RESEARCH ARTICLE

# Formulation and evaluation of domperidone pellets prepared by powder layering technology

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The goal of the present study is to evaluate the influence of the formulation and operating conditions on pellet preparation by the pan technique. The effect of initial core weight on the physical parameters of pellets as well as to conduct stability study was also the goal of this study. For this domperidone maleate was selected as the model drug. Pellets were prepared by layering of powdered drug on sugar-based cores. Inert cores were intermittently treated with micronized drug powder and binding solution. This treatment led to the formation of multiple layers of drug particles around an inert core resulting in the production of pellets that can further be coated by different polymers to obtain modified release formulations. Scanning electron microscopy was employed to image the surface morphology of the prepared pellets. Drug loading efficiency, % yield, size, and shape uniformity of pellets were increased along with increasing the initial core weight. Drug content and dissolution study were performed by following HPLC and UV–Visible method. About 50% and 80% drug was released within 7.72 m and 13.66 m respectively in 0.1N HCl media (pH 1.2). Physical appearance of the prepared pellets, potency, moisture content, pellets size and shape, dissolution data, release rate constant, diffusion exponent ($P<.05$) over the stability period showed that the system is efficient for the production of highly stable formulations. This study also showed the good performance of the conventional coating pan system in obtaining instant release domperidone pellets prepared by the powder layering technique.

***Key words:*** *Domperidone, physical parameters, powder layering, stability study*

## INTRODUCTION

Coating pans have been used in pharmaceutical coating operations since the early 19th century when they were used extensively for sugar coating.[1] The first pelletization process for developing a sustained release dosage form in the coating pan can be traced to the 1956 patent by Blythe. This process involved layering a drug powder onto nonpareils using syrup as the adhesive solution. There have been 30 years of research and development experience in the powder layering technology since that patent, and a variety of products have been successfully developed and introduced into the market.[2] With time, the manufacture of pellets in conventional coating pans has developed from the art of earlier years into a much more sophisticated and controlled process. The basic components of conventional coating pan system are the rotating pan, air supply system, spray system, powder addition system, and air–exhaust system. In the powder layering technology, pellets are usually prepared by loading the micronized powders on the solid cores. Cores are usually prepared using one of the following processes: compaction, surface layering, or agglomeration.[3] Among these methods, the surface-layering technique is an appealing approach. Generally, this pelletization method involves the using of inert substrates, such as sugar spheres, and their enlargement by intermittently spraying a binder solution[4] and applying the active substance powder in a rotating coating pan or in a fluidized bed[5] Once the drug beads are prepared, they may be further coated with a protective coating to allow a sustained or prolonged release of the drug.[6]

Using a multiple-unit dosage form, pellets offer several advantages: Pellets disperse freely in the gastrointestinal tract and thus maximize drug absorption, reduce peak plasma fluctuations, and minimize side effects; high local concentrations of drug are avoided; there is flexibility in the development of oral dosage forms as pellets,[7-10] so different drug substances (e.g. incompatible drugs) can be formulated and blended into a single dosage form; and immediate- and controlled-release pellets can be mixed to achieve the desired release pattern.[7-10]

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The aim of the present study was to evaluate the influence of the formulation variables and operating conditions on the pellet preparation by conventional pan layering technology. For instance, the following parameters were considered: (i) effect of initial cores; (ii) effect of lubricant; (iii) percent yield; (iv) physical parameters; (v) surface morphology; and (v) size of the final pellets. Surface morphology has a great role on pellets quality and its stability. In this study the surface morphology of the prepared pellets was examined by scanning electron microscopy (SEM). To evaluate the stability of the prepared pellets in different stability conditions was also the goal of this study. For these purposes, domperidone maleate was considered as the model drug. Domperidone is a dopamine antagonist with antiemetic properties, used in the treatment of nausea and vomiting. Micropelletization technique, a possible approach for ensuring maximum dissolution with enhanced wet ability, and uniform pellet size almost spherical were used to achieve the smooth gastric transit of drug.[11] It is rapidly absorbed following oral administration with peak plasma concentrations occurring at approximately 30 to 60 min.[12]

## MATERIALS AND METHODS

### Material

Domperidone Maleate (Sri Krishna Pharma Ltd., India), Nonpareil Seeds (Eskayef Bangladesh Ltd), Maize Starch (Cerestar, Netherland), Purified Talc (Asian Mineral, Thailand), Kollidon 30 (BASF, Germany), Isopropyl Alcohol (Exxonmobil, USA), Hydrochloric Acid (Merck, Germany).

### Method

*Preparation of domperidone pellets*

The powder layering method was chosen to prepare the domperidone maleate beads. The required amount of polyvinyl pyrrolidone (Kollidon 30) was dissolved in Isopropyl alcohol according to Table 1 to prepare binding solution (concentration 10%w/w). Domperidone maleate powder, purified talc, and maize starch were passed through 80 mesh separately to discard any coarse particle present and the sieved materials were weighed [Table 1] and mixed properly in a double polythene bag manually for 5 min. Required amount of desired size (30/36) white nonpareil seeds (NPS) was loaded onto conventional coating pan (Ganson, India) and pan was rotated at 36 r/min and spraying of binding solution was started at a rate of 12 g solution/min. After 5 min, the mixture of domperidone maleate powder, purified talc, and maize starch was loaded manually on sugar-based NPS at a rate of 100 g powder/10 min. The solution spray rate and powder dosing rate was kept constant throughout the whole process. The inlet air temperature was 40-42°C and bed temperature was 30-33°C. After completion of the process, drug loaded pellets was dried at 60°C for 7 h in hot air oven (Non-perforated tray drier) and the batch is termed as F1. Same process was followed to manufacture the batches F2, F3, and F4 according to Table 1 where the quantity of raw materials varied. The dried pellets were used to perform several physical tests [Table 2].

**Table 1: Formulation of domperidone pellets (weights are in g)**

| Materials | Formulation code | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| Domperidone maleate | 165 | 260 | 390 | 780 |
| Nonpareil seeds (NPS*) | 1500 | 3500 | 5500 | 11000 |
| Purified talc | 120 | 210 | 275 | 550 |
| Maize starch | 450 | 855 | 1050 | 2100 |
| Polyvinylpyrrolidone (K-30) | 90 | 175 | 210 | 420 |
| Isopropyl alcohol upto | 900 | 1750 | 2100 | 4200 |
| Total batch size | 2325 | 5000 | 7425 | 14850 |

*Size 30/36 mesh

*Sieve test*

Sieve analysis of the dried pellets was performed by using USA Standard Sieve Series (Newark, New Jersey, USA).

*Moisture content*

The moisture content (% loss on drying; % LOD) of the dried and sieved pellets (18/24) was determined by using Mettler Toledo Halogen Moisture Analyzer (Model: HB43, USA) where the working temperature was 105°C.

*% Friability*

The friability test of the drug loaded beads (18/24) was performed for 10 min at 24 r/min by using Electrolab EF-2 Friabilator (India).

*Bulk density*

Bulk density of the dried and sieved pellets (18/24) was determined by using Stampfvolumeter bulk density detector (Model: Stav 2003, Germany) after performing 100 strokes to measuring cylinder containing a 20 g sample.

*Assay*

The quantity of domperidone in the prepared pellets (18/24) was determined by following the high performance liquid chromatography (Shimadzu ClassVP, Kyoto, Japan) method.[13]

*In vitro dissolution study*

The dissolution of domperidone pellets (18/24) was studied by Erweka (Germany) dissolution tester USP (XXVIII) using USP apparatus 2 (Paddle method). Domperidone pellets equivalent to 10 mg of domperidone was poured in 900 ml of 3.65 g/l hydrochloric acid medium at 37°±0.5 C with a rotation of 50 r/min for 30 min. At the end of 30 min, the media was taken and drug content was determined spectrophotometrically at 286 nm.[13]

**Encapsulation and packaging**

After performing the relevant tests, 18/24 size pellets were taken only from batch F4 (due to higher yield value and better physical properties) and encapsulated at a fill weight of 245.10 mg in size 2 (body-powder blue opaque and cap light blue opaque) shell (Associated Capsules Ltd, India) using Automatic Encapsulation Machine (Sejong, Korea). Strips (Aluminium-PVDC) were prepared by using Horn Noack Blister Machine (Germany) and leak test was performed then set for stability study for next 3 months at RT, 40°C, 40°C/75%RH, and 30°C/70%RH conditions in 3 different stability chambers (Thermolab -1000 L, India for 40°C; Memmert UFP 2016, Germany for 40°C/75%RH and Newtronic QCL 2016, India for 30°C/70%RH). After each month, dissolution test and other physical tests were performed and presented in Table 3.

**Scanning electron microscope**

Scanning electron microscope (SEM) was used to study the morphology of the prepared pellets as such without any coating around the pellets during analysis. SEM was performed using Hitachi (Model: S-3400 N, Japan) scanning electron microscope at 5 kV having different magnifications.

**Statistical analysis**

The statistical analysis was performed by multiple regression analysis using Microsoft Excel. To evaluate the contribution of each factor with different levels on responses, two-way analysis of variance (ANOVA) was performed using Sigma Stat software (Sigma Stat 2.03, SPSS, Chicago, IL). The $P < .05$ was considered to be significant.

## RESULTS AND DISCUSSION

Domperidone maleate was loaded on nonpareil seeds by powder layering technology. The prepared pellets were used to perform several physical tests with *in vitro* dissolution using the USP paddle method. Then 3 months' stability study was performed at RT, 40°C, 40°C/75%RH, and 30°C/70%RH conditions. The results of different tests were plotted in different fashions.

**Physical characterization**

Initially the color of the pellets was white to off-white and no difference in color was found from batch to batch. So formulation variables have no effect on the color of the pellets. But it was observed that in case of low core (NPS) weight (Formula F1), the size and shape of the pellets were not spherical [Figure 1A] which might be due to improper powder loading against the solution spray rate as well as improper seeds rolling against the pan rolling. The SEM was also revealed that for low initial load the surface of the pellets become rough enough and powder was not loaded uniformly around the dummy seeds [Figure 1B]. So a minimum effective load should be maintained to get the spherical and uniform size pellets as well as for better yield value. The shape and size become spherical and uniform gradually along with an increase in initial core weight. Formula F4 provides maximum percent of pellets within 18/24 size [Table 2]. The spherical shape was also represented by the scanning electron micrographs of the pellets [Figure 1C–D]. The initial core weight also has greater effect on the powder loss. In case of formula F3 and F4, higher percent yield (90.22% and 92.57%, respectively) was

**Table 2: Physical parameters of domperidone pellets prepared by powder layering technology***

| Parameters | Formulation code | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| Appearance | White to off-white spherical pellets | White to off-white spherical pellets | White to off-white spherical pellets | White to off-white spherical pellets |
| % Product yield | 76.18 | 84.36 | 90.22 | 92.57 |
| Drug loading efficiency (%) | 78.32 | 87.53 | 97.09 | 98.79 |
| Loss on drying (%) | 2.06±0.45 | 1.92±0.08 | 1.84±0.15 | 1.87±0.33 |
| % Potency | 4.37±2.04 | 3.58±1.11 | 4.01±1.32 | 4.08±1.07 |
| % Dissolution (30 min) | 73.45±3.77 | 81.52±5.14 | 97.73±3.21 | 94.25±2.01 |
| % Friability | 1.12%±0.08 | 0.59%±0.01 | 0.37%±0.05 | 0.43%±0.01 |
| Bulk density (g/cm$^3$) | 0.89±0.02 | 0.92±0.03 | 0.91±0.04 | 0.88±0.02 |

*Three samples run for each trial except % yield

**Table 3: Physical parameters of domperidone pellets at different time intervals during stability study in four different conditions (Formula F4, *N*=3)**

| Para-meters (%) | Initial | 1 month | | | | 2 months | | | | 3 months | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | RT | 40°C | 40°C/ 75%RH | 30°C/ 70% RH | RT | 40°C | 40°C/ 75% RH | 30°C/ 70% RH | RT | 40°C | 40°C/ 75% RH | 30°C/ 70% RH |
| Loss on drying | 1.87 | 1.84 | 1.84 | 1.81 | 1.86 | 1.84 | 1.79 | 1.85 | 1.82 | 1.83 | 1.75 | 1.82 | 1.77 |
| Potency change | 100 | 99.23 | 99.04 | 98.84 | 99.42 | 98.84 | 99.04 | 98.65 | 99.23 | 97.69 | 98.27 | 97.03 | 99.04 |

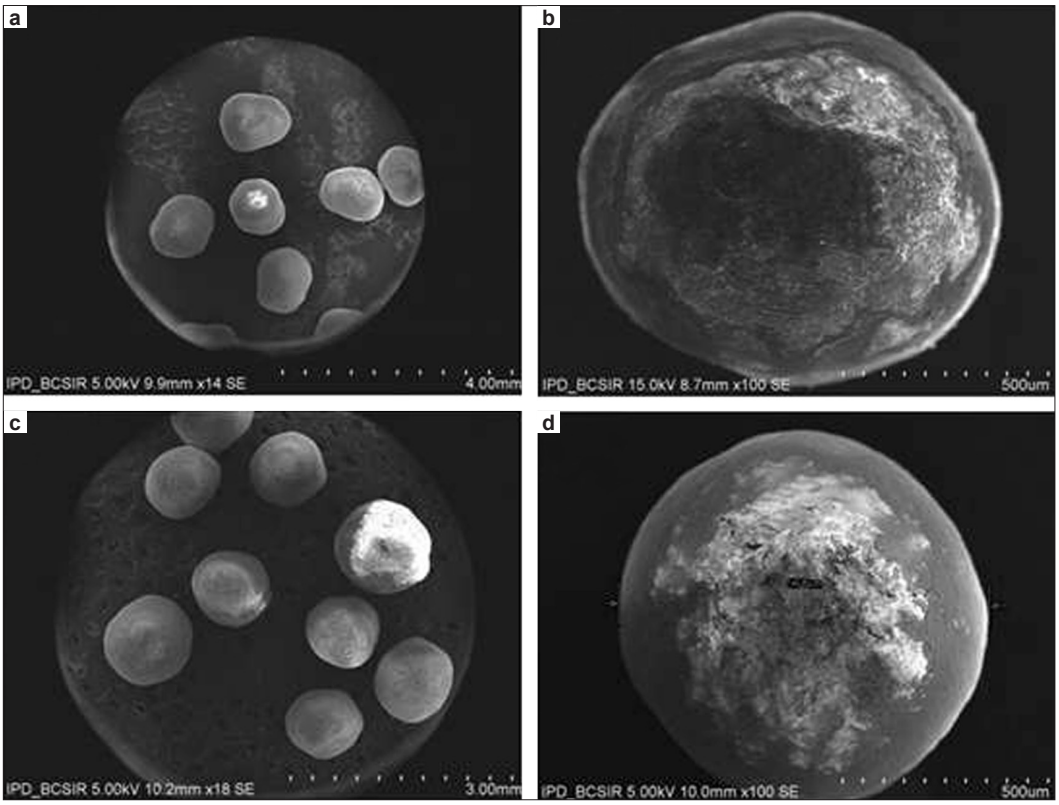


**Figure 1:** Scanning electron micrographs of domperidone pellets (18/24) prepared by powder layering technology. (a) Pellets of formula F1 (nonspherical shape). (b) Pellets of formula F1 (partially powder loaded surface). (c) Pellets of formula F4 (spherical shape). (d) Pellets of formula F4 (cracks on surface)

obtained. The formula of F3 and F4 is same but batch weight is twice for F4. About 30%, 20%, 12%, and 7% pellets were found outside the desired limit (18/24) for the formula F1, F2, F3, and F4, respectively [Figure 2]. So it was revealed that higher the initial core weight, higher the percent yield as well as higher the uniform size of pellets. The size of initial core was 30/36 and formula F1 contains maximum amount of powder mix (31.61%) so percent load will be maximum which might lead to form larger size of pellets. So it is necessary to adjust the ratio of initial core to powder mix by keeping the core size fixed. For the batches having low initial load (F1 and F2) the potency of the pellets was found to be 4.37% and 3.58%, respectively, which were much less as compared to the theoretical values (drug loading efficiency 78.32% and 87.53%, respectively). This might be due to improper loading of powder blend forming agglomeration rather than powder layering on the dummy seeds. For F3 the potency of domperidone in the prepared beads was found to be 4.01% (±1.32 SD) which indicates that the powder mixture was uniformly loaded on the nonpareil seeds and the manufacturing process was >97% efficient [Table 2]. This efficiency was also supported by formula F4 [Table 2] where the initial load was twice than F3. Again it was found that an amount of lubricant has a significant effect on potency as well as % yield. Potency, % yield and uniformity of pellets were increased [Table 2] along with decreasing the quantity of lubricant [Table 1].

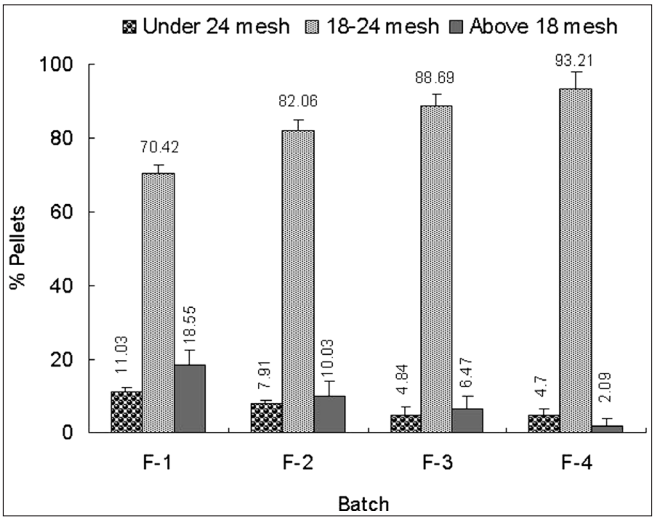


**Figure 2:** Sieve analysis of powder layered pellets of different batches

The friability test reveals that 1.12% weight loss [Table 2] occurred for formula F1 which might be due to irregular shape and large surface area of pellets [Figure 1a] as well as surface roughness [Figure 1b]. The least friability was found for formula F4 (0.43%) which might also be due to large surface area of pellets [Figure 1c] and presence of few cracks at the surface of the pellets [Figure 1d]. Friability decreases along with increase in uniformity of pellets size and shape [Table 2]. The results showed that the prepared pellets are less friable

and have strength enough to withstand the mechanical forces. Sieve test indicates that in all cases maximum amount of pellets have the size range between 18 and 24 mesh [Figure 2]. In case of formula F1 about 11% pellets were below 24 mesh which indicates the unloaded amount of powder mix as well as partially loaded or unloaded dummy seeds [Figure 1b]. Also about 19% pellets lie above 18 mesh which reflects the powder agglomeration and pellets agglomeration due to maximum amount of binder (3.87%) as well as improper ratio of initial load, powder application rate and solution spray rate. Hydrophobic lubricant might also have some effect on that by inhibiting the powder mix to bind on seeds surface. The percent of powder and ball growth were decreased gradually [Figure 2] after increasing the amount of initial core as well as by decreasing the amount of lubricant and binder [Table 1]. For the formula F4 about 93.21% pellets were within 18/24 mesh size [Figure 2] which reflects the uniform powder loading on the NPS. The uniformity was also reflected by Figure 1C. About 2.09% pellets were above 18 mesh which reflects minimum agglomeration or twinning of pellets during processing. Also amount of smaller granules or unloaded powder (about 4.70% below 24 mesh) was found minimum. In each testing parameter, the variation of the results found from three different samples was within the limit of ±5% and S.D. was found as little as 0.01 [Table 2] which indicates that the values were much more closure to each other.

The bulk density of the pellets was found 0.88 g/ml. As the potency of the pellets is 4.08% and dose of domperidone is 10 mg, so the fill weight of the pellets will be 245.10 mg. This value seemed to be suitable to fill the pellets containing 10 mg domperidone in 2 size or 3 size empty gelatin shell. As in 2 size shell the fill weight is 296 mg and 333 mg having a bulk density 0.8 g/ml and 0.9 g/ml respectively, whereas in 3 size shell the fill weight is 240 mg and 270 mg having bulk density 0.8 g/ml and 0.9 g/ml, respectively.[14] During encapsulation, the average fill weight per capsule was 245.10 mg where weight variation and S.D. were found to be ±5% and ±1.02, respectively.

**Dissolution study**

The dissolution of the domperidone pellets run for 30 min in 0.1N HCl media. It was revealed that 20.23%, 62.41%, 85.07% and 94.25% drug was released in 5, 10, 20 and 30 min, respectively. About 50% and 80% drug was released within 7.72 min and 13.66 min, respectively [Table 4]. About 100% drug was released within 30 min [Figure 3a–d]. This might be due to the disintegrant property of polyvinylpyrrolidone[15,16] as well as it enhances the dissolution of poorly soluble drugs from solid dosage forms.[17,18] As the pellets have a larger surface area, so they become contacted with the dissolution media very easily and quick dissolution of the drug might also be enhanced. This finding was also supported by the Scanning Electron Micrographs. The burst release can be explained by the cracking present in the pellets surface [Figure 1d] which enhances the dissolution medium to penetrate into the core of the pellets.

**Stability study**

The color and shape of the pellets were found to be unchanged even at the end of 3 months' stability study in all conditions except 40°C/75%RH. In 40°C/75%RH the color of the pellets becomes slightly yellowish which is negligible, but shape of the pellets remains same. The color change might be related to the excipients, as after 3 months at 40°C/75%RH the potency of the pellets was found 97.03% which is close to the initial value [Table 3]. No agglomeration or stickiness among the pellets in the capsule or pellets with the capsule surface was observed during the stability period. The % LOD value was decreased slightly from its initial value in most cases [Table 3]. No major change in potency of the products was observed (>97%) from the storage conditions [Table 3] which reflects that the formulated pellets are stable. In each month the dissolution of the domperidone pellets was performed for the samples stored in four different conditions. The $t_{50\%}$, $t_{80\%}$, $Q_{20}$, release rate constant ($k$), and diffusion exponent ($n$) at different time intervals showed no major difference over the stability period [Table 4]. The calculation was performed based on the following equations:

$$T_{50\%} = (0.5/k)^{1/n}$$

$$T_{80\%} = (0.8/k)^{1/n}$$

where $k$ is the release rate constant and $n$ is the diffusion exponent. The value of $k$ and $n$ were determined graphically.

**Table 4: Multiple regression output for dependent variables* (Formula F4)**

| Parameter | Initial | Room temperature | | | 40°C | | | 40°C/75%RH | | | 30°C/70%RH | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1M | 2M | 3M | 1M | 2M | 3M | 1M | 2M | 3M | 1M | 2M | 3M |
| $Q_{20}$ | 85.07 | 81.02 | 88.32 | 84.25 | 83.02 | 79.32 | 84.25 | 78.02 | 82.32 | 86.25 | 81.02 | 88.32 | 89.25 |
| $t_{50\%}$ | 7.72 | 7.02 | 6.60 | 5.51 | 4.97 | 7.15 | 5.72 | 9.23 | 7.31 | 6.12 | 5.96 | 7.02 | 8.13 |
| $t_{80\%}$ | 13.66 | 12.77 | 12.15 | 10.96 | 10.06 | 13.13 | 11.37 | 15.52 | 12.90 | 11.70 | 11.65 | 12.78 | 13.83 |
| $r^2$ | 0.825 | 0.889 | 0.840 | 0.837 | 0.919 | 0.857 | 0.832 | 0.856 | 0.905 | 0.869 | 0.879 | 0.810 | 0.831 |
| $k$ | 2.705 | 2.700 | 2.723 | 2.560 | 2.631 | 2.592 | 2.495 | 2.732 | 2.858 | 2.623 | 2.522 | 2.690 | 2.929 |
| $n$ | 0.823 | 0.786 | 0.767 | 0.684 | 0.667 | 0.774 | 0.684 | 0.908 | 0.828 | 0.726 | 0.701 | 0.784 | 0.884 |

*$Q_{20}$ indicates percentage drug release at 20 min; $t_{50\%}$, time required for 50% drug release; $t_{80\%}$, time required for 80% drug release; $r^2$, correlation coefficient; $k$, release rate constant; $n$ diffusion exponent.; M, month

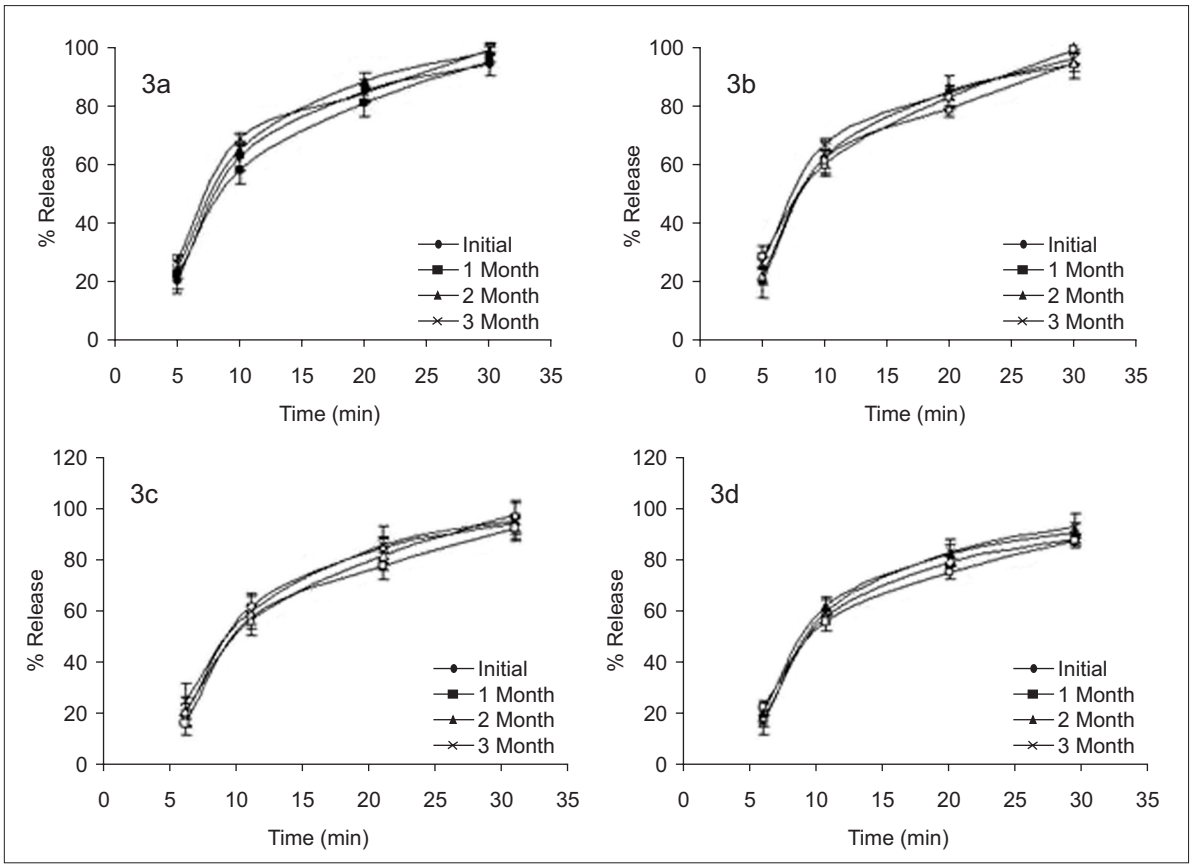


**Figure 3:** Release of domperidone from drug layered pellets in 0.1N HCl (Formula F4, *N* = 3): (a) at room temperature; (b) at 40°C; (c) at 40°C/ 75% RH; (d) at 30°C/ 70% RH

Mean dissolution time can also be calculated by the following equation:[19]

$$MDT = (n/n+1).\ k^{-1/n}$$

The ANOVA test was performed for statistical methodology. The tabulated *F* value for 3 and 12 degree of freedom and 1% level of significance $F_{.01,3,12}$ is 5.95.[20] It was observed that the calculated *F* values for four different conditions were found to be <5.95 [Table 5], so null hypothesis cannot be rejected and conclude that the mean variation among initial, 1 month, 2 month, and 3 month dissolution study [Figure 3a-d] does not differ significantly. So these data indicate the instant and stable dissolution profile of domperidone from the prepared pellets.

**Table 5: Results of analysis of variance for measured response (% drug release).* (Formula F4)**

| Condition | Parameters | df | SS | MS | Significance F |
|---|---|---|---|---|---|
| Room temperature | Treatment | 3 | 89.01 | 29.67 | 0.0286 |
| | Error | 12 | 12433.13 | 1036.09 | |
| | Total | 15 | 12522.15 | 834.81 | |
| 40°C | Treatment | 3 | 40.05 | 13.35 | 0.0137 |
| | Error | 12 | 11694.62 | 974.55 | |
| | Total | 15 | 11734.67 | 782.31 | |
| 40°C/75% RH | Treatment | 3 | 68.05 | 22.68 | 0.0213 |
| | Error | 12 | 12731.73 | 1060.98 | |
| | Total | 15 | 12799.78 | 853.32 | |
| 30°C/70% RH | Treatment | 3 | 46.07 | 15.36 | 0.0141 |
| | Error | 12 | 13037.54 | 1086.46 | |
| | Total | 15 | 13083.61 | 872.24 | |

*df indicates degree of freedom; SS, sum of square; MS, mean sum of square

## CONCLUSION

The present study confirmed the good performance of the conventional coating pan system in obtaining domperidone instant release pellets by a powder layering technique. For powder layering process, minimum effective load is essential to attain better yield value. Moreover, during the initial formulation trials, the careful evaluation of the process variables is necessary to optimize the powder layering process. The physical parameters of the pellets found consistent over the stability period. The results generated in this study showed that the selection of excipients for manufacturing of domperidone pellets by powder layering technology was found suitable to design a stable pellet dosage form ensuring quick dissolution and better physical parameters.

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