ORIGINAL ARTICLE

Exploring Adsorption Phenomena in Pharmaceutical Formulation Design: A Systematic Quality-By-Design Approach for Agomelatine-Loaded Liquisolid Compact Tablets

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Abstract

Introduction: In our quest to maximize the therapeutic potential of Agomelatine, we embarked on a study wherein we formulated it into liquisolid compact tablets, strategically designed to enhance its dissolving performance and unlock its antidepressant efficacy. **Materials and Methods:** Employing the Quality by Design (QbD) methodology, specifically a randomized, non-block, central composite design with a response surface study type, quadratic model, and version 13.0.5.0, we meticulously developed nine alternative formulations (F1-F9). The non-volatile solvent, polyethylene glycol 400, played a pivotal role, with the non-volatile solvent loading factor (X_1) and the excipient ratio of carrier to coating material (X_2) serving as key independent variables. Evaluation of the formulations centered on two critical parameters: the angle of repose (Y_1) and *in-vitro* percentage drug release (Y_2). Employing Kawakita and Heckel's methods, we discerned the dense nature of compact particles and their favorable compaction properties. The addition of Aerosil 200 alongside microcrystalline cellulose showcased improved compressibility through plastic deformation. Comprehensive pre- and post-compressional parameter assessments were established in Indian Pharmacopiea standard procedures. The release order kinetics were analyzed using DD solver as a statistical tool. **Results:** It pointed to the (F8) liquisolid formulation as particularly impactful, out shining other alternatives. Tablets were successfully fabricated using the direct compression method (F10). Our study extended to assess the similarity factor (f_2) with a marketed sample (Agoprex 25 mg) and conducted stability studies for 90 days in line with ICH guidelines. Post 90 days, an analysis of variance demonstrated a $P = 0.386$, surpassing the threshold of $P > 0.05$, indicating negligible variation in *in-vitro* dissolution parameters. **Conclusion:** Our research underscores the effectiveness of liquisolid encapsulation as a distinctive strategy, significantly elevating the dissolving performance of Agomelatine and, consequently, enhancing its antidepressant efficacy. The application of QbD principles, coupled with a meticulous analysis of formulation variables and thorough tablet property evaluations, has yielded valuable insights, paving the way for an optimized liquisolid compact tablet formulation for agomelatine.

Key words: Agomelatine liquisolid compact tablets, DD solver, *in-vitro* drug release, non-volatile solvent, quality by design

INTRODUCTION

Oral medicine administration is preferred due to its numerous advantages, including cost-effectiveness and high patient compliance. When medications are ingested orally, they undergo dissolution in the stomach and subsequent absorption into the bloodstream through the gastrointestinal tract (GIT). As a result, the process of dissolution plays a critical role in regulating the rate of oral

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absorption, particularly for poorly water-soluble drugs.[1,2] Conversely, an extensive review of various literature sources reveals that nearly 40% of newly developed drugs face substantial challenges in addressing issues related to their diminished solubility and limited permeation within the GIT, resulting in compromised drug absorption and overall bioavailability.[3] This study introduces several innovative technological breakthroughs that have been documented to effectively mitigate the water solubility concerns associated with active pharmaceutical ingredients (API). Several methodologies have been identified, encompassing the dispersion of API into suitable carriers, exemplified by the rapid-dissolving ondansetron tablets,[4] solid crystal engineering,[5] micronization to reduce solid substance size,[6] complex formation,[7] emulsification,[8] the creation of fast-dissolving agomelatine films,[9] and the incorporation of carriers within mesoporous structures.[10] Notably, the recent formulation of medicines into liquisolid compacts has shown significant promise in enhancing their dissolution performance and oral bioavailability.[11] Through the dissolution of the medication into an appropriate physical blend of carrier and coating material, followed by the compression of the resultant liquisolid compact, the drug becomes highly compressible and resistant to degradation in the presence of a non-volatile solvent. The solubilization and loading of the drug onto the carrier are facilitated by the non-volatile solvent. An enhanced level of oral bioavailability is a distinctive attribute of liquid-solid compacts, attributed to their ability to expedite wetting and dissolution of the medication. The transformation of powder compacts into liquid tablets enables the incorporation of medications while they are in a liquid state conducive to absorption. As an illustration of ideal candidates, carbamazepine, utilized in epilepsy management,[12] atorvastatin for lipid and triglyceride reduction,[13] and fenofibrate controlling pancreatic inflammation[14] stand out among medications whose solubility has been augmented through liquisolid compact utilization. Notably, agomelatine, a potent antidepressant, has emerged as a forefront contender in the battle against depression. Functioning as an agonist at melatonin receptors (MT_1 and MT_2) and an antagonist at serotonin (5-HT_2C) receptors, agomelatine targets the relevant 5-HT_2C receptors in antidepressant therapy. Its interaction with melatonin receptors further leads to improved sleep quality, highlighting its therapeutic potential. Agomelatine, acknowledged for its anxiolytic properties, holds potential for the treatment of anxiety disorders.[15] However, it falls into bio-pharmaceutics classification class-2 and exhibits minimal solubility in water, registering at only 1.2 mg/mL.[16] Consequently, the elevation of its bioavailability and therapeutic efficacy necessitates enhancing its solubility and dissolution rate, much like the strategies employed in the formulation of Amorphous solid dispersion of Agomelatine[17] and Agomelatine-PEG solid dispersions.[18] Within the scientific literature, a variety of methods have been documented to enhance the solubility of agomelatine. Among these methodologies are agomelatine nanostructured carriers,[19] the formulation of nano-based transdermal patches,[20] the creation of mucoadhesive-loaded agomelatine,[21] controlled release approaches for agomelatine,[22] co-crystallization techniques for agomelatine,[23] salt formation strategies for agomelatine,[24] and more contemporary approaches such as novel amorphous preparations of agomelatine.[25]

In addition, recent studies exploring the use of liquisolid compact technology to enhance agomelatine's solubility and dissolution performance have been reported in the literature.[26-28] However, these investigations primarily focus on revealing *in-vitro* evaluation parameters, warranting a more comprehensive examination of the behavioral characteristics of the formulated compounds. Quality by design (QbD) encapsulates the concept of enhancing comprehension of both product and process while minimizing the investment of time, finances, and effort.[29-31] An integral facet of quality-based design, designs of experiments (DoE) is particularly esteemed for its capacity to elucidate the intricate interplay among various variables.[32,33] Numerous investigations have substantiated that the incorporation of QbD and DoE techniques is instrumental in devising high-performance products.

QbD, a technique aimed at enriching the understanding of both product and process, operates with a modest initial investment in terms of time, finances, and effort.[32-35] Within the realm of QbD, DoE occupies a significant role[36] as they effectively unveil the correlations among diverse factors. As demonstrated by several studies, the integration of QbD and DoE methodologies has yielded valuable insights in the creation of products with exceptional performance.

MATERIALS AND METHODS

Materials

A gift sample of agomelatine was acquired from Aurobindo Pharmaceuticals Private Ltd., situated in Hyderabad, India. The required ingredients were procured from Himedia Chemicals Private Ltd., located in Mumbai, India. These ingredients encompassed MCC grade PH102 (Avicel) serving as the carrier, colloidal silicon dioxide (Aerosil 200) employed as coating material, croscarmellose sodium for its super disintegrating properties, and magnesium stearate contributing to the glidant effect. In addition, the ingredients included tween 20 and 80, glycerin, propylene glycol (PG), as well as polyethylene glycol (PEG) 200 and 400, among others.

Fabrication of agomelatine liquisolid compact tablets

Calculation of liquid loading factor (Lf)

To establish their liquid Lf, a mortar was filled with the requisite quantity (5 g) of a physical mixture of excipients, including various carriers such as lactose, microcrystalline cellulose, and dibasic calcium phosphate. Subsequently, the powder was

combined with the appropriate non-volatile solvent, PEG400, in increments of 0.1 mL. Following each incremental addition, the mixture was meticulously blended using a pestle to ensure uniform distribution of the solvent among the solid particles. Ultimately, to prevent clumping of the powder, the appropriate amount of liquid was incorporated, and the final weight was documented.[37] The liquid Lf was determined by applying the formula $L_f = W/Q$, with W representing the final weight and Q denoting the amount of solvent added.[38]

Following the procedure outlined by Spireas and Bolton,[37] Agomelatine liquisolid compacts were formulated. The process commenced with the preparation of the medication solution, wherein the drug was dissolved in PEG 400 and subsequently poured onto a powdered amalgamation of Avicel 200 and Aerosil 400. Care was taken to avoid excessive trituration, preventing undue reduction of particle size, during a thorough mixing period of 15 min, executed using a mortar and pestle. Post this stage, the powder was further blended for an additional 15 min following the introduction of croscarmellose sodium as a disintegrating agent, ensuring the attainment of a consistent texture. For lubrication purposes, magnesium stearate was incorporated into the powder mixture and stirred for 5 min. The tablets were manufactured employing the direct compression technique, with a fixed compression force of 4 tons, employing a single-station tablet press (Cadmach Corporation, Ahmadabad, India), featuring a punch dimension of 9mm in diameter. The tablets were manually fed into the machine and expelled after each compression cycle. In a parallel manner, traditional tablets were also prepared utilizing the same powder blend; however, the non-volatile solvent was omitted before the direct compression of the powder mass into tablets. The design of Agomelatine liquisolid tablets were depicted in Table 1.

$$R^* = Q/q \quad (1)$$

R=Excipient ratio, Q=Carrier weight, q=Amount of coating material,

$$L_f^* = W/Q \quad (2)$$

L_f^*=Liquid load factor, W=Weight of the liquid, Q=Weight of the carrier.

QbD-based systematic optimization of liquisolid compact tablets

Employing QbD principles, we systematically enhanced the efficiency and safety of our liquisolid compact tablet through a well-designed experimental approach. The central composite design was employed to optimize the main material properties, the liquid L_f, and the excipient ratio (R), each at three levels (low, medium, and high), utilizing an alpha value of 1 for maximum efficiency. The description of agomelatine liquisolid compacts preparation, encompassing F1-F9, as well as the direct compressible tablets (F10), can be found in Table 3. Conversely, Table 2 delineates the various experiment trials, presenting the combinations of study variables in both coded and actual groups.

The formulated liquisolid tablet experimental formulations underwent testing, evaluating micromeritic properties such as flow pattern through parameters such as the angle of repose (θ) and the percentage of drug release (%) as dependable responses (Y_1 and Y_2) respectively. Furthermore, we made investigation how far variations in Lf and excipient ratio would affect the behavior of agomelatine liquisolid compacts.

Characterization of Agomelatine liquisolid compacts powders

Solubility analysis

To assess the drug's solubility, tests were conducted in both distilled water and various suitable non-volatile solvents, including glycerin, PEG, Tweens, and PG. Each vial containing the solvents was supplemented with a predetermined quantity of the drug, after which consistent stirring was sustained using a water bath maintained at 37±1°C for a duration of 48 h. Subsequent to the incubation period, the drug concentration in each solvent was quantified in comparison to a blank sample, employing a UV-visible spectrophotometer for further analysis (Lab India Instruments, India).[39]

Drug-Excipient compatibility studies of prepared liquisolid compacts physical mixture

For FT-IR analysis, the materials were thoroughly blended with KBr to form discs, following which spectra were measured

Table 1: Design of agomelatine liquisolid compacts from central composite design

Formulation code	Load factor (L_f) (X_1)	Excipient ratio (R) (X_2)
F1	0	1
F2	0	0
F3	−1	1
F4	−1	−1
F5	1	−1
F6	0	−1
F7	1	1
F8	1	0
F9	−1	0

Table 2: Translation of coded level into actual units

Factors	Minimum (−1)	Centre (0)	Maximum (+1)
Load factor (L_f)	0.2	0.4	0.6
Excipient ratio (R)	5	10	15

Table 3: Formulation composition of agomelatine liquisolid compact tablets

Ingredient mg	F1	F2	F3	F4	F5	F6	F7	F8	F9	(DCT) F10
Agomelatine	25	25	25	25	25	25	25	25	25	25
PEG (400)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	-
MCC (Avicel 102)	113.5	113.5	227	227	75.6	113.5	75.6	75.6	227	151.3
Colloidal silicon dioxide (Aerosil 200)	7.56	11.35	15.13	45.40	15.12	22.70	5.04	7.56	22.70	26.48
Croscarmellose sodium	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75
Magnesium stearate	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Lactose	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
R*	15	10	15	5	5	5	15	10	10	-
L_f	0.4	0.4	0.2	0.2	0.6	0.4	0.6	0.6	0.2	-
Total weight (mg)	350	350	350	350	350	350	350	350	350	350

Table 4: Evaluation of different flow properties of agomelatine-liquisolid compacts

Formulation batch	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner's ratio	Angle of repose (Θ)
F1	0.365±0.12	0.521±0.27	15.27±1.13	1.34±0.04	28.17±1.23
F2	0.387±0.13	0.526±0.17	16.27±1.21	1.42±0.01	27.14±1.30
F3	0.412±0.14	0.589±0.11	17.38±1.10	1.31±0.08	27.18±1.36
F4	0.425±0.03	0.599±0.22	17.99±1.01	1.37±0.03	26.13±1.37
F5	0.364±0.16	0.512±0.32	17.13±1.02	1.39±0.04	29.15±1.05
F6	0.423±0.07	0.521±0.18	15.41±1.25	1.41±0.07	26.15±1.31
F7	0.426±0.33	0.531±0.62	15.23±1.04	1.44±0.06	28.13±1.08
F8	0.391±0.37	0.534±0.01	16.14±1.03	1.37±0.04	25.13±1.07
F9	0.378±0.42	0.532±0.22	16.32±1.07	1.41±0.06	26.14±1.09
F10 (DCT)	0.362±0.17	0.533±0.21	17.23±1.25	1.44±0.05	30.17±1.34

The Data presented as mean ±S.D. (n=3), n is the number of observations

utilizing an FT-IR spectrometer covering the range of 4000–400 cm^{-1} (Shimadzu, India). A sample mass of 5 mg was mixed with 100 mg of KBr powder, and the resulting mixture was compressed under vacuum conditions at a pressure ranging from 11,000 to 12,000 pounds per square inch for a duration of two to three minutes. Subsequently, FT-IR analysis was carried out on the produced disc, and the acquired spectra were subsequently subjected to comparison.[40]

Drug-excipient compatibility by thermal analysis

To evaluate the stability of the dosage form and its compatibility with both the medication and excipients, DSC analysis was employed. The automated thermal analyzer (DSC Q20, Perkin Elmer, India) was utilized to record thermal spectra for both the pure API and the optimized formulation of liquisolid compact (F8). Furthermore, thermogravimetric analysis was conducted on materials that were subjected to heating and cooling in aluminum pans over a temperature range spanning from 30 to 300°C.[41]

Micrometric properties fabricated liquisolids

Conforming to the testing protocols detailed in USP-NF 40, the powder mixture from each batch underwent micrometric characterization to assess various powder flow properties. These properties encompass Bulk and True density, Hausner's ratio, Carr's Index, and the Angle of repose.[41]

Determination of liquisolid powders flow properties

In general, the flow properties of liquisolid can be performed by selecting the classic fixed funnel method.

$$\theta = tan^{-1} {}^{h}\!/_{r} \quad (3)$$

Where θ is the angle of repose, h, and r, say the height and radius of the powder pile.

Mathematical modeling of powder characteristics[43]

Kawakita analysis

In line with conventional procedures, the study was conducted by first weighing out a specified amount (10 g) of the powder, which was then introduced into a glass measuring cylinder having a volumetric capacity of 50 mL. The initial volume (V_0) at rest was accurately measured. Subsequently, mechanical tapping was initiated, and the resulting height of the powder column (V_N) was recorded after a set number of taps. Ultimately, the flow properties of the powders were assessed utilizing Kawakita analysis, as per Equation (4).

$$\frac{N}{C} = \frac{N}{C} + \frac{1}{ab} \quad (4)$$

Where N represents the total number of taps, and coefficients a and b are devised to signify the compatibility of particles and the extent of volume reduction due to tapping, respectively. The parameter C, denoting the volume reduction achieved by tapping, is calculated by dividing the initial volume (V_0) by the tapped volume (V_N), as described by Equation (5).

$$C = \frac{(VO - VN)}{VO} \quad (5)$$

Compaction studies

By precisely measuring a quantity of 200 mg of powder, we subjected it to crushing within a hydraulic pellet press cavity equipped with a die (Navayug Co. Ltd., India) under pressures ranging from 10 to 100 kg/cm². Initially, the dimensions of the compacts, including thickness and diameter, along with their weight distribution, were determined. Subsequently, the density of the resulting compacts (ρA) was calculated.

Heckel analysis

The compaction of physical mixture was determined by Heckel equation. The above equation is mathematically denoted as

$$In\frac{1}{1-\rho r} = Kp + A \quad (6)$$

$$\rho_T = \frac{\rho A}{\rho T} \quad (7)$$

Evaluation of post-compressional parameters of liquisolid compact tablets

Post-compressional parameters were evaluated, encompassing measurements for tablet thickness, friability, hardness, weight variation, disintegration time, and drug content for every batch of liquisolid tablets. These evaluations were conducted following the procedures outlined in USP-NF protocols.

Estimation of *in-vitro* percentage drug release

To obtain the *in-vitro* dissolution profiles, both liquisolid compacts and conventionally compressed tablets underwent dissolution testing using a USP-II dissolution test apparatus. The dissolution studies were conducted within a dissolution medium of 6.8 pH buffer, totaling 900 mL, at a controlled temperature of 37°C ± 0.5°C, and a rotation speed of 50 rpm. Subsequently, samples of 5 mL were collected at 5-min intervals over a duration of up to 60 min. To ensure sink conditions, the dissolution fluid was replenished with 5 mL of fresh dissolution medium after each sample collection. The collected samples underwent filtration and were then subjected to spectrophotometric analysis at 236 nm.[43]

Drug release kinetics and mechanism analysis[45,46]

To elucidate the drug release kinetics and mechanisms of Agomelatine liquid solid compact tablets, the In-vitro dissolution profiles for all formulations were systematically evaluated. These profiles were subjected to a range of appropriate models, including zero-order kinetics, first-order kinetics, Higuchi's plot, and the Korsmeyer–Peppas (K-P) model. The statistical tool DD Solver software was employed for this analysis.[46]

In this assessment, crucial parameters such as the adjusted regression values (r^2 adjusted), the range of Akaike Information Criterion (AIC), and the Model selection criterion (MSC) values played a pivotal role.[48] These parameters generated distinct values that formed the basis of comparison. By analyzing these values, it became possible to determine the best-fitting models that elucidate the release order mechanism for the various formulations ranging from F1-F9 and pure DCT (F10). This systematic approach provides insights into the kinetics and mechanisms governing the drug release from the different formulations.

Stability studies according to ICH guidelines

In accordance with the ICH guidelines, stability studies were undertaken to determine the true shelf-life of the optimized agomelatine liquisolid tablets (F8). These tablets were subjected to controlled conditions, specifically maintained at a temperature of 40°C and a relative humidity (RH) of 75%, over a span of 90 days. The objective of these studies was to gain insight into the tablets' stability and to ascertain their potential performance and quality over an extended period under these specified conditions.

Comparison of *in-vitro* dissolution profiles by similarity factor (f_2)[49]

The primary objective of this study was to conduct a comparative analysis between the *in-vitro* dissolution profiles of the optimized formulation of agomelatine liquisolid compact tablets (F8) and the commercially available Agoprex (25 mg) tablets. To achieve this, a model-independent method was employed. Mathematically expressed, this method allows for a robust comparison of the dissolution behaviors of the two formulations. The focus was on understanding the release patterns of both formulations and drawing meaningful comparisons, facilitating insights into their respective performance characteristics.

$$f_2=50\times\log\{[1+(1/n)\Sigma|R_t-T_t|^2]^{-0.5}\times 100\} \quad (8)$$

Here, similarity index factor (f_2), observations in number (n), R_t and T_t indicate the percentage amount of drug to be dissolved from both formulations (reference and test).

RESULTS AND DISCUSSION

Figure 1 presents the solubility data of the pure medication (agomelatine) in various solvents. Among different non-volatile solvents tested, PEG 400 emerged as the chosen carrier for agomelatine due to its high surface adsorption and porous nature.

The development of the liquisolid compact involved employing carriers such as cellulose, starch, and lactose, chosen for their characteristics. In tandem, microcrystalline cellulose 102 was selected as a carrier, while colloidal silicon dioxide powder (Aerosil 200) was designated as a coating agent in preliminary experimental trials, incorporating these excipients. Utilizing the experimental design outlined in Table 3, a series of liquisolid compact formulations (F1-F9) and direct compressible formulations (F10) was also formulated.

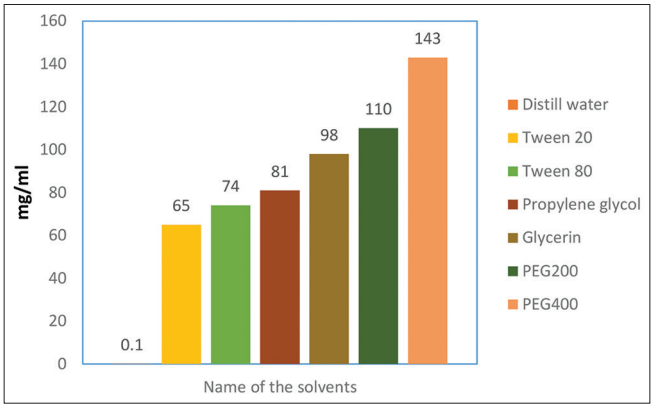

Figure 1: Solubility of Agomelatine in different solvents

Drug-excipient compatibility studies by FT-IR analysis

Figures 2 and 3 provide a visual representation of the FT-IR spectra of various samples, including the pure drug, the drug mixed with carefully selected excipients, and the drug combined with the optimal formulation (F8). When scrutinizing the FTIR spectra, a comparison between the pure drug and a physical mixture of the drug with excipients reveals prominent peaks at specific ranges: the C=C of pure Agomelatine spanning from 1433 to 1457, C-N stretching ranging between 1253 and 1360, C-O-C stretching at 1027-1212, 1054, 1254, 1054, and 1214, and C=O stretching at 1625–1630. In addition, N-H stretching was identified within the 3248–3449 range. Upon evaluating the spectral analysis of both the pure drug and the optimized formulations, no significant alterations were observed in the wave number or intensity of the peaks. This outcome suggests the absence of any substantive interaction between the medication and the selected polymers.

Thermal analysis of physical mixture by differential scanning calorimeter (DSC)

Figures 4 and 5 visually represent the DSC thermograms of two samples: Pure Agomelatine (API) and the optimized

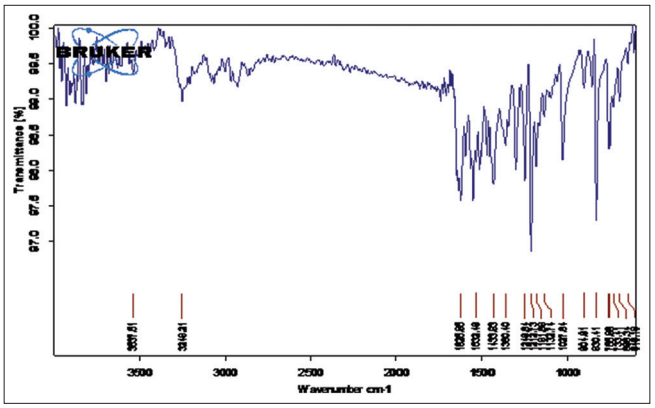

Figure 2: FT-IR spectra of pure agomelatine

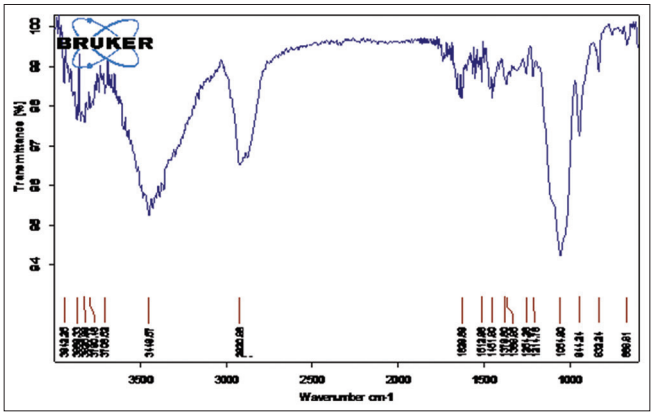

Figure 3: FT-IR spectra of optimized liquisolid formulation (F8)

liquisolid compact formulation (F8). Analysis of these DSC thermograms did not disclose any notable interactions between the drug and excipients. In the case of the pure medication, a distinct melting point is evident, characterized by an endothermic peak at 199.01°C. Remarkably, this peak vanishes in the liquisolid compact formulation. The transition of the drug from a solid crystalline state to an amorphous state accounts for this disappearance, signifying a significant transformation.

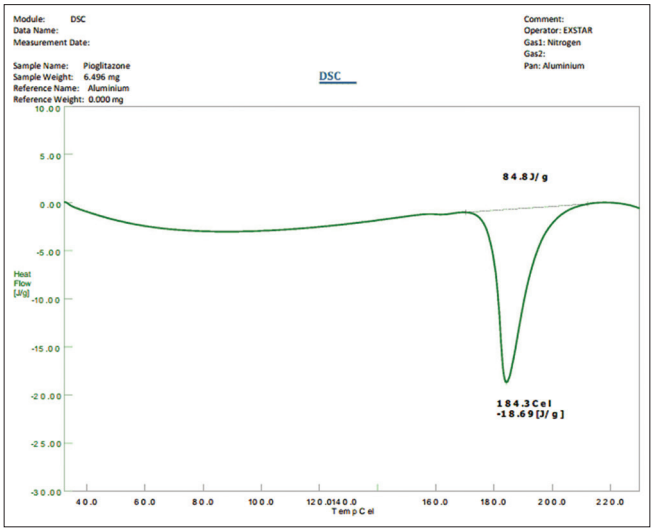

Figure 4: DSC spectra of pure Agomelatine powder

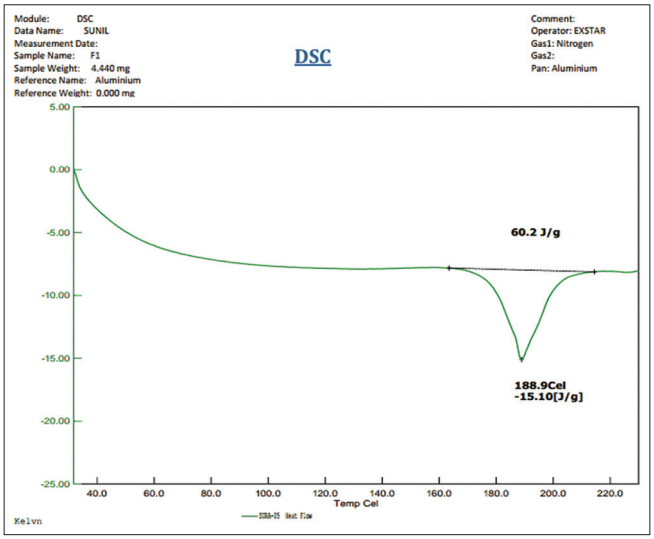

Figure 5: DSC spectra of optimized formulation (F8)

Evaluation of agomelatine liquisolid compacts flow properties

Table 4 provides a comprehensive compilation of parameters and corresponding values for the flow properties of different formulations. Once again, it was determined that among all the formulated variations, formulation F8 exhibited the most favorable flow behavior.

Micrometric characterization

Kawakita analysis

The plot depicting the relationship between the number of taps and N/C was generated for both pure agomelatine and the optimized fabricated liquisolid compact powder mixture [as illustrated in Figure 6]. Notably, tapping the liquisolid powder evinced a linear correlation between and, while the act of tapping the conventional powder mix resulted in a delayed time and established a linear relationship for powder flow.

Heckel analysis

Figure 7 presents a Heckel plot that illustrates the alteration in compression force's impact on the crushing strength of the fabricated liquisolid powder. This plot revealed a curved parallel relationship between the mentioned parameters, thereby aiding in the preservation of material properties. In contrast, a linear correlation between compression pressure and tensile strength was evident in the case of the traditional powder blend. Furthermore, a saturation effect was observed in the standard powder mixtures, wherein a distinct decrease in elastic recovery was noted under high compression pressure, signifying a loss of this specific property.

Table 5: Summary of ANOVA and regression analysis (R^2) from response surface method of agomelatine liquisolid compacts (n=3 values)

Parameters	Response	X_o	X_1	X_2	X_{12}	X_1^2	X_2^2	Model lack of fit
Angle of repose (Y_1)	Coefficients	27.14	1.99	1.01	−0.0175	0.98	0.01	In significant
	P-value	<0.0001	<0.0001	<0.0001	0.0008	<0.0001	0.0002	
	Regression values							
	R^2=1.000		Adjusted R^2=1.000		Predicted R^2=1.000			
Percentage of drug release (Y_2)	Coefficients	95.30	2.81	3.66	0.290	−2.20	−1.67	In significant
	P-value	0.0002	0.0001	<0.0001	0.1196	0.00014	0.0031	
	Regression values							
	R^2=0.9985		Adjusted R^2=0.9960		Predicted R^2=0.9822			

Application of response surface method for optimization of agomelatine

The polynomial equation (Eq. 9) demonstrated an effective fit for all the selected responses, affirming the suitability of the quadratic polynomial model. This was evident through the noteworthy significance of the ANOVA model, coupled with a nominal lack of fit value ($p = 0.0001$ in each instance). The evaluation of correlation coefficients yielded r^2 values between 1.0 for the angle of repose (Y_1) and 0.9985 for the percentage drug release (Y_2), with a minimal PRESS value of 0.0002.

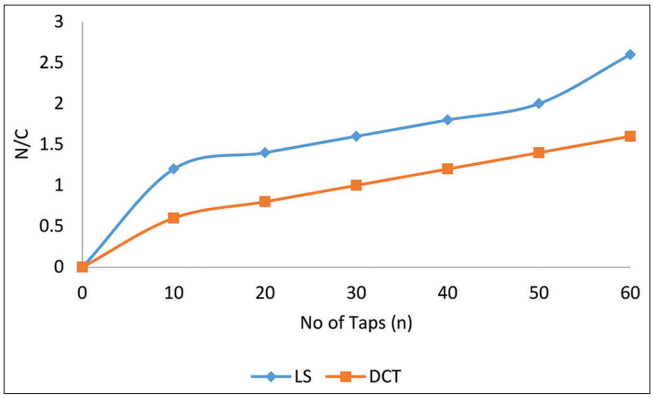

Figure 6: Kawakita plot for powder flow property

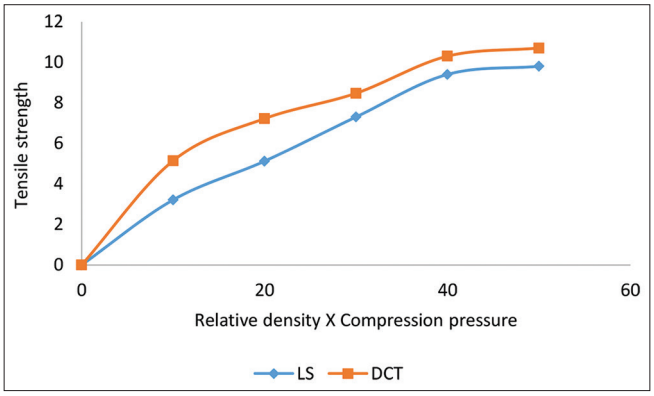

Figure 7: Heckle plot depicting the powder compaction property

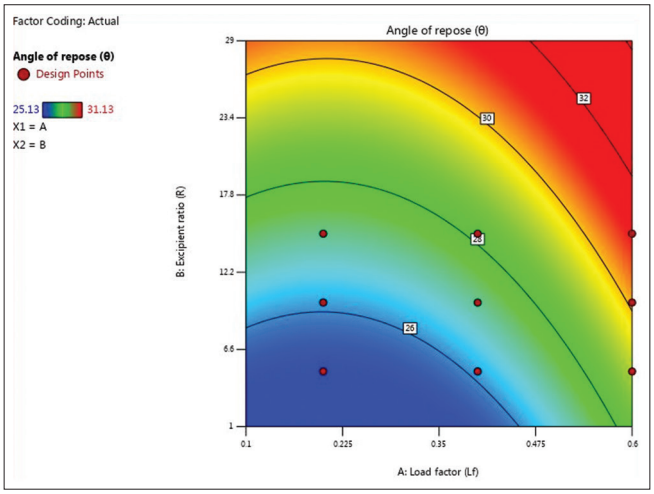

Figure 8: 2D angle of repose (θ)contour plot

$$\text{Angle of repose } (Y_1) = +27.14 + 10.99X_1 + 22.01X_2 - 0.0175X_1X_2 + 0.9883X_1^2 + 0.0183\,X_2^2 \quad (9)$$

Figures 8 and 9 depict the variation in pharmaceutical liquid content. Notably, a liquisolid medication concentration exceeding 0.4% leads to a decline in flow ability. This is attributed to incomplete absorption of the excessive liquid by the carrier and coating materials, resulting in the formation of adhesive agglomerates. However, the assessment of blends with L_f values above 0.4-0.6 was hindered by severe sticking issues. A similar trend is observed in Figure 8, which represents the quantity of liquid medicine. The flowability of the drug diminishes as the proportion of liquid to solid drops below 0.40. Here again, the challenge of incomplete liquid absorption by the carrier and coating materials leads to sticky agglomerates. The L_f value exceeding 0.4–0.6 is impractical due to excessive sticking. Consequently, the optimal range for the liquid load factor L_f within Avicel® combinations was found to be between 0.4 and 0.6.

In-vitro percentage drug release (Y_2)

The impact of increases in liquid volume and excipient ratio on the blends studied differed with regard to the percentage drug release (Y_2).

$$\text{Percentage drug release } Y_2 = +95.30 + 6.81\times1 + 13.66X_2 + 0.2900X_1X_2 - 2.20\,X_1^2 + 1.67\,X_2^2 \quad (10)$$

Figures 10 and 11 provide evidence of the influence of the load factor L_f (X_1) and excipient ratio R (X_2) on the flow ability of liquisolid powder formulations. When liquid medication concentration increased while maintaining the same excipient ratio, the effects on the blends' permeability varied. According to the polynomial equation, the L_f (X_1) amplifies the quantity of drug that becomes more soluble in the liquid solvent. This promotes an increased retention

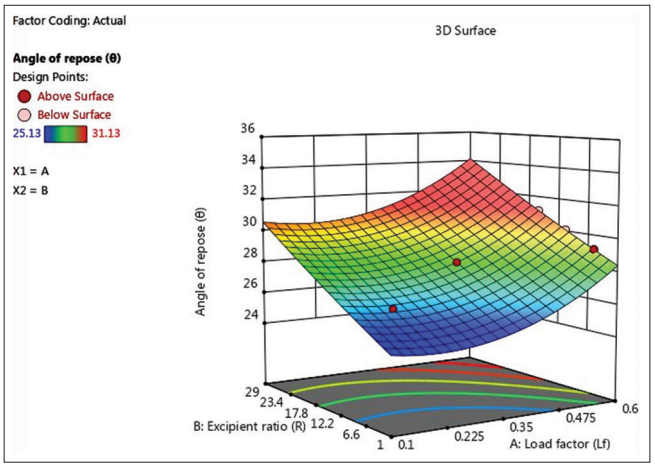

Figure 9: 3D angle of repose (θ)RSM plot

of drug within the liquid-carrier-coating system, effectively forming a drug reservoir. Consequently, the polynomial equation displays a positive sign, indicating a greater loading of drug into the liquid-carrier-coating system, ultimately leading to a higher percentage of drug release compared to agomelatine by the direct compression method.

Unlike the load factor, the excipient ratio (X_2) exerts an impact on the percentage of drug release (Y_2). With increasing drug quantity, the fabricated liquisolid system transitions into a more saturated and wet state. This progression eventually culminates in the formation of loose aggregates or a precipitation-like state, signifying the initiation of solvent liquefaction. To emulate the creation of loose aggregates within the liquisolid system, it becomes essential to elevate the excipient ratio of carrier to coating within the range of 5–15. This adjustment facilitates the absorption and adsorption of excess liquid from the drug solution, effectively rendering the liquisolid system drier and more spherical. Furthermore, the spherical nature of the liquisolid system enhances its specific surface area, allowing for increased penetration of the liquid medium. Consequently, the polynomial equation bears a positive sign, signifying that an augmentation in the excipient ratio corresponds to an increase in the percentage of drug release.

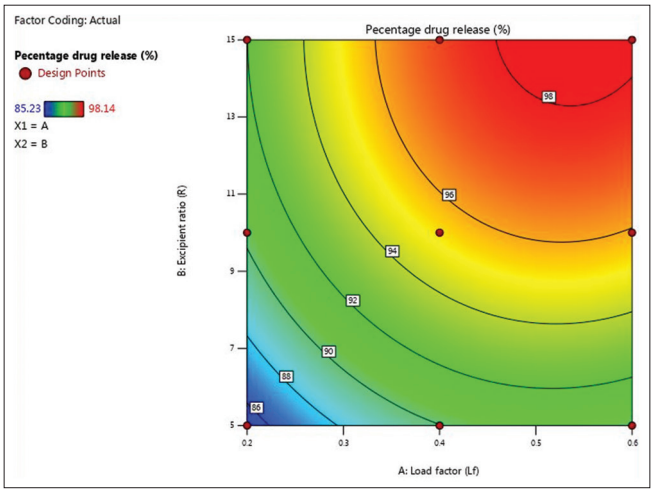

Figure 10: 2D- Percentage drug release contour plot

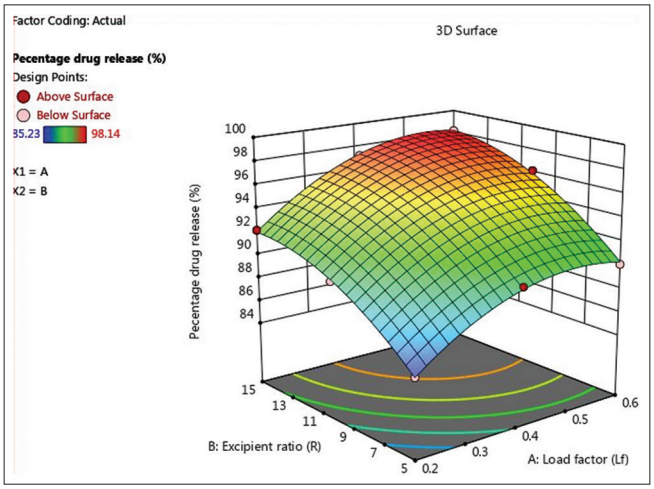

Figure 11: 3D RSM percentage drug release plot

Selection criterion for optimization of fabricated liquisolid compacts containing agomelatine

When dealing with two response variables, such as the Angle of repose (Y_1) and *In-vitro* percentage drug release (Y_2), the application of numerical optimization alongside a desirability function value approaching 1 aid in selecting the most optimal formulation. Among the array of tested formulas, F8 demonstrated the closest alignment with the desired outcomes for all response factors. Figures 12 and 13 illustrate this visually, where the yellow area delineates

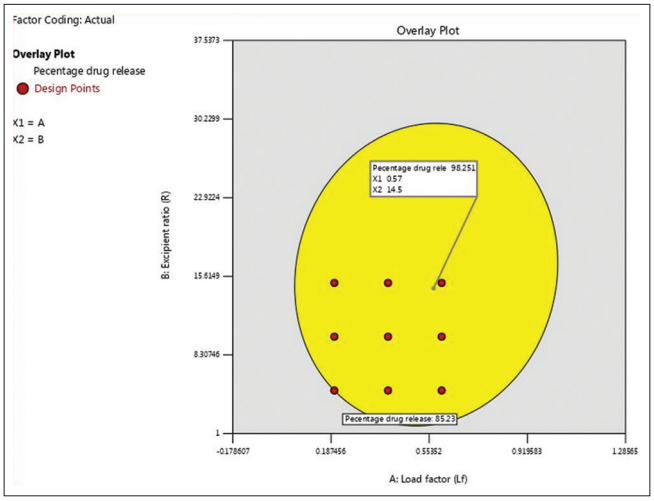

Figure 12: Overlay plot for all response variables for optimized agomelatine liquisolid compacts

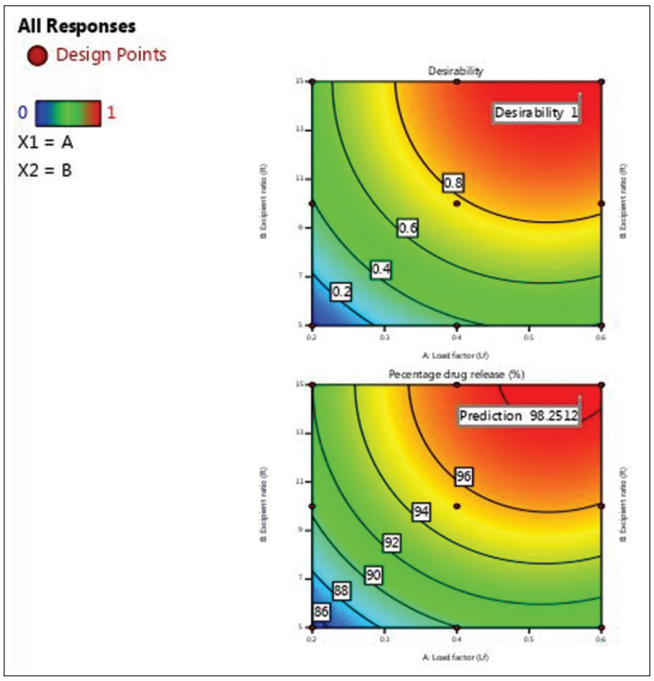

Figure 13: Desirability plot of all response variables for optimized agomelatine liquisolid compacts

the design space, and the highlighted point indicates the constituent components of the optimum formulation as well as the projected values for the responses and the summary of ANOVA and regression analysis results were depicted in Table 5.

Evaluation of the prepared liquisolid compact formulations F-F9

For oral medication, tablets should possess a balance of durability to withstand handling while also being sufficiently soft to dissolve in the body and effectively deliver the intended medicine. Table 6 outlines the technical attributes of various liquisolid compact formulations. Notably, among the formulations developed, F8 emerged as the most compressible. It exhibited superior characteristics in terms of tablet thickness was found to be (4.52 ± 0.02 mm), hardness (3.2 ± 0.016 kg/cm^2), friability (0.46 ± 0.12), weight variation (250.06 ± 0.17), disintegration time (3.98 ± 0.15), and drug content was noted (98.41 ± 0.38), finally a significant percentage of drug release achieved (98.14 ± 1.16) within the designated timeframe.

In-vitro drug release study

Figure 14 visually presents a comparison of the *in-vitro* drug release profiles across different formulations. This assessment includes direct compressible tablets containing the pure medication, which were observed under specific and suitable conditions using pH 6.8 phosphate buffer as the medium. Notably, both the liquisolid compact tablet formulation (F8) and the tablets subjected to direct compression (F10) exhibited complete drug release, measuring 98.14 ± 1.16% and 85.23 ± 1.28%, respectively, within a 60-min timeframe. It is noteworthy that the current investigation highlights the pronounced enhancement in drug release achieved through the fabricated liquisolid compact tablet formulation in comparison to the tablets created through the direct compression process.

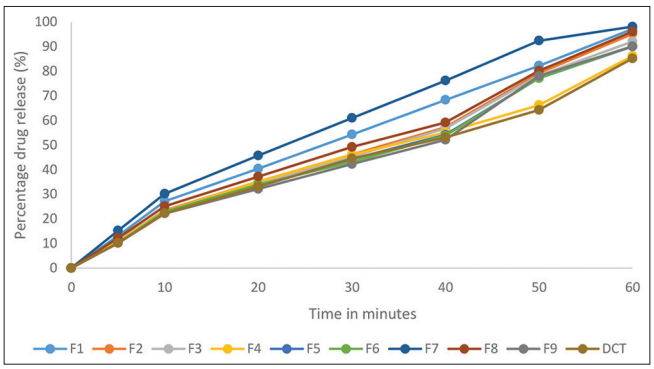

Figure 14: *In-vitro* Comparative dissolution profiles of agomelatine liquisolid compact tablet from (F1-F9) and directly compressible tablet (F10) in pH 6.8 buffer.
The Data is presented as mean± S.D. (*n*=3)

Release order kinetics

In the assessment of release orders for the fabricated agomelatine liquisolid compact formulations from batches F1-F9 and F10, the DD solver model software was employed. This software served as a powerful tool for deciphering the intricate release patterns. By utilizing a range of mathematical models, the study yielded insightful results were shown in Table 7.

From the zero-order model, the F8 formulation exhibited a notable r^2 value of 0.9741, indicating a robust correlation between the model and the observed data. Correspondingly, the AIC value was calculated as 38.47, while the MSC value reached 3.514. In the context of first-order studies, the model F8 formulation resulted in a higher r^2 value of 0.9884, confirming the model's strong fit. The recorded AIC value was 2937, and the MSC value stood at 4.962.

Shifting focus to the Higuchi Model, formulation F8 demonstrated an r^2 value of 0.9746, signifying the model's excellent alignment with the experimental data. The AIC value was determined as 34.28, while the MSC value reached 3.871. Notably, the inclusion of Hixon-Crowell release order analyses revealed that for formulation F8, the r^2 value was 0.9858, AIC value was 38.17, and MSC value was 3.641.

Extending the investigation, the Korsmeyer–Peppas equation provided deeper insights into formulation F8. The model suggested an r^2 value of 0.9719, in strong agreement with the data. The calculated AIC value was 39.51, while the MSC value was 4.215. Notably, the exponent release (n) value stood at 0.413, indicating a Fickian diffusion-type mechanism governing the release.

Where, r^2 is regression co-efficient, AIC, and MSC, etc.

In this comprehensive study, various mathematical models were used to explore and explain the complex patterns of drug release from different formulations of agomelatine liquisolid compacts along with direct compressible tablets. Through detailed analysis, these models offered detailed insights into the release kinetics. As a result, a better understanding of how the formulations release their contents over time was achieved.

Stability studies were conducted to ascertain the true shelf-life of the optimized agomelatine liquisolid compacts tablets. Formulation F8 underwent these tests at 40°C and 75% RH conditions. Over 3 months, the formulations underwent comprehensive analysis, evaluating overall tablet properties such as hardness, friability, and drug content. The study also included *in-vitro* dissolution evaluations.

In the *in-vitro* dissolution studies, an analysis of variance (ANOVA) was performed. The obtained $P = 0.386$ surpassed the threshold of $P > 0.05$, indicating insignificant variation in

Table 6: Evaluation post-compressional studies of formulations F1-F9 and DCT tablets

Formulation batch	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	Weight variation (mg)	Disintegration time (min)	Drug content (%)
F1	4.52±0.01	3.0±0.112	0.49±0.12	350.01±0.12	4.02±0.12	98.74±0.54
F2	4.45±0.05	3.6±0.117	0.46±0.11	248.11±0.02	4.43±0.11	99.47±0.71
F3	4.41±0.02	3.7±0.124	0.48±0.19	351.09±0.03	4.62±0.13	99.63±1.42
F4	4.39±0.09	4.3±0.145	0.29±0.17	350.06±0.14	5.23±0.14	99.33±0.62
F5	4.57±0.07	4.1±0.007	0.38±0.15	249.08±0.11	4.81±0.16	98.65±0.54
F6	4.64±0.05	4.1±0.008	0.43±0.13	351.03±0.17	4.90±0.14	99.24±0.57
F7	4.72±0.03	2.8±0.131	0.53±0.14	349.07±0.15	4.23±0.13	99.26±0.47
F8	4.52±0.02	3.2±0.016	0.46±0.12	350.06±0.17	3.98±0.15	98.41±0.38
F9	4.47±0.04	3.2±0.013	0.48±0.14	349.07±0.15	4.81±0.10	99.25±0.76
F10 (DCT)	4.49±0.05	4.5±0.143	0.51±0.13	350.02±0.18	5.43±0.17	98.37±0.18

Data are presented as mean±SD. (*n*=3), *n* is the number of observations

Table 7: Summary data release order kinetics of optimized formulation (F8) from DD solver software

Release order parameters	Zero order (k0)	First order (k1)	Higuchi model (kH)	Hixon-Crowell (kHC)	Korsmeyer-Peppas (kKP)	*n*
Adjusted r^2	0.9741	0.9884	0.9762	0.9920	0.9719	0.413
r^2	0.9741	0.9884	0.9746	0.9858	0.9719	
AIC	38.47	29.37	34.28	38.17	39.51	
MSC	3.514	4.962	3.871	3.641	4.215	

Table 8: Summary data of single factor analysis of variance for optimized agomelatine liquisolid compact (F8) during stability storage conditions

Groups	Count	Sum	Average	Variance		
Before 3 months	8	414.02	51.7525	1198.181		
After 3 months	8	1102.94	137.8675	73005.94		
ANOVA						
Source of Variation	SS	df	MS	F	*P*-value	F crit
Between Groups	29663.17	1	29663.17	0.799502	0.386356	4.60011
Within Groups	519428.8	14	37102.06			
Total	549092	15				

Where, SS: Sum square, df: Degree of freedom, Ms: Mean square value, F: Fisher's value. If F is ≥ 1, the model is significant, If *P*<0.05, the model is significant

the *in-vitro* dissolution parameters. The results are depicted in Table 8. Furthermore, the optimized F8 formulation's performance was compared to the commercial Agoprex 25 mg. This comparison utilized the similarity factor (f_2) assessment, resulting in an impressive f_2 value of 79. This value highlighted a remarkable resemblance between the dissolution profiles of the F8 formulation and Agoprex 25 mg.

The thorough stability studies highlighted the positive characteristics of the optimized F8 formulation for 3 months under controlled temperature and humidity. Remarkably, the dissolution behavior of F8 closely mirrored that of the established Agoprex 25 mg, suggesting a promising equivalence between the two formulations.

CONCLUSIONS

Through the implementation of the liquisolid technique, we have effectively enhanced the drug release rate, pharmacokinetics behavior, and overall performance of agomelatine, a medication known for its limited solubility. Leveraging a QbD-based experimental design approach,

we have gained a deeper understanding of the formulation's behavior and successfully identified the most optimal solution that aligns with our objectives. Our analysis of FT-IR spectra has substantiated the absence of significant interactions between the chosen excipients and the medication. The Kawakita study conducted indicated a reduced cohesiveness of particles within liquisolid compacts, owing to their dense density. Furthermore, the presence of plastic deformation in colloidal silicon dioxide and microcrystalline cellulose suggests an improved compressibility. A noteworthy outcome emerged in terms of agomelatine's dissolving rate within liquisolid formulations, attributed to enhanced wetting mechanisms, amplified particle surface area, and a transition from crystalline to amorphous form. In summation, the application of liquisolid compact technology has been identified as a promising and novel strategy, effectively enhancing both the bioavailability and dissolution rate of agomelatine.

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