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FORMULATION AND EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM BY SOLVENT CASTING METHOD

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ABSTRACT

Transdermal drug delivery leads direct access to the systemic circulation through the skin which bypasses drugs from the hepatic first pass metabolism leading to increase bioavailability. Tramadol HCl has been selected as model drug because it has low bioavailability. It exhibit all physicochemical characteristics required for the transdermal patch. Transdermal patches of Tramadol HCl were prepared by solvent casting method using different polymers i.e. HPMCK4M, HPMCK15M, HPMCE5.Propyleneglycol was used as plasticizer and methanol was used to dissolve the drug. Water was used as solvent to dissolve the polymer.The prepared formulations were evaluated for drug content uniformity, *in vitro* diffusion study, thickness, tensile strength, moisture content, folding endurances etc. Amongst all formulation, formulation F3 had more desirable characteristic & shows 88.36% drug release in 12hr. Release kinetic can be described by Higuchi model with anomalous diffusion as a release mechanism. The Transdermal patch formulated from HPMCK4M, HPMCK15M and HPMCE5 showed satisfactory physicochemical properties.The ratios of hydrophilic polymers HPMCK4M, HPMCK15M and HPMCE5 good moisture content property, good tensile strength, folding endurances and *in-vitro* drug release. So, it can be concluded that such a matrix type patches of HPMCK4M, HPMC K15M and HPMCE5 could be a good carrier in transdermal delivery of Tramadol HCl.FTIR studies showed there were no incompatibilities between drug and other excipients.

INTRODUCTION

Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Transdermal patches are polymeric formulations which when applied to skin deliver the drug at a predetermined rate across dermis to achieve systemic effects. Transdermal dosage forms, though a costly alternative to conventional formulations, are becoming popular because of their unique advantages.Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal drug delivery. [1-5] Development of controlled release transdermal dosage form is a complex process involving extensive efforts. This article describes the methods of preparation of different types of transdermal patches *viz.*, matrix patches, reservoir type, membrane matrix hybrid patches, drug-inadhesive patches and micro reservoir patches. In addition, the various methods of evaluation of transdermal dosage form have also been reviewed. [6-10]

Further the conventional dosage forms used for the control of infection, pain and fertility may cause side effects like nausea, vomiting, gastric irritation and toxicity if they are consumed for long duration. Continuous I.V. infusion has been recognized as a superior mode of systemic drug delivery that can be tailored to maintain a constant and sustained drug level within a therapeutic concentration range for as long as required for effective treatment. It also provides a means of direct entry into the systemic circulation of drugs that are subjected to hepatic first-pass metabolism and/or suspected of producing gastro-intestinal incompatibility.Unfortunately, such a mode of drug administration entails certain health hazards and therefore necessitates continuous hospitalization during treatment and requires close medical supervision. [11-15]

Transdermal drug delivery can closely mimic the slow intravenous infusion, without its potential hazards and also offer another most important advantage in allowing the patient to terminate the drug therapy by simply removing the patch at any desired time if toxicity develops. Drugs like estrogens, testosterone, and nitroglycerine when administered orally will be inactivated by gastrointestinal enzymes or environmental difference. Such drugs can now be delivered directly into systemic circulation by a noninvasive transdermal route. On the contrary, transdermal drug delivery mode is not suitable for all drugs, which may be the reason for the fact that only few drugs have been successfully designed and commercialized

by different companies. [16-21] The skin acts as a formidable barrier to the penetration of drugs and other chemicals; it does have certain advantages which make it an alternative route for systemic delivery of drugs. Transdermal drug delivery system involves the passage of substances from the skin surface through the skin layers, into the systemic circulation.The skin has been commonly used as a site for topical administration of drugs, when the skin serves as a port for administration of systemically active drugs. The drug applied topically is distributed following absorption, first into the systemic circulation and then transported to the target tissue, which can be relatively remote from the site of drug application to achieve its therapeutic action. [22-24]

Advantages of Transdermal patches

- Provide relatively steady and sustained drug concentration in plasma in contrast to conventional systems where peaks and troughs are a common feature.
- Variability due to factors such as pH intestinal motility, food intake, etc, which make vast difference in the bioavailability of the drugs given through oral route, are not existent.
- The hepatic first pass metabolism is avoided.
- A constant rate of absorption is possible in a vast variety of adverse patient population.
- Ease of administration and patient convenience.
- Drug input terminable by mere removal of the Transdermal patches.
- Drugs that cause gastro intestinal upset can be good candidates for Transdermal delivery because this method avoids direct effects on stomach and intestine.
- Increased therapeutic value due to avoidance of hepatic first pass effect, gastro intestinal irritation and low absorption problem.
- Drugs that are having short biological half-life can be given by this therapeutic systems and it also reduces dosing frequency.
- Transdermal patches are used for cessation of tobacco smoking.
- Another advantage is convenience, especially notable in patches that require only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy.

Disadvantages of Transdermal patches

- Can be used only for drugs, which require very small plasma concentrations for action.
- Local irritation and arythmea are possible. Enzymes in epidermis or derived from micro organisms present on the skin may denature the drugs.

- Another significant disadvantage of Transdermal drug delivery is that skin is less permeable because it serves as protective barrier for the entry of foreign particles.
- In order to maintain constant release states, transdermal patches must contain surplus of active drug. [25-29]

MATERIALS AND METHODS

Materials

Tramadol HCl is procured from the Sura labs ,hyd., HPMC K4M, HPMC K15M, HPMC E5, Glycerine are the gifted samples from ESSEL fine chem.,Mumbai, Propylene glycol, Methanol are obtained from the SD fine chem limited. Mumbai.

Preparation of Transdermal patches

Transdermal patches containing Tramadol HCl were prepared by solvent casting method using varying ratios of different grades of polymers and plasticizers in different concentrations as shown in the table 1.

Procedure for patch preparation

The Matrix type Transdermal patches of Tramadol Hydrochloride was prepared by the Solvent casting method. Briefly, Solution I was prepared by dissolving polymers HPMCK-4M, HPMCK-15M, HPMCE5 in different ratios in water and was allowed to stir for 2 hours and kept for overnight swelling. Solution II was prepared by dissolving the accurately weighed quantity of Tramadol Hydrochloride in methanol. Then the drug solution added slowly to the polymer solution and stirred on a magnetic stirrer to obtain uniform solution. Propylene glycol was used as a plasticizer.Then the solution was poured on the Petri dish having the area of 18.8cm^2 and dried at room temperature. Then the patches were cut into 2X1cm^2 patches. Drug incorporated for each patch was 100 mg. The dried patches were wrapped in butter paper and stored in a closed container away from light and in cool place.

Formulation design

Table 1: Composition of formulation

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tramadol HCl(mg)	100	100	100	100	100	100	100	100	100
HPMC K4M(mg)	25	50	100	---	---	---	---	---	---
HPMC K15M(mg)	---	---	---	25	50	100	---	---	---
HPMC E5(mg)	---	---	---	---	---	---	50	100	200
Methanol(ml)	5	5	5	5	5	5	5	5	5
Oleic acid(ml)	1	1	1	1	1	1	1	1	1
Propylene glycol(ml)	2	2	2	2	2	2	2	2	2
Water(ml)	10	10	10	10	10	10	10	10	10
Glycerin(ml)	1	1	1	1	1	1	1	1	1

RESULTS AND DISCUSSION

Compatibility studies by FTIR

The drug and excipient compatibility studies were carried out by FTIR study. The study showed peaks for the corresponding functional groups in Tramadol HCl. When the study was carried out with the combination of Tramadol HCl and polymers, there was no major changes in the peaks. Hence there was no interaction with the polymers were shown in the figure 1.

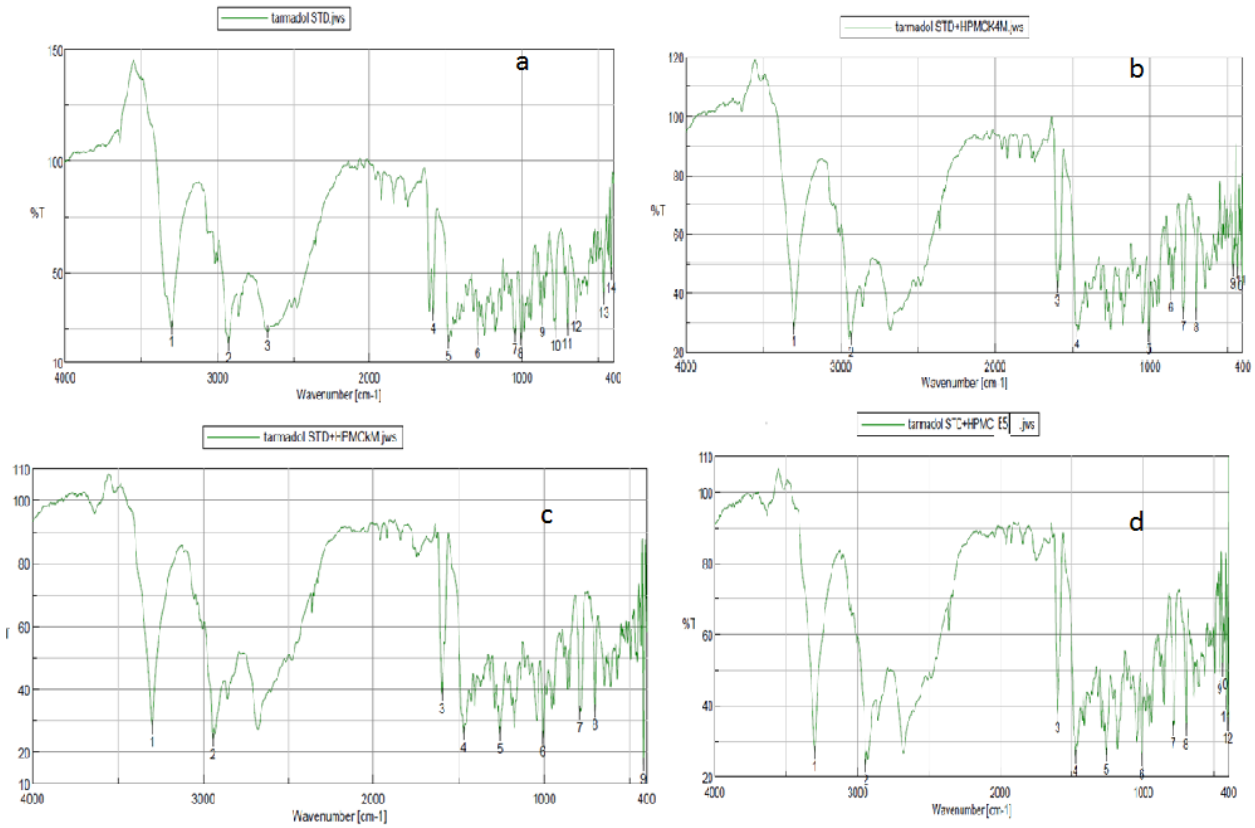

Figure 1: a) FTIR Spectra of Tramadol b)**FTIR Spectra of Tramadol +HPMCK4M c) FTIR Spectra of Tramadol +HPMCK100M** d) **FTIR Spectra of Tramadol +HPMCE5**

Pre-formulation studies

Preliminary identification test were either carried out or obtained from literature survey for pure drug on the following parameters:

Solubility

Tramadol HCl is free soluble in methanol,ethanol and slightly soluble in acetone. As the solubility of Tramadol HCl in isotonic phosphate buffer pH 7.4 is very low, methanol was used as a co-solvent to enhance the solubility of drug in phosphate buffer pH 7.4. It was found that by using methanol at a concentration of 30% v/v in isotonic phosphate buffer pH 7.4, a solubility of 1 mg/ml of Tramadol HCl was achieved. Hence 30% v/v methanolic

isotonic phosphate buffer (MPB) pH 7.4 was used as a solvent for establishing the standard calibration curve of Tramadol HCl & as an acceptor medium for in vitro release studies.

Partition coefficient

The Octanol-water partition coefficient (log P) value of 3.97 indicates high lipophilicity character of Tramadol HCl and the drug may possess high permeability.

Evaluation Parameters

Table 2: Result of Evaluation Parameters of Batch F1-F9

Code	Average Weight (mg)	Mean Thickness (mm)	Moisture Content (%)	Drug Content (%)	Folding Endurance	Tensile Strength (Kg/Cm2)
F1	102.3±2.510	0.110±0.013	3 ± 0.957	101.29%±0.5	300 ± 2.33	0.442±0.015
F2	104.3±3.491	0.140±0.036	4 ± 0.942	98.35%±0.58	310 ± 0.66	0.622±0.045
F3	108.6±3.055	0.274±0.026	3 ± 0.642	97.37%±0.62	317 ± 1.66	0.742±0.021
F4	109.6±2.605	0.255±0.032	5 ± 0.744	99.71%±0.07	322± 0.51	0.409±0.012
F5	111.0±3.605	0.231±0.012	4 ± 0.956	97.95%±0.08	300 ± 2.33	0.602±0.023
F6	114.5±4.601	0.294±0.021	4 ± 0.749	90% ±0.56	305 ± 1.66	0.715±0.019
F7	117.4±2.331	0.294±0.022	7 ± 0.442	99.90%±0.75	302 ± 1.34	0.842±0.002
F8	119.2±4.461	0.294±0.036	6 ± 0.882	96.13%±0.05	307 ± 2.66	0.848±0.007
F9	121.3±3.071	0.302±0.042	5 ± 0.242	98.5% ±0.38	311 ± 1.03	0.880±0.014

Physical appearance: All the Transdermal patches were visually inspected for colour, clarity, flexibility.

Weight of the patch

Drug loaded patches (4x4 cm2) were tested for uniformity of weight. The patches were found uniform. The average weight of the patch found was found to be in the range of 102.3 to 121.7 mg. as the polymer content increase, the weight of the patch also increased as shown in the table 2.

Thickness of the patch

All the patches have uniform thickness throughout as shown in the table 2. Average thickness was found to be in the range of 0.11 to 0.30mm. As the polymeric content increases, the thickness of the patch also increases.

Moisture content

Moisture content in F1 to F10 were found to be in the range of 3 to 7% as shown in table 2.

Drug content determination

It was determined for all formulation by UV spectrophotometer method shown in table 2.The data obtained from triplicate studies were analyzed for mean and standard deviation. The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 90.13% to 101.29 %.

Tensile strength

Ideal Transdermal patch should be flexible, elastic and strong enough to withstand breakage due to stress caused during its residence in the mouth. The tensile strength shows the strength and elasticity of the patch. A soft and weak polymer is characterized by a low TS; a hard and brittle polymer is defined by a moderate TS, a soft and tough polymer is characterized by a moderate TS, whereas a hard and tough polymer is characterized by high TS. Tensile Strength increased with the increase in polymeric content. Maximum TS was exhibited by F9 patch (0.848±0.007 kg/cm2) and minimum was exhibited by F1 (0.442±0.015 kg/cm2) as shown in the table 2.

Folding endurance

Folding endurance measures the ability of patch to withstand rupture as shown in the table 2. Patch did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point. Folding endurance did not vary when the comparison was made between plain patch and drug loaded patch.

In vitro drug release studies

The drug release profiles of Transdermal patches of Tramadol HCl were shown in figure 2 and their release data were shown in table 3. The drug release was governed by the amount of matrix forming polymer. An increase in polymer concentration causes an increase in the viscosity of the gel as well as formation of a gel layer with a longer diffusion path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate however, the difference is insignificant among the formulations. Formulation F3 showed maximum drug release (88.36%), whereas formulation F9 showed lowest release of (62.46%) among the series.

Table 3: *In vitro* diffusion release data of factorial batch F1 to F9

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	23.25±0.04	24.67±0.03	25.64±0.06	23.68±0.02	22.91±0.03	22.34±0.05	18.67±0.02	13.85±0.04	14.65±0.01
1	30.24±0.06	31.91± 0.05	32.47±0.02	26.42± 0.05	26.42± 0.08	24.54± 0.01	20.22± 0.03	18.45± 0.02	18.52± 0.06
2	33.52± 0.04	34.31± 0.09	38.72±0.08	31.67± 0.06	29.41± 0.05	28.62± 0.02	26.21± 0.08	24.49± 0.04	23.46± 0.05
3	36.47± 0.01	37.85± 0.01	43.65±0.04	33.91± 0.07	32.35± 0.04	31.22± 0.08	29.41± 0.06	27.76± 0.08	26.39± 0.03
4	39.51± 0.05	41.86± 0.07	46.12±0.05	35.49±0.08	35.73± 0.09	36.47± 0.06	31.81± 0.07	30.46± 0.09	29.85± 0.02
5	41.38± 0.02	45.83± 0.05	49.71±0.01	38.18± 0.09	38.94± 0.04	40.45± 0.04	34.42± 0.04	34.97± 0.07	31.74± 0.08
6	43.56±0.08	49.72± 0.02	53.84±0.08	41.58± 0.04	42.82± 0.01	44.47± 0.07	38.44± 0.06	38.85± 0.06	35.73± 0.07
7	49.48± 0.06	53.64± 0.08	58.86±0.07	44.82± 0.05	46.57± 0.06	51.48± 0.02	41.48± 0.03	41.67± 0.05	39.46± 0.05
8	56.37± 0.07	57.49± 0.05	62.38±0.04	49.47± 0.01	52.41± 0.05	54.72± 0.06	43.49± 0.08	44.27± 0.01	43.49± 0.06
9	60.31± 0.05	63.42± 0.04	68.48±0.06	55.58± 0.02	57.22± 0.02	59.93± 0.05	46.59± 0.01	49.49± 0.04	47.72± 0.08
10	63.65± 0.06	68.31± 0.06	75.56±0.03	63.35± 0.03	64.86± 0.08	68.43± 0.04	57.6± 0.06	54.72± 0.08	52.49± 0.04
11	68.87± 0.07	73.49± 0.04	79.58±0.06	68.68± 0.07	68.54± 0.07	71.37± 0.06	60.22± 0.05	59.37± 0.07	56.61± 0.08
12	71.56± 0.08	75.49± 0.08	88.36±0.03	69.97± 0.04	71.62± 0.05	74.91± 0.08	63.44± 0.04	67.88± 0.01	62.46±0.04

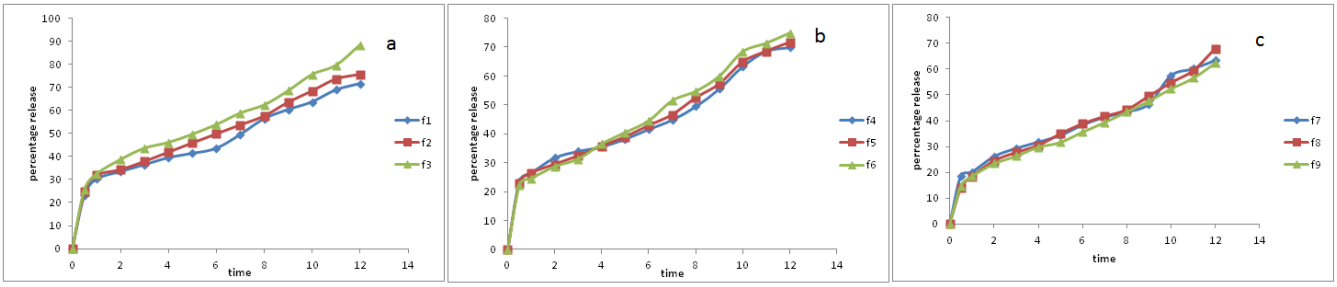

Figure 1: drug release of profile of all formulations

Kinetics of invitro drug release(curve fitting analysis)

To study the drug release kinetics of Transdermal patch of Tramadol HCl, different kinetic equations were applied to interpret the release from matrices .the linear nature of curves obtained for zero-order and first-order, Higuchi and Korsemeyer –peppas model demonstrated by very close and higher R^2 values suggests that the release from the formulations may follow any one of these models.The kinetic invitro dissolution profile of best formulation(f3) were fitted into zero, first, Higuchi and Peppas equations.They showed highest linearity with Higuchi order release. Data of the in vitro diffusion release was fit into different equations and kinetic models to explain the release kinetics of Tramadol HCl from transdermal patches. The kinetic models used were zero-order equation, first-order equation, and Korsemeyer Peppas models. The drug release profile of F3 showed highest linearity with Higuchi mechanism release as the R^2 value was found to be 0.970 as shown in the figure 2.

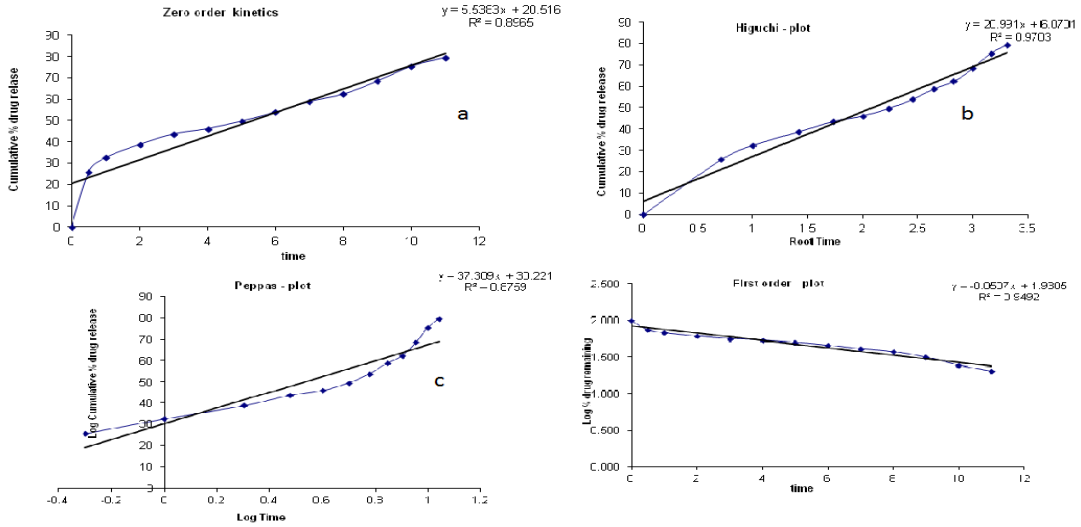

Figure 2: a)Zero order kinetics graph b)**Higuchi release graph** c)**Peppas release graph d)First order kinetics graph**

CONCLUSION

Oral drug delivery has significant drawbacks such as poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. To overcome these difficulties Tramadol HCl was formulated as transdermal drug delivery system. The Transdermal patch formulated from HPMCK4M,HPMCK15M, and HPMCE5 showed satisfactory physicochemical properties. Good correlation was observed between drug release and drug permeation study in-vitro.It can be concluded that such a patches of HPMCK4M,HPMC K15M and HPMCE5 could be a good carrier in transdermal delivery of Tramadol HCl. It may also concluded that adhesion of transdermal drug delivery device to skin membrane leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drug.The standard graph was plotted in pH 7.4 phosphate buffer. All the formulated Transdermal patches were visually inspected for color, clarity, flexibility ,checked for flatness, physical parameters such as Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and all the results were found to be within the pharmacopoeial limits. The prepared Tramadol HCl Transdermal patches were evaluated for In-vitro permeation studies using dialysis membrane, among all the 9 formulations F3 formulation was shown 88.36% cumulative drug release within 12 hours. The kinetics of In-vitro permeation studies using dialysis membrane for F3 formulation was plotted and the F3 formulation followed the Higuchi mechanism of drug release. Drug excipient compatibility studies were carried for pure drug and polymers, it was evident from the results that there were no interactions between drug and polymers.

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