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DESIGN, DEVELOPMENT AND EVALUATION OF NAPROXEN SODIUM BILAYER TABLET

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Abstract:

An oral drug delivery device provides a continuous oral release of the medication during its gastrointestinal (GI) transit. The popularity of the oral route may be partly due to its ease of administration and the widespread belief that the medication is effectively absorbed while passing through the gastrointestinal tract with meals. It is the preferred and advised method of administration for drugs with systemic effects. Due to patient acceptance, convenience of administration, and a low-cost production method, oral medication is frequently the first route examined in the discovery and development of new pharmacological agents and pharmaceutical formulations

The present study that appropriate combination of Naproxen Sodium with Aloe vera powder was suitable for the adequate sustained release. The Bilayer tablet of Naproxen Sodium and Aloevera powder was successfully formulated and prepared. The formulation T1, T3 and T4 were optimized formulations. Therefore the study proves that Naproxen Sodium can be successfully released in a sustained manner along with the Aloe vera powder by the use of the Bilayer tablet.

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INTRODUCTION:

An oral drug delivery device provides a continuous oral release of the medication during its gastrointestinal (GI) transit. The popularity of the oral route may be partly due to its ease of administration and the widespread belief that the medication is effectively absorbed while passing through the gastrointestinal tract with meals. It is the preferred and advised method of administration for drugs with systemic effects. Due to patient acceptance, convenience of administration, and a low-cost production method, oral medication is frequently the first route examined in the discovery and development of new pharmacological agents and pharmaceutical formulations

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties that relieves pain, fever, swelling, and stiffness. It is commonly used as sodium salt. Naproxen itself is rapidly and completely absorbed from the GI tract with an *in-vivo* bioavailability of 95%. Naproxen is extensively metabolized to 6-0-desmethyl naproxen and both parent and metabolites do not induce metabolizing enzymes. The elimination half-life of Naproxen is approximately 15 hours. Most of the drug is excreted in the urine and a small amount (< 5%) of the drug is excreted in the faeces. Since Naproxen is extensively bound to plasma albumin, so it may be more efficient to deliver this drug in its sustained-release dosage form .However, its ability to inhibit prostaglandin synthesis may be involved in the anti inflammatory effect. The mechanism of action of naproxen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase (COX) activity. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity, while inhibition of COX-2 provides anti inflammatory activity

Aloe vera is used as medicine for centuries, most commonly to treat sunburn, rashes, burns, wounds and other skin conditions . It may also help ease digestion problems like heartburn and constipation, reduce blood sugar in people with diabetes, fight cavities and condition and strengthen hairs. Aloe vera is widely available as a distilled juice, dietary supplements, and ingredient in shampoos, face creams, body lotions and skin ointments. Although the stems of the aloe plant and the gooey gel inside can be eaten raw or cooked, they may be unsafe if consumed in excess.

It has been recently discovered for both the aloe vera and whole leaf extract include the ability to improve the bioavailability of co-administered vitamins in human subjects. Due to its absorption enhancing effect Aloe vera gel may be employed to effectively deliver poorly absorbable drugs through the oral route of drug administration. And the dried powder which is obtained from Aloe vera gel was successfully used to manufacture directly compressible matrix type tablets. And which shows the slow release over an extended period of time and thereby showing potential to be used as an excipient in modified release dosage forms.

Figure 1. Aloe Vera Plant

Aloe vera contains two classes of Aloins:

1. **Nataloins** which yields picric acid and oxalic acid with nitric acid, and do not give a red colouration with nitric acid
2. **Barbaloins** which yields aloetic acid ($C_7H_2N_3O_5$), chrysammic acid ($C_7H_2N_2O_6$), picric acid and oxalic acid with nitric acid, being reddened by the acid. The plant produces at least 6 antiseptic agents such as lupeol, salicyclic acid, urea nitrogen, cinnamonic acid, phenols and sulphur. They kill or control mold, bacteria, fungus and viruses. Lupeol and Salicyclic acid present in the juice which acts as very effective pain-killer.

Medicinal Properties:

Aloe vera extracts shows Antimicrobial activity. Also use in the treatment of pimples, acne and mouth ulcers. It has also been used to control bleeding, itching of piles and relief from arthritic pain. Pharmacologically it is an immunity booster and detoxifies the system. It is recommended in adjuvant therapy with antibiotics, NSAID's and chemotherapy to eliminate drug induced gastritis and other adverse effects. Used in Diabetes type 2, arthritis, eye disease, tumour, spleen enlargement, liver complaints, vomiting, bronchitis, asthma, jaundice and ulcers. Relieves constipation, maintains a good gastric pH, helps in inflammatory bowl diseases, non-ulcers dyspepsia, gastric and duodenal ulcers. And a dietary supplement in pre and post operative patients, postmenopausal women and in cases of osteoporosis.

MATERIALS AND METHODS:

MATERIALS:

Naproxen Sodium was obtained as a gift sample from Glenmark Pharmaceuticals, Mumbai, Aloe vera powder was form General store, Buldana, HPMC grades were form Lupin Pharmaceuticals, Aurangabad, Carboxyl Methyl Cellulose was obtained from Research Lab, Crosscaemellose Sodium was obtained from Lupin Pharmaceuticals, Aurangabad, Microcrystalline cellulose(Avicel pH 101) was obtained from Ozone Internationals, Sodium Starch Glycolate was obtained from Research lab

METHODS:

Naproxen Sodium Sustained Release Layer:

Transfer Naproxen Sodium through sieve no.120

⇓

Also transfer the HPMC, CMC, Crosscarmellose Sodium, Lactose through sieve no. 120

⇓

Dry mix it in a motor pestle & then add sufficient amount of water or starch paste as a granulating fluid

⇓

After granulation, pass the dumb mass through sieve no. 20

⇓

Then dry the granules in the hot air oven at >50^0C

⇓

Pass the dried granules from sieve no. 22

⇓

Add Magnesium stearate & Talc to the granules

⇓

Then punch the 1st layer of the tablet

Aloe Vera Powder Immediate Release Layer:

Transfer Aloe vera powder through sieve no. 120

⇓

Also transfer the MCC(Avicel pH 101), Sodium Starch Glycolate through sieve no. 120

⇓

Dry mix it in a motor pestle & then add sufficient amount of water as a granulation fluid

⇓

After Granulation, pass the dumb mass through sieve no. 20

⇓

Then dry the granules in the hot air over at >50^0C

⇓

Pass the dried granules from sieve no. 22

⇓

Add Magnesium stearate & Talc to the granules

⇓

Then punch the 2nd layer of the tablet

Characteristics of Granules:

Bulk Density: Bulk density is defined as the mass of the many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume. Bulk density is the weight of a volume unit of powder and is usually expressed in g/cm^3, kg/m^3. Bulk density is usually determined by measuring the volume of 100 gm of powder in 250ml graduated cylinder after exposure to compaction by standardized tapping.

Bulk Density = Mass/ Volume (g/ml)

Tapped Density: Tapped density of a powder is the ratio of mass of the powder to the volume occupied by the powder after it has been tapped for a defined period of time. The tapped density of a powder represents its random dense packing.

Tapped Density = Mass/ Final volume (g/ml)

Compressiblity Index: The Carr's index is an indicator of the compressibility of a powder. It is named after the scientist Ralph J. Carr, Jr. The Carr's index is frequently used in pharmaceutics as an indication of the compressibility of a powder. In a free-flowing powder, the bulk density and tapped density would be close in value, therefore, the Carr's index would be small. On other hand, in a poor-flowing powder where there are greater interparticle interactions, the difference between the bulk and tapped density observed would be greater, therefore the Carr's index would be larger. The Carr's index is calculated by the formula-

Carr's Compressiblity Index = [(TD-BD)×100]/TD

Where, TD = Tapped Density

BD = Bulk Density

Table 1. Compressibility Index

Sr. No.	Carr's Index (%)	Flowability
1	Excellent	0-10
2	Good	10-15
3	Fair	16-20
4	Passable	21-25
5	Poor	26-31

Hausner's Ratio: The Hausners ratio is the no.that is correlated to the flowability of a powder or granular material. It is named after the engineer Henry H. Hausner.

H = $^{\rho}$T / $^{\rho}$B

Where, **$^{\rho}$T =** Bulk Density, **$^{\rho}$B =** Tapped Density

Table 2. Hausner's Ratio

Sr. No.	Hausner's ratio	Flowability
1	Excellent	1.00-1.11
2	Good	1.12-1.18
3	Fair	1.19-1.25
4	Passable	1.26-1.34
5	Poor	1.35-1.45

Angle of Repose: The angle of repose is the maximum angle that the plane of powder makes with the horizontal surface on rotation. Angle of repose is helpful in assessment of flow properties of particles which could be further related to packing densities and mechanical arrangements of particles. The angle of repose of granules was determined by the fixed funnel and free standing cone method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface.

Tan Θ = h/r

Where, h = height of the powder heap,

r = radius of the powder heap,

Θ = angle of repose.

Table 3. Significance of Angle of Repose

Sr. No.	Angle of Repose	Flow Property
1	< 25	Excellent
2	25-30	Good
3	30-40	Passable
4	< 40	Poor

FTIR Study:

The Fourier transform infrared (FTIR) spectra of pure drug (naproxen sodium), pure drug with other excipients (HPMC,CMC,Crosscarmellose Sodium, Aloe vera powder, MCC, Sodium Starch Glycolate) were recorded using a FTIR spectrophotometer. The smoothing of the spectra and the baseline correlation procedures were applied. The FTIR measurements were performed in the scanning range of 4000-400 cm−1 at ambient temperature.

Evaluation of Tablet:[28,29]

Hardness: Hardness is the force which is required to break the compressed tablet. It was measured using Monosanto tablet hardness tester. It is expressed in kg/cm^2.

Thickness and Diameter: Thickness & Diameter of the tablet is determined by the verniercaliper . Least count of the verniercaliper is 0.1mm.

Weight Variation test: Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average. The uniformity of weight was determined accordingly to IP specification. As per USP not more than two of individual weight should deviate from average weight by more than 5% and none deviate more than twice that percentage.

Friability test: RochesFriabilator is used to test friability of the tablet. Tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of six inches with each revolution. Pre weighed samples of 10 tablet and

place in the friabilator for 4 min 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not loose more than 1% of their weight.
The friability (F) is calculated by the following formula-

F = Wt (initial) – Wt (final)/ Wt (initial) × 100
Disintegration time: The time required for disintegration of six tablets, placed in each tube of basket rack assembly of disintegration test apparatus speed of 28-32 cpm, was measured using distilled water maintained at 37± 2^0C.

Drug content uniformity: Drug content uniformity was calculated by crushing 20 tablets and blend equivalent weight of 200mg of drug was weighed and dissolved in suitable quantity of 0.1 N HCl. The solution was then filtered and diluted accondingly, drug content was then analysed using UV spectroscopy at 232nm.

RESULT AND DISCUSSION:

Characterization of Granules:
The granules of Naproxen Sodium and Aloe vera powder was prepared by Wet Granulation method. The granules were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio. The angle of repose of different formulation batches from T1 to T6 was found to be from 24.98 to 39.2 ^{0}. The angle of repose was less than 40° for few of the formulation batches of granules, indicating passable flow behavior. Similarly, bulk density and tap density of all the formulation batches from T1 to T6 were found to be from 0.33 to 0.476 g/ml and from 0.480 to 0.616 g/ml, which is good flow properties of the granules. The Carr's index of all formulation batches was in the acceptable range from 18.75 to 26.22. The Hausner ratio of all formulation batches from T1 to T6 was found to be from 1.23 to 1.35. The Hausner ratio less than 1.35 indicates good and passable flowability.

FTIR Study:
The IR spectra of Naproxen Sodium showed the peaks at 3400 cm^{-1}(O-H), 2900 cm^{-1}(C-H), 1722 cm^{-1} (C=O), 1461 cm^{-1} (C=C), 1156 cm^{-1} (C-O), 1028 cm^{-1} (C-H alkenes out of the plane bend), 857 cm^{-1} (C-H aromatic out of the plane bend).
FTIR spectrum of the physical mixture of drug and polymer showed the peak at 3295cm−1 due to the presence of O-H, at 1252 cm−1 due to the presence of C–O stretch, the C = C (aromatic stretch) at 1602 cm−1, –CH3 bend at 1481 cm−1. Therefore, FTIR study concluded that no interaction occurred between the drug and polymer.

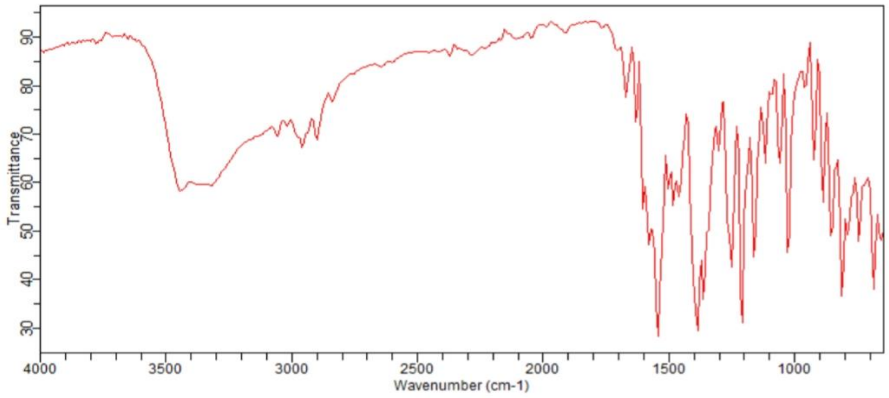

Figure 2. FTIR of Naproxen Sodium

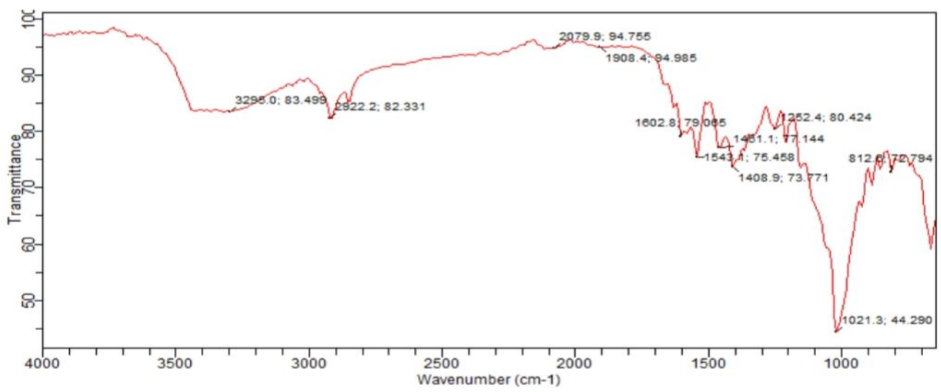

Figure 3. FTIR of Naproxen Sodium with other excipients

In Vitro drug release study of Naproxen Sodium:
The release rate of Naproxen Sodium from tablets was determined. The dissolution test was performed using United States Pharmacopoeia (USP) type II (paddle) apparatus,900 ml of 0.1N HCl at 37 ± 0.5°C and 50 rpm. A sample 5ml of the solution was withdrawn from the dissolution apparatus at the appropriate time for 4hrsand the samples were replaced with fresh dissolution medium. The samples were diluted into a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 232 nm using a Shimadzu UV/Visible double-beam spectrophotometer. Percentage drug release was calculated. The drug content was calculated using the equation generated from standard calibration curve. The % drug release was calculated.

In vitro drug release study of Aloe vera Powder:
The release rate of Aloe vera powder from tablets was determined. The dissolution test was performed using United States Pharmacopoeia (USP) type II (paddle) apparatus, 900 ml of 0.1 N HCl at 37± 0.5°C and 50 rpm. A sample 5ml of the solution was withdrawn from the dissolution apparatus at the appropriate time for 4hrs min and the samples were replaced with fresh dissolution medium. The samples were diluted into a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 254 nm using a Shimadzu UV/Visible double beam spectrophotometer. Percentage drug release was calculated. The drug content was calculated using the equation generated from standard calibration curve. The % drug release was calculated.

The in vitro drug release studies of the Bilayer Tablet i.e., T1 to T6 showed 95.23%, 90.12%, 96.76%, 97.9%, 89.34%, 92.20% drug release within 12 hrs Different dissolution media were used for the remaining formulation batches of Bilayer Tablet to perform in vitro drug release studies. Formulation T1, T3, T4 showed maximum release of the drug form the bilayer tablet. Which contains HPMC K100M, HPMC K15M, Crosscarmellose Sodium in varing concentrartion.

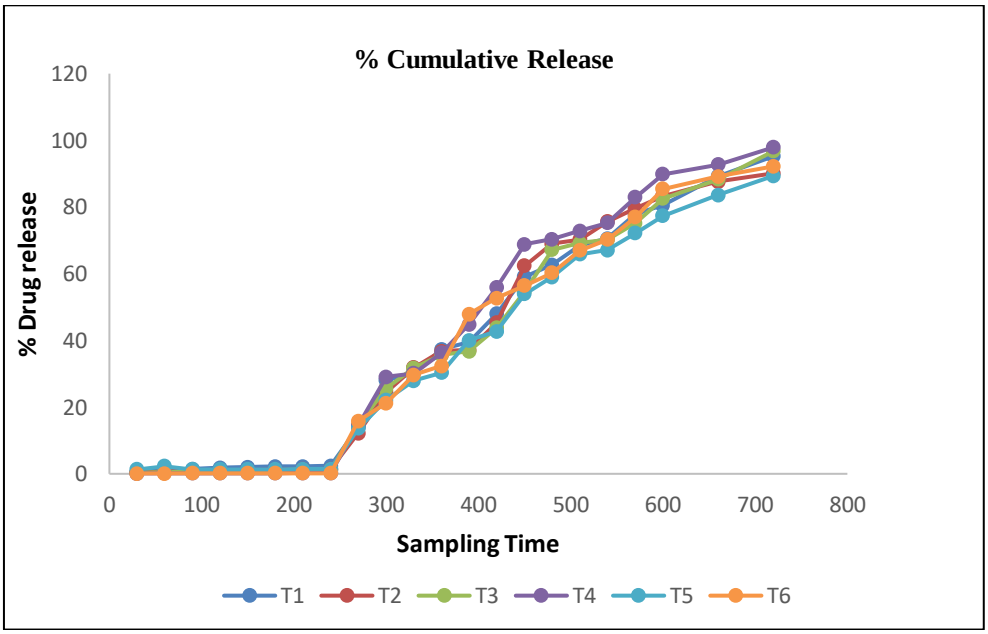

Figure 4. % Cumulative Drug Release

Differential Scanning Calorimetry:
The DSC of pure Naproxen is shown in the Figure 5, while the DSC profiles of the polymers is shown in the Figure 6 and 7. DSC is one of the most common applications to determine and predict the physicochemical interaction between components in a formulation. The thermogram of pure Naproxen Sodium showed a sharp endothermic peak at 156.9^{0}C due to melting. The broad peak in the DSC profiles of Naproxen Sodium with polymer might be corresponded to the melting and decomposition .The melting point of a substance is closely related to its solubility through latent heat of fusion, which is the amount of heat generated during melting or fusion.

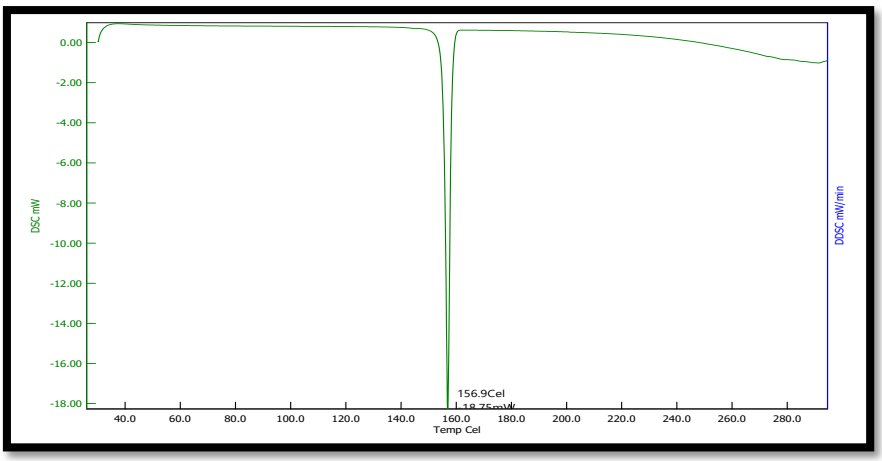

Figure 5. DSC of pure drug Naproxen

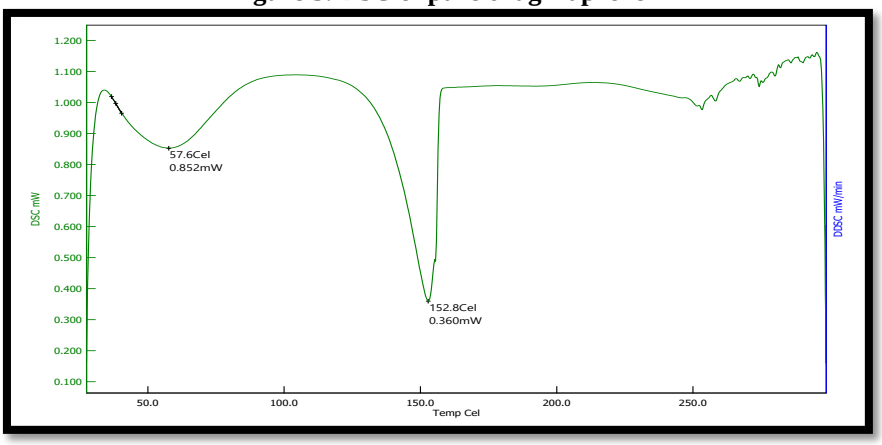

Figure 6. DSC of Naproxen sodium and HPMC K100M

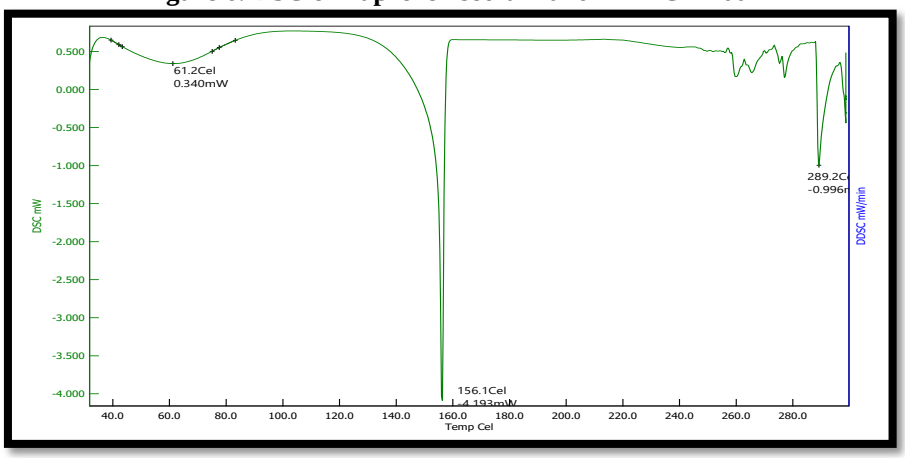

Figure7. DSC of Naproxen Sodium and HPMC K15M

CONCLUSION:

It is concluded that the present study that appropriate combination of Naproxen Sodium with Aloe vera powder was suitable for the adequate sustained release. The Bilayer tablet of Naproxen Sodium and Aloevera powder was successfully formulated and prepared. The formulation T1, T3 and T4 were optimized formulations. Therefore the study proves that Naproxen Sodium can be successfully released in a sustained manner along with the Aloe vera powder by the use of the Bilayer tablet.

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