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Original Article

Development and Evaluation of Orally Disintegrating Tablets of Pramipexole Using Full Factorial Design

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Abstract

Pramipexole is the mostly prescribed drug in patients with Parkinson disease. The incidence of Parkinson disease is related to aging and mostly developed in elderly people with difficulty in swallowing or dysphagia. In the current study we aimed to develop an orally fast disintegrating tablet (ODT) of pramipexole as a preferable alternative in geriatric patients. Hence, the fast disintegration is a critical for ODTs, the effects of four different superdisintegrants including, crospovidone, croscarmellose, sodium starch glycolate, and agar were evaluated on physical characteristics of the tablets. All of the formulations were prepared through direct compression method using aspartame and mannitol as taste masking agents. The flow properties of all of the mixtures were in the acceptable limits. Croscarmellose and Avicel® were chosen as the best superdisintegrants which resulted in the lowest disintegration time and the least friability. In subsequent studies, a 3^2 full factorial design was adopted to assess the impact of different amounts of croscarmellose and Avicel®. The overall results suggest that the tablet containing 2.5 mg croscarmellose and 70 mg Avicel® as superdisintegrants is the best formulation. Mean hardness, disintegration time, friability, and the drug release percent during 5 min for the optimized formulation were confirmed 42.05 ± 4.6 Kg/cm^2, 24.98 ± 6.8 Sec, 0.13 %, and 95.52 ± 2.23% , respectively.

Keywords: Pramipexole, Full factorial design, Orally disintegrating tablets, superdisintegrants, crospovidone, croscarmellose

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1. Introduction

Although conventional oral administration is the preferred and the most convenient route of drug administrations, it has some certain drawbacks. Poor absorption and enzymatic degradation of drugs within the gastrointestinal tract could result in reduced bioavailability of conventional oral administration (1). Bioavailability is also

limited by hepatic first-pass metabolism, which produces some metabolites that do not greatly contribute to clinical benefit and may even rise substantial toxicity (1,2). In some patients, taking tablets is not possible because of gastric mucosal irritation, bowel obstruction, frequent emesis, or severe dysphagia. In addition, an estimated 50% of the general population reports inconvenience in swallowing tablets and hard gelatin capsules, which results in a high incidence of noncompliance and the consequent compromises in efficacy (2). This is most common among pediatric and geriatric patients, but also occurs in those who are ill or who are busy or traveling and do not have convenient access to water. Such problems can be resolved by means of orally disintegrating tablets (ODTs). Upon contact with salvia, ODTs are rapidly disintegrated in oral cavity and released their drug content in the salvia. Drugs could be partially absorbed from the mouth, pharynx, and esophagus as the salvia passes down through the stomach. Based on literature survey, oral bioavailabilities of some drugs have been significantly enhanced following ingestion of ODTs compared to conventional tablet dosage forms. (3). For instances, selegiline ODTs markedly reduced presystemic metabolism of the drug and improved clinical efficacy in patients with Parkinson disease (4). In another study ondansetron ODT was prepared to be used in patients having difficulty in swallowing conventional oral tablets (5). In some other studies dicyclomine, alfuzosin, and olanzapine were developed as ODTs to increase patient compliance and consequently increase efficacy (6, 7). Pramipexole is a nonergot dopamine agonist which has been widely used in treatment of patients with Parkinson disease. Currently pramipexole is formulated as conventional tablets containing 0.125 to1 mg pramipexole (8). Most of patients with Parkinson disease are geriatric people that have difficulty in swallowing tablets which results in a high incidence of non-compliance and the consequent compromises in efficacy. Moreover, most of the Parkinson patients experience hypersalivation, thus orally disintegrating tablets could be more beneficial than conventional tablets. Based on the literature review there is no reports on development of ODTs of pramipexole. The objective of the present study was to prepare orally disintegrating tablets of pramipexole. The main criteria for mouth disintegrating tablets is to disintegrate or dissolve rapidly in oral cavity in specified limit time, without need of water and should have pleasant mouth feel (9). In the present study a variety of superdisintegrants were selected and tablets were prepared by direct compression method using different additives. Full factorial design was used to optimize and evaluate the effect of different superdintegrants including croscarmellose sodium, crospovidone, sodium starch glycolate, and agar on characteristic of ODTs.

2. Materials and Methods

2.1. Materials

Pramipexole was supplied from Farabi pharmaceutical company (Iran). Sodium starch

glycolate and natural agar were provided from Nutriroma, India. Croscarmellose and Crospovidone purchased from Sigma Chemical Co. (St. Louis, MO). Aspartame, Avicel® PH102, Talc, Magnesium stearate, Mannitol were obtained from Merck (Germany).

2.2. Methods

In a preliminary study, four different superdisintegrants, crospovidone, croscarmellose, sodium starch glycolate, and agar with different concentrations were evaluated. The composition of different formulations have been shown in table 1. All of the ingredients were mixed using a glass mortar and pestle for 5minutes according to Table 1. Magnesium stearate and talc were added in the final step and mixing continued for one minute. This blend was subjected to the analysis of pre-compression parameters including Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio. Tablets were compressed by mattresss 7 on a single punch tableting machine (Erweka A R 4100, Germany). The tablets were evaluated for friability, weight variation, hardness and in vitro disintegration time.

2.2.1. Angle of Repose

Angle of repose is defined as the maximum angle possible between the surfaces of a pile of powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose as following equation:

$\tan \theta = h/r$

Where θ is the angle of repose, h is stands for the height of the pile, and r represents the radius of the base of the pile

Table 1. Formulations of pramipexole ODTs, in a preliminary study with four different super disintegrants.

Ingredients (mg)	A_1	A_2	A_3	B_1	B_2	B_3	C_1	C_2	C_3	D_1	D_2	D_3
Pramipexole	1	1	1	1	1	1	1	1	1	1	1	1
Agar	5	7.5	10	-	-	-	-	-	-	-	-	-
croscarmellose	-	-	-	5	7.5	10	-	-	-	-	-	-
crospovidone	-	-	-	-	-	-	5	7.5	10	-	-	-
Sodium starch glycolat	-	-	-	-	-	-	-	-	-	5	7.5	10
Avicel PH102	40	40	40	40	40	40	40	40	40	40	40	40
Aspartame	2	2	2	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Mg. Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Mannitol	146	143.5	141	146	143.5	141	146	143.5	141	146	143.5	141
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

2.2.2. Bulk Density (D_b) and Tapped Density (D_t)

A suitable amount of powder from each formulation was lightly shaken to break agglomerates and introduced into a 10 mL measuring cylinder. After initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from a height of 2.5 cm at 2 seconds intervals. The tapping was continued until no further change in volume was noted. Bulk density (D_b) and tapped bulk density (D_t) were calculate using following formula (10):

$$Db = \frac{weight\ of\ powder}{\text{volume of the packing}}$$

$$\text{Dt} = \frac{\text{weight of powder}}{\text{tapped volume of the packing}}$$

2.2.3. Carr Index

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

$$\text{Carr's index} = \frac{Dt - Db}{\text{Dt}} \times 100$$

2.2.4. Hausner's Ratio

It is determined by comparing the tapped density to the bulk density and it is expressed as:

$$\text{Hausner ratio} = \frac{\text{Dt}}{\text{Db}}$$

Where Dt is tapped density of the powder and Db is bulk density of the powder.

2.2.5. Evaluation of Tablet Properties

2.2.5.1. Weight Variation

The test was performed according to specifications given in the USP. Randomly, 20 tablets were selected after compression and the average weight was determined. None of the tablets deviated from the average weight by more than ± 7.5% (11).

2.2.5.2. Friability Test

This test was performed to determine the effects of friction and shock. Preweighed sample of 10 tablets was placed in the Erweka friabilator and rotated at 25 rpm for about 4 minutes. The tablets were dedusted and reweighed, and the friability percentage was calculated using equation. Compressed tablets should not lose more than 1% of weight (12).

$$\text{friability \%} = \frac{\text{initial weight of tablets} - \text{Final weight}}{\text{initial weight of tablets}}$$

2.2.5.3. Hardness Test

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The hardness of the tablets was determined by diametral compression using Erweka hardness tester (13).

2.2.5.4. Thickness Test

The thickness was measured by placing tablet between two arms of the vernier calipers. Five tablets were taken and their thickness was measured (13).

2.2.5.5. Disintegration Time Test

The in vitro disintegration studies were carried out using a Digital Tablet Disintegration test Apparatus (Erweka ZT-Germany). One tablet was placed in each of the six tubes of the basket assembly and then disk was added to each tube. This assembly was then suspended in a one-liter beaker containing water with its temperature being maintained at 37±2 ºC. The basket was then moved up and down through a distance of 5 to 6 cm, at the frequency of 28 to 32 cycles per minute. The time required for complete disintegration of the tablet was recorded (11).

2.2.6. Experimental Design and Analysis

Based on preliminary study croscarmellose and Avicel® were chosen as best superdisintegrants which caused the lowest disintegrating time and the least friability. In subsequent studies, a 3^2 full factorial design was adopted to optimize the amount of croscarmellose and Avicel®. Table 2 displays two independent variables, croscarmellose and Avicel®, and their levels selected in the optimization study. A set of formulations corresponding to all possible combinations of factor levels were prepared. All experiments were performed in triplicate. Four studied responses were included: The hardness, friability, Disintegration time and the drug release percent. The experimental results were then analyzed by the Design Expert software version 7 (Stat-Ease, Inc., Minneapolis, Minnesota, USA) to extract independently the main effects of these factors, followed by the analysis of variance (ANOVA) to determine which factors were statistically significant. Identifying controlling factors and qualifying the magnitude of the effects were also emphasized. An overview of the formulations

Table 2. Definition and trial levels of factors in full factorial design used in production of pramipexole ODTs.

Studied variable	Level 1	Level 2	
Croscarmellose (mg)	5	2.5	3.75
Avicel (mg)	20	50	70

Table 3. Formulations of pramipexole ODTs generated by a 3^2 full factorial design.

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pramipexole	1	1	1	1	1	1	1	1	1
Croscarmellose	5	2.5	3.75	3.75	5	3.75	5	2.5	2.5
Avicel	70	50	70	50	20	20	50	70	20
Aspartame	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Mg.Stearate	3	3	3	3	3	3	3	3	3
Mannitol	116	138.5	117.25	137.25	166	167.25	136	118.5	168.5
Total weight	200	200	200	200	200	200	200	200	200

investigated in the present work is listed in Table 3.

2.2.7. Content Uniformity

Ten tablets of each formulation were crushed and powder equivalent to 1mg of pramipexole was suspended in approximately 50 mL of 0.1 N HCl and shaken for 15 minutes. Final volume was adjusted to 100 mL with 0.1 N HCl and filtered (Whatman No.1 filter paper). After serial dilution the absorbance of final solution was recorded at 267 nm using UV/Vis spectrophotometer against a reagent blank and the content was compared from a calibration curve prepared with standard pramipexole in 0.1 N HCl (11).

2.2.8. In vitro Dissolution Studies

Six tablets of each formulation were used in the dissolution experiments. The dissolution rates of pramipexole were determined in USP 24 type II apparatus (paddle method, Erweka DT 6RGermany) at 37 ºC in 900 ml phosphate buffer solution (pH 6.8) with the rotation speed of 50 rpm. At appropriate time intervals, 5 mL of sample was withdrawn and an equal volume of medium was added to maintain the volume constant. Samples were analyzed spectrophotometrically at 267 nm. A linear correlation ($r^2 > 0.999$) was obtained over the range of 0.25–15µg/mL. High precision and accuracy were also obtained (CV: 1.49–5.68%, error: 1.21–4.62%). The obtained dissolution data was plotted as percent cumulative drug released versus time (11).

3. Results and Discussion

3.1. Preliminary Studies

3.1.1. Powder Flow Properties

In preliminary study four different superdisintegrants were studied. The Powder flow properties were analyzed and shown in Table 4. For all of the formulations Carr's index were obtained in the range of 10.34 to 18.51 and Hausner's ratio were below 1.25 which indicated good compressibility and flow ability.

The tablets were prepared using the direct compression method. All of the formulations passed the weight variation test. The hardness of all tablets was found in the range of 28.5 - 38.8 kg/cm^2. Friability was observed to be less than 1% which was an indication of good resistance of the tablets. Disintegration times varied from 16 to 41 Sec and it was the least in the formulations containing croscarmellose and Avicel®. According to these results croscarmellose and Avicel® containing formulations were selected to participate in optimization studies.

3.2. Full Factorial Design

The precompression properties of different formulations prepared by design by Expert Design 7 were also within the acceptable range. The Carr's index indicated good powder flow properties with good compressibility (data are not shown).

Orally disintegrating tablets were prepared using the direct compression method. All of the formulations passed the weight variation and the content uniformity test. The hardness of all the tablets was found in the range of 20.5 -72.9 kg/cm2. The results of friability, in vitro

Table 4. Powder flow properties in the preliminary mixtures.

F	Bulk density g/cm3	Tap density g/cm3	Angle of Repose	Carr's Index	Hausner's Ratio
A1	0.41	0.52	29.03	20.46	1.25
A2	0.43	0.52	28.25	17.97	1.21
A3	0.43	0.54	31.01	19.62	1.24
B1	0.43	0.52	28.85	16.89	1.20
B2	0.44	0.52	29.60	16.31	1.19
B3	0.42	0.53	31.04	17.77	1.19
C1	0.41	0.53	32.05	20.7	1.28
C2	0.44	0.53	27.95	17.07	1.20
C3	0.43	0.54	29.57	19.55	1.24
D1	0.42	0.51	31.04	19.88	1.21
D2	0.43	0.52	32.06	16.21	1.24
D3	0.43	0.52	29.67	17.97	1.21

disintegration time and percent drug released during 5 min (QT5) are shown in Table 5. Fig 1-3 shows the effects of different amounts of croscarmellose and Avicel® on hardness, disintegration time, and friability of the formulations, respectively. The drug was completely released from all of the formulations during 5 min and no significant differences (P value> 0.05) were observed between different formulations.

3.3. Prediction of the Optimized Formulation

Computer optimization process and a desirability function determined the effect of the levels of independent variables (croscarmellose and Avicel®) on the responses. The optimized formulation was selected based on the set criteria including constraints and target goals of all dependent variables. The constraints of hardness were 20.45 to 72.9

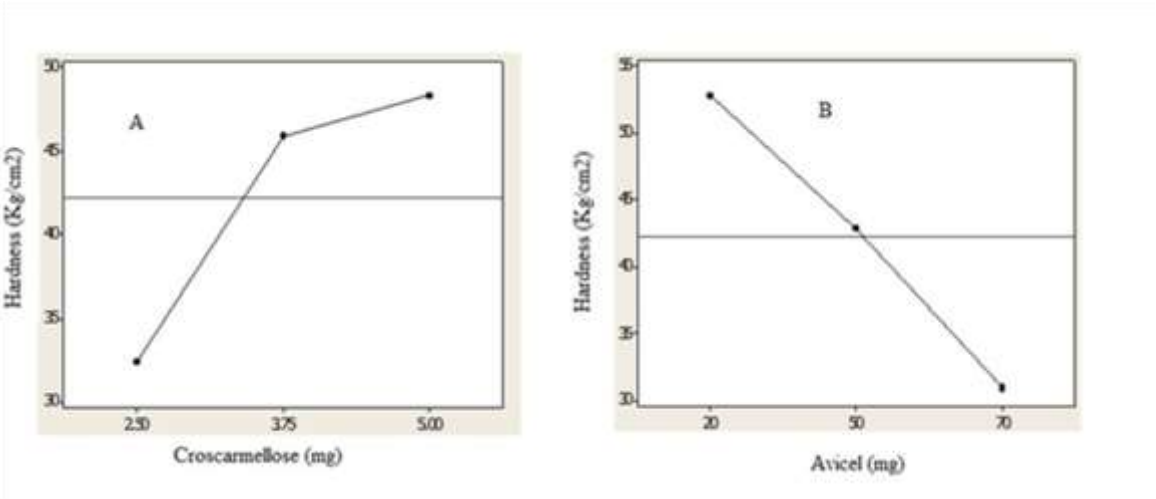

Figure 1. Effect of different levels of (A) croscarmellose and (B) Avicel on hardness.

Kg/cm^2 with targeting the hardness in the range of 30-50 Kg/cm^2, the range of disintegration times were 12 to 55 sec, while the target was minimum value of disintegration time, for the friability the constraints were 0.13 to 1.45 % with the goal of minimum value, and for the release percent the target was considered in the range of the measured value. Accordingly, the predicted optimized formulation by the software would contain 2.5 mg croscarmellose and 70 mg Avicel®. To confirm the predicted model, the optimized formulation was prepared, and the observed responses were measured and listed in Table 6. The acceptable agreement between the observed values and the values predicted by the software and the negligible error percent confirm the validation and reliability of our method as well as its adequate precision for the prediction of optimized conditions in the domain of levels chosen for the independent variables.

3.4. Discussion

Table 5. Physical properties of pramipexole ODT prepared by 3^2 full factorial design.

F	Weight variation (mg)	Disintegrating time (sec)	Hardness kg/cm²	Friability %	% Drug Release Q_{T5}	Content Uniformity(mg)
F1	201.85 ±2.51	15.5 ± 2.73	23.8 ± 1.93	0.95	95.52	0.923±0.01
F2	201.6 ± 2.70	17.33 ± 2.06	34.6 ± 7.42	0.65	91.67	0.957±0.03
F3	200 ± 3.45	12 ± 1.54	26.9 ± 2.28	1.11	95.52	0.928±0.01
F4	202 ± 3.45	22 ± 1.54	38 ± 3.43	0.73	92.95	0.950±0.03
F5	201.15 ± 4.9	36.83 ± 1.32	65.05 ± 3.8	0.50	91.67	0.925±0.02
F6	202.15 ± 3.23	55.33 ± 11.21	72.9 ± 8.92	0.40	87.73	0.962±0.04
F7	204.55 ± 3.01	25.33 ± 3.67	56 ± 3.46	0.42	91.67	0.920±0.02
F8	200.35 ± 2.41	25.5 ± 1.37	42.05 ± 4.6	0.13	95.52	0.943±0.03
F9	197.9 ± 17.78	15 ± 2.6	20.45 ± 11.24	1.45	96.81	0.895±0.00

Table 6. Predicted versus actual responses obtained for the optimized formulation.

Parameters	Drug Release Q_{T5} (%)	Friability (%)	Hardness (kg/cm²)	Disintegrating time (sec)
Actual value	95.52 ± 2.23	0.13	42.05 ± 4.2	25.5±1.6
Predicted value	93.98	0.2	45.62	24.98
Error (%)	1.63	35	1.33	2.08

Figure 3. Effect of different levels of (A)croscarmellose and (B) Avicel on friability.

Pramipexole is one of the mostly prescribed drugs in elderly people who suffer from Parkinson disease. It is currently available as conventional orally tablets. The incidence of Parkinson disease is related to aging and mostly developed in elderly peoples with difficulty in swallowing or dysphagia. Thus, the development of the ODT of pramipexole could be a preferable alternative to conventional oral rout, in improving the quality of life and patient acceptability. In the current study we aimed to develop ODT of pramipexole and evaluated the effect of using different disintegrating agents in physical properties of the tablets. The proper choice of superdisintegrants and their consistency of performance are of importance to the formulation of a rapidly disintegrating dosage form. Here, we performed a preliminary study to choose the best disintegrant between croscarmellose, crospovidone, agar, sodium starch glycolate, and Avicel®. Based on the results, croscarmellose and Avicel® fabricated the formulations with the lowest disintegrating

time and the least friability. In the following study a 3^2 full factorial design with three levels was applied to optimize the amount of each disintegrant. Nine formulations were prepared in our laboratory and subsequently evaluated in terms of the responses. As shown in Table 5 and Fig 1 the hardness was significantly increased by increasing the amount of croscarmellose and decreasing the amount of Avicel® Disintegration time is one of the main criteria in ODTs. As they should be rapidly disintegrated in buccal cavity without need for water. As expected, by increasing the amount of Avicel®, the formulations were more rapidly disintegrated, While increased amount of croscarmellose increased the disintegration times (fig 2). In the study conducted by Bansal et al (14) croscarmellose more than 10% significantly increased the disintegration time which is in accordance with our results. It can be attributed to the gelling property of croscarmellose at high concentrations which prevents the disintegration of the tablets. By increasing the croscarmellose, the friability was significantly decreased which is due to the effect of croscarmellose on hardness of tablets, while increasing the amount of Avicel did not significantly affect the friability. In another similar study (5), ODT of ondansetron was prepared and increasing the amount of croscarmellose increased the hardness and decreased the friability of the formulations. As an indicated in Table 5 the drug content was completely released from all of the formulations during 5 min which would contribute to higher bioavailability of ODT compared to conventional form.

4. Conclusion

In the current study we aimed to prepare ODT of pramipexole to improve the quality of life and patient acceptability. The flow properties of the drug and the excipients were good in all of the formulations. The overall results suggest that the tablet containing 2.5 mg croscarmellose and 70 mg Avicel® as superdisintegrants is the best formulation.

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