Prototype Formulation Development Of Ebastine Using Hydrophilic Surfactants

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ABSTRACT:

The purpose of this study was to evaluate the effect of different hydrophilic excipients to enhance the dissolution rate of poorly water-soluble drug using conventional spray granulation process. Poorly water soluble drug Ebastine was studied with Gelatin (35 bloom), Low viscosity Hypromellose USP Type 2910 (E5LV) and poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (Poloxamer 188). The study was carried out in the two steps in which first step involves the evaluation of the mentioned hydrophilic excipients individually at different concentrations and second step involves the evaluation of different concentrations in combination using design of experiments. The selected hydrophilic surfactants were dissolved in quantity sufficient purified water and the resulting solution is sprayed on to the drug and excipients mixture present in the fluid bed processor. The resulting granulate is dried for sufficient duration in the same fluid bed processor then blended with suitable excipients and compressed to tablets using a rotary tablet press. The drug release was characterized by subjecting dissolution testing of the tablets using USP Apparatus II (Paddle), 50 rpm, 900 mL acetate buffer PH 4.5 with 0.1% SLS at 37°C. The combination of hydrophilic excipients enhanced the drug dissolution relative to alone excipients in the study and also relative to marketed drug product. The results concludes that rate and extent of drug dissolution can be enhanced by using combination of hydrophilic surfactants in conventional spray granulation approach. The mechanism for dissolution enhancement is believed to be a microenvironment surfactant effect facilitated by keeping the Gelatin, HPMC and drug particles in close proximity during drug dissolution. Also, it is believed to be a function of self-emulsification mechanism of Poloxamer. Using appropriate hydrophilic surfactants, the conventional manufacturing methods may provide a cost effective, quicker, readily scalable alternative for formulating poorly water-soluble drugs.

KEYWORDS: Ebastine, Hydrophilic surfactants, Drug release, Solubility enhancement, Design of experiments.

INTRODUCTION:

The issue of poor solubility of active pharmaceutical ingredients (APIs) is one of the biggest limitations for drug development. It is a matter of concern, as the bioavailability depends on the dissolution of drug in the gastrointestinal fluids. The main determinants of the dissolution kinetics in vivo are solubility and surface area of the particles. The solubility is a function of the crystal lattice energy and the affinity of solid phase to the solvent. Thus, three groups of strategies that have been implemented to improve the rate of dissolution and solubility rely on: (1) the reduction of the intermolecular forces in solid phase, (2) the enhancement of the solid–solvent interaction, and (3) the increase of the surface area available for solvation (according to the Noyes–Whitney equation) [1]. Due to the fact that almost 50% of currently marketed drugs and over 70% of new chemical entities exhibit low solubility in water, numerous techniques have been developed to overcome this problem [2]. Common strategies include pH adjustment, formation of salts, co-solvency, formation of co-crystals and inclusion complexes, particle size reduction, supercritical fluid technology (SCF), and self-emulsification [3,4]. Recently, nanotechnology has emerged as a technique that leads to the formation of robust delivery systems. Numerous attempts have been applied to obtain several types of delivery systems, i.e., micelles [5], liposomes [6], capsules [7,8], protein nano containers [9], and silica-based nanoparticles

[10,11]. Poorly water-soluble drugs have been frequently processed with hydrophilic polymers, as the molecular dispersion of drug molecules within the matrix provides better dissolution of the drug. Moreover, when the systems were further formulated into the nanoparticles, the results were more pronounced [12–14]. The main factors affecting the choice of a particular method are the physicochemical characteristics of drugs and carriers. Solid dispersions are commonly formed to enhance the water solubility of APIs; however, the number of marketed products arising from that strategy is rather low. This is a result of the thermal instability of drug and carrier during preparation of systems, a poor in vitro–in vivo correlation, and instability during storage [15]. However, the simplicity of preparation, low cost, and great improvements in the dissolution of poorly water-soluble drugs have made the solid dispersions widely investigated. Experimental and theoretical approaches have been involved to determine the thermodynamic properties of APIs dispersed in polymer matrices as well as the mechanisms and factors affecting their stability [16–18]. The concept of solid dispersion—one of the earliest methods of solubility enhancement—was introduced in 1961 by Sekiguchi and Obi, who prepared eutectic mixtures containing microcrystalline drug and a water-soluble carrier [19–22]. Although crystalline forms provide high stability and chemical purity, the lattice energy barrier is the major limitation affecting the dissolution rate. Thus, amorphous carriers such as polyvinylpyrrolidone (PVP) [23,24] and hydroxypropylmethyl cellulose (HPMC) [25,26] have been introduced to prepare amorphous solid dispersions (ASDs). The highly water-soluble amorphous carriers provide stabilization of APIs, increasing the wettability and dispersibility of the drug [27–29]. They limit the precipitation of a drug in water; however, the supersaturation may lead to precipitation and recrystallization of APIs, which negatively affects the bioavailability of the drug. To face this problem, surface active agents or self-emulsifiers such as poloxamers (PLXs) [30,31], Tween 80 [32], or sodium lauryl sulfate (SLS) [33] have been introduced. They improve the dissolution rate as well as physical and chemical stability of the supersaturated system. Surfactants or emulsifiers enhance the miscibility and thus limit the recrystallization rate of the drug. Moreover, they are able to absorb onto the outer layer of drug particles or form micelles encapsulating drug particles, effectively preventing drug precipitation [34]. On the other hand, many surfactants can absorb moisture, which may result in phase separation during storage, an increase in drug mobility, and conversion from the amorphous or metastable form to the more stable crystalline one. They may change the physical properties of the matrix, increase the water content and cause adverse side effects in vivo. [35] Thus, their use has to be cautious and their amounts well adjusted. Among the strategies that allow for obtaining solid dispersions, solvent methods are often used. In these techniques the drug and the carrier are dissolved in a volatile solvent such as ethanol [36] or Pharmaceutics 2019, 11, 130 3 of 22 methylene chloride–ethanol mixture [37] that is further evaporated. It requires sufficient solubility of the drug as well as the carrier in the solvent. Moreover, the type of used solvent, the temperature, and rate of its evaporation are of key importance due to the fact that the concentration of residual solvent needs to be below the detection limit after drying. One of the strategies utilized to fulfill that requirement is the use of low-toxicity solvent mixtures, e.g., water with ethanol, which decreases the amount of each solvent in dry formulation. However, this strategy sometimes fails due to insufficient dissolution of components at a given ratio [35].

Poloxamers are the nonionic surfactants widely used in pharmaceutical formulations as emulsifiers, wetting agents and solubilizers. They have been introduced into solid dispersions to enhance solubility and dissolution profiles of poorly water-soluble APIs from solid dosage forms [38,39]. Gelatin, a water-soluble and biodegradable protein derived from collagen, has many applications in the food and pharmaceutical industries. In addition to conventional drug formulations, gelatin and gelatin derivatives have been investigated as novel systems designed for the solubility enhancement of poorly soluble drugs [40]. Low viscosity HPMC Type 2910 (E5LV) is widely used pharmaceutical excipient investigated for solubility enhancement of poorly soluble drugs [41].

Ebastine was used as a model drug. Ebastine (EBA) is a H1 receptor inverse agonist used for common cold and different types of allergic diseases (Korfitis C et al., 2017). It is a second generation antihistaminic drug assigned to Biopharmaceutics Classification System (BCS) class II because of poor water solubility and high membrane permeability [42].

In the present work, we study the effect of hydrophilic surfactants such as Gelatin (35 bloom), low viscosity Hypromellose Type 2910 (E5LV) and Poloxamer®188 on dissolution enhancement of the poorly water soluble drug Ebastine (EBA). These excipients were dissolved in suitable amount of water and sprayed on to the drug-excipient mixture using fluid bed processor.

MATERIAL AND METHODS:

Materials

Ebastine was obtained as a generous gift from Micro labs, India. Gelatin was a kind gift from Nitta gelatin, India, Hypromellose (HPMC E5 LV) was gifted by Colorcon, India and Poloxamer kindly donated by BASF Corporation, Mumbai, India. Cellulose, microcrystalline and Crospovidone were gifted by DuPont, Colloidal silicon dioxide was gifted by Evonik, India and Magnesium stearate was a kind gift from Nitika chemicals, India.

Methods

Solubility studies:

Saturation solubility studies were carried out for Ebastine in different aqueous media with 0.1% sodium lauryl sulphate i.e. pH 1.2 Hydrochloric acid buffer, 4.5 Acetate buffer and 6.8 Phosphate buffer. Excess quantity of Ebastine was added to 250 mL of the mentioned media, shaken for 12 hours, samples were withdrawn at 6th and 12th hour time interval and analyzed for quantity of Ebastine dissolved.

Selection of dissolution medium:

The dissolution apparatus selected is Ph.Eur. Type II i.e. Paddle, which is commonly used for dissolution testing of conventional dosage forms. The lower acceptable paddle rotation speed of 50 rpm was selected to keep the agitation rate at lower level during dissolution, to achieve the discriminating power of the dissolution method. The dissolution medium selected was 900 mL of acetate buffer pH 4.5 with 0.1% sls, 50 rpm, Type II (Paddle) using sampling time points of 5, 10, 15, 30 and 60 minutes. This medium was selected based on the saturation solubility studies of pure API. The usual experimental conditions mentioned in the guideline on the investigation of bioequivalence (London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) can be started with 50 rpm paddle speed. The drug release from the Reference medicinal product (Ebast® Tablets, 20 mg) and test product was characterized using the mentioned conditions.

Reference medicinal product:

Ebastine tablets 20 mg (Brand name: Ebast®) manufactured by Micro labs, India was purchased from the market and used for physicochemical evaluation.

In-vitro drug release studies:

In-vitro dissolution studies of test and reference products were carried out in 900 mL of acetate buffer, pH 4.5 with 0.1% sodium lauryl sulfate, 50 RPM, Type II (Paddle) using sampling time points of 5, 10, 15, 30 and 60 minutes. The temperature was maintained at 37 ± 0.5°C. 5mL aliquots were withdrawn at each time point and filtered using a 0.45µ nylon filters and replaced with 5mL of fresh dissolution medium. The filtered samples were analyzed using HPLC UV detector using C18 stainless steel column 100 mm long, 4.6 mm internal diameter filled with octadecylsilyl silica chemically bonded with silica gel particles of 5 µm diameter at wavelength of 255 nm. A solution of mixture of buffer, acetonitrile in the ratio of 30:70 (v/v) was used as the mobile phase. Dissolution tester make was Electrolab and model TDT-08L was used for dissolution testing.

Buffer preparation: Add 6.8 mL of orthophosphoric acid in 1000 mL of water mix well, add 6 mL of diethyl amine and adjust pH-6.0 ± 0.1 by using diethyl amine.

Mobile phase: Mix the above Buffer and Acetonitrile in the ratio of 30:70 and mix well, then filter through 0.45 µm Filter and degass it.

Chromatographic conditions: Hypersil, ODS 150 mm x 4.6 mm, 5 µm, Flow rate 1.5 mL/minute, detection-UV, 255 nm, Injection volume-100 µL, Run time about 9 minutes. Column temperature-40°C and Elution-Isocratic.

Preparation of Ebastine Tablets:

Ebastine with the particle size distribution of d(90) less than 10 µm was selected for the formulation development. Spray granulation process was handled by using a laboratory-scale fluid bed processor (Model: GPCG 1.1, Glatt GmbH, Germany). After the top spray process in GPCG 1.1, granules were blended with other extra granular ingredients in a small double cone blender. The resultant lubricated blend was compressed in to tablets using rotary compression machine. The process parameters of spray granulation were mentioned below.

Table-1: Process parameters for spray granulation

Parameters of spray granulation in GPCG 1.1					
Inlet Temperature (ºC)	Product Temperature (ºC)	Exhaust Temperature (ºC)	Air flow (cfm)	Atomization air pressure (kg/cm^2)	Spray rate (g/min)
60 ± 10	28-42	29-41	30-50	1.0-1.5	5-15

Formulation Design:

Screening of Hydrophilic polymers:

Formulation screening experiments were planned with different polymers i.e. Gelatin, Hyprmellose and Poloxamer at different concentrations alone and in combination. Screening experiments were conducted using polymers alone at the level of 1.5%, 2.25% and 3%. Optimization experiments were conducted using combination of polymers at the same level mentioned. Optimization was planned using design of experiments.

Table-2: Formulation screening trials for polymer selection

	Ingredients	**EB01**	**EB02**	**EB03**	**EB04**	**EB05**	**EB06**	**EB07**	**EB08**	**EB09**
	% of polymer w.r.t core	1.50	2.25	3.00	1.50	2.25	3.00	1.50	2.25	3.00
S. No.	**Stage-A: Polymer solution**	**mg/ tab**	**mg/ tab**	**mg/ tab**	**mg/ tab**	**mg/ tab**	**mg/ tab**	**mg/ tab**	**mg/ tab**	**mg/ tab**
1	Ebastine	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
2	Gelatin (35 Bloom Strength)	3.00	4.50	6.00	-	-	-	-	-	-
3	Hypromellose (5 Cps)	-	-	-	3.00	4.50	6.00	-	-	-
4	Poloxamer (P 188)	-	-	-	-	-	-	3.00	4.50	6.00
5	Water Purified	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Stage B: Spray granulation									
1	Cellulose, microcrystalline PH 101	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00
2	Mannitol SD 200	85.00	83.50	82.00	85.00	83.50	82.00	85.00	83.50	82.00
	Total	**188.0**	**188.0**	**188.0**	**188.0**	**188.0**	**188.0**	**188.0**	**188.0**	**188.0**

Optimization of Hydrophilic polymers:

Optimization experiments were conducted using combination of polymers at the level of 1.5%, 2.25% and 3%. Optimization was planned using design of experiments.

Table-3: Details of optimization trials using Central Composite Design

Factors: Control Variables		**Levels**	
		-1 (low)	**+1 (high)**
Gelatin (35 Bloom Strength)		1.50	3.0
Hypromellose (5 Cps)		1.50	3.0
Poloxamer (P 188)		1.50	3.0
Responses	**Quality Target Product Profile**	**Acceptable Ranges**	
Dissolution at 5 min (%)	Report the results	To be defined	
Dissolution at 10 min (%)	Report the results	To be defined	
Dissolution at 15 min (%)	Report the results	To be defined	
Dissolution at 30 min (%)	Report the results	To be defined	
Dissolution at 60 min (%)	Report the results	To be defined	

Table-4: Details of HME process optimization trials using Central Composite Design

Standard	ID	Run	Block	Type	Factor 1 A: Gelatin (mg)	Factor 2 B: Hypromellose (mg)	Factor 3 C: Poloxamer (mg)
15	0	1	Block 1	Center	4.5	4.5	4.5
1	1	2	Block 1	Factorial	3	3	3
4	4	3	Block 1	Factorial	6	6	3
12	12	4	Block 1	Axial	4.5	6	4.5
2	2	5	Block 1	Factorial	6	3	3
17	0	6	Block 1	Center	4.5	4.5	4.5
16	0	7	Block 1	Center	4.5	4.5	4.5
5	5	8	Block 1	Factorial	3	3	6
13	13	9	Block 1	Axial	4.5	4.5	3
18	0	10	Block 1	Center	4.5	4.5	4.5
14	14	11	Block 1	Axial	4.5	4.5	6
6	6	12	Block 1	Factorial	6	3	6
10	10	13	Block 1	Axial	6	4.5	4.5
3	3	14	Block 1	Factorial	3	6	3
11	11	15	Block 1	Axial	4.5	3	4.5
19	0	16	Block 1	Center	4.5	4.5	4.5
7	7	17	Block 1	Factorial	3	6	6
8	8	18	Block 1	Factorial	6	6	6
9	9	19	Block 1	Axial	3	4.5	4.5

Preparation of Tablets:

Extra granular materials of Crospovidone, Colloidal silicon dioxide and Magnesium stearate were sifted through ASTM # 30 mesh and added to the ASTM # 30 mesh passed spray granulated material. This blend was subjected for mixing for 10 minutes in a double cone blender at 20 rpm. This lubricated blend was subjected for compression using rotary compression machine and round punches. The same procedure was used for all formulation optimization experiments.

Solid-state characterization:

The percentage of crystallinity was measured by using differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD) techniques. Make/model of DSC was Mettler Toledo/823. Make/model for XRD: Bruker AXS/D8 focus or equivalent, X-ray tube: Cu. (K-Alpha 1, λ=1.5406A°), Detector: Lynx Eye, K-beta filter: Nickle, start position: 3°, End position: 40°, Scan type: Locked coupled & continuous, rotation speed: 30 rpm, Time: 0.5 seconds, Step size: 0.016°, Divergence slit: 0.6 mm, receiving slit: 3 mm.

RESULTS AND DISCUSSION:

Screening of Polymers:

Table-5: Composition and tablet parameters of formulation optimization trials

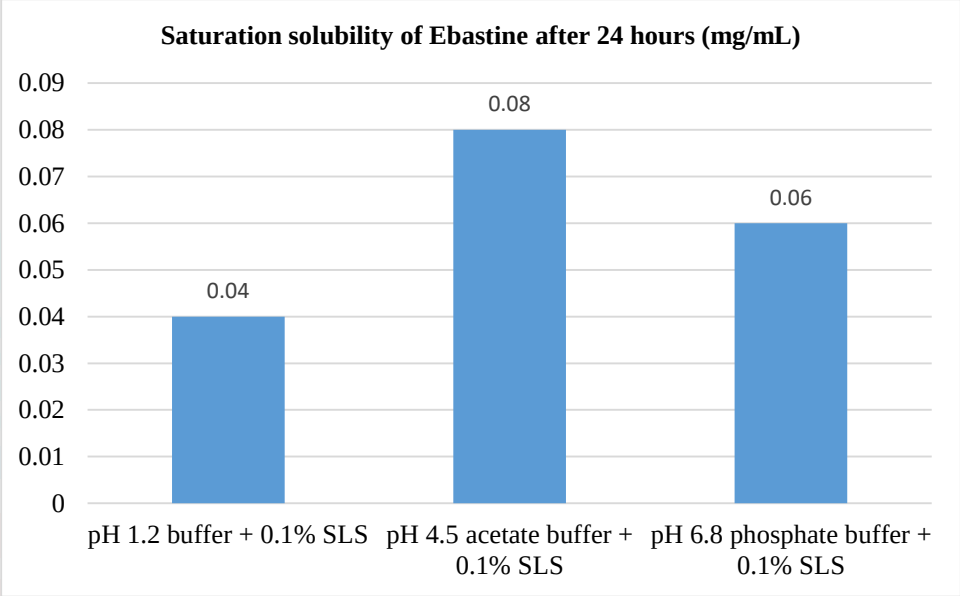
	Ingredients	**EB01**	**EB02**	**EB03**	**EB04**	**EB05**	**EB06**	**EB07**	**EB08**	**EB09**
	% of polymer to core	**1.50**	**2.25**	**3.00**	**1.50**	**2.25**	**3.00**	**1.50**	**2.25**	**3.00**
S. No.	**Stage-A: Polymer solution**	**mg/ tab**	**mg/ tab**	**mg/ tab**	**mg/ tab**	**mg/ tab**	**mg/ tab**	**mg/ tab**	**mg/ tab**	**mg/ tab**
1	Ebastine	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
2	Gelatin (35 Bloom Strength)	3.00	4.50	6.00	-	-	-	-	-	-
3	Hypromellose (5 Cps)	-	-	-	3.00	4.50	6.00	-	-	-
4	Poloxamer (P 188)	-	-	-	-	-	-	3.00	4.50	6.00
5	Water Purified	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Stage B: Spray granulation									
1	Cellulose, microcrystalline PH 101	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00
2	Mannitol SD 200	85.00	83.50	82.00	85.00	83.50	82.00	85.00	83.50	82.00
	Stage C: Lubrication and compression									
1	Crospovidone	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
2	Colloidal silicon dioxide	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
3	Magnesium stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Total weight of the tablet	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**
	Parameters of the tablets									
1	Average weight (mg)	204.3	202.6	201.4	206.3	205.1	202.1	203.7	202.5	202.6
2	Thickness (mm)	2.45-2.60	2.55-2.64	2.40-2.55	2.59-2.62	2.55-2.61	2.54-2.65	2.45-2.64	255-2.66	2.55-2.67
3	Average Hardness (Newton)	70	72	75	68	73	73	74	72	75
4	Disintegration time (min)	2’50”	2’22”	3’55”	2’55”	3’30”	3’55”	3’50”	4’05”	4’50”
5	Friability (%)	0.13	0.10	0.06	0.11	0.05	0.04	0.10	0.04	0.06

Table-6: Saturation solubility data of Ebastine

pH of Media	Quantity dissolved (mg/ml)	Sink Factor*	Suitability for dissolution test
pH 1.2 buffer	0.0	0.0	No
pH 4.5 acetate buffer	0.0	0.0	No
pH 6.8 phosphate buffer	0.0	0.0	No
pH 1.2 buffer + 0.1% SLS	0.04	1.80	No
pH 4.5 acetate buffer + 0.1% SLS	0.08	3.60	Yes
pH 6.8 phosphate buffer + 0.1% SLS	0.06	2.70	No

* sink factor is calculated by solubility (mg/ml) of API (Drug) x 900/20

Figure-1: Saturation solubility of Ebastine

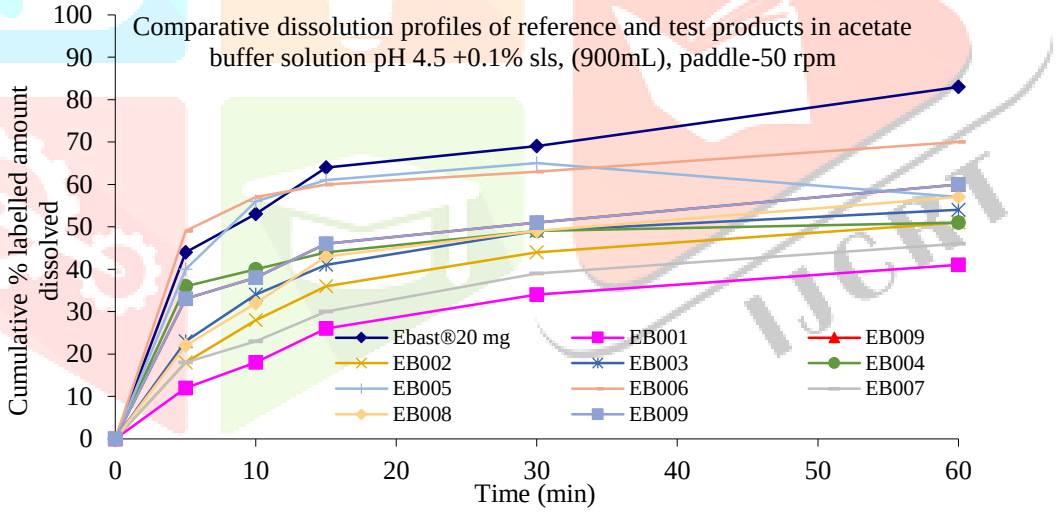


Discussion: Saturation solubility study of Ebastine in different aqueous buffers revealed that no solubility was observed in plain aqueous buffers and inclusion of 0.1 % surfactant increased the solubility. The solubility of Ebastine was higher in acetate buffer pH 4.5 + 0.1% SLS media and achieved the desired sink condition (i.e. more than 3). Based on the above solubility data pH 4.5 acetate buffer + 0.1% SLS media was selected for evaluation of Eabstine 20 mg tablets.

Table – 7: Summary of dissolution profiles of Ebastine tablets in acetate buffer pH 4.5 + 0.1% SLS (900 mL), Paddle – 50rpm.

% Drug release in acetate buffer pH 4.5 + 0.1% SLS (900 mL), Paddle – 50rpm					
Time (Min)	**5**	**10**	**15**	**30**	**60**
Reference, Ebast® 20 mg	44	53	64	69	83
% RSD	12.42	8.98	6.89	5.77	6.23
EB001 (1.5% of Gelatin)	12	18	26	34	41
% RSD	8.98	7.63	7.4	5.64	4.33
EB002 (2.25% of Gelatin)	18	28	36	44	51
% RSD	6.55	5.82	4.32	3.11	2.98
EB003 (3% of Gelatin)	23	34	41	49	54
% RSD	7.44	5.23	4.81	6.77	5.82
EB004 (1.5% of Hypromellose)	36	40	44	49	51
% RSD	5.78	4.21	4.01	3.89	3.23
EB005 (2.25% of Hypromellose)	40	56	61	65	57
% RSD	6.22	5.32	4.55	3.22	3.1
EB006 (3% of Hypromellose)	49	57	60	63	70
% RSD	7.44	6.56	4.09	3.94	2.88
EB007 (1.5% of Poloxamer)	18	23	30	39	46
% RSD	6.66	5.09	4.26	6.27	3.55
EB008 (2.25% of Poloxamer)	22	32	43	49	57
% RSD	5.05	4.11	4.9	3.28	3.91
EB009 (3% of Poloxamer)	33	38	46	51	60
% RSD	12.42	8.98	6.89	5.77	6.23

Figure-2: Comparative of dissolution profiles of Ebastine Tablets and reference product (Ebast®) in acetate buffer solution pH 4.5 (900 mL), Paddle – 50rpm.



Discussion: The drug release from different formulations revealed that the reference formulation exhibited higher release than the test products. The test formulation with 3% hypromellose exhibited higher rate of release than all test formulations in the study. Hydrophilic surfactant alone in the concentration of 1.5 % to 3% were not sufficient to achieve the required dissolution in the selected media. Therefore, evaluation of combination of polymers were considered important to obtain complete drug release using spray granulation technique.

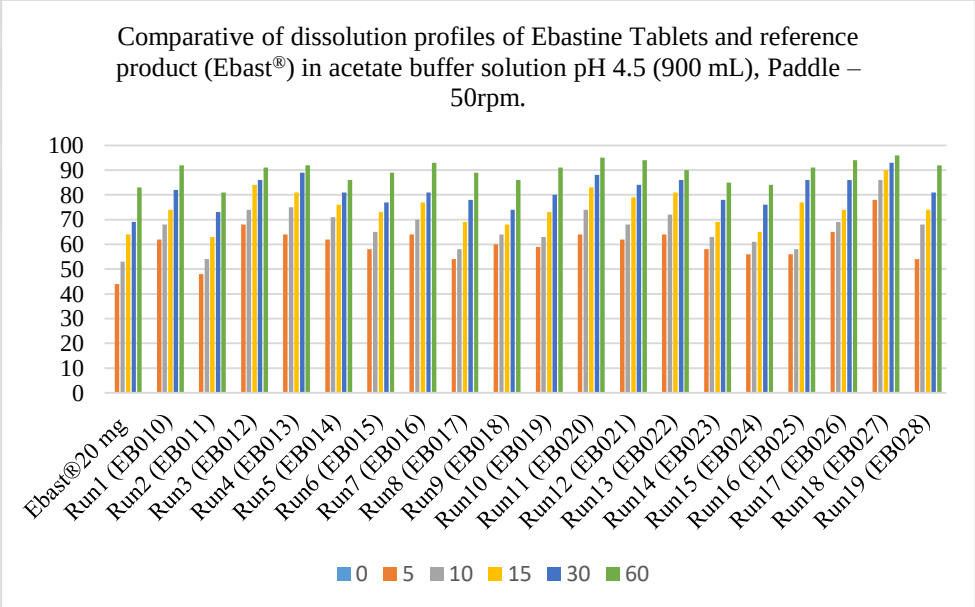
Optimization of Polymers:

Fitting of the data to the model and data analysis

Table-8: Experimental results of the process optimization of hydrophilic surfactants using Central Composite Design

Run	Factor 1 A: Gelatin (mg)	Factor 2 B:Hypromellose (mg)	Factor 3 B: Poloxamer (mg)	% Drug dissolved				
				Y_1: Dissolution at 5 min (%)	Y_2: Dissolution at 10 min (%)	Y_3: Dissolution at 15 min (%)	Y_4: Dissolution at 30 min (%)	Y_5: Dissolution at 60 min (%)
1	4.5	4.5	4.5	62	68	74	82	92
2	3	3	3	48	54	63	73	81
3	6	6	3	68	74	84	86	91
4	4.5	6	4.5	64	75	81	89	92
5	6	3	3	62	71	76	81	86
6	4.5	4.5	4.5	58	65	73	77	89
7	4.5	4.5	4.5	64	70	77	81	93
8	3	3	6	54	58	69	78	89
9	4.5	4.5	3	60	64	68	74	86
10	4.5	4.5	4.5	59	63	73	80	91
11	4.5	4.5	6	64	74	83	88	95
12	6	3	6	62	68	79	84	94
13	6	4.5	4.5	64	72	81	86	90
14	3	6	3	58	63	69	78	85
15	4.5	3	4.5	56	61	65	76	84
16	4.5	4.5	4.5	56	58	77	86	91
17	3	6	6	65	69	74	86	94
18	6	6	6	78	86	90	93	96
19	3	4.5	4.5	54	68	74	81	92
Reference Product (Ebast® Tablets)				44	53	64	69	83

Figure-3: Comparative of dissolution profiles of Ebastine Tablets and reference product (Ebast®) in acetate buffer solution pH 4.5 (900 mL), Paddle – 50rpm.



The drug release at 5 minutes and 60 minutes were subjected for statistical evaluation.

Effect of formulation variables on dissolution of Ebastine at 5 minutes:

The release of Ebastine at 5 minutes time point for the studied variables ranges from 48-78%. The % drug release is low when the concentrations of Gelatin, Hypromellose and Poloxamer are low (3 mg per tablet per each ingredient); whereas the percentage of the drug release is high with higher concentration of these excipients (6 mg per tablet per each ingredient). The Analysis of Variance (ANOVA) results for 5 minutes time point are presented below. The linear relationship existing between the concentration of excipients and drug release.

Table- 09: ANOVA for response surface linear model

Source	Sum of Squares	Degrees of freedom	Mean Square	F - Value	p-value Prob > F	
Model	635.50	3	211.83	32.75	< 0.0001	Significant
A- Gelatin	302.50	1	302.50	46.77	< 0.0001	
B-Hypromellose	260.10	1	260.10	40.21	< 0.0001	
C-Poloxamer	72.90	1	72.90	11.27	0.0043	
Residual	97.03	15	6.47			
Lack of Fit	56.23	11	5.11	0.50	0.8352	Not significant
Pure Error	40.80	4	10.20			
Cor Total	732.53	18				

The Model F-value of 32.75 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case all excipients in the study i.e. Gelatin, Hypromellose and Poloxamer are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. The "Lack of Fit F-value" of 0.50 implies the Lack of Fit is not significant relative to the pure error. There is 83.52% chance that a "Lack of Fit F-value" this large could occur due noise. Non-significant lack of fit is good.

Table- 10: Values of different statistical terms

Parameter	Value
Standard Deviation	2.54
Mean	60.84
C.V. %	4.18
PRESS	158.03
R-Squared	0.8675
Adjusted R-Squared	0.8411
Predicted R-Squared	0.7843
Adequate Precision	22.794

The "Predicted R-Squared" of 0.7843 is in reasonable agreement with the Adjusted R-Squared of 0.8411. Adequate Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. The obtained Adequate Precision value of 22.794 indicates an adequate signal. Therefore this model can be used to navigate the design space.

Table- 11: Values of different statistical terms

Factor	Coefficient estimate	Degrees of freedom	Standard error	95% Confidence Interval Low	95% Confidence Interval High	VIF
Intercept	60.84	1	0.58	59.60	62.09	
A-Gelatin	5.50	1	0.80	3.79	7.21	1.00
B-Hypromellose	5.10	1	0.80	3.39	6.81	1.00
C-Poloxamer 188	2.70	1	0.80	0.99	4.41	1.00

Final Equation in Terms of Actual Factors:

Release at 5 minutes = +20.94 +3.66*Gelatin+3.40*Hypromellose+1.80*Poloxamer

From the equation it can be concluded that Gelatin, Hypromellose and Poloxamer have positive impact on the drug release at 5 minutes.

Figure-4: Different statistical plots for effect of formulation variables on dissolution of Ebastine at 5 minutes

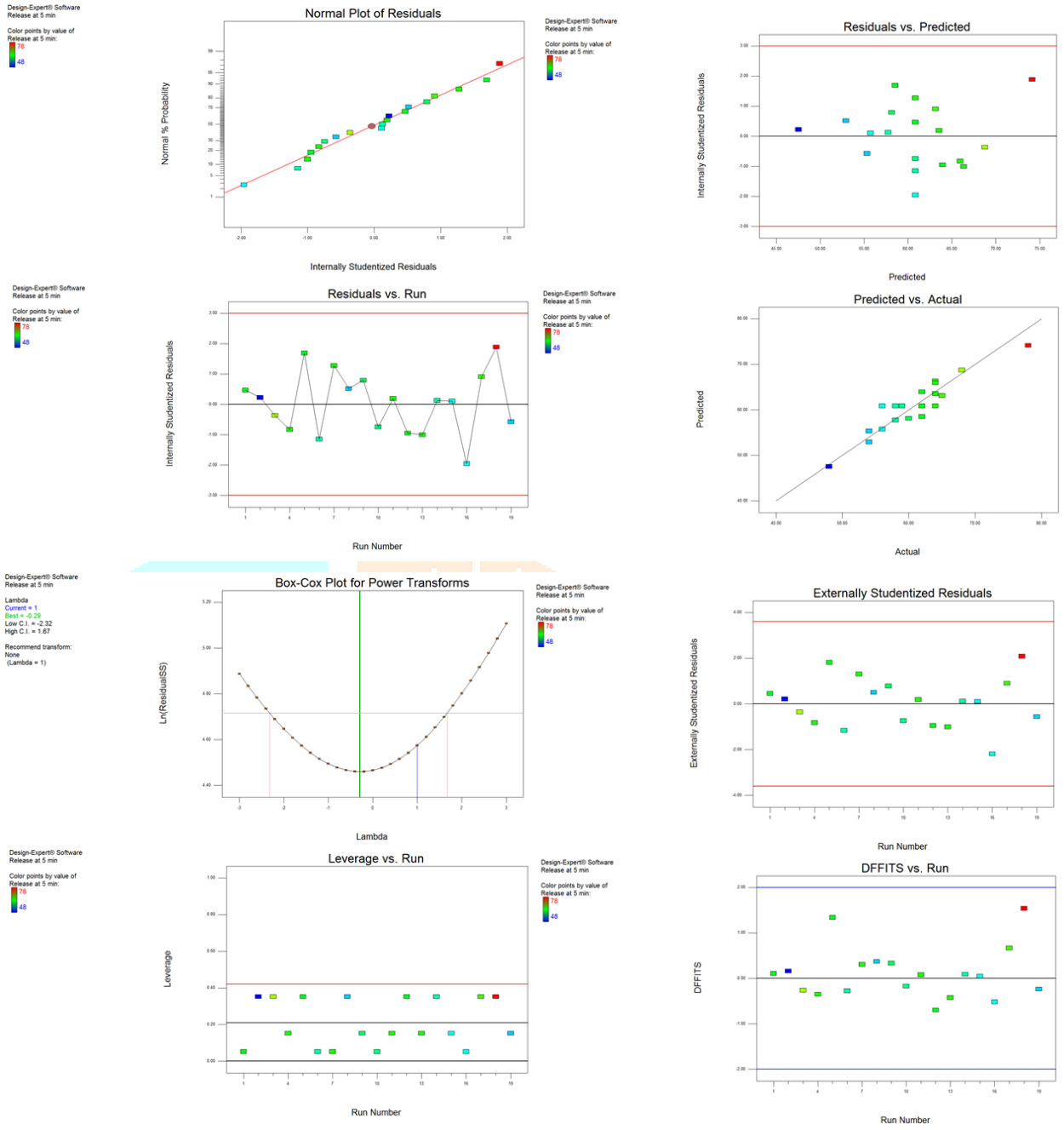


Figure-5: Cook's distance and 3D plots for effect of formulation variables on dissolution of Ebastine at 5 minutes

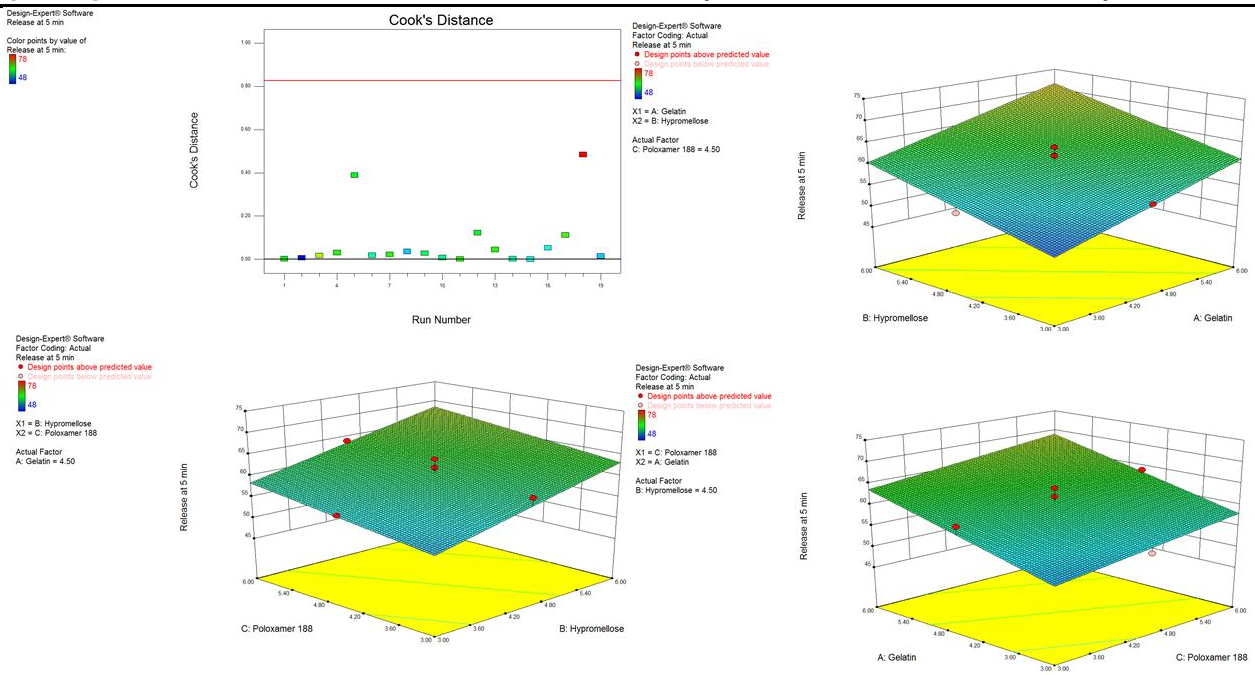

Design-Expert® Software
Release at 5 min
Color points by value of
Release at 5 min:
78
48
Cook's Distance
Cook's Distance
Run Number
Design-Expert® Software
Factor Coding: Actual
Release at 5 min
Design points above predicted value
Design points below predicted value
78
48
X1 = A: Gelatin
X2 = B: Hypromellose
Actual Factor
C: Poloxamer 188 = 4.50
Release at 5 min
B: Hypromellose
A: Gelatin
Design-Expert® Software
Factor Coding: Actual
Release at 5 min
Design points above predicted value
Design points below predicted value
78
48
X1 = B: Hypromellose
X2 = C: Poloxamer 188
Actual Factor
A: Gelatin = 4.50
Release at 5 min
C: Poloxamer 188
B: Hypromellose
Design-Expert® Software
Factor Coding: Actual
Release at 5 min
Design points above predicted value
Design points below predicted value
78
48
X1 = C: Poloxamer 188
X2 = A: Gelatin
Actual Factor
B: Hypromellose = 4.50
Release at 5 min
A: Gelatin
C: Poloxamer 188

Table- 12: Diagnostics case statistics for dissolution at 5 minutes

Standard Order	Actual Value	Predicted Value	Residual	Leverage	Internally Studenized Residual	Externally Studenized Residual	Influence on Fitted DFFITS	Cook's Distance	Run Order
1	48	47.54	0.46	0.353	0.224	0.217	0.16	0.007	2
2	62	58.54	3.46	0.353	1.69	1.814	1.339	0.389	5
3	58	57.74	0.26	0.353	0.126	0.122	0.09	0.002	14
4	68	68.74	-0.74	0.353	-0.363	-0.352	-0.26	0.018	3
5	54	52.94	1.06	0.353	0.517	0.504	0.372	0.036	8
6	62	63.94	-1.94	0.353	-0.949	-0.946	-0.698	0.123	12
7	65	63.14	1.86	0.353	0.908	0.902	0.666	0.112	17
8	78	74.14	3.86	0.353	1.885	2.085	1.539	0.484	18
9	54	55.34	-1.34	0.153	-0.573	-0.56	-0.238	0.015	19
10	64	66.34	-2.34	0.153	-1	-1	-0.425	0.045	13
11	56	55.74	0.26	0.153	0.11	0.106	0.045	0.001	15
12	64	65.94	-1.94	0.153	-0.83	-0.82	-0.348	0.031	4
13	60	58.14	1.86	0.153	0.794	0.783	0.332	0.028	9
14	64	63.54	0.46	0.153	0.196	0.189	0.08	0.002	11
15	62	60.84	1.16	0.053	0.468	0.455	0.107	0.003	1
16	64	60.84	3.16	0.053	1.276	1.305	0.308	0.023	7
17	58	60.84	-2.84	0.053	-1.148	-1.161	-0.274	0.018	6
18	59	60.84	-1.84	0.053	-0.744	-0.733	-0.173	0.008	10
19	56	60.84	-4.84	0.053	-1.956	-2.189	-0.516	0.053	16

Effect of formulation variables on dissolution of Ebastine at 60 minutes:

The release of Ebastine at 60 minutes time point for the studied variables ranges from 81-96%. The % drug release is low when the concentrations of Gelatin, Hypromellose and Poloxamer are low (3 mg per tablet per each ingredient); whereas the drug release is high with higher concentration of these excipients (6 mg per tablet per each ingredient). The Analysis of Variance (ANOVA) results for 60 minutes time point are presented below. The linear relationship existing between the concentration of excipients and drug release.

Table- 13: ANOVA for response surface linear model

Source	Sum of Squares	Degrees of freedom	Mean Square	F - Value	p-value Prob > F	
Model	235.30	3	78.43	20.41	< 0.0001	Significant
A- Gelatin	25.60	1	25.60	6.66	0.0209	
B-Hypromellose	57.60	1	57.60	14.99	0.0015	
C-Poloxamer	152.10	1	152.10	39.58	< 0.0001	
Residual	57.65	15	3.84			
Lack of Fit	48.85	11	4.44	2.02	0.2603	Not significant
Pure Error	8.80	4	2.20			
Cor Total	292.95	18				

The Model F-value of 20.41 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case all excipients in the study i.e. Gelatin, Hypromellose and Poloxamer are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. The "Lack of Fit F-value" of 2.02 implies the Lack of Fit is not significant relative to the pure error. There is a 26.03 % chance that a "Lack of Fit F-value" this large could occur due noise. Non-significant lack of fit is good.

Table- 14: Values of different statistical terms

Parameter	Value
Standard Deviation	1.96
Mean	90.05
C.V. %	2.18
PRESS	88.20
R-Squared	0.8032
Adjusted R-Squared	0.7639
Predicted R-Squared	0.6989
Adequate Precision	17.565

The "Predicted R-Squared" of 0.6989 is in reasonable agreement with the Adjusted R-Squared of 0.7639. Adequate Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. The obtained Adequate Precision value of 17.565 indicates an adequate signal. Therefore this model can be used to navigate the design space.

Table- 15: Values of different statistical terms

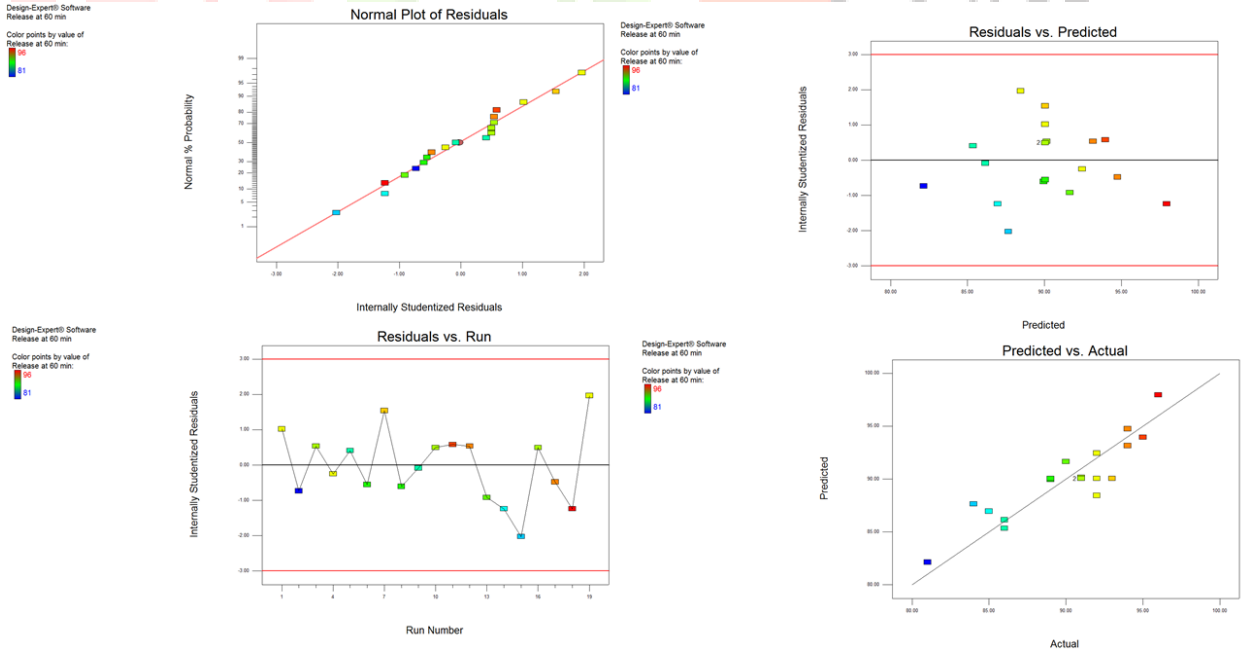
Factor	Coefficient estimate	Degrees of freedom	Standard error	95% Confidence Interval Low	95% Confidence Interval High	VIF
Intercept	90.05	1	0.45	89.09	91.01	
A-Gelatin	1.60	1	0.62	0.28	2.92	1.00
B-Hypromellose	2.40	1	0.62	1.08	3.72	1.00
C-Poloxamer 188	3.90	1	0.62	2.58	5.22	1.00

Final Equation in Terms of Actual Factors:

Release at 60 minutes = +66.35 +1.06*Gelatin+1.60*Hypromellose+2.60*Poloxamer

From the equation it can be concluded that Gelatin, Hypromellose and Poloxamer have positive impact on the drug release at 60 minutes.

Figure-6: Different statistical plots for effect of formulation variables on dissolution of Ebastine at 60 minutes



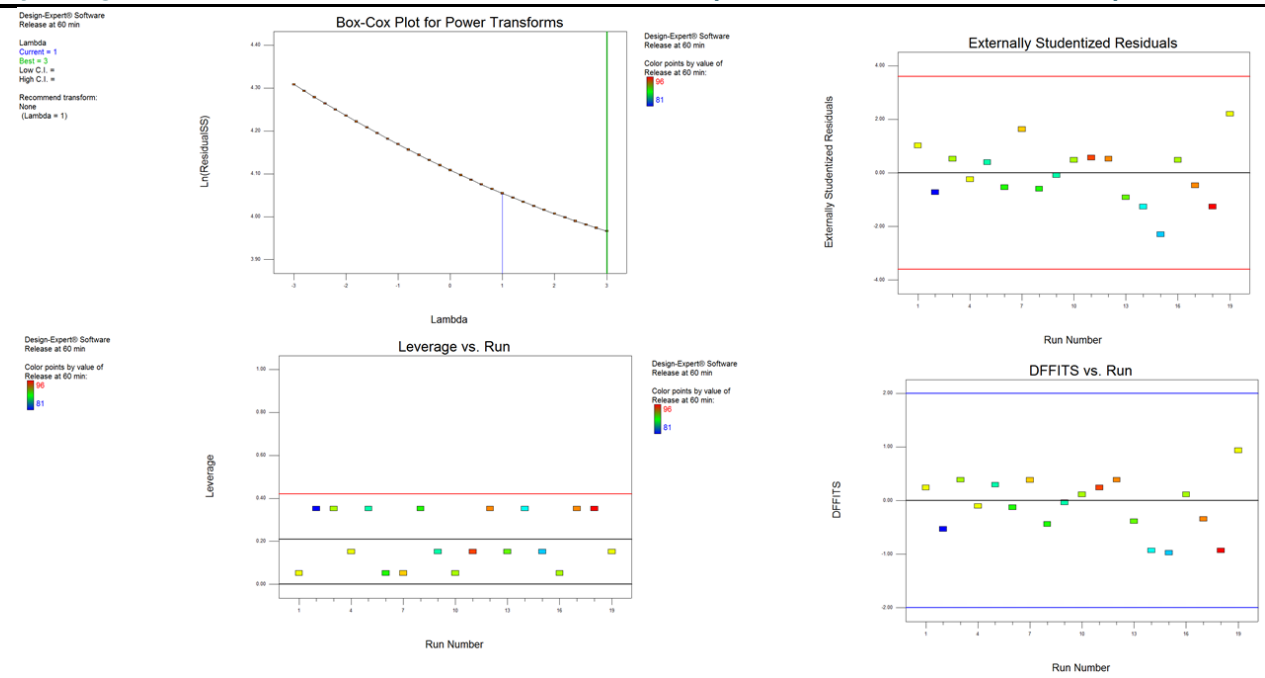


Figure-7: Cook's distance and 3D plots for effect of formulation variables on dissolution of Ebastine at 60 minutes

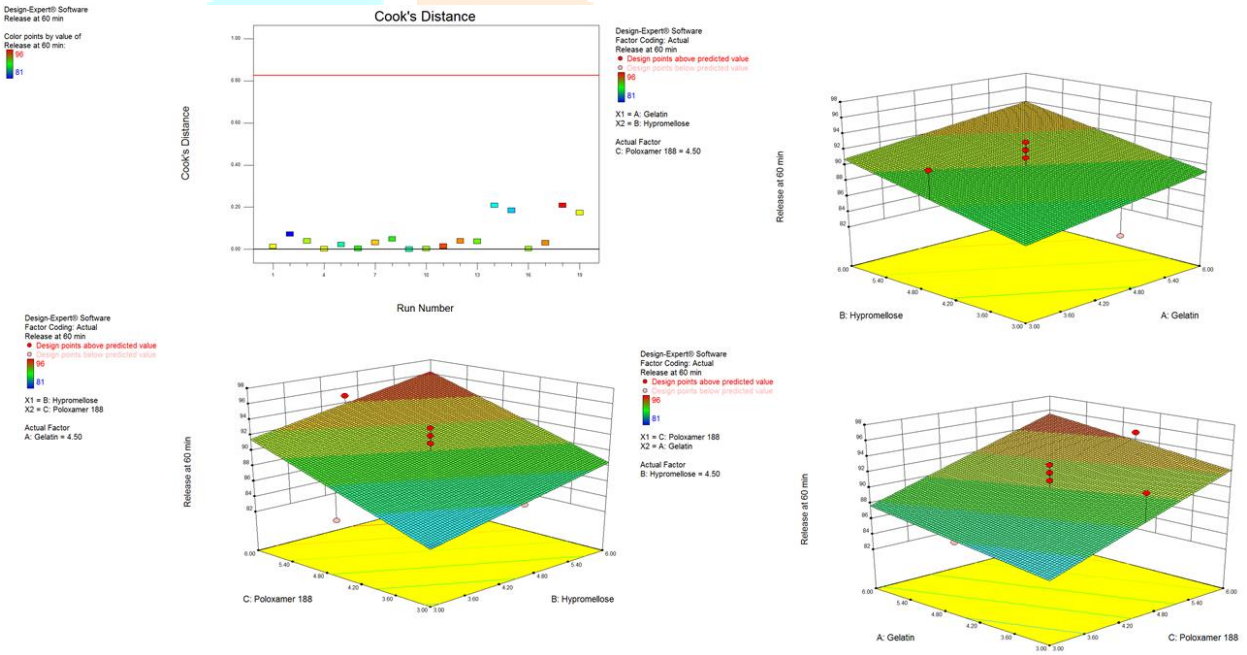


Table- 16: Diagnostics case statistics for dissolution at 60 minutes

Standard Order	Actual Value	Predicted Value	Residual	Leverage	Internally Studenized Residual	Externally Studenized Residual	Influence on Fitted DFFITS	Cook's Distance	Run Order
1	81.00	82.15	-1.15	0.353	-0.731	-0.719	-0.531	0.073	2
2	86.00	85.35	0.65	0.353	0.410	0.399	0.294	0.023	5
3	85.00	86.95	-1.95	0.353	-1.238	-1.262	-0.932	0.209	14
4	91.00	90.15	0.85	0.353	0.537	0.524	0.387	0.039	3
5	89.00	89.95	-0.95	0.353	-0.604	-0.591	-0.436	0.050	8
6	94.00	93.15	0.85	0.353	0.537	0.524	0.387	0.039	12
7	94.00	94.75	-0.75	0.353	-0.477	-0.465	-0.343	0.031	17
8	96.00	97.95	-1.95	0.353	-1.238	-1.262	-0.932	0.209	18
9	92.00	88.45	3.55	0.153	1.966	2.204	0.935	0.174	19
10	90.00	91.65	-1.65	0.153	-0.916	-0.911	-0.386	0.038	13
11	84.00	87.65	-3.65	0.153	-2.024	-2.294	-0.973	0.184	15

12	92.00	92.45	-0.45	0.153	-0.251	-0.243	-0.103	0.003	4
13	86.00	86.15	-0.15	0.153	-0.085	-0.082	-0.035	0.000	9
14	95.00	93.95	1.05	0.153	0.580	0.567	0.241	0.015	11
15	92.00	90.05	1.95	0.053	1.021	1.022	0.241	0.014	1
16	93.00	90.05	2.95	0.053	1.545	1.627	0.384	0.033	7
17	89.00	90.05	-1.05	0.053	-0.552	-0.538	-0.127	0.004	6
18	91.00	90.05	0.95	0.053	0.496	0.484	0.114	0.003	10
19	91.00	90.05	0.95	0.053	0.496	0.484	0.114	0.003	16

The design was navigated to get the target parameters to get a desired dissolution profile.

Figure-8: Overlay plot of formulation variables on responses

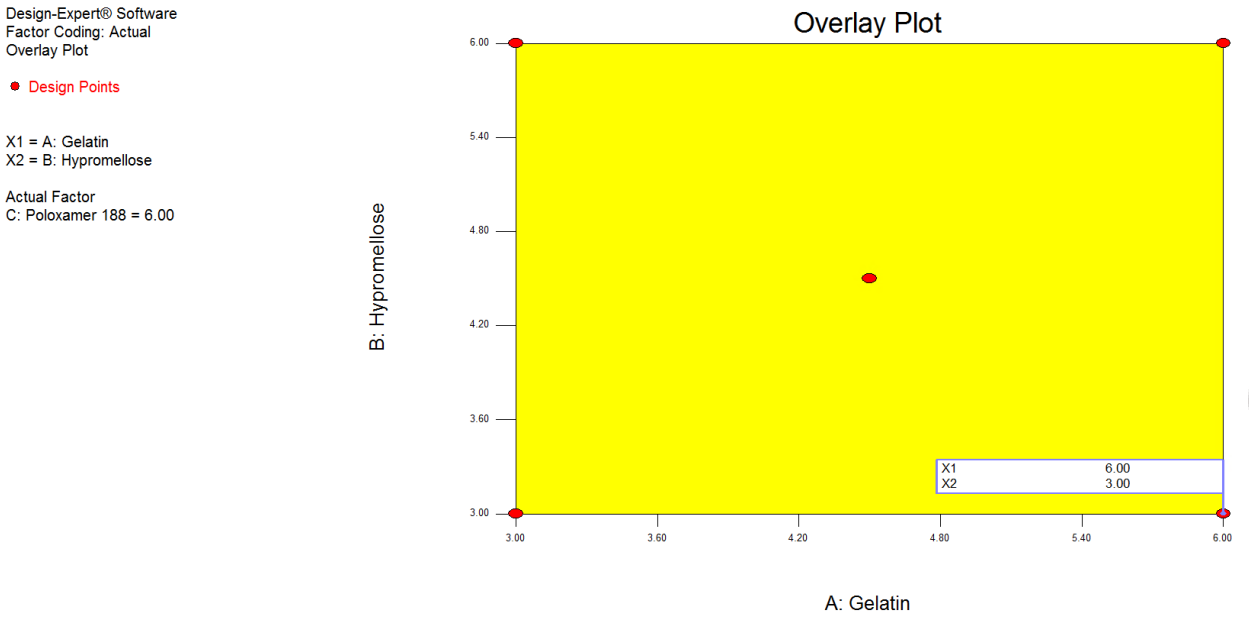


Table- 17: Summary of solutions provided for the optimization

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A:Gelatin	is in range	3	6	1	1	3
B:Hypromellose	is in range	3	6	1	1	3
C:Poloxamer 188	is in range	3	6	1	1	3

No.	Gelatin	Hypromellose	Poloxamer	Desirability	No.	Gelatin	Hypromellose	Poloxamer	Desirability
1	4.50	4.50	6.00	1.000	24	4.08	5.62	5.15	1.000
2	6.00	6.00	3.00	1.000	25	3.29	4.63	5.86	1.000
3	6.00	3.00	3.00	1.000	26	5.75	5.16	3.95	1.000
4	4.50	4.50	4.50	1.000	27	4.13	4.48	5.83	1.000
5	4.50	3.00	4.50	1.000	28	4.34	4.55	4.49	1.000
6	3.00	6.00	3.00	1.000	29	4.78	4.20	3.46	1.000
7	6.00	4.50	4.50	1.000	30	4.64	3.52	3.59	1.000
8	3.00	3.00	6.00	1.000	31	3.59	5.67	5.03	1.000
9	6.00	6.00	6.00	1.000	32	3.84	5.83	5.49	1.000
10	3.00	3.00	3.00	1.000	33	3.98	4.72	3.29	1.000
11	6.00	3.00	6.00	1.000	34	3.58	3.98	4.94	1.000
12	3.00	6.00	6.00	1.000	35	3.87	5.88	5.97	1.000
13	4.50	4.50	3.00	1.000	36	5.93	3.73	5.88	1.000
14	3.00	4.50	4.50	1.000	37	4.21	5.79	3.53	1.000
15	4.50	6.00	4.50	1.000	38	4.23	5.29	5.97	1.000

16	4.61	4.18	4.09	1.000	39	5.62	5.78	3.06	1.000
17	4.25	4.32	3.17	1.000	40	3.17	3.53	5.21	1.000
18	3.93	5.72	3.11	1.000	41	5.66	4.15	3.20	1.000
19	5.03	5.03	4.54	1.000	42	5.61	3.93	5.43	1.000
20	5.74	3.21	5.26	1.000	43	3.39	5.34	3.50	1.000
21	5.51	5.42	3.14	1.000	44	3.21	5.60	5.07	1.000
22	4.58	4.61	4.31	1.000	45	3.21	4.82	3.52	1.000
23	4.20	4.37	3.30	1.000	-	-	-	-	-

From the solutions, No. 9 and 11 trials are manufactured using same set of experimental conditions and subjected to statistical evaluation.

Table- 18: Parameters of selected solution (B. No. EB032)

Name of the dependent factor	**B. No. EB032**		
A: Gelatin	6.00		
B: Hypromellose	3.00		
B: Poloxamer	6.00		
Response variable	**Observed value**	**Predicted value**	**Prediction Error**
Dissolution of Ebastine at 5 minutes (%)	61	63.94	-4.81
Dissolution of Ebastine at 15 minutes (%)	83	80.26	3.30
Dissolution of Ebastine at 60 minutes (%)	95	93.15	1.94

Response	**Prediction**	**Std Dev**	**SE Mean**	**95% CI low**	**95% CI high**
Release at 5 min	63.94	2.54	1.51	60.72	67.16
Release at 10 min	70.72	4.11	2.44	65.51	75.93
Release at 15 min	80.26	3.01	1.78	76.46	84.07
Release at 30 min	85.15	2.66	1.58	81.78	88.52
Release at 60 min	93.15	1.96	1.16	90.67	95.63

Response	**SE Pred**	**95% PI low**	**95% PI high**	**95% TI low**	**95% TI high**
Release at 5 min	2.96	57.64	70.25	51.88	76.01
Release at 10 min	4.79	60.52	80.92	51.21	90.24
Release at 15 min	3.50	72.81	87.71	66.01	94.52
Release at 30 min	3.10	78.55	91.76	72.52	97.79
Release at 60 min	2.28	88.29	98.01	83.85	102.45

Table- 19: Parameters of selected solution (B. No. EB033)

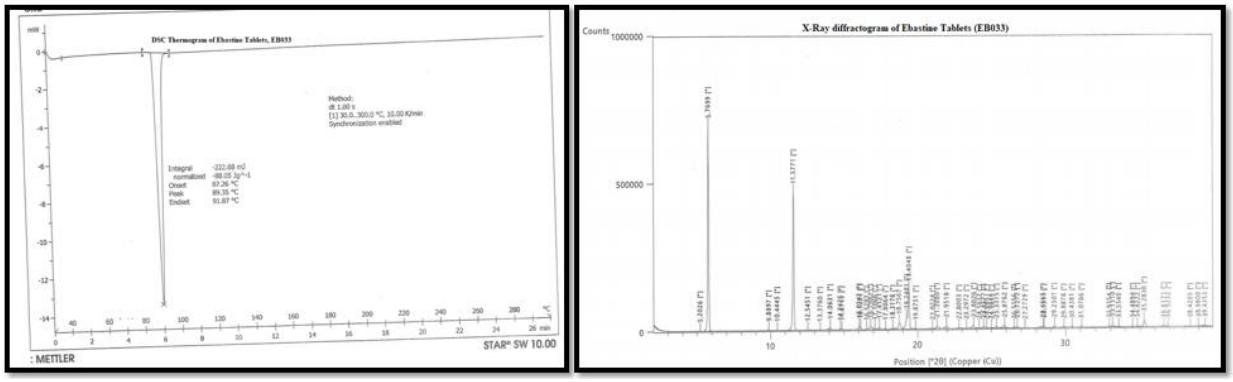
Name of the dependent factor	**B. No. EB033**		
A: Gelatin	6.00		
B: Hyprmellose	6.00		
B: Poloxamer	6.00		
Response variable	**Observed value**	**Predicted value**	**Prediction Error**
Dissolution of Ebastine at 5 minutes (%)	76	74.14	2.45
Dissolution of Ebastine at 15 minutes (%)	91	89.47	1.68
Dissolution of Ebastine at 60 minutes (%)	97	97.95	-0.979

Response	**Prediction**	**Std Dev**	**SE Mean**	**95% CI low**	**95% CI high**
Release at 5 min	63.94	74.1421	2.54331	1.51029	70.923
Release at 10 min	70.72	81.7211	4.11446	2.44328	76.5133
Release at 15 min	80.26	89.4632	3.00538	1.78468	85.6592
Release at 30 min	85.15	93.1526	2.66392	1.58191	89.7809
Release at 60 min	93.15	97.9526	1.9604	1.16414	95.4713

Response	**SE Pred**	**95% PI low**	**95% PI high**	**95% TI low**	**95% TI high**
Release at 5 min	2.95794	67.8374	80.4468	62.0785	86.2057
Release at 10 min	4.78523	71.5216	91.9205	62.2051	101.237
Release at 15 min	3.49533	82.013	96.9133	75.2079	103.718
Release at 30 min	3.09822	86.5489	99.7563	80.5169	105.788

Release at 60 min	2.27999	93.0929	102.812	88.6539	107.251

Figure-9: DSC and x-Ray diffractograms for the selected solution



Discussion: The selected hydrophilic surfactant combinations in the DoE were appropriate to provide desired responses i.e. dissolution at different time points. The higher concentration of polymers resulted higher drug release and linear relationship was established between the variables and responses. The combination of polymers exhibited the positive effect on the drug release and optimum concentration of the hydrophilic surfactant can be selected based on the desired dissolution profiles. Therefore, this DoE outcome can be considered for selecting appropriate level of studied polymers and design space can be established. Furthermore, the dissolution enhancement is believed to be due to maintenance of micro-environment concentration around the drug particles. DSC thermogram and XRD diffractograms of formulation revealed that the API remains in the crystalline form and complies to initial.

CONCLUSIONS:

In the present study, it was found that the formulation screening with one factor at a time approach produced reliable information on the selection of suitable polymers. The optimization data revealed that the combination of polymers produced desirable drug dissolutions and exhibited linear relationship with the concentration of polymers studied. Hydrophilic surfactants at the level of 3 % of each produced enhanced rate and extent of dissolution significantly when compared to the reference product. The DSC thermogram and X-Ray diffractogram of the final formulation revealed that the API is present in the crystalline state.

In conclusion, the prototype formulation of Ebastine with combination of hydrophilic surfactants produced desirable drug release using conventional spray granulation technique. Using appropriate hydrophilic surfactants, the conventional manufacturing methods may provide a cost effective, quicker, readily scalable alternative for formulating poorly water-soluble drugs.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

REFERENCES:

1. References 1. Williams, H.D.; Trevaskis, N.L.; Charman, S.A.; Shanker, R.M.; Charman, W.N.; Pouton, C.W.; Porter, C.J.H. Strategies to Address Low Drug Solubility in Discovery and Development. Pharmacol. Rev. 2013, 65, 315–499. [CrossRef] [PubMed]
2. Di, L.; Kerns, E.H.; Carter, G.T. Drug-Like Property Concepts in Pharmaceutical Design. Curr. Pharm. Des. 2009, 15, 2184–2194. [CrossRef] [PubMed]
3. Kawabata, Y.; Wada, K.; Nakatani, M.; Yamada, S.; Onoue, S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. Int. J. Pharm. 2011, 420, 1–10. [CrossRef] [PubMed]
4. Krupa, A.; Descamps, M.; Willart, J.F.; Jachowicz, R.; Danède, F. High energy ball milling and supercritical carbon dioxide impregnation as co-processing methods to improve dissolution of tadalafil. Eur. J. Pharm. Sci. 2016, 95, 130–137. [CrossRef] [PubMed]
5. Rios-Doria, J.; Carie, A.; Costich, T.; Burke, B.; Skaff, H.; Panicucci, R.; Sill, K. A Versatile Polymer Micelle Drug Delivery System for Encapsulation and In Vivo Stabilization of Hydrophobic Anticancer Drugs. J. Drug Deliv. 2012, 951741. [CrossRef]
6. Bader, R.A.; Silvers, A.L.; Zhang, N. Polysialic Acid-Based Micelles for Encapsulation of Hydrophobic Drugs. Biomacromolecules 2011, 12, 314–320. [CrossRef]
7. Luo, R.; Venkatraman, S.S.; Neu, B. Layer-by-Layer Polyelectrolyte–Polyester Hybrid Microcapsules for Encapsulation and Delivery of Hydrophobic Drugs. Biomacromolecules 2013, 14, 2262–2271. [CrossRef]
8. Szafraniec, J.; Błazejczyk, A.; Ku´s, E.; Janik, M.; Zaj ˛ac, G.; Wietrzyk, J.; Chłopicki, S.; Zapotoczny, S. Robust ´ oil-core nanocapsules with hyaluronate-based shells as promising nanovehicles for lipophilic compounds. Nanoscale 2017, 47. [CrossRef]
9. Han, Y.; Shchukin, D.; Yang, J.; Simon, C.R.; Fuchs, H.; Möhwald, H. Biocompatible Protein Nanocontainers for Controlled Drugs Release. ACS Nano 2010, 4, 2838–2844. [CrossRef]
10. Juère, E.; Florek, J.; Bouchoucha, M.; Jambhrunkar, S.; Wong, K.Y.; Popat, A.; Kleitz, F. In Vitro Dissolution, Cellular Membrane Permeability, and Anti-Inflammatory Response of Resveratrol-Encapsulated Mesoporous Silica Nanoparticles. Mol. Pharm. 2017, 14, 4431–4441. [CrossRef]
11. Meka, A.K.; Jenkins, L.J.; Dàvalos-Salas, M.; Pujara, N.; Wong, K.Y.; Kumeria, T.; Mariadason, J.M.; Popat, A. Enhanced Solubility, Permeability and Anticancer Activity of Vorinostat Using Tailored Mesoporous Silica Nanoparticles. Pharmaceutics 2018, 10, 283. [CrossRef] [PubMed]
12. Mazumder, S.; Dewangan, A.K.; Pavurala, N. Enhanced dissolution of poorly soluble antiviral drugs from nanoparticles of cellulose acetate based solid dispersion matrices. Asian J. Pharm. Sci. 2017, 12, 532–541. [CrossRef]
13. Kim, M.-S.; Baek, I. Fabrication and evaluation of valsartan-polymer-surfactant composite nanoparticles by using the supercritical antisolvent process. Int. J. Nanomed. 2014, 9, 5167–5176. [CrossRef] [PubMed]
14. Tran, T.H.; Poudel, B.K.; Marasini, N.; Chi, S.-C.; Choi, H.-G.; Yong, C.S.; Kim, J.O. Preparation and evaluation of raloxifene-loaded solid dispersion nanoparticle by spray-drying technique without an organic solvent. Int. J. Pharm. 2013, 443, 50–57. [CrossRef] [PubMed]
15. Van den Moter, G. The use of amorphous solid dispersions: A formulation strategy to overcome poor solubility and dissolution rate. Drug Discov. Today 2012, 9, e79–e85. [CrossRef] [PubMed]
16. Le-Ngoc Vo, C.; Park, C.; Lee, B.-J. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. Eur. J. Pharm. Biopharm. 2013, 85, 799–813. [CrossRef]
17. Maniruzzaman, M.; Pang, J.; Morgan, D.J.; Douroumis, D. Molecular modeling as a predictive tool for the development of solid dispersions. Mol. Pharm. 2015, 12, 1040–1049. [CrossRef] [PubMed] Pharmaceutics 2019, 11, 130 20 of 22
18. Vasconcelos, T.; Marques, S.; das Neves, J.; Sarmento, B. Amorphous solid dispersions: Rational selection of a manufacturing process. Adv. Drug Deliv. Rev. 2016, 100, 85–101. [CrossRef] [PubMed]
19. Sekiguchi, K.; Obi, N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull. 1961, 9, 866–872. [CrossRef]

20. Sekiguchi, K.; Obi, N.; Ueda, Y. Studies on absorption of eutectic mixture. II. Absorption of fused conglomerates of chloramphenicol and urea in rabbits. Chem. Pharm. Bull. 1961, 12, 134–144. [CrossRef]
21. Goldberg, A.H.; Gibaldi, M.; Kanig, J.L. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. I. Theoretical considerations and discussion of the literature. J. Pharm. Sci. 1965, 54, 1145–1148. [CrossRef] [PubMed]
22. Chiou, W.L.; Riegelman, S. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci. 1971, 60, 1281–1302. [CrossRef] [PubMed]
23. Sharma, A.; Jain, C.P. Preparation and characterization of solid dispersions of carvedilol with PVP K30. Res. Pharm. Sci. 2010, 5, 49–56. [CrossRef] [PubMed]
24. Gupta, P.; Kakumanu, V.K.; Bansal, A.K. Stability and solubility of celecoxib-PVP amorphous dispersions: A molecular perspective. Pharm. Res. 2004, 21, 1762–1769. [CrossRef] [PubMed]
25. Lim, H.-T.; Balakrishnan, P.; Oh, D.H.; Joe, K.H.; Kim, Y.R.; Hwang, D.H.; Lee, Y.-B.; Yong, C.S.; Choi, H.-G. Development of novel sibutramine base-loaded solid dispersion with gelatin and HPMC: Physicochemical characterization and pharmacokinetics in beagle dogs. Int. J. Pharm. 2010, 397, 225–230. [CrossRef]
26. Alonzo, D.E.; Gao, Y.; Zhou, D.; Mo, H.; Zhang, G.G.Z.; Taylor, L.S. Dissolution and precipitation behavior of amorphous solid dispersions. J. Pharm. Sci. 2011, 100, 3316–3331. [CrossRef] [PubMed]
27. Frank, K.J.; Rosenblatt, K.M.; Westedt, U.; Holig, P.; Rosenberg, J.; Magerlein, M.; Fricker, G.; Brandl, M. Amorphous solid dispersion enhances permeation of poorly soluble ABT-102: True supersaturation vs. apparent solubility enhancement. Int. J. Pharm. 2012, 437, 288–293. [CrossRef] [PubMed]
28. Sun, D.D.; Lee, P.I. Evolution of supersaturation of amorphous pharmaceuticals: The effect of rate of supersaturation generation. Mol. Pharm. 2013, 10, 4330–4346. [CrossRef]
29. Chauhan, H.; Hui-Gu, C.; Atef, E. Correlating the behavior of polymers in solution as precipitation inhibitor to its amorphous stabilization ability in solid dispersions. J. Pharm. Sci. 2013, 102, 1924–1935. [CrossRef]
30. Passerini, N.; Albertini, B.; González-Rodríguez, M.L.; Cavallari, C.; Rodriguez, L. Preparation and characterisation of ibuprofen–poloxamer 188 granules obtained by melt granulation. Eur. J. Pharm. Sci. 2002, 15, 71–78. [CrossRef]
31. Eloy, J.O.; Marchetti, J.M. Solid dispersions containing ursolic acid in Poloxamer 407 and PEG 6000: A comparative study of fusion and solvent methods. Powder Technol. 2014, 253, 98–106. [CrossRef]
32. Joshi, H.N.; Tejwani, R.W.; Davidovich, M.; Sahasrabudhe, V.P.; Jemal, M.; Bathala, M.S.; Varia, S.A.; Serajuddin, A. Bioavailability enhancement of a poorly water-soluble drug by solid dispersion in polyethylene glycol–polysorbate 80 mixture. Int. J. Pharm. 2004, 269, 251–258. [CrossRef] [PubMed]
33. Moes, J.; Koolen, S.; Huitema, A.; Schellens, J.; Beijnen, J.; Nuijen, B. Pharmaceutical development and preliminary clinical testing of an oral solid dispersion formulation of docetaxel (ModraDoc001). Int. J. Pharm. 2011, 420, 244–250. [CrossRef] [PubMed]
34. Ghebremeskel, A.N.; Vemavarapu, C.; Lodaya, M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Stability testing of selected solid dispersions. Pharm. Res. 2006, 23, 1928–1936. [CrossRef] [PubMed]
35. Chaves, L.L.; Vieira, A.C.C.; Reis, S.; Sarmento, B.; Ferreira, D.C. Quality by Design: Discussing and Assessing the Solid Dispersions Risk. Curr. Drug Deliv. 2014, 11, 253–269. [CrossRef] [PubMed]
36. Kumar, N.; Jain, A.K.; Singh, C.; Kumar, R. Development, characterization and solubility study of solid dispersion of terbinafine hydrochloride by solvent evaporation method. Asian J. Pharm. 2008, 2, 154–158. [CrossRef]
37. Tabbakhian, M.; Hasanzadeh, F.; Tavakoli, N.; Jamshidian, Z. Dissolution enhancement of glibenclamide by solid dispersion: Solvent evaporation versus a supercritical fluid-based solvent-antisolvent technique. Res. Pharm. Sci. 2014, 9, 337–350. [PubMed]
38. Kolašinac, N.; Kachrimanis, K.; Homšek, I.; Grujı´c, B.; Đuri´c, Z.; Ibri´c, S. Solubility enhancement of desloratadine by solid dispersion in poloxamers. Int. J. Pharm. 2012, 436, 161–170. [CrossRef]
39. Shah, T.J.; Amin, A.F.; Parikh, J.R.; Parikh, R.H. Process Optimization and Characterization of Poloxamer Solid Dispersions of a Poorly Water-soluble Drug. AAPS Pharm. Sci. Technol. 2007, 8, E18–E24. [CrossRef]

40. Sumio Chono, Eri Takeda, Toshinobu Seki, Kazuhiro Morimoto Enhancement of the dissolution rate and gastrointestinal absorption of pranlukast as a model poorly water-soluble drug by grinding with gelatin. International Journal of Pharmaceutics 347 (2008) 71–78.
41. Shawn A. Mitchell , Thomas D. Reynolds 1, Tina P. Dasbach A compaction process to enhance dissolution of poorly water soluble drugs using hydroxypropyl methylcellulose, International Journal of Pharmaceutics 250 (2003) 3 /11[CrossRef]
42. Paul Van Cauwenberg, Tine De Belder & Lien Sys, A review of the second-generation antihistamine ebastine for the treatment of allergic disorders, Drug evaluation, 2004 Asheley publications Ltd, ISSN 1465-6566.