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FORMULATION AND EVALUATION OF BILAYER TABLETS FOR SUSTAINED RELEASE OF SAXAGLIPTIN

Ankit Pal, Anil Nagar, Dr. Umesh Kumar Jain*

Bhopal institute of Science & Technology- Pharmacy, Bhopal, M. P.

***Corresponding Author: Dr. Umesh Kumar Jain**

Bhopal institute of Science & Technology- Pharmacy, Bhopal, M. P.

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ABSTRACT

In bilayer tablet A single or two different active pharmaceutical ingredients can be incorporated.They are also used for the separation of incompatible active pharmaceutical ingredients.The surface area of drug layer is modified by sandwiching. It can be controlled by one or two inactive layers and make them to achieve the swellable (or) erodible barriers for modified release. It is used for the fixation of a combination of different active pharmaceutical ingredients. Life-cycle of the drug product is increased

KEYWORDS: Bilayer tablet, controlled release, drug delivery, In vitro Drug Release, Consolidation.

INTRODUCTION

Bilayer tablet means a type of multi-layered tablet which have two layers instead of a single layer. It is formulated when two incompatible drugs are combined together in the same formulation. For the combination of different APIs bilayer technique is used. It is also used for the administration of fixed dose. It prolongs the life cycle of drug products. Chewing device and floating tablets are the novel drug delivery system for gastro- retentive drug delivery. The surface area of API layer is modified by sand witching. It can be controlled by one or two inactive layers and make them to achieve the swellable (or) erodible barriers for modified release. For the controlled release of the API, it should be separated from one layer to another layer by utilizing the functional property[1,2] These are the solid unit dosage forms and have greater capability amongst all oral dosage forms. As compared with various other dosage forms, their cost is very low. It is compact and lighter. For packaging and stripping, it is easiest and cheapest.It is very much easy for swallowing and least tendency to hang-up. Coating technique helps to mask the objectionable odor and bitter taste masking. It is very much suitable for production on a large scale. It has a very high chemical stability and microbial stability. Identification of product is easy and rapid. It does not require additional steps for embossing and/or monogrammed punch facing.[3-5]

In a situation of paediatric and insensible subjects, it is very difficult to administer. Dense compacts, amorphous nature and low density character are found in certain drugs Drugs which have slow dissolution, poor wetting, ideal absorption in the Gastro Intestinal Tract, faces difficulty in formulation and manufacturing into a tablet Encapsulation or coating is required for bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen.[6]

METHODOLOGY

Method of preparation of immediate release tablet

The drug was mixed with a suitable disintegrant for 20 mins and poured into a porcelain mortar. After that it was passed through the sieve (#60). For the mixing of this blend, Silicon dioxide and magnesium stearate were used. For compression of the tablets fixed funnel method was used. Flat faced punch rotary tablet machine was used for this process. 1% of magnesium stearate has been used in all the formulations. 5 to 8% of disintegrants were added to the tablets.[7]

Table 1: Composition of saxagliptin IR tablet (F1 to F10).

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Saxagliptin	20	20	20	20	20	20	20	20	20	20
MCC	52	32	22	42	42	32	42	12	15	17
Croscarmellose	5	-	10	-	20	-	25	10	-	15
Mag. stearate	1	1	1	1	1	1	1	1	1	1
Aerosil	1	1	1	1	1	1	1	1	1	1
Cross povidone	5	10	15	25	-	30	-	10	35	15
Starch	5	10	15	05	10	15	20	25	5	10
Erythrosine	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2

Method of preparation of floating sustained release tablet

For the preparation of tablets, drug and HPMC were mixed with other excipients. The powdered ingredients were mixed uniformly and subjected to wet granulation technique by using isopropyl alcohol. The wet mass was passed through the sieve no 16 and the resulting granules were dried into an oven at a temperature of 50^0C. After the completion of drying, these granules were passed through sieve no. 12. Then around 5 to 8% magnesium stearate was mixed with these granules.[8,9]

Table 2: Composition of saxagliptin SR tablet (F1 to F10).

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Saxagliptin	40	40	40	40	40	40	40	40	40	40
HPMC K4M	85	45	-	-	60	55	45	45	35	-
HPMC K100M	-	40	60	55	-	-	-	-	10	35
Lactose	110	110	110	110	110	110	110	110	110	110
Magnesium stearate	1	1	1	1	1	1	1	1	1	1
Aerosil	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35
Starch	5	10	20	-	25	-	30	-	35	-
Sodium bicarbonate	5	10	20	30	40	50	-	60	-	30
PVP K-30	-	-	-	5	-	10	-	15	-	20
Talc	1	1	1	1	1	1	1	1	1	1
Isopropyl alcohol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

Evaluation of formulation

Pre-compression parameters

The flow properties of granules of saxagliptin floating sustained release (before compression) were evaluated in terms of bulk density, tapped density, angle of repose, Carr's index & Hausner's ratio, as per the procedure.The studies were done in triplicate (n=3).[10]

Post compression parameters

Weight Variation Test

The weight variation test was done by weighing 20 tablets individually, calculating their average weight and comparing the individual weights to the average weight obtained.

Hardness

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling during manufacture, packaging and shipping. The Inweka hardness tester was used to check the hardness of random 20 prepared tablets.[11]

Friability test

The friability was determined by first weighing 10 tablets after dusting and placing them in a Roche friabilator, which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of the tablet was recorded and the percent friability was calculated.[12]

Thickness

The thickness of the tablet was mostly related to the tablet hardness and was used as an initial control parameter. The thickness of the tablets was measured using vernier callipers. Twenty tablets were randomly selected.[13]

Drug content

Ten tablets were taken and crushed with the help of sonication, drug equivalent quantity was dissolved in 0.1N HCl and volume was made up to 100 ml. By using Whatman filter paper, drug solution was filtered. For obtaining the 10µg/ml concentration solution was treated with 0.1N HCl. By measuring the absorbance of the solution, the drug.[14]

Dissolution test

USP dissolution apparatus type II was used for the dissolution of different batches of saxagliptin floating sustained release tablets. The dissolution study was performed out in pH 1.2 HCl buffer for the 16 hrs (900 ml). It was maintained at 37∘C ± 0.5∘C of temperature with a 50 RPM stirring rate. Each sample was drawn at

regular interval of time and the remaining volume was made up by fresh solvent. Whatman filter paper was used for filtration and by using UV-Visible spectrophotometer; observance was recorded against a blank.[15]

Wetting time

Randomly a tablet was taken and put it into 2 layers of absorbent paper. The absorbent paper was wetted by using pH 1.2 HCl buffer and the unused buffer was drained out from the petridish. The stopwatch was used to the record the time required for the buffer to diffuse from the wetted absorbent paper into the entire tablet. The test was executed three times and mean ± Standard Deviation was calculated.[16]

Bilayer tablet preparation

From the optimized batch of saxagliptin, [immediate release part] and in saxagliptin, [sustained release part] were selected for the formulation of bilayer tablets. As per the procedure, granules of [immediate release part] and blend powder of [sustained release part] were prepared separately. In rotary bilayer tablet compression machine (single sided press), one by one these layers were filled and compressed.[17]

Floating property study

The time taken by tablet to emerge on the surface of the medium is known as floating lag time (FLT) and duration of time the dosage form constantly remains on the surface of the medium is called total floating time (TFT). For this study, one tablet from each batch was taken in USP XXIII type II dissolution apparatus containing 900 ml of 0.1 N HCl. The study was performed using the paddle at a rotational speed of 50 rpm. The time taken for tablet to emerge on the surface of the medium and the duration of time the tablet constantly remained on the surface of the medium was recorded as the floating lag time and TFT respectively.[18]

Table 3: Optimized formulation of bilayer tablet.

Immediate release layer		Sustained release layer	
Ingredients (mg)	**S-IR**	**S-SR**	
Saxagliptin	20	**Saxagliptin**	40
MCC	42	**HPMC K4M**	45
Croscarmellose sodium	-	**HPMC K100M**	40
Magnesium stearate	1	**Lactose monohydrate**	110
Aerosil	1	**Magnesium stearate**	1
Cross povidone	25	**Aerosil**	1.35
Starch	05	**Starch**	10
Erythrosine	1	**Sodium bicarbonate**	10
Talc	2	**PVP K-30**	-
		Talc	1
		Isopropyl alcohol	Q.S.

RESULT

Table 4: Pre-compression parameters of saxagliptin IR tablets (n=3).

Batch	Angle of Repose (^{0})	Bulk density (g/mL)	Tapped bulk (g/mL)	Compressibility Index (%)	Hausner's Ratio
F1	29.58±0.18	0.28±0.17	0.30±0.029	14.59±0.016	1.10±0.04
F2	30.56±0.14	0.28±0.16	0.31±0.028	8.88±0.012	1.12±0.023
F3	30.15±0.15	0.28±0.14	0.29±0.030	12.63±0.014	1.20±0.017
F4	29.35±0.18	0.29±0.16	0.30±0.028	10.48±0.015	1.16±0.016
F5	30.45±0.19	0.28±0.13	0.31±0.027	8.37±0.017	1.18±0.05
F6	31.82±0.16	0.28±0.17	0.30±0.029	7.55±0.018	1.19±0.016
F7	30.55±0.14	0.27±0.18	0.29±0.028	8.52±0.016	1.10±0.012
F8	29.45±0.16	0.29±0.19	0.30±0.025	11.02±0.014	1.09±0.007
F9	30.59±0.17	0.30±0.17	0.31±0.026	10.56±0.013	1.08±0.006
F10	31.25±0.19	0.31±0.18	0.30±0.023	9.15±0.015	1.03±0.004

Table 5: Post compression parameters of saxagliptin IR tablets.

Code	Disintegration Time (Seconds)	Drug content	Wetting Time (secs)	Water Uptake
F1	190.52±35.25	100.0±1.13	224.33±8.64	235.33±7.63
F2	53.18±13.99	99.5±1.01	40.33±3.05	238.33±7.64
F3	36.67±5.60	100.7±1.99	52.00±2.00	366.33±14.57
F4	35.38±6.55	101.2±0.09	25.66±1.52	395.00±7.13
F5	79.69±24.38	99.5±1.22	175.00±8.14	339.33±47.64

F6	108.8516.19	100.5±1.34	59.00±52.02	312.36±74.95
F7	55.52±14.30	99.5±2.99	161.00±10.50	346.00±18.58
F8	55.56±34.2	98.52±2.13	53.55±1.11	235.33±7.63
F9	109.25±33.56	99.0±1.97	89.12±1.99	230.33±7.64
F10	115.89±33.86	100.56±2.45	95.55±2.01	239.33±47.64

As per the information obtained in literature survey, lower the value of wetting time of tablets, lesser will be the time taken by tablet to disintegrate. F4 formulation showed the lowest wetting time amongst all the formulations. And the water uptake capacity was found to be highest in F4 formulation with a value of 395 mg per tablet. Fast disintegration and dissolution of tablets was caused by higher water uptake.

Results of floating sustained release tablets.

Table 6. Post compression parameters of saxagliptin SR tablets

Code	Total floating time (hours)	Floating lag time (sec)	Swelling index (%)	WettingTime (sec)	Maximal Water Uptake
F1	>8	3:01	12.4±1.11	140.66±1.52	395.00±7.55
F2	>12	0:92	13.8±0.59	77.33±3.05	399.14±39.45
F3	>8	2:41	13.3±1.45	152.00±2.00	366.33±4.57
F4	>8	2:19	13.4±3.12	224.33±8.64	238.33±7.63
F5	>12	2:12	13.6±2.45	175.00±8.14	339.33±47.64
F6	>8	2:06	13.35±0.99	332.00±2.02	312.36±74.95
F7	>6	1:60	13.7±2.11	161.00±0.50	346.00±18.58
F8	>8	1:53	13.5±0.78	132.33±5.5	350.02±17.28
F9	>8	1:40	12.6±1.87	152.16±2.9	356.09±16.38
F10	>8	1:20	12.7±2.09	135.66±4.5	358.03±16.48

The *in-vitro* buoyancy study was conducted for all the batches, where the lowest floating lag time (FLT) was bserved for F2 formulation which contained HPMC K100M. For the formulation of bilayer tablets, optimized batch F4 and batch F2 of were selected.

In vitro buoyancy study of bilayer tablet

The gas generation technique was used for formulating tablets in which sodium bicarbonate was added. *In vitro* buoyancy parameters of bilayer tablet are shown in Table The buoyancy/floating lag time (BLT) was found to be 8 minutes with total floating time (TFT) of 12.67 hours. The maximal water uptake capacity of the bilayer tablet was reported to be 404.56 mg per tablet. (++) in table indicates that the matrix of the bilayer tablet remained intact during more than 8 hours of dissolution.

Table 7: Saxagliptin immediate and sustain release from bilayer tablet.

Time (Minutes)	Cumulative % drug release (Saxagliptin IR layer)	Time (Hrs)	Cumulative % drug release (Saxagliptin SR layer)
0	0	0.5	5.19±1.25
5	15.28±0.95	1	15.87±2.19
10	39.15±2.15	2	31.67±0.95
15	58.75±1.27	4	43.02±1.14
20	71.25±0.27	6	50.19±1.25
25	89.19±0.75	8	62.48±0.25
30	95.65±0.85	10	72.85±0.48
35	98.24±1.28	12	89.49±0.58
40	99.29±0.87	14	97.29±1.85
45	99.56±1.85	16	99.98±2.48

From the in-vitro dissolution study of bilayer tablet, it was concluded that 99.29% of saxagliptin was released within 40 minutes. On the other hand, within 16 hours of dissolution study, 99.98% of saxagliptin were released.

CONCLUSION

Bilayer tablet means a type of multi-layered tablet which have two layers instead of a single layer. It is formulated when two incompatible drugs are combined together in the same formulation. For the formulation of bilayer tablets, optimized batch F4 and batch F2 of were selected. From the in-vitro dissolution study of bilayer tablet, it was concluded that 99.29% of saxagliptin was released within 40 minutes. On the other hand, within 16 hours of dissolution study, 99.98% of saxagliptin were released.

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