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Binders for colon specific drug delivery: an in vitro evaluation

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Abstract

The aim of the present study was to develop a single unit, site-specific drug formulation allowing targeted drug release in the colon. Tablets were prepared using polysaccharides or synthetic polymer as binders. These included xanthan gum, guar gum, chitosan and Eudragit E. Indomethacin was used as a model drug. The prepared tablets were enteric coated with Eudragit-L 100 to give protection in the stomach. The coated tablets were tested in-vitro for their suitability as colon specific drug delivery systems. The drug release studies were carried out in simulated stomach environment (pH 1.2) for 2 h followed by small intestinal environment at pH 6.8. The dissolution data obtained from tablets demonstrates that the dissolution rate of the tablet is dependent upon the type and concentration of polysaccharide/polymer used as binder. The results demonstrate that enteric coated tablets containing 3% chitosan as a binder, showed only 12.5% drug release in the first 5 h, which is the usual upper gastrointestinal transit time, whereas, tablets prepared using guar gum as binder, were unable to protect drug release under similar conditions. Preparations with xanthan gum as a binder formed time-dependent release formulations. When used in a concentration of 5.92% in the tablets, 28% drug release was observed in the usual upper gastrointestinal tract conditions. It was also found that enteric coated preparation formulated with 8.88% of Eudragit E as binder could be used to carry water insoluble drug molecules to the colon especially in IBD. The above study shows that chitosan could be successfully used as a binder, for colon targeting of water insoluble drugs in preference to guar gum when used in the same concentration. Additionally, formulations developed with chitosan and Eudragit E would be highly site specific since drug release would be at a retarded rate till microbial degradation or polymer solubilization takes place in the colon.

Keywords: Colon specific drug delivery; Colon targeting; Chitosan; Guar gum; Xanthan gum; Eudragit E

1. Introduction

Until recently, colon was considered as a site for water reabsorption and residual carbohydrate fermentation. However, it is currently being viewed as a site for drug delivery. Colonic drug delivery is not only restricted to treatment of local disorders but also for systemic drug delivery. This part of GIT is also being considered as a site for administration of protein and peptide drugs (Reddy et al., 1999). This is because colon provides a less hostile environment for drugs due to low diversity and intensity of digestive enzymatic activities, and a near neutral pH. Moreover, colon

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transit time may last for upto 78 h, which is likely to increase the time available for drug absorption. Further, considering that this site is more responsive to absorption enhancers, its suitability as a site for drug administration appears promising. Additionally, colonic delivery of drugs may be extremely useful when a delay in drug absorption is required from a therapeutic point of view e.g. in case of diurnal asthma, angina, arthritis, etc. (Kinget et al., 1998).

Different systems are being developed for the purpose of site-specific drug delivery to the colon. These include (a) Systems developed with pH-sensitive polymers (Leopold, 1999) (b) Time-dependent formulations (MacNeil and Stevens, 1990) (c) Enzyme controlled release systems (Sinha and Kumria, 2001a,b). One or a combination of the above approaches is utilized to achieve colon-specific drug delivery. However, analyzing the marketed products clearly shows a preference for using enteric polymers, being the simplest and most viable technique for the above purpose (Leopold, 1999). Though, these systems effectively resist drug release under acidic conditions of the stomach, a considerable amount of drug may be released in the small intestine before it reaches the colon. Also, as the pH-difference between the small and large intestine is not very pronounced (Evans et al., 1988), these systems do not allow reproducible drug delivery (Ashford et al., 1993a,b; Leopold and Eikeler, 2000).

Site-specific drug delivery to the colon may be achieved by different approaches. Ideally, the approach based on a combination of pH-dependent and time-controlled release mechanism seems encouraging. pH-dependent release can be assured by enteric coating and drug release can be delayed further for a predetermined time during transit through the small intestine. Time-controlled release system may be, swellable, soluble coating, or a matrix type, which can resist the release of majority of drug from the formulation for an additional 3 h (i.e. the usual small intestinal transit time) and can deliver drug primarily to the colon.

Conventionally, various polysaccharides/polymers are used in the tablet formulations to retard drug release. These have been used either as matrices or as a coating material. For matrices, generally, a high concentration of polymer is required. Alternatively, these can be used as binders in tablets. A solution of these polysaccharides/polymers as binders probably on drying enables the granules to be coated by them (Yen, 1964; Banakar, 1992). Thus, varying the polysaccharide/polymer and their concentration affects drug release from the prepared tablet. Based on the above assumption, three different polysaccharides namely, guar gum, xanthan gum, chitosan and a pH sensitive polymer, Eudragit-E were selected for the present study.

The aim of the present study was to formulate a dosage form which was enteric coated to prevent drug release in the stomach and had an additional lag phase in the formulation to retard drug release in the small intestine. Though enteric coated systems with such lag phases have been developed earlier, but being relatively complex systems, their large scale manufacturing requires a lot of technological advancement and skills (MacNeil and Stevens, 1990; Niwa et al., 1995). So, an attempt was made to formulate a dosage form, which could be formulated easily, using the usual tableting techniques and usual tableting ingredients, with little modification in the method of processing of the ingredients.

2. Material and methods

2.1. Materials

Indomethacin was a generous gift from Indian Drugs and Pharmaceuticals Limited (Gurgaon) India. Guar gum (M.W. 220 000) was procured from Himedia Laboratories Limited, India. Chitosan (degree of deacetylation $>85\%$) was obtained from Central Institute of Fisheries, Kochi, India. Xanthan gum (USNF) was gifted by Dabur Research Foundation, Sahibabad, India. All other ingredients used in the preparation and coating of tablets were of Analytical Pharmacopoeial.

Table 1
Quantity of binder in g for 75 tablets

Serial number	Formulation code	Xanthan gum	Guar gum	Chitosan	Eudragit E	Percentage of binder
1	CH3	–	–	0.300	–	1.77
2	CH4	–	–	0.400	–	2.37
3	CH5	–	–	0.500	–	2.96
4	GG3	–	0.300	–	–	1.77
5	GG4	–	0.400	–	–	2.37
6	GG5	–	0.500	–	–	2.96
7	EE5	–	–	–	0.500	2.96
8	EE7	–	–	–	0.750	4.44
9	EE10	–	–	–	1.00	5.92
10	EE15	–	–	–	1.5	8.88
11	XG5	0.500	–	–	–	2.96
12	XG7	0.750	–	–	–	4.44
13	XG10	1.00	–	–	–	5.92

2.2. Methods

2.2.1. Preparation of binder solutions

Binder solutions of the polysaccharides were prepared by mixing the weighed amount of polysaccharide (as per Table 1) with distilled water. In case of chitosan a 1% v/v solution of acetic acid in distilled water was used. This mixture was allowed to stand with intermittent mixing for 0.5 h, so as to enable the polysaccharides to swell. The paste thus formed was then used as a binder for the powder mix during wet granulation. In case of Eudragit E. the polymer was dissolved in 10 ml of acetone and this mixture was used as a binder. The quantities of polysaccharide/polymer used were as mentioned in Table 1.

2.2.2. Preparation of granules

All the powdered ingredients were weighed, mixed and granulated with the binder solution/paste prepared as above. This mixture was thoroughly blended manually and passed through a sieve with a nominal aperture of 1 mm. The granules prepared were dried in a tray drier at a temperature between 30 and 40 °C for 4 h. The dried granules were screened, mixed with lubricants and stored for tableting.

2.2.3. Preparation of tablets

Tablets weighing 225 mg containing 25 mg of indomethacin were individually punched on a single punch tableting machine (Modern Engineering Works, New Delhi, India) using 7.9 mm concave die-punch. The tablets had a hardness between 5 and 7 kg/cm^2. Various tests were performed on the prepared tablets viz., content determination, friability, disintegration, etc.

2.2.4. Coating of tablets

Each batch of the tablet was coated with a 12.5% w/v solution of Eudragit L-100, using a pan coating equipment. PEG-400 (1.25% w/w) was used as a plasticizer. The percent weight increase of each batch of tablet after coating varied between 2.1 ± 0.05% w/w.

2.2.5. Swelling studies

Uncoated tablets with xanthan gum and guar gum as binder in varying concentrations, were subjected to swelling studies (Talukdar and Kinget, 1995; Sujja-areevath et al., 1998) at a temperature of 37 °C and at a pH of 6.8, using the same buffer that was used for dissolution studies. Swelling studies were conducted in triplicate for each binder concentration. Radial swelling of tablet width was noted, manually from time to time (Figs. 1 and 2).

2.2.6. Drug release studies

The ability of the prepared tablets to retard drug release in the physiological environment of the stomach and the small intestine was assessed by

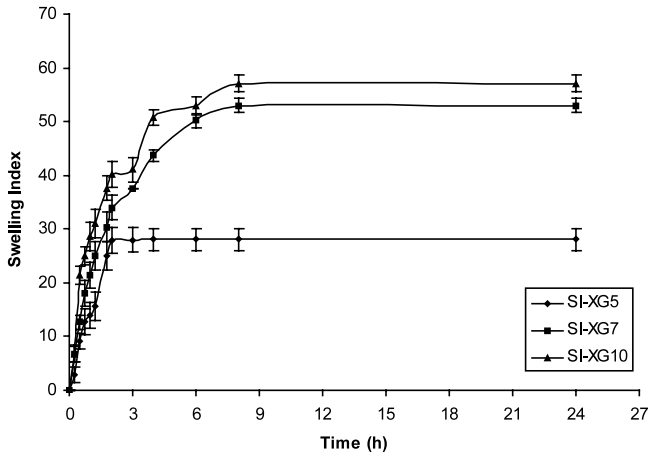

Fig. 1. Swelling index vs. time graph of XG tablets at 6.8 pH (37 °C).

conducting drug release studies in simulated stomach and small intestinal pH, respectively. The changing pH media, Method 1, USP 23, for delayed release tablets was used. Dissolution test was conducted in USP 1 apparatus at 75 rpm and a temperature of 37 °C. Initial drug release studies were conducted in 750 ml of 0.1N HCl for 2 h. Then, 250 ml of 0.2 M trisodium phosphate was added to the dissolution media and the pH adjusted to 6.8. Samples were withdrawn after regular intervals of time to evaluate drug release. These were analyzed spectrophotometrically at a wavelength of 318 nm.

3. Results and discussion

For the formulation of a delivery system for colon targeting, it is an essential prerequisite that the drug release should be minimal until the dosage form reaches the colon. The normal transit time in the stomach is 2 h (though this may vary). The transit time in small intestine is relatively constant and is 3 h. So, after gastric emptying, the drug release from the dosage form is to be retarded during transit through the small intestine (3 h). To overcome the variation in transit time of stomach the tablets prepared were enteric coated. None of

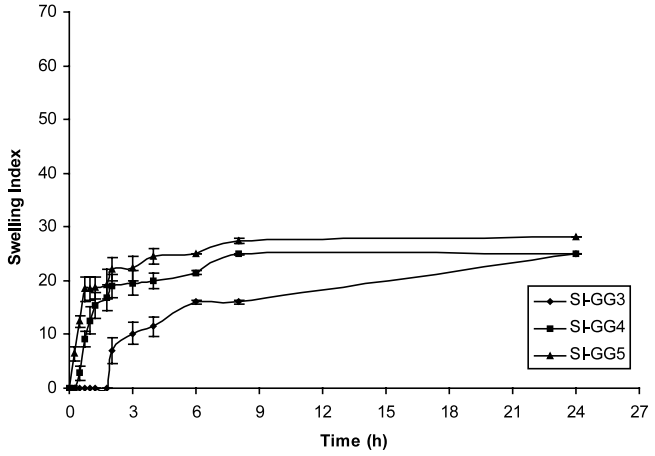

Fig. 2. Swelling index vs. time graph of GG tablets at 6.8 pH (37 °C).

the tablets showed drug release during the first 2 h in 0.1N·HCl. When the pH was changed to 6.8, enteric layer dissolved and further drug release rate was dependent upon the type and concentration of binder used in the tablets.

3.1. Xanthan gum as binder

XG tablets did not show any drug release during the initial 2 h in the acidic media due to the enteric coating but once the pH was changed to 6.8, drug release started, but at a retarded rate. Drug release from XG5 tablets in the next 3 h was 26% and a total of 72% of the drug was released in 24 h. Increasing the concentration of XG from 2.96% (XG5) to 4.44% (XG7), decreased the initial amount of drug released, showing 25% release in the next 3 h but the total amount of drug release in 24 h was increased to 86%. Further, increase in concentration of xanthan gum to 5.92% (XG10), though, initially reduced drug release, but this was followed by a rapid drug release and nearly 100% drug was released in 20 h.

The initial decrease in drug release rate (Fig. 3) on increasing the concentration of xanthan gum can be explained on the basis that a higher binder concentration led to an increase in hardness of the tablet, while the porosity and capillary pore sizes were reduced (Upadrashta et al., 1992). This in-turn reduced the wicking of water into the tablet and consequently the swelling and drug release rates are slowed.

These tablets showed a considerable swelling at a pH of 6.8 (Fig. 1) and the drug was dispersed in the swollen matrix formed by the polysaccharide. The release of the active principle (drug) by a matrix system is generally produced by two simultaneous mechanisms: (a) erosion or attrition of the outermost, least consistent gel layer, (b) dissolution of the active principle in the liquid medium and diffusion through the gel barrier when formed (Lapidus and Lordi, 1968; Feely and Davis, 1988; Alderman, 1984).

However, it has been reported that when water solubility of the drug is low, as is in the case of indomethacin, the possibility of release by diffusion is practically zero and release takes place by surface erosion (Lapidus and Lordi, 1966; Nigalaye et al., 1990).

Studies carried out on swellable matrices have shown that as the concentration of the swellable polymer is increased in the formulation, the gel thickness increases upon swelling. This increases the diffusion path length, which in turn decreases the drug release from the tablet (Talukdar and Kinget, 1995). However, in the present study though, upon increasing the polysaccharide concentration, the swelling increased, but after a certain lag phase, the drug release was increased rather than being decreased, as is normally expected from a matrix tablet. This can be explained

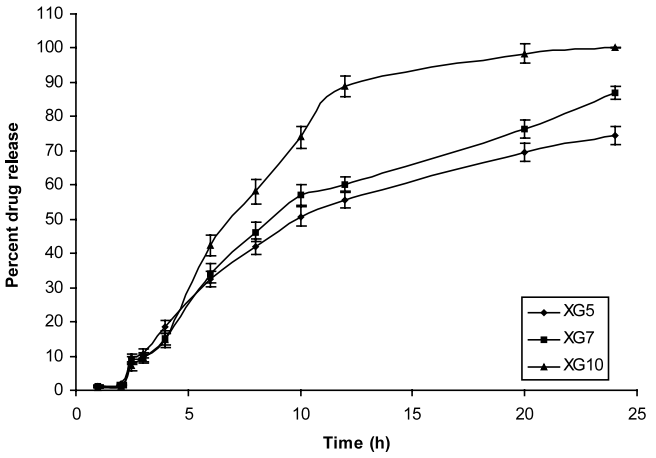

Fig. 3. Percent drug release vs. time graph of XG tablets.

on the basis that these tablets upon swelling form rather loose gels due to a very low concentration of the polysaccharide. Since the release of drug from these matrices takes place by polysaccharide erosion, which further depends upon the gel consistency (Marcos et al., 1991), looser the gels, the more susceptible the matrix is to erosion and faster is the drug release. This accounts for the drug release behavior in case of XG tablets. Hence, after an initial lag phase (time taken by the tablet to swell) increase in concentration of binder in XG tablets increases swelling and drug release.

This study shows that time-controlled release systems for colon targeting can be formulated using XG as a binder which initially retards drug release due to the lag time required for swelling and after swelling, a rapid drug release was obtained.

3.2. Guar gum as a binder

The cumulative percent drug release versus time profile for GG tablets show a rather rapid drug release after second hour of dissolution showing that as the enteric layer dissolved, the gum used as a binder could not effectively retard drug release. In GG3 tablets with a concentration of 1.77% of gum, drug release could not be retarded. Increasing the concentration of guar gum in the tablet from 1.77 to 2.37% and then to 2.96% did retard the drug release profile further but a significant reduction was not observed. The percent drug release versus time graph shows that as much as 62, 58 and 50% drug release was observed in the first 5 h of dissolution of GG3, GG4 and GG5 tablets, respectively (Fig. 4). Complete drug was release from the tablets at around 20th h.

With increase in concentration of gum in GG tablets increase in swelling index (Fig. 2) was observed but the drug release was not much affected and no optimum lag time was achieved as required to bypass the drug release in upper parts of GIT. This may be due to lower swelling of guar gum tablets and also probably, the concentration of the gum present was not sufficient to retard the drug release.

3.3. Chitosan as a binder

Studies using chitosan as a binder showed that at a concentration of 1.77% (in CH3 tablets), the drug release in the initial 5 h was 17%. Increasing the concentration of chitosan in the formulation from 1.77 to 2.37% in CH4, and then to 2.96% in CH5 tablets further retarded drug release from the dosage form. Percent drug release at 5 h was reduced to 14% in CH4 tablets and further to 12.5% in CH5 tablets. The total amount of drug released from CH3, CH4, and CH5 tablets was around 76%, 63% and 46%, respectively in 24 h (Fig. 5, Table 2).

This decrease in release rate on increasing the concentration of chitosan can be explained on the basis that as the concentration of binder in the system is increased, hardness, porosity & capillary sizes are reduced. This reduces the wicking of water into the tablet, which reduces the disintegration and dissolution processes. These tablets formulated using chitosan did not show any swelling in basic environments, so drug release due to swelling & polymer erosion was minimized. This explains why the rate of drug release was not as high as in the case of other swellable gums.

Thus, systems formulated using chitosan as a binder have been found to protect majority of drug release during the usual upper GIT transit time of 5 h. However, there have been a number of reports where chitosan has been found to be digested by the microflora of the colon. Enteric-coated chitosan capsules have been known to be site specific for the colonic delivery of drug molecules, since they release the drug upon bacterial degradation in the colon (Tozaki et al., 1997, 1999). On similar lines, once these CH tablets reach the colon, chitosan shall be broken down by the microflora of the colon and the total amount of drug shall be released from the dosage form. These tablets can also tolerate variation in upper GIT transit time, since the rate of drug release before arrival into the colon remain retarded. These tablets seem to be highly site specific because drug shall be released only upon specific bacterial degradation of the binding agent i.e. chitosan in the colon.

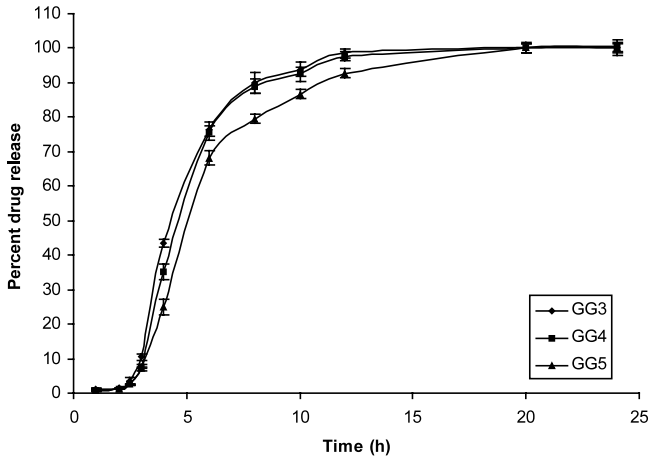

Fig. 4. Percent drug release vs. time graph of GG tablets.

3.4. Eudragit E as binder

Enteric coated system with Eudragit E as binders protected drug release for an initial 2 h in acidic media. In the basic environment (pH 6.8) the enteric layer dissolves, and Eudragit-E, being soluble only at lower pH values (lower than 5) finds an unfavorable environment for dissolution and thereby drug release was retarded (Fig. 6). However, a concentration of 2.96% (i.e. in EE5 tablets) was not able to protect drug release from the tablets and a sharp increase in drug release was observed with-in the next 1 h and 80% of drug release was observed in the next 3 h. Upon increasing the concentration of the binder Eudragit E in the tablet to 4.44% (EE7 tablets) the drug release during the first 5 h of dissolution was retarded showing percent drug release of around 27% as against 80% in EE5 tablets. Further increase in concentration of binder to 5.92 and then to 8.88% in EE 10 and EE 15 tablets, reduced percent drug release in first 5 h to 23% and 17%, respectively. The total amount of drug released in 24 h reduced from 100 to 99% followed by 79 and then 50% in EE5, EE7, EE10 and EE15 tablets, respectively (Table 2).

This reduction in rate of drug release upon increasing the concentration of binder can be explained on the assumption that upon drying of granules a film is formed by the binder over the

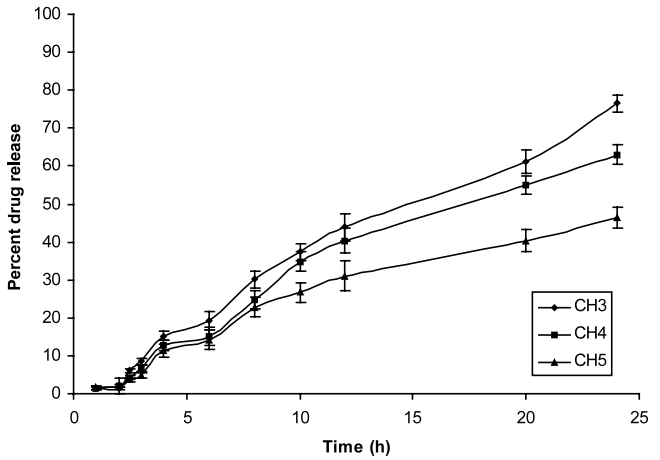

Fig. 5. Percent drug release vs. time graph of CH tablets.

Table 2
Cumulative percent drug release from the tablets at varying time intervals

	Tablet code	Percent drug release (2 h)	Percent drug release (5 h)	Percent drug release (24 h)
1	CH3	0	17	76
2	CH4	0	14	63
3	CH5	0	12.5	46
4	GG3	0	62	100
5	GG4	0	58	100
6	GG5	0	50	100
7	EE5	0	80	100
8	EE7	0	27	99
9	EE10	0	23	79
10	EE15	0	17	50
11	XG5	0	26	72
12	XG7	0	25	86
13	XG10	0	28	100

granules (Yen, 1964; Banakar, 1992). The thickness of the film depends upon the concentration of binder used. As concentration of binder was increased, thicker film of Eudragit E was formed around the granules, which retarded the drug release because of being insoluble at a pH of 6.8.

These systems especially EE15 tablets seem to be promising systems for delivery of drugs to the colon in case of inflammatory bowel disease (IBD), when the pH of the colon is lowered to between 2.3 and 4.7 (Roediger et al., 1984; Fallingborg et al., 1993; Sasaki et al., 1997), since Eudragit E is soluble at a pH below 5.

4. Conclusion

These systems seem to be promising for delivery of water insoluble drugs to the colon. The use of 5.97% of xanthan gum as binder could formulate time-controlled release formulations, which could carry a high percentage of drug to the terminal ileum or the colon. Also systems formulated using chitosan as binders seem to be highly site specific due to release of majority of drug only upon breakdown by the bacterial microflora of the colon. These formulations could act as colon specific drug delivery systems using as low as 3%

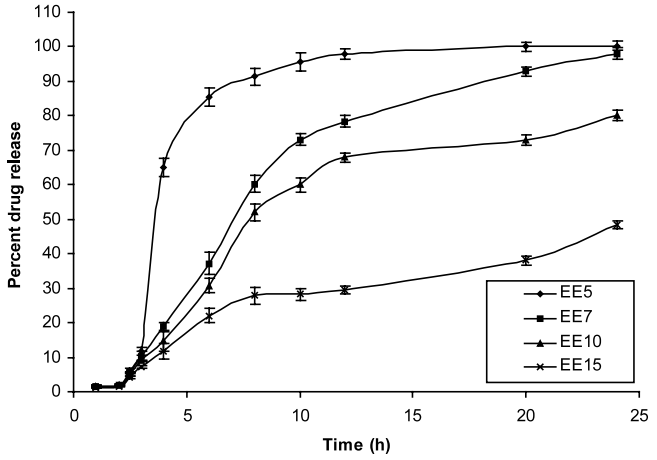

Fig. 6. Percent drug release vs. time graph of EE tablets.

of chitosan as binders. Such a low concentration of chitosan has shown high site specificity. An additional advantage of these systems is that they could be formulated easily, using the usual tableting and coating techniques. Systems formulated using upto 3% of guar gum could not carry the drug to the colon.

Systems formulated with 8.88% of Eudragit E as binders could be used to deliver water insoluble drugs site-specifically to the colon in IBD.

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