Bull. Pharm. Sci., Assiut University, Vol. 47, Issue 1, 2024, pp.83-100.

Bulletin of Pharmaceutical Sciences
Assiut University
Website: http://bpsa.journals.ekb.eg/

EXPLORATION OF THEORETICAL AND PRACTICAL EVALUATION ON VARDENAFIL HYDROCHLORIDE TRIHYDRATE ORODISPERSIBLE TABLET BY LIQUISOLID POWDER COMPACT TECHNIQUE

Kajal Shinde[1], Ganesh R. Gadekar[1], Rohit R. Shah[1], Mangesh A. Bhutkar[2], Dheeraj S. Randive[2], Somnath D. Bhinge[3*], Amol D. Patil[4], Bahubali N. Patil[1]

[1]*Department of Pharmaceutics, Appasaheb Birnale College of Pharmacy, Sangli-416416, Maharashtra, India*
[2]*Department of Pharmaceutics, Rajarambapu College of Pharmacy, Kasegaon, MS ,415404, INDIA*
[3]*Department of Pharmaceutical Chemistry, Rajarambapu College of Pharmacy, Kasegaon, MS,415404, INDIA*
[4]*Department of Pharmacology, Appasaheb Birnale College of Pharmacy, Sangli-416416, Maharashtra, India*

Liquisolid powder compacts (LSPs) have demonstrated their ability to enhance solubility, thereby enabling the effective oral delivery of several drugs from Class II and IV of Biopharmaceutics Classification System (BCS). Our objective in this study was to develop and assess an orodispersible liquisolid compact containing Vardenafil hydrochloride trihydrate (VHT), with the aim of enhancing the dissolution characteristics of VHT through the utilization of a straightforward, scalable, and economical liquisolid compact technique. Different liquid vehicles for instance PEG400, Tween 20, PEG200, Tween 80 and propylene glycol were investigated in solubility studies. Among them, PEG400 (non-volatile solvent) was preferred in order to formulate the LSPs. For the quality-based design, process attribute optimization studies were done using 3^2 full factorial study design. The effect of % drug concentration (X1) and super disintegration concentration (X2) on response drug release percentage (Y1) and disintegration period (Y2) was evaluated with Design Expert (Stat ease Version 9.0.3). The results obtained from fourier transform infrared spectroscopy (FTIR) studies indicated the absence of any interaction among the polymers used and the drug moiety. X-ray diffraction (XRD) and Differential scanning calorimetry (DSC) Scanning Electron Microscopy (SEM) analyses provided evidence of the change of the VHT from crystalline nature to an amorphous form. The utilization of the Vardenafil hydrochloride trihydrate liquisolid method proved its efficiency in improving the dissolution profile and biopharmaceutical characteristics of a drug with limited solubility in aqueous media

Keywords: *Factorial design, Vardenafil Hydrochloride Trihydrate, Dissolution rate, Liquisolid compacts, Mathematical model*

INTRODUCTION

Vardenafil hydrochloride trihydrate (VHT) is oftenly recommended for the management of erectile dysfunction, which exhibits its functioning as a phosphodiesterase-5 (PDE5) inhibitor[1]. Additionally, recent studies have indicated the potential of PDE5 inhibitors in the effective treatment of primary pulmonary hypertension[2]. It is evident that phosphodiesterase-5 (PDE5) is present in the smooth muscle of the arterial wall within the lungs. Therefore, patients with primary pulmonary hypertension have been prescribed Vardenafil HCl trihydrate for its effective management. It is worth noting that

Received : 30/9/2023 & Accepted : 5/12/2023

*Corresponding author: Dr. Somnath Devidas Bhinge, E-mail: somu1245@yahoo.co.in

phosphodiesterase-5 (PDE5) is abundantly expressed in lung tissue, making it a promising target for the management of primary pulmonary hypertension[3]. With respect to selectivity, it surpasses both Tadalafil and Sildenafil as a phosphodiesterase-5 (PDE5) inhibitor and exhibits ten times greater potency than Sildenafil. The sole advantage of Vardenafil HCl trihydrate over Sildenafil is its lack of inhibitory effects on phosphodiesterase-6, which can sometimes lead to rare side effects like altered color perception[4, 5].

Belonging to BCS class II, this hydrophobic drug features a relatively shorter half-life (4-5 hrs) and exhibits 15% bioavailability[6]. The intent of this study was to enhance the water solubility and in-vitro release of VHT, thereby improving its dissolution profile. By preparation of Orodispersible tablets in combination with liquid-like technology i.e. Orodispersible liquisolid compact of Vardenafil HCL trihydrate it gives rapid action and reduces first pass hepatic effect. After being administered orally, BCS class II drugs, which are typified for their negligible aqueous solubility, pose hurdles in terms of their appreciable absorption from the gastrointestinal tract (GIT). These drugs therefore possess limited bioavailability owing to their deficient and deferred absorption. The hindered systemic absorption is principally accredited to their little aqueous solubility, which also hampers their solubility in gastric fluid upon oral intake. In conformity with the Noyes-Whitney equation, the dissolution rate of a drug moiety is dependent upon its solubility, making the solubility of the drug substance a crucial determining factor.

The technique known as "Liquisolid compact" proves to be a valuable approach in enhancing the dissolution profile, aqueous solubility and consequently an improvement in the extent of absorption of drugs that possess low water solubility. This method was initially pioneered by Spireas et al. in 1998. Several liquid drug moieties, solutions and suspensions of drug have been successfully converted in to non-volatile solvents. It is achieved with the aid of mixtures of powders that are non-adhesive, easily flowable, and capable of compression. This transformation is facilitated by incorporating the suspension or solution with selectively chosen carriers and coating materials[7]. In this system, drugs with low solubility have the potential to exist in a solubilized state, exhibiting almost molecular dispersion[8]. As a result, the utilization of the liquisolid system can lead to improved drug release profile, thereby enhancing bioavailability. This improvement can be attributed to multiple factors, including an increase in surface area of the drug along with greater solubility in aqueous media and more wettability of the drug particles[9]. A novel mathematical technique is exploited to calculate the precise amounts of powder excipients, including carrier materials and coatings, required to achieve development of liquisolid systems. For the quality-based design, process attribute optimization studies were performed using the 3^2 full factorial study design. The effect of % drug concentration (X1) and super disintegration concentration (X2) on response percentage drug release (Y1) and disintegration time (Y2) was evaluated using Design Expert (9.0.3).

MATERIALS AND METHODS

Maceleods Pharmaceutical Ltd., Palghar generously provided Vardenafil hydrochloride trihydrate as a gift, while Neusilin US2 was generously presented by Gangval Chemicals Private Limited, Palghar. Syloid 244FP was gifted by Grace Davidsons, Mumbai. Crosspovidone was purchased from Qualichems fine Chem. Vadodara. PEG400 was gifted by Mohini Organics Pvt Ltd. Directly compressible Mannitol and Magnesium stearate were purchased from Medispray Labs, Satara.

Saturated solubility study

It involved using different solvents (non-volatile), namely propylene glycol, PEG 400, PEG 200, Tween 20, Tween 80, and distilled water. To prepare saturated solutions, each solvent was supplemented with an excessive quantity of the drug and shaken on an Orbital shaker for 48 hours at a constant vibration and temperature of 25 ± 0.5°C. Subsequently, the solutions underwent filtration, dilution, and analysis utilizing a UV spectrophotometer set at a wavelength of 216 nm[10].

Development of Orodispersible liquisolid compact of VHT by use of the 3^2 factorial design

The creation of the liquisolid compacts involved the utilization of a full factorial

design[11-14]. The study investigated 2 independent factors, with each factor being examined at 3 different levels. This led to a total of nine potential combinations for the experimental trials. The independent variables preferred for the investigation included % of drug concentration in the liquid medication (cd %) and the concentration of the superdisintegrant. In case of the dependent variables, the percent drug release and Disintegration time (DT) were chosen. **Table 1** contains the various levels of the independent variables, while **Table 2** outlines the corresponding levels of the dependent variables. The data obtained from various batches regarding the percent drug release and disintegration time were analyzed using multiple regression analysis with the aid of Design Expert Software. Additionally, response surfaces were plotted based on the obtained results.

Formulation of Orodispersible liquisolid compact of VRD using a Mathematical model

The determination of ingredient quantities was based on the liquid retention potentials (Φ-values) of the powder excipients[7, 15]. Neusilin® US2 and Syloid® 244FP exhibited liquid retention potentials of 0.88 and 3.7, respectively. **Eq. 1** was employed to calculate the fluid loading factor, which relied on the excipient ratio value, R, and the fluid retention potential[7, 15].

$$LF = (\Phi\mathrm{Ca} + \Phi\mathrm{Co}) \times 1/\mathrm{R} \quad \ldots\ldots\ldots\ldots\ldots\ldots (\mathbf{1})$$

Wherein, Lf stands for Liquid load factor; ΦCa refers to flowable liquid retention potential of carrier material; ΦCo is the flowable liquid retention potential of coating material

was utilized to ascertain the optimal quantities of the carrier (Q).

$$LF = W/Q \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (\mathbf{2})$$

Wherein, W refers to Weight of liquid medication; Q stands for the amount of carrier

has been presented to determine the optimal quantities of the carrier material (Q) and the coating material (q).

$$R = Q/q \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (\mathbf{3})$$

Where, q refers to the amount of coating material

Angle of slide measurement (Φ value)

The gradual addition of the liquid medication was carried out to a pre-determined quantity of powdered material (10 g). Subsequently, the resulting mixture was positioned at one end of a metal plate with excessive polish. By gradually tilting the metal plate on one side while keeping the other side on the ground, the angle formed between the plate and the floor was measured as the sliding angle. An approximate sliding angle value of 33 indicated the optimal interaction between the powder carrier and the specific liquid vehicle, thereby exhibiting favorable properties[16].

Development of liquisolid system of VHT

In a 20 mL glass beaker, the required amount of Vardenafil HCL trihydrate (5mg per tablet) and PEG400 were combined and heated gradually until complete solubilization of the drug occurred which was then incorporated into a fixed quantity of carrier (Q) and coating (q) materials (as shown in **Table 3**), following the three phases proposed by Spireas et al., During the phase one, the powdered excipient along with liquid medicine were mixed for about one minute at an approximate rate of one rotation/sec, to ensure proper and uniform distribution of the liquid contents within the powder. Whereas, in the second phase, the liquid/powder mixture was spread over the surface of a mortar uniformly and left as such for about 5 min. This ensured imbibing of the drug solution into the internal core of the powder contents. In the last phase, the powder was scrapped off from surface of the mortar with the aid of a spatula and further blended with the selected disintegrant for 30 seconds, following the same mixing procedure as described in the first phase. The powder blend underwent lubrication by adding magnesium stearate (2 mg), and mannitol was included as a diluent, along with aspartame (4 mg) for each tablet. Finally, the formulation was compressed into tablets[17].

Table 1: Coded and actual values of the Variables of 3^2 factorial design**.**

Coded Value	Actual Value	
	X1 (Drug concentration)	X2 (Superdisintegrant Concentration)
-1	10	8
0	12	10
+1	14	12

Table 2: Observed responses from 3^2 factorial design**.**

Batch Code	Variables in coded form		Drug release (%)	Disintegration time (seconds)
	X_1	X_2		
F1	1	1	82.13±0.12	20.10±0.52
F2	0	0	86.28±0.42	22.01±0.67
F3	0	-1	84.44±0.56	26.21±0.69
F4	1	0	80.67±0.66	23.09±0.14
F5	0	1	88.76±0.06	20.22±0.56
F6	1	-1	78.55±0.40	28.43±0.05
F7	-1	-1	95.77±0.77	29.54±0.23
F8	-1	1	99.08±0.59	19.32±0.18
F9	-1	0	96.41±0.97	21.00±0.54

Table 3: Composition of different Vardenafil Hydrochloride trihydrate liquisolid compacts according to mathematical model and 3^2 factorial design.

Batch code	F1	F2	F3	F4	F5	F6	F7	F8	F9
VHT conc.(%w/w)	14	12	12	14	12	14	10	10	10
Liquid medication (W)	35.71	41.66	41.66	35.71	41.66	35.71	50	50	50
Neusilin US2 as carrier (Q) (mg)	33.53	39.11	39.11	33.53	39.11	33.53	46.94	46.94	46.94
Syloid 244FP as coating material (q) (mg)	1.67	1.95	1.95	1.67	1.95	1.67	2.34	2.34	2.34
Crospovidone as Superdisintegrant conc.(%)	12	10	8	10	12	8	8	12	10
Total Weight (mg)	120	130	120	120	130	110	140	150	150

Characterization of liquisolid formulation

Flow property

Determination of the flow properties of the liquisolid systems included measurement of the angle of repose and estimation of Carr's index, and Hausner's ratio. For determination of the angle of repose both methods, namely the fixed funnel method and the free-standing cone methods were used. Whereas, estimation of Carr's index, and Hausner's ratio involved determination of Bulk density and tap density[16].

Hardness and Friability

A Monsanto tester was employed to assess the hardness of the orodispersible liquisolid compact. The "hardness factor," which was calculated as the average of 06 measurements, was determined and recorded. To assess weight variation, twenty tablets were individually weighed on an electronic balance in compliance with the Indian Pharmacopoeia (IP), and the average weight was determined which was further compared with the individual tablet weight. Roche friabilator, Digital micrometer and Pharma Test Disintegration Tester

(VEEGO) were used to determine the friability, thickness and Disintegration time of the tablets respectively by adopting the standard set procedures[16, 18].

Drug content

The tablet was pulverized, and the resultant powder was added to a volumetric flask (100ml capacity containing 40 ml of methanol). The flask was vigorously agitated to facilitate solubilization of the contents. The resultant solution were centrifuged at 5000 rpm for 30 min. Thereafter; methanol was added to adjust the volume, thereby obtaining a standard solution. Subsequently, appropriate dilutions were made and the absorption of the solution was measured at a wavelength of 216 nm[11].

Wetting period and water absorption efficiency

This is an important criterion for rapidly dissolving tablets, indicating the effectiveness of superdisintegrant and refers to the time required for penetration of water in to the surface of the tablet. The procedure for determination of wetting time involved use of a circular sheet of tissue paper placed on the Petri plate filled with 10 ml of phosphate buffer 6.8 and a certain amount of amaranth solution until it turned red. The dye solution was utilized to detect wetting occurring on the surface of the tablet.

***In-vitro* disintegration time**

It was assessed for 6 tablets per batch using the Disintegration test apparatus (Veego), wherein, a tablet was placed in one of the six tubes within the basket, thereafter a disc was added to each tube, and the device was operated with phosphate buffer (900 ml, pH 6.8) at a constant temperature (37±0.5°C). The basket underwent a uniform up-and-down motion at a speed of 30 cycles/ min and the duration (measured in seconds), for the tablet to fully dissolve in the apparatus without leaving any visible residue was noted and documented[19, 20].

In-vitro dispersion time

This examination is conducted to verify the disintegration of prepared tablets in salivary fluid, particularly when intended for use as an orodispersible tablet[21]. The in vitro dispersion time was assessed by placing a tablet into a measuring cylinder filled with 6 mL of simulated salivary fluid with a pH of 6.8. Three prepared tablets were randomly chosen from each formulation (F1-F9), and the in vitro dispersion time was recorded.

***In-vitro* drug release**

It was conducted with the aid of a USP (Type II) paddle machine, which comprises a bath and dissolving beakers maintained at a constant temperature (37± 0.5ºC). For the dissolution testing, a total volume of 900 mL of phosphate buffer 6.8 was utilized as the dissolution media and filled into the basket. One of the beakers is kept filled with the phosphate Buffer to maintain the sink environment. Paddle rotation speed has been adjusted to 50 revolutions per minute. The tablet was placed into the dissolution beaker containing the phosphate buffer 6.8 and the dissolution was carried out. At 30 second intervals, an aliquot of 5 ml was removed for 3 minutes. The condition of the sink was maintained by substituting 5 ml of phosphate buffer 6.8. After filtering, the sample solutions were diluted with the dissolving medium and subjected to analysis using a UV spectrophotometer (V-730, Jasco-Japan) at a wavelength of 216 nm. The total amount of released drugs was determined through accurate calculations[22]. The release kinetic profiles were evaluated employing mathematical models, specifically Zero order, First order, Higuchi, and Korshmayer Peppas. The equations corresponding to these mathematical models are indicated in equations (**3**) through (**6**)[23].

Zero order: $Q = K_o t$ …… **(3)**

Q: Amount of drug released at time t, Ko: zero order rate constant, t: time in hours

First order:

$\text{Log } Q_t = \text{Log } Q_o + \frac{kt}{2.303}$ …… **(4)**

Log Qt: Drug amount remaining to be released at time t, Log Q_o:drug amount remaining to be released at zerohr, K: release rate constant

Higuchi:

$Q = KH\ t1/2$ …… **(5)**

Q is amount of drug released at time t,KH is release rate constant

Korsmeyer- peppas:

$\frac{Mt}{M\infty} = Kt^n$ …… **(6)**

Mt = amount of drug released at time t, M∞= amount of drug released at infinite time

$\frac{Mt}{M\infty}$= fraction of drug release, n= diffusion exponents

Fourier transform infrared spectroscopy (FTIR) studies

It was performed on pure Vardenafil hydrochloride trihydrate (VHT), Neusilin® US2, Syloid® 244FP, PEG400, Crosspovidone, and the optimized batch F8 using an FTIR spectrometer (Alpha 2, Bruker, Germany). The scanning range covered 3500-1000 cm^{-1}.The resulting spectra were presented as percent transmittance versus wavenumber (cm^{-1})[24].

Differential scanning calorimeter (DSC) studies

Thermotropic properties were assessed using DSC (Differential Scanning Calorimetry) with the DSC-3 STARe system (METTLER TOLEDO, Switzerland, sr.no. B820851798). Pure drug, Vardenafil hydrochloride (VRD) and a sample from the optimized batch were accurately weighed and sealed in aluminum sample holders. Thermograms were captured by starting from room temperature and gradually heating up to 300 ºC at a rate of 10 ºC/min. A nitrogen flow of 20 ml/min was maintained throughout the process to ensure an inert atmosphere[25].

X –Ray diffraction (XRD) studies

Powder X-ray diffraction studies were employed to analyze the crystallinity of both the pure drug Vardenafil hydrochloride trihydrate and the optimized formulation. The powder X-ray diffraction profiles were obtained using an X-ray diffractometer (Ultima IV, Rigaku Corporation, Japan) equipped with CuKα radiation (nickel filtered; graphite monochromator)[24, 26].

Scanning Electron Microscopy (SEM)

The surface morphology of formulation F8 and VHT was analyzed using SEM. The dry powder of both formulations was placed on an electron microscope brass stub, which underwent ion sputter coating with gold. Digital images of the optimized batch were captured through randomized scanning of the stub at different magnifications.

Statistical analysis

One way ANOVA was utilized as a statistical tool to determine statistical significance. GraphPad prism (Trial version 9, Boston MA) was employed for the analysis. Significant results were recorded when $P<0.05$ at 95% confidence interval.

A multiple comparison post hoc Tukey's assay was used to confirm significant difference among the test groups.

RESULT AND DISCUSSION

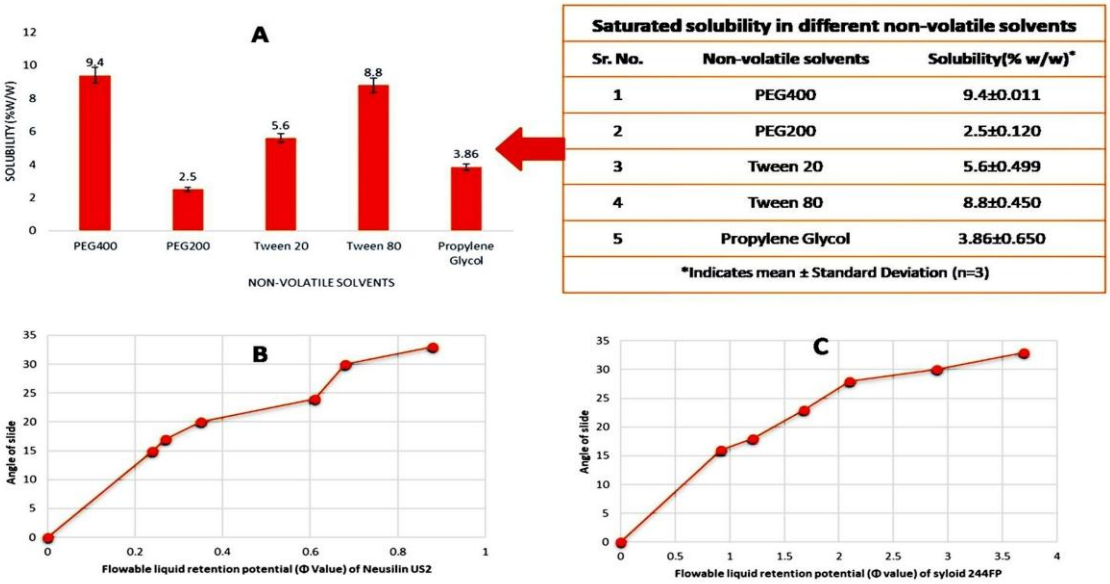
Result

Saturated solubility study

It was determined in various solvent systems, including propylene glycol, PEG400, PEG200, Tween 20, and Tween 80, as depicted in **Fig. 1A**. The obtained results were compiled and presented in **Fig 1A**. For the fast disintegrating liquisolid compaction formulation to provide enhanced drug release, the solvent selection should be the one in which the drug solubility is highest and complete. PEG 400 was chosen as the preferred formulation ingredient for the Liquisolid system, aiming for the rapid release of Vardenafil hydrochloride trihydrate[27].

Angle of slide measurement (Φ value)

It is an important parameter that is helpful in determining the liquid retention potential, which has a vital role as far as formulation of a liquisolid tablet is concerned. **Fig. 1B** and **1C** highlight the correlation between the slide angle and the corresponding Φ-value of Neusilin® US2 and Syloid® 244FP when used with the PEG400 liquid vehicle. By utilizing the ΦCa and ΦCo values of the liquid vehicle, the calculation of Lf was performed, enabling the determination of the optimal amounts of carrier and coating materials necessary to attain dry, fluid, and compressible powder systems[27].



Saturated solubility in different non-volatile solvents		
Sr. No.	Non-volatile solvents	Solubility(% w/w)*
1	PEG400	9.4±0.011
2	PEG200	2.5±0.120
3	Tween 20	5.6±0.499
4	Tween 80	8.8±0.450
5	Propylene Glycol	3.86±0.650
*Indicates mean ± Standard Deviation (n=3)		

Fig. 1: Solubility of the drug in various non-volatile solvents A) Flowable liquid retention potential of Neusilin® US2 B) Flowable liquid retention potential of Syloid® 244FP C).

Flow property

The overall bulk density of F1-F9 formulations was found to range between 0.44 and 0.50 g/ml. The tapped density estimates of the measured F1-F9 formulations ranged between 0.51 and 0.59 gm/ml. Whereas, the optimized Batch F8 had a bulk and tapped density of 0.50±0.13 and 0.55±0.64 respectively. Based on the densities (bulk and tapped) estimates of the formulations, it can be concluded that the powder mixture has good packing capabilities. In this study, an extensive analysis was conducted on batches labeled F1 through F9 to determine their respective tapped density values. These measurements were meticulously taken, yielding the following results: Batch F1-F9 exhibited a tapped density in the range of 0.51±0.66 to 0.59±0.06 g/cm³ Whereas, the optimized Batch F8 had a tapped density of 0.55 g/cm³ with a standard deviation of ±0.64 g/cm³.These values offer valuable insights into the tapped density variations among different batches, playing a crucial role in quality control and process optimization endeavors. In **Table 4**, we observe the micrometric properties of pre-compression liquisolid powders within various batches, with a focus on their Hausner's Ratios. These results reveal notable variations across the batches, with Hausner's Ratios ranging from 1.07±0.05 to 1.23±0.54, signify differing levels of precision in these measurements. Whereas, the optimized Batch F8 had a Hausner's ratio of 1.10 with a standard deviation of ±0.55, which proved its impact on flow properties, dosing accuracy, drug release control, and overall product quality. The standard Carr's index value is between 0-10percent which indicates excellent compressibility properties. A value between 10-15% indicates good compressibility and Values between 16-20% indicate Fair compressibility. For formulation batch F8 its value is 9.09% indicates excellent compressibility. For Batches F2, F3, F5, F7, and F9 the values where ranged from 12.5-14.54% which indicates Good flow property and batches F1,F4, and F6 the values ranged as 17.24-8.96% which indicates Fair compressibility property. For formulation batch F7 and F8 its value is 1.07 and 1.1 indicates excellent flow property of powder. For F2, F3, F5, and F9 the values were ranged as 1.15-1.18 which indicates good flow property of powder, and batches F1 and F4 the value is 1.23-1.22 which indicates Fair flow property.

The angle of repose was observed to lie within the range of 25-30, indicating excellent flow properties, 31-35, demonstrating good flow, and 36-40, indicating fair flow properties of the powder. In case of formulation batch F7, F8, and F9 the value were ranged as 27.71-29.68 which indicates excellent flow property, batches F2, F3, F5, and F6 the value ranged as 31.56-35 which indicates good flow property, and Batch F1 and F4 shows 37.20 and 36.82 which indicates fair flow property of powder.(**Table 4**) [28, 29].

Table 4: Micrometric properties of prepared pre-compression liquisolid powders**.**

Batches	Bulk density (gm/ml)*	Tapped density (gm/ml)*	Hausner's Ratio	Carr's index (%)*	Angle of repose (°)*
F1	0.47±0.22	0.58±0.09	1.23±0.54	18.96±0.39	37.20±0.07
F2	0.49±0.03	0.58±0.43	1.18±0.36	14.03±0.09	35.00±0.34
F3	0.44±0.74	0.51±0.66	1.15±0.04	13.72±0.11	34.67±0.63
F4	0.48±0.21	0.59±0.06	1.22±0.17	18.64±0.66	36.82±0.06
F5	0.47±0.05	0.55±0.43	1.17±0.07	14.54±0.87	31.56±0.66
F6	0.48±0.16	0.58±0.78	1.20±0.69	17.24±0.08	34.41±0.35
F7	0.49±0.08	0.56±0.28	1.07±0.05	12.50±0.42	28.21±0.20
F8	0.50±0.13	0.55±0.64	1.10±0.55	9.09±0.14	27.71±0.44
F9	0.49±0.45	0.57±0.11	1.15±0.39	13.33±0.58	29.68±0.08

*Indicates mean ± Standard Deviation (n=3).

Hardness and Friability

Table 5 presents the outcomes of post-compression parameters of the orodispersible liquisolid compacts of VHT. Thickness of the orodispersible liquisolid compacts in batches F1-F9 ranged from 2.85 to 3.80 mm. The hardness of F1-F9 batches oro-dispersible liquisolid compacts was between 2.51- 3.8 kg cm^{-1}. This was within acceptable limits for Fast-dissolving tablets, i.e.2.50-3.50kg cm^{-1}. For the average weight of the tablets between 110-250 mg, the % deviation according to the Pharmacopeia limit is known to be 7.5 %.All F1-F9 formulations were found to be compliant with the Pharmacopoeial limits. Oral dissolution tablets have an acceptable friability of less than 1%. All F1-F9 batches had values in the range of 0.12% to 0.53 % or within the allowable range[30].

Drug content

The acceptable limits for drug content are 85% to 115% of the average. All F1-F9 formulations had acceptable values of 97.11 to 99.97%. (**Table 5**)[30]

Wetting period and water absorption efficiency

The efficacy of the super disintegrating agents is determined by the wetting period of the tablets. The least amount of time it takes for the media to get to the surface of the tablet. The best is the efficiency of the superdisintegrant which tends to quickly absorb water by capillary action. The wetting time of the batches F1-F9 was between 8-21 sec. Among these formulations F1, F5 and F8 indicated that rapid wetting incorporated 12% concentration super disintegrator. The water absorption ratio was ranged 103-145 % for batches F1-F9. (**Table 6**)[18].

***In-vitro* disintegration time**

This is an important consideration in the case of rapidly disintegrating tablets. The limit for disaggregation from tablet to administration is less than 30 seconds. It was found between 19-28 seconds on the F1-F9 batches (**Table 6**). The tablet that quickly disintegrated was the one with 10% drug concentration and 12% superdisintegrant ie.19 sec. **Fig. 2A** and **2B** depict the 3D surface plot and contour plot, respectively, showing the effect of variables on the disintegration time of the formulation. It can be observed that as the drug concentration and superdisintegrant concentration decrease, the disintegration time of the formulation increases. When drug concentration is high, the disintegration period decreases. Thus it can be concluded that the drug concentration has an inverse effect on the disintegration period. At a higher superdisintegrant concentration, the disaggregation of the drug units is increased, leading to rapid disintegration and therefore a decrease in disintegration time. The superdisintegrant concentration, therefore, has an inverse relation to the disintegration period. To calculate the purpose of the optimization of the disintegration period to less than 30 seconds, the drug concentration is reduced and the superdisintegrant concentration is increased[30].

***In-vitro* dispersion time**

It was considered complete and uniform across all batches and the values for F1-F9 batches were between 17.50±0.64 to 30.22±0.05 (**Table 6**).

***In-vitro* drug release**

Its values ranged from 78.55-99.08% in six minutes for F1-F9 formulations (**Table 6**).

The greatest drug release has been established with the formulation F8 i.e. 99.08% formulated with 10% drug concentration and 12% superdisintegrant concentration. (**Fig. 3**)

This could be due to the larger specific area of Neusilin US2 which resulted in the adsorption and absorption of liquid drugs into Neusilin pores and mesoporous. The particles of the medicinal product are solubilized or suspended in a PEG 400 and when the formulation disintegrates, the liquid medicinal product is dispersed in the dissolution media. The improved dissolution of the formulation may be ascribed to the heightened wettability, increased aqueous solubility, and the greater surface area which facilitated prompt dissolution. There was a tendency to reduce the rate of dissolution with an increase in drug concentration from 10% to 14%. Higher drug concentration may lead to its precipitation within the carrier and coating excipients, potentially explains this phenomenon. Another reason of prime importance is the part of molecular dissolved drug in the liquid vehicle i.e. Fm Value For 10% drug concentration (F7-F9) Fm was 94%. For F2, F3, and F5 formulations with a drug concentration of 12%, Fm was 78%, while for F1,F4, and F6 formulations with a concentration of 14% it was 67%.Since the solubilized portion of the drug is highest at a low concentration of 10%, the result has been an increased rate of dissolution with these formulations. **Fig. 2C** and **2D** exhibit the response surface plot and contour plot, respectively, showcasing the impact of the factors on the percentage release of the drug in the formulation. The observed pattern indicates that a reduction in drug concentration and an increase in superdisintegrant concentration result in an elevation of the percentage release of the drug. When the drug concentration goes down, the result is an increase in the fraction of the dissolved molecular entity of the drug that would increase its release. There is an inverse relationship to the drug release. When the super disintegration concentration is increased the drug release also increases. To enhance drug release, it is advised to decrease the concentration of the drug and increase the concentration of the superdisintegrant, as it has been observed that these adjustments have a positive impact on drug release[17, 22, 31]. Kinetic models, as indicated in **Table 7**, were employed. The best-fitted model for the prepared formulation was the Higuchi model.

Table 5: Thickness, Hardness, Weight variation, Friability and Drug content of Orodisperible liquisolid compacts VHT**.**

Batch code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)*	Friability (%)	Drug Content (%)
F1	3.14±0.57	3.8±0.73	120.4±0.05	0.53±0.32	98.66±0.04
F2	3.08±0.32	3.5±0.07	130.1±0.28	0.12±0.87	98.02±0.24
F3	2.98±0.08	2.6±0.29	120.7±0.69	0.17±0.59	98.24±0.55
F4	3.20±0.22	3.22±0.45	120.3±0.47	0.38±0.05	97.34±0.67
F5	3.41±0.65	3.8±0.41	130.8±0.98	0.35±0.20	98.12±0.87
F6	2.85±0.73	3.12±0.19	110.7±0.71	0.16±0.19	97.11±0.09
F7	3.42±0.15	2.51±0.04	140.3±0.06	0.48±0.82	99.08±0.38
F8	3.67±0.07	2.7±0.58	150.3±0.49	0.17±0.65	99.97±0.13
F9	3.80±0.09	2.8±0.37	150.2±0.55	0.41±0.50	99.33±0.89

*Indicates mean ± Standard Deviation (n=3)

Table 6: Wetting time, Water absorption ratio, In-vitro disintegration time and % Drug release of Orodisperible liquisolid compacts of VHT**.**

Batch code	Wetting time (Sec)*	Water absorption ratio (%)*	In-vitro Disintegration time(Sec)*	In-vitro dispersion time (Sec)*	%Drug release in 6min
F1	10.00±0.81	129.70±0.45	20.12±0.52	18.00±0.33	82.13±0.12
F2	15.00±0.45	117.00±0.55	22.00±0.67	23.47±0.19	86.28±0.42
F3	21.01±0.11	103.00±0.69	26.50±0.69	25.35±0.64	84.44±0.56
F4	16.09±0.08	115.30±0.30	23.00±0.14	21.36±0.98	80.67±0.66
F5	8.00±0.67	137.00±0.21	20.09±0.56	19.50±0.34	88.76±0.06
F6	18.05±0.88	108.00±0.09	28.70±0.05	28.56±0.28	78.55±0.40
F7	17.00±0.06	112.60±0.11	29.99±0.23	30.22±0.05	95.77±0.77
F8	9.00±0.82	145.00±0.78	19.57±0.18	17.50±0.64	99.08±0.59
F9	13.09±0.17	119.00±0.33	21.56±0.54	20.34±0.66	96.41±0.97

*Indicates mean ± Standard Deviation (n=3).

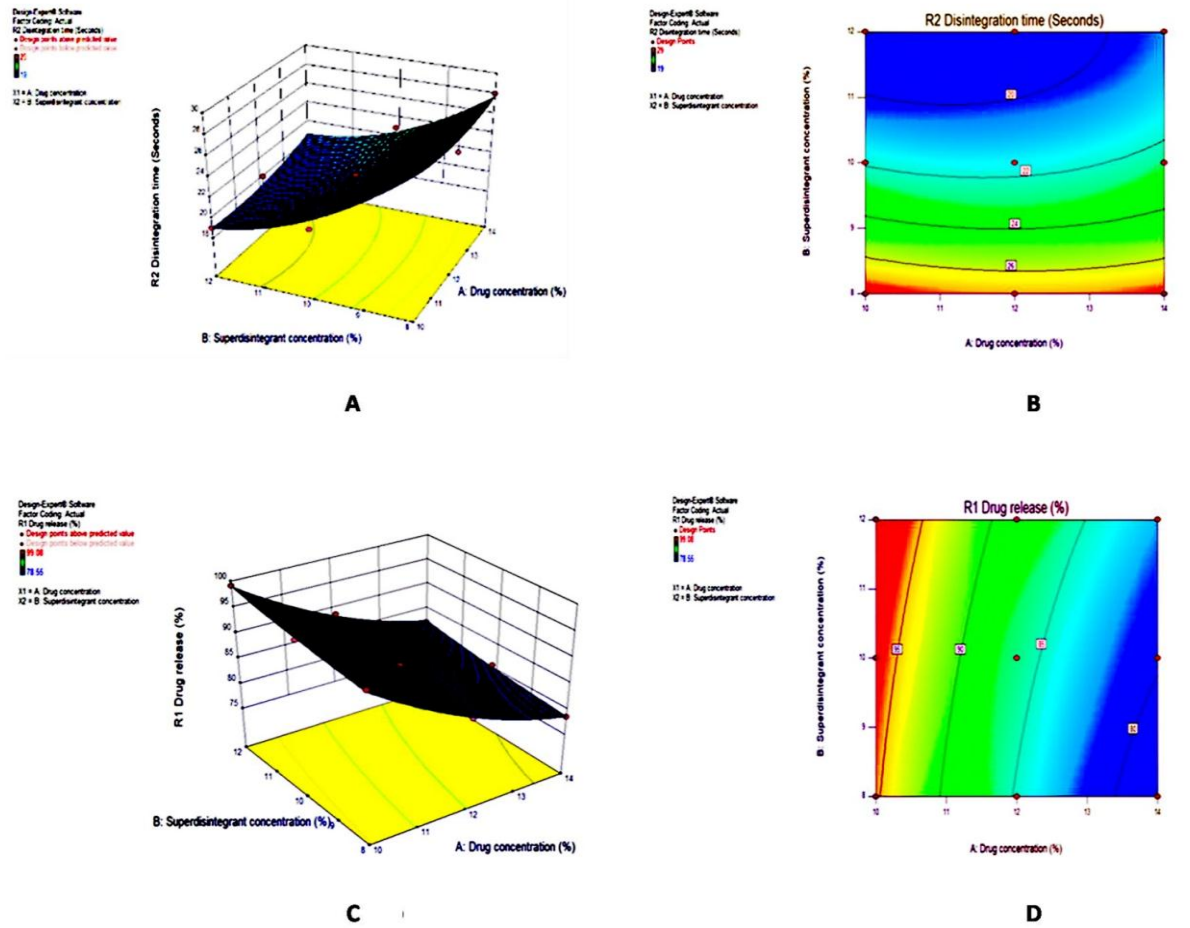


Fig. 2: Disintegration time 3D response surface plot and A) contour plot B) % drug release 3D response surface plot C) contour plot D).

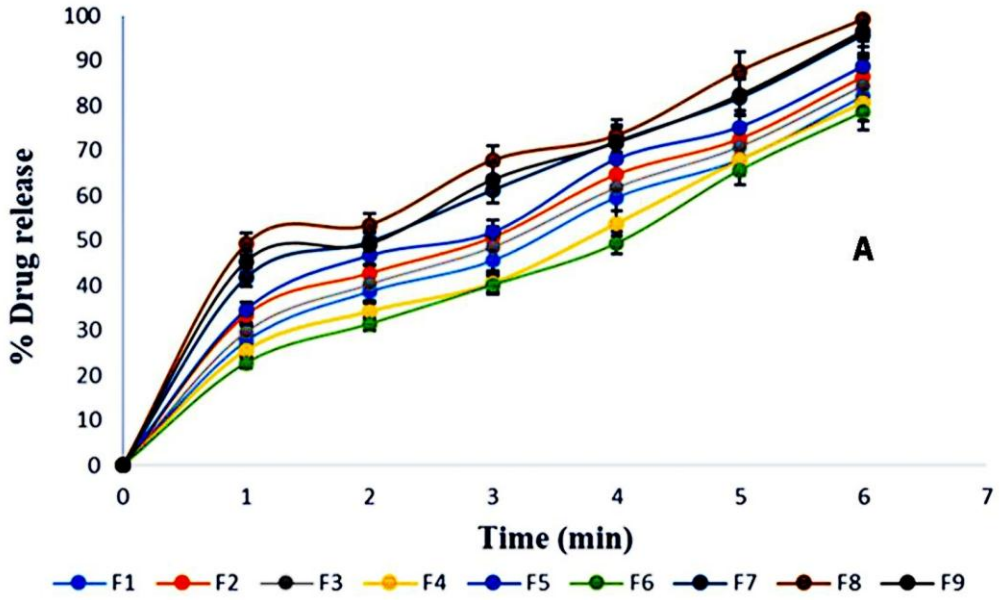


Fig. 3: Dissolution profile of F1-F9 batehes.

Table 7: *In-vitro* VHT release kinetics from optimized F8 formulation

Formulations	**Zero order**	**First order**	**Higuchi model**	**Kor's peppas**
	r^2	**r^2**	**r^2**	**r^2**
Optimized Batch F8	0.8836	0.7684	0.9793	0.7984

Factorial Design study and optimization of the process variables

Drug release (in vitro type) and disintegration period were identified as dependent variables. From the nine analyses, the results were used to create a predictor equation with independent type variables such as drug concentration (X1) and super disintegration concentration (X2)[11, 17].

Impact of formulation variables on release profile

Equation (7) provides information about the influence of formulation variables, namely drug concentration (X1) and percentage of superdisintegrant concentration (X2), on the amount of drug release (**7**).

Drug Release = +86.27 –8.32*A +1.87 *B +0.067 *AB +2.28 *A^2 +0.34 *B^2 …….. (**7**)

Impact of formulation variables on Disintegration time

Equation (8) describes the impact of formulation variables, specifically drug concentration (X1) and the percentage of superdisintegrant concentration (X2), on the disintegration time (**8**).

Disintegration Time = +21.56+0.33*A-4.00*B+0.50*AB+0.67*A^2+1.67 *B^2… (**8**)

Analysis of Variance

The regression model exhibited excellent predictability with R^2 values of 0.9981 and 0.9581 for response variables R1 and R2, respectively. The significant F-values of 312.22 for R1 and 13.07 for R2 indicated that the models were statistically significant, with a very low probability (0.03% and 3.00%, respectively) that such large F-values could arise due to random variation. The corresponding P-values of 0.0003 for R1 and 0.0300 for R2 further confirmed the significance of the models. The regression analysis generated quadratic equations for both response variables R1 and R2[32].

Fourier transform infrared spectroscopy (FTIR) studies

The potential interaction between VHT and excipients was assessed using FTIR spectroscopy measurements. **Fig. 4** present the data acquired in the form of spectra, illustrating the relationship between % transmittance and wavenumber (cm^{-1}). The FTIR spectra **(Fig. 4)** of PEG400 exhibited characteristic peaks corresponding to various functional groups. These included O-H, C-O stretch, CH2 (alkane), C-H stretch (aliphatic), at specific wavenumbers of 3437.78, 1067.52, 1353.54, and 2867.45 cm^{-1}, respectively. The crospovidone exhibited characteristic peaks, including C-N, C=O, CH2 (alkene), and C-H, at specific wavenumbers of 1278.45, 1657.70, 1365.58, and 2901 cm^{-1}, respectively. The FTIR spectrum of Neusilin US2 revealed a characteristic Si-O stretch at a specific wavenumber of 1007.89 cm-1. Similarly, the FTIR spectrum of Syloid 244FP displayed characteristic peaks, including Si-O stretch at a specific wavenumber of 1090.54 cm^{-1}. The FTIR spectrum of VHT showed characteristic peaks corresponding to various functional groups, namely C-N, CH2, S=O, N-H, C=O, C=N, HCl, and O-H, at specific wavenumbers of 1282.31, 1349.13, 949.89, 3340.31, 1705.71, 1633.68, 717.60, and 3246.39 cm^{-1}. The FTIR analysis of physical mixture of VHT and added polymer revealed slight changes in characteristic peaks of functional groups, specifically C-N, CH2, S=O, N-H, C=O, C=N, HCl, and O-H, at specific wavenumbers: 1280.90, 1358.80, 955.67, 3358.26, 1748.26, 1643.67, 727.66, and 3216.13. cm-1. **(Fig. 4).** However, the FTIR spectra of the optimized batch exhibited the same peaks as those obtained in the spectra of pure VHT, with slight shifts in wavenumber. It demonstrated characteristic peaks of functional groups, namely C-N, CH2, S=O, N-H, C=O, C=N, HCl, and O-H, at specific wavenumbers: 1289.09, 1355.93, 940.03, 3397.23, 1748.53, 1646.57, 704.06, and 3260.93 cm^{-1}. The presence of a carbonyl group facilitates hydrogen bonding interactions and intermolecular interactions. Therefore, the observed shift in the carbonyl peak in the formulation spectra signifies the existence of these interactions, which are crucial for the formation of an amorphous solid dispersion (ASD).

Differential scanning calorimeter (DSC) studies

With intent to determine the thermal properties and gain initial understanding of the physicochemical behavior, a DSC analysis was conducted on both the pure VHT and the optimized batch F8. **Fig. 5A**, depicts the DSC thermogram, which provides significant insights. The thermogram of Vardenafil hydrochloride trihydrate (VHT) in its pure form displayed a noticeable endothermic peak at 223°C, which provided confirmation about its crystalline nature. Additionally, an endothermic peak at 100°C is indicative of loss of H_2O. In contrast, the DSC thermogram of the optimized batch shows the absence of an endothermic event near its melting point, indicating the conversion of crystalline VHT into an amorphous state[25, 33].

X –Ray diffraction (XRD) studies

Both the pure drug VHT (**Fig 5B**) and the optimized batch F8 (**Fig. 5C**) underwent examination of their XRD patterns. The XRD spectra of the pure VHT displayed prominent and well-defined peaks, indicating its crystalline state. In contrast, the spectra of the optimized batch F8 exhibited a lack of distinct peaks, suggesting its amorphous nature. Based on this analysis, it can be concluded that the liquisolid compact technique, combined with appropriate excipients, resulted in the conversion of VHT into an amorphous form, leading to an improved dissolution release profile[33].

SEM

The morphological characteristics of VHT and the optimized liquisolid batch F8 were analyzed using SEM. The SEM image for VHT (**Fig. 6**) revealed needle-like crystal forms, whereas the liquisolid compact (**Fig. 6**) displayed the absence of the needle-like crystalline shape characteristic of the pure API. This observation suggests that VHT has been solubilized in the liquid system, indicating that although the API is in a solid dosage form[34], it is held in a powdered substrate in a solution or nearly dispersed state. This phenomenon contributes to an increase in drug solubility.

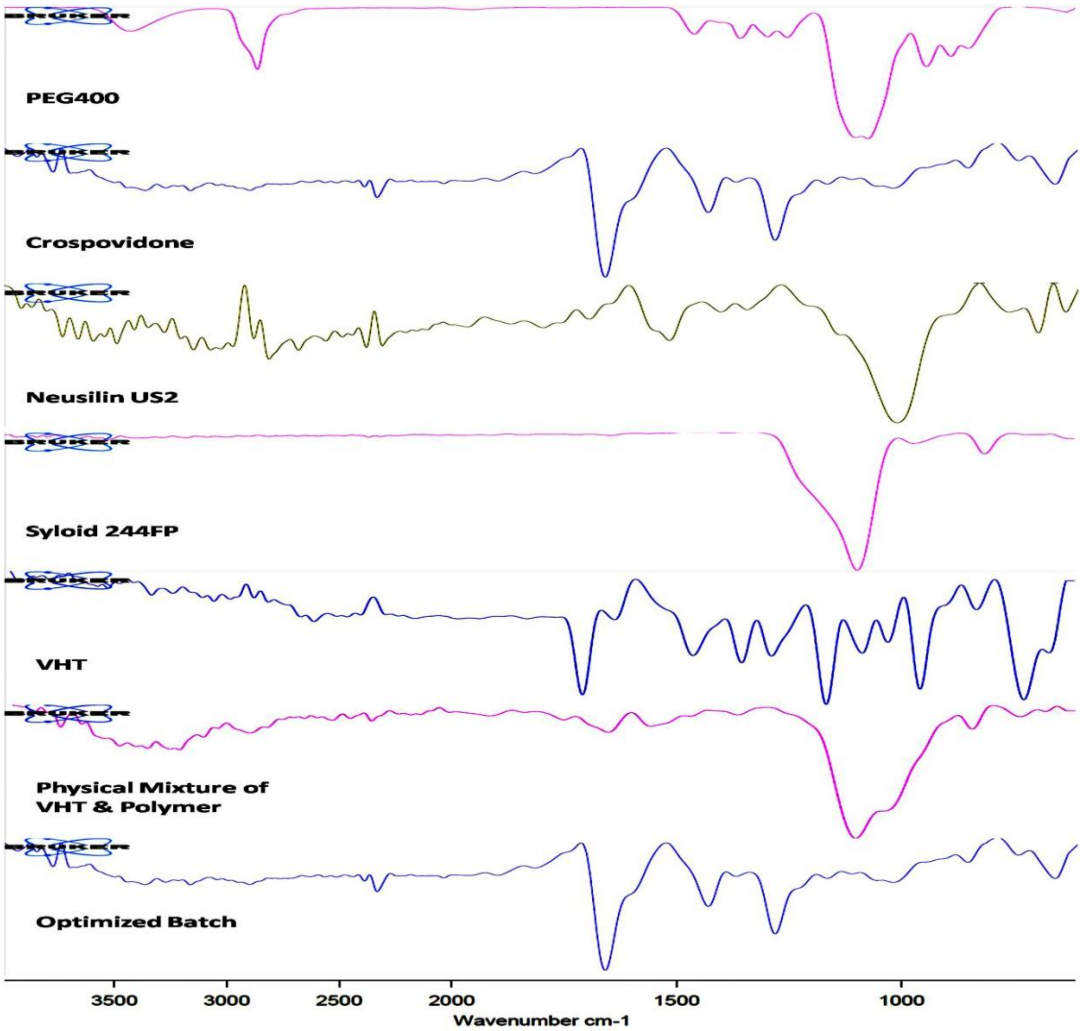


Fig. 4: FTIR analysis of excipients, VHT, physical mixture (excipients and VHT) and optimized batch.

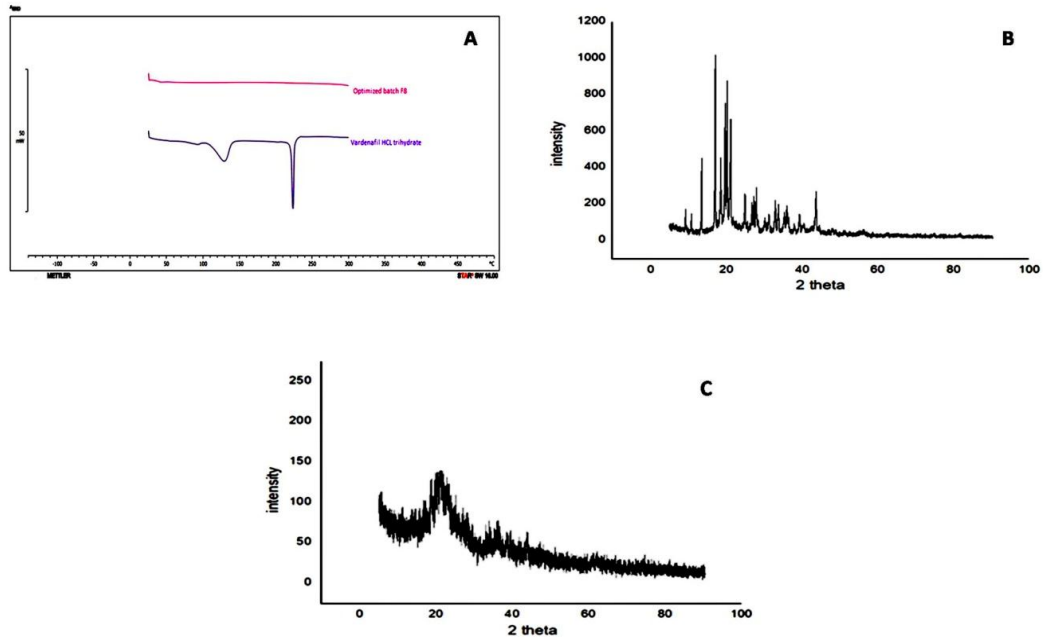


Fig. 5: DSC of pure drug and optimized batch F8 A) X-ray diffraction of Vardenafil HCL trihydrate B) X-ray diffraction of optimized batch F8 C).

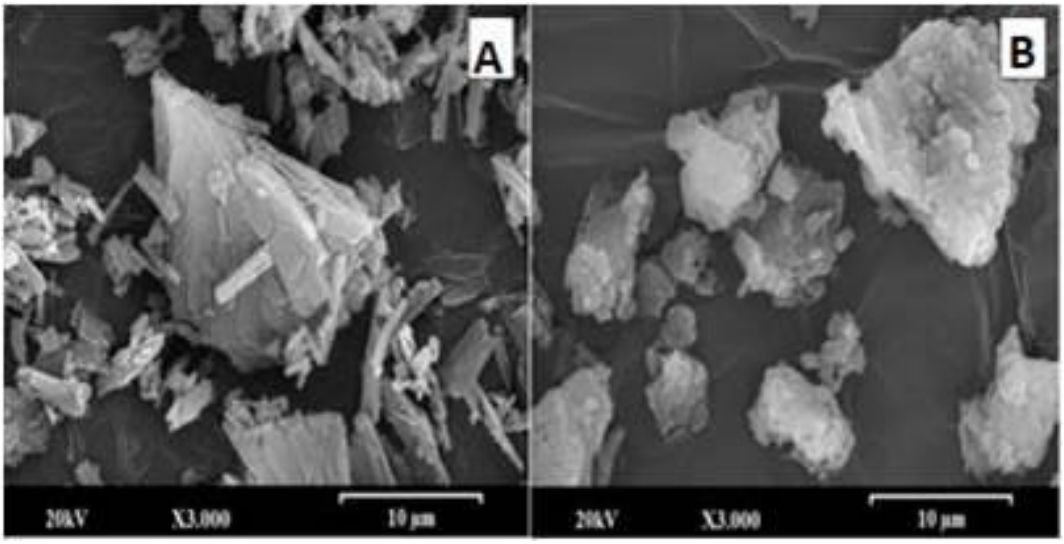


Fig. 6: SEM analysis of VHT A) Optimized Batch B)**.**

Discussion

Vardenafil hydrochloride trihydrate (VHT) exhibits greater selectivity and potency compared to sildenafil, being ten times more potent. Unlike sildenafil, VHT does not inhibit phosphodiesterase-6, which helps prevent alterations in color perception, a rare side effect associated with sildenafil usage. VHT, being a hydrophobic drug moiety is classified as a within Class II of BCS thereby exhibiting low solubility in aqueous environments. This limited solubility hampers its absorption and reduces its bioavailability following oral administration. Furthermore, approximately 85% of VHT undergoes degradation during the first pass, resulting in a remarkably low absolute oral bioavailability of only 15%. This value is notably lower than the oral bioavailability of other cGMP PDE 5 inhibitors. Consequently, it is needed to come up with a formulation that can provide improved solubility, better absorption of VHT while bypassing the first-pass metabolism. Our work is an attempt to enhance the solubility and improve the in-vitro release of Vardenafil hydrochloride trihydrate (VHT) by formulating Orodispersible liquisolid compact of Vardenafil HCL trihydrate, which can give rapid action and reduce first-pass effect. Study outcomes have showcased the potential of liquisolid compacts as a straightforward, scalable, and economical approach to augment the solubility as well as dissolution characteristics of a poorly soluble drug namely Vardenafil hydrochloride trihydrate.

Conclusion

The efficient use of the Vardenafil hydrochloride trihydrate liquisolid method verified its utility to achieve improvement in the dissolution rate along with its biopharmaceutical characteristics for a drug with relatively poor water solubility. By employing the 32 FFD design approach, the formulation behavior was better understood, and the finest formulation was identified considering achievement of the desired objectives. Incorporation of Vardenafil hydrochloride trihydrate into liquisolid formulations significantly increased its dissolution rate through mechanisms such as improved wetting, increased surface area of the drug particle and transformation from crystal structure to amorphous state. Further, the DSC and XRD studies provided confirmation regarding the loss of its crystalline nature in case of Vardenafil hydrochloride trihydrate upon its formulation as a liquisolid. Considering factors such as viscosity and solubility, the selection of the liquid vehicle play a decisive role in improving the dissolution profiles of poorly water-soluble drugs in liquisolid formulations. Moreover, an essential step in formulation of a successful liquisolid tablets is determining the maximum liquid retention potential (Φ-value).

Abbreviations

VHT: Vardenafil hydrochloride trihydrate; FTIR: Fourier transform infrared spectroscopy; XRD: X-ray diffraction; DSC: Differential

scanning calorimetry; BCS: Biopharmaceutics Classification System; LSPs: Liquisolid powder compacts; PDE5: phosphodiesterase-5; GIT: Gastrointestinal tract; DT: Disintegration time; FTIR: Fourier Transform Infrared spectroscopy.

REFERENCES

1. H. A. Al-Gethmy, U. A. Fahmy, N. A. Alhakamy, O. A. Ahmed and K. M. El-Say, "Optimization of the factors affecting the absorption of vardenafil from oral disintegrating tablets: A clinical pharmacokinetic investigation", ***Pharmaceutics***, 11(1), 1-13 (2019).
2. Z. C. Jing, Z. X. Yu, J. Y. Shen, B. X. Wu, K. F. Xu, X. Y. Zhu, L. Pan, Z. L. Zhang, X. Q. Liu, Y. S. Zhang and X. Jiang, "Vardenafil in pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled study", ***Am J Respir Crit Care Med***, 183(12), 1723-1729 (2011).
3. H. O. Ammar, M. I. Tadros, N. M. Salama and A. M. Ghoneim, "Ethosome-derived invasomes as a potential transdermal delivery system for vardenafil hydrochloride: development, optimization and application of physiologically based pharmacokinetic modeling in adults and geriatrics", ***Int J Nanomed,*** 15, 5671–5685 (2020).
4. Y. F. Fan, R. Zhang, X. Jiang, L. Wen, D. C. Wu, D. Liu, P. Yuan, Y. L. Wang and Z. C. Jing, "The phosphodiesterase-5 inhibitor vardenafil reduces oxidative stress while reversing pulmonary arterial hypertension", ***Cardiovasc Res,*** 99(3), 395-403 (2013).
5. U. A. Fahmy, "Nanoethosomal transdermal delivery of vardenafil for treatment of erectile dysfunction: optimization, characterization, and in vivo evaluation", ***Drug Des Dev Ther***, 9, 6129-6136 (2015).
6. A. S. Lila, E. Gomaa, F. E. Ghazy and A. A. Hasan, "Treatment of pulmonary arterial hypertension by vardenafil-solid dispersion lozenges as a potential alternative drug delivery system", ***J Drug Deliv Sci Technol,*** 55, 101444 (2020).
7. M. Lu, H. Xing, J. Jiang, X. Chen, T. Yang, D. Wang and P. Ding, "Liquisolid technique and its applications in pharmaceutics", ***Asian J Pharm Sci,*** 12(2), 115-123, (2017).
8. D. R. Komala, K. Y. Janga, R. Jukanti, S. Bandari and M. Vijayagopal, "Competence of raloxifene hydrochloride loaded liquisolid compacts for improved dissolution and intestinal permeation", ***J Drug Deliv Sci Technol,*** 30, 232-241 (2015).
9. K. Sanka, S. Poienti, A. B. Mohd and P. V. Diwan, "Improved oral delivery of clonazepam through liquisolid powder compact formulations: in-vitro and ex-vivo characterization", ***Powder Technol***, 256, 336-344 (2014).
10. N. Chella, N. Narra and T. Rama Rao, "Preparation and characterization of liquisolid compacts for improved dissolution of telmisartan", ***J Drug Deliv***, 692793, (2014).
11. F. J. Sayyad, S. L. Tulsankar and U. B. Kolap, "Design and development of liquisolid compact of candesartan cilexetil to enhance dissolution", ***J Pharm Res***, 7(5), 381-388, (2013).
12. T. S. Mulla, V. R. Salunkhe, S. D. Bhinge and N. Mohire, "Formulation, Design And Optimization Of Antidiabetic Drug Loaded Microspheres", ***Polym Bull***, 80, 6171-6196, (2023).
13. P. Patil, V. Salunkhe, S. Bhinge and S. Patil, "Formulation optimization and evaluation of Glycyrrhetinic Acid Loaded PLARosome using Factorial design: In-vitro anti-ulcer activity", ***J Indian Chem Soc***, 98, 100199 (2021). https://doi.org/10.1016/j.jics.2021.100199
14. Q. A. Patil, I. S. Patil, R. U. Mane, D. S. Randive, M. A. Bhutkar and S. D. Bhinge, "Formulation optimization and evaluation of Cefdinir nanosuspension using 2^3 Factorial design", ***Marmara Pharm J***, 22(4), 587-598, (2018).
15. S. Spireas, T. Wang and R. Grover, "Effect of powder substrate on the dissolution properties of methyclothiazide liquisolid

compacts", ***Drug Dev Ind Pharm***, 25(2), 163-168, (1999).
16. N. Tiong and A. A. Elkordy, "Effects of liquisolid formulations on dissolution of naproxen", ***Eur J Pharm Biopharm***, 73(3), 373-384, (2009).
17. B. Jaydip, M. Dhaval, M. M. Soniwala and J. Chavda, "Formulation and optimization of liquisolid compact for enhancing dissolution properties of efavirenz by using DoE approach", ***Saudi Pharm J***, 28(6), 737-745, (2020).
18. H. M. Tawfeek, W. Faisal and G. M. Soliman, "Enalapril maleate orally disintegrating tablets: Tableting and in vivo evaluation in hypertensive rats", ***Pharm Dev Technol***, 23(5), 496-503, (2018).
19. B. Vraníková, J. Gajdziok and P. Doležel, "The effect of superdisintegrants on the properties and dissolution profiles of liquisolid tablets containing rosuvastatin", ***Pharm Dev Technol,*** 22(2), 138-147, (2017).
20. K. M. Hosny, N. A. Alhakamy, M. A. Almodhwahi, M. Kurakula, A. M. Almehmady and S. S. Elgebaly, "Self-nanoemulsifying system loaded with sildenafil citrate and incorporated within oral lyophilized flash tablets: preparation, optimization, and in vivo evaluation" ***Pharmaceutics,*** 12(11), 1124. (2020).
21. P. D. Chaudhari, S. P. Chaudhari and S. R. Kohle, "Formulation and evaluation of fast dissolving tablets of famotidine"' ***Indian Drugs.*** 42(10), 641-649 (2005).
22. K. J. Parikh and K. K. Sawant, "Solubilization of vardenafil HCl in lipid-based formulations enhances its oral bioavailability in vivo: a comparative study using Tween-20 and Cremophor-EL", ***J Molecul Liq***, 277, 189-199, (2019).
23. S. Amarachi, Chime & Onunkwo and Godswill & Onyishi, Ikechukwu, "Kinetics and mechanisms of drug release from swellable and non swellable matrices: A review" ***Res. J. Pharm. Biol. Chem. Sci.*** 4(2), 97-103 (2013).
24. Y. Javadzadeh, M.R. Siahi, S. Asnaashari and A. Nokhodchi, "Liquisolid technique as a tool for the enhancement of poorly water-soluble drugs and evaluation of their physicochemical properties", ***Acta Pharma,*** 57(1), 99-109 (2007).
25. A. A. Elkordy, E. A. Essa, S. Dhuppad and P. Jammigumpula, "Liquisolid technique to enhance and to sustain griseofulvin dissolution: Effect of choice of non-volatile liquid vehicles", ***Int J Pharm***, 434(1-2), 122-132, (2012).
26. J. Baranauskaite, D. M. Kopustinskiene, R. Masteikova, J. Gajdziok, A. Baranauskas and J. Bernatoniene, "Effect of liquid vehicles on the enhancement of rosmarinic acid and carvacrol release from oregano extract liquisolid compacts", ***Colloids Surf A***, 539, 280-290, (2018).
27. B. Vraníková and J. Gajdziok, "Liquisolid systems and aspects influencing their research and development", ***Acta Pharma***, 63(4), 447-465, (2013).
28. A. Noorjahan, B. Amrita and S. Kavita, "In vivo evaluation of taste masking for developed chewable and orodispersible tablets in humans and rats", ***Pharma Dev Technol***, 19(3), 290-295, (2014).
29. P. M. Sabale, N. D. Grampurohit, D. D. Gaikawad, M. V. Gadhave, G. M. Shingade and G. Shaik, "Liquisolid technique for enhancement of dissolution properties of fenofibrate", ***Int J Pharm Sci Res***, 3(5), 1481-1488 (2012).
30. H. A. Al-Gethmy, U. A. Fahmy, N. A. Alhakamy, O. A. Ahmed and K. M. El-Say, "Optimization of the factors affecting the absorption of vardenafil from oral disintegrating tablets: A clinical pharmacokinetic investigation", ***Pharmaceutics,*** 11(1), 11-19 (2019).
31. N. R. Jadhav, P. V. Irny, U. S. Patil, "Solid state behavior of progesterone and its release from Neusilin US2 based liquisolid compacts", ***J Drug Del Sci Technol***, 38, 97-106, (2017).
32. B. Bonthagarala, V. Dasari, V. Kotra, S. Swain and S. Beg, "Quality-by-Design based development and characterization of pioglitazone loaded liquisolid compact tablets with improved biopharmaceutical attributes", ***J Drug Del Sci Technol***, 51, 345-355, (2019).

33. T. Vojinović, D. Medarević, E. Vranić, Z. Potpara, M. Krstić, J. Djuriš and S. Ibrić, "Development of ternary solid dispersions with hydrophilic polymer and surface adsorbent for improving dissolution rate of carbamazepine", ***Saudi Pharm J***, 26(5), 725-732 (2018).

34. R. R. Vakhariya, V. R. Salunkhe, M. A. Bhutkar and S. D. Bhinge, "Design, development and optimization of ramipril solid lipid nanoparticles using solvent emulsification and evaporation method" ***Nanosci Nanotech Asia***, 11(01), 42-52 (2021).

Bull. Pharm. Sci., Assiut University, Vol. 47, Issue 1, 2024, pp 83-100.

نشرة العلوم الصيدليـــــة
جامعة أسيوط

BULL. PHARM. SCI. Assiut Univ.

التقييم النظري والعملي للأقراص القابلة للتشتت لعقار هيدروكلوريد الفاردنافيل ثلاثي الهيدرات بتقنية المسحوق السائل المضغوط

كاجال شيندي[١] – غانيش آر جاديكار[١] – روهيت آر شاه [١] – مانجيش إيه بوتكار[٢] – ديراج إس راندیف [٢] – سومناث دي بينج[٣*] – أمول دي باتيل[٤] – باهوبالي إن باتيل [١]

[١]قسم الصيدلانيات، كلية أباصاحب بيرنيل للصيدلة، سانجلي–٤١٦٤١٦، ماهاراشترا، الهند

[٢]قسم الصيدلانيات، كلية راجارامبابو للصيدلة، كاسيجاون،٤١٥٤٠٤، ماهاراشترا ، الهند

[٣]قسم الكيمياء الصيدلية، كلية راجارامبابو للصيدلة، كاسيجاون،٤١٥٤٠٤، ماهاراشترا ، الهند

[٤]قسم الفارماكولوجى، كلية أباصاحب بيرنيل للصيدلة، سانجلي–٤١٦٤١٦، ماهاراشترا، الهند

أثبتت مضغوطات المسحوق السائلة (LSPs) قدرتها على تعزيز القابلية للذوبان، وبالتالي تمكين التوصيل الفموي الفعال للعديد من الأدوية من الفئتين الثانية والرابعة من نظام تصنيف المستحضرات الصيدلانية الحيوية (BCS). كان الهدف من هذه الدراسة هو تطوير وتقييم مركب سائل صلب قابل للتشتت يحتوي على عقار هيدروكلوريد الفاردنافيل ثلاثي الهيدرات (VHT)، بهدف تعزيز خصائص ذوبان وذلك خلال استخدام تقنية جديدة واضحة وقابلة للتطوير واقتصادية أيضا.وتم فى هذه الدراسة استعمال بعض المركبات السائلة المختلفة مثل PEG400 و20 Tween و80 PEG200 و Tween والبروبيلين جليكول لدراسات الذوبان للعقار. وتم التوصل إلى تفضيل PEG400 لإعطائه أعلى قيمة ذوبانية وذلك من لأجل صياغة (LSPs).

وقد تم اختيار تصميم مناسب لتأكيد الجودة فى النتائج ، وقد تم إجراء دراسات تحسين سمات العملية باستخدام تصميم دراسة عاملية (٢٣) كاملة. وقد تم تقييم تأثير النسبة المئوية لتركيز الدواء (X1) وتركيز التفكك الفائق (X2) على نسبة إطلاق الدواء المستجيب (Y1) وفترة التفكك (Y2) باستخدام Design Expert Stat easy) الإصدار ٩.٠.٣).

وأشارت النتائج التي تم الحصول عليها من دراسات التحليل الطيفي للأشعة تحت الحمراء (FTIR) إلى عدم وجود أي تفاعل بين البوليمرات المستخدمة و الدواء . كما أظهرت تحليلات حيود الأشعة السينية (XRD) وقياس السعرات الحرارية للمسح التفاضلي (DSC) والمجهر الإلكتروني (SEM) دليلاً على تغير (VHT) من الطبيعة البلورية إلى شكل غير متبلور (غير متجانس).

وتوصلت النتائج إلى أنه باستخدام طريقة معالجة هيدروكلوريد الفاردنافيل ثلاثي الهيدرات السائلة أثبتت كفاءتها في تحسين صورة الذوبان والخصائص الصيدلانية الحيوية لدواء ذي قابلية ذوبان محدودة في الوسط المائي.