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# FORMULATION AND IN-VITRO EVALUATION OF FAST DISSOLVING TABLETS OF GEFITINIB

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**Abstract:**

*Objective: The main objective of the Oral disintegrating tablets is to enhance absorption and bioavailability of the drug by Preparation of standard calibration curve for Gefitinib and by Preparation of rapidly disintegrating tablets of Gefitinib by using direct compression of the solid dispersion prepared.*

*Method: Solid dispersions are prepared by using different carriers like Urea. Here, required weighed quantities of drug and Urea are weighed and are made to dissolve in 10-20 ml of Methanol .Then using magnetic stirrer with hot plate the solvent is evaporated and clear film of drug and carrier was obtained. Then the amount of drug equivalent to 25mg and carrier equivalent to 50 mg are weighed and to it the remaining ingredients are added .The tablets are prepared by Direct compression.*

*Result: The results obtained in the in-vitro drug release were tabulated for F1 to F12 formulations. The formulations F1,F2,F3 showed release upto 79.78%,81.67%,92.45% respectively. The formulations F4,F5,F6 showed release of 98.28%,92.18%,90.28% while the formulations F7,F9 showed drug release of 94.45%,94.45% while the formulations F10,F12 showed drug release of 86.52%,83.88%. The drug release was completely achieved in a short duration of time. Finally, % drug release of formulation v/s time (in min) was estimated.*

*Conclusion: Among all the 12 formulations F4, F7, F9 are the better formulations showed high in-vitro dissolution rate than the other formulations, of which F4 was expected formulation for rapid release.*

*Key Words: Gefitinib, Rapidly disintegrating tablets, Direct compression, Solid dispersion.*

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## INTRODUCTION:

Solid dispersion systems illustrated in literature to enhance the dissolution properties of poorly water soluble drugs. Such as solubilization of drugs in solvents, salt formation, complex forms with cyclodextrin and sometimes particle size reduction also utilized to improve the dissolution of poorly water soluble drugs. On other hand solid dispersion system offers variety of formulations by using excipients to enhance dissolution of poorly water soluble drugs for oral administration [1-4].

When the solid dispersion is exposed to aqueous media, the carrier will dissolves and the drug releases as fine colloidal particles in the media. The resulting enhanced surface area shows higher dissolution rate and bioavailability of poorly water soluble drugs. In solid dispersion drug dissolves immediately to saturate the gastrointestinal tract (GIT) fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron to nano size. Solid dispersion technique was demonstrated by Sekiguchi and Obi. They investigated the faster absorption of poorly water-soluble drugs such as sulfathiazole by the formation of eutectic mixture with a water-soluble and physiologically inert carriers like urea [5].

In solid dispersions, molecular dispersions represents on particle size reduction, after carrier dissolution the drug is molecularly dispersed in dissolution medium. Solid dispersions apply this principle for solid dispersions to drug release by creating a mixture of poorly water soluble drug and highly soluble carriers, if higher surface area is formed, resulting enhanced dissolution rate and bioavailability [6-11].

Gefitinib is a drug used for certain breast, lung and other cancers. Gefitinib is an EGFR inhibitor, like erlotinib, which interrupts signaling through the epidermal growth factor receptor(EGFR) in target cells. Therefore, it is only effective in cancers with mutated and overactive EGFR [12].

In this work, the compatibility of the ingredients was obtained by the FT-IR method. The fast dissolving tablet of Gefitinib and Croscarmellose sodium (Ac-Di-Sol), sodium starch glycolate and Crosspovidone as superdisintegrants. Their addition process is also studied. The effect of selected process parameters on critical properties of dispersible tablets were studied, like effect of disintegration time, friability, hardness and wetting time. The stability study as per the ICH guidelines was carried out for time period of three months.

## MATERIALS AND METHOD:

Gefitinib was gift sample from Wanbury Ltd, india Crospovidone from Wanbury ltd, india, Sodium starch glycolate from Huadong medicine co. Ltd,
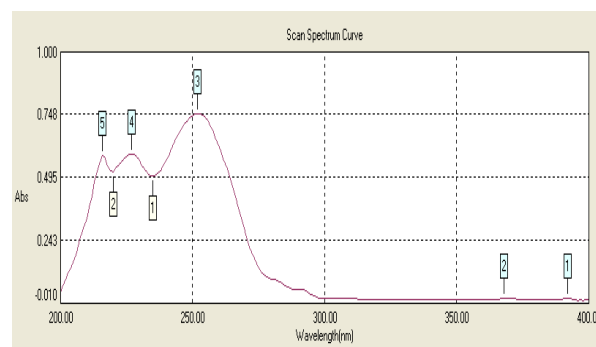
Croscarmellose sodium from Shin Etsu Chemicals, Ltd, Lactose BASF Ltd.

### Methodology:
**Determination of UV Absorption maxima:**
Gefitinib solution was prepared in 0.1 N HCL and diluted suitably. The UV spectrum of the solution was taken on double beam Spectrophotometer. The Solution exhibited UV maxima at 252.0nm

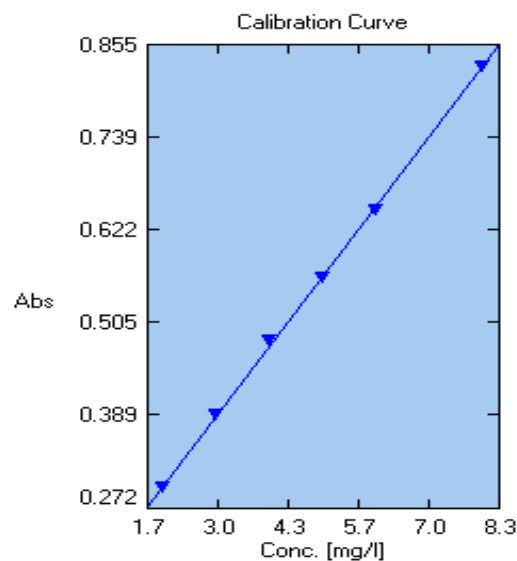### Preparation of Standard Calibration Curve of Gefitinib:

100 mg of Gefitinib was accurately weighed and dissolved in little amount of ethanol and prepare the final volume up to 100 ml with 0.1 N HCl (pH 1.2) to prepare stock solution. The 1 ml of stock solution was further diluted with 0.1 N HCl (pH 1.2) in 100ml to get 10μg/ml (working standard). Then 2ml, 3ml, 4ml, 5ml, 6ml, 8ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 0.1N HCl to prepare 2μg, 3μg, 4μg, 5μg, 6 μg and 8μg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 200-400 nm against 0.1 N HCl (pH 1.2) as blank. The absorbances so obtained were tabulated as in Table below. Calibration curve was constructed and shown in Fig. The method was validated for linearity, accuracy and precision. The results of standard curve preparation are shown in

### Gefitinib –peak in 0.1N HCl (PH=1.2)



**Fig 1: Gefitinib Peak Maxima**

### Standard Calibration curve of Gefitinib:

Concentration and absorbance obtained for calibration curve of Gefitinib in 0.1 N hydrochloric acid buffers (pH 1.2):

**Table 1: Gefitinib Absorbances at Different Concentrations**

| No. | Type | Concentration (µg/ml) | Absorbance |
|-----|------|------------------------|------------|
| 1 | standard | 2 | 0.298 |
| 2 | standard | 3 | 0.390 |
| 3 | standard | 4 | 0.484 |
| 4 | standard | 5 | 0.563 |
| 5 | standard | 6 | 0.649 |
| 6 | Standard | 8 | 0.829 |



**Fig 2: Standard Calibration Curve of Gefitinib**

**Tablet Formulation:**

**Formulation of Gefitinib Dispersible Tablet by Direct- Compression and solid dispersion method:**

All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-12 station with 8mm flat punch, B tooling.

Each tablet contains 200mg gefitinib and other pharmaceutical ingredients as listed in the table 2.

Solid dispersions are prepared by using different carriers like Urea. Here, required weighed quantities of drug and Urea are weighed and are made to dissolve in 10-20 ml of Methanol .Then using magnetic stirrer with hot plate the solvent is evaporated and clear film of drug and carrier was obtained. Then the amount of drug equivalent to 25mg and carrier equivalent to 50 mg are weighed and to it the remaining ingredients are added. The tablets are prepared by Direct compression. Tablets prepared are studied for in-vitro dissolution rate and are evaluated.

**Table 2: Composition of Preliminary Trials for Gefitinib Dispersible Tablets**

| Ingredients (in mg) | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ | $F_9$ | $F_{10}$ | F11 | $F_{12}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gefitinib | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Sodium starch glycolate | 25 | 50 | 75 | | | | | | | 25 | 25 | |
| Crosscarmellose sodium | | | - | 25 | 50 | 75 | | | | 25 | | 25 |
| Cross povidone | - | | | | | | 25 | 50 | 75 | | 25 | 25 |
| Urea | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Talc | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Magnesium Stearate | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Micro crystalline Cellulose(PH-101) | Qs | Qs | Qs | Qs | Qs | Qs | Qs | Qs | Qs | Qs | Qs | Qs |
| TOTAL(mg) | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

**Evaluation Parameters:**
**Pre-compression parameters:**
**Bulk Density ($D_b$):**

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

$$D_b = M / V_b$$

Where, M is the mass of powder

$V_b$ is the bulk volume of the powder.

**Tapped Density ($D_t$):**

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by,

$$D_t = M / V_t$$

Where,

M is the mass of powder

$V_t$ is the tapped volume of the powder.

**Angle of Repose ($\Theta$):**

The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

**Tan ($\Theta$) = h / r**

$\Theta = \tan^{-1}$ **(h / r)**

Where,

$\Theta$ is the angle of repose.

h is the height in cm

r is the radius in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the

height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

**Table 3: Angle of Repose as an Indication of Powder Flow Properties**

| S. No. | Angle of Repose($^0$) | Type of Flow |
|--------|-----------------------|--------------|
| 1 | <20 | Excellent |
| 2 | 20-30 | Good |
| 3 | 30-34 | Passable |
| 4 | >34 | Very Poor |

**Carr's index (or) % compressibility:**

It indicates powder flow properties.

It is expressed in percentage and is given by,

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where,

Dt is the tapped density of the powder and

Db is the bulk density of the powder.

**Table 4: Relationship between % compressibility and flow ability**

| S.no. | %Compressibility | Flow ability |
|-------|------------------|--------------|
| 1 | 5-12 | Excellent |
| 2 | 12-16 | Good |
| 3 | 18-21 | Fair Passable |
| 4 | 23-33 | Poor |
| 5 | 33-38 | Very Poor |
| 6 | <40 | Very Very Poor |

**Hausner ratio:**

Hausner ratio is an indirect index of ease of powder flow. It is calculated by ,

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where, $D_t$ is the tapped density, $D_b$ is the bulk density.

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

**Post -compression parameters:**

**Weight variation:**

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in table No. 5:

**Table 5: Weight Variation Specification as per IP:**

| Average Weight of Tablets | %Deviation |
|---|---|
| 80 mg or less | ±10 |
| More than 80 mg but less than 250 mg | ±7.5 |
| 250 mg or more | ±5 |

**Hardness:**

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in $kg/cm^2$.

**Thickness:**

Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

**Friability (F):**

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

**Wetting time:**

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

$$dl/dt = r¡cos\Theta/(4hl)$$

Where,
 **l** is the length of penetration,
 **r** is the capillary radius,
 **¡** is the surface tension,
 **h** is the liquid viscosity,
 **t** is the time, and
 **Ө** is the contact angle.

It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37ºC.Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

**In-Vitro Drug Release:**

Release of the drug *in vitro*, was determined by estimating the dissolution profile.

**Dissolution Test:**

USP II Paddle apparatus was used and paddle was allowed to rotate at 50 rpm, acid buffer 0.1N HCL (pH 1.2, 900 ml) was used as a dissolution medium.

**Packing:**

The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped with aluminum.

**Testing Parameters:**

The stored samples were evaluated for Weight variation, Hardness, Disintegration Time, Friability, Wetting Time and Drug content at the interval of 1 month.

## RESULTS AND DISCUSSION

Rapidly disintegrating tablets of Gefitinib were prepared to enhance the overall bioavailability by using solid-dispersion technique and direct compression .The Total 12 formulations prepared of which, F1 to F9 are prepared by using single super disintegrant (SSG,CCS,CP) and in F10,F11,F12 formulations combination of superdisintegrants are used (SSG+CCS,CCS+CP,SSG+CP) respectively, compositions of these formulations are tabulated above.

**Standard plot:**

The standard caliberation curve of Gefitinib was obtained by plotting Absorbance vs Concentration. The table of standard plot shows the absorbance values.The peak maxima of Gefitinib was found to be 252.0 nm. The correlation coeffiecient of 0.9998 was obtained within the concentration ranges of 2-10 mg/ml. The calculation of drug content, in-vitro release and stability studies are based on this calibration curve.

**Drug-Excipient compatibility studies:**

To study the compatibility of drug with various polymers, IR spectra of the drug and formulations were carried out. The obtained spectrum shows compatibility between the drug and formulation components.

**Evaluation of Tablets**:

**Pre-compression parameters:**
**Angle of repose:** The results obtained are obtained within the range of 24 - 30º for all the formulations, which indicates good flow property.
**Bulk density:** The loose bulk density and tapped density for all the formulations varied from the values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped density. This results help in calculating % Compressibilty index of the powder.

**Percentage Compressibility:** This parameter was determined by Carr's index. The percent compressibility for all the 12 formulations lie within the range.

**Post-Compression parameters:**
All the formulations were subjected for organoleptic, physical and chemical evaluations.

**Thickness test**: The thickness of the tablets were measured. The values were almost uniform in specific method. The values range between 2.2-2.7 mm, calculated for 3 mean values.

**Hardness test:** The hardness test was performed by Monsanto tester. The hardness was maintained to be within 2.0–3.0 kg/cm$^2$, as these are rapidly disintegrating tablets. The results obtained were within the range of 2.0-2.5 kg/cm$^2$, indicates good mechanical strength and sufficient hardness which influences the disintegration time of the tablets.

**Friability test:** The study results are tabulated, found well within the approved range (<1%) in all the formulations. Intial formulations were found to worn out may be due to excess fines or improper formulation, but are found within the limits indicates good mechanical strength.

**Weight Variation Test:** All the tablets passed weight variation test as the % weight variation was within the pharmacopeial limits of ±7.5%.It was found to be from 198.0 to 202.0 gm. The weights of all tablets were found to be uniform.

**In- vitro disintegration time:** The internal surface of tablets that is pore size distribution, water penetration into tablets and swelling of disintegrating substance are suggested to be the mechanism of disintegration.

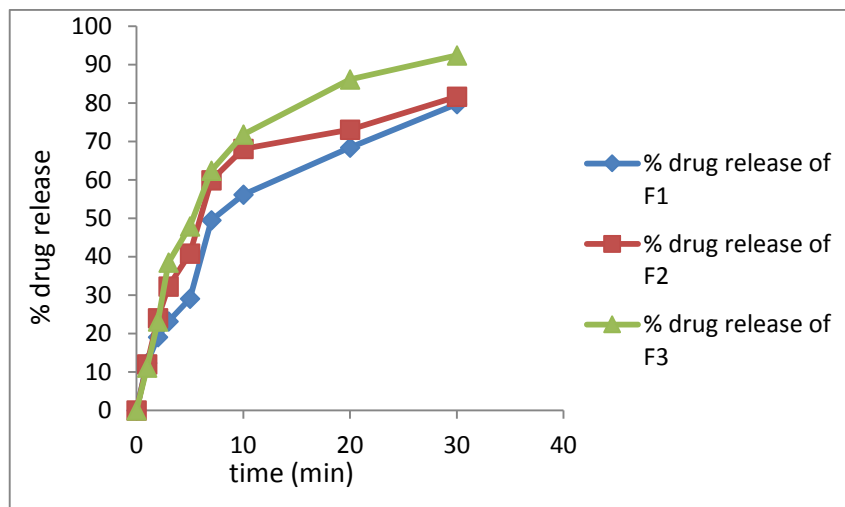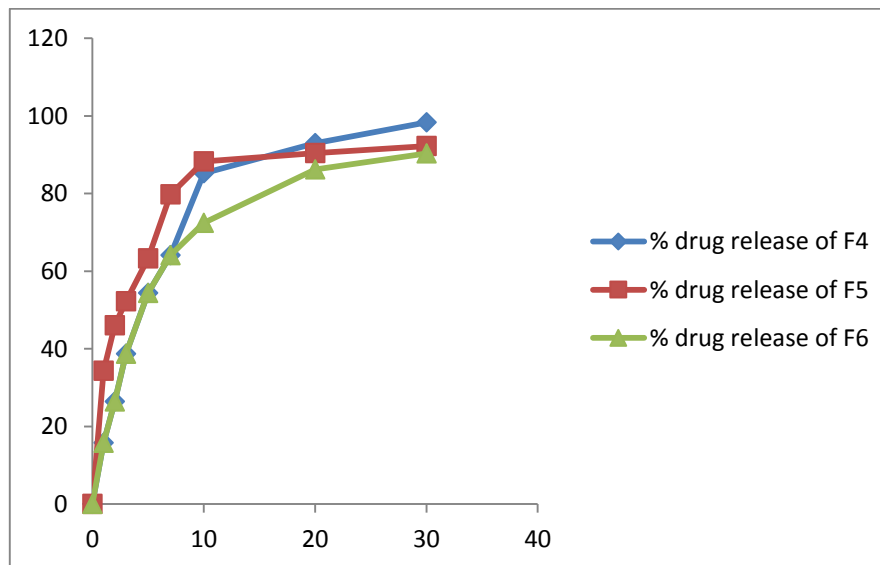All formulations showed disintegration time less than 40 seconds.

**Wetting Time:** Wetting is closely related to inner structure of tablets. The values were tabulated. The wetting time of all the formulations was very fast. This may be due to ability of swelling and also capacity of absorption of water. solid dispersions prepared showed rapid wetting time showing rapid water absorption capacity than the other formulations.

*In-vitro* **Dissolution Studies:** All the 12 formulations were subjected for the in-vitro dissolution studies using tablet dissolution tester USPXXIII .The samples were withdrawn at different time intervals and analysed at 252nm % drug release was calculated from the absorbance observed.

The results obtained in the in-vitro drug release were tabulated for F1 to F12 formulations. The formulations F1,F2,F3 showed release upto 79.78%,81.67%,92.45% respectively. The formulations F4,F5,F6 showed release of 98.28%,92.18%,90.28% while the formulations F7,F9 showed drug release of 94.45%,94.45% while the formulations F10,F12 showed drug release of 86.52%,83.88%. The drug release was completely achieved in a short duration of time. Finally, % drug release of formulation v/s time (in min) was estimated.

**Table 6: Dissolution Profile and Percentage Drug Release of All Formulations (%):**

| Time (min) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 12.31 | 12.00 | 11.13 | 15.8 | 34.31 | 15.8 | 25.54 | 37.02 | 25.54 | 0 | 0 | 25.00 |
| 2 | 19.1 | 23.96 | 23.15 | 26.4 | 46.05 | 26.4 | 37.38 | 56.76 | 37.38 | 0 | 0 | 27.51 |
| 3 | 23.17 | 32.27 | 38.49 | 38.7 | 52.19 | 38.7 | 54.65 | 68.03 | 54.65 | 25.54 | 37.02 | 33.14 |
| 5 | 29.07 | 40.79 | 47.92 | 54.35 | 63.25 | 54.35 | 61.24 | 82.98 | 61.24 | 37.38 | 56.76 | 42.50 |
| 7 | 49.50 | 59.92 | 62.45 | 64.13 | 79.73 | 64.13 | 76.87 | 97.05 | 76.87 | 54.65 | 68.03 | 52.56 |
| 10 | 56.15 | 68.06 | 71.85 | 85.2 | 88.25 | 78.2 | 86.52 | - | 86.52 | 61.24 | 82.98 | 60.05 |
| 20 | 68.39 | 73.12 | 86.17 | 92.92 | 90.4 | 89.92 | 91.43 | - | 91.43 | 76.87 | 97.05 | 74.92 |
| 30 | 79.78 | 81.67 | 92.45 | 98.28 | 92.18 | 90.28 | 94.45 | - | 94.45 | 86.52 | - | 83.88 |



**Fig 3: Percentage Drug Release Of Formulations (F₁,F₂,F₃)**



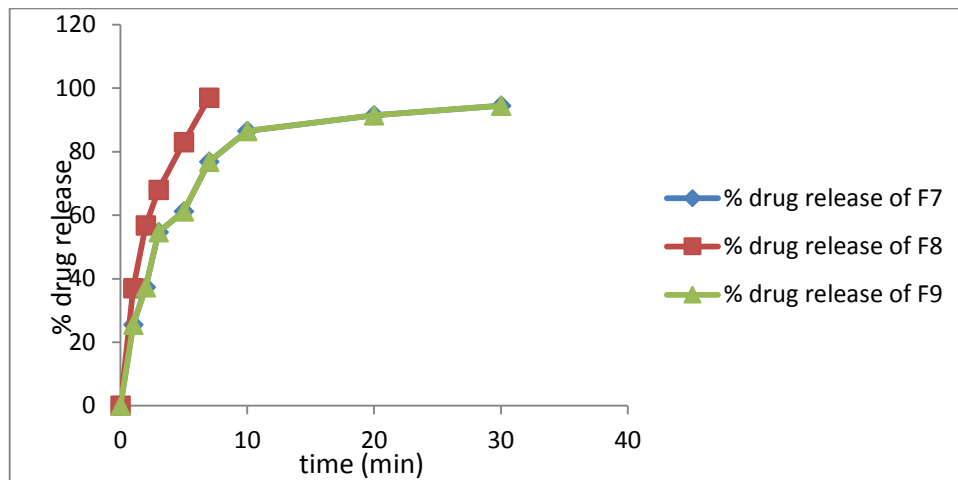**Fig 4: Percentage Drug Release Of Formulations (F₄,F₅,F₆)**

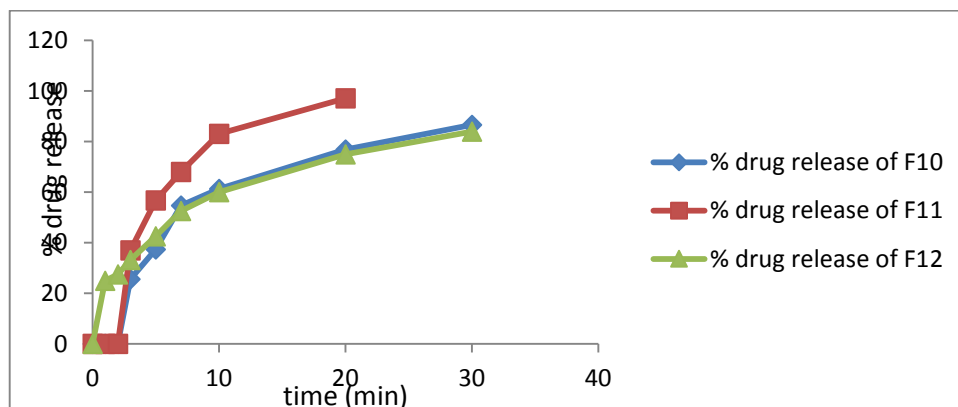**Fig 5: percentage Drug Release Of Formulations ($F_7$,$F_8$,$F_9$)**



**Fig 6: Percentage Drug Release Of Formulations ($F_{10}$,$F_{11}$,$F_{12}$)**

**Table 7: Results of Pre-compression Parameters of Gefitinib Tablets:**

| Formulations | Bulk Density (gm/cm³) | Tap Density (gm/cm³) | Carr's Index (%) | Angle Of Repose(Θ) |
|---|---|---|---|---|
| $F_1$ | 0.59 | 0.72 | 18.517 | 28.82 |
| $F_2$ | 0.59 | 0.69 | 14.49 | 30.09 |
| $F_3$ | 0.57 | 0.66 | 13.64 | 29.56 |
| $F_4$ | 0.56 | 0.65 | 15.84 | 27.90 |
| $F_5$ | 0.59 | 0.69 | 14.49 | 24.56 |
| $F_6$ | 0.61 | 0.70 | 12.86 | 26.86 |
| F7 | 0.59 | 0.71 | 16.90 | 25.72 |
| F8 | 0.559 | 0.70 | 15.71 | 24.78 |
| F9 | 0.59 | 0.69 | 14.49 | 24.84 |
| F10 | 0.58 | 0.64 | 13.57 | 26.74 |
| F11 | 0.57 | 0.62 | 13.54 | 25.18 |
| F12 | 0.58 | 0.64 | 14.52 | 26.47 |

**Table 8: Results of Post-Compression Parameters of Gefitinib Tablet:**

| Formulations | Weight variation (mg) (n=10) | Hardness (kg/cm$^2$) (n=3) | Thickness (mm) (n=3) | Disintegration Time (sec) | Friability (%) | Wetting time (sec) |
|---|---|---|---|---|---|---|
| $F_1$ | 199.5±1.109 | 2.3±0.15 | 2.5±0.04 | 36±2.4 | 0.6633 | 45 |
| $F_2$ | 200.4±1.198 | 2.4±0.18 | 2.4±0.05 | 30±1.2 | 0.6103 | 38 |
| $F_3$ | 201.8±1.071 | 2.5±0.09 | 2.4±0.08 | 26±2.0 | 0.6035 | 32 |
| $F_4$ | 198.9±2.152 | 2.3±0.19 | 2.5±0.02 | 32±1.5 | 0.5356 | 40 |
| $F_5$ | 198.5±2.178 | 2.2±0.18 | 2.3±0.11 | 28±2.0 | 0.5200 | 36 |
| $F_6$ | 199.2±2.052 | 2.4±0.08 | 2.5±0.06 | 22±3.6 | 0.7480 | 30 |
| F7 | 201.3±1.254 | 2.2±0.15 | 2.4±0.86 | 18±2.8 | 0.7739 | 26 |
| F8 | 200.0±1.588 | 2.4±0.09 | 2.6±0.01 | 16±3.2 | 0.7187 | 25 |
| F9 | 200.0±1.018 | 2.2±0.18 | 2.5±0.02 | 15±3.2 | 0.7854 | 20 |
| F10 | 197.9±2.154 | 2.3±0.19 | 2.5±0.02 | 32±1.5 | 0.5356 | 40 |
| F11 | 199.5±2.478 | 2.2±0.18 | 2.3±0.11 | 28±2.0 | 0.5200 | 36 |
| F12 | 199.8±2.054 | 2.4±0.08 | 2.5±0.06 | 22±3.6 | 0.7480 | 30 |

## CONCLUSION:

The rapidly disintegrating tablets of Gefitinib is the first selective inhibitor of epidermal growth factor receptor can be formulated by direct compression of the formulation made using urea as the drug disperses actively in the carrier(Solid dispersion). Hardness and friability of all the formulations indicated tablets were mechanically stable and percentage weight variation and drug content uniformity found within limits.

Among the superdisintegrant Crospovidone showed better drug release either used alone or in combination with other superdisintegrant. Also showed the maximum drug release of all the formulations when used along with solid dispersion preparation with urea. Among all the 12 formulations F4, F7, F9 are the better formulations showed high in-vitro dissolution rate than the other formulations, of which F4 was expected formulation for rapid release.

This work needs to be proved effective by its bioavailability, pre-clinical and clinical studies.

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