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Formulation and Evaluation of Bilayer Tablet of Metformin Hydrochloride and Sitagliptin Phosphate Using Tamarind Seed Mucilage

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ABSTRACT: ***The main aim of present study is to formulate and evaluated bilayer tablet of Metformin Hydrochloride and Sitagliptin Phosphate as fixed dose combination tablets for effective treatment of type II diabetes mellitus. Here an attempt was made to reduce the dose, dosage frequency and reduce side effect of Metformin Hydrochloride and to provide synergistic action of drugs. Preformulation studies including drug excipient compatibility were conducted for both drugs. Different formulation of sustained release, Metformin Hydrochloride was prepared by using natural hydrophilic polymer e.g. Tamarind seed mucilage and were evaluated. Sitagliptin Phosphate immediate release formulations were prepared using synthetic superdisintegrants microcrystalline cellulose and were evaluated. Based on the in-vitro dissolution data MF3 & SG8 were selected as the best formulations from Metformin Hydrochloride and Sitagliptin Phosphate respectively. Bilayer tablet were prepared by slightly compressing Metformin Hydrochloride (MF3) and then final compression was made by placing Sitagliptin Phosphate (SG8) layer on it with final hardness 5.0 and they were evaluated. From the bilayer tablet % cumulative drug release of Sitagliptin Phosphate release 98.6 % in 30 minutes and second layer Metformin Hydrochloride release 97.9 % in 12 hrs. From the study, it was found that, Tamarind seed mucilage has good polymeric activity which was able to sustain the release for 12 hours.***
Keywords: Bilayer tablet, Tamarind seed mucilage, Metformin Hydrochloride, Sitagliptin Phosphate.

1.0 INTRODUCTION

In recent years, pharmaceutical drug product manufacturers have oriented their product development activities to fixed dose combination (FDCs) for the treatment like type 2 diabetes, hypertension, pain, and HIV/AIDS to mention a few.

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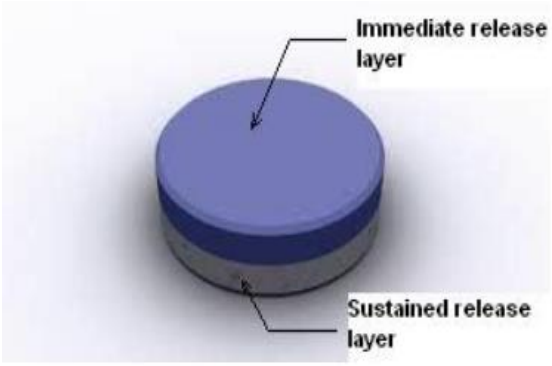

Figure No. 1.0: Bilayer tablet

Several different approaches are employed to deliver the FDCs product to the patients such as multilayer tablet.[20] compression coating, active coating[1,2] Bilayer floating tablet[3,4] and buccal/mucoadhesive delivery system.[5,6] Bilayer tablets can be a primary option to avoid chemical incompatibilities between APIs by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). [6,7]

Bilayer tablets are tablet, manufactured by compressing two different granulations feed into a die continuation, one on top of another, in layers. Each layer comes from a separate feed frame with characteristic weight control.[8]

In this study extended release layer compressed using tamarind seed mucilage which was used as a polymer to extend the release of Metformin hydrochloride from extended release layer, and immediate release layer compressed using microcrystalline cellulose which was used as superdisintegrates to immediate the release of Sitagliptin phosphate from immediate release layer.

2.0 MATERIAL AND METHOD

Metformin hydrochloride was obtained by Ipca Laboratories limited, Ratlam (M.P.) as a giftsample and Sitagliptin phosphate was obtained by Torrent Pharma as a gift sample, Tamarind Seed purchased from local market, Sodium Starch glycolate, Microcrystalline Cellulose, Magnesium Stearate, Talc, Potassium Dihydrogen Phosphate, Sodium hydroxide, Hydrochloric acid, Potassium chloride, Silica Gel G, Methanol, Ammonia, Glacial acetic acid were purchased from local authorized dealer.

2.1 Extraction of mucilage from tamarind seed: Raw seeds of tamarind were cleaned with distilled water to remove any extra pulp. Then 250gm of cleaned seeds were broken into small pieces and grounded into fine powder. Powder were taken into a 1000ml beaker containing 500 ml water and boiled on water bath at 80-100^{o}C with a constant stirring till a viscous solution was obtained. The solution was filtered using muslin cloth to throw away the undissolved fraction,

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and the supernatant was dried at 40°C for overnight. Then the dried material was called as tamarind kernel powder.[9]

TSP was prepared from this tamarind kernel powder by following method.

20 gm of tamarind kernel powder was taken and added in 200ml of distilled water, and slurry was prepared. The slurry was boiled for 20 minutes with continuous stirring at a water bath. The resulting solution was kept overnight to settle most of the protein and fibers. This solution was then centrifuged for 20 minutes at 5000 rpm. The supernatant was separated and twice volume of ethanol poured into it with continuous stirring. The precipitate was dried at 40°C. The dried film obtained was crushed to fine powder, passed through sieve no. 12.[10]

2.2 Preformulation Study:

2.2.1 Determination of λmax

2.2.1.1 Metformin hydrochloride

➢ **Preparation of standard stock solution Metformin hydrochloride**

- **Standard stock solution (1):** Metformin Hydrochloride (100 mg) was accurately weighed and transferred into a 100ml volumetric flask and dissolved and the volume was made up to 100ml using distilled water to obtain a standard stock solution of drug concentration of 1000µg/ml.

- **Standard stock solution (2):** 100µg/ml standard stock solution of Metformin hydrochloride from the above was prepared by pipetting 1 ml of stock solution to a 10ml volumetric flask and making it up to 10ml with distilled water.

- **Determination of λmax Metformin hydrochloride:** 2 ml of the above standard stock solution (2) solution was diluted to 10ml with the same solvent to get a concentration of 20µg/ml. The UV spectrum of final solution was scanned in the range of 200 – 400 nm by UV spectrophotometer against distilled water as blank. [11]

2.2.1.2 Sitagliptin phosphate

➢ **Preparation of standard stock solution of Sitagliptin phosphate:** Sitagliptin phosphate (100 mg) was accurately weighed and transferred into a 100ml volumetric flask. And make up the volume up to 100 ml to obtain a standard stock solution of drug concentration of 1000µg/ml.

- **Determination of λmax Sitagliptin phosphate:** From the above standard stock of Sitagliptin phosphate 250µg/ml was prepared by pipetting 2.5 ml of stock solution to a 10ml volumetric flask and making it up to 10 ml with distilled water to obtain 250µg/ml. 250µg/ml solution of Sitagliptin phosphate was taken and the UV spectrum of solution was scanned in the range of 200 – 400 nm by UV spectrophotometer against distilled water as blank. [12]

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2.2.2 Preparation of Calibration curve

➢ **Preparation of Calibration curve of Metformin hydrochloride in Distilled water**

- **Standard stock solution (1):** Metformin hydrochloride (100 mg) was accurately weighed and transferred into a 100ml volumetric flask and dissolved and the volume was made up to 100ml using distilled water to obtain a standard stock solution of drug concentration of (1000µg/ml).
- **Standard stock solution(2):** From the above standard stock solution of Metformin hydrochloride (100µg/ml) was prepared by pipetting 1 ml of stock solution to a 10ml volumetric flask and making it up to 10ml with distilled water.

Preparation of calibration curve: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25 2.5 ml was pipetted out from standard stock solution (2) and diluted to 10ml with distilled water to give the final concentration of 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 22.5 25µg/ml respectively. Absorbance at λmax against distilled water as a blank was taken and the calibration curve was plotted. [11]

➢ **Preparation of Calibration curve of Sitagliptin phosphate in Distilled water:** Accurately weighed 100mg of Sitagliptin phosphate and dissolved in 100ml of water to make the concentration (1000µg/ml). then 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5ml was pipetted out and diluted to 10ml with distilled water to give the final concentration of 50, 100, 150, 200, 250, 300, 350, 400, 450, 500 µg/ml respectively & the absorbance at λmax against distilled water as a blank was taken and the calibration curve was plotted. [13]

2.2.3 Drug excipient interaction study

Drug excipient interaction study of Metformin hydrochloride and Sitagliptin phosphate: The physical mixtures of drugs were prepared in 1:1 ratio and then passed through sieve # 30. Samples of drug Metformin hydrochloride and excipients were placed in closed and labeled vial. Then the vials were stored under conditions at 40˚C temp and at 75% RH in humidity chamber. Physical and chemical observations of the mixtures were done on 0^{th} day, 30^{th} day by TLC. [14, 15]

3.0 Method

Table no. 1.0 & 2.0 enlist no. of different excipients with its ratio of mixing with tamarind seed mucilage, where tamarind seed mucilage used as polymer[16], microcrystalline cellulose used as disintegrating agent[18], magnesium stearate used as lubricant[19],sodium starch glycolate used as superdisintegrate [17].

Sustained release blend containing 500 mg Metformin hydrochloride was prepared by prepared by shifted drug and excipients through sieve no. #40 then shifted material was mixed rapidly for 5 minutes and again passed through sieve no #40. Sufficient quantity of water was added to the mixture slowly and was kneaded for 2-5 minutes. Then the kneaded mass was passed through

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sieve no #16 to obtained granules then the granules were dried in a oven at 50°C for 1 hrs Then the granules were lubricated with magnesium stearate and talc. [20]

Immediate release blend of Sitagliptin phosphate was prepared by shifted Sitagliptin and other excipient (SSG, MCC) through sieve no #40. the shifted powder were thoroughly mixed for 5 minutes and again passed through sieve no #40 for maintaining uniformity of particle size then the mixture was lubricated for 2 minutes with magnesium stearate which was already passed through sieve no #60. [20]

Optimized layer of Metformin hydrochloride Granules were first introduced into die cavity, a slight compression was made and then optimized Sitagliptin blend was introduced into the die cavity followed by final compression with optimum hardness to form a bilayer tablets. Compression was made by using rotary tablet compression machine with 12mm deep concave punches plan on both side.[21]

- Metformin hydrochloride sustained release layer

S. No.	Name	MF 1	MF 2	MF 3	MF 4	MF 5	MF 6	MF 7	MF 8	MF 9
1	Metformin Hydrochloride	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg
2	Tamarind seed mucilage	75 mg	75 mg	75 mg	50 mg	50 mg	50 mg	100 mg	100 mg	100 mg
3	Microcrystalline cellulose	75 mg	25 mg	50 mg	25 mg	75 mg	50 mg	50 mg	75 mg	25 mg
4	Magnesium stearate	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
5	Talc	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg

Table No. 1.0: Formulation and optimization of sustained release layer of metfromin hydrochloride

- Sitagliptin phosphate immediate release layer

S. No.	Name	SG 1	SG 2	SG 3	SG 4	SG 5	SG 6	SG 7	SG 8	SG 9
1	Sitagliptin phosphate	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
2	Sodium starch glycolate	20 mg	20 mg	20 mg	10 mg	10 mg	10 mg	30 mg	30 mg	30 mg
3	Microcrystalline cellulose	45 mg	15 mg	30 mg	15 mg	45 mg	30 mg	30 mg	45 mg	15 mg
4	Magnesium stearate	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg
5	Talc	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg

Table No. 2.0: Formulation and optimization of immediate release layer of Sitagliptin phosphate

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4.0 Post compression Evaluation of bilayer tablet [22]

4.1 Thickness: Thickness of the tablets was calculated by the use of vernier calipers as shown in table no 6.0.

4.2 Weight variation test: Randomly selected 20 tablets and weighed individually and average weight was calculated. not more than 2 of individual weight deviate from the average weight. No tablet must differ by more than double the relevant percentage.

4.3 Friability: Friability was determined by using roche tablet friability apparatus, for tablets with an average weight of more than 0.65gm. 10 tablets were taken and weighed accurately and placed in the drum and rotated 100 times. Removed the tablets, removed dust from them and weighed them accurately, maximum loss of weight not greater than 1.0 % is acceptable for most tablets.

% Friability = weight before test - weight after test / weight after test × 100

4.4 Hardness: Hardness of the tablet was determined by using the Monsanto hardness tester.

4.5 Swelling index: The swelling behavior of Metformin hydrochloride tablets was determined at 37 ± 0.5°C in phosphate buffer pH 6.8, over 6 hrs. Formulations were individually kept in a Petri dish containing 50 ml of the buffer solution. At the end of the specific period the tablet was removed, blotted with a tissue paper and weighed. The extent of swelling was calculated by following formula and result shown table no 7.0. [25]

Swelling index: weight after swelling-weight before swelling / weight before sweelling×100

4.6 Drug content: 10 tablets were weight and powder. Then accurately a quantity of the powder containing about 0.1 gm of sample substances was taken and shacked it with 70 ml water for 15 minutes, diluted to 100 ml with water and filter. Than Diluted 1 ml of filtrate to 10 ml of water. Further diluted 1 ml to 10ml of with water. And absorbance of resulting solution was measured at λmax. And the drug content was calculated which results shown in table no 6.0.[23]

4.7 Drug release: drug release of bilayer tablet was estimated using USP type II Dissolution apparatus (paddle) according to method describe in Indian pharmacopeia as follows

Method: 900 ml of 0.1 N Hydrochloric acid was placed in the vessel and the apparatus was assembled. The temperature at 36.5°C to 37.5°C and paddle speed 100 rpm was maintained. Than the dosage form was placed in the apparatus and sample volume was taken and replaced with same media. Then after 2 hrs drained the acid from the vessel and add 900 ml pH 6.8 phosphate buffer that has previously been warmed to 36.5° to 37.5°C and then operate the apparatus at same operation as previous. [24]

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5.0 Results and Discussion

5.1 Determination of wavelength using UV spectrophotometric analysis:

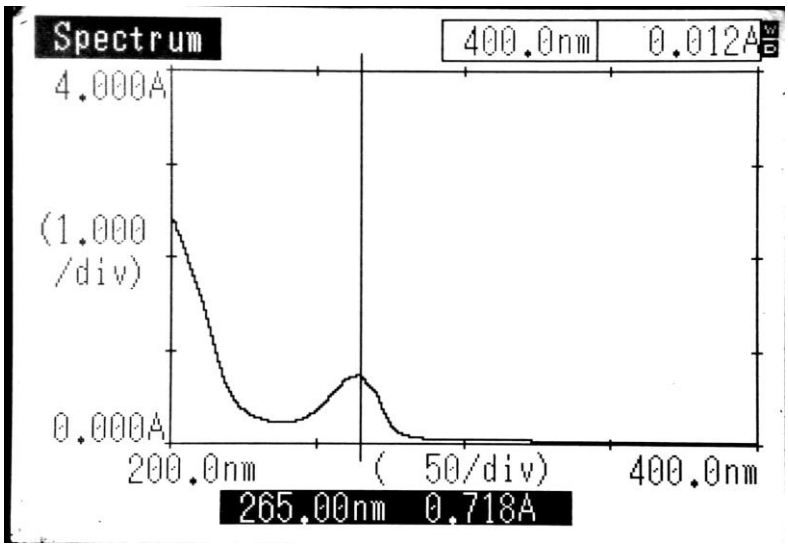

Figure No. 2.0: λ max of Metformin hydrochloride

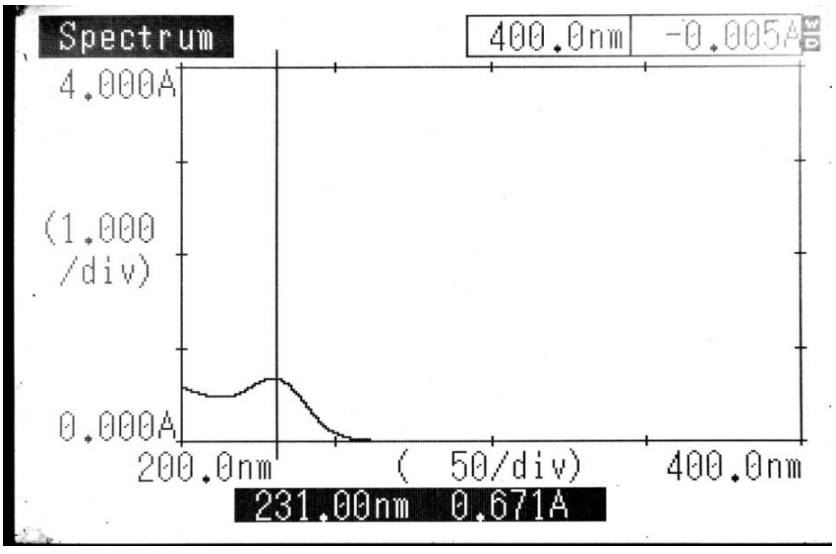

Figure No. 3.0: λ max of Sitagliptin phosphate

Maximum wavelength of Metformin hydrochloride was found at 231 & Sitagliptin phosphate was found at 265.

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5.2 The calibration Curve of Metformin hydrochloride: The calibration curve of Metformin hydrochloride in distilled water was prepared at 231 nm and show below:

Table No 3.0: Absorbance data of Metformin hydrochloride in water

S. No.	Concentration (µg/ml)	Absorbance (mean ± standard deviation)
1	2.5	0.202 ± 0.016
2	5	0.286 ±0.011
3	7.5	0.429 ± 0.013
4	10	0.586 ±0.006
5	12.5	0.686 ±0.018
6	15	0.859 ±0.007
7	17.5	0.981 ±0.012
8	20	1.109 ±0.002
9	22.5	1.243 ±0.007
10	25	1.452 ±0.013

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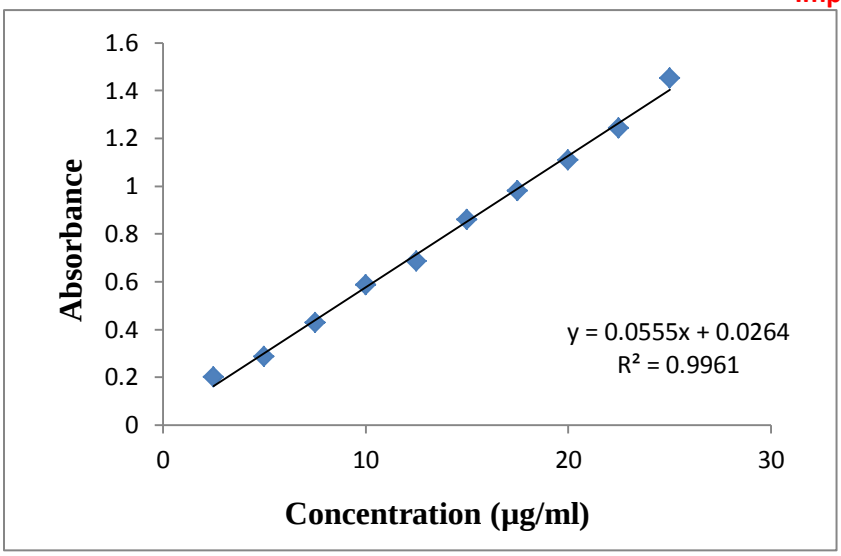

Figure No 4.0: Calibration curve of Metformin hydrochloride in distilled water at 231 nm.

5.3 The calibration Curve of Sitagliptin phosphate: The calibration curve of Sitagliptin phosphate in water was prepared at 265nm and show below:

Table No 4.0: Absorbance data of Sitagliptin phosphate in water

S. No.	Concentration (µg/ml)	Absorbance (mean ± standard deviation)
1	50	0.135±0.012
2	100	0.258±0.009
3	150	0.371±0.013
4	200	0.535 ±0.004
5	250	0.708 ±0.003
6	300	0.852 ±0.007
7	350	0.970 ±0.019
8	400	1.167 ±0.007
9	450	1.347±0.015
10	500	1.486±0.012

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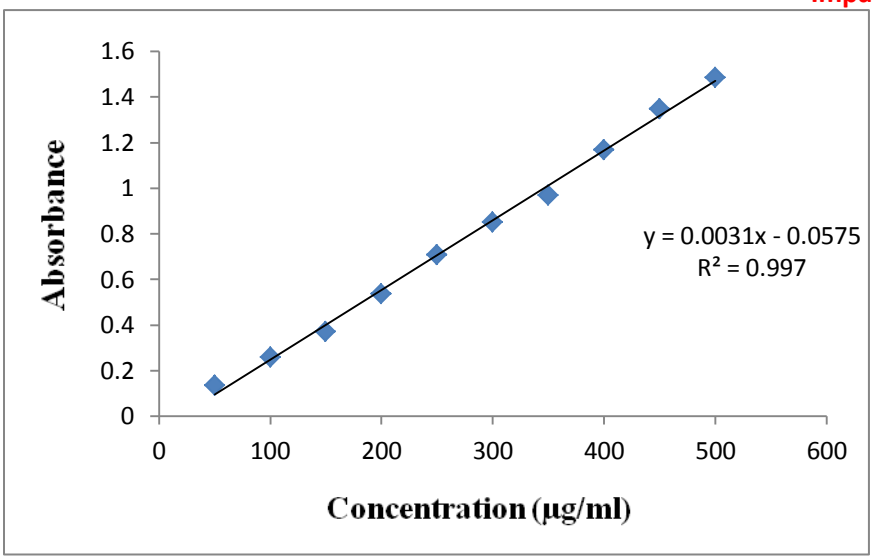

Figure No. 5.0: Calibration curve of Sitagliptin phosphate in distilled water

5.4 Drug Excipient interaction study:

The drug was found to be compatible with various excipients which were selected for formulation of bilayer tablet the compatibility was assessed by TLC (thin layer chromatography).

Table 5.0: List of drug excipient retention factor

S. NO.	Drug Excipient Ratio (1:1)	Initial appearance Present day		Final appearance After 15 days	Retention factor Present day	Retention factor After 15 days
1	Metformin hydrochloride	White crystalline powder		No change	0.67	0.66
2	Metformin hydrochloride: mucilage	Pale brown powder	No change	0.64	0.64	
3	Metformin hydrochloride: MCC	White mixture	No change	0.64	0.65	
4	Metformin hydrochloride: magnesium state	White mixture	No change	0.68	0.65	
5	Metformin hydrochloride: Talc	White mixture	No change	0.66	0.67	
6	Metformin hydrochloride: all excipient	Brownish white powder	No change	0.67	0.67	
7	Sitagliptin phosphate	Off White powder	No change	0.80	0.81	

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8	Sitagliptin phosphate:sodium starch glycolate	White mixture	No change	0.88	0.88
9	Sitagliptin phosphate: MCC	White mixture	No change	0.87	0.89
10	Sitagliptin phosphate: magnesium state	White mixture	No change	0.83	0.85
11	Sitagliptin phosphate : Talc	White mixture	No change	0.88	0.89
12	Sitagliptin phosphate: all excipient	White mixture	No change	0.88	0.88

5.5 Post compression Parameter: Result of optimized tablets were as follows:

Table No. 6.0: post compression parameter of bilayer tablet

S.No.	Thickness (Mean ± SD)	Hardness (Mean ± SD)	Weight variation (mg) (Mean ± SD)	Friability (Mean ± SD)	Drug content (Mean ± SD)	
					Metformin hydrochloride	Sitagliptin Phosphate
1	5.6 ± 0.05	4.9 ± 0.25	768 ± 6.70	0.43 ± 0.19	98.37 ± 0.43	99.95 ± 0.08

- **Swelling index of bilayer tablet**

Table No. 7.0: Swelling index of bilayer tablet

S. No.	Time (hour)	Swelling Index % (Mean ± SD)
1	1	36.79 ± 0.7
2	2	50.86 ± 0.6
3	3	58.8 ± 0.3
4	4	66.48 ± 0.4
5	5	72.04 ± 0.6
6	6	84.80 ± 0.3

Swelling behavior of bilayer tablet shown in table no. 7.19 and it was observed that bilayer tablet was swelled 84.8 % within 6 hours.

- **In vitro drug release of bilayer tablet:**

Drug release was determined according to procedure of I.P. and results shown in table no. 7.20 and it was observed that immediate release layer of bilayer tablet release its 98.6 % drug release in 30 minutes and after that sustained release layer of bilayer tablet started to release its drug and 97.96 % of drug was released up to 12 hours.

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Table No. 8.0: % cumulative drug release of bilayer tablet

S.No.	Time	% Cumulative drug release of bilayer tablet (Mean ± SD)	
		Sitagliptin phosphate	Metformin hydrochloride
1	5 min	47.4 ± 0.73	-
2	10 min	56.2 ± 1.05	-
3	15 min	61.3 ± 0.70	-
4	20 min	80.6 ± 0.65	-
5	25 min	93.8 ±0.61	-
6	30 min	98.6 ±0.68	-
7	1 hr	-	8.1 ± 0.52
8	2 hr	-	17 ± 0.76
9	3 hr	-	28.1 ± 0.59
10	4 hr	-	39 2 ± 0.52
11	5 hr	-	48.9 ±0.82
12	6 hr	-	53 ± 0.43
13	12 hr	-	97.96 ± 0.58

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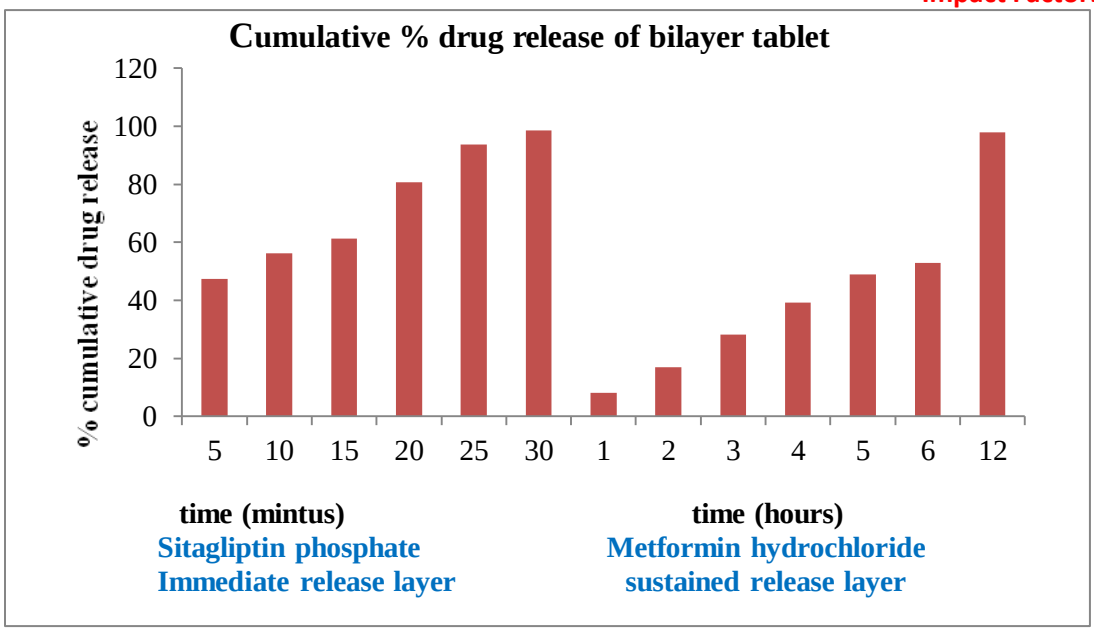

Figure No. 6.0: % cumulative drug release of bilayer tablet

6.0 CONCLUSION

The bilayer tablet was made which was consist of two layer one was sustained release Metformin hydrochloride and immediate release Sitagliptin phosphate. Metformin hydrochloride sustained release layer was made using natural polymer e.g. tamarind seed mucilage which was show good sustained release activity. Sitagliptin phosphate immediate release layer was made using sodium starch glycolate which was also show good immediate release activity. Bilayer tablet was compressed without chipping, capping ad sticking and after post compression evaluation study the tablet was showing good properties with uniform drug content. It was also concluded that drug & tamarind seed mucilage ratio influenced the release of drug from the formulation.

Based on the in-vitro dissolution data MF3 & SG8 were selected as the best formulations from Metformin Hydrochloride and Sitagliptin Phosphate respectively.

% cumulative drug release of Sitagliptin Phosphate release 98.6 % in 30 minutes and second layer Metformin Hydrochloride release 97.9 % in 12 hrs from the bilayer tablet.

From the study, it was found that, Tamarind seed mucilage is acceptable because it has good polymeric activity which was able to sustain the release upto 12 hours.

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