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DESIGN, DEVELOPMENT AND EVALUATION OF STOMACH SPECIFIC *IN SITU* GEL FOR ANTIBIOTICS: CEFDINIR

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ABSTRACT

The purpose of this research work was to design, development and evaluation of stomach specific in situ gel for cefdinir. Cefdinir stomach specific in situ gels were prepared by ionic gelation method by using different concentration of sodium alginate and matrix forming polymers and $CaCO_3$ was used as CO_2 as well as Ca^{++} generating agent for ionic gelation and floating. Primarily drug excipient interactions were carried out by using FTIR spectras showed that there was no interaction. All the formulated in situ gels were evaluated for there physical appearance, drug content, rheological, floating behaviors. Results of these parameters were within the pharmacopoeial limits. In vitro drug release studies revealed that the F7 & F16 formulations were best formulation among all, because release pattern was similar to theoretical one. Mechanism of drug release studies of optimized formulation showed zero order followed by non fickian type drug release. Finally, stability studies of optimized formulation showed the formulations were found to be stable.

KEY WORDS

GRDD, Cefdinir, in situ gel, control release, stomach specific.

INTRODUCTION

Oral drug delivery system is the most widely exploited rout of administration among all routes for systemic delivery of drugs via different pharmaceutical dosage form because traditional belief that by oral administration, drug is as well absorbed as the foodstuffs that are ingested daily. Oral controlled release dosage forms have been developed over past few decades due to their considerable therapeutic advantages. However, this approach is bedilled with several physiological difficulties such as inability to restrain and locate the CDDS within the desired region of the git due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time i.e. 2-3hr through the major absorption zone i.e. stomach and upper part of the intestine can results in incomplete drug release from the DDS leading to reduced efficacy of the administered dose. Therefore, control of placement of a drug delivery system in a specific region of the git offers advantages for a variety of important drugs characterized by narrow absorption window. Gastroretentive DDS possess the ability of retaining the dosage form in git particularly in the stomach for long periods of time to release the drug. These systems offer many advantages like improving their bioavailability, therapeutic efficacy, reduction of dose and reduction in fluctuation in therapeutics levels minimizing the risk of resistance especially in case of antibiotics **[1-5]**.

Several approaches are used for the formulation of gastroretentive systems such as bioadhesive,

floatation, sedimentation, expansion, swellable and modified shape systems. But many researches on all these systems are belonged to the solid dosage forms. These solid dosage forms suffer from the swallowing problems for geriatric, pediatrics and bedridden patient and choice of accidental burst release also more. To overcome these problems in recent years considerable attention has been focused on the development Gastroretentive liquid dosage forms (GRLDF) i.e. *in situ* gel formulations. The oral use of liquid pharmaceutical has generally been justified on the basis of ease of administration to those individuals who have difficulty swallowing solid dosage forms and better patient compliance **[6]**.

Stomach specific *in situ* gel forming systems are a rebellion in oral drug delivery. Stomach specific *in situ* gel is liquids at room temperature but undergo gelation when in contact acidic pH. Alginates show characteristic ion binding for multivalent cations and this forms the basis for their gelling properties. The alginate binding leads to the formation of covalent bonds leading to the perception of the insoluble hydrogel. crosslinking processes stiffen and roughen the polymer and reduce the swelling in solvents. This generally leads to a reduction in the permeability of different solutes hindering the release of embodied drugs in alginate matrices, allowing these systems to be used in controlling the drug release. The soluble sodium alginate was cross-linked with calcium chloride resulting in the formation of the insoluble calcium alginate **[7-10]**.

Cefdinir is third generation cephalosporin with broad spectrum antibiotic. Cefdinir has a narrow absorption window in upper part of GIT thus showing low oral bioavailability is 21% and short biological half life (1.7 hr). Cephalosporin drugs shows incidence of antibiotic-associated colitis, which might have been caused by the high concentration of antibiotic entering the colon. To avoid the drug absorption in the colon gastro-retentive dosage form would be required to ensure drug delivery within drug-absorbable intestinal regions. Cefdinir is administer with the antacid as its activity is lost due to increase in the gastric pH suggested that the absorption of drug is confined mainly to the upper part of the gastrointestinal tract.

The objective of present research work was to develop stomach specific *in situ* gel of cefdinir. The use of natural biodegradable polymer sodium alginate and other polymers were used for this purpose at various concentrations and combinations.

MATERIALS AND METHODS

Materials

Cefdinir was obtained as a gift sample from Aurobindo Pharma Ltd., Hyderabad, HPMC (K4M and K100M) were kindly gifted by Dr. Reddy's Laboratories, Hyderabad. All other materials and solvents used were of analytical grade or pharmaceutical grade.

Methods

Drug excipient interactions: drug excipient interaction can be estimated by using FTIR.

Fourier transforms infrared spectroscopy (FTIR)

FTIR study was carried to check the presence of any drug polymer interaction. IR spectra for pure drug and stomach specific *in situ* gel formulation were recorded in the scanning range of 400 – 4000 cm^{-1} in FTIR spectrophotometer (FTIR 8400 S, Shimadzu, Japan). Spectra were shown in Figure 1.

Preparation of stomach specific *in situ* Gel for Cefdinir: Cefdinir was passed from 60# sieve while other inactive ingredients were passed from 40# sieve. Then aqueous solutions of HPMC (K 4 M & K 100 M) and natural gum were prepared. Cefdinir was gradually added to the above solution while stirring on a magnetic stirrer so that there was proper and homogeneous dispersion of the drug. In a another beaker, different concentrations of sodium alginate solutions as shown **Table 1** were prepared by adding the alginate to purified water containing sodium methyl paraben and sodium propyl paraben and heating to 60°C. After cooling to below 40°C, both solutions were mixed while stirring on magnetic stirrer. Then appropriate amount of calcium carbonate was added while stirring. The above formulation was sonicated in a bath sonicator for 15 minutes and then pH and viscosity of the solutions were determined, then pH of solution was adjusted to 5.5 - 6.5 with 0.1N sodium hydroxide solution **[11-14]**.

Table 1: Composition of Cefdinir stomach specific *in situ* gels

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Cefdinir (mg)	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
Guar gum	-		1	1.5	1.5	1.5	1.5	1.5						-	-	-	-	-
Pectin									1.5	1.5	1.5	1.5	1.5					
HPMC K4M (%)	-		-	-	-	-	-	-	-	-				1	1	1	1	1
Sodium alginate (%)	1	1.5	1	1	1.5	2	2.5	3	1	1.5	2	2.5	3	1	1.5	2	2.5	3
CaCO3 (%)	2.5		2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5				2.5	2.5	2.5	2.5	2.5
Sodium citrate (%)	0.3		0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3				0.3	0.3	0.3	0.3	0.3
Methyl paraben and propyl paraben (9:1) (%)	0.2		0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2				0.2	0.2	0.2	0.2	0.2
Water	Up to 100ml																	

Physical appearance and pH

Formulations of stomach specific *in situ* gels for Cefdinir antibiotic were tartan for their clarity and the type of the solutions. Check the time required for gel when formulation were placed in 0.1N HCl and type of gel formed. The pH of formulations was measured using a calibrated digital pH meter at 27°C. The measurements of pH of each data were in triplicate and the average values are given in **Table 2**.

Rheological Behaviors

Viscosities of the stomach specific formulations were determined using a Brookfield digital viscometer with spindle S34 at 200 rpm and temperature of formulations were maintained at 25±1°C before each measurement. Increasing the concentration of a dissolved or dispersed substance generally gives rise to increasing viscosity (i.e. thickening). Viscosities of all formulation were depicted in **Table 2**.

Density

For stomach specific system density is an important parameter and which less than the stomach fluid density (< 1.004). The Densities of all formulations were measured by forming gel of 5ml solutions were placed in measuring cylinder and weight of this gel was noted by using calibrated balance. Finally, the densities of different formulations were noted in triplicate.

Floating behavior

5ml of the stomach specific *in situ* gel was placed in 100 ml of the simulated gastric fluid (0.1N HCl, pH 1.2) at 37 ± 0.5°C temperature. The mixture was stirred at 100 rpm with a magnetic stirrer and floating lag time and duration of floating were noticed in triplicate, and then report the average value in **Table 2**.

Determination of drug content

Accurately weighed quantity, 5 ml of stomach specific *in situ* gel (Equivalent to 150mg of Cefdinir) was measured and transferred to 200ml volumetric flask, then make up the volume with 0.1N HCl. Shake the solution for 30 min followed by 15 min sonication. Sonicated solution was filtered using 0.45µ membrane filter. From this solution 10ml of sample was withdrawn and diluted with 0.1N HCl. Determine the amount of Cefdinir using standard curve in UV spectrophotometer then depicted the values in **Table 2**.

Table 2: Evaluation characteristics of Cefdinir stomach specific *in situ* gel

Formulation code	Physical appearance	pH	Density (gm/cm^3)	Viscosity (cps)	*In vitro* gellation	FLT (sec)	Drug Content	DF' (hr)
F 1	clear	5.8	0.523 ±0.008	110	++	22	99.11±1.15	8
F 2	clear	6.1	0.586±0.010	150	++	31	98.21±1.27	10
F 3	clear	6.2	0.555 ±0.012	180	++	41	97.38±1.09	12
F 4	clear	5.7	0.612±0.014	200	+++	47	96.58±1.72	12
F 5	clear	5.8	0.632±0.009	223	+++	50	98.98±1.32	12
F 6	viscous	6	0.601±0.011	252	+++	52	97.39±1.55	12
F 7	viscous	6.3	0.633±0.007	278	+++	58	99.29±0.99	12
F 8	viscous	5.6	0.634 ±0.018	320	+++	69	99.12±0.92	12
F 9	clear	5.9	0.526±0.012	132	++	32	98.65±1.21	9
F 10	clear	6.2	0.547 ±0.009	154	++	37	98.99±1.43	12
F 11	clear	6.5	0.627±0.011	202	++	48	98.01±1.85	12
F 12	clear	5.8	0.645±0.008	218	+++	52	97.28±1.62	12
F 13	clear	5.9	0.675 ±0.010	282	+++	59	99.13±0.67	12
F 14	clear	6.2	0.539±0.015	213	+++	35	99.37±1.66	10
F 15	clear	6.3	0.558 ±0.014	302	+++	42	98.98±1.17	12
F 16	viscous	6.4	0.634±0.006	355	+++	46	97.25±1.08	12
F 17	viscous	6.5	0.647±0.008	452	+++	52	96.98±1.73	12
F 18	viscous	5.9	0.659±0.015	612	+++	69	98.27±1.22	12

***In vitro* drug release study**

The drug release study was performed in USP 26 dissolution test using apparatus II (paddle apparatus) (Electrolab, TDT- 06T, Mumbai, India) at 37 ± 0.5°C and 50 rpm using 900 ml of 0.1N HCl as a dissolution medium (n=3). 5 ml of stomach specific *in situ* gels equivalent to 150mg Cefdinir was used for the test. 10 ml of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45 µ membrane filter, diluted and analyzed spectrophotometrically. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample **[15-20]**.

Kinetics modeling of drug dissolution profiles

Cumulative amount drug release at various time intervals of all the batches was fitted to Zero order, First order (Wagner, 1969; Gibaldi, 1967), Higuchi model (Higuchi, 1996; Higuchi 1963) and peppas models to ascertain the kinetic modeling of the drug release.

Stability studies

Optimized formulation was filled in a suitable glass contained and well stoppered with cap. Stability studies were carried out for 3 month at 45°C/75% RH according to ICH and WHO guidelines for the drug content, *in vitro* dissolution, gelling capacity, floating behavior and appearance of the formulated cefdinir stomach specific *in situ* gel solution **[21-24]**.

RESULTS AND DISCUSSION

Cefdinir is broad spectrum, third generation cephalosporin. Cefdinir has a low oral bioavailability 21% and short biological half life (1.7 hr) with narrow absorption window in upper part of GIT. Maintenance of plasma drug concentration is necessary to avoid the bacterial infections of the ear, sinus, throat, and skin. In order to maintain all these cefdinir formulation in the form of gastroretentive drug delivery systems. In all gastroretentive drug delivery systems stomach specific *in situ* gels are more

trustworthy because of easy administration to pediatrics, geriatric and young patients. These systems are liquids at room temperature and undergo gelation when it contact with acidic pH in stomach.

First drug and excipient interactions were estimated by using FTIR studies. These studies can be concluded that there was no interaction as shown in Figure 1 between cefdinir and selected excipients. So, these excipients can be compatible with drug and used for further studies. Cefdinir stomach specific *in situ* gels were formulated by using different concentrations of ionic gelation polymer sodium alginate and matrix forming polymers HPMC, guar gum and pectin. When these cefdinir stomach specific *in situ* gel were come into contact with 0.1N HCl, $CaCO_3$ liberate the CO_2 and Ca^{++} ions. These Ca++ ions react with sodium alginate to form a Ca^{++} alginate gel and formed CO_2 was entrapped in the gel to float as shown in **Figure 2**. Formulated gels were evaluated for their physical appearance and pH showed that as the concentration of polymer increases, the viscosity increases but gave a clear solution at room temperature and pH was slightly neutral to alkaline nature.

Rheological properties of prepared solutions were important for oral administration for easy spreadability and pourability. Rheological properties of all formulations illustrated that increase in concentration of polymer and sodium alginate increases the viscosity of solutions as shown in **Table 2** but these were easily pourable from the container.

Density is an important parameter for gastroretentive drug delivery systems; these were estimated after forming the gel in 0.1N HCl. Densities of all formulated cefdinir stomach specific *in situ* gels were in the range of 0.523 ±0.008 to 0.659±0.015 gm/cm^3 shown in **Table 2**. All formulations having the densities values less the gastric fluid, which can be easily floated in the gastric contents.

Floating behaviors of prepared cefdinir stomach specific *in situ* gels having floating lag time in the range of 22 to 69 sec and duration of floating was greater than 12hr. The Drug content of all formulations were found to be in the range of 96.58±1.72% - 99.37±1.66% as shown in **Table 2**. The values are acceptable and indicating homogenous distribution of drug throughout gel

The Cumulative % drug releases of the various formulations were shown in **Figure 3 & 4**. In all the formulations as the sodium alginate concentration increases with decrease in the amount of drug releases but sodium alginate alone was not sufficient to produce the drug relapse as that of theoretical one. So in order go get the desired drug release combination of gelling polymer sodium alginate and other matrix forming polymers were used in the study. F 7 and F 16 formulations gave the better control release as similar to that of theoretical containing the guar gum and HPMC K4M as a matrix forming polymers. Further, the best formulation is selected based on the *in vivo* performance.

To understand the mechanism of drug release dissolution data of all formulation were fitted in to different kinetic model and result were estimated based on the regression coefficient and slope in peppas model. Results of these models indicated that optimized formulation follows the zero order, non fickian drug transport mechanism. (**Table 3).**

Finally, optimized F 7 and F 16 formulations were subjected to stability studies according to the ICH guidelines and results of the various evaluation parameters were shown **Table 4 & 5**. After stability studies, the formulations F 7 and F 16 was more stable at accelerated condition.

Table 3: Mechanism of drug release from all cefdinir stomach specific *in situ* gel formulations

Formulations	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	n (slope)
F 1	0.8854	0.7205	0.9244	0.9476	0.4972
F 2	0.8451	0.7153	0.9284	0.9605	0.5288
F 3	0.9070	0.9608	0.9292	0.9718	0.6262
F 4	0.9561	0.8978	0.9275	0.9797	0.6813
F 5	0.9578	0.7655	0.9340	0.9821	0.7456
F 6	0.9860	0.6325	0.9325	0.9841	0.7994
F 7	0.9980	0.5356	0.9312	0.9986	0.7564
F 8	0.9959	0.9254	0.9316	0.9816	0.9034
F 9	0.7475	0.7369	0.9430	0.8278	0.5072
F 10	0.9693	0.8040	0.9239	0.9722	0.6832
F 11	0.9719	0.7503	0.9302	0.9862	0.7520
F 12	0.9858	0.6372	0.9318	0.9770	0.7816
F 13	0.9962	0.8998	0.9305	0.9872	0.9242
F 14	0.8451	0.7153	0.9284	0.9605	0.5288
F 15	0.9561	0.8978	0.9275	0.9797	0.6813
F 16	0.9984	0.5095	0.9311	0.9915	0.8123
F 17	0.9978	0.9273	0.9287	0.9941	0.8923
F 18	0.9878	0.9063	0.9272	0.9655	0.8845

Table 4: Stability studies of optimized F 7 cefdinir stomach specific *in situ* gels

Parameters		Before storage [a,b]	After storage [a,b]
	Drug content (%)	99.29 ± 0.99	98.58 ± 1.12
	Viscosity (cps)	278	275
Floating Behavior	**Floating lag time (Sec)**	58 ± 3	60 ± 4
	Duration of floating (hr)	12	12
Dissolution	***In vitro* gelation**	Very good	Very good
	Similarity factor	91.25 %	

[a] Storage at 45°C/75% RH for three months.
[b] Mean ± SD, *n* = 6

Table 5: Stability studies of optimized F 16 cefdinir stomach specific *in situ* gels

Parameters		Before storage [a,b]	After storage [a,b]
	Drug content (%)	98.25±1.08	97.58 ± 0.99
	Viscosity (cps)	355	275
Floating Behavior	**Floating lag time (Sec)**	46 ± 4	48 ± 2

		Duration of floating (hr)	12	12
ion	**Dissolut**	***In vitro* gelation**	Very good	Very good
		Similarity factor	87.87 %	

[a] Storage at 45°C/75% RH for three months.
[b] Mean ± SD, *n* = 6

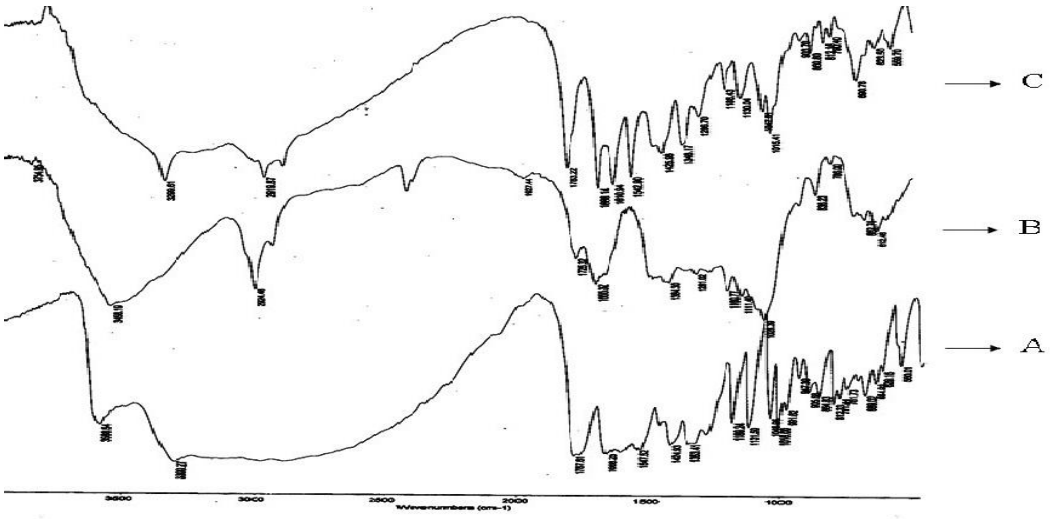

Figure 1: FTIR spectra of A) Pure Cefdinir B) Placebo formulation C) F 7 Formulation

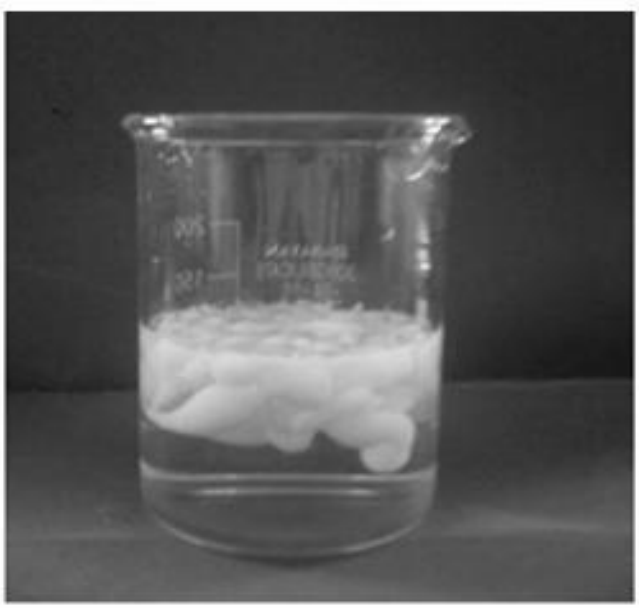

Figure 2: *in situ* gelation and floating of optimized F 7 formulation

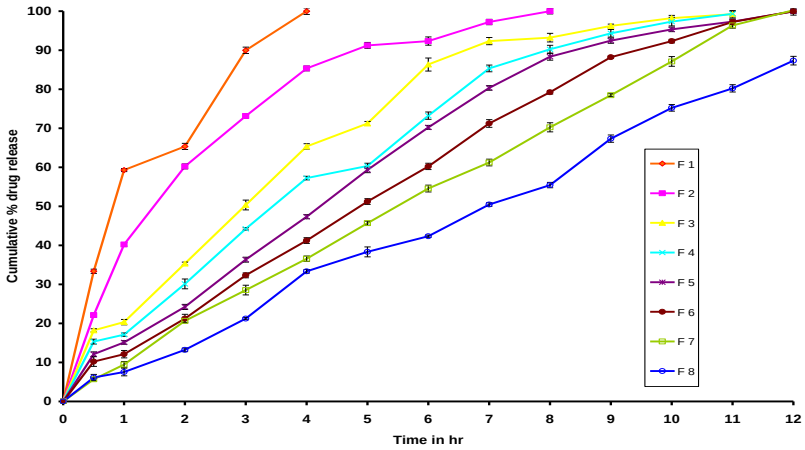

Figure 3: Cumulative % drug release studies from F 1 to F 8 formulations of cefdinir stomach specific *in situ* gels

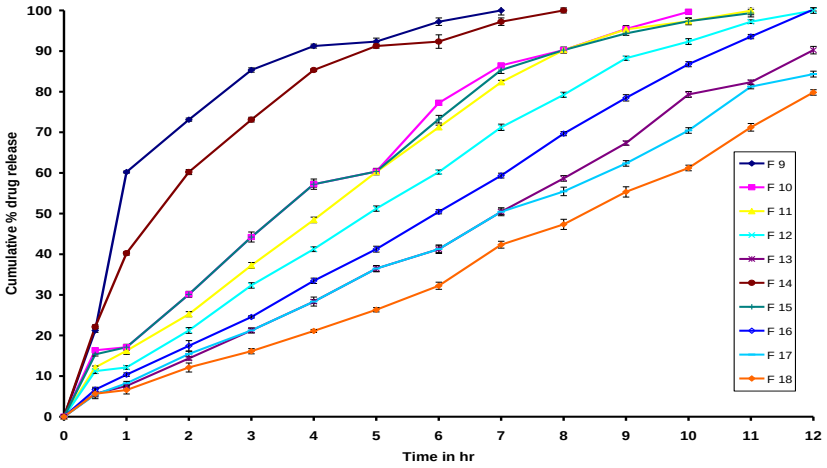

Figure 4: Cumulative % drug release studies form F 9 to F 18 formulations of cefdinir stomach specific *in situ* gels

CONCLUSION

In this research work, we successfully developed and optimized cefdinir stomach specific *in situ* gels which exhibit a unique combination of floatation and ionic gelation for prolonged residence in the stomach. The optimized F 7 & F 16 formulation showed a satisfactory physical appearance, drug content, rheological and floating behaviors. *In vitro* dissolution rate is similar to that of theoretical release. Mechanism of drug release studies revealed optimized formulations showed zero order followed by non fickian transport. Finally stability studies showed that optimized formulations were stable for prolonged period of time. Further in vivo assessment is necessary to get best optimized formulation.

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