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Research Article

Mechanistic Evaluation of the Effect of Sintering on Compritol® 888 ATO Matrices

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Abstract. The present research studied the effect of sintering technique in the development of a controlled release formulation for ketorolac tromethamine. The method consisted of mixing drug and wax powder (Compritol® 888 ATO) along with lactose as diluent and talc as lubricant followed by direct compression at room temperature. The compressed fluffy matrices were kept at 80°C for 1, 2, and 3 h for sintering. The sintered tablets were characterized by their physical parameters and *in vitro* dissolution profile. The sintering time markedly affected the drug release properties of Compritol® 888 ATO matrices. It is notable that the release rate of ketorolac tromethamine from matrices was inversely related to the time of sintering. This may be due to the increase in the extent and firmness of sintering which further compacts the mass so that drug release is affected. Contact angle measurement and scanning electron microscopy analysis indicated that heat treatment caused the wax to melt and redistribute. This redistributed wax formed a network-like structure in which the drug along with lactose is entrapped. This particular formed matrix is responsible for retarding the drug release. Fourier transform infrared spectroscopy results did not show any drug–wax interaction due to sintering. Differential scanning calorimetric and powder X-ray diffraction studies ruled out the occurrence of solid solution and polymorphic changes of the drug. Drug release from the wax tablets with or without sintering was best described by the Higuchi equation.

KEY WORDS: controlled release; scanning electron microscopy (SEM); sintering; wax.

INTRODUCTION

Controlled release drug delivery is one of the widely used technologies in dosage form design, and intensive research has been undertaken in achieving better drug product effectiveness reliability and safety. Wax has been used as matrix in pharmaceutical controlled release dosage forms since decades (1). Waxes provide several advantages that include good stability at varying pH and moisture levels and effective retardation of highly water-soluble drug from the matrix (2).

Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder or in a compact by application of heat (3). This concept in pharmaceutical science is relatively recent, but research interests relating to this process have been growing. According to studies carried out, controlled release polymeric systems of rifampacin were prepared by mixing the drug and ethylene vinyl acetate copolymer, which were then compressed at room temperature. These matrices were exposed at 60°, 70°, and 80° for 1.5, 3, and 4.5 h for sintering. The sintering time markedly affected the drug release properties of the ethylene vinyl acetate copolymer matrices. The percent release decreased as the sintering temperature was increased for all formulation (4,5). The release followed a diffusive mechanism with first-order release kinetics. A similar effect was seen when rifampicin was replaced with theophylline (6) and when ethylene vinyl acetate copolymer was replaced with EudragitRL100 matrices (7). In another approach, thermal treatment of tablets containing Eudragit RS or RL in their structure above the glass transition temperature of the respective polymer was found to decrease drug release (8).

Ketorolac tromethamine is a non-steroidal anti-inflammatory drug usually given in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. The dose of conventional tablet is 10 mg three times a day. Due to high water solubility and short plasma half-life, development of oral controlled release formulation of this drug is highly desirable (9,10).

Compritol 888 ATO composed of glyceryl behnate (an atomized mixture of mono-, di-, and tribehenate of glycerol) has been used as retard material for sustained release dosage forms. It has low fusion point and hydrophilic–lipophilic balance value of 2. This glyceride mixture is known to exhibit a complex polymorphism depending on many parameters such as crystallization rate or temperature of storage (11). The crystalline lattice of Compritol 888 ATO is composed of very small amounts of the unstable alpha polymorphic form characteristic of triacylglycerols, which disappear after thermal stress (12).

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The current study aimed to investigate the effect of sintering on the release of ketorolac tromethamine from Compritol 888 ATO matrices and also investigate the changes in the properties of the drug and/or wax during the sintering process.

MATERIALS AND METHODS

Gift sample of ketorolac tromethamine USP was provided by Ranbaxy Lab Ltd, Goa. India. Compritol® was provided by Gattefosse, France while lactose and talc by Loba Chemie Ltd. Mumbai. All chemicals were used as received.

Preparation of Compritol® 888 ATO Matrix Tablets

A formulation containing ketorolac tromethamine and Compritol® 888 ATO in a ratio of 1:1 was prepared as per Table I. The components of each formulation were mixed together by geometric mixing for a period of 10 min. Tablets of 150-mg weight were directly compressed using 6-mm diameter punches on a rotary tablet compression machine (Mini Press-II MT, Rimek). The prepared tablets were assayed by UV spectrophotometric method at 322 nm.

Sintering of Matrix Tablets

The prepared tablets were then subjected to thermal treatment by placing on aluminum foil and subjecting to sintering (3,8,13) at 80°C for 1, 2, and 3 h in hot air oven (Labhosp, Mumbai).

In Vitro Release Studies

Drug release was evaluated by conventional *in vitro* dissolution testing. The dissolution test for wax matrix tablet was performed in triplicate using dissolution test apparatus II (DA 6D Veego) at 100 rpm in 900 ml distilled water at 37°C. Aliquots of 5 ml were periodically withdrawn and the sample volume replaced with an equal volume of fresh dissolution medium. The samples were filtered through Whatman filter paper and 1 ml of sample was made up to 10 ml with distilled water and solutions analyzed at 322 nm by UV spectrophotometer (JASCO, V-530, Japan). Cumulative percentage drug release was calculated using PCP Disso v2.08 Software (Poona College of Pharmacy, Pune).

Scanning Electron Microscopy

Scanning electron microscopy (SEM) photomicrographs were taken by scanning electron microscope (JSM-6360) for studying surface morphology of sintered matrix tablet before and after sintering. Each sample was mounted to an aluminum stub using double-sided adhesive tape and then coated with gold palladium alloy using JEOL/EO fine coat sputter. The surfaces of the tablet were coated with platinum under an argon atmosphere. The samples were then examined with ×200 and ×1,000 magnification using a scanning electron microscope (JEOL JSM-6360A).

Table I. Formulation Composition of Wax Matrix Tablet (150 mg)

Sr. no.	Ingredients	Quantity
1	Ketorolac tromethamine USP	40 mg
2	Compritol ATO888	40 mg
3	Lactose	q.s.
4	Talc	7.5 mg

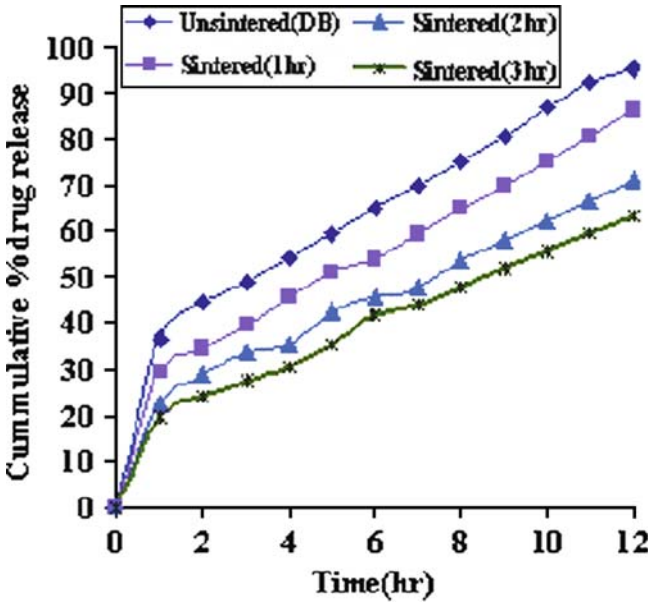

Fig. 1. Effect of sintering on the release of ketorolac tromethamine from Compritol® 888 ATO matrices

Wettability (13)

The contact angle between purified water and tablet surfaces was determined by placing 10 µl of water on the surface of the tablet using micropipette. Photographs of the drop in contact with water were taken. Amaranth red was added to the water to ensure proper visibility of the drop.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared spectroscopy (FTIR) spectra (ranging 400–4,000 cm^{-1}) of ketorolac tromethamine, Compritol® 888 ATO, and a physical mixture of ketorolac tromethamine and Compritol® 888 ATO before and after heat treatment were investigated using (460plus, Jasco) using the KBr disk method.

DSC Studies

The differential scanning calorimetric (DSC) thermograms of ketorolac tromethamine, Compritol® 888 ATO, and a physical mixture of ketorolac tromethamine and Compritol® 888 ATO before and after heat treatment were recorded using differential scanning calorimeter (DSC 823 Mettler Toledo, Japan). Approximately 2 to 5 mg of each sample was heated in a closed pierced aluminum pan from 30° to 300° at a

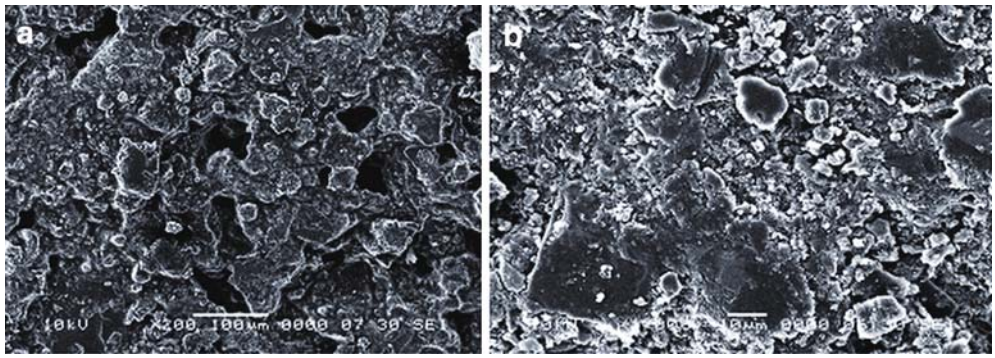

Fig. 2. Scanning electron microscope images of **a** unsintered and **b** sintered tablet surfaces

heating rate of 10°C/min under a stream of nitrogen at a flow rate of 50 ml/min.

PXRD Analysis

Powder X-ray diffraction (PXRD) patterns of ketorolac tromethamine, Compritol® 888 ATO, and a physical mixture of ketorolac tromethamine and Compritol® 888 ATO before and after heat treatment were investigated using powder X-ray diffractometer (PW 1729 X-ray Generator, Philips, The Netherlands). The X-rays were Ni-filtered CuKα1 radiation with 40 kV and 30 mA over 0–100°/2θ.

Stability Studies

To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines. Prepared formulations were kept in humidity chamber (Remi Instrument Ltd., Mumbai) maintained at 40°C and 75% relative humidity (RH) for 3 months. The sample was analyzed for the physical changes and percent drug content at interval of 7, 15, 30, 60, and 90 days.

RESULTS

Preparation of Compritol® 888 ATO Matrix Tablets

One hundred tablets of 150 mg each were directly compressed using 6-mm diameter punches on a rotary tablet compression machine (Mini Press-II MT, Rimek). Hardness of tablets was kept to 5–6 kg/cm^2. The assay of the tablets was within the official limits and was in the range of 97–99%.

In Vitro Release Studies

The drug release profiles of formulations were studied. The drug release profiles of ketorolac tromethamine from Compritol® 888 ATO matrices are shown in Fig. 1. Unsintered tablets showed higher drug release compared to tablets subjected to sintering at 80°C. Among the tablets subjected to sintering, desired drug retardation was when tablets were sintered for 3 h. Drug release from all tablets shows Higuchi diffusion-controlled matrix release. It was also noted that as the duration of sintering increased, the retardation of drug release was increased (Fig. 1).

Scanning Electron Microscopy

Figure 2 shows the micrographs of surface of the tablet before and after sintering for period of 3 h at 80°C.

Wettability

The effect of sintering on the wettability of the tablet surfaces was established by taking the photographs of the tablet surfaces on which the drop of purified water containing amaranth red was placed. The contact angle of sintered tablet was greater than that of unsintered tablet, as shown in Fig. 3. This clearly indicates that sintering decreases the wettability of tablet surfaces.

Fourier Transform Infrared Spectroscopy

To investigate the interaction during sintering, the FTIR spectra of ketorolac tromethamine, Compritol® 888 ATO, and a physical mixture of ketorolac tromethamine and compritol® 888 ATO before and after sintering were recorded (Fig. 4). In the spectrum of ketorolac tromethamine, major peaks 3,350 cm^{-1} [NH stretch]; 1, 725 cm^{-1}[C = O stretch(acid)]1, 167 cm^{-1} [C = *O* stretch(diaryl ketone)]; and 3,450 cm^{-1} [OH (acid)] were seen in subsequent spectra.

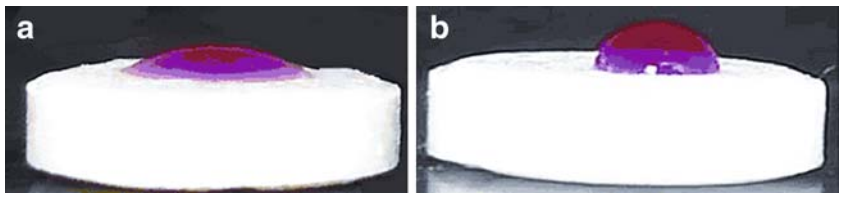

Fig. 3. Photoimages showing contact angle of water with **a** unsintered tablet and **b** sintered tablets

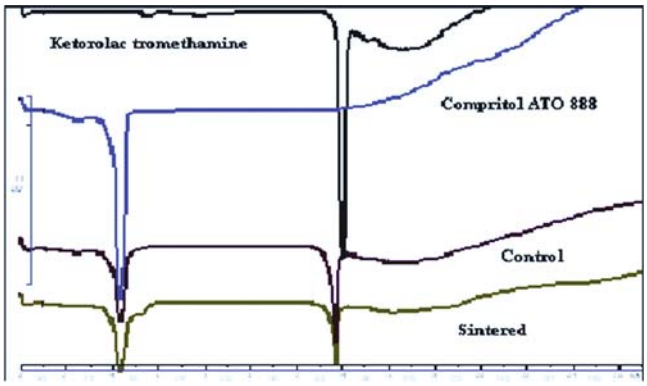

Fig. 4. DSC thermograms of ketorolac tromethamine, Compritol® 888 ATO, unsintered (control), and sintered tablets

DSC Studies

DSC spectra of ketorolac tromethamine, Compritol® 888 ATO, and a physical mixture of ketorolac tromethamine and Compritol® 888 ATO before and after sintering are shown in Fig. 5.

PXRD Analysis

X-ray diffractograms of ketorolac tromethamine, Compritol® 888 ATO, and a physical mixture of ketorolac tromethamine and Compritol® 888 ATO before and after sintering were recorded (Fig. 6). The figure shows two peaks in its diffraction pattern at 2θ=21.33, 23.45. The X-ray diffraction peaks for the ketorolac tromethamine pure

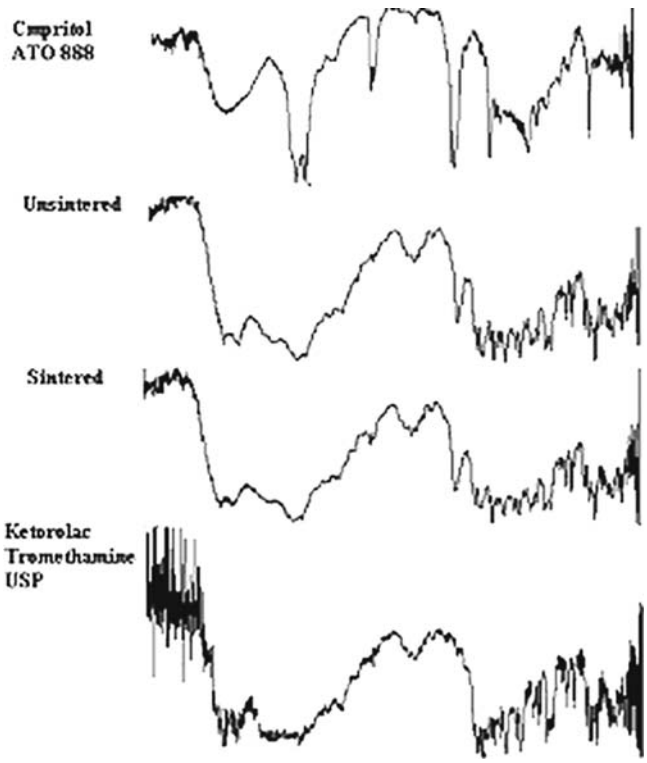

Fig. 5. FTIR of ketorolac tromethamine, Compritol® 888 ATO, unsintered (control), and sintered tablets

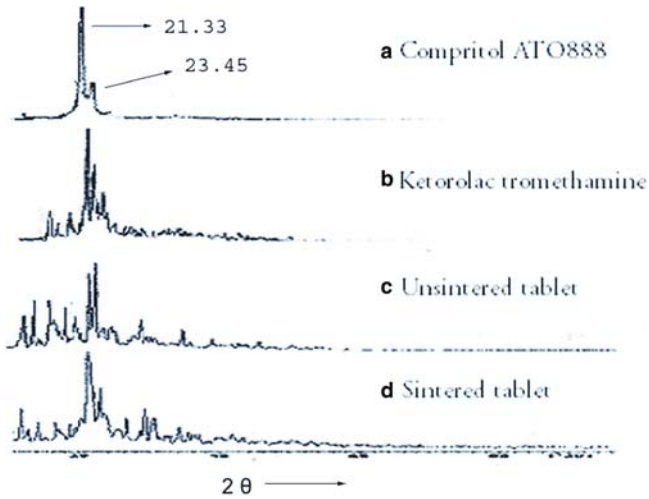

Fig. 6. X-ray diffraction spectra of ketorolac tromethamine, Compritol® 888 ATO, unsintered (control), and sintered tablets

powder occurs at 2θ=12.62, 13.99, 16.43, 17.04, 18.41, 20.10, 22.07, 22.89, and 29.39, which shows that ketorolac tromethamine exists in crystalline form.

Stability Studies

The stability studies of prepared formulations revealed no significant changes in the physical parameters when stored at temperature and humidity conditions of 40±2°C/75±5% RH. Samples were withdrawn and retested for drug content after intervals of 7, 15, 30, 60, and 90 days. Percent drug content was found in all the prepared formulations ranging from 95.21±0.41 to 97.61±0.37, indicating that no significant reduction in the content of the active drug was observed over a period of 3 months; the percent drug contained is found within a specified limit of USP. Therefore, there was no evidence of degradation of drug quantity.

DISCUSSION

In this work, we studied the mechanism of the effect of sintering on the release of ketorolac tromethamine as a model drug. SEM, PXD, FTIR, and DSC were used to demonstrate the suggested mechanism. Unsintered tablets showed higher drug release in 12 h, whereas with sintering at 80°C for 1, 2, and 3 h, percent drug release was found to decrease, which indicated that increasing the sintering time decreased the drug release rate from the matrices. Table II shows the values of coefficients and release rate constants for the unsintered and sintered (3 h) tablets. The *R* values indicate that Higuchi matrix model is the best-fit model for both sintered and unsintered tablets. This is further substantiated by Higuchi square root law (Fig. 7). As seen in Fig. 2, the surface of the tablet is smoother after heat treatment. SEM micrographs of the surface of the tablets after sintering show that a thin film-like structure covers the entire surface, indicating that heat treatment causes the wax to melt, redistribute, and coat drug and excipient particles, thus creating new surfaces with lower wettability and which is responsible for the retardation of drug release from matrix

Table II. Coefficients and Release Rate Constants for Different Models

Sr. no.	Formulation	Model	*R*	*k*
1	Unsintered	Zero Order	0.8850	−0.0472
		First Order	0.8985	27.5878
		Korsemeyer Peppas	0.9985	−0.2035
		Hixon Crowell	0.9662	8.4338
		Higuchi Matrix	0.9935	25.7140
2	Sintered (1 h)	Zero Order	0.8718	7.0792
		First Order	0.9800	−0.1114
		Korsemeyer Peppas	0.9958	19.9201
		Hixon Crowell	0.9561	−0.0316
		Higuchi matrix	0.9983	20.8353
3	Sintered (2 h)	Zero order	0.8332	7.1753
		First order	0.9104	−0.1811
		Korsemeyer Peppas	0.9958	26.8916
		Hixon Crowell	0.9733	−0.0412
		Higuchi matrix	0.9979	24.3104
4	Sintered (3 h)	Zero order	0.8845	4.0471
		First order	0.9902	−0.0718
		Korsemeyer Peppas	0.9969	16.3213
		Hixon Crowell	0.9802	−0.0194
		Higuchi matrix	0.9976	14.9491

tablets. The duration of sintering also affected the porosity, with tablets sintered for 1 h showing higher porosity as compared to those sintered for 3 h.

Contact angle is indicative of the wettability of the tablet surface. It is an important physical property that will have a far-reaching impact on the release of the drug especially from a hydrophobic wax matrix. This indicates a decrease in the wettability of the sintered tablet. The surface of the tablets made from direct compression consists of a heterogeneous mixture of the ingredients of the tablet. After sintering, the hydrophobic wax is more uniformly dispersed through the compact, and this leads to a decrease in the wettability of the tablet surface. This is evidenced by the higher contact angle and further contributes to the retardation of drug release from matrix tablet. When the tablets are exposed to temperatures over the melting point of the incorporated wax, the wax present in liquid state will move through the matrix of the tablet and get filled between the pores of the matrix without affecting the overall shape of the tablet. This coating of the drug particles is generally referred to as *in situ* micro-coating (14).

During the heat treatment, there are possibilities of interaction between wax and drug which could have an impact on the retardation of drug release.

Comparison of the spectra of physical mixtures and heat-treated samples of ketorolac tromethamine with Compritol® 888 ATO showed no difference in the position of the absorption bands. The spectra can be simply regarded as the superposition of those of ketorolac tromethamine and Compritol® 888 ATO. This observation ruled out the possibility of chemical interaction and complex formation between these two components by sintering.

DSC was used to examine the thermal behavior of pure drug and formulation. The thermogram of ketorolac tromethamine shows a very sharp endothermic peak at 171°C and Compritol 888 ATO shows sharp endothermic at approximately 72°C. Comparison of the spectra of physical mixture (control) and sintered sample shows that no change has occurred after sintering of sample. Therefore, there is no evidence of drug interaction or complexation during manufacturing process and on sintering. Often, DSC is used to investigate the polymorphic behavior of the compounds, but X-ray diffraction is a much more suitable technique for the identification of the polymorphs because of their distinctive diffraction pattern (12).

Polymorphic structure of a drug is an important parameter which influences the dissolution rate and bioavailability of drug (15). To evaluate the effect of sintering, X-ray diffractograms were taken. Compritol® 888 ATO shows two peaks that are due to lipidic polymorphism. This further reveals that these two peaks are due to the lateral packing of fatty acid chains specifically designated as sub-α, α, β`, and β, each of them corresponding to a particular lateral organiza-

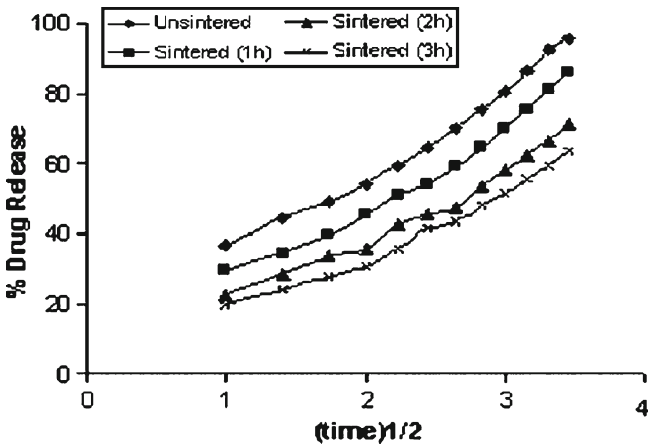

Fig. 7. Higuchi square root plot

tion of hydrocarbon chains (14). The diffraction peaks for ketorolac tromethamine were located in the same position for both physical mixture (control) and sintered sample. These results further indicate the absence of any crystalline change during the heat treatment.

CONCLUSION

Sintering is defined as bonding of adjacent particle surfaces in a mass of compact by the application of heat. Our study showed that drug release prolongation after sintering can be attributed to the melting and redistribution of the wax in the tablet matrix structure. Drug release from all tablets shows Higuchi diffusion-controlled matrix release. Sintering of the tablets results in melting and redistribution of the wax throughout the matrix and a possible change in the nature of the pores within the matrix. FTIR results did not show any drug–wax interaction due to heat treatment. DSC and PXD studies ruled out the occurrence of solid solution and polymorphic change of the drug.

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