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Optimization of Superdisintegrants Concentration in Designing of Mouth Dissolving Tablets of Solid Dispersion of Domperidone by Using response surface methodology

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Abstract

This research involves preparation of mouth dissolving tablets of solid dispersions of Domperidone by direct compression method using various concentrations of superdisintegrants in combination i.e. Croscarmellose Sodium and crospovidone. For optimization, a 3^2 (two-factor three-level) factorial design is being used in which 2 factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations for every four selected solid dispersion batches (9x4=36 formulations + one blank). The amount of Croscarmellose Sodium (X_1) and crospovidone (X_2) was selected as independent variables. The disintegration time, percentage friability and percent drug release were selected as dependent variables. All the active powder blends were evaluated for pre-compression parameters (viz. angle of repose, Carr's index, Hausner ratio, etc.) and the tablets were evaluated for post-compression parameters (viz. weight variation, hardness, and friability, wetting time, disintegration time, water absorption ratio, and in vitro drug release studies). Optimization was done using the software (Design Expert® 11.0.4), predicted responses of which were validated.

Keywords: Tablet, Domperidone, Solid Dispersion, Mouth dissolving.

Introduction

Drugs are rarely administered in their original pure state due to various issues like stability, proper dose strength, etc. They are administered in various dosage forms after converting it into a suitable stable formulation [1]. The aim of dosage form is to administer a drug at a therapeutic concentration to a particular site of action for a specified period of time [2]. Oral routes of drug administration are widely used up to 50-60% of total dosage forms [3]. Several orally administered drugs have a less bioavailability due to their poor water solubility. In Biopharmaceutics classification system, drugs with decreased aqueous or water solubility, slow dissolution rate and increased membrane permeability are categorized as Class II drug [4].

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Since for BCS class II drugs, rate determining step is release of drug from the dosage form and its solubility in the gastric fluid, so increasing the solubility leads to increases the bioavailability for BCS class II drugs [5,6,7,8,9]. Solid dispersion is one of the many techniques available to enhance drug dissolution and bioavailability of poorly water-soluble drugs. Further, such formulations can be dispensed in the form of fast dissolving tablets which disintegrate and/or dissolve rapidly in saliva; thus may help in improving the bioavailability of such drugs.

When the solid dispersion comes in contact with the aqueous medium, the inert carrier or polymer dissolves quickly thereby releasing the drug, the increased surface area produces a higher dissolution rate thus increasing the bioavailability of the poorly soluble drug. Vomiting is the common problem for all the age groups. Domperidone, an antiemetic and prokinetic is one of the effectively used in vomiting / motion sickness, having less side effects, with half life of 7.5 hours but poorly soluble in water and hence less bioavailable [10].

The purpose of this research is to prepare solid dispersions of Domperidone, an antiemetic drug and employing them with superdisintegrants in different

concentrations in the development of mouth dissolving tablets. The superdisintegrants will use in this study are croscarmellose sodium and crospovidone. Tablets will be prepared by direct compression technique and will be evaluated for uniformity of weight, thickness, hardness, friability, disintegration time (DT) and dissolution study. Factorial design will use for the optimization of tablets and to see the effect of concentration of superdisintegrants in the development of MDTs.

Materials & Methods

Materials. Domperidone (API), Polyethylene Glycol (PEG-4000, 6000), Polyvinyl Pyrrolidone (PVP K-30, 90), Croscarmellose Sodium, Crospovidone, Mannitol, Aspartame, Microcrystalline Cellulose was obtained as a gift sample from Wockhardt Research Centre, Aurangabad, Maharashtra, India. Talc, Magnesium Stearate, Lactose were procured from R.S. Enterprises, Jaipur, India manufactured by Central Drug House (P) Ltd – CDH, New Delhi, India. All chemicals used were of analytical grade.

Methods

Preparation of solid dispersions of Domperidone

Solid dispersions (SDs) of Domperidone (DOM) prepared by fusion method with polymers PEG (4000 and 6000) and PVP (K30 and K90) in drug to polymer ratio 1:4 used for preparing mouth dissolving tablets [11,12].

Preparation of Mouth Dissolving Tablets of Domperidone Solid Dispersion by Direct Compression Method

Preliminary trial batch were prepared by direct compression technique using single punch tablet machine. Thirty Seven MDT formulations each weighing 200 mg, were prepared by using solid dispersion of Domperidone Maleate (equivalent to 10mg in each tablet) along with a mixture of Croscarmellose Sodium and Crospovidone, at different concentrations 2% to 8% w/w. Batches were prepared by mixing combination of Superdisintegrants, AvicelPH102, Mannitol and Lactose in a glass mortar and pestle and were lubricated with 2% w/w Talc and 2% w/w Magnesium stearate. Finally mixed powder blends were converted into tablets using a single-punch tablet compression machine.

Solid dispersions SDP414, SDP614, SDK314 and SDK914 were used for formulation of mouth dissolving tablets. The composition and codes of formulations are shown in table 1 to 4. Batch **D1** consist of pure Domperidone without using its solid dispersion.

Table 1: Composition and codes of SD P414 mouth dissolving tablets

Ingredient (mg)	Formulation Codes									
	D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**
SD P414*(DOM)	-	50	50	50	50	50	50	50	50	50
Domperidone	10	-	-	-	-	-	-	-	-	-
Croscarmellose Sodium	-	2	2	2	4	4	4	6	6	6
Crospovidone	-	2	4	6	2	4	6	2	4	6
Mannitol	20	10	10	10	10	10	10	10	10	10
Aspartame	1	1	1	1	1	1	1	1	1	1
Talc	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4	4	4
AvicelPH102	30	30	30	30	30	30	30	30	30	30
Lactose	131	97	95	93	95	93	91	93	91	89

* Solid Dispersion containing PEG-4000, Drug to Polymer Ratio: 1:4

Table 2: Composition and codes of SD P614 mouth dissolving tablets

Ingredient (mg)	Formulation Codes								
	D11	**D12**	**D13**	**D14**	**D15**	**D16**	**D17**	**D18**	**D19**
SD P614#(DOM)	50	50	50	50	50	50	50	50	50
Croscarmellose Sodium	2	2	2	4	4	4	6	6	6
Crospovidone	2	4	6	2	4	6	2	4	6
Mannitol	10	10	10	10	10	10	10	10	10
Aspartame	1	1	1	1	1	1	1	1	1
Talc	4	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4	4
AvicelPH102	30	30	30	30	30	30	30	30	30
Lactose	97	95	93	95	93	91	93	91	89

Solid Dispersion containing PEG-6000, Drug to Polymer Ratio: 1:4

Table 3: Composition and codes of SD K314 mouth dissolving tablets

Ingredient (mg)	Formulation Codes								
	D20	**D21**	**D22**	**D23**	**D24**	**D25**	**D26**	**D27**	**D28**
SD K314[$](DOM)	50	50	50	50	50	50	50	50	50
Croscarmellose Sodium	2	2	2	4	4	4	6	6	6
Crospovidone	2	4	6	2	4	6	2	4	6
Mannitol	10	10	10	10	10	10	10	10	10
Aspartame	1	1	1	1	1	1	1	1	1
Talc	4	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4	4
AvicelPH102	30	30	30	30	30	30	30	30	30
Lactose	97	95	93	95	93	91	93	91	89

[$] Solid Dispersion containing PVP-K30, Drug to Polymer Ratio: 1:4

Table 4: Composition and codes of SD K914 mouth dissolving tablets

Ingredient (mg)	Formulation Codes								
	D29	**D30**	**D31**	**D32**	**D33**	**D34**	**D35**	**D36**	**D37**
SD K914[^](DOM)	50	50	50	50	50	50	50	50	50
Croscarmellose Sodium	2	2	2	4	4	4	6	6	6
Crospovidone	2	4	6	2	4	6	2	4	6
Mannitol	10	10	10	10	10	10	10	10	10
Aspartame	1	1	1	1	1	1	1	1	1
Talc	4	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4	4
AvicelPH102	30	30	30	30	30	30	30	30	30
Lactose	97	95	93	95	93	91	93	91	89

[^] Solid Dispersion containing PVP-K90, Drug to Polymer Ratio: 1:4

Evaluation of Powder Blends: All formulation powder bland batches were evaluated for precompression studies viz. angle of repose, bulk density, tapped density, Carr's consolidation index, and Hausner's ratio as per the official methods [13, 14, 15].

Evaluation of Compressed Tablets

Tablet Thickness

From each batch ten tablets were taken of and their thickness was recorded using Eureka Thickness Tester. The data is shown in Table 5.

Hardness

Hardness of the MDT of each batch was determined using Monsanto hardness tester. It is expressed in kg/cm^2. The data is shown in Table 5.

Weight Variation

All the batches of compressed MDT's were subjected to weight variation test, as per IP-2010 [16]. Twenty tablets were taken and weighted individually; their average weight was calculated and compared with the individual tablet weight to notice the variation in tablet weights. The data is shown in Table 5.

Friability

Friability of tablets was determined using Roche friabilator. Sample of 20 pre-weighed MDTs were placed in a friabilator and revolve at a speed of 25 rpm for 4 min [17]. Now dust removed from the tablets, weighed again, and percentage weight loss (friability) was calculated.

$$\% \text{ Friability} = \{1 - \frac{Wo}{W}\} \times 100 \quad \textbf{...Eq.1}$$

Where, W_0 is initial weight of the tablets before the test and W is the weight of the tablets after test. Results are presented in Table 5.

Wetting Time

Five circular tissue papers were placed in a petridish of 10 cm diameter. Ten milliliters of phosphate buffer pH 6.8 containing a water-soluble dye (Amaranth), was added to the petridish to check complete wetting of the tablet surface. A tablet was cautiously placed on the surface of the tissue paper in the petridish containing dye solution at 25°C and wetting time was noted using a stopwatch as the time required for dye solution to reach the upper surface of the tablets and to completely wet. These results were carried out in repetition of three [18,19]. The data is shown in Table 5.

***In vitro* Disintegration Test** [20,21]

Bi et al. recommended the use of a modified dissolution apparatus (a paddle method), in place of the conventional disintegration apparatus [20]. The

disintegration time of MDTs is determined by means of the disintegration test for conventional tablets that is described in the official monographs.

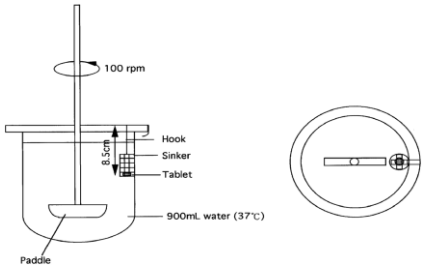

Figure 1: Modified Dissolution Apparatus for Disintegration of MDT's [20]

In this study, 900 ml of phosphate buffer pH 6.8 maintained at 37°C was used as the disintegration fluid and a paddle at 100 rpm used as stirring element. Disintegration time was noted when the tablet disintegrated and passed completely through the screen of the sinker (height 3–3.5 mm, width 3.5–4 mm and submersed at a depth of 8.5 cm from the top with the help of a hook).

Content Uniformity [22]:

Randomly selected twenty tablets from each trial batch were weighed and then powdered in a glass mortar with pestle. The weight equivalent to 10 mg of powdered DOM was taken and dissolved in 10 ml of methanol in volumetric flask. The volume was then adjusted to 100 ml with phosphate buffer pH 6.8. An aliquot of 2.5 ml of the above 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 284 nm and drug content was determined using calibration curve. The mean value and standard deviation of all the formulations were calculated.

%Drug Content =Sample Absorbance/ Standard Absorbance x 100.....**Eq.2**

***In vitro* Release study [23,24]:**

The *in vitro* release studies of all the formulations were carried out using USP type II dissolution test apparatus. The tablets were placed in dissolution bowls containing 900 ml of phosphate buffer pH 6.8 maintained at 37ºC ± 0.5 and stirred at 50 rpm. Samples (5 ml) were collected by manual programming at different time intervals (1, 2, 4, 6, 8, 10, 15 min) and replaced with fresh dissolution medium. The absorbance was determined spectrophotometrically at 284 nm. Comparison of dissolution profiles were constructed as shown in fig. 2 to 5. Cumulative drug release was calculated on the basis of mean amount of DOM present in the respective tablet by the formula:

Amount released (mg) =

$$\frac{\text{Concentration} \times \text{Bath volume} \times \text{Dilution factor}}{1000} \quad \text{.....Eq.3}$$

Percent drug release (PDR) =

$$\frac{\text{Amount released}}{\text{Drug content}} \times 100 \quad \text{.....Eq.4}$$

Factorial Design:

To see the effect of superdisintegrants on dependent variables and to know the actual amount of 2 superdisintegrants on the desirable properties of mouth dissolving tablets a 3^2 randomized full factorial design was used in which 2 factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations for every four selected solid dispersion batches (9x4=36 formulations + one blank means without superdisintegrants) [25,26]. The amount of Croscarmellose Sodium (X_1) and crospovidone (X_2) was selected as independent variables. The disintegration time, percentage friability and percent drug release were selected as dependent variables. Following polynomial equation is used to see the effect of independent variables on dependent variables

$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1X_2$ **Eq.5**

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate nonlinearity.

Result & Discussion

Pre-compression Evaluation

The results of bulk density and tapped density ranged from 0.45 ± 0.02 to 0.61 ± 0.01 and 0.54 ± 0.02 to 0.70 ± 0.04 respectively. The results of angle of repose (18.12 ± 0.11 to 26.36 ± 0.15) indicated good flow properties which were further supported by Carr's index (12.86 to 17.12) and Hausner's ratio data (1.15 to 1.21). Results are shown in table

Post-compression Evaluation Average tablet thickness (Table No. 5) was found to be consistent throughout the batch. Tablet thickness ranges between 4.01mm to 4.05mm. As these tablets are rapidly

disintegrating. Tablet hardness ranges between 2.12 kg/cm^2 to 2.83 kg/cm^2. Uniformity of weight of the MDTs was assessed and the average weight for all formulations was found to be between 198-203 mg which was within in the prescribed limits i.e. ±7.5% (185 to 215 mg).The wetting time in all the formulation was very fast except D1 (100 seconds) which may be due to absence of solid dispersion of Domperidone. It ranges between 24 to 45 seconds which is depend on the concentration of superdisintegrants in the tablets.

The friability of all formulations was found to be less than 1.0%. Friability was found to be in the range of 0.2- 0.54%. Disintegration time of prepared MDTs was in the range of 20-45 seconds. The disintegration time was found to follow in the following order; Crosscarmellose<Crospovidone and PVP<PEG. As the concentration of superdisintegrants in the formulations was increased the disintegration time was found to decrease. The percent drug content of the tablets was found between 96.40% to 100.72% of Domperidone. Drug content of all the formulations was found to be within the limits.

Table 5: Evaluation of Post-compression/Tablet parameters

Form. Code	Uniformity of Thickness (mm) (n =10)	Diameter (mm) (n = 3)	Hardness (kg/cm^2) (n=3)	Weight Variation(mg) (n = 20)	Wetting time (s) (n=5)	Drug Content Uniformity (n = 10) (%)
D1	4.04 ± 0.02	8.02 ± 0.01	2.69 ± 0.02	202 ± 3.34	98-103	97.56 ± 0.25
D2	4.02 ± 0.01	8.05 ± 0.02	2.25 ± 0.03	201 ± 2.60	41-45	99.71 ± 0.12
D3	4.03 ± 0.01	8.00 ± 0.01	2.47 ± 0.01	203 ± 3.70	39-42	97.04 ± 0.23
D4	4.01 ± 0.03	8.04 ± 0.01	2.53 ± 0.03	202 ± 2.95	36-40	98.85 ± 0.56
D5	4.01 ± 0.02	8.02 ± 0.01	2.29 ± 0.01	199 ± 3.67	40-44	98.29 ± 0.78
D6	4.00 ± 0.06	8.03 ± 0.02	2.45 ± 0.04	201 ± 3.12	35-39	99.62 ± 0.28
D7	4.02 ± 0.04	8.03 ± 0.03	2.23 ± 0.02	200 ± 2.15	33-37	98.47 ± 0.45
D8	4.03 ± 0.02	8.04 ± 0.01	2.62 ± 0.03	202 ± 1.82	31-35	97.33 ± 0.12
D9	4.05 ± 0.01	8.01 ± 0.03	2.51 ± 0.02	201 ± 2.16	28-32	99.24 ± 0.45
D10	4.04 ± 0.02	8.02 ± 0.01	2.59 ± 0.02	202 ± 2.45	26-30	97.67 ± 0.67
D11	4.02 ± 0.01	8.05 ± 0.02	2.15 ± 0.03	201 ± 2.12	40-44	99.82 ± 0.78
D12	4.03 ± 0.01	8.00 ± 0.01	2.37 ± 0.01	203 ± 2.70	38-41	97.15 ± 0.13
D13	4.01 ± 0.03	8.04 ± 0.01	2.43 ± 0.03	202 ± 1.95	35-39	98.96 ± 0.34
D14	4.01 ± 0.02	8.02 ± 0.01	2.49 ± 0.01	199 ± 2.57	39-43	98.4 ± 0.89
D15	4.00 ± 0.06	8.03 ± 0.02	2.35 ± 0.04	201 ± 1.82	34-38	99.73 ± 0.09
D16	4.02 ± 0.04	8.03 ± 0.03	2.13 ± 0.02	200 ± 2.15	32-36	98.58 ± 0.35
D17	4.03 ± 0.02	8.04 ± 0.01	2.52 ± 0.03	202 ± 1.82	30-34	97.44 ± 0.25
D18	4.05 ± 0.01	8.01 ± 0.03	2.51 ± 0.02	201 ± 1.96	27-31	99.35 ± 0.29
D19	4.04 ± 0.02	8.02 ± 0.01	2.79 ± 0.02	202 ± 2.34	25-29	97.5 ± 0.12
D20	4.03 ± 0.01	8.03 ± 0.03	2.65 ± 0.03	201 ± 2.80	40-44	99.65 ± 0.25
D21	4.01 ± 0.03	8.04 ± 0.01	2.57 ± 0.01	203 ± 2.73	38-41	96.98 ± 0.26
D22	4.01 ± 0.02	8.01 ± 0.03	2.43 ± 0.03	202 ± 2.95	35-39	98.79 ± 0.74
D23	4.00 ± 0.06	8.02 ± 0.01	2.39 ± 0.01	198 ± 1.87	39-43	98.23 ± 0.87
D24	4.02 ± 0.04	8.05 ± 0.02	2.25 ± 0.04	201 ± 2.72	34-38	99.56 ± 0.43
D25	4.03 ± 0.02	8.00 ± 0.01	2.23 ± 0.02	200 ± 2.35	32-36	98.41 ± 0.32

D26	4.05 ± 0.01	8.04 ± 0.01	2.12 ± 0.03	202 ± 2.52	30-34	97.27 ± 0.87
D27	4.04 ± 0.02	8.02 ± 0.01	2.31 ± 0.02	201 ± 2.56	27-31	99.18 ± 0.47
D28	4.02 ± 0.01	8.03 ± 0.02	2.49 ± 0.02	202 ± 2.34	25-29	97.59 ± 0.87
D29	4.03 ± 0.01	8.03 ± 0.03	2.55 ± 0.03	201 ± 1.90	39-43	99.74 ± 0.98
D30	4.01 ± 0.03	8.04 ± 0.01	2.67 ± 0.01	203 ± 2.70	37-40	97.07 ± 0.65
D31	4.01 ± 0.02	8.01 ± 0.03	2.83 ± 0.03	202 ± 2.75	34-38	98.88 ± 0.43
D32	4.00 ± 0.06	8.02 ± 0.01	2.19 ± 0.01	198 ± 2.87	38-42	98.32 ± 0.98
D33	4.02 ± 0.04	8.05 ± 0.02	2.35 ± 0.04	201 ± 2.92	33-37	99.65 ± 0.25
D34	4.03 ± 0.02	8.00 ± 0.01	2.53 ± 0.02	200 ± 2.45	31-35	98.5 ± 0.21
D35	4.05 ± 0.01	8.04 ± 0.01	2.62 ± 0.03	202 ± 1.82	29-33	97.36 ± 0.12
D36	4.04 ± 0.02	8.02 ± 0.01	2.51 ± 0.02	201 ± 2.16	26-30	99.27 ± 0.25
D37	4.02 ± 0.01	8.03 ± 0.02	2.65 ± 0.03	201 ± 2.80	24-28	99.65 ± 0.25

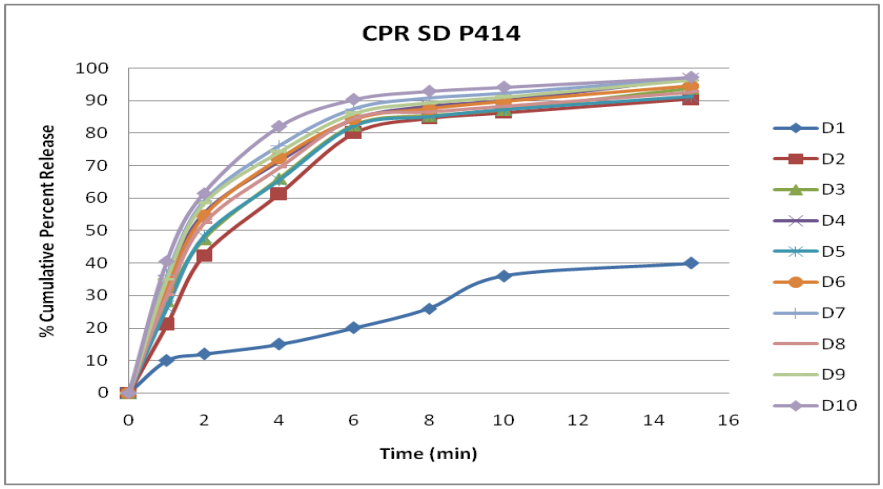

Fig. 2: Comparison of % Drug release of MDT prepared from Plain Domperidone (D1) and SD P414 (D2-D10)

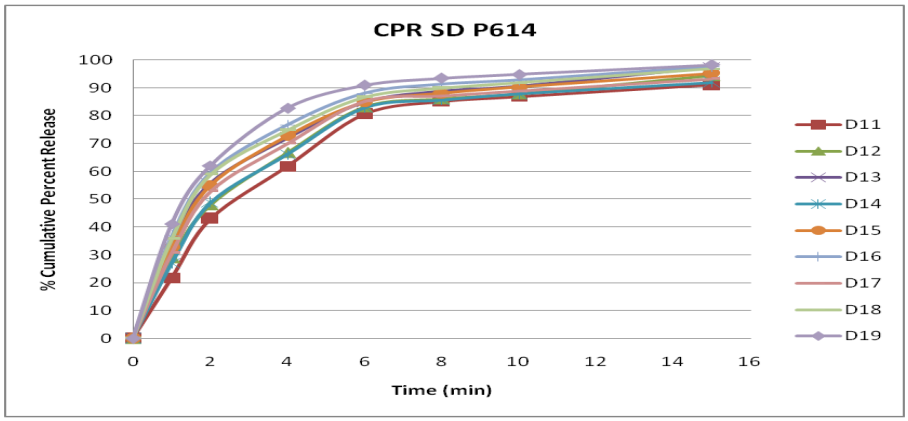

Fig. 3: Comparison of % Drug release of MDT prepared from SD P614 (D11-D19)

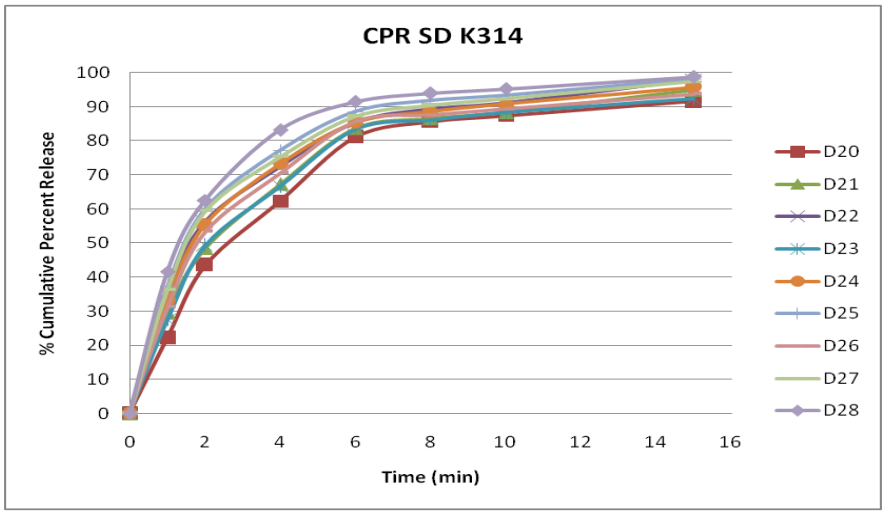

Fig. 4: Comparison of % Drug release of MDT prepared from SD K314 (D20-D28)

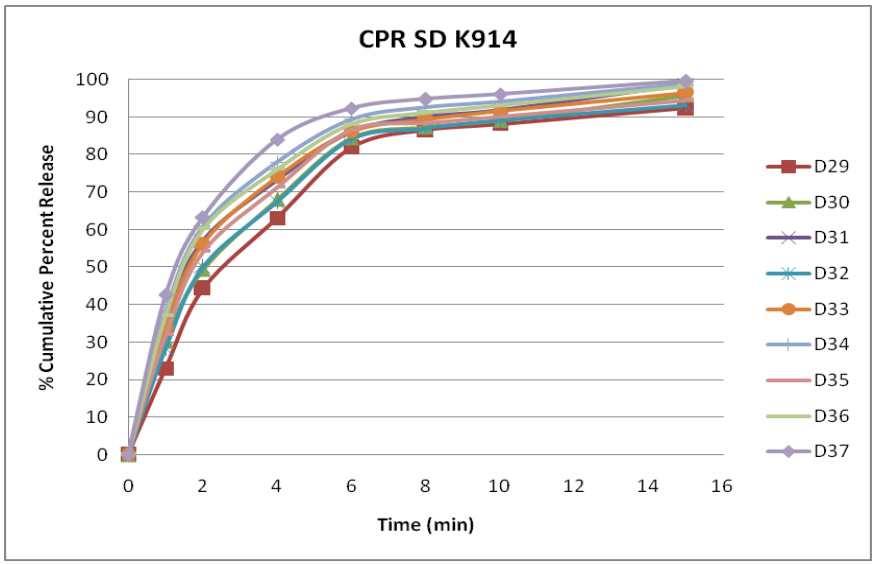

Fig. 5: Comparison of % Drug release of MDT prepared from SD K914 (D29-D37)

Optimization of Superdisintegrants Concentration:

Effect of Superdisintegrants on *in vitro* Disintegration Time

The response surface plot demonstrated the effect of amount of Croscarmellose Sodium (X_1) and crospovidone (X_2) on disintegration time (DT) (Y_1). The polynomial equation indicated that disintegration time was significantly decreased from 39 → 33 → 28 (of SD P414), 37 → 31 → 26 (of SD P614), 38 → 34 → 27 (of SD K314), 36 → 28 → 24 (of SD K914); and from 34 → 30 → 25 (of SD P414), 33 → 28 → 23 (of SD P614), 35 → 29 → 22 (of SD K314), 30 → 25 → 20 (of SD K914) at low and high level of Croscarmellose Sodium, respectively, as the concentration of the crospovidone was increased. The DT value was changed from 39 → 36 → 34 (of SD P414), 37 → 35 → 33 (of SD P614), 38 → 37 → 35 (of SD K314), 36 → 32 → 30 (of SD K914); and from 28 → 27 → 25 (of SD P414), 26 → 24 → 23 (of SD P614), 27 → 24 → 22 (of SD K314), 24 → 22 → 20 (of SD K914) at low and high levels of crospovidone, respectively, as the concentration of Croscarmellose Sodium was increased. Increased concentration of crospovidone has significant effect on DT at low concentration of Croscarmellose Sodium, whereas it has a little effect on DT at high concentration of Croscarmellose Sodium. Increased concentration of Croscarmellose Sodium exhibited a random effect on DT value at low level of crospovidone and little effect at high level of crospovidone.

Effect of Superdisintegrants on Friability

The response surface plot demonstrated the effect of amount of Croscarmellose Sodium (X_1) and crospovidone (X_2) on Friability (Y_2). The polynomial equation indicated that friability was decreased from 0.35 → 0.30 → 0.25 (of SD P414), 0.32 → 0.27 → 0.22 (of SD P614), 0.33 → 0.28 → 0.23 (of SD K314), 0.30 → 0.25 → 0.20 (of SD K914); and from 0.54 → 0.50 → 0.45 (of SD P414), 0.51 → 0.48 → 0.42 (of SD P614), 0.52 → 0.49 → 0.44 (of SD K314), 0.45 → 0.40 → 0.39 (of SD K914), at low and high level of Croscarmellose Sodium, respectively, as the concentration of the crospovidone was increased. The friability value was increased from 0.35 → 0.49 → 0.54 (of SD P414), 0.32 → 0.45 → 0.51 (of SD P614), 0.33 → 0.46 → 0.52 (of SD K314), 0.30 → 0.43 → 0.49 (of SD K914); and from 0.25 → 0.34 → 0.45 (of SD P414), 0.22 → 0.31 → 0.42 (of SD P614), 0.23 → 0.32 → 0.44 (of SD K314), 0.20 → 0.30 → 0.40 (of SD K914), at low and high levels of crospovidone, respectively, as the concentration of Croscarmellose Sodium was increased. Increased concentration of crospovidone significantly decreases friability at low & high concentration of Croscarmellose Sodium. Increased concentration of Croscarmellose Sodium exhibited insignificant increases in friability at low & high level of crospovidone.

Effect of Superdisintegrants on Percent Drug Release

The response surface plot demonstrated the effect of amount of Croscarmellose Sodium (X_1) and crospovidone (X_2) on Percent Drug Release (PDR) (Y_3). The polynomial equation indicated that PDR was increased from 90.5 → 93.8 → 96.8 (of SD P414), 91.1 → 94.4 → 97.4 (of SD P614), 91.6 → 94.9 → 97.9 (of SD K314), 92.4 → 95.7 → 98.7 (of SD K914); and from 92.6 → 94.6→ 97.2 (of SD P414), 93.2 → 96.9→ 98.2 (of SD P614), 93.7 → 97.4→ 98.8 (of SD K314), 94.5 → 98.2→ 99.6 (of SD K914), at low and high level of Croscarmellose Sodium, respectively, as the concentration of the crospovidone was increased. The PDR was increased from 90.5 → 91.3 → 92.6 (of SD P414), 91.1 → 91.9 → 93.2 (of SD P614), 91.6 → 92.4 → 93.7 (of SD K314), 92.4 → 93.3 → 94.5 (of SD K914); and from 96.8 → 97 → 97.2 (of SD P414), 97.4 → 97.6 → 98.2 (of SD P614), 97.9 → 98.1 → 98.8 (of SD K314), 98.7 → 98.9 → 99.6 (of SD K914), at low and high levels of crospovidone, respectively, as the concentration of Croscarmellose Sodium was increased. Increased concentration of crospovidone significantly increases PDR at low & high concentration of Croscarmellose Sodium. Increased concentration of Croscarmellose Sodium exhibited little increases in PDR at low & high level of crospovidone.

Coded values	Actual values (mg)	
	X_1	X_2
-1	2	2
0	4	4
1	6	6

Table 6: 3^2 Full Factorial Design Layout

Batch Codes	Variable Levels in Coded Form		Disintegration Time	% Friability	% Drug Release
	X_1	X_2	DT (sec)	F (%)	Disso (%)
3^2 Full Factorial Design Layout (MDT of SD P414)					
D2	-1	-1	39	0.35	90.5
D3	-1	0	33	0.3	93.8
D4	-1	1	28	0.25	96.8
D5	0	-1	36	0.49	91.3
D6	0	0	32	0.39	94.6
D7	0	1	27	0.34	97.0
D8	1	-1	34	0.54	92.6
D9	1	0	30	0.5	94.6
D10	1	1	25	0.45	97.2
OPT	0.09	0.22	30.56	0.4	95.0
3^2 Full Factorial Design Layout					
D11	-1	-1	37	0.32	91.1
D12	-1	0	31	0.27	94.4

D13	-1	1	26	0.22	97.4
D14	0	-1	35	0.45	91.9
D15	0	0	30	0.36	95.2
D16	0	1	24	0.31	97.6
D17	1	-1	33	0.51	93.2
D18	1	0	28	0.48	96.9
D19	1	1	23	0.42	98.2
OPT	0.19	-0.17	30.24	0.4	95.0
3^2 Full Factorial Design Layout (MDT of SD K314)					
D20	-1	-1	38	0.33	91.6
D21	-1	0	34	0.28	94.9
D22	-1	1	27	0.23	97.9
D23	0	-1	37	0.46	92.4
D24	0	0	32	0.38	95.7
D25	0	1	24	0.32	98.1
D26	1	-1	35	0.52	93.7
D27	1	0	29	0.49	97.4
D28	1	1	22	0.44	98.8
OPT	0.13	-0.01	31.58	0.4	95.87
3^2 Full Factorial Design Layout (MDT of SD K914)					
D29	-1	-1	36	0.3	92.4
D30	-1	0	28	0.25	95.7
D31	-1	1	24	0.2	98.7
D32	0	-1	32	0.43	93.3
D33	0	0	26	0.38	96.5
D34	0	1	22	0.3	98.9
D35	1	-1	30	0.49	94.5
D36	1	0	25	0.45	98.2
D37	1	1	20	0.4	99.6
OPT	-0.002≈0	-0.52	29.02	0.39	94.99

Table 7: Summary of Results of Regression Analysis (MDT of SDP414)

Response (full model)	**b_0**	**b_1**	**b_2**	**b_{12}**	**b_{11}**	**b_{22}**
MDT of SD P414						
Disintegration Time	31.778	**-1.833**	**-4.833**	0.500	-0.167	-0.167
% Friability	0.402	**0.098**	**-0.057**	0.003	-0.008	0.007
% Drug Release	94.367	**0.550**	**2.767**	**-0.425**	-0.050	-0.100
MDT of SD P614						
Disintegration Time	29.667	**-1.667**	**-5.333**	0.250	0.000	0.000
% Friability	0.372	**0.100**	**-0.055**	0.003	-0.003	0.002
% Drug Release	95.300	**0.900**	**2.833**	-0.325	0.300	-0.600
MDT of SD K314						
Disintegration Time	31.778	**-2.167**	**-6.167**	-0.500	-0.167	**-1.167**
% Friability	0.387	**0.102**	**-0.053**	0.005	-0.005	0.000
% Drug Release	95.789	**0.917**	**2.850**	-0.300	0.317	-0.583
MDT of SD K914						
Disintegration Time	26.000	**-2.167**	**-5.333**	0.500	0.500	1.000
% Friability	0.374	**0.098**	**-0.053**	0.003	-0.022	-0.007
% Drug Release	96.611	**0.917**	**2.833**	-0.300	0.283	-0.567

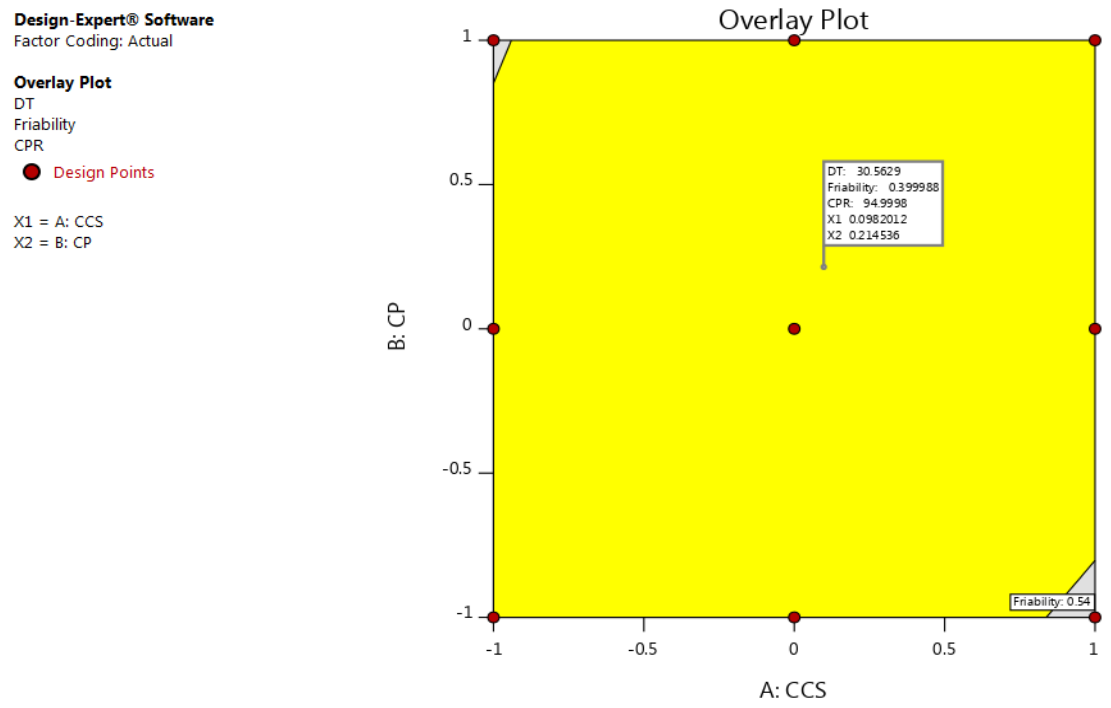

Fig. 6: Overlay Plot for Predicted Optimized Formulation of SD P414

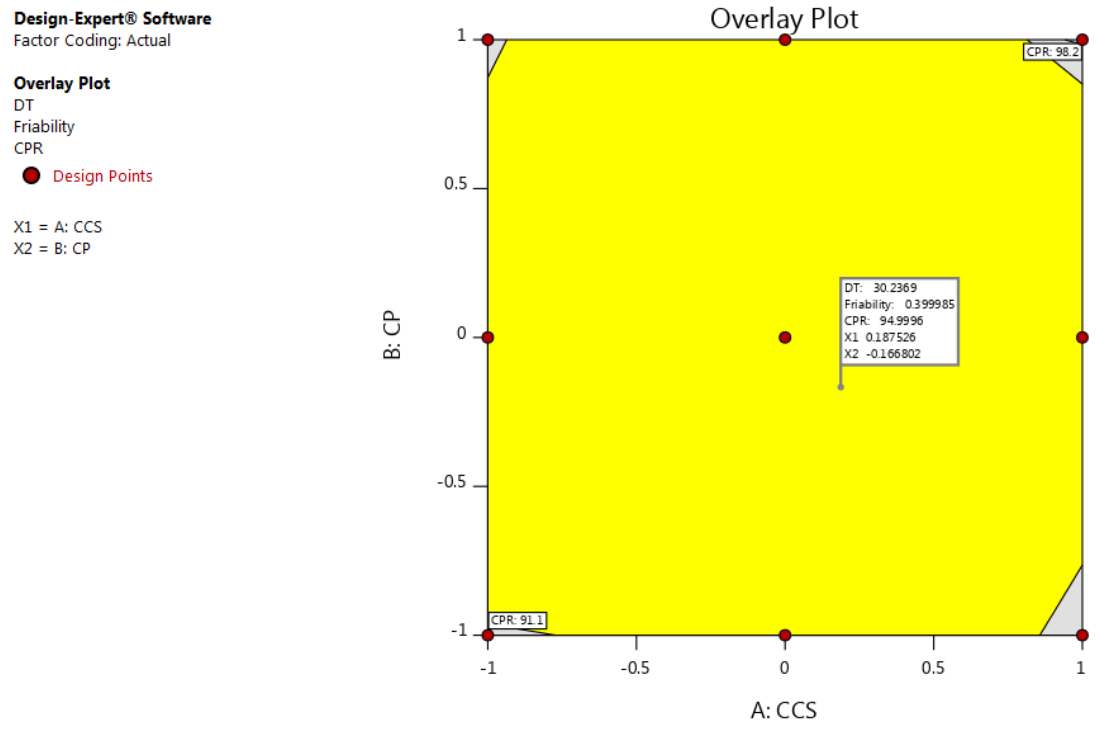

Fig. 7: Overlay Plot for Predicted Optimized Formulation of SD P614

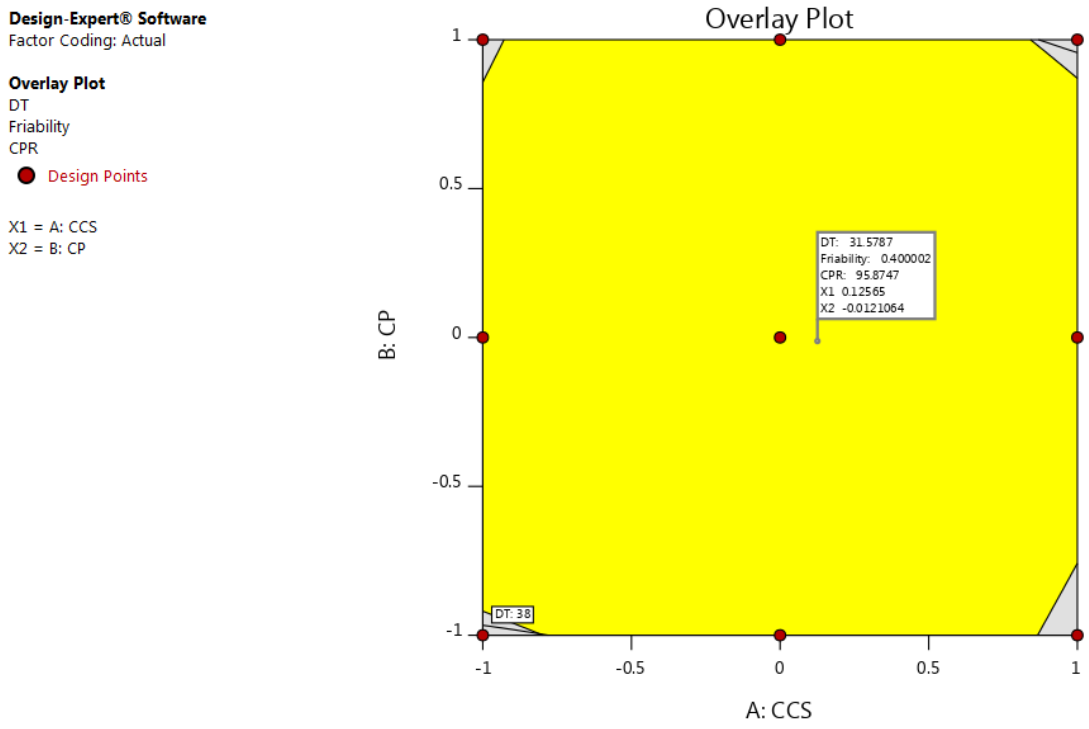

Fig. 8: Contour Plot for Predicted Optimized Formulation of SD K314

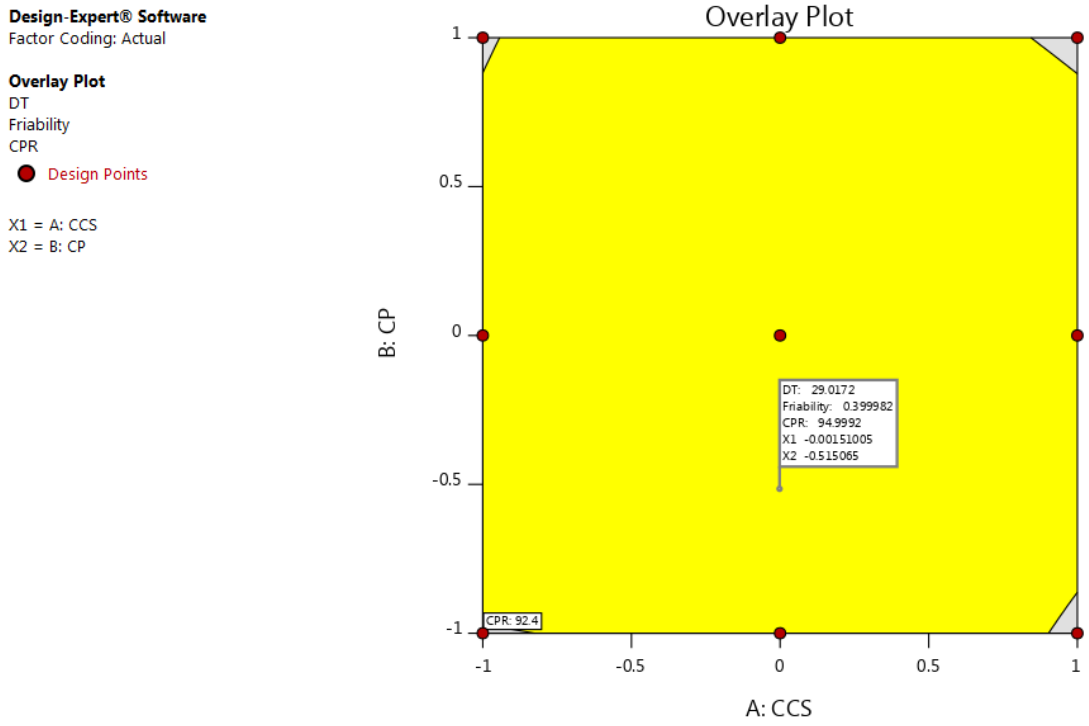

Fig. 9: Overlay Plot for Predicted Optimized Formulation of SD K915

Conclusion

Mouth dissolving tablets of Domperidone solid dispersion (prepared using four different combinations of drug with two different polymers in ratio 1:4) were formulated and optimized using 3^2 factorial design. Two independent variables i.e. amount of

Croscarmellose Sodium and crospovidone at three levels were selected on the basis of preliminary studies. As the concentration of superdisintegrants in the formulations was increased the disintegration time was found to decrease. It was found that increased concentration of crospovidone cause decrease in disintegration time and increased percent drug release and has very little effect of increasing concentration of croscarmellose sodium. All the formulations show maximum (>90%) drug release in minimum time. Design-Expert® (11.0.4) software was used for design & optimization of batches and response surface plots & contour plots were drawn, and optimum formulations were selected by desirability plots. For various response variables, polynomial mathematical models were generated using multiple regression analysis, and found to be statistically significant ($P<0.05$). Optimized formulations were further used for preparing optimized mouth dissolving tablets.

References

1. Aulton ME. Pharmaceutics - The science of dosage from design. 2001, 2nd edition, pp 7-37. London: Churchill Livingstone
2. Satinder Kakar, Ramandeep Singh, Manisha Shah. Formulation and evaluation of orodispersible tablets of tramadol hydrochloride. FABAD Journal of Pharmaceutical Sciences. 2013 ; 38(2):73-81
3. Meenu Bhatt, Satinder Kakar, Ramandeep Singh. A Review On Floating Drug Delivery System. International Journal Of Recent Advances In Pharmaceutical Research. 2015; 5(2):57-67
4. Rinaki E, Valsami G, Macheras P. Quantitative biopharmaceutics classification system: The central role of dose/solubility ratio. Pharm Res. 2003;20:1917–25.
5. Yellela SRK. Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. Journal of Bioequivalence & Bioavailability. 2010;2(2):28-36.
6. Edward KH, Li D. "Solubility," in Drug like Properties: Concept, Structure, Design and Methods, from ADME to Toxicity Optimization, p. 56, Elsevier, 2008.
7. Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. International Journal of Pharmaceutical Sciences Review and Research. 2010;5(1):41-51.
8. Sharma D, Soni M, Kumar S, Gupta GD. Solubility enhancement—eminent role in poorly soluble drugs. Research Journal of Pharmacy and Technology. 2009;2(2):220-224.
9. Kumar A, Sahoo SK, Padhee K, Kochar PS, Sathapathy A, Pathak N. Review on solubility enhancement techniques for hydrophobic drugs. Pharmacie Globale. 2011;3(3):001-007.
10. Tripathi K.D. "Antiemetics". In: Essentials of Medical Pharmacology, Jaypee Brothers Medical Publishers (P) LTD, New Delhi, Fifth Edition, Reprint 2004. 601-604.
11. Chiou WL, Reigelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971;60(9):1281-1302.
12. Serajuddin A. Solid dispersion technique. J Pharm Sci. 1999;88(10):891-900.
13. Marshall K, Lachmann Liberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd edition. Varghese publishing house, Mumbai. 1987;67-69.
14. Subrahmanyam CVS. Textbook of physical pharmaceutics. Delhi: Vallabh Prakashan; 2005:210-228.
15. Y. Bi, "Preparation and evaluation of a compressed tablet rapidlydisintegrating in the oral cavity," Chemical and Pharmaceutical Bulletin, vol. 44, no. 11, pp. 2121–2127, 1996.
16. Uniformity of Weight of Single-Dose Preparations. Indian Pharmacopoeia. Indian Pharmacopoeia Commission: Government of India, Ministry of Health and Family Welfare, Controller of Publications, Delhi. 2010;1:192.
17. Friability of Uncoated Tablets. Indian Pharmacopoeia. Indian Pharmacopoeia Commission: Government of India, Ministry of Health and Family Welfare, Controller of Publications, Delhi. 2010;1:193.
18. Battu SK, Repay MA, Maunder S, Rio MY. Formulation and evaluation of rapidly disintegrating tablet Fenoverine tablets: Effect of Superdisintegrants, Drug Dev. Ind. Pharm. (2007);33:1225-1232.
19. Bi Y, Sunada H, Yonezawa Y, Danjo K, Otsuka A, Iida K. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem. Pharm. Bull. 1996;44:2121–2127.
20. Bi Y, Sunada H, Yonezawa Y, Danjo K, Otsuka A, Iida K. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem. Pharm. Bull. 1996;44:2121–2127.
21. Narazaki R, Harada T, Takami N, Kato Y, Ohwaki T. A new method for disintegration studies of rapid disintegrating tablet. Chem. Pharm. Bull. 2004,52:704–707.

22. Uniformity of Content of Single-Dose Preparations. Indian Pharmacopoeia. Indian Pharmacopoeia Commission: Government of India, Ministry of Health and Family Welfare, Controller of Publications, Delhi. 2010;1:192-193.

23. Dissolution Test. Indian Pharmacopoeia. Indian Pharmacopoeia Commission: Government of India, Ministry of Health and Family Welfare, Controller of Publications, Delhi. 2010;1:189-192.

24. Dissolution. United States Pharmacopoeia. USP 30 NF 25. 711(1-4).

25. Gohel MC, Parikh RK, Brahmbhatt BK, Shah AR. Preparation and assessment of novel coprocessed superdisintegratnt consisting of crospovidone and sodium starch glycolate. AAPS Pharm Sci Tech. 2007;8(1):Article 9.

26. Jeong SH, Park K. Development of sustained release fast-disintegrating tablets using various polymer-coated ion-exchange resin complexes. Int J Pharm. 2008;353:195–204.

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