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Original Article

OPTIMIZATION MUCOADHESIVE BUCCAL FILM DOSAGE FORM OF SODIUM VALPROAT USING A SIMPLEX LATTICE DESIGN APPROACH

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Abstract

Sodium valproate is a first choice as anti-convulsants for partial epilepsy, bipolar disorders (psychotic disorders) and migraine therapy. Many dosage forms designed for modified release of Sodium valproic in tablets have disadvantages including frequent use and increased toxicity. So it is necessary to design other dosage forms that are comfortable for the patient and still maintain the therapeutic dose. The buccal mucoadhesive film was chosen to overcome these problems. In the preparation of buccal mucoadhesive films, this study used variations of chitosan and sodium carboxymethylcellulose (SCMC) as carrier films by solvent casting technique using the simplex lattice design approach. Several parameters characteristic of the quality of the dosage form of the film such as weight, film thickness, surface pH, swelling index, measurement of fold resistance, mucoadhesive residence time, uniformity of drug content and percentage of drug release were selected as dependent variables. From these results it is known that the thickness, swelling index and the mucoadhesive residence time are influenced significantly by the selected polymers. The simplex lattice design analysis by the software design expert 10.0 showed that the desirability of optimum parameters of film contained at chitosan and SCMC in a ratio of 0.64:0.36 as the recommendation. The dissolution test was performed to determine the recommended release profile of the buccal mucoadhesive film. The Kinet DS 3.0 software obtained a fitting model for release profile as follows Michaelis-Menten kinetics.

Keywords: Mucoadhesive Buccal Film, Sodium valproat, SCMC, Simplex lattice design

Introduction

Buccal drug delivery systems have advantages such as excellent accessibility, presence of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms, direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability, Low enzymatic activity, Suitability for drugs or excipients that mildly and reversibly damages or irritates the mucosa, Painless administration, Easy drug withdrawal, Facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation, Versatility in designing as multidirectional or unidirectional release systems for local or systemic actions [1] [2]

The ideal drug candidates in the buccal drug delivery system include drugs that are easily absorbed only by passive diffusion, odorless and have a molecular weight between 200-500 daltons, have natural lipophilic and hydrophilic properties, are tasteless and have a stable pH, which is very good for delivery systems. buccal medicine. Banarjee, et. al (2015) conducted a review of drugs with high potential as potential drug candidates in the development of fast dissolving film preparations. Included in the review is vaproic acid which is used as an anti-epileptic drug.

Valproic acid and its pharmaceutically acceptable salts are useful for treating various forms of epilepsy as well as certain other disorders. Valproic acid is considered a first line therapy for treating petit mal, monoclonic seizures, generalized and partial motor seizures, absence and infantile spasms. Recently, Valproic acid was also approved for the treatment of partial epilepsy, bipolar disorders (psychotic disorders) and migraine.

Pharmacokinetically Valproic acid can bind very high protein at 87 - 95%, low clearance at 6-20 ml/h/kg (Leppik and Birnbaum, 2010). Valproic acid is classified into a class 2 Biopharmaceutic Classification System (BCS) drug, which includes drugs that have low solubility and high permeability. Various attempts have been made to overcome the problem of solubility by converting it to the form of Salt, which is solid. The sodium salt of valproic acid is hygroscopic. This hygroscopicity is a problem in the production of compressed tablet formulations.

Sodium valproate has been developed in oral, intra parenteral, rectal dosage forms[6], transdermal patch[7]. Even for the purpose of repeated use, delayed-release tablets have also been developed. Drugs with doses not exceeding 125 mg – 325 mg are more suitable in the form of extended-release products because they can provide several advantages, including

limiting the size of the delivery system dosage, reducing the frequency of dosing (twice a day), avoiding first-pass metabolism, increasing patient compliance and maintaining therapeutic effect with a single daily dose.

The buccal route of drug delivery may be useful in the treatment of chronic disease such as epilepsy. Buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form the buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally. However, buccal preparations should be made in a thin and small film size for easy application. This preparation is formulated in the form of a matrix that has mucoadhesive ability in order to maintain long contact with the buccal area and release the active ingredients. This matrix acts by swelling or dissolving, undergoing surface erosion with little or no mass erosion. Then the surface area of the matrix decreases with time, with concomitant drug release. The mechanism of drug release across the membrane involves the diffusion of water through the membrane into the interior of the nucleus, dissolution of the drug and then diffusion of the drug into the surrounding fluid. [8]

Ideally, the pharmaceutical oral adhesive delivery system should contain mucosal adhesives, penetration promoters, and enzyme inhibitors. Mucosal adhesives are used to maintain close and long-term contact between the formulation and the absorption site, and permeation enhancers are mediated by the mucosa (transmucosal delivery) or drug penetration into the deepest layers of the epithelium (mucosal delivery). Enzyme inhibitors ideally protect the drug from degradation by mucosal enzymes. The barrier properties of the buccal mucosa are a major limitation in the development of oral adhesive delivery systems. So that in the manufacture of buccal mucoadhesive films, it is necessary to pay attention to critical factors, one of which is the choice of polymer. This preparation uses a combination of chitosan polymer and sodium carboxymethylcellulose. Chitosan was chosen because it has very high swelling ability and very slow erosion ability as a film. One of the limitations of the use of chitosan is that its mucoadhesive properties are reduced when applied to a neutral pH or more than 6.5. This is due to the reduced ionic interaction between the positively charged amino groups of chitosan and the negative charge of the mucosal layer. Therefore, to overcome the shortage of chitosan polymer, it is necessary to add another polymer to the preparation which in this case is Sodium Carboxymethylcellulose (SCMC). SCMC can act as an additive that functions to protect the adhesion of the product to body tissues from damage, besides that it is also used to localize and modify the release kinetics of the active ingredient (Rowe et al., 2009). SCMC has a COO- group in an acidic environment, so that the bond that will occur between SCMC and mucosal components is hydrogen bonding (El-Kamel, 2002).

Based on the research of Irawan and Farhana (2011) using a combination of chitosan and SCMC in the manufacture of the theophylline tablet mucoadhesive system, the optimum formula was obtained which resulted in optimum theophylline release kinetics at chitosan 8.38 – 10.91% and SCMC 28.84 – 29.09%.

2. Material and Methods

2.1 Material

The tools used in this study were Double Beam UV/Vis Spectrophotometer (Simadzu 1280), Analytical Scale (OHAUS Pioneer) with a sensitivity of 0.0001 g, Micro Pipette (SOCOREX) 50 – 1000 L, centrifuge (Effendorf Minispin), glass tools such as measuring flasks, beakers, measuring cups and test tubes as well as other laboratory support equipment.

The material used for this experiment is Sodium valproate obtained from PT. Otto Pharmaceutical Lab, Depacote ® Extended Release (AbbVie Ltd, Imported and packed by PT. Abbott Indonesia), Chitosan from Sigma Aldrich, Carboxymethyl cellulose-Na (Bratachem), Propylene glycol (Bratachem), Pharmacoat 606 (Bratachem), Acetic acid (Bratachem)

2.2. Optimization of buccal film mucoadhesive sodium valproat

The optimization was performed on the Chitosan and SCMC bases by using SLD design. The concentration of Chitosan and SCMC were chosen as independent variables in 8 runs.

2.4 Manufacture of *mucoadhesive Bukal film*

Buccal mucoadhesive film sodium valproic of Chitosan/SCMC and their combinations were prepared by solvent-casting method. SCMC was left overnight in water solvent at room temperature to produce a clear and bubble-free solution. Chitosan was dissolved using 1% acetic acid and stirred using a magnetic stirrer at 500 rpm for 2 hours until all the mass was dissolved. Sodium valproate powder was dissolved in propylene glycol and citric acid, respectively. The mixture was homogenized with a varimixer. The solution is poured into molds and allowed to dry at room temperature and a flexible film is formed. Pharmacoat 606 was dissolved in 95% ethanol and poured into a mold as a backing membrane.

2.3 Formulation of mucoadhesive buccal film sodium valproate

The formula design was made using the proportion ratio of chitosan and SCMC concentrations using design expert 10.0 with the simplex lattice design method, the composition was obtained as follows:

Table 1. Design optimization result of mukoadhesif buccal Film Sodium Valproat

Material	Formula of buccal film muchoadhesif (mg)							
	F1	F2	F3	F4	F5	F6	F7	F8
Sodium Valproat	250	250	250	250	250	250	250	250
Chitosan	0	11,25	33,75	45	22,5	0	45	22,5
SCMC	45	33,75	11,25	0	22,5	45	0	22,5
Propilenglikol	60	60	60	60	60	60	60	60
Pharmacoat 606	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Citric Acid	3	3	3	3	3	3	3	3
Total	300	300	300	300	300	300	300	300
Note F1-F8 = Formula 1 – Formula 8								

2.3 Evaluation of sodium valproat film buccal mukoadhesif

1) **Weight**

The uniformity test of the preparation was determined by the method of weight uniformity and content uniformity. Weight uniformity is determined based on the number of weight deviations from the average of all tested weights. Weight uniformity test was carried out by weighing 20 films from each formula randomly using an analytical balance. Then calculated the average and standard deviation of each formula.

$$CV = \frac{SD}{X} X\ 100\ \%$$

2) ***Thickness*** **of Film**

The uniformity of the film size affects the ease of use of the film. The uniformity of the film size should range from 0.5-1 mm while the diameter ranges from 1-2 cm

3) **Surface *pH***

The pH test of the film surface was carried out to determine the pH of the resulting film. The resulting film must have a neutral pH so that it is not irritating when used on the human mucosa. The surface pH test was carried out by first soaking the patch in a phosphate buffer solution of pH 6.8 for 2 hours at room temperature. The pH measurement is done by dipping the digital pH meter into the solution medium, then the pH is recorded.

4) ***Swelling index***

Patches were cut into 1×1 cm2 Percentage moisture absorption and weighed accurately and kept immersed in 50 ml phosphate buffer pH 6.8. Taken out and weighed at 10,20, 30 minutes intervals till a constant weight was obtained.

5) ***Measurement* of Folding Endurance**

Three patches of each formulation of size 2×2 cm2 Surface pH of the patches were cut using a sharp blade. Folding endurance was determined by repeatedly folding a small strip of patch at the same place till it broke. The number of time the patch could be folded at the same place without breaking gave the value of folding endurance. The mean value is calculated [9]

6) **Mucoadhesive residence time**

Mucoadhesion time test is a measurement of how long the resulting film can stick to the rabbit mucosa [1]. The film was moistened with phosphate buffer pH 6.8 and attached to the Buccal mucosa of the rabbit attached to the watch glass by applying pressure for 20 seconds. The watch glass was hung and immersed in 200 mL of phosphate buffer pH 6.8 (temperature 37±0.5°C) with a stirring speed of 50 rpm to stimulate the buccal cavity environment.[10]

7) **Drug Content Uniformity**

The content uniformity test was carried out by taking as many as 10 films at random and then cut into small pieces. Each film was dissolved in 100 mL of phosphate buffer pH 6.8 and sonicated for 15 minutes. 1 ml of the solution was taken from 100 ml of phosphate buffer pH 6.8 transferred to a 10 ml volumetric flask and added 2 ml of methanol and 0.8 ml of iodine solution. The solution was allowed to stand for 30 minutes, then chloroform was added until the volume was reached. The absorbance was measured using a Double Beam UV/Vis

Spectrophotometer (Simadzu 1280), at a wavelength of 361 nm and the absorbance values were recorded.

8) **Preparation of standard stock of sodium valproate and reagent solution**

Stock standard solutions of sodium valproate 800 g/mL, 200 g/mL and 50 g/mL, which were prepared separately in methanol were reacted with Iodine. Sodium valproate (5mM≈1.2 mg/mL) in chloroform and iodine (5 mg/mL).

9) **Calibration Graph**

Aliquots (200–1600 L) of standard stock solution of sodium valproate (50 g/mL) were transferred into a series of 10-mL volumetric tubes. The volume was adjusted to 2 mL with methanol and 0.8 mL and iodine solution was added. The solution was allowed to stand for 30 minutes, then refined with chloroform and the absorbance was measured at 361 nm with respect to the standard solvent. Absorbance values are plotted against concentrations to create a calibration graph.

10) Measurement of Dissolving Time

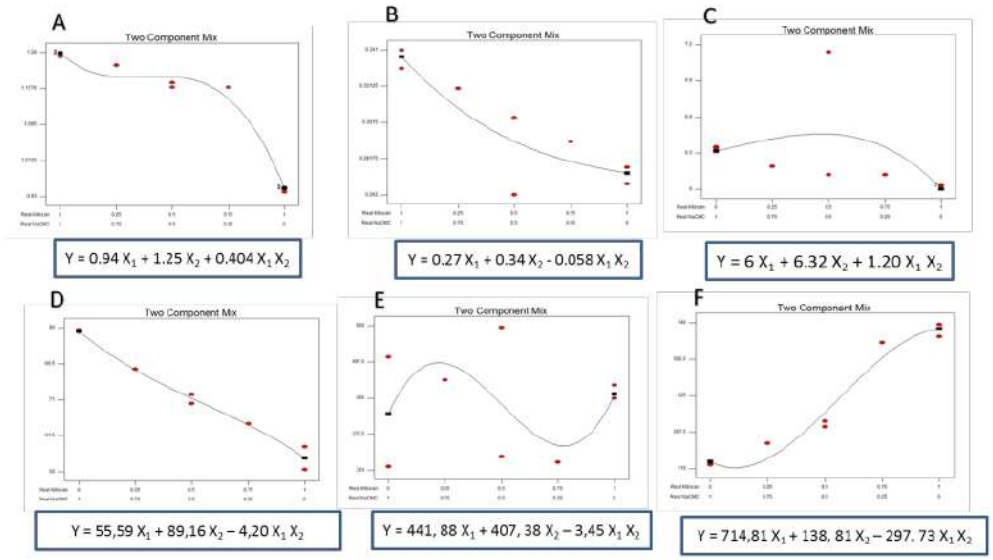
Type II dissolution test was used for in vitro test of buccal film release. The dissolution media used phosphate buffer (pH 6.8) 900 ml, temperature 37 ± 0.5 °C and speed of 50 rpm. Using a waterproofing adhesive, the film is attached to the padel. 5 ml samples were taken at intervals of 5, 10, 15, 30, 45, 60 minutes and at the same time the same amount of dissolution medium was added with phosphate buffer to maintain equilibrium conditions. The 5 ml sample was transferred to a 10 ml volumetric flask and added 2 ml of methanol and 0.8 ml of iodine solution. The solution was allowed to stand for 30 minutes, then chloroform was added until the volume was reached. The absorbance was measured with a Double Beam UV/Vis Spectrophotometer (Simadzu 1280) at a wavelength of 361 nm and values were recorded.[11]

3. Result and Discussion

Unsystematic description of the quality of the initial matrix without the active compound followed by important qualities related to the release of the active drug while discussing what the data mean and the correlations between the data

In this study, we used computer software designed and developed at the same time to understand the relationship between polymers (chitosan and SCMC) that are widely used as mucosal adhesive polymers. The results show that computer

software and design of experiments can reduce the number of experimental formulations and predict the optimal buccal sodium valproate formulation with a mucosal adhesive film with appropriate properties.



A : Thickness
B : Weight
C : pH Surface
D : Swelling Indeks
E : Folding endurance
F : Muchoadhesif Residence Time

Fig. 1 The contour plot of predicted pre-model formulations : (A) thickness, (B) weight, (C) pH Surface, (D) swelling indeks, (E) folding endurance and (F) mucoadhesive residence time.

In fig 1 shows the Thickness of film test results, weight and swelling index decreased linearly with the effect of decreasing SCMC concentration. The swelling index test results show that the swelling index value with SCMC concentration produces a larger swelling index value due to the stronger water absorption ability, the use of hydrophilic polymers will increase the ability of the wetted film and make it easier for water to penetrate into the film. The swelling index value decreased with increasing the concentration of chitosan.

The results of measuring the surface pH of the effect of chitosan and SCMC showed that the pH of the resulting preparation had met the criteria for the buccal pH range of 5.6-7. The surface pH of this film corresponds to the Buccal pH to prevent possible irritation.

The folding resistance results show that the value of all formulations is more than 300 times. From the results of this test, it can be seen that the resulting film meets the requirements, namely the preparation of the film is said to be good if it has a folding resistance value of greater than 300 times.

The results of the mucoadhesive test showed that the mucoadhesive value was influenced by the solubility of the polymer, the coefficient of hydrogen bonding capacity, the swelling index, the concentration of the polymer and the environment. The results showed that increasing the concentration of SCMC chitosan and decreasing the concentration of chitosan will increase the mucoadhesive power. This factor is influenced by the solubility of the chitosan polymer, which affects polymer corrosion when interacting with the environment. Oral membranes with low polymer concentrations will reduce the number of polymer chains per unit that will penetrate and cause an imbalance of interactions between polymer and mucus. Increasing the amount of polymer in the mucosa can prolong the duration and increase the resistance to mucosal adhesion.

Table 2 Results of Mucoadhesive Buccal Test for Sodium Valproate Film

Response	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8
Thickness (mm)	0,25 ± 0,01	0,23 ± 0,01	0,17 ± 0,01	0,16 ± 0,01	0,18 ± 0,01	0,26 ± 0,01	0,15 ± 0,01	0,19 ± 0,01
Weight(gm)	0,331 ± 0,16	0,32 ± 0,36	0,291 ± 0,59	0,268 ± 0,81	0,262 ± 1,03	0,341 ± 1,23	0,277 ± 1,46	0,304 ± 1,68
Content Uniformity	248,62	244, 51	233,05	244,7	225,12	247,95	229,61	233,24
Surface pH	6,35 ± 0,13	6,19 ± 0,09	6,12 ± 0,09	6,03 ± 0,08	7,14 ± 0,10	6,34 ± 0,08	6,03 ± 0,08	6,12 ± 0,09
Swelling Indeks	89,43 ± 2.39	79,10 ± 2.10	64,61 ± 2.42	58,56 ± 4.5	69,96 ± 3.21	88,83 ± 2.35	52,56 ± 1.72	72,30 ± 2.3
10	43	55	25	17	28	53	22	29
20	87	64	30	43	47	79	42	45
30	98	84	54	65	62	81	58	63
Folding Endurance	506	466	324	457	557	316	434	334
Mucoadhesive Residence Time (minute)	126	220	655	680	315	135	733	290

Figure 2. Mucoadhesive film buccal Sodium valproat

Table 3 Analysis Anova

No	Parameter	Mean ± SD	CV	P	remark
1.	Thickness	0,15 ± 0,024	2,08	0,0007	significant
2.	Weight	0,30 ± 0,018	6,12	0,0831	Not significant
3.	Surface pH	6,29 ± 0,41	6,59	0,7164	Not significant
4.	Swelling Indeks	71,92 ± 2,30	3,20	0,0005	significant
5	Folding Endurance	424 ± 107,07	25,24	0,8068	Not significant
6.	Mucoadhesive Residence time	394,25 ± 62,96	15,97	0,0023	significant

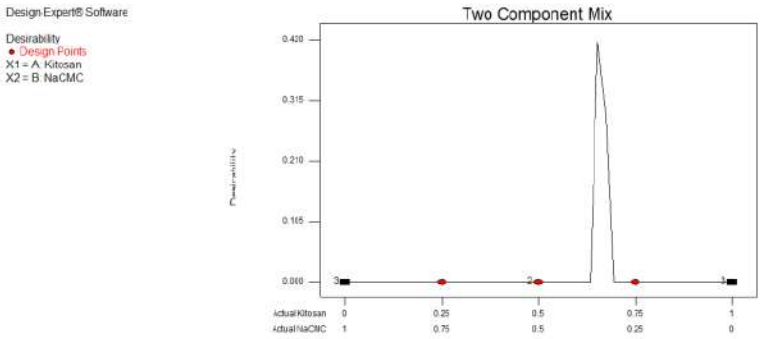


Figure 3. Grafik Nilai Desirability

The results of the analysis using software design expert 10.0 show that chitosan and SCMC polymers can increase mucoadhesive abilities which will support the preparation to last longer in the environment and be able to release drugs optimally. So that the optimum formula was determined based on the highest predictive mucoadhesive strength. Based on

Figure 3, the optimum formula was chosen with a concentration ratio of Chitosan : SCMC = 0.64 : 0.36.

Table 4. Data confirming the optimization formula for predictions with a ratio of Chitosan : SCMC = 0.64 : 0.36

Response	Prediction	Optimasi
Thickness	0.18	0.14
Weight	0.29	0.27
Surface pH	6.24	6.20
Swelling Index	67.26	65.35
Folding Endurance	424	388
Muchoadhesive Residence time	480	510

The results of the experimental preparations carried out by t test analysis showed that there was no significant difference between the predicted response and the response of the optimization formula with a Sig (2-tailed) Equal variances assumed value of 0.992.

Solubility Measurement

Solubility is defined as the process of dissolving a drug from a preparation in a certain medium. The dissolution test was performed to determine the release profile of the buccal mucoadhesive film of sodium valproate. The test was carried out at 370C and the dissolution medium was phosphate buffer pH 6.8. Determination of the standard curve for sodium valproate in isotonic phosphate buffer pH 6.8, the absorption was measured using a Simadzu 1280 Double Beam UV/Vis Spectrophotometer at a maximum absorption wavelength of 361 nm. The standard curve was obtained from the relationship between concentration and absorption. The experimental results in Figure 2 show the standard curve for sodium valproate following the linear regression line equation Y = 0.0407x + 0.126 with an r value of 0.995. This data was used to determine the concentration of sodium valproate.

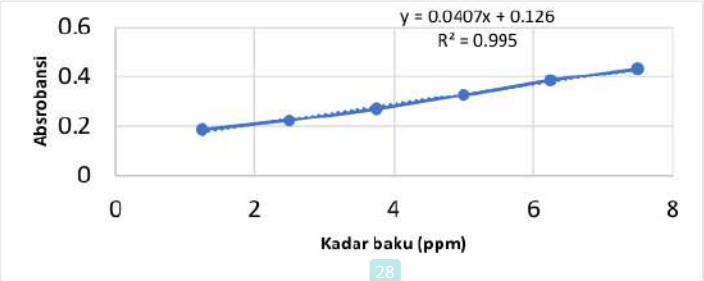


Figure 4. Standard curve of sodium valproate

The results of the drug release test using the Kinet DS3.0 software obtained a fitting model for release for the optimum buccal mucoadhesive film formula. This model can be influenced because the polymer used has the influence of hydrogen bonding factors, solubility and polymer erosion ability when interacting with environmental media.

Tabel 5. Model Fitting For Optimization Formulation

Mathematical model							
Order of reaction (zero)	Order of reaction (first)	Korsmeyer-Peppas	Weibull	Hickson-Crowell	Higuchi	Michaelis-Menten	Hill equation
0,0934	0,1326	0,4499	0,3739	0,1188	-0,4441	0,8114	0,2935

The optimization formula follows Michaelis-Menten kinetics. Cross-linking occurs between chitosan and SCMC. This binding mechanism is due to the nature of SCMC as it dissolves in water with chitosan to form hydrogels, closing matrix cavities and preventing drug release. Changes in water-insoluble properties release the drug onto the film in a stable release system. The hydrophilic polymer has the ability to expand into hydrogels in a liquid medium due to the crosslinked matrix, which makes them insoluble in water and absorbs only water.

4. Conclusion

1. Mucoadhesive film of sodium valproate appears to be an acceptable dosage form for the treatment of epilepsy. This film showed acceptable and desirable properties. Finally, it is clear that the application of design of experiments is a useful tool in the development of the desired film dosage form.

2. All formulas meet the requirements of the Indonesian Pharmacopoeia based on the physical assessment supported by the results of the factorial planning analysis.. The use of polymer and the concentration used can affect the release profile of the drug in vitro. The results showed that the optimal formula for mucoadhesive buccal film was the concentration ratio of Chitosan : SCMC = 0.64 : 0.36.

5. Patents

There is no patent resulting from the work reported in this manuscrip

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Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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