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# Formulation development and evaluation of medroxyprogesterone acetate injectable suspension

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## ABSTRACT

The aim of the present work is to develop sustained release parenteral drug delivery system of contraceptive drug i., e medroxyprogesterone acetate. The formulation was prepared by sterile combining of API and excipient powders by rapid stirring method. Different excipients used in the formulation are PEG 3350, Poloxamer -188, Polysorbate-80, Benzyl alcohol and Sodium chloride. The prepared parenteral suspension was evaluated for all official parameters like sedimentation volume, measurement of zeta potential, pH, viscosity, osmolality, dissolution, assay, particle size determination, and stability studies. The dissolution profile was found to be more when compared with the innovator formulation. Stability studies were also conducted at 25ºC / 60% RH and 40ºC / 75% RH conditions up to 3M.All the parameters evaluated are within the specified limits.

**Keywords:** Medroxy progesterone acetate, PEG 3350, Poloxamer-188, injectable suspension.

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## INTRODUCTION

The parenteral route is the most preeminent and common form of drug delivery system. This system generally avoids the drug related problems which were associated with the oral route are acid degradation, hepatic metabolism (first pass effect), enzymatic action in the intestine, unpredictable pharmacokinetic parameters (solubility, absorption, distribution etc..,). Site specific drug delivery can also be achieved by this route[1].

To overcome the loopholes various approaches like microemulsions[2], liposomes, solid dispersion techniques, cubosomes and complexation with cyclodextrins are adopted. Though there reasonable success has been achieved employing these techniques but still some of the draw backs were there such as poor stability, low drug loading capacity, increased toxicity, complex manufacturing method[3].

### Depot systems

A depot is an injection, either administered intramuscularly or subcutaneously which usually deposits the drug at the site of injection as a mass, from which it gets absorbed and distributed to the tissue which surrounds it. This system usually releases the active compound in a consistent manner over a long period. The main advantage of long-acting depot injection includes decreased dosing frequency which in turns increases the patient compliance; more consistent serum concentration can be gained[4].

Parenteral suspensions are thermodynamically unstable heterogeneous systems in which the insoluble drug particles are dispersed or suspended in the dispersion medium (such as aqueous or non-aqueous vehicles). Particle size should be less than 5 µm[5]. Medroxy progesterone structurally resembles progesterone and it is widely used as contraceptive or hormone replacement therapy[6]. The overall aim of the present work was to formulate the parenteral depot suspension and illustrate the particle size, pH, in- vitro drug release profile and stability parameters with that of innovator product.

## MATERIALS AND METHODS

Medroxy progesterone acetate was obtained from Crystal pharma as a gift sample. Polyethylene glycol 3350 was purchased from Sigma Aldrich, USA. Polysorbaten80, poloxamer-188, benzyl alcohol, sodium chloride and sodium hydroxide were obtained from Merck chemicals Ltd., Mumbai. All other chemicals and reagents used were of analytical reagent (AR) grade.

### Preformulation studies[7]

Preformulation is the study that yields necessary information related to physicochemical properties of drug candidate in order to develop safe, effective and stable dosage form. This study includes

- Physical characterization of API
- Solubility of API
- Drug-excipient compatibility study

### Preparation of aqueous suspension

Aqueous suspension of medroxy progesterone acetate was prepared by rapid stirring method. Accurately weighed quantity of PEG-3350, poloxamer 188, Polysorbate 80, benzyl alcohol and sodium chloride was dissolved in Milli-Q water by continuous stirring. The API was added during stirring condition, at least for 45 minutes[8]. The formulation design for medroxy progesterone acetate suspension is represented (Table No. 1).

**Table 1: Formulation design of Medroxy progesterone acetate injectable suspension**

| S.No | Name of the ingredients (mg/mL) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Medroxy progesterone Acetate | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| 2. | Polyethylene glycol 3350 | 27.1 | 26.9 | 28.5 | - | - | - | 28.1 | 27.7 | 26.9 |
| 3. | Poloxomer 188 | - | - | - | 1.0 | 1.50 | 2.0 | 0.80 | 1.20 | 2.0 |
| 4. | Polysorbate 80 | 2.41 | 2.41 | 2.41 | 2.41 | 2.41 | 2.41 | 2.41 | 2.41 | 2.41 |
| 5. | Sodium chloride | 8.68 | 8.68 | 8.68 | 8.68 | 8.68 | 8.68 | 8.68 | 8.68 | 8.68 |
| 6. | Benzyl alcohol | 4.45 | 7.10 | 8.88 | 5.6 | 6.90 | 9.16 | 7.5 | 6.80 | 8.88 |
| 7. | Sodium hydroxide (0.1N) | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| 8. | Hydrochloric acid (0.1N) | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| 9. | Water for injection | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |

### In-vitro Dissolution studies

In-vitro dissolution test was carried out by using USP type-IV apparatus (Flow through cell)[9]. 900 mL of pH 7.4 phosphate buffer and 0.50 % SLS was used as dissolution medium. Basket was rotated at 50 rpm and temperature was maintained at 37 ± 0.5ºC. Sampling was done at regular intervals and they are analysed by HPLC.

### Physical characterization of suspension

- Particle size and zeta potential
- pH
- Osmolality
- Viscosity

## RESULTS AND DISCUSSION

**Table 2: Physical characterization of API**

| S.No | Description | Results |
|---|---|---|
| 1. | Colour | White |
| 2. | Appearance | Crystalline powder |
| 3. | Taste | Bitter |
| 4. | odor | Odorless |

### X-Ray diffraction study

Sharp peaks were observed in the X-Ray diffractogram indicates crystalline nature of API.

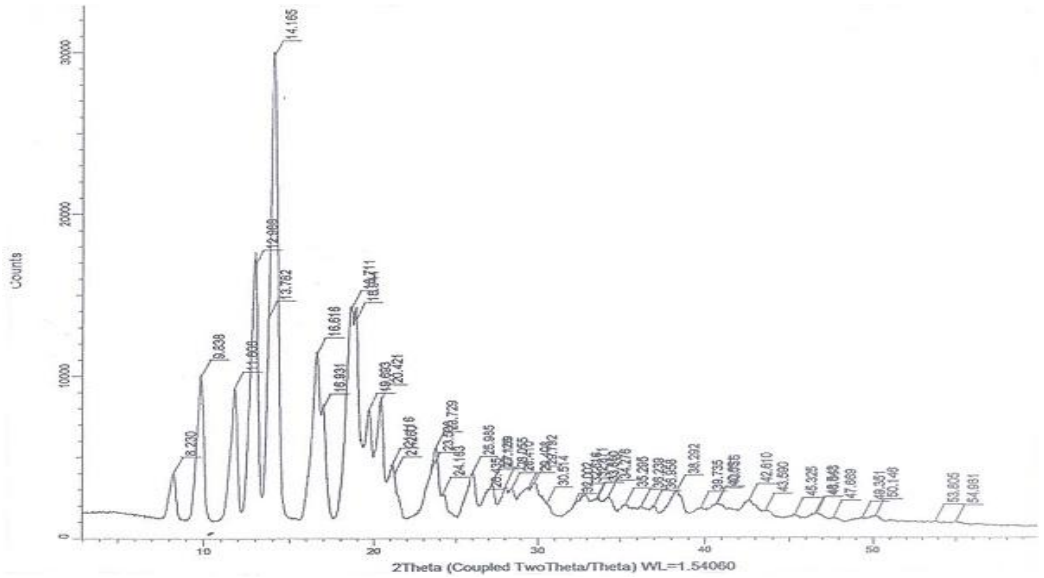


**Figure 1: XRD of Medroxy progesterone acetate**

**Table 3: Solubility of API in different media**

| Solvent system | Solubility (mg/mL) |
|---|---|
| Purified water | 0.0033 |
| 0.1 N Hcl | 0.0003 |
| pH 4.5 acetate buffer | 0.0004 |
| pH 6.8 phosphate buffer | 0.0002 |
| pH 7.4 phosphate buffer | 0.0014 |
| Water + 0.5 % SLS | 0.355 |
| 0.1 N Hcl + 0.5 % SLS | 0.352 |
| pH 4.5 acetate buffer + 0.5 % SLS | 0.383 |
| pH 6.8 phosphate buffer + 0.5 % SLS | 0.329 |
| pH 7.4 phosphate buffer + 0.5 % SLS | 0.449 |

**Drug-Excipient compatibility studies by FTIR**

FTIR method was adopted to study the compatibility with drug and excipients. Medroxy progesterone acetate shows characteristics absorption bands at 3424.31cm-1 for O-H, 2947.26cm-1 for C-H stretching, 1731.79cm-1 for C=O stretching and 1410.27cm-1C=C bending. There were no extra peaks observed in the spectrum when API in combination with excipient. A figure 1, 2 & 3 represents the compatibility between drug and the excipients mixture.

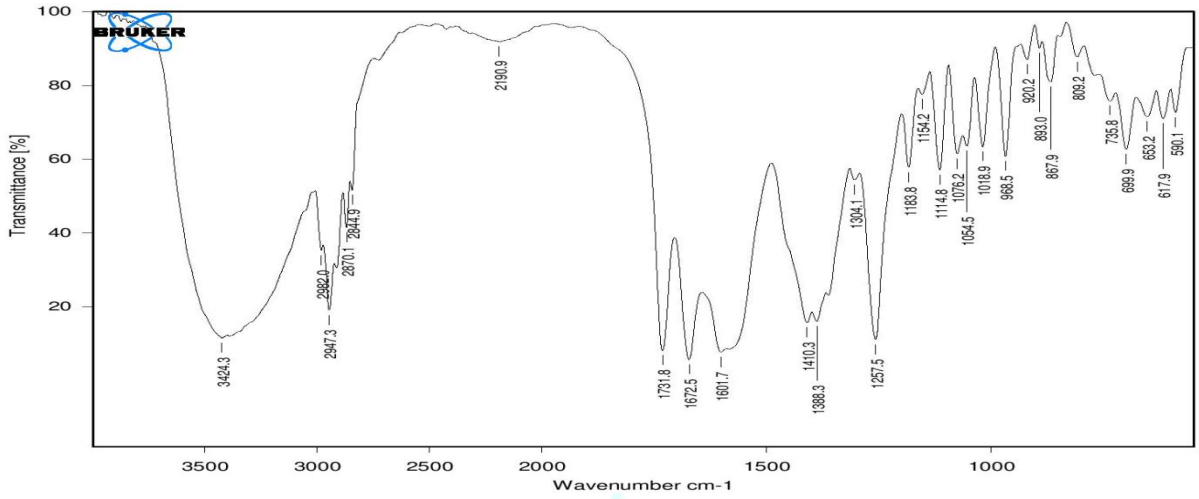


**Figure 2: FTIR Spectrum of pure API**

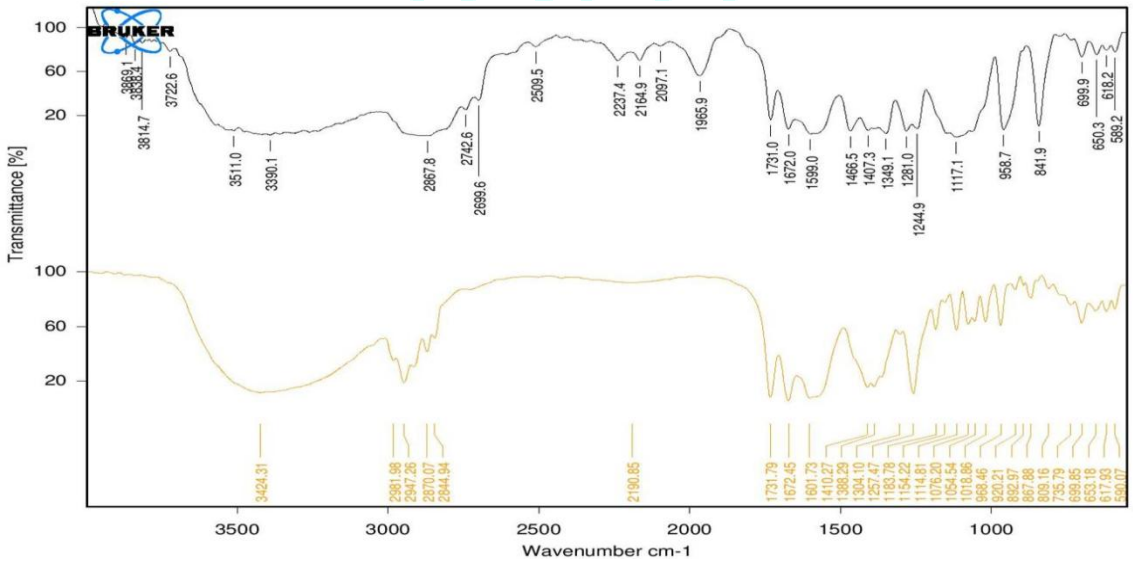


**Figure 3: FTIR Spectrum of medroxy progesterone acetate with PEG 3350**

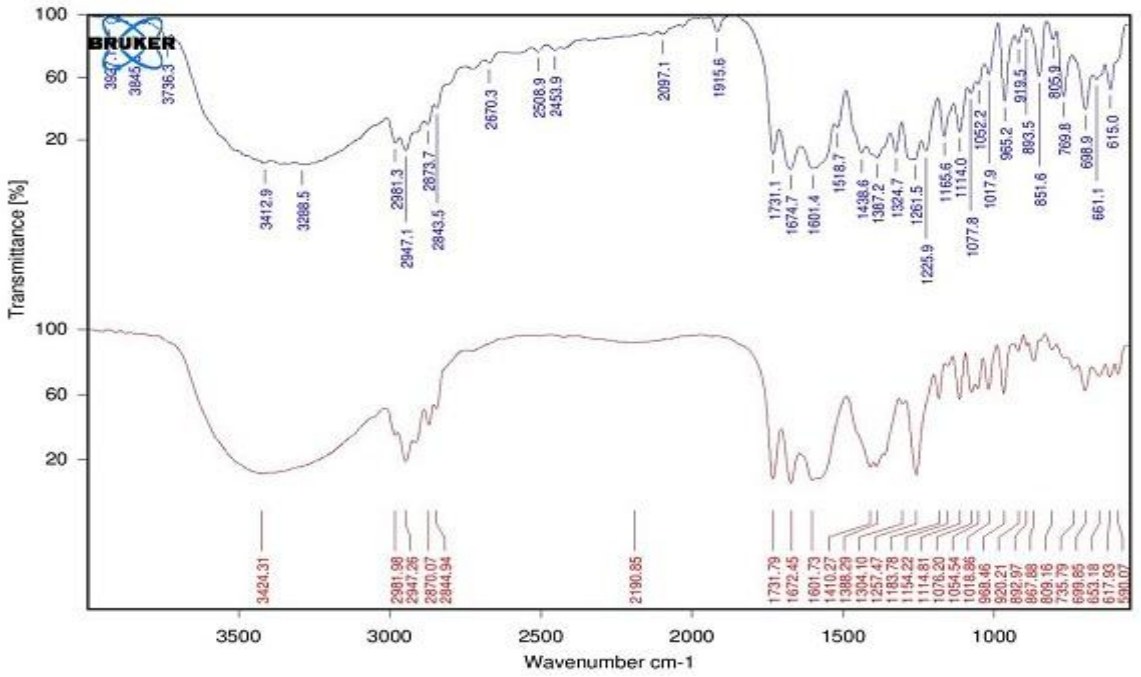


**Figure 4: FTIR Spectrum of medroxy progesterone acetate with Poloxamer-188**

### Assay

The assay percentage of innovator and optimized formulation was 100.2±0.5 and 99.8±0.69 respectively. Assay was within the limit and matches with the innovator.

### Dissolution studies

The drug release profiles are obtained for the innovator and different formulations F1, F2, F3, F4, F5, F6, F7, F8, and F9. Cumulative % drug release of Optimized formulation F9 0, 41±0.79, 67±1.52, 73±0.99, 83±0.75, 89±1.13, 95±0.98, 101±0.69 respectively. The innovator shows the drug release 0, 43±0.91, 65±0.97, 72±0.45, 81±0.79, 88±0.98, 93±1, 99±1.36 respectively. Among all formulations, F9 trial shows the increased drug release pattern than innovator.

**Table 4: Drug content**

| Test | Assay (96%-103% USP) |
|---|---|
| RLD | 100.2±0.51 |
| F1 | 98.5±1.02 |
| F2 | 100.9±0.98 |
| F3 | 98.7±0.59 |
| F4 | 101.5±0.12 |
| F5 | 97.9±0.85 |
| F6 | 95.9±1.05 |
| F7 | 97.8±0.39 |
| F8 | 98.1±0.78 |
| F9 | 99.8±0.69 |

Mean±standard deviation (n=3)

**Table 5: Cumulative Percentage drug release of profiles**

| Trials | Time (hrs) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 6 | 8 | 12 |
| **F1** | 0 | 39±0.5 | 58±0.63 | 67±0.20 | 79±1.29 | 87±0.91 | 92±1.23 | 96±1.49 |
| **F2** | 0 | 48±0.21 | 66±0.82 | 72±0.85 | 80±2.15 | 84±0.67 | 91±0.87 | 97±1.54 |
| **F3** | 0 | 29±0.82 | 49±0.71 | 65±1.09 | 71±1.1 | 79±0.98 | 87±1.25 | 93±1.49 |
| **F4** | 0 | 52±1.14 | 63±1.49 | 71±2.1 | 80±0.79 | 87±1 | 91±1.53 | 96±1.65 |
| **F5** | 0 | 35±0.75 | 51±1.13 | 62±0.98 | 71±0.83 | 83±0.8 | 89±0.86 | 93±0.79 |
| **F6** | 0 | 27±1.05 | 46±0.99 | 59±1.45 | 71±0.29 | 87±1.23 | 95±2.7 | 98±1.13 |
| **F7** | 0 | 50±0.91 | 61±0.84 | 73±1.25 | 79±0.87 | 86±1.4 | 88±1.11 | 95±2.1 |
| **F8** | 0 | 32±0.85 | 56±1 | 69±1.05 | 75±1.15 | 87±1.21 | 90±1.98 | 94±0.94 |
| **F9** | 0 | 41±0.79 | 67±1.52 | 73±0.99 | 83±0.75 | 89±1.13 | 95±0.98 | 101±0.69 |
| **RLD** | 0 | 43±0.91 | 65±0.97 | 72±0.45 | 81±0.79 | 88±0.98 | 93±1 | 99±1.36 |

**Note:** All the values are expressed as mean± SD, n=3

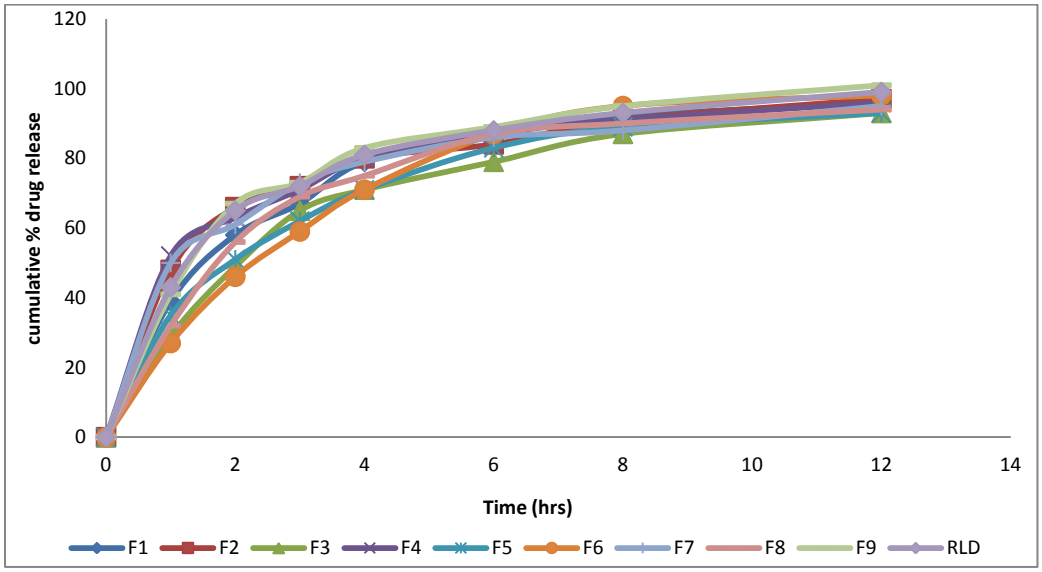


**Figure 5: Cumulative % drug release of formulations F1-F8 and RLD**

**Table 6: Physical characterization**

| Trials | Size (nm) | Zeta potential (mV) | pH (3.0 -7.0) | Osmolality (mOsmol/kg) (350-410) | Viscosity (cps) (6.0-9.0) |
|---|---|---|---|---|---|
| F1 | 1243±11.47 | -33.7±0.49 | 5.67 | 375 | 6.15 |
| F2 | 1190±32.7 | -21.9±3.14 | 6.12 | 367 | 6.19 |
| F3 | 1210±21.18 | -28.5±2.89 | 6.67 | 364 | 6.23 |
| F4 | 1240±19.8 | -19.8±4.1 | 6.49 | 376 | 6.12 |
| F5 | 1160±45.1 | -31.8±0.56 | 5.97 | 361 | 6.51 |
| F6 | 1290±12.5 | -29.7±2.47 | 6.21 | 374 | 6.37 |
| F7 | 1310±5.14 | -34.2±0.31 | 6.60 | 361 | 6.64 |
| F8 | 1180±19.2 | -25.9±2.73 | 6.01 | 359 | 6.29 |
| F9 | 1105±17.94 | -38.1±0.21 | 6.80 | 381 | 6.95 |
| RLD | 1132±7.8 | -35.4±0.64 | 6.78 | 379 | 6.92 |

Mean±standard deviation (n=3)

**Table 7: Sedimentation study analysis**

| Time (hrs) | F9 F=Vs/Vi | RLD F=Vs/Vi |
|---|---|---|
| 1 | 1.00 | 1.00 |
| 2 | 1.00 | 1.00 |
| 4 | 0.99 | 0.98 |
| 8 | 0.99 | 0.95 |
| 24 | 0.97 | 0.91 |
| 48 | 0.94 | 0.89 |
| 72 | 0.90 | 0.89 |
| 96 | 0.90 | 0.89 |
| 120 | 0.90 | 0.89 |

**Note: Vs -** Volume of sediment in mL, **Vi** – Initial volume & **F** – Sedimentation volume

**Table 8: 3M stability data of optimized formulation F9**

| Formulation | F9 | F9 | RLD | RLD |
|---|---|---|---|---|
| **Stability conditions** | **25ºC / 60% RH** | **40ºC / 75% RH** | **25ºC / 60% RH** | **40ºC / 75% RH** |
| **Drug content** | 100.1±0.6 | 98.8±1.23 | 99.8±0.69 | 98.4±1.07 |
| **pH** | 6.79 | 6.76 | 6.77 | 6.74 |
| **Osmolality** | 381 | 379 | 378 | 376 |
| **Viscosity** | 6.94 | 6.89 | 6.91 | 6.88 |
| **Dissolution** | 101.17±0.58 | 100.8±0.6 | 98.87±1.63 | 98.28±1.94 |
| **Particle size (nm)** | 1112±10.58 | 1125±7.2 | 1145±5.89 | 1175±4.17 |

**Report:**

There were no marked changes observed in the 3M stability of optimized formulation F9 and innovator at 25ºC / 60% RH and 40ºC / 75% RH conditions. It indicates that optimized formulation F9 shows good stability like that of innovator.

## CONCLUSION

The goal of the investigation was to develop a sustained release parenteral drug delivery system of contraceptive drug i., e medroxy progesterone acetate which was administered intramuscularly. Drug excipient compatibility was performed and the spectrums show compatibility. The formulation was optimized and evaluated for the parameters of parenteral preparations. The dissolution profile of optimized was more when compared with the innovator formulation.3M stability data at 25ºC / 60% RH and 40ºC / 75% RH conditions generated and it shows good stability. Hence, this product was developed to get increased compliance with decreasing the dosing frequency. A stable pharmaceutically equivalent product was developed.

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