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Oral Controlled-Release Dosage Forms. I. Cellulose Ether Polymers in Hydrophilic Matrices

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ABSTRACT

An appropriately designed controlled-release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery to the target tissue. Hydrophilic matrices are an interesting option when developing an oral controlled-release formulation. The present study focuses on oral controlled-release dosage forms and the application of cellulose ether polymers in hydrophilic matrices.
***Key Words**. Controlled-release matrices; Hydrophilic matrices; Cellulose ether polymers; Hydroxypropylmethylcellulose; HPMC*

INTRODUCTION

The use of controlled-release technology in the formulation of pharmaceutical products has become increasingly important in the last few years. In particular, the interest awakened by hydrophilic matrices is completely justified in view of their biopharmaceutical and pharmacokinetics advantages over conventional dosage forms (1–3). This work summarizes the advantages of drug controlled-release therapy and briefly outlines the relevant physicochemical and biological properties of a drug that affect controlled-release performance. In order to define "matrix" system, all parameters required to characterize it are discussed and a classification is proposed. In addition, polymer factors affecting matrix dissolution, such as polymer hydration,

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polymer composition, polymer viscosity, drug solubility, polymer/drug proportion, and polymer/drug or polymer/additive interactions, are presented and discussed.

ADVANTAGES AND DISADVANTAGES OF ORAL CONTROLLED-RELEASE DOSAGE FORMS

The principal goal of controlled-release dosage forms is the improvement of drug therapy as assessed by the relationship between advantages and the disadvantages of the use of controlled-release systems (1,4–6). Among the advantages, we mention the most important:

minimization or complete annihilation of the patient compliance problems;
reduction of both local and systemic side effects;
less potentiation or reduction in drug activity with chronic use;
minimization of drug accumulation in body tissues with chronic dosing; and
minimization or annihilation of "peaks" and "valleys" in the drug blood level, improving efficiency in treatment. In fact, drugs with short half-lives require frequent dosing to maintain constant therapeutic levels.

Besides the positive aspects of these pharmaceutical dosage forms, some disadvantages have been pointed out, such as:

difficulty or impossibility of quick stoppage of pharmacological action drug, when serious poisoning or intolerance occurs;
reproducibility of action affected by the rate of the gastric emptying;
little or no efficacy of pharmaceutical dosage form, if the drug is not absorbed by intestinal mucosa;
difficulty of adjusting the posology to several interindividual pharmacokinetics;
release rate dependent on pharmaceutical dosage form integrity;
large size of pharmaceutical dosage form;
low bioavailability in some cases; and
greater cost than conventional dosage forms.

Limitations of Preparation

The preparation of controlled-release dosage forms is subject to several variables of considerable importance. The oral administration route remains the most popular, in spite of a number of problems. This includes the potential for chemical degradation under various pH conditions in the gastrointestinal tract, the influence of gastric emptying, and its dependence on food.

The physicochemical and biological properties of drug are also important:

Dose, the amount of drug in oral controlled-release dosage form, is approximately two or three times greater than the amount of oral conventional dosage forms.

Aqueous solubility, the drug solubility in water, is a very important factor that affects its incorporation into oral pharmaceutical dosage forms. The drugs with high or low solubility are not chosen for this kind of pharmaceutical forms (7,8).

Partition coefficient explains the ability of a drug to cross the biological membranes and interact with the receptor. As a first approximation, the more effectively a drug crosses membranes, the greater is its activity. Drugs with a partition coefficient that is either extremely higher or lower are poorer candidates for formulation into controlled-release dosage forms (1).

pKa allows to determine the un-ionized form of a drug and, together with the partition coefficient O/A, allows to expect its absorption (9).

Drug stability, i.e., the drug must be stable under biological fluids; otherwise, it is necessary to use methods avoiding its contact with the site of gastrointestinal tract where instability has occurred.

Molecular weight, the ability of a drug to diffuse through polymeric membranes, is a function of its diffusion coefficient. Drugs with molecular weights greater than 500–700 have a lower diffusion coefficient, which makes their use in controlled-release forms difficult (10).

Biological half-life, is the principal limitation, although it is difficult to define upper and lower limits for the value of half-life of a drug that best suits it for controlled-release formulation; it is accepted that a drug with a half-life between 2 and 6 hr must be used (1).

Absorption, a rapid rate of absorption of the drug relative to its release is essential if the system is to be successful (10).

Therapeutic index is defined in the following equation:

$$TI = TD\ 50/ED\ 50$$

where TD 50 is the medium toxic dose and ED 50 is the medium effective dose. A drug is safer when its TI is higher than 10 (11).

DEFINITION AND CLASSIFICATION OF HYDROPHILIC MATRICES

The matrix system is most often used for a drug controlled-release from a pharmaceutical dosage form (12). Among the innumerable methods used in controlled release of drugs from a pharmaceutical dosage form, the matrix system is the most frequently applied; it is a release system for delay and control of the release of a drug that is dissolved or dispersed in a resistant support to disintegration (13). To define matrix, it is necessary to know the characteristics that differentiate it from other controlled-release pharmaceutical dosage forms. Hence, the following must be considered:

the chemical nature of support (generally, the supports are formed by polymeric nets);
the physical state of the drug (dispersion under molecular or particulate form, or both);
the matrix shape and alterations in volume as a function of time;
the routes of administration (oral administration remains the most widely used but other routes are adaptable); and
the release kinetics model (in accordance with Higuchi's equation, these systems are considered to have one linear release rate as a function of the square root of time).

The classification of matrix systems can be based on several criteria, namely:

matrix structure;
release kinetics (must be zero-order release);
controlled-release properties (diffusion, erosion, swelling); and
chemical nature and properties of applied materials.

Paying attention to the last criterion, the matrix systems can be classified in accordance with Table 1 (13).

HYDROPHILIC MATRICES

The formulation of the drugs in gelatinous capsules or, more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in the field of controlled release (2). In fact, a matrix is defined as a well-mixed composite of one or more drugs with a gelling agent (hydrophilic polymer) (14). These systems are called swellable controlled-release systems (15).

Materials

The polymers used in the preparation of hydrophilic matrices are divided into three broad groups:

1. Cellulose derivatives: methylcellulose 400 and 4000 cPs; hydroxyethylcellulose; hydroxypropylmethylcellulose (HPMC) 25, 100, 4000, and 15,000 cPs; and sodium carboxymethylcellulose.
2. Noncellulose natural or semisynthetic polymers: agar-agar; carob gum; alginates; molasses; polysaccharides of manose and galactose; chitosan; and modified starchs.
3. Polymers of acrylic acid; carbopol 934, the most used variety.

Although many polymeric systems have been applied, hydrosoluble polymers such as cellulose ethers (one group of semisynthetic cellulosic derivatives) are perhaps the most often used.

Table 1

Abstract of Matrix Systems Classification

Mineral Matrices	Hydrophilic Matrices	Inert Matrices	Lipidic Matrices	Biodegradable Matrices
Drug retained in the support	Unlimited swelling, delivery by diffusion	Controlled delivery by diffusion	Delivery by diffusion	Non-lipidic
Drug adsorbed on the support	Limited swelling, controlled delivery through swelling		Delivery by surface erosion	

HPMC (with its variety dependent on viscosity and proportions between its substituents) is most widely used in matrix tablets and other types of controlled-release pharmaceutical dosage forms (16) because of its characteristics, namely, non-toxic nature of polymer, its capacity to incorporate active principles, manufacture of matrix tablets by direct compression without previous granulation, and non-pH dependence (15,17–19).

HPMC is made by reacting purified cellulose with appropriate free agents (methylchloride and propyleneoxide) in the presence of caustic soda (20). It does not have an ionic charge and therefore will not complex with metal salts.

The Preparation Process

The well-deserved attention of hydrophilic matrices in recent years is justified by their safe forms and their inherent advantage of the entire controlled-release dosage over other systems (1), as follows:

- with proper control of the manufacturing process, reproducible release profiles are possible. The variability associated with them is lower than that obtained with coated-release forms (2,21);
- there is an immediate release of a small amount of active principal but there is no risk of "dumping" a large part of the dose (22);
- their large capacity to incorporate drugs, which allows them to release large doses (1);
- the preparation processes are very simple. The matrix tablets can be made by direct compression or through conventional dry or wet granulation methods (2,23); and
- a class of inexpensive substances with official organizations' acceptance (20,23).

Drug Release Mechanism

One of the proposed mechanisms for drug release from matrices of HPMC implies water penetration in the matrix (with drug dissolution on the surface, causing its immediate release), hydration and swelling of HPMC (with its expansion), diffusion of the dissolved drug, and the erosion of gelatinous polymer layer (15,24–26). In accordance with the results of Alderman (23), the quick formation of gelatinous viscous layer resulting from hydration is considered to be the first essential step for obtention of delivery/release of drug from HPMC matrices (a corroborated phenomenon by Pham and Lee (19)).

When the water reaches the center of the tablet (or other pharmaceutical dosage forms), and the concentration of drug falls below solubility value, or the release rate of drug begins to reduce, the time lag in the changing of release mechanism is recorded. In fact, for HPMC content increases and drug release decreases, the transition of Higuchi's diffusion to mechanism case II is observed (27).

Papadimitriou et al. (28) have verified that drug release (especially water soluble) of HPMC matrices is affected by swelling method nature. This phenomenon was evidenced when studies with HPMC (Methocel K 100 M) matrices were performed exhibiting impermeable coatings on one or both matrix faces and allowing the observation of preferential swelling directions (29). It was thus demonstrated that the release rate from the matrix decreases with the increase of coating surface. However, the release rate by exposed area stays unalterable and the drug is released at constant rate by exposed surface, albeit with different kinetics (30).

The studies on the influence of the included air in polymeric matrices containing hydrosoluble drugs (31) concluded that this air has a primordial role in the formation of gelatinous layer. It promotes alterations of the release kinetics proposed by T. Higuchi (32) and W. Higuchi (33), and subsequently adjusted by Lapidus and Lordi (34).

Models

All authors agree that drug release from a matrix is controlled by diffusion through the polymeric matrix, obeying Fick's laws (1st and 2nd):

$$Y = -D\frac{\delta C}{\delta X}$$

$$\frac{\delta C}{\delta t} = D\frac{\delta^2 C}{\delta X^2}$$

where Y represents the diffusional material flux; D, the diffusion coefficient of the drug; C, the concentration of the drug; and X, the distance of diffusion.

In this section, several physical models relative to drug release from matrices are considered, selected from the most significant models. However, it is important to note that each pharmaceutical dosage form has a drug release mechanism that is dependent on the pH, the drug, and its own polymeric support. The first proposed model for drug release from ointment bases containing

drugs in suspension was Higuchi's model (32), in accordance with this equation:

$$Q = (2\ A\ D\ C_s t)^{1/2}$$

where Q is the amount of drug released from fatty suspension; A, the concentration of drug per unit volume; D, the diffusion coefficient (constant), C_s, the solubility of drug; and t, representing time. The equation is derived from a system described as follows:

- the suspended drug is in a fine state such that the particles are much smaller in diameter than the thickness of the layer;
- the amount of drug, A, per unit volume, is substantially greater than C_s; and
- the surface of which the drug ointment is applied is immiscible with respect to the ointment, and constitutes a perfect sink for the released drug.

Higuchi's model (32) had successive improvements in the following years, namely, with homogeneous and heterogeneous solid matrices (35). Similarly, Lapidus and Lordi (34,36) have brought the previous equation up-to-date, defining the cases where the drugs are soluble or insoluble in water. Developments that followed were presented by Bamba et al. (37,38), in which the penetration rate of water was limitative.

It is important to refer to the developed model by Korsmeyer et al. (39) because it is most recent and draws much attention. This model relates the drug fractional release with potency time:

$$\frac{Mt}{M\infty} = kt^n \tag{1}$$

or,

$$\log \frac{Mt}{M\infty} = \log k + n \log t \tag{2}$$

where $\frac{Mt}{M\infty}$ is the fractional release of the drug, t denotes the release time, K represents a constant incorporating structural and geometric characteristics of the release device, and n is the time exponent indicative of the release mechanism. This equation includes two drug transport mechanisms (in unlimited swelling systems): Fickian diffusion ($n = 0.5$ for square root of time kinetics); and case II transport (n = 1 for zero-order release kinetics—that means drug release independent of time). These equations were verified by Peppas and Franson (24), Peppas et al. (40), Peppas and Sattin (41), and Bowstra and Junginger (42). The geometrical pharmaceutical dosage form is important (43,44), especially in this release model where the diffusional exponent has several values in accordance with the geometrical form (2,45). This equation is useful when it is not possible to apply Higuchi's model.

The classification above has been successfully used by Ford et al. (46) to characterize the release of a number of different drugs from HPMC matrices. If one plots the logarithm of the fractional release versus the logarithm of time (in minutes), the slope of the graph will give one value of the n exponent. In order for Eq. (2) to be applicable, the intercept of the graph must pass through the origin, i.e., log K must be zero. This correction of data can be achieved by correcting the sampling time data of cumulative fractional release versus the square root of time. The sampling times are then corrected by linear regression so that the graph passes through the origin (46,47).

The drug release kinetics and its exhibition of Fickian or case II drug transport can also be mechanistically analyzed using a novel dimensionless analysis. The physical conditions that determine the kinetics of drug release from swellable matrix were studied by Peppas and Franson (40) who introduced the swelling interface number, S_w. This number compares the mobility of the solvent front relative to drug mobility in the presence of polymer relaxation and is defined as:

$$S_w = \frac{v \cdot d(t)}{D}$$

where v is the velocity of the penetrating swelling front, $d(t)$ representes the time-dependent gel thickness, and D is the drug diffusion coefficient in the swollen phase. The number compares the relative mobilities of the penetrant and of the drug in a matrix undergoing macromolecular relaxation of the polymer.

Values of S_w near unity indicate anomalous transport, whereas values much greater than 1 indicate Fickian diffusion, and values much lower than 1 indicate case II transport. The number S_w is inherentely related to one-dimensional transport and the relaxation rate at the numerator possesses the dimensions of a surface over time. In a three-dimensional matrix, the swelling front movement is dominated by the movement of the dissolution front, since the rate of the swelling front is a constant but the thickness of the gel layer is time-dependent. Therefore, it seems important to consider a new dimensionless number, the swelling area

number S_a, where the relaxation rate is given by the increase in area of the matrix (dissolution front rate).

S_a is defined by the expression:

$$S_a = \frac{1}{D} \cdot \frac{dA}{dt}$$

where $\frac{dA}{dt}$ is the rate of releasing area change and D is the drug diffusion coefficient in the swollen polymer. The advantage of the new number in comparison with the S_W is that it is easier to have data about the expanding area of the matrix as a function of time (48,49).

PARAMETERS AFFECTING DRUG RELEASE

The study of drug release from hydrophilic matrices requires a knowledge of properties and interactions of the polymers used as the binder.

Polymer Hydration

It is important to study the hydration/swelling process for the maximum number of polymers and polymeric combinations. The more important steps in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer–polymer linkings with the simultaneous forming of water–polymer linkings, separation of polymeric chains, swelling, and finally, dispersion of polymeric chain in dissolution medium.

The Methocel K polymer, because of its low content in methoxyl groups, hydrates quickly which justifies its application in controlled-release matrices (50). Several studies about matrice (HPMC) hydration were conducted by Alderman (23), Kararli and Catalano (51), and Rajabi-Siahboomi et al. (52,53). The obtained results by Rajabi-Siahboomi et al. showed that larger-sized fractions of HPMC hydrated more rapidly than smaller fractions, which contradicted Alderman (23). On the other hand, it was demonstrated that this factor is only important when the matrix has a low HPMC content (54). Again, the data contradicted the supposition of Alderman (23) that coarser fractions hydrate more slowly; after 60 min, however, both samples imbibed the same amount of water. The first minutes of hydration are the most important, because they correspond to the time when the protective gel coat is formed around matrices containing HPMC (55).

In accordance with Joshi and Wilson (56), the water influences the stability, rheological behavior, and transport properties of many substances. It was verified that misoprostol stability in HPMC matrices is affected by the polymer–water interaction. In areas with low relative humidity, the increase of content in water and HPMC plastification lead to growing of degradation rate of misoprostol (51).

The swelling of HPMC can be one of the parameters that influence and control the drug release, because it exhibits an inverse relationship between the HPMC constant rate swelling and constant rate dissolution by Higuchi's equation (25). In a matrix, the presence of a drug promotes the alteration of the pathway as the water binds to the cellulose ether (57,58). The thermal analysis shows a variation promoted by water distribution in HPMC gels, in the presence of propranolol hydrochloride (59).

Polymer Composition

In paying attention to the complex composition of polymer cellulose ethers, several reactions are possible. As hydroxyl groups, they can be reacted covalently with many species, both mono- and poly-functional, in order to stabilize and insolubilize their structure. The intermolecular reactions include: formation of acetals with monofunctional aldehydes, formation of hemiacetals or acetals with dialdehydes, formation of ether or methylene links with reagents containing methylol groups, and formation of ether links with epoxides, ethylene imine derivatives, sulfones, and labile chlorine compounds. Under very dilute solutions, some of these reactions may proceed intramolecularily (60).

Dahl et al. (61) evaluated the influence of alteration in metoxyl/hydroxypropyl ratio on the drug release rate. They observed that in matrices obtained by granulation, the drug dissolution rate was directly proportional to hydroxypropyl content, and good results were obtained when HPMC had a content greater than 7.5%.

The modifications observed by alteration of size particles, proportion of metholxyl/hydroxylpropyl substituents, and relative humidity of the HPMC powders were evaluated, and it was concluded that the two last studied fractions have significant effect (62).

Polymer Viscosity

With cellulose ether polymers, viscosity is used as an indication of matrix weight (63). Increasing the molecular weight or viscosity of the polymer in a matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater the viscosity of the

gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution (23,64).

In accordance with Avan and Brossard (65), the viscosity of the gelling agent slows or speeds the initial process of hydration (without altering the release rate), which confirms the studies conducted by Salomon et al. (66,67). Chou and Ayres (68) evaluated the drug release from polymeric matrices according to their viscosity. Recently, Vázquez et al. (69) demonstrated that the decreasing of the matrix viscosity makes the drug diffusion easier.

Some studies were done to evaluate the reaction between polymer viscosity and drug release from a matricial system (70). The penetration rate of water in hydrophilic matrices is determined by the equilibrium between promotive forces of admission of water and those that act against its admission—viscosity forces. Insofar as the movement of hydrosoluble drug through gelatinous layer is controlled by diffusion, it must obey the equation to Einstein-Stokes; and the process is slower in more viscous mediums. As long as the matrix swells, the relative polymer concentration decreases with hydration and dilution. This allows the decreasing of viscosity and concomitantly a decreasing of the forces that act against the admission of liquid into the matrix.

Wan et al. (18) developed studies that demonstrate that when the molecular weight increases, the liquid retention rate decreases and an obturation of pores can occur, which is explained by the increasing of viscosity.

Works applying the differential scanning calorimetry (DSC) allowed conclusion that HPMC hydration is affected by temperature. With the increase of gel temperature, the HPMC loses hydration water, followed by decrease in relative viscosity. With the successive decrease of hydration water, polymer–polymer interactions occur, primarily as a result of methoxyl substitutes (hydrophobic), causing a large increase in relative viscosity. This is the gelification point (2,71).

Drug Solubility

Several parameters have been evaluated in in vitro soluble drug release, namely, drug size particles and their granules before compression and drug concentration, which showed that they constituted determining parameters (72). These studies were conducted with attention paid to Higuchi's equations (35).

Some studies demonstrate that the compression of HPMC particles from controlled-release matrix tablets can lead to biodisponsibility differences. This phenomenon is particularly noted with slightly soluble drugs, as a result of internal tension that occurs during the hydration and swelling of matrix (62,73).

Release studies, applying a flow-through cell and observing the evolution of matrice dissolution, lead to the conclusion that release kitectics of hydrosoluble drugs is mainly regulated by the swelling process—diffusion. In the case of HPMC with high viscosity, the drug is largely released and the polymeric matrix stays more or less intact (30,74).

The characteristics of used drugs can also affect the drugs' release. The soluble drugs released in water (propranol hydrochloride) is mainly controlled by drug diffusion through the gel; the insoluble drugs are released in water by gel erosion (16).

Polymer/Drug Proportion

Studies completed by Salomon et al. (66) demonstrate that the release rate increases for lower amounts of HPMC. In turn, Shah et al. (75) advocated the application of the mechanism proposed by Korsmeyer et al. (39) to optimize the drug release profiles, previously selecting the concentration of HPMC.

The proportion of polymer is generally used as a control variable in drug rate delivery. In the case of water soluble drugs, this proportion is calculated from Higuchi's equation (35). With slightly soluble drugs, that proportion is dependent on gel consistency, since it is affected by gel proportion (2,76,77).

Polymer/Drug Interaction

Studies applying differential scanning calorimetry (DSC) and dissolution tests showed that diclofenac sodium substantially reduces the thermal gelation of HPMC, and that the matrices cannot actuate (78,79); it has been used as a polyvinilic alcohol (80,81).

The evolution of water concentration profile was calculated from HPMC matrices with different molecular weights. The swelling of a matrix is divided into three stages: gel layer, swelling gelatinous layer, and dry core. The thermal analyte of cellulose ether polymers demonstrated that the drug–polymer interaction occurs at hydrated gel layer around the matrix tablet and is partially responsible for the drug release modulation (82).

Ford et al. (22,83) developed studies using water-soluble drugs (e.g., promethazine hydrochloride) to evaluate the temperature effects on drug release from matrices with several degrees of viscosity and HPMC K

15M. They concluded that drug release decreases with the increase of HPMC content, and the increase of temperature leads to an increase of the release rate. The equations applied are derived from Higuchi (32) and from Franson and Peppas (40).

Propranolol hydrochloride and tetracycline hydrochloride demonstrate an important role in the HPMC matrix swelling. The mechanism for this phenomenon must be the salt formation with the polymer and the modification of HPMC gel characteristics (58,59).

On the other side, the variation of drug concentration, at a constant amount of HPMC matrix, leads to the conclusion that as long as the drug concentration decreases, so does the matrix capacity to attain the controlled-release drug (84).

Polymer/Additive Interactions

The obtainment of technologically acceptable formulations requires, in addition to the drug and the gelling agent, the presence of other excipients, in particular, diluents and lubricants whose presence can markedly affect release (2).

The role accomplished by the incorporation of additives has been studied. It is important to note that the presence of tensioactive agents in HPMC matrices leads to the decrease of drug release with the influence of pH medium (because the alteration of ionic state of drug or tensioactive agent can change this behavior).

The mechanism for the decreasing of drug release is the ionic interaction between drug and tensioactive agent. It leads to the formation of a complex with low solubility, as is verified by the HPMC matrix erosion mechanism (85).

Ford et al. (46) evaluated the incorporation of additives on drug release rate. Studies by the same authors (87) noted the influence of anionic tensioactive agents on the release of propranolol hydrochloride from HPCM matrices, and concluded that the drug release occurred more slowly.

Abrahamsson et al. (88) demonstrated that the choice of solubilizer must be carefully evaluated because of the possibility of interactions between the solubilizer and the release rate controlling excipients of the dosage form.

Another work was performed by Lapidus and Lordi (36), applying diluents (soluble or insoluble) to verify that their addition in large amounts, lead to a different drug release rate. Panomsuk et al. (77) evaluated the lactose influence and concluded that this additive does not affect the swelling mechanism, but generally interferes with the drug, which was confirmed by Gao et al. (89).

The additives that modify the pH matrix have been used to regulate the drug release rate (90). Recently, Mandal (91) evaluated the influence of binder agents on indomethacin release rate from HPMC matrices and verified that these additives change the degree of swelling and the ease with which HPMC constitutes the gelatinous layer, increasing the drug release when the amount of water is increased (derived from drug granulation).

This review article can conclude that ether cellulose polymers (especially HPMC), on account of its specific characteristics, have been used largely in hydrophilic matrices for oral controlled-release systems that can be developed for tablet or capsule dosage forms.

The interactions occurring within a hydrophilic matrix can be quite complicated as demonstrated by several described studies. However, each mechanism can be explained and anticipated in the formulation of the matrix through an understanding of polymeric properties.

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