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FORMULATION OF OLMESARTAN FAST DISSOLVING TABLETS USING STEVIA AS SWEETNER

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Abstract

Solubility is an important physicochemical factor affecting absorption of drug and it's therapeutic effectiveness. The present research work is to improve the solubility and dissolution rate of olmesartan medoxomil by complexation with HP β-Cyclodextrins. The inclusion complexes were prepared by lyophilization and solvent evaporation method. The prepared complexes were characterized by scanning electron microscopy (SEM) and by X-Ray Diffractometry. The XRD spectra of olmesartan/ hydroxylpropyl β-Cyclodextrins solid complexes showed that olmesartan medoxomil could form inclusion complex with hydroxylpropyl β-Cyclodextrins in solid state. From the prepared inclusion complexes, fast dissolving tablets were formulated by using superdisintegrants like calcium silicate and sodium starch glycolate in various concentrations. Prepared tablets were evaluated for physical parameters and drug release by *in vitro* dissolution studies. Complexation of olmesartan medoxomil with hydroxylpropyl β-Cyclodextrins significantly improved the solubility of the drug, drug dissolution speed, improved the mechanical properties of tablets produced by direct compression. Stevia as sweetener has good mouth feeling property help to change perception of medication as bitter pill particularly in geriatric patients.

Keywords: Olmesartan medoxomil, HPβ-Cyclodextrins, Calcium Silicate, Stevia, Orodispersible tablets.

Introduction

An increased demand for more patient friendly dosage forms has been observed since past few years. The oral route of drug administration is the most preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective swallowing a dosage form is a comfortable and a familiar means of taking medication. Although oral route of administration is preferred for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption results in poor bioavailability and is most common among the problems that can be encountered when delivering an active agent via oral route. Solubility behaviour of a drug plays a key role for its oral bioavailability. For some drugs solubility presents a challenge to the development of a suitable formulation for oral administration [1].

Recent developments in technology have presented viable dosage alternatives for paediatric, geriatric, bedridden, nauseous or non compliant patient. Traditional tablets and capsules administered with 250 ml of water may be inconvenient or impractical for such patients. Hence, fast dissolving tablets (FDTs) are a perfect fit for them. FDTs dissolves or more commonly disintegrate rapidly in the saliva without the aid of water. Also, this dosage form offers an advantage of convenience of administration while travelling where they may not be accesses to water. The fast dissolving/disintegrating dosage forms are well established in the management of pain, inflammation, vomiting, headache and hypertension. Several methods have been reported for preparing FDTs dosage forms. Fast dissolving tablets are also known as mouth-dissolving tablets, melt-in mouth tablets, the time for disintegration of fast disintegrating tablets is generally considered to be less than one minute. The fast dissolving solid dosage form turns into a soft paste or liquid form for easy swallowing, and thus it is free of risk of choking. Fast dissolving technology offers following advantages like improved compliance/added convenience, no water needed, no chewing needed, better taste and improved stability [2-3].

In the present work use of stevia as sweetener has been investigated in the preparation of FDT. Steviol glycosides are recently included in the European Union (EU) list of permitted sweeteners. Steviol glycosides are extracted from the shrub Stevia rebaudiana which is native to Paraguay, where the leaves have a history of use as a sweetener for over a century. Steviol and rebaudioside A are not mutagenic at doses and routes of administration at which they are administered to humans. Two review studies found no health concerns with stevia or its sweetening extracts [4-5].

In the present investigation, olmesartan medoxomil was selected as a drug candidate for developing Fast dissolving drug delivery system [6]. Olmesartan medoxomil was selected as a drug candidate for improving its solubility and dissolution rate by inclusion complexes using hydroxylpropyl β-Cyclodextrins (HP-βCD) as carriers prepared by lyophilization and solvent evaporation method. Highly hydrophilic cyclodextrin derivatives like HP-βCD have been used in the formulation of poorly water soluble drugs thereby enhancing the oral bioavailability through the formation of inclusion complexes [7-10].

Material and Nethods

Materials

Olmesartan Medoxomil (OLM) was a gift sample from M/S Apotex pharma Pvt Ltd, Bangalore, Calcium silicate (CS), Sodium starch glycolate (SSG) and HP-βCD were commercially procured from yarrow chem. Ltd, Mumbai, Potassium dihydrogen phosphate, Sodium hydroxide, Methanol and ethanol were procured from S.D Fine Chem., Ltd., and Mumbai. All other materials used were of pharmacopoeial grade and commercially procured.

Preparations of cyclodextrin inclusion complexes

All the binary mixtures were prepared in a 1:1 molar ratio of drug and HPβ-CD on the basis of the results obtained from the preliminary phase solubility studies [Akbari et al., 2011]. The poorly soluble olmesartan medoxomil was incorporated into the HPβ–cyclodextrins polymer by using the following different two different techniques. They are lyophillization and solvent evaporation method.

Lyophilization: Specified quantity of olmesartan and HPβ-CDs were weighed and added with minimum amount of water. This dispersion was rapidly solidified by freezing in a lyophilizer. Shin Freeze drier (Shin Lab Co., Ltd). The solvent in the dispersion was sublimed under a pressure of 10 M torr and condensed onto a -40 ºC condenser. After the solvent was completely removed, the powder

Solvent evaporation method: OLM and HPβ-CDs were mixed in 1:1 molar ratio and 10ml of ethanol solution of OLM was added to slowly to 10 ml aqueous solution of HPβ-CD followed by stirring at 500-600 rpm using magnetic stirrer at 37^0C for 24 hr. The solvents were then evaporated at 40-50^0C. The resultant solids were pulverized and then sieved through 100 # [12].

Evaluation of inclusion complexes

Estimation of drug content for inclusion complexes

Inclusion complexes of OLM equivalent to 40 mg was weighed and transferred into a 100ml volumetric flask. To this small quantity of methanol was added to dissolve and shaken occasionally for about 15 minutes and the volume was made up to 100ml by adding 6.8 p^H buffer. The solution was filtered by using a Whattman filter paper. The filtrate was subsequently diluted with 6.8 p^H buffer and the absorbance was measured at 256nm using 6.8 p^H buffers as blank. This test was repeated six times (N=6). The amounts of OLM estimated from different complexes were depicted in table 4,5 .

Characterization of inclusion complexes

The prepared inclusion complexes are characterized by Scanning Electron Microscopy and PXRD.

Scanning Electron Microscopy (SEM)

The samples (Pure drug and inclusion complexes) were coated with a thin gold layer by sputter coater unit (SPI, Sputter, USA). Then, the SEM photographs were taken by a scanning electron microscope (Scanning electron microscope JSM-6390, Japan) operated at an accelerated voltage of 15kV. The results were shown in figure.5.

X- Ray diffraction of powder (XRD):

The powder crystallinity nature of the OLM and the OLM inclusion complexes were studied by using Bruker D8 Advance XRD with copper target instrument. The conditions were maintained at 40 Kv, with 40 MA current at room temperature. The scanning rate employed was 0.1 0 /sec over a range of 2θ values from 30 to 450.

Preparation of olmesartan medoxomil fast dissolving tablets from inclusion complexes

Fast dissolving tablets of OLM with taste masked inclusion complex (equivalent to 40mg of drug) were prepared by direct compression method. The superdisintegrants (Cross carmellose sodium) in varying concentration (10-15%) were used to develop the tablets. The weight of all the tablet formulations was maintained uniformly by using microcrystalline cellulose (p^H 102) as diluents and stevia as natural sweeting agent. The compositions of various tablet formulations were given in tables 2, 3. The materials were individually weighed, passed through sieve no: 80 and blended for 15 minutes by using double cone blender. The powder mixture was then lubricated with 1% magnesium stearate and directly compressed as tablets using 10 station rotary tablet compression machine to produce tablets weighing 300 mg. To minimize the processing variables all batches of tablets were compressed, under identical condition and were shown in the table 1..

Evaluation of Tablets

Physical parameters such as weight variation, hardness, friability, disintegration, wetting time, water absorption ratio were evaluated for prepared tablets and there results shown in table no.25-26. The prepared fast dissolving tablets were further evaluated for physical parameters like drug content, wetting time, water absorption ratio and for moisture uptake studies.

***In Vitro* Dissolution Studies**

Dissolution studies on each tablet formulation were performed in a calibrated 8 station dissolution test apparatus (LABINDIA) equipped with paddles (USP apparatus II method) employing 900 ml of 6.8 pH buffer as a dissolution medium. The paddles were operated at 50 rpm and temperature was maintained at 37º C ± 1º C throughout the experiment. The samples (10 ml) were withdrawn at 5, 10, 15, 20, 30 and 45 minutes and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples with drawn at various time intervals were suitably diluted with same dissolution medium and the amount of the drug dissolved was estimated by ELICO double beam U.V spectrophotometer at 256 nm. The dissolution studies on each formulation were conducted in triplicate. From the dissolution profiles various parameters were calculated. The dissolution profiles for all formulations were shown in figure 3 and 4 and were as the *in vitro* dissolution parameters were given in the table 4**.**

Accelerated stability Studies

The formulations which showed good invitro performance were subjected to accelerated stability studies. The tablet formulations subjected to accelerated stability studies at a temperature and relative humidity of 25 ± 2^0C, 60 ± 5% RH for 6 months and 40 ± 2^0C, 75 ± 5% RH for 3 months. Then the samples of each type of formulations were evaluated for the earlier mentioned physical parameters.

Evaluation of FDT for Mouth Feel

In order to evaluate the efficiency of stevia as a sweetener mouth fell test was carried out on the placebo tablets. The FDT placebo tablets were prepared containing stevia and three volunteers were asked to keep the FDT in mouth for few seconds and asked for mouth feel. The volunteers were suggested to give the ratings whether the tablets are pleasant, acceptable or unacceptable.

Results and Discussion

In the present investigation, Olmesartan medoxomil was selected as a drug candidate for developing inclusion complex formulations using HPβ-CDs by lyophillization and solvent evaporation methods. The prepared complexes were characterized by SEM and P-XRD analysis to understand the state of the complex. The SEM images of pure olmesartan drug was observed as irregular shaped crystals while the images of the prepared inclusion complexes were regular in shape with smooth and regular surface. The P-XRD patterns of pure OLM showed characteristic high diffraction peaks where as the diffraction patterns of complexes showed decrease in the peak intensity which is the indication of complex formation.

From the prepared inclusion complexes fast dissolving tablets were prepared by using superdisintegrants CS and SSG. The direct compression process was found to be suitable for compressing the tablet formulations as fast dissolving tablets. The compositions of OLM FDT were given in the table 1. Tablet formulations were further evaluated for physical parameters. All the tablet formulations were found to be stable were within the I.P specified limits for weight uniformity, friability, and drug content. Moisture uptake studies for orodispersible tablets were conducted to assess the stability of formulation. The results indicated that tablets containing high concentration of superdisintegrants get softened and absorb more atmospheric moisture.

Fast dissolving tablets of olmesartan were prepared by using superdisintegrants CS and SSG in different concentrations i.e., 10 and 15%. Tablet formulations were further evaluated for physical parameters. Moisture uptake studies for orodispersible tablets were conducted to assess the stability of formulation. The results of physical parameters evaluation were given in table 2 and 3.

The dissolution studies of orodispersible tablets were performed in pH 6.8 buffer by using USP-II paddle method. Based upon the data obtained from the dissolution studies, various parameters such as T_{50}, DE_{30}% and first order and zero order release rate constants were estimated. The drug release from all the tablet formulations were found to release the drug at a faster rate than compared to pure drug and other formulations containing SSG as disintegrant. The drug release of tablet formulations containing complexes prepared by lyophillization method in the presence of superdisintegrant CS was found to be faster when compared with the other formulations which was due to porous and pluffy formation of complexes by lyophilization. The rate of drug release of tablet formulations was found to be linear with first order rate constant. The r^2 values of all tablet formulations were in the range of 0.92 to 0.99. The dissolution profiles for all formulations were shown in figure 3 and 4 and were as the *in vitro* dissolution parameters were given in the table 4**.**

The optimized tablet formulations subjected to accelerated stability studies preparation and stored in thermo stated oven at a temperature and relative humidity of 25 ± 2^0C, 60 ± 5% RH for 6 months and 40 ± 2^0C, 75 ± 5% RH for 3 months. Then the samples of each formulation were evaluated for the earlier mentioned physical parameters and all the results were found to be ideal without any major deviations.

From the mouth feel evaluation studies it was reported that the formulations containing stevia as sweetener are quite acceptable with a pleasant taste. From these studies it may be suggested that the use of natural sweeteners as an alternatives to artificial sweeteners is a best alternative in the formulation of FDT.

Conclusion

The present study has shown that it is possible to increase the solubility and dissolution rate of poorly soluble drug olmesartan medoxomil by preparing it

as inclusion complexes with HP β-cyclodextrins. The inclusion complexes exhibited faster dissolution characteristics as compared to that of pure drug. This was due to solubilizing effect of the complexing agent .It was found that the inclusion complex prepared by the lyophillization method released the drug rapidly than the pure drug and other formulations prepared by solvent evaporation method.

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Conflict of Interest Declaration

The author(s) declare that they have no competing interests.

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Table: 1 Composition of OLM FDT

Ingredients (mg/Tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Drug+HPβ CD complex (eq 40mg) **L**	150.4	150.4	150.4	150.4	-	-	-	-
Drug+HPβ CD complex (eq 40mg) **S.E**	-	-	-	-	150.4	150.4	150.4	150.4
Calcium Silicate	30	45	-	-	30	45	-	-
Sodium Starch Glycolate	-	-	30	45	-	-	30	45
Mannitol	30	30	30	30	30	30	30	30
Avicel p^H 102	86.6	71.6	86.6	86.6	71.6	86.6	71.6	86.6
Stevia	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total wt (mg)	300	300	300	300	300	300	300	300

L : Complexes Prepared by Lyophillization Method
S.E: Complexes Prepared by Solvent Evaporation Method

Figure 1 (b): SEM Photograph of Olmesartan Medoxomil

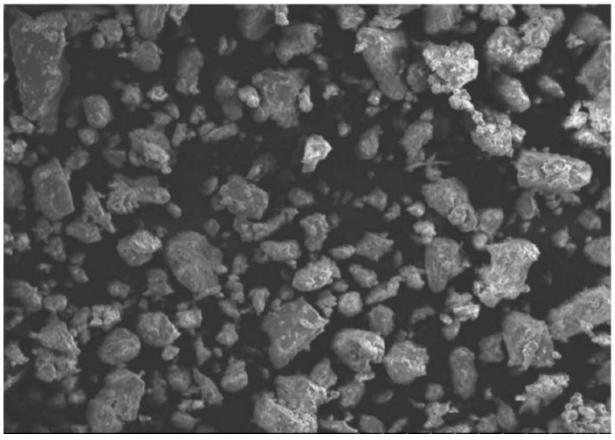


Figure 1 (b): SEM Photograph of Inclusion Complex (Lyophilization)

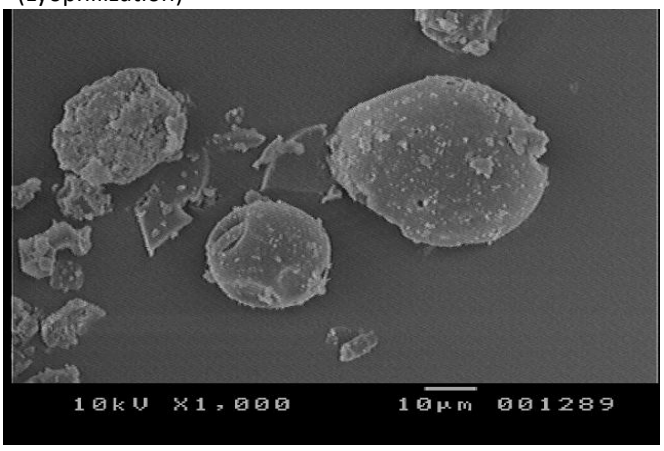
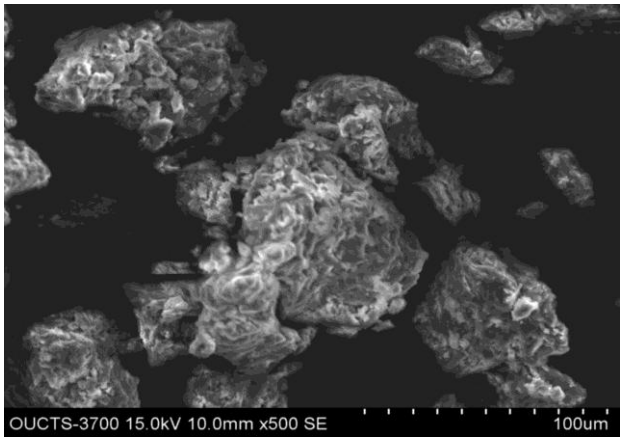


Figure 1(c): SEM Photograph of Inclusion Complex (solvent evaporation method)



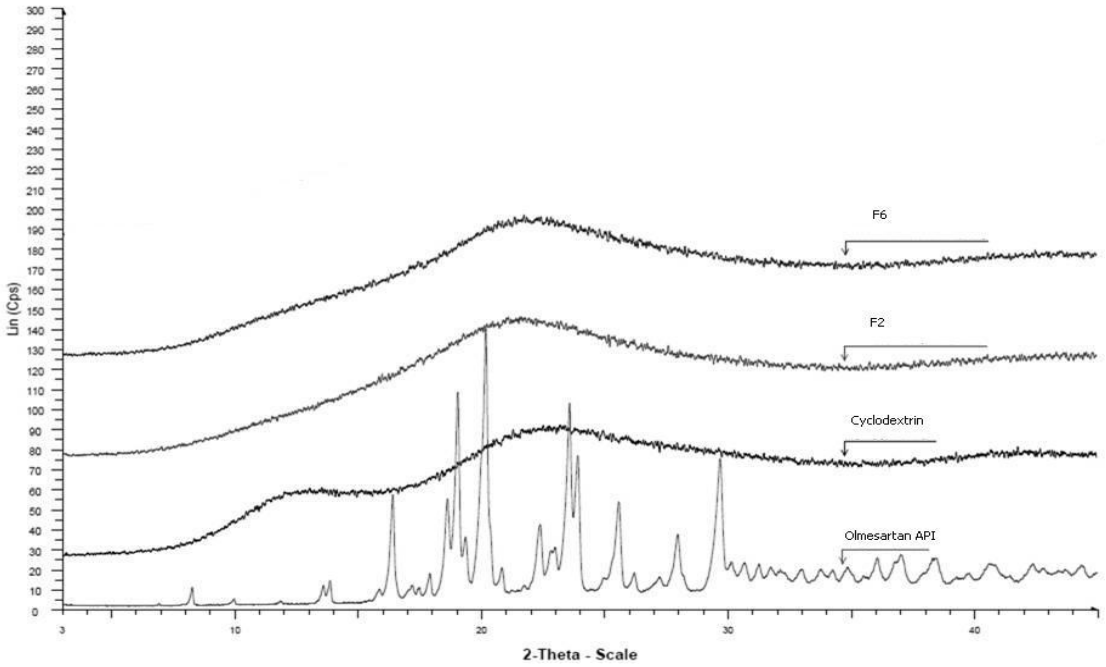


Figure 2: XRD Images of OLM Pure Drug and Optimized Formulations

S.NO	Tablet Formulation	Weight uniformity (mg/tablet)	Friability loss (%)	Hardness (kg/cm^2)	Drug content* (mg)
1	F1	300±2	0.55	3.5±0.5	40±0.5
2	F2	300±2	0.62	3.5±0.5	39±0.5
3	F3	299±2	0.76	3.5±0.5	39±0.5
4	F4	300±2	0.55	3.4±0.5	39±0.5
5	F5	300±1	0.65	3.4±0.5	40±0.5
6	F6	298±2	0.80	3.4±0.5	40±0.5
7	F7	301±2	0.70	3.4±0.5	39±0.5
8	F8	301±2	0.60	3.4±0.5	40±0.5

Table 2: Physical Parameters of OLM FDT

S.NO	Tablet Formulations	Wetting time (seconds)	Water absorption ratio	*In Vitro* Disintegration time (seconds)	Moisture Uptake (%)
1	F1	28±2	78.4	18±5	4.6±1.4
2	F2	32±3	84.0	15±3	5.7±1.8
3	F3	26±5	72.8	22±3	3.8±2.0
4	F4	28±3	76.8	20±4	4.2±1.6
5	F5	24±3	71.8	24±4	4.6±1.4
6	F6	27±3	77.2	21±2	4.9±2.0
7	F7	22±3	68.2	22±2	4.9±2.0
8	F8	25±3	74.2	25±2	4.9±2.0

Table 3: Evaluation Parameters of OLM FDT.

S.NO	Tablet Formulations	T_{50} %	DE_{30} %	Zero order		First order		Hixson Crowell	
				R^2	K (mg/min)	R^2	K (min^1)	R^2	K ($mg^{1/3}$)
1	F1	6	66.6	0.558	2.001	0.956	0.110	0.774	0.014
2	F2	2	73.3	0.463	2.011	0.989	0.140	0.713	0.010
3	F3	8	55	0.594	1.896	0.963	0.082	0.886	0.019
4	F4	4	61.6	0.587	1.674	0.977	0.091	0.829	0.016
5	F5	8	53.3	0.678	2.014	0.988	0.076	0.844	0.018
6	F6	6	58.3	0.549	2.011	0.984	0.082	0.815	0.017
7	F7	10	58.3	0.441	1.981	0.986	0.072	0.815	0.017
8	F8	8	58.3	0.447	1.920	0.988	0.062	0.815	0.017

Table 4: *In Vitro*** Dissolution Parameters of OLM FDT

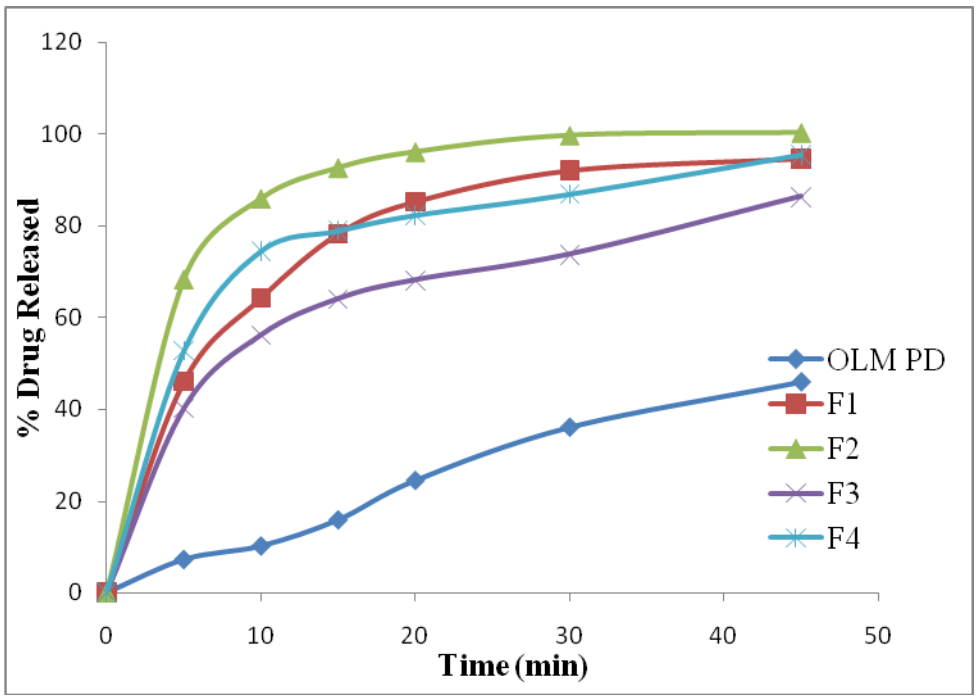


Figure 3: Drug Release Profiles OLM - FDTs

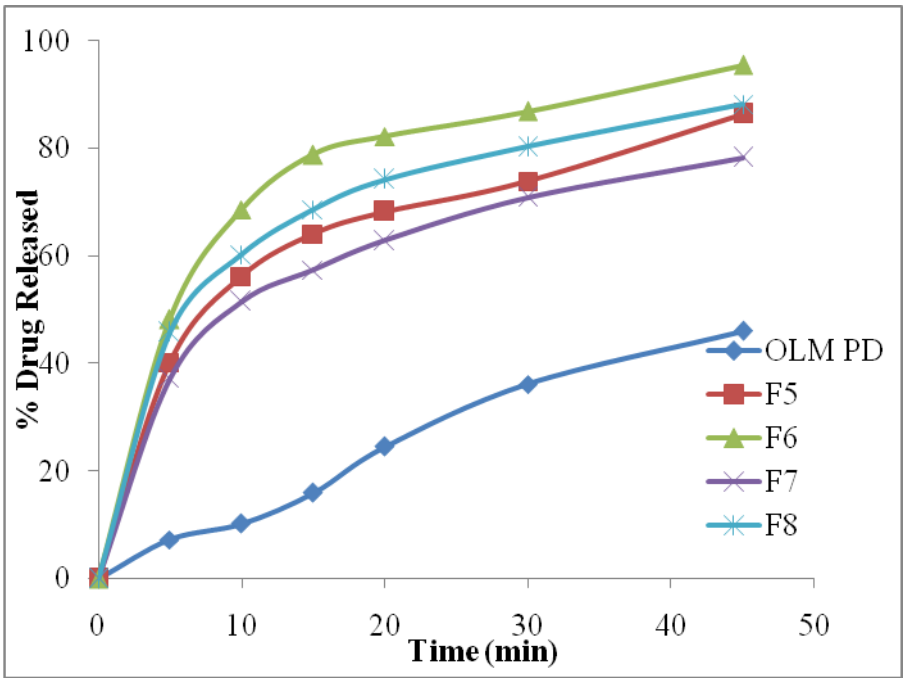


Figure 4: Drug Release Profiles of OLM - FDTs