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Original research paper

Formulation of meloxicam gel for topical application: *In vitro* and *in vivo* evaluation

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Skin delivery of NSAIDs offers several advantages over the oral route associated with potential side effects. In the present investigation, topical gel of meloxicam (MLX) was formulated using *N*-methyl pyrrolidone (NMP) as a solubilizer and Carbopol Ultrez 10® as a gelling polymer. MLX gel was evaluated with respect to different physicochemical parameters such as pH, viscosity and spreadability. Irritation potential of MLX gel was studied on rabbits. Permeation of MLX gel was studied using freshly excised rat skin as a membrane. Anti-inflammatory activity of MLX gel was studied in rats and compared with the commercial formulation of piroxicam (Pirox® gel, 0.5 % *m*/*m*). Accelerated stability studies were carried out for MLX gel for 6 months according to ICH guidelines. MLX gel was devoid of any skin irritation in rabbits. After 12 h, cumulative permeation of MLX through excised rat skin was 3.0 ± 1.2 mg cm^{-2} with the corresponding flux value of 0.24 ± 0.09 mg cm^{-2} h^{-1}. MLX gel exhibited significantly higher anti-inflammatory activity in rats compared to Pirox® gel. Physicochemically stable and non-irritant MLX gel was formulated which could deliver significant amounts of active substance across the skin *in vitro* and *in vivo* to elicit the anti-inflammatory activity.

Keywords: meloxicam, gel, stability, skin permeation, skin irritation, anti-inflammatory activity

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Meloxicam (MLX) is a potent non-steroidal anti-inflammatory drug (NSAID) belonging to the enolic acid class. It preferentially inhibits COX-2 and is therefore used for the treatment of rheumatoid arthritis, osteoarthritis, and other joint diseases (1). Although MLX is well tolerated orally compared to other NSAIDs, it is associated with ulcerogenicity, bellyache and indigestion. This makes administration of MLX unsuitable for patients with gastric ulcer (2). Oral MLX administration is also associated with drug interactions (3).

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Skin delivery represents an attractive alternative to oral administration due to its numerous advantages, including avoidance of GI irritation, minimum systemic toxicity, avoidance of hepatic metabolism (4) and provision of steady plasma levels (5). It has been demonstrated that local administration of NSAIDs promotes analgesia. A small oral dose of MLX (7.5/15 mg per day), low relative molecular mass (354.1) and excellent tissue tolerability (6) make MLX a good candidate for topical delivery.

A few investigations are reported on the topical delivery of MLX such as using penetration enhancers (7), hydrogels (8) and microemulsions (9). However, none of these have established the *in vivo* pharmacodynamic activity of topically applied MLX.

The specific aims of the present investigation were to formulate a topical gel of MLX and evaluate it for: (*i*) different physicochemical properties, (*ii*) stability as per IGH guidelines, (*iii*) skin irritation in rabbits, (*iv*) permeation across excited rat skin and (*v*) anti-inflammatory activity in rats compared to Pirox® gel.

EXPERIMENTAL

Materials

Meloxicam (MLX) was received as a gift sample from Sun Pharmaceutical Industries Ltd., (India). *N*-methyl pyrrolidone (NMP) (Pharmasolve® ISP International, USA), Solutol HS 15 (BASF, India), Transcutol P (Colorcon Asia Pvt. Ltd., India) and Carbopol Ultrez-10 (Noveon Ltd., India) were also received as gift samples. Pirox® gel, 0.5 %, *m*/*m* (Cipla, India) was purchased from the local pharmacy. Potassium dihydrogen phosphate, sodium chloride, Tween 80, propylene glycol, triethanolamine, sodium acetate, acetic acid and methanol (HPLC grade) were purchased from S.D. Fine Chemicals Ltd., (India). Membrane filters (0.22 μm) were purchased from Pall Life Sciences, India. Doubly distilled water was used whenever required.

HPLC analysis of MLX

MLX samples (solubility, skin permeation and stability studies) were quantified by an in-house HPLC method. The HPLC apparatus consisted of a Jasco PU-2080 Plus Intelligent HPLC pump equipped with a Jasco UV-2075 Intelligent UV/VIS detector (Jasco, Japan), a Rheodyne 7725 injector (Rheodyne, USA) and Jasco Borwin Chromatography Software (version 1.50).

Isocratic separation was performed using a Spherisorb ODS-2, RP-18 column (4.6 × 250 mm, 5 μm particle size). The mobile phase comprised methanol/acetate buffer pH 4.5 (45:55, *V*/*V*). The flow rate and injection volume used were 1.3 mL min^{-1} and 20 μL, respectively. The detection wavelength was set at 363 nm. Under these conditions, MLX eluted at 8.81 min. The method was linear in the concentration range 0.2–100 μg mL^{-1}; the *LOD* and *LOQ* values were 0.1 and 0.33 μg mL^{-1}, respectively. The method was validated with respect to inter- and intra-day accuracy and precision as per ICH guidelines (10). These were determined in terms of the recovery of known amounts of MLX. Repeated analysis was performed for three concentrations of MLX (0.25, 10 and 50 μg mL^{-1}) on the same day to determined intra-day variability and on two different days to estab-

lish inter-day variability. The relative standard deviation was less than 2 % in both cases. The mean MLX recovery ranged between 95.3 and 100.9.

Solubility studies

Solubility of MLX was determined in Solutol HS 15 (polyethylene glycol hydroxystearate), *N*-methyl pyrrolidone, propylene glycol, Transcutol P (diethylene glycol monoethyl ether) and Tween 80 (polyoxyethylene sorbitan monooleate) by the shake flask method. Briefly, an excess amount of MLX was added to each vial containing 5 mL of the selected solubilizer. After sealing, the mixtures were subjected to mechanical agitation for 72 h in an isothermal shaker (Remi, India) at 37 ± 1 °C, followed by centrifugation at 5000 rpm for 15 min and filtration through a membrane filter prior to HPLC analysis.

Formulation of MLX gel

NMP was selected as the vehicle to formulate MLX gel. To formulate 1 % (*m*/*m*) gel, MLX (100 mg) was dissolved in varying amounts of NMP (8–15 %, *m*/*m*). Carbopol Ultrez 10® was dispersed in water under continuous stirring using an overhead stirrer at 1000 rpm until it yielded a homogenous dispersion. To the MLX solution, Carbopol Ultrez 10® dispersion (0.5–1 %, *m*/*m*) was added under continuous stirring to yield a homogenous dispersion, which in turn was neutralized with triethanolamine to obtain a transparent gel. MLX gel formulations with different amounts of NMP and Carbopol Ultrez 10® were formulated. Formulation F4 (Table I) was selected for further studies based on its transparency, composition and viscosity.

Evaluation of MLX gel

To determine the drug content, approximately 1 g of MLX gel was weighed in a 100-mL volumetric flask, dissolved in methanol and diluted suitably prior to HPLC analysis. Viscosity of MLX gel was determined using a Brookfield synchrolectric viscometer, model RVT (Brookfield Engineering Laboratories, Inc., USA). To determine the spredability of MLX gel, 0.5 g of gel was placed within a circle of 1 cm diameter pre-marked on a glass plate, over which a second glass plate was placed. A weight of 500 g was allowed to rest on the upper glass plate for 5 min. The increase in the diameter due

Table I. Composition of different MLX formulations

Ingredient	Composition (%, *m*/*m*)				
	F1	F2	F3	F4	F5
MLX	1	1	1	1	1
NMP	8	8	8	10	15
Carbopol Ultrez 10®	0.5	0.75	1.0	0.75	0.75
Triethanolamine	1.5	1.75	2.0	1.0	0.5
Water (q. s.)	100	100	100	100	100

to gel spreading was noted. The pH of the 10 % (*m*/*m*) gel Equiptronics, India was determined using a digital pH meter (model Eq-610).

In vitro *release studies*

In vitro release of MLX gel was studied by the method described by Joshi *et al*. (11). Briefly, USP (12) type II apparatus assembled with a small stainless steel disk designed to hold the gel at the bottom was used for this purpose. Phosphate buffer saline, pH 7.4 (500 mL) equilibrated at 32 ± 0.5 °C was used as medium. MLX gel (2 g) was placed on the disk in order to ensure that the release surface was as flat as possible. The disk assembly was gently inserted at the bottom of the dissolution vessel and the paddle rotation speed was 25 rpm. Aliquots (2.0 mL) were withdrawn at predetermined intervals and an equivalent volume of dissolution medium was replaced. The amount of MLX released was quantified by HPLC analysis.

Stability

Physicochemical stability of MLX gel was studied by subjecting MLX gel samples to accelerated stability conditions at 25 °C/60 % RH, 30 °C/60 % RH and 40 °C/75 % RH as per ICH guidelines for a period of 6 months (13). The stability samples (n = 3) were analyzed for drug content, pH, viscosity and spreadability at 0, 30, 60, 90 and 180 days.

Skin permeation

Skin permeation of MLX was studied using freshly excised hairless abdominal skin of a male Wistar rat (250 g, 8 weeks), which was housed individually in the animal house with food and water given *ad libitum*.

The rat was sacrificed by decapitation. Then, the hairs in the abdominal area of the animal were carefully cut as short as possible with scissors. In the next step, the skin was surgically removed, cleaned of muscle, fat or vasculature, and kept at –4 °C for 24 h before the experiment. Skin samples were mounted on a modified Franz diffusion cell (A = 0.785 cm^2) with the dermal skin surface exposed to the receiver phase and the stratum corneum remained in contact with the donor compartment. The receiver phase used was phosphate buffer saline, pH 7.4 (10 mL) maintained at 32.0 ± 0.1 °C. MLX gel (0.4 g) was placed in the donor compartment. Receiver phase (3.0 mL) was withdrawn after 1, 2, 4, 6, 8, and 12 h and an equivalent volume of phosphate buffer added to the receiver compartment. The amount of MLX permeated was quantified by HPLC analysis.

Skin irritation

Draize patch test was used on rabbits to evaluate the irritation potential of MLX gel (14). White New Zealand rabbits of either sex (2.75 ± 0.25 kg, 8–9 weeks) were supplied by Nicholas Piramal Research Centre, Mumbai, India, and were housed individually in the animal house with food and water given *ad libitum*.

Rabbits were divided into three groups (n = 3): group 1 – no application (control), group 2 – placebo gel without MLX, and group 3 – MLX gel. The back of the rabbits was

clipped free of hair 24 h prior to the formulation application. Formulation, 0.5 g of each was applied on the hair-free skin of rabbits by uniform spreading over an area of 4 cm^2. The skin surface was observed for any visible change such as erythema (redness) after 24, 48 and 72 h of the formulation application. The mean erythemal scores were recorded depending on the degree of erythema: no erythema = 0, slight erythema (barely perceptible-light pink) = 1, moderate erythema (dark pink) = 2, moderate to severe erythema (light red) = 3, and severe erythema (extreme redness) = 4.

Anti-inflammatory activity

Anti-inflammatory effect of topically applied MLX gel was determined in male Wistar rats (210 ± 10 g, 6–8 weeks) by the carrageenean induced paw edema method (15, 16). For this purpose, rats were divided into three groups (n = 6): group 1 – control (no treatment), group 2 – Pirox® gel, group 3 – MLX gel. They were housed individually in the animal house with food and water given *ad libitum*.

Briefly, 30 min after formulation application (0.5 g), rats of both treated groups were challenged by a subcutaneous injection of a 1 % (m/V) solution of carrageenean in saline (0.1 mL) into the plantar site of the right hind paw. The paw volume was measured using a Ugo Basile 7140 plethysmometer (Italy) just before and 1, 2, 3, 4 and 6 h after carrageenean administration. The percent inhibition of edema at any time was calculated for each rat and the difference between MLX gel and Pirox® gel was evaluated statistically.

Animal care and handling throughout all three experimental procedures described above were performed in accordance with the CPCSEA guidelines. The experimental protocols were approved by the Animal Ethical Committee of the Institute of Chemical Technology, Mumbai, India.

Statistics

Statistical analysis was performed using either a paired Student's t-test or ANOVA.

RESULTS AND DISCUSSION

Solubility

Solubility studies helped to rationalize the choice of vehicle for gel formulation. MLX is poorly soluble in water (0.012 mg mL^{-1}, Fig. 1). Among the different solubilizers screened, MLX exhibited the highest solubility in NMP (135 mg mL^{-1}) and the lowest in propylene glycol (0.5 mg mL^{-1}). Solubility of MLX in Solutol HS 15, Transcutol P and Tween 80 was 9.5, 5.4 and 5.0 mg mL^{-1}, respectively. NMP was selected as the vehicle of choice to formulate MLX gel, based on its solubilization capacity and penetration enhancing effect on hydrophilic and hydrophobic actives as well as dermal acceptability (17, 18).

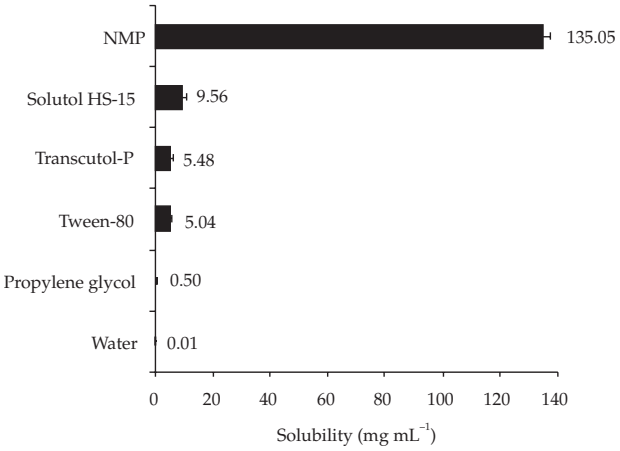

Fig. 1. Solubility of MLX in different solubilizers (mean ± SD, n = 3).

Formulation and evaluation of MLX gel

Due to higher concentration of NMP, formulations F4 and F5 were transparent in appearance compared to F1, F2 and F3 (Table I). Concentration of Carbopol Ultrez-10® was optimized on the basis of the desired viscosity and spreadability. Carbopol Ultrez--10® at a concentration of 0.5 %, *m*/*m* produced a gel of fluid consistency, whereas a gel of high viscosity and lower spreadability was obtained at 1 %, *m*/*m*, concentration (data not shown). Optimum viscosity and spreadability were obtained at Carbopol Ultrez-10® concentration of 0.75 %, *m*/*m*.

Formulations F4 and F5 were transparent in appearance and had the desired viscosity; however, F4 was selected for further studies because of its lower concentration of NMP. MLX content of the F4 gel was found to be 100.3 ± 1.2 % (n = 3) of the theoretical value (1 %, *m*/*m*). Viscosity of MLX gel was found to be 7.6×10^6 mPa s. The pH value of MLX gel was 7.35 ± 0.01 (n = 3), which is a physiologically acceptable pH and in principle devoid of any skin irritation.

Spreadability of the topically applied formulation is an important property considering patient compliance. Formulations with higher spreadability values allow ease of application and thereby increased surface area available for drug permeation. The increase in MLX gel diameter following the spreadability test was found to be 7.6 cm (n = 3), which is indicative of good spreadability.

In vitro *release of MLX gel*

In vitro release of the drug from the topical dosage form gives an idea of the amount of free active drug available for partitioning into the stratum corneum. *In vitro* release of MLX from the gel followed first order kinetics (R^2 = 0.9584, k = –0.0275 min^{-1}) and corresponding release after 5 and 30 min was 28 and 70 %, respectively. At the end of 60 min, 98.0 % of the applied amount of MLX was released in the dissolution medium (Fig. 2). Rapid dissolution of MLX gel could be attributed to solubilization of MLX by NMP. This

observation suggests that the entire amount of MLX loaded in the gel would be available for partitioning into the stratum corneum.

Stability

MLX gel subjected to accelerated stability conditions exhibited respectable stability with respect to drug concentration except at 40 °C/75 % RH (Table II). The MLX assay values for the samples stored at 25 °C/60 % RH were found to range between 100.0 and 99.4 % after 1, 2, 3 and 6 months of storage and compared to the initial value of 100.3 % the observed differences in assay values were not statistically significant. The assay values for the MLX samples stored at 30 °C/60 % RH were found to be between 100.1 and 97.0 % at the same time points as before and the observed differences in assay values were still not significantly different. However, the assay values for the MLX samples stored at 40 °C/75 % RH were 95 ± 0.7, 100.3 ± 1.2, 97.9 ± 1.1 and 96.1 ± 0.8 after 1, 2, 3 and 6 months, respectively, indicating loss of MLX after six months. This maximal decrease in assay value for the samples stored at 40 °C/78 % RH was aproximately 4 %.

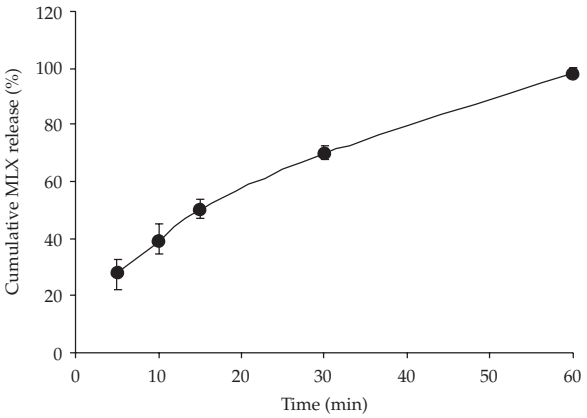

Fig. 2. *In vitro* release profile of MLX from developed gel using USP paddle over disk method (mean ± SD, n = 6).

Table II. Chemical stability of MLX in gel during stability testing

Month	MLX content (%)[a]		
	25 °C/60 % RH	30 °C/60 % RH	40 °C/75 % RH
0		100.3 ± 1.2[b]	
1	100.0 ± 1.6	100.1 ± 0.5	99.5 ± 0.7
2	99.5 ± 0.2	99.3 ± 1.4	100.3 ± 1.2
3	99.4 ± 0.6	98.5 ± 1.3	97.9 ± 1.1
6	99.8 ± 1.6	97.0 ± 0.5	96.1 ± 0.8[b]

[a] Mean ± SD, n = 3.
[b] Statistically significant difference *vs.* time zero: p = 0.003.

Skin permeation

Skin permeation of MLX followed first order kinetics (R^2 = 0.9947, k = –0.0364 h^{-1}). The amount of MLX released after 6 and 12 h was 2.2 ± 1.2 and 3.0 ± 1.2 mg cm^{-2} (Fig. 3). The corresponding MLX flux was 0.24 ± 0.09 mg cm^{-2} h^{-1}. About 58 % of the applied amount of MLX was permeated across the skin. This clearly indicates that the developed formulation has a great potential to deliver MLX across the skin. Although we did not attempt to establish the mechanism of MLX permeation through skin, we believe that the high permeation of MLX from the developed gel is a result of the high concentration gradient across the skin (due to solubilized MLX) and also due to the permeation enhancing effect of NMP. NMP acts by partitioning into the stratum corneum where it alters the barrier function of the membrane (19) and this effect leads to enhancement of skin permeation of the active drug. Therefore, NMP as a vehicle has played an important role for increasing skin permeation of MLX. Considering the oral dose of MLX the same amount can be delivered topically by using a 2.5-cm^2 patch.

Skin irritation

Placebo and MLX gels were devoid of any irritation potential and no edema formation was observed in any case. Irritation score (primary skin irritation index) for MLX gel was zero, which indicated its safety and acceptability for topical administration.

Anti-inflammatory activity

In the anti-inflammatory activity test using carrageenean as the phlogistic compound, Pirox® and MLX gel exhibited anti-inflammatory activity up to 6 h (Fig. 4) and peak activity was observed between 2–6 h for both formulations. MLX gel exhibited significantly higher anti-inflammatory activity compared to Pirox® gel ($p < 0.05$). MLX gel application resulted in 10 % inhibition at the end of 1 h and it further increased to 30 %

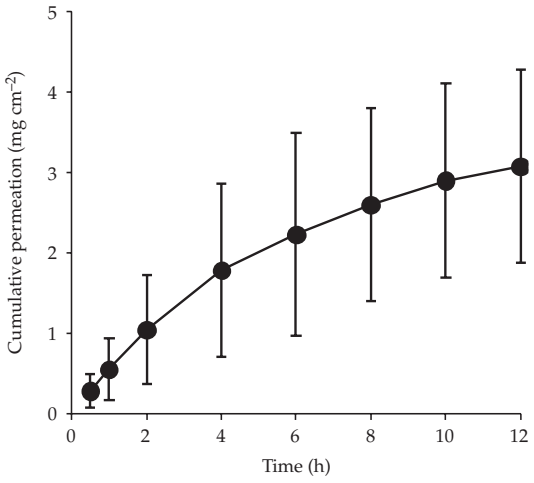

Fig. 3. *In vitro* skin permeation of MLX through rat skin (mean ± SD, n = 6).

from 2 to 6 h. Inhibition produced by the application of Pirox® gel was 6 and 15 % after 1 and 2 h respectively, and it remained constant up to 6 h. The observed activity difference between MLX gel and Pirox® gel was around two-fold. Since no topical formulation of MLX is available on the market, Pirox® gel (0.5 %, *m*/*m* piroxicam) was used for comparison to study the anti-inflammatory activity. The results confirm the fact that a significant amount of MLX was delivered from the gel through skin to induce the anti-inflammatory effect. Furthermore, it also proves the penetration enhaning effect of NMP *in vivo*, which was not established to date.

CONCLUSIONS

The results present a physicochemically stable and non irritant topical gel of MLX that could deliver a significant amount of meloxicam across the skin. MLX gel exhibited two-fold higher anti-inflammatory activity compared to Pirox® gel.

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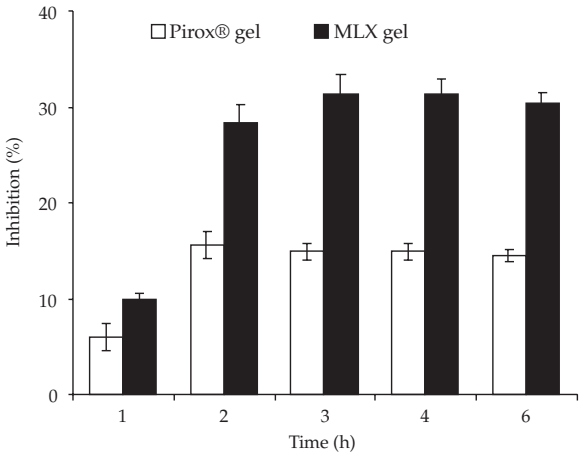

Fig. 4. Anti-inflammatory studies on MLX and Pirox® gels in rats (mean ± SD, n = 6).

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S A Ž E T A K

Gel meloksikama za topičku primjenu: *In vitro* i *in vivo* vrednovanje

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Primjena nesteroidnih protuupalnih lijekova na kožu ima nekoliko prednosti nad peroralnim načinom primjene uz koju se vežu određene nuspojave. U radu je opisana priprava gela meloksikama (MLX) za topičku primjenu. U pripravi gela korišten je *N*-metil pirolidon (NMP) kao otapalo i Carbopol Ultrez 10® kao polimer za geliranje. Određivani su različiti fizikokemijski parametri kao što su pH, viskoznost i razmazljivost. Potencijalna iritacija MLX gela testirana je na kunićima, a svojstvo permeacije na svježim izrescima kože štakora. Protuupalno djelovanje praćeno je na štakorima i uspoređeno s registriranim pripravkom piroksikama (Pirox® gel, 0,5 % *m/m*). Testovi ubrzanog starenja MLX gela rađeni su tijekom 6 mjeseci prema ICH protokolu. Dobiveni rezultati ukazuju da MLX gel nimalo ne iritira kožu kunića. Kumulativna permeacija nakon 12 h bila je 3,0 ± 1,2 mg cm^{-2}, s odgovarajućem vrijednošću fluksa 0,24 ± 0,09 mg cm^{-2} h^{-1}. MLX gel pokazao je značajno jače protuupalno djelovanje u odnosu na Pirox® gel. Pripravljeni gel je stabilan, ne iritira kožu, te *in vitro* i *in vivo* doprema kroz kožu ljekovitu tvar u dovoljnoj količini da ispolji protuupalno djelovanje.

Ključne riječi: meloksikam, gel, stabilnost, permeacija kože, iritacija kože, protuupalno djelovanje

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