoxetine | Bioavail |
| Benadryl Fastmelt | Diphenhydramine | Pfizer |
| Zolpidem FDT | Zolpidem tartarate | Bioavail |

## MATERIALS

Oseltamivir Procured From Cipla Limited provided by **SURA LABS**, Crospovidone, SSG, Magnesium stearate, Talc, Mannitol are procured from Merck Specialities Pvt Ltd, Mumbai, India

## METHODOLOGY

### Construction Of Calibration Curve Of Oseltamivir

- Accurately weighed 10mg of drug was transferred to 10 ml volumetric flask and dissolved in methanol, this was considered as stock solution (I).
- To 1 ml of stock solution (I) 9 ml of pH 6.8 phosphate buffer was added and this was considered as stock solution (II).

- From stock solution (II) 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1ml, were taken and was made up the volume to 10ml with pH 6.8 Phosphate buffer to get respective concentrations of (2, 4, 6, 8 and 10) µg/ ml.
- Prepared samples were analyzed by using ultraviolet double beam spectrophotometer at $\lambda_{max}$ 218nm.
- The calibration curve was plotted by taking concentration on x-axis and absorbance on y-axis.

**Preparation Of Oseltamivir Fast Dissolving Tablets**

**Preparation Of Oseltamivir Fast Dissolving Tablets By Direct Compression Method**

- Drug different concentrations of sublimating agent and super disintegrates were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes.
- The obtained blend was lubricated with Mg stearate and glidant (Talc) was added and mixing was continued for further 5 minutes.
- The resultant mixture was directly compressed into tablets by using 8mm round flat faced punch of rotary tabletting machine. Compression force was kept constant for all formulations.

**Table 3. Composition Of Oseltamivir Fast Dissolving Tablet.**

| Materials (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Oseltamivir | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 |
| Solutab | 10 | 20 | 30 | - | - | - | - | - | - |
| Explotab | - | - | - | 10 | 20 | 30 | - | - | - |
| polyplasdone XL | -- | -- | -- | -- | -- | -- | 10 | 20 | 30 |
| Talc | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Mg stearate | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MCC | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |
| Total weight of tablet | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

**EVALUATION OF PRE-COMPRESSION PARAMETERS OF POWDER BLEND**

Angle Of Repose, Bulk Density, Tapped Density, Carr's Index, Hausner's Ratio (H).

**EVALUATION OF POST COMPRESSION PARAMETERS OF OSELTAMIVIR FDTs:**

Various tests performed are:

- Weight variation test
- Thickness measurement
- Hardness
- Friability
- Drug Content uniformity
- Wetting time and Water absorption ratio
- *In vitro* dispersion Time
- *In vitro* disintegration Time
- *In vitro* dissolution studies

***IN VITRO* DISSOLUTION STUDIES:**

- **Method:** Dissolution test was carried out by using USP type II apparatus. The paddle was rotated at 50 rpm. pH 6.8 Phosphate buffer was used as dissolution medium (900ml) and was maintained at 37 ± 1$^{o}$C. Samples of 5ml were withdrawn at predetermined intervals (5, 10, 15, 20, 30, 45 and 60), filtered and replaced with 5ml of fresh dissolution medium.
- The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the drug at 218nm by using ultraviolet double beam spectrophotometer. Each dissolution study was performed for three times and mean values were taken.

**Fourier Transform Infrared Spectroscopy (FTIR)**

- FTIR studies were performed on drug, optimized formulation using AGILENT FTIR. The samples were analyzed between wave numbers 4000 and 400 cm$^{-1}$.

## RESULTS AND DISCUSSION

### DETERMINATION OF $\lambda_{MAX}$ AND PREPARATION OF CALIBRATION CURVE OF OSELTAMIVIR

The regression coefficient was found to be 0.999 which indicates a linearity with an equation of Y=0.028x-0.000. Hence, beer - lambert's law was obeyed.

**Table 4. Calibration curve data of Oseltamivir in pH 6.8 phosphate buffer at $\lambda_{max}$ of 218nm**

| Concentration (µg/mL) | Absorbance |
|---|---|
| 0 | 0 |
| 5 | 0.148 |
| 10 | 0.275 |
| 15 | 0.425 |
| 20 | 0.576 |
| 25 | 0.712 |

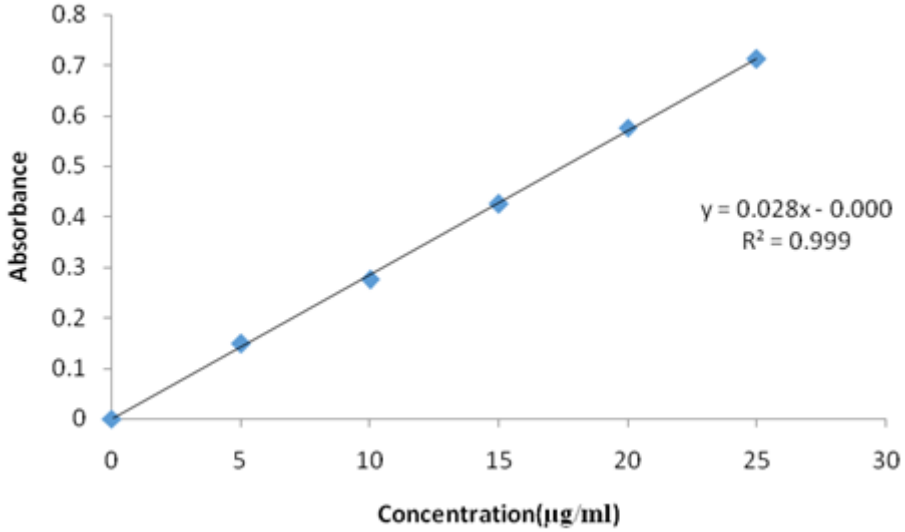


**Fig. 4. Calibration curve of Oseltamivir**

## EVALUATION OF PRE - COMPRESSION PARAMETERS OF POWDER BLEND

**Table 5. Evaluation of pre-compression parameters of powder blend**

| Formulation Code | Angle of Repose | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr's index (%) | Hausner's Ratio |
|---|---|---|---|---|---|
| F1 | 25.01 | 0. 59 | 0.57 | 14.03 | 1.16 |
| F2 | 26.8 | 0. 46 | 0.67 | 16.41 | 1.19 |
| F3 | 27.7 | 0. 32 | 0. 54 | 18.75 | 1.23 |
| F4 | 25.33 | 0.54 | 0.64 | 15.62 | 1.18 |
| F5 | 25.24 | 0.52 | 0.65 | 18.46 | 1.22 |
| F6 | 28.12 | 0. 46 | 0. 56 | 15.15 | 1.17 |
| F7 | 27.08 | 0.58 | 0.69 | 15.94 | 1.18 |
| F8 | 25.12 | 0.48 | 0.67 | 15.78 | 1.18 |
| F9 | 26.45 | 0.54 | 0.65 | 16.92 | 1.25 |

- For each formulation blend of drug and excipients were prepared and evaluated for various pre-compression parameters described earlier in methodology chapter.

- The bulk density of all formulations was found in the range of (0.32-0.59**)** and tapped density was in range of (0.54-0.69).

- The Carr's index and Hausner's ratio was calculated from tapped density and bulk density.

## EVALUATIONS OF POST COMPRESSION PARAMETERS OF OSELTAMIVIR FDTs

**Table 6: Evaluation of post compression parameters of Oseltamivir Fast dissolving tablets**

| Formulation codes | Average Weight (mg) | Hardness (kg/cm2) | Friability (% loss) | Thickness (mm) | Drug content (%) |
|---|---|---|---|---|---|
| F1 | 195 | 3.5 | 0.52 | 3.8 | 99.76 |
| F2 | 200 | 3.0 | 0.54 | 3.9 | 99.45 |
| F3 | 197 | 3.4 | 0.51 | 3.9 | 99.34 |
| F4 | 201 | 3.5 | 0.55 | 3.9 | 99.87 |
| F5 | 199 | 3.4 | 0.56 | 3.7 | 99.14 |
| F6 | 203 | 3.2 | 0.45 | 3.6 | 98.56 |
| F7 | 205 | 3.1 | 0.51 | 3.4 | 98.42 |
| F8 | 196 | 3.3 | 0.49 | 3.7 | 99.65 |
| F9 | 197 | 4.0 | 0.55 | 4.0 | 99.12 |

**Weight variation and thickness:** All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown above. The average tablet weight of all the formulations was found to be between (196 to 203).

**Hardness and friability:** All the FDT formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown above. The average hardness for all the formulations was found to be between **(3.0 to 4.0) Kg/cm$^2$** which was found to be acceptable (Avinash *et al*., 2010).

- Friability was determined to evaluate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the FDT formulations were evaluated for their percentage friability using Roche friabilator and the results are shown above. The average percentage friability for all the formulations was between **0.45 to 0.59**, which was found to be within the limit.

• **Drug content:** All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown above. The assay values for all the formulations were found to be in the range of **(98.45**±0.57 **to 100.56**±0.74**).** According to IP standards, the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.

**Table 7. Evaluation of post-compression parameters of Oseltamivir Fast dissolving tablets**

| Formulation | Disintegration time (seconds) | Wetting time (seconds) | *In vitro* dispersion time (sec) | %Water absorption ratio |
|---|---|---|---|---|
| **F1** | 26 | 16 | 28 | 86 |
| **F2** | 15 | 9 | 21 | 99 |
| **F3** | 32 | 23 | 15 | 98 |
| **F4** | 25 | 14 | 24 | 85 |
| **F5** | 16 | 25 | 20 | 92 |
| **F6** | 28 | 18 | 12 | 99 |
| **F7** | 16 | 13 | 25 | 83 |
| **F8** | 45 | 20 | 19 | 88 |
| **F9** | 26 | 10 | 13 | 96 |

• ***In vitro*** **disintegration time:** *In vitro* disintegration studies showed from 15 to 35 secs. These results indicate that increasing the concentration of sublimating agent in the tablets results in the formation of more pores form on tablets that are less likely to break up or dissolve easily in water.

**Wetting time:** Wetting time to the time required to wet completely when kept motionless on the tissue paper in a petridish.

• All the FDT formulations were evaluated for their wetting time as per the procedure described in the methodology section, and the results are shown above.

- The average wetting time for all the formulations was in the range of **(9 to 25)** seconds.
- It was also observed that formula F6 which had the least wetting time also had the minimum disintegration time showing a strong correlation between disintegration time and wetting time.

***In vitro* dispersion time:**

The *in vitro* dispersion time for all formulations was found to be in a range of **12 to 28** seconds.

**Water Absorption ratio:** All the formulations were evaluated for water absorption ratio according to the procedure described in methodology section and the results are shown above.

- Water absorption ratio is directly proportional to dissolution rate profile as higher the water absorption ratio faster the dissolution.

***IN VITRO* DRUG RELEASE STUDIES OF OSELTAMIVIR**

**Table 8: Dissolution data of Oseltamivir containing solutab**

| Time ( min ) | CUMULATIVE PERCENT DRUG DISSOLVED | | |
|---|---|---|---|
| | % DR F1 | % DR F2 | % DR F 3 |
| 0 | 0 | 0 | 0 |
| 5 | 25.85 | 49.54 | 35.41 |
| 10 | 43.61 | 58.43 | 68.51 |
| 15 | 56.38 | 70.25 | 98.34 |
| 20 | 75.14 | 83.54 | |
| 30 | 86.74 | 96.45 | |
| 45 | 93.12 | | |
| 60 | | | |

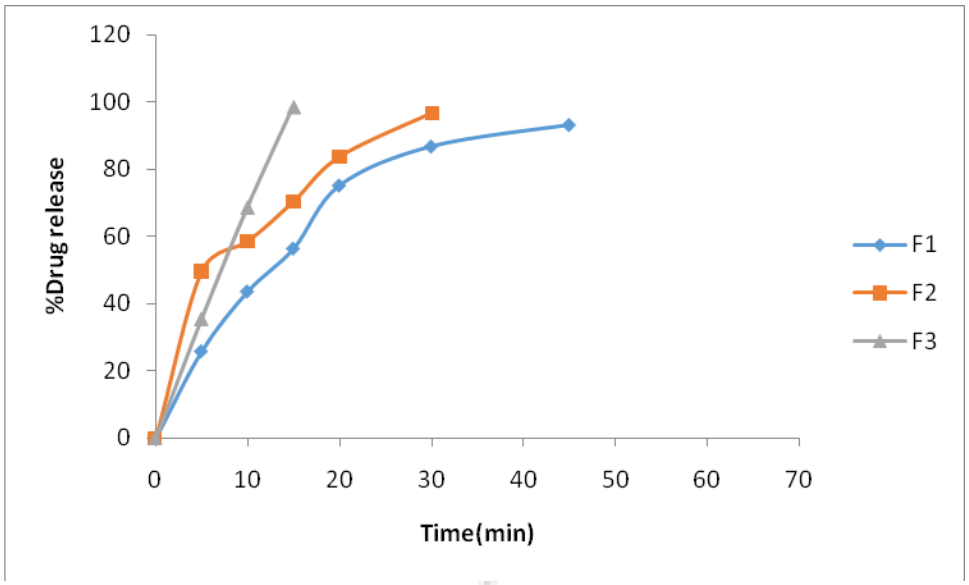


**Figure 5: Graph representing dissolution data of Oseltamivir containing solutab**

**Table 9. Dissolution data of Oseltamivir containing explotab**

| Time ( min ) | CUMULATIVE PERCENT DRUG DISSOLVED | | |
|---|---|---|---|
| | % DR F4 | % DR F5 | % DR F 6 |
| 0 | 0 | 0 | 0 |
| 5 | 8.45 | 25.12 | 34.54 |
| 10 | 15.46 | 39.46 | 43.12 |
| 15 | 35.15 | 46.73 | 55.15 |
| 20 | 46.78 | 55.14 | 61.24 |
| 30 | 57.46 | 70.51 | 79.31 |
| 45 | 70.23 | 83.61 | 91.87 |
| 60 | 89.67 | 95.47 | |

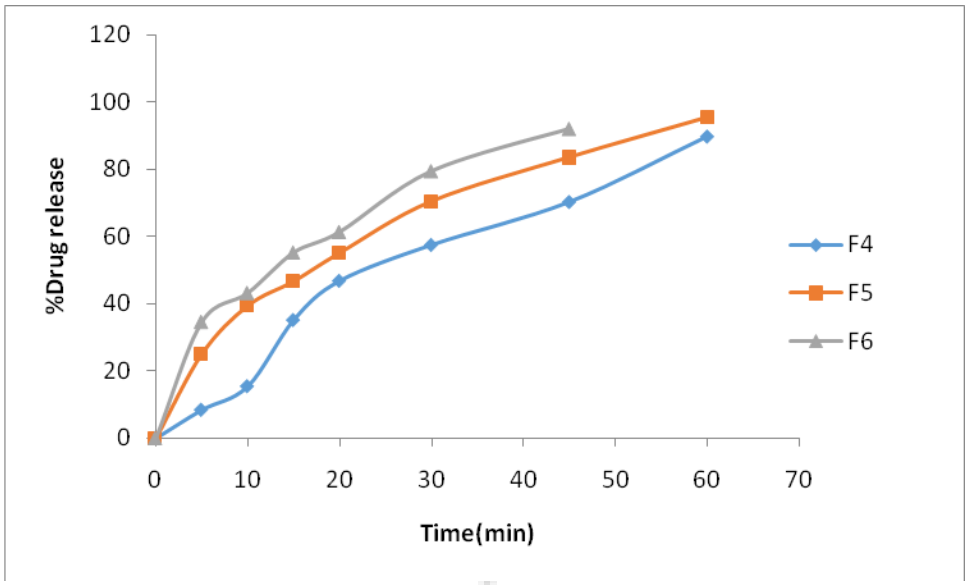


**Figure 6. Graph representing dissolution data of Oseltamivir containing explotab**

**Table 10: Dissolution data of Oseltamivir containing polyplasdone XL**

| Time ( min ) | CUMULATIVE PERCENT DRUG DISSOLVED | | |
|---|---|---|---|
| | % DR F7 | % DR F8 | % DR F9 |
| 0 | 0 | 0 | 0 |
| 5 | 37.15 | 20.45 | 20.36 |
| 10 | 48.34 | 45.46 | 45.42 |
| 15 | 57.12 | 62.58 | 63.26 |
| 20 | 73.42 | 70.51 | 79.13 |
| 30 | 82.16 | 83.61 | 94.15 |
| 45 | 90.02 | 96.45 | |
| 60 | 96.13 | | |

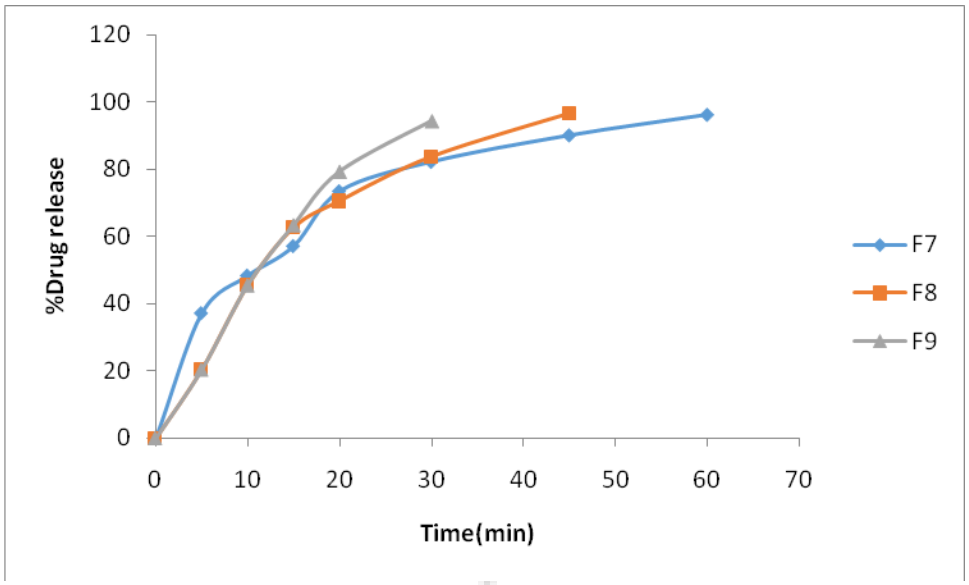


**Figure 7. Graph representing dissolution data of Oseltamivir containing polyplasdone XL**

Three different super disintegrants are solutab, explotab, poilyplasdone XL. These formulations were shown good drug release. Among all formulations, formulation F3 containing solutab was shown maximum drug release at 15 min. Hence, F3 formulation was concluded as optimised formulation.

## CONCLUSION

The present study was done on fast dissolving tablets of Oseltamivir using super disintegrants. Drug wavelength was determined and standard graph plotted in pH 6.8 Phosphate buffer at 218nm. The regression coefficient was found to be 0.999 which indicates a linearity with an equation of Y=0.028x-0.000. Hence, beer - lambert's law was obeyed.

Prepared blend was evaluated for pre-compression studies such as bulk density, tapped density, Carrs index, Hausners ratio and angle of repose. Those pre-compression parameters were found to be within limits.

After completion of pre-compression studies, required powder blend was weighed and compressed using tablet compression machine (LAB PRESS). Those compressed tablets were kept for post compression evaluation studies such as weight variation, thickness, hardness, friability, disintegration and *in vitro* dispersion tests.

From the dissolution data, tablets containing solutab in the concentration 30mg showed maximum drug release at 15 min. Hence, F3 formulation was concluded as optimised formulation.

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