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Original Article

FORMULATION AND EVALUATION OF BILAYER TABLET CONTAINING DICLOFENAC SODIUM AS SUSTAINED RELEASE AND ALOE VERA GEL POWDER AS IMMEDIATE RELEASE

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ABSTRACT

Objective: The objective of the present investigation is to design formulate and characterized the bilayer tablet containing Diclofenac sodium and Aloe Vera gel powder. In which diclofenac sodium is sustained release and Aloe Vera gel powder is immediate release. In order to produce a single dosage form containing two different classes, drug are widely prescribed by the physician to have better patient compliance.

Methods: Bilayer tablet was prepared by direct compression, The immediate release layer of Aloe Vera gel powder was prepared by using different excipients such as starch, sodium starch glycolate, lactose, talc etc. sustained release layer of diclofenac sodium was prepared by using HPMC K4M, lactose, Talc Magnesium stearate, talc etc. for preparation of bilayer tablet sodium starch glycolate are use as super disintegrants in immediate release tablet and HPMC K4M are use as controlled release polymer. Various Preformulation parameter i.e. Identification, melting point, compatibility study, solubility are checked. Micromeritics properties of powder blend such as bulk density, tapped density, hausner's ratio, Carr's index, angle of repose are performed. Post-compression parameter was done such as hardness, friability, weight variation, drug content uniformity, thickness, *in vitro* drug release.

Results: Result was found within the limit of the standard of optimized formulation. The drug release of the tablet was in the range of 82 to 92%in 8 h.

Conclusion: Bilayer tablet was prepared by optimized batches of both layers. The prepared tablets showed satisfactory results for various evaluation parameters. The optimized formulation based on all the parameter A1 (Sodium starch glycolate) is selected for the immediate release layer and D3 (HPMC K4M) was selected for the controlled release layer. The drug release mechanism was found to be zero order release depends upon diffusion.

Keywords: Bilayer tablet, Diclofenac sodium, Aloe Vera gel powder, HPMC K4M, Immediate release, Sustained release, Direct compression

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INTRODUCTION

The purpose of any drug delivery system is to provide a therapeutic amount of the drug to the proper site of action in the body to maintain the desired drug concentration. Oral rout is most convenient route of the administration dosage form. Tablet is a convenient dosage form acceptable by patients and physicians. Bilayer tablet is suitable for sequential release of two drugs in which one is immediate release and another is sustained release [1]. The fixed-dose Combinations of two or more active drugs produced in a single dosage form. The advantages of combination therapy to reduce the number of the dosage form in prescription and maintain administrative cost as well as improving patient compliance. The present study is about to find out the solution to reduce the incidence of diclofenac sodium-induced GI injury and other severe GI problems. This problem is overcome by preparing the bilayer tablet of diclofenac sodium with Aloe vera gel powder. Diclofenac sodium is a non-steroidal anti-inflammatory drug which has analgesic and antipyretic activity. Diclofenac is used to treat pain, menstrual pain, dysmenorrhea, ocular inflammation, osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. The primary mechanism responsible for its analgesic, anti-inflammatory and antipyretic action is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase and it appears to inhibit DNA synthesis. Inhibition of COX also decreases prostaglandins in the epithelium of the stomach, making it more sensitive to corrosion by gastric acid, which is responsible for the cause of ulcer [2]. Diclofenac is absorbed 100% orally, 99% protein bound, metabolized and excreted both in urine and bile. The elimination half-life is 1.2 to 2 h hence, diclofenac is suitable for sustained release layer [3]. Aloe Vera Gel Powder is the natural anti-ulcer medicine. Which Acts by directly interact with the H^2receptor on parietal cells which is responsible for decreases gastric acid secretion by direct interaction with acid. It is a poorly soluble drug with a short biological half-life of 4 hr and its absorption from the gastrointestinal tract (GIT) is rate limited [4] hence aloe vera choose for immediate release. Present study is to prepared bilayer tablets of Diclofenac Sodium (SR) by using HPMC as controlled release polymer in sustained release layer along with other excipients and aloe vera gel powder (IR) using SSG super disintegrants in an immediate release [5]. Both layers are compressed by direct compression methods. To evaluate blends in terms of Angle of repose, Bulk and tapped density, Carr's index, Hausner's Ratio and to evaluate Bi-layer matrix tablets in terms of hardness, weight variation, friability, thickness, drug content uniformity, *In vitro* dissolution studies in 1.2 and 6.8 pH [6].

MATERIALS AND METHODS

Material

Sample was procuring from Diclofenac sodium (), HPMC K4M, Talc (Thermosil fine chem.) Aloe vera gel powder (maple biotech pvt ltd bhosari, Pune) starch, sodium starch glycolate, (research lab) Lactose, (Sahyadri scientific supply) Magnesium Stearate (Hilab chemicals) were sample is analytical grade.

Method

Formulation of bilayer tablet was prepared by direct compression method. Immediate release layer was prepared by using different super disintegrants (sodium starch glycolate).

Drug and above super disintegrants were passed through the 40# sieve and transfer into polybag and mix up to 3 min. Then add other excipients to the above mixture. Finally, add (glidant) talc into the blend.

Another layer was also prepared by direct compression; drug and polymer (HPMC k4M) were pass through the 40# sieve transfer into polybag and mixed properly up to 3 min. Other excipients were mixed well and finally added Magnesium Stearate in the above blend and were mixed for 2 min.

Finally above optimized batch blends were compressed by rotary tablet compression machine (Make-CREATE INDUSTRIES, MODEL-LP-8GMP).

Table 1: Formulation of immediate release aloe vera gel powder

S. No.	Ingridients	Weight (mg)		
		A1	A2	A3
1	Aloe Vera gel Powder	100	100	100
2	Starch	7	8	9
3	SSG	5	4	3
4	Lactose	33	33	33
5	Talc	5	5	5
6	Color	q. s	q. s	q. s
	Total	150	150	150

Table 2: Formulation of sustained release diclofenac sodium

S. No.	Ingridients	Weight (mg)		
		D1	D2	D3
1	Diclofenac sodium	50	50	50
2	HPMC K4M	12	20	28
3	Lactose	128	120	112
4	Talc	5	5	5
5	Magnesium stearate	5	5	5
	Total	200	200	200

Preformulation study: [7, 8]

Identification test by U. V vis. spectrophotometer

A. For diclofenac sodium:

25 mg of diclofenac sodium was weighed accurately and transferred it to 25 ml volumetric flask. Dissolved it in ethanol and make the volume up to 25 ml with respective solvent. This was considered a stock solution (1000 mcg/ml). Further dilutions were made with this stock solution and scanned in the range of 400-200 nm using respective blank in UV spectrophotometer (SHIMADZU U. V 1800).

B. For Aloe vera gel powder

25 mg Aloe vera gel powder was weighed accurately and transferred it to 25 ml volumetric flask. Dissolved it in methanol and make the volume up to 25 ml with respective solvent. This was considered a stock solution (1000 mcg/ml). Further dilutions were made with this stock solution and scanned in the range of 400-200 nm using respective blank in UV spectrophotometer.

Melting point determination [8]

Melting point of diclofenac sodium and aloe vera gel powder was determined by using melting point apparatus by capillary method.

Determination of solubility [8]

Qualitative Solubility

Qualitative solubility analysis of drugs was done by dissolving 5 mg of drug in 5 ml solvent such as distilled water, methanol, ethanol, chloroform, phosphate buffer (7.4), ether.

Compatibility study, by FT-IR spectroscopy [7]

The powdered substance of the tablet was mix, dried potassium bromide (IR grade) ratio of sample is should be 1:100 mg, i. e 1 mg sample: 100 mg KBr. are compressed to form transparent pellets. The sample was scanned from 4000 to 400 cm^{-1}at ambient temperature. (Perkin Elmer Spectrum-65)

Pre-compression evaluation [7]

Bulk density

Bulk density was determined by introducing the power blend into measuring cylinder and the total volume was measured and also total powder weight was measured. The bulk density was calculated by using formula.

Bulk density (BD) = weight of powder/bulk volume.

Tapped density

Tapped density was determined by tapping the cylinder by using the tapped density apparatus. Tapped the cylinder up to 100 times and then measure the tapped volume and calculate the tapped density by using formula.

Tapped Density (TD) = weight of powder/tapped volume.

Hausner's ratio

Hausner's ratio bulk density as to tapped density is the number that is correlated to the flowability of a powder or powder blend. It is calculated using formula,

Hausner's ratio = tapped density/bulk density.

Compressibility index

Compressibility index was calculated by formula,

Carr's index (%) = Tapped density–bulk density/tapped density* 100

Angle of repose

The angle of repose of powder blend of each layer of each formulation was determined by fix funnel method. The blend was poured through funnel separately until apex of pile so formed just touch the tip of the funnel. The angle of repose was calculated by using formula

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

h is height of pile; r is the radius of pile.

Post-compression evaluation [6]

Uniformity weight

Uniformity weight of the tablet was determined by selecting 20tablet randomly. This selected tablet weighing individually and the weight of individual tablet was compared with average weight.

Thickness

Thickness of the tablet was measured by using vernier calliper. 5 tablets were selected and thickness was measured in (mm).

Table 3: Limits for tablet weight variation test

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
>324	5%

Hardness

Hardness is an important parameter of evaluation of tablet. The resistance of the tablet to break under the condition of handling, transportation and storage depend upon hardness. The hardness of the tablet was measured by using Monsanto hardness tester. The unit of hardness is expressed in term of kg/cm^2.

Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. 10 tablets are weighed and placed in the (roche friabilator) apparatus they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked. The percentage friability was determined by the formula:

% friability = [initial weight–final weight/initial weight]*100

Content uniformity

For diclofenac sodium

10 tablets were taken and crushed into morter to form a powder. From that, sample equivalent to 50 mg of drug was taken and transferred to 100 ml volumetric flask. Ethanol (20 ml) was added dissolve the drug and volume were made up to mark with methanol, this was filtered. From the filtrate 1 ml was taken and diluted with pH 6.8 phosphate buffer and absorbance of this solution was measured by using U. V-spectrophotometer at 275 nm (SHIMADZU; U. V1800).

For aloe vera gel powder

10 tablets were taken and crushed into morter to form a powder. From that, sample equivalent to 100 mg of drug was taken and transferred to 100 ml volumetric flask. Methanol (20 ml) was added dissolve the drug and volume were made up to mark with methanol, this was filtered. From the filterate 1 ml was taken and diluted with pH 6.8 phosphate buffer and absorbance of this solution was measured by using U. V-spectrophotometer at 262 nm (SHIMADZU; U. V1800).

***In vitro* drug dissolution studies**

***In vitro* drug release was studied for immediate release tablet (Aloe vera gel powder)**

In vitro drug release was studied using USP II (paddle) apparatus, (Electrolab TDT-08L) with 900 ml of dissolution medium maintained at 37±1 °C for 15 h, at 50 rpm. 0.1 N HCl (pH 1.2). 5 ml of sample was withdrawn in 10 min time intervals. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. Collected samples were analyzed by U. V spectrophotometrically at 262 nm, and cumulative percent drug release was calculated.

***In vitro* drug release was studied for sustained release tablet (Diclofenac sodium)**

The *In vitro* dissolution study for the Diclofenac sodium sustained release tablets were carried out in USP type-II dissolution test apparatus (Electrolab TDT-08L) (Paddle type) using 900 ml of phosphate buffer pH 6.8 at 50 rpm and temperature 37±0.5 °C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed by measuring the absorbance at 275 nm using UV Visible spectrophotometer and calculate the percentage drug release.

***In vitro* drug release was studied for bilayer tablet**

The release of bilayer tablets was determined using USP Type II (Paddle) dissolution apparatus (Electrolab TDT-08L) under sink condition. The dissolution medium was 900 ml of a 0.1N HCl solution (pH=1.2), at 370c±0.20c for 1hour. Then dissolution media replace by phosphate buffer (6.8pH). The stirring speed was 50 rpm. Aliquot of the solution was collected at the specific interval were replaced with fresh dissolution medium. The Aloe vera gel powder and Diclofenac sodium were analyzed spectrophotometrically at 262 nm and 275 nm respectively using simultaneous equation method.

RESULTS AND DISCUSSION

Pre-formulation studies

The UV absorption of 10 µg/ml in methanol for Aloe vera gel powder is 262 nm in the range of 200-400 nm exhibit maximum and in case of Diclofenac sodium at 275 nm.

Melting point, solubility and compatibility study of both drugs are carried out and the result is including in table 4.

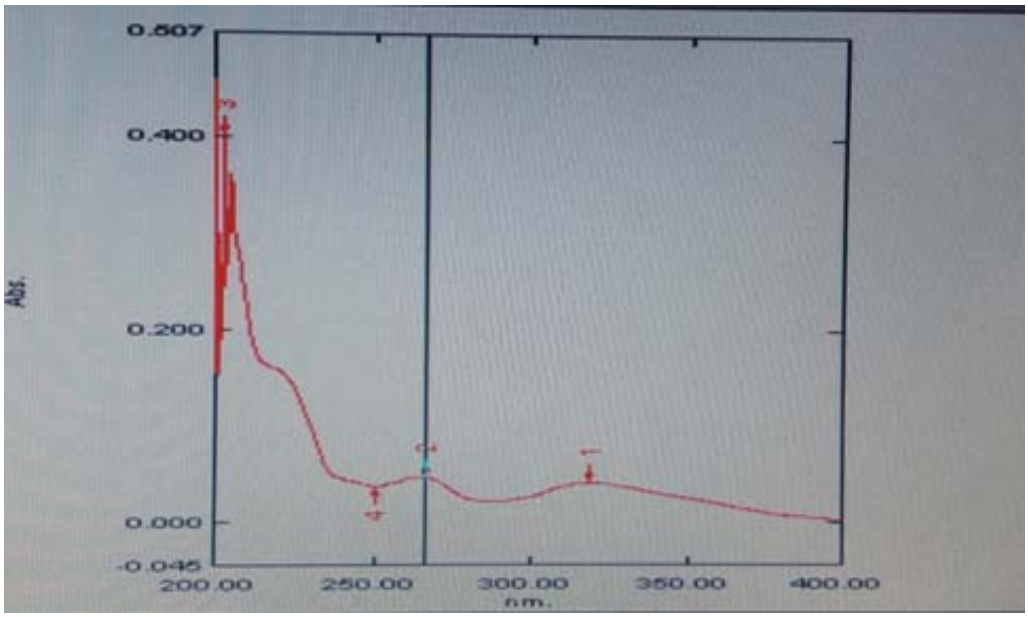

Fig. 1: Absorbance maxima of aloe vera gel powder

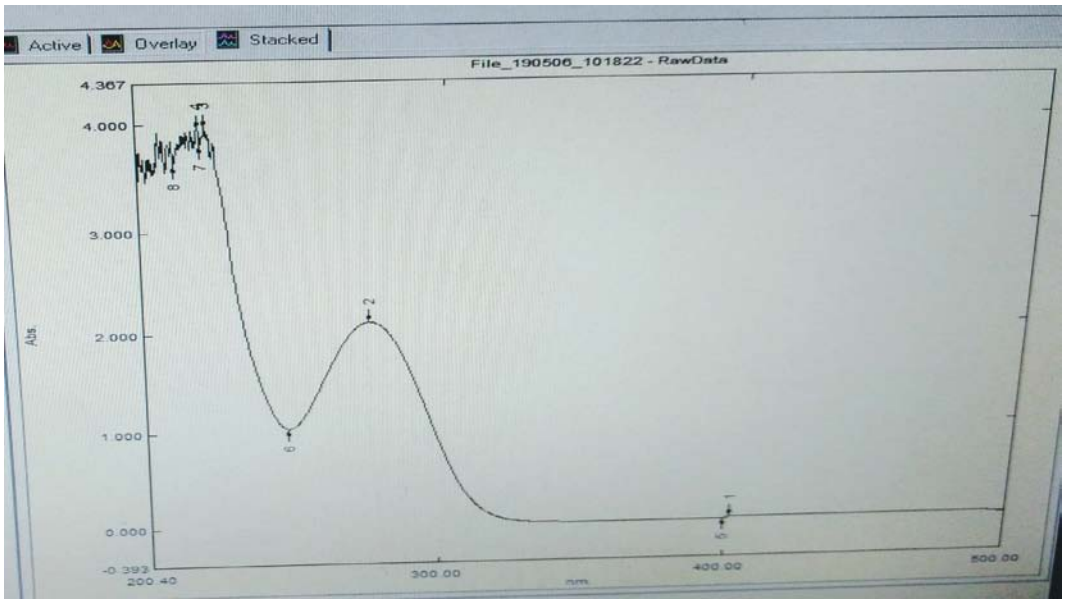

Fig. 2: Absorbance maxima of diclofenac sodium

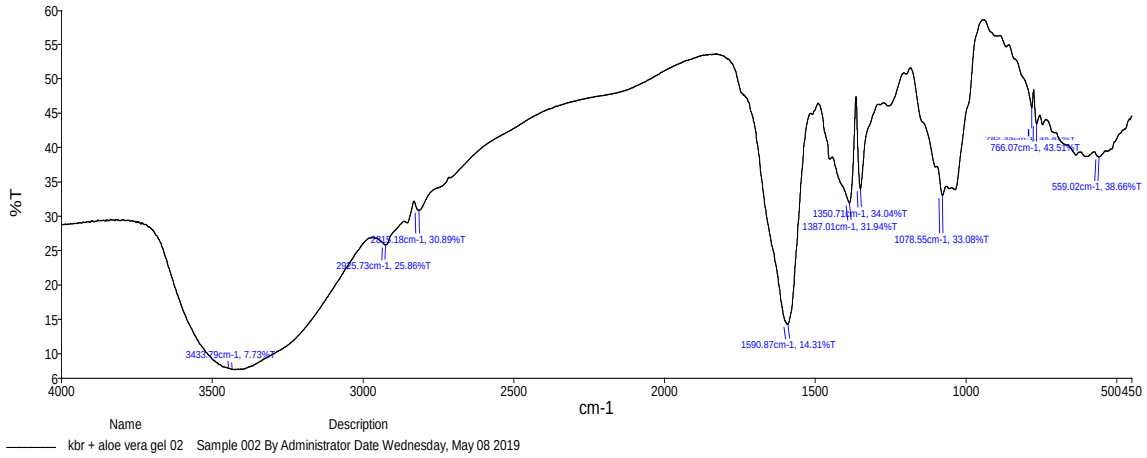

Fig. 3: FTIR of Aloe vera gel powder

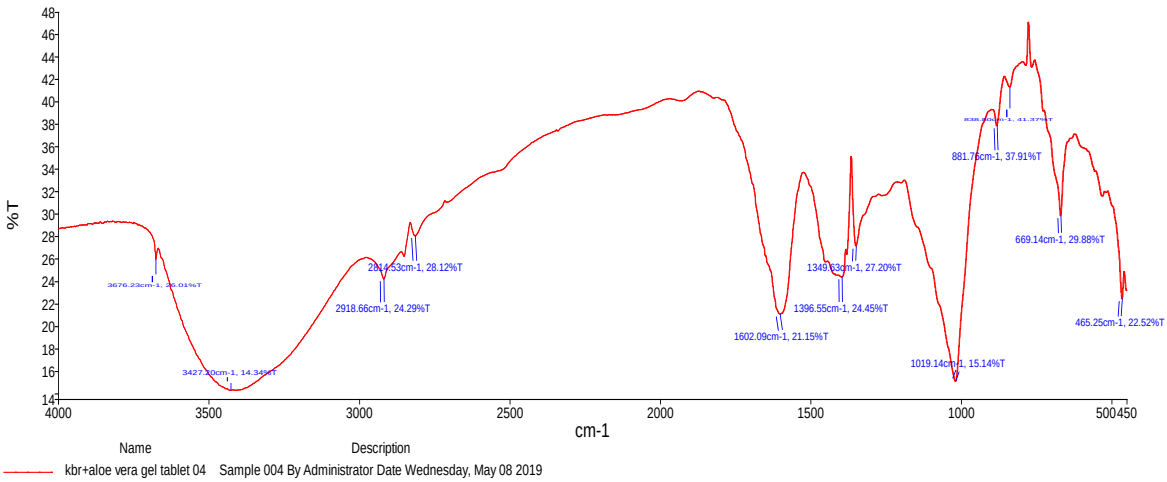

Fig. 4: FTIR of Aloe vera gel powder tablet

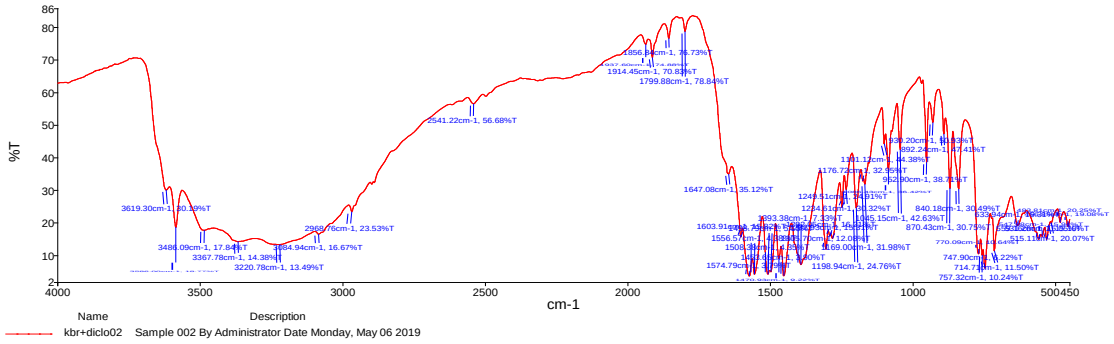

Fig. 5: FTIR of diclofenac sodium

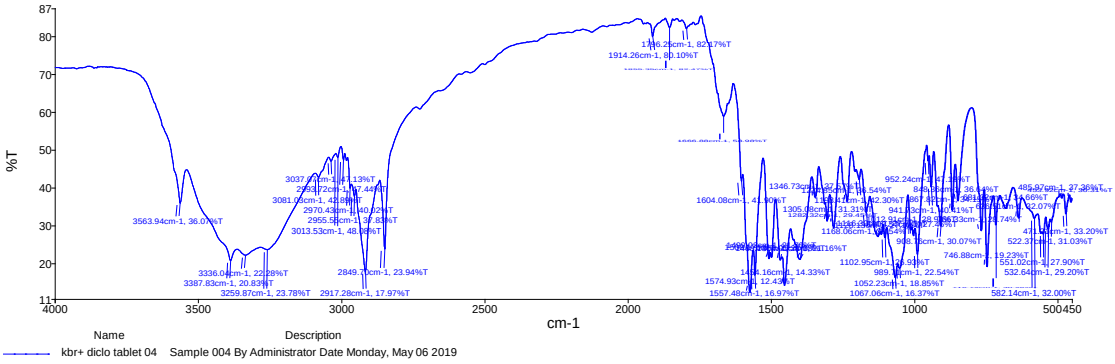

Fig. 6: FTIR of diclofenac sodium tablet

Table 4: Preformulation study of aloe vera gel powder and Diclofenac sodium

S. No.	Parameter	Aloe vera gel powder	Diclofenac sodium
1	Identification by U. V Vis spectrophotometer.	262 nm (ʎ max)	275 nm (ʎ max)
2	Melting Point	224 °C	289 °C
3	Solubility	Highly Soluble in water, ethanol, methanol, phosphate buffer, poorly soluble in chloroform.	Soluble in water, methanol, ethanol, phosphate buffer, insoluble in ether sparingly soluble in acetone.
4	Compatibility study	compatible	Compatible

Pre-compression evaluation

The micromeritic properties such as of bulk density, tapped density, Angle of repose, compressibility index, and Hausner's of Aloe vera gel powder immediate release layer blend and Diclofenac sodium sustained release layer were studied. The overall results were shown in table No5. The value of bulk density indicates good packing characteristics. The compressibility index of the formulation Indicating poor flow properties of powder which were further confirmed by determining the angle of repose, it is in the range of 16 ° to 26 ° which indicates good flow properties.

Table 5: Pre-compression evaluation of immediate release powder blend (Aloe vera gel powder)

S. No.	Parameter	A1	A2	A3
1	Bulk density (g/ml)	64.36	66.10	61.94
2	Tapped density (g/ml)	75.23	78.63	73.80
3	Compressibility index (%)	14.44%	15.93%	16.07%
4	Hausner's ratio	1.16	1.18	1.19
5	Angle of repose (degree)	22.6 °	24.90 °	24.63 °

Table 6: Pre-compression evaluation of sustained release powder blend, (diclofenac sodium)

S. No.	Parameter	D1	D2	D3
1	Bulk density (g/ml)	56.67	60.5	58.20
2	Tapped density (g/ml)	68.1	69.6	66.70
3	Compressibility index (%)	16.1%	13.07%	12.87%
4	Hausner's ratio	1.20	1.16	1.14
5	Angle of repose (degree)	20 °	21.5 °	24.2 °

Post-compression evaluation of tablet

The prepared tablets were evaluated for weight variation, dissolution test, thickness, hardness uniformity of dosage units and friability. The weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average.

The hardness of each batch of the tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm2. The hardness of 6 tablets was determined using

The Friability was determined by first weighing 10 tablets after dusting and placing them in a friability tester (Roche friabilator), which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of tablet was recorded and the percent friability was calculated.

The thickness of the each 10 tablets was measured with the Varnier Caliper. All test value are included. Drug content uniformity and *In vitro* drug release determined according to the USP requirements. Test values are including in table 9.

Table 7: Post-compression evaluation of immediate release tablet

S. No.	Parameter	A1	A2	A3
1	Uniformity weight(mg)	149 mg	147 mg	153 mg
2	Thickness(mm)	3.0	3.1	3.0
3	Hardness(kg/cm^2)	3.2 kg/cm^2	3 kg/cm^2	3.5 kg/cm^2
4	Friability (%)	0.84%	0.67%	0.91%
5	Drug content	97.54	98.10	96.92
6	% Drug release	90.21%	89.75%	87.82%

Table 8: Post-compression evaluation of sustained release tablet

S. No.	Parameter	A1	A2	A3
1	Uniformity weight(mg)	199 mg	203 mg	201 mg
2	Thickness(mm)	3.5	3.5	3.7
3	Hardness(kg/cm^2)	6.5 kg/cm^2	7 kg/cm^2	6.2 kg/cm^2
4	Friability (%)	0.54%	0.91%	0.80%
5	Drug content	95.40	91.50	96.92
6	% Drug release	91.21%	86.35%	82.12%

Table 9: Post-compression evaluation of bilayer tablet of A1 and D3 Optimized batch

S. No.	Parameter	A1D3
1	Uniformity weight(mg)	349 mg
2	Thickness(mm)	3.5 mm
3	Hardness(kg/cm^2)	5.2 kg/cm^2
4	Friability (%)	0.90%
5	Drug content (immediate release)	97.21
	Drug content (Sustained release)	95.49
6	% drug release (immediate release)	93.80%
	% drug release (Sustained release)	84.26%

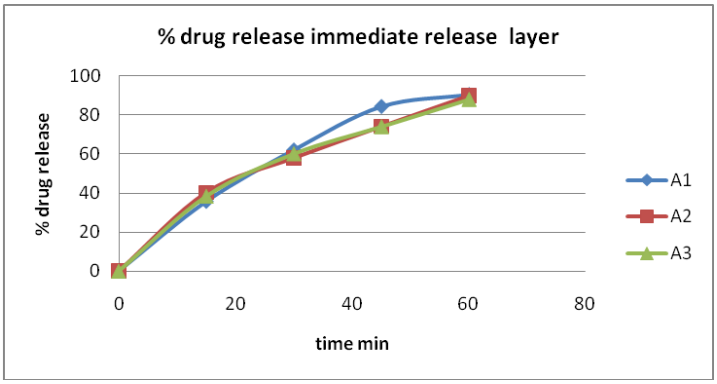

Fig. 7: % Drug release immediate release layer (Aloe vera gel powder)

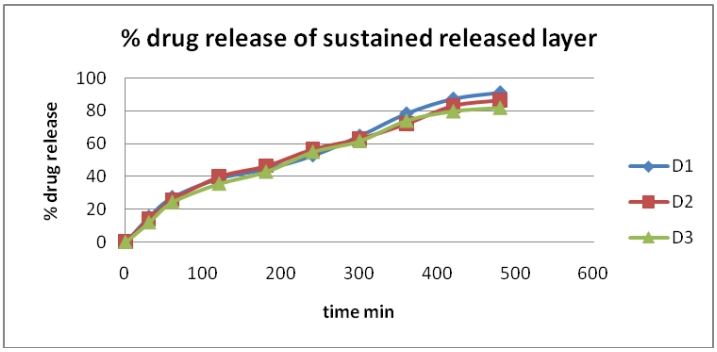

Fig. 8: % Drug release of the sustained released layer (diclofenac sodium)

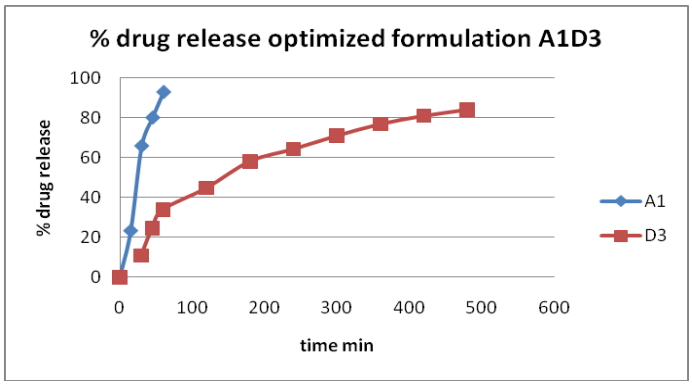

Fig. 9: % Drug release optimized formulation A1, D3

Table 10: Drug release kinetics of Aloe vera gel powder

Time (H)	cumulative % drug released	% drug remaining	Square root time	log cumu % drug remaining	log time	log Cumu % drug released	% Drug released	Cube root of % drug remaining (Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
15	20.5	79.5	3.873	1.900	1.176	1.312	20.5	4.300	0.342
30	66	34	5.477	1.531	1.477	1.820	45.5	3.240	1.402
45	80.2	19.8	6.708	1.297	1.653	1.904	14.2	2.705	1.937
60	93.01	6.99	7.746	0.844	1.778	1.969	12.81	1.912	2.730

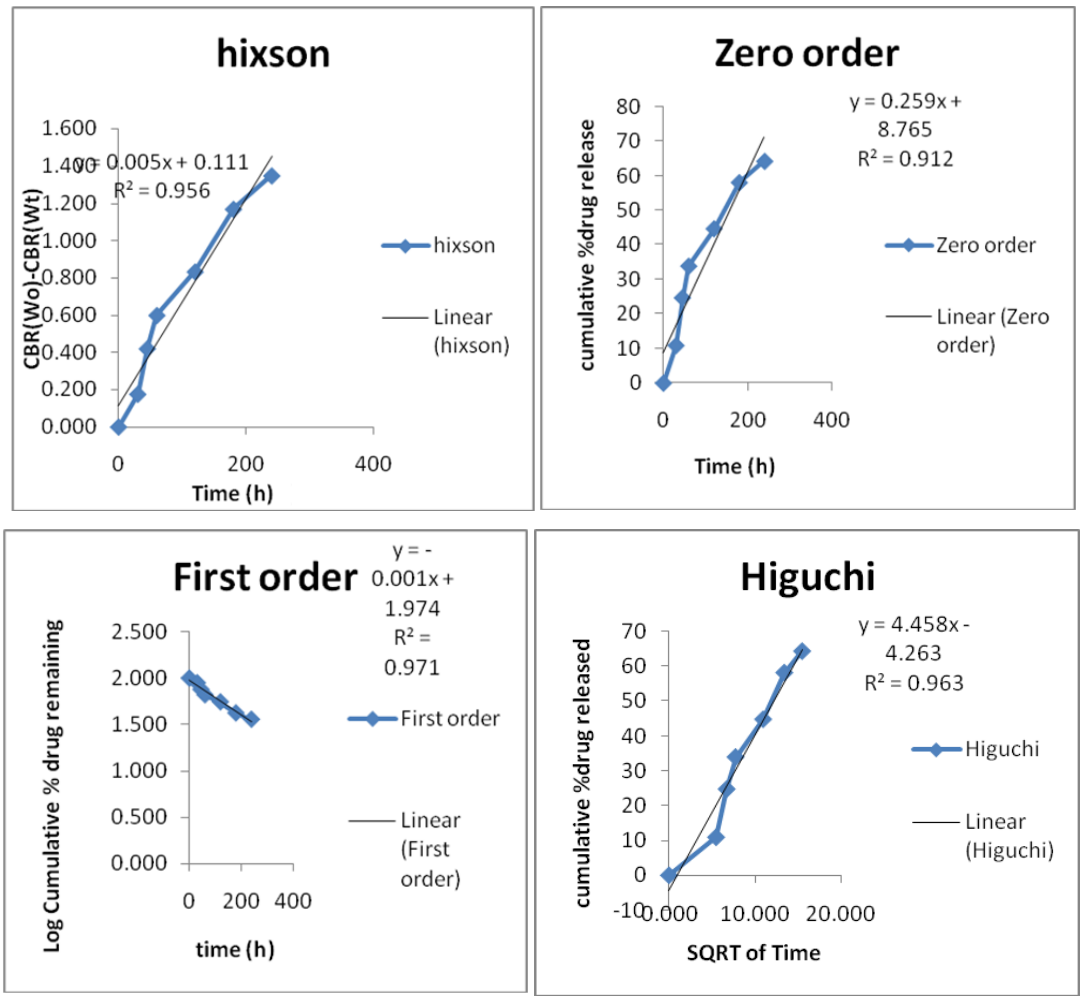

Fig. 10: Drug release kinetic of immediate release layer (Aloe vera gel)

Table 11: Drug release kinetics of diclofenac sodium

Time (H)	Cumulative % drug released	% drug remaining	Square root time	log cumu % drug remainining	log time	log cumu % drug released	% Drug released	Cube root of % drug remaining (Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
30	10.92	89.08	5.477	1.950	1.477	1.038	10.92	4.466	0.176
45	24.73	75.27	6.708	1.877	1.653	1.393	13.81	4.222	0.420
60	33.92	66.08	7.746	1.820	1.778	1.530	9.19	4.043	0.599
120	44.75	55.25	10.954	1.742	2.079	1.651	10.83	3.809	0.833
180	58.12	41.88	13.416	1.622	2.255	1.764	13.37	3.473	1.169
240	64.28	35.72	15.492	1.553	2.380	1.808	6.16	3.293	1.349
300	70.97	29.03	17.321	1.463	2.477	1.851	6.69	3.073	1.569
360	76.83	23.17	18.974	1.365	2.556	1.886	5.86	2.851	1.791
420	80.98	19.02	20.494	1.279	2.623	1.908	4.15	2.669	1.973

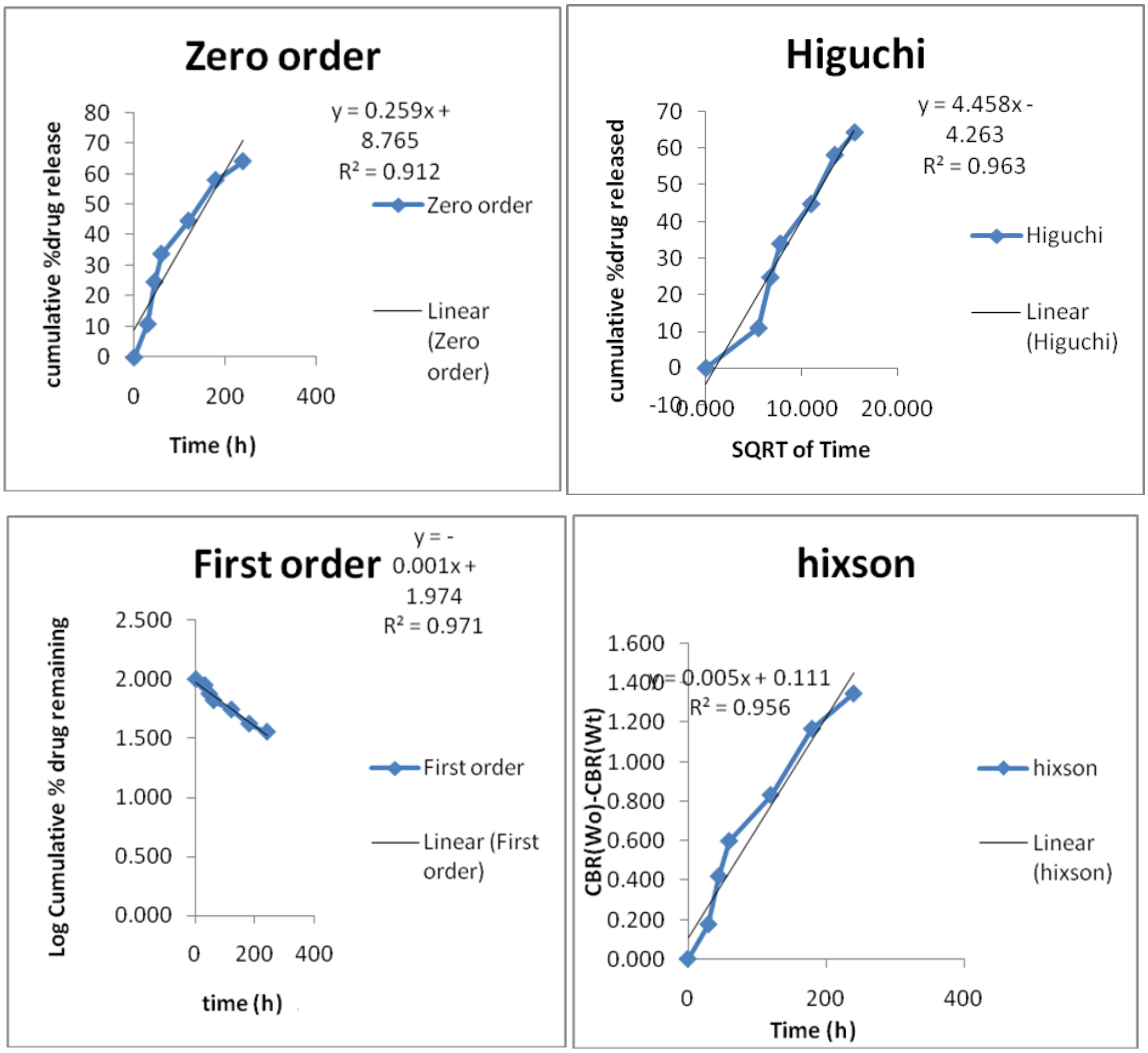

Fig. 11: Drug release kinetic of sustained release layer (diclofenac sodium)

Kinetic models

Dissolution data of above bi-layered tablet was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

CONCLUSION

The prepared tablets showed satisfactory results for various evaluation tests such as tablet dimension, hardness, friability, weight uniformity, drug content and *in vitro* dissolution study. The optimized formulation based on all the parameter A1 (Sodium starch glycolate) is selected for the immediate release layer and D3 (HPMC K4M) was selected for the controlled release layer. The drug release mechanism was found to be zero order release; dependent on both drug diffusion and polymer relaxation. The bilayer tablets of Aloe vera gel powder and Diclofenac sodium useful for NSAID with antiulcer Aloe vera gel powder.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declare none

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