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In vitro-in vivo correlation as a tool for predicting bioavailability of aspirin liquisolid tablets

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ABSTRACT

Background: Aspirin is widely utilized for cardiovascular event prevention and fever management, making it one of the most frequently prescribed medications. It boasts a singular mechanism of action, specifically targeting thromboxane A2 production to prevent platelet activation, unmatched by other antiplatelet agents. The majority of commercial aspirin products are plagued by gastrointestinal side effects and inconsistent absorption, ultimately reducing their bioavailability and therapeutic potential. These observations underscore the critical need for aspirin formulation that exhibit optimal absorption and minimized variability. The liquisolid process is an age-long approach for improving oral drug solubility and absorption.

Methods: Herein, we formulated different aspirin liquisolid tablets (ALS1-ALS15) and exposed them to pre and post-compression studies to identify the optimized formulation, after which we compared and investigated the predicted plasma concentration-time profiles of aspirin prototype drug from *in vitro* dissolution results using a mathematical convolution approach for *In vitro-in vivo* correlation (IVIVC) study.

Results: All formulations had near-excellent flowability. The differential scanning calorimetry and Fourier transform infra-red spectral showed no major interactions between aspirin crystals and the excipients used in this study. Formulation ALS5 exhibited preferred physicochemical properties and was therefore chosen as the optimal formula. The time to attain peak plasma concentration was similar for both the test and the reference product (0.5 h). In contrast, their maximum plasma concentration deviates by 1.23 and 21.75 percent from the authentic reference values derived from the literature.

Conclusion: The percentage of predicted errors achieved revealed that the convolution technique could predict plasma drug levels of aspirin liquisolid tablets as per FDA guidelines.

1. Introduction

The oral route remains the most popular method for drug administration due to its simplicity and patient compliance. However, for oral drugs to be effective, they must achieve a certain concentration in the blood stream, which is heavily influenced by their solubility[1].

Recently, the Liquisolid (LS) technique has gained prominence as a promising method for enhancing drug solubility and bioavailability. This technique is also believed to optimize other drug-related physicochemical parameters such as permeability, stability, tabletability, and thermal properties, as well as the enhancement of therapeutic response and pharmacological properties of the active pharmaceutical ingredients[2]. The liquisolid technique has successfully enhanced the solubility of several poorly soluble drugs, including carbamazepine, famotidine, indomethacin, furosemide, hydrocortisone, piroxicam, naproxen, prednisolone, ezetimibe, chlorpheniramine, digoxin, clofibrate, nifedipine, gemfibrozil, etoposide, lacidipine, hydrochlorothiazide,

methyclothiazide, spironolactone, and ibuprofen[2]. The Liquisolid process involves dissolving or suspending a poorly soluble drug in a non-volatile solvent, which is then transformed into a free-flowing powder that can be compressed into a solid form[3]. This process is an easy and affordable way to increase the solubility of lipophilic drugs in water by increasing the surface area for release, improving the drug's ability to dissolve in water, and enhancing the wetness of the drug particles.

Aspirin is a BCS (Biopharmaceutical Classification System) Class II drug that was found in the 18th century as a medicine for reducing inflammation[4]. Over time, it has been found to also help with treating fever, preventing heart problems, and even fighting colorectal cancer[5]. It is poorly water-soluble and could cause gastrointestinal disturbance (due to decreased Prostaglandin E_2 and Prostacyclin I_2 secretion). The pharmacological effect of aspirin depends on the dose and mechanism of action of the cyclooxygenase enzyme[4]. Orally, it requires high successive dosing due to its broad first-pass metabolic effect. It has a pKa value of 3.5 owing to the presence of the carboxylic group[6]. Partially it is absorbed into the gastric mucosa, and majorly in the duodenal mucosa. About 75 % of the absorbed drug undergoes a first-pass effect in the intestinal wall and the liver[4]. Although the plasma drug level is dose-dependent, the maximum time (Tmax) is about an hour[4]. The salicylate form is about 80-90 % plasma-albumin bound with a volume of distribution of 0.1-0.2 L/Kg. Aspirin dissociates into an acetyl cation (responsible for the mechanism of action), and a salicylate anion (which reacts with the proton of serine 529 of platelet COX-1 to form salicylic acid)[4]. It has an elimination half-life of about 2-3 hours at a single analgesic dose with first-order kinetics[6]. At higher doses of about 325-650 mg/4-6 hours, aspirin blocks COX-2 thereby relieving pain, inflammatory process, and fever, but also inhibits the vasodilator and antiplatelet effect on the vascular wall[6]. About 10 % of the salicylate is eliminated via urine unmetabolized, and 75 % is salicyluric acid[4].

This study aimed to evaluate the effect of the LS technique on the solubility of aspirin and predict its pharmacokinetic properties via the *in vitro-in vivo* correlation study. The purity analysis and the characterization of the drug-excipient mixture were performed using Differential Scanning Calorimeter (DSC) and Fourier Transformed Infrared (FT-IR) respectively. In analyzing the drug profile, *in vitro* dissolution testing was carried out. The outcome of this study revealed an enhanced dissolution profile with a preferred pharmacokinetic property compared to the marketed aspirin 75 mg tablet.

Materials and Methods

Materials

Aspirin crystals, sodium acetate trihydrate, and glacial acetic acid used in this study were products from Merck Darmstadt, Germany; Tween 20 and Propylene glycol (PG) were produced in India by Loba Chemie; and Glycerol was manufactured by Himedia, India. Avicel PH-102, Aerosil 300, and polyvinyl pyrrolidone (PVP) were made in the UK by Fisher Scientific while magnesium stearate and talc were from FMC Corp, UK.

Methods

Solubility study

Solubility of aspirin were tried out in different non-volatile liquid to find the best one for the study. The liquid tested were glycerol, propylene glycol (PG), tween 20, a mixture of propylene glycol and tween 20 (1:1), propylene glycol and glycerol (1:1), and tween 20 and glycerol (1;1). Accurately, 500mg of aspirin was weighed and then dispersed in 10 ml of each of the various solvents listed above and placed on the incubator shaker for 3 hours at room temperature to achieve a nearly cleared solution. The solutions were filtered and the residue was left to dry in an oven set at 60 degrees. After this, the dried residue was weighed and the solubility percentage was extrapolated[2]. We selected the solvent with the greatest solubility percentage for more research.

Liquid retention study

The ability of the non-volatile solvent to hold the drug and other excipients without leakage was determined using:

$$\Phi Lf = \Phi CA + \Phi CO\ (\frac{1}{R})$$

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ΦCA and ΦCO signify the flowability potential for the carrier and coating materials to retain liquid; whereas ΨCA and ΨCO are the compressible potentials for liquid retention of the carrier and coating materials; and R is the excipient ratio expressed as:

R=Q/q

Where Q is the quantity of the carrier material, and q is the quantity of coating material[2].

Compression of the LS tablets

A total of Fifteen batches of LS compacts (ALS 1 – ALS 15) of 50 tablets, each containing 75mg aspirin were dispersed in a non-volatile solvent to generate a liquid medication (Table 1). A mixture containing the carrier and coating

material already determined by the retention ratios was properly triturated in a mortar for about 10 minutes with the liquid medication[7].The lubricant and glidant were also incorporated into the mixture and compressed with the aid of a single-station tableting machine.

Pre-compression evaluation

Characterization of Drug-Excipient mixture: The pre-mixed formulations for tableting were checked for interactions within the tablet matrix, Fourier-transform infrared spectrophotometer (Magna-IR, 560 spectrometers; Perkin Elmer, USA) was used; to evaluate how physical properties of the formulation changed along with temperature against time, a Differential Scanning Calorimeter (DSC- 60, Shimadzu; Japan) was used[7].

Powder flow properties: Angle of repose (Θ), Carr's compressibility index (CI), and Hausner ratios (HR) of batches were tested using methods outlined in previous studies[3].

Post compression evaluation

Uniformity in weight of tablets, tablet hardness, percentage friability, the time it takes for a tablet to disintegrate, and drug content were assessed using official compendia methods[8].

Dissolution testing: A pre-calibrated USP apparatus I dissolution tester (RC-6, China) was used to generate in vitro dissolution profiles. A 500 mL acetate buffer (pH 4.5) prepared by mixing 29.9 g of sodium acetate with 16.6 mL of glacial acetic acid with sufficient water to produce 10 L was placed in each vessel and allowed to equilibrate to 37±0.5 ºC. A tablet from a batch was placed in each of the vessels and the equipment operated at 50 rpm for 45 min. At a pre-determined time, the withdrawal of samples and replacement with an equal amount of the buffer, followed by the measurement of the absorbance of the filtered samples at 265 nm was carried out using the dissolution medium in the reference cell as the blank[9].

A standard calibration curve of aspirin was prepared by dissolving 50 mg of pure aspirin in 100 ml of acetate buffer (pH 4.5) to obtain a concentration of 500 g/ml of standard stock solution. Various concentration ranging from 10 to 150 g/ml were prepared from the stock solution serially. A calibration equation of y=0.0032x+0.011; R^2=0.998 was obtained when the concentration values were plotted against those of absorbance at 265 nm[9].

In vitro-in vivo (IVIVC) kinetic study

Using drug release profiles from dissolution testing, the discrete drug release values were extrapolated.

The rate of elimination for the first-order reaction was calculated using the difference in predicted drug quantity values at different time.

ke=(*In C1-In C2/(t2-t1*)

C1 and C2 are predicted drug quantities in blood at times t1 and t2, while Ke is the elimination rate constant for first-order[2]

The anticipated blood level profile was obtained by employing the values of bioavailability and predicted concentration to that of the average body weight of an adult, and volume of distribution.

predicted conc.at times=predicted total blood amount ×F/Vd×body wt

F and Vd are bioavailability and volume of distribution respectively

Percent predicted error (% PE) is the difference between observed and predicted parameters to that of the observed parameter[2].

% PE=(Observed parameter -Predicted parameter) ×100/Observed parameter

Pharmacokinetic parameters for aspirin tablet

Authentic pharmacokinetic parameters for aspirin tablets obtained from literature are as follows:

Bioavailability; F is 0.68, Volume of distribution; Vd is 0.10 L/Kg, peak plasma concentration; Cmax is 7.31 µg/mL, Tmax is 0.5 h, area under the curve; AUC is 6.21 µgh/mL; average body weight of an adult human is 62.00 kg[3,4,5,6,7].

Results

In our study, we found that aspirin dissolves best in a mixture of propylene glycol and glycerol, followed by propylene glycol alone, glycerol alone, a mix of propylene glycol and tween 20, and finally tween 20 alone (fig. 1)

DSC and FTIR studies showed that the drug retained its crystalline structure and chemical properties in the liquisolid mixture (fig. 2 and 3)

The angle of repose values was near excellent, while the Hausner ratio and Carr's index values confirm the free-flowing ability of all the formulations (Table 2)[11]

Most batches met the 0.2 % deviation for thickness and diameter, and variations in tablet weight within a single batch were insignificant for all formulations as no more than two tablets vary from the average weight by more than 5 %[11]. ALS1, ALS2, ALS3, ALS4, ALS5, ALS7, ALS8, and ALS14 met the 4-10 KgF specifications for crushing strength. ALS8, ALS13, ALS14, and ALS15 failed to meet the compendial specification for percentage friability. Disintegration time was within specification (< 15 mins) for all batches. Some variants like ALS1, ALS2, ALS3, ALS 5, ALS7, ALS10, and ALS15 release at least 80 % of its active ingredient in 30 min as specified in official guidelines (fig 4a & 4b). Others like ALS4, ALS5, ALS6, ALS9, ALS10, ALS12, ALS13, and ALS15 contain between 90% and

110% of the specified ingredient amount[12]

The optimized formulation (ALS5) showed good predictability of in vivo profiles using the convolution algorithm (fig 5; table 3,4,5,6,7).

Discussion

Key to improving the solubility of a poorly soluble drug is its ability to dissolve in a specific solvent. The chemical properties and lipophilic nature of both propylene glycol and glycerol provided the synergistic effect toward solubilizing the aspirin crystals[2]. The ratios of ingredients used were successful in absorbing the propylene glycol/glycerol mixture in the tablet without any liquid leaking out.

Figure 2 and 3 provides details about the melting point, crystallinity, decomposition, and changes in heat capacity to understand the state of the drug inside the matrix, and how the various excipients interact. The DSC graph of the pure drug (ASP) shows a clear peak at around 118 ^{0}C, indicating its melting point as a crystalline substance. The DSC thermogram of the liquisolid mixture (ALS) was almost the superposition of the pure drug. When comparing the FTIR spectra of the test samples and the reference, the deviations were not too striking because the main absorption band features of the acetylsalicylic acid were present in both (see figure 3). By looking at the functional groups in the pure drug, we were able to match them to that of ALS sample by comparing the vibrating bands in their spectra. In both samples, the characteristic bands of the C=O vibration from the vinyl ester group were in the region 1750-1650 cm^{-1}[10]. The valence radiation of the aromatic acid was noticed in the region of 1999-1990 cm^{-1}. It was also noticed that around 1600-1400 cm^{-1} another valence vibration of the aromatic core occurs. The valence vibrations of the C-O group from acid and ester appeared in the region between 1200 and 950 cm^{-1}, while those of C-H vibration were seen around 2999-2900 cm^{-1}, and those of O-H were in the region of 3330-3000 cm^{-1} [10]. This is an indication that the interactions between the ASP and the excipients used were insignificant.

The formulated tablets were subjected to quality control parameters and the results are presented in table 2. The powder blends had good flow properties, and the formulations met quality control parameters for thickness, diameter, and weight variations. A failed hardness test tablet will adversely impact friability, disintegration, dissolution, and eventually bioavailability. The porous nature of Avicel could be responsible for this robust property exhibited by our formulations; as Avicel constitutes mostly a cluster of small subunits bound together by hydrogen bonds[2]. The ALS5 formula was found to have better qualities hence it was selected as the optimized brand for more research.

In vitro drug release profiles can help predict how a drug will behave in the body, which can save time and money during the development of new medicines[13]. This is why the idea of *in vitro-in vivo* correlation (IVIVC) is important in biopharmaceuticals. There are two methods for establishing IVIVC: convolution and deconvolution. Convolution involves predicting *in vivo* drug profiles from dissolution data, while deconvolution involves estimating dissolution profiles from *in vivo* data. Here, we utilized the convolution approach. The convolution method is preferred as it doesn't require human subjects and avoids the challenge of defining a suitable dissolution test for products with different *in vivo* release properties. The publicity of this concept has increased over the years which has led to the creation of specific terms, methods, and rules for how it works. Therefore, IVIVC defines the relationship between a parameter derived from a biological attribute produced by a dosage form and the physicochemical characteristics of the same dosage form[13]. *In vitro* profiles obtained under dissolution experimental conditions from ALS5 and the commercial brand were used as the input function in the convolution algorithm to calculate the expected in vivo profiles. The IVIVC correlation plots of predicted versus in vivo observed data for the tablet samples are presented in Table 3-6. The predictability of the correlations established was evaluated by internal validation[14,15] which involved extrapolating the percentage predicted errors of Cmax and Tmax as shown in Tables 4 & 6. ALS5 and the reference product both reached their highest concentration levels (7.22 and 5.71 µg/mL) at the same time (0.5 hours) and then decreased quickly (fig 5). The fast absorption of ALS5 is the reason why its highest concentration value (Cmax) is higher than the commercial brand[15]. The estimated highest plasma concentration (Cmax) was only 1.23% different from the actual value for the test product and 21.75% different for the reference product. However, the errors in predicting the time it takes to reach the highest concentration (Tmax) were the same (0%) for both products, as shown in Table 7. The % PE values for Cmax and Tmax indicated that the convolution technique accurately predicted ALS5 plasma drug levels according to FDA guidelines, since values were lower than 10%[14].

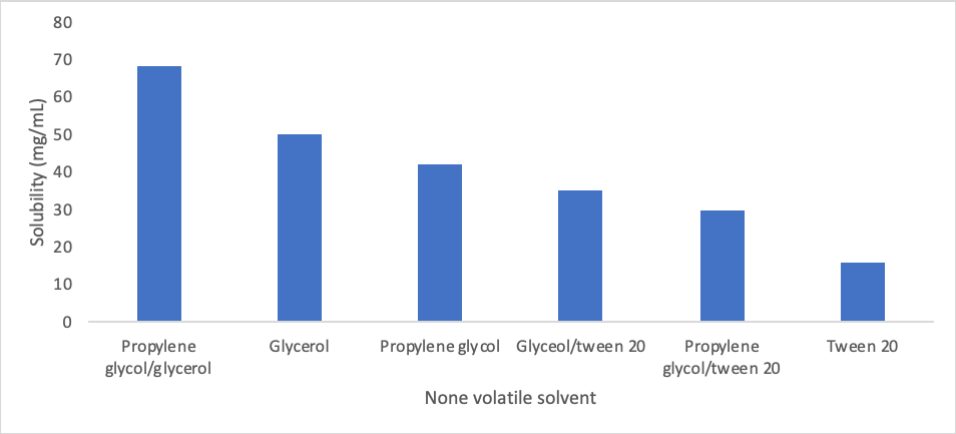

Fig. 1. Plot of solubility of aspirin crystals in some selected non-volatile solvents.

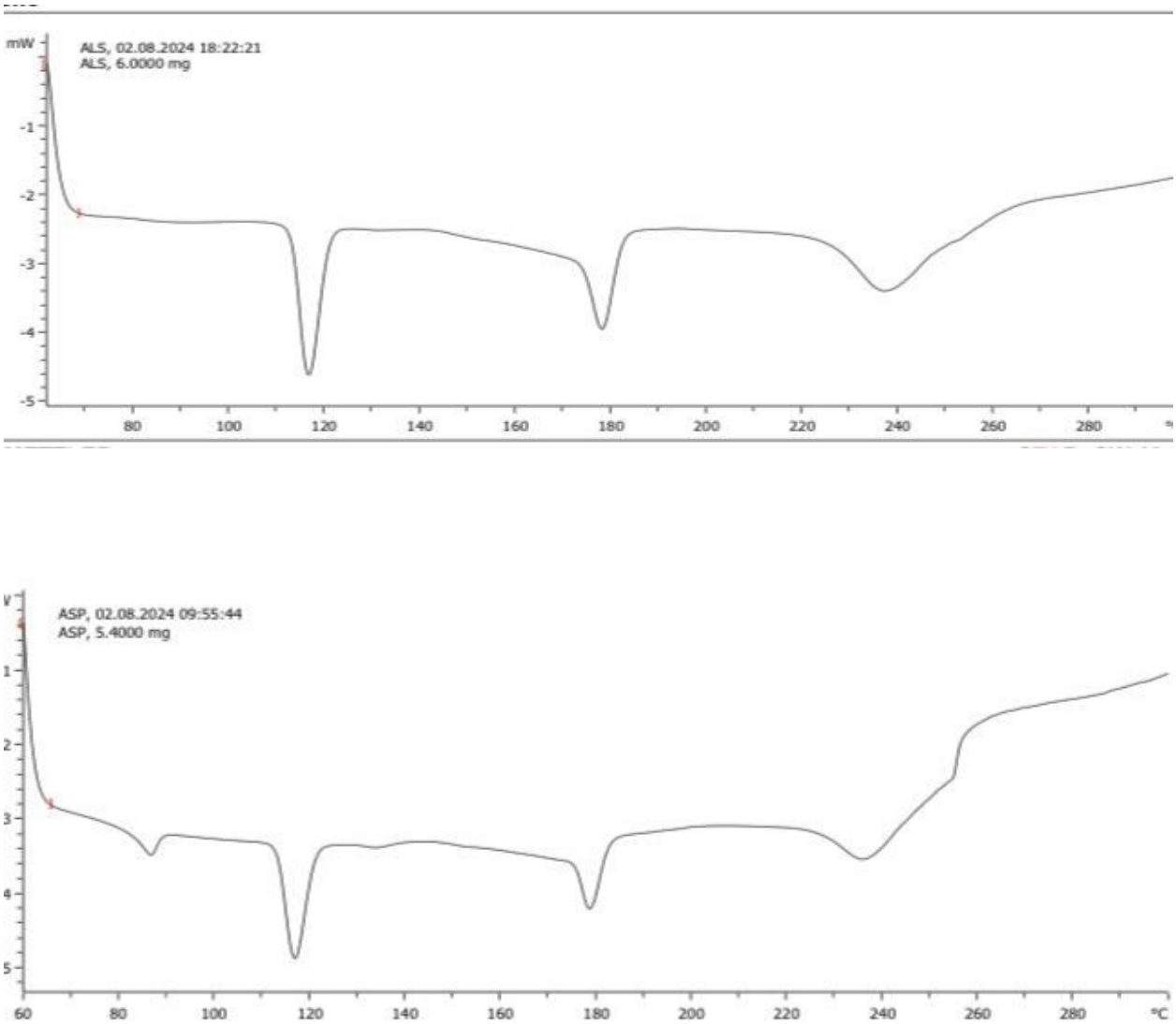

Fig. 2 DSC thermogram for pure aspirin crystal (ASP) and aspirin liquisolid tablet mixture (ALS).

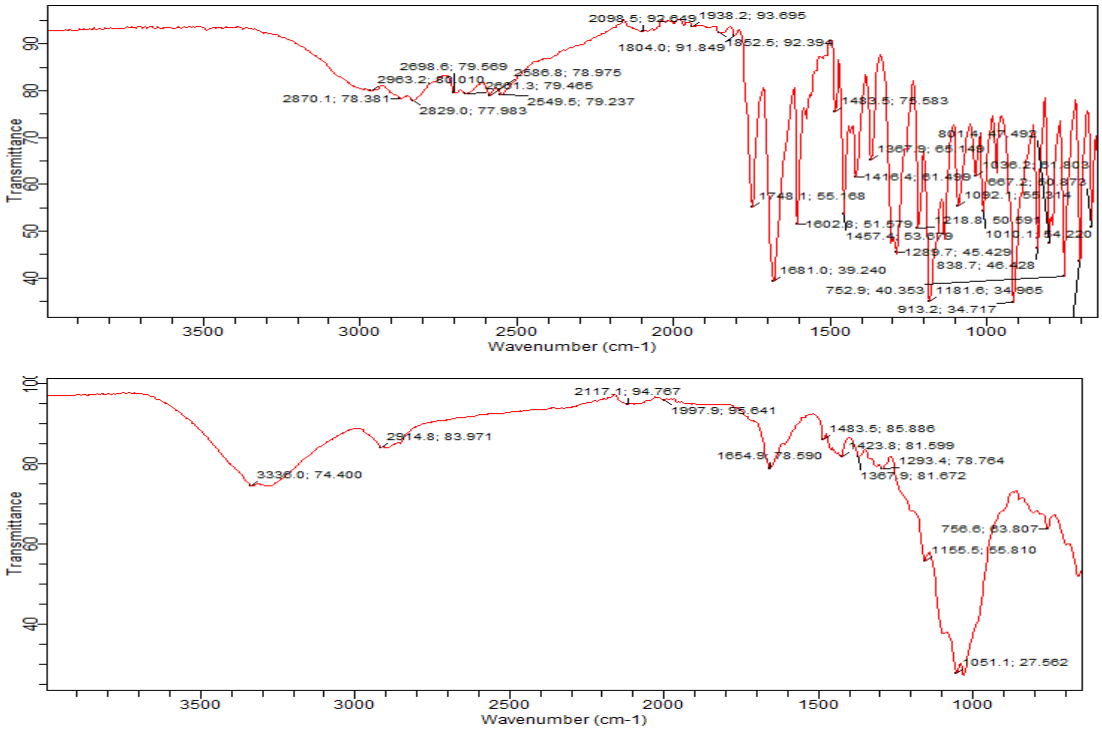

Fig. 3 FTIR spectra for pure aspirin crystals and that of aspirin liquisolid tablet mixture

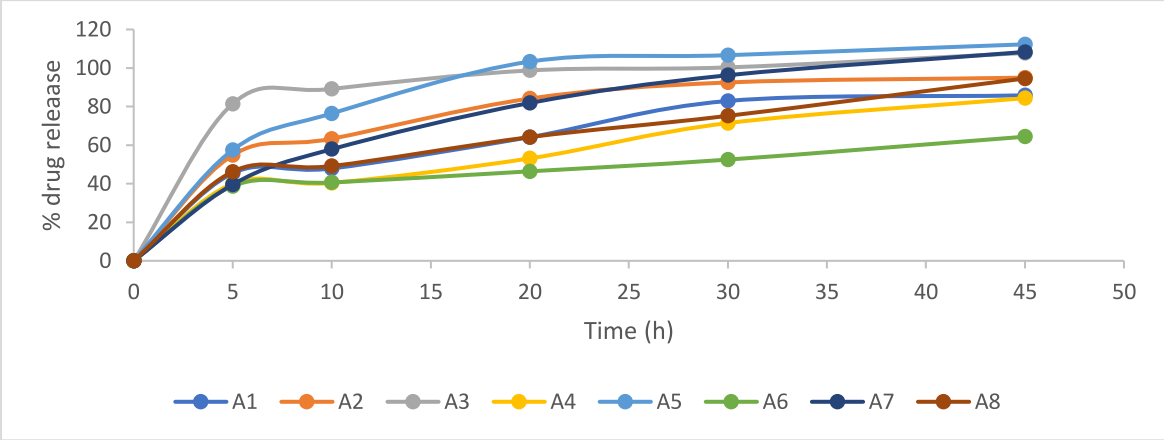

Fig. 4.a Dissolution profiles for liquisolid formulation ALS1 to ALS8.

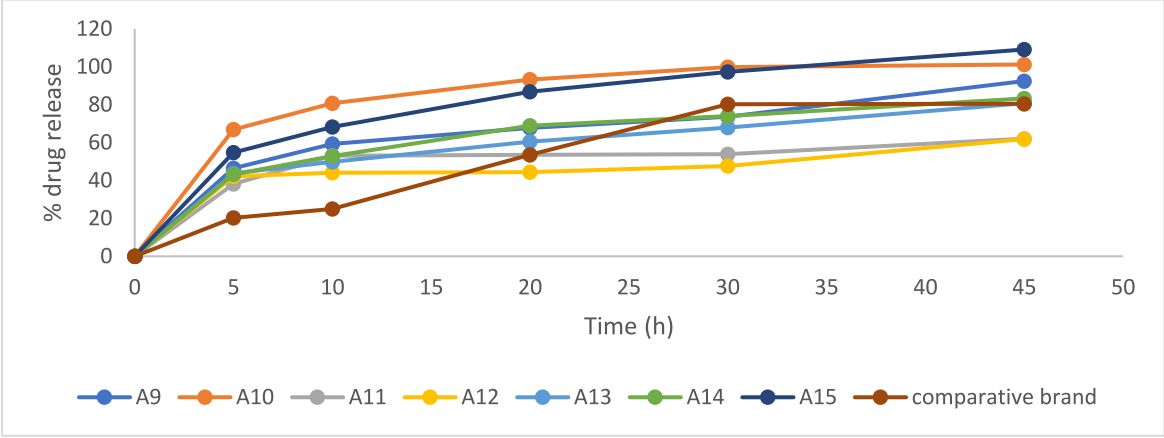

Fig. 4. B Dissolution profiles for liquisolid formulation ALS9 to ALS15 with the comparative brand

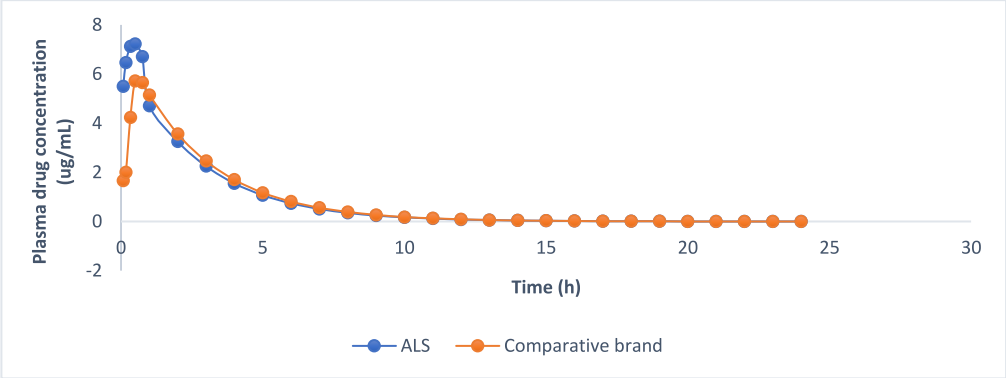

Fig. 5 Plasma drug concentration-time profile derived from *in vitro* dissolution profiles for ALS5 and comparative brand

Table 1. Tablet composition.

	API	Solvent	Q	Q	PVP	Talc	MGS	Total (mg)
ALS 1	75	50	400	20	27.25	2.73	5.45	580.43
ALS 2	75	40	400	20	26.75	2.68	5.35	569.78
ALS 3	75	30	400	20	26.25	2.63	5.25	559.13
ALS 4	75	20	400	20	25.75	2.58	5.15	548.48
ALS 5	75	10	400	20	25.25	2.53	5.05	537.83
ALS 6	75	50	400	40	28.25	2.83	5.65	601.73
ALS 7	75	40	400	40	27.75	2.78	5.55	591.08
ALS 8	75	30	400	40	27.25	2.73	5.45	580.43
ALS 9	75	20	400	40	26.75	2.68	5.35	569.73
ALS 10	75	10	400	40	26.25	2.63	5.25	559.13
ALS 11	75	50	400	80	30.25	3.03	6.05	644.33
ALS 12	75	40	400	80	29.75	2.98	5.95	633.68
ALS 13	75	30	400	80	29.25	2.93	5.85	623.03
ALS 14	75	20	400	80	28.75	2.88	5.75	612.38
ALS 15	75	10	400	80	28.25	2.83	5.65	601.73

*API=active pharmaceutical ingredient, Q=carrier material, q=coating material, PVP=polyvinyl pyrolidone, MGS= magnesium stearate. Unit of measurements were all in mg.

Table 2 Some pre-compression and post-compression study results

Tablets	AR	HR	CI	T	D	H	F	Dt	WV	A
ALS1	28.5±0.9	1.8±0.6	12.2±0.4	5.7±0.2	12.9±0.1	5.3±2.3	0.2	0.1±0.6	568.5±0.1	81
ALS2	19.9±0.2	0.2±1.1	14.1±1.1	5.6±0.1	12.8±0.2	8.3±1.8	0.9	0.6±0.4	552.6±0.1	72
ALS3	14.8±2.3	0.5±1.7	12.5±2.2	5.4±0.0	12.8±0.2	7.9±1.0	0.5	0.5±0.3	517.0±0.1	60
ALS4	19.1±2.4	1.1±0.5	12.5±0.9	5.5±0.1	12.9±0.1	7.3±1.6	0.4	0.7±0.6	526.8±0.8	90
ALS5	23.1±1.5	0.1±0.1	10.1±3.1	5.5±0.0	12.8±0.1	9.9±0.4	0.5	0.8±0.0	521.9±0.1	93
ALS6	31.3±0.3	0.6±2.9	13.0±2.1	5.6±0.1	12.9±0.4	1.4±0.5	0.4	0.3±0.7	573.7±0.2	95
ALS7	21.0±2.1	0.3±0.2	14.1±0.3	5.5±0.3	12.9±0.4	7.2±2.9	0.5	0.4±0.1	551.2±0.1	77
ALS8	19.2±4.2	0.2±1.2	14.7±0.6	5.5±0.1	12.9±0.3	7.0±1.6	1.7	0.2±0.5	555.3±0.2	79
ALS9	11.1±2.6	0.2±0.9	10.1±0.8	5.5±0.0	12.8±01	1.8±0.9	0.6	0.1±0.2	555.1±0.2	93
ALS10	25.6±0.4	0.2±0.3	11.3±1.6	5.6±0.1	12.8±0.3	2.6±0.2	0.8	0.5±1.9	539.0±0.1	102
ALS11	15.7±0.6	0.1±0.2	11.7±1.1	5.6±0.1	12.9±0.3	1.5±3.7	2.3	0.6±0.9	611.2±0.1	81
ALS12	33.6±1.6	0.9±1.1	12.1±6.2	5.8±0.0	12.9±0.1	2.9±8.2	0.7	0.2±0.5	624.5±0.9	91
ALS13	22.1±9.3	1.2±0.7	10.8±8.0	6.4±0.1	12.9±0.5	2.1±4.1	1.4	0.2±0.2	614.4±0.0	101
ALS14	20.7±0.8	1.0±1.6	14.4±0.3	5.8±0.0	12.8±0.1	5.7±1.5	1.1	0.6±0.0	593.1±0.8	74
ALS15	28.5±1.1	0.1±0.8	11.1±1.4	5.7±0.0	12.9±0.1	2.7±2.7	1.1	0.4±0.2	580.4±1.5	93
				5.5±0.0	12.9±1	1.5±1.3	1.3	0.4±0.0	515.1±0.1	116

*AR=Angle of repose (^{0}), HR=Hausner ratio, CI=Carr's compressibility index, T=thickness (mm), D=diameter (mm), WV=weight variation (mg), F=friability (%), H=hardness (KgF), Dt=disintegration time (min), A=assay (%) test.

Table 3. Percent dissolution at different times with correlated quantities gotten within the sampling interval for ALS5

T	CPR	AR	DAR
0.08	66.87	50.15	50.15
0.17	80.83	60.62	10.47
0.33	93.33	70.00	9.38
0.5	99.79	74.84	4.84
0. 75	101.25	75.94	1.10

*AR= Amount of drug release (mg), CPR= cumulative percent drug release (%), DAR= discrete quantity of drug release within sampling interval (mg), T= time (hours)

Table 4 Calculated drug level at different times from ALS5

T	PBA					PTQ	PC
0.08	50.15					50.15	5.50
0.17	48.52	10.47				58.99	6.47
0.33	45.74	9.87	9.38			64.99	7.13
0.5	42.95	9.27	8.81	4.84		65.87	7.22
0.75	39.16	8.45	8.03	4.41	1.10	61.15	6.71
1	27.05	7.70	3.18	4.02	1.00	42.95	4.71
2	18.68	5.32	2.20	2.78	0.69	29.67	3.25
3	12.90	3.68	1.52	1.92	0.48	20.50	2.25
4	8.91	2.54	1.05	1.32	0.33	14.15	1.55
5	6.15	1.75	0.72	0.92	0.23	9.77	1.07
6	4.25	1.21	0.50	0.63	0.16	6.75	0.74
7	2.94	0.84	0.34	0.44	0.11	4.67	0.51
8	2.03	0.58	0.24	0.30	0.08	3.23	0.35
9	1.40	0.40	0.16	0.21	0.05	2.22	0.24
10	0.97	0.28	0.11	0.14	0.04	1.54	0.17
11	0.67	0.19	0.08	0.10	0.02	1.06	0.12
12	0.46	0.13	0.05	0.07	0.02	0.73	0.08
13	0.32	0.09	0.04	0.05	0.01	0.51	0.06
14	0.22	0.06	0.03	0.03	0.01	0.35	0.04
15	0.15	0.04	0.02	0.02	0.01	0.24	0.03
16	0.11	0.03	0.01	0.02	0.00	0.17	0.02
17	0.07	0.02	0.01	0.01	0.00	0.11	0.01
18	0.05	0.01	0.01	0.01	0.00	0.08	0.01
19	0.03	0.01	0.00	0.01	0.00	0.05	0.01
20	0.02	0.01	0.00	0.00	0.00	0.03	0.00
21	0.02	0.01	0.00	0.00	0.00	0.01	0.00
22	0.01	0.00	0.00	0.00	0.00	0.01	0.00
23	0.01	0.00	0.00	0.00	0.00	0.01	0.00
24	0.01	0.00	0.00	0.00	0.00	0.01	0.00

*PBA= predicted blood quantity after oral absorption (mg), PC= predicted concentration at times (g/ml), PTQ= predicted total blood quantity following oral absorption (mg), T= time following absorption (hours).

Table 5. Percent dissolution at different times with correlated quantities obtained within sampling interval for reference tablet.

T	CPR	AR	DAR
0.08	20.23	15.17	15.17
0.17	25.01	18 .76	3.57
0.33	53.50	40.13	21.37
0.5	80.30	60.23	20.1
0.75	80.51	60.38	0.15

*AR= Amount of drug release (mg), CPR= cumulative percent drug release (%), DAR= discrete quantity of drug release within sampling interval (mg), T= time (hours)

Table 6 Calculated drug level at different times from comparative brand

T	PBA					PTA	PC
0.08	15.17					15.17	1.66
0.17	14.68	3.57				18.25	2.00
0.33	13.84	3.37	21.37			38.58	4.23
0.5	12.99	3.16	20.07	20.10		56.32	5.72
0.75	11.85	2.88	18.29	18.32	0.15	51.49	5.65
1	10.80	2.63	16.68	16.71	0.14	46.96	5.15
2	7.46	1.81	11.52	11.54	0.09	32.42	3.56
3	5.15	1.25	7.96	7.97	0.06	22.39	2.46
4	3.56	0.86	5.50	5.51	0.04	15.47	1.70
5	2.46	0.60	3.80	3.80	0.03	10.69	1.17
6	1.70	0.41	2.62	2.63	0.02	7.38	0.81
7	1.17	0.28	1.81	1.82	0.01	5.09	0.56
8	0.81	0.20	1.25	1.25	0.01	3.52	0.39
9	0.56	0.14	0.86	0.87	0.01	2.44	0.27
10	0.39	0.09	0.60	0.60	0.00	1.68	0.18
11	0.27	0.06	0.41	0.41	0.00	1.15	0.13
12	0.18	0.04	0.28	0.29	0.00	0.79	0.09
13	0.13	0.03	0.20	0.20	0.00	0.56	0.06
14	0.09	0.02	0.14	0.14	0.00	0.39	0.04
15	0.06	0.01	0.09	0.10	0.00	0.26	0.03
16	0.04	0.01	0.06	0.07	0.00	0.18	0.02
17	0.03	0.01	0.04	0.05	0.00	0.13	0.01
18	0.02	0.00	0.03	0.03	0.00	0.08	0.01
19	0.01	0.00	0.02	0.02	0.00	0.05	0.01
20	0.01	0.00	0.01	0.02	0.00	0.04	0.00
21	0.01	0.00	0.01	0.01	0.00	0.03	0.00
22	0.00	0.00	0.01	0.01	0.00	0.02	0.00
23	0.00	0.00	0.01	0.01	0.00	0.02	0.00
24	0.00	0.00	0.00	0.00	0.00	0.00	0.00

*PBA= predicted blood quantity after oral absorption (mg), PC= predicted concentration at times (g/ml), PTQ= predicted total blood quantity following oral absorption (mg), T= time following absorption (hours).

Table 7 Predicted and observed pharmacokinetic parameters for ALS5 and comparative brand, along with their correlated percentage prediction error

PARAMETERS	PV	ALS5 OV (% PE)	CB OV (% PE)
C max	7.31	7.22 (1.23)	5.72 (21.75)
T max	0.5	0.5 (0)	0.5 (0)

*C_{max} =peak plasma concentration (g/ml), T_{max} =time to reach maximum concentration (hours), OV= observed values, % PE= percentage predicted error, PV= predicted values

Conclusion

The study demonstrated that aspirin can be successfully formulated into liquisolid tablets with improved solubility and dissolution properties. The choice of excipients, particularly propylene glycol and glycerol, played a crucial role in enhancing the solubility of aspirin. The IVIVC study showed that the optimized formulation (ALS5) had good predictability of in vivo profiles. In conclusion, the results suggest that liquisolid technology can be a promising approach for improving the bioavailability of poorly soluble drugs like aspirin.

References

1. Mir AM, Karim OB, Khosro A, Javad S, Solmaz A (2017) Enhancement of ketoconazole dissolution rate by the liquisolid technique. *Acta Pharmaceutics, 68:325-336.* https://doi.org.10.2478/acph-2018-0025
2. Bhola J, Mori D, Soniwala MM, Jayant C (2022) Formulation and optimization of liquisolid compact for improving the dissolution profile of efavirenz by using DoE approach. *Saudi Pharmaceutical Journal, 28:737-745.* https://doi.org/10.1016/j.jsps.2020.04.016
3. Marzia C, Paola M, Maurizio V, Letizia B (2022) Development and characterization of liquisolid tablets based on mesoporous clays or silicas for improving glyburide dissolution. *Pharmaceutics, 12:1-18.* https://doi:10.3390/pharmaceutics12060503
4. Maria RB, Jorge AG, Haydee C, Ana MM, John J (2022) In vitro bioequivalence of acetylsalicylic acid and implications in public health. *Dissolution Technologies, 29:1-10* dx.doi.org/10.14227/DT290322PGC1
5. Shathala HK, Jayaprakash V, Muniganti R, Jaswanth GBH, Karthika P (2021) Enhancement of solubility and dissolution rate of acetylsalicylic acid via co-crystalization technique: a novel ASA-Valine cocrystal. *International Journal of Applied Pharmaceutics, 13(1):1-7.* http://dx.doi.org/10.22159/ijap.2021v13i1.40054
6. Braham D, Manjusha C, Vikas B (2020) Preparation, characterization and evaluation of aspirin: benzoic acid cocrystals with enhanced pharmaceutical properties. *Future Journal of Pharmaceutical Sciences, 6:32-48.* https://doi.org/10.1186/s43094-020-00052-y
7. Nawal AR (2017) Preparation and in vitro evaluation of lacidipine oral liquid solid tablet as an approach of solubility and dissolution rate enhancement. *International Journal of Applied Pharmacy, 10:145-153.* http://dx.doi.org/10.22159/ijap.2018v10i1.22313
8. Doaa HA, Mohamed AI, Gamal Z, Mohammed AA, Heba AA (2022) The role of sodium lauryl sulfate on the formulation of directly compressed tablets containing simvastatin and aspirin: effect on drugs dissolution and gastric mucosa. *Saudi Pharmaceutical Journal, 30:635-645.* http://doi:10.1016/j.jsps.2022.02.006
9. Yeyet CS, Arini S, Jessie SP, Heni R (2009) Dissolution test of various low-dose acetylsalicylic acid preparations marketed in Indonesia. *Medical Journal of Indonesia, 18:161-166.* https://doi.org/10.13181/mji.v18i3.355
10. Gabriela M, Aurel P (2014) Studies of different types of aspirin by spectrophotometric methods *ACTA Chemica IASI, 22:155-164.* http://doi:10.2478/achi-2014-0013
11. Pranaya RB, Krishna SA (2019) Preparation of aspirin-loaded ethyl cellulose nanoparticles by nanoprecipitation technique. *SOJ Pharmacy & Pharmaceutical Sciences, 6(2):1-3.*
12. Noriko H, Taigi Y, Yoshiaki F, Hidehiro N, Takehiko (2023) A study on pharmacokinetics of acetylsalicylic acid mini-tablets in healthy adult comparison with the powder formulation. *Pharmaceutics, 15:1-11.* http://doi:10.3390/pharmaceutics15082079
13. Lakshmi K, Yash C, Preeti P, Ghanshyam DG, Dilpreet S (2024) Advancement in solubilization approaches: A step towards bioavailability enhancement of poorly soluble drugs. *Life, 13:1-33.* http://doi:10.3390/life13051099
14. Dominick JA, Jayne P, Efthymios ND, David JS, James S (2022) Pharmacokinetic and pharmacodynamic profile of a novel phospholipid aspirin formulation. *Clinical Pharmacokinetics,* 61:465-479 http://doi:10.1007/s40262-021-01090-2
15. Duanduan C, Wenyuan Q, Xiaohui L, Xiaoyu X, Lingyun D (2023) Pharmacokinetic study of enteric-coated sustained-release aspirin tablets in healthy Chinese participants. *Drug Design, Development and Therapeutics, 17:2421-242.* http://doi:10.2147/DDDT.S409524