ORIGINAL ARTICLE

# Formulation and Development Modified Release Apremilast Pellets

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## Abstract

**Aim:** The aim of the present study is to develop and evaluate modified release apremilast pellets for the treatment of rheumatoid arthritis (RA). This disease directly depends on the circadian rhythm of the body, i.e. the maximum joint stiffness generally higher during the morning. The modified release apremilast pellets can be taken before bedtime and capable of releasing drug after a predetermined lag time. **Materials and Methods:** Apremilast pellets were prepared employing carboxymethyl tamarind kernel powder (CMTKP) as a novel natural excipient using the extrusion-spheronization technique. The apremilast pellets were prepared using blend of microcrystalline cellulose (MCC), lactose, TKP, and crospovidone. The process variables such as spheronizing speed, amount of spheronizing aid (MCC), and binder (TKP) were optimized and reported. **Results and Discussion:** The obtained pellets were subjected for determination of percentage yield, hardness, physicochemical properties, and particle size analysis. The prepared pellets were further coated with Eudragit L100 release rate retardant polymer, using fluidized bed processor by Wurster technique. Increasing the level of the Eudragit L100 coating retarded the water uptake and thus prolongs the lag time for the release of the drug. The 10% Eudragit L100 coating gave the least release in 0.1 N HCl in 2 h, in next 5 h 97.4% release was observed in phosphate buffer. **Conclusion:** A significant result obtained with the study indicates that modified release pellets prepared by extrusion-spheronization technique can successfully be further explored and employed in the treatment of RA as well as other diseases characterized by circadian rhythm.

**Key words:** Apremilast, carboxymethyl tamarind kernel powder, Eudragit L100, extrusion, spheronization

## INTRODUCTION

Multiparticulate dosage form is pharmaceutical formulations where the active substance is in the form of a number of small independent subunit such as pellets, granules, microparticle, and mini-tablets. Multiparticulate drug delivery systems are specifically suitable for achieving sustained or delayed release oral formulations with a lower risk of dose dumping. Pellets are small free-flowing, systematically produced, spherical or semi-spherical solid units. Pellets are the agglomerates of about size ranging from 0.5 mm to 2.0 mm, obtained from diverse starting materials of fine powders or granules of bulk drugs and excipient utilizing different pelletization techniques.[1-3]

Extrusion spheronization has five steps. Those are mixing, wet massing, extrusion, spheronization, and finally drying. A first step involves dry mixing of pharmaceutically active ingredient with excipients to achieve homogenous powder dispersion. Second step is wet massing of the dry mixture with the addition of binder solution. An extrusion is a third step consists of shaping the wet mass into long rod-shaped particles of uniform diameter. The fourth step of spheronization includes breaking of rod-shaped particles into smaller particles and rounding them to form spheres. The fifth and final step includes drying of pellets.[4-6]

Rheumatoid arthritis (RA) is a morning symptoms of are linked to the circadian abnormal increase in night inflammation is linked with the morning symptoms of rheumatoid arthritis (RA) which is chosen by inadequate cortisol secretion under conditions of active disease. Therefore, exogenous glucocorticoid treatment is recommended in RA at low dose is it may partially act like

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a "replacement therapy." The prevention/treatment of the night upregulation of the immune/inflammatory reaction (and related flare of cytokine synthesis) has been shown to be more effective when exogenous glucocorticoid administration is obtained with a night time-release formulation. Large- scale trials documented the modified release of prednisolone has more efficacies for low dose glucocorticoid long term treatment in RA conditions than morning prednisolone is documented, explaining a greater significant reduction in joint stiffness in morning. Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 h. It has been recognized in several diseases such as asthma, arthritis, duodenal ulcer, cardiovascular diseases, diabetes, neurological disorders, and hyperlipidemia.[7-9]

Apremilast is a small molecule inhibitor of PDE4, an enzyme that breaks down cyclic adenosine monophosphate (cAMP). In inflammatory cells, PDE4 is the dominant enzyme responsible for this reaction. The resulting increase in cAMP levels downregulates expression of a number of pro-inflammatory factors such as tumor necrosis factor-alpha, interleukin 17, interleukin 23, and many others, and upregulates the anti-inflammatory interleukin 10.

## MATERIALS AND METHODS

### Materials

Apremilast obtained as gift sample by Lupin Research Park, Aurangabad, Maharashtra. Microcrystalline cellulose (MCC) (Avicel PH-101), lactose and crospovidone were purchased from Loba chemicals. Tamarind Kernel powder (TKP) was purchased from a research lab.

### Methods

#### *Formulation of apremilast pellets*

The apremilast core pellets were prepared using wet granulation method by extrusion and spheronization technique. Powder mixture of apremilast, lactose, MCC, and crospovidone was mixed in a mortar for 20 min. This was followed by addition of binding liquid consisting of TKP in water. The obtained wet mass was passed through BSS sieve no.16 to get the extrudates. The prepared extrudates were then transferred to spheronizer (Shakti Pharmatech) at different spheronizing speed to obtain pellets. The prepared core pellets were dried in hot air oven at 37°C for 30 min. Five batches were prepared (F1–F5), shown into optimize the process parameters by evaluation of physical properties of pellets. The factorial design was applied for the preparation of further batches (F6–F14), as shown in Table 1, at optimized conditions of process parameters. Nine batches were prepared using $3^2$ factorial designs as shown in Table 2.

### Coating of apremilast pellets

The prepared dried core pellets were coated with Eudragit L100 solution of various concentrations, F15-5%, F16-8%, and F17-10%, using fluidized bed processor (ACG, Miniquest-F). The coating solution was prepared by dissolving Eudragit L100 in ethanol and was stirred to obtain a clear solution. The plasticizer was added into coating solution and solution was further agitated for at least 30 min. The coating process parameters were as followed: Inlet temperature, 40°C; product temperature, 35°C; atomizing air pressure, and 1 bar and spray rate 2 ml/min. Coated pellets were removed from the coating chamber and stored in a closed container for further evaluation.

**Table 1:** Composition of core apremilast pellets

| Batch No. | Ingredients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Drug (g) | MCC (g) | Lactose (g) | Crospovidone (g) | TKP (g) | Water (ml) | Total weight (g) | Spheronization speed (rpm) | Spheronization time (s) |
| F-1 | 1.3 | 10 | 6.7 | 1 | 1 | q.s. | 20 | 700 | 55 |
| F-2 | 1.3 | 10 | 6.7 | 1 | 1 | q.s. | 20 | 750 | 72 |
| F-3 | 1.3 | 10 | 8.7 | 1 | 1 | q.s. | 20 | 800 | 90 |
| F-4 | 1.3 | 10 | 6.7 | 1 | 1 | q.s. | 20 | 850 | 135 |
| F-5 | 1.3 | 10 | 6.7 | 1 | 1 | q.s. | 20 | 900 | 149 |
| F-6 | 1.3 | 8 | 8.7 | 1 | 1 | q.s. | 20 | 800 | 90 |
| F-7 | 1.3 | 8 | 7.7 | 1 | 2 | q.s. | 20 | 800 | 94 |
| F-8 | 1.3 | 8 | 6.7 | 1 | 3 | q.s. | 20 | 800 | 98 |
| F-9 | 1.3 | 10 | 6.7 | 1 | 1 | q.s. | 20 | 800 | 90 |
| F-10 | 1.3 | 10 | 5.7 | 1 | 2 | q.s. | 20 | 800 | 92 |
| F-11 | 1.3 | 10 | 4.2 | 1 | 3 | q.s. | 20 | 800 | 94 |
| F-12 | 1.3 | 12 | 4.7 | 1 | 1 | q.s. | 20 | 800 | 94 |
| F-13 | 1.3 | 12 | 3.7 | 1 | 2 | q.s. | 20 | 800 | 98 |
| F-14 | 1.3 | 12 | 2.7 | 1 | 3 | q.s. | 20 | 800 | 94 |

**Table 2:** Optimization of formulations using $3^2$ factorial designs

| Batch No. | $X_1$* MCC (g) | $X_2$** TKP (g) |
|---|---|---|
| F-6 | −1 | −1 |
| F-7 | −1 | 0 |
| F-8 | −1 | 1 |
| F-9 | 0 | −1 |
| F-10 | 0 | 0 |
| F-11 | 0 | 1 |
| F-12 | 1 | −1 |
| F-13 | 1 | 0 |
| F-14 | 1 | 1 |

*$X_1$=MCC (g): −1=8, 0=10, +1=12, **$X_2$=TKP (g): −1=1, 0=2, +1=3, MCC: Microcrystalline cellulose, TKP: Tamarind kernel powder

## Evaluation of pellets

### *Standard calibration curve of apremilast in 0.1N HCl*[10]

About 10 mg of apremilast accurately weighed and was dissolved in 100 ml 0.1N HCl in 100 ml volumetric flask to get 100 µg/ml. This solution was further diluted with 0.1NHCl to got solutions in the concentration range of 1–10 µg/ml. The absorbance of these solutions was determined spectrophotometrically at 230.5 nm.

### *Standard calibration curve of apremilast in phosphate buffer pH-6.8*[11]

About 10 mg of apremilast accurately solutions in the concentration range of 1–10 µg/ml. The absorbance of these solutions was determined spectrophotometrically at 230 nm weighed and was dissolved in 100 ml phosphate buffer pH-6.8 in a 100 ml volumetric flask to get 100 µg/ml. This solution was further diluted with phosphate buffer pH-6.8 to get.

### *Drug-excipient compatibility study*[12,13]

The interaction study of drug and excipient was performed by Fourier-transform infrared (FTIR) spectroscopic analysis. FTIR spectra of the drug, polymer and the physical mixture of drug and polymer were recorded on a FTIR spectrometer (FTIR-8400 S, Shimadzu, Japan) in the range 4000–400 $cm^{-1}$ and observed for the interaction between drug and excipient.

### *Particle size analysis*[13]

The size distribution of the pellets (batch F1-F5) was determined using mechanical sieve shaker (Make-Kumar). A series of BSS standard stainless steel sieves of number 10, 12, 16, 22, 36, and 44 were arranged in order of decreasing aperture size. An accurately weighed amount of drug-loaded pellets (10 g) from each batch was placed on the uppermost sieve. The sieves were shaken for a period of 10 min and the material retained on each sieve was weighed separately. Graph of the arithmetic means size versus percentage weight retained was plotted to analyzed pellets size.

## Physicochemical properties of apremilast[10,14-16]

### *Bulk density*

Bulk density was determined by placing weighed amount of pellets into 100 ml graduated cylinder and volume was measured. Bulk density calculated using formula: Bulk density=Mass/Volume

### *Tapped density*

Tapped density determined by USP method. Pellets were filled in 100 ml graduated cylinder of tap density tester which was operated for a fixed number of taps until the powder bed volume reached a minimum. Tapped density was calculated by formula: Tapped Density=Mass/Tapped volume

### *Hausner's ratio*

Hausner's ratio gives an idea regarding the flow of the pellets. Hausner's ratio was calculated by the equation: Hausner's ratio = Tapped density/Bulk density

### *Carr's index*

The Carr's index was calculated by comparing bulk density and tapped density of the pellets using the formula: Carr's index = (Tapped density–Bulk density/Tapped density) × 100

### *Angle of repose*

Angle of repose was determined using the fixed funnel method. The angle of repose was calculated from the height (h) and average radius(r) of powder cone, using formula, Angle of repose ($\theta$) = $\tan^{-1} h/r$.

### *Determination of %yield*

The percentage yield of pellets was calculated by the formula: %yield of pellets = Practical yield of pellets/Amount of powder mixture × 100

### *Hardness*[17]

The hardness of the pellets was determined using digital hardness tester (Make-Veego). 20 pellets were taken randomly and analyzed for hardness. The average value was calculated.

### *Drug content*

Pellets were grounded using mortar pestle, and 100 mg of powder was transferred into 50 ml volumetric flask containing methanol and volume was made to 50 ml. The mixture was sonicated for 10 min to ensures complete extraction of the drug. The solution was filtered through a Whatman filter paper. The 1 ml of the filtrate was taken and diluted up to 10 ml with methanol. The absorbance was measured spectrophotometrically at 230.5 nm.

### *Pellets shape*[18]

The pellets shape of optimized formulation was studied by optical microscopy. The sample was taken on the glass slide and observed with ×10 objective.

### *In vitro* drug release study[11-13,19,20]

### *Dissolution of apremilast pellets in 0.1 N HCl*

Drug release studies of optimized apremilast pellets batch were performed by USP dissolution apparatus-I (Veego Instruments). The dissolution studies were carried out with 900 ml 0.1N HCl as dissolution medium at 37 ± 0.5°C at 50 rpm for 2 h. Pellets equivalent to 20 mg of apremilast were weighed and transferred to the dissolution apparatus. At 15 min of time interval, a 10 ml aliquot was withdrawn and immediately replaced by the same volume of fresh medium to maintained sink condition. The aliquot was filtered through Whatman filter paper, and absorbance was measured at 230.5 nm. Drug release was calculated using a standard curve.

### *Dissolution of apremilast pellets in phosphate buffer pH 6.8*

Drug release studies of optimized apremilast pellets batch were performed by USP dissolution apparatus-I (Veego Instrument). The dissolution studies were carried out with 900 ml of phosphate buffer pH6.8 kept at 37 ± 0.5°C. The basket was rotated at 50 rpm. Pellets equivalent to 20 mg of apremilast were weighed and transferred to basket dissolution apparatus. At 30 min of the time interval, a 10 ml aliquot of dissolution medium was withdrawn and immediately replaced by the same volume of fresh medium to maintained sink condition. Then, an aliquot was filtered through Whatman filter and absorbance was measured at 230.0 nm. Drug release was calculated using a standard curve.

### *Dissolution of apremilast coated pellets*

The optimized apremilast pellets batch was further coated with different concentration of coating solution and *in vitro* release of apremilast was performed using USP apparatus type-I (Basket method). The dissolution was carried out with 900 ml of 0.1 N HCl as dissolution medium for first 2 h followed by phosphate buffer pH6.8 for next 5 h at 37 ± 0.5°C. The speed was maintained at 50 rpm. Pellets equivalent to 20 mg of apremilast were weighed and transferred to the dissolution apparatus. At 30 min of time interval, a 10 ml aliquot of dissolution medium was withdrawn and immediately replaced by the same volume of fresh medium to maintained sink condition. Then, an aliquot was filtered through Whatman filter and absorbance was measured at 230.0 nm.

### *Differential scanning calorimeter (DSC)*

The optimized apremilast coated batch F16 was characterized by the DSC analysis. The DSC patterns were recorded on a Mettler Toledo 61000 USA, DSC system. Sample analysis was performed in an aluminum pan, 1 mg of sample weight was used approximately and it was performed under nitrogen purging at flow rate of 20 ml/min, sample were heated from 40°C to 300°C at rate of 10°C per min.

### *Scanning electron microscopy (SEM)*

The surface morphology of optimized coated pellets was examined using the SEM. SEM was performed using Carl Zeiss Supra 5, Germany SEM. The pellets samples were mounted directly onto aluminum staged, and where sputtered coated with gold/palladium mixture for 1 min under an argon atmosphere. The coated pellets were mounted onto stubbed using double-sided adhesive tape.

## RESULTS AND DISCUSSION

### Standard calibration curve of apremilast

Calibration curves of apremilast were taken in 0.1N HCl and phosphate buffer pH 6.8, as shown in Figure 1. The coefficients of regression are close to one indicating linearity of response in the concentration range of 1–10 µg/ml.

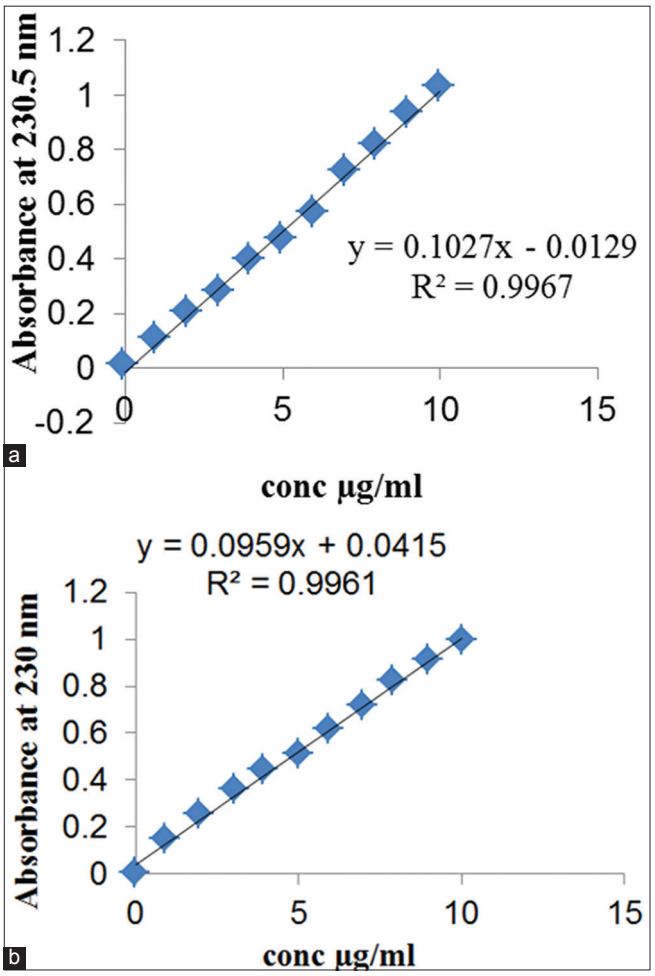


**Figure 1:** Calibration curve of apremilast in 0.1N HCl and pH 6.8

**Table 3:** Evaluation of apremilast pellets

| Batch No. | % yield | Diameter (mm) | Hardness (kg/cm²) | Bulk density (g/ml) | tapped density (g/ml) | Hausner's ratio | Carr's index (%) | Angle of repose (°) |
|---|---|---|---|---|---|---|---|---|
| F-1 | 52.62 | 1.62 | 0.024 | 0.595 | 0.640 | 0.929 | 7.01 | 25.96 |
| F-2 | 54.69 | 1.26 | 0.021 | 0.582 | 0.627 | 0.928 | 7.17 | 28.45 |
| F-3 | 65.32 | 0.91 | 0.012 | 0.52 | 0.57 | 1.09 | 8.77 | 25.22 |
| F-4 | 59.23 | 0.43 | 0.021 | 0.628 | 0.686 | 0.935 | 6.12 | 27.2 |
| F-5 | 56.19 | 0.58 | 0.018 | 0.660 | 0.704 | 0.937 | 6.25 | 26.84 |
| F-6 | 65.32 | 0.91 | 0.012 | 0.52 | 0.57 | 1.09 | 8.77 | 25.22 |
| F-7 | 64.9 | 0.92 | 0.066 | 0.517 | 0.55 | 1.06 | 7.27 | 28.75 |
| F-8 | 67.9 | 0.96 | 0.095 | 0.571 | 0.68 | 1.05 | 16.66 | 28.41 |
| F-9 | 75.65 | 0.99 | 0.125 | 0.548 | 0.614 | 1.11 | 8.97 | 26.64 |
| F-10 | 79.1 | 0.98 | 0.156 | 0.572 | 0.614 | 1.07 | 6.84 | 27.12 |
| F-11 | 72.75 | 0.82 | 0.195 | 0.693 | 0.732 | 0.946 | 5.36 | 28.10 |
| F-12 | 86.48 | 0.91 | 0.235 | 0.425 | 0.514 | 1.084 | 5.72 | 28.98 |
| F-13 | 86 | 0.95 | 0.284 | 0.419 | 0.520 | 1.058 | 5.55 | 29.03 |
| F-14 | 93.7 | 0.94 | 0.316 | 0.541 | 0.631 | 1.166 | 14.28 | 25.18 |

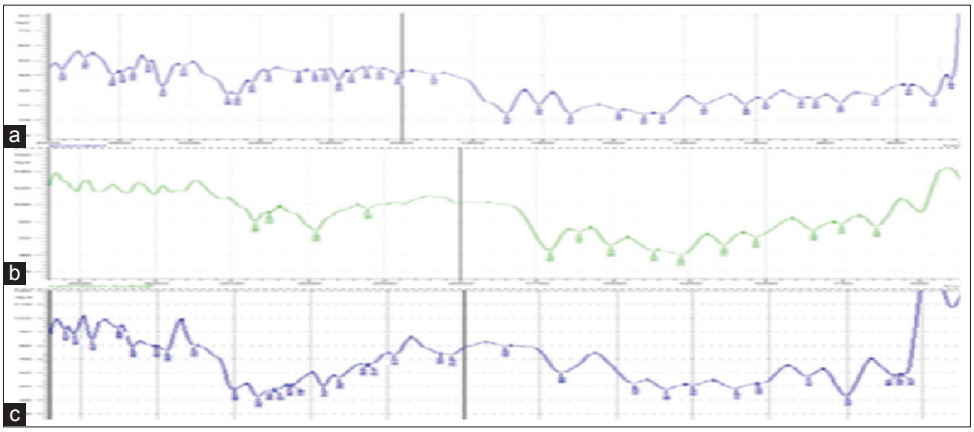


**Figure 2:** Fourier-transform infrared spectrum of apremilast (a), apremilast and Eudragit L100 (b), and apremilast formulation (c)

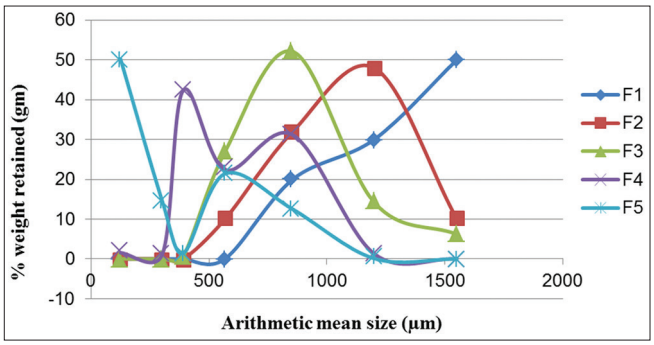


**Figure 3:** Particle size distribution curve

## Drug-polymer compatibility study by FTIR

The FTIR spectra of the pure drug showed a functional peak at 3635.00, 3518.28, 2985.91, 2204.71, 1703.20, 1386.86, and 657.25 cm-, while physical mixture shows peaks at 3654.93, 3518.20, 2914.19, 2204.71, 1697.63, 1385.71, and 658.39 $cm^{-1}$ with negligible shift in wave number it might be due to the presence of amorphous nature of the polymer used. The FTIR spectra of drug and physical mixture indicate compatibility of apremilast and Eudragit L100 as shown in Figure 2.

## Optimization of spheronization speed

Five batches of apremilast pellets (F1–F5) were prepared at different spheronization speed, i.e. 700–900 rpm. At lower spheronization speed, i.e. 700–750 rpm (Batch F1, F2) formation of larger size pellets with no sphericity was observed. At speed 800 rpm (Batch F3) spherical pellets were obtained with an optimal size range. At higher speed 850–900 rpm (Batch F4, F5) there was the formation of spherical pellets with smaller size range as shown in Figure 3. The speed was kept constant (800 rpm) for further formulation batches (F6–F14).

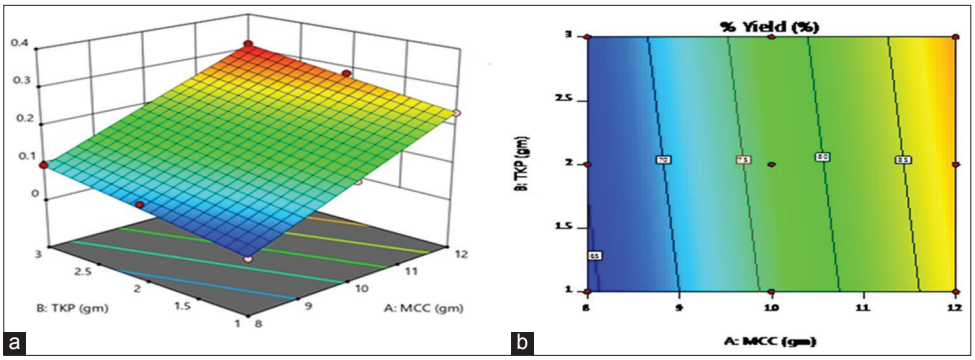


**Figure 4:** (a) Response surface plot showing the influence of the concentration of microcrystalline cellulose and tamarind kernel powder on the percentage yield of pellets. (b) Contour plot showing the relationship between various levels of two independent variables.

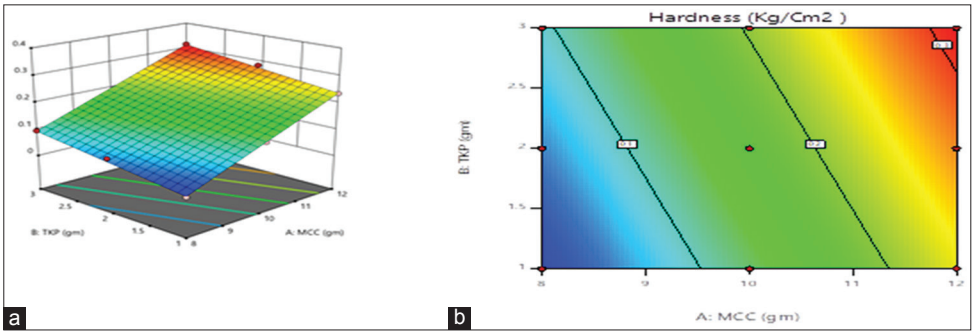


**Figure 5:** (a) Response surface plot showing the influence of the concentration of microcrystalline cellulose and tamarind kernel powder on the hardness of pellets. (b) Contour plot showing the relationship between various levels of two independent variables

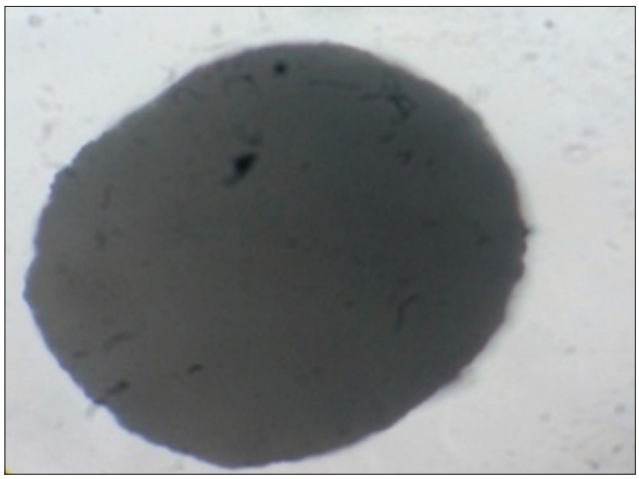

**Figure 6:** Microphotograph of pellets (batch F14)

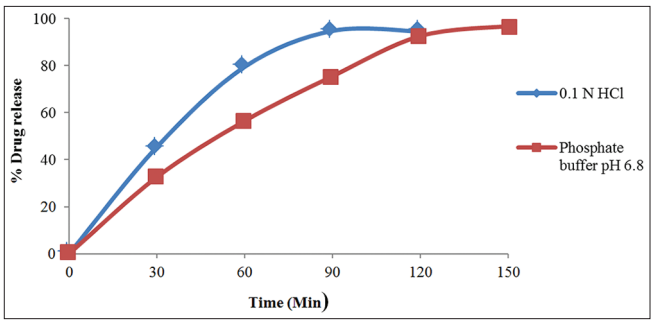


**Figure 7:** Cumulative percentage drug release apremilast pellets in 0.1 N HCl and phosphate buffer pH 6.8

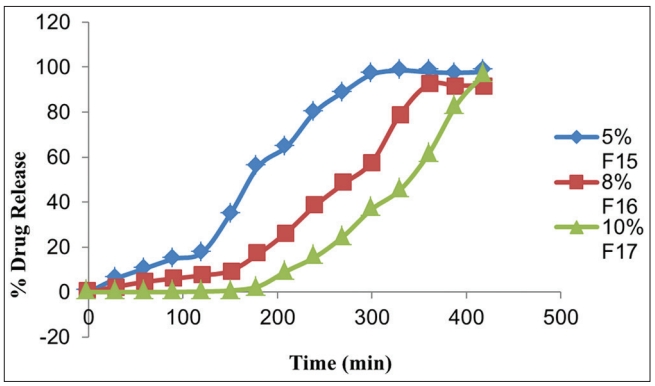


**Figure 8:** Cumulative percentage drug release in 0.1 N HCl (for 2 h) and phosphate buffer pH 6.8 (for next 5 h)

## Optimization of spheronizing aid and binder

To optimize the concentration of spheronizing aid and binder, nine batches were prepared (F6–F14). The concentration of MCC and TKP used was 8–12 g and 1–3 g m, respectively. Increasing the concentration of MCC leads to higher percentage yield of pellets, whereas a significant increase in hardness was observed with increasing concentration of TKP. Batch (F14) prepared with 12 g MCC and 3 g TKP showed good physicochemical properties. Table 3 shows various evaluation parameters. To withstand the mechanical Stress during subsequent coating process, pellets obtained in batch (F14) were selected for further coating.

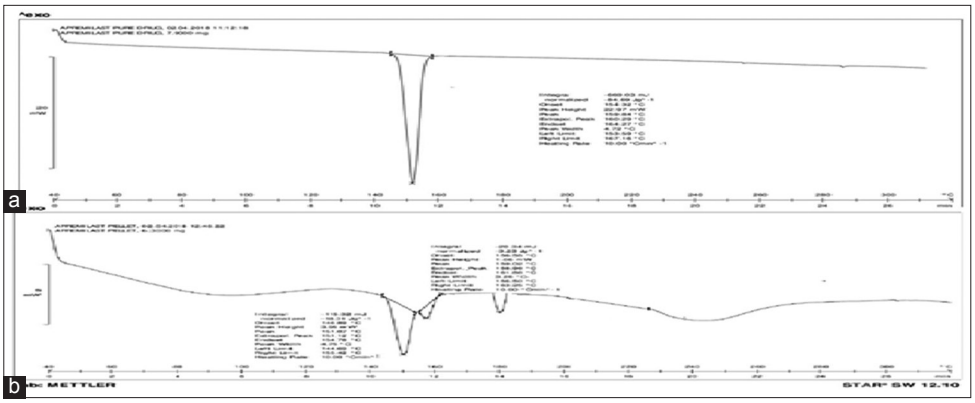

**Figure 9:** Differential scanning calorimeter thermogram of pure apremilast (a) and optimized batch F17 (b)

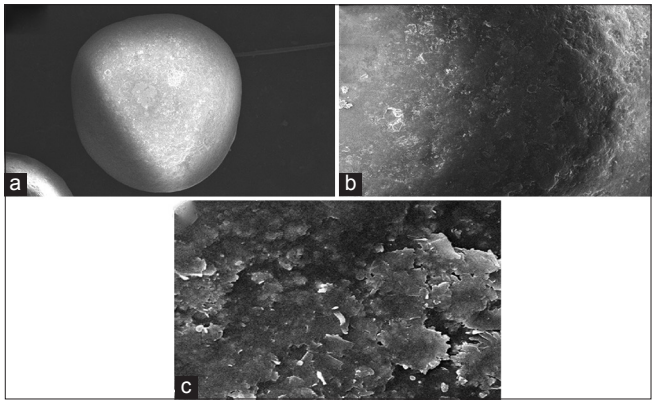

**Figure 10:** Scanning electron microscopy images of optimized formulation batch F17- (a) ×105, (b) ×500, (c) ×1000

% Yield (Y1) and hardness ($Y_2$) were used to generate polynomial equation from design expert 11.0.0. Mathematical relationships generated for the studied response variables are expressed in the following equations 1 to 2.

$$\% \text{ Yield } (Y_1) = 17.23 + 5.75MCC + 0.98TKP \quad (1)$$

$$\text{Hardness } (Y_2) = 0.40 + 05MCC + 0.039TKP \quad (2)$$

### Effect on %yield

From Equation 1, it can be seen that positive coefficient of $X_1$ (concentration of MCC) indicated an increase in the percentage yield ($Y_1$) with an increase in the concentration of MCC up to certain concentration. The positive coefficient of $X_2$ (concentration of TKP) indicates a slightly increase in response with an increase in the concentration of TKP. The equation obtained was a linear equation which showed the effect is linear. The response plot and counterplots are Figure 4. The plot indicates the effect of concentration of MCC and TKP on percentage yield of apremilast loaded pellets.

### Effect on hardness

From Equation 2, it can be seen that positive coefficient of $X_1$ indicated an increase in the pellet hardness ($Y_2$) with an increase in the concentration of TKP. The positive coefficient of $X_2$ indicated an increase in response ($Y_2$) that is pellet hardness with an increase in the concentration of MCC up to certain concentration. The equation obtained was a linear equation. The response plot and counterplots in Figure 5. Indicate a relative effect of concentration of MCC and TKP on pellet hardness of apremilast loaded pellets [Figure 6].

### Optimization of coating

The batch F14 was further coated with Eudragit L100 to obtained weight gain of 5%, 8%, and 10%, respectively.

### *In vitro* dissolution study

The percentage drug release of apremilast from pellets (F14) in 0.1 N HCl shown 96.6% in 90 min and in phosphate buffer pH 6.8 shown 96.8% in 150 min as shown in Figure 7. The percentage drug release behavior of coated pellets changed due to the variation in the coating percentage. 5% and 8% (F15 and F16) coating had shown more drug release in the acidic media (0.1N HCl) as compared to 10% coating (F17) for initial 2 h. These pellets showed 97.4% drug release in phosphate buffer pH 6.8 for the next 5 h as shown in Figure 8. From all the above observations of coated formulation, 10% coating level formulation is suitable for the successful sustained release of apremilast for 7 h.

### DSC

The endothermic peak obtained in thermogram of pure apremilast at 152.7°C can attribute to the melting point of apremilast, slightly change was observed in thermogram of formulation while addition endoderm at 182.2°C represents the peak of Eudragit L100. Thus, the thermogram showed that the apremilast and Eudragit L100 are compatible with each other since there is no significant difference in the endothermic peak of pure drug and formulation batch F17 as shown in Figure 9.

### SEM

The SEM studies the pellets shown spherical shape of pellets with outer smooth surface due to the polymer coating. Pellets size was observed between 0.880 and 1.109 mm as shown in Figure 10.

## CONCLUSION

The apremilast pellets batch (F-14) prepared with MCC (12 g) and TKP (3 g) spheronized at 800 rpm were found to be optimized. The optimized batch had shown good physicochemical properties, hardness, and percentage yield. The optimized pellets were coated with Eudragit L100 as release rate retardant polymer. It was observed that increasing the level of Eudragit coating retarded the drug release in 0.1N HCl and pH 6.8 phosphate buffer. The study suggested that 10% Eudragit coating gave the least drug release in 0.1N HCl in 2 h. In the next 5 h 97.4%, drug release was observed in phosphate buffer. Thus, delayed release followed by sustained release was obtained with coated pellets (10% level). A significant result obtained with the study indicates that modified release pellets prepared by extrusion-spheronization technique can successfully be further explored and employed in the treatment of RA as well as other diseases characterized by circadian rhythm.

## REFERENCES


1. Muley S, Nandgude T, Poddar S. Extrusion–spheronization a promising pelletization technique: In-depth review. Asian Journal of Pharmaceutical Sciences. 2016 Dec 1; 11(6): 684-99.
2. Sharma A, Chaurasia S. Multiparticulate drug delivery system: pelletization through extrusion and spheronisation. Int. Res. J. Pharm. 2013; 4(2): 6-9.
3. Gavali H, Nair D, Patel D. Multiparticulate drug delivery system and their processing techniques. World Journal of Pharmaceutical Research, 2015; 4(6): 1949-1960.
4. Sai ML, Adithya BS, Jenya NK, Mohammad G, Nadendla RR. Extrusion and spheronization: an indispensible technique in formulation development. 2017; 2(2):457-46.
5. Sahoo GP, Parashar B. Pharmaceutical Processing–A Review on Spheronization Technology. Journal of Pharmaceutical Research and Opinion. 2013; 3(9): 65-8.
6. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, Van Der Heijde D, Landewé R, Nash P, Pricop L, Yuan J, Richards HB. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. New England Journal of Medicine. 2015 Oct 1; 373(14): 1329-39.
7. Sajan J, Cinu TA, Chacko AJ, Litty J, Jaseeda T. Chronotherapeutics and chronotherapeutic drug delivery systems. Tropical Journal of Pharmaceutical Research. 2009; 8(5): 467-475.
8. Ashwini D, Asif K, Ramana MV, Mitul P, Omkar D. Chronotherapy: A novel drug delivery system. International journal of research in Ayurveda & Pharmacy. 2011; 2(6):1692-700.
9. Hire N, Gudsoorkar V, Bhise K, Upasani C, Nandgude TD, Dalvi H. Microparticulate drug delivery system for topical administration of itraconazole. Asian J Pharm. 2007 Apr;1:83-8.
10. Muley S, Nandgude T, Poddar S. Formulation and Optimization of Lansoprazole Pellets Using Factorial Design Prepared by Extrusion-Spheronization Technique Using Carboxymethyl Tamarind Kernel Powder. Recent patents on drug delivery & formulation. 2017; 11(1): 54-66.
11. Patil SM, Mishra RV, Shirolkar SV. Development and Evaluation of Sustain Release Simvastatin Pellets. Research Journal of Pharmacy and Technology. 2017; 10(8): 2467-2473.
12. Diggikar SS, Nandgude TD, Poddar SS. Formulation of Modified Release Pellets of Montelukast Sodium. Research Journal of Pharmacy and Technology. 2018; 11(1): 31-37.
13. Nandgude TD, Bhise KS, Gupta VB. Characterization of hydrochloride and tannate salts of diphenhydramine. Indian journal of pharmaceutical sciences. 2008; 70(4): 482-486.
14. Law MF, Deasy PB. Use of hydrophilic polymers with microcrystalline cellulose to improve extrusion–spheronization. European journal of pharmaceutics and biopharmaceutics. 1998; 45(1): 57-65.
15. Nandgude T, Bhise K. Characterization of drug and polymers for development of colon specific drug delivery system. Asian Journal of Biomedical and Pharmaceutical Sciences. 2011; 1(4): 17-21.
16. Prashant R, Rakesh M, Nandgude T, Sushilkumar P. Solubility and dissolution enhancement of albendazole by spherical crystallization. Asian Journal of Biomedical and Pharmaceutical Sciences. 2016; 6(52): 09-14.
17. Lavanya K, Senthil V, Rathi V. Pelletization technology: a quick review. International Journal of Pharmaceutical Sciences and Research. 2011; 2(6): 1337-1355.
18. Rahman MA, Ahuja A, Baboota S, Bali V, Saigal N, Ali J. Recent advances in pelletization technique for oral drug delivery: a review. Current drug delivery. 2009; 6(1): 122-129.
19. Nandgude T, Maria S, Bhise K. Formulation and evaluation of fast disintegrating tablet of Diphenhydramine Tannate. Asian Journal of Pharmaceutics. 2006; 1(1) 41-45.
20. Mishra R, Nandgude T. Spherical Crystallization for Solubility and Dissolution Enhancement of Meloxicam by Neutralization Method. Pharmaceutical Process Development. 2016; (2): 74-81.


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