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Research Article

# EFFECT OF POLYMERS ON DISSOLUTION PROFILE OF VENLAFAXINE HYDROCHLORIDE PELLETS

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**ABSTRACT**
The present invention concerns with the development of modified release capsules of Venlafaxine hydrochloride which are designed to modify the drug release by sustained release action.
The present study was carried out by advanced pelletization technique. Sustained release capsules of Venlafaxine hydrochloride were formulated by using the pelletization process by drug layering on inert sugar pellets by using sucrose and Hypermellose 606 as a binder. The drug layered pellets were coated by using the HPMC, CMC & with Eudragit grades as a coating material, P.E.G-6000 as a plasticizer, aerosil and magnesium stearate as a glidant & Isopropyl alcohol and water used as solvent materials to sustain the drug release.
Formulation of venlafaxine hydrochloride pellets has been done by two stages drug loading and coating. Loading of pellets has been done by coating pan method and the coating has been done by FBC. The coated pellets size and shape is observed during processing.
The coated pellets is filled in capsules size no.2 and these pellets were evaluated for appearance ,angle of repose, compressibility, Hausner's ratio, Friability test, sieve analysis disintegration and dissolution test were performed & capsules were also evaluated for assay, weight variation, content uniformity, disintegration and in-vitro dissolution tests and observed & they are within range. There is no physicochemical interaction between drug and excipient's.
**KEY WORDS:** Venlafaxine hydrochlorid, Pelletization Technique, HPMC, EUDRAGIT, CMC.

## INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form. Nowadays most of the pharmaceutical scientists are involved in developing an ideal DDS.The design of oral sustain drug delivery system should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose. Pellets[2]: Pellets are described to be produced systematically, as geometrically defined agglomerate obtained from diverse starting materials using different processing conditions. They are free-flowing, spherical or semi-spherical solid units with a size range of about 0.5 mm to 1.5 mm and that are intended mostly for oral administration[1,2].

## ANTIDEPRESSANT

An antidepressant is a medication used primarily in the treatment of depression. Venlafaxine is used primarily for the treatment of depression, general anxiety disorder, social phobia, panic disorder, and vasomotor symptoms. Venlafaxine is well absorbed and extensively metabolized in the liver. Venlafaxine half-life is 5±2 hours. Objective of present study is to formulate, Venlafaxine hydrochloride SR pellets to observe the dissolution profile of the polymers in regard with the drug[3,4].

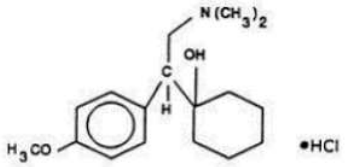
## OBJECTIVE AND PLAN OF WORK

Aim of the present research study is to develop Venlafaxine hydrochloride sustained releases coated pellets using HPMC, Eudragit(dependent and independent), CMC by using drug layering solution method by pelletization technique. Target of our study is to formulate the Sustained release Venlafaxine hydrochloride pellets by drug layering solution method and improve the release rate of the drug by 20 hours and compare with the reference product. To achieve this goal we have to formulate and evaluate the pellets &capsules. The formula will be finalized by comparing the in-vitro dissolution profile with that of the reference product

## DRUG PROFILE

### Venlafaxine Hydrochloride[3,4]

**Therapeutic category**
Antidepressant drug.
**Structure**



venlafaxine hydrochloride

**Chemical name**
(RS)-1-[2-dimethylamino-1-(4-methoxyphenyl) - ethyl] cyclohexanol
**Molecular weight**
313.87g/ml
**Molecular formula**
$C_{17}H_{27}NO_2$·HCL
**Description**
It is a white to off-white crystalline solid.
**Appearance**
White crystal
**Solubility**
It is having solubility of 572 mg/ml in water. Its octane: water partition co-efficient is 0.43.
**Melting point**
Melts between 215 to 217 degrees
**Loss of drying**
1.0% maximum is determined.
**Heavy metals**
Maximum 20 ppm
**Mechanism of action[4]**
Venlafaxine is a bi-cyclic antidepressant, and is usually categorized as a serotonin-nor-epinephrine reuptake inhibitor (SNRI), but it has been referred to as a

serotonin-nor-epinephrine-dopamine reuptake inhibitor (SNDRI). It works by blocking the transporter "reuptake" proteins for key neurotransmitters affecting mood, thereby leaving more active neurotransmitters in the synapse. The neurotransmitters affected are serotonin and nor-epinephrine. Additionally, in high doses it weakly inhibits the reuptake of dopamine, with recent evidence showing that the nor-epinephrine transporter also transports some dopamine as well, since dopamine is inactivated by nor-epinephrine reuptake in the frontal cortex, which largely lacks dopamine transporters: therefore, venlafaxine can increase dopamine neurotransmission in this part of the brain.

**Pharmacokinetic properties**[4]

Venlafaxine is well absorbed, with at least 92% of an oral dose being absorbed into systemic circulation. It is extensively metabolized in the liver via he CYP2D6 isoenzyme to desvenlafaxine (O-desmethylvenlafaxine), which is just as potent a serotonin-nor epinephrine reuptake inhibitor as the parent compound, meaning that the differences in metabolism between extensive and poor metabolizes are not clinically important in terms of efficacy. Side effects, however, are reported to be more severe in CYP2D6 poor metabolizes. Steady-state concentrations of venlafaxine and its metabolite are attained in the blood within 3 days. Therapeutic effects are usually achieved within 3 to 4 weeks. No accumulation of venlafaxine has been observed during chronic administration in healthy subjects. The primary route of excretion of venlafaxine and its metabolites is via the kidneys. The half-life of venlafaxine is relatively short, and, therefore, patients are directed to adhere to a strict medication routine, avoiding missing a dose. Even a single missed dose can result in the withdrawal symptoms.

**Dose:** 75 to 150mg daily, in divided doses.

**Side Effects**

More common side effects include decreased sexual drive, restlessness, difficulty sitting still, skin rash, hives, and itching. Less common side effects include fever and/or chills, and pain in joints or muscles.

## MATERIALS AND METHODS

| | |
|---|---|
| Venlafaxine Hydrochloride | Grk Pharma |
| Sugar Spheres#20 | Meghana, Hyderabad |
| Aerosil | Sigma Aldrich, Bangalore |
| Surcose | Sigma Aldrich, Bangalore |
| Hypromellose | Sigma Aldrich, Bangalore |
| Eudragit | Basf, Germany |
| CMC | Basf, Germany |
| HPMC K4M | Feicheing, E |
| Poly Ethylene Gylcol-6000 | Clarient |
| Magnesium stearate | Sigma Aldrich,Bangalore |

**Composition of venlafaxine hydrochloride capsules**

**Formulation of Venlafaxine Hydrochloride Core Pellets**

| Ingredients | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| Venlafaxine Hydrochloride | ___ | 33 | 33 | 27 |
| Sugar Pellets (#20#24) | ___ | 35 | 45 | 50 |
| Aerosil | ___ | 1 | 0.8 | 0.60 |
| Sucrose | ___ | 13.58 | 7.35 | 12.02 |
| **Binder solution** | | | | |
| Sucrose | ___ | 10.5 | 4.45 | 3.00 |
| Hypromellose (HPME 606) | ___ | 0.4 | 0.4 | 0.38 |
| Purified water | ___ | QS | QS | QS |

**Formulation of Venlafaxine HCL coated pellets**

| Ingredients | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 |
|---|---|---|---|---|---|---|---|---|
| Venlafaxine Hydrochloride | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 |
| Sugar Pellets (#20#24) | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Aerosil | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 |
| Sucrose | 12.02 | 11.52 | 15.02 | 16.86 | 12.52 | 14.66 | 12.66 | 9.80 |
| **Binder solution** | | | | | | | | |
| Sucrose | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.20 | 3.20 |
| Hypromellose (606) | 0.38 | 0.38 | 0.38 | 0.38 | 0.38 | 0.38 | 0.38 | 0.38 |
| Purified water | QS | QS | QS | QS | QS | QS | QS | QS |
| **Sr coating** | | | | | | | | |
| Eudragit independent | 5 | 10 | ___ | ___ | ___ | ___ | ___ | ___ |
| CMC | ___ | ___ | 6 | ___ | ___ | ___ | ___ | ___ |
| Eudrragit L 100(dependent) | ___ | ___ | ___ | 3.13 | 9 | ___ | ___ | ___ |
| HPMC K4M | ___ | ___ | ___ | ___ | ___ | 8.02 | 7.13 | 10.0 |
| P.E.G-6000 | 1.0 | 0.5 | 1 | 0.34 | 0.5 | 0.34 | 0.34 | 0.34 |
| Magnesium stearate | 4 | 1 | 1 | 2.69 | 1 | 1.64 | 2.69 | 2.68 |
| I.P.A | QS | ___ | ___ | ___ | ___ | ___ | QS | QS |
| Purified Water | QS | QS | QS | QS | QS | QS | QS | QS |
| | 99.9 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |

## EVALUATION PARAMETERS AND PROCEDURE FOR CORE AND SR COATED PELLETS

### Angle of repose[5]

The angle of repose has been used in several branches of science to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles.

### Bulk density and tapped density

$$\text{Bulk density} = \frac{W}{V_0};$$

$$\text{Tapped density} = \frac{W}{V_f}$$

Where, W = weight of the pellets; $V_0$ = initial volume; $V_f$ = final volume

### Compressibility index[6]

$$\text{Compressibility index} = 100 \times \left(\frac{(\rho_{tapped} - \rho_{bulk})}{\rho_{tapped}}\right)$$

### Drug content

Weigh initially 5 gm of sample, crushed the pellets in a mortar and weighed accurately a quantity equivalent to 50 mg of venlafaxine HCL and shaken with 60 ml of methanol in 200 ml volumetric flask and diluted the volume with methanol. 5ml of this solution is diluted to 100 ml with methanol. The absorbance of resulting solution is measured at maximum about 226 nm. The content of Venlafaxine hydrochloride is calculated from the absorbance obtained by repeating the procedure using Venlafaxine Hydrochloride in place of substance.

## EVALUATION OF CAPSULES FILLED WITH VENLAFAXINE HCL SR COATED PELLETS

### Weight variation

Twenty capsules were selected at random,weighed individually and an average weight is calculated not more than two capsules deviate from average weight .

### Disintegration Test

The capsules are placed in the basket rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37°c ±5°c and observed over the time described in the individual monograph. To fully satisfy the test capsules must disintegrate completely into a soft mass having no palpably firm core, and only some fragments of the gelatin shell.

### In-vitro dissolution test[7]

For capsules place 1000ml of dissolution medium in each vessel and allow the medium to equilibrate to a temperature of 37 ±0.5°C .place one capsules in each of the basket and operate the apparatus at 100 rpm for specific time. With draw10ml of the solution from each vessel and replace with equal volume of fresh dissolution medium at specific time intervals. Filter the solution through 0.45microns membrane filter and discard first few ml of the filtrate. Dissolution study was carried out in pH 6.8 buffer for 2,4,6, 8, 10 , 12, 18 and 20 hours and assay was done by HPLC method.The results are shown in table

### Procedure

### Standard Preparation

Tranfer 48.0 mg of Venlafaxine Hydrochloride into 25 ml volumetric flask add10ml of mobile phase sonicate to dissolve.

Make up to volume with mobile phase. Transfer the solution through 0.45µ nylon filter paper.

**Table 1. Dissolution Parameters**

| | |
|---|---|
| Dissolution Unit | USP Apparatus I (Basket), equipped with Basket shafts to meet USP<711> criteria |
| Temperature | 37°C±0.5°C |
| RPM | 100 |
| Medium | Water |
| Medium Volume | 900 ml |
| Sample Volume | 10 ml |

### Preparation of venlafaxine Hcl Standard Stock Solution in buffer solution, pH 6.8

A Standard Solution of Venlafaxine HCL was prepared by dissolving accurately weighed 100 mg of Venlafaxine HCL with little quantity of phosphate buffer solution, pH 6.8 in a 100 ml volumetric flask. The volume was made up to 100 ml with phosphate buffer solution, pH 6.8 to obtain a stock solution of 1000µg/ml.

Accurately weighed quantity of venlafaxine hydrochloride (100 mg) was dissolved in little quantity of phosphate buffer solution, pH 6.8, and volume was made up to 100ml.From this, 1ml of solution was pippeted out into a volumetric flask and volume was made up to 100ml. Appropriate aliquots were taken into different volumetric flask and volume was made up to 10ml with phosphate buffer solution, pH 6.8, So as to get drug concentration of 4 to 24µg/ml. The absorbencies of these drug solutions were estimated at $\lambda_{max}$ 226 nm.

**Table 2: Standard plot of Venlafaxine Hydrochloride in Phosphate Buffer solution, pH 6.8**

| Concentration(µ/ml) | Absorbance 226nm AM±SD |
|---|---|
| 0 | 0.00±0.000 |
| 4 | 0.16±0.001 |
| 6 | 0.33±0.003 |
| 8 | 0.51±0.002 |
| 12 | 0.68±0.002 |
| 16 | 0.85±0.001 |
| 20 | 1.038±0.002 |

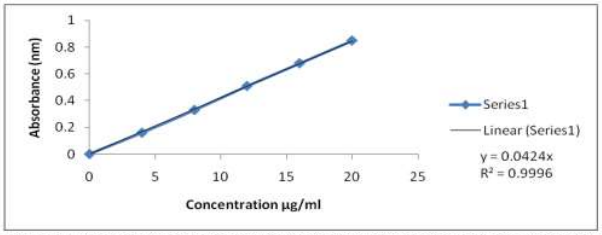



**Figure 1 Calibration curve of Venlafaxine Hydrochloride in Phosphte buffer solution, PH 6.8, at 226 nm**

### Evaluation of Core Pellets (F1-F4)

**Table 3: Evaluation of Core Pellets**

| Formulation | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| Angle of repose(degrees) | - | 52.56 | 43.61 | 30.46 |
| Bulk density(gm/ml) | - | 0.714 | 0.754 | 0.56 |
| Tappeddensity(gm/ml) | - | 0.740 | 0.785 | 0.60 |
| Compressibility index (%) | - | 10.57 | 9.09 | 6.66 |
| Hausner's ratio | - | 1.06 | 1.04 | 1.07 |
| Loss on drying (%) | - | 2.05 | 1.57 | 0.97 |
| Friability (%) | - | 0.266 | 0.197 | 0.266 |
| Drug content (%) | - | 97.65 | 99.86 | 101.08 |

## Evaluation of Sustained release Coated Pellets (F4-F11)

**Table 4: Evaluation of Sustained release Coated Pellets (F4-F11)**

| Formulation | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 |
|---|---|---|---|---|---|---|---|---|
| Angle of repose (degrees) | 32.6 | 29.0 | 31.8 | 27.84 | 27.8 | 28.4 | 28.32 | 29.87 |
| Bulk density (gm/ml) | 0.628 | 0.621 | 0.614 | 0.614 | 0.655 | 0.694 | 0.702 | 0.66 |
| Tapped density (gm/ml) | 0.778 | 0.728 | 0.712 | 0.712 | 0.742 | 0.785 | 0.790 | 0.703 |
| Compressibility index (%) | 19.2 | 14.6 | 13.7 | 13.06 | 11.7 | 11.5 | 11.1 | 6.11 |
| Hausner's ratio | 1.23 | 1.17 | 1.15 | 1.15 | 1.13 | 1.13 | 1.12 | 1.06 |
| Loss on drying (%) | 2.05 | 1.75 | 2.25 | 2.10 | 2.08 | 1.99 | 1.97 | 1.85 |
| Friability (%) | 0.214 | 0.175 | 0.326 | 0.563 | 0.459 | 0.523 | 0.143 | 0.965 |
| Drug content (%) | 100.56 | 96.75 | 98.78 | 99.04 | 99.86 | 99.9 | 100.01 | 100.02 |

**Table 5: Sieve Analysis for Sustained release Coated Pellets**

| Sieve no | Percentage of sample retained in each sieve (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 |
| 16 | 9.1 | 10.9 | 11.2 | 12.4 | 13.4 | 11.8 | 12.4 | 12.6 |
| 20 | 20.9 | 29.1 | 29.0 | 30.4 | 42.8 | 46.3 | 52.2 | 52.2 |
| 24 | 70.0 | 60.0 | 60.8 | 57.2 | 43.8 | 41.9 | 35.4 | 35.2 |

**Table 6: Evaluation of Venlafaxine HCL SR Coated Capsules (F4-F11)**

| Formulations | Weight variation in (mg) ± S.D | Drug content (%) | Cumulative % Drug content of 10 capsules |
|---|---|---|---|
| F4 | 227.8 ± 1.02 | 100.56 | 99.73 |
| F5 | 229.2 ± 0.07 | 96.75 | 98.00 |
| F6 | 226.9 ± 1.01 | 98.78 | 100.60 |
| F7 | 227.8 ±0.06 | 99.04 | 101.04 |
| F8 | 228.4 ± 1.0 | 99.86 | 99.97 |
| F9 | 225.9 ±1.02 | 99.9 | 99.21 |
| F10 | 227.0 ± 0.6 | 100.1 | 101.88 |
| F11 | 227.0 ± 0.6 | 100.2 | 101.29 |

**Table 7: Disintegration tests**

| Parameter | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 |
|---|---|---|---|---|---|---|---|---|---|
| Disintegration time in min. | 4.30 | 4.50 | 4.40 | 5.10 | 4.50 | 4.50 | 4.55 | 5.05 | 4.25 |

**Table 8: Comparison of In-Vitro Evaluation of SR Coated Pellets with Reference product Formulations (F4-F11)**

| Time in hrs | Percenstage drug release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Effexor 75mg | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 14.2 | 13.6 | 33.6 | 11.2 | 10.2 | 22.3 | 19.5 | 12.6 | 10.2 |
| 6 | 42.6 | 22.7 | 55.3 | 39 | 21.2 | 42 | 35 | 23.6 | 24.9 |
| 8 | 60.2 | 46.9 | 75.6 | 55 | 32.1 | 56.9 | 52.35 | 47.8 | 33.5 |
| 10 | 73.7 | 67.6 | 86.4 | 73.2 | 60.3 | 72.6 | 70.45 | 68.3 | 62.9 |
| 12 | 81.4 | 76.1 | 98.9 | 82.6 | 69.6 | 79.7 | 78.9 | 78.1 | 79.8 |
| 18 | 90.4 | 81.3 | ND | 90.6 | 76 | 87.4 | 85.3 | 83.2 | 85.5 |
| 20 | 97.8 | 91.1 | ND | 95.8 | 83.1 | 96.6 | 95.3 | 94 | 96.2 |

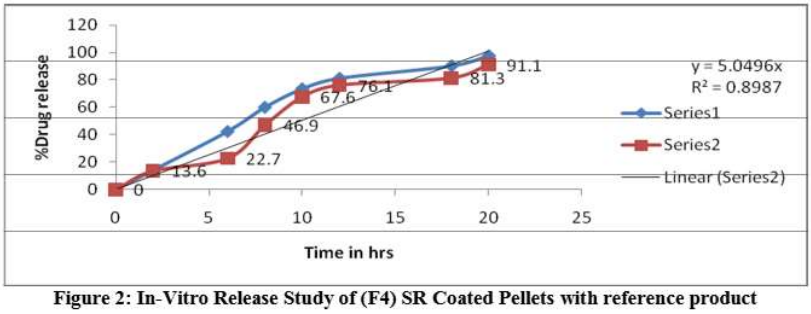



**Figure 2: In-Vitro Release Study of (F4) SR Coated Pellets with reference product**

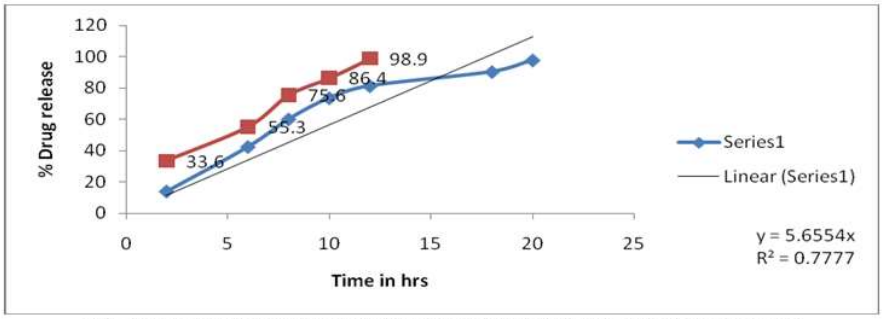



**Figure 3: In-Vitro Release Study of (F5) SR Coated Pellets with Reference product**

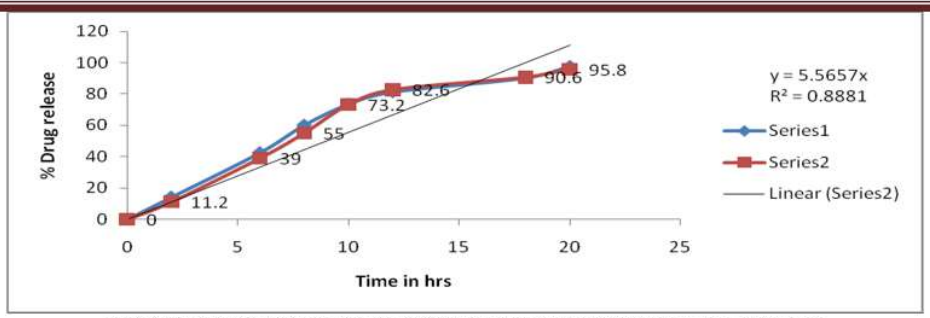



**Figure 4: In-Vitro Release Study of (F6) SR Coated Pellets with Reference product**

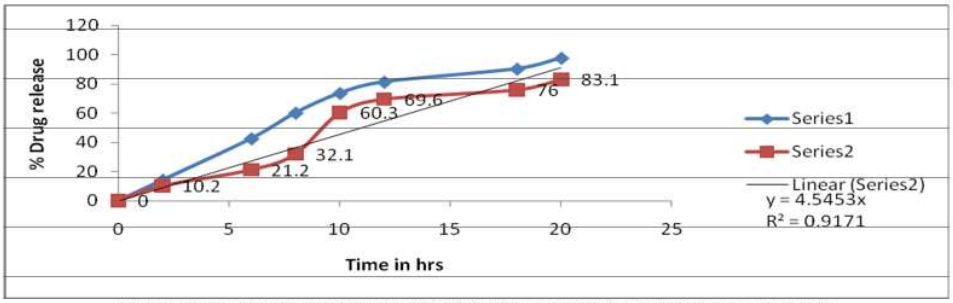



**Figure 5: In-Vitro Release Study of (F7) SR Coated Pellets with Reference product**

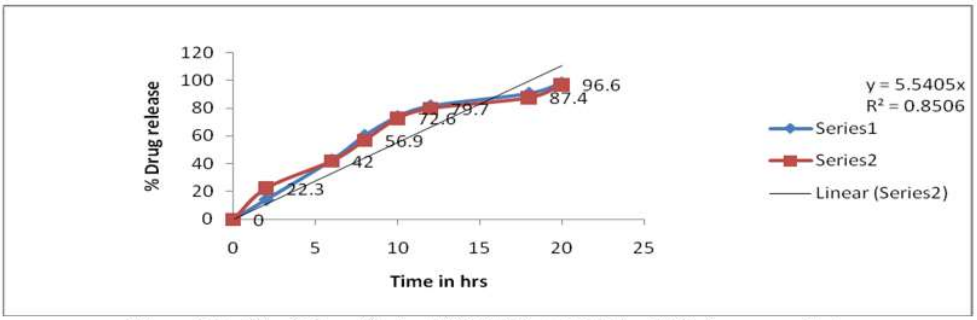



**Figure 6: In-Vitro Release Study of (F8) SR Coated Pellets with Reference product**

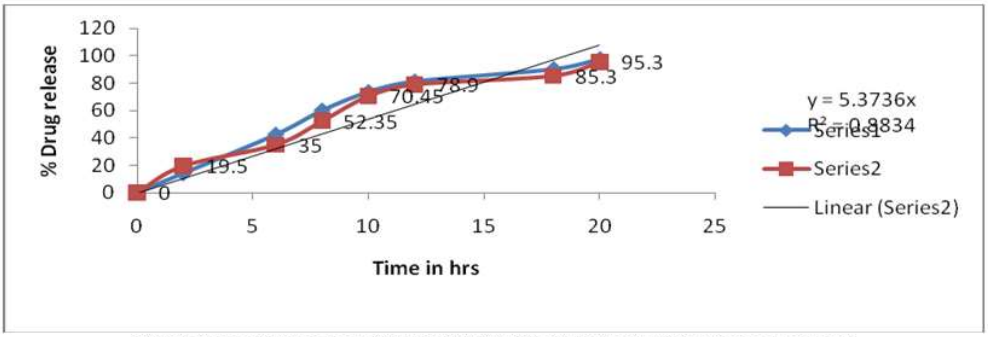



**Figure 7: In-Vitro Release Study of (F9) SR Coated Pellets with Reference product**

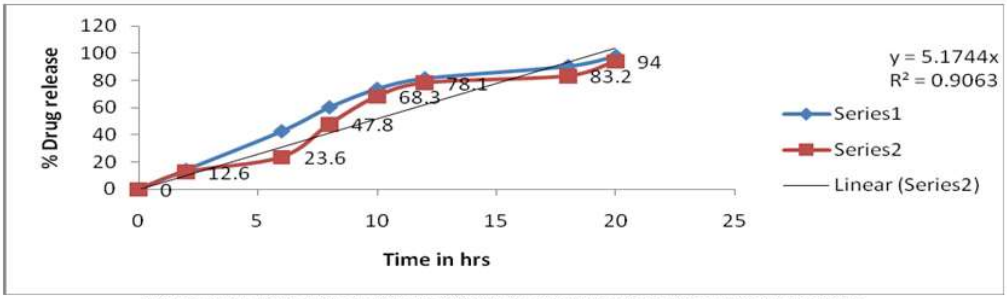



**Figure 8: In-Vitro Release Study of (F10) SR Coated Pellet with Reference product**

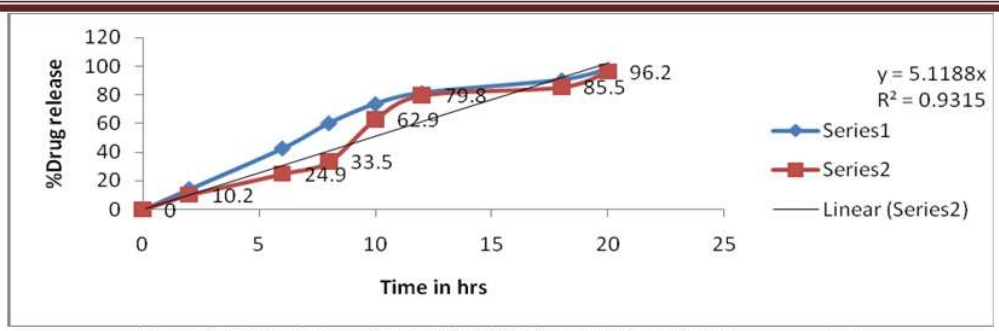



**Figure 9: In-Vitro Release Study of (F11) SR Coated Pellets with Reference product**

## CONCLUSION

When we come to discussion and conclusion of SR coated pellets, the release in the starting hours is controlled by increasing the concentration of HPMCin the formulations in F10 formula and the plasticizer is also increased. It was observed that the release profile of the pellets were good by using HPMC polymer, when compared with the Eudragit's (independent), Eudragit's (dependent) L100 & CMC.

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