# Formulation and evaluation of controlled release transdermal microneedles of rotigotine

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**Abstract**

Rotigotine is a novel, non-ergot dopamine agonist delivered using a transdermal microneedle device. Microneedle transdermal patches integrate hypodermic needles and transdermal patches to address the inherent constraints of both injections and patches. The aim of this work was to develop a minimally invasive, polymeric microneedle patch and assess the fabricated biodegradable microneedles through in vitro methods. The polymeric microneedle arrays were constructed from polyvinyl alcohol (PVA) and Eudragit NM 30D via the micromolding process in aseptic circumstances. The synthesized transdermal microneedle patches were assessed for FT-IR analysis, DSC analysis, drug content, in vitro drug release, and stability evaluation. Polyvinyl alcohol (PVA) and Eudragit NM 30D were deemed safe for the manufacturing of rotigotine

microneedle patches, as no interactions were seen between the drug and the polymers. The improved rotigotine microneedle patches demonstrated a 97.8 ± 0.9% in vitro drug release over 8 hours. The six-month stability testing demonstrated that there were no significant changes in the optimized formulation. The findings indicate that PVA and Eudragit-based microneedle patches constitute a practical and effective method for transdermal drug administration, presenting opportunities for further advancement in controlled release applications.

Keywords: Rotigotine, Polyvinyl alcohol, Eudragit, Microneedle Patch

## 1. Introduction

Dopamine agonists serve as an efficacious symptomatic intervention for the initial phases of Parkinson's disease (PD) (Pringsheim et al., 2021; Choi et al., 2025; Bonuccelli et al., 2009). Most currently available dopamine agonists necessitate a thrice-daily oral dose schedule, which may lead to suboptimal compliance (Hollerhage et al., 2024; Canovas et al., 2014). Therefore, there is a necessity for new therapies that are effective, safe, well-tolerated, user-friendly, and enhance compliance.

Rotigotine is a novel, non-ergot D3, D2, and D1 dopamine agonist designed within a silicone-based transdermal delivery system (Jost 2020; Rascol et al., 2009). Pharmacokinetic investigations indicate that the rotigotine transdermal patch delivers dose-proportional and consistent plasma concentrations of rotigotine for 24 hours (Elshoff et al., 2015). Prior clinical studies demonstrated that the rotigotine transdermal patch is safe, well tolerated, and effective in individuals with both early and advanced-stage Parkinson's disease (Rascol et al., 2009; Elshoff et al., 2015; Elshoff et al., 2012). This study examined the efficacy and safety of the rotigotine transdermal microneedle patch in the initial phases of PD.

## 2. Materials and Methods

### Materials

Ajanta Pharma, located in Mumbai, was the supplier of rotigotine. SD Fine Chemicals Ltd, located in Mumbai, India, supplied Eudragit NM 30D, polyvinyl

alcohol, glycerin, and propylene glycol. Furthermore, many analytical-grade chemicals and solvents were employed in this work.

## Methods

### Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR measurements of Rotigotine and its excipients were acquired using the conformist KBr pellet method (Bruker, Germany). Each sample was individually pulverized with anhydrous KBr, followed by the compaction of the pellet under hydraulic pressure. FT-IR spectroscopy was performed within the wavelength range of 400 to 4000 $cm^{-1}$.

### Differential Scanning Calorimetry (DSC)

DSC experiments on rotigotine and the rotigotine-loaded microneedle patch were performed at the Sophisticated Instrumentation Centre for Applied Research and Testing (SICART) in Vallabh Vidhyanagar, Gujarat, India, to evaluate the thermal stability of the microneedle patch. Meticulously measured samples were positioned in the DSC sample holder, and the DSC 8000 (Perkin Elmer, US) was employed to document calorimetric curves inside the temperature range of -35 to 400ºC, utilizing a heating rate of 0.1 to 100ºC/min in a nitrogen atmosphere.

### Preparation of rotigotine transdermal microneedle patchs

The micromolding method was employed to fabricate rotigotine microneedle patches. A magnetic stirrer was employed to completely dissolve PVA in hot water for two hours to obtain a suitable solution. Subsequently, eudragit NM 30D and propylene glycol were included into the polymeric solution. Subsequently, a medication (6 mg) and glycerin were incorporated, resulting in a homogenous solution achieved through mechanical stirring, followed by degassing with a sonicator (REMI Instrument, India). Additionally, to facilitate the total evaporation of the solvent, this solution was meticulously poured into the mold (area = 24 $cm^2$) and allowed to remain at room temperature for 72 hours. To fabricate transdermal microneedle patches carrying around 1mg of medicine, the patches were meticulously sectioned into 2 × 2 $cm^2$ pieces. These

films were encased in aluminum foil for further experimental utilization. A total of nine formulations were developed, as illustrated in Table 1.

**Table 1: Different batches of rotigotine loaded microneedle patches**

| Sr. No. | PVA (mg) | Eudragit NM 30D (mg) | Glycerine (ml) | Propylene glycol (ml) | Water up to (ml) |
|---|---|---|---|---|---|
| F1 | 65 | 2.5 | 1 | 1 | 10 |
| F2 | 70 | 2.5 | 1 | 1 | 10 |
| F3 | 75 | 2.5 | 1 | 1 | 10 |
| F4 | 65 | 5 | 1 | 1 | 10 |
| F5 | 70 | 5 | 1 | 1 | 10 |
| F6 | 75 | 5 | 1 | 1 | 10 |
| F7 | 65 | 7.5 | 1 | 1 | 10 |
| F8 | 70 | 7.5 | 1 | 1 | 10 |
| F9 | 75 | 7.5 | 1 | 1 | 10 |

PVA – polyvinyl alcohol

## Drug content

100 cc of a phosphate buffer at pH 6.8 solubilized the constructed microneedle patch (2×2 $cm^2$). The solution was analyzed using a UV spectrophotometer (Shimadzu, 1800) at 272 nm, following appropriate dilutions. The reference standard curve, established with a rotigotine solution at a concentration range of 0-45 µg/ml, was utilized to calculate the rotigotine content ($R^2$=0.9997). Each microneedle patch sample was subjected to sextuplicate testing. The drug contents of the microneedle patches were determined using the formula: rotigotine content (%) = Quantity of drug entrapped / Theoretical drug content.

## *In vitro* drug release

A dialysis membrane facilitated drug release from a pure drug solution and transdermal microneedle patches. To facilitate adequate sample diffusion from the membrane, the dialysis membrane was immersed in phosphate buffer at pH 6.8 overnight. A dialysis bag was suitably filled with 1 mg of a drug-containing solution and microneedle patches, then incubated at 37ºC with a shaking speed of 50 rpm in 15 ml of phosphate buffer at pH 6.8. A 2 ml sample was extracted, and an equal volume of freshly prepared phosphate buffer at pH 6.8 was

immediately added at each designated time interval. A UV-visible spectrophotometer (Schimadzu-1800) was employed to evaluate the aliquots at a wavelength of 272 nm. The drug release evaluation tests were conducted in sextuplicate. Mathematical models were employed to ascertain the kinetics of drug release from transdermal microneedle patches following in vitro disintegration.

### Stability study

The aim of the stability study was to assess the physical stability of the rotigotine microneedle patches under increased relative humidity and storage temperature. The rotigotine microneedle patches were stored in a stability chamber for six months at a temperature of 25 ± 2ºC and a relative humidity of 60 ± 5% (REMI Instrument, India). The rotigotine microneedle patches were systematically assessed for percentage drug content and drug release at consistent time intervals during testing.

## 3. Results and Discussion

### Fourier Transform Infrared Spectroscopy (FT-IR)

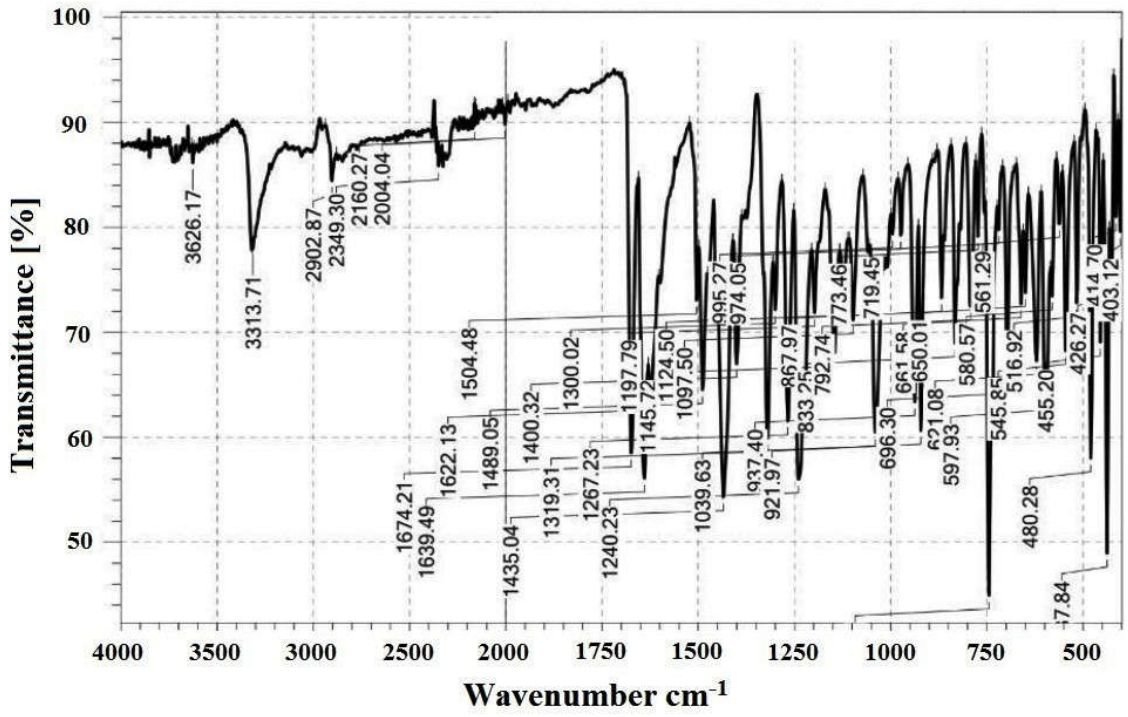



**Figure 1A. FT-IR spectra of rotigotine**

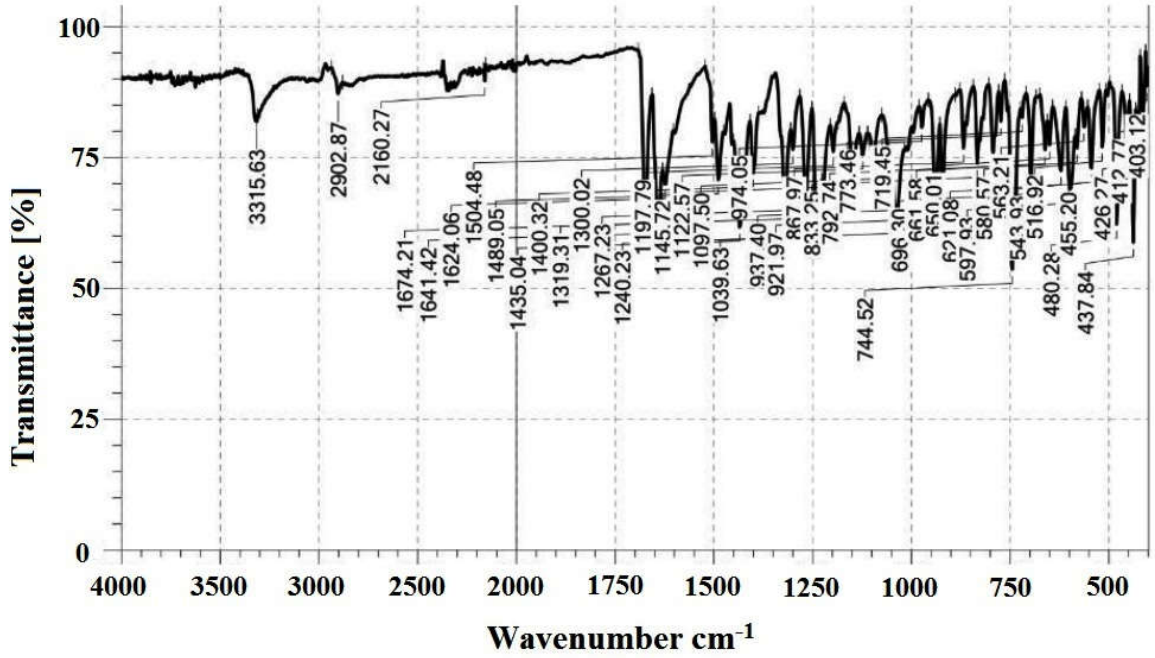



**Figure 1B. FT-IR spectra of rotigotine + excipients**

Figure 1A presents the FT-IR spectra of rotigotine, the physical mixture of rotigotine, PVA, and all excipients. The naphthalene ring of Rotigotine exhibits distinctive absorption bands at 3313.71 $cm^{-1}$ attributed to C-H stretching vibrations, with peaks at 1435.04, 1489.05, and 1504.48 $cm^{-1}$ corresponding to aromatic C=C stretching, and C-H out-of-plane bending peaks at 773.46, 792.74, 833.25, and 967.97 $cm^{-1}$, along with distinctive absorption bands at 1097.50 and 1124.50 $cm^{-1}$ due to C-N stretching vibrations. The FT-IR spectra of the physical mixture, as shown in Figure 1B, exhibit a characteristic absorption band at 3315.63 $cm^{-1}$, attributed to C-H stretching vibrations. All peaks associated with aromatic C=C stretching and C-H out-of-plane bending have virtually identical intensity. Consequently, it was concluded that no definitive chemical reaction occurred between the medication and the excipients, as evidenced by the absence of a novel characteristic absorption band of rotigotine simultaneously.

## Differential Scanning Calorimetry (DSC)

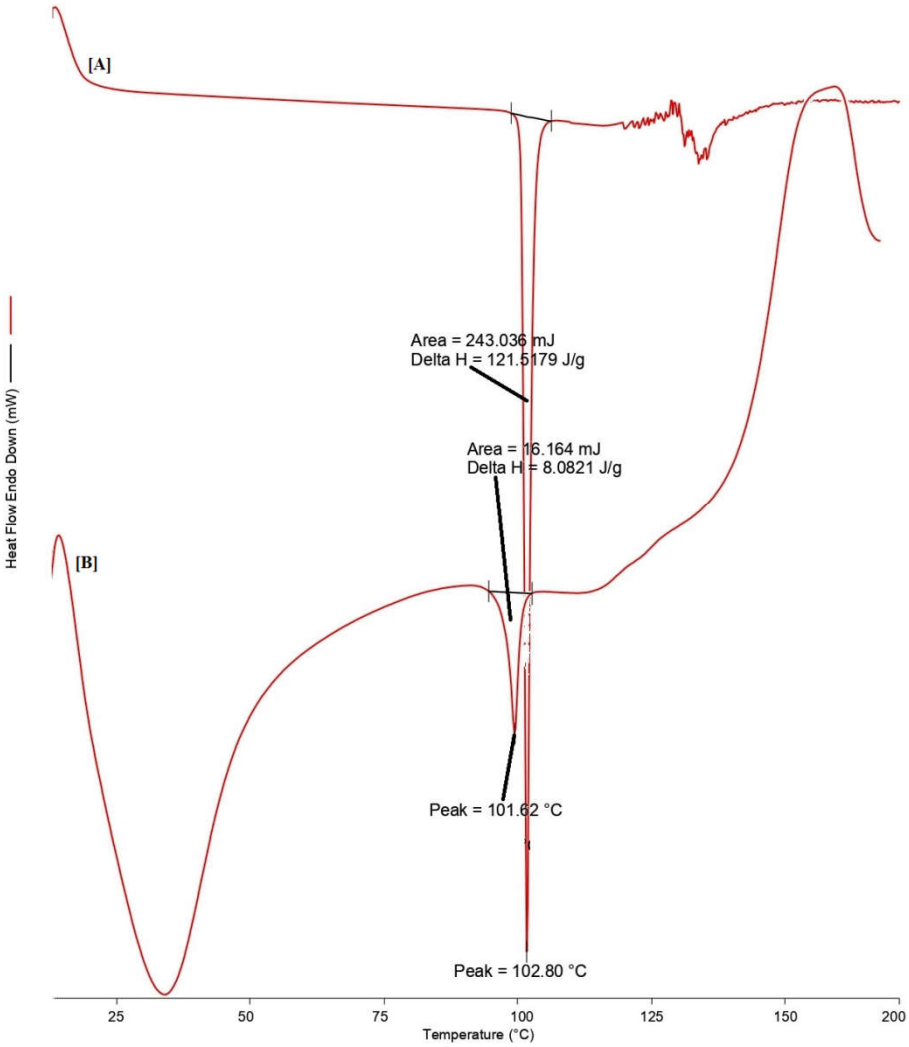



**Figure 2. DSC curve of [A] rotigotine; [B] rotigotine patch**

The thermal properties of rotigotine in our fabricated microneedle patches were analyzed using DSC curves (Figure 2). The DSC curve of Rotigotine (Figure 2A) exhibited an endothermic peak at 102.80ºC. The endothermic events corresponding to the melting of the pure drug and the evaporation of water during crystallization were evident on the curve pertaining to the microneedle patch at 35.74ºC and 101.62ºC, respectively (Figure 2B). The reduced melting point of rotigotine in the formulation indicated uniform incorporation of the drug into the polymeric matrix.

**Drug content**

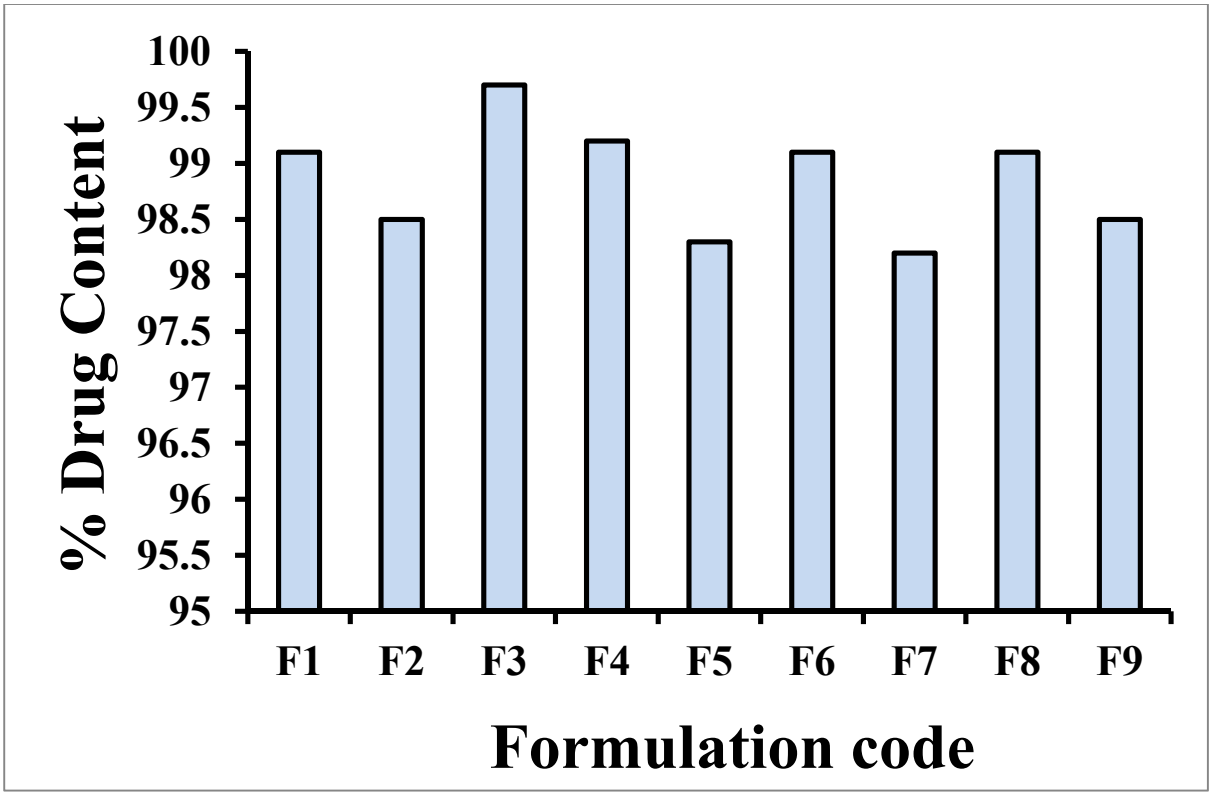



**Figure 3. % drug content of formulations**

Analysis of drug content was conducted for all manufactured transdermal systems using a conventional method, with findings illustrated in Figure 3. The produced transdermal films exhibited nearly consistent drug content, varying from 98.2% to 99.7%. This indicates that the method used to produce the patches achieved consistent medication content and minimal variability.

### *In vitro* drug release

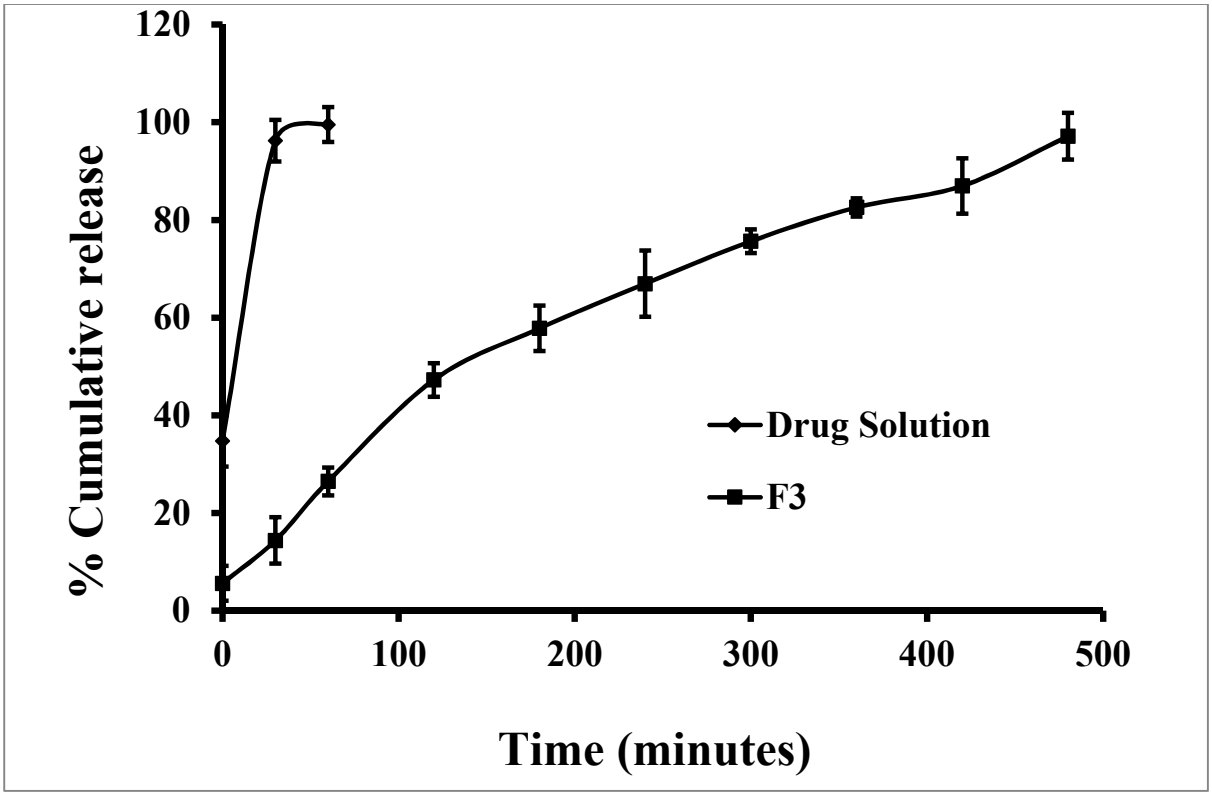
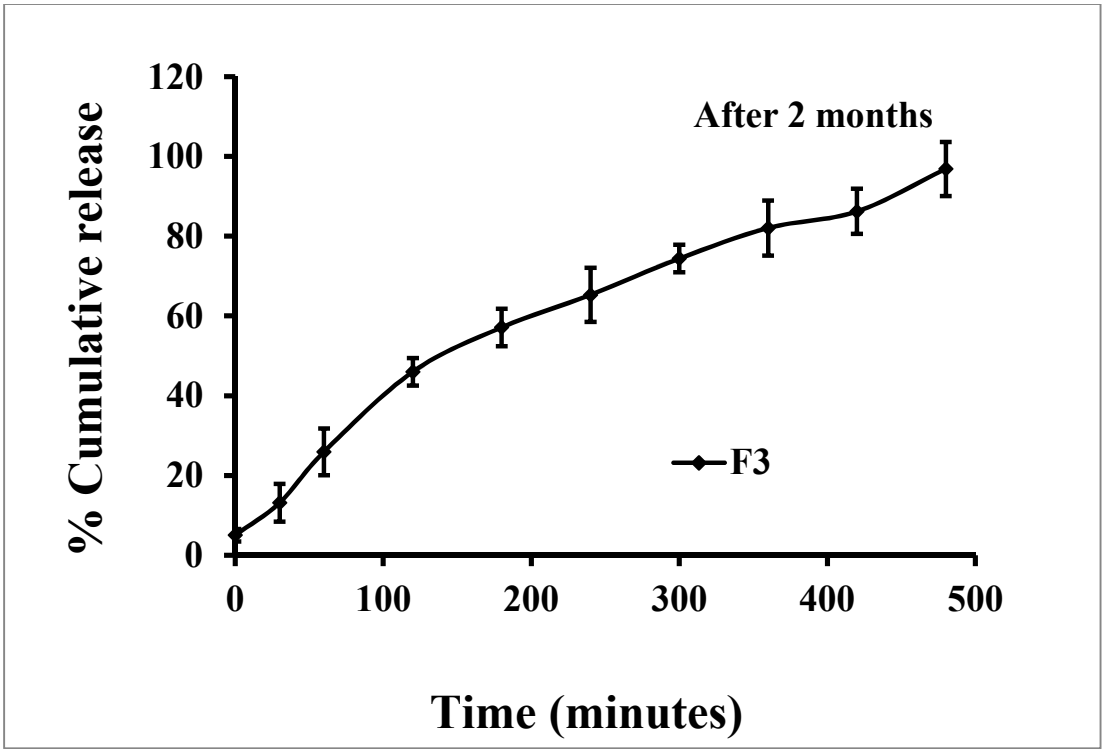


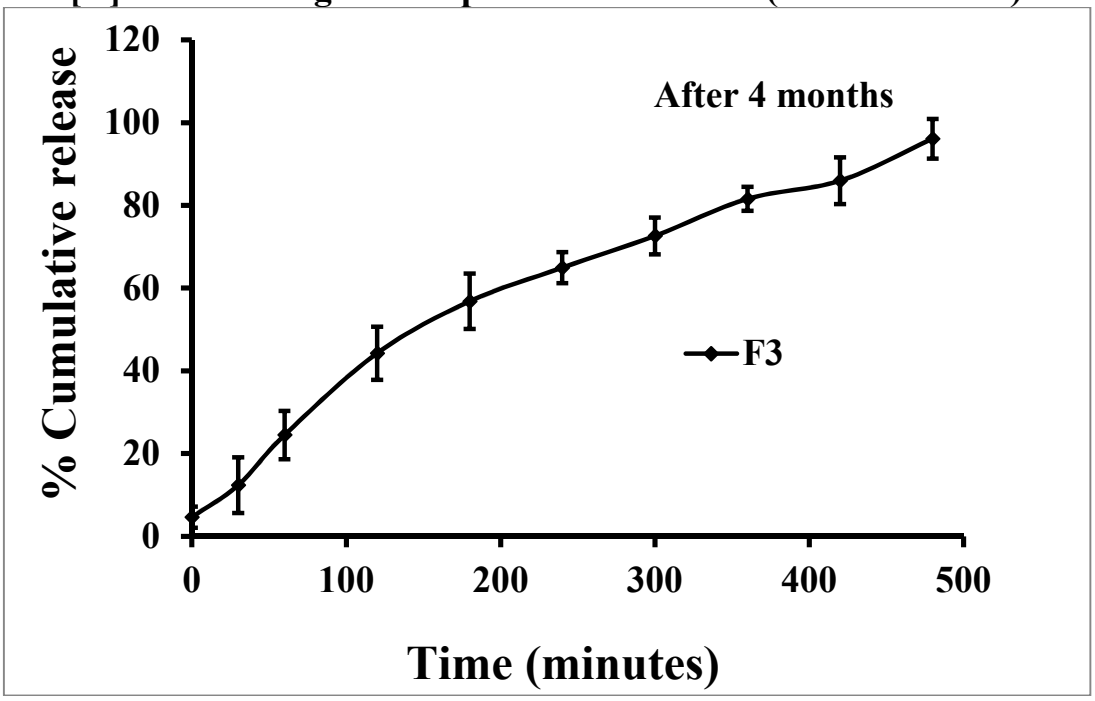

**Figure 4. *In vitro* drug release profile of rotigotine patch**

The release profile of rotigotine solution and rotigotine microneedle patch in phosphate buffer at pH 6.8 and 37ºC indicated that nearly 100% of the rotigotine solution was released within 1 hour, whereas the cumulative release of rotigotine from the microneedle patch was approximately 97.12% after 8 hours (Figure 4), underscoring the pronounced sustained release characteristics of the rotigotine-loaded microneedle patch. The cumulative drug release from the drug-loaded microneedle patch and the release duration were analyzed using the zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell equations. The optimal result for the drug-loaded microneedle patch was observed with first-order drug release kinetics ($r^2 = 0.9725$), indicating the onset of diffusion kinetics from the drug-polymer matrix.

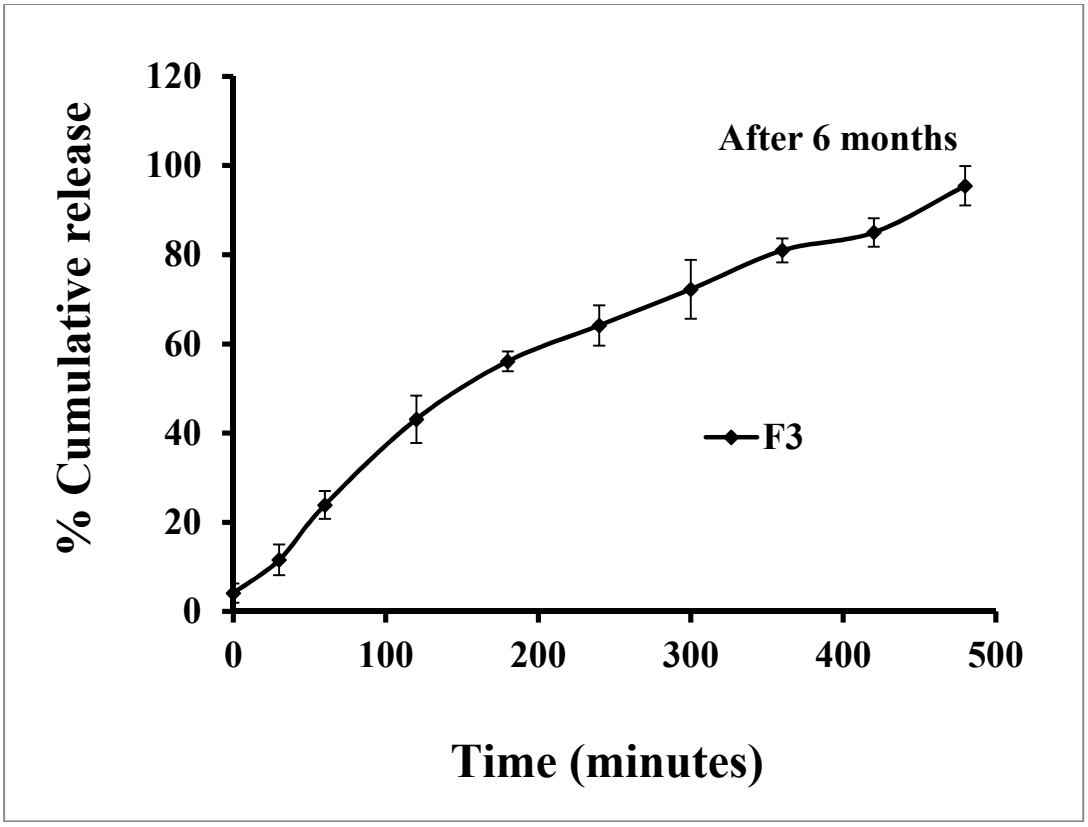
**Stability study**



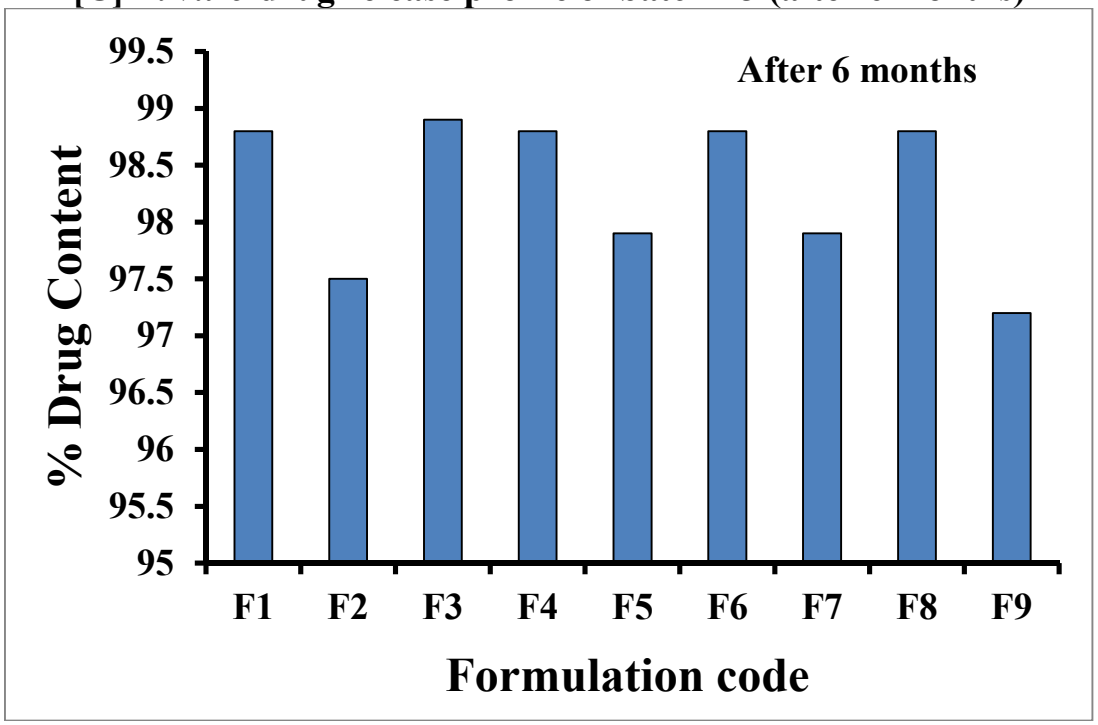

**[A] *In vitro* drug release profile of batch F3 (after 2 months)**




**[B] *In vitro* drug release profile of batch F3 (after 4 months)**




**[C] *In vitro* drug release profile of batch F3 (after 6 months)**




**[D] % drug content of batch F3 (after 6 months)**

**Figure 5. Stability study of batch F3**

Stability studies of the produced formulations were conducted to assess the release behavior and structural alignment. Stability investigations of the

optimized rotigotine-loaded microneedle patch (batch F3) conducted over six months revealed little alterations in the percentage of drug content. The drug release profile exhibited minimal variations, indicating strong compatibility between the drug and excipients (Figure 5).

## 4. Conclusion

This study highlights the importance of rotigotine in the development of drug-loaded microneedle patches, assessing the compatibility of all excipients, drug content, in vitro drug release, and a six-month stability evaluation. The results indicated that drug-loaded microneedle patches exhibited a significantly prolonged release compared to the traditional formulation. This study highlights the potential applicability of rotigotine-loaded microneedle patches in the medical treatment of PD.

## Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

## Acknowledgements

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## References

1. Pringsheim, T., Day, G.S., Smith, D.B., Rae-Grant, A., Lincking, N., Armstrong, M.J., de Bie, R.M.A., Roze, E., Miyasaki, J.M., Hauser, R.A., Espay, A.J., Martello, J.P., Gurwell, J.A., Billinghurst, L., Sullivan, K., Fitts, M.S., Cothros, N., Hall, D.A., Rafferty, M., Hagerbrant, L., Hastings, T., O'Brien, M.D., Silsbee, H., Gronseth, G., Lang, A.E. (2021). Dopaminergic therapy for motor symptoms in early Parkinson disease practice guideline summary. *Neurology*, 97(20), 942-957.
2. Choi, J., Horner, K.A. (2023). Dopamine Agonists. *In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.* 2025 January.
3. Bonuccelli, U., Dotto, P.D., Rascol, O. (2009). Role of dopamine receptor agonists in the treatment of early parkinson's disease. Parkinsonism & Related Disorders, 15(Suppl. 4), S44-S53.

4. Hollerhage, M., Beckepe, J., Classen, J., Deuschl, G., Ebersbach, G., Hopfner, F., Lingor, P., Lohle, M., Maab, S., Potter-Nerger, M., Odin, P., Woitalla, D., German Parkinson's Guidelines Group, Trenkwalder, C., Hoglinger, G.U. (2024). Pharmacotherapy of motor symptoms in early and mid-stage parkinson's disease: guideline "Parkinson's disease" of the german society of neurology. *Journal of Neurology*, 271, 7071-7101.
5. Canovas, A.A., Piudo, R.L., Ruiz-Espiga, P.G., Burguera, J.A., Arillo, V.C., Castro, A., Linazasoro, G., Del Val J.L., Vela, L., Martinez Castrillo, J.C. (2014). Dopaminergic agonists in Parkinson's disease. *Neurologia*, 29(4), 230-241.
6. Jost, W.H. Rotigotine for treating parkinson's disease. (2020). *NeuroPsychopharmacotherapy*, 1-17.
7. Rascol, O., Perez-Lloret, S. (2009). Rotigotine transdermal delivery for the treatment of parkinson's disease. *Expert Opinion on Pharmacotherapy*, 10(4), 677-691.
8. Elshoff, J.P., Cawello, W., Andreas, J.O., Mathy, F.X., Braun, M. (2015). An update on pharmacological, pharmacokinetic properties and drug-drug interactions of rotigotine transdermal system in Parkinson's disease and restless legs syndrome. *Drugs*, 75(5), 487-501.
9. Elshoff, J.P., Braun, M., Andreas, J.O., Middle, M., Cawello, W. (2012). Steady-state plasma concentration profile of transdermal rotigotine: an integrated analysis of three, open-label, randomized, phase I multiple dose studies. *Clinical Therapeutics*, 34(4), 966-978.