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Original Article

Investigating the Effect of Mixed Hydrotropy Approach on Solubility Enhancement of Felodipine

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ABSTRACT

Poorly soluble drugs are sources of concern in pharmaceutical formulations. Hydrotropes are compounds that enhance the solubility of insoluble materials in solvents. The hydrotropic solubilization concept is one of the most effective methods for avoiding the usage of organic solvents. The present research study used a hydrotropy strategy in order to enhance the solubility of felodipine implementing a mixed hydrotropic molecule. The experiment was carried out by assessing the medication's solubility in combinations with hydrotropic agents. Sodium benzoate, nicotinamide, and sodium citrate were used at 10%w/v concentrations. Sodium benzoate and nicotinamide as a mixed hydrotropic agent increase the solubility of felodipine significantly in comparison with the other hydrotropic combination and its aqueous solubility. By using a solvent evaporation method, three formulas of felodipine mixed hydrotropic solid dispersions at different ratios were prepared. The drug content of prepared formulae has been established, FTIR, XRD, SEM, and dissolution studies. The achieved findings disclosed the solubility of felodipine increases synergistically by mixed hydrotropy six times in comparison with aqueous solubility of pure drug, F1(1:2) shows highest dissolution rate. FTIR results suggest no interaction between drug and hydrotropic agents. Reduced crystallinity was observed in XRD and SEM. The notion of mixed hydrotropic solid dispersion was demonstrated to be a cost-effective way for increasing the bioavailability of medications with low water solubility.

Keywords: Hydrotropy approach, Felodipine, Enhancement of solubility, Mixed hydrotropic agents, Solvent evaporation method.

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INTRODUCTION

Bioavailability and drug solubility have the most impact on efficiency of a medicine and optimization of drug therapy.[1] Solubility is one of the critical factors for achieving pharmacological response.[2] The hydrotropic solubilization concept is one of the most effective methods for avoiding the usage of organic solvents.[3]

Hydrotropes include both hydrophilic and hydrophobic components, but their hydrophobicity is less than that of the surface-active agents. The efficacy of hydrotrope solubilization can be assessed by its combination of hydrophilic and hydrophobic components. A molecule's hydrotropic potency increases when the hydrophobic component loads up and the hydrophilic component loads down.[4] Despite the widespread usage of hydrotropic drugs, little is understood about how hydrotropy works. Numerous hypotheses and research investigations are being attempted in order to acquire a better understanding of the hydrotropy mechanism.[5]

The active ingredient for hydrotrope formulation in the current investigation was Felodipine (FLP) Which is chemically described as 1,4-dihydro-derivative (Figure 1), clinically classified under vasoselective calcium antagonists, in addition it is completely excreted as metabolites and undergoes extensive metabolism in the gut and liver.[6,7]

Due to felodipine's low oral bioavailability, poor water solubility, and substantial first pass metabolism, dissolution augmentation is required to produce the optimum pharmacological response. A range of formulation solutions, including nanoparticles, solid dispersions, and microparticles, were created to improve felodipine solubility in order to increase oral bioavailability.[8,9]

FLP has the distinct benefit that it's more selective as a vasodilator and having fewer cardiac effects than other calcium channel blocker, however it only has a 15% bioavailability after oral administration.[10]

As solubilizing agents, sodium benzoate, urea, nicotinamide, sodium citrate, and sodium acetate have all been utilized in the literature. Solid dispersion techniques have been used to improve

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the rate of absorption and/or total bioavailability of weakly water-soluble medicines. The most prevalent ways for producing hydrotropic solid dispersions include solvent evaporation, fusion, and fusion-solvent processes.[11]

The fundamental benefit of the Hydrotropic Solid Dispersion (HSD) method is that it does not require any organic solvent, making it simple to use. If necessary, low-temperature evaporation is utilized to remove excess water from the mixture.[12]

The present research work is focused to enhance solubility of FLP using hydrotropic solubilization technique with different hydrotropic agents' combination.

MATERIALS AND METHODS

Materials

FLP was purchased from Kathy for chemicals and equipment's distribution in the Middle East. Sodium benzoate and nicotinamide were bought from central drug house pvt. Ltd., Delhi, India, trisodium citrate was acquired from Loba chemic pvt. Ltd., Mumbai, India. All other chemicals were of analytical reagent grade.

Methods

Calibration curves of FLP

Calibration curves of FLP in water

The stock solution was produced by dissolving 100 mg of FLP pure powder, which was accurately weighed, in 30 mL of ethanol, and then adding 100 mL of water containing 0.5% tween 80 in a volumetric flask. A UV-visible spectrophotometer was used to test the absorbance at 364 nm for several standard solutions that were created from stock solution. (Shimadzu, Japan).[13]

Calibration curves of FLP in 0.1N HCl

To prepare the stock solution, a precisely weighed 100 mg of FLP pure powder was dissolved in 30 mL of ethanol and the final volume was made up to 100 mL of 0.1 N HCl with 1% tween 80 in a volumetric flask. Different standard solutions were made from stock solution, and the absorbance was measured in a UV spectrophotometer at 364 nm using a UV-visible spectrophotometer (Shimadzu, Japan).

Calibration curves of FLP in Ethanol

To make a stock solution, 100 mg of FLP was carefully weighed and dissolved in 100 mL of ethanol in a volumetric flask. After preparing various reference solutions, the absorbance was measured in a UV spectrophotometer at 364 nm using a UV-visible spectrophotometer (Shimadzu, Japan).

Determination of Equilibrium solubility of FLP

The equilibrium solubility of FLP was measured in Distilled Water (DW) and solutions of mixture of hydrotropic agents at a concentration of 10% w/v as mentioned in (Table 1). An excess amount of FLP was added to 5 mL vials containing distilled water and mixed hydrotropic solutions and shaken in an incubator shaker at a speed of 200 rpm for 24 hr. These solutions were allowed to equilibrate for 24 hr before being centrifuged at 2000 rpm for 5 min. Supernatants were filtered using Whatman filter paper No. 41, diluted appropriately, and spectrophotometrically measured at 364 nm using a Shimadzu Ultraviolet (UV) visible spectrophotometer (Japan).[14,15]

The following formula was used to compute enhancement ratios in solubility:

$$\text{Enhancement ratio} = \frac{\text{solubility of drug in hydrotropic solution}}{\text{solubility of drug in water}}$$

Preparation of Hydrotropic Solid Dispersion (SDs)

FLP and a hydrotropic blend in various ratios [1:2], [1:4] and [1:8] were precisely weighed. Hydrotropic agents (sodium benzoate and nicotinamide) were dissolved in a 100 mL beaker containing the smallest (possible) volume of DW at 80°-85°C on magnetic stirrer and then FLP was added. Stirring was continued until a semisolid was obtained in the beaker (after a substantial amount of water was evaporated), which was distributed in thin layers on watch glasses for speedy drying. The watch lenses were dried in oven at 40°C. After nearly complete drying, the solid dispersion powder was passed through a sieve mesh size 70, yielding a hydrotropic solid and stored in tightly closed container for further studies.[16,17]

Evaluation of hydrotropic solid dispersion containing FLP

Saturated Solubility Study of FLP in Mixed Hydrotropic SDs

A saturation solubility test was carried out to evaluate the solubility of FLP in the prepared SDs. Extra amounts of SDs (F1, F2, and F3) were added to vials holding (10 mL) of DW. The vials were shaken for 24 hr at 37±0.5°C using a mechanical bath shaker. A syringe filter with a grade of 0.45 µm was employed for filtration the solution. Appropriate volume of the filtrate was diluted with water and measured at 364 nm using a UV spectrophotometer.

Determination of Drug Content in Mixed Hydrotropic Solid Dispersions

Drug content of FLP in the prepared Mixed hydrotropic SDs that contain a blend of hydrotropic agents (sodium benzoate, sodium citrate, and nicotinamide) was analyzed in order to get the actual amount of drug in each formula. A weight of each formula equivalent to 10 mg of FLP was carefully weighed and dissolved in ethanol in 50 mL volumetric flask. The solutions were agitated for 30 min before being filtered through Whatman filter

Table 1: Equilibrium solubility Studies of FLP in hydrotropic blends.

hydrotropic blends	Concentration % w/v	Individual concentration % w/v
SB⋆+N⋆	10	5
N+SC⋆	10	5
SB+SC	10	5
*N: Nicotinamide	SB⋆: Sodium Benzoate	SC⁎: Sodium Citrate

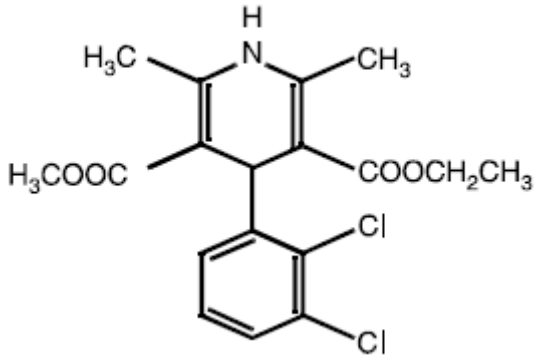


Figure 1: Chemical Structure of Felodipine.

paper 41 and properly diluted before being analyzed for drug concentration with a UV-visible spectrophotometer at 364 nm, The analysis was carried out three times. The following equation was used to compute the average drug content.[18]

$$\text{Content uniformity} = \frac{\text{Actual drug amount in solid dispersion}}{\text{Theoretical drug amount in solid dispersion}} \times 100$$

Dissolution rate studies

Using a USP II dissolution equipment with a paddle stirrer, the dissolution profile of FLP from pure powder and formulae of mixed hydrotropic SDs (F1, F2, and F3) were investigated in 0.1N HCl solution (pH 1). A sample of SDs equal to 5 mg of FLP was tied in a mesh cloth and placed in a dissolution jar with 500 mL of dissolution fluid. The temperature was maintained at 37±0.5°C throughout the experiment, and the paddle's rotational speed was set to 50 rpm. At predetermined intervals, samples of the 5 mL dissolving medium were removed and replaced with fresh samples of the same volume. The samples' drug content was examined using an absorbance measurement at 364 nm.[19,20]

Fourier Transforms Infrared Spectroscopy (FTIR)

After performing the necessary background removal, the FTIR spectrum of the medication and the optimized hydrotropic solid dispersion were recorded using an FTIR spectrophotometer (BRUKER, USA) connected with an ATR system. Each spectra was examined in the 400-3600 cm^{-1} analytical range.[21,22]

Powder X-ray diffraction (PXRD)

Analytical XRD equipment (XRD-6000, Shimadzu, Japan) was used to analyze the powder X-ray diffractograms of the pure medication and the chosen formula. The scanning range was between 10° and 80° on a scale of 2θ, with a 10°/min scan speed. The electric current's intensity and voltage were 40 KV and 30 mA, respectively.[23,24]

Scanning Electron Microscopy (SEM)

Both the form and solid-state physical structure of pure drug, as well as the most suitable formula of mixed hydrotropic solid dispersion, have been examined using SEM. The images taken with a SEM were captured using a VEGA (TESCAN) scanning electron microscope with an accelerating voltage ranging from 0.5 to 30 KV.[25,26]

Statistical analysis

All experiments have been conducted in triplicate, and findings were expressed as means standard deviation. Both the two-sample t-test and one-way Analysis of Variance (ANOVA) were used independently. When the estimated *p* values were less than 0.05, the variation was considered statistically significant. Comparison of Dissolution Data Profiles, DDsolver Software Program was used.

RESULTS AND DISCUSSION

UV spectrophotometric scan of FLP wavelength λ_{max} and calibration curves of felodipine in different medias were shown in Figure 2 (A, B, C and D).

Equilibrium solubility of FLP in mixed hydrotropic solutions

The results of solubility of FLP in mixed hydrotropic solution using sodium benzoate, nicotinamide and sodium citrate were listed in Table 2 and Figure 3, and the higher solubility was obtained in solution containing a combination of sodium benzoate and nicotinamide hydrotropic agents at 10% w/v and showed that the solubility of FLP was increased six times in this hydrotropic blend in comparison with water. So, this hydrotropic compound was chosen to be used in the preparation of solid dispersion.

Determination of drug content and saturation solubility of mixed hydrotropic solid dispersion

The drug content of all solid dispersion formulations at the ratios given below have been found to be within pharmacopoeia guidelines, ranging from 95%±0.33 to 105%±0.4, as revealed in Table 3. It points out that the drug is evenly distributed throughout all powder forms. For saturation solubility, the solubility of drug in the prepared MHSD* was raised in all formulas as shown in Table 3, and these results suggest that hydrotrope improves the solubility of drugs with low water solubility.[27]

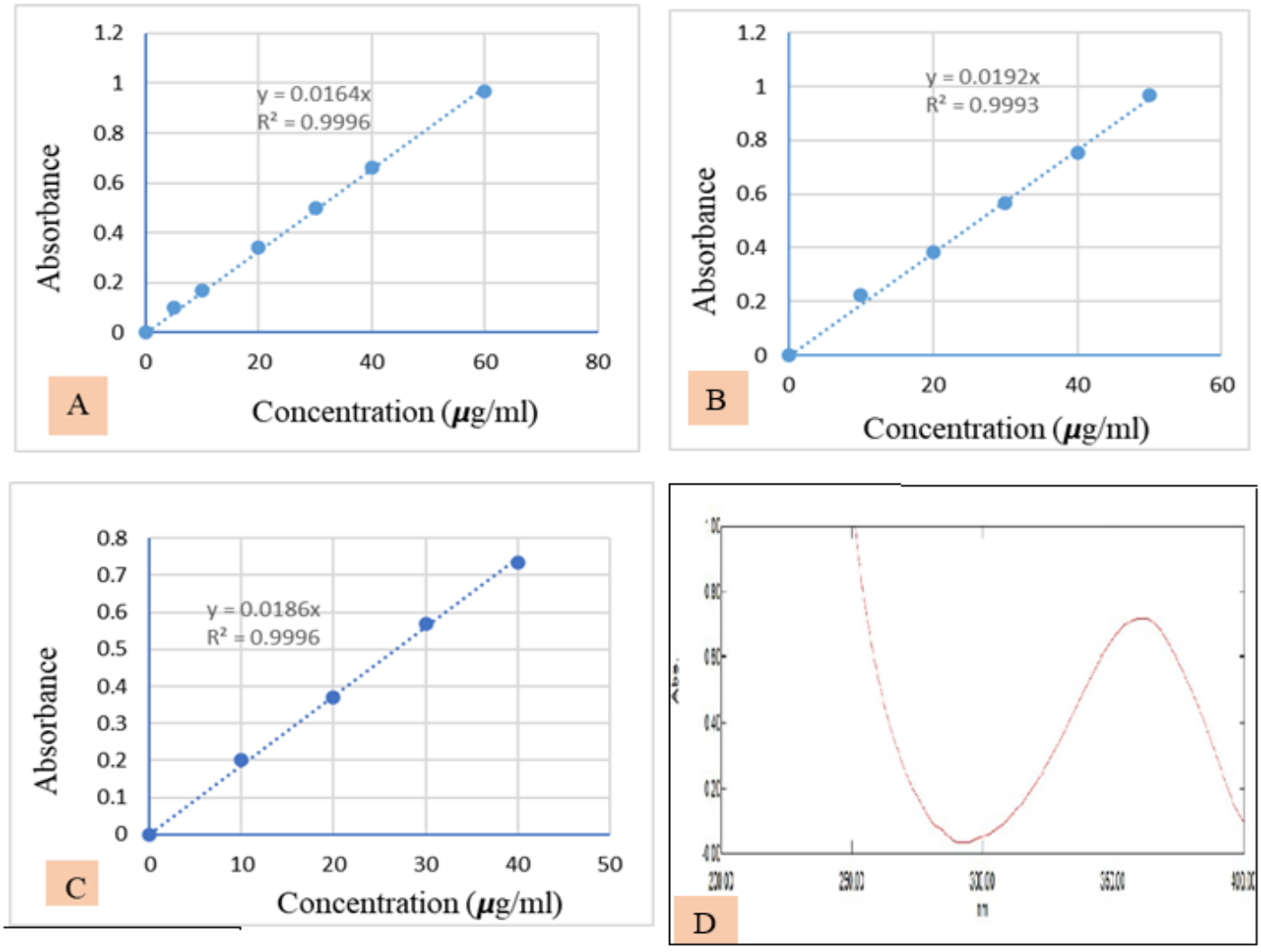


Figure 2: Calibration curves of FLP in water (A), ethanol (B),0.1N HCl (C) and UV Spectrophotometric scan of FLP wavelength [λ_{max}] (D).

Table 2: Equilibrium solubility of Felodipine in mixed hydrotropic solutions.

Mixed hydrotropic solution	Concentration % w/v	Individual concentration % w/v	Solubility (µg/mL)	Solubility enhancement ratio
SB+N	10	5	1.65±0.2	6
SB+SC	10	5	0.98±0.23	3.5
SC+N	10	5	0.83±0.1	3
Water	----	------	0.28±0.3	------

Some of the most likely mechanisms by which a hydrotrope might improve solubility are the formation of complexes between hydrotropes and drugs, a breakdown in the structure of the water molecule, and self-stacking organization of hydrotropic molecules contrary to the solute in the solution, and this is the most widely embraced.[28]

Dissolution rate studies

The results of the *in vitro* release study at 0.1N HCl are shown graphically in Figure 4, which shows that 40% drug release from pure drug at 30 min, while 90%, 86% and 48% drug released from F1 (1:2), F2 (1:4) and F3 (1:8) respectively. Hence, the dissolution rate of FLP was improved significantly *p*-value 0.001 ($p<0.05$) when it is prepared as hydrotropic solid dispersion. Comparison in the release profile of FLP in the overall time from F1 and F2, it is considered no significant difference between them (*p*-value 0.44) at 1:2 and 1:4 ratio respectively. However, the optimized formula was selected based on desirability calculations in order to attain maximum dissolution efficiency percent at 15 min $\%DE_{15}$ and as well as minimum MDT.[29] So $\%DE_{15}$ of F1 and F2 was 58%

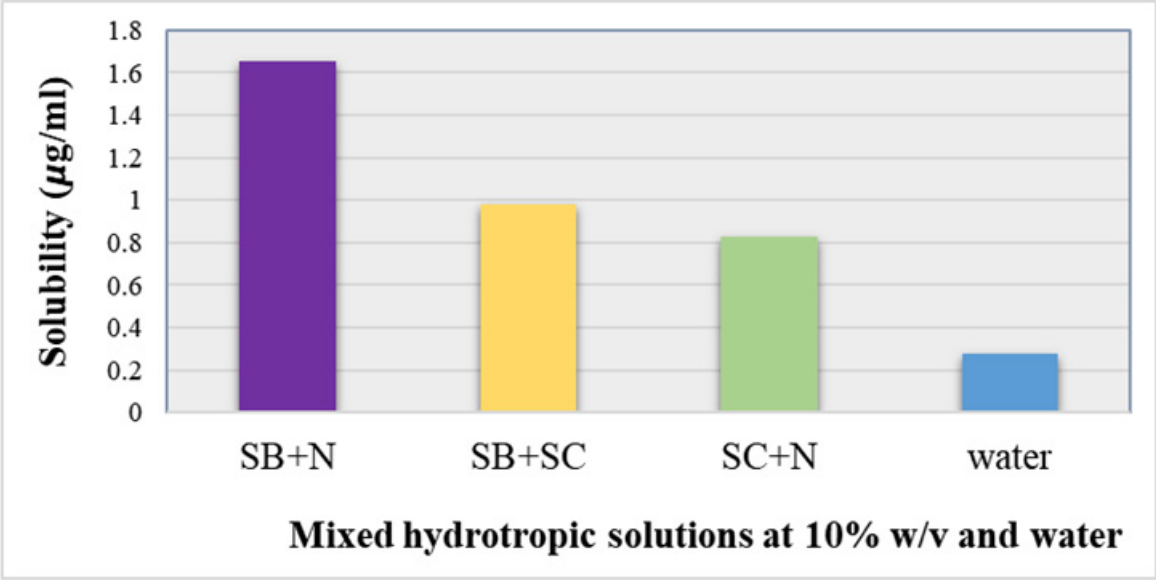


Figure 3: solubility of FLP in mixed hydrotropic solutions.

Table 3: Drug content and Saturation solubility of drug in MHSD. ∗

Drug: hydrotropic agent ratio	% drug content	Solubility of FLP in solid dispersion (µg/mL)
F1 MHSD (1:2)	95%±0.33	3 ±0.1
F2 MHSD (1:4)	102%±0.67	2±0.14
F3 MHSD (1:8)	105±0.4	2.3±0.2

∗MHSD: Mixed hydrotropic solid dispersion.

and 39% respectively, while MDT for each one was 5 and 12 respectively, from those parameters it was clear that formulae F1 delivered the highest enhancement effect on FLP dissolution and release rates.

Fourier Transforms Infrared Spectroscopy (FTIR)

From the FTIR spectra of FLP (Figure 5 A), it was observed that the peak attributed to the stretching vibration of the amino group presents at 3367 cm^{-1}, while stretching vibration of methyl C-H at 2838, 2948 cm^{-1}, bending vibration of methyl C-H at 1380 cm^{-1}. Skeletal C-C vibration was appeared at 726 cm^{-1}, aromatic ring and C-H stretch were observed at 1493 and 2980 cm^{-1} respectively. Stretching vibration of C=O was at 1687 cm^{-1}, these characteristic peaks indicate the purity and crystallinity of felodipine.[10,30]

In the FTIR spectra of F1 mixed hydrotropic SD at ratio (1:2), similarities can be seen with FTIR of pure drug as shown in (Figure 5 B). However, peaks have shifted into the low range, and the spectrum for selected hydrotropic solid dispersion formulation supports the existence of small intermolecular interactions between hydrotropic agents and drug. The modest magnitude of the peak shift is most frequently used to identify the weak interactions. The creation of hydrogen bonds could be the cause of the observed decrease in the intensities of FLP's distinctive absorption bands in the solid dispersion's formula.

Powder X-ray Diffraction (PXRD) results

Characteristic peaks of FLP at 2θ of 10.3°, 23.3° and 32.7° with high intensity were seen in Figure (6 A) indicating that FLP is in crystalline form, those characteristic peaks were appeared in the mixed hydrotropic solid dispersion F1 at ratio (1:2) (Figure 6 B) at low intensity with diffuse pattern of peaks may indicate the conversion to the amorphous form.[31,32]

Scanning electron Microscopy

As a result of its great magnification and resolution, scanning electron microscopy has been constantly employed for evaluating the solid-state characteristics of substances. SEM analysis of pure FLP powder revealed a plate-like shape with ragged edges as demonstrated in (Figure 7 A), this could validate the crystalline structure of pure medication.[33] While SEM of F1 MHSD at ratio 1:2, FLP had been found to be diffused as well as deposited on the surface of hydrotropic agents. Furthermore, the probability of the FLP original structure disappearing in these dispersions may confirm a decrease in crystallinity as shown in (Figure 7 B).

CONCLUSION

Mixed hydrotropic solid dispersions of FLP were prepared using the solvent evaporation method with the successful hydrotropic blends of sodium benzoate and nicotinamide. The highest dissolution rate was achieved from F1 formula at drug: hydrotropic agent ratio (1:2). The methods suggested would be cost-effective, convenient, and efficient. As a result of the research, it is possible to construct mixed HSD of weakly water-soluble medicines.

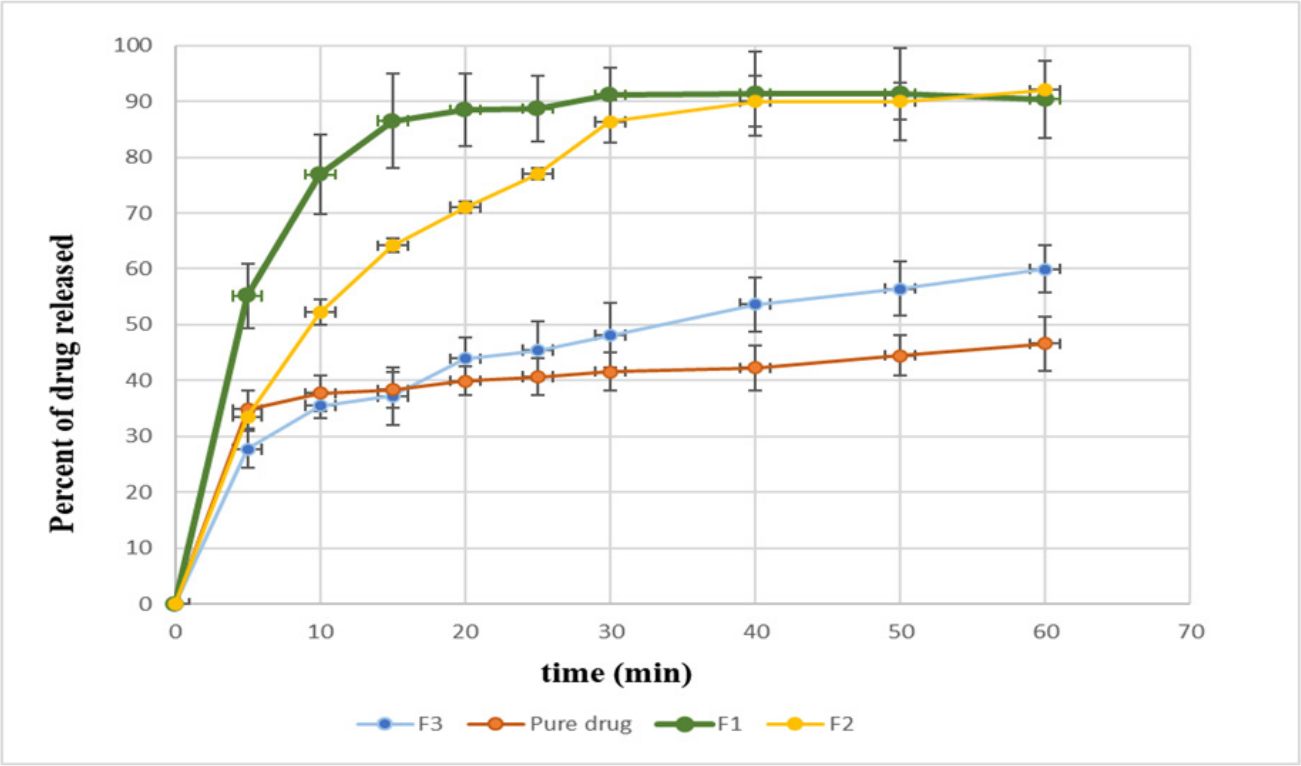
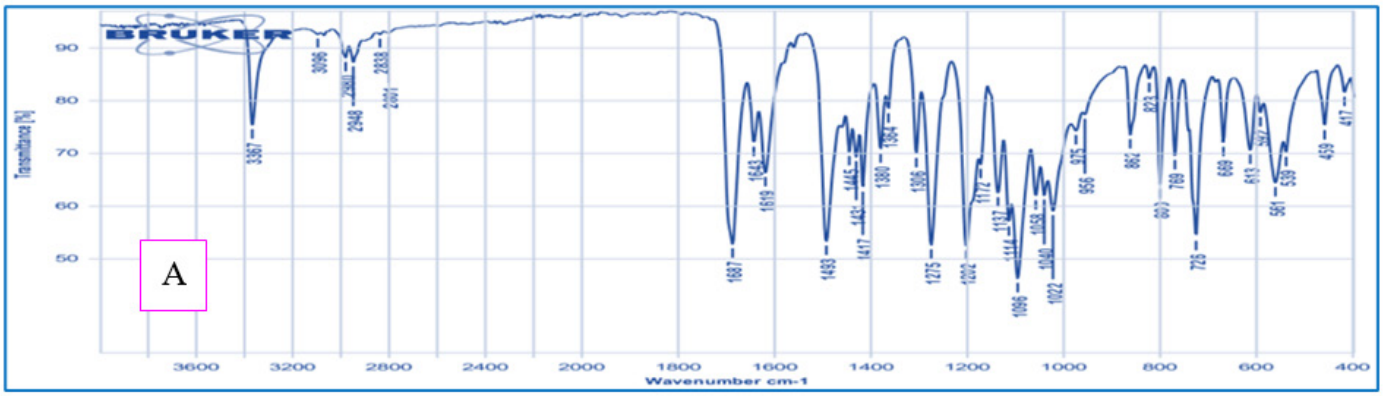


Figure 4: *In vitro* release profile from pure drug and MHSDs.



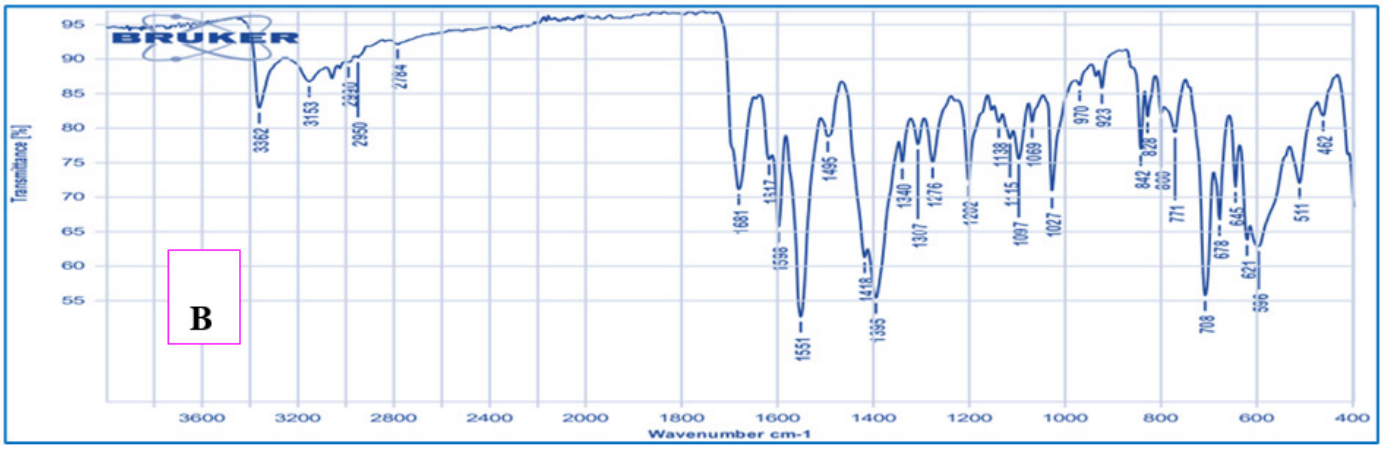


Figure 5: A: FTIR of FLP and B: FTIR of F1 MHSD at 1:2 ratio.

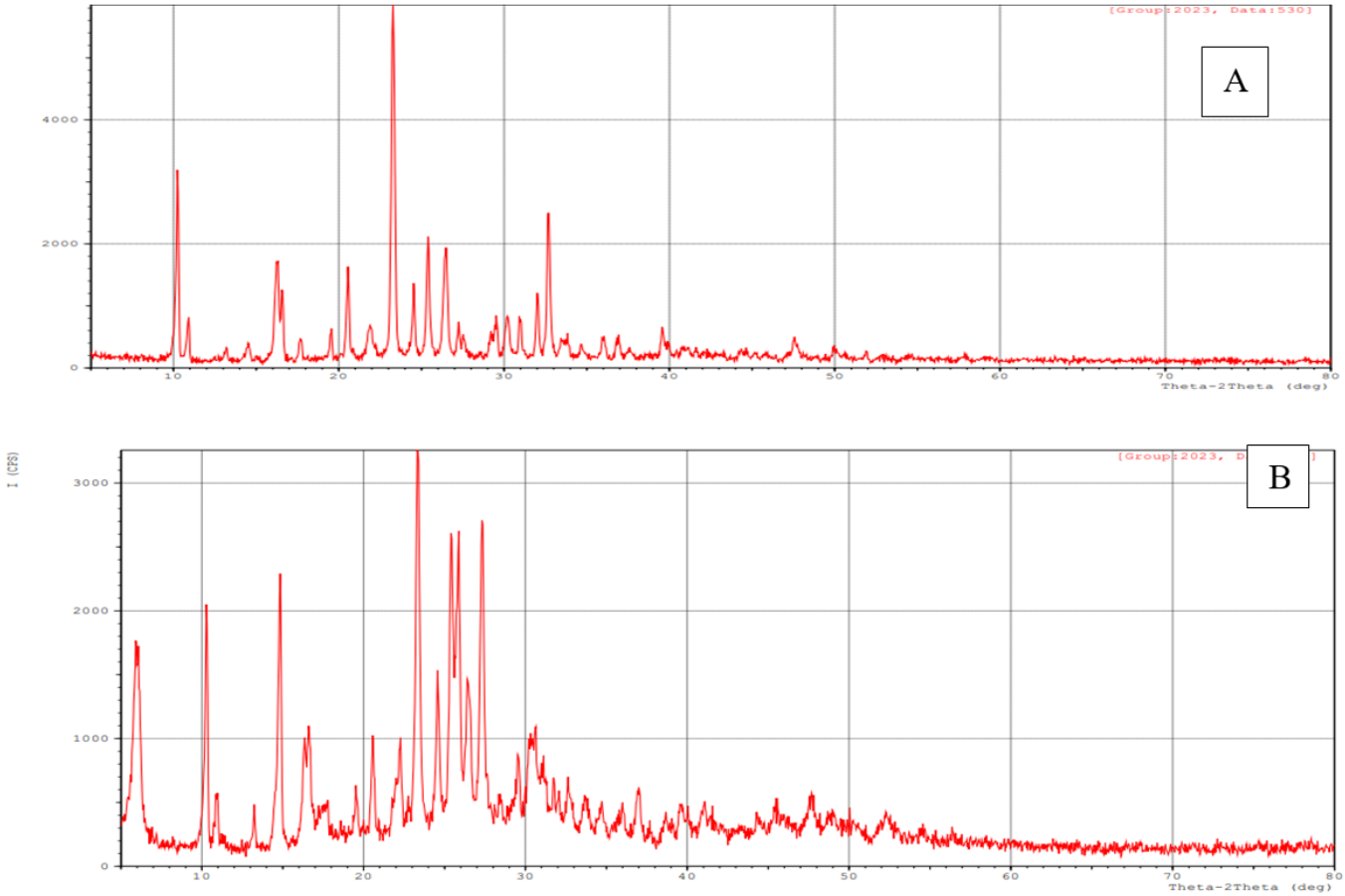


Figure 6: A: PXRD of FLP and B: PXRD of F1 MHSD at 1:2 ratio.

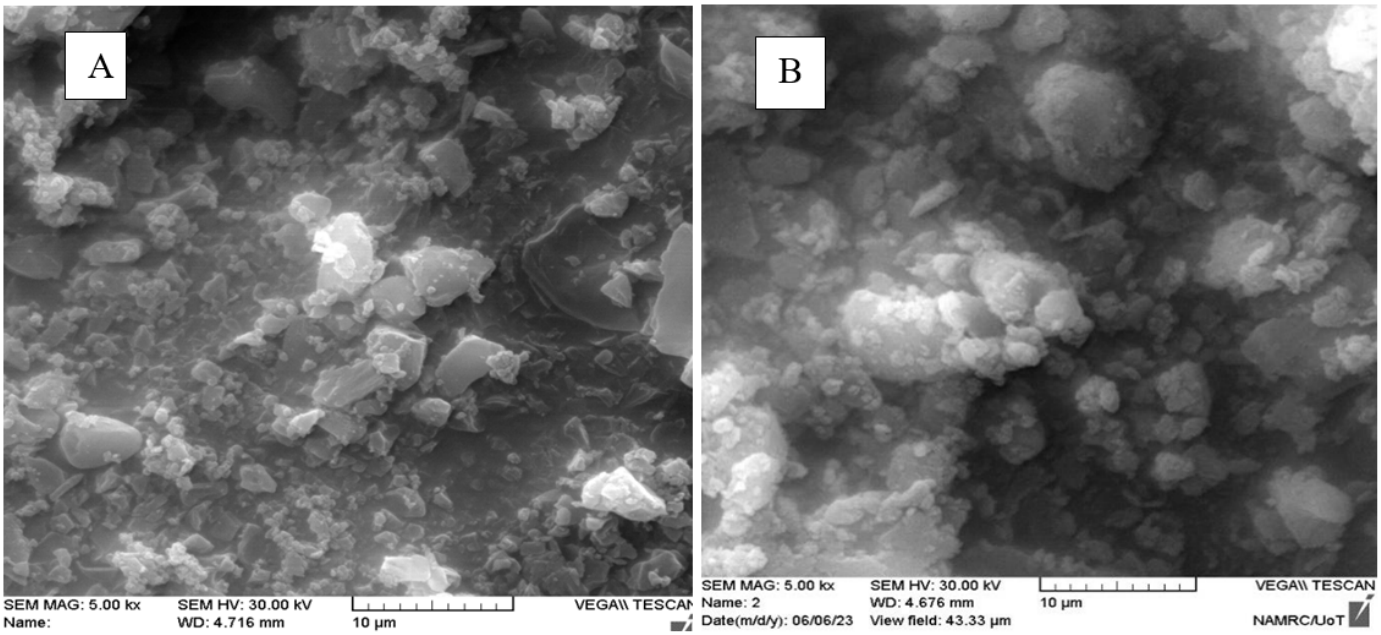


Figure 7: A: SEM of FLP powder and B: SEM of F1 MHSD at 1:2 ratio.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

FLP: Felodipine; **HCl:** Hydrochloric acid; **UV:** Ultraviolet; **DW:** Distilled water; **No:** Number; **w/v:** Weight/volume; **SD:** Solid dispersion; **MHSDs:** Mixed hydrotropic solid dispersion; **N:** Nicotinamide; **SB:** Sodium benzoate; **SC:** Sodium citrate; **FTIR:** Fourier transforms infrared spectroscopy; **PXRD:** Powder X-ray diffraction; **SEM:** Scanning electron microscopy; **ANOVA:** Analysis of variance.

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