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# Formulation and Evaluation of Oseltamivir Phosphate Immediate Release Tablets by Using Compression Coating Technique

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**Keywords:** Oseltamivir phosphate, influenza virus, immediate release, compression coating technology.

**ABSTRACT**

Oseltamivir phosphate is used for the treatment of influenza virus infections. It is an ethyl ester prodrug which gets hydrolyzed for conversion to the active form. Oseltamivir carboxylate which is a viral neuraminidase inhibitor. Oseltamivir phosphate is a water-soluble, bitter drug with good oral bioavailability. It is available as a capsule and oral suspension for reconstitution before use. The Present study includes formulation and evaluation of Oseltamivir phosphate immediate-release tablets with compression coating technique. Immediate release tablets of oseltamivir phosphate have been prepared and subsequently, compression coated to mask the bitter taste of the drug.The Oseltamivir tablets were prepared by using various excipients like Methyl carboxy cellulose, sodium carboxy Methyl Cellulose, cross Povidone& sodium starch glycolate. The tablet formulations (F1 to F7) were prepared and evaluated for various parameters like hardness, friability, disintegration and dissolution studies. The prepared compression coated tablets containing oseltamivir phosphate core tablet were found to give release up to 100% within 60 min. The compression coated tablet was compared to marketed capsule dosage form of oseltamivir phosphate. Though capsule gave quicker release, compression coated tablet also achieved the complete dissolution within 60 min. Formulations with higher release F3, F5 & F7 were considered as optimized formulations. The compression coated tablets were evaluated for stability for a period of 3 months at $40^0$C/75%RH.Stability study indicated that the optimized formulations were stable with good drug release after 3 months study.

## INTRODUCTION:

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs using various dosage forms. Oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration and cost-effective manufacturing process. Tablets may be defined as the solid unit dosage form of medicament or medicaments with or without suitable excipients and prepared either by molding or by compression.[1-5] A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.[6,7] The compressed tablet is the most popular dosage form in use today. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets.

Compression coating of a tablet is compressing a coat around a core tablet. It involves the compaction of granular materials or powder around a preformed tablet core using specially designed tableting equipment. If any drug tends to discolor readily or develop mottled appearance because of oxidation or sunlight, these problems can be minimized by incorporating the core in core tablet. Compression coating can be used to conceal unpleasant taste, provide a barrier for a substance irritating to the stomach or one inactivated by gastric juice.

Oseltamivir phosphate[8,9]is an anti-viral drug used for the treatment of infections with the influenza virus. Oseltamivir phosphate is water soluble, the bitter drug with good oral availability. At present, there is no tablet dosage form available for oseltamivir phosphate. Tablets are unit solid dosage forms and are of widely accepted because of its convenience of self-administration, cost-effective manufacturing and better patient compliance. The objective of the present investigation is to formulate oseltamivir phosphate immediate-release tablets. Since it has bitter taste the aim was to develop taste masked tablet dosage form employing compression coating technology.

**MATERIALS:**

Oseltamivir phosphate, Microcrystalline cellulose, Aerosil, Sodium carboxy methyl cellulose, Sodium starch glycolate, Lactose monohydrate, Mannitol, Magnesium Stearate, Talc, Sucrose, dextrose.

**METHOD:**

**Pre Compression parameters for core material blend:**

As Per the formula, a required quantity of each ingredient was taken and blended gently in a mortar. The powder blend was studied for the pre-compression parameters like angle of repose, bulk density, tapped density, compressibility index & hausners' ratio.

**Preparation of core tablet:**[2,3]

Core tablets were prepared by direct compression. As per the formula is given in the table1, the drug and excipients were weighed accurately. They were thoroughly blended in geometrical proportions in a mortar and then lubricants were added through sieve 100on to the powder blend and again blended properly. The resulting blend was compressed to form tablets using the 8mm circular flat faced punches on tablet compression machine.

**Table 1: Composition of Tablet Core**

| **Materials** | **f1 (mg)** | **f2 (mg)** | **f3 (mg)** | **f4 (mg)** | **f5 (mg)** |
|---|---|---|---|---|---|
| Oseltamivir phosphate | 98.53 | 98.53 | 98.53 | 98.53 | 98.53 |
| Microcrystalline cellulose | 50.47 | 35.47 | 35.47 | - | - |
| Cros Povidone | 15 | 30 | - | 30 | 10 |
| Magnesium stearate | 10 | 10 | 10 | 10 | 10 |
| Sodium starch glycolate | - | - | 30 | - | - |
| Aerosil | 20 | 20 | 20 | 20 | 20 |
| Sodium CMC | - | - | - | 35.47 | 50.47 |
| Total | 194 | 194 | 194 | 194 | 194 |

**Evaluation of core tablets**[2, 3]**:**

The prepared tablets were evaluated for Assay, weight variation, thickness, hardness, friability, drug content and *in-vitro* dissolution studies.

**Assay:**

Five tablets were selected at random and average weight was calculated. Tablets were powdered in a mortar. Quantity equivalent to 98.53mgof oseltamivir phosphate was dissolved in 100ml of 0.1N HCl by subjecting to sonication for 5 mins. The solution was filtered and required dilutions were made and analyzed spectrophotometrically at 240nm for oseltamivir phosphate.

**Weight variation:**

Twenty tablets were selected at random and weighed individually. The average of twenty tablets was calculated. Individual weights of the tablets were compared with the average weight and percentage deviation was calculated.

**Hardness:**

The strength of the tablet is expressed as the tensile strength ($Kg/cm^2$).The tablet crushing strength is the force applied to break a tablet along the diameter. It was measured using a tablet hardness tester(Monsanto hardness tester).a tablet was placed between two anvils of hardness tester, force was applied to the anvils, and the crushing strength that causes the tablet to break was recorded in $kg/cm^2$.Three tablets from each formulation batch were tested randomly and the average reading was noted.

**Friability:**

Friability of the tablets was determined using Roche friabilator (Electro lab, India).

This device consists of a plastic chamber that is set revolve around 25rpm for 100 revolutions dropping the tablets at a distance of 6 inches for each revolution. Pre-weighed sample of 10 tablets were placed in the friabilator and operated for 100 revolutions, again tablets were reweighed. The friability (F %) is given by the formula

$$F\% = (1-W_0/W) \times 100$$

Where, $W_0$ is wt. of the tablets before the test and W is the weight of tablets after the test.

**Disintegration test:**

The disintegration time of the tablets was determined in the disintegration apparatus (electro lab) in the 0.1N HCl medium maintained at 37±0.5°C and were allowed to undergo the disintegration. After the complete disintegration at the set temperature, the time for disintegration of individual tablets were noted down.

***In-vitro* dissolution study of core tablet:**

The *In-vitro* dissolution studies of core tablets was studied using USP Dissolution Apparatus II (paddle type)

Procedure- 900ml of dissolution medium i.e. 0.1NHCl was taken and transferred to dissolution baskets. The medium was maintained at temperature of 37±0.5°C and paddles were operated at 50rpm.Tablet was placed in each of the basket .5ml of sample was withdrawn through filter from each vessel at regular intervals of time 5, 10,15,30,45 60 min. The medium was replaced immediately with 5ml of respective fresh 0.1NHCl after sampling to maintain the sink conditions. The samples were then collected and analysed by UV spectrophotometer. Dilutions were made if required.

**Formulation of compression coated tablet:**

Compression coated tablets were formulated using various excipients like mannitol, lactose monohydrate which are sweet and water soluble. The aim in compression coat material selection is to mask the bitter taste of drug and also impart stability.

**Pre-compression parameters of coat material:**

The coating materials as per the formulas are given in the table were thoroughly blended in a mortar. The blend was evaluated for pre-compression parameters. Pre-compression parameters were carried out as described in previous section.

**Preparation of compression coated tablet:**

Compression coated tablets were prepared by compression coating of prepared 8mm core tablets into 12mm diameter compression coated tablets using coat materials. The composition of outer coat was taken as given in the table. Compression coating was done by placing half the compression coating blend or granules into the die cavity of 12mm diameter, then

manually placing the core tablet on the powder bed centrally. Further remaining half quantity of compression coating material was added over the core tablet. Then finally compression coating was done using tablet compression machine.

**Table 2: composition of the compression coated tablets:**

| **Ingredients (mg)** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** |
|---|---|---|---|---|---|---|---|
| CORE | f1 core | f2 core | f3 core | f4 core | f5 core | f1 core | f5 core |
| lactose | 86 | 86 | 86 | 86 | 86 | 86 | 86 |
| Magnesium stearate | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Talc | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Mannitol | - | 90 | - | 90 | - | - | - |
| dextrose | - | - | 90 | - | - | 90 | 90 |
| sucrose | 90 | - | - | - | 90 | - | - |
| total | 400 | 400 | 400 | 400 | 400 | 400 | 400 |

**Evaluation of compression coated tablets:**

The compression coated tablets were evaluated for weight variation, hardness, friability, thickness, disintegration studies were carried out.

**Stability study:** All the compression coated tablets were subjected to preliminary stability studies at 40ºC±2ºC/75%±2%RH for period of three months. Each tablet was individually wrapped in aluminium foil and packed in polyvinyl pyrrolidine bottle and put at above specified condition in a heating humidity chamber for 3 months. For every one month tablets analyzed for the appearance, drug content and *in-vitro* drug release.

**RESULTS AND DISCUSSION:**

**ANALYTICAL METHOD DEVELOPMENT FOR ESTIMATION OF OSELTAMIVIR PHOSPHATE:**

An ultraviolet spectrophotometric method based on measurement of absorbance at 240nm in 0.1 N HCl media was used for estimation of oseltamivir phosphate. The method was

validated for linearity(r=0.99) and precision (%C.V<4%). It was found that it obeyed the **B**eers Lambert's law.

**Table 3: Standard graph of oseltamivir phosphate:**

| Concentration (µg/ml) | Absorbance(n=3) (X±s.d) | % C.V. |
|---|---|---|
| 2 | 0.09± 0.03 | 2.82 |
| 4 | 0.18± 0.04 | 3.28 |
| 6 | 0.24± 0.02 | 3.97 |
| 8 | 0.32±0.02 | 2.71 |
| 10 | 0.41±0.02 | 3.93 |
| 12 | 0.49±0.02 | 4.02 |

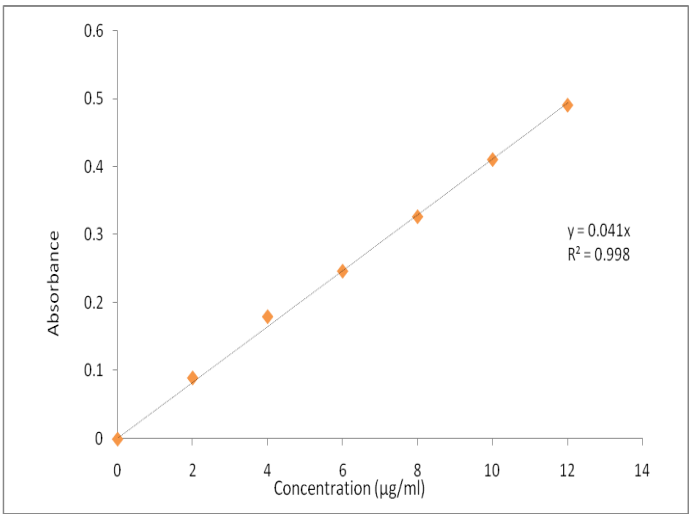


**Figure 1: Standard curve of Oseltamivir phosphate**

**DRUG EXCIPIENT COMPATIBILITY STUDY:**

Excipient compatibility was evaluated using FTIR spectrum studies.IR spectrum was recorded from 4000 $cm^{-1}$ to 400$cm^{-1}$. The spectrums of the physical mixture were observed for characteristic peaks of oseltamivir phosphate.

IR spectrum of pure drug suggests the presence of ester bond at 1720cm-1, amine group at 3354cm-1, amide at 1662 cm-1 that are present in oseltamivir phosphate. It was observed that there was no change in the characteristic peaks of a drug in the FTIR spectra of drug and excipient mixtures as shown in figures suggesting that there were no physical or chemical interactions and there is no functional alteration of a drug with the excipients used.

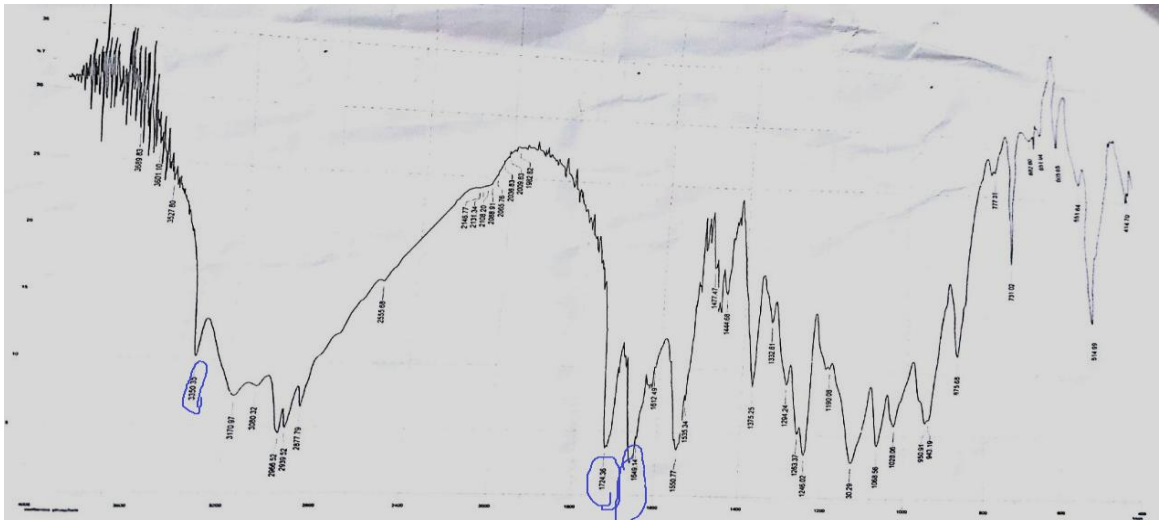

**Figure 2: FTIR spectra of Oseltamivir phosphate (pure drug)**

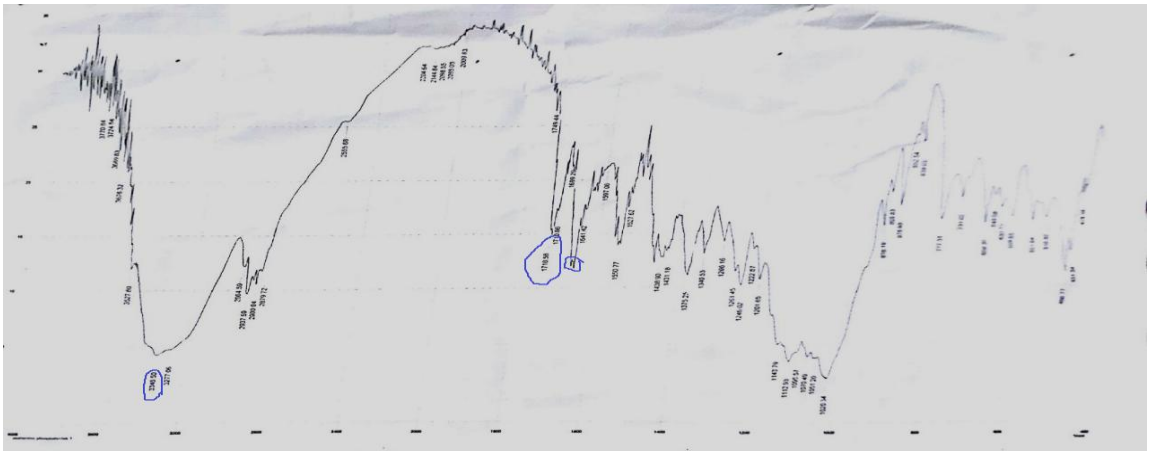

**Figure 3: FTIR spectra of (F4 formulation)**

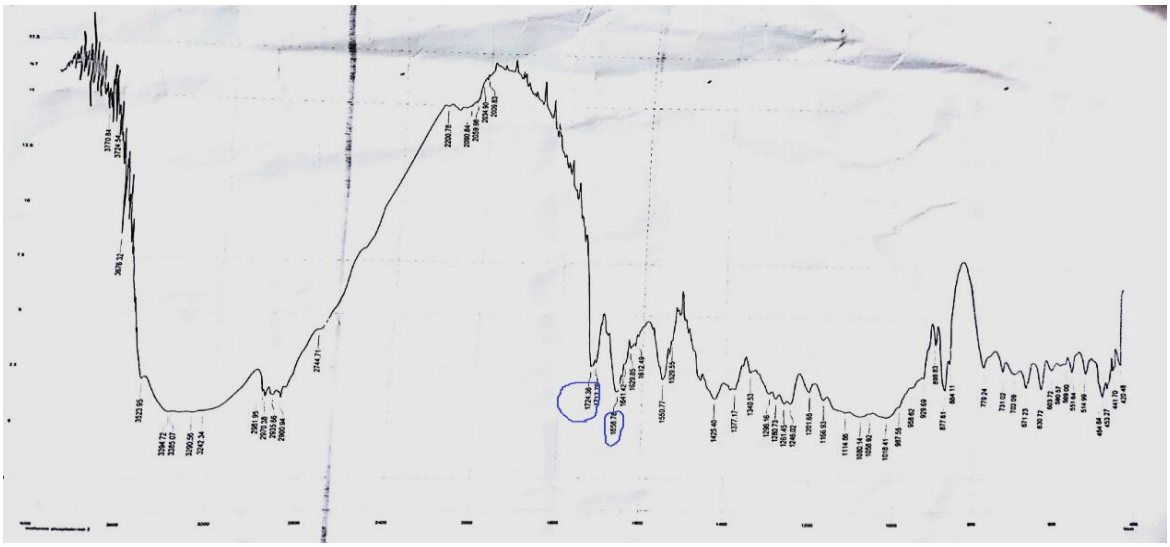

**Figure 4: FTIR spectra of (F5 formulation)**

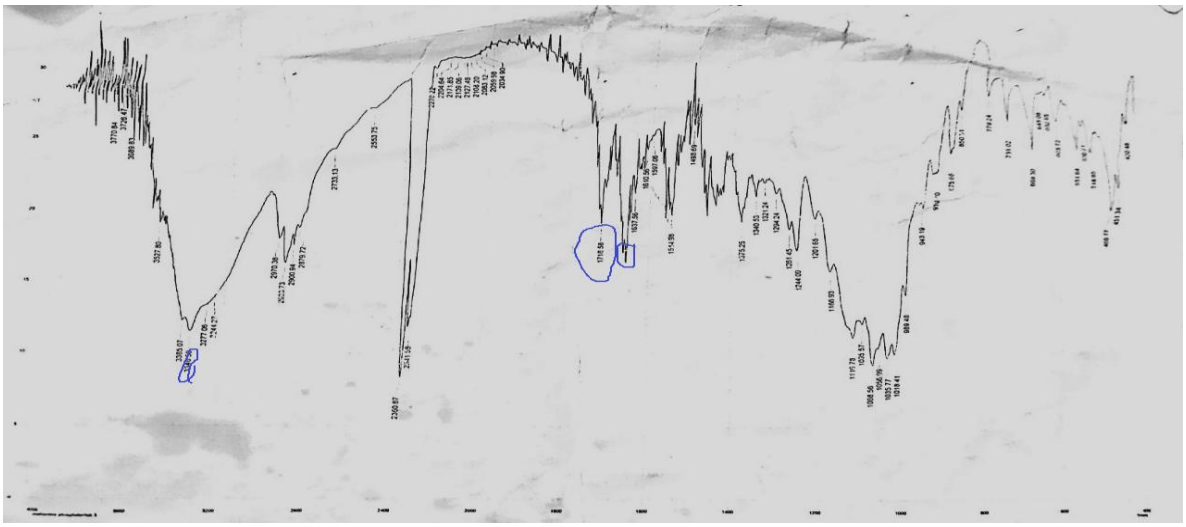

**Figure 5: FTIR spectra of (F7 formulation)**

**Table 4: Precompression parameters of core tablet powder blend:**

| Sr. No. | Powders | Bulk density ($gm/cm^3$) | Tapped density ($gm/cm^3$) | Angle of repose (Ɵ) | Compressibility index (%) | Hausner's ratio |
|---|---|---|---|---|---|---|
| 1 | f1 | 0.642±0.014 | 0.753±0.004 | 20.80±1.03 | 13.0 | 1.17 |
| 2 | f2 | 0.665±0.012 | 0.732±0.003 | 15.43±1.09 | 14.4 | 1.10 |
| 3 | f3 | 0.645±0.011 | 0.770±0.002 | 20.62±1.05 | 14.6 | 1.19 |
| 4 | f4 | 0.600±0.02 | 0.765±0.001 | 20.65±0.92 | 11.20 | 1.27 |
| 5 | f5 | 0.583±0.024 | 0.772±0.005 | 21.35±1.08 | 12.5 | 1.34 |

**Table 5: Oseltamivir phosphate core tablet characteristics:**

| Formula code | %weight variation | Hardness ($kg/cm^3$) n=5 | Friability (%) n=1 | Thickness (mm) n=3 | Disintegration Time(min) (n=3) | Assay (n=5) |
|---|---|---|---|---|---|---|
| F1 | 1.03 | 3-4 | 0.12 | 2-3 | 15 | 98.45±0.13 |
| F2 | 1.5 | 3-4 | 0.1 | 2-3 | 13 | 96.36±0.56 |
| F3 | 1.06 | 4-5 | 0.10 | 2-3 | 12 | 98.16±0.80 |
| F4 | 0.98 | 4-5 | 0.12 | 2-3 | 10 | 99.15±0.36 |
| F5 | 1.4 | 3-4.5 | 0.105 | 2-3 | 10 | 99.24±0.48 |

**Table 6: *In-vitro* drug release study of oseltamivir core tablet:**

| Time(mins) | %drug released f1 | f2 | f3 | f4 | f5 |
|---|---|---|---|---|---|
| 5 | 12.07±1.8 | 10.23±1.3 | 11.36±1.0 | 12.3±2.0 | 13.2±2.0 |
| 10 | 20.04±1.2 | 23.20±1.5 | 25.23±1.5 | 29.63±2.3 | 30.2±1.1 |
| 15 | 45.02±2.5 | 44.23±1.6 | 45.36±1.7 | 46.23±1.5 | 49.2±1.3 |
| 30 | 85.92±2.0 | 80.32±2.0 | 89.36±1.3 | 82.39±1.6 | 89.41±1.6 |
| 45 | 99.13±1.0 | 95.01±1.2 | 98.86±1.6 | 99.07±1.2 | 100±1.0 |

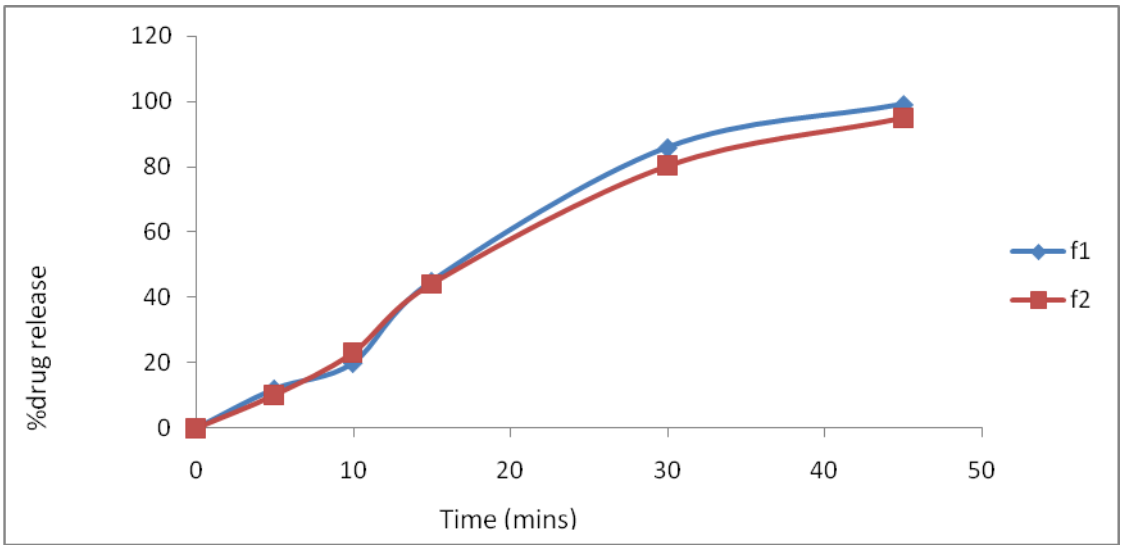


**Figure 6: % Drug release vs time graph of oseltamivir phosphate core tablets (f1 and f2)**

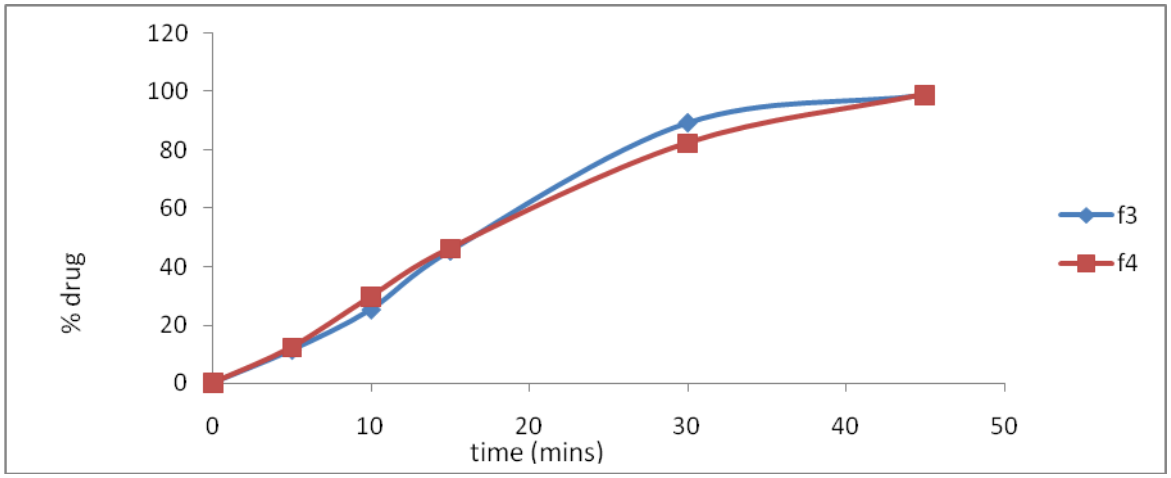


**Figure 7: % Drug release vs time graph of oseltamivir phosphate core tablets (f3 and f4)**

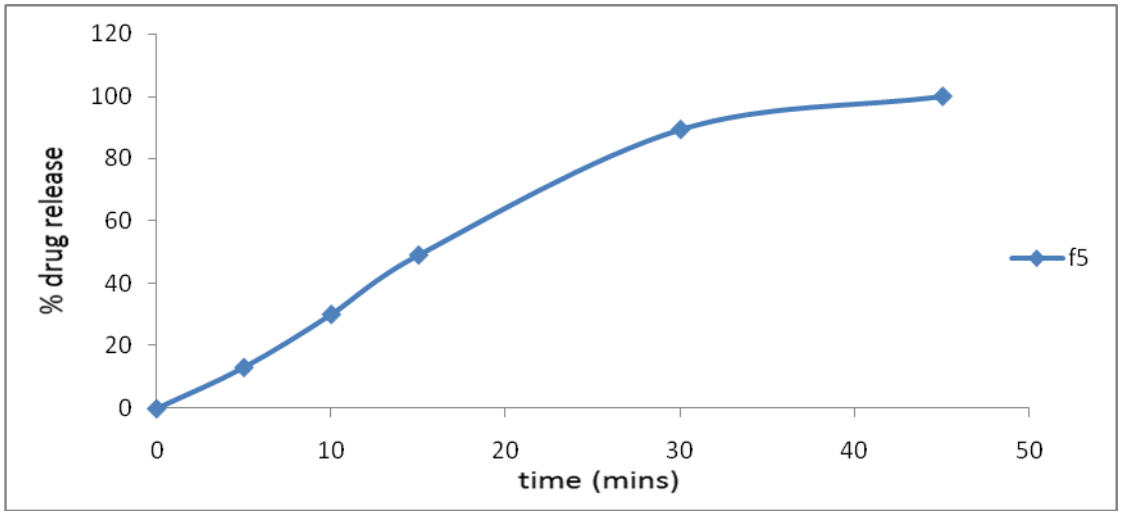


**Figure 8:% Drug release vs time graph of oseltamivir phosphate core tablets (f5)**

**Precompression properties of coat material:**

All formulation blends were studied for an angle of repose, bulk density, tapped density, compressibility index and Hausner ratio. The results showed that all formulations showed good flow properties.

**Table 7: Pre compression parameters of coat material:**

| Formula code | Angle of repose(Ɵ) (n=3) | Bulk density ($gm/cm^3$) (n=3) | Tapped density($gm/cm^3$) (n=3) | Hausner's ratio | Compressibility Index |
|---|---|---|---|---|---|
| F1 | 18.2±0.98 | 0.56±0.003 | 0.65±00.008 | 1.16 | 16.67 |
| F2 | 24.3±0.82 | 0.45±0.002 | 0.50±0.006 | 1.11 | 23.0 |
| F3 | 25.1±0.36 | 0.46±0.005 | 0.56±0.003 | 1.21 | 11.8 |
| F4 | 23.6±0.56 | 0.69±0.012 | 0.79±0.005 | 1.14 | 25.3 |
| F5 | 28.9±0.90 | 0.65±0.004 | 0.72±0.004 | 1.10 | 13.24 |
| F6 | 22.1±0.76 | 0.56±0.021 | 0.77±0.006 | 1.27 | 13.65 |
| F7 | 25.06±1.08 | 0.56±0.008 | 0.66±0.005 | 1.17 | 17.89 |

**Table 8: Evaluation of compression coated tablets:**

| Time | % Drug released (X±S.D) | | | | | | |
|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
| 5 | 22.93±1.3 | 24.93±1.9 | 23.62±1.0 | 31.20±1.3 | 30.10±1.2 | 22.93±1.9 | 24.66±1.2 |
| 10 | 38.75±1.2 | 36.5±2.3 | 44.95±1.3 | 43.83±1.2 | 47.36±1.3 | 28.05±1.8 | 32.18±1.6 |
| 15 | 56.81±2.0 | 54.55±1.6 | 65.51±1.4 | 60.09±1.1 | 65.9±1.6 | 30.70±1.4 | 65.87±1.5 |
| 30 | 78.00±1.7 | 67.07±1.3 | 79.77±1.7 | 80.03±1.9 | 85.2±1.5 | 44.33±1.5 | 81.74±1.6 |
| 45 | 85.75±1.6 | 76.85±1.4 | 83.34±1.5 | 92.03±2.0 | 95.86±1.2 | 54.83±1.2 | 93.80±1.8 |
| 60 | 99.4±1.2 | 90.92±1.5 | 96.23±1.2 | 99.79±2.3 | 100 | 87.53±1.3 | 100 |

**Table 9: *In-vitro* drug release profile of compression coated tablets**

| Formula code | Assay (n=5) | %weight variation (n=1) | Hardness (n=3) | Thickness(mm) (n=3) | Friability (%) (n=3) | Disintegration time(min) (n=3) |
|---|---|---|---|---|---|---|
| F1 | 98.43±0.2 | 0.66 | 2.9 | 4.1±0.04 | 0.10±0.34 | 14 |
| F2 | 98.15±0.3 | 1.12 | 3.8 | 4.13±0.03 | 0.11±0.24 | 12 |
| F3 | 98.75±0.4 | 0.89 | 4.2 | 3.6±0.05 | 0.15±0.13 | 13.5 |
| F4 | 97.71±0.2 | 0.98 | 3.8 | 4.3±0.06 | 0.12±0.35 | 10.5 |
| F5 | 98.54±0.2 | 1.2 | 4.0 | 3.9±0.02 | 0.11±0.30 | 12.4 |
| F6 | 98.15±0.1 | 1.3 | 3.7 | 4.05±0.01 | 0.106±0.12 | 14.2 |
| F7 | 99.08±0.3 | 0.98 | 3.9 | 4±0.03 | 0.11±0.15 | 10 |

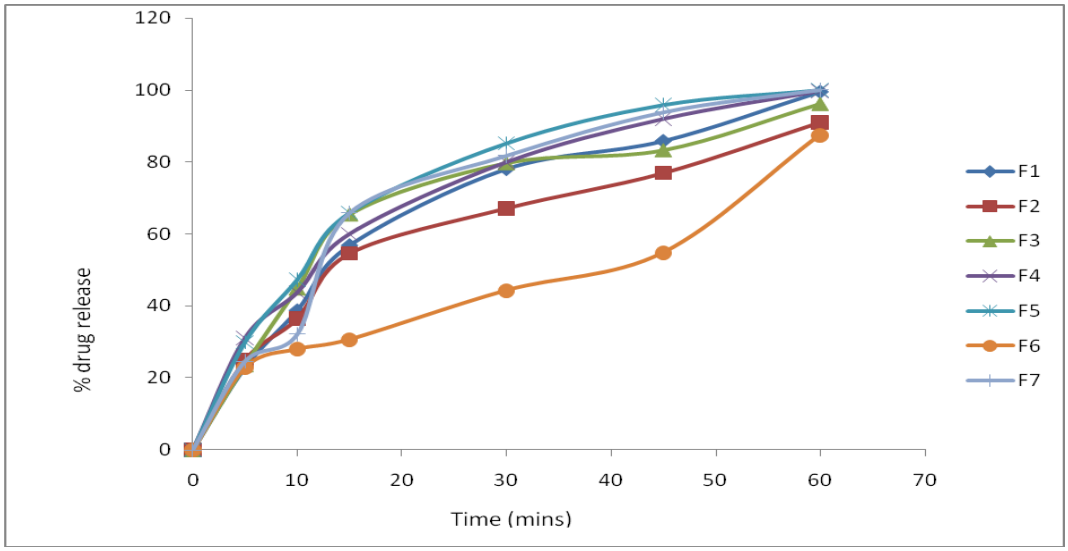


**Figure 9: %drug release vs time graph of compression coated tablets.**

**Table 10: Stability Profile of optimized formulations:**

| F.no | Before stability | | | | After stability | | | |
|---|---|---|---|---|---|---|---|---|
| | Hardness | color | % drug release (n=3) | % drug content (n=3) | Hardness | color | % drug release | % drug content |
| F4 | 3-4.5 | White | 99.7±1.0 | 99.1±2.3 | 3-3.5 | white | 89.3±2.3 | 97.9±2.3 |
| F5 | 3-4.5 | white | 100±1.2 | 99.2±1.2 | 3-3.5 | white | 90.2±1.2 | 98.0±1.1 |
| F7 | 3-4.5 | white | 100±2.0 | 99.5±1.6 | 3-3.5 | white | 90±1.1 | 98.4±1.5 |

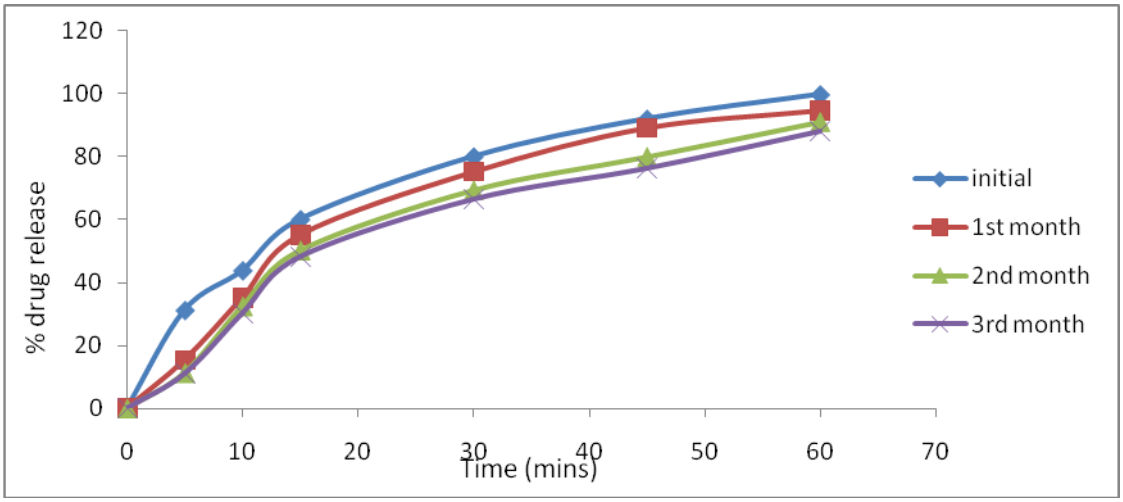


**Figure 10: Stability profile of F4 formulation**

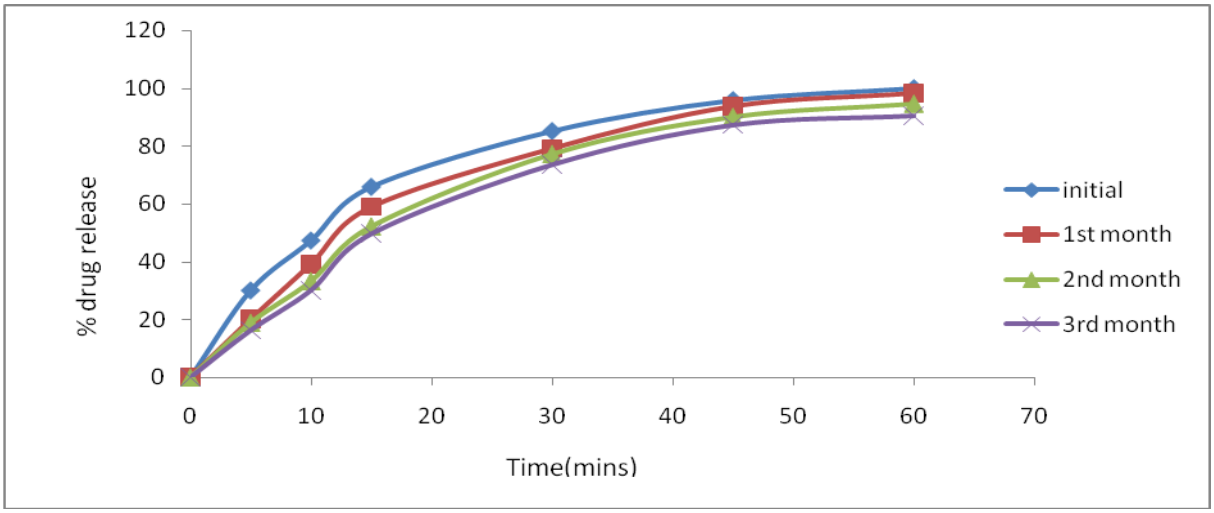


**Figure 11: Stability profile of F5 Formulation**

**Table 12: *In-vitro* dissolution profile after stability testing of F7 formulation:**

| Time | %drug release | | | |
|---|---|---|---|---|
| | before | After 1 month | After 2 months | After 3 months |
| 5 | 24.66±1.9 | 19.88±1.5 | 15.9±2.1 | 14.6±1.2 |
| 10 | 32.18±2.1 | 29.46±1.4 | 25.4±1.8 | 20.6± 1.39 |
| 15 | 65.87±1.4 | 45.92±1.9 | 43.5±1.5 | 40.2±1.5 |
| 30 | 81.74±1.3 | 64.9±1.3 | 60.8±1.2 | 56.3±1.02 |
| 45 | 93.80±1.6 | 85.3±1.1 | 82.9±1.4 | 79.6±1.2 |
| 60 | 100 | 95.45±2.0 | 90.4±1.9 | 87.2±1.8 |

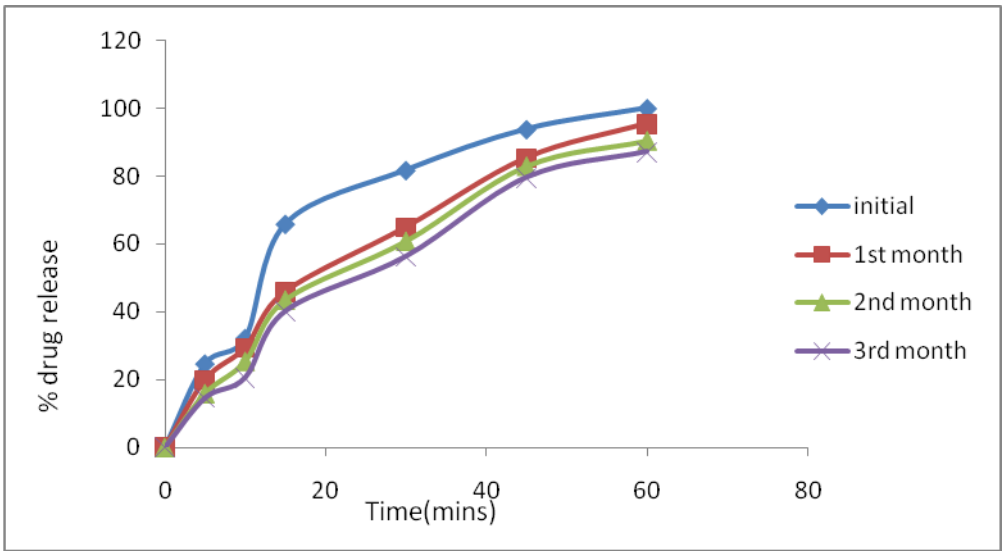


**Figure 12: Stability profile of F7 formulation**

**Table 13: Comparative dissolution study of compression coated tablet & marketed capsule dosage form of oseltamivir phosphate:**

| Time | % drug released | | | |
|---|---|---|---|---|
| (mins) | Capsule(Marketed formulation) | F5 | F7 | F4 |
| 5 | 36.0±2.2 | 30.10±2.0 | 24.66±2.2 | 31.20±1.0 |
| 10 | 64.3±1.8 | 47.36±1.8 | 32.18±2.0 | 43.83±1.5 |
| 15 | 85.9±1.4 | 65.9±1.4 | 65.87±1.1 | 60.09±2.0 |
| 30 | 102. ±2.1 | 85.2±1.0 | 81.74±2.5 | 80.03±2.1 |
| 45 | | 95.86±2.0 | 93.80±2.3 | 92.03±1.6 |
| 60 | | 100±1.5 | 100±2.0 | 99.79±1.2 |

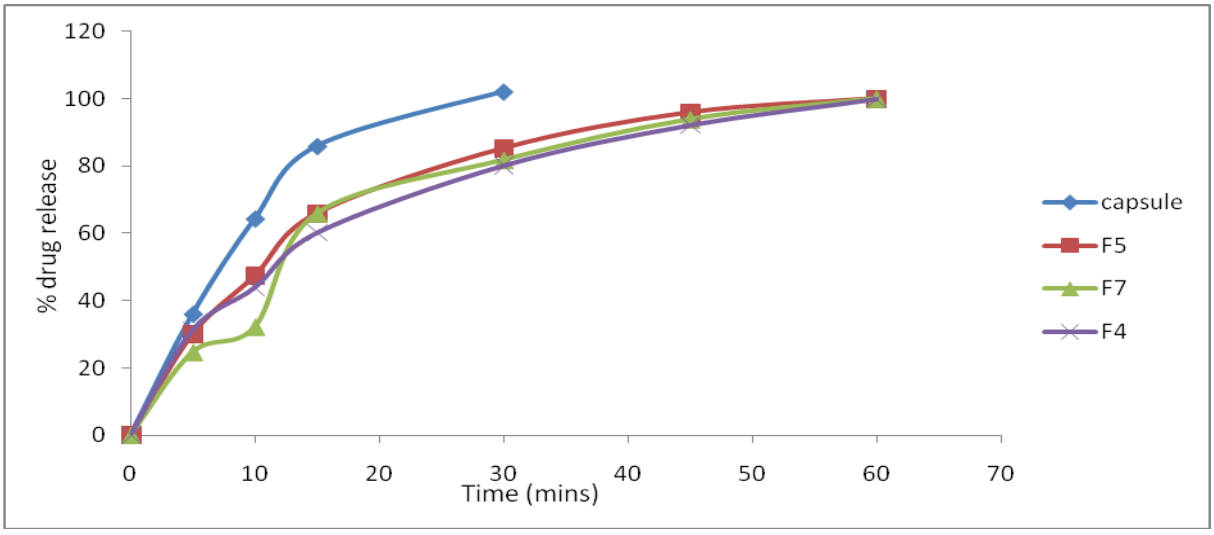


**Figure 13: Comparative % drug release of marketed product with F5, F7, and F4**

**DISCUSSION:**

Our aim was to develop immediate release taste masked tablet dosage form employing compression coating technology. Core tablets were prepared by direct compression. In this procedure, powder blend was studied for pre-compression parameters and the tablets were punched. The prepared tablets were evaluated for weight variation, thickness, hardness, friability and *in-vitro* dissolution studies which were found to be within the limits.

Compression coated tablets were prepared by compression coating of prepared 8mm diameter core tablets into 12mm diameter compression coated tablets using coat materials like lactose monohydrate, mannitol, sucrose etc. For these prepared tablets pre-compression parameters for powder blend and evaluation tests were studied. From the results of dissolution study

compression coated tablets (F5 & F7) showed complete dissolution within 60 min. These were compared with the marketed product (capsule). The drug release from the capsule was quicker but the release obtained from the compression coated tablets also meets the IP specification.

Compression coated tablets were subjected to accelerated stability studies at 40°C ±2 °C/75%±2% RH for 3 months. Tablets were analyzed for the appearance, hardness, drug content and *in-vitro* drug release. In the preliminary investigation of Oseltamivir phosphate compression coated tablets that was done before, the dissolution got delayed after stability studies of 2months.In this present study, we could achieve similar dissolution profiles for formulations F5 & F7 after 3 months stability study. Hence we conclude that our aim of preparing the compression coated tablets with better stability could successfully be achieved.

## CONCLUSION

The prepared compression coated tablets containing oseltamivir phosphate core tablet were found to give release up to 100% within 60 min. Formulations with higher release F3, F5 & F7 were considered as optimized formulations. The compression coated tablets were evaluated for stability for a period of 3 months at 40 °C/75%RH.A stable immediate release tablet of oseltamivir phosphate could be successfully developed. Compression coating technologies have proved to be efficient coating method to impart stability and overcome the bitter taste of the drug.

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