Original Article

A Novel Combination For Scope And Medical Management Of Fibriods

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Abstract

One of the main causes of morbidity in women of reproductive age is uterine. These widespread tumours are thought to be caused by a number of variables, but this just furthers our lack of understanding of their pathophysiology. The effects of fibroids on a woman's menstrual cycle or pelvic pressure symptoms are the most typical ways in which they present . The best diagnostic method for uterine fibroids appears to be ultrasound, with magnetic resonance imaging. The medical treatment toolbox has grown with the recent arrival of aromatase inhibitors and selective progesterone receptor modulators (SPRMs). A common therapy for fibroids that spares the uterus and preserves fertility is uterine artery embolization (UAE). The number of minimal access treatment alternatives has recently risen with the use of radiofrequency (VizAblateTM and AcessaTM) or ultrasound waves (MRgFUS) for uterine fibroid ablation.

Keywords: leiomyoma, menorrhagia, ultrasonography, selective progesterone receptor modulators, embolization, myomectomy.

INTRODUCTION

Fibroids is now a days a growing issue in case of women's at the age of 30-60 years. Fibroids are unnatural growths that form in or on the uterus of women. These tumours can occasionally grow extremely large, resulting in excruciating stomach pain and irregular periods. Other times, they have no noticeable effects at all. Usually benign or noncancerous, the growths. There is no known cause of fibroids. [1-4].

Uterine fibroids are addressed as myomas or leiomyomas is the common benignant uterine tumours, and mostly 20%–40% women during their reproducing age are incident of it .

It is a mangling tumours of the smooth muscle cells in and around uterine and consist of large quantity of extracellular matrix which contain collagen, fibronectin, and proteoglycan. They are multiple in number, can vary from a few millimetres to as massive growths of 20 cm diameter or more in size[5.6]. They are oestrogen- and progesterone-dependent tumours, which are uncommon before monarchy, prevalent throughout reproductive life, and greatly enlarge after menopause. However, the pharmacology is mainly unclear. Fibroids can cause irregular uterine bleeding, dyspareunia and pelvic pain, rectus or bladder obstruction, and fertility issues. The severity of a patient's clinical symptoms is not influenced by a tumour's size.

Fibroids can be known as : [7 -10]

leiomyoma

myomas

uterine myomas

fibromas

Most women, however, don't have any symptoms and might never be aware that they have fibroids.

Causes of fibroids [11]

There can be many reasons for the development of fibroids in the women's womb

Some of the basic reasons are

Hormonal Changes :

The ovaries create hormones like progesterone and oestrogen. Every menstrual cycle, they damage the inner lining, which might result in the development of fibroids.

Family History:

Family history like ancestors having it is carried forwarded to the generation .

Pregnancy: Your body produces more progesterone and oestrogen when you're pregnant. which in the majority of cases affect pregnant women can result in fibroids.

Symptoms[12 -15]

The type of tumours you have, as well as their location and size, will affect your symptoms. Heavy monthly bleeding and trouble getting pregnant may be brought on by submucosal fibroids.

There won't be any symptoms if your tumour is really minor or if you are going through menopause. Both during and after menopause, fibroids decrease. This is due to a decrease in oestrogen and progesterone levels, two hormones that encourage the formation of fibroid, in menopausal women.

Heavy bleeding with blood clots before, during, or after your menstruation.

- discomfort during intercourse;

- pain in the pelvic or lower back;

- increased menstrual cramping;

- menstruation that lasts longer than usual;

- increase in urination.

- feeling full or pressure in your lower abdomen

- Abdominal edoema or hypertrophy.

Fibroid histology [16–18]

The patient must visit a gynaecologist for an evaluation in order to receive a proper diagnosis. This test is used to determine the health, dimensions, and shape of your uterus. You might additionally require the following tests:

1) Ultrasonography: An ultrasound produces images of your uterus on a screen using high-frequency sound waves. This will enable the doctor to examine any fibroids and the internal structures of the object. Since the ultrasound wand is placed inside the vagina during a transvaginal ultrasonography, it is closer to the uterus and may produce sharper images. [14-15].

2) Pelvic Magnetic Resonance imaging (MRI): Using detailed imaging, your uterus, ovaries, and other pelvic organs are captured on camera. [19].

MATERIAL AND METHOD

Material and instrument used

Table 1. List of drug and other excipients used.

Sr. No.	Ingredients	Grade	Suppliers
1.	Ulipristal Acetate	Pure grade	Alembic Pvt Ltd, Mumbai
2.	Mifepristone	Pure grade	Alembic Pvt Ltd, Mumbai
3	PEG 6000	Pure grade	Loba Chemi Mumbai, India
4	PEG 4000	Pure grade	Loba Chemi Mumbai, India
5.	Avicel 101	Pure grade	Loba Chemi Mumbai, India
6.	Lactose monohydrate	Pure grade	Loba Chemi Mumbai, India
7.	Starch	Pure grade	Loba Chemi Mumbai, India
8.	Magnesium stearate	Pure grade	Loba Chemi Mumbai, India

Preformulation study
The received sample of Ulipristal acetate and Mifepristone was subjected to the Pre-formulation studies.

Organoleptic properties
The drug sample's colour, smell, and look were evaluated.

Melting point determination:
By using a capillary technique, the melting point of the drug sample was established.

UV Spectroscopy:

A) Ulipristal acetate

Determination of maximum absorbance in dissolution media (λ max)[25]
The medication was produced as a stock solution (100 g/ml) in methanol. Using a UV-Visible double beam spectrophotometer, the UV spectrums in the 200-400 nm region were recorded (Agilent Technologies, carry 60). Maximal absorption's wavelength (max) was identified.

Standard Calibration Curve of Ulipristal acetate in dissolution media

B) Mifepristone

Determination of maximum absorbance in dissolution media (λ max) [25]
Stock solution (100 µg/ml) of drug was prepared in Methanol. The UV Spectrums were recorded in range 200-400 nm by using UV-Visible double beam spectrophotometer (Agilent Technologies, carry 60). The wavelength of maximum absorption (λ max) was determined.

Standard Calibration Curve of Mifepristone in dissolution media.

Determination of solubility
Saturation solubility of the both drugs was determined in distilled water and various buffers (acetate buffer 4.4, 0.1N HCL, pH 6.4 to 7.4). The 10ml distilled water or buffer of required pH taken in 25ml amber coloured volumetric flask.[14] These volumetric flask were kept in orbital shaking water bath. The shaking was carried out for 48 hours with the speed of 50 rpm and temperature 37 ± 0.5º C. Then the resulting samples were filtered using syringe filter with pore size 0.22 µm. The filtrate were collected and after suitable dilutions with same solvent the absorbance of drug was analysed with UV visible spectrophotometer.

Drug and polymer compatibility study[29]

Fourier Transform Infrared Spectroscopy (FTIR)
The study was conducted with an intention to check the compatibility of polymer i.e. PVP K-30 with Ulipristal acetate and mifepristone. Also, it helps to check the suitability of polymers for the preparation of solid dispersion.[22] A Shimadzu FTIR spectrometer (IR Affinity 1Model, Japan) was used to study the FTIR spectrum.. The sample of both drug and physical mixture of both drugs were prepared separatory with KBr after drying in hot air oven for about 1 hr. then kept in desiccators before scanning the spectra between the ranges of 4000 to 500 cm^{-1} .

Solvent evaporation method[25-28]

PVP K-30 was used in various ratios to create solid dispersions using a solvent evaporation technique (1:0.5, 1:1 and 1:2 of the drug: polymer). By continuously agitating with a magnetic stirrer for an hour at room temperature, the appropriate amount of medication and the carrier were dissolved using a small amount of methanol. Using a rotary evaporator maintained at 40 °C, the solvent was entirely evaporated under reduced pressure. The generated solid dispersions underwent additional drying in a 40° oven for 24 hours. The entire batch of solid dispersions that resulted from this was scraped, ground in a mortar, and sieved through a 60-mesh sieve. Then, until they were used, all solid dispersions were held in the desiccator in amber glass bottles.[1]

Table 2. Formulation of solid Dispersion

Sr no.	Formulation code	Ratio of solid dispersion (Drug :Polymer)
1	F1	1:0.5
2	F2	1:1
3	F3	1:2

Characterization of solid dispersion

Solid dispersion that exhibited a better result was chosen from the findings of experiments on solubility and dissolution. Solid dispersion was used for additional evaluation in order to determine whether there was any interaction between the drug and polymer as well as what characteristics of polymers make them useful for enhancing solubility and bioavailability. In the current investigation, FT-IR, DSC, XRD, and SEM were used to describe the solid dispersion of both medicines. [1]

Percentage yield

Percentage yield of solid dispersion by using various ratio of drug and carrier was determined by using formula.

$$\% \text{ yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Drug Content:[14]

A volumetric flask containing precisely weighed solid dispersion (10 mg) and 5 ml of methanol was agitated with a vortex mixer for 1 minute to determine the drug content. The volume reached 10 ml. The content of Ulipristal acetate and Mifepristone was then determined spectrophotometrically at 302 nm and 304 nm, respectively. The solution was then filtered and diluted.

FORMULATION & PREPARATION OF SOLID DISPERSION TABLET

Table 3. Composition of Ulipristal acetate solid dispersion tablet.

Ingredient	Quantity in batch (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	30	3030	30	30	30	30	30	30	30
Lactose monohydrate	235	237	240	235	237	240	235	237	240
Povidone	12	12	12	13	13	13	15	15	15
Cross carmallose	15	15	15	15	15	15	15	15	15
Magnesium stearate	3	3	3	3	3	3	3	3	3
Isopropyl alcohol	qs	qs	qs	qs	qs	qs	qs	qs	qs

Table 4 . Composition of Mifepristone solid dispersion tablet.

Ingredient	Quantity in batch (mg)

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	200	200	200	200	200	200	200	200	200
Silica colloidal anhydrous	2	2	2	2	2	2	2	2	2
Corn starch	102	105	108	102	105	108	102	105	108
Povidone	10	10	10	12	12	12	14	14	14
Micro crystalline cellulose	45	45	45	45	45	45	45	45	45
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Isopropyl alcohol	qs	qs	qs	qs	qs	qs	qs	qs	Qs

Preparation of Tablet Using Direct Compression Method - Weigh all the ingredients accurately. All the powders were blended by geometric dilution method using mortar and pestle. Binder was added to powder and after that compress the powder directly using direct compression method.

Pre-Compression Evaluation of Powder

Bulk Density -

$$\text{Bulk Density} = \text{Mass (gm)} / \text{Bulk Volume (mL)}$$

Tapped Density

$$\text{Tapped Density} = \text{Mass (gm)} / \text{Tapped Volume (mL)}$$

Carr's Index (%)

$$\text{CI (\%)} = [\text{(Tapped density} - \text{Bulk density)} / \text{Tapped density}] \times 100$$

Hausner's Ratio

$$\text{HR} = \text{Tapped density} / \text{Bulk density}$$

Factorial design[11]

Two or more elements are evaluated concurrently using a factorial design. Combinations of different degrees of the components make up the treatments. When conducting studies to clarify the effects of various elements or circumstances, a factorial design is utilised. The preferred designs for simultaneously determining the impact of various elements and their interactions are factorial ones.

Factor:[20] It is a predetermined variable, like concentration, temperature, lubricant, drug, or nutrition. Qualitative or quantitative factors are also acceptable. Names rather than numbers are given to the qualitative aspects. A quantitative factor is given a numerical value.

Level: The values or identities that have been given to a factor are its levels. Examples of levels for the factor "temperature" include 30°C and 50°C. 0.1 molar and 0.3 molar for "concentration," "drug" and "placebo" for "drug treatment," respectively. Factorial experiments are made up of runs or trials that include all possible combinations of all stages and levels of all possible components.[7]

Optimization

For those involved in formulation research, the optimization of pharmaceutical formulations with relation to one or more qualities has always been a topic of relevance and attention. The goal is to create a mathematical representation of the responses.

In general, the technique entails creating a number of formulations and systematically changing their ingredient concentrations.[1] Using the software Design Expert®, various computations for the current optimization research were carried out (Design Expert trial version 8.0.7.1; State-Ease Inc., Minneapolis, MN, USA). For a systemic analysis of polymer combinations, a two-factor, three-level complete factorial design was employed.

Comparison of In Vitro Dissolution Profiles:

Difference factor (f1):

The difference factor, which measures the relative error between the two curves, determined the percent (%) difference between the two curves at each time point.[15]

$$f_t = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} X\ 100$$

Where n is the number of time points, Rj and Tj are the percent dissolved of the reference and test products at each time point.

Stability studies:

Stability studies are one of the most crucial aspects of the registration of pharmaceutical products and were a crucial component of the medication development programme. The goal of stability testing is to demonstrate how the quality of a drug substance or drug product changes over time under the influence of various environmental factors, such as temperature, humidity, and light.[9] Stability testing also makes it possible to determine the ideal storage conditions, re-test intervals, and self-half-lives. Stability assessment pathway was used to determine degradation products and route. The tablets in these investigations were kept in appropriate containers or blister packages, and a stability study was carried out in accordance with ICH criteria.

Storage conditions

Accelerated: - 40 ºC ± 2 ºC /75 % RH ± 5 % RH

As per ICH guidelines, the samples for stability analysis must be exposed to an environment of 40˚C ± 2˚C / 75 % RH ± 5 % RH for a period of 6 months. As per the standard protocol the samples must be analysed at 0, 1, 2, 3 and 6 months' time points.

Accelerated stability studies were performed for the final optimized formulation. Samples were analysed at 1, 2, 3 months' time points.

RESULT AND DISCUSSION

Preformulation study

Preformulation study of Ulipristal Acetate

API characterization

Table 5: Organoleptic properties of Ulipristal acetate

Sr. No.	Name of property	Specification
1.	Colour	White
2.	Odour	Unpleasant
3.	Nature	Crystalline

Table 6: Melting point of Ulipristal acetate

Sr.no.	Melting point	Reference range	Average melting point
1	182℃		

2	184℃	183-185℃	183℃
3	183℃		

Melting point of Ulipristal acetate was reported to be 183℃, which is in range as studied in previous literature (183-185℃). Hence the drug can be stated as pure.

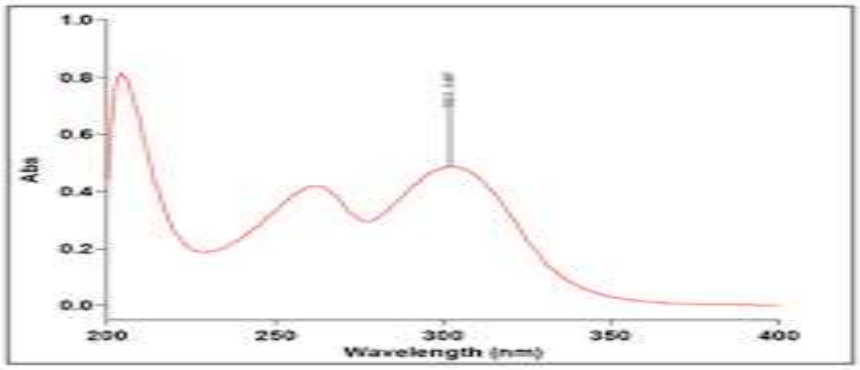

Fig 1 : UV Spectra of pure Ulipristal acetate in methanol

Absorption maximum was found to be at 302 nm. Hence 302 nm was selected as λ max for further studies.

Calibration curve of Ulipristal acetate in methanol

Table: 7 : Different concentration & absorbance of Ulipristal acetate

Sr.no.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.112
3	20	0.206
4	30	0.314
5	40	0.401
6	50	0.513
7	60	0.637

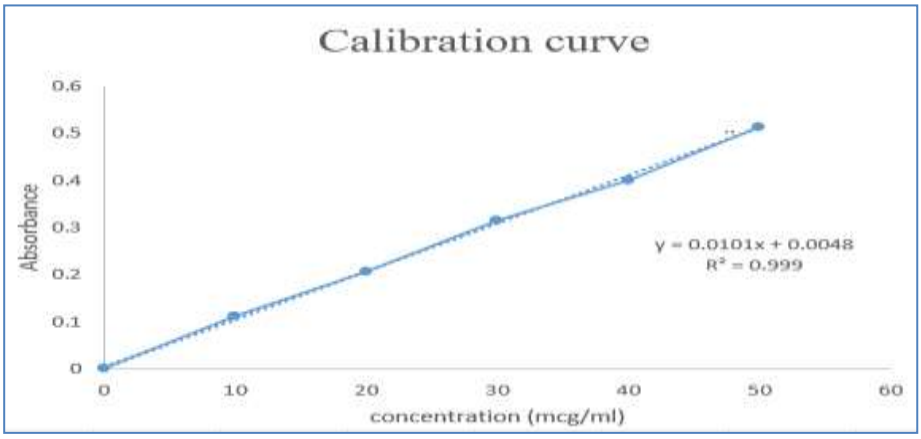

Fig 2 : Calibration curve of Ulipristal acetate in methanol.

Table 8 : Parameters of calibration curve

Sr.No.	Parameter	Finding

1	Wavelength detection	302 nm
2	Correlation coefficient	Y= 0.0101x + 0.0048
3	Regression equation	R^2 = 0.999

Preformulation study of Mifepristone

API characterization

Table 9 : Organoleptic properties of Mifepristone

Sr. No.	Name of property	Specification
1.	Colour	Yellow
2.	Odour	Unpleasant
3.	Nature	Amorphous

Identification of pure drug

Melting Point

Table 10 : Melting point of Mifepristone

Sr.no.	Melting point	Reference range	Average melting point
1	193℃		
2	196℃	191-196℃	194.33℃
3	194℃		

Melting point of Mifepristone was found to be 194.33℃, which is in range as given in literature (191-196℃). Hence the drug can be stated as pure.

UV Spectroscopy

Determination of λ max

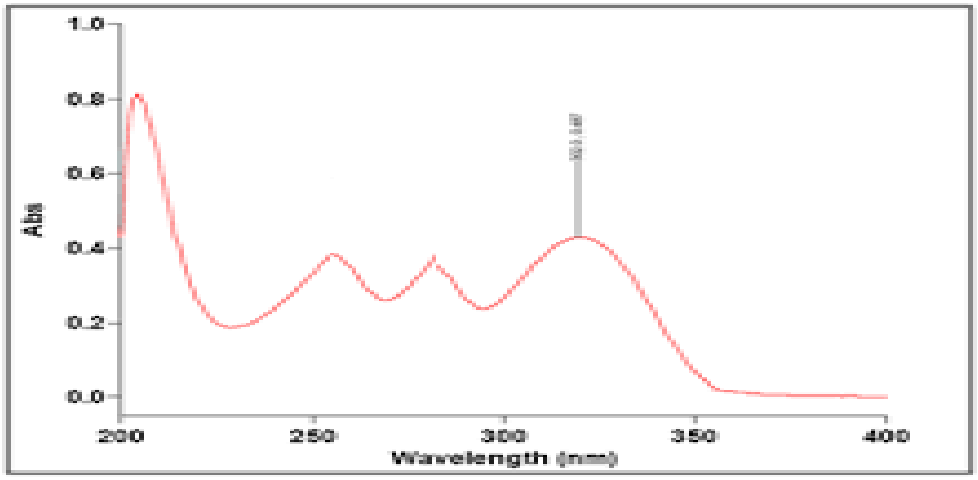

Fig 3: UV Spectra of pure Mifepristone in methanol

Absorption maximum was found to be at 304 nm. Hence 304 nm was selected as λ max for further studies.

Calibration curve of Mifepristone in methanol

Table: 11 : Different concentration & absorbance of Mifepristone

Sr.no.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.172
3	15	0.269
4	20	0.341
5	25	0.405
6	30	0.499
7	35	0.584

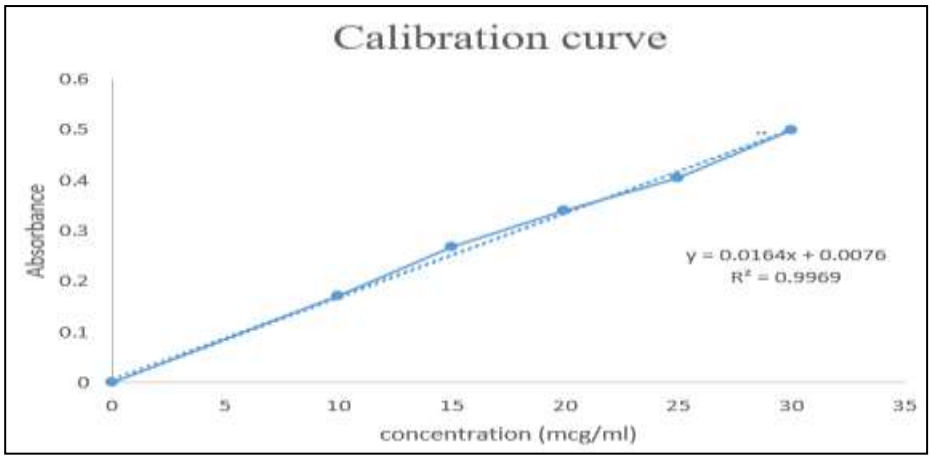

Fig 4 : Calibration curve of Mifepristone in methanol.

Table 12: Parameters of calibration curve

Sr.No.	Parameter	Finding
1	Wavelength detection	304 nm
2	Correlation coefficient	Y= 0.0164x +0.0076
3	Regression equation	R^2 = 0.9969

Characterization of solid dispersion:

Fourier-transfer infrared (FTIR) analysis

To determine if any interaction between drug and polymer FTIR spectroscopy of drug, PVP K30 6000 and solid dispersion was carried out.

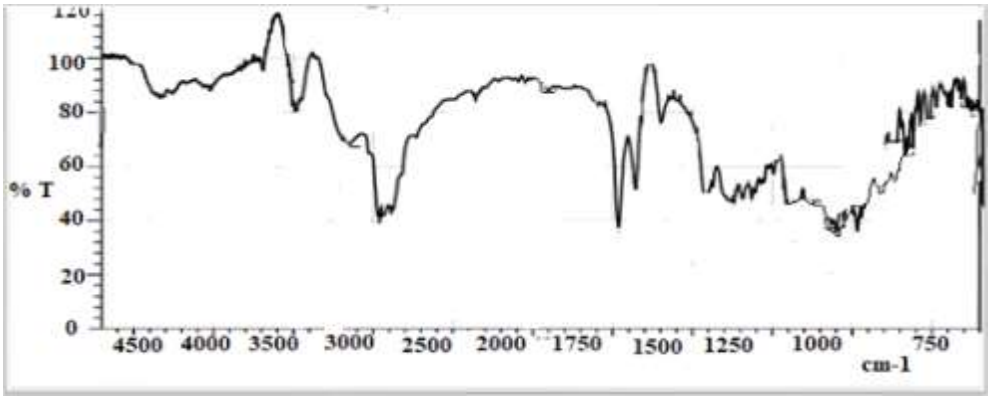

Fig 5 : FTIR spectra of Ulipristal acetate

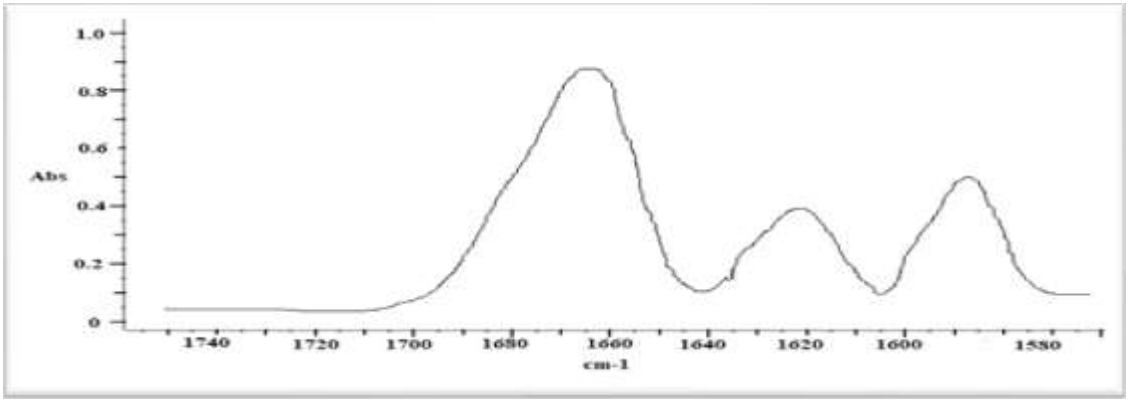

Fig 6 : FTIR spectra of Mifepristone

Table 13. Interpretation of the FTIR spectra

Material	Functional group	Standard IR range (cm^{-1})	Observed range (cm^{-1})
Ulipristal acetate	C-N Stretching	1350-1250	1314.51
	C – H Stretching	3300 – 2500	2962.71
	C = O Stretching	2400 – 2000	2358.02
Mifepristone	C = O Stretching	1730 – 1715	1731.14
	C - N Stretching	1685 – 1666	1678.10
	N-H bending	1650-1550	1640,1620
PEG 6000	C = O Stretching	3500 – 3200	2877.79
	C –O Stretching	1150 – 1085	1103.02
Solid dispersion	O – H Stretching	3500 – 3200	2891.34
	O = C = O Stretching	2400 – 2000	2238.43
	O = C = O Stretching	2400 – 2000	2166.10
	C = O Stretching	1710 – 1685	1684.85
	C = O Stretching	1710 – 1685	1653.99
	C –O Stretching	1150 – 1085	1111.02

From the FTIR study, no considerable changes observed in the positions of absorption bands and bonds of various functional groups are present in the drugs. This observation shows that no prominent changes in the characteristic peaks of Ulipristal acetate and Mifepristone in solid dispersion. From the FTIR spectra it is found that there is no interaction between both drugs and polymer.

Differential scanning calorimetry (DSC) analysis

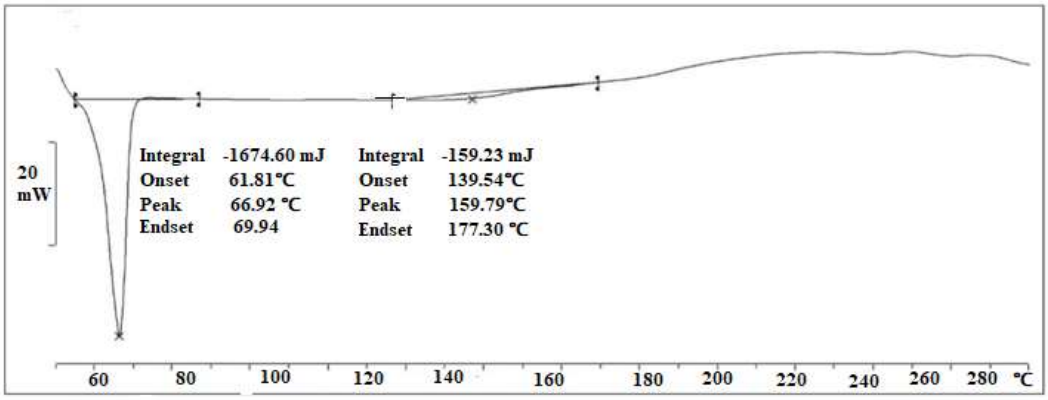

Fig 7 : DSC thermogram of Solid dispersion of ulipristal acetate

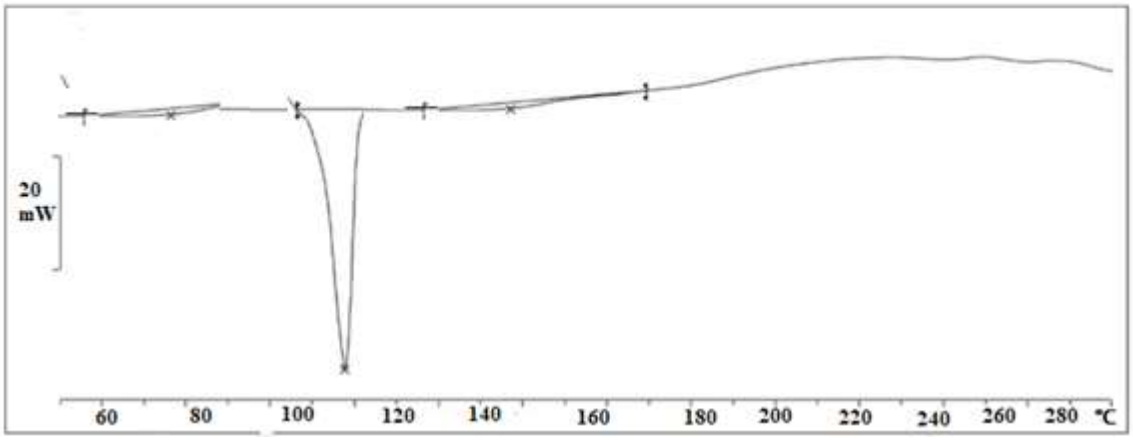

Fig 8 : DSC thermogram of Solid dispersion of mifepristone

X-ray diffraction (XRD) analysis

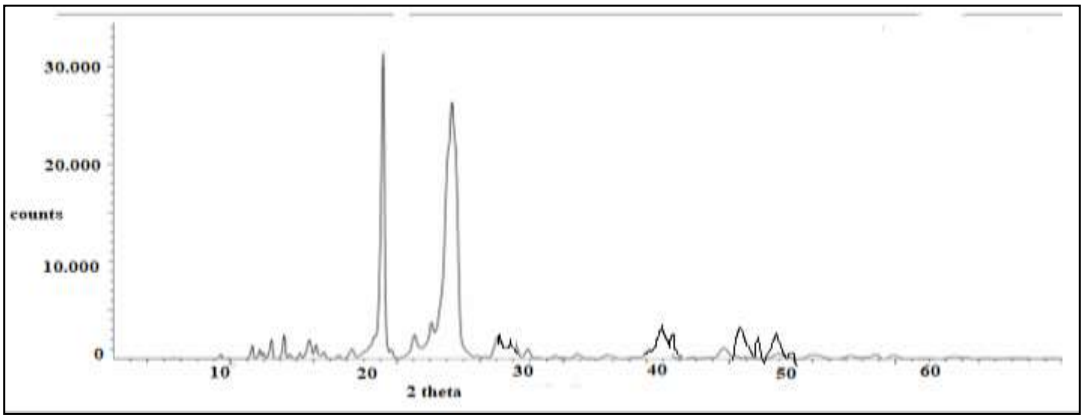

Fig 9 : XRD spectra of solid dispersion of ulipristal acetate

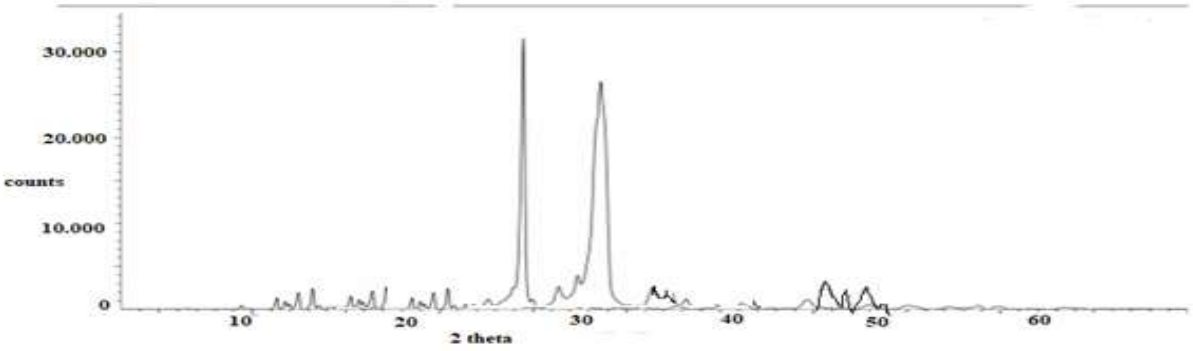

Fig 10 : XRD spectra of solid dispersion of mifepristone

The XRD diffractogram of pure Ulipristal acetate shows that the drug was in crystalline nature as shown by numerous peaks observed at 2θof 32.96^0, 26.35^0, 20.89^0, 19.03^0, 17.24^0, 14.69^0, 13.10^0, 11.19^0, 6.49^0, 4.46^0 etc. as shown in figure 10 and Mifepristone shows that the drug was in amorphous in nature as shown by several peaks observed at 2θof 36.76^0 ,28.45^0, 19.03^0,18.98^0, 15.45^0, 13.87^0, 7.98^0 etc as shown in fig.22.The pure PVP K30 showed two peaks with high intensity at 2θ and d-spacing of 9.41 and 4.65 A^0, 23.34 and 3.78A^0.The extent of crystallinity influences the dissolution of the drug. An amorphous or metastable form dissolve at faster rate. Some changes in the position of both drugs in solid dispersion is noted. The characteristics peaks of both drugs in solid dispersion significantly decrease when solid dispersion is prepared by melting method. From the above result it was concluded that crystalline and amorphous nature of the both drug is not maintained, and reduction of intensities of both drug in PEG6000 preparation suggest that the quality of the crystals was changed. The result of the study shows that Ulipristal acetate and Mifepristone present in the amorphous form in solid dispersion and it shows agreement with other studies.

Table 14 : Percentage yield

Percentage yield of Ulipristal acetate and Mifepristone solid dispersion prepared by solvent evaporation method.

Data represented as mean standard deviation (n = ±3)

Sr no.	Formulation code	Ratio of solid dispersion (drug: polymer)	Percentage yield (%) of Ulipristal acetate	Percentage yield (%) of Mifepristone
1	F1	1:0.5	84.81±0.45	87.81±0.41
2	F2	1:1	93.56±0.39	96.56±0.37
3	F3	1:2	95.76±0.19	91.76±0.14

The percentage yield of all the solid dispersion was determined and found that solid dispersion prepared by solvent evaporation method method. Batch F3 of Ulipristal acetate and .batch F2 of Mifepristone shows highest percentage yield.

Table 15 : Solubility study of solid dispersion

Solubility study of solid dispersion prepared by fusion method.

Data represented as mean standard deviation (n = ±3)

Sr no.	Formulation code	Ratio of solid dispersion (Drug: polymer)	Solubility (mcg/ml) of Ulipristal acetate	Solubility (mcg/ml) of Mifepristone
1	F1	1:0.5	16.06±0.23	13.06±0.23
2	F2	1:1	17.86±0.75	24.86±0.71
3	F3	1:2	20.64±0.97	21.64±0.87

The solubility of all the solid dispersions was executed in distilled water. Ulipristal acetate shows 5.95 ug/ml and Mifepristone shows 6.87 ug/ml solubility which is very low. The result obtained for all the solid dispersion preparation showing increase in solubility. This might be due to the more intimate contact between drug and carrier and conversion of crystalline nature of drug to amorphous nature. The solid dispersion prepared by solid evaporation method shows more significant increase in the solubility. It was also noted that an increase in the ratio of drug to carrier from 1:0.5 to 1:2, marked improvement in the solubility of drug was noted and highest increase in the solubility was a shown by batch F3 of Ulipristal acetate and batch F2 of Mifepristone.

Table 16 : Drug content

Drug content of solid dispersion prepared by solvent evaporation method.

Data represented as mean standard deviation (n = ±3)

Sr no.	Formulation code	Ratio of solid dispersion (Drug: polymer)	Drug content (%) of Ulipristal acetate	Drug content (%) of Mifepristone
1	F1	1:0.5	79.67±0.87	82.34±0.98
2	F2	1:1	86.21±0.69	85.45±0.23
3	F3	1:2	89.56±0.86	80.65±0.66

The drug content of all solid dispersion was measured and it was found that solid dispersion prepared by solvent evaporation method. F3 batch of Ulipristal acetate and F2 batch of Mifepristone shows better drug content.

Table 17 : In-vitro drug release

Time (min)	% drug release of Ulipristal acetate			% drug release of Mifepristone		
	F1	F2	F3	F1	F2	F3
0	0	0	0	0	0	0
5	10.563	14.678	20.688	11.798	19.792	20.688
10	32.565	41.432	52.689	38.688	41.090	41.890
15	67.781	74.984	79.573	69.899	77.892	76.792
30	86.787	88.987	95.893	89.874	96.682	91.674

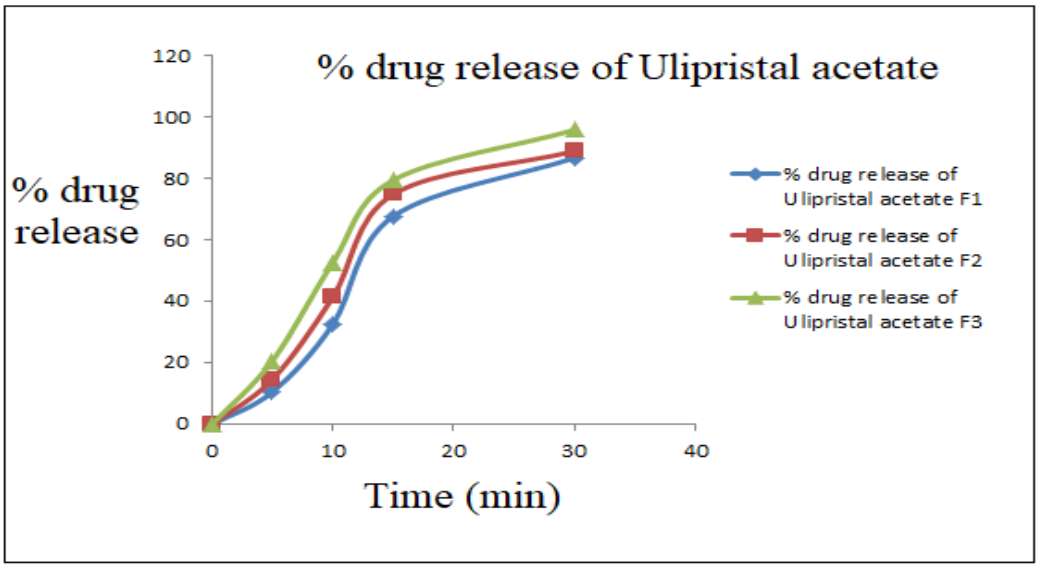

Fig 11 : Graphical representation of comparative drug release of F1 to F3 Batch of Ulipristal acetate

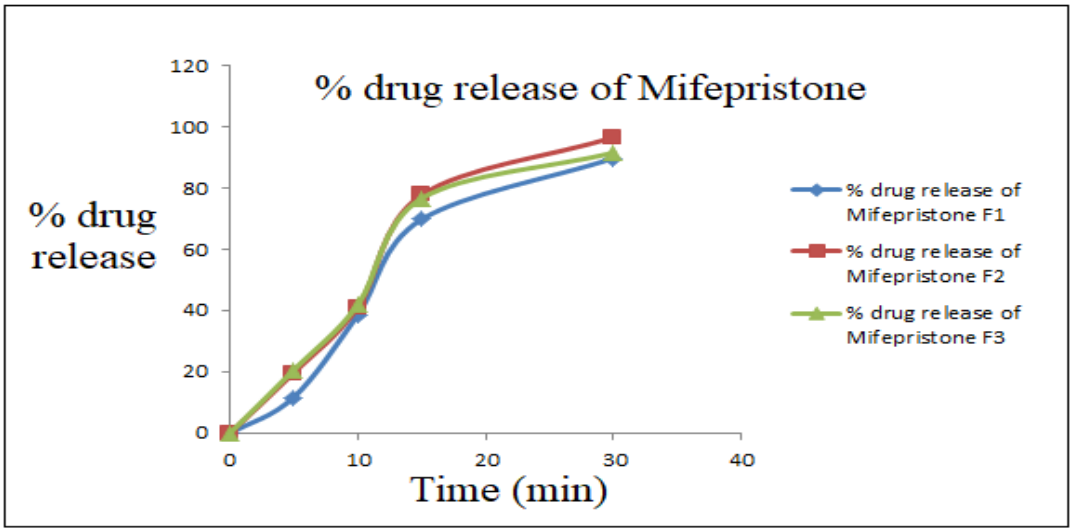

Fig 12 : Graphical representation of comparative drug release of F1 to F3 Batch of Mifepristone

EVALUATION OF TABLET DOSAGE FORM

Table 18 : Pre-compression evaluation of powder blend formulation of Ulipristal acetate

S.N.	Parameter	Ulipristal acetate	Solid dispersion (F3 batch)
1	Angle of repose	33.42º	27.74º
	Inference	Passable	Good
2	Bulk density (gm/ml)	0.18	0.1
3	Tapped density (gm/ml)	0.25	0.116
4	Carr's index (%)	28	13.79
	Inference	Poor	Good
5	Hausner's ratio	1.38	1.16
	Inference	Poor	Good

Table 19 : Pre-compression evaluation of powder blend formulation of Mifepristone

S.N.	Parameter	Mifepristone	Solid dispersion (F2 batch)
1	Angle of repose	31.43º	26.89º
	Inference	Passable	Good
2	Bulk density (gm/ml)	0.19	0.1
3	Tapped density (gm/ml)	0.26	0.12
4	Carr's index (%)	26	14.65
	Inference	Poor	Good
5	Hausner's ratio	1.35	1.15
	Inference	Poor	Good

Table 20 : Post compression evaluation

Properties	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Drug content (%)	Disintegration (sec)
F1	0.283	3.7	0.51	3.10±0.014	98.40	5.0
F2	0.281	3.9	0.55	3.10±0.012	99.13	1.30
F3	0.283	4.0	0.60	3.20±0.016	91.54	3.20
F4	0.280	4.0	0.55	3.12±0.012	99.73	5.20
F5	0.282	4.1	0.62	3.15±0.020	95.58	3
F6	0.280	4.2	0.63	3.20±0.024	95.22	1.20
F7	0.284	4.3	0.65	3.25±0.018	94.74	2.20
F8	0.283	4.4	0.55	3.30±0.010	93.09	3.05
F9	0.281	4.5	0.61	3.10±0.012	93.85	2.45

Table 21: In-Vitro Drug Release Study

In vitro dissolution of Ulipristal acetate solid dispersion tablet for F1-F9 batch

Time (min)	Percentage drug Release of Ulipristal acetate								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	5.635	15.531	23.342	19.517	19.525	19.588	15.783	19.838	18.967
10	41.813	45.997	49.444	50.232	48.931	54.653	42.063	54.633	44.711
15	74.122	85.12	81.034	85.066	86.940	88.063	81.276	95.009	84.932
30	98.603	99.884	97.509	95.010	97.525	93.636	95.259	98.657	96.376

Table 22 : In-Vitro Drug Release Study

In vitro dissolution of Mifepristone solid dispersion tablet for F1-F9 batch

Time (min)	Percentage drug Release of Mifepristone								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	28.98	31.97	29.34	37.62	29.66	29.52	25.53	29.55	29.05
10	45.80	55.75	58.31	45.40	47.98	61.94	46.85	50.43	49.23
15	70.23	67.12	77.45	76.65	72.30	77.69	76.25	73.63	67.54
30	99.20	98.39	96.89	98.34	98.26	97.86	98.3	98.01	98.27

Table 23 : Formulation of F1 to F9 batches of Ulipristal acetate

Ingredient	Quantity in batch (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	30	3030	30	30	30	30	30	30	30
Lactose monohydrate	235	237	240	235	237	240	235	237	240
Povidone	12	12	12	13	13	13	15	15	15
Cross carmallose	15	15	15	15	15	15	15	15	15
Magnesium stearate	3	3	3	3	3	3	3	3	3
Isopropyl alcohol	qs	qs	qs	qs	qs	qs	qs	qs	qs

Analysis of variance and model equation

In the next steps, significance of this influence was statistically confirmed by ANOVA test. According to applied 3^2 experimental design 9 experiments were performed to optimize the formulation method of solid dispersion to get maximum drug release in terms of response. The obtained results were entered in design expert software 7.0.0.

Table No 24 : Analysis of variance and model equation (% drug release)

Source	Sum of squares	df	Mean square	F-value	P-Value Prob> F
Model	31.52	5	6.30	14.37	0.0263
A-Lactose monohydrate	0.30	1	0.30	0.69	0.4661
B-Povidone	5.42	1	5.42	12.36	0.0390
AB	1.22	1	1.22	2.79	0.1937
A2	13.76	1	13.76	31.37	0.0112
B2	10.81	1	10.81	24.63	0.0157
Residual	1.32	3	0.44		
Cor Total	32.83	8			

Counter plot

Figure show the counter plot of lactose monohydrate and povidone is actual factor. It shows as lactose monohydrate concentration increases the percentage release also increases at some level and then there is decrease in % drug release as concentration of lactose monohydrate increases. povidone concentration increases, % drug release was found to be decreased at some level and then there is increase in % drug release as concentration of povidone increases.

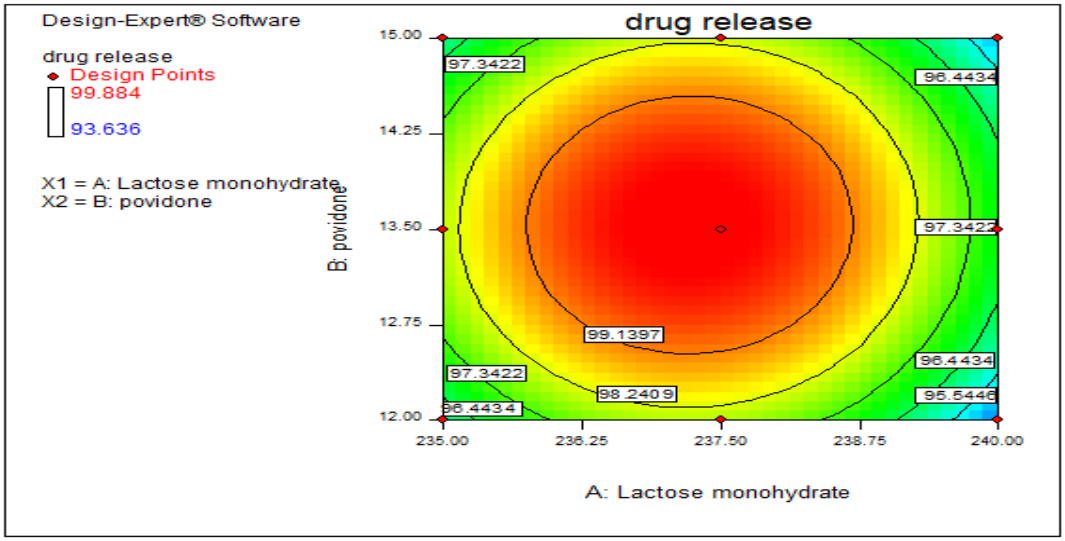

Fig 13 : Contour plot the effect of lactose monohydrate and povidone On % Drug release

Three Dimensional Graphical Presentations 3D surface

The 3D in figure shows that as increase in concentration of lactose monohydrate, it shows increase in drug release at some level and then there is decrease in % drug release as concentration of lactose monohydrate increases. It was concluded from the graph that the factor A have significance effect on the drug release.

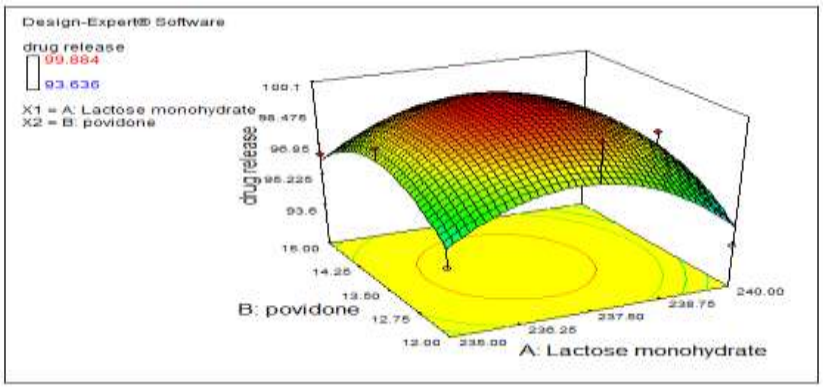

Fig 14 : 3D Surface Plot of % Drug Release of Ulipristal acetate with Respect to Lactose monohydrate and povidone

COMPARISON WITH MARKETED TABLET

ULIPRISTAL ACETATE

Marketed tablet: Fibristal

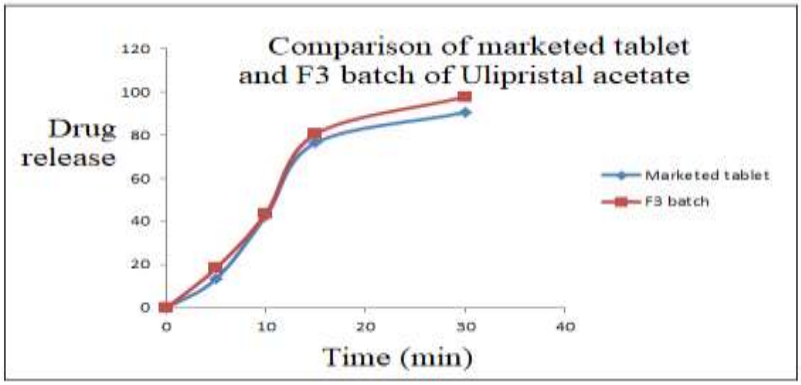

Fig 15 : In-vitro drug release of marketed tablet and optimized batch (F3) of Ulipristal acetate

From the above graph, it shows that there is increase in drug release of F3 batch due to the solid dispersion.

MIFEPRISTONE

Marketed tablet : Mifeprex

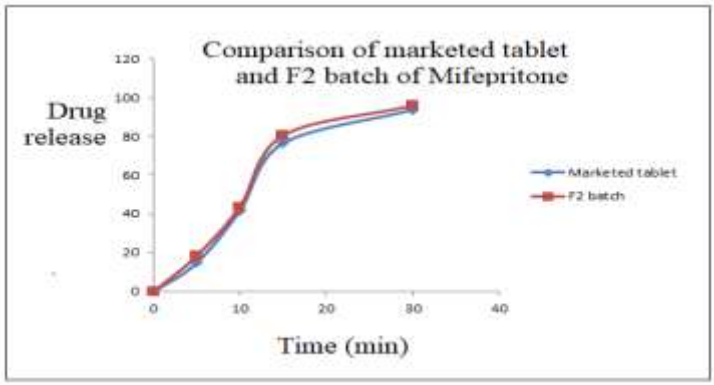

Fig 16 : In-vitro drug release of marketed tablet and optimized batch (F2) of Mifepristone

From the above graph, it shows that there is slight increase in drug release of F2 batch due to the solid dispersion.

STABILITY STUDIES[1]

According to ICH requirements, stability experiments on the optimized formulation were conducted. We examined a number of factors, including drug content and in vitro drug release, before and after 30, 60, and 90 days of stability. The following table displays the findings of stability investigations. Results of stability studies revealed that even under conditions of elevated temperature and humidity, the above-mentioned parameter did not significantly alter. The produced formulation is therefore stable and not significantly impacted by high humidity and temperature conditions, as shown by the stability studies.

Table 25 : Stability study of Optimized Batch of Ulipristal acetate formulation

Time (day)	Drug content (%)	In vitro drug release (%)
0	99.40	99.20
30	97.89	98.56
60	97.10	98.02
90	96.25	97.36

Table 26 : Stability study of Optimized Batch of Ulipristal acetate formulation

Time (day)	Drug content (%)	In vitro drug release (%)
0	99.40	99.20
30	97.89	98.56
60	97.10	98.02
90	96.25	97.36

Table 27 : Stability study of Optimized Batch of Mifepristone formulation

Time(day)	Drug content(%)	In vitro drug release(%)
0	99.29	99.34
30	98.97	98.92
60	97.62	97.05
90	96.89	96.90

SUMMARY AND CONCLUSION

Uterine fibroids are a major cause of morbidity in reproductive-age of women (and sometimes even after menopause). There are several factors attributed to the development and incidence of these common tumours, but this only adds to their relatively unknown pathogenesis. Fibroids are most commonly manifested by their impact on a woman's menstrual cycle or by symptoms of pelvic pressure. Fibroids are most commonly manifested by their impact on a woman's menstrual cycle or by symptoms of pelvic pressure. For preparation of solid dispersion, Ulipristal acetate and Mifepristone are used which are for

the fibroid treatment. The polymer used was PVP K-30 in the preparation of Ulipristal acetate and Mifepristone solid dispersion. Preformulation study was carried out using raw materials. Solid dispersion were formulated by using solvent evaporation method. The study was carried out on drug content and in vitro drug release from solid dispersion. All the formulations were subjected for evaluation. Results of pre-formulation studies, percentage yield, drug content and in-vitro drug release, have shown satisfactory results. The In-vitro study of formulations showed a significant release of Ulipristal acetate and Mifepristone. The data obtained for both the formulations were statistically analyzed by Design Expert Software 7.0.0. the Ulipristal acetate and Mifepristone solid dispersion tablets were prepared using 3^2 factorial design. From the evaluation of tablets, F3 batch of Ulipristal acetate and F2 batch of Mifepristone was found to be optimized which follows zero order and higuchi kinetics and drug release pattern respectively.

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