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FORMULATION AND EVALUATION OF ORMELOXIFENE FAST DISSOLVING TABLETS

Abdul Hasan Sathali. A*, Ramanathan. M

Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai- 625 020, Tamil Nadu, India

ABSTRACT

The objectives of the present work were to enhancedissolution and solubility of slightly water soluble ormeloxifene hydrochloride and formulate fast dissolving tablets. The research work was two-phase process; the first phase was to enhance the solubility and dissolution of ormeloxifene. For this object drug was processed with different solid dispersion techniques like kneading, co precipitation, melting and solvent evaporation technique with β-cyclodextrin and PEG 6000 carrier. The second phase approach was, to formulate as fast dissolving tablet by using the resulted solid dispersion product by direct compression method by using various superdisintagrents. Solid dispersion mixtures were characterized by differential scanning calorimetry, x-ray diffraction studies, and Fourier transform infrared spectroscopy. The solubility and dissolution rate of Ormeloxifene HCl was remarkably increased in the above methods. It was concluded that, Kneading method has produce best increase in solubility and dissolution for Ormeloxifene then other methods. The overall results showed that ormeloxifene fast dissolving tablet formula (F8) using crospovidone ,croscarmillose sodium and sodium starch glycolate (combined superdisintegrants) showed shortest disintegration time, superior drug release profile, high water absorption ratio. In addition the selected formulation had an acceptable hardness and friability and stability,so it was concluded that combined superdisintegrant formula with mannitol diluent was more opt to make Ormeloxifene fast dissolving tablet.

Keywords: *Ormeloxifene, superdisintegrants, kneading, dissolution, disintegration time and solid dispersion.*

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***Address for Correspondence**

Abdul Hasan Sathali. A, Professor and Head, Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai- 625 020, Tamil Nadu, India

INTRODUCTION

Fast dissolving tablet form is very popular because of ease of self-administration, compact in nature, easy to manufacture and it can be delivered in accurate dose. Some drugs having poor bioavailability due to poor aqueous solubility and thus results slow dissolution rate in the biological fluids. Dissolution is rate limiting step for oral bioavailability of products. Solubility is the major challenges in pharmaceutical tablet formulations; all drugs must possess some degree of aqueous solubility. For pharmacological response solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation. Poorly water-soluble drug candidates often emerge from contemporary drug discovery programme[1]

Solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. There are many techniques which are used to enhance the aqueous solubility. The ability to increase aqueous solubility can thus be a valuable aid to increase efficiency and reduce side effects for certain drugs. Therapeutic effectiveness of a drug depends upon the bioavailability and solubility. Due to advanced research &development, there are varieties of new drugs and their derivatives are available, but most of the drug candidates fail to reach market due to poor bioavailability, even though these drugs might exhibit potential pharmacodynamic activities. The basic aim of the further formulation and development section is to make that drug available at proper site of action within optimum dose.

Fast dissolving tablets are those, when put on tongue, disintegrate rapidly releasing the drug which dissolve or disperses in the saliva. The faster the drug dissolves into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly

greater than those observed from conventional tablets dosage form. The European pharmacopoeia adopted the term "Orodispersible tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. According to European pharmacopoeia, the ODT should disperse/disintegrate in less than 3minutes.[2]

Ormeloxifene hydrochloride indicated for emergency contraceptive and dysfunctional uterine bleeding, making fast dissolving tablet is most opt for these indications. The basic approach in the development of fast dissolving tablet by use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate, polyvinyl pyrollidone etc, which provide instantaneous disintegration of tablet after putting on tongue, there by release the drug in saliva.

MATERIALS AND METHODS

Ormeloxifene hydrochloride was obtained as a gift sample from HLL Life care Ltd, Belgaum, (KA). Crospovidone, Croscarmellose sodium, sodium starch glycolate and Micro Crystalline Cellulose was obtained from High Purity Laboratory Chemicals Pvt Ltd, Mumbai. β-cyclodextrin was obtained from Hi Media Laboratories Pvt Ltd, Mumbai. PEG 6000was obtained from S.D Fine Chemicals Ltd, Mumbai. All other chemicals used were of analytical grade and were used without further purification.

Determination of λ max for ormeloxifene in distilled water and phosphate buffer pH (6.8)

Ormeloxifene hydrochloride solution 10 µg/ml in distilled water and phosphate buffer pH 6.8 solutions are prepared, then scanned by a UV spectrophotometer at wavelengths ranging from 400nm to 200nm, the λmax for solution was determined.[3]

Calibration of ormeloxifene in distilled water and phosphate buffer pH (6.8)

An accurately weighed quantity (100mg) of pure drug Ormeloxifene HCl was dissolved in sufficient amount of methanol and made up to 100ml with Distilled water and phosphate buffer pH 6.8 respectively to produce 1mg/ml solution. From this 10ml of the solution is pipette-out and made up to 100ml with distilled water and phosphate buffer pH 6.8 respectively. From this 5 to 25ml ispipette-out and diluted to 100ml with distilled water and phosphate buffer pH 6.8 respectively. The solutions are scan within the range of 200nm-400nm in UV-Spectrophotometer. The absorbance of the solutions was measured at 278nm by using UV spectrophotometer and distilled water and phosphate buffer pH 6.8 was used as blank solution respectively. The calibration graph is drawn by taking concentration in X-axis and respective absorbance in Y-axis to get a straight line as per Beers law.

COMPATIBILITY STUDIES FOR DRUG AND EXCIPIENTS

Compatibility studies were carried out to check the interactions between the drug and excipients. This information was needed for selection of excipients with the drug for the formulation of solid dispersion. Infrared spectrophotometry and Differential scanning calorimetry studies are the two techniques used to check the compatibility studies between drug and polymers.

Fourier Transform-Infra Red (FT-IR) Studies

Ormeloxifene hydrochloride and β-cyclodextrin, ormeloxifene hydrochloride and PEG-6000 are subjected to Fourier Transform Infra-Red Spectroscopy studies (Shimadzu, Japan).Samples are prepared using KBr disc method and spectra are recorded over the range 600-4500 per cm. Spectra are analyzed for drug-carrier interaction and functional groups involved in the complexation process.[4]

Differential Scanning Colorimetric (DSC) studies:

The possibility of drug and carrier / polymer interaction was investigated by Differential scanning calorimetry (DSC 200 TA Instruments, USA). The DSC thermograms of pure drug and the polymers were recorded to study the interactions between drug and polymers. The samples were separately sealed in aluminium cells and set in a thermal analyzer.[5]The thermal analysis was performed at a scanning rate of 10^0C per minute over a temperature range of 50^0-200^0.

FORMULATION AND EVALUATION OF SOLID DISPERSIONS

Solid dispersion of Ormeloxifene hydrochloride is prepared by following methods

Kneading method

Melting method

Co precipitation method

Solvent evaporation method

Kneading method

β-cyclodextrin was placed as per formula ratio in a mortar, a small quantity of methanol was added to it while triturating to get slurry like consistency. Then the drug was slowly incorporated into the slurry and trituration was further continued for one hour. Slurry was then air dried at 25°C for 24 hours, pulverized, passed through sieve and stored in desiccators over fused silica gel[5].

Melting method

The carriers PEG 6000 were taken in a china dish and heated upto 60ºC in a water bath, until the mixture melts completely. The drug (Ormeloxifene hydrochloride) was added to the molten carrier and mixed thoroughly. The dispersion is cooled to ambient condition. Solidified mass was crushed, pulverized and passed through sieve and stored in desiccators[5].

Co precipitation method

As per the formula ratio the carrier ß-cyclodextrin 20% w/w solution was prepared purified water at 75°C.An appropriate molar ratio of drug (ormeloxifene hydrochloride) was added to the solution, which was cooled down to room temperature while continuously stirring and shaking. During the cooling, the solid drug ß-cyclodextrin complex precipitated.[7]

Solvent evaporation method

Ormeloxifene and the carrier (PEG – 6000) as per the ratio of 1:1, 1:2, 1:3, and 1:4 were dissolved in a minimum amount of methanol. The solvent was removed by evaporation at the temperature 40°C for 1hour.

resulting residue was dried for 2 hour and stored overnight in desiccators. After drying the residue was ground in a mortar and sieved through a mesh. The resultant solid dispersions were stored in desiccators until further investigation8. All solid dispersion technique formula was shown in table.1.The

Table 1. Solid dispersion formula

S. No	F. Code	Method	Ratio	Composition
1	K1	Kneading	1:1	Drug : BCD
2	K2	Kneading	1:2	Drug : BCD
3	K3	Kneading	1:3	Drug : BCD
4	K4	Kneading	1:4	Drug : BCD
5	M1	Melting	1:1	Drug : PEG 6000
6	M2	Melting	1:2	Drug : PEG 6000
7	M3	Melting	1:3	Drug : PEG 6000
8	M4	Melting.	1:4	Drug : PEG 6000
9	C1	Co precipitation	1:1	Drug : BCD
10	C2	Co precipitation	1:2	Drug : BCD
11	C3	Co precipitation	1:3	Drug : BCD
12	C4	Co precipitation	1:4	Drug : BCD
13	S1	Solvent evaporation	1:1	Drug : PEG 6000
14	S2	Solvent evaporation	1:2	Drug : PEG 6000
15	S3	Solvent evaporation	1:3	Drug : PEG 6000
16	S4	Solvent evaporation	1:4	Drug : PEG 6000

Estimation of percentage yield

Percentage yield is calculated to know about percent yield or efficiency of any method, thus it helps in selection of appropriate method of production. Solid dispersions are collected and weighed to determined practical yield from the following formula[9].

$$\text{Percentage Yield} = \frac{\text{Practical mass (solid dispersion)}}{\text{Theoretical mass (drug + carrier)}}$$

Determination of Drug Content

The pure drug and solid dispersions equivalent to 10mg of Ormeloxifene hydrochloride are weighed accurately and dissolved in methanol. The solution is filtered, diluted suitably with distilled water and drug content is analyzed by UV –Spectrophotometer[5,8].

***In vitro* Dissolution Studies**

Invitro dissolution studies of pure drug Ormeloxifene hydrochloride, and solid dispersions (SDs) are performed by using dissolution test apparatus (USP type II) at the paddle rotation speed of 50 rpm in 900ml of distilled water and temperature was maintained at 37°C ± 0.5°C. Samples equivalent to 10mg of Ormeloxifene solid dispersion product was filled in hard gelatin capsules for dissolution studies. Samples were collected at regular interval of time (10, 20, 30, 40, 50, 60 minutes). The absorbance of the samples was measured at 278 nm after suitable dilution using appropriate blank**.** The dissolution experiments were conducted in triplicate[13].

Powder X Ray Diffraction Studies (PXRD)

Powder x-ray diffraction patterns (XRD) of the pure drug, and solid dispersion was recorded with an x-ray diffractometer (XD, Shimadzu, Japan) using copper as x-ray target, a voltage of 40 KV, a current of 30mA and within1.5404 angstrom wavelength.. The diffraction patterns were run at 2.4 degree / min over the 2θ range of 2-50 degree[5].

Solubility Studies

Solubility study was assessed out according to the method of Higuchi and Cannors. The solubility of ormeloxifene pure drug, and solid dispersion were determined in distilled water and phosphate buffer pH 6.8. Samples are equivalent to 10mg of drug was taken and to this 10ml of respective medium was being added in 250ml conical flask, and shaken for 24 hours at room temperature on Rotary Flask Shaker. The entire samples are protected from light by wrapping the flask by aluminum foil. After 24 hours samples were filtered through whatman filter paper and aliquots were suitably diluted and assayed by spectrophotometrically[5].

Preformulation study for Fast dissolving tablets

Fourier Transform-Infra Red (FT-IR) Studies

Spectra were analyzed for drug-carrier interaction and functional groups involved in the complexation process[4].

Angle of Repose

The friction forces in a loose powder can be measured by the angle of repose (θ) by funnel method. It is an indicative of the flow properties of the powder[2].

Bulk Density

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 was called the bulk volume. From this the bulk density was calculated[2].

Tapped Density

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 should be less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume should be noted. Tapping was continued until the difference between successive volumes is less than 2 % in a bulk density apparatus[2].

Percentage of compressibility (or)Carr's index

It indicates powder flow properties. It is expressed in percentage. It should be below 16% which indicates a powder having good flow property.

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow[2]. Lower hausner ratio (<1.25) indicates better flow properties than higher ones.

Precompression drug Content

10mg equivalent of Ormeloxifene solid dispersion drug complex was dissolved in sufficient amount of methanol and made up to 100ml of phosphate buffer pH 6.8. From this solution 10ml was pipette out into 100ml volumetric standard flask and volume was made to 100ml with buffer. The absorbance of the solution was measured at 278nm using buffer as blank and the content of ormeloxifene was estimated[10].

Formulation of ormeloxifene fast dissolving tablets

An accurately weighed quantity (equivalent to 30 mg ormeloxifene) of solid dispersion complex was mixed with superdisintegrant (Sodium starch glycolate, Crospovidone, Croscarmellose Sodium), microcrystalline cellulose, PVP K-30 and Mannitol, in geometrical dilution method as per formula in the table 2(a) and 2(b). Then Magnesium streate and Talc are added, mixed thoroughly and compressed into tablets by using single punching tablet machine to produce flat faced tablets. The average tablet weight is 250mg, with 8mm diameter[11]. Ormeloxifene fast dissolving tablet formula was shown in table 2(a &b).

Table 2(a): Ormeloxifene FDT formula

Ingredients [mg]	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10
Ormeloxifene SD complex Eq. to 30mg	150	150	150	150	150	150	150	150	150	150
MCC	-	-	-	25	25	25	-	-	25	-
SSG	12.5	25	37.5	12.5	25	37.5	12.5	12.5	12.5	-
Croscarmellose	-	-	-	-	-	-	12.5	12.5	12.5	12.5
Crospovidone	-	-	-	-	-	-	-	12.5	12.5	-
PVP K-30	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mannitol	75	62.5	50	50	37.5	25	62.5	50	25	75

Table 2 (b) Ormeloxifene FDT formula

Ingredients [mg]	F 11	F 12	F13	F 14	F 15	F 16	F 17	F 18	F 19	F 20
Ormeloxifene SD	150	150	150	150	150	150	150	150	150	150
MCC	-	-	25	25	25	25	25	-	-	-
SSG	-	-	-	-	-	12.5	-	-	-	-
Croscarmellose	25	37.5	12.5	25	37.5	12.5	12.5	-	-	-
Crospovidone	-	-	-	-	-	-	12.5	12.5	25	37.5
PVP K-30	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mannitol	126	100	100	75	50	75	75	150	125	100

Post compression evaluation of fast dissolving tablet

Thickness and diameter

Tablet thickness and diameter can be measured using a simple procedure. Five tablets were taken and their thickness and diameter was measured using Vernier calipers[12].

Hardness

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in

formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time[2]. Hardness was measured by hardness tester.

Weight variation test

20 tablets were selected randomly from the lot and weighted individually to check for weight variation[2].

Friability test

Friability of the tablet was determined by 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. Preweighted 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[2].

Uniformity of drug content

Twenty tablets of each formulation were weighed and crushed in mortar and the powder equivalent to 10mg of Ormeloxefine hydrochloride was weighed and dissolved in methanol, the volume was made up to 100ml with pH 6.8 phosphate buffer. From the stock solution 1ml sample was withdrawn and diluted to 10ml with pH 6.8 phosphate buffer, The absorbance was measured at wavelength 278nm using UV-Visible spectrophotometer[12].

***Invitro* drug release studies**

Dissolution studies of all tablets were performed using dissolution tester (Paddle type, LABINDIA 2000, India). Tablets were added to the 900 ml of Phosphate buffer pH 6.8 at 37°C ± 0.5°C, which was stirred with a rotating paddle at 50 rpm. 5ml samples were withdrawn at the time interval of 5, 10, 15, 20, 25, 30, 40, 50, and 60minutes, by the same time equal volume of fresh medium was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test. Assay carried out using UV spectrophotometer[13] (Shimdzu 1700UV-Visible Spectrophotometer, Japan) at 278nm.

Solubility studies[5]

Solubility study was assessed out according to the method of Higuchi and Connors. The solubility of Ormeloxifenepure drug and fast dissolving tablets are determined in distilled water and phosphate buffer pH 6.8. Samples equivalent to 10 mg of drug was taken and to this 10 ml of respective medium was being added in 250 ml conical flask, and shaken for 24 hours at room temperature on rotary flask shaker (Secor, India). The entire samples are protected from light by wrapping the flask by aluminum foil. After 24 hours samples are filtered through whatmann filter paper No. 42 and aliquots are suitably diluted and assayed by spectrophotometer at 278 nm.

Disintegration time

The test was carried out on 6 tablets using the apparatus specified in IP 2010 distilled water at 37°C±2°C was used as a disintegration medium and the time in seconds taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in second[14].

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed[2].

Wetting Time

Five circular tissue papers of 10 cm diameter were placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin (water-soluble dye) was added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time[2].

Stability study (Temperature Dependent)

The fast dissolving tablet stored under following conditions for a period prescribed by ICH guidelines for accelerated studies. $40^0 \pm 2^0$ C, &RH 75 %± 5 %. The tablets were withdrawn a specified period and analysed for physical characterization such as visual defects, hardness, Friability, disintegration and Dissolution etc[14,16].

RESULTS AND DISCUSSION

FT-IR studies for Solid dispersion:

FT-IR spectrum of the pure drug, PEG 6000, Betacyclodextrin and physical mixtures was recorded, it was shown inFigure-1a,b&c Pure Ormeloxifene hydrochloride spectra showed sharp characteristic peaks at 1619.29, 1507.42, 1157.33, and 608.55 cm^{-1}.All the above characteristic peaks appear in the IR spectrum of physical mixtures indicates that there is no modification or interaction between drug and carriers.

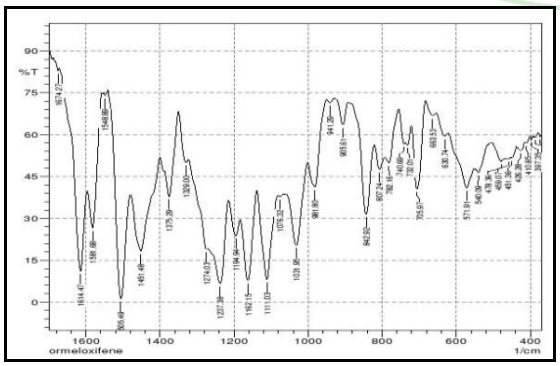


Fig 1 (a) FT-IR of ormeloxifene

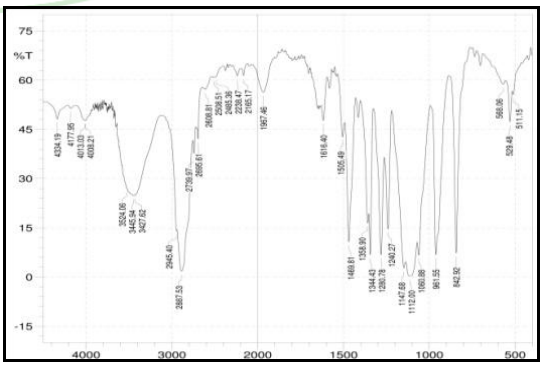


Fig 1(b) FT-IR of ormeloxifene andPEG-6000

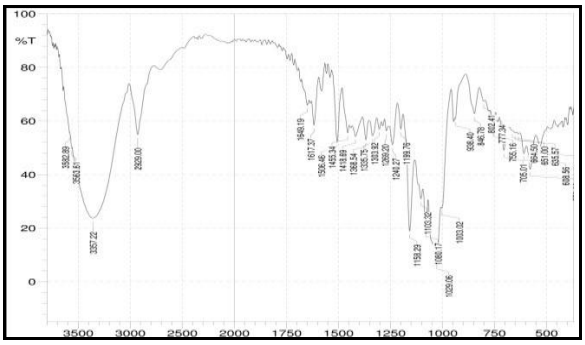


Fig 1(c) FT-IR of ormeloxifene and BCD

Percentage Yield

The percentage yield of solid dispersions ranged from 83.6%-96.88% which indicates that there is no considerable loss in the yield during the physical mixing process The percentage yield of the solid dispersion M3 was found to be high (96.88%) as compared to the other formulations. It is shown in table.3

Drug Content

The drug content of the prepared solid dispersions was found to be in the range of 86.39 % to 95.40% which indicated the uniform distribution of drug in the formulation**.** The results shown in table 3

Table 3: Percentage of yield and drug content

Sl.No	F. Code	Method	% of yield	Drug content
1	K1	Kneading	83.60 ± 1.07	87.01 ± 2.94
2	K2	Kneading	88.33 ± 2.02	88.67 ± 1.89
3	K3	Kneading	85.19 ± 1.75	89.70 ± 1.39
4	K4	Kneading	96.60 ± 0.77	86.54 ± 4.61
5	M1	Melting	91.72 ± 1.79	93.26 ± 1.39
6	M2	Melting	95.35 ± 1.60	94.17 ± 0.52
7	M3	Melting	96.88 ± 0.31	95.40 ± 1.58
8	M4	Melting	91.44 ± 1.81	86.04 ± 2.02
9	C1	Co precipitation	87.45 ± 2.09	86.30 ± 0.81
10	C2	Co precipitation	90.08 ± 0.61	86.39 ± 1.83
11	C3	Co precipitation	92.72 ± 1.93	88.37 ± 1.39
12	C4	Co precipitation	94.82 ± 1.02	88.75 ± 2.92
13	S1	Solvent evaporation	90.05± 1.58	87.08 ± 0.59
14	S2	Solvent evaporation	93.97± 1.68	89.30 ± 1.53
15	S3	Solvent evaporation	94.93 ± 1.40	91.74 ± 0.92
16	S4	Solvent evaporation	88.90 ± 0.56	85.65 ± 1.77

* SEM 3

***In vitro* Dissolution Studies:**

The cumulative percentage of pure drug (Ormeloxifene hydrochloride) release, at the end of one hour was found to be 40.90%.In kneading method the release profile were found to be 55.09% (K1), 68.59%(K2), 75.97%(K3) and91.77 %(K4) after 1 hour. In Melting method the release profile were found to be 42.18 % (M1), 44.32 % (M2), 56.90 % (M3) and 63.45 % (M4) after 1 hour**.** In the Co-precipitation method the release profile were found to be 46.09 % (C1), 55.56 % (C2), 66.66 % (C3) and 81.75 % (C4) after 1 hour. In Solvent evaporation method the release profiles was found to be 46.10% (S1), 49.67 % (S2), 54.20% (S3) and 70.57 %(S4) after 1 hour. The results are shown in figure 2(a, b, c &d). From the overall release profile results it was observed that the formulation K-4 (1:4 ratio) is higher than other formulations**.**

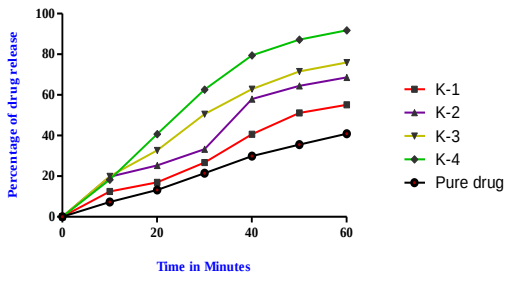


Fig 2(a) Dissolution study-Kneadin

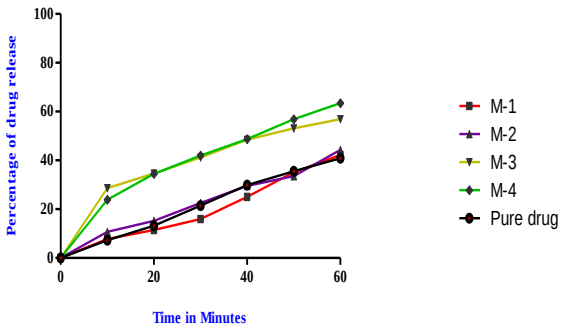
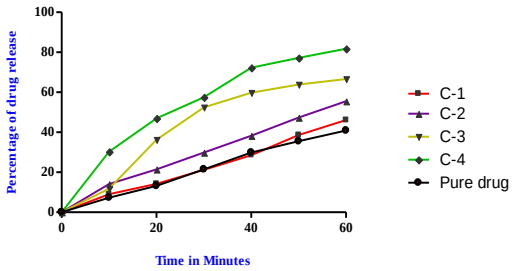


Fig 2(b) Dissolution study - Melting



2(c) Dissolution study-Co precipitation

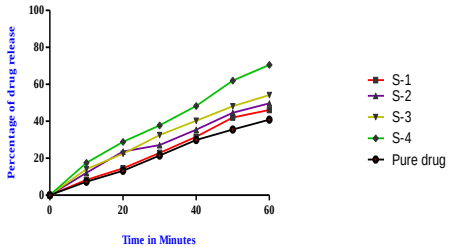


Fig 2(D) Dissolution study-Solvent evaporation

Best formulation:

The best formulation was selected based on the results obtained from the drug *invitro* release studies. From the result it was observed that, kneading method using beta cyclodextrin carrier was found to have greater dissolution rate of 91.77% (K-4) after 1hour, so it was considered as best formulation. The order of drug release profile is

Pure drug < Physical mixture <Solid dispersion

The drug dissolution was increase in both, physical mixtures and solid dispersion product. It happens because of the enhanced wettability, hydrophilic nature of the carriers and possibility of reduced crystallinity of the drug and conversion of amorphous form of the drug.

Powder X Ray Diffraction Studies (PXRD):

The XRPD patterns of pure drug (Ormeloxifene) and kneading mixture (K-4) was confirmed that the characteristic peaks were not preserved that indicated the crystalline state was changed, it is shown in figure 3a&b

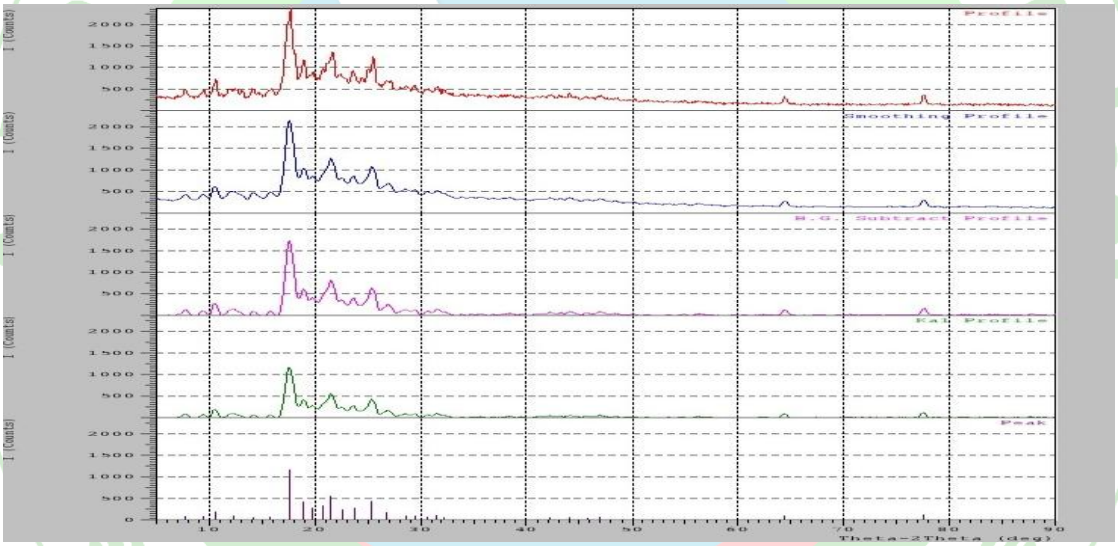


Fig 3(a) XPRD- Ormeloxifene

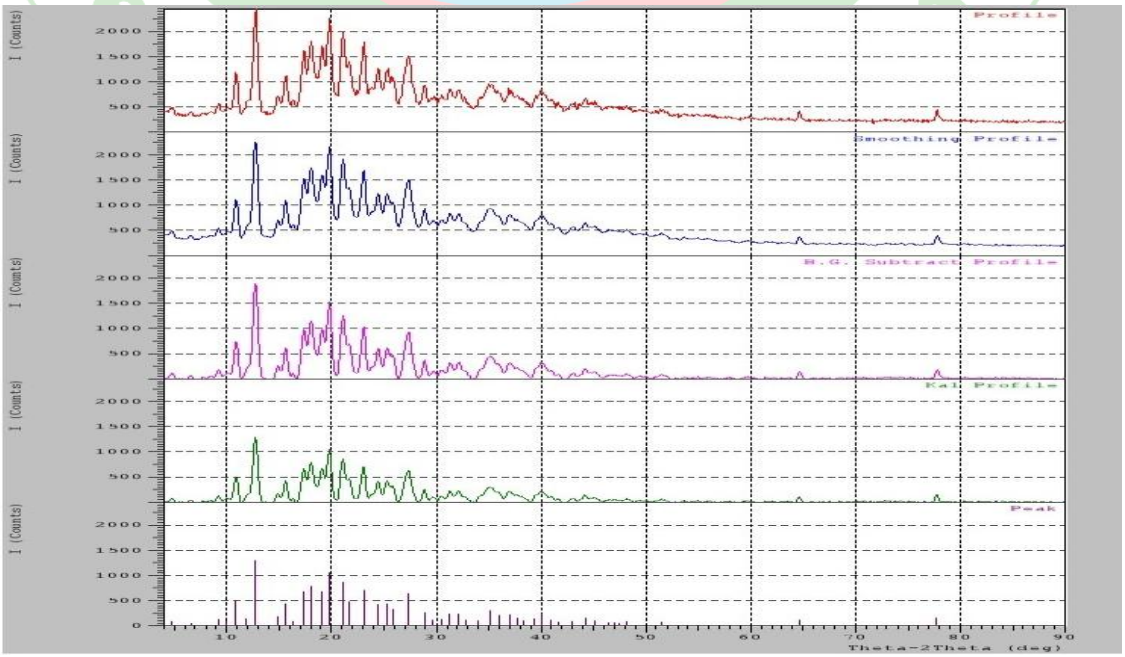


Fig 3(b) XPRD-Solid dispersion product (K-4)

Differential Scanning Calorimetric (DSC) Studies:

An endothermic peak corresponding to the melting point of pure drug was prominent in best formulation. Which suggested clearly that there was no interaction between the drug and the polymers and the drug was existed in its unchanged form. It is shown in figure 4(a) & 4(b)

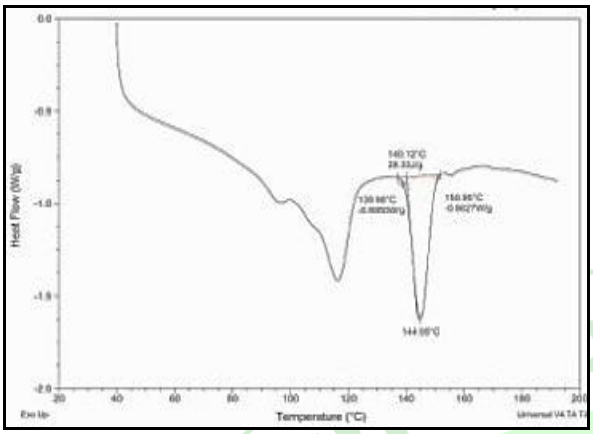


Fig 4 (a): DSC-Ormeloxifene

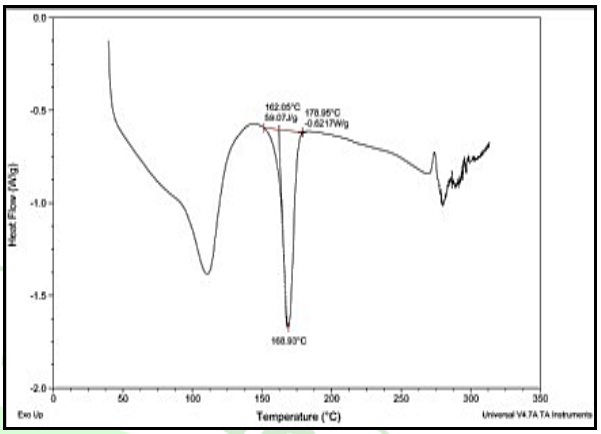


Fig 4 (b): DSC-Solid dispersion product (K-4)

Solubility Studies of Solid Dispersions:

It was observed that the solid dispersion product (K-4) showed high solubility in water (0.556mg/ml) and phosphate buffer pH 6.8 (0.603mg/ml) as compared to pure drug solubility in water (0.266 mg/ml) and phosphate buffer pH 6.8 (0.3 mg/ml) it was shown in figure 5. It clearly indicate the enhancement of solubility

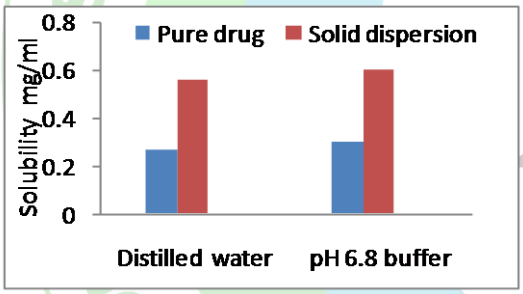


Fig 5. Solubility study

Preformulation studies for fast dissolving tablet formulation

Fourier Transform Infrared Spectroscopic studies:

IR Spectrum of the best formulation (K4) and SSG, CCS, CP, PVP K30, MCC was recorded. The pure Ormeloxifene spectra showed sharp characteristic peaks at, 1619.29, 1507.42, 1157.33, and608.55 cm^{-1}. All the above characteristic peaks appear in the IR spectrum which indicates that there was no interaction between drug and carriers.It was shown in figure 6

Angle of Repose:

The angle of repose of all the formulations ranged from 20˚.88' to 29˚.16'.The results indicated that all the formulations exhibited good flow properties. The results of angle of repose for all the formulations were shown in table 4.

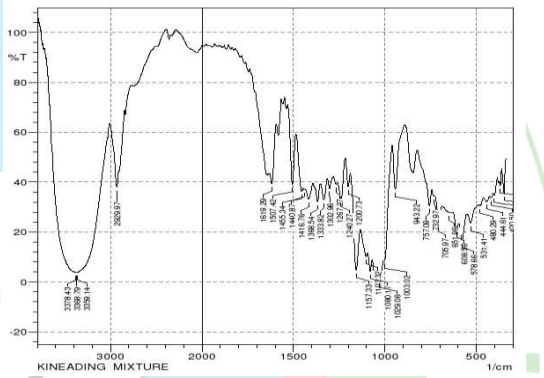


Fig. 6: FT-IR of Ormeloxifene (K4), SSG, CCS, CP, PVP K30 and MCC

Bulk density:

The bulk density of all the formulations was in the range of 1.16 to 1.25g/cm^3.The values of bulk density showed that the blend was not tightly packed and indicated good flow properties. The results of bulk density for all the formulations were shown in table 4.

Tapped Density:

The tapped density of all the formulations were in the range of 1.34 to 1.48 g/cm^3.The results indicated that the blends of all the formulation had good flow properties. The results of tapped density for all the formulations were shown in table 4.

Carr's Compressibility Index:

The compressibility index of all the formulations ranged from 11.34 to 15.8 %.This value below 16% it indicated the powder having good flow property and good propensity of compression. The results of compressibility for all formulations were shown in table 4.

Hausner's Ratio:

The Hausner's ratio of all the formulations ranged from 1.15 to 1.19. It was less than 1.25 indicated better flow property of blend. The results of Hausner's ratio for all the formulations were shown in table 4.

Table 4. Preformulation study for Ormeloxifene fast dissolving tablets

F-Code	Angle of repose	Bulk Density	Tapped Density	% of Compressibility	Hausner ratio
F-1	24.54 ± 1.84	1.23 ± 0.02	1.45 ± 0.02	14.87 ± 2.85	1.17± 0.03
F-2	25.68 ± 1.66	1.25 ±0.04	1.48 ± 0.02	17.51 ± 0.26	1.19 ± 0.02
F-3	23.09 ± 0.22	1.19 ± 0.01	1.39 ± 0.02	14.08 ± 1.96	1.15 ± 0.03
F-4	24.15 ± 2.30	1.22 ± 0.01	1.41 ± 0.02	13.02 ± 1.53	1.14 ± 0.02
F-5	20.95 ± 0.94	1.17 ± 0.01	1.36 ± 0.01	13.96 ± 0.17	1.15 ± 0.05
F-6	28.64 ± 0.43	1.23 ± 0.02	1.45 ± 0.02	14.90± 0.10	1.17 ±0.04
F-7	29.85 ± 0.71	1.22 ± 0.01	1.38 ± 0.00	11.34 ± 1.66	1.12 ± 0.02
F-8	20.95 ± 0.85	1.19 ± 0.01	1.39 ± 0.02	14.08 ± 1.96	1.16 ± 0.02
F-9	22.55 ± 3.50	1.17 ± 0.01	1.34 ± 0.05	15.21 ± 1.25	1.17 ± 0.01
F-10	29.16 ± 2.73	1.18 ± 0.01	1.36 ± 0.01	13.22 ± 1.20	1.14 ± 0.01
F-11	23.14 ± 0.60	1.19 ± 0.01	1.40 ± 0.02	15.17 ± 1.67	1.17 ± 0.02
F-12	21.64 ± 1.91	1.18 ± 0.01	1.37 ± 0.01	13.85 ± 2.04	1.15 ± 0.02
F-13	20.88 ± 0.61	1.19 ± 0.01	1.40 ± 0.02	14.91 ± 1.22	1.17 ± 0.02
F-14	22.63 ± 1.23	1.18 ± 0.01	1.39 ± 0.02	15.29 ± 1.33	1.17 ± 0.02
F-15	22.39 ± 1.27	1.16 ±0.03	1.37 ± 0.01	15.31 ± 1.07	1.17 ± 0.01
F-16	21.94 ± 0.53	1.18 ± 0.01	1.38 ±0.00	14.48 ± 1.25	1.16 ± 0.01
F-17	21.25 ± 1.56	1.18 ± 0.01	1.37 ± 0.01	13.86 ± 0.17	1.15 ± 0.01
F-18	23.78 ± 1.46	1.21 ± 0.03	1.40 ± 0.02	13.50 ± 1.42	1.15 ± 0.02
F-19	21.70 ± 1.67	1.18 ± 0.01	1.40 ± 0.02	15.80 ± 0.14	1.18 ± 0.00
F-20	22.39 ± 0.20	1.17 ± 0.01	1.38 ± 0.00	14.97 ± 1.10	1.17 ± 0.01

* SEM 3

Thickness and Diameter:

The thickness of the tablet in all formulation was 3.5 to 3.7 mm and the diameter of the tablet in all formulation was 8mm. The results indicate all the formulations had uniform size and shape. The results were shown in table 5.

Hardness:

The hardness of the tablets of all the formulations was found to be 4kg/cm^2.The result indicated that all the tablets had a good mechanical strength. The results of the hardness for all the formulations were shown in table 5.

Weight Variation Test:

The weight of all the tablets from each formulation was in the range from 245.7 mg to 248.76 mg. It was found all the tablets passed weight variation test, as the percentage weight variation was within the acceptable limits of 7.5%.The results were shown in table 5.

Friability test:

The results showed that the friability of all the formulation was ranged from 0.56 % to 0.72%.Friability of all the formulation was lesser than 1 % which indicated the tablets had a good mechanical resistance. The results were shown in table 5.

Uniformity of drug Content:

The drug content in the content of all the formulations was found to be in the range of 97.06 % to 99.66 %. The results indicated all the formulations were within the acceptable limits as per USP limits. The results were shown in table 5.

In-vitro drug release Studies:

The ormeloxifene fast dissolving tablet dissolution profile range from 33.17 % to 80.49 % at 15 minutes, it was shown in figure 7(a-g). The dissolution drug release rate was found to be comparatively less in formulation containing sodium starch glycolate. The maximum increased in the dissolution drug release rate was observed with the combination of crospovidone, croscarmellose sodium and sodium starch glycolate containing formulation. The order of the dissolution rate with various superdisintegrants was found to be Combination of disintegrants > crospovidone > croscarmellose sodium > SSG This study indicated that combination of superdisintegrants was produce better drug release rate than using alone. The formulation F-8dissolution study was produce 80.49% at 15 minutes, which complies with WHO guild line (WHO Uganda., 2009). Many factors contributed for faster drug release rate such as rapid disintegration, smaller particle size, decrease in agglomeration of particles, increased wettability and decreased crystallinity of drug.

Table.5: Post compression evaluation of Ormeloxifene FDT

F-Code	Weight uniformity	DC(mg)± SD	Hardness (kg/cm2)	Thickness (mm)	Friability (%)
F -1	244.35 ± 3.34	29.73 ± 0.17	4	3.7	0.61
F -2	243.62 ± 4.52	29.4 ± 0.45	4	3.6	0.7
F -3	248.49 ± 3.30	29.41 ± 0.12	4	3.7	0.68
F -4	248 ±4. 22	29.89 ± 0.82	4	3.7	0.69
F -5	246.04 ± 3.73	29.20 ± 0.35	4	3.7	0.72
F -6	248.11 ± 2.89	29.47± 0.30	4	3.7	0.67
F -7	247.32 ± 1.9	29.32 ± 0.34	4	3.7	0.63
F -8	248.76 ± 2.09	29.33 ± 0.34	4	3.7	0.71
F -9	247.98 ± 2.39	29.39 ± 0.17	4	3.7	0.7
F -10	247.6 ± 2.69	29.81 ± 0.47	4	3.7	0.56
F -11	247.1 ± 1.73	29.47 ± 0.21	4	3.7	0.67
F -12	146.35 ± 1.2	29.37 ± 0.34	4	3.6	0.66
F -13	246.98 ± 1.38	29.40 ± 0.17	4	3.6	0.56
F -14	248.3 ± 1.28	29.66 ± 0.43	4	3.7	0.70
F -15	246.69 ± 1.42	29.19 ± 0.27	4	3.7	0.63
F -16	246.93 ± 1.02	29.12 ± 0.11	4	3.6	0.69
F -17	247.17 ± 1.28	29.10 ± 0.27	4	3.6	0.63
F -18	247.14 ± 0.99	29.31 ± 0.34	4	3.7	0.69
F -19	247.45 ± 0.95	29.37 ± 0.30	4	3.7	0.60
F -20	245.7 ± 2.79	29.22 ± 0.34	4	3.7	0.69

* SEM 3

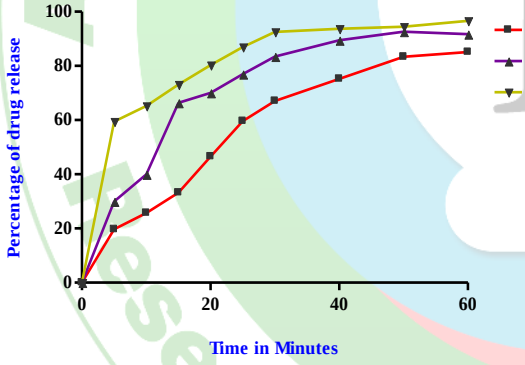


Fig 7 (a): Dissolution ormeloxifene (F1 to F3)

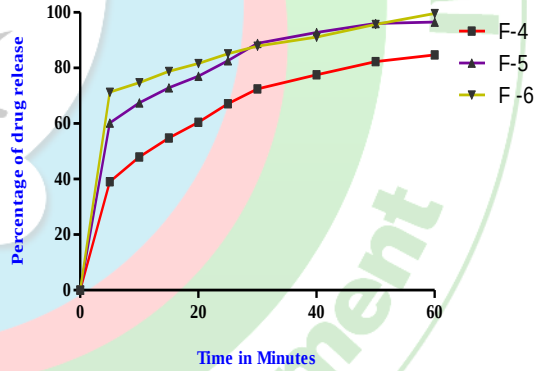


Fig 7(b): Dissolution ormeloxifene (F4to F6)

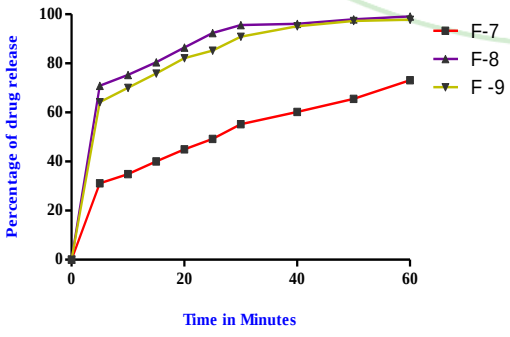


Fig 7 (c): Dissolution ormeloxifene (F7 to F9)

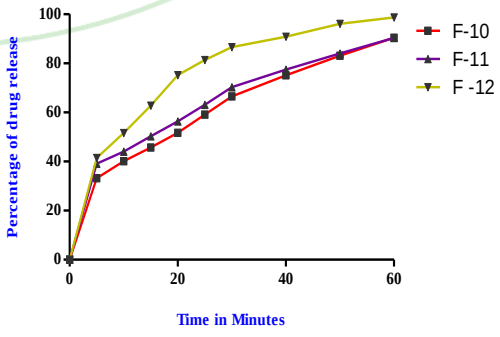


Fig 7 (d): Dissolution ormeloxifene (F10 to F12)

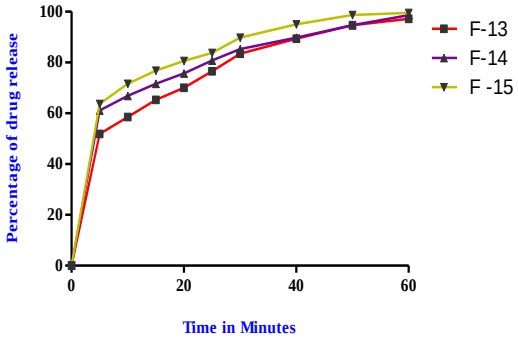


Fig 7 (e): Dissolution ormeloxifene(F13to F15)

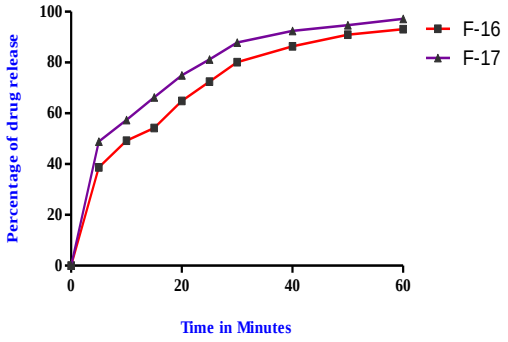


Fig 7 (f): Dissolution ormeloxifene (F16 to F17)

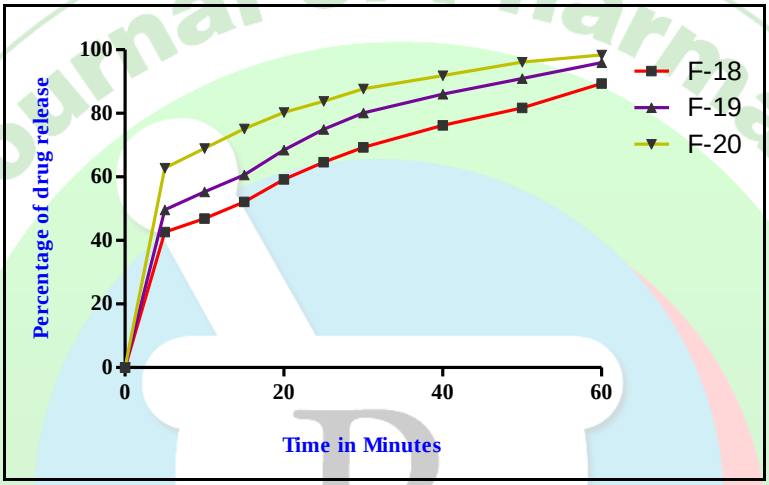


Fig 7 (g): Dissolution ormeloxifene (F18 to F20)

Solubility studies:

The solubility study was conducted with pure drug, solid dispersion product and fast dissolving tablet (F-8) using distilled water and phosphate buffer pH 6.8. It was observed that the fast dissolving tablet F-8 (0.79mg/ml) has highest solubility in water and phosphate buffer pH 6.8 (0.81 mg/ml) compared to pure drug in distilled water (0.26mg/ml) and phosphate buffer pH 6.8 (0.3 mg/ml).Results are shown in table 6.

Table 6: Solubility studies

Medium	Pure drug [mg/ml]	Solid dispersion [mg/ml]	Fast dissolving tablet [mg/ml]
Distilled water	0.266 ± 0.01	0.556 ± 0.01	0.79 ± 0.01
pH 6.8 buffer	0.3 ± 0.01	0.603 ± 0.01	0.81 ± 0.02

* SEM 3

Disintegration Time:

The results of disintegration of all the tablets were found to be lesser than 180 seconds. So all the formulation satisfied the criteria of fast dissolving tablets. Formulation F8 tablet disintegrate rapidly in shortest time of 58 seconds.

In vitro disintegration study explained that there was decrease in disintegration time with successive addition of superdisintegrant concentration in formulation but comparatively co-processed formulations(combination of superdisintegrants) take least time for disintegration. Such a difference in disintegration time between all these formulations indicates that in combination of superdisintagrant formulation may increase in capillary action which may have led to improved water uptake. The results were shown in table 7.

Water Absorption Ratio:

The results showed that as concentration of superdisintegrant increased water absorption ratio was also increased. Formulation F8 containing showed highest water absorption ratio (73.75%) than other formulation. The reason for high water absorption ratio for F-8 formulation, the combined superdisintegrant action of water wicking mechanism and capillary action into porous network of tablet, resulting rapidly absorbs water into its network than formulation prepared with other combination of superdisintegrants. The results of water absorption ratio of all the formulation were shown in table 7.

Wetting Time:

The results indicated that the concentration of superdisintegrant and type of superdisintegrant influences wetting time. Formulation F8 shows lesser wetting time than other formulation.

This may be due to fact that superdisintegrant perform their action of Crospovidone capillary action, Croscarmellose sodium wicking and swelling action and Sodium starch glycolate disintegrate the tablet by swelling mechanism, on combine effect of these three leading to shorter wetting time. The results of wetting time of all the formulations were shown in table 7.

Table 7: Post compression evaluation studies

F- code	Disintegration Time[Sec]	Water absorption Ratio(%)	Wetting Time[Sec]
F -1	166.33 ±1.52	9.87 ±1.17	228.33 ±2.08
F -2	145.66 ±2.08	18.20 ±1.33	178.33 ±1.52
F -3	88.33 ±1.52	45.25 ±2.04	116.33 ±1.52
F -4	129.66 ±2.08	21.08 ±1.72	153.33 ±2.51
F -5	86.33 ±1.52	40.37 ±1.11	126.33 ±1.15
F -6	72.33 ±2.08	57.61 ±1.34	62.66 ±1.52
F -7	155.66 ±1.52	13.34 ±0.05	181.66 ±1.52
F -8	58.33 ±1.52	73.75 ±2.27	53.66 ±1.52
F -9	70.33 ±2.51	71.59 ±2.66	59.66 ±1.52
F -10	137.66 ±1.52	12.57 ±1.34	159.66 ±1.52
F -11	148.33 ±1.52	20.80 ±0.28	162.66 ±1.52
F -12	127.66 ±1.52	19.28 ±0.76	147.66 ±1.52
F -13	123.33 ±1.52	27.82 ±1.39	141.66 ±1.52
F -14	87.66 ±1.52	49.27 ±0.42	134.66 ±0.57
F -15	86.33 ±2.08	72.94 ±1.97	120.66 ±081
F -16	143.66 ±1.52	26.36 ±0.23	152.33 ±1.15
F -17	126.33 ±1.15	26.93 ±0.25	131.66 ±0.57
F -18	146.33 ±2.08	22.68 ±0.38	155.66 ±1.52
F -19	129.33 ±0.57	32.09 ±0.60	126.33 ±0.57
F -20	87.33 ±2.081	52.00 ±0.13	99.33 ±2.30

*SEM 3

Best formulation selection:

Among twenty formulations, the best was selected on the basis of lowest disintegration time, rapid drug release profile, higher water absorption ratio, short wetting time. Formulation F-8 showed lowest disintegration tine of 58 seconds, faster drug release rate of 80.49 in 15 minutes,

95.63%in 30 minutes, comparatively high water absorption ratio of 73.75%, and shortest wetting time of 53 seconds. In those parameter would drive theF-8 as a best formulation comparatively.

Differential Scanning Calorimetric (DSC) Studies:

DSC thermogram of F-8 formulation was recorded. An endothermic peak corresponding to the melting point of pure drug was prominent in the best formulation. So it suggested clearly that there was no interaction between the drug and the polymers and the drug was existed in its unchanged form, it shown in figure 8.

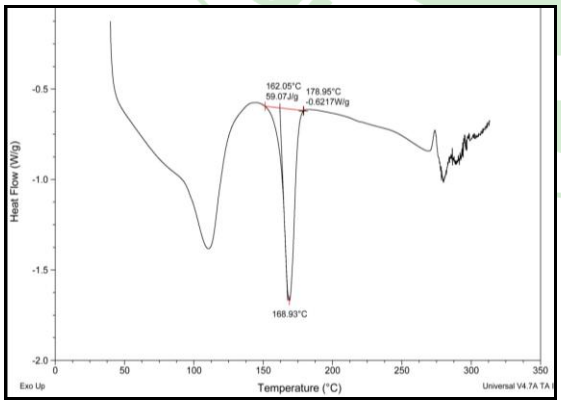


Fig. 8 (a): DSC Thermodram of Kneading Mixture

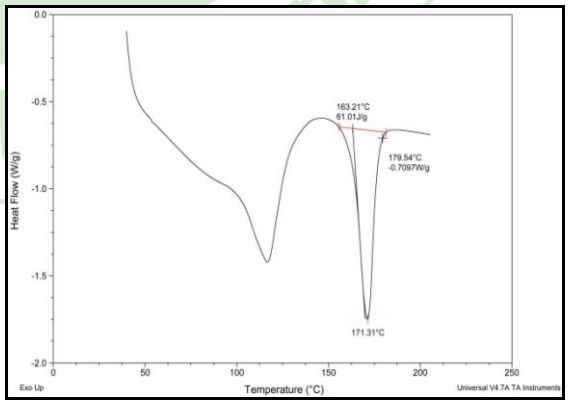


Fig. 8 (B): DSC Thermodram of FDT Best Formulation (F8)

Powder X Ray Diffraction Studies (PXRD):

These results confirmed that Ormeloxifene was transferred amorphous form. It shown in figure 9**.**

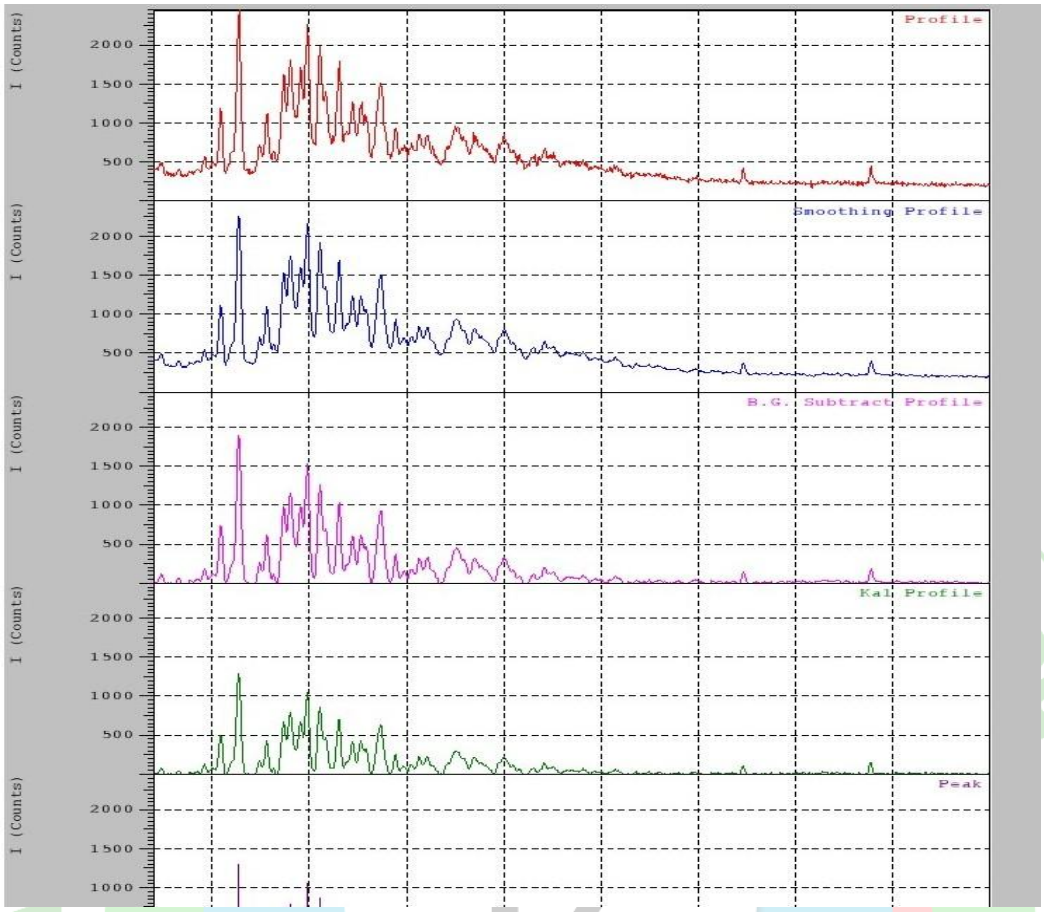


FIG. 9 (a): XRD of Kneading Mixture

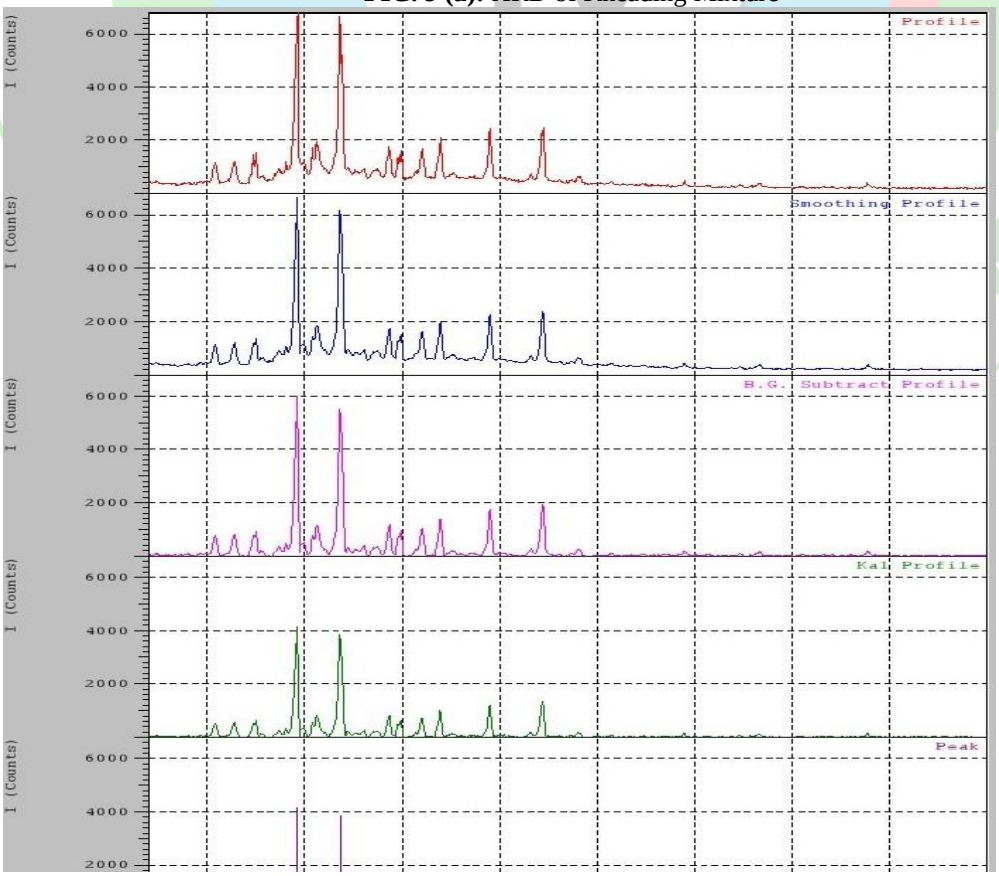


Fig. 9 (B): XRD of FDT Best Formulation (F8)

Stability study (Temperature Dependent):

The stability studies of best formulation (F-8) was carried out at an ambient temperature and relative humidity($40^0C\pm2^0C$, RH75%±5%) for a period of 60 days to find out any physicochemical changes in the fast dissolving tablet as per modified International Conference On Harmonization (ICH) guidelines. Periodically samples were withdrawn to estimate the drug content. The results was in table 8, which indicates that there is no significant change in quality parameters.

Table 8: Stablity studies

Parameter	Initial	After 10 days	After 20 days	After 30 days	After 45 days	After 60 days
Physical appearance	Off white	Off White	Off white	Off white	Off white	Off white
Hardness[kg/cm^2]	4	4	4.3	4.3	4.3	4.3
Water absorption ratio [%]	73.75	73.75	73.75	73.75	73.60	73.60
Wetting time [seconds]	53	53	56	56	56	56
Disintegration time [Sec]	58	58	59	59	60	60
Drug content [%]	97.76	97.63	97.62	97.62	97.58	97.58
Drug release % (15Minuts)	81	81.00	80.96	80.95	80.95	80.95

CONCLUSION

It was concluded that ormeloxifene hydrochloride can be successfully formulated as fast dissolving tablets with using superdisintegrants by direct compression method. The formulation containing combination of crospovidone, cros carmellose sodium and sodium starch glycolate superdisintegrant was found to be outstanding than other formulations in terms of disintegration time, rate of drug release, water absorption and wetting time, solubility and stability.

ACKNOWLEDGEMENT

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