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Solubility Enhancement and Optimization of Fast dissolving tablets of Domperidone using 3² Full Factorial Design

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Abstract

The aim of the research work was to develop and optimize fast dissolving tablets of Domperidone by direct compression technique. Due to the solubility issues with Domperidone, the solid dispersion technique was used using fusion and freeze drying method. For the investigation purpose, a 3^2 full factorial design was used to know the joint influence of two formulation variables, Sodium starch Glycolate and crospovidone. The formulated tablets were evaluated for its percent friability and their disintegration time. The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating dosage form, tablets should be prepared using an optimum concentration of sodium starch glycolate and a crospovidone. A contour plot was also presented to graphically represent the effect of the independent variables on the disintegration time 30 s and percent friability 0.5 %. A checkpoint batch was also prepared to prove the validity of the evolved mathematical model. The optimized tablet should be prepared with an optimum amount of Sodium starch Glycolate (2.08 mg), and Crospovidone (2.58 mg) which disintegrated in the 30 seconds, with friability of 0.5% and of drug release within- 5 min. The optimized approach aided both the formulation of fast dissolving tablets and the understanding of the effect of formulation processing variables on the development of formulation.

Key words: Fast dissolving tablet, Domperidone, factorial design, Response Surface, contour plot

Introduction

The oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. The most popular solid dosage forms are tablet and capsule. One drawback of these dosage forms however is the difficulty to swallow. Dysphasia or difficulty in swallowing is seen nearly 35% in the general population. This disorder is also associated with number of medical conditions including stroke, Parkinson's disease, AIDS, head and neck radiation therapy and other neurological disorders including cerebral palsy.[1-3]

Many elderly persons will have difficulties in taking conventional solid dosage form (tablets and capsules) because of their hand tremors and dysphasia. Swallowing problems are also common in young individuals because of their under developed muscular system.

Other groups, who may experience problems in swallowing solid dosage form, are the mentally ill, the developmentally disabled, uncooperative patients and reduced liquid intake plans or nausea. In some cases such as motion sickness, sudden episode of allergic attack or coughing and an unavailability of water, swallowing of tablets may become difficult.[4]

To fulfill these medical needs, the pharmaceutical technologist have devoted considerable effort to develop a novel type of dosage form for oral administration, the Fast Dissolving Tablet (FDT), tablet that disintegrates and dissolves rapidly in saliva without need of water. The fast dissolving tablets usually dissolve in oral cavity within 15 to 60 s. The faster the drug goes into solution, the quicker the absorption and onset of clinical effects. The development of fast dissolving tablets also provides line extension in the market place.[1-4]

To avoid such problems the fast dissolving tablet of Domperidone was prepared with the aim to minimize nausea and vomiting also tablet of domperidone will help in rapid and complete absorption in the gastrointestinal tract in order to achieve therapeutic success.

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Material and Methods

Materials

Domperidone was obtained as a gift sample from Cipla, Baddi, India. Ac-disol, Sodium starch Glycolate, Crospovidone and Avicel PH 102 were purchased from Signet Chemicals, Mumbai, India. Dextrose, Talc and Magnesium Stearate were purchased from Loba Chemie, Mumbai. All other chemicals used were of analytical grade.

Development of Solid dispersion of Domperidone

The solubility of domperidone in alkaline pH is reduced and due to the oral bioavailability of 13–17% and this drug is classified with class-II (poor solubility and high permeability) in BCS classification. In order to improve the therapeutic effectiveness of domperidone the solid dispersion techniques were used to improve solubility.

Preparation of physical mixture and solid dispersion

Solid dispersion of domperidone (DOP) was prepared in three mass ratios (1:1, 1:3 and 1:5 w/w) with fusion method and lyophilization technique with Poloxamer 407 (PXM) as hydrophilic carrier. The formulations prepared were compared with physical mixture of drug and polymer. Formulation with best results was chosen for evaluations.

Physical mixture

Physical mixtures of DOP and PXM in (1:1, 1:3 and 1:5w/w) ratios was prepared by mixing the two components in geometric proportion in a mortar for 10 minutes so as to obtain a homogeneous mixture. The resulting mixtures were sieved through # 60 mesh sieve (Endecott's, London) and stored in air-tight containers until further evaluation.

Fusion method

PXM was melted by heating up to 70°C was and kept in a porcelain dish and a proper amount of drug was added to obtain a homogenous dispersion. The mixture was cooled sieved through a 100-mesh screen, and stored in a screw-cap vial at room temperature for further use.

Freeze dried (lyophilized) solid dispersions

All SD preparations containing different ratio (1:1, 1:3 and 1:5w/w) of DOP and PXM were prepared using freeze drying method. DOP was weighed and was dispersed into 100 mL of PXM solution, the dispersion being stirred with the help of a magnetic stirrer. 25% liquid ammonia was added drop wise and stirred until a clear solution was obtained. The sample was freezed to a temperature of -45ºC (Freezer Unicryo) and lyophilized in a freeze dryer (Vertis Sentry, Freeze Mobile, 25SL, Gardiner, NY, USA) at a temperature of -40ºC and vacuum of 90 x 10^{-3} Mbar. The freeze dried mass was then sifted through # 60 mesh sieve and stored in air-tight containers until further evaluation.

Table 1: Compressibility parameters of various formulations of solid dispersion

Method	Ratio (DOP:PXM)	Bulk Density (g/cc)	Tapped Density (g/cc)	Hausner's Ratio	Compress-ibility Index (%)	Angle of Repose (º)
Physical Mixture	1:1 (SD1)	0.219 ±0.02	0.295 ±0.01	1.071 ±0.012	6.604 ±1.33	28.34 ±1.36
	1:3 (SD2)	0.316 ±0.01	0.336 ±0.01	1.065 ±0.024	5.621 ±1.23	29.91 ±1.22
	1:5 (SD3)	0.397 ±0.01	0.405 ±0.02	1.048 ±0.013	4.556 ±1.42	31.15 ±1.17
Fusion	1:1(SD4)	0.287 ±0.04	0.311 ±0.02	1.059 ±0.015	5.623 ±1.22	22.44 ±1.16
	1:3(SD5)	0.336 ±0.01	0.347 ±0.05	1.073 ±0.010	6.792 ±1.01	22.99 ±1.09
	1:5(SD6)	0.403 ±0.05	0.433 ±0.06	1.065 ±0.003	6.076 ±1.23	23.56 ±1.13
Lyophilization	1:1(SD7)	0.398 ±0.03	0.416 ±0.04	1.069 ±0.006	6.422 ±1.08	22.59 ±1.16

1:3(SD8)	0.412 ±0.01	0.435 ±0.01	1.057 ±0.016	5.432 ±1.09	23.32 ±1.13
1:5(SD9)	0.462 ±0.07	0.484 ±0.02	1.082 ±0.027	7.601 ±1.24	24.22 ±1.43

Evaluation of solid dispersions

Table 2: % Drug content and aqueous solubility of various formulations of solid dispersion

Formulation code	% Drug content	Solubility (X 10⁻⁴mg/ml)
Pure drug (DOP)	90.3±0.2	9.71±0.03
SD1	91.4±0.1	16.13±0.02
SD2	92.7±0.3	35.91±0.31
SD3	93.5±0.8	49.32±0.27
SD4	94.2±0.4	18.73±0.14
SD5	95.7±0.2	41.13±0.43
SD6	97.9±0.1	59.65±0.27
SD7	97.1±0.3	24.34±0.04
SD8	98.9±0.7	45.09±0.31
SD9	99.7±0.05	71.83±0.52

Note: The Solubility column header reads $(X\ 10^{-4}\text{mg/ml})$.

Superdisintegrant addition technique

Preparation of co-processed Superdisintegrants

The preparation of co-processed superdisintegrants is as follows: the blend of various superdisintegrants was prepared to factorial design batches.

Physical Mixture

The physical mixture of sodium starch glycolate and crospovidone was prepared by mixing them together in glass pestle motor.

Co-processed by solvent evaporation method

The preparation of co-processed superdisintegrants was as follows: blends of SSG and crospovidone in different ratio total weight of 10 g were added to 50 ml of isopropyl alcohol. The contents of beaker were mixed on a stirrer. The temperature was maintained between 65-70ºC and stirring continued till isopropyl alcohol was evaporated. The wet coherent mass was sieved through sieve no. #100, the powder was dried using tray drier at 60ºC for 20 minutes[21].

Co-processed by lyophilization method

The blends of SSG and crospovidone in various ratios in total weight of 10 g were added to 50 mL of isopropyl alcohol in round bottom flask. The contents of the RBF were lyophilized for 10 to 12 hrs. The powder was dried further for the moisture removal using oven at 50º C temperature[21].
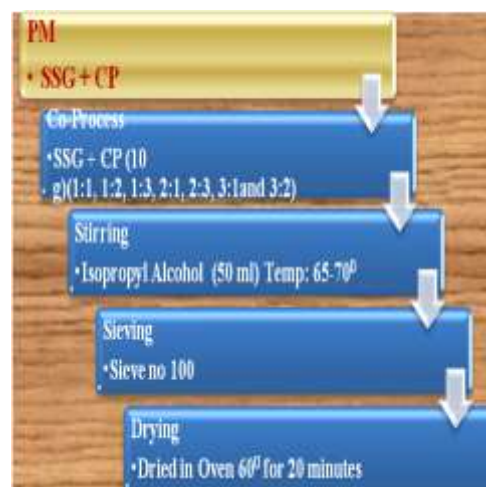
Figure 1: Preparation of Physical Mixture, Co-processed Superdisintegrants & Lyophilization Method

Figure 2: Particle Size Analysis

Evaluation of co-processed superdisintegrant blends
Particle size analysis

The microscope technique was used in testing the particle size distribution of superdisintegrants and their blends. The particle size of the disintegrants was evaluating to prepare the slides of powder and observed under the microscope. In order to test the swelling of superdisintegrant in water and sorenson's buffer (pH 6.8, saliva pH), disintegrant powder was first dispersed in a small volume of liquid and it was ultrasonicated for 10 minutes. The suspension was transferred using pipette to a on the glass slide.
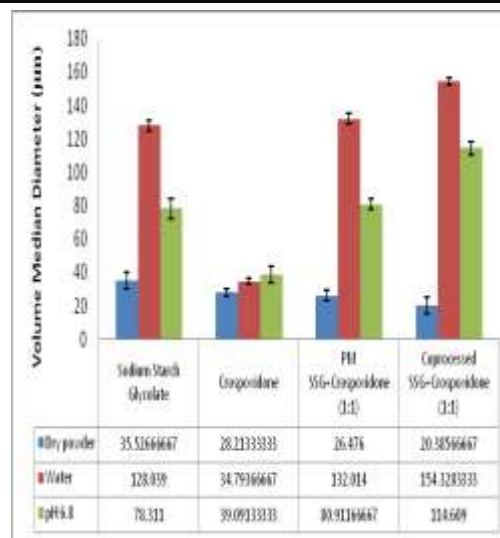
Mass- volume relationship and flow properties
For the mass-volume relationship bulk density (ρ_b), tapped density (ρ_t), hausner's ratio (RH = ρ_t / ρ_b) and compressibility index ($Ic = 100(\rho_t - \rho_b) / \rho_b$) was determined with the bulk/tapped densitometer. The angle of repose was calculated using funnel method. The blend was poured through a glass funnel that can be raised vertically until a specified cone height (h) was obtained. Radius of the conical pile (r) was measured and angle of repose (θ) was calculated using the formula tan θ = h/r[12-18]. The results are shown in Table 3.

Table 3: Evaluation of Superdisintegrant blends

Batch	Ratio	Bulk Density (g/cc)	Tapped Density (g/cc)	Hausner's Ratio	Compressibility Index (%)	Angle of Repose (°)
SSG	-	0.759 ±0.005	0.945 ±0.004	1.250 ±0.004	20.029 ±0.234	36.18 ±0.174
Crospovidone	-	1.244 ±0.020	1.858 ±0.015	1.494 ±0.034	33.039 ±1.519	44.02 ±1.010
Physical Mixture (SSG+ Crospovidone)	1:1	0.891 ±0.008	1.157 ±0.040	1.299 ±0.039	22.946 ±2.268	37.83 ±1.714
Co processed (SSG+ Crospovidone)	1:1	0.624 ±0.002	0.700 ±0.004	1.122 ±0.004	10.856 ±0.332	22.42 ±0.626
Lyophilized (SSG+ Crospovidone)	1:1	0.620 ±0.002	0.695 ±0.004	1.120 ±0.004	9.856 ±0.291	21.02 ±0.626

n=6, ±SD

Preparation of Fast Dissolving Tablets (FDT) using co-processed superdisintegrant blends

Tablets formulated by using single punch tablet machine (Cadmach, Ahmedabad) to produce flat faced tablets weighing 100 mg each with a diameter of 5 mm. A minimum of 50 tablets were prepared for each batch. The superdisintegrants in different ratios were used to prepare the tablets. All the ingredients were shown in Table 4 were passed through sieve no. 60 and were co-grounded in a glass pestle motor[3-5]. Before compression tablet blends was tested for mass-volume (bulk density, tapped density, Hausner's ratio, compressibility index) and flow properties (Table 5). Tablets were evaluated for post compression parameters (Table 6).

Table 4: Formulation of Drug Tablets with Superdisintegrants

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10 *	F11 #	F12 $
Domperidone+ Poloxamer 407	50	50	50	50	50	50	50	50	50	50	50	50
Ac-Di-Sol	2	3	4									
Sodium Starch Glycolate				2	3	4				2	2	2
Crospovidone							2	3	4	2	2	2
Avicel PH102	35	35	35	35	35	35	35	35	35	35	35	35
Dextrose	10	10	10	10	10	10	10	10	10	10	10	10
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2

*- Physical Mixture, # Coprocessed, $ Lyophilized

Table 5: Characterization of Tablet Blends

Formulation Codes	Parameters				
	Bulk Density (g/cc)	Tapped Density (g/cc)	Hausner's Ratio	Compressibility Index (%)	Angle of Repose (º)
F1	0.371 ±0.012	0.395 ±0.013	1.071 ±0.012	6.604 ±1.330	23.34 ±1.363
F2	0.408 ±0.015	0.436 ±0.012	1.065 ±0.024	5.621 ±1.233	25.19 ±1.221
F3	0.383 ±0.023	0.405 ±0.021	1.048 ±0.013	4.556 ±1.422	27.35 ±1.007
F4	0.387 ±0.004	0.421 ±0.002	1.059 ±0.015	5.623 ±1.221	24.44 ±1.126
F5	0.406 ±0.013	0.427 ±0.005	1.073 ±0.010	6.792 ±1.012	25.99 ±1.096
F6	0.403 ±0.025	0.433 ±0.006	1.065 ±0.003	6.076 ±1.231	23.56 ±1.132
F7	0.409 ±0.034	0.436 ±0.014	1.069 ±0.006	6.422 ±1.086	26.59 ±1.165
F8	0.384 ±0.013	0.405 ±0.017	1.057 ±0.016	5.432 ±1.097	26.32 ±1.136
F9	0.396 ±0.017	0.424 ±0.023	1.082 ±0.027	7.601 ±1.242	25.22 ±1.432
F10	0.405 ±0.006	0.429 ±0.023	1.095 ±0.010	8.756 ±1.134	23.59 ±1.243
F11	0.399 ±0.023	0.417 ±0.012	1.059 ±0.015	5.594 ±1.123	25.62 ±0.968
F12	0.402 ±0.005	0.422 ±0.007	1.067 ±0.023	6.294 ±1.324	23.54 ±0.847

Table 6: Post-Compression Characterization

F. Codes	Parameters							
	Thickness (mm)	Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Wetting Time (s)	Dispersion Time (s)	Disintegration Time (s)	Drug content in (%)
F1	5.436 ±0.012	100.667 ±2.082	3.6 ±0.152	0.612 ±0.042	74 ±4.01	112 ±1.52	98 ±1.52	85 ±3.21
F2	5.421 ±0.015	99.333 ±1.528	3.2 ±0.187	0.626 ±0.038	66 ±2.51	102 ±2.93	84 ±2.93	88 ±4.11
F3	5.414 ±0.011	101.000 ±2.646	3.3 ±0.165	0.665 ±0.057	54 ±3.21	90 ±2.04	63 ±2.04	78 ±3.46
F4	5.425 ±0.011	103.332 ±1.528	3.4 ±0.170	0.690 ±0.048	39 ±2.08	81 ±2.08	51 ±2.08	81 ±2.28
F5	5.437 ±0.009	101.00 ±2.646	3.1 ±0.178	0.608 ±0.028	62 ±2.21	107 ±3.01	87 ±3.01	83 ±2.11
F6	5.412 ±0.011	99.667 ±2.082	3.3 ±0.095	0.602 ±0.031	58 ±1.98	95 ±1.51	76 ±1.51	89 ±4.11
F7	5.445 ±0.008	102.667 ±1.528	3.4 ±0.165	0.579 ±0.041	41 ±2.31	79 ±1.98	59 ±1.98	91 ±1.11
F8	5.425 ±0.017	106.00 ±2.646	3.6 ±0.187	0.547 ±0.052	32 ±1.52	73 ±2.02	42 ±2.02	92 ±3.89
F9	5.431 ±0.014	108.333 ±1.528	3.2 ±0.179	0.679 ±0.036	87 ±4.93	121 ±4.01	106 ±4.01	90 ±4.20
F10	5.408 ±0.012	102.333 ±2.517	2.9 ±0.134	0.656 ±0.053	75 ±3.87	109 ±3.21	58 ±3.21	93 ±3.18
F11	5.421 ±0.018	103.667 ±2.887	3.2 ±0.178	0.599 ±0.056	58 ±2.65	88 ±2.22	41 ±2.22	94 ±2.98
F12	5.396 ±0.013	104.00 ±2.517	2.9 ±0.126	0.512 ±0.058	48 ±1.85	78 ±3.48	26 ±1.89	97 ±4.21

Optimization of Formula for FDT prepared by superdisintegrant technique

Preparation of Full factorial design batches

A 3^2 full factorial design was used. In this design 2 factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations[23,24]. The amount of SSG (X_1) and the amount of crospovidone (X_2) was selected as independent variables. The disintegration time and percentage friability were selected as dependent variables. A polynomial term was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1$$

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.

Preparation method of fast dissolving tablets

The raw materials were passed through a no. 100 screen prior to mixing. Domperidone, SSG, crospovidone, microcrystalline cellulose and lactose were mixed using a glass mortar and pestle. The blends were lubricated with 2% w/w talc and 2% w/w magnesium stearate. The blends ready for compression were converted into tablets using a single-punch tablet machine (Cadmach, Ahmedabad, India).
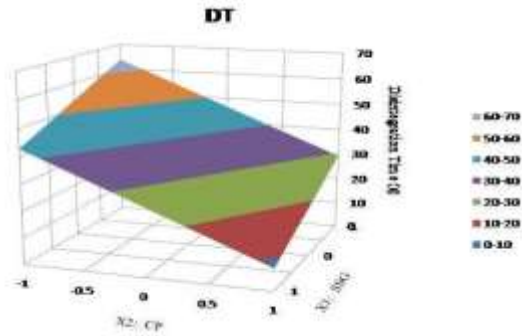
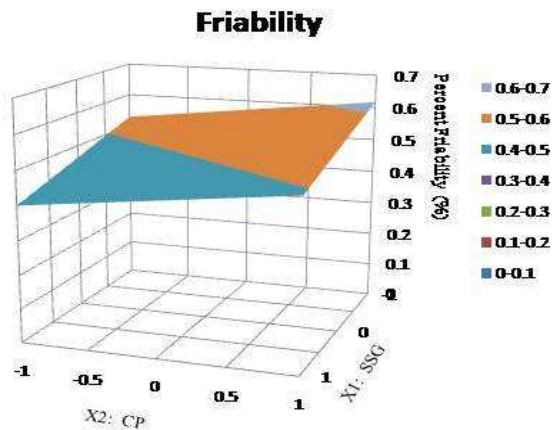**Figure 4: Response Surface for Disintegration Time**
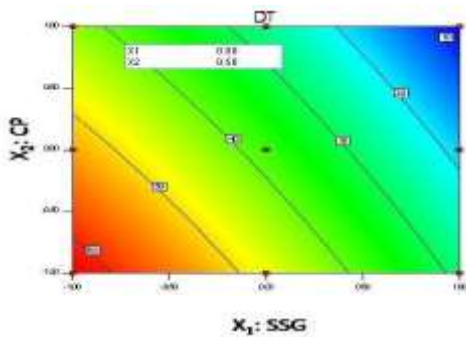

Figure 6: Response Surface for Percent Friability

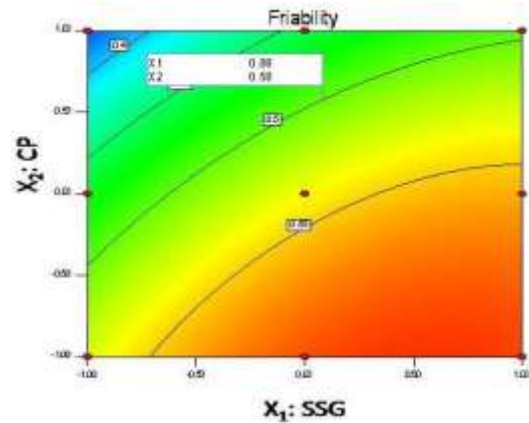**Figure 7: Contour Plot for Disintegration Time**

Figure 8: Contour Plot for Percent Friability

Optimization of the FDT formulations

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 (ie, positive or negative).

After application of full factorial design and with help of polynomial terms the optimized tablet was produced which have targeted to the disintegration time 30 s and 0.5% percent friability. The optimization was done with the help of software Design Expert 7.1.6. The optimized amount of the co-processed SSG and crospovidone was incorporated in the tablet formulation (OPT) which was also used as the check point of the regression analysis model. The response surface prediction plots were formulated with the help of the software.

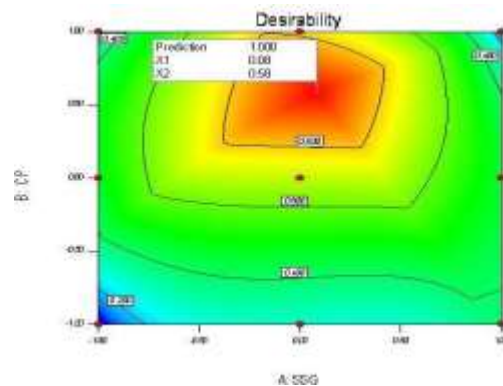**Figure 9: Response Surface for Optimized Formulation**

Table 10: Optimization of Fast Dissolving Tablet

Constraints			
Name	**Goal**	**Lower Limit**	**Upper Limit**
SSG	is in range	-1	1
Crospovidone	is in range	-1	1
DT (s)	is target = 30	7	62
Friability (%)	is target = 0.5	0.349	0.602
Solution			
SSG (X_1)	**Crospovidone(X_2)**	**DT (s)**	**Friability (%)**	**Desirability**
0.08	0.58	30	0.499	1.000

Development of Optimized FDT formulations

The optimized fast dissolving tablet was prepared with the best amount of co-processed superdisintegrant suggested by the software. The prepared tablets were evaluated for its physiochemical properties.

Table 11: Development of Optimized Formulation

Formulation	OPT 1 (mg)
Domperidone	50
Sodium Starch Glycolate	2.08
SBC+CA	-
Camphor	-
Crospovidone	2.58
Avicel PH 102	31.34
Dextrose	10.
Talc	2.00
Magnesium Stearate	2.00
Evaluation	
Weight (mg)	100.024±2.358
Hardness (kg/ cm²)	3.2±0.135
Friability (%)	0.498±0.028
Wetting time (s)	25±1.98
Disintegration time (s)	31±2.01
Drug Content (%)	98.35±2.325

n=6, ±SD

Content uniformity

Ten randomly selected tablets were weighed and average weight was calculated, the tablets were powdered in a glass mortar pestle. The weight equivalent to 100 mg domperidone was weighed. The weighed amount was dissolved in 100 ml of Sorenson's buffer (pH 6.8) and the solution was filtered. An aliquot of 1.0 ml from this solution was diluted appropriately with Sorenson's buffer (pH 6.8) in separate volumetric flask. The content in each formulation was determined spectrophotometrically at 285 nm.

***In vitro* dissolution study**

In vitro dissolution study for optimized tablet and marketed tablet were carried out using USP paddle method at 50 rpm in 900 ml of Sorenson's buffer (pH 6.8) as dissolution media, maintained at 37±0.5ºC. 5 ml of aliquot was withdrawn at the specified time intervals (1 minute), filtered through whatmann filter paper and assayed spectrophotometrically at 285 nm. An equal volume of fresh medium, pre warmed at 37ºC, was replaced into the dissolution media after each sampling to maintain the constant volume throughout the study.

The various kinetic treatments were applied to the dissolution data. The *in vitro* dissolution data obtained were subjected to a zero order and first order kinetics to understand the release profile and release mechanism. When a graph of the cumulative percentage drug released from the tablet against time was plotted, zero order release was observed and the plot obtained was found to be linear, indicating that the release rate is independent of concentration.

Table 12: Dissolution Release Profile of Optimized Fast Dissolving Tablet

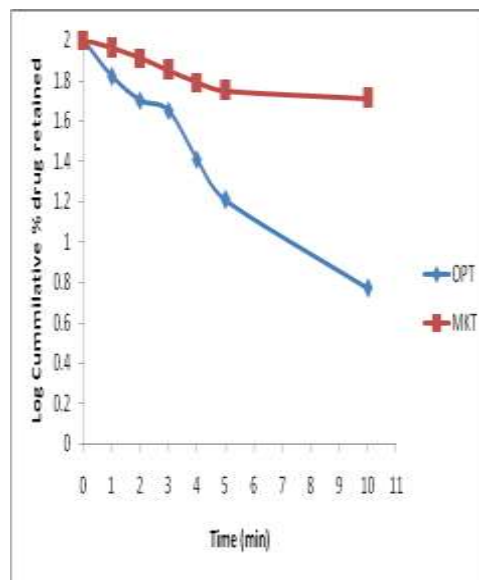| Time (min)	Cumulative Mean Percent Drug Released ± S.D.	
	OPT (Lyophilized)	**MKT**
0	0.00	0.00
1	35.81±1.40	11.33±2.10
2	54.06±1.61	20.67±1.16
3	61.08±1.62	31.11±2.51
4	78.33±1.91	41.19±2.10
5	85.70±1.82	49.84±1.61
10	95.27±2.05	50.38±2.40

n=6, ±SD
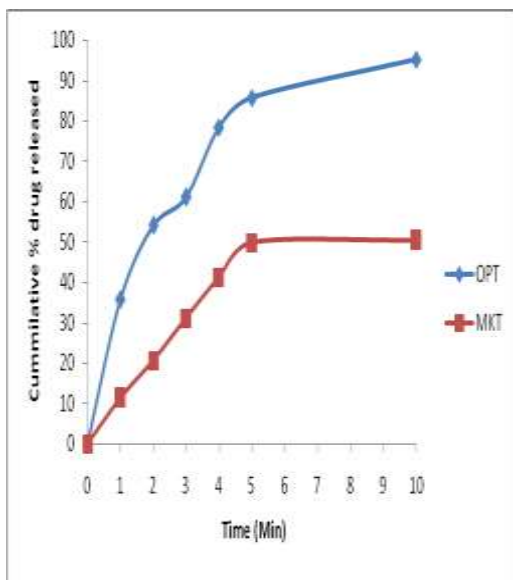
Figure 10: Comparison of Zero Order Release Profile

Table 13: Dissolution Release Profile of Optimized Fast Dissolving Tablet

Time (min)	Log Cumulative Mean Percent Drug Retained ± S.D.	
	OPT (Lyophilized)	MKT
0	2	2
1	1.8±0.021	1.96±0.021
2	1.70± 0.023	1.91±0.014
3	1.65±0.054	1.85±0.042
4	1.41±0.025	1.79±0.031
5	1.21±0.045	1.75±0.053
10	0.775±0.089	1.71±0.074

n=6, ±SD

Figure 11: Comparison of First Order Release Profile

Table 14: Fit of Various Kinetic Models for Tablets of Domperidone

Formulation Code	Zero Order		First Order	
	R^2	K (mg/min)	R^2	K (min^{-1})
OPT 1	0.730	8.468	0.975	0.306299

Conclusion

The Fast dissolving tablets of Domperidone were successfully prepared by direct compression technique; twelve formulations with varying quantity of Sodium starch glycolate and Crospovidone were prepared. Among all formulations F12 showed the best results with DT26 Seconds and Friability 0.512%, on the basis of results this batch was further selected for optimization. The pre-compression characterization of mixed blends was done for determination of mass volume relationship and flow properties. The results of bulk density, tapped density, Hausner's ratio, compressibility index and angle of repose indicated good compressibility and flow characteristics of the formulated mixed blends. Further using 3^2 factorial design totals nine formulations were prepared by Lyophilization technique. Using polynomial equation the effect of independent variables X_1 (SSG) and X_2 (CP) on dependent variables Y_1 (DT) and Y_2 (friability) was checked. The desirability of the models was found very near to one, so, these models can be used to navigate the design space. The amount of independent variables was calculated for DT 30 s, friability 0.5% and 90% drug release after 5 min. The optimized amount of independent variables was obtained easily

by software and these amounts were incorporated in the check point batches. The optimized tablets were prepared and evaluated for physiochemical properties. The results indicated that the formulation satisfied all the criteria of the fast dissolving tablet.

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