DESIGN AND CHARACTERIZATION OF MICROEMULSION GEL FOR TRANSDERMAL DRUG DELIVERY SYSTEM OF DULOXETINE HYDROCHLORIDE

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ABSTRACT

Objective: The objective was to improve the bioavailability, stability of formulation, and skin permeability of Duloxetine HCl.

Method: Microemulsion was prepared with oleic acid as oil, water, and S_{mix} ratio of tween 20 to propylene glycol (1:3). Pseudo-ternary phase diagrams were constructed to determine the region of existence of microemulsions prepared using oil titration method. Optimization of formulations was done based on the *in vitro* diffusion studies. The microemulsion was gelled using carbopol 934p and HPMCK 100 as the gelling agent.

Result: After the analysis of different evaluation parameter and drug release, the F3 batch was selected as a promising formulation for delivery of duloxetine HCl as a microemulsion gel for transdermal drug delivery with 79.607% drug release in 10 h.

Conclusion: It was observed that transdermal microemulsion gel can be formulated successfully for duloxetine HCl with improved bioavailability. Among the other batches, the F3 batch was selected as an optimized batch because all the evaluation parameters results are satisfactory. From stability data, the formulation was found to be stable as no phase separation or turbidity was observed in the formulation after 3 months.

Keywords: Transdermal, Duloxetine HCl, Microemulsion gel, Phase diagrams.

INTRODUCTION

Transdermal drug delivery offers many advantages over other traditional routes; however, the barrier nature of the skin made it difficult for most of the drugs to be delivered through it [1]. Transdermal drug delivery system has several advantages such as ability to deliver the drug into systemic circulation by avoiding first-pass metabolism, avoids drug degradation in the gastrointestinal tract, and improves bioavailability [2]. A remarkably broad range of transdermal formulations is available, ranging from simple solutions and lotions, though commonly used creams, ointments, gels, and patches. While selecting a suitable dosage form drug, physicochemical properties such as solubility, pKa, and lipophilicity must be taken into consideration [3-5]. Duloxetine HCl (Fig. 1) [N-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine] is a selective serotonin and noradrenaline reuptake inhibitor, approved by the USFDA for the treatment of major depressive disorders [6]. Microemulsion gel, as the name suggests they are the combination of microemulsion and gel. The term "microemulsion" refers to a thermodynamically stable, isotropic clear dispersion of two immiscible liquids, such as oil and water, which is stabilized by an interfacial film of surfactant and cosurfactant molecules [7]. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into a microemulsion-based gel. The direct oil-in-water system is used to entrap lipophilic drugs, whereas hydrophilic drugs are encapsulated in the reverse water-in-oil system. Microemulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin.

MATERIALS AND METHODS

Duloxetine HCl was a gift sample from CTX Life science Pvt. Ltd., Gujarat. HPMCK100, Propylene glycol, NaOH were procured from Chemdyes Corporation, Gujarat. Carbopol 934p and oleic acid were procured from Research Lab Finchem, India. Tween 20 was procured from Encore

Chemicals. Methanol was procured from Thomas Baker Pvt. Ltd., India. All reagents used were of analytical grade.

Methods

Solubility studies [8-11]

The solubility of duloxetine HCl was determined in various excipients such as oils, surfactant, and cosurfactant. Excess amount of duloxetine HCl was added to 2 ml of each excipient and vortex-mixed. They were stirred in a rotary shaker at 37±0.5°C. All samples were centrifuged at 3000 RPM for 15 min using a laboratory centrifuge. The supernatant was filtered, suitably diluted with methanol, and analyzed spectrophotometrically at λ_{max} of 290 nm using a Double beam UV-Visible spectrophotometer.

Construction of ternary phase diagram [12]

Pseudoternary phase diagrams comprises oil, S_{mix}, and water were developed using the oil titration method, specific ratio of S_{mix} (1:1,1:2,1:3,2:1, and 3:1), water were taken in test tubes and vortexed for 5 min followed by addition of oil with a micropipette, the addition of oil was continued until addition of one more drop produce turbidity. They were also visually observed for phase clarity and flowability. The volume of oil phase was noted, and phase diagrams were then constructed using chemix software.

Formulation of microemulsions [13]

The microemulsion formulations were prepared using oleic acid as oil phase, Tween 20 as a surfactant and propylene glycol as cosurfactant based on the solubility studies, as the drug was having the highest solubility in these solvents. The ratios were selected from the constructed pseudo-ternary phase diagrams. Using the oil phase titration method microemulsions were prepared. Microemulsions were prepared by mixing the surfactant mixture and aqueous phase at the constant stirring rate. The drug was added to the oil phase, and methanol was added to enhance the solubility of drug in oil phase,

followed by dropwise addition of oil phase to aqueous phase at constant stirring rate until microemulsions were formed.

Formulation of microemulsion gels
Microemulsions were prepared, and then HPMC K100 and Carbopol 934p were added to it. This mixture was then kept for soaking to 24 h. Next day pH of the gels was adjusted using NaOH solution. Compositions of duloxetine HCl loaded microemulsion gels are given in Table 1.

Characterization of microemulsion gel

Appearance
The prepared formulation was inspected visually for their color, appearance, and consistency.

pH
The pH values of formulations were measured by a pH meter. The pH meter was calibrated before each use with buffer solution of pH 4.0, 7.0, and 9.0. The measurement of pH of the formulation was done [14].
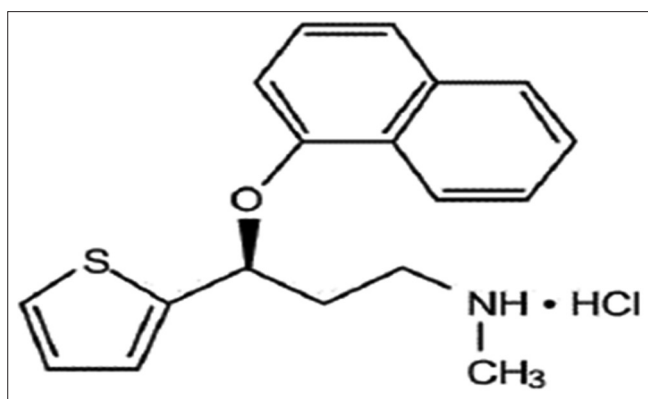
Viscosity
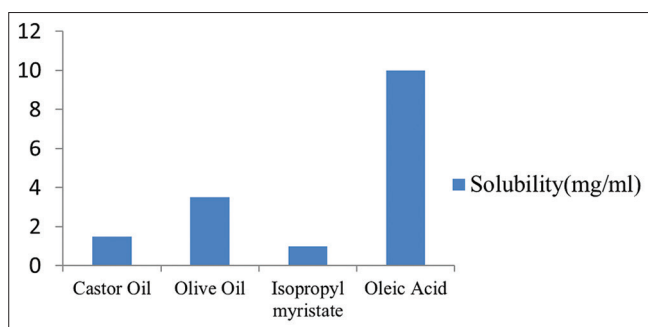The viscosities of formulations were measured with a Brookfield Viscometer DV–II+PRO, equipped with spindle no. LV1 and spindle code 61. The spindle was dipped in the preparation and rotated at ambient temperature at 100 RPM for 5 min [15].

Globule size and zeta potential
The mean droplet size and zeta potential were determined by photon correlation spectroscopy using the Zetasizer (Malvern Instruments, UK). Each sample was diluted to a suitable concentration with filtered double-distilled water. Globule size analysis was performed at 25°C with an angle of detection at 90°C. Size and zeta potential of formulations were obtained directly from the instrument [14].

Spreadability
Two glass slides were taken, and onto one slide, an excess of 3 g of gel was placed. Then, another glass slide was placed such that gel sandwiched between two glass slides. The top slide was subjected to a stress of 50 g by putting weight on it. Then, the time (in seconds) required by the gel to travel a distance of 10 cm was noted. A shorter time interval indicates better spreadability [13].
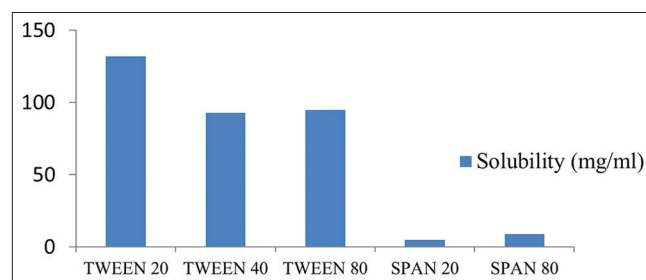

Fig. 1: Duloxetine HCl drug structure

Fig. 3: Solubility of drug in surfactants

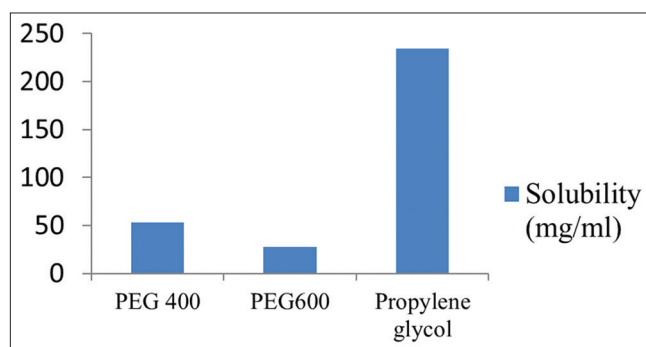**Fig. 2: Solubility of drug in different oils**

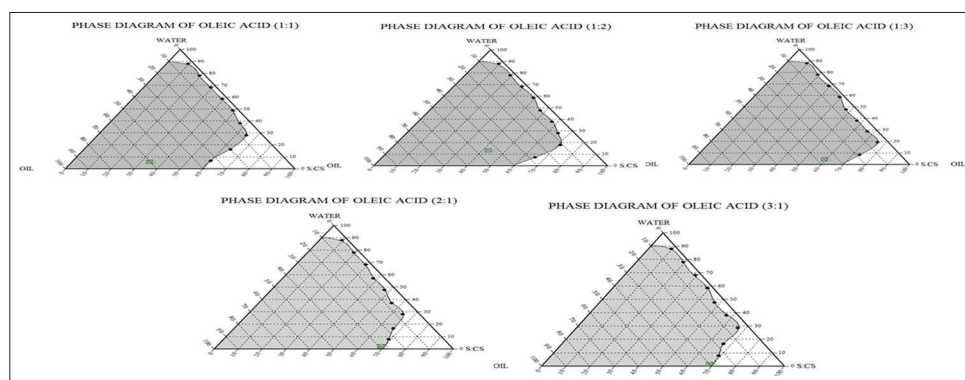**Fig. 4: Solubility of drug in cosurfactants**

Fig. 5: Phase diagram of oleic acid in different ratios of Tween 20 and propylene glycol
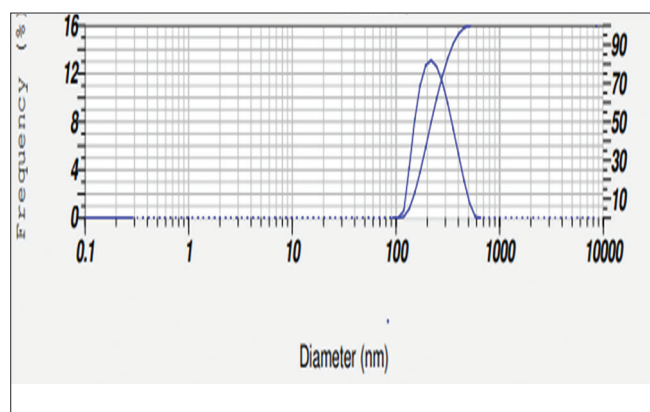
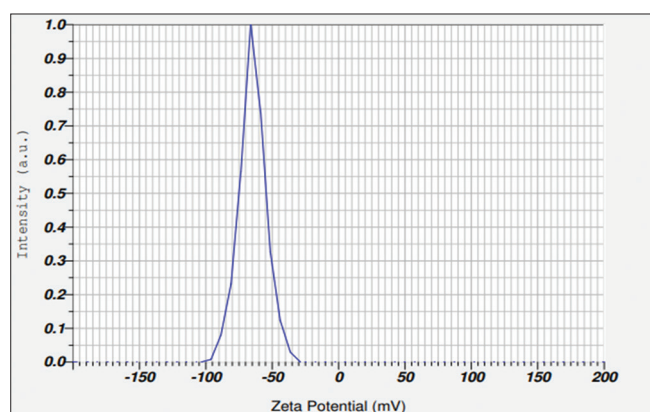**Fig. 6: Globule size of optimized batch F3**

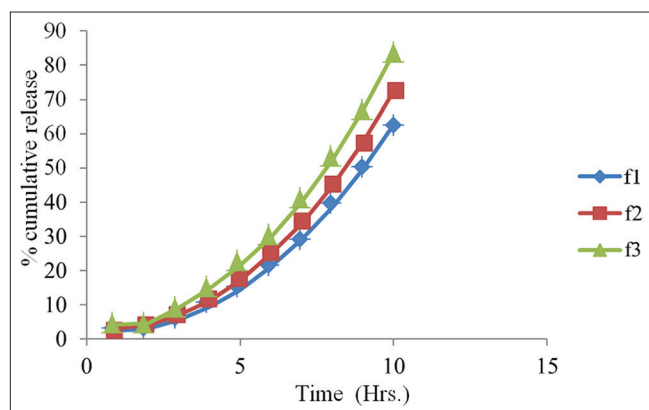**Fig. 7: Zeta potential of optimized batch F3**

Fig. 8: Cumulative % drug release of F1- F3 formulation

In-vitro drug release studies [13]

Drug release studies were performed using Franz diffusion cell employing a Millipore membrane (Millipore membrane 0.45 µm). Millipore membrane was initially soaked in pH 7.4 phosphate buffer solution for 24 h. It was then clamped between the donor and receptor compartments of the Franz diffusion cell. The receptor compartment was filled with pH 7.4 phosphate buffer solution and was magnetically stirred throughout the experiment at 100 RPM. The donor compartment contained an appropriate amount (2 g) of the formulation. Aliquots (1 ml) of sample were withdrawn from the receptor compartment at specified time intervals for 10 h and were replaced with fresh buffer solution to maintain sink conditions. The samples were analyzed for drug concentration using UV-Visible double beam spectrophotometer at 289 nm. The drug concentration was calculated using the standard calibration curve.

Table 1: Composition of microemulsion gel formulation

Ingredients	F1	F2	F3
Duloxetine HCl	0.115 g	0.4 g	1.1 g
Oleic acid	11.5 ml	11.1 ml	9 ml
Tween 20: PG (1:3)	55.7ml	58 ml	63.6 ml
Water	33 ml	31 ml	27.3 ml
Methanol	-	1 ml	1 ml
HPMC K100	0.6 g	0.6 g	0.6 g
Carbopol 934p	1 g	1 g	1 g
NaOH	q.s.	q.s.	q.s.
Total	100 g	100 g	100 g

Table 2: Evaluation of Microemulsion gel

Sr.No.	Parameters	F1	F2	F3
1.	Appearance	Off-white	Off-white	Off-white
2.	pH	6.59	6.23	6.72
3.	Viscosity (cp)	19.2	20.6	22.2
4.	Globule size (nm)	269	263	260
5.	Zeta potential (mV)	−58.2	−60.1	−64.8
6.	Spreadability (s)	40	37	34

Table 3: *In vitro* drug release of F1-F3 formulation shows percentage of cumulative drug release

Time (h)	F1	F2	F3
1	2.19±0.27	2.82±0.47	4.073±0.27
2	2.82±0.24	3.52±0.47	4.464±0.23
3	5.25±0.36	6.34±0.71	8.302±0.75
4	8.85±0.49	10.65±0.72	13.627±1.02
5	13.71±0.59	16.14±1.06	20.053±1.44
6	20.13±1.06	23.50±1.41	27.967±1.65
7	27.81±1.42	32.28±1.80	37.840±2.05
8	36.75±1.53	42.86±2.03	49.753±2.10
9	47.79±1.67	55.55±2.18	63.543±2.81
10	60.64±1.77	70.05±2.62	79.607±3.77

Release kinetics of optimized batch [16]

Model-dependent methods are based on different mathematical functions, which describe the dissolution profile. Mathematical modeling aids in predicting the drug release rates and diffusion behavior of these systems by the solution of an appropriate model, thereby reducing the number of experiments needed. The model-dependent approaches included as follows;
- Zero-order kinetic models.
- First-order kinetic model.
- Higuchi model.
- Korsmeyer–Peppas model (the power law).
- Hixson–Crowell model.

Stability studies [17,18]

The optimized batch is subjected to stability studies at 30°C±2°C at 65% RH±5% RH for duration of 3 months. Stability of the stored formulations was evaluated by visually inspecting the formulations for phase separation or turbidity.

RESULTS AND DISCUSSION

Solubility studies

Solubility of drug in different oils

The solubility of duloxetine HCl in various oils was analyzed to select oil for microemulsions.

The maximum amount of drug was found to be dissolved in oleic acid, i.e., 10 mg/ml. Hence oleic acid was selected as oil phase for the formulation. As shown in Fig. 2.
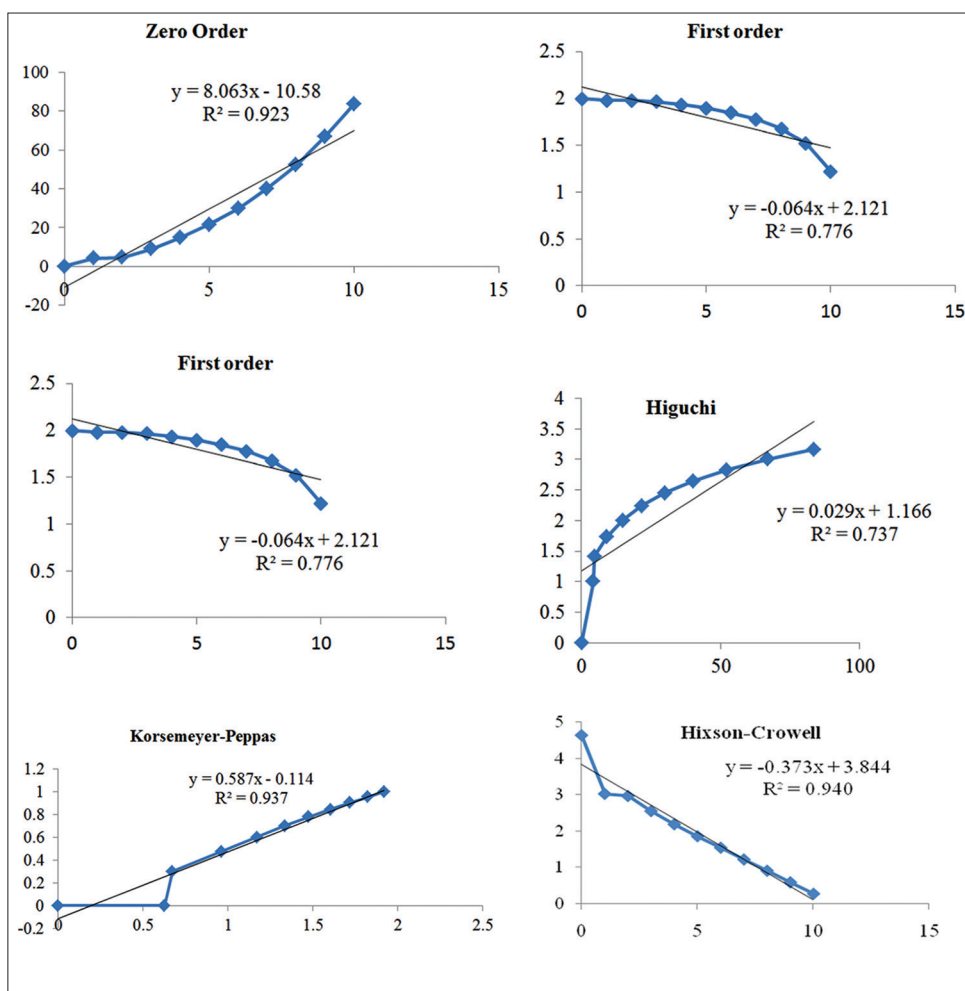
Fig. 9: (a-e) Release kinetic study of optimized batch F3

Table 4: Release kinetics of optimized batch F3

Batch no.	Zero-order	First order	Higuchi	Kors. Meyer peppas	Hix. crow	Best-fit model
F3	0.9236	0.7769	0.7379	0.9375	0.9407	Hix. crow

Table 5: Stability studies at 30°C±2°C at 65% RH±5% RH for 3 month

Parameters	1 month	2 month	3 month
Appearance	Off-white	Off-white	Off-white
pH	6.71	6.70	6.71
Viscosity (cp)	21.8	21.9	22.1
Globule size (nm)	261	260	260
Zeta potential (mV)	-64.7	-64.6	-64.7
Spreadability (s)	35	34	34

Solubility of dug in surfactants

The solubility of duloxetine HCl in various surfactants was analyzed to select surfactant for microemulsions.

The maximum amount of drug was found to be dissolved in Tween 20, i.e. 132 mg/ml. Hence, Tween 20 was selected as surfactant for the formulation. As shown in Fig. 3.

Solubility of drug in cosurfactants

The solubility of duloxetine HCl in various cosurfactants was analyzed to select cosurfactant for microemulsions.

The maximum amount of drug was found to be dissolved in propylene glycol, i.e., 234 mg/ml. Hence, propylene glycol was selected as cosurfactant for the formulation. As shown in Fig. 4.

Construction of ternary phase diagram

Fig. 5 represents the pseudo-ternary phase diagrams of oleic acid with various ratios of Tween 20 and propylene glycol. It was found that the area of microemulsion became enlarged as the Smix reached (1:3) ratio.

Characterization of microemulsion gel

Physical appearance

The prepared gels were checked for their color, appearance, and consistency and were having a smooth, homogenous texture and off-white appearance. As shown in Table 2.

pH

The pH of the formulations was found to be between 6.23 and 6.72. The results are shown in Table 2.

Viscosity

The viscosity of all three batches was measured using Brookfield Viscometer DV–II+PRO. The results are shown in Table 2.

Globule size and zeta potential

The globule size and zeta potential were measured for all three batches. F3 batch showed optimum result. As shown in Table 2 and Figs. 6 and 7. Figs. 6 and 7 show particle size distribution and zeta potential of the formulation F3. The particle size of the microemulsion gel was found to be 260 nm, and zeta potential was found to be −64.8 mV which indicates that the particles of microemulsion gel are negatively charged which provide electrostatic stabilization. The polydispersity index was found to be 0.594 which indicates narrow particle size distribution.

Spreadability

Spreadability of the formulations was determined. The results were shown in Table 2, indicating that the optimal gel formulations have shown good spreadability in <1 min.

In vitro drug release of F1-F3 formulation shows percentage of cumulative drug release

Drug release studies were performed using Franz diffusion cell employing a Millipore membrane. pH 7.4 phosphate buffer was used as the release medium. Drug release was found to be the highest for the formulation F3 (79.607%) at 10th h. As shown in Table 3 and Fig. 8.

Among all the batch, batch F3 showed a significant release as compared to other formulations.

Release kinetics of optimized batch

The Release kinetics of optimized batch F3 were studied, and the F3 batch showed higher correlation with Hixon–Crowell. The result was shown in Fig. 9 and Table 4.

Stability studies

The optimized batch was kept for stability studies at 30°C±2°C at 65% RH±5% RH for 3 months. As shown in Table 5.

CONCLUSION

The study demonstrated that the microemulsion gel formulation can be employed to improve the stability of formulation and skin permeability of duloxetine HCl. Microemulsion was prepared with oleic acid as oil, water, and S_{mix} ratio of TWEEN 20: PG (1:3). F3 was found to be stable with the globule size of 260 NM and percentage of drug release was found to be 79.607% in 10 h using carbopol 934p and HPMC K100 as the gelling agent. It can be concluded that microemulsion gel can be formulated successfully for duloxetine HCl with improved bioavailability. From stability data, the formulation was found to be stable as no phase separation or turbidity was observed in the formulation after 3 month.

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AUTHOR'S CONTRIBUTION

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Ms. Karishma Tole collected the data, analyzed the data, all the laboratory work performed, wrote the introduction, discussion and the material and method part. Dr. Ganesh Deshmukh proof-read the whole manuscript as well as helps in designing and conducting the study.

CONFLICTS OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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