

Formulation and Evaluation of Sustain Release Tablets of Ramipril

B.Venkateswara Reddy*, K.Navaneetha
 Department of Pharmaceutics, St. Pauls College of Pharmacy,
 Turkayamjal, Hayathnagar, R.R. Dist., Andhra Pradesh, India
 *basu.pharmacist@gmail.com



ABSTRACT

Objective: Sustained release tablets of ramipril were prepared in order to increase the half life (3 hours) of the drug and to reduce the adverse events associated with ramipril, a drug used in treatment of hypertension.

Methods: The tablets were prepared by direct compression method and evaluated for various parameters. HPMC K15, HPMC E15 and HPMC K4 were used as sustain release polymers.

Results: IR spectroscopic studies indicating that the drug is compatible with all the excipients and there was no drug-polymer interaction. The results of preformulation studies indicate that the powder blend has good flow properties. Tablets prepared by direct compression method are evaluated for thickness, hardness test, friability test, uniformity of weight, drug content estimation. All the formulation were found to be good appearance without showing any chipping, capping and sticking defects and all parameters were also passed the test.

Conclusion: When comparing all formulation, F1 containing HPMC K15 showed a sustained release of 98.7% at end of 16th hour. Percentage drug release obtained from sustained release tablets of ramipril were subjected for kinetic treatment for kinetic treatment to know the release order and was found that F1 formulation follow zero order release and follow the mechanism of both diffusion and erosion.

Keywords: Ramipril, Sustain Release Tablets, hypertension

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form. Nowadays most of the pharmaceutical scientists are involved in developing an ideal DDS. This ideal system should have advantage of single dose for whole duration of the treatment and it should deliver the drug directly at specific site.^[1] The design of oral sustain drug delivery system (DDS) should be primarily aimed to achieve the more predictability and reproducibility to control the

drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.^[2]

For most of the drugs, conventional methods of formulation are quite effective. However some drugs are unstable, toxic and have a narrow therapeutic range, exhibit extreme solubility problems, require localization to a particular site in the body or require strict compliance or long-term use. In such cases a method of continuous administration of drug is desirable to maintain fixed plasma drug levels. The goal in designing sustained or sustained delivery

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systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ.^[3,4]

The therapy of many chronic diseases requires a repeated dosing of a drug. Drugs having a short half life have to administer up to several times daily within short intervals. To reduce the application frequently sustained formulations have been developed.^[5]

Traditional drug delivery system has been characterized by immediate release and repeated dosing of the drug which might lead to the risk of dose fluctuation, this arises the need of a Formulation with control release that maintain a near-constant or uniform blood level.^[6]

Sustain release with the introduction of extended release matrix tablet have proved to be an effective tool to control the release of drug without involving the complex production procedures. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous sustain release oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs. However generating such a system requires certain consideration of which the half life and the pharmacological action of the drug form an essential part. But making a consideration of the drawbacks seen with the conventional drug delivery system (repeated

dosing and dose fluctuation) the sustain release helps to achieve the following goals:^[7, 8]

- Uniform release of drug over prolong period of time.
- Reduced dosing frequency.
- Less fluctuating blood levels.

In many instances, conventional method is more preferred to deliver the drug, but some drugs are unstable and toxic by frequently dosing. These kinds of drug have narrow therapeutic range and face solubility difficulties. In such cases, sustained drug delivery system is used, which maintain the drug plasma level in the therapeutic index.

The drug chosen for the present investigation was ramipril, orally active Antihypertensive agent. It is effectively used in the treatment of Hypertensive. Unlike sulfonylurea, metformin usually does not produce hypoglycemia in diabetic and non-diabetic individuals. So, it is more appropriately referred to as antihyperglycemic agent and found to be well-tolerated and safe on chronic use. On oral administration, it is absorbed through upper part of GI tract and absolute bioavailability of ramipril is approximately 50- 60%. Ramipril negligibly bounds to plasma proteins. It is excreted unchanged in the urine and does not undergo hepatic metabolism. It has a plasma elimination half-life of 3 hours. Its daily oral dose is 0.5 to 3 g/day in divided doses. Recommended dosage of conventional tablets is 3 times a day.^[9] As the dose of ramipril is 10 mg (marketed immediate release formulations of ramipril are available in of (10mg, 20mg and 25 mg) it is found to be suitable for development of a sustained release dosage form. Ramipril has a biological half-life of 3 hours. Hence, it requires three-times a day dosing. Therefore, ramipril is suitable candidate for development of a sustained release dosage form. Adverse events associated with ramipril use are often gastrointestinal in nature (e.g.

anorexia, nausea, vomiting, and occasionally diarrhea, etc.). These adverse events may be partially avoided using sustained release dosage form.

MATERIALS AND METHODS

Materials: Ramipril was obtained as a gift sample from Aurobindo Pharma Ltd. HPMC K15, HPMC E15 and HPMC K4 were obtained from Colorcon Asia Pvt. Ltd, Goa. Carbopol was obtained from Jayman chemicals, Mumbai. Microcrystalline cellulose was obtained from FMC biopolymers, Mumbai. Magnesium stearate from S.D.Fine chemicals, Mumbai..

Compatibility Studies of Ramipril and Formulation Components:

The compatibility of drug and polymers under experimental conditions is important prerequisite before formulation. It is therefore

necessary to confirm that the drug does not react with the polymer and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation. Infrared spectrum of the representative Ramipril and excipients were taken. The study was conducted on Thermo Nicolet (FTIR-200). The spectra's were run from 4000 to 400 cm^{-1} .

Preparation of tablets^[10]

The direct compression technique was followed to manufacture the ramipril tablets. Ramipril was passed through 30- mesh sieve. Polymers and microcrystalline cellulose were passed through 40-mesh sieve. Required amount of drugs as well as polymer and excipients were weighed and transferred into the double cone blender. The blend was then lubricated by required quantity of magnesium stearate.

Table no.1 Composition of Various Tablets Formulations of Ramipril

Ingredients	F1	F2	F3	F4	F5	F6
Ramipril	10	10	10	10	10	10
Hpmc K15	10	20	30	10	10	10
Hpmc E15	---	---	---	10	---	---
Hpmck4	---	---	---	---	10	---
Carbopol	---	---	---	---	---	10
Microcrystalline Cellulose	275	265	255	265	265	265
Mg. Stearate	5	5	5	5	5	5

Each tablet weight 300mg

Physical Properties of ramipril and Powder Blend of Tablet Batches

Bulk density^[11]

Bulk density is a ratio between a given mass powder of granules and its bulk volume. A quantity of 5g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 100ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cm to 2- seconds

intervals. The bulk density was calculated in gm/cm^3 by the formula

$$\text{Bulk density} = M/V_0$$

Where, M=mass of powder taken; V_0 =apparent volume

Tapped Density

Tapped density is a ratio between a given mass of powder or granules and constant or fixed volume of powder or granules after tapping. A quantity of 5g of powder from each formula, previously lightly shaken to break any

agglomerates formed, was introduced into a 100ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cm to 2- seconds intervals. The tapping was continued until no further change in volume was noted. The Tapped density was calculated in gm/cm^3 by the formula

$$\text{Tapped density} = M/V_f$$

Where, M=weight of sample powder taken; V_f =tapped volume

Compressibility index ^[12]

The compressibility of the powder was determined by the Carr's compressibility index.

Angle of repose ^[13]

Angle of repose is a defined as the maximum angle possible between the surface of the pile of powder and horizontal plain. The Angle of repose of the powder or granules was determined by fixed funnel method to assess the flow properties of powder or granules. Angle of repose of the granules was determined height cone method. A funnel was fixed to a desired height and granules were filled in it. They were allowed to flow on a graph paper fixed on a horizontal surface. The Angle of repose (θ) was calculated using the following formula

$$\tan \theta = h/r \text{ or } \theta = \tan^{-1} h/r$$

Where, h =height; r =diameter of the pile.

EVALUATION OF TABLETS

Post compression parameters

All the prepared tablets were evaluated for following official and unofficial parameters.

Hardness ^[14]

Hardness is force required to break tablet across the diameter. The Hardness of a tablet is an indication of its strength. The tablets should to stable to mechanical stress during handling and transportation. The tablet was placed

horizontally in content with the lower plunger of the Monsanto hardness tester and zero reading was adjusted. The tablet was than compressed by forcing upper plunger until the tablets breaks. Thus force was noted. The hardness of ten tablets was measured using Monsanto Hardness tester. It is expressed in kg/cm^2 .

Friability ^[15]

Friability is the loss of weight of tablets in the container/package, due to removal of fine particle from the surface. The friability of the tablets was determined using Roche friabilator. It is expressed in percentage (%). 10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for four minutes. After four minutes the tablets were weighed again. The % friability was determined following the formula

% Friability =

$$\frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

Weight Variation ^[15]

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test. The % deviation was calculated by using the following formula percentage deviation =

$$\frac{\text{Individual weight}-\text{avg weight}}{\text{avg weight}} * 100$$

Estimation of drug Content ^[15]

To ensure the consistency of dosage units, each unit in a batch should have active substance content within narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of an active substance in each dosage unit.

Ten tablets were weighed and average weight is calculated. All the ten tablets were crushed in mortar. Powder equivalent to 50mg of ramipril was dissolved in 250ml distilled water and shaken for 20 mins. Solution was filtered and 5

ml filtrate was diluted to the 100ml using distilled water. Absorbance of resultant solution was measured at 235 nm using distilled water as blank. Amount of drug present in one tablet was calculated.

Dissolution Study

The vitro drug release sample were carried out using type-II (paddle type). The dissolution medium 900ml 0.1N Hcl was placed in to dissolution flask maintain temperature of $37 \pm 0.5^\circ\text{C}$ and rpm of 50. One Ramipril tablet was placed in each basket dissolution apparatus. The apparatus run for 24 hours sample measuring 5ml. Where withdrawn after every 4 hours upto 24 hours using 5 ml pipette. The fresh dissolution was replaced every time with the same quantity of the sample. Collected sample with suitability diluted 0.1N Hcl and analyzed at 235nm using 0.1N Hcl as a blank. The percentage drug release was calculated.

Kinetic analysis of dissolution data ^[16-22]

The results of in vitro release profile obtained for all the formulations were fitted modes of data treatment as follows

1. Log cumulative percent drug remaining versus time (First order)
2. cumulative percent drug release versus square root of time (Higuchi model)
3. Log cumulative percent drug release versus time (Zero order)
4. cumulative percent drug released versus log time (Koysmeyers model)

RESULTS AND DISCUSSION

IR spectral analysis:

FTIR studies conducted on pure drug and mixture of drug and polymer (Figures 1, 2 and 3) showed that there is no marked interaction between drug and selected polymer. The graphs obtained indicate that the drug is compatible with the polymer used.

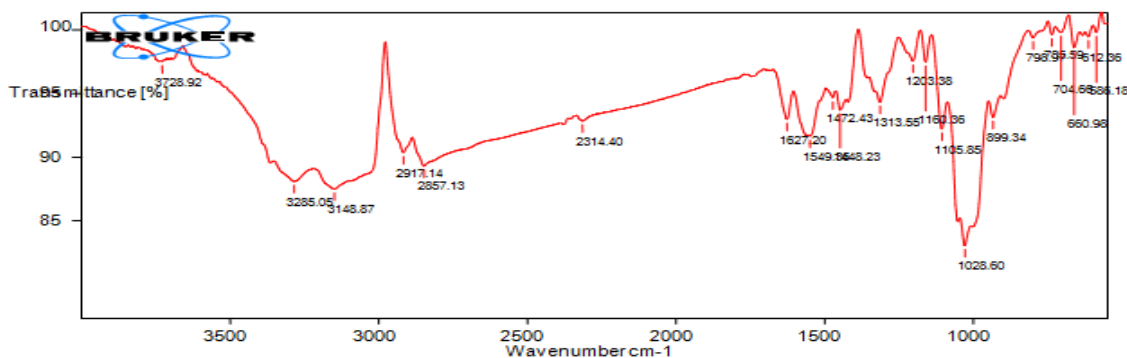


Figure no 1: FT-IR spectra of pure ramipril

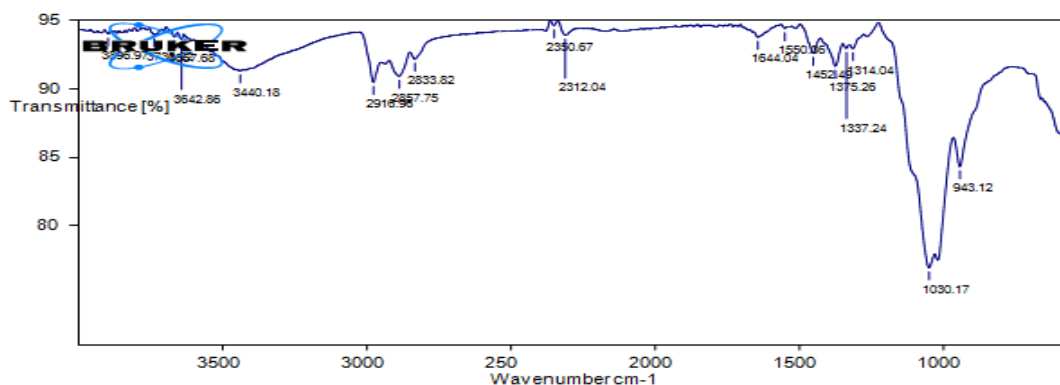


Figure no 2: FT- IR spectra of HPMC K15

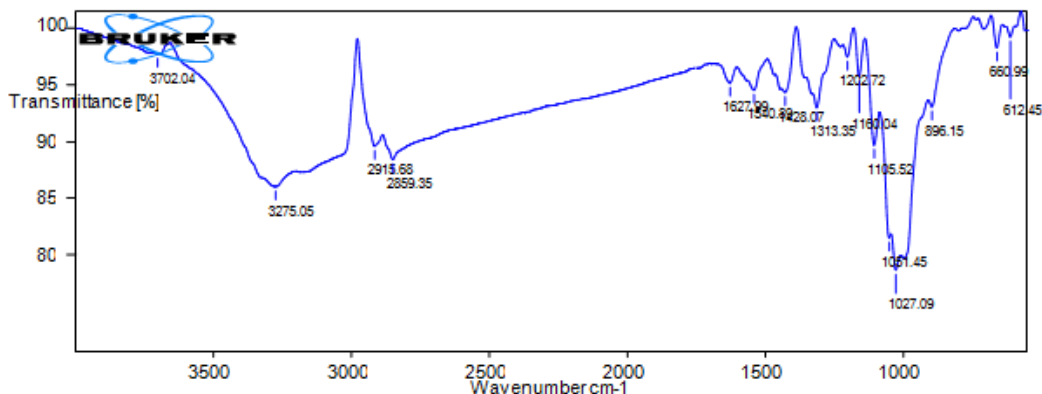


Figure no 3: FT-IR spectra of ramipril with HPMC K15

Precompression parameters:

The results of precompression parameters are represented in the table 2. The bulk density of all the formulations was found to be in the range of 0.41-0.46gm/cm³. The tapped density was found to be in the range of 0.52-0.57 gm/cm³. The angle of repose of all the formulation was below 30. If the angle of repose is within 30, it indicates excellent flow property of the granules. The compressibility index of all the formulation exists in the range of 18-21. It indicates that the granules showed good flow character. The results of the hausner's ratio of all the formulation is between 1.21 - 1.26. It shows good flow behavior of the granules or powder. The results indicate that all formulation show good flow property.

Table no 2: Evaluation of Granular Properties

Formulations	Angle of repose (θ)	Bulk density gm/cm ³	Tapped density gm/cm ³	Carr' s index (%)	Hausner ratio (%)
F1	26	0.42	0.57	17.85	1.21
F2	25	0.46	0.57	19.23	1.23
F3	27	0.44	0.54	18.51	1.22
F4	25	0.44	0.55	20.37	1.25
F5	26	0.44	0.54	18.51	1.22
F6	27	0.41	0.52	20.68	1.26

Post compression parameters:

The formulated ramipril sustained release tablets were evaluated for various physico-chemical parameters

Thickness

Thickness must be controlled to facilitate packaging. The results showed that the tablets of all the formulations showed uniform thickness.

Hardness

Oral tablets normally have a hardness of 4-10 kg/cm². The hardness of the tablets was tested using Monsanto hardness tester and results are presented in the table no.3. The hardness of the all formulation was within range of 6-7 kg/cm². So all the formulated tablets passes the test.

Weight variation test

Twenty tablets of each formulation were selected randomly and weighed individually. Here the actual weight of one tablet is 300mg. All the formulated tablets passes the test.

Friability

Friability was carried out Roche friabilator 10 preweighed tablets with revolution adjusted to 100 revolutions. After 100 revolutions, the tablets are dusted and weighed. A maximum weight loss of not more than 1% of the weight of the tablet being tested during the friability test is considered generally acceptable. The friability of all the formulated tablets was within 1%. It revealed that adhesion of tablet ingredient is good.

Drug Content uniformity

From each formulation equivalent to 50mg of ramipril was dissolved in 100ml of water. The solution was diluted with water and the content of ramipril was estimated spectrophotometrically at 235nm. The results are presented in the table no.3. As per IP, the content uniformity should be in the range of 90-110. The results showed that the percentage of ramipril in all formulations was ranging 96-98%. It revealed that drug is uniformly dispersed in the formulation and confirms the homogeneous mixing of the drug and the polymer. So all the formulated tablets passes the test.

Table no 3: Evaluation of Tablets

Formulations	Thickness	Hardness kg/cm ²	Friability (%)	Wt variation	Drug content (%)
F1	3.2	6.02	0.52	300	98
F2	3.5	5.99	0.07	301	96.5
F3	3.4	6.33	0.19	299	96
F4	3.1	6.09	0.49	300	97
F5	3.3	6.11	0.40	301	95
F6	3.2	6.19	0.33	300	98

Invitro release Study

Invitro release studies were performed to evaluate the dissolution character of ramipril sustained release tablets using four polymers with different ratio. Results of the invitro release studies of all formulation are presented in the table no.4. The graphical representation of the data are shown in the figure no.4

The percentage drug release of F1 formulation after 16 hours using HPMC K15 was found to be 98.9%(ramipril : HPMC K15 1:1) and F4 formulation contain HPMC E15 was 62.9%(ramipril :HPMC E15 1:1).The remaining formulation increase the polymer ratio like(1:2 ,1:3).They decrease the cumulative drug release.

It was found that the cumulative percentage drug release of the formulation,F1(98.9%) more than F4(62.9%).The cumulative percentage of drug release in the formulation F1(98.9%) showed sustained release than F2.

When comparing the percentage release of ramipril from the formulation F1 using HPMC K15(1:1 ratio)the formulation F4 using HPMC E15 (1:1 ratio), the drug release was in sustained release manner in the formulation F1.

Table no 4: Dissolution data of Ramipril Sustained Release tablets

TIME (hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	25.0	21.7	33.5	19.6	23.2	23.2
4	42.3	20.5	45.2	37.4	22.7	22.7
8	74	19.6	29.8	53.94	22.2	22.2
16	98.9	20.5	30.1	63.4	21.1	21.1
20	---	19.4	29.4	62.9	20.4	20.4

In vitro drug release

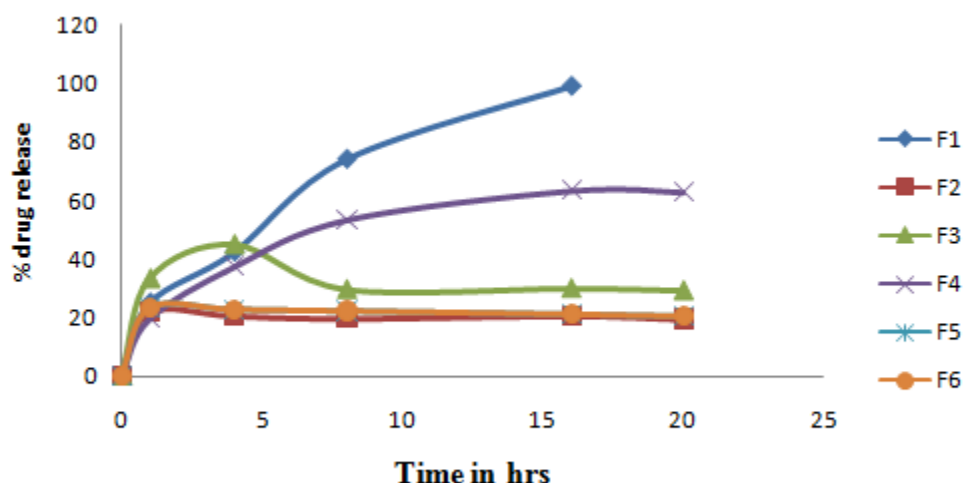


Figure no 4: In Vitro release drug release plot for formulation F1-F6

Curve fitting analysis

To know the mechanism of drug release from these formulations, the data were treated according to zero order, first order, Higuchi model and Krosmeier model. The release rate kinetic data for F1 formulation are shown in the table no.5. When the data were plotted according to zero order, the formulation showed a high linearity, with regression co-efficient values (R^2) was 0.975

Diffusion is related to transport of drug from the dosage matrix into the invitro study fluid depending on the concentration. This is explained by Higuchi's model. The release profile of drug from F1 formulation could be best expressed by Higuchi's model equations, as the plot showed high linearity co-efficient value (R^2) was 0.994

By using Krosmeier model, if $n=0.45$ it is fickian diffusion, if $n=0.45-0.89$ it is non fickian transport. Here F1 formulation showed n value between 0.458-0.843. So F1 formulation follows non-fickian transport mechanism.

Table no 5: Kinetic studies of optimum formulation F1

Time in hrs	sqrt time	log time	%cumulative release	log %cumulative release	drug retained	log %cumulative drug release retained
1	1.0	0	25.0	1.393	75	1.875
4	2.0	0.602	42.3	1.629	57.7	1.761
8	2.828	0.903	74	1.829	26	1.414
16	4	1.204	98.9	1.995	1.1	0.041

Table no 6: Kinetic values obtained from F1 plot formulation

Formulation n	Zero order r^2	First order r^2	Higuchi r^2	Korsmeyer peppas r^2	n	Best of fit
F1	0.955	0.947	0.980	0.992	0.527	korsmeyer peppas

CONCLUSION

Sustained release tablets of ramipril were prepared with four polymer and preformulation studies, tablets evaluation studies, IR spectral studies, dissolution studies were performed. The results are presented. Preformulation studies such as angle of repose, bulk density, tapped density, compressibility index, and hausner's ratio were performed and results showed that all the parameter are within the limits. Tablets were prepared by direct compression method and evaluated for thickness, hardness test, friability test, uniformity of weight, drug content estimation. All the formulation were found to be good

appearance without showing any chipping ,capping and sticking defects and all parameters were also passed the test. IR spectroscopic studies indicating that the drug is compatible with all the excipients and there was no drug-polymer interaction. When comparing all formulation, F1 showed a sustained release of 98.7% at end of 16th hour. Percentage drug release obtained from sustained release tablets of ramipril were subjected for kinetic treatment for kinetic treatment to know the release order and was found that F1 formulation follow zero order release and follow the mechanism of both diffusion and erosion.

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