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Solubility Enhancement of Poorly Soluble Antiemetics: Development & Optimization of Fast-Disintegrating Tablets of Cinnarizine and Dimenhydrinate using Solid Dispersion Technique

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ABSTRACT:

Introduction: By generating a high-energy, metastable system that enhances surface area and encourages amorphization, the solid dispersion technique has become a reliable and adaptable method for accelerating the pace at which hydrophobic medications dissolve. **Objective:**This study's main goal is to create and improve fast-disintegrating tablets (FDTs) containing dimenhydrinate (DIM) and cinnarizine (CIN) using the solid dispersion (SD) technology in order to significantly improves their solubility-limited bioavailability.**Methods:**The fusion method was used to create solid dispersions (SDs) of cinnarizine. Coprocessed super disintegrants such as sodium starch glycolate and crospovidone were used to create orodispersible tablets. A 3^2 full factorial design effectively modeled the influence of two superdisintegrants—Sodium Starch Glycolate (SSG) and Crospovidone (CP). **Results:**The fabricated optimized tablet (OPT FKM) exhibited excellent pharmaceutical properties. Very rapid disintegration 32-35 seconds, crucial for quick onset of action. Drug release 87.2% (Cinnarizine) and 92.7% (Dimenhydrinate) release within just 15 minutes, far exceeding the performance of the pure drugs and meeting the target of rapid drug availability.**Conclusion:**this research demonstrates a potent two-pronged formulation strategy: first, the solid dispersion technique fundamentally overcame the solubility limitation of the drugs (especially Cinnarizine), and second, the engineered fast-disintegrating tablet platform ensured the rapid liberation and presentation of the dissolved drug for absorption.

KEY WORDS: Cinnarizine, Dimenhydrinate, Orodispersible, SSG, Crospovidone

1. Introduction:

At the site of absorption, all medications from a certain dose form that must be absorbed must be present as a solution. One of the main issues with the creation and formulation of new chemical entities is their poor solubility in water.[1, 2] A drug's bioavailability and, ultimately, its solubility affect its therapeutic efficacy. Achieving the proper medication concentration in the systemic circulation and starting the necessary pharmacological reaction depend on solubility and dissolving rate. These days, only 8% of new pharmaceutical moieties show notable solubility and permeability.[3]

A major problem in pharmaceutical development is that many weakly water-soluble medications have a low rate of dissolution, which often limits their oral bioavailability.[4] Two common antiemetic medications, cinnarizine and dimenhydrinate, are classified as Class II in the Biopharmaceutics Classification System (BCS) due to their poor aqueous solubility, which might result in inconsistent and insufficient absorption. This calls for the development of methods to improve their solubility and dissolving properties.[5-6]

Micronization, amorphous drug manufacturing, and the creation of solid dispersions with hydrophilic carriers are only a few of the techniques used to improve the solubility of drugs that are poorly soluble in water.[1, 7] Solid dispersions are collections of solid products composed of two or more different components, often a hydrophilic matrix and a hydrophobic medication. Pharmaceuticals that are insoluble in water dissolve their carriers in aqueous solutions, releasing the medication as minuscule colloidal particles. For this reason, solid dispersion systems can speed up the drug's rate of dissolution and boost its bioavailability.[8-9]

By producing a high-energy, metastable system that increases surface area and encourages amorphization, the solid dispersion technique has become a reliable and adaptable method to increase the dissolution rate of such hydrophobic medicines.[10] A promising synergistic approach is created when paired with the creation of fast-disintegrating tablets (FDTs), which provide the benefits of quick disintegration without water and improved patient compliance, which is especially advantageous for those who are nauseous or vomiting.[11-12]

Oro-dispersible tablets (ODTs), a newly developed drug delivery method, are a clever tactic to increase marketing and extend patency.[13] Orodispersible dosage forms are proven to be effective in treating headaches, pain, inflammation, and nausea. Numerous technologies have been documented to enhance the dissolving properties of poorly soluble medications and boost bioavailability following oral absorption, and there are useful research papers available for the development of ODT.[14-15]

In order to greatly improve their solubility and guarantee a prompt initiation of therapeutic action, this study is concentrated on the creation and methodical optimization of fast-disintegrating tablets comprising solid dispersions of cinnarizine and simple dimenhydrinate.[16]

2. Materials and Methods:

2.1. Materials

API was obtained as a gift sample from M/s Mylan Lab Pvt. Ltd., Hyderabad. Sodium Starch Glycolate (SSG), Crospovidone (CP)was purchased from S.D. Fine Chem. Ltd., Mumbai.Avicel, Mg Stearate, Mannitoland Talcwere purchased from Merck Pvt. Ltd, Mumbai.

2.2. Methods

2.2.1 Formulation of Solid Dispersion

Using the fusion method, solid dispersions (SDs) of the drug cinnarizine were made at four mass ratios: 1:1, 1:2, 1:3, and 1: 4. PEG-6000 and PVP-K30 polymers were melted by heating them to a maximum of 165°C in a porcelain dish. A suitable quantity of the medication was added to the molten mass, and it was continuously agitated until a homogeneous dispersion was achieved.

2.2.2Prepration and Optimization of Drug MDTs

Preparation of the Blend

SD and mannitol were passed through sieve #60. Avicel was passed through sieve #20 and all other ingredients were passed through sieve #80. Ingredients were blended in a polybag

Pre-Compression Studies[17-20]

The powder blends, before subjecting to compression, were firstly evaluated for sufficient flow properties using various characteristic parameters such as bulk density, tapped density, compressibility index and angle of repose.

Bulk Density:

Apparent bulk density (ρ_b) of all the powder blends was determined bypouring the blend into a graduated cylinder.

$$\rho_b = \frac{M}{V_b}$$ Where $V_b$isbulk volume and M is weight of powder

Tapped Density: The measuring cylinder containing a known mass of blend was tapped 100 times using density apparatus. The constant minimum volume (V_t) occupied in the cylinder after tapings and the weight (M) of the blend was measured by using formula

$$\rho t = M/Vt$$

Compressibility Index: The simplest way for measurement of flow of the powder is its compressibility, an indication of the ease with which a material can be induced to flow.

$$I = (\rho t - \rho b)/(\rho t) \times 100$$

Angle of Repose

Angle of repose (θ)was determined using funnel method. The powder blend was poured on to a paper through a funnel that can be raised vertically until a specified cone height (h) was obtained.Radius of the heap (r) was measured and angle of repose (θ) was calculated as follow:

$$\tan \theta = h/r$$

Hausner's Ratio

Hausner ratio is an indirect index of ease of powder flow. The characterization of blends is an important aspect and gives an idea of the characteristics of final preparation.Compressibility affects the hardness, size of the tablet and further its disintegration and release.

$$\text{Hausner ratio} = \rho_t / \rho_b$$

Preparation of Oro-dispersible Tablets[21-22]

Preparation of physical mixture and co-processed superdisintegrants: The physical mixture of sodium starch glycolate and crospovidone was prepared by mixing them together in glass pestle motor. The co-processed super-disintegrant was prepared as follows:

Microwave Technology: Blends of SSG and crospovidone in different ratios were combined with 50 ml of isopropyl alcohol, weighing 10 g in total. The beaker was placed in the microwave oven, and most of the ethyl alcohol evaporated after heating was continued at a temperature between 65 and 700.

Prepration and Optimization of Drug MDT's:

MDT formulations each weighing 250mg, were prepared by using solid dispersion of Cinnarzine (equivalent to 60 mg in each tablet)&Dimenhydrinate 40mg along with a mixture of Sodium starch glycolate and Crospovidone, at different concentrations viz. 2% to6% as these super-disintegrants work best in between range of 2% to 8%. Batches were prepared using combination of Super-disintegrants. [21-22].

Table 1Formulation of Factorial Design Batches of PVP K-30 SD of drug (Microwave Technology**)**

Ingredients	FKM1	FKM2	FKM3	FKM4	FKM5	FKM6	FKM7	FKM8	FKM9
Cinnarzine SD 1:3	60	60	60	60	60	60	60	60	60
Dimen	40	40	40	40	40	40	40	40	40
SSG	2.5	2.5	2.5	5	5	5	7.5	7.5	7.5
Crospovidone	2.5	5	7.5	2.5	5	7.5	2.5	5	7.5
Avicel PH 102	50	50	50	50	50	50	50	50	50
Mannitol 20%	50	50	50	50	50	50	50	50	50
Talc 5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mg. stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Lactose (qs)	250	250	250	250	250	250	250	250	250
Superdisint. %	2	3	4	3	4	5	4	5	6

FKM- **F**actorialBatch of PVP **K**-30 SDprepared by **M**icrowave Technology

Optimization of MDTs of factorial FKM batches:

The study aims to find the optimal levels of two formulation variables (X1 and X2, likely quantities of excipients like a super-disintegrant) to minimize Disintegration Time (DT) and maximize Drug Release for two drugs: Cinnarizine (Cinn) and Dimen-hydrinate (Dimen).To optimize a fast-dissolving tablet formulation containing two poorly soluble drugs (Cinnarizine and Dimenhydrinate) by finding the ideal combination of two super-disintegrants.

Evaluation of Compressed Tablets[23-26]

a. General Appearance

This includes tablet's size, shape, color, presence or absence of an odor, taste, surface texture.

b. Tablet Thickness

Ten tablets from each batch were taken and their thickness was recordedusing Eureka Thickness Tester. The data is shown in Table.

c. Hardness

Hardness of the ODTs of each batch was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked & hardness of the same tablets from each formulation was determined.The data is shown in Table.

d. Weight Variation

All the prepared batches of ODTswere subjected to weight variation test, as per IP. Twenty tablets were taken and weighted individually; their average weight was calculated and compared with the individual tablet weight for any change produced.

e. Friability: Friability of tablets was determined using Roche friabilator. Sample of pre-weighed 20 MDTs were placed in a plasticchambered friabilator attached to a motor revolving at aspeed of 25 rpm for 4 min. The tablets were then de-dusted,reweighed, and % friability wascalculated.

f. Wetting Time: Five circular tissue papers were placed in a petri dish of 10cm diameter. Ten milliliters of phosphate buffer pH 6.8containinga water-soluble dye (Amaranth), was added to the petridish. The dye solution was used to identify completewetting of the tablet surface.

Water Absorption Ratio (R): The weight of the tablet prior to placement in the petridishwas noted (w_b) utilizing a CAS digital balance. The wettedtablet was removed and reweighed (w_a). WaterAbsorptionratio, R, was then determined according to the followingequation

$$R = 100 \times (w_a - w_b) / w_b$$

***g. In-vitro* Disintegration Test**

Disintegration of fast disintegrating tablets is achieved in the mouth owing to the action of saliva, however amount of saliva inthe mouth is limited and no tablet disintegration test was found inUSP and IP to simulate *in vivo* conditions.Todetermine disintegration time, 6 ml of water was placed inside the vessel in such way that 4 ml of the mediawas below the sieve and 2 ml above the sieve. Tablet was placed onthe

sieve and the assembly was then placed on a shaker.The time at which all the particles pass through the sieve wastaken as a disintegration time of the tablet.

h. Content Uniformity: An aliquot of 2.5 ml of stock solution was taken and diluted to 10 ml with phosphate buffer pH 6.8 in separate volumetric flask. The absorbance of above sample was determined spectrophotometrically at 257 nm and content was determined using calibration curve.

% Drug Content = Sample Absorbance/ Standard Absorbance x 100

***i. In vitro* Release study:** The tablets were placed in dissolution vessel containing 900 ml of phosphate buffer pH 6.8maintained at 37ºC ± 0.5 and stirred at 50 rpm. Samples (6 ml) were collected periodically at different time intervals (1, 2, 4, 6, 8, 10, 15 min) and replaced with fresh dissolution medium. The absorbance was determined spectrophotometrically at 257 nm.

3. Results and Discussion:

3.1 Characterization of Solid Dispersions:

The UV-spectroscopic method was used to determine the drug content in each solid dispersion, and the results are displayed in table. Cinnarizine solid dispersions were found to have a drug concentration ranging from 96.85% to 99.65%.

Table 2:Drug Content in Cinnarizine Solid Dispersion

Formulation code of Solid dispersion (with PEG)	Drug content (%) n=3	Formulation code of Solid dispersion (with PVP K30)	Drug content (%) n=3
CSD P11	96.85 ± 1.86	CSD K11	98.25 ± 1.13
CSD P12	98.78 ± 1.25	CSD K12	98.72 ± 1.26
CSD P13	99.25 ± 1.18	CSD K13	99.65 ± 1.54
CSD P14	99.28 ± 1.35	CSD K14	99.4 ± 1.08

3.2 *In vitro* drugrelease of SD: Solid dispersion formulations of Cinnarizine were found to enhance the dissolution of the drug. The enhancement was found to be dependent on the amount of the polymer (PEG 6000, polyvinylpyrrolidone (PVP)) used. Q_{30} (amount of drug released in 30 min) in drug to polymer ratio 1:1 was noted to be in the range of 78-80% while in ratio 1:2, 1:3 and 1:4 it was found to be 85-88%, 93-96% and 93-96% respectively as compared to 51 % in case of pure Cinnarizine. No significant increase in the dissolution of Cinnarizine was observed when drug to polymer ratio was further increased from 1:3 to 1:4.

Table 3: *In vitro* dissolution of pureCinnarizine& its SD in HCl buffer pH 1.2

Formulation Code	PERCENT DRUG RELEASED AT DIFFERENT TIME INTERVALS					
	5 min	10 min	15 min	20 min	25 min	30 min
Pure Cinnarizine	15.58±0.85	24.13±1.10	33.52±1.22	42.36±1.2	48.18±1.08	51.00±1.02
CSD P11	20.45±1.1	35.45±1.05	46.36±1.0	51.75±1.15	68.78±1.12	78.56±1.25
CSD P12	24.78±1.26	38.22±1.68	50.85±1.8	62.24±1.48	72.75±1.68	85.96±1.24
CSD P13	28.12±1.21	42.45±1.12	54.59±1.45	66.46±0.65	80.12±0.8	93.58±1.24
CSD P14	28.75±0.45	43.78±0.78	54.5±1.12	66.85±1.28	82.35±1.75	94.12±2.15
CSD K11	23.26±0.85	38.98±1.02	49.8±0.8	57.45±1.45	71.65±0.86	80.12±1.25
CSD K12	27.41±1.32	41.87±1.2	53.32±0.75	66.86±1.36	76.85±0.8	88.65±1.22
CSD K13	31.5±0.65	45.38±1.11	57.85±0.75	71.58±1.05	84.2±2.28	96.15±2.65
CSD K14	32.2±0.5	46.1±0.58	58.25±1.16	72.5±0.86	86.65±1.65	96.42±2.22

Discussion: Based on the presented data, it can be concluded that the formulation of Cinnarizine as a solid dispersion significantly enhances its in-vitro dissolution rate compared to the pure drug. The extent of this enhancement is directly proportional to the amount of hydrophilic polymer (PEG 6000 & PVP K30) used, up to a saturation point. A critical threshold exists at a **drug-to-polymer ratio of 1:3**, beyond which no further dissolution improvement is achieved, indicating that this ratio provides the optimal balance of polymer-mediated solubilization and dispersion for Cinnarizine under the studiedconditions. On the basis of outcome **PVP K30 Polymer** uses for further study.

3.3 Optimization of MDTs of factorial FKM batches:

The fitted equation was generated relating the responses disintegration time and percentage friability to the transformed factor. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative).After application of 3^2 factorial designs and with help of polynomial terms the optimized tablet was produced which have targeted to the disintegration time 30s, 0.3% percent friability and 95% percent drug release.

Table 4: 3^2 Full Factorial Design Layouts (MDT of FKM)

Batch Codes	Variable Levels in Coded Form		Disintegration Time	% Drug Release	% Drug Release
	X_1	X_2	DT (sec)	Cinn	Dimen
FKM1	2.5	2.5	45	78.31	84.31
FKM2	5	2.5	41	80.13	86.13
FKM3	7.5	2.5	39	82.42	88.42
FKM4	2.5	5	42	81.65	85.65
FKM5	5	5	38	83.43	88.43
FKM6	7.5	5	35	85.64	90.64
FKM7	2.5	7.5	39	82.62	87.62
FKM8	5	7.5	35	85.83	90.83
FKM9	7.5	7.5	37	87.03	94.03
OPT	7.5	7.5	34.16	87.08	93.52

X_1 indicates amount of Sodium starch Glycolate (mg); X_2, amount of Crospovidone (mg)

3.3.1 Effect of Formulation parameters on Disintegration Time (Y1):

- **Overall Performance:** All formulations disintegrate very rapidly (35-45 seconds), confirming the efficacy of using dual superdisintegrants.
- **Individual Effects:**

Crospovidone (X2) appears more potent for rapid disintegration. Compare:

- ✓ FKM1 (2.5% SSG, 2.5% CP): 45 sec
- ✓ FKM3 (2.5% SSG, 7.5% CP): 39 sec → Big improvement from CP.
- ✓ FKM2 (7.5% SSG, 2.5% CP): 41 sec → Moderate improvement from SSG.

The fastest DT (35 sec) is achieved at high Crospovidone levels, whether SSG is low or high (FKM6, FKM8).

Interaction: The combination isn't simply additive. The best results come from pushing one disintegrant very high while modulating the other

3.3.1 Effect of Formulation parameters on % Drug Release(Y2):

General Trend: Dimenhydrinate release is consistently 5-6% higher than Cinnarizine across all batches, attributable to its slightly better solubility.

Individual Effects on Release:

Crospovidone (CP) has a stronger positive influence on drug release. Increasing CP (compare FKM1->FKM3 or FKM7->FKM8) consistently gives a bigger jump in release than increasing SSG by the same amount (FKM1->FKM2).

SSG also improves release, but its effect might plateau or even slightly reverse at very high levels when combined with high CP (see FKM4 vs. FKM3).

Optimization of the Mouth Dissolving Tablet

The response's disintegration time and percentage release were related to the converted factor by the fitted equation. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative)

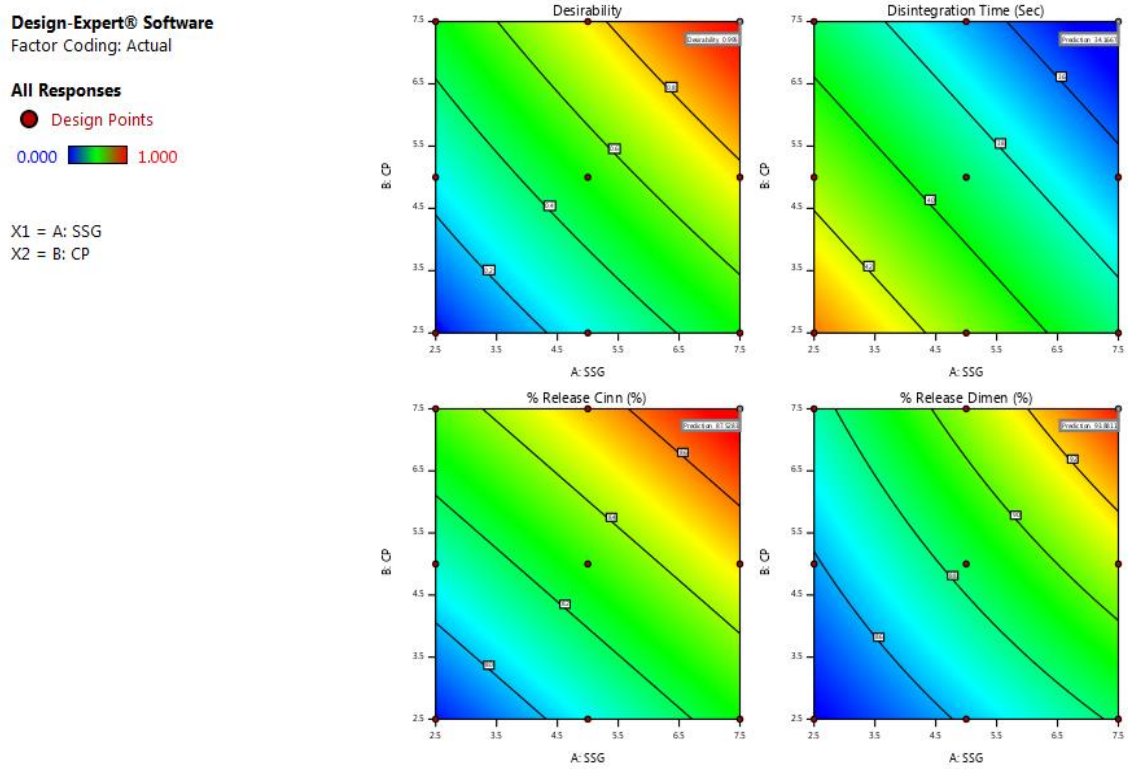

Fig. 1: Contour Plot of Optimized formulation FKM (showing Desirability)

Table 5: Summary of Results of Regression Analysis (MDT of FKM)

	Intercept	A	B	AB	A^2	B^2
Disintegration Time	39	**-2.5**	**-2.33333**			
p-values		**0.0093**	**0.0125**			
% Release Cinn	83.0067	**2.085**	**2.43667**			
p-values		**0.0002**	**< 0.0001**			
% Release Dimen	88.4511	**2.585**	**2.27**	**0.575**		
p-values		**< 0.0001**	**< 0.0001**	**0.0060**		

The optimized tablet was created using full factorial design and polynomial terms, with a minimum disintegration time of 35 seconds and a maximum drug release of 83.00% for cinnarzine and 88.45% for dimenhydrinate. The optimized amount of the co-processed Sodium starch Glycolate and crospovidone was incorporated in the tablet formulation (OPT) which was also used as the check point of the regression analysis model. The software was used to create the response surface prediction plots.

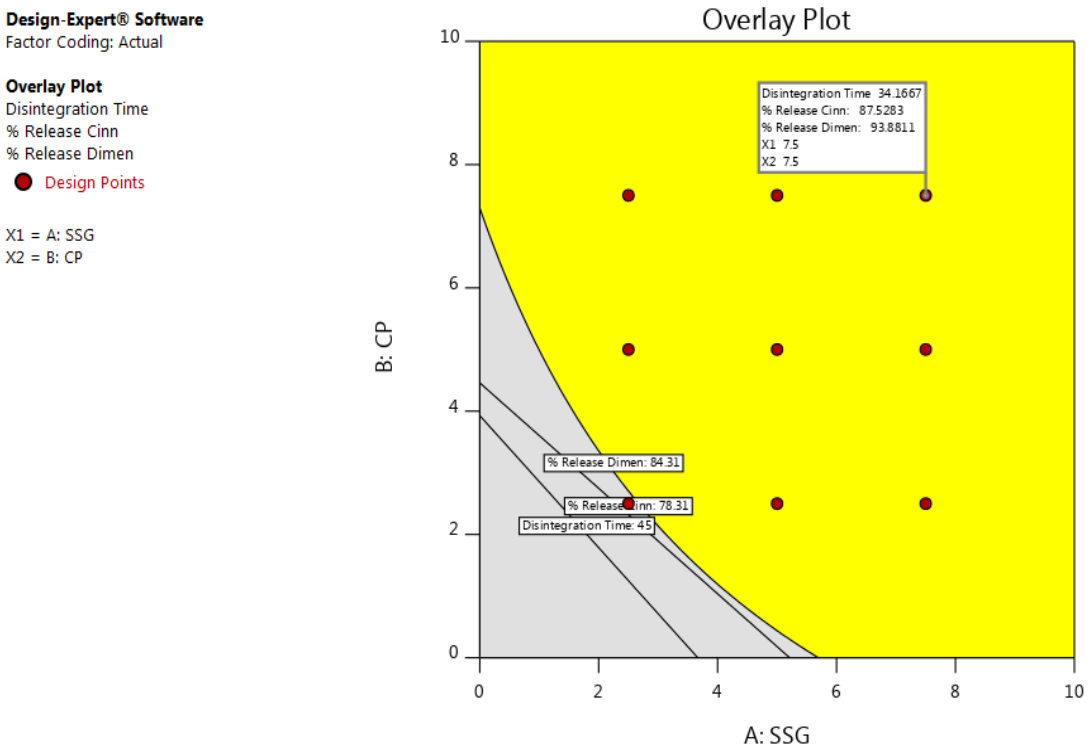

Fig. 2: Overlay Plot for Predicted Optimized Formulation of FKM

Table 6 Optimization of Mouth Dissolving Tablet (FKM)

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A:SSG	is in range	2.5	7.5	1	1	3
B:CP	is in range	2.5	7.5	1	1	3
Disintegration Time	minimize	35	45	1	1	3
% Release Cinn	maximize	78.31	87.03	1	1	3
% Release Dimen	maximize	84.31	94.03	1	1	3
Solution						
SSG	CP	Disintegration Time	% Release Cinn	% Release Dimen	Desirability	
7.5	7.5	34.16	87.52	93.88	0.995	Selected

Discussion:

Optimal Formulation: The selected solution (SSG=7.5, CP=7.5) represents the optimal combination of the two formulation variables (Super-disintegrants and Co-Processed Excipient) within the tested design space.

Excellent Performance: The solution achieved an overall Desirability Score of 0.995 (on a scale of 0 to 1). This indicates a near-perfect balance and achievement of all five conflicting goals simultaneously.

The high levels of both SSG and CP (at their upper limits) are the key factors driving the superior performance. This combination results in:

- Very fast disintegration (34.16s), which is crucial for rapid drug release.
- Exceptionally high drug release percentages for both active ingredients, surpassing the target thresholds significantly.

The formulation with 7.5% SSG and 7.5% CP is highly recommended. It is the optimal, robust formulation that delivers **fast-disintegrating tablets with excellent and complete drug release profiles** for both Cinnarizine and Dimenhydrinate, successfully fulfilling all predefined pharmaceutical quality objectives.

Development of Optimized Mouth Dissolving Tablet:

The optimal quantity of super-disintegrant recommended by the software was used to make the optimum Mouth Dissolving tablet. The super-disintegrants both SSG and Crospovidone are required different amount for the preparation of optimized tablets of selected batch of solid dispersions ofcinnarzine and dimenhydrinate.

Table 7: Development & Evaluation of Optimized Formulation

Ingredients/Formulation	OPT FKM (F1) (mg)
Cinnarizine SD	40
Dimenhydrinate	60
SSG	7.5
Crospovidone	7.5
Avicel PH 102	45
Mannitol	30
Talc	3.75
Mg. stearate	3.75
Lactose (qs)	150
Evaluation	
Weight (mg)	247 ±1.34
Hardness (kg/cm^2)	3.65 ± 0.02
Wetting time (s)	32-34
Cinnarzine Content (%)	99.1±0.1
Dimenhydrinate Content (%)	98.7±0.1
Friability (%)	0.35 ± 0.03
Disintegration time (s)	32-35
Cinnarzine release (%) Q_{15}	87.2
Dimenhydrinate release (%) Q_{15}	92.7

Table 8: Comparison of Percent drug release of Optimized formulations

Time (min)	Percent Drug Release (CPR)OPT FKM (F1)	
	Cinn Release	Dimen Release
1	21.5	23.2
2	36.1	45.5
4	52.3	58.3
6	66.8	75.4
8	75.4	80.6
10	82.1	87.8
15	87.2	92.7

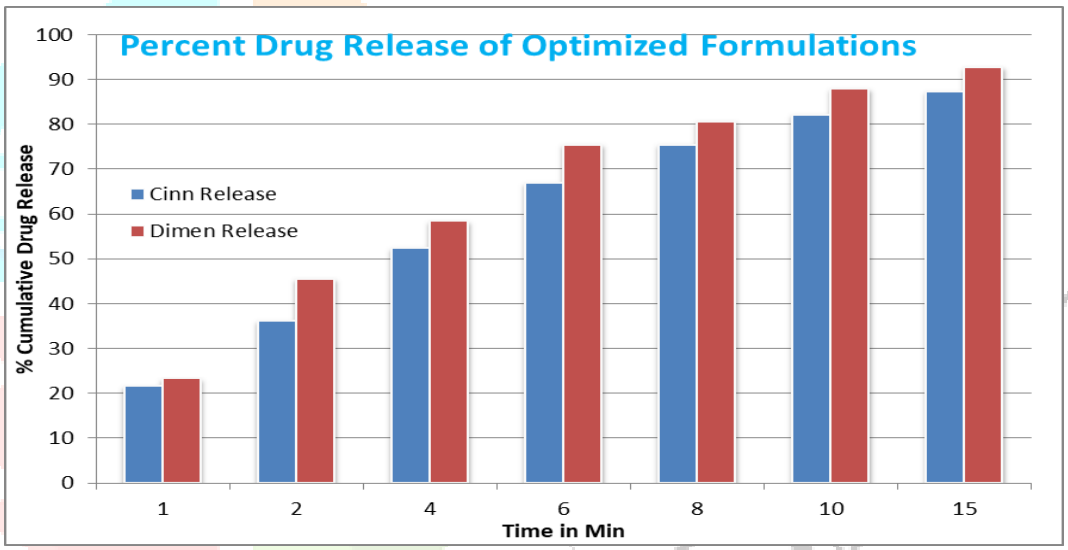

Fig. 3: Comparison of Percent drug release of Optimized formulations

Conclusion:

The study successfully achieved its primary objective of enhancing the solubility and dissolution of the poorly soluble antiemetics Cinnarizine and Dimenhydrinate by developing and optimizing a fast-disintegrating tablet (FDT) formulation using the solid dispersion technique. The final optimized tablet represents a significant advancement over the pure drugs, offering rapid disintegration, excellent drug release, and robust mechanical properties suitable for patient use, particularly for those experiencing nausea and vomiting.

The extent of dissolution enhancement was directly dependent on the polymer ratio, with an optimal drug-to-polymer ratio of 1:3 identified. Beyond this ratio (1:4), no significant further improvement was observed, establishing a cost-effective and efficient formulation point. Based on performance, PVP K30 was selected as the preferred polymer for further development.

A 3^2 full factorial design effectively modeled the influence of two superdisintegrants—Sodium Starch Glycolate (SSG) and Crospovidone (CP)—on the critical quality attributes of disintegration time and drug release.Statistical analysis revealed that Crospovidone had a more pronounced individual effect on both accelerating disintegration and enhancing drug release for both active ingredients.The synergistic combination of both superdisintegrants at high levels yielded the best performance.

The optimized formulation (7.5% SSG and 7.5% CP) was predicted and validated to achieve a near-perfect balance of all targets with a desirability score of 0.995.Superior Drug Release achieved 87.2% (Cinnarizine) and 92.7% (Dimenhydrinate) release within just 15 minutes, far exceeding the performance of the pure drugs and meeting the target of rapid drug availability.

CONFLICT OF INTEREST:

No conflicts of interest are mentioned by the researchers. The composition and writing of the document are the sole responsibility of the writer.

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