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Influence of natural polymer coating on novel colon targeting drug delivery system

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Abstract A novel colon targeted tablet formulation was developed using natural polysaccharides such as chitosan and guar gum as carriers and diltiazem hydrochloride as model drug. The prepared blend of polymer-drug tablets were coated with two layers, inulin as an inner coat followed by shellac as outer coat and were evaluated for properties such as average weight, hardness and coat thickness. In vitro release studies of prepared tablets were carried out for 2 h in pH 1.2 HCl buffer, 3 h in pH 7.4 phosphate buffer and 6 h in simulated colonic fluid (SCF) in order to mimic the conditions from mouth to colon. It was observed that 4% w/v of rat cecal contents in saline phosphate buffer (SCF) incubated for 24 h provides suitable conditions for in vitro evaluation of the formulations prepared. The drug release from the coated system was monitored using UV/ Visible spectroscopy. In vitro studies revealed that the tablets coated with inulin and shellac have controlled the drug release in stomach and small intestinal environment and released maximum amount of drug in the colonic environment. Among the polymers used, chitosan was found to be the suitable polymer for colon targeting. The study revealed that polysaccharides as carriers and inulin and shellac as coating materials can be used effectively for colon targeting of drugs for treating local as well as systemic disorders.

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Introduction

Generally the small intestine is considered as the primary site for drug absorption and thus it is a preferred part of gastrointestinal tract (GIT) for targeting the drugs with various controlled release technologies. Colon targeting drug delivery systems have attracted many researchers due to distinct advantages such as near neutral pH, longer transit time and reduced enzymatic activity. Colon specific drug delivery not only increases the bioavailability of the drug at the target site, but also reduces the dose required as well as reduces the side effects. In the recent studies, colon targeted drug delivery systems are gaining importance to treat local pathologies of the colon (crohn's disease, inflammatory bowel disease, colonic cancer) and also for the systemic delivery of protein and peptide drugs. This is because the peptide and protein drugs gets destroyed or inactivated in acidic environment of the stomach or by pancreatic enzymes in the small intestine [1]. Drug targeting to colon would also be useful when a delay in drug absorption is desired from therapeutic point of view, such as treatment of diseases that have peak symptoms in the early morning like nocturnal asthma, angina or arthritis [2, 3].

Various approaches such as prodrugs, pH-dependant, time-dependant and microflora-activated systems have been developed for colon specific drug delivery. Among the different approaches, the use of polymers, specifically biodegraded by colonic bacterial enzymes holds greater promise [4, 5]. The bacteria present in the colon such as *Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Lactobacillus, Clostridium* etc., secrete a wide range of reductive and hydrolytic enzymes such as β-glucuronidase, β-xylosidase, β-galactosidase, α-arabinosidase, nitroreductase, azoreductase, deaminase, urea hydroxylase etc. These

enzymes are responsible for biodegradation of di-, tri- and polysaccharides [6–9]. One of the latest techniques developed for colon specific drug delivery is CODES^{TM}. This is a unique technique wherein the polysaccharides degraded by bacteria are coupled with pH sensitive polymeric coats. As schematically presented in Fig. 1, a typical configuration of CODES^{TM} consists of a core tablet coated with three layers of polymeric coating. The first coating (next to the tablet core) is an acid soluble polymer such as Eudragit and outer coating is an enteric coat such as cellulose acetate phthalate (CAP) with an hydroxy propyl methyl cellulose (HPMC) barrier layer in between them. This has been designed in order to prevent any interaction between the oppositely charged polymers. The core tablet is comprised of any polysaccharide, which gets degraded by colonic microflora. During its transit through GIT, CODES^{TM} remains intact due to the enteric protection, but the enteric and barrier coat will dissolve in the small intestine. The inner coat, eudragit restricts the drug release in the small intestinal environment. Upon entry into the colon, the bacteria will enzymatically degrade the polymer coat and the core thereby releasing the drug in the colon.

In the present study, naturally occurring and biodegradable polymers such as chitosan and guar gum have been selected for preparation of tablet core. Inulin is used as inner coat and shellac is used as enteric coat. Chitosan is polysaccharide derived from naturally occurring chitin by alkaline deacetylation and has favourable biological properties such as nontoxicity [10], biocompatibility [11], biodegradability [12] and low chemical reactivity. It is soluble in acidic pH and insoluble in basic environment of small intestine. Upon entering into colon it gets degraded by enzymes secreted by colonic microflora. Many systems such as capsules, microcapsules, tablets etc., are formulated using chitosan for colon specific drug delivery. Guar gum is a naturally occurring biodegradable [13, 14] galactomannan derived from the seeds of *Cyamopsis tetragonalobus*. It hydrates and swells in water forming viscous colloidal dispersions. The gelling retards the drug release from the tablets. Guar gum is extensively studied for colon targeting in the form of matrix tablets and as a compression coat material. Inulin is polysaccharide obtained from plants such as onion, garlic, chicory, artichoke etc. Only enzymes secreted by microflora of colon degrade inulin. Shellac is a resinous secretion of the insect *Laccifer lacca* and it is used as enteric coat to prevent the drug release from the tablet in stomach. The drug selected for the present study is diltiazem hydrochloride, which is used in the treatment of early morning angina.

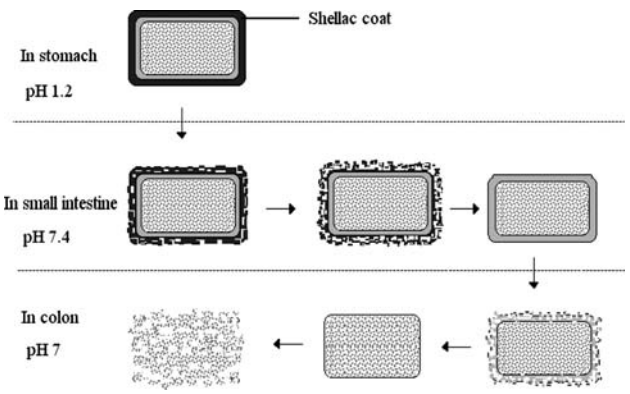

Fig. 1 Schematic representation of tablet design and mechanism of drug release

Materials and methods

Materials

Diltiazem HCl was a gift sample from M/s Divis Laboratories, Hyderabad, India. Diltiazem HCl (Fig. 2) is a white, odorless, crystalline powder freely soluble in water and methanol. Chitosan was procured from M/s Marine Chemicals, Cochin, India. Guar gum, inulin and shellac were procured from M/s Loba Chemie, Mumbai, India. All other ingredients used were of analytical grade.

Preparation of diltiazem HCl-polymer matrix tablets

Preliminary studies had demonstrated that directly compressed pure chitosan and guar gum formulations lacked the required mechanical strength. Therefore all the core tablets were prepared by wet granulation technique. Accurately weighed quantities of drug, polymer (chitosan) and binder (PVP K-30, 3% w/w) were physically mixed with a mortar and pestle. Required quantity of the solvent (ethanol) was added and the same was mixed thoroughly to form a mass suitable for preparation of granules. The dough mass was passed through sieve # 22 to form granules which were dried in an oven at 50 °C. The granules were mixed with required quantities of diluent (lactose) and lubricant (talc, 3% w/w) and were compressed to form tablets in a 10 station rotary tablet machine (Rimek, Mumbai, India) at 10 rpm and using 9 mm round concave

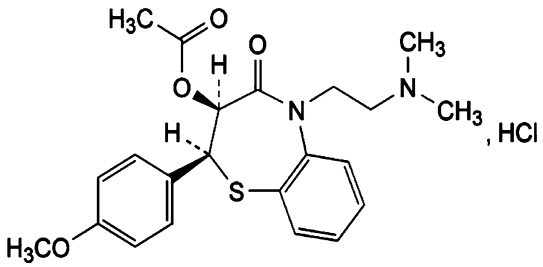

Fig. 2 Chemical structure of Diltiazem hydrochloride

punches at an optimum pressure. In this research article author selected two naturally occurring, biocompatible polymers namely, chitosan and guar gum as a carrier. Three formulations of 300 tablets each were prepared with different amount of chitosan viz., 25, 50 and 75% w/w of the tablet and sample code is CF1, CF2 and CF3 respectively. The total weight of each tablet was 300 mg containing 60 mg of diltiazem hydrochloride drug. The similar compositions were considered for the preparation of guar gum based matrix tablets (GF1, GF2 and GF3 code for 25, 50 and 75% of guar gum respectively). The prepared core tablets were evaluated for tablet properties such as hardness, thickness, weight variation, percent friability and drug content. Friability test has been performed on the tablets for ensuring the mechanical strength of the tablet. It has been carried out using Electrolab friability tester (EF-2). Drug content studies were carried out to evaluate the amount of drug present in the prepared tablet.

Coating of the prepared tablets

For the inner coat, a solution of inulin (10% w/v) in hot water (80 °C) was used to get the desired weight gain (coat) on the tablets. Triethyl citrate (1.5% w/w of inulin) and poly ethylene glycol (PEG 6,000, 4% w/w of inulin) were used as plasticizers and magnesium stearate (12% w/w of inulin) was added to reduce the tackiness of the tablets. For the outer coat (enteric coat), a solution of shellac (20% w/v) in ethanol was used to get the desired weight gain over the tablets. PEG 6000 (4% w/w of shellac) was used as plasticizer. Both the coating solutions were passed through a 0.3 mm sieve prior to coating.

The prepared matrix tablets were coated with the inulin solution by spray coating. The influences of degree of coating of inulin on chitosan-drug blend system have been studied i.e., 2, 3 and 4% w/w of inulin coat on matrix tablets. After drying of the inulin coated tablets, a second layer was coated with shellac to a weight gain of 2.5% w/w. Coating of the tablets has been carried out in a conventional coating pan (Ram Scientific Suppliers, Bangalore, India) at an inlet temperature of 55 °C, pan rotation speed of 15 rpm, spray pressure of 4 kg/cm^2 and a spray rate of 10 ml/min. A pilot type spray gun (Bullows 630) fitted with a 1 mm atomizing nozzle was used to spray the solution. The coated tablets were evaluated for hardness and drug content.

UV/Visible spectroscopy

The wavelength of maximum absorbance (λ_{max}) of diltiazem hydrochloride drug was determined by scanning a known concentration of sample solution in the wavelength region 200–400 nm by using Shimadzu 1601 UV/ Visible spectrophotometer. The λ_{max} was found to be 237 nm and this wavelength was used for further studies.

FTIR spectrophotometry

In order to evaluate the integrity and compatibility of the drug in the formulations, IR spectra of the drugs and its formulations were obtained by FTIR spectrophotometer (Perkin Elmer-1,000, Japan) using potassium bromide pellet method.

Scanning electron microscopy (SEM)

The degree of coating and the uniformity of coat on the polymer-drug blend (core) tablet was measured by scanning electron microscopy (Joel- LV-5600, USA).

In vitro dissolution studies

Dissolution testing of colon delivery systems with the conventional basket method has usually been conducted in different buffers for different periods of time to simulate the GI tract pH and transit time that the colon specific delivery systems might encounter in vivo. Dissolution studies were carried out using USP XXII dissolution apparatus, basket type at 100 rpm and 37 ± 1 °C. In vitro drug delivery studies were carried out for 2 h in 900 ml of 1.2 pH (HCl buffer), 3 h in 900 ml of 7.4 pH (phosphate buffer) and for 6 h in 100 ml of SCF [15–18].

Preparation of SCF

To evaluate the performance of colon specific delivery systems triggered by colon specific bacteria, animal cecal contents of rats, rabbits and pigs have been utilized as alternative dissolution medium. Because of the similarity of human and rodent colonic misroflora, predominantly comprising *Bifidobacteria*, *Bacteroides* and *Lactobacillus*, rat cecal contents were used for dissolution studies. 4% w/v of rat cecal contents in pH 7 saline phosphate buffer, incubated for 24 h was used as simulated colonic fluid (SCF). Incubation of the prepared solution was carried out in order to induce the enzyme concentration. This is to simulate the conditions of human colon wherein large amount of cecal contents will be present. During all the processes, the solution was kept bubbled with carbon dioxide to maintain anaerobic condition as the bacteria

present in cecal contents are predominantly anaerobic. Dissolution studies were carried out in both incubated and unincubated SCF to check the effect of incubation over drug release.

Peppas model fitting [19]

Koresmeyer–Peppas model is one of the mathematical expression to evaluate the mechanism of drug delivery. The Koresmeyer–Peppas equation is as follows;

$$M_t/M_\infty = 1 - A\,(\exp^{-kt}) \quad (1)$$

$$\log\,(1 - M_t/M_\infty) = \log A - kt/2.303 \quad (2)$$

where, M_I/M_∞ is the fractional amount of drug released and t is the time in h. In this study, the release constant, k and constant, A were calculated from the slopes and intercepts of the plot of In $(1 - M_t/M_\infty)$ versus time t.

Results and discussion

The core tablets prepared were having an average diameter of 9 mm. Percentage weight variation, percent friability and content of active ingredient for all the formulations were found to be well within United States Pharmacopoeia (USP) standards. The tablets were coated with two polymer layers, i.e., inner or first layer of coating by inulin and outer layer by shellac. The polymer coated tablets were evaluated for hardness and drug content. The data obtained for coated and uncoated tablets are given in Table 1. From the table it is clear that the hardness of the core tablets increased as the amount of polymer concentration in the tablet increased. Formulations containing 75% w/w of polymer (CF3 and GF3) showed maximum hardness among the three ratios selected (25%, 50% and 75%). The estimated drug content before and after coating of the tablets is given in Table 1. From the table it was noticed that, the percentage of drug content lies in the range 98.1–100.4 and 97.7–99.06 for before and after coating operation of the tablets respectively. This result clearly indicates that a slight reduction in drug content occurred during coating operation and this is expected.

The IR spectra of diltiazem drug and its coated formulations were found to be identical (Fig. 3). The characteristic IR absorption peaks of diltiazem at 2966 (aliphatic C–H stretch), 2837 (O–CH_3 stretch), 2393 (amine HCl), 1679 (lactam C=O stretch), 839 (o-substituted aromatic C–H out of plane deformation) and 781 cm^{-1} (p-substituted aromatic C–H out of plane deformation) were obtained. The FTIR spectra of the pure drug as well as coated formulations indicated that no chemical interaction occurred between the diltiazem and the polymers used. But, a slight shift in absorption peaks position was noticed. This result revealed that physical interaction occurred between drug and the polymer. SEM microphotograph of the 75% chitosan-drug tablet coated with inulin and shellac is shown in Fig. 4. The SEM microphotograph revealed that the coating was uniform and tablets were found to have an inner coat (inulin 4% w/w) of about 30 μm and an outer coat (shellac 2.5% w/w) of about 20 μm.

The plot of cumulative drug release as a function of time is shown in Fig. 5. Drug release studies was carried out in saline phosphate buffer, pH 7 with and without rat cecal contents, indicated that drug release was more in presence of rat cecal contents (Fig. 5). In vitro release studies were carried out for GF3 formulation using incubated and unincubated SCF. The effect of incubation on cumulative percent drug release from guar gum formulation (GF3) is shown in Fig. 6. When the unincubated SCF was used, the drug release from the tablet was only about 60% at the end of the dissolution study. But, when incubated SCF was used, a marginal increase in drug release was noticed.

Table 1 Evaluation data obtained for coated and uncoated tablets

Formulation code	Uncoated tablets[a]					Coated tablets[a]	
	% weight variation	Thickness (mm)	Hardness (kg/ cm^2)	Friability (%)	% Drug content	Hardness (kg/ cm^2)	% Drug content
CF1	−2.4 to + 3.9	4.97 ± 0.15	5.4 ± 0.63	0.88 ± 0.92	99.9 ± 0.41	6.0 ± 0.63	97.8 ± 0.46
CF2	−2.0 to + 2.2	4.92 ± 0.12	5.9 ± 0.96	0.84 ± 0.71	98.1 ± 0.83	6.1 ± 0.96	97.7 ± 0.71
CF3	−3.5 to + 2.2	5.05 ± 0.16	6.5 ± 0.71	0.712 ± 0.51	99.1 ± 0.77	6.8 ± 0.71	98.1 ± 0.25
GF1	−2.4 to + 3.2	4.89 ± 0.15	5.5 ± 0.71	0.712 ± 0.51	99.2 ± 0.41	5.9 ± 0.71	98.3 ± 0.28
GF2	−2.6 to + 3.2	4.93 ± 0.13	5.8 ± 0.48	0.78 ± 0.411	100.4 ± 0.11	6.0 ± 0.48	99.06 ± 0.41
GF3	−2.6 to + 3.5	4.95 ± 0.18	6.1 ± 0.48	0.78 ± 0.411	98.9 ± 0.77	6.7 ± 0.48	97.7 ± 0.46

[a] mean ± SD, n = 3, Code - CF1, CF2 and CF3 for 25, 50 and 75% of chitosan and GF1, GF2 and GF3 for 25, 50 and 75% of guar gum polymer as carrier in 300 mg of tablets

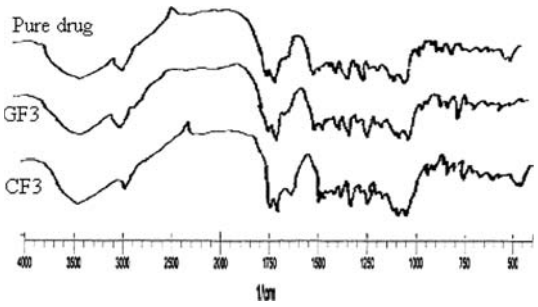

Fig. 3 FTIR spectra of pure drug and optimized formulations

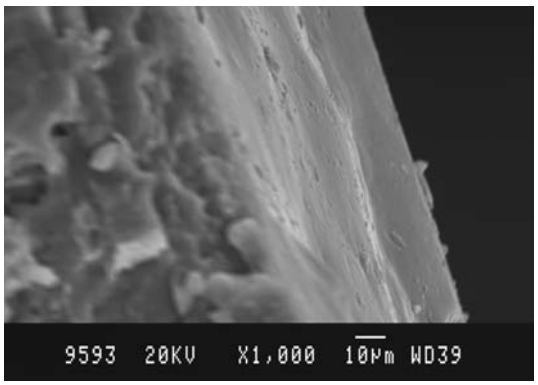

Fig. 4 SEM microphotograph of chitosan-drug matrix tablet coated with inulin and shellac

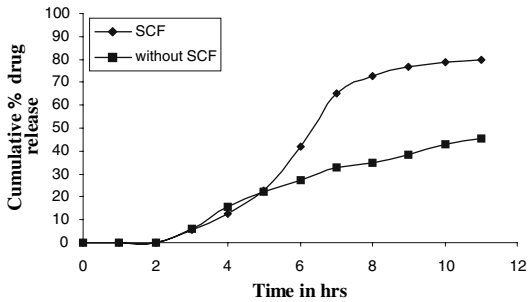

Fig. 5 Drug release profile of GF3 formulation in presence and absence of cecal contents (4% w/v rat cecal contents)

At the end of 11 h of dissolution, 80% of the drug was released from the polymer-drug blend tablet. This is because of the multiplication of bacteria present in the cecal content, which got multiplied during incubation period and the enzymes secreted by the bacteria have enhanced the rate of biodegradation of the coated and matrix polysaccharides used. Hence, for all the drug release studies incubated SCF was used. Drug release studies have been carried out for 2, 3 and 4% w/w of inulin coated tablets (GF3 formulation) for 3 h in phosphate buffer of pH 7.4 to ascertain the influence of coating on degree of drug release from the tablets in the small intestinal environment before reaching colon. The results indicated that the drug release of about 28, 24 and 21% from 2, 3 and 4% w/w of

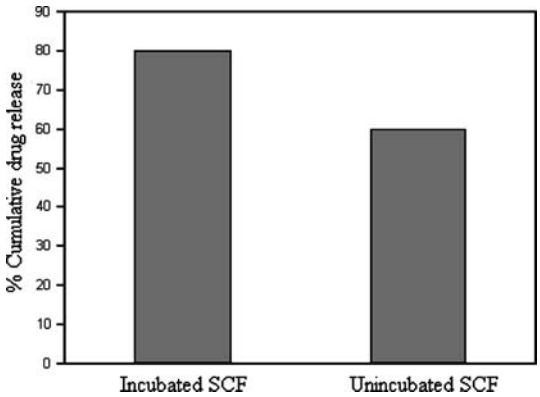

Fig. 6 Bar graph showing cumulative percent drug release from the tablets (GF3) in incubated and unincubated SCF

inulin coated tablets. The results inferred that the inulin at 4% w/w coat is effective in controlling the drug delivery from the tablets in small intestinal environment.

In vitro studies revealed that the formulations containing 25 and 50% of polymer could not show sustained release whereas, the formulations CF3 and GF3 (75% w/w of chitosan and guar gum) showed sustained drug release from the coated tablets over a period of time. Chitosan and guar gum formulations containing 25 and 50% w/w of polymer, released entire drug within 6 and 8 h of dissolution respectively. On the other hand tablets containing 75% w/w of chitosan or guar gum showed only about 74.2 and 80% of drug release at the end of 11 h of dissolution. That means the order of drug delivery from the coated tablets with reference to polymer concentration is; $25 > 50 > 75\%$.

The formulations CF3 and GF3 were found to show no drug release in pH 1.2 buffer (stomach environment) and showed a low amount of about 19 and 21% of the drug in pH 7.4 phosphate buffer (small intestinal environment) and released the remaining amount of drug in the colonic environment (Fig. 7). Drug delivery studies revealed that the tablets coated with shellac (2.5% w/w), prevented the drug release in stomach environment and inulin coated tablets (4% w/w) have limited the drug release in small intestinal environment. On reaching the colonic

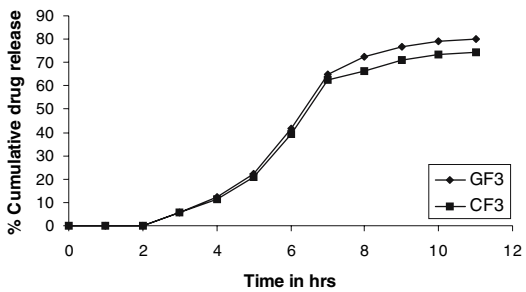

Fig. 7 Drug release profile of GF3 and CF3 formulations for 2 h in pH 1.2, 3 h in pH 7.4 and 6 h in SCF

Table 2 Data obtained from Peppas model fitting for the polymer coated optimized formulations

Parameters	CF3	GF3
Release constant (k) $\times 10^2$	4.54	4.07
Constant (A)	2.2584	2.0383
Regression coefficient (R^2)	0.9619	0.9610

environment, the inulin coat gets biodegraded in the bacteriological media and the drug present in the core gets exposed to the bacteriological solution. The bacteria present in the solution breakdown the polysaccharide units and the drug gets released.

The data obtained from in vitro drug release studies was fit into Peppas model. From the plot of log M_t/M_∞ versus t, the parameters such as release constant (k), constant (A) and the regression coefficient (R^2) were calculated and are given in Table 2. In all the cases the value of A were found to be more than 2. This result indicates that the release of drug from the polymer matrix formulations was found to be super case-II transport, i.e., drug release by more than one mechanism.

Conclusions

In vitro release studies of the prepared formulations with and without rat cecal contents (SCF) indicated that rate of drug delivery enhanced in the presence of rat cecal contents, which enhance the rate of biodegradation of the polymers used. This is due to the presence of enzymes secreted by the bacteria present in the cecal contents. The drug release studies were conducted in incubated and unincubated simulated colonic fluid. The data obtained from these studies indicated that the drug release was more in case of incubated fluid. This is due to the presence of high concentration of enzymes caused by the multiplication of the bacteria. This enhanced the biodegradation of the polymers used. Hence, incubated SCF was used for in vitro dissolution studies. From the dissolution data, it was clear that shellac protected the release of drug from the tablets in the stomach environment, while inulin controlled the drug release in small intestine. Comparison of the release profiles of the drug indicated that, drug release depends on the nature of the matrix and amount of polymer coated. When chitosan was used as matrix material, it had shown a maximum effect in controlling the drug release, followed by guar gum. Polymers at a concentration of 75% w/w of tablet showed controlled drug release. These are the optimized composition for effective drug delivery. The A value obtained from Peppas model fitting was more than two, which indicates that the drug release followed super case-II transport i.e., release of the drug from tablets was by more than one mechanism. With the present experimental work, it can be concluded that, chitosan proved to be the most suitable polymer amongst the polymers selected for the study. The study revealed that natural polymers can be used for selective delivery to colon for the treatment of local as well as systemic disorders.

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