

# Preparation and Characterization of a Novel Optimum Modified Liquisolid Compact to Enhance the Dissolution Profile of Mifepristone

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## ABSTRACT

Most drugs used to treat vaginal disorders are administered orally or parenterally. Mifepristone (MFP) is a Biopharmaceutical Classification System class IV drug that is currently used to abort pregnancies under 70 days long. To improve bioavailability, a modified liquisolid compact (MLSC) formulation has been proposed for vaginal administration for off-label treatment of uterine fibroids. The MLSC was prepared using ultrasonication with pre-screened excipients to minimize the bulk of the final formulation and enhance properties for commercial viability. The MLSC formulation was evaluated for physical properties (including morphology, uniformity, wettability) and in vitro dissolution of MFP. The results showed 85–90% of MFP was released in 90 mins at a pH range of 1.2–7.4, and dissolution in water supports pH-independent dissolution process. Faster dissolution at vaginal fluid pH may minimize the associated adverse effects of the dose. The physical modification of MFP as an MLSC formulation improved dissolution and absorption for potential vaginal administration.

**KEYWORDS:** Dissolution, powder characterization, site specificity, probe sonication, pH-independent release

## INTRODUCTION

Approximately 20–80% of women develop uterine fibroids (UF) by age 50 (1). General treatments for UF include invasive therapy and some oral medications like contraceptive pills and progestational agents, or parenteral injections of gonadotropin-releasing hormone (GnRH) agonists, i.e., leuprolide acetate and intrauterine devices. The United States FDA has approved MYFEMBREE (relugolix, estradiol, and norethindrone acetate; Pfizer and Myovant Sciences), a once-daily pill for managing heavy menstrual bleeding associated with UF in premenopausal women, with a treatment duration of up to 24 months (2, 3). Recent domestic and international clinical studies have demonstrated that 3 months of mifepristone (MFP) treatment can significantly reduce the size of UF to achieve complete amenorrhea, improve anaemia-related bleeding, lessen clinical symptoms, and reduce the size of UF (4, 5). Due to the hepatic first-pass

effect and low drug solubility at physiological pH, the drug's oral bioavailability is reported to be 40% (6).

Conventional oral MFP formulations fail to meet the need for therapeutic concentration and the patient may get dose-related adverse effects (7–9). Researchers have attempted to increase the physiological availability of MFP by developing various delivery systems, altering the route of administration, and creating multiple carrier systems (10, 11). UF is a localized disorder in which intrauterine distribution through the vaginal site is considered an ideal approach. Although site-specific drug delivery for the localized treatment of UF has not gained much attention, intravaginal MFP administration can improve the treatment of localized disorders (10). MFP is considered a Biopharmaceuticals Classification System (BCS) class IV drug on the basis of insufficient permeability of MFP on Caco-2 cells (11, 12). Therefore, augmentation of both solubility and permeability of MFP is essential to get the

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in vivo therapeutic response. The current study aims to enhance MFP's bioavailability with physical alterations and changing the route of administration.

Various methods have been studied to improve drug solubility and dissolution in pharmaceutical formulations, including a liquid-solid compact (LSC) formulation (9, 13–15). The amount of bulk in a traditional LSC may be unattainable for designing formulations like tablets, capsules, topical preparation, and others (16). Therefore, the modified liquisolid compact (MLSC) formulation was proposed to improve solubility of MFP at the physiological pH range of 1–7.4, using an ultrasonicator and polymer precipitation inhibitor (15). The ultrasonicator technique has resulted in maximum solubility augmentation compared to the traditional LSC method (15). The MLSC formulation was selected to provide pH-independent dissolution and maximize drug solubility into the compact with a co-solubilizer, potentially resulting in additional bulk reduction and extending commercial viability (17).

## METHODS

### Materials

The MLSC was prepared with blend of polyethylene glycol (PEG) and vitamin ETPGS (d- $\alpha$ -tocopheryl polyethylene glycol 1000 succinate) in a 1:1 ratio (% w/w), then precipitation enhancer (polyvinyl pyrrolidone [PVP] K30, 2% w/v) was added, followed by carrier (Avicel pH 101) and adsorbent (Aeroperl 300) in a 5:1 ratio.

MFP was procured from Pellucid Pharma, Ahmedabad, India. Methanol, propylene glycol (PG), tween 80, PEG 400, PEG 600, glycerin, and PVP K30 were purchased from Loba Chemie (Mumbai, India). Capmul MCM30 was gifted from Abitec (USA). Capryol 90, Lauroglycol, Plurol Oleique, and Avicel (pH 101, 102, and 112) were procured

from FMC Biopolymer (Ireland). Aerosil 200, 300, and Aeroperl 300 were obtained from Evonik Industries AG (Germany). Vitamin ETPGS was procured from Sigma Aldrich USA. All the other solvents and reagents used were analytical grade.

### Modified Liquisolid Compact (MLSC) Preparation

The process for MSLC preparation is depicted in Figure 1.

#### Selection of Non-Volatile Liquid Solubilizer

All excipients and solvents were selected, considering their safety, using the inactive ingredient database. The solubilizer was selected using the saturated solubility studies. The solubility of MFP was studied in various non-volatile liquids, including PEG 200, PEG 400, PEG 600, glycerin, tween 80, Capmul MCM30, Lauroglycol, and Plurol Oleique (18). Vitamin ETPGS in the concentration range of 0.5–2% w/v and PVP K30 in the range of 1–3% w/v was also studied for MFP solubility in the presence of a selected blend of solvents that act as a precipitation inhibitor (19). An ultrasonic processor (VCX 500, Vibra-Cell) was utilized to get maximum solubility into the selected blend; sonication time 10 sec intervals for 5 min at 40 °C.

#### Selection of Solid Carrier

The binding capacity method was used to select a suitable solid carrier for the liquid blend. Avicel pH 101, 102, and 112 were selected as carrier materials. The addition of 0.1 mL of the liquid blend to 1 g of carrier material was continued until an acceptable range of Carr's index was attained (18).

#### Selection of Adsorbent Material

Flowability of the compact is a valuable attribute for processing into a solid dosage form. Aerosil 200, Aerosil

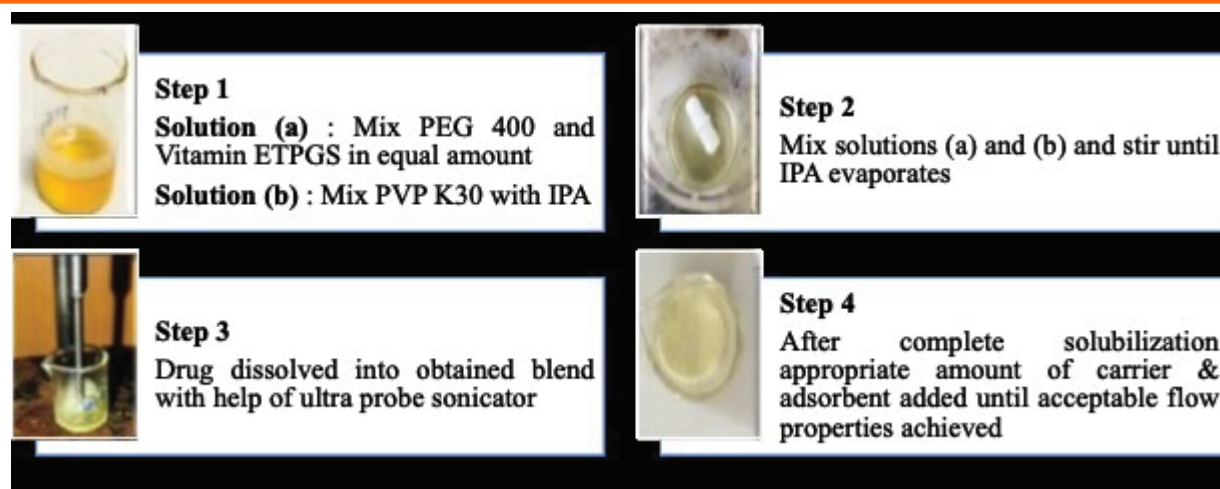


Figure 1. Method for preparation of modified liquisolid compact. IPA: isopropyl alcohol; PVP K30: polyvinylpyrrolidone; PEG: polyethylene glycol.

300, and Aeroperl 300 were screened, and final compacts were evaluated for flow characteristics like Carr's index and angle of repose.

### **Physical Appearance, Flow Properties, and Drug Content of MLSC**

Morphology of the MLSC was assessed using a scanning electron microscope (SEM) (JSM 6010 LA, USA). The samples were mounted on an aluminum stub with double-sided adhesive tape to ensure the specific adhesion of the inserts. A platinum coating was used to reduce thermal disturbance. An applied voltage was used to image the coated samples (20). Powder x-ray diffraction (XRD, D2-phase, Bruker) was used to determine the physical state of MLSC. The patterns were documented via Ni-filtered Cu K $\alpha$  at 40 kV voltage, 20 mA, and steps of 0.02° for 2 seconds, with a scanning speed of 0.01° per second in the intermission 2 $\theta$  at 10–45 (21).

Flow properties (i.e., angle of repose) were determined by the fixed funnel method (22).

To assess content uniformity, a 44-mg MLSC, equivalent to 10 mg of MFP, was weighed and solubilized in 10 mL methanol. The solution was placed in a vortex mixer (CM-101 plus, REMI) at 1000 rpm for 2 hours. The solution was filtered by a 0.4- $\mu$ m syringe filter and measured using a validated high-performance liquid chromatography (HPLC) (W2998 PDA, Waters Alliance, Australia) method with a C8 column reverse-phase (Zorbax SB-C8, 5  $\mu$ m, 150  $\times$  4.6 mm). The mobile phase was methanol, acetonitrile, water (50:25:25% v/v/v) with a flow rate of 0.8 mL/min, run time 10 min, injection volume 20  $\mu$ L, and sample 304 nm (unpublished literature) using a linear equation.

Triplicate batches were prepared, and the average value was considered for further characterization.

### **Fourier Transform Infrared Spectroscopy (FTIR)**

Interactions between the drug and excipients in the MLSC were studied using Fourier transform infrared spectroscopy (FTIR) (NICOLET 6700, Thermo Scientific, USA) (23). In the analysis, a sample was triturated with KBr before being compacted into pellets (4–5 tons) by the press for 4–5 minutes. The prepared pellet was 10–15% of the formulation with dry KBr. The sample was scanned in the FTIR spectra of 4000–500 cm<sup>-1</sup>.

### **Wettability**

The wettability of a drug particle significantly affects the dissolution rate of the formulation because wetting is a prerequisite to dissolution (24). Wettability of powders was measured using the Washburn method with a tension force tensiometer (Sigma 700/701). The contact angle was

calculated from the weight increase over time when the powder sample was in contact with the liquid. Wetting was measured by the change in mass over time during the liquid phase. When the mass starts to remain constant, no more liquid can penetrate, which was considered the endpoint of measurement.

### **Headspace Gas Chromatography**

Residual solvent, i.e., isopropyl alcohol utilized to dissolve PVP K30, is rigorously monitored and regulated at a level that cannot impact drug safety potential. Headspace gas chromatography (Turbo matrix 40 Perkin Elmer) was used to identify the residual solvent in MLSC (25). Chromatographic conditions were as follows: Elite 624 column (1.80  $\mu$ m, 30 m  $\times$  0.32 mm), 7 °C/min, injection temp: 210 °C, oven temp: 60 °C, 2-min hold, detector temp: 250 °C, carrier gas: nitrogen, carrier flow: 14 psi. Headspace conditions were as follows: gas temp 80 °C, needle temp 85 °C). A sample was put in a locked vessel and heated to an identified temperature profile. The vapor in the container was tested for analysis.

### **In Vitro Drug Release**

MFP has pH-dependent solubility, so the U.S. Food and Drug Administration recommends two dissolution conditions using apparatus 2 (paddle): 75 rpm with 900 mL of 0.01 N HCl and 50 rpm with 900 mL of pH 1.8 KCl. Maximum solubility is reported at pH 1–3 (26). An optimum MLSC formulation was proposed to improve drug release in a physiological pH range of 1–7.4. Dissolution tests were performed with acetate buffer pH 1.2, phosphate buffer pH 4.5, 6.8, and 7.4, and water for vaginal application according to Dobaria et al. (i.e., 25 mL, 50 rpm, 37  $\pm$  0.5 °C, with sampling at 15, 30, 45, 60, and 90 min; 1-mL samples were withdrawn and filtered through a 0.45- $\mu$ m filter for analysis). For discriminating the dissolution profiles of MFP and MLSC, 0.5% Tween 80 was added to the media. The sample amount withdrawn was replaced with fresh dissolution medium (same volume, kept at 37 °C). Each dissolution test was carried out in triplicate. A validated HPLC method of MFP was performed using an HPLC system (E2695, Waters Alliance) and Empower 3 software, equipped with a photodiode array (PDA) detector, Phenomenex C18 column (5  $\mu$ m, 250  $\times$  4.6 mm) at 304 nm. The same dissolution method was used for all media.

### **Dissolution Efficiency**

Dissolution efficiency (DE) was calculated as the area under the dissolution curve up to a specific time *t*, expressed as a percentage of area of the release assay curve and the rectangle that represents 100% dissolution (28).

### Drug Release Kinetics

The release data from the optimized MLSC formulation were subjected to several kinetic models, i.e., zero-order, Korsmeyer–Peppas, Higuchi, and first-order, to demonstrate the release mechanism of MFP from the MLSC (21, 26).

### Stability

Stability tests were performed to determine the formulation's stability and shelf life. MLSC was filled into capsules, packed under aluminum foil, and sealed to represent specific packaging. The optimized MLSC formulation was subjected to an accelerated stability study for 6 months as per ICH Q1(R2) (29). Parameters including the angle of repose, physical appearance, drug content, and dissolution were studied during certain intervals.

## RESULTS AND DISCUSSION

MFP's maximum solubility (15–16 mg/mL) was achieved in PEG 400. With the help of ultrasonication, drug particle size was reduced, and solubility increased to 90–100 mg/mL. Co-solubilizers (vitamin ETPGS and PVP K30) were added during ultrasonication to reduce bulk and improve solubility. Solubility study results with PEG 400, vitamin ETPGS, and PVP K30 showed maximum solubility augmentation (290–300 mg/mL) compared to PEG 400 alone. A blend of PEG 400, vitamin ETPGS, and PVP K30 in the ratio of 1:1:2 was used for the optimized MLSC formulation.

Binding capacity was used to select the suitable carrier material for the liquid blend of the drug. Avicel pH 101 was selected as it showed the highest binding capacity (0.5 mL/g), whereas Avicel pH 102 and pH 112 had 0.2 and 0.17 mL/g binding capacity, respectively. Aeroperl 300, having the lowest Carr's index (13.24), was selected as an adsorbent material to impart flow properties, whereas Aerosil 200 and 300 had 15.02 and 17.74 Carr's index values, respectively.

### Physical Properties of MLSC

SEM and XRD studies showed reduced crystallinity of MFP in the MLSC formulation compared to the pure drug, as shown in Figure 2.

The SEM image of MLSC shows reduced crystallinity of MLSC compared to the drug. On the other hand, the XRD pattern of the drug revealed prominent peaks at 21.2°, 16.4°, 18.6°, 20°, 21.5°, 23.2°, 26.5°, demonstrating MFP's crystalline nature. The XRD pattern of the MLSC exhibited weak peaks compared with the pure drug. Partial amorphization of the drug was seen in the range

of 20–30°, which was due to presence of the hydrophilic chain of vitamin ETPGS.

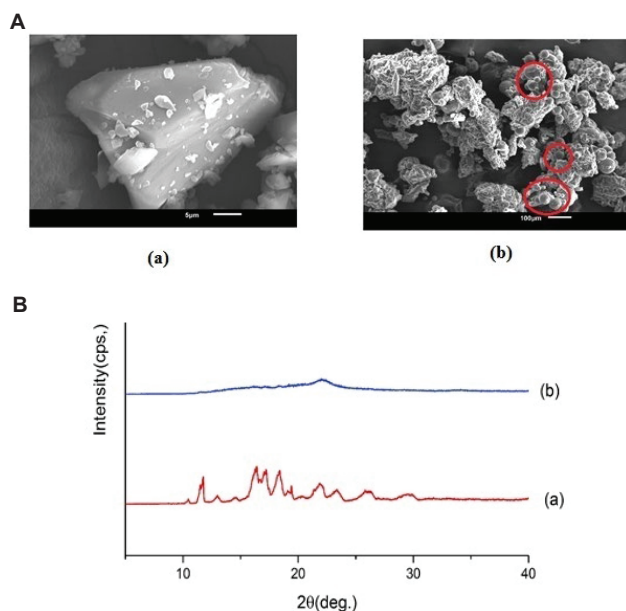


Figure 2. (A) Scanning electron microscope (SEM) images and (B) x-ray diffraction (XRD) graph of (a) mifepristone and (b) modified liquisolid compact formulation.

Flowability was assessed using the angle of repose. Values in the range of 25–27 suggest excellent flow properties. Drug content was 98–99%, which is within the appropriate specification range for uniformity per *Indian Pharmacopoeia*. The yield from triplicate batches was 95–97%, indicating the suitability of the preparation method.

### FTIR

All characteristic peaks of MFP were retained in the final MLSC formulation, which shows the drug's compatibility with the formulation.

The FTIR spectra of the drug showed distinctive peaks, which comprised peaks at 3381  $\text{cm}^{-1}$  for -OH (hydroxyl group), 2878  $\text{cm}^{-1}$  for C-H stretching (methyl and methylene groups), and at 1655 and 1517  $\text{cm}^{-1}$  for C-H stretching (aromatic nucleus). In the optimized batch FTIR, the analysis revealed lower intensity of existing characteristic peaks of MFP, which confirmed the absence of any physical interaction with excipients used in the preparation of MLSC.

### Wettability

Using the Washburn method at the end of 5 minutes, the maximum weight gain observed for the drug was 300 mg, whereas for MLSC it was 530 mg. This shows increased wettability of the MLSC formulation compared with pure MFP. This observation may be related to augmentation

of the drug's solubilizer blend, which could further act as a surface-active agent and reduce hydrophobicity of the drug particles.

### Headspace Gas Chromatography

In the MLSC composition, isopropyl alcohol was used as an organic solvent to dissolve PVP K30. The limit was 0.83 ppm, which is acceptable for pharmaceutical formulations (i.e., limit of 5000 ppm) (30, 31).

### In Vitro Drug Release

Comparative in vitro drug release profiles of the drug and MLSC in various dissolution media are shown in Figure 3. Drug release from API dispersion was approximately 4.5% after 90 min due to the presence of Tween 80. In vitro drug release profiles of the drug at various pH levels show the pH-dependent solubility of the drug. In comparison with MFP, the dissolution rate of all MLSC formulations was remarkably enhanced. Possible reasons for the improvement in dissolution include conversion of MFP from its crystalline to amorphous state and improved wettability (32).

and 14.66–15.33%, respectively. This further indicates excellent improvement in the dissolution rate of MFP from prepared MLSCs as compared to other methods reported for dissolution enhancement of MFP (33, 34).

Table 1. Dissolution Efficiency (DE) of Drug and MLSC at Various pH Levels

Dissolution Medium pH	DE of MFP (%)	DE of MLSC (%)
1.2	0.76	15.33
4.5	0.43	15.16
6.8	0.21	14.66
7.4	0.23	15.33
Water (7.0)	0.38	15.33

MFP: mifepristone; MLSC: modified liquisolid compact

### Drug Release Kinetics

The drug release mechanism follows the zero-order model ( $R^2 = 0.9233$ ), which indicates pH-independent release of MFP from the MLSC.

### Stability

After 6 months, none of the parameters deviated from their acceptable range. Dissolution was carried out in water, considering the pH-independent dissolution of MFP from the MLSC formulation. No significant changes were observed in the rate of dissolution at selected sampling intervals, as shown in Table 2. Therefore, the MLSC formulation was stable.

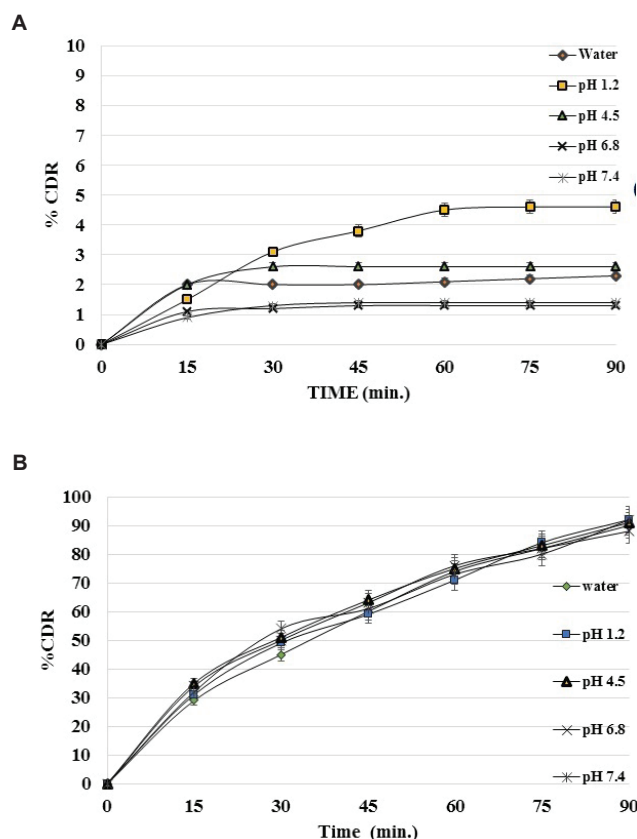


Figure 3. In vitro dissolution profile of the (a) mifepristone and (b) modified liquisolid compact formulation. CDR: cumulative drug release.

### Dissolution Efficiency

DE values at various pH levels are shown in Table 1. The DE of MFP and MLSC were in the range of 0.21–0.76%

Table 2. Stability Study of the MLSC Formulation

Parameters	0 month	3 months	6 months
Appearance	Yellowish white	Yellowish white	Yellowish white
Angle of repose	25 ± 1	26 ± 1	26 ± 1
Cumulative drug release (%)			
15 min	35 ± 2	36 ± 2	35 ± 2
45 min	64 ± 2	65 ± 2	64 ± 2
90 min	91 ± 2	90 ± 2	90 ± 2
Assay %	99.2 ± 1	99.3 ± 1	99.2 ± 1

\* CDR: Cumulative Drug Release; MLSC: Modified liquisolid compact

### CONCLUSION

Popular treatments for UFs include surgery, intramuscular injectable formulations, and various oral medications. The impact of adding MFP to the targeted delivery route may be limited by its solubility. The physical modification of MFP into an MLSC formulation successfully improved dissolution and absorption for potential vaginal administration, which may improve efficacy of treatment for UF and reduce dose-related effects.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest and financial disclosure concerning this study.

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