International Journal of Pharmaceutical and Bio-Medical Science

ISSN(print): 2767-827X, ISSN(online): 2767-830X

Volume 03 Issue 10 October 2023

Page No: 521-529

DOI: https://doi.org/10.47191/ijpbms/v3-i10-03, Impact Factor: 6.858

Formulation and Evaluation of Bilayer Anti-Diabetic Tablet of Murayya Koeinigii and Spinach Olaracea

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ABSTRACT

The purpose of this study was to develop and evaluate bilayer tablet for the immediate and controlled release of murayya koeinigii and spinach oleracea for effective treatment of diabeties (Type 2). The immediate release layer was prepared by using super disintegrants- starch powder and the sustained release layer was prepared by using polymer like acaia, HPMC E5 and Methyl cellulose. Before preparation of the tablets, all the preformulation parameters were checked and the tablet of murayya koeinigii and spinach oleracea were prepared by direct compression method and was evaluated for physical characteristics like hardness, weight variation, drug content and friability. In vitro release of drug was performed USP type II dissolution test apparatus using distilled water buffer as dissolution media and dissolution was continued for 10 hrs for the sustained release layer. It was found that all the formulations were within the limit of the standard. The drug release of the tablet was in the range of 67%-99% in 10 h. The drug release pattern of formulation F5 was fitted in different kinetic models which showed highest regression for zero order kinetics with Koresmeyer Peppas through non-fickian type of drug release mechanism. Hence It was concluded that the F5 formulation showed the optimum result as a bilayer tablet for the effective treatment of diabeties (Type 2).

KEYWORDS: Sustained release, Bilayered tablet, Herbal tablet, Diabetes mellitus

ARTICLE DETAILS

Published On:
17 October 2023

Available on:
https://ijpbms.com/

INTRODUCTION

Diabetes mellitus represents a cluster of metabolic disorders marked by persistent high blood sugar levels, which arise from shortcomings in insulin secretion, insulin function, or both. These metabolic abnormalities affect the processing of carbohydrates, lipids, and proteins, all of which hinge on insulin's role as an anabolic hormone. The inadequate response to low insulin levels and the resistance of target tissues, primarily skeletal muscles and adipose tissue, as well as to a lesser extent, the liver, at the level of insulin receptors, signal transduction systems, and/or effector enzymes or genes, contribute to these metabolic irregularities. The type and duration of diabetes determine the intensity of symptoms. Some diabetes patients, notably those with type 2 diabetes in the early stages of the disease, may remain asymptomatic. In contrast, individuals with pronounced hyperglycemia, particularly children with an absolute lack of insulin, may experience symptoms like excessive urination, excessive thirst, increased appetite, weight loss, and blurred vision. If left uncontrolled, diabetes can escalate to a state of stupor, coma, and potentially fatal outcomes, primarily due to keto acidosis or, albeit rarely, nonketotic hyper osmolar syndrome. Factors contributing to type 2 diabetes, whether they are irreversible, such as age, genetics, race, and ethnicity, or modifiable, like dietary choices, physical activity, and smoking habits, play a pivotal role in its development and management. (1)

Curry leaf (Murraya koenigii) is one of 1600 species and 150 genera in the Rutaceae family [2]. According to research, it is native to South Asia, most notably Bangladesh, India, and Sri Lanka [3]. Murraya koenigii was employed for the first time between the first and fourth centuries AD. The entire plant is regarded as tonic and stomachic and has been used historically [4]. Along with Mitha Neem in Hindi and Surabhinimba in Sanskrit, Karuveppilai is also found in Tamil [5]. Curry leaf plants can be used as a hedge and attractive shrub because of their complex leaves [6]. The M. koenigii plant's green leaves are used to cure a variety of conditions, including edema, bruises, piles, diarrhea, inflammation, itching, and new cuts. The roots have a purgative effect. They are energising and utilised for general body aches. Snake bites can be treated with the bark [7-8].

The Amaranthaceae family includes spinach (Spinacia oleracea L.), a dark green leafy vegetable related to beets and chard. [9]. Spinach (English), Chhurika (Sanskrit), Palak (Hindi, Gujarati, and Marathi), Palakh (Kashmiri), Palang (Bangla), Pasalai (Tamil), and Mathrubhumi (Telugu) are some of the common names for Spinacia oleracea [10]. Possibly the most nutrient- dense vegetable eaten in the US is spinach, with broccoli coming in second. [11] . A cool-season perennial vegetable, spinach (Spinacia oleracea L.) can be consumed raw, cooked, canned, frozen, in baked goods, soups, and other dishes[12]. Indian vegetarian diets heavily emphasize vegetables. According to research, fruits and vegetables account for 95% of the country's total -carotene availability, with green leafy vegetables accounting for 52%.and mangoes accounting for 90 percent of this total (38%) [13] .

Bilayer Tablet

The notion of a bi-layer tablet has long been used to create formulations with sustained release. To maintain the drug's release, this tablet may have one (bi layer) fast-releasing layer. The pharmacokinetic advantage is based on the assumption that when a drug is released from the fast-releasing layer, the blood concentration increases abruptly. However, once the sustaining layer is released, the blood level is kept consistent [14]. Oral sulfonylurea hypoglycaemic drugs' mechanisms of action may also include extrapancreatic effects. [15]

Type of bilayer tablets [16,17]

a. Single side tablet press
b. Double sided tablet press
c. Bilayer tablet press with displacement monitoring

MATERIALS AND METHODS

Standard graph:

Preparation of standard graph of murayya koeinigii and spinacia olaracea :

Preparation of primary stock solution: 100 mg of a mixture of plant components were precisely weighed and then added to a 100 ml volumetric flask. Plant products can be made to dissolve by adding small amounts of distilled water, and using distilled water, the volume can be increased to 100 ml.

Preparation of standard solutions:

Pipette 1, 2, 3, 4, 5, and 6 ml of the secondary stock solution into a different 10 ml volumetric flask, and then fill the remaining space with distilled water to make it up to 10 ml, which contains 10, 20, 30, 40, 50, and 30 g/ml of plant extracts from the spinacia olarace and the murayya koeinigii, respectively

The 470 nm wavelength was used to scan the standard solutions, and the associated absorbances were recorded. After that, a standard graph was generated by placing the concentration on the X-axisand the absorbance on the Y-axis.

PREPARATION OF BILAYER TABLETS OF MURAYYA KOEINIGII AND SPINACIAOLARACEA: BY DIRECT COMPRESSION METHOD:

- **Preparation of Immediate release layer**

Starch powder acts as a disintegrating agent and diluent. Magnesium stearate acts as a lubricant. The tablets were prepared by using direct compression method.

- **Preparation of Sustained release tablets**

Murrayya koenigii can be made into a dosage form with prolonged release. Different ratios of acacia and ethyl cellulose are employed as polymers to achieve the desired effect. As a binder, ethyl cellulose is used. In the formulations for sustained release, binder is important. As a lubricant, magnesium stearate is used. The direct compression approach was used to formulate the tablets.

- **Preparation of Bilayered tablet**

In this process, the first step sustained release powder are weighted accurately and fed in to die cavity of tablet punching machine. The next step involves immediate release powder are fed in to die cavity and compressed so that final hardness can be achieved. After preparation of tablets, the tablets are subjected for evaluation.

COMPOSITION OF BILAYER LAYERED TABLET

Table1: Composition of bilayer layered tablet

Layers	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Immediate release layer	Spinach powder	20	20	20	20	20	20	20	20	20
	Starch powder	72	70	65	60	55	70	65	60	55
	Lactose	106	100	95	90	85	100	95	90	85
	Polyethylene glycol (PEG)	-	08	18	28	38	-	-	-	-
	Polyvinyl pyrolidine	-	-	-	-	-	08	18	28	38
	(PVP)									

Amaranths	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	2	2	2	2	2	2	2	2	2
Murayya koenigii	36	36	36	36	36	36	36	36	36
Acacia	80	75	70	65	60	75	70	65	60
Ethyl cellulose	176	170	165	160	150	140	145	155	165
Methylcelluose	-	11	21	31	46	-	-	-	-
HPMC E5	-	-	-	-	-	41	41	36	31
Magnesium stearate	8	8	8	8	8	8	8	8	8
	500	500	500	500	500	500	500	500	500

POST-COMPRESSION EVALUATION PARAMETER FOR FORMULATED TABLETSOF PIPER BETEL:

1. Weight variation test:

Weighing all twenty tablets of each formulation yielded the average weight. The %deviation was calculated using the formula below.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

In accordance with the Indian Pharmacopoeia's guidelines, the weight variation's percentagedifference must not exceed 10%.

2. **Diameter and Thickness**- Using Vernier Calipers diameter and thickness of each tabletwere measured and noted.

3. **Hardness**- A Monsanto hardness tester was used to assess the tablets. Tablets of each formulation's hardness were examined and recorded.

4. **Friability** The friability was determined using the Roche friabilator, which is given as apercentage. 20 tablets were taken after being weighed (W initial). Selected tablets that had been preweighed were placed in the friabilator, which rotated for 4 minutes at a speed of 25 rpm (100 revolutions). The tablets were then taken out of the chamber, cleaned, and weighedonce more (W final). Next, the% friability was determined using

F= {(W initial)- (W final)/ (W initial)}×100

5. Drug Content [18]

The average weight of 20 tablets was determined after a random selection of them. The tablets were crushed in a mortar, and then an exact weight of the average tablet weight was removed andput into a volumetric flask measuring 100 mL. To dissolve the drug, a small amount of methanol was added to the mixture, and the volume was then adjusted using the appropriate medium. To ensure that the drug was completely dissolved, the container was stored for an hour while being shook occasionally. After filtering, the proper dilutions were created. The final step was to detectdilutions using a spectrophotometer to calculate the medication content. The drug's content should fall between 90 and 110% of standard dose.

6. In vitro dissolution studies [19][20]

Using USP type II apparatus (paddle type), in vitro dissolving tests of bilayer tablets of Murayya koeinigii and Spinacia olaracea were conducted. The dissolution vessel was filled with 900ml of pH 7 distilled water, and the medium's temperature was then set to 37±0.50C. One tablet was added to each dissolving vessel after the paddle's rotational speed was set to 50 rpm.For ten hours, 10ml of solution was taken out of the dissolving vessels every hour, and the samples were then replaced with 10ml of brand-new dissolution medium. Using a UV spectrophotometer, the solution's absorbance at 470 nm was determined.

7. Drug release kinetics [21][22]

The results of an in-vitro dissolution research of a formulation that showed good parameters were investigated using different kinetics equations (zero order, first order, Higuchi model, and Korsmeyer Peppas) in order to determine the precise mechanism of drug release from the dosageform.

8. Stability Studies [22]

The purpose of stability testing is to provide evidence on how the quality of drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. The optimized bilayer tablets were subjected to stability studies (as per ICH guidelines) at 40°C ± 2°C/75% ± 5% RH in a humidity chamber. The products were evaluated for their physical characteristics and *in vitro* drug release profiles over a period of 3 months.

RESULTS

Standard graph

- **Standard graph of Murrayya koenigii and spinacia oleracea:**

The standard plot of murayy koenigii and spinacia olaraceaa in distilled water was shown in figure. The data of absorbance

was shown in table. The correlation coefficient obtained was 0.9937

Table 2: Data of standard plot of Murrayya koenigii and spinacia olaracea of distilled water

Concentration (µg/ml)	Absorbance
0	0
10	0.035±0.02
20	0.051±0.05
30	0.077±0.01
40	0.10±0.02
50	0.127±0.01

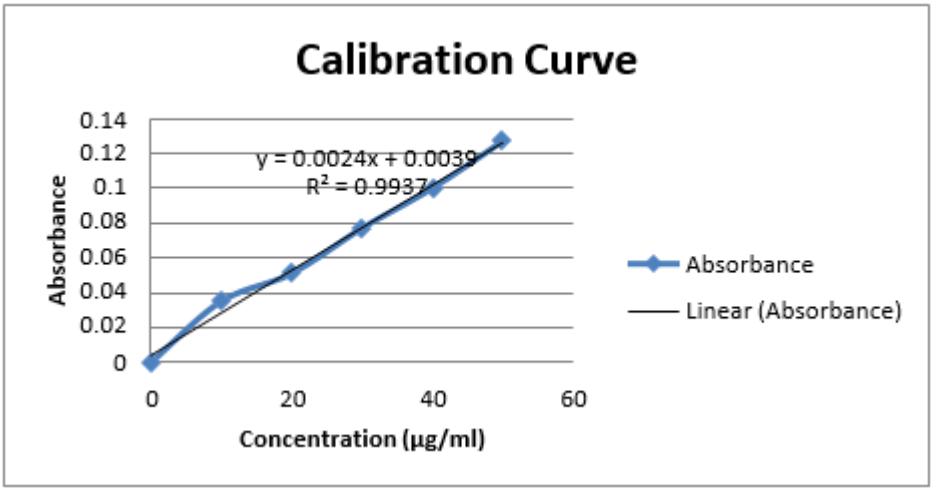

Fig-1: Standard graph of murayya koeinigii and spinacia oleraceaDrug-Excipient Compatibility Studies by FT-IR

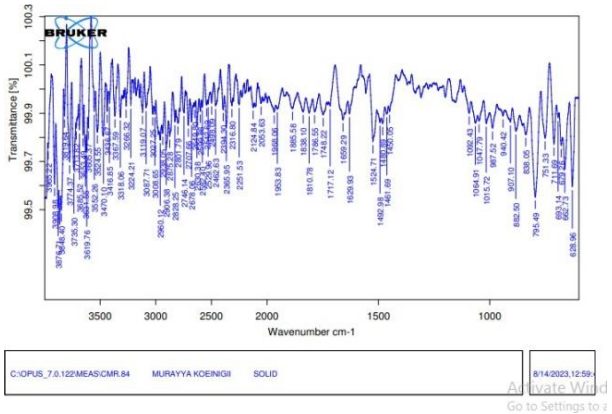

Fig2: FTIR of Murrayya koeinigii

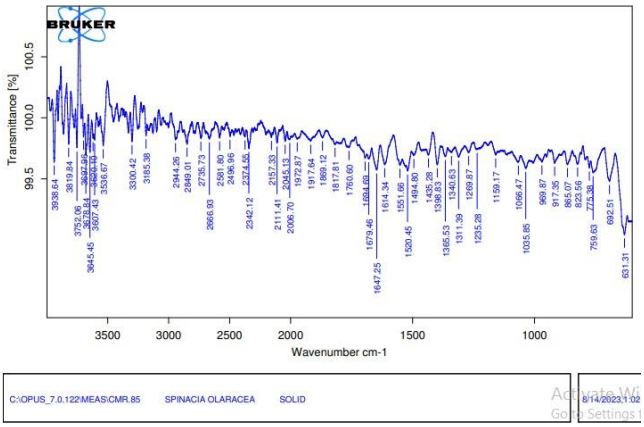

Fig3: FTIR of spinacia olaracea

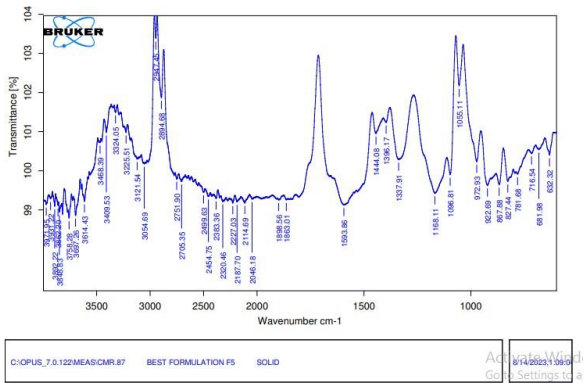

Fig4: FTIR of Best formulation

The compatibility of drugs with their respective excipients was studied by FT-IR spectroscopy (Bruker, India). The scanning was performed 20 times at scanning speed 2 mm/sec with resolution of 4 cm^{-1} over the region 4000–400 cm^{-1}. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks, and appearance of new peaks due to polymer interaction.

Precompression Parameters of Bilayered tablet

Table 3: Precompression Parameters of Bilayered tablet

Formulation	Bulk density*g/cm^3	Tapped density*g/cm^3	Carrs index* g/cm^3	Hausner'srati	Angle repose*
F1	0.45±0.014	0.55±0.014	12.11±0.017	1.02±0.014	21.36±0.014
F2	0.41±0.015	0.56±0.018	12.41±0.014	1.09±0.017	22.89±0.014
F3	0.46±0.018	0.59±0.013	12.99±0.017	1.11±0.017	21.90±0.012
F4	0.49±0.017	0.60±0.011	13.17±0.015	1.04±0.014	25.01±0.017
F5	0.44±0.018	0.57±0.017	12.40±0.016	1.03±0.016	25.91±0.018
F6	0.42±0.014	0.54±0.016	14.24±0.015	1.07±0.017	21.01±0.017
F7	0.50±0.017	0.56±0.014	13.75±0.011	1.03±0.024	23.64±0.014
F8	0.45±0.014	0.58±0.017	13.57±0.017	1.18±0.011	22.73±0.014
F9	0.43±0.014	0.52±0.016	12.47±0.012	1.16±0.014	24.11±0.017

The bulk density, tap density, carrs index, hausners ratio, angle of repose were determined andreported in table3. All the parameters were within the acceptable limits

Evaluation of post compression parameter of Bilayer tablet:Table4: Post compression parameter of Bilayer tablet

Formulation	Thickness	Hardness(kg/cm^2)	Weight variation (mg)	Friablity(%)	Drug content(%)
F1	3.5±0.019	5.8±0.012	491.01±0.014	0.53±0.017	97.34±0.019
F2	3.9±0.024	5.6±0.013	499.37±0.012	0..37±0.016	98.27±0.017
F3	3.7±0.012	5.9±0.014	463.27±0.017	0.38±0.015	98.83±0.016

F4	4.1±0.013	6.1±0.017	489.09±0.016	0.29±0.014	97.90±0.017
F5	4.7±0.012	6.0±0.014	496.07±0.017	0.34±0.027	99.98±0.018
F6	4.8±0.012	5.7±0.015	491.14±0.019	0.29±0.017	97.64±0.017
F7	3.9±0.014	6.1±0.016	482.37±0.027	0.33±0.016	99.01±0.018
F8	4.1±0.019	5.7±0.015	489.37±0.017	0.53±0.018	97.95±0.024
F9	4.0±0.013	5.5±0.017	488.90±0.019	0.29±0.024	96.48±0.017

The thickness of all formulations was in the range 3.5-4.8mm. The hardness ranged from 5.5-6.1 kg/cm^2. All formulations passed the USP requirements for friability and uniformity of weight Table No.4

Table 5: In Vitro Dissolution Data for Batches F1 – F9

Time in	**Cummulative % drug release**								
min	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	**0**	0	0	0	0
5	17.32±0.01	17.32±0.10	34.64±0.10	33.33±0.03	**26.95±0.01**	26.65± 0.02	21.65± 0.10	28.64± 0.21	31.49±0.21
10	24.74±0.01	25.00±0.01	35.25±0.10	38.57±0.10	**31.22±0.03**	34.64± 0.21	31.49± 0.32	36.74± 0.01	44.1±0.29
20	26.96±0.02	28.64±0.02	39.74±0.01	43.59±0.02	**33.07±0.21**	37.75± 0.32	35.25± 0.03	43.3±0 .02	49.49±0.10
30	28.39±0.03	31.22±0.32	46.63±0.10	45.3±0.21	**56.7±0.031**	39.85± 0.010.0 1	43.3±0. 10	49.38± 0.03	53.29±0.29
60	36.66±0.03	34.44±0.02	52.04±0.10	50.29±0.01	**58.33±0.10**	44.61± 0.21	44.1±0. 01	53.29± 0.29	55.87±0.27
120	37.63±0.01	38.42±0.21	58.93±0.02	52.7±0.03	**67.14±0.32**	48.1±0. 10	49.49± 0.34	55.3±0 .27	58.75±0.32
180	39.11±0.02	56.77±0.27	62.99±0.02	54.95±0.27	**71.34±0.34**	52.04± 0.01	53.29± 0.41	60.08± 0.34	62.9±0.01

240	44.41±0.03	67.36±0.10	64.67±0.21	56.29±0.29	**77.09±0.41**	55.79± 0.27	57.74± 0.21	65.58± 0.32	63.6±0.34
300	49.07±0.01	70.18±0.21	66.29±0.10	61.33±0.29	**79.19±0.01**	57.21± 0.34	59.54± 0.03	68.25± 0.34	74.06±0.02
360	51.45±0.12	72.38±0.01	67.57±0.03	63.29±0.37	**85.92±0.41**	58.89± 0.02	62.01± 0.10	71.14± 0.02	79.87±0.03
420	54.29±0.02	75.93±0.02	72.52±0.10	70.82±0.32	**87.9±0.41**	61.86± 0.03	64.45± 0.10	74.23± 0.21	84.43±0.21
480	67.45±0.02	81.7±0.27	73.62±0.21	78.53±0.01	**90.82±0.27**	62.47± 0.29	68.25± 0.32	76.71± 0.01	87.5±0.41
540	70.17±0.02	83.36±0.10	80.21±0.29	86.25±0.27	**97.3±0.34**	65.33± 0.41	70.32± 0.41	80.21± 0.29	90.55±0.10
600	73.92	87.84	88.48	92.46	**99.29**	67.12	71.97	82.84	94.25

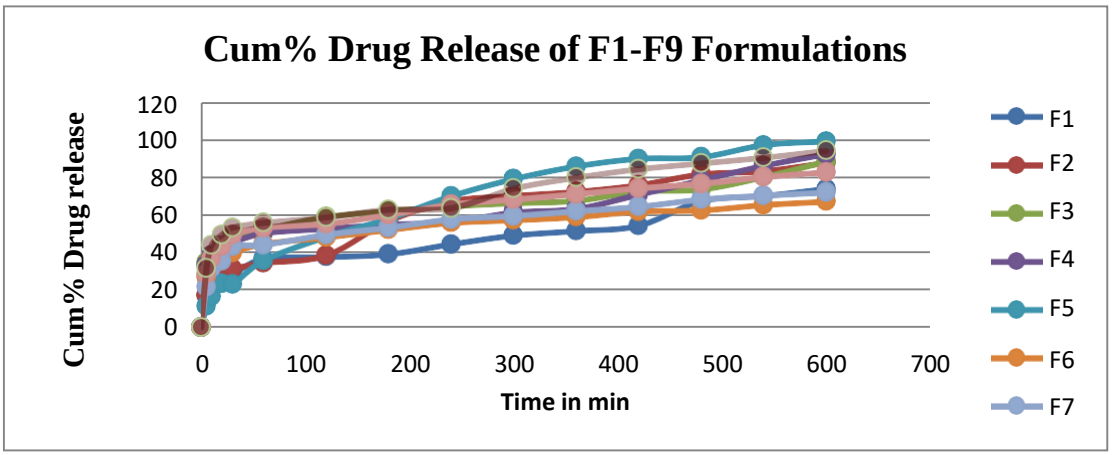

Fig 5: Cum% Drug Release of F1-F9 Formulations

From the in vitro profile for bilayer tablet of murayya koeinigii and spinacia oleracea from F1 to F9 the drug released was found to be 73.92%, 87.84% ,88.48%, 92.46%, 99.29%, 67.12%, 71.97%, 82.84%, 94.25%, respectively at the end of 10hrs. From this release profile, it was evident that the formulation F5 was suitable.

Table 6: Treatment of Dissolution Data into Different Models of Bilayered tablet

Formulation	Zero order		First order		Higuchi Plot		Krosmeyer – Peppas plot	
	n	R^2	n	R^2	n	R^2	n	R^2
F1	0.1318	0.9475	0.704	0.8494	3.0192	0.9349	0.5913	0.9234
F2	0.1373	0.9567	0.6039	0.8228	3.8435	0.9352	0.5711	0.9023
F3	0.1576	0.9555	0.8043	0.9078	3.8826	0.9669	0.7073	0.9458
F4	0.1753	0.9135	0.7945	0.8632	3.7052	0.9141	0.7671	0.9604
F5	0.182	0.9862	0.6044	0.9131	3.6446	0.9001	0.7026	0.9816
F6	0.1391	0.9617	0.7341	0.9616	2.9687	0.9781	0.6427	0.9619
F7	0.1736	0.9833	0.7044	0.9235	3.052	0.9352	0.6919	0.9699
F8	0.1618	0.9399	0.7042	0.9449	3.4569	0.9661	0.6689	0.9393
F9	0.1692	0.9461	0.7043	0.9411	3.7739	0.9778	0.6789	0.9673

The results of the optimized bilayer tablet's dissolution data were fitted to different drug release kinetic models, including the Zero-Order, First Order, Higuchi, and Peppas models, in order to determine the drug's release mechanism. The table no. 6 displays the calculated R2 and n values. According to the findings, all formulations follow zero-order over first order. Sustained release formulations that fit in zero-order rather than first-order are acceptable.

Stability study

Table 7: Stability study of optimized formulation

TEST	Time (Days)			
	0	**30**	**60**	**90**
Weight variation	496.07±0.017	496.05±0.017	496.03±0.016	496.02±0.016
Hardness	6.0±0.014	6.0±0.014	5.9±0.014	5.9±0.014
Drug content %	99.9	99.8	99.6	99.5
In vitro dissolution	99.2	99.19	99.11	99.02

Optimized formulations of bilayer tablet were subjected to stability studies as per ICH guidelines. Various parameters such as weight variation , hardness, drug content, and in vitro dissolution profile release were measured before and after 30, 60 and 90 days of stability. Results of stability studies are shown in table no.7.Physical appearances of all formulations were unaffected or did not show any significant changes.

CONCLUSION

The aim of this study is to Design and Evaluate Bilayered tablet of murayya koeinigii and spinacia oleracea belongs to antidiabetic agents. In this Bilayered tablet of murayya koeinigii released the drug for immediate action. For sustained release Acacia, Ethyl cellulose are used with spinacia oleracea. The evaluation parameters are weight variation, hardness, thickness, drug content and In- vitro studies were carried out. In-vitro dissolution studies are performed using distilled water as buffer, F-5 formulation shows good sustained effect for a longer period of time up to 10hrs.

REFERENCE

I. Akram T Kharroubi and Hisham M Darwish, Diabetes mellitus: The epidemic of the century.
II. Rizkalla SW. Glycemic index: Is it a predictor of metabolic andvascular disorders? CurrOpin Clin Nutr Metab Care 2014; 17:373-8.
III. Sangam, S., Naveed, A., Athar, M., Prathyusha, P., Moulika, S., and Lakshmi, S. (2015). International Journal of Health Sciences and Research. 5(1), 156–164 .
IV. Mustafa, D., and Oktavia, R. (n.d.). Research Journal

of Pharmaceutical, Biological and Chemical Sciences Optimization Formalin Transport Through Bulk Liquid Membrane Technique. September – October. 7(1250), 1250–1255.

V. Ajay S, Rahul S, Sumit G, Mishra A, and Gaurav A. (2011). Asian Journal of Pharmacy and Life Science Comprehensive review: Murraya koenigii Linn. 1(4).

VI. Henry AB, Trimen. A hand-book to the flora of Ceylon. Dulau and Co; 2015, 1–1893.

VII. Parmar, C. and Kaushal, M.K. (1982). Murraya koenigii. In: C. Parmar and M.K. Kaushal (Eds), Wild Fruits(pp. 45–48). New Delhi: Kalyani Publishers.

VIII. Gajaria, T.K.; Patel, D.K.; Devkar, R.V.; Ramachandran, A.V. Flavonoid rich extract of Murraya koenigii alleviates in-vitro LDL oxidation and oxidized LDL induced apoptosis in raw 264.7 Murine macrophage cells. J. Food Sci. Technol. 2015, 52, 3367–3375. [CrossRef]

IX. Dhawan S and Singla AK: Performance liquid chromatographic analysis: application to invitro and in-vivo Journal of Chromatographic Science 2003; 41: 295-300.

X. Gutierrez RM, Velazquez EG, Carrera SPP. Spinacia oleracea Linn considered as one of themost perfect foods: A pharmacological and phytochemical review. Mini reviews in medicinal chemistry. 2019;19(20):1666- 1680.

XI. Kirtikar KR, Basu BD. Indian Medicinal plants. Deharadun: International Book Distributors. 2005; 8:2078-2079.

XII. Morelock TE, Correll JC. Spinach. In Vegetables I (pp. 189-218). Springer, New York, NY,2008.

XIII. Ozkan IA, Akbudak B, Akbudak N. Microwave drying characteristics of spinach. Journal of food engineering. 2007; 78(2):577-583.

XIV. Shukla A, Bansal S and Mishra MK: Formulation and evaluation of mucoadhesive buccal tablets of glipizide, research article. International Journal of Pharmaceutical Science Letter 2015; 5 (6): 636-643.

XV. Sandhan S, Sapra K and More J: Formulation and evaluation of sustained release matrix tablets, original research article. International Journal of Pharmceutical and Biological Research 2013; 1(4): 89-94.

XVI. Badugu LR and Gunti R: Estimation in commercial drugs by RP-HPLC, research article. International Journal of Atoms and Molecules, 2012; 2(1): 103-108.

XVII. Radhika PR, Pal TK and Sivakumar T: Formulation and evaluation of sustained release matrix tablets, original article. Iranian Journal of Pharmaceutical Science 2009; 5(3): 205- 214.

XVIII. C. H. Harika, Y. R. J. Rao, S. K. Gousia Parvin, and S. S. Sastry, "Formulation and evaluation of immediate release tablets of Nebivolol Hydrochloride," *International Journal of Pharmaceutical Archives*, vol. 2, no. 11, pp. 251–258, 2013.

XIX. Indian Pharmacopoeia, *Indian Pharmacopoeia*, vol. 3, Worldwide Book Service, 2014.

XX. United States Pharmacopoeia 34, vol. 3, pp. 3611–3614, 2011

XXI. V. Thanda, S. Firoz, C. Yerram, A. Vikram, S. K. Divya, and K. T. Murali, "Design and characterisation sustained release matrix tablets of Repaglinide using natural polymers," *International Journal of Pharmacy*, vol. 2, pp. 73–83, 2012.

XXII. G. H. Kumar, K. Jaganathan, R. S. Kumar, and P. Peruma, "Formulation and *in-vitro* evaluation of bilayer floating tablets of Metformin hydrochloride and Sitagliptin phosphate," *International Journal of Advanced Pharmaceutics*, vol. 2, no. 2, pp. 64–81, 2012.