DEVELOPMENT OF ORAL FORMULATIONS USING SPRAY DRIED SOLID DISPERSION TECHNOLOGY

Synopsis of the PhD thesis submitted to

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a. Title of the Thesis and abstract:

DEVELOPMENT OF ORAL FORMULATIONS USING SPRAY DRIED SOLID DISPERSION TECHNOLOGY

Abstract:

Solid Dispersion (SD) technology is one of the most widely preferred solubility enhancement methods, especially for Biopharmaceutics classification system Class II and IV drugs. Since the last decade, its application for the dual purpose of solubility enhancement and modified release using novel carriers has been in demand for its added advantages. Spray drying is a commercially accepted technique with high aspects of scalability and product characteristics. The current study used spray dried dispersion (SDD) to design a site-specific formulation of weakly basic drug Posaconazole (POS) using novel carriers Soluplus® & Gelucire 43/01, and a delayed release formulation of the Proton pump Inhibitor (PPI) Esomeprazole magnesium trihydrate (ESM) using dual purpose carrier Hydroxy propyl methyl cellulose acetate succinate- medium grade (HPMCAS-MF) for enteric release and solubility improvement. The novel carriers not only enhanced solubility, but inhibited precipitation of saturated drug solutions in crystalline form that may improve absorption and bioavailability of drug. Both formulations were optimised using Design of Experiment (DOE), considering significant formulation and process variables. The optimised spray dried dispersion were characterised based on Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Powder X-ray Diffraction (PXRD), and Scanning Electron Microscopy (SEM) and also evaluated for solubility, *in-vitro* drug release, residual solvent content, and stability testing. The design space was developed via overlay plot based on constraints specified to attain the desired response and validated using three checkpoint batches with desirability 1. FTIR spectra showed API-polymer compatibility. *In-vivo* roentgenography & pharmacokinetic study of POS SDD were performed in New Zealand rabbit and male Sprague-Dawley rats respectively. The proposed delayed release approach avoided compression, coating with enteric polymers, and the development of multi-particulate pellet-based formulations, improving manufacturing feasibility.

b. Brief description on the state of the art of the research topic

Solid dispersion (SD) is one of the preferred methods to overcome solubility limited bioavailability of API with low aqueous solubility (1). Apart from traditional binary SD including insoluble drug and SD carrier, it is also possible to design a multi-component SD, wherein more than two components are used to improve formulation as well as therapeutic efficacy simultaneously (2). Since last 2 decades, hydrophobic and hydrophilic swellable polymers are also preferred as SD carrier to retard the dissolution of drug for the designing of

controlled or sustained release formulations. Controlled release SD bypass the risk of a burst release of drug due to dispersion of drug molecules in carrier/s that lead to desired release rate (3). Recently many novel polymers have been researched and extensively used in SD Technology. The most widely used amphiphilic cellulosic SD carrier is HPMCAS. The block graft copolymer Soluplus® is SD carrier of choice due to excellent solubilization, extrudibilty as well as stabilization properties (4).

Spray Drying is one of the most prevalent and recommended procedures in SD preparation with excellent product attributes and scalability (5). Spray dried powder is ideally homogeneous, amorphous, and stable, and may be incorporated into several Oral Solid Dosage forms (OSD), such as capsules, tablets and sachets (6).

c. Definition of the Problem

According to the statistics, about 40% of the currently available drugs and 60% of new chemical entities (NCE) are poorly soluble in water and face bioavailability problem. So, the major constraint for formulation scientist is to find an efficient approach to enhance the solubility of the API (Active Pharmaceutical Ingredient) to increase the dissolution rate of formulation (7,8).

Posaconazole, being a weakly basic drug with pka values of 3.6 and 4.6, exhibits higher solubility in the acidic environment of the stomach with pH 1-2, especially in the fasting state. Thus, like most weakly basic drugs, it tends to precipitate from the supersaturated solution upon entry into the upper small intestine due to its alkaline pH (9–11). Eventually, the absorption rate and bioavailability become lower and highly variable, along with the possibility of sub-therapeutic concentration as observed in the marketed oral suspension (12).

Like all the PPIs, Esomeprazole too exhibits pH dependant solubility. It shows fleeting degradation in the gastric pH with the gradual improvement in the stability as the pH exceeds the value of 6.8 (13). To minimise deterioration in the gastric pH of the upper GIT, the majority of marketed PPIs are manufactured as delayed release formulations in form of multi-particulate drug delivery system (DDS) or enteric coated products (14).

Objectives and Scope of work

1. To improve the solubility of BCS Class II drugs POS and ESM using SD technology.
2. To utilize Spray Drying Technology for SD to obtain SDD with excellent processing attributes.
3. To explore novel SD carriers namely, Soluplus®, HPMCAS and Gelucire 43/01, wherein the latter two served dual purposes of solubility enhancement and site specificity.
4. To develop a gastro-retentive formulation of weakly basic drug POS to overcome the problem of pH-dependent solubility.

5. To develop a delayed-release formulation of PPI ESM to overcome the problem of pH-dependent stability.

d. Original contribution by the thesis

This study investigated the use of novel SD carriers using industrially applicable and feasible spray drying technique to achieve solubility improvement of BCS class II drugs POS & ESM. Soluplus® and Gelucire 43/01 were utilized to develop a novel gastro-retentive formulation of POS; wherein Soluplus® provided excellent solubilisation & stabilization, whereas Gelucire 43/01 is a waxy lipid providing floating behaviour & sustained release. The saturation and precipitation of a weakly basic drug upon intestinal transit due to pH dependant solubility, may be avoided by this approach, enabling proper absorption and bioavailability of POS.

The second formulation incorporated HPMCAS-MF to develop a delayed release formulation of ESM, wherein the SD carrier served dual purpose of solubility enhancement, and enteric release with solubility above pH 6. The developed SDD encapsulated in hard gelatin capsule dosage form was sufficient to procure the delayed release, eliminating the need of enteric coating and/or multi-particulate dosage form prevalent in marketed formulation, which may significantly contribute to product development cost reduction and ease the scale up of the formulation.

e. Methodology of Research, Results / Comparisons

Pre-formulation studies

Identification of pure drug was done by Melting point and UV scanning. Drug polymers interaction was analysed by FTIR study.

Analytical Study

Standard calibration curve of POS was prepared in 0.1 N HCl & methanol.

Standard calibration curve of ESM was prepared in 0.1 N HCl, Phosphate buffer solution pH 6.8 (PBS pH 6.8) and methanol.

1. Posaconazole Gastro-retentive Oral Formulation

Preparation of ASD by spray drying technique

A magnetic stirrer was used to dissolve POS in a solvent system of DCM (Dichloromethane): water: IPA (1:1:3), along with SD carriers Gelucire 43/01 and Soluplus®, hydrophilic gum PEO WSR 303 (Poly Ethylene Oxide Water Soluble Resin), and anti-adherent Aerosil (Colloidal Silicon Dioxide). PEO was selected as a swellable polymer to allow drug release from SD matrix and Aerosil was used as an anti-adherent to reduce the stickiness of waxy lipid. After being thoroughly mixed on a magnetic stirrer, the resultant dispersion was spray dried. With the atomization air pressure set at 2 kg/cm^2 and the aspirator speed set at 65 m^3/hr, a micro

spray drier (Cronimach Machinary, model no. CRO-MSD161, Evaporation capacity: 1 L/hr H20) was utilized for spray drying in a co-current mode with 0.7 mm dual-fluid nozzle (15).

Optimization of formulation using 3^2 Full Factorial Design (FFD)

A quadratic model of analysis was created using Full Factorial Design (FFD) as a part of Design of Experiment (DOE) to optimize formulation variables after finalization of process variables According to Design Expert 11 (StatEase, Minneapolis, MN), nine trials were conducted. Table1 shows FFD trial runs along with the dependent and independent variables.

Table 1: 3^2 Full Factorial Design (FFD) with Evaluation Data

Run	X1	X2	X1 POS: Soluplus Ratio	X2 POS: Gelucire Ratio	% Yield	% Drug content (n=3)	% Buoyancy (n=3)	Solubility (µg/ml) (n=3)	Q_8 (0.1 N HCl) (n=2)
B1	-1	-1	1:0.5	1:2.75	71.5	93.96±3.36	94.34 ± 0	1504±12	102.56±0.75
B2	0	-1	1:1	1:2.75	72.7	94.85±4.58	89.64 ± 4.85	1865±36	103.92±0.744
B3	+1	-1	1:1.5	1:2.75	75.1	98.45±1.23	89.06 ± 4.41	2176±86	105.86±0.47
B4	-1	0	1:0.5	1:3	70.44	96.49±2.97	91.45 ± 5.11	1945 ±33	97.25±1.04
B5	0	0	1:1	1:3	72.8	93.84±2.51	93.87 ± 5.14	2332±27	98.47±0.64
B6	+1	0	1:1.5	1:3	78.8	92.09±3.7	89.37 ± 4.18	2556±55	102.31±0.78
B7	-1	+1	1:0.5	1:3.25	70.9	94.00±2.36	93.84 ± 2.43	2303±38	91.10±0.62
B8	0	+1	1:1	1:3.25	68.2	96.6±1.94	95.42 ± 3.82	2641±43	92.53±0.28
B9	+1	+1	1:1.5	1:3.25	73.9	95.6±1.88	93.75 ± 3.47	2936±41	94.25±0.21
API								710±15	

INDEPENDENT VARIABLES IN FFD

SR NO	VARIABLES	LEVELS OF VARIABLES		
		-1	**0**	**+1**
1	POS: Soluplus Ratio	1:0.5	1:1	1:1.5
2	POS: Gelucire Ratio	1:2.75	1:3	1:3.25

DEPENDENT VARIABLES IN FFD

SR NO	RESPONSE
1	Solubility (mg/ml)
2	% CDR in 0.1 N HCl in 8 hours (Q_8)

Table 2 provides a description of the regression analysis conducted using the Quadratic model for all of the chosen dependent variables. The statistical analysis of the Model F values and lack of fit for each dependent variable indicated that the chosen regression model was statistically significant and exhibited a good fit with minimal potential for extraneous variability.

Solubility Full model = 2306.11+319.33 A+389.17 B – 9.75AB – 42.67 A2 – 40.17 B2 + ε

Solubility Reduced model = 2306.11+319.33 A+389.17 B + ε

Q_8 Full model = 98.95+1.92 A- 5.74 B – 0.035AB + 0.578A^2 – 0.971 B^2 + ε

Q_8 Reduced Model = 98.95+1.92 A- 5.74 B + ε

Wherein

A & B are Main Effects

AB is a 2-way Interaction Effect, A^2 & B^2 are Curvature effects

Ɛ is an Experimental error

Based on the verified model and the graphical optimization using the overlay plot, the optimum batch was chosen as Check point batch 1 (CP1) based on increase in SDD solubility compared to API and the most favourable controlled % CDR in the gastric pH.

Table 2: Regression Analysis by Quadratic model and Model Validation

ANOVA ANALYSIS FOR SOLUBILITY			
Source	**F-value**	**p-value**	
Model	**439.40**	**0.0002**	**Significant**
A-Soluplus Concentration	879.85	**< 0.0001**	
B-Gelucire Concentration	1306.74	**< 0.0001**	
AB	0.5468	0.5132	
A^2	5.24	0.1061	
B^2	4.64	0.1202	
Std. Dev.	26.37	**R^2**	0.9986
Mean	2250.89	**Adjusted R^2**	0.9964
C.V. %	1.17	**Predicted R^2**	0.9881
		Adeq Precision	65.8110

ANOVA ANALYSIS FOR Q_8 (% drug release in 0.1N HCl)			
Source	**F-value**	**p-value**	
Model	80.82	0.0021	Significant
A-Soluplus Concentration	39.99	0.0080	
B-Gelucire Concentration	359.45	0.0003	
AB	0.0089	0.9308	
A^2	1.22	0.3507	
B^2	3.43	0.1610	
Std. Dev.	0.7418	**R^2**	0.9926
Mean	98.69	**Adjusted R^2**	0.9803
C.V. %	0.7516	**Predicted R^2**	0.9214
		Adeq Precision	25.2825

Constraints			
Name	**Goal**	**Lower Limit**	**Upper Limit**
A: Soluplus Concentration	is in range	0.5	0.75

B: Gelucire Concentration	is in range	2.75	2.9
Solubility	is in range	1504	2000
Q8	is in range	90	100
Check point Batches for Model Validation			
Soluplus Conc (g)	**Gelucire Conc (g)**	**Solubility (µg/ml)**	**Q8 (%)**
0.537	2.898	1805.582	99.836
0.560	2.895	1817.649	99.950
0.618	2.898	1869.657	99.989

Evaluation & Characterization of POS SDD

% Yield

Product yield was estimated by dividing the obtained amount of SDD by the total weight of API and excipients added to the relevant batch (16). The data of all 9 batches are depicted in bar graph of Fig 1A.

% Drug content (Assay)

Product equivalent to 50 mg of POS was dissolved in methanol and the sample was filtered using Whatman filter paper, diluted as needed, and then subjected to ultraviolet (UV) examination at 259 nm (17). The data confirmed that the % assay falls within the acceptable range of 90-110% as shown in Fig 1B.

Saturation Solubility study

Excessive sample [drug/SDD] was dissolved in 10 ml of 0.1N HCl in a stoppered glass container, shaken for 48 hours in a 37±0.5°C water bath in orbital shaker, centrifuged at 2000 rpm for 10 minutes, and analysed at 255 nm after filtering (0.45µm) & diluting the supernatant (18). The solubility values (µg/ml) for all experimental batches were determined within a range of two to three times that of the API and are presented in Fig 1C.

In-vitro Dissolution study

The product was subjected to an *in-vitro* dissolution study using a USP Apparatus II (paddle) operating at 50 rpm in 0.1N HCl at 37 ± 0.5°C temperature for a duration of 8 hours (19). All batches exhibited controlled drug release, achieving a CDR of over 90% within a period of 8 hours as demonstrated in Fig 2. The % CDR at 8 hrs (Q_8) for all 9 batches is summarized in Fig 1D. The release kinetics study data analyzed using DD-Solver software fits korsemeyer peppas model with non-fickian diffusion (n=0.88), based on the adjusted R^2-value, which was in close proximity to 0.999, the AIC (Akaike Information Criteria) value that was lowest, and the MSC (Model Selection Criteria) value that exceeded 4. Due to n component nearer to 0.89 value, the erosion mechanism was greater than diffusion mechanism and the drug release followed zero-order kinetics rather than first order kinetics.

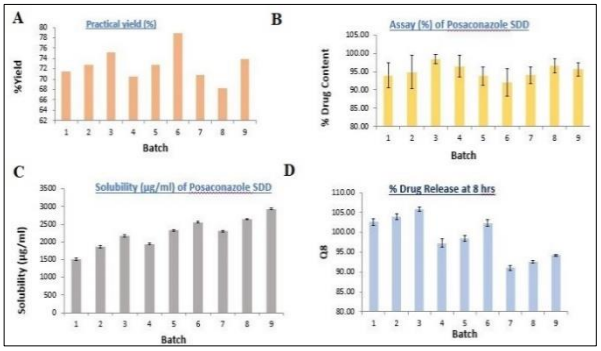

Fig 1 Evaluation of POS SDD

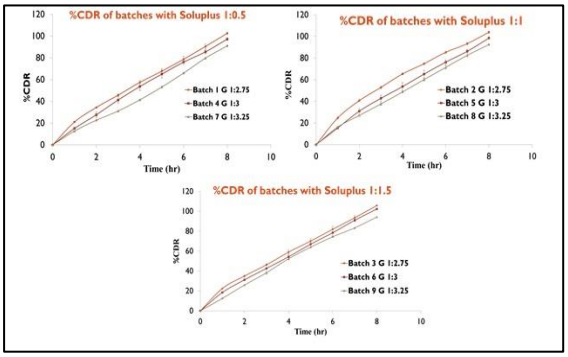

Fig 2 % CDR of POS SDD

Differential scanning calorimetry (DSC)

The DSC thermograms were acquired using the PerkinElmer Thermal Analyzer under inert conditions with a nitrogen flow rate of 10 ml/min. The heating process was carried out at 30 °C to 350 °C at a scanning rate of 20 °C per minute (17). Figure 3 displays the DSC thermograms of the pure POS and SDD. Pure drug shows sharp endothermic peak at a temperature of 170.91°C which had disappeared in POS SDD curve.

Powder X-ray Diffraction (PXRD)

The study utilized a Powder X-ray Diffractometer D8 DISCOVER (Bruker) to compare the PXRD spectra of the POS SDD and pure POS as depicted in Fig 4. The scan angles were varied between 0° and 80° over a 2θ spectrum (20). The API demonstrated a prominent peak at 2θ values of 16.33°, which suggested its crystalline nature. The PXRD pattern of the SDD exhibited a lack of discernible peaks, thereby confirming the conversion of crystalline drug into amorphous form within the SDD.

Particle size

The Particle Size Analyzer (HORIBA Scientific SZ-100) was utilized to evaluate the mean particle size through the application of Dynamic Light Scattering (DLS) as shown in Fig 5A (21). The average of the three distinct measurements was considered to determine mean value of 2067.5 nm (Z-average).

Scanning electron microscope (SEM)

Figure 5B displays the surface morphology analysis conducted via scanning electron microscopy (SEM) on the optimized batch (22). The visual depiction validated the spherical shape and fibrous texture of the SDD powder.

Residual solvent Detection by HS-GC/MS

According to the Headspace-Gas Chromatography/Mass Spectrometry (HS-GC/MS) (Shimadzu GCMS-QP2020 NX) analysis of the SDD sample, it was found that there were no residual solvent peaks of DCM (class II solvent with a limit of 3000 ppm) or IPA (class III solvent with a limit of 5000 ppm) in the chromatogram (20).

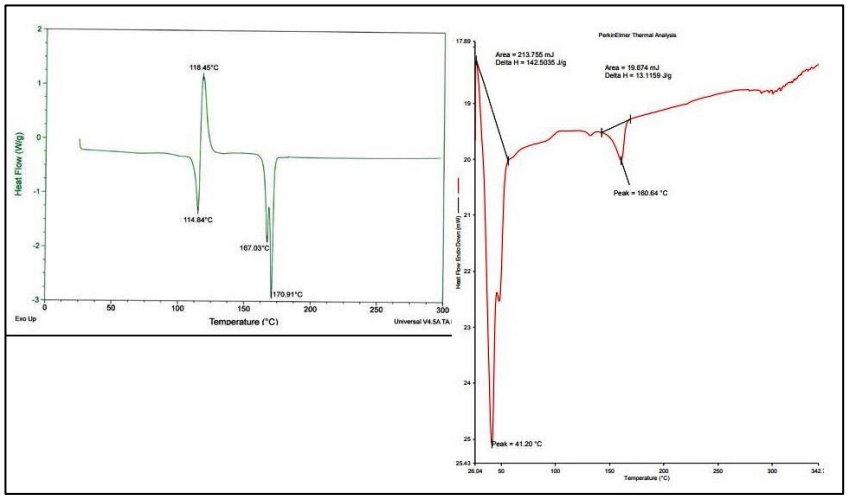

Fig 3
DSC Thermograms of the pure POS and SDD

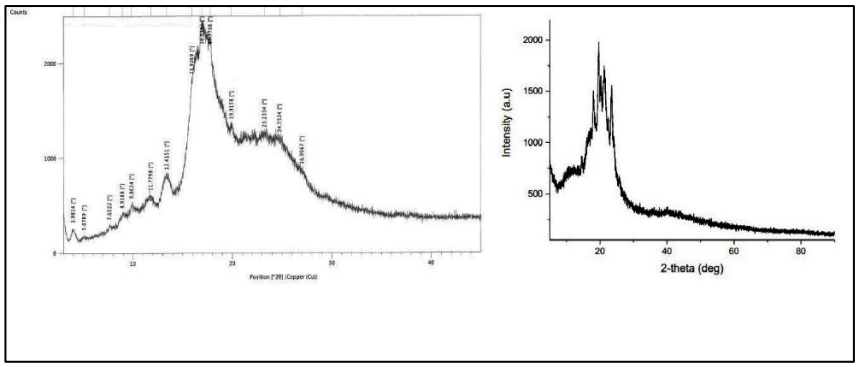

Fig 4
PXRD spectra of the pure POS and POS SDD and

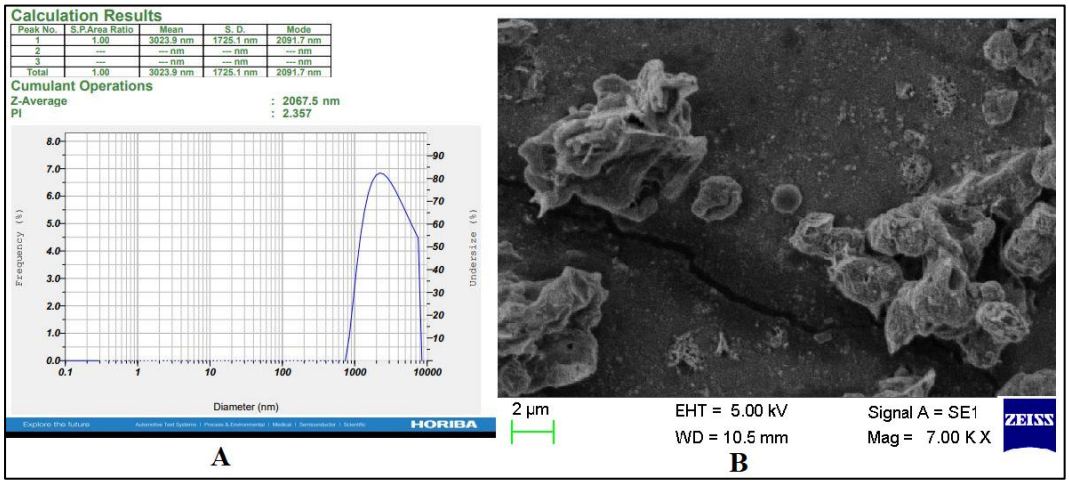

Fig 5 (A) Particle size distribution; (B) Surface Morphology Analysis by SEM

Stability Study

The optimized batch of SDD, encapsulated in capsule shell was subjected to an Accelerated stability study as per the International Conference on Harmonization (ICH) guidelines for six months in a stability chamber (Patel Instrument Pvt. Ltd.) at a temperature of 40°C ± 2°C and a relative humidity of 75% ± 5% RH (23). All parameters indicated that the final outcomes were statistically significant in comparison to the initial data and product was stable.

Roentgenography in Rabbit for site-specificity

The optimized POS SDD underwent an *in-vivo* gastro-retention study utilizing radiography technique in a healthy New Zealand white rabbit by substituting 10% of the drug component with barium sulphate ($BaSo_4$) (24). X-ray images were captured of the animal's abdominal region in an upright position at various intervals of time, including 0 hours (prior to the administration of the formulation), 2 hours, 5 hours, and 7 hours, as shown in Fig 6 along with the interpretation.

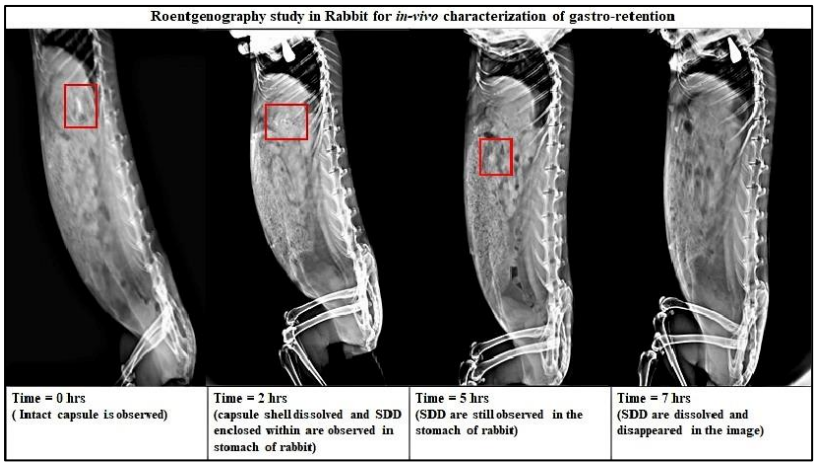

Fig 6 Roentgenography study in rabbit for *in-vivo* characterization of gastro-retention

Pharmacokinetic study in Male Sprague Dawley Rats

The study utilized male Sprague-Dawley rats weighing 250 g (ranging from 225-275 g), procured from the Preclinical Department of Zydus Research Centre Ahmedabad, with 3 experimental groups, each consisting of 6 rats. Two groups were fed optimized POS SDD in the fasting and fed states, whereas the third group was administered the standard oral formulation (Noxafil suspension) after overnight fasting, at a dose of 40 mg/kg of POS. The study involved the retro-orbital blood sampling technique (0.15-0.3ml, NMT 1.5ml per day per rat) at specific time intervals of 0.5, 0.75, 0.92, 1.33, 3.5, 6, 8, 24, 48, and 72 hours from both test groups and the third standard group while the rats were under isoflurane anesthesia. The Plasma drug concentration was analysed by High Performance Liquid Chromatography (Isocratic HPLC, Model: LC-2000). Non-compartmental pharmacokinetic analysis was performed using PK Solver to derive important pharmacokinetic parameters as depicted in Table 3. The data derived were checked for statistical significance using the 2-way Annova test, followed by Sidak's multi-comparison test with $\alpha = 0.05$ and P value <0.05 as shown in Fig 7.

Table 5 Pharmacokinetic Data Analysis using PK Solver

PK Solver 2.0 Non-Compartmental Analysis of Plasma Data after Extravascular Input	
Time Unit: h	**Dose**: 10 mg
Conc Unit: **µg/ml**	**Method**: **Linear Trapezoidal**

Parameter	Fasting (mean±SEM)	Fed (mean±SEM)	Noxafil (mean±SEM)
Ke (1/h)	0.011±0.001	0.019±0.017	0.019±0.002
$t_{1/2}$ (h)	62.194±3.521	37.565±3.233	37.899±4.429
t_{max1} (h)	1.330±0	3.500±0	6.000±0
C_{max1} (µg/ml)	8.513±0.165	1.163±0.0245	2.073±0.247
t_{max2} (h)	24 ±0	24 ±0	24 ±0
C_{max2} (µg/ml)	2.994±0.092	1.838±0.03	2.887±0.151
AUC $_{0\text{-}t}$ (µg/ml*h)	161.867±5.413	103.769±2.47	144.32 ±10.084
AUC $_{0\text{-}inf\_obs}$ (µg/ml*h)	314.021±1.638	145.322±9.69	212.101±28.408
MRT $_{0\text{-}inf\_obs}$ (h)	96.498±4.528	59.576±4.49	63.355±6.17
Vz/F_obs (mg)/(µg/ml)	2.858±0.164	3.719±0.078	2.589±0.041
Cl/F_obs (mg)/(µg/ml)/h	0.032±0.0001	0.069±0.004	0.049±0.006

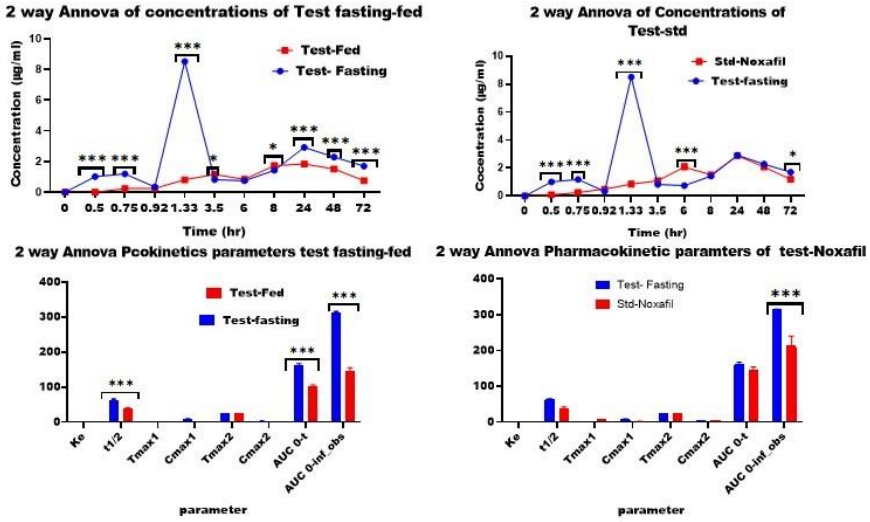

Fig 7 Two-way Annova comparison of concentration and pharmacokinetic parameters

2. Esomeprazole Delayed Release Oral Formulation

Preparation of ASD by spray drying technique

ESM and HPMCAS-MF were dissolved in a solvent system comprising of methanol: water: Acetone (1:2:7) using magnetic stirrer following the procedure described in POS formulation.

Optimization of formulation using Box-Behnken Design (BBD)

The final formulation components and the significant process parameters like Feed Flow rate (FFR) and inlet temperature were optimization by Response Surface Methodology based on the review of literature, and the range for proceeding optimization design was confirmed based on the preliminary trials. Table 4 depicts the 15 experimental runs generated utilizing BBD as per Design Expert 13, including the details of variables, responses and levels used. Considering the effects of factors on the responses recorded and the suitable constraints decided, the 3 check

point batches with desirability 1 were scrutinized for the model validation as enumerated in Table 4. CP3 was selected as optimized batch for further characterization.

Table 4 Box-Behnken Design (BBD) Matrix & Check point Analysis

Experimental Batch	X1	X2	X3	X1 ESM: HPMCAS-MF	X2 FFR (ml/min)	X3 Inlet temperature (°)
B1	-1	-1	0	1:1	4	100
B2	+1	-1	0	1:3	4	100
B3	-1	+1	0	1:1	8	100
B4	+1	+1	0	1:3	8	100
B5	-1	0	-1	1:1	6	80
B6	+1	0	-1	1:3	6	80
B7	-1	0	+1	1:1	6	120
B8	+1	0	+1	1:3	6	120
B9	0	-1	-1	1:2	4	80
B10	0	+1	-1	1:2	8	80
B11	0	-1	+1	1:2	4	120
B12	0	+1	+1	1:2	8	120
B13	0	0	0	1:2	6	100
B14	0	0	0	1:2	6	100
B15	0	0	0	1:2	6	100

INDEPENDENT VARIABLES IN BBD

SR NO	VARIABLES	LEVELS OF VARIABLES		
		-1	**0**	**+1**
1	ESM: HPMCAS-MF Ratio	1:1	1:2	1:3
2	Feed flow rate (FFR) (ml/min)	4	6	8
3	Inlet temperature of Spray dryer (°)	80	100	120

DEPENDENT VARIABLES IN BBD

SR NO	RESPONSE
1	% Yield
2	Solubility (mg/ml)
3	% CDR in 0.1 N HCl in 2 hours (Q_2)

Check point Batch	HPMCAS-MF conc (g)	FFR (ml/min)	Inlet Temp (°)	Solubility (mg/ml)	Yield (%)	Q_2 (%)
CP1	2.361	4.099	94.649	1.379	75.133	7.971
CP2	2.387	4.122	98.819	1.391	75.396	7.902
CP3	**2.492**	**4.038**	**97.899**	**1.449**	**75.963**	**7.806**

The regression analysis by Quadratic model for all the selected dependent variables are described in Table 5 and the models generated are listed below.

Solubility Full model = 1.21+ 0.4665A – 0.0059B – 0.0031C +0.0015AB – 0.015AC – 0.0142BC + 0.113 A^2 – 0.0278 B^2 + 0.0512 C^2 + ε

Solubility Reduced model = 1.21+ 0.4665A+ 0.113 A^2 + ε

% Yield Full Model = 68.67+ 0.875A – 6B – 1.13C – 0.25AB + 0.0AC + 0.25BC + 1.67A^2 + 0.4167 B^2 – 8.33C^2

% Yield Reduced Model = 68.67+ 0.875A – 6B – 1.13C + 1.67A^2 + ε

Q_2 Full Model = 8.11 – 1.9A – 0.2475B – 0.1832C +0.1335AB – 0.27AC – 0.0615BC + 0.8653 A^2 + 0.2268 B^2 – 0.2902 C^2 + ε

Q_2 Reduced Model = 8.11 – 1.9A + 0.8653 A^2 + ε

Table 5 Regression Analysis by Quadratic model for Dependent Variables

	SOLUBILITY			% Yield			Q_2		
Source	**F-value**	**p-value**		**F-value**	**p-value**		**F-value**	**p-value**	
Model	61.93	**0.0001**	**S**	94.95	**< 0.0001**	**S**	36.37	**0.0005**	**S**
A-HPMCAS	538.27	**< 0.0001**	**S**	8.96	**0.0303**	**S**	283.07	**< 0.0001**	**S**
B-FFR	0.0854	0.7819		421.46	**< 0.0001**	**S**	4.82	0.0795	
C-InletTemp	0.0242	0.8826		14.82	**0.0120**	**S**	2.64	0.1649	
AB	0.0028	0.9600		0.3659	0.5717		0.7013	0.4405	
AC	0.2783	0.6204		0.0000	1.0000		2.87	0.1511	
BC	0.2511	0.6376		0.3659	0.5717		0.1488	0.7155	
A^2	14.57	**0.0124**		15.01	0.0117		27.19	0.0034	
B^2	0.8817	0.3908		0.9381	0.3773		1.87	0.2300	
C^2	2.99	0.1442		375.23	< 0.0001		3.06	0.1406	
R^2	0.9911				0.9942			0.9850	
Adjusted R^2	0.9751				0.9837			0.9579	
Predicted R^2	0.8586				0.9694			0.8006	

*S= significant, p-value < 0.05 is significant

Evaluation & Characterization of ESM SDD

% Yield, % Drug content (Assay) & Saturation Solubility study in PBS pH 6.8

These parameters were evaluated in the similar way as described in POS formulation. The data for all 15 batches are depicted in Fig 8.

In-vitro Dissolution study

The CDR study was performed in 0.1N HCl for 2 hrs and for another 2 hours in PBS pH 6.8, as described earlier and data are represented in Fig 9. The % CDR complied with USP product monograph of DR formulation stating that 'NMT 10% of the labelled amount of esomeprazole is dissolved in 0.1 N hydrochloric acid, up to 2 hrs and NLT 75% (Q) of the labelled amount of esomeprazole is dissolved at 30 min in phosphate buffer pH 6.8'. Q_2 values of all the 15 batches is shown in Fig 8. The release kinetics after the lag time of 2 hrs fits Korsmeyer-Peppas

(K-Peppas) model with Fickian Diffusion (n< 0.45), based on the values of adjusted R^2 near to 0.999, Akaike Information Criteria (AIC) value in range of 30-40 and MSC (Model Selection Criteria) value >4.

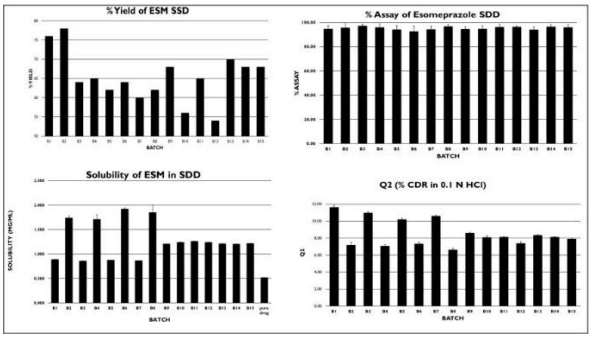

Fig 8 Evaluation of ESM SDD

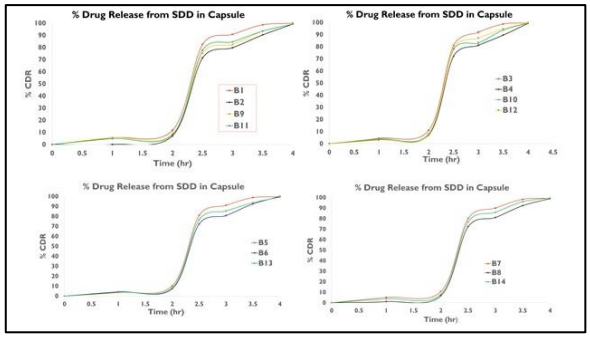

Fig 9 % CDR of ESM SDD

Differential scanning calorimetry (DSC) & Powder X-ray Diffraction (PXRD)

The DSC thermograms and PXRD spectra of pure ESM and ESM SDD, as described in Fig 10, were procured as discussed earlier. Both the curves confirmed the conversion of crystalline drug to amorphous form in SDD.

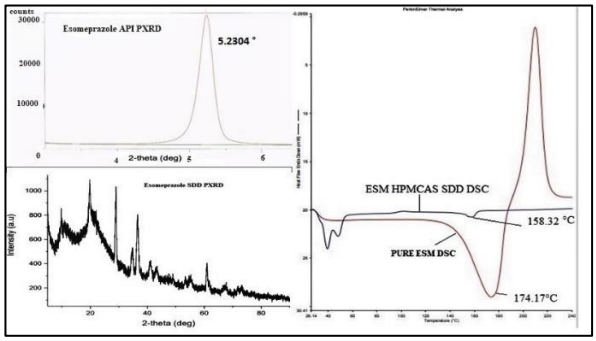

Fig 10 DSC thermogram and PXRD spectra

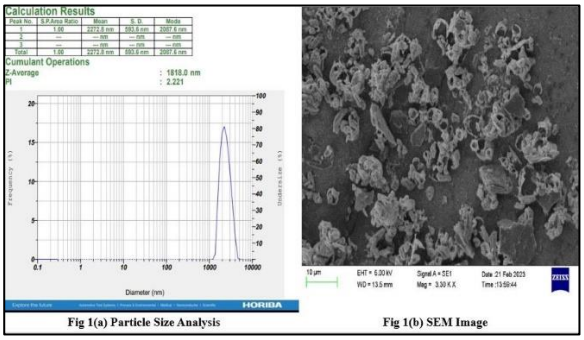

Fig 1(a) Particle Size Analysis **Fig 1(b) SEM Image**

Fig 11 Particle size analysis and SEM

Particle size & Scanning electron microscope (SEM)

The particle size analysis and surface morphology study were conducted as described earlier, and the results are mentioned in Fig 11.

Residual solvent Detection by HS-GC/MS & Stability Study

These studies were conducted as discussed earlier. The residual curve confirmed the absence of organic solvents (acetone and methanol) peaks in optimized formulation, used in spray drying process. The product was stable for 6 months as per ICH guidelines.

f. Achievements with respect to objectives

In the present study, an SDD based oral gastro-retentive formulation was developed using an industrially feasible spray drying technique for the controlled release of the weakly basic drug POS in the gastric environment, where its solubility is higher compared to intestinal pH. The gastric retention of dosage form reduced the intestinal precipitation of POS, improving the stability of amorphous form and bioavailability of POS. The major limitation of variable

bioavailability of standard Noxafil oral suspension may be overpowered by the developed novel formulation.

The developed ESM SDD encapsulated in hard gelatin capsule was sufficient to procure the delayed release, avoiding the degradation of proton pump inhibitor in gastric pH along with eliminating the need of enteric coating and/or multi-particulate dosage form, prevalent in marketed formulation. The said concept combined with Spray Drying Technique, may significantly contribute to product development cost reduction and ease the scale up of the formulation.

g. Conclusion

The ternary ASD of POS was prepared using carriers Soluplus®, which has an excellent solubilization properties, and lipid polymer Gelucire 43/01, which has floating and sustained release properties by spray drying technique. The ratio of SD carriers was optimized based on DOE using Full Factorial Design. The final optimized formulation was decided from the Design Space of an overlay plot having desirability 1 for the selected constraints. The optimized batch of SDD possessed almost 2-folds enhanced solubility compared to the API, along with controlled release in simulated gastric pH for 8 hours. The release kinetics evaluated by the DD Solver confirmed K-peppas model with zero order kinetics. The selected SDD batch fulfilled all the required characteristics desired for the compatibility and complexation between API and carrier confirmed by FTIR, DSC, and PXRD studies. The particle size of the optimized batch was also in the micron range, supporting the improved solubility of the BCS Class II drug. The developed SDD was sufficient to obtain gastric retention with no floating lag time, > 8hrs floating duration and > 90% buoyancy. The developed SDD encapsulated in capsule shell was stable as per ICH guidelines. The gastro-retention was confirmed through an *in-vivo* roentgenography study in rabbit. The pharmacokinetics study executed in male Sprague-Dawley rats proved the efficiency of the developed formulation in comparison to the marketed formulation using PK Solver and statistically analysed by two-way ANNOVA using GraphPad prism 8.

SDD based oral formulation was developed for the delayed release of PPI Esomeprazole magnesium. The significant process and formulation variables were optimized based on DOE concept using Box-Behnken Design, a preferred Response Surface optimization method. The final optimized formulation was decided from the Design Space of overlay plot having desirability 1 for the selected constraints. The optimized batch of SDD possessed almost 3-folds enhanced solubility compared to the API along with the at least 90% dose retention in final dosage form during the transit from gastric pH to intestinal pH. Both these targets were solely achieved by the SD carrier HPMCAS-MF having excellent solubilization properties and

solubility above pH 6. Hence, this approach may be extended to any API having stability issues in upper GIT or for the API having absorption window in lower GIT. The selected SDD batch fulfilled all the required characteristics desired for the compatibility and complexation between API and carrier confirmed by FTIR, DSC and PXRD studies. The particle size of the optimized batch was also in micron range supporting the improved solubility. The optimized batch was stable for 6 months as per ICH guidelines.

h. Copies of papers published (Attached as Annexure I)

Sr No.	Details
Papers Published/ accepted	
1	Solid dispersion technology as a formulation strategy for the fabrication of modified release dosage forms: A comprehensive review. Authors : Kaushika Patel, Shreeraj Shah, Jaymin Patel Publication date: 18 April 2022, Issue: June 2022 Source: DARU Journal of Pharmaceutical Sciences Volume: 30, Issue: 1, Pages165-189 Publisher: Springer International Publishing, DOI: 10.1007/s40199-022-00440-0
2	Development of Delayed Release Oral Formulation Comprising Esomeprazole Spray Dried Dispersion utilizing design of experiment as an optimization strategy. Authors : Kaushika Patel, Jaymin Patel, Shreeraj Shah Accepted date: 22/08/23 Source: AAPS PharmSciTech DOI : 10.1208/s12249-023-02642-4 Publisher: Springer International Publishing

i. References

1. Xu W, Sun Y, Du L, Chistyachenko YS, Dushkin AV, Su W. Investigations on solid dispersions of valsartan with alkalizing agents: Preparation, characterization and physicochemical properties. Journal of Drug Delivery Science and Technology [Internet]. 2018; 44 (October 2017): 399–405. Available from: https://doi.org/10.1016/j.jddst.2018.01.012.

2. De Mohac LM, Caruana R, Pavia FC, Cavallaro G, Giammona G, Licciardi M. Multicomponent solid dispersion as a formulation strategy to improve drug permeation: A case study on the anti-colorectal cancer irinotecan. Journal of Drug Delivery Science and Technology. 2019 Aug 1; 52:346–54.

3. Tran HTT, Park JB, Hong KH, Choi HG, Han HK, Lee J, et al. Preparation and characterization of pH-independent sustained release tablet containing solid dispersion granules of a poorly water-soluble drug. International Journal of Pharmaceutics [Internet]. 2011; 415(1–2):83–8. Available from: http://dx.doi.org/10.1016/j.ijpharm.2011.05.052.

4. Nair AR, Lakshman YD, Anand VSK, Sree KSN, Bhat K, Dengale SJ. Overview of Extensively Employed Polymeric Carriers in Solid Dispersion Technology. AAPS PharmSciTech. 2020; 21(8).

5. Bhujbal SV, Mitra B, Jain U, Gong Y, Agrawal A, Karki S, et al. Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies. Acta Pharmaceutica Sinica B [Internet]. 2021; 11(8):2505–36. Available from: https://doi.org/10.1016/j.apsb.2021.05.014.

6. Li Y, Mann AKP, Zhang D, Yang Z. Processing impact on in vitro and in vivo performance of solid dispersions—a comparison between hot-melt extrusion and spray drying. Pharmaceutics. 2021 Aug 1; 13(8).

7. De Mohac LM, Raimi-Abraham B, Caruana R, Gaetano G, Licciardi M. Multicomponent solid dispersion a new generation of solid dispersion produced by spray-drying. Journal of Drug Delivery Science and Technology [Internet]. 2020; 57(April):101750. Available from: https://doi.org/10.1016/j.jddst.2020.101750.

8. Alam MA, Ali R, Al-Jenoobi FI, Al-Mohizea AM. Solid dispersions: A strategy for poorly aqueous soluble drugs and technology updates. Expert Opinion on Drug Delivery. 2012; 9(11):1419–40.

9. Kambayashi A, Dressman JB. Predicting the Changes in Oral Absorption of Weak Base Drugs under Elevated Gastric pH Using an In Vitro–In Silico–In Vivo Approach: Case Examples—Dipyridamole, Prasugrel, and Nelfinavir. Journal of Pharmaceutical Sciences. 2019 Jan 1; 108(1):584–91.

10. Hens B, Brouwers J, Corsetti M, Augustijns P. Supersaturation and Precipitation of Posaconazole Upon Entry in the Upper Small Intestine in Humans. Journal of Pharmaceutical Sciences [Internet]. 2016; 105(9):2677–84. Available from: http://dx.doi.org/10.1002/jps.24690.

11. Gutsche S, Krause M, Kranz H. Strategies to overcome pH-dependent solubility of weakly basic drugs by using different types of alginates. Drug Development and Industrial Pharmacy. 2008 Dec; 34(12):1277–84.

12. Li J, Bukhtiyarov Y, Spivey N, Force C, Hidalgo C, Huang Y, et al. In Vitro and In Vivo Assessment of the Potential of Supersaturation to Enhance the Absorption of Poorly Soluble Basic Drugs. Journal of Pharmaceutical Innovation. 2020 Dec 1; 15(4):591–602.

13. Kanwar K, Gautam SP. Qualitative Portrayal of Esomeprazole Magnesium by Exploring Diverse Analytical and Investigative Approaches. Journal of Pharmaceutical Research International. 2021 Jul 1; 52–68.

14. Srebro J, Brniak W, Mendyk A. Formulation of Dosage Forms with Proton Pump Inhibitors: State of the Art, Challenges and Future Perspectives. Pharmaceutics. 2022 Oct 1; 14(10).

15. Pohlen M, Lavrič Z, Prestidge C, Dreu R. Preparation, Physicochemical Characterisation and DoE Optimisation of a Spray-Dried Dry Emulsion Platform for Delivery of a Poorly Soluble Drug, Simvastatin. AAPS PharmSciTech. 2020 May 1; 21(4).

16. Szabó E, Galata DL, Vass P, Hirsch E, Csontos I, Marosi G, et al. Continuous formulation approaches of amorphous solid dispersions: Significance of powder flow properties and feeding performance. Pharmaceutics. 2019 Dec 1; 11(12).

17. Rani Avula P. Quality By Design Approach For Development Of Amorphous Solid Dispersions Of Efavirenz By Melt-Quench Technique. Vol. 9, Volatiles & Essent. Oils. 2022 p. 43–59.

18. Abdelhaleem Ali AM, Khames A, Alrobaian MM, Hamaidi M, Abourehab MAS. Glucosamine-paracetamol spray-dried solid dispersions with maximized intrinsic dissolution rate, bioavailability and decreased levels of in vivo toxic metabolites. Drug Design, Development and Therapy. 2018; 12:3071–84.

19. Mustafa WW, Fletcher J, Khoder M, Alany RG. Solid Dispersions of Gefitinib Prepared by Spray Drying with Improved Mucoadhesive and Drug Dissolution Properties. AAPS PharmSciTech. 2022 Jan 1; 23(1).

20. Surti N, Mahajan AN, Patel D, Patel A, Surti Z. Spray dried solid dispersion of repaglinide using hypromellose acetate succinate: in vitro and in vivo characterization. Drug Development and Industrial Pharmacy. 2020 Oct 2; 46(10):1622–31.

21. Ajiboye AL, Nandi U, Galli M, Trivedi V. Olanzapine loaded nanostructured lipid carriers via high shear homogenization and ultrasonication. Scientia Pharmaceutica. 2021 Jun 1; 89(2).

22. Muqtader Ahmed M, Fatima F, Abul Kalam M, Alshamsan A, Soliman GA, Shaikh AA, et al. Development of spray-dried amorphous solid dispersions of tadalafil using glycyrrhizin for enhanced dissolution and aphrodisiac activity in male rats. Saudi Pharmaceutical Journal. 2020 Dec 1; 28(12):1817–26.

23. De PK, Sahana B, Rakshit S. Enhancement of Dissolution rate and stability study of Ofloxacin Solid dispersion. Available from: www.pelagiaresearchlibrary.com

24. Diós P, Szigeti K, Budán F, Pócsik M, Veres DS, Máthé D, et al. Influence of barium sulfate X-ray imaging contrast material on properties of floating drug delivery tablets. European Journal of Pharmaceutical Sciences. 2016 Dec 1; 95:46–53.