Research Article

INVESTIGATION OF THE IMPACT OF CELLULOSE ACETATE COATING ON THE RELEASE PATTERN OF FREELY SOLUBLE DRUG: METOPROLOL SUCCINATE

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ABSTRACT

This study is aimed to develop and evaluate cost-effective cellulose acetate (CA)-polyvinyl pyrrolidone (PVP) film coating that can effectively control the release of freely water soluble drug, metoprolol succinate (MS) and to match that of release profile with its marketed tablet formulation. Simple core tablets of MS were compressed and coated with a solution composed of semipermeable rate controlling polymer, CA and water soluble pore forming polymer, PVP. Drug-excipient interaction was investigated by both physical observation and differential scanning calorimetry (DSC). The effect of formulation parameters such as the ratio of CA to PVP, tablet coating weight gain, effect of pH on the *in-vitro* drug release were evaluated. Surface morphology of the CA coating membrane was examined by scanning electron microscope (SEM). Release profile of the optimized formulation at different pH conditions was determined and the similarity factor (*f*₂) with marketed tablet release profile was calculated. It was observed that drug release rate increased with a decrease in the ratio of cellulose acetate to PVP and decreased with increased weight gain of the coating membrane. Among all the formulations, the formulation with CA and PVP at a ratio of 85:15 %w/w and 9 % weight gain showed matching release profile to the marketed tablet formulation with *f*₂ value of 72.25. Developed MS formulation showed pH independent drug release. This study proved that CA-PVP polymer coating could effectively control the release rate of freely water soluble drugs for up to 24 h. Once a day CR formulation of metoprolol succinate pharmaceutically equivalent to marketed formulation was developed.

Keywords: Metoprolol succinate, cellulose acetate, controlled release tablet, tablet coating, pore-former, pharmaceutical equivalence.

INTRODUCTION

Developing oral controlled release tablets for freely water soluble drugs with a constant release rate has always been challenging to the pharmaceutical technologist. Polymeric matrix tablets are most commonly employed for this application in pharmaceutical industry. In this study, efforts were made to evaluate the applicability of simple and economical cellulose acetate (CA)-polyvinyl pyrrolidone (PVP) coating in controlling the release of highly water soluble drug without using any rate controlling polymers in the tablet matrix. Cellulose acetate is the most commonly used coating material as the semi-permeable membrane for osmotic or controlled release drug delivery. It is also used for taste-masking and tableting. Cellulose acetate has many advantages for using in sustained release formulations, which include i) water insolubility, making it insoluble throughout gastrointestinal tract ii) soluble in various organic solvents, making it easy to prepare coating solutions and mixing with other additives such as plasticizers iii) miscibility with various water soluble additives that permit the permeability characteristics of the resultant films to be changed readily iv) biocompatible and non-biodegradable, thus used only in oral formulations v) non-toxic, non-irritant and non-allergenic¹. Cellulose acetate forms a semi-permeable membrane coating which is permeable to aqueous fluids but substantially impermeable to the components of the core. In order the drug permeable, water-soluble materials/particles as a pore-former are usually added to CA coating layers. After administration of the dosage form, the pore-former dissolves in situ and forms pores or channels in the coating, making the polymer coating micro-porous, and inducing drug release²⁻⁶. Among various pore-formers studied so far, water-soluble hydrophilic polymers like hydroxyl propyl methyl cellulose and

PVP are most commonly used due to their desirable compatibilities with polymeric coat materials^{7,8}. In this study PVP is used because of its good solubility in organic solvents used for making coating solutions. Metoprolol succinate was selected as model drug for the evaluation of CA-PVP coating technology due to three main reasons i) freely water soluble ii) to improve patient compliance and reduce side effects iii) long absorption window. Metoprolol, a β 1-selective adrenergic blocking agent, is one of the most commonly prescribed drugs for the treatment of patients with hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction and heart failure. Metoprolol has short elimination half-life of 3-4 h and extensive first pass metabolism, there by requiring two to three times daily dosing in large number of patients, which often leads to non-compliance. Antihypertensive patients require maintaining constant blood plasma levels of drug to control the blood pressure. Administering extended release dosage forms can lead to reduction in dosing frequency and reduction in plasma level fluctuations of drug to control the blood pressure and consequently potential side effects can be minimized. Thus, there is a strong clinical need and market potential for MS controlled release formulations. Various controlled release tablet formulations of MS are available in the market, but there was no study reported on application of cellulose acetate coating for altered drug release of metoprolol⁹. In human, absorption of metoprolol is rapid and complete. Metoprolol is not absorbed from the stomach, but absorbed well from all segments of small intestine (duodenum, jejunum, and ileum) and colon¹⁰⁻¹². Due to its high permeability throughout GIT, metoprolol is ideal choice for the development once a day CR tablet. This study was undertaken to evaluate the application of cellulose acetate-polyvinyl pyrrolidone coating blend in developing once a day controlled release tablet formulation for highly water soluble drug, metoprolol

succinate. Formulation variables such as pore-former concentration and coating weight gain were studied and optimized to achieve the desired release profile. Optimized formulation was evaluated *in-vitro* for its pharmaceutical equivalence to the marketed tablet formulation, and release pattern in different pH conditions.

MATERIALS AND METHODS

Metoprolol succinate was purchased from Dr. Reddy's laboratories, Hyderabad, India. Mannitol (Pearlitol 160c) and lactose were obtained from Roquette India Ltd, Mumbai, India. Low viscosity grade cellulose acetate was purchased from Eastman Chemicals Ltd, Kingsport, Tennessee, U.S.A. Polyvinyl pyrrolidone (Kollidone K30) was purchased from BASF Corporation, Mumbai, India. Colloidal silicone dioxide (Aerosil® 200) was purchased from Evonik Industries, Parsippany, NJ, U.S.A. and magnesium stearate was from Merck Ltd, Mumbai, India. Polyethylene glycol was obtained from Viswaat Chemicals Ltd, Mumbai, India. Isopropyl alcohol and dichloromethane are of commercial grade.

Drug-excipient compatibility study

The possibility of drug-excipient interaction was investigated by both physical observation and differential scanning calorimetry (DSC). Briefly, metoprolol succinate was mixed with all excipients to be used in formulations at 1:1 ratio and kept at $5 \pm 3^\circ\text{C}$ and $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH conditions for one month and monitored every week for any color changes. Powder samples for DSC analysis prepared by crushing tablets in mortar. All the samples, pure drug, placebo tablets, core tablets of MS and coated tablets of MS were separately sealed in aluminum pans and subjected for analysis in Perkin Elmer DSC (Pyris 1, Waltham, MA). The thermal analysis was performed in a nitrogen atmosphere at a heating rate of $10^\circ\text{C}/\text{min}$ over a temperature range of 25°C to 200°C .

Preparation and characterization of metoprolol succinate tablets

Composition of the metoprolol succinate core formulation is depicted in Table 1. Core tablets of MS were prepared by wet granulation method and the batch size was kept as 1000 tablets. MS was mixed with diluents, mannitol and lactose and passed through sieve #40. Then the blend was mixed for 10 min in a polybag. The dry blend was granulated with povidone (PVP K30) solution in isopropyl alcohol. The mass was dried at 45°C to get a loss on drying (LOD) value between 1 to 1.5 % and sized through sieve #20. These granules were lubricated with magnesium stearate and colloidal silicon dioxide and compressed with 10 mm oval biconcave punches using 16-station rotary compression machine (Cadmach, Ahmadabad, India) keeping hardness at about 16 kps. These core tablets were characterized for size, weight variation, hardness, friability, content uniformity, and *in-vitro* drug release following USP guidelines.

Cellulose Acetate coating of MS core tablets

Formulae of five coating formulations were depicted in Table 2. The core Tablets of MS were coated in an automated perforated pan coater (Ganscoater, Gansons Ltd, Thane, India). The coating solution is composed of cellulose acetate, PVP K30, PEG 400 dissolved in 1:1 ratio of isopropyl alcohol and dichloromethane. In the preparation of coating solution, cellulose acetate was dissolved in the mixture of IPA and DCM by stirring for 15 min. PVP K30 was dissolved in a small portion of IPA and this portion was added to cellulose acetate dissolved portion under stirring. After forming a clear solution, PEG 400 was added and stirring was continued for 10 more minutes to achieve uniformity. Coating parameters were optimized to get finest quality of coating and optimized parameters were summarized in Table 3. Core Tablets of MS were placed in the

coating pan rotating at low speed of 2 rpm and hot air was passed through the tablet bed. Coating process was started once the required bed temperature was attained. During the coating process few tablets were taken randomly and their percent weight gain was recorded and the coating was continued until the desired weight gain was obtained. After completing coating, tablets were allowed for curing at 45°C - 50°C for 15 min.

In-vitro release analysis

In-vitro drug release of MS tablets ($n = 6$) was determined using the dissolution method mentioned in United States Pharmacopeia (USP) monograph. Dissolution parameters include, USP apparatus II, 500 mL of pH 6.8 phosphate buffer, paddle speed 50 RPM, medium temperature $37 \pm 0.5^\circ\text{C}$. 10 mL of samples were removed from the dissolution apparatus (Disso 2000, Lab India, Thane, India) at regular time intervals up to 24 h (1, 2, 4, 8, 12, 16, 20, and 24 h) and replaced with the same volume of fresh dissolution medium. Samples were filtered through $0.45\ \mu\text{m}$ membrane filter and analyzed by UV-Visible spectrophotometer (Cary C50, Varian Inc., Palo Alto, CA, USA) at 223 nm to determine the cumulative percent drug release. All the inactive ingredients showed no absorption interference for the analysis of metoprolol succinate at 223 nm.

Determination of similarity factor (f2 Value)

Similarity factor (f_2) values are calculated using the following formula

$$f_2 = 50 \cdot \log \left\{ 1 + \left(\frac{1}{n} \right) \sum_{t=1}^n (R_t - T_t)^2 \right\}^{-0.5} \cdot 100$$

Where, R_t and T_t are the cumulative percentage dissolved at each of the selected 'n' time point of the reference and test product respectively

Scanning electron microscopy

To better understand the mechanism of drug release, surface morphology of the coating membranes of the optimized formulation before and after dissolution was examined by scanning electron microscope (SEM). The samples were placed on a spherical brass stub (12 mm diameter) with a double backed adhesive tape. The tablets (coated tablets before dissolution studies) were mounted as such on the specimen stub. On other hand, small sample of the coating membrane was carefully cut from the exhausted shells, after 24 h of the dissolution studies, and dried. The mounted samples were sputter coated for 10 min with platinum using fine coat ion sputter (JFS-1600, Joel, Japan) and examined under SEM (JSM-6100, Joel, Japan).

Effect of pH on drug release

To evaluate the drug release behavior of the formulation throughout the GIT with different pH conditions, *in-vitro* release studies were conducted in media of different pH. The release media was pH 1.2 buffer; pH 4.5 acetate buffer, pH 6.8 phosphate buffer.

RESULTS AND DISCUSSION

Drug-excipient compatibility study

Pre formulation study involving the compatibility of excipients used in formulation with metoprolol succinate was performed initially. After one month incubation of drug-excipient mixtures at $5 \pm 3^\circ\text{C}$ and $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH, there were no physical signs of discoloration or change in consistency were observed. This indicates no physical interaction between drug and excipients. To further confirm differential scanning calorimetry (DSC) was used. The DSC thermo grams of pure metoprolol succinate, placebo tablets, MS core tablets, and MS coated tablets are depicted in Figure 1.

Appearance of new additional peaks or disappearance of existing peaks was not seen in the thermographs of MS tablets. Drug exhibited a sharp melting endotherm in the core as well as coated formulations. From the DSC thermo grams it was clear that no specific interaction between the drug and excipients used in the present formulation.

Preparation and characterization of MS core tablets

According to United States Pharmacopeia (USP) 190 mg of metoprolol succinate is equivalent to 200 mg of metoprolol tartarate. Based on this, 190 mg/tablet of metoprolol succinate was used in this study. Metoprolol succinate has poor flow property with Carr's index and Hausner's ratio of 36 % and 1.57, respectively. Wet granulation was used to increase its flow ability and PVP K-30 is used as a binder. Mannitol and lactose were used as fillers to increase the bulk of the tablet, magnesium stearate was used as lubricant, and colloidal silicone dioxide used as glidant. Final formulation blend (with all excipients depicted in Table 1) showed good flow properties with Carr's index and Hausner's ratio of 14.2 % and 1.16, respectively. Results of the quality control tests performed on the metoprolol succinate uncoated tablets are listed in Table 4. MS core tablets showed complete drug release in 2 h. In order to extend the drug release for 24 h, these core tablets were subjected for controlled release coating.

Cellulose acetate coating of core tablets

In this study cellulose acetate was used as rate controlling polymer. Water soluble polymer PVP K30 was used as pore-former and PEG400 was used leachable plasticizer. In the optimization of coating formula i.e. to get similar release profile to that of marketed formulation, ratio of cellulose acetate to pore-former, PVP K30 were changed constantly. Addition of plasticizer reduces the internal stress of coating, flexibility of the polymer chains and produces a less porous network⁸. In the current formulation PEG400 was used as plasticizer. Plasticizer, PEG 400 was kept constant i.e., 10 % of total solid polymer content (10 % of cellulose acetate + PVP K30). Solvent system is also same for every formulation i.e., isopropyl alcohol (IPA) and dichloromethane (DCM) in the ratio of 1:1. Four coating formulations with different cellulose acetate and PVP K30 ratios (CA01, CA02, CA03, and CA04) were applied to core MS tablets at both 9 % and 12 % weight gain and tested for their *in-vitro* release profile. Coating parameters were optimized to get a flawless and quality coating.

In-vitro drug release

As depicted in Table 5, USP has mentioned release specifications for metoprolol succinate extended release tablets. Marketed product was subjected for dissolution study and determined *in-vitro* drug release. As shown Table 5, it showed 97.1 % cumulative present release in 24 h and met USP release specifications. Cellulose acetate-PVP film coating was evaluated for controlling the release of freely water soluble drug metoprolol succinate for a period of 24 h in similar to its marketed product. Dissolution profile of metoprolol succinate tablets coated with film formulations CA01, CA02, CA03, and CA04 at both 9 % and 12 % weight gain were illustrated in Figures 2-5. The ratio of cellulose acetate to PVP K30 was increased from trail to trial in order achieve a desired release profile in equivalence to marketed tablet formulation. CA01 formulation having equal ratio of cellulose acetate and PVP K30 showed much faster drug release. 9 % weight gain tablet showed 98.4 ± 2.8 % release in 8 h; whereas 12 % weight gain tablet showed 96.8 ± 3.1 % release within 12 h. Faster drug release rate was attributed to the high amount of pore-former or low amount of CA. To decrease the rate of drug release, the ratio of CA to PVP K30 further increased to 60:40 in CA02 formulation. Drug release rate

was controlled in CA02 formulation in comparison to CA01 formulation, but still fallen above the USP sections for MS controlled release tablets with 98.0 ± 3.9 % release in 12 h from 9 % weight gain tablet, whereas 97.8 ± 2.9 % release within 16 h from 12 % weight gain tablet. Drug release rate was further controlled with CA03 formulation having CA to PVP K30 in ratio of 70:30, but fallen little above the USP specification. 9 % weight gain tablet release rate was faster than 12 % weight gain tablet. The amount of pore-former has to be decreased further to decrease the rate of drug diffusion. Drug release from CA04 formulations with CA to PVP K30 ration of 85:15 at both weight gains (9 % and 12 %) fallen well within USP specifications and the release profile appeared very close to that of marketed formulation.

Effect of pore-former concentration and coating weight gain on drug release

To understand the effect of pore forming agent concentration on release of drug release, dissolution profile 9 % weight gain tablets of four formulations with varying CA:PVP ratios were plotted together (Figure 6A). The pore former, PVP, concentration was expressed as the percent weight of cellulose acetate. For example CA02 formulation is composed of 12 g of PVP and 28 g CA, which means pore-former PVP concentration, is 42.8 % of CA concentration. In this manner the pore-former concentration in CA01, CA02, CA03 and CA04 formulations is 100 %, 66.7 %, 42.8 % and 17.4 % wt/wt (of cellulose acetate), respectively. It is clearly evident that the level of pore-former had direct effect on drug release. As the percentage of pore-former increases, the membrane becomes more porous after coming into contact with the aqueous environment, resulting in faster drug release. It can be clearly understood by comparing the cumulative percent drug release at 8 h time. Release from tablets with pore-former concentration of 100 %, 66.7 %, 42.8 % and 17.4 % wt/wt was found to be 97.4 ± 3.5 %, 87.8 ± 1.9 %, 69.9 ± 2.7 % and 50.5 ± 3.3 %, respectively. To study the effect of coating weight gain on drug release, metoprolol succinate core tablets were coated with CA04 formulation for different coating weight gains i.e. 6 %, 9 %, 12 % and 15 % wt/wt. Release profile from these tablets was shown in the Figure 6B. It is clearly evident that drug release decreases with an increase in weight gain of the membrane. It can be clearly understood by comparing the cumulative percent drug release at 12 h time. Release from tablets with different coating weight gains 6 %, 9 %, 12 % and 15 % was found to be 88.8 ± 2.5 %, 76.3 ± 2.2 %, 64.8 ± 1.88 % and 35.1 ± 3.1 %, respectively.

Similarity to innovator's tablet (f2 Value)

There are several methods for dissolution profile comparison. f2 is the simplest among those methods proposed by Moore and Flanner⁶. It is a model independent of mathematical approach to compare the dissolution profile using two factors f1 and f2.

$$f1 = \left\{ \frac{\sum_{t=1}^n |R_t - T_t|}{\sum_{t=1}^n R_t} \right\} \cdot 100$$

$$f2 = 50 \cdot \log \left\{ 1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right\}^{-0.5} \cdot 100$$

Where, R_t and T_t are the cumulative percentage dissolved at each of the selected 'n' time point of the reference and test product respectively

The factor f1 is proportional to the average difference between the two profiles, whereas factor f2 is inversely proportional to the average of squared difference between the two profiles, with emphasis on the larger difference among all the time points. The factor f2 measures the closeness between the two profiles. Because of the nature of measurement, f1 was described as difference factor, and f2 as similarity factor. When the two profiles are identical, f2 = 100. An average difference of 10 % at all measured time point's results in f2 value of 50. FDA has set a public standard of f2 value in the range of 50-100 to indicate similarity between two dissolution

profiles¹³. f2 values of the developed formulations were delineated in Table 6. Accordingly, CA03/12 %, CA04/9 % and CA04/12 % trials showed similarity to the marketed tablet. However, other formulations were not similar. Among all developed formulations, CA04/9 % weight gain formulation's release profile is very close to that of the marketed tablet. So it is considered as the best and optimized formulation.

Scanning electron microscopy

Cellulose acetate membranes of optimized formulation, CA04/9 %, obtained before and after dissolution were studied by SEM. As shown in Figure 7A, membranes obtained before dissolution was uniform and clearly showed nonporous region. After 24 h dissolution, the membrane clearly showed pores of less than 0.3 μm size (Figure 7B and 7C) owing to the dissolution of PVP K30. The leaching of PVP from the membrane leads to formation of pores, and thus the release of drug takes place. In a previous study with sorbitol as pore-former, the pore size in the CA coating membrane after dissolution was reported as 1 -15 μm , which is significantly higher than that of formulation developed in this study⁴. The lower

pore-size occurred with PVP in current formulation due to the fact that PVP polymer due to its longer chain length intrigued into the cellulose polymer coating. But this is not possible with carbohydrate pore-formers such as sorbitol, mannitol and lactose.

Effect of gastric pH on drug release

The optimized formulation, CA04/9 % weight gain, was subjected to *in-vitro* release studies in buffers with different pH. The release profile was showed in Figure 8. There are no significant differences in the release profiles at three different pH conditions, demonstrating that the drug release from the developed formulation is independent of pH of release media. This can minimize the variability and bioavailability *in-vivo*, releasing the drug linearly throughout the gastro intestinal tract (GIT). Metoprolol succinate absorbs almost equally through all segments of GIT excluding stomach. So pH indent drug release from developed tablets improves *in-vivo* bioavailability. The results are in consistent with the previous reports^{14,15}.

Table 1: Composition of metoprolol succinate core tablet

Component	% w/w	mg/tablet
Metoprolol Succinate, USP	47.5	190
Mannitol, NF	16.25	65
Lactose, NF	30.25	121
Povidone, K-30 USP	4	16
Magnesium stearate, NF	1	4
Colloidal silicone dioxide, NF	1	4
Total tablet weight	100	400

Table 2: Coating compositions of metoprolol succinate formulations

Formulation code	CA01	CA02	CA03	CA04
Cellulose acetate: PVP K 30	50:50	60:40	70:30	85:15
Cellulose acetate (g)	20	24	28	34
PVP K 30 (g)	20	16	12	6
PEG 400 (g)	4	4	4	4
IPA (ml)	400	400	400	400
DCM (ml)	600	600	600	600

*Total solid content 4.4 % w/v, *Plasticizer PEG 400 added 10 % of total solid polymer (10 % of CA + PVP K 30)

Table 3: Optimized coating parameters

Parameter	Value
Spray rate	24 mL/min
Pan speed	5.4 rpm
Inlet temperature	40°C
Outlet temperature	35°C
Atomization	1 kg/cm ²
Fan	1.2 kg/cm ²

Table 4: Results of the quality control (QC) tests on the core tablets of MS

Tablet weight (mg)	400 $\pm$ 6.25
Thickness (mm)	4.68 $\pm$ 0.015
Diameter (mm)	9.92 $\pm$ 0.02
Hardness (kps)	16 $\pm$ 0.9
Friability (%)	0.18 %

Table 5: Dissolution profile of marketed tablet and USP release specifications for metoprolol succinate extended release tablets

Time (hours)	Cumulative percent drug release of marketed MS extended release tablet	USP release specification of MS extended release tablets
1	9.57 $\pm$ 0.62	Not more than 25 %
2	15.3 $\pm$ 0.57	
4	28.7 $\pm$ 0.74	Between 20 % and 40 %
8	52.5 $\pm$ 0.71	Between 40 % and 60 %
12	74.6 $\pm$ 1.88	
16	83.2 $\pm$ 0.90	
20	93.6 $\pm$ 1.10	Not less than 80 %
24	97.1 $\pm$ 1.50	

Table 6: Calculated f₂ values of coated MS tablets

Formulation #	% weight gain	f ₂ values	Similarity in comparison to marketed product as per FDA standards
CA01	9 %	7.76	Dissimilar
	12 %	10.22	Dissimilar
CA02	9 %	11.48	Dissimilar
	12 %	15.48	Dissimilar
CA03	9 %	22.14	Dissimilar
	12 %	63.30	Similar
CA04	6 %	42.10	Dissimilar
	9 %	77.78	Similar
	12 %	55.50	Similar
	15 %	22.29	Dissimilar

Figure 1: DSC thermogram of a) pure drug, MS b) placebo tablet c) uncoated MS tablet d) coated MS tablet

Figure 2: *In-vitro* drug release profile of coated tablets, formulation #CA01 with 9 % and 12 % weight gain in comparison to marketed tablet formulation Figure 3: *In-vitro* drug release profile of coated tablets, formulation #CA02 with 9 % and 12 % weight gain in comparison to marketed tablet formulation Figure 4: *In-vitro* drug release profile of coated tablets, formulation #CA03 with 9 % and 12 % weight gain in comparison to marketed tablet formulation Figure 5: *In-vitro* drug release profile of coated tablets, formulation #CA04 with 9 % and 12 % weight gain in comparison to marketed tablet formulation

Figure 8: *In-vitro* drug release of optimized formulation, CA04 in pH 1.2, 4.5 and 6.8 buffers Figure 6: A) *In-vitro* drug release of coated tablets (9 % weight gain) containing variable amounts of pore-former B) *In-vitro* release from CA04 tablets coated for 6, 9, 12 % and 15 % weight gains

Figure 7: SEM of the surface of the coating before (A) and after dissolution studies (B and C)

CONCLUSION

Results of this study showed that cellulose acetate-polyvinyl pyrrolidone polymer coating could effectively control the release rate of freely water soluble drugs for up to 24 h. Release rate from these tablets depends on the concentration of pore-former and coating thickness. Desired release profile can be achieved by adjusting the ratio of cellulose acetate to pore-former and coating thickness. It was also proved the release from these developed tablets is pH independent, which is ideal release pattern for controlled release formulations. Once a day metoprolol succinate tablets pharmaceutically equivalent to marketed formulation was successfully developed using CA-PVP film coating.

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