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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF MUCOADHESIVE TABLETS OF OFLOXACIN USING NATURAL GUMS

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ABSTRACT

The present study concerns the development of mucoadhesive tablets of ofloxacin which were designed to prolong the gastric residence time after oral administration. Ofloxacin is a fluoroquinolone antibacterial agent which is highly effective against gram positive and gram negative bacteria. Different types of natural gums such as guar gum, locust bean gum and their combinations were used to formulate the mucoadhesive ofloxacin tablets. Tablets were prepared using wet granulation method and were evaluated for parameters such as Weight variation, Hardness, Friability, Drug content, Swelling index, *in vitro* drug release study, *in vitro* mucoadhesive strength study. All the formulation showed compliance with pharmacopieal standards. Among all the formulations, F7 with the combination of guar gum and locust bean gum showed greater *in vitro* drug release (98.23% at the end of 12 hrs), good swelling and better mucoadhesive strength than using a single gum and other gum combinations. So, the formulation (F7) was selected as optimized. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer–Peppas (n value is 0.615). Stability studies were carried out according to ICH guideline which indicates that formulation F7 was stable.

Keywords: Mucoadhesive tablets, Ofloxacin, Guar gum, Locust bean gum

INTRODUCTION

The primary aim of oral controlled drug delivery system is to deliver drugs for longer period of time to achieve better bioavailability, which should be predictable and reproducible. But this is difficult due to number of physiological problems such as fluctuation in the gastric emptying process, narrow absorption window and stability problem in the intestine.[1] To overcome these problems, different approaches have been proposed to retain dosage form in stomach. These include bioadhesive or mucoadhesive systems,[2] swelling and expanding systems,[3,4] floating systems[5,6] and other delayed gastric emptying devices.

Bioadhesion may be defining as the state in which two materials, at least one of which is biological in nature, are held together for extended period by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucous membrane the phenomenon is referred to as mucoadhesion.[7] Bioadhesive formulations use polymers as the adhesive component. These polymers are often water soluble and when used in a dry form, they attract water from the mucosal surface and this water transfer leads to strong interaction. These polymers also form viscous layers when hydrated with water, which increases the retention time over the mucosal surfaces leads to adhesive interactions.[8]

The principle of mucoadhesive preparation offers a simple practical approach and is particularly useful to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug.[9]

Ofloxacin is a fluoroquinolone antibacterial agent which is highly effective against gram positive and gram negative bacteria.[10] Ofloxacin exhibits pH dependent solubility. The solubility of ofloxacin in water is 60 mg/ml at pH value ranging from 2 to 5, falls to 4 mg/ml at pH 7 (near isoelectric pH).[11] Thus it is more soluble in acidic pH and slightly soluble at neutral or alkaline condition (intestinal environment). Hence an attempt was made to develop gastroretentive delivery system of ofloxacin by using natural gum such as guar gum, locust bean gum which would increase the bioavailability of ofloxacin and also to reduce frequency of administration, thereby improving patient compliance and therapeutic efficacy.

MATERIALS AND METHODS

Materials

Ofloxacin was obtained as gift sample from Blue Cross Laboratories Ltd, Mumbai. Guar gum was obtained from Himedia Mumbai, Locust bean gum was obtained from Research Lab Fine Chemical Industries Mumbai. All other ingredients used were of analytical grade.

Preparation of mucoadhesive tablets

Mucoadhesive tablets were prepared by conventional wet granulation. The powder mix was granulated with 5% w/w PVP-K30 in isopropyl alcohol. The wet mass was passed through sieve # 16 and the granules were dried at 60°C for 1 hrs in a hot air oven. The dried granules were passed through sieve # 22 and lubricated with magnesium stearate and talc by further blending for 3 min. Tablets were compressed at 500 mg weight on a 10 station mini rotary tableting machine with 12 mm flat-shaped punches. Tablets of Batch F1-F3 and F4-F6 contain only single mucoadhesive polymer having concentration 25%, 30%, and 35% respectively. Whereas Batch F7-F9 contain combination of mucoadhesive polymers with total polymer concentration of 30%.

Evaluation of granules

The angle of repose was measured by using funnel method,[12] which indicates the flow ability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD)[13] were measured using the formula: LBD= weight of the powder / volume of the packing. TBD= weight of the powder / tapped volume of the packing. Compressibility index[14] of the granules was determined by using the formula:

$$CI\ (\%) = [(TBD-LBD/TBD)] \times 100.$$

Evaluation of tablets

All prepared mucoadhesive tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods.[15] The weight variation was determined by taking 20 tablets using an electronic balance (type ER182A, Afcoset, Mumbai, India). Tablet hardness was determined using a Monsanto tablet hardness tester (MHT-20, Campbell Electronics, Mumbai, India). Friability was determined by testing 10 tablets in a friability tester (FTA-20, Campbell Electronics) for 4 minutes at 25 rpm.

Table 1: Composition of different formulations

Ingredients (mg /tablet)	Formulation F1	F2	F3	F4	F5	F6	F7	F8	F9
Ofloxacin	200	200	200	200	200	200	200	200	200
Guar gum	125	150	175	-	-	-	113	75	37
Locust bean gum	-	-	-	125	150	175	37	75	113
Magnesium stearate	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
MCC	98	73	48	98	73	48	73	73	73
PVP K30	12	12	12	12	12	12	12	12	12

Total weight of tablet-500mg

Drug content

Five tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets (100 mg) was extracted with 0.1N HCl (pH 1.2 buffer) and the solution was filtered through 0.45 µ membranes. Each extract was suitably diluted and analyzed spectrophotometrically at 294 nm.

Swelling study of formulations[16]

Swelling study of individual batch was carried out using USP dissolution apparatus-II (rotating paddle), in 900 ml of 0.1N HCl which is maintained at 37±0.5°C, rotated at 100 rpm. Weight of individual tablet was taken prior to the swelling study (W1). The tablet was kept in a basket. The tablet was removed every one hour interval up to 12 hour and excess water removed carefully using filter paper. The swollen tablets were re-weighed (W2); Percent hydration (swelling index) was calculated as shown in table 4 using following formula,

% Swelling Index = {(W2) – (W1)/ (W1)} x 100

Where W1- initial weight of tablet, W2- weight of the swollen tablet.

In vitro mucoadhesion studies[17, 18, 19]

The mucoadhesive strength of the tablets was measured on modified physical balance. The apparatus consist of a modified double beam physical balance in which the right and left pan were with lighter pans. The left side of the balance was made heavier than the right side by placing a 5 g weight on left side pan. Another Teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward protrusion of 2 cm height and 1.5 cm diameter on one side. This was kept in the beaker, which was then placed below the left hand set of the balance. The goat gastric mucus membrane was used as the model membrane and pH 1.2 buffer solution was used as the moistening fluid. The goat stomach mucosa was kept in tyrode solution at 37°C for 2 hr. The underlying mucus membrane was separated and washed thoroughly with a pH 1.2 buffer

solution. It was then tied to a Teflon-coated glass slide and this slide was fixed over the protrusion in the Teflon block using a thread. The block was then kept in a beaker containing pH 1.2 buffer solution at a level that just touches the membrane so as to moisten the membrane. By keeping a 5 g weight on the right pan that two sides were balanced. The beaker with the Teflon block was kept below the left hand setup of the balance. The tablet was stuck on to the lower

side of the left hand side pan. The 5 g weight from the right pan was then removed. This lowered the left pan along with the tablet over the membrane with the weight of 5 g. This was kept undisturbed for 3 min. Then the weight on the right hand side was added in an increment of 0.5 g until the tablet just separates from the membrane surface. The excess weight on the right pan i.e.

total weight minus 5 g was taken as the measure of the mucoadhesive strength from the mucoadhesive strength, the force of adhesion was calculated using following formula;

Force of adhesion (N) = Mucoadhesive strength/100 × 9.81.

***In vitro* drug release study**

In-vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 100 rpm. The dissolution medium consisted of 900 ml of 0.1N HCl (pH 1.2), maintained at 37 + 0.5°C. The dissolution samples were collected at every 1 hour interval and replaced with an equal volume of 0.1N HCl to maintain the volume constant. The sample solution was diluted sufficiently and analyzed at 294nm using an UV spectrophotometer (Labindia, Mumbai, India). The study was performed in triplicate.

Drug release kinetics (Curve fitting analysis)

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were fitted into zero order, first order Higuchi model and Korsmeyer's equation release models.[18, 19]

Stability studies

To assess the drug and formulation stability, stability studies were done according to ICH guidelines. [20] The optimized formulation was subjected to stability study at 40 ± 2ºC and 75 ± 5% RH for 90 days. The samples were evaluated for physical changes, hardness, friability, drug content, mucoadhesive properties and percentage drug release during the stability studies.

RESULTS AND DISCUSSION

FTIR spectroscopy

The pure drug ofloxacin and the solid admixture of drug and various polymers used in the preparation of mucoadhesive tablet formulations were characterized by FT-IR spectroscopy to know the compatibility. As shown in figure 1-2, there was no significant difference or the characteristic peak of pure drug was unchanged in spectrum of optimized formulation.

Characterization of powder blend

Granules prepared for compression of mucoadhesive tablets were evaluated for their flow properties, the results were shown in Tables 2. Angle of repose was in the range of 25.30± 1.34 to 29.74 ± 0.73 which indicates excellent flow of the powder for all formulations. The bulk density of the powder formulation was in the range of 0.3806 ± 0.012 to 0.4188 ±0.027gm/ml; the tapped density was in the range of 0.4517 ± 0.017 to 0.4854 ± 0.018 gm/ml, which indicates that the powder was not bulky. The Compressibility index was found to be in the range of 9.83 ± 1.76 to 15.74 ± 0.48, indicating compressibility of the tablet blend is good. These values indicate that the prepared granules exhibited good flow properties.

Physicochemical evaluation of mucoadhesive tablets

The ofloxacin mucoadhesive tablets were off-white, smooth, and flat shaped in appearance. The results of physicochemical characterizations are shown in Tables 3. The thickness of mucoadhesive tablets were measured by vernier caliper and were ranged between 3.72±0.06 to 3.74±0.06 mm. Weight variation for different formulations were found to be 498.5±1.677 to 551.2±1.337 mg, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. The hardness of the mucoadhesive tablets was measured by Monsanto tester and was controlled between 6.2±0.312 to 6.7±0.167 kg/cm^2. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The percentage of drug content for F1 to F9 was found to be in between 97.81% to 100.37% of ofloxacin it complies with official specifications.

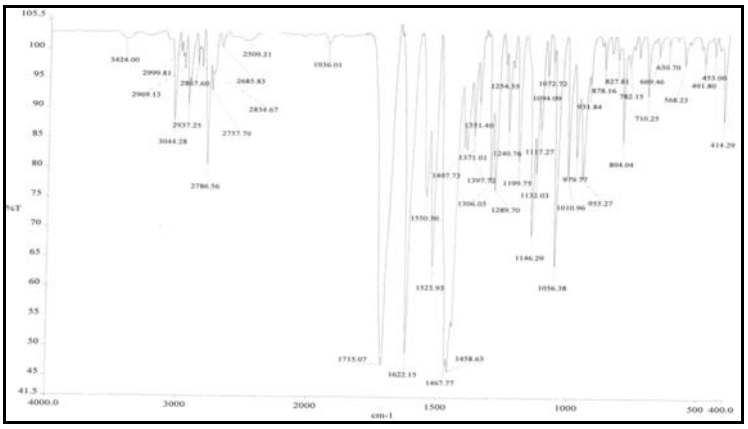

Fig. 1: FTIR Spectroscopy of pure drug

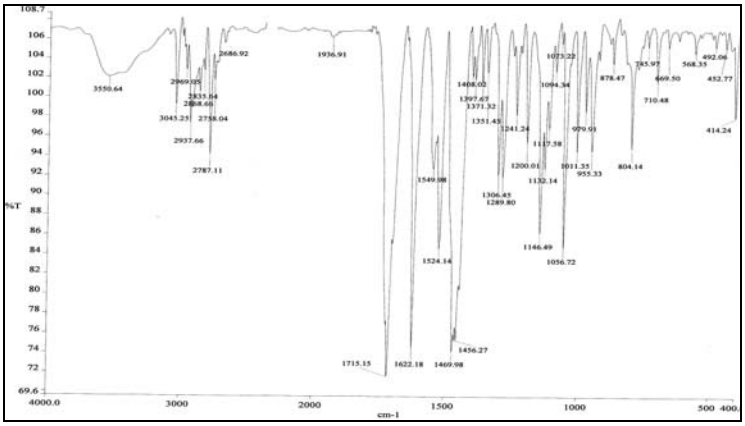

Fig. 2: FTIR Spectroscopy of formulation F7

Table 2: Granules properties of formulations F1 to F9 of Ofloxacin mucoadhesive tablets

Formulation No.	Angle of repose*	Loose bulk density (LBD) (g/ml) *	Tapped bulk density (TBD) (g/ml) *	Compressibility index (%)*
F1	27.31 ± 1.08	0.4132 ± 0.021	0.4854 ± 0.018	14.88 ± 1.41
F2	25.30 ± 1.34	0.4098 ±0.017	0.4545 ± 0.019	9.83 ± 1.76
F3	26.56 ± 1.81	0.4032 ± 0.003	0.4629 ± 0.011	12.89 ± 1.58
F4	25.40 ± 1.53	0.3806 ± 0.012	0.4517 ± 0.017	15.74 ± 0.48
F5	28.54 ± 1.81	0.4111 ± 0.014	0.4728 ± 0.013	13.04 ± 1.78
F6	26.40 ± 1.44	0.4188 ±0.027	0.4746 ± 0.016	11.75 ± 1.36
F7	29.74 ± 0.73	0.3968 ± 0.017	0.4408 ± 0.013	11.97 ± 0.61
F8	27.47 ± 1.03	0.4065 ± 0.013	0.4761 ± 0.013	14.63 ± 0.71
F9	27.40 ± 1.53	0.3906 ± 0.025	0.4587 ± 0.016	14.87 ± 0.58

* (n=3, ±S.D.)

Table 3: Tablet properties of formulations F1 to F9 of Ofloxacin mucoadhesive tablets

Formulation No.	Hardness* (kg/cm^2)	Thickness* (mm)	% Friability	Weight Variation*(mg)	% Drug content
F1	6.3±0.218	3.73±0.04	0.534	500.2±1.844	99.35
F2	6.5±0.113	3.74±0.03	0.47	498.5±1.677	98.50
F3	6.2±0.312	3.73±0.05	0.654	499.2±1.877	99.37
F4	6.7±0.167	3.72±0.06	0.667	500.3±1.566	100.37
F5	6.4±0.239	3.75±0.04	0.445	499.6±1.132	97.81
F6	6.6±0.347	3.73±0.04	0.545	551.2±1.337	98.44
F7	6.4±0.212	3.74±0.05	0.321	499.8±1.323	99.65
F8	6.3±0.442	3.74±0.06	0.484	500.6±0.434	99.06
F9	6.5±0.243	3.73±0.05	0.652	501.3±1.678	98.75

* (n=3, ±S.D.)

Swelling index

Swelling index was performed for all the batches (F1-F9) up to 12 hrs. The results were shown in Table 4. It was found that swelling index are directly proportional to the concentration of the gum, as the gum concentration increases there is increase in swelling index. Thus, the viscosity of the gum had major influence on swelling process, matrix integrity, as well as adhesion property. Graphical representation swelling index of all the batches were shown in figure 3.

Table 4: Swelling Index of mucoadhesive tablets

Time in 'hrs'	Swelling index (%) Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	14	16	29	17	23	41	21	24	19
2	32	38	54	39	48	67	44	43	40
3	51	61	73	63	69	91	63	67	65
4	73	81	90	87	91	112	89	91	92
5	94	104	117	121	112	147	111	116	117
6	111	119	135	145	147	176	126	137	151
7	133	135	149	173	176	198	145	161	176
8	141	152	167	185	198	222	159	179	206
9	153	177	194	190	222	245	181	198	223
10	160	203	216	197	245	261	206	220	236
11	168	217	228	201	261	273	222	237	259
12	170	210	222	205	273	298	238	256	269

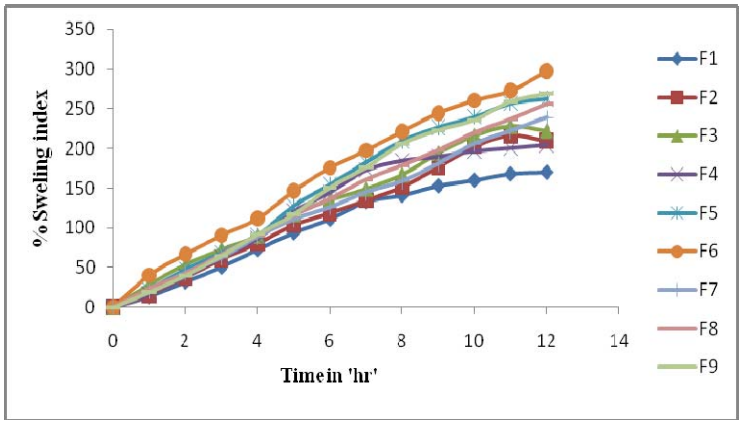

Fig. 3: Swelling Index of mucoadhesive tablets F1-F9

Table 5: In vitro mucoadhesive strength study of the prepared mucoadhesive tablets

Formulation code	Mucoadhesive strength* (g)	Mucoadhesion force (N)
F1	17.27±0.45	1.69
F2	23.22±0.34	2.27
F3	26.11±0.67	2.56
F4	19.67±0.38	1.92
F5	22.13±0.78	2.17
F6	24.47±0.54	2.40
F7	25.51±0.65	2.50
F8	23.74±0.39	2.32
F9	24.08±0.57	2.36

* (n=3, ±S.D.)

***In vitro* mucoadhesive study**

The *in vitro* mucoadhesive study was performed on modified physical balance and measures the mucoadhesive strength (g) requires to detach the tablet. The mucoadhesive characteristics were affected by the concentration of the gum. Increase in concentration of gum increases mucoadhesive strength of formulation. Batch F3 with 35% guar gum shows greater mucoadhesive strength. The results were shown in Table 5.

***In vitro* release study**

In vitro dissolution studies of all the formulations of mucoadhesive tablets were carried out in 0.1N HCl (pH 1.2). The study was performed for 12 hrs. The variation in drug release was due to different concentrations of polymer in all the 12 formulations. When % drug release was plotted versus time (figure 4), it was observed that for increase in polymer concentration from 25%-35%, a decrease in the release rate.

This might be due to increase in diffusional path length, which the drug molecule may have to travel and also it might attributed to the different diffusion and swelling behavior of the polymer.

Among all the formulations, batch F7 showing greater drug release 98.23% at the end of 12 hour also it showing better mucoadhesive property thus it was considered as an optimized formulation.

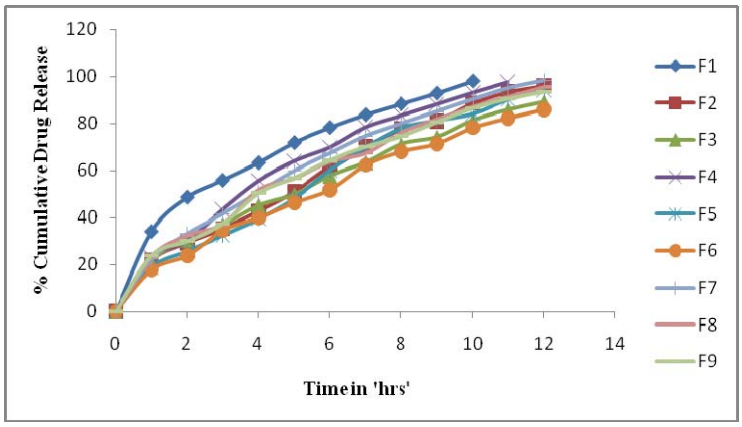

Fig. 4: Drug release profile of mucoadhesive tablets F1-F9

Drug release kinetics

The drug release data were fitted to models representing zero order (cumulative amount of drug released vs. time), first order (log percentage of drug unreleased vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time), and Korsmeyer's equation (log cumulative percentage of drug released vs. time) kinetics to know the release mechanisms. All the formulations in this investigation could be best expressed by higuchi's classical diffusion equation, as the plots showed high linearity (R^2 : 0.984 to 0.998) indicates that the drug release follows diffusion mechanism. To confirm the diffusion mechanism, the data were fitted into Korsmeyer–Peppas equation. All the formulations showed values ranging from 0.453 to 0.705, indicating that non-Fickian/anomalous diffusion (If the exponent n=0.45, then the drug release follows the Fickian diffusion, and if 0.45 < n < 0.89, then it is said to be non-Fickian or anomalous release). The results were shown in table 6.

Table 6: Kinetic values obtained from different plots of formulations F1 to F9

Formulations	Zero order plots◘	First order plots▪	Higuchi's plots●	Korsmeyer et al's plots□	
	R^2	R^2	R^2	R^2	Slope(n)
F1	0.893	0.915	0.998	0.998	0.453
F2	0.974	0.983	0.983	0.982	0.646
F3	0.965	0.972	0.990	0.993	0.586
F4	0.950	0.969	0.993	0.988	0.635
F5	0.974	0.974	0.984	0.981	0.705
F6	0.976	0.935	0.989	0.992	0.667
F7	0.954	0.915	0.998	0.981	0.615
F8	0.958	0.958	0.991	0.989	0.589
F9	0.954	0.923	0.992	0.986	0.594

◘Zero order equation, $C=K_0 t$, ▪First order equation, Log C=log C⍰-Kt/2.303, ●Higuchi's equation, Q= Kt½, ⍰Korsmeyer et al's equation, Mt/Mα= Ktn.

Stability studies:

The optimized mucoadhesive tablets (F7) was selected for stability study. The tablets were investigated at 40°C/75%RH for 3 months. From the data, the formulation is found to be stable under the conditions mentioned before since there was no significant change in the percentage amount of drug content (Table 7). Thus, it was found that the mucoadhesive tablets of ofloxacin (F7) were stable under these storage conditions for at least 3 months.

Table 7: Stability study (40 °C/75%RH) of Optimized Formulation (F7)

parameters	1st month	2nd month	3rd month
Physical appearance	Off white, smooth, flat faced	Off white, smooth, flat faced	Off white, smooth, flat faced
Hardness(kg/cm²)	6.41	6.43	6.40
Friability(%)	0.325	0.330	0.331
Drug content (%)	99.70	99.68	99.74
Mucoadhesive strength (g)	25.78	25.58	25.65
In vitro release (%) 12 hr.	98.15	98.29	98.38

CONCLUSION

Mucoadhesive tablets containing ofloxacin can be prepared successfully by using wet granulation technique. Tablets were subjected to various evaluation parameters such as Weight variation, Hardness, Friability, Drug content, Swelling index, *in vitro* drug release study, *in vitro* mucoadhesive strength study. It was revealed that tablets of all batches had acceptable physical parameters. FT-IR studies revealed that there was no interaction between ofloxacin and other excipients used in the tablets.

It was found that increase in the polymer concentration will increase swelling index, mucoadhesive strength but decrease drug release. Tablets of batch F7 combination of guar gum and locust bean gum have better *in vitro* drug release than the other formulations, and also showing good mucoadhesive strength. The drug release kinetics follows Higuchi model and the mechanism was found to be non Fickian/anomalous.

The stability studies were carried out according to ICH guideline which indicates that the selected formulation was stable. The

present study shows that natural gum can be used effectively in the preparation of mucoadhesive drug delivery system.

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