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FORMULATION AND OPTIMIZATION OF DOMPERIDONE FAST DISSOLVING TABLET BY WET GRANULATION TECHNIQUES USING FACTORIAL DESIGN

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Abstract: The purpose of this study is to prepare fast dissolving tablets of Domperidone by wet granulation. In the present research study, Sodium Starch Glycolate, was taken as super disintegrant and starch paste as a binder for the study. Here the Domperidone (anti-emetic) is taken as the model drug for the study and wet granulation as a method for preparation of the Fast Dissolving Tablet. The disintegrant incorporated during the wet granulation process as extra granular incorporation. A 3^2 full factorial design was applied to investigate the combine effect of 2 formulation variable: Superdisintegrants and starch paste. Here the concentration of Superdisintegrants and concentration of starch paste were taken as independent variable, X_1 and X_2 respectively. The effect of Disintegration time, wetting time, Q_{30} and friability were investigated as dependent parameters. The optimized batch obtained from the factorial design was compared with the marketed products. The stability study of the optimized batch is also done at 40 ^oC and 75%RH.

Keywords: Domperidone, Wet Granulation, Sodium Starch Glycolate, Disintegration Time, Q_{30}.

FDT : Fast Dissolving Tablets
SSG : Sodium Starch Glycolate
X_1 : Dependent Variable 1, Concentration of Sodium Starch Glycolate
X_2 : Dependent Variable 2, Concentration of Starch Paste
Q_{30} : Cumulative Amount of Drug Release after 30min
IP : Indian Pharmacopoeia
DOM : Domperidone
mg : Milligram
cm : Centimeter
ml : Milliliter
D.T. : Disintegration Time
USP : United States Pharmacopoeia
RH : Relative Humidity
f_2 : Similarity Factor
MDT : Mean Dissolution Time

Introduction

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. Of the various dosage forms administered orally, the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids, and because it is more tamperproof than capsules[1-4]. The bioavailability of drug is dependent on in vivo disintegration, dissolution, and various physiological factors. In recent years, scientists have focused their attention on the formulation of quickly disintegrating tablets. The task of developing rapidly disintegrating tablets is accomplished by using a suitable diluents and superdisintegrant.

The domperidone is selected as the model drug which comes under anti-emetic class. Domperidone is optimized suits for preparation of FDT as it has longer half life and in case of vomiting it required quick release.

Sodium starch glycolate was chosen because of its high swelling capacity. Moreover, the disintegrant efficiency of sodium starch glycolate is unimpaired by the presence of hydrophobic excipient such as lubricants. Sodium starch glycolate exhibits good flow (angle of repose <36º). The bulk density of sodium starch glycolate is 0.756 g/cm^3.

$A3^2$ full factorial design is applied for the optimization of the fast dissolving tablets of the Domperidone. The concentration of Superdisintegrants (Sodium starch glycolate, X_1) and amount of binder (Starch paste, X_2) were taken as independent variable. The dependent variables selected are disintegration time, wetting time, Q_{30} and friability to find out effect of independent variables on dependent variables.

Materials and Methods

Material

Domperidone, Ac-di-sol and Crospovidone were received as a gift sample from Torrent Research Center (Ahmedabad, India). Lactose (IP), Starch, Magnesium Stearate and talc were purchased from the S.D. Fine Chem. Ltd., Mumbai.

Preparation of Domperidone Fast Dissolving Tablets

Different fast dissolving tablets formulations were prepared by wet granulation method. All the powders were passed though 80 mesh sieve. Required quantity of drug and excipient mixed thoroughly. Mixture was than granulated using starch paste and granules were made. Granules were dried at 40°C for about 15 min. After drying super disintegrant was added externally. Talc and magnesium stearate were finally added as glident and lubricant respectively. The blend was compressed using Rotary Tablet Machine-12 Station. Each tablet contained 10 mg of DOM. Formulation of preliminary trail, full factorial layout and composition of factorial batches was shown in table 1, 2 and 3 respectively.

Table 1. Formulation of preliminary trial

Ingredient	F_1	F_2	F_3	F_4	F_5
Drug	10	10	10	10	10
SSG	12	12	12	15	21
Starch (paste)	18	24	30	18	18
Lactose	251	245	239	248	242
Mg stearate	3	3	3	3	3
Talc	6	6	6	6	6
Total Wt.	300	300	300	300	300

*All the ingredients are in mg

Table 2. Full Factorial Design Layout

Batch code	X_1	X_2
F_6	-1	-1
F_7	0	-1
F_8	1	-1
F_9	-1	0
F_{10}	0	0
F_{11}	1	0
F_{12}	-1	1
F_{13}	0	1
F_{14}	1	1

Coded value	Amount of superdisintegrant (SSG) in mg X_1	Amount of binder (starch paste) in mg X_2
-1	12	15
0	18	18
1	24	21

Table 3. Formulation using 3^2 full factorial designs.

Formulations Code→	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}
Drug	10	10	10	10	10	10	10	10	10
SSG	12	18	24	12	18	24	12	18	24
Starch	15	15	15	18	18	18	21	21	21
Lactose	254	248	242	251	245	239	248	242	236
Mg-stearate	3	3	3	3	3	3	3	3	3
Talc	6	6	6	6	6	6	6	6	6
Total wt.	300	300	300	300	300	300	300	300	300

Evaluation of the prepared tablets properties

The tablet geometry was determined by a means of a micrometer (Baty Co, Ltd, Sussex, England), while the tablet breaking strength (hardness) and the tablet friability were determined using Monsanto hardness tester and Rochi fribilator, respectively. The disintegration and wetting times were measured[10]. Briefly, the disintegration time (DT) was measured using a modified disintegration method. For this purpose, a petri dish (10-cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of the petri dish and the time for the tablet to disintegrate completely into fine particles was noted. On the other hand, the wetting time was measured as follows: A filter paper was kept in a petridish having diameter of 10 cm and containing 15 ml of purified water. A tablets having small amount of amaranth powder on the upper surface and tablet was placed on the filter paper. The time required to developed red color on the upper surface of the tablets was recorded as wetting time[6, 10].

In-vitro dissolution profile of prepared Domperidone FDT

The release rate Domperidone from fast dissolving tablets was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl (pH=1.2), at 37 □ 0.5□C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at different time interval. The samples were replaced with fresh dissolution medium of same quantity. Absorbance of these solutions was measured at 284 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve. Release profile of the preliminary batches and factorial batches were shown in the figure 1 and figure 2.

Full Factorial Design

$A3^2$ full factorial design was used in the present study to optimized formulation. In this design 2 factors evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The amount of super disintegrating agent, SSG (*X1*), and the amount of binder, starch paste (*X2*), was selected as independent variables. The disintegration time, wetting time, friability and Q_{30} were selected as dependent variables.[10]

Comparison of optimized batch with marketed tablets

The optimized tablet formulation (F_7) was compared with marketed fast dissolving tablets of Domperidone for in vitro drug release profile and Mean Dissolution Time (MDT) were considered for comparison.

Accelerated stability study of optimized batch

In order to determine the change in *in-vitro* release profile on storage, stability study of batch F_7 was carried out at 40^0 C in a humidity chamber having 75% RH. Sample were withdrawn after three-week interval and evaluated for change in in-vitro drug release pattern, hardness and disintegration time. The similarity factor (f_2) was applied to study the effect of storage on formulation F_7. [1-3]

Result

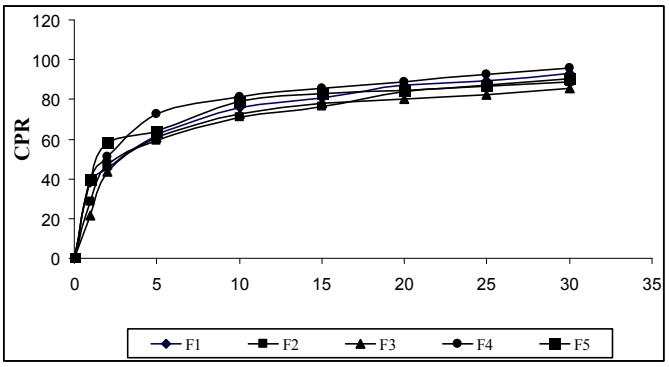
Results of preliminary trail

In preliminary study, different batches were prepared as per the composition given in Table 1. All the batches were evaluated for in vitro dissolution study as per the procedure. Results of different evaluation parameters were shown in table 4. Hardness, disintegration time, wetting time and friability of all preliminary batches were found between 3to12 kg/Cm^2, 38to70 sec, 40to75 sec and 0.29to 47 %. The release of drug for all the batches was between 85to95. Release profile of all the preliminary batches were shown in Figure 1. It was found that Batch F_4 gives desirable fast release action. Moreover, hardness, disintegration time, wetting time and friability of tablet were found 4±0.2 kg/Cm^2, 38sec, 40 sec and 0.42 %. It gives more than 95% release of drug with in 30 min. Therefore, the composition of batch F_4 was selected for further evaluation by factorial design.

Table 4. Physical parameters of preliminary trails

Batch	Disintegration time (sec)	Wetting time (sec)	Hardness (n=10)	Friability	Q_{30}
F_1	46	49	5.6±0.211	0.39	92.99
F_2	57	60	7.3±0.270	0.28	88.61
F_3	70	75	12.1±0.259	0.24	85.58
F_4	38	40	4±0.2	0.42	95.82
F_5	42	45	3.1±0.122	0.45	90.29

Fig. 1 Cumulative Percentage Release Profile of Preliminary Batches



Results of 3^2 Full Factorial Designs

On the basis of the preliminary trials in the present study a 3^2 full factorial design was employed to study the effect of independent variables, i.e. amount of superdisintegrant (SSG, X_1) and the amount binder(starch paste,X_2) on dependent variables like disintegration time, wetting time, friability and Q_{30}. The results as summarized in table 5 clearly indicate that all the dependent variables are strongly dependent on the selected independent variables as they show a wide variation among the nine batches (F_6 to F_{14}).

Table 5. Effect on dependent variable

Batches	Independent variable		Dependent variables			
	SSG	Starch Paste	Disintegration time (sec)	Wetting time (sec)	Friability (in %)	Q_{30}
F_6	-1	-1	35	39	0.4	91.52
F_7	0	-1	28	29	0.43	96.77
F_8	1	-1	27	31	0.49	95.62
F_9	-1	0	41	44	0.38	92.99
F_{10}	0	0	37	40	0.35	94.41
F_{11}	1	0	40	42	0.33	95.25
F_{12}	-1	1	45	54	0.27	92.15
F_{13}	0	1	40	46	0.3	91.82
F_{14}	1	1	39	41	0.31	90.79

Independent variable	Real value		
	Low (-1)	Medium (0)	High (1)
SSG (X_1)	12	16	18
Starch paste(X_2)	15	18	21

Comparison of optimized batch with marketed tablets

The optimized tablet formulation (F_7) was compared with marketed FDT of Domperidone tablets for in vitro drug release profile and Mean Dissolution Time. Percentage of drug dissolved in 30 min (Q_{30}) and Mean Dissolution Time were considered for comparison. Results are shown in table 6 and comparative release profile is given in Figure 3.

Accelerated stability study of optimized batch

Sample withdrawn after three month showed no change in *in-vitro* drug release profile (Figure 4). The value of similarity factor was 90.81 (Table 5) indicating good similarity of dissolution profile before and after stability studies. Results of the stability study shoe no remarkable change in the release profile of the Domperidone FDT after the stability. All the results of stability were shown in table 5.

Discussion

Factorial Equation for disintegration and Percentage friability

Concerning disintegration time, the results of multiple linear regression analysis showed that the coefficients b1 bear negative sign and b2 bear a positive sign. Therefore, increasing the concentration of superdisintegrant (SSG) is expected to decrease the disintegration time while increasing the concentration of binder (starch paste) is expected to increases the disintegration time. Sodium starch glycolate 6% w/w and starch paste 5% were selected as the optimum concentration that showed minimal disintegration time of 28 seconds. It was observed that further increase in concentration of binder led to the increase in disintegration time. Such delay in disintegration may be because of the tight binding between molecules which ultimately slow down the water uptake by the tablets and thus super disintegrant do not get sufficient water to swell.

The water uptake by the tablet is facilitated by the starch, while the tablet disintegration is facilitated by the swelling force exhibited by sodium starch glycolate at their optimum concentration. When higher percentage of starch paste is used, higher binding between granules is expected in the tablets and tablet became harder, so an increase in the concentration of starch leads to a decrease in friability. This was confirmed by the negative sign of the coefficient b2. As indicated by negative sign of the coefficient b1, the increase in the incorporated amounts of sodium starch glycolate resulted in increase in the friability due to its less compressibility which ultimately results in weak tablets.

$$\text{Disintegration time} = 37.44 - 2.5\,X_1 + 5.66X_2 + 0.5X_1X_2 + 2.83X_1^2 - 3.66X_2^2$$

$$\text{Friability} = 0.417 + 0.03X_1 - 0.058X_2 - 0.01X_1X_2 - 0.0066X_1^2 - 0.0216X_2^2$$

Factorial Equation for wetting time and Q_{30}

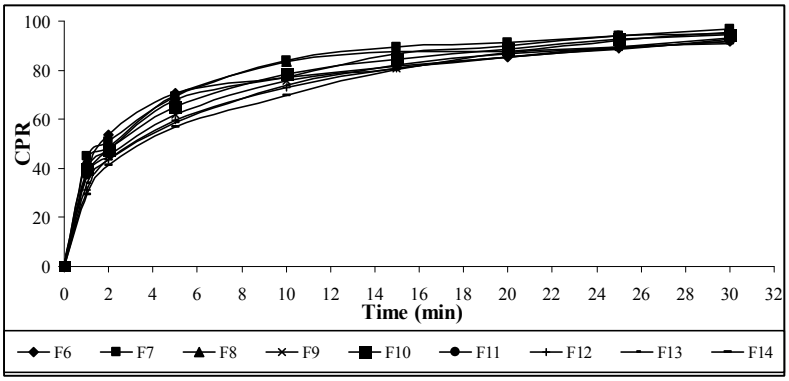
The in vitro dissolution after 30min varied from 90 to 97 and showed good correlation coefficient (0.9109). Concerning dissolution, the results of multiple linear regression analysis showed that both the coefficients b1 and b2 bear an opposite sign. More amount of sodium starch glycolate were expected to increase the drug release due to the faster disintegration of the tablets, therefore increasing the concentration of sodium starch glycolate is expected to increase the drug release after 30min. While as indicated by negative sign of the coefficient b_2, increase in the amount of binder decrease the release of the drug after 30min due to more hard tablets which.

From the multiple regression analysis, both the coefficients b1 and b2 bear an opposite sign for wetting time of tablets. Additions of more amount of sodium starch glycolate, wetting period of tablets were decrease while the increase the amount of starch pastes wetting time increase. That means increasing concentration of superdisintegrant agent decrease the wetting time. Sodium starch glycolate 6% wt/wt and starch paste 10% wt/wt were selected as the optimum concentration that showed minimal wetting time of 29 sec with 96.77% drug release in 30 min.

$$\text{Wetting time} = 40 - 3.33X_1 + 6.5X_2 - 0.5X_1X_2 + 3X_1^2 - 2.5X_2^2$$

$$Q_{30} = 95.03 + 0.88X_1 - 1.52X_2 - 1.36X_1X_2 - 1.28X_1^2 - 1.10X_2^2$$

Fig. 2 Cumulative Percentage Release Profile of Factorial batches



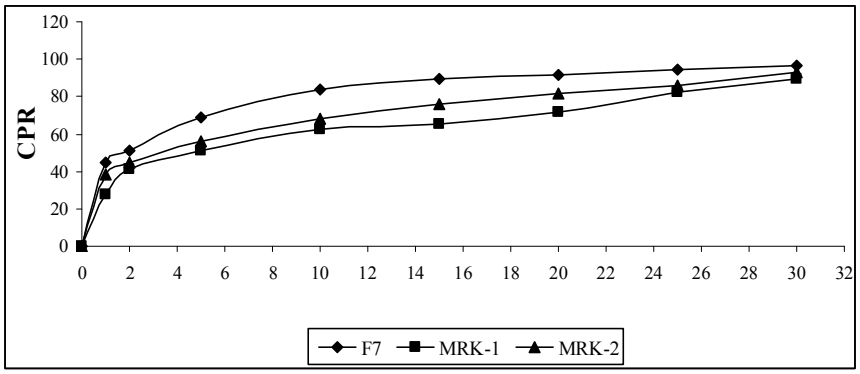
Selection of optimized domperidone fast dissolving tablets and its comparison with marketed tablet

The selection of the optimized formulation depends on disintegration time, wetting time, Q_{30} and friability. The disintegration time of batch F_8 is 27sec, means tablet disintegrate faster than other but its friability is also high which is not suitable for the fast dissolving tablets. To develop effective fast dissolving formulations, it is important to determine the disintegration time, friability and its dissolution profile. So considering all the parameters related to the fast dissolving formulation, batch F_7 was found to be the optimized batches among all other batches.

Table 6. Comparison of formulation F_7 with marketed tablets.

Product	% Drug release after 30 min (Q_{30})	Mean Dissolution Time
Market product (MRK-1)	89.03	4.1
Market product (MRK-2)	93.1	4.8
Formulation F_7	96.77	2.92

Fig. 3 Comparative release profile of the optimized batch with Marketed Preparation



Stability Study

Results of the stability study show no remarkable change in the release profile of the Domperidone FDT. Disintegration time of the tablets is increased after the stability study, which may be due to moisture absorption by the tablets. Storage msut be done in controlled humidity.

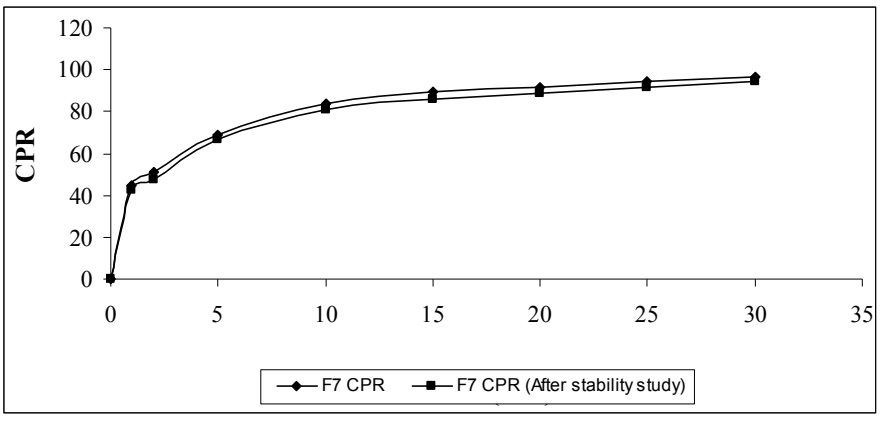
Conclusion

It was concluded that by adopting a systematic formulation approach, an optimum point could be reached in the shortest time with minimum efforts.

Table 7. Results of stability study of optimized batch

Time (Min)	CPR of F_7 (Initial)	CPR of F_7 (After storage at 40° C and 75%RH for 3 months)
0	0	0
1	45.08	42.92
2	50.92	47.56
5	69.15	66.85
10	83.88	80.96
15	89.31	86.25
20	91.51	89.01
25	94.13	91.94
30	96.77	94.27
Similarity factor (f_2) = 81.09		
Disintegration time	28 sec	35 sec
Wetting time	29 sec	38 sec
MDT (min)	2.92	3.01

Fig. 4 Comparative release profile of the optimized batch before and after stability study



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