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# FORMULATION AND EVALUATION OF MIRTAZAPINE ORAL THIN FILM

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**ABSTRACT**

The aim of this present investigation was to develop a rapid dissolving oral polymeric film, using the solvent casting method, having good mechanical properties, instant disintegration and dissolution, an acceptable taste in the oral cavity. Mirtazapine is a tetracyclic antidepressant drug mainly in patients affected by depression The present investigation was undertaken with the objective of formulating of the Mirtazapine rapid dissolving oral thin films allowing fast reproducible drug dissolution in oral cavity thus bypassing first pass metabolism, to enhance the convenience and compliance by the elderly and pediatric patients .Nine formulation of films with drug were prepared using both natural and synthetic polymers like HPMC E6 and Sodium Alginate. Propylene glycol was used as plasticizers. Citric acid was used as a saliva stimulating agent. Synthetic Aspertame was used as sweetening agent. The resultant films were evaluated for weight variation, assay, content uniformity, folding endurance, thickness, tensile strength, percent elongation, surface pH, *in vitro* disintegration and *in vitro* dissolution. The F4 formulation showing the best results. the disintegration time is only 3.5 second. and was releasing upto 100.8% of drug within 20 minutes.

**Keywords:** Mirtazapine , solvent casting method, Oral thin film and HPMC E6.

## INTRODUCTION

More recently, fast-dissolving films are gaining interest as an alternative to fast-dissolving tablets to definitely eliminate patients' fear of chocking and overcome patent impediments. Fast-dissolving films are generally constituted of plasticized hydrocolloids or blends made of thereof that can be laminated by solvent casting or hot-melt extrusion

The oral route is one of the most preferred routes of drug administration as it is more convenient, cost effective, and ease of administration lead to high level of patient compliance. The oral route is problematic because of the swallowing difficulty for pediatric and geriatric patients who have fear of choking. Patient convenience and compliance oriented research has resulted in bringing out safer and newer drug delivery systems. Recently, fast dissolving drug delivery systems have started gaining popularity and acceptance as one such example with increased consumer choice, for the reason of rapid disintegration or dissolution, self-administration even without water or chewing.

Mirtazapine is a tetracyclic antidepressant used mainly in patients affected by depression[1,2]. The novel antidepressant mirtazapine has a dual mode of action. It is a noradrenergic and specific serotonergic antidepressant (NaSSA) that acts by antagonizing the adrenergic alpha2-autoreceptors and alpha2-heteroreceptors as well as by blocking 5-HT2 and 5-HT3 receptors[3,4]. It enhances, therefore, the release of nor epinephrine and 5-HT1A-mediated serotonergic transmission. Increased activation of the central 5-$HT_{1A}$ receptor is thought to be a major mediator of efficacy of Mirtazapine .This dual mode of action may conceivably be responsible for mirtazapine's

rapid onset of action. Mirtazapine is extensively metabolized in the liver. The cytochrome (CYP) P450 isoenzymes CYP1A2, CYP2D6, and CYP3A4 are mainly responsible for its metabolism. The objectives of present investigation were to formulate and evaluate the oral thin film of Mirtazapine by the help of both natural and synthetic polymer and to study the various formulation variables that affects invitro release and bioavailability Mirtazapine.

## MATERIALS AND METHODS

### MATERIALS

Mirtazapine was procured from Dr.Reddy Lab, Hyderabad India. HPMC E6 , propylene glycol, CMC and Crosscar mellose was purchased from Sigma-Aldrich (Bangalore). Sodium Alginate, aspartame ,citric acid was recived as a gift sample from Macleod's Pvt. Ltd, Mumbai (India).

### Method of formulation of Oral thin film

The OTF were prepared by the method of solvent casting technique employing 'O' shape ring placed on a glass surface as substrate by using different concentration of both synthetic and natural polymers like Hydroxy Propyl Methyl Cellulose (HPMC E6),CMC and Na Alginate,

The calculated quantities of polymers were dispersed in water. An accurately weighed Mitrazapine was incorporated in polymeric solutions after levigation with 25 % w/w propylene glycol which served the purpose of plasticizer as well as penetration enhancer. The solution was mixed occasionally to get semisolid consistency. citric acid was added to formulation as saliva stimulating agent, Then the solution was subjected to sonication in a bath sonicator to remove the air bubbles Then this were casted on a glass surface employing 'O' shape ring is covered with funnel to controlling the evaporation of solvent and allowed to dry at room temperature over night. The dried film were separated and the backing membrane used was aluminium foil. Then the formulations were stored in desiccators until further use.

The films were evaluated for imperfections and cuts, peel ability without rupturing, folding and cracking endurance and surface roughness (Table 1: Different Formulation of oral thin film of Mirtazapine).

### EVALUATION OF ORAL THIN FILM

### FTIR studies

Compatibility of drug and polymers was studied using Fourier Transform Infrared (FTIR) spectroscopy. FTIR Spectrum was recorded between 600-4000 cm-1 using Shimadzu 160a, Kyoto, Japan by KBr Disc method.

### Mechanical Properties

Film thickness was evaluated using thickness tester (MitutoyoCo. Ltd., Japan, 0.001 mm capacity) at five locations and the mean thickness was calculated. Tensile strength was determined using Universal Testing machine (Model AGS10kNG, Shimadzu, Japan) with load cell of 1kN. FDFs of size 7 x 1 cm2 were placed between two clamps held 5 cm apart. The films were pulled by the clamp at a rate of 10 mm/min. Load vs. displacement data were recorded until the specimen broke. This data was then converted to stress vs. strain. Tensile strength and percentage elongation was calculated for each specimen by standard reported methods. [9] The folding endurance was measured manually by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. properties were measured in triplicate and reported as mean and standard deviation

### The Percentage moisture absorption (PMA)

This test was carried out to check the physical stability of films at high humid conditions. In the present study the moisture absorption capacity of the Mirtazapine films were determined by keeping the preweighed films in desiccator at room temperature for 72 hours. Then they were taken out and exposed to 79.5% relative humidity (saturated solution of aluminum chloride). Average percentage moisture absorption of three films can be calculated by following equation

**Percentage moisture absorption =**

$$\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

### Percentage moisture loss (PML)

This test was also carried to check the integrity of Mirtazapine films at dry condition. Three 2cm diameter films was cut and weighed accurately and kept in desiccators' containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. Average percentage moisture loss of three films was found out.

**Percentage moisture Loss =**

$$\frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

### Weight Variation

Weight variation is studied by individually weighing 10 randomly selected Mirtazapine

films and calculating the average weight. The average weight should not deviate significantly from the average weight.

**Surface pH**

The surface pH of Mirtazapine fast dissolving oral thin films was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral strip was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the film.

**Drug content**

Drug content of all batches of Mirtazapine thin films was determined by UV-spectrophotometric method. For this one strip of 4 cm2 was dissolved in 100ml of pH 6.8 buffer. Then the solution was suitably diluted and the absorbance was recorded at 289 nm.

**Uniformity of drug content**

The uniformity of dosage units of the oral film preparation was tested using 10 preparations, and the content of montelukast sodium was determined by UV-spectrophotometry. The acceptance value (AV) of the preparation is less than 15%, according to the JP15. 6.0%. AV for JP15 was calculated according to the following equation:

$$AV = |M - X| + ks$$

Where, *M* is label claim (100%), *X* the average (%) of individual contents, *k* the acceptability constant (2.2), and *s* is the standard deviation.

**MIRTAZAPINE ORAL THIN FILMS SOLID STATE EVALUATION**

**In vitro disintegration time**

A glass Petri dish (6.5 cm diameter) was filled with 10 ml of water and the film was carefully placed in the center. The set up was left undisturbed. The time for the film to completely disintegrate into fine particles was noted. The test was performed four times on each formulation and mean value was reported.

**In vitro dissolution studies**

The *in-vitro* release studies were performed in phosphate buffer solution (pH 6.8, 100 ml) at 37 ºC using a modified dissolution apparatus. The modified dissolution apparatus consisted of a 250 ml beaker as a receptor compartment and an open end tube as a donor tube. The magnetic stirrer assembly with an attached hot plate was adopted for the study. The dissolution medium consisted of 100 ml of phosphate buffer (pH 7.5) maintained at 37 ± 1°C by means of a thermo-regulated hot plate. Film was placed into the donor chamber of the assembly separated from the medium by a semi-permeable membrane. The donor tube was then dipped into the receptor compartment containing dissolution medium, which was maintained at 37 ± 1°C and stirred at a constant speed of 100 rpm using a magnetic bead. One milliliter samples were withdrawn at predetermined time intervals for all the batches. For each sample withdrawn, an equivalent volume of phosphate buffer was replaced to the dissolution medium to maintain constant volume and sink condition. A ten-fold dilution of each of the withdrawn sample was made and the diluted solutions were thereafter analyzed spectrophotometrically at 289nm.

**Stability Studies**

For stability testing the optimized formulation (F4) were stored under controlled conditions of 40°C±2°C and 75%±5% RH over a period of 3 months according to the ICH guidelines. During storage the films were evaluated for their physical appearance, disintegration time, drug content and *invitro* dissolution studies.

**RESULTS AND DISCUSSION**

**FTIR studies**

The FTIR spectra of Mirtazapine showed a characteristic peaks of Mirtazapine appeared at 3245 (N-H stretching), 711 (C-Cl stretching). It was observed that there were no changes in these main peaks in the FTIR spectra of a mixture of drug and excipients. The FTIR study demonstrates that no physical or chemical interactions of Mirtazapine with other excipients (Fig. 1: FTIR of pure drug Mirtazapine and Fig. 2: FTIR of Physical mixture of Optimized Formula F4).

**Surface pH**

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the rate of hydration of the polymers, the surface pH of the films was determined. The observed surface pH of the formulations was found to be in the range of 6.52±0.03 to 6.80±0.01. The results are found that there is no significant difference of surface pH in all the formulations and the pH range lies with in the range of salivary pH i.e. 6.5 to 6.8, hence do not cause irritation and achieve patient compliance. Surface pH values of all the formulations are represented in table no- 2.

**Percentage Moisture Absorption and Percentage Moisture Loss**

Checking the physical stability of the film at high humid conditions and integrity of the film at dry conditions, the films were evaluated for PMA and PML. The observed results of PMA and PML were shown in the tabular column. (Table No. 2). The percentage Moisture uptake in the formulation F6 has shown the highest value of moisture absorption 14.21±0.06. This may be due to the presence of higher concentrations of Na. Alginate along with HPMC E6.

**Water Vapour Transmission**

Water vapor transmission rate through various films was given in table 2 Water vapor transmission studies indicated that all the films were permeable to water vapour. The formulation F8 has shown maximum water vapor transmission of among all the films. This may be due to the presence of high amount of Crosscar mellose.

**Thickness and Weight of films**

The film thicknesses were observed by using digital vernier caliper and found to be in the range of 0.20±0.01 mm to 0.65±0.01 mm. The weight of the films was found to be in the range of 212.12±1.06 mg to 169.18±0.9 mg.

**Folding endurance**

The folding endurance was found vary near to 300 in case of all the formulations. This makes the system acceptable for movement of mouth, indicating good strength and elasticity. Folding endurance test results indicated that the films would maintain the integrity with buccal mucosa when applied and has good plasticity.

**Drug content estimation**

The observed results of content uniformity indicated that the drug was uniformly dispersed and with minimum intra batch variability.

**Disintegration time**

In vivo Disintegrating time is defined as the time (seconds) at which a film breaks when brought into the contact with water or saliva. All the formulations were found to disintegrate within 6sec. Formulation F4 showed less disintegration time i.e.3.56 sec and formulation F6 showed more disintegration time i.e. 6.4 second. with the increase concentration of Cross carmellose the disintegration time decreases (Table 2: Physicochemical evaluation of oral thin films of mirtazapine).

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**In-vitro drug release studies**

Distinguishable difference was observed in the release of Mitrazapine in all formulations. The results and data of *in vitro* studies are shown in the Table No: 3 .Formulations F4 is showing fast and complete release within 20second. With increasing concentration of HPMC E6 and Crosscar mellose together have great effect on drug release process.In-vitro dissolution graphs are mentioned in figure no-3 & 4 .More amount of drug release in short span of time supports the faster action of the dosage form (Table 3: In-vitro drug release data for oral thin film of Mitrazapine).

**Stability studies**

When the oral film preparation was stored either in the aluminum package or under unwrapped condition at 40 ◦C and 75% in humidity for 4–8 weeks, no apparent changes in the shape, color or flexibility were observed.

**CONCLUSION**

Fast dissolving films fulfill all the aforementioned requirements of potential solid oral dosage form for local delivery of Mitrazapine . Fast dissolving film when placed in the oral cavity quickly gets hydrated, sticks onto the site of application and then disintegrates to release the drug . Thus, a fast dissolving film is a unique solid oral dosage form and has valuable advantages . The film preparation met the criteria of Acceptance value in the dosage uniformity test for JP15 and USP27, moreover, it revealed an excellent stability and dissolution profile.

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**Table 1: Different Formulation of oral thin film of Mirtazapine**

| INGREDIENTS | FORMULATION | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Mitrazapine | 20 | 20 | 20 | **20** | 20 | 20 | 20 | 20 | 20 |
| HPMC E6 (%) | 2 | 3 | 4 | **5** | - | - | - | - | - |
| Na Alginate(%) | - | - | - | **-** | 2 | 3 | 4 | 5 | 6 |
| CM(%) | 2.5 | 5 | 7.5 | **10** | 2.5 | 5 | 7.5 | 10 | 2.5 |
| CMC(%) | - | - | 5 | **-** | - | - | 4 | 3 | 2.5 |
| Polyglycol(%) | 2.5 | 2.5 | 2.5 | **2.5** | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Citric acid(%) | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 |
| Aspertame(mg) | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 |
| Water | Q.S | Q.S | Q.S | **Q.S** | Q.S | Q.S | Q.S | Q.S | Q.S |

**Table 2: Physicochemical evaluation of oral thin films of Mitrazapine**

| Formulation Code | Surface pH ± SD | PMA ± SD | PML± SD | WTR ± SD | Disintegration time(secs) ± SD | Thickness (mm) ± SD | Weight of films in mg ± SD | Drug Content in mg |
|---|---|---|---|---|---|---|---|---|
| F1 | 6.74±0.005 | 5.20±0.07 | 5.57±0.12 | 10.18±0.35 | 5.14±0.72 | 0.24±0.01 | 40.93±1.55 | 19.5 |
| F2 | 6.85±0.005 | 7.38±0.04 | 5.14±0.72 | 7.67±0.34 | 4.14±0.2 | 0.62±0.01 | 49.18±0.9 | 19.1 |
| F3 | 6.83±0.015 | 9.24±0.09 | 4.74±0.1 | 7.17±0.34 | 3.99±0.02 | 0.47±0.01 | 39.53±0.81 | 18.5 |
| F4 | 6.64±0.050 | 10.32±0.11 | 4.14±0.2 | 6.4±0.35 | 3.56±0.02 | 0.59±0.01 | 46.31±0.58 | 18.6 |
| F5 | 6.6±0.015 | 12.13±0.09 | 4.08±0.03 | 5.98±0.08 | 4.74±0.1 | 0.65±0.02 | 41.37±0.85 | 19.4 |
| F6 | 6.52±0.03 | 14.21±0.06 | 3.88±0.02 | 5.39±0.32 | 6.4±0.35 | 0.31±0.01 | 42.12±1.06 | 19.5 |
| F7 | 6.67±0.004 | 11.23±0.23 | 5.71±0.02 | 5.86±0.24 | 5.25±0.72 | 0.44±0.01 | 42.9±0.65 | 18.8 |
| F8 | 6.76±0.005 | 10.26±0.23 | 6.71±0.01 | 10.21±0.30 | 4.82±0.1 | 0.39±0.01 | 41.37±0.92 | 19.2 |
| F9 | 6.75±0.015 | 10.32±0.11 | 3.88±0.02 | 7.17±0.34 | 4.26±0.2 | 0.31±0.01 | 43.9±0.65 | 19.4 |

**Table 3: In-vitro drug release data for oral thin film of Mitrazapine**

| TIME (Mins) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 2 | 9 | 6 | 9 | 18 | 6 | 9 | 12 | 10 | 28 |
| 4 | 14 | 13 | 27 | 27 | 16 | 17 | 30 | 28 | 28 |
| 6 | 23 | 20 | 36 | 37 | 24 | 25 | 41 | 36 | 34 |
| 8 | 36 | 33 | 52 | 46 | 38 | 40 | 49 | 47 | 46 |
| 10 | 42 | 40 | 65 | 69 | 45 | 44 | 62 | 56 | 57 |
| 12 | 52 | 45 | 70 | 75 | 53 | 50 | 74 | 70 | 72 |
| 15 | 60 | 52 | 76 | 89 | 64 | 56 | 78 | 75 | 80 |
| 20 | 78 | 59 | 78 | 101.8 | 69 | 79 | 82 | 84 | 83 |

**FTIR REPORT**

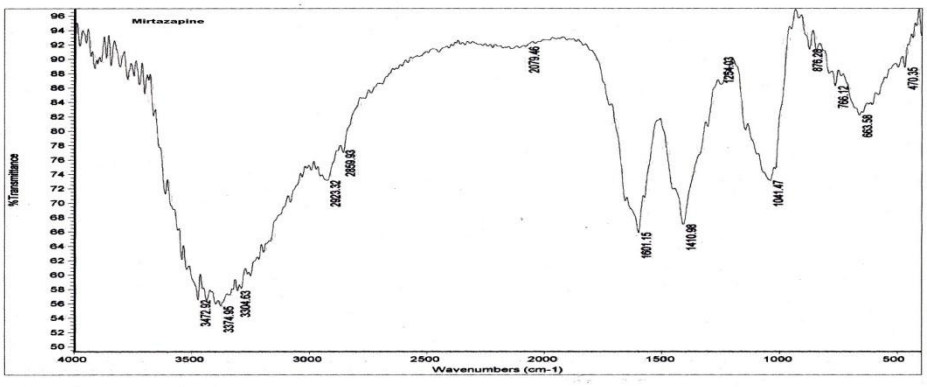


**Fig. 1: FTIR of pure drug Mirtazapine**

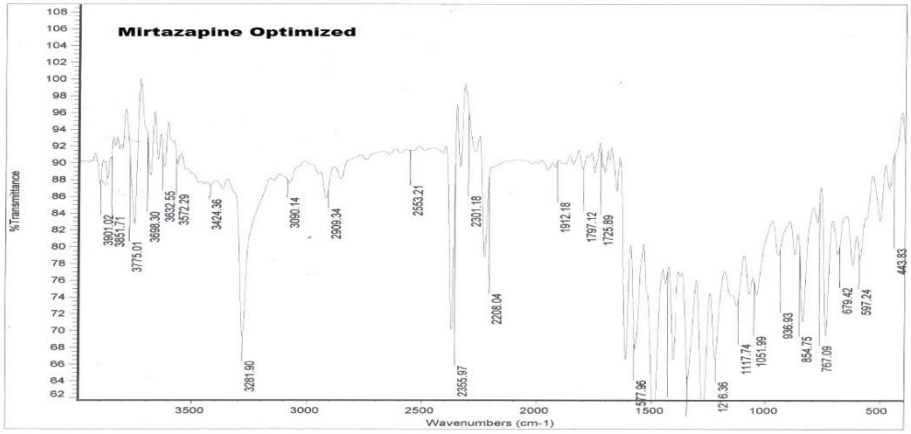


**Fig. 2: FTIR of Physical mixture of Optimized Formula F4**

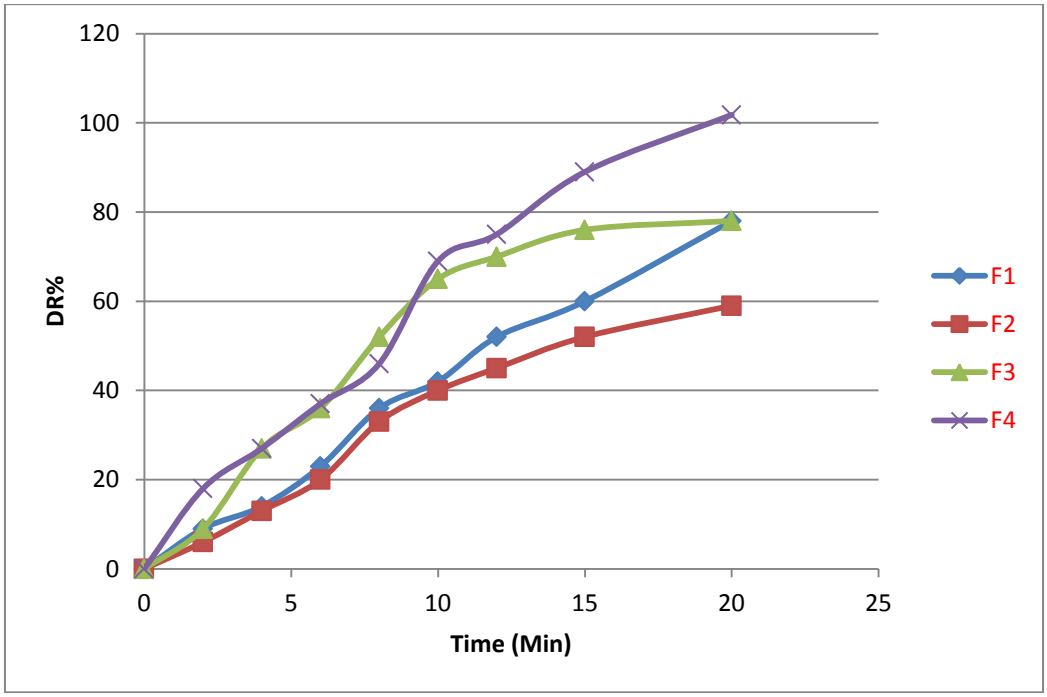


**Fig. 3: In-vitro drug release profile of formulations from F1-F5**

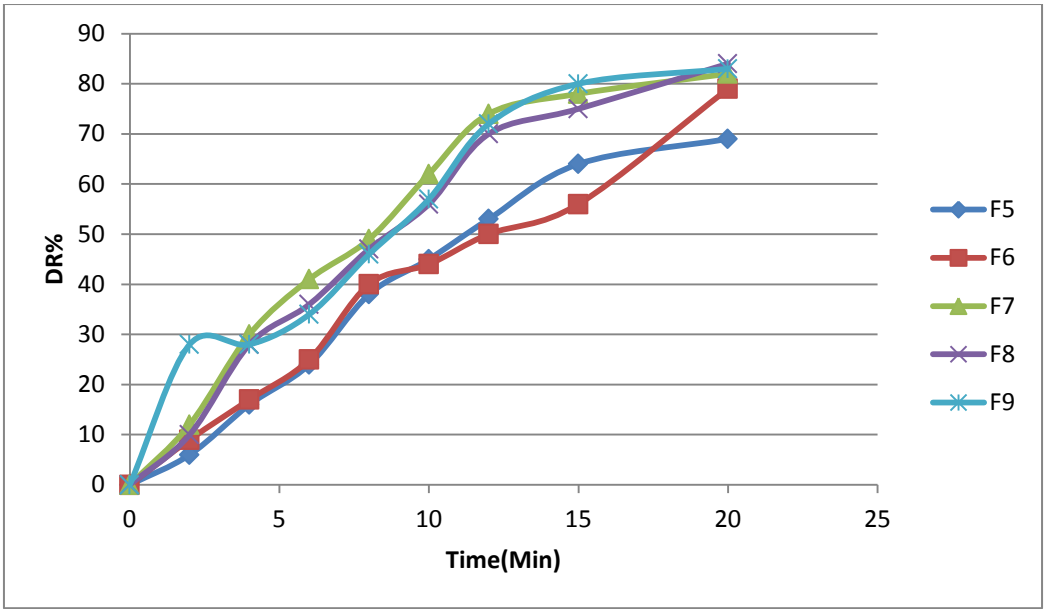


**Fig. 4: In-vitro drug release profile of formulations from F6-F9**

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