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Original Article

Solubility Enhancement of Diacerein Through Liquisolid Technology: A Formulation Perspective

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ABSTRACT

Liquisolid systems present an effective technique for improving the dissolution rate and oral bioavailability of poorly water-soluble drugs. The objective of this study is to formulate and evaluate Diacerein liquisolid compacts using Tween 80 as the liquid vehicle, Neusilin and Fujicalin as carriers, and Aerosil 200 as a coating material. Sodium starch glycolate and magnesium stearate were used as disintegrants and lubricants, respectively. Pre and post-compression parameters such as flow properties, hardness, friability, drug content, and disintegration time were measured. The *in vitro* release characteristics of the pure drug, marketed capsules (as reference), and liquisolid technique (test sample) were studied. Among all the formulations, FSC3 had the highest dissolving efficiency (DE) of 53.109% at 60 minutes, exceeding the marketed product's DE of 44.972%. FTIR analysis revealed no drug-excipient incompatibility, and all tested formulations fulfilled, pharmacopeial requirements for flow and mechanical characteristics.

Overall, the study demonstrates that the liquisolid technique significantly improves the dissolution of Diacerein, indicating its potential to boost the physicochemical properties of poorly soluble drugs.

KEYWORDS: liquisolid compacts, Diacerein, Solubility enhancement, poorly aqueous soluble, formulation development.

1. Introduction

Solubility plays a critical role in drug bioavailability, particularly in oral formulations. However, approximately 70% of new drug candidates and 40% of marketed immediate-release oral drugs suffer from low aqueous solubility, leading to poor absorption and inconsistent therapeutic effects. This presents a major challenge for the pharmaceutical industry in developing effective formulations with enhanced dissolution and bioavailability. [1,2]

Diacerein, a BCS Class II drug, a chondroprotective agent, is administered orally at a dose of 50 mg per day. Its absolute oral bioavailability ranges from 35% to 56%. [3]. Several strategies have been explored to improve solubility, including micronization, nanonization, cyclodextrin complexation, solid dispersions. While liquid dosage forms can enhance solubility, they are prone to stability issues and incompatibilities. In contrast, solid dosage forms such as tablets offer advantages like better stability, ease of handling, longer shelf life, and cost-effective large-scale production. [4,5]

Liquisolid technology is an innovative approach that transforms liquid drugs, suspensions, or drug solutions into free-flowing, compressible powders using porous carriers like microcrystalline cellulose and coating agents like colloidal silica. Non-volatile liquid vehicles, such as propylene glycol, polyethylene glycols, and glycerine, play a crucial role in this conversion. By increasing the surface area, solubility, and wettability of drug particles, liquisolid systems significantly enhance drug dissolution, leading to better gastrointestinal absorption and improved bioavailability. Additionally, they help overcome challenges like poor wettability, variable dissolution rates, and erratic drug release seen in conventional formulations. [6,7]

2. Materials and Methods

Diacerein was purchased from Chorus Labs Pvt Ltd, Karnataka. PEG 300, PEG 400, Tween 20, Tween 80, Brij 35, Kolliphor RH40, Magnesium stearate, and Sodium starch glycolate were procured from S.D. Fine- Chem. Ltd, Mumbai. Neusilin, Aerosil 200, and Fujicalin were sourced from Aurobindo Pharma Ltd, Hyd. All the chemicals and reagents were of analytical grade and were used as obtained.

2.1. Solubility Determination in Non-Volatile Solvents

Diacerein solubility was assessed in PEG 300, PEG 400, Tween 80, Tween 20, Brij 35, Kolliphor RH40, and water to select the optimal solvent. Excess drug was added to each solvent and shaken in an orbital shaker at 25°C for 48 hours. The saturated solutions were then filtered through Whatman filter paper, and the filtrate was analysed using UV spectrophotometry at 343 nm **[8].**

2.2. Angle of Slide (Θ) Determination

The angle of slide assessed the flow properties and flowable liquid-retention potential (ϕ) of Neusilin and Fujicalin with

Tween 80. Admixtures of 10g Neusilin and 5g Fujicalin with varying liquid vehicle concentrations (0.2–2.0 w/w) were placed on a polished tile and tilted until the powder began to slide, defining the angle of slide [9].

2.3. Load Factor Calculation

Drug-loaded liquid medication was blended with a carrier-coating admixture, and the loading factor (Lf) was determined using Lf = W/Q, where W is the liquid medication weight and Q is the carrier concentration. Neusilin (10 g) or Fujicalin (5 g) was mixed with the liquid vehicle for 10 minutes, and the calculated Lf value guided the required carrier and coating material amounts [10,11].

2.4. Compressible Liquid Retention Potential (Ψ) Determination

Various liquid-carrier admixtures with different liquid-solid weight ratios were prepared, similar to the angle of slide method. Each admixture was compressed into a tablet to assess maximum hardness, observing for liquid squeeze-out. The Ψ-value was defined as the highest liquid-to-carrier ratio before liquid squeeze-out occurred [12].

2.5. Preparation of Liquisolid Compacts

Diacerein liquisolid compacts were prepared using Neusilin and Fujicalin as carriers, Tween 80 as the liquid vehicle, and drug concentrations of 5%, 10%, and 15% w/w. The drug and non-volatile solvent were accurately weighed, blended until fully dissolved, and then mixed with carrier and coating materials. The three-stage mixing process involved (1) initial blending for uniform distribution, (2) a five-minute absorption phase for drug penetration, and (3) final blending with sodium starch glycolate. The carriers transformed the wet mixture into a free-flowing dry powder with optimal compression properties. Sodium starch glycolate, magnesium stearate, and Aerosil 200 (R=20) were incorporated as a disintegrant, lubricant, and coating agent, respectively. The final blend was evaluated for flowability and compressed into tablets using a multi-rotary press with 12mm biconvex punches to ensure appropriate tablet hardness [13,14].

2.6. Precompression studies

Flow properties were measured in triplicate for diacerein and liquisolid compact tablets using standard pharmacopoeial methods. [15].

2.6.1. Angle of repose

The angle of repose is the maximum angle between a powder heap and the horizontal, indicating powder flow properties. It was determined by pouring powder from a 2 cm height and calculating the angle using the formula $\Theta = \tan^{-1}(h/r)$, where h is the height and r is the average radius.

2.6.2. Compressibility Index (% CI)

Carr's compressibility index measures flow properties and packing ability. It is calculated using bulk (Db) and tapped density (Dt) as: CI (%) = (Dt - Db)/Dt] x 100.

2.6.3. Hausner's Ratio

Hausner's ratio assesses flowability and packing efficiency, with values close to 1 indicating good flow and packing properties. It is calculated as:

Hausner's ratio = Dt/Db

Where Dt, is tapped density and Db is bulk density.

Table 1. Formulation composition NSC 1- NSC 3 with Neusilin as carrier material

S.no	Ingredients	Quantity (mg/tab)		
		NSC 1	**NSC 2**	**NSC 3**
	Drug conc. In tween 80 (%w/w)	5%	10%	15%
1	Diacerein(mg)	50	50	50
2	Tween80 (mg)	95	449	283
3	Neusilin (mg)	104	350	237
4	Aerosil 200 (mg)	5	20	14
5	SSG (mg)	30	30	30
6	Magnesium stearate (mg)	1	1	1
	Unit dose weight (mg)	285	900	615

Table 2. Formulation composition FSC 1- FSC 3 with Fujicalin as carrier material

Sno	Ingredients	Quantity (mg/tab)		
		FSC 1	**FSC 2**	**FSC 3**
	Drug conc. In tween 80 (%w/w)	5%	10%	15%
1	Diacerein(mg)	50	50	50
2	Tween80 (mg)	940	450	283
3	Fujicalin (mg)	237	158	555
4	Aerosil 200 (mg)	12	11	26
5	SSG (mg)	30	30	30
6	Magnesium stearate (mg)	1	1	1
	Unit dose weight (mg)	1270	700	945

2.7. Evaluation of compressed tablets

2.7.1. Post-compression studies

2.7.1.1. Physical Appearance

The general appearance of a tablet, including its size, shape, color, odor, and taste, is crucial for consumer acceptance and ensuring uniformity between batches. [16].

2.7.1.2 Size and Shape

Tablet dimensions are controlled, with thickness as the only variable, measured using a micrometer and maintained within ±5% of the standard value. [17].

2.7.1.3. Weight Variation

As per USP guidelines, 20 tablets were weighed individually and compared to the average weight. The batch met the requirements if not more than two tablets deviated beyond the specified limit, and none exceeded twice that limit. [18].

2.7.1.4. Hardness

5 tablets from each batch were selected, and hardness was measured using hardness tester to find the average tablet hardness or crushing strength. [18].

2.7.1.5. Friability

Friability was determined by taking 6 tablets. Tablet samples were weighed accurately and placed in Roche friabilator and operated for the given specification (4 min at 25 rpm) [18].

2.7.1.6. Drug content

Ten tablets from each formulation were powdered. The powdered sample equivalent to 100 mg of drug was transferred to a 100 mL volumetric flask containing 100 mL of 0.1 N hydrochloric acid solutions. The contents were shaken up to 30 min. The drug content was determined by measuring the absorbance at 343nm. [17].

2.7.1.7. Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. The apparatus was run for 10 minutes, and the basket was lifted to observe whether all of the tablets had disintegrated. [17].

2.7.1.8. In vitro drug release

In vitro drug release of the samples was carried out using USP-type II dissolution apparatus (paddle type) at 100 rpm in 900 ml of 0.1N HCl at 37 ± 0.5 °C. At different time intervals, 5 mL of the sample was withdrawn and filtered. The fresh dissolution medium was replaced every time with the same quantity of the sample. Collected samples were analyzed at 343 nm. The percentage cumulative drug release (% CDR) was calculated. [17].

2.8. Comparison of dissolution profiles

To compare dissolution profiles between two drug products, model-dependent, statistical analysis and model-independent methods can be used [19,20]. Dissolution profiles of formulations were compared on the basis of dissolution efficiency (DE) and mean dissolution time (MDT) with marketed formulation.

2.9. FTIR – Spectroscopy

The FT-IR studies were carried out to confirm the compatibility of diacerein with the excipients used in the formulation. The FT-IR scans for the pure drug and physical mixtures of drug and different excipients were recorded on FTIR spectrophotometer (IR Sipirit – X, Shimadzu). The spectrum was recorded in the wavelength region of 4000-400 cm^{-1} and shown in Figure 4- 3. The characteristic absorption peaks were observed for the pure drug.

3. Results

3.1. Saturation solubility studies

The solubility of diacerein was evaluated in various non-volatile solvents (PEG 300, PEG 400, Tween 20, Tween 80, Kolliphor RH40, Brij 35, and water) at 25°C. Tween 80 showed the highest solubility, making it ideal for liquisolid formulations, as higher solubility enhances drug dissolution in the liquid vehicle before adsorption onto carriers, improving drug release.

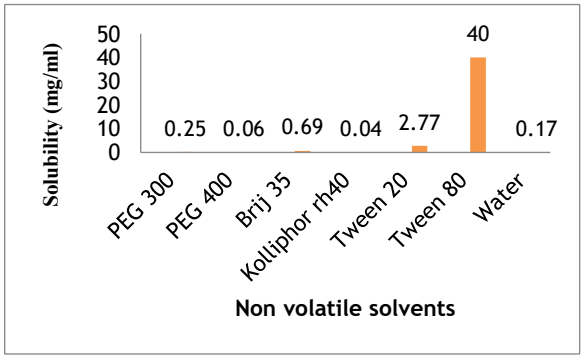

Fig 1. Solubility of diacerein in various non-volatile solvents

3.2. Determination of angle of slide (Θ) of powder excipients (Neusilin and Fujicalin)

The optimum angle of the slide was considered to be 33°. For the Neusilin-Tween 80 admixture, the angle of slide was 33.5° at ϕ = 1.4, while for Fujicalin, it was 32.9° at ϕ = 0.6, ensuring acceptable flow. These values help determine the required carrier amount for a free-flowing, non-adherent, and readily compactable liquisolid formulation.

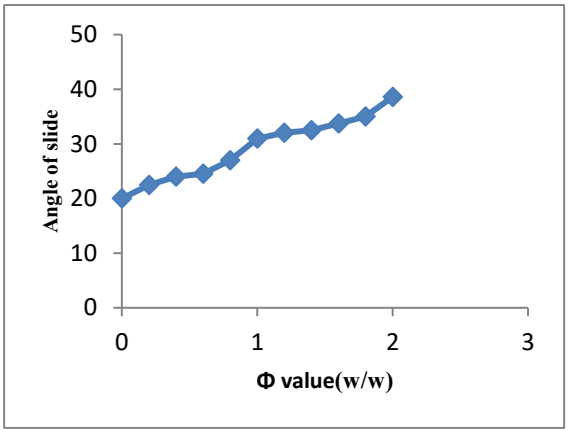

Fig 2. Angle of slide of admixture of Neusilin and Tween 80

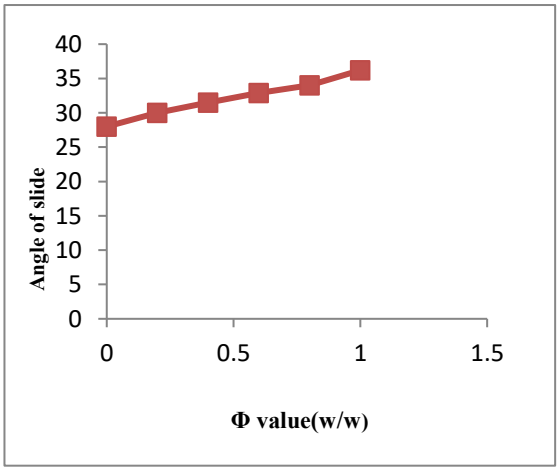

Fig 3. Angle of slide of admixture of Fujicalin and Tween 80

3.3. Determination of compressible liquid retention potential (Ψ value)

Compressible liquid retention potential (Ψ value) was determined for the prepared admixtures. Neusilin tween 80 admixtures, i.e., 0.2 to 2.0 and fujicalin tween 80 admixtures 0.2 to 1.0, during tablets, the liquid squeezes out at 1.4 for neusilin and 0.6 for fujicalin. Therefore, the values previous to these were considered as the compressible liquid retention potential. From the load factor with proper flow and compressible liquid retention potential values, it can be concluded that neusilin can retain liquid medication with proper flow without any liquid squeezing out phenomenon in the ratio of 1.4 and in the case of fujicalin it was found to be 0.6. For optimal flow properties (Θ ≈ 33°), the flowable liquid retention potential (ϕ) was determined. The Neusilin-Tween 80 admixture had an angle of slide of 33.95° with a corresponding ϕ value of 1.4, while the Fujicalin-Tween 80 admixture had an angle of slide of 32.9° with a ϕ value of 0.6.

3.4. Flow Properties of Powder Excipients

Tween 80/carrier admixtures with varying liquid vehicle concentrations were prepared and evaluated for bulk and tapped density to determine Hausner's ratio and Carr's index, as per the described methods.

Table 3. Flow properties of Neusilin in Tween 80

ϕ values (w/w)	Bulk density (g/cc)	Tapped density (g/cc)	Hausner's ratio	Carr's index (%)
0.0	0.48±0.08	0.58±0.02	1.20	17.0
0.2	0.51±0.02	0.58±0.08	1.148	12.9
0.4	0.55±0.05	0.66±0.06	1.132	11.7
0.6	0.5±0.01	0.58±0.08	1.11	10
0.8	0.45±0.04	0.55±0.05	1.22	18.198
1.0	0.47±0.06	0.55±0.05	1.165	14.23
1.2	0.43±0.04	0.5±0.01	1.101	13.2
1.4	**0.41±0.06**	**0.47±0.06**	**1.144-Good**	**12.6 Good**
1.6	0.38±0.04	0.45±0.04	1.18	15.41
1.8	0.4±0.04	0.45±0.04	1.135	11.89

*Each value has an average of three determinations

Table 4. Flow properties of Fujicalin in Tween80

Formulations	Weight variation(mg)* *(A.M± S.D)	Hardness (kg/cm^2) * (A.M±S.D)	Friability (%) *(A.M±S.D)	Disintegration Time(min)* (A.M±S.D)	Drug content (%)* (A.M± S. D)
NSC 1	284.63± 0.035	3.4±0.04	1.046±0.04	4.16±0. 040	98.25± 0.86
NSC 2	900±0.01	5.02±0. 191	0.85±0. 096	4.73±0. 642	99.47± 0.14
NSC 3	615±0.957	4.62±0. 426	0.886±0 .06	4.166±0 .763	98.65± 0.88
FSC 1	1270.50 ±0.02	3.322± 0.237	0.763±0 .066	3.76±0. 251	99.61± 0.12
FSC 2	700.152 ±0.00	5.344± 0.263	0.93±0. 051	3.46±0. 533	98.45± 0.54
FSC 3	945.656 ±0.01	4.46±0. 160	0.923±0 .066	5.13±0. 320	99.18± 0.12

3.5. Formulation development

3.5.1 Pre-compression parameter of formulation blends of NSC 1-3 and FSC 1-3

Pre-compression parameters of NSC 1-3 and FSC 1-3 were evaluated to assess flow properties, with results shown in Table 5.

Table 5. Pre-compression parameter of formulation blend of NSC 1-3 and FSC 1-3

LSC	Hausner's ratio (%)	Compressibility index (%)	Angle of repose (Θ)
NSC 1	1.15	20	31.2±1.32
NSC 2	1.21	18.5	33.5±2.16
NSC 3	1.0	10	30.94±2.16
FSC 1	1.21	18	32.96±1.001
FSC 2	1.15	13.3	37.2±1.37
FSC 3	1.21	17.7	33.4±1.604

*Each value is an average of three determinations

The formulation blends exhibited passable to good flow, with Hausner's ratio ranging from good to moderate and compressibility index from fair to passable.

3.6. Evaluation of liquidsolid tablets

Evaluation tests of formulation NSC 1-3, FSC 1-3 tablets were studied and reported in Table 3- 5. All tablet batches met USP specifications, with percent deviation within limits (Table 6), ensuring uniformity. Formulations had a hardness of 3.3-5.3 kg/cm² (Table 6). NSC 2, 3 and FSC 2, 3 exhibited good mechanical strength, meeting the acceptable limit of ≥4.5 kg/cm².NSC 2, 3 and FSC 1, 2, 3 had friability <1%, meeting USP limits, indicating good mechanical resistance. NSC 1 exceeded 1%, making it non-compliant. Tablets disintegrated within 3-5 minutes, slightly higher for an immediate-release formulation. This delay may be due to sodium starch glycolate forming a viscous gel layer, hindering penetration of the disintegration medium. Drug content was consistently above 98%, ensuring uniform API distribution across all formulations.

Table 6. Post-compression evaluation tests of formulation NSC 1-3, FSC 1-3 tablets

Formulations	Weight variation (mg)* *(A.M±S.D)	Hardness (kg/cm^2) * (A.M±S.D)	Friability (%) *(A.M±S.D)	Disintegration Time(min)* (A.M±S.D)	Drug content (%)* (A.M±S. D)
NSC 1	284.63±0 .035	3.4±0.0 4	1.046±0. 04	4.16±0.0 40	98.25± 0.86
NSC 2	900±0.01	5.02±0. 191	0.85±0.0 96	4.73±0.6 42	99.47± 0.14
NSC 3	615±0.95 7	4.62±0. 426	0.886±0. 06	4.166±0. 763	98.65± 0.88
FSC 1	1270.50± 0.02	3.322±0 .237	0.763±0. 066	3.76±0.2 51	99.61± 0.12
FSC 2	700.152± 0.00	5.344±0 .263	0.93±0.0 51	3.46±0.5 33	98.45± 0.54
FSC 3	945.656± 0.01	4.46±0. 160	0.923±0. 066	5.13±0.3 20	99.18± 0.12

3.7. *In-vitro* dissolution studies

NSC 1-3 and FSC 1-3 formulations were subjected to *In-vitro* dissolution studies in 0.1 N hydrochloric acid solution. The corresponding dissolution profile was presented, and the comparative *in vitro* dissolution profile was given in Figures 4 - 6.

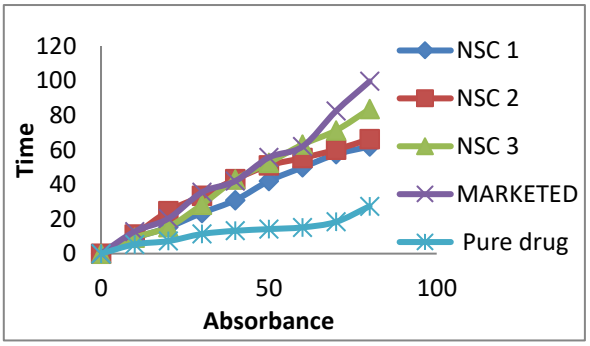

Fig 4. *In vitro* drug release of the drug from tablets of batches NSC1-3, marketed and pure drug

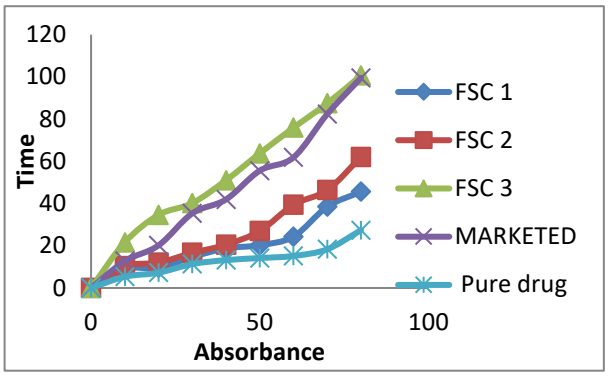

Fig 5. *In vitro* drug release of the drug from tablets of batches FSC1-3, marketed and pure drug

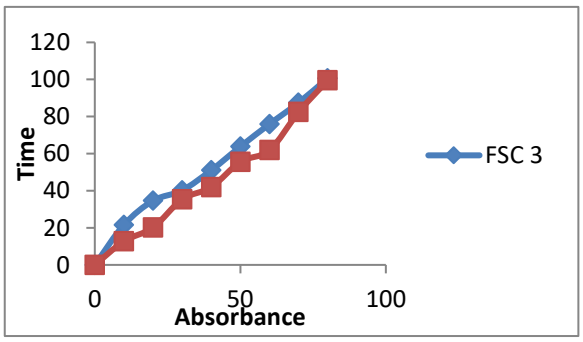

Fig 6. *In vitro* drug release of the drug from tablets of batch FSC 3 and marketed.

Fig 4 & 5 illustrates the *in vitro* drug release profile of the liquisolid formulations, pure drug and marketed formulation. All the liquisolid compacts showed higher drug release than pure drug. The results showed that there was significant difference between the release profile of the pure drug and liquisolid compacts. The enhanced dissolution rates of liquisolid compacts compared to pure drug may be attributed to the fact that, the drug is already in solution in Tween 80, while at the same time, it is carried by the powder particles (Aerosil, Neusilin or Fujicalin). Thus, its release is accelerated due to its markedly increased wettability and surface availability to the dissolution medium. The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Tween 80 facilitates wetting of drug particles by decreasing interfacial tension medium and tablet surface. The formulations having high drug concentration in tween 80 showed rapid drug release. An increase in concentration of drug in tween 80 increases the dispersion of drug at molecular level which may further enhance the dissolution rate of the drug.

From the results of different batches prepared by two different carriers, it was found that Fujicalin proved to be the superior carrier than Neusilin. Further Diacerein liquisolid compacts dissolution profile was compared with markted capsules (Durajoint). FSC3 exhibited drug release profile similar to Durajoint capsules.

DE is commonly applied for comparison of dissolution profiles to decide better formulation. The marketed formulation showed 44.972%. DE of optimized liquisolid formulation FSC3 was found to be 53.109 % at the end of 60 min. Higher DE indicated that liquisolid compact has significantly enhanced dissolution. MDT of marketed formulation was found to be 43.8 min, while that of formulation FSC3 was 37.78 min. Lower MDT values indicated faster release of drug from the liquisolid formulation. Finally, on the basis of total drug release, Tablet hardness, DE (%), and MDT, formulation FSC3 showed promising *in vitro* results.

3.8. FTIR Spectroscopy

IR spectrum of diacerin shown in Figure 6, an absorption band was observed, peaks 3068.7 cm−1 (=C-H), 1764.86 cm−1 (C=O (ester)),1657.21(C=O (COOH) and1256 cm−1 (C-O). These peaks can be considered as characteristic peaks of diacerin and were not affected and prominently observed in IR spectra of diacerin along with oil and carrier materials shown in Fig 7. Characteristic peaks of the individual excipients were also retained; also, no new peak was found in the drug-loaded mixture of the excipients to be formulated in liquisolids. This indicates that there is no interaction between the drug and excipients.

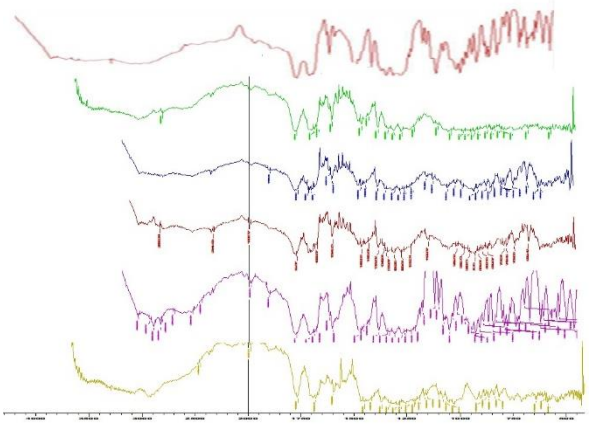

Fig 7. Overlay IR of (A) drug (Diacerein), (B) Neusilin, (C) Aerosil 200, (D) Fujicalin, (E) Magnesium stearate, (F) Sodium starch glycolate.

4. Conclusions

The results suggest that liquisolid compacts of diacerein can be successfully prepared using novel carriers such as Neusilin and Fujicalin combined with non-volatile solvents like Tween 80. Both Fujicalin and Neusilin exhibited excellent potential for loading the non-volatile solvent while preserving favourable flow properties and enhancing dissolution compared to pure drug and marketed formulation. Notably, formulation FSC3 demonstrated a lower mean dissolution time (MDT) and higher dissolution efficiency than the commercially available formulation. These findings highlight the promising potential of liquisolid technology to improve the therapeutic efficacy of poorly water-soluble drugs like diacerein.

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Conflicts of Interest: The authors declare no conflict of interest.

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