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DESIGN AND DEVELOPMENT OF SUBLINGUAL TABLETS CONTAINING POORLY SOLUBLE CINNARIZINE DRUG BY USING SPRAY DRYER TECHNOLOGY

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ABSTRACT

The aim of present investigation was formulation and development of Cinnarizine Sublingual Tablets. Study started from the Preformulation study of the drug. Drug belonged to BCS class-II and had low solubility properties. So, solubility enhancement technique is used namely spray drying technology. Solid dispersion technique is used to introduce solubility enhancer into the drug. The flow properties of API were found to be good enough, hence direct compression technique was used for tablet preparation. While studying IR spectrum, it was concluded that there was no interaction between drug and other

excipients. Initially feasibility trials were taken to optimize three super disintegrants. Tablets were found acceptable in physical parameters evaluation. After preliminary screening, it was concluded that Crospovidone showed fastest rate of drug release. Based on that satisfactory batch considering for further factorial screening. 3^2 factorial design was applied by taking Crospovidone and Mannitol as independent factors. Factorial batch F1-F9 prepared by using direct compression method. Physical and chemical evaluation was done for all batches. Finally, from overlay plot Checkpoint batch (S1) was prepared and post compression parameters were evaluated and compared with optimised factorial batch F2 and found satisfactory. Finally optimized factorial batch F6 was loaded for stability study for 1 month and evaluation was done and found acceptable. Hence, F6 was the optimized formulation. Disintegration time was not more than 1 min which is good and desirable for sublingual dosage form. Its wetting time is 33 sec; and drug content was found to be100.0%.

By looking all the above parameters, it is concluded that F6 formulation is optimizedformulation from all the batches and passes the entire evaluation test including stability studies.

Keywords: Cinnarizine, motion sickness, Sublingual tablets, Crospovidone, Spray drying

INTRODUCTION

Cinnarizine is H1 receptor antihistaminic and use in motion sickness. Motion sickness is the uncomfortable dizziness, nausea and vomiting that people experience when their sense of balance and equilibrium is disturbed by constant motion **[1]**. Cinnarizine is a weakly basic and also lipophilic property compound with low aqueous solubility. It also able to cross the blood brain barrier by simple diffusion **[2]**. Because of this property cinnarizine is able to exert its effects on cerebral blood flow in the brain. It is antihistaminic drug having half-life of 3-4 hours. Cinnarizine is extensively metabolized via CYP2D6. Cinnarizine has fewer side effects as compared to other antihistaminic used in motion sickness **[3]**. Cinnarizine is used for motion sickness, vertigo, meniers disease, vomiting and useful in vestibular.

Therefore, the present work is aimed to formulate sublingual tablets of cinnarizine for improving patient compliance and rapid onset of action. Ease of Administration to the patient such as paediatric, geriatric & psychiatric patients. To prevent hepatic impairment by bypassing first pass metabolism **[4]**. No need of water to swallow the dosage form. Fast dissolution and absorption of the drug, which will produce quick onset of action. Some drugs are absorbed from the mouth, pharynx and oesophagus as saliva passes down into the stomach **[7, 8]**. In such cases bioavailability of drug is increased. Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects. Good mouth feel property helps to change the perception of medication as bitter

pill particularly in pediatric patient. This offers new business opportunity like product differentiation, product promotion, patent extensions and life cycle management **[10]**.

Spray Drying:

It is a method of changing a dry powder from a liquid or slurry by rapidly drying with a hot gas. This is the preferred method of drying of many thermally-sensitive materials such as foods and pharmaceuticals or materials which may require extremely consistent, fine particle size. Air is the heated drying medium; however, if the liquid is a flammable solvent such as ethanol or the product is oxygen-sensitive then nitrogen is used **[3]**.

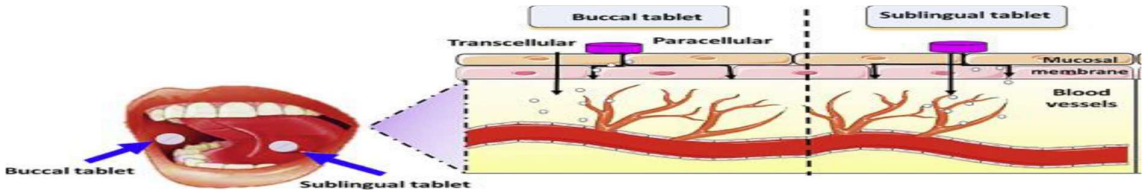

Figure:1 Buccal and sublingual tablet drug delivery

Spray-Dried Technology:

Spray-dried dispersions (SDDs) are usually amenable for incorporation into a variety of final oral dosage forms, including capsules, tablets and sachets. According to **Figure 2** One advantage of spray drying is how readily excipients can be incorporated into the process. As long as the excipient is soluble in a spray solvent, it can be included in the formulation **[3-4]**. If the drug is not prone to degradation under acidic conditions, ionizable cellulosic polymers are often a good excipient choice because of their high glass transition temperature and low hygroscopicity in a solid state. At physiological pH of the intestine, the side chains on these polymers ionize and form amphiphilic coil structures that inhibit API crystallization and maintain supersaturation **[8-10]**.

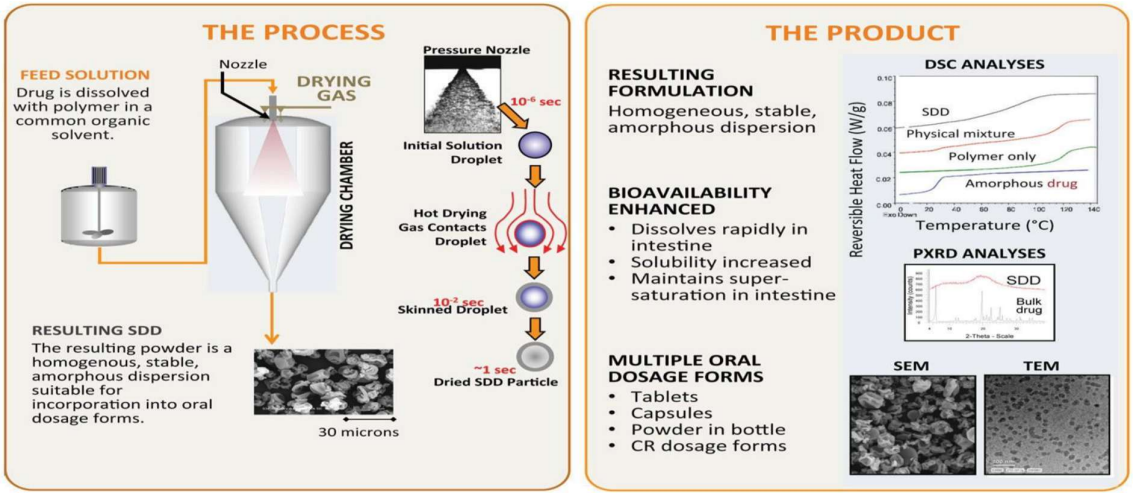

Figure 2: Spray Dried technology

MATERIALS AND METHODS:

Cinnarizine Drug and cyclodextrin solubilizer are received from Nest Healthcare Pvt. Ltd PVPK30 Carrier, Mannitol Sweetener, Magnesium stearate Lubricant, Microcrystalline Cellulose Diluent, Citric acid Saliva stimulant, Cross carmellose sodium Cross povidone Super disintegrant received from S.D.fine chemicals, Ahmedabad

Method of Preparation

Solid dispersion technique used For Solubility Enhancement of Cinnarizine: The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or the melting-solvent method **[4]**. The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates and consequently, the bioavailability of poorly water-soluble drugs.

Preparation of Solid Dispersions of Cinnarizine with carriers

Solid dispersions containing cinnarizine and carrier in the proportion of 1:1, 1:2 and 1:3 were prepared by fusion method and solvent evaporation method. Solid dispersions of drug with carrier (B-Cyclodextrine, PVP K30) were prepared by fusion method. In this method, cinnarizine was dissolved in acetone, and the solution was incorporated into the melt of carrier (B-Cyclodextrine, PVP K30) at 165°, by pouring into it. It was kept in an ice bath for sudden cooling **[4, 5]**. The mass was kept in the desiccator for complete drying. The solidified mass was scrapped, crushed, pulverized, and passed through sieve no 80 mesh.

Solid dispersions of drug with B-Cyclodextrine and PVP K30were prepared by solvent evaporation method. In this method, accurately weighed quantities of carriers (B-Cyclodextrine, PVP K30) in the stated proportions were carefully transferred into boiling test tubes, and dissolved in acetone **[4]**. To these solutions, accurately weighed quantities of cinnarizine were added, and allowed to dissolve. The solution was transferred to a Petri dish, the solvent was allowed to evaporate at room temperature, and the dispersions were dried at room temperature for 1 h, and then dried at 65° for 6 h in a hot air oven. The mass obtained in each case was crushed, pulverized, and sifted through sieve no 80 mesh. Sublingual tablets prepared by using Direct compression method **[15]**.

EXPERIMENTAL WORK [15]

Preformulation is defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.

Preformulation studies are the starting step in the rational development of dosage form of a drug substance. The objectives of Preformulation studies are to develop a

portfolio of information about the drug substance, so that this information is useful to develop formulation.

Solubility

Check the solubility of the API by adding the known quantity of the API powder in respective solvent. Calculate the mg/ml and record the results.

Loose Bulk Density: Weigh accurately 10 g of drug (M), which was previously passed through 20 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V0). Calculate the apparent bulk density in gm/ml by the given formula

Bulk density = Weight of powder / Bulk volume….(1)

Tapped bulk density: Weigh accurately 10 g of drug, which was previously passed through 20 # sieve and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute

Tapped Density = Weight of powder/Tapped volume …….(2)

Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) x100]/TD ……(3)

Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material.

Hausner's Ratio = TD / BD……..(4)

Angle of repose

The angle of repose of API powder was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan Ø = h/r$ …….(5)

Where, h and r are the height and radius of the powder cone respectively.

Table 1: Composition and batch code of solid dispersion of cinnarizine with carrier

Batch code	Carrier	Ratio of drug and carrier	Method of preparation	Drug content (%)
PV1	PVP K30	1:1	Fusion	87.32
PV2	PVP K30	1:2	Fusion	89.21
PV3	PVP K30	1:3	Fusion	88.78
PV4	PVP K30	1:1	Solvent evaporation	86.78
PV5	PVP K30	1:2	Solvent evaporation	85.75
PV6	PVP K30	1:3	Solvent evaporation	90.89
CD1	ß-cyclodextrine	1:1	Fusion	92.43
CD2	ß-cyclodextrine	1:2	Fusion	96.02
CD3	ß-cyclodextrine	1:3	Fusion	91.21
CD4	ß-cyclodextrine	1:1	Solvent evaporation	89.90
CD5	ß-cyclodextrine	1:2	Solvent evaporation	93.88
CD6	ß-cyclodextrine	1:	Solvent evaporation	95.74

Table 2: Percentage release of cinnarizine from PVP K 30 solid dispersion

Time (min)	Pure	PV1	PV2	PV3	PV4	PV5	PV6
5	16.57	22.90	20.87	22.93	22.08	24.23	26.42
10	25.62	36.97	37.34	39.43	39.42	43.53	48.11
15	31.81	58.31	67.21	65.75	69.53	78.67	82.19
20	43.57	77.08	84.21	85.87	86.59	91.33	93.52
30	53.62	85.43	88.19	93.22	91.63	94.82	96.81

Table 3: Percentage release of Cinnarizine from ß-cyclodextrine Solid dispersion

Time (min)	Pure	CD1	CD2	CD3	CD4	CD5	CD6
5	15.61	21.91	22.55	22.76	22.08	24.23	26.42
10	29.82	37.90	40.01	39.97	39.40	49.53	46.10
15	31.73	58.43	69.32	67.74	68.73	77.69	79.09
20	49.64	78.38	84.25	86.83	86.42	89.93	86.32
30	55.71	86.49	88.72	94.22	90.79	96.77	90.71

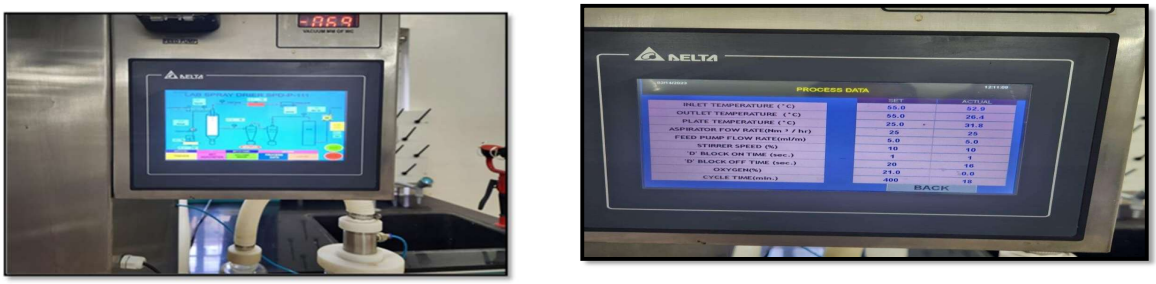

Figure 3 a, b: Spray dryer operating parameter

Table 3 shows CD5 Batch is found to be satisfactory and dried by novel technique used in pharmaceutical industry which is spray dried technology. According **Figure 4** Optimized batch is run in spray dryer by using acetone as solvent and various leading parameter of spray dryer.

Table 4: Formulation of Preliminary Batches

Ingredients (mg)	P1	P2	P3	P4	P5	P6	P7	P8	P9
SD (Cinnarizine +CD)	60	60	60	60	60	60	60	60	60
Mannitol	29	24	19	29	24	19	29	24	19
Magnesium stearate	1	1	1	1	1	1	1	1	1
Microcrystalline Cellulose	15	15	15	15	15	15	15	15	15
Citric acid	15	15	15	15	15	15	15	15	15
Cross Carmellose sodium	10	15	20	-					
Cross povidone	-	-	-	10	15	20	-	-	-
Sodium starch Glycolate	-	-	-	-	-	-	10	15	20
Total	130	130	130	130	130	130	130	130	130

Preliminary screening was done by preparation of 9 preliminary batches with the use of different super disintegrants. Crospovidone, Croscarmellose sodium and sodium starch glycollate were used different concentrations to prepare preliminary batches.

Table 4 shows All the batches were analysed for pre and post compression parameters and from that formulation P5 was found to give good and satisfactory results.

Based on results of preliminary batches of fastest drug release, P5batch which contains 15 mg of Crospovidone gave satisfactory drug release. Hence P5 batch composition selected for factorial design. Design and formulation of factorial batches are given below.

Table 5: Formulation coding of factorial batches

Formulation	Coded value	Coded value	Actual Value X1	Actual Value X2
	X1	X2	Amount of Cross povidone	Amount Of Mannitol
F1	-1	-1	13	20
F2	0	-1	15	20
F3	1	-1	17	20
F4	-1	0	13	24
F5	0	0	15	24
F6	1	0	17	24
F7	-1	1	13	28
F8	0	1	15	28
F9	1	1	17	28

Table 6: Formulation of Factorial Batches (F1 to F9)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
SD (cinnarizine +cyclodextrine)	60	60	60	60	60	60	60	60	60
Mannitol	20	20	20	24	24	24	28	28	28
Crospovidone	13	15	17	13	15	17	13	15	17
Microcrystalline Cellulose	21	19	17	17	15	13	13	11	9
Citric acid	15	15	15	15	15	15	15	15	15
Magnesium stearate	1	1	1	1	1	1	1	1	1
Total weight	130	130	130	130	130	130	130	130	130

Factorial batches were prepared as mentioned in above **Table 6**, namely F1 to F9. Amongst them, formulation F6 shown fastest drug release as desired. The pre and post compression parameters were evaluated and from the data of all the 9 factorial batches, Design Expert 13 software was used for optimization of concentration of both factors X1 and X2.

RESULTS AND DISCUSSION

Drug-Excipients Compatibility Studies

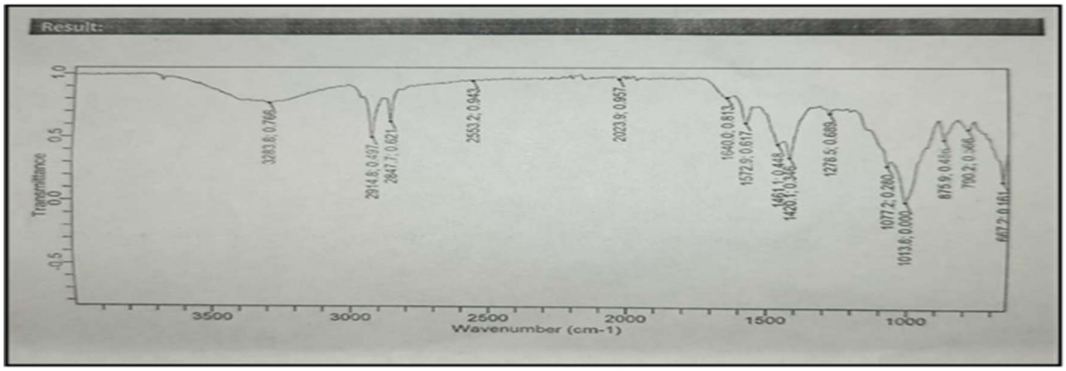

Figure 4: FTIR spectra of Cinnarizine and excipients

Table 7: Precompression studies of Preliminary Batches

Formulation	Bulk Density (gm/mL)	Tapped Density (gm/mL)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (θ)
P1	0.49	0.61	19.67	1.24	28.55°
P2	0.47	0.51	7.84	1.08	23.22°
P3	0.5	0.54	7.4	1.08	22.98°
P4	0.48	0.58	17.24	1.2	27.45°
P5	0.46	0.66	30.3	1.43	29.19°
P6	0.43	0.46	6.52	1.06	22.33°
P7	0.51	0.56	8.92	1.09	24.52°
P8	0.5	0.59	15.25	1.18	26.91°
P9	0.48	0.56	14.28	1.16	26.57°

Table 8: Disintegration Time, Wetting time and Drug content

Formulation	Disintegration time	Wetting Time (Sec)	Drug Content (%)
P1	42	39	89.27
P2	53	40	88.21
P3	52	41	86.3
P4	47	38	79.6
P5	49	41	86.9
P6	37	32	93.22
P7	45	44	87.71
P8	47	42	83.2
P9	44	47	89.2

Table 9: In-vitro Drug release studies of Preliminary batches

Time (min)	P1	P2	P3	P4	P5	P6	P7	P8	P9
0	0	0	0	0	0	0	0	0	0
4	19.22	21.56	9.87	8.92	17.58	29.73	12.23	19.88	14.37
8	34.89	46.56	35.44	34.25	36.27	73.56	37.74	35.66	32.2
12	55.63	61.18	59.72	48.66	51.74	88.23	59.22	58.85	56.22
16	59.44	65.37	64.85	58.58	65.92	92.31	68.85	80.67	79.53
20	69.21	71.97	70.43	71.91	81.23	97.43	80.97	93.49	89.79

Results obtained from Design Expert 13 Software-

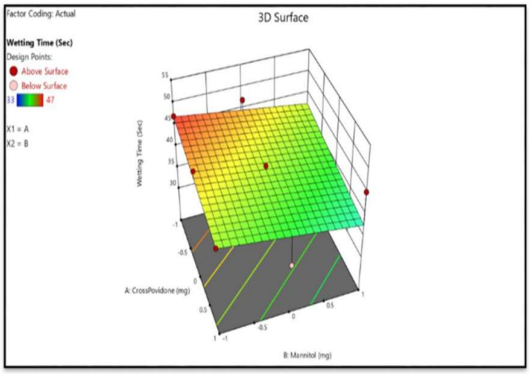

Figure 5: 3D surface graph of Wetting time

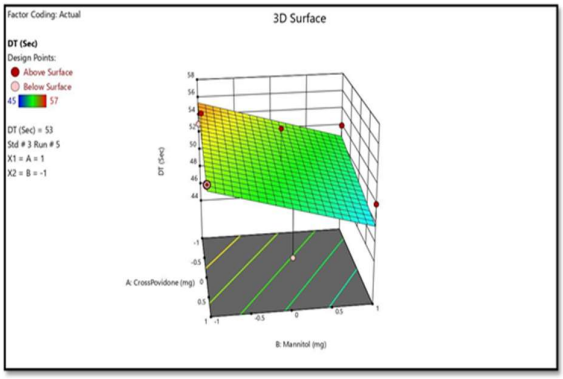

Figure 6: 3D surface graph of Disintegration time

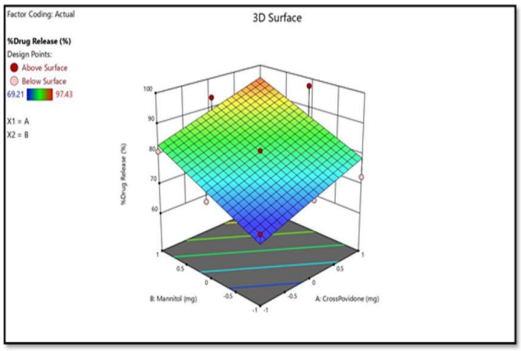

Figure 7: 3D Surface for Drug release

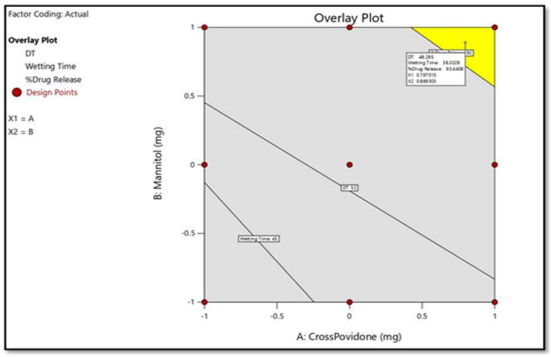

Figure 8: Overlay Plot

P-values less than 0.0500 indicate model terms are significant. In this case there areno significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Table 10: Comparison of checkpoint batch and factorial batch

Post compression	Predicted value	Experimental value
Disintegration time(sec)	53.89	50.34
Wetting time (sec)	44.39	41.78
% Drug content	72.45	89.63

Stability Studies

Stability study of optimized formulation F6 was carried out by keeping the tablets in stability chamber for 1 month at 400 C ± 20 C and 75% RH± 5%. All the post compression parameters were evaluated. Formulation was found stable and no any critical observation seen during stability.

CONCLUSION

The aim of the present study was to develop and optimize oral sublingual tablets of model drug Cinnarizine to give quick onset of action by rapidly disintegrating in a few seconds without the need of water with better patient compliance. In such cases, bioavailability of drug is significantly

greater and adverse event is reduced than those observed from conventional tablet dosage form. Sublingual tablets of Cinnarizine can be successfully prepared by direct compression method using selected super disintegrants with Crospovidone, Croscarmellose and Sodium starch glycolate for the better patient compliance and effective therapy. The relative efficiency of these super disintegrants is to improve the disintegration and dissolution rate of tablets.

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