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Original Research Article

Formulation and Evaluation of Bilayer Tablet of Metformin HCl and Sitagliptin

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Abstract:

The treatment of Type 2 Diabetes Mellitus (T2DM) often necessitates a combination therapy to achieve optimal glycemic control. Metformin HCl, a biguanide, and Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, are commonly prescribed together due to their complementary mechanisms of action. This study aims to develop and evaluate a bilayer tablet containing Metformin HCl and Sitagliptin, designed to provide immediate release of Sitagliptin and extended-release of Metformin HCl. The bilayer tablets were formulated using direct compression and wet granulation techniques, and various parameters including shape of tablet, tablet dimension, weight variation, hardness, friability, drug content, and in vitro dissolution profiles were evaluated. The results indicated that the formulated bilayer tablets met the desired specifications for physical characteristics and demonstrated effective controlled release, thereby enhancing patient compliance and therapeutic efficacy.

Keywords: Type 2 Diabetes Mellitus, immediate release, extended-release, in vitro dissolution profiles.

Introduction

Bilayer tablets are an innovative drug delivery system designed to deliver two different drugs or two different release profiles of the same drug in a single dosage form. This technology is particularly beneficial in managing diseases requiring multi-drug therapy or where a combination of immediate and sustained release is desired.[1] The bilayer tablet consists of two distinct layers, each formulated with different drug release characteristics. [2,3]

The management of Type 2 Diabetes Mellitus (T2DM) often requires a combination of medications to effectively control blood glucose levels. Metformin HCl and Sitagliptin are two such medications commonly used. Metformin HCl, a biguanide, works primarily by decreasing hepatic glucose production and increasing insulin sensitivity, while Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, works by increasing incretin levels, which inhibit glucagon release, thereby increasing insulin secretion.[4] A bilayer tablet combining these two drugs can improve patient compliance by simplifying the medication regimen and ensuring synchronized drug release. [5,6]

Methodology

- **Formulation of Metformin HCl Layer**

Various versions of extended-release floating tablets of the Metformin HCl layer

(F1-F10) were created using the wet granulation technique, incorporating different excipients such as HPMC K100 M, Sodium CMC as a polymer to slow down release, PVP K 30 as a binding agent, Sodium Bicarbonate to serve as an effervescent agent, and Magnesium Stearate as a lubricant.

- **Formulation of Sitagliptin Immediate Release Layer**

Various forms of sitagliptin IR tablets were manufactured using the Direct Compression process. These tablets included the active ingredient along with various excipients such as microcrystalline cellulose, sodium starch glycolate, Gallen gum, poly vinyl pyrrolidine as well as magnesium stearate. [7,8]

Evaluation of The Bilayer Tablets

a) Shape of Tablets

The form of the tablet was checked by examining it under a microscope.

b) Tablet Dimensions

A set of calibrated vernier callipers have been employed to measure the thickness and diameter. Thickening of bilayer tablets was assessed on an individual basis after they were randomly selected.

c) Hardness

The strength of the tablet determines its hardness, which is its capacity to endure mechanical shocks during storage, shipping, and handling prior to use by a patient. The Pfizer hardness tester was used to assess the tablet hardness of each formulation. The unit of measurement for hardness was kg/cm^2. The hardness of each batch was determined by randomly selecting three tablets.[9]

d) Friability

The tumbling mechanism, which spins at 25 rpm and drops the twenty tablets six inches after each rotation, was loaded with precise weights. The tablets have been weighed and the percentage of friability was determined using the procedure after 4 minutes (or 100 rotations).

$$\% \text{ Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

e) Weight variation test

We used an electronic balance (Shimatzu) to weigh twenty tablets at random from each batch. Twenty tablets were weighed and their standard deviations determined. [10]

f) Drug content of the Bilayer tablets

The twenty tablets were ground into a fine powder after being precisely measured. In order to prepare the solution, 10 milligrams of Metformin HCl and 1 milligram of Sitagliptin were weighed then dissolved in distilled water. The mixture was then subjected to sonication for 10 minutes and filtered using Whatman's filter paper no.41. Following the removal of the initial few milliliters, a series of dilutions was used to generate tablet samples of varying concentrations. These samples were then scanned in multi-component mode across the 400-200 nm range and examined at the 233 and 267 nm wavelengths.

g) In-Vitro Dissolution Study of The Bi Layered Tablet

The dissolution test for bilayer tablets was conducted over a 12-hour period utilizing an Electrolab USP type II (paddle) dissolving Testing Apparatus. At a temperature of 37±0.50 C, 900 ml of 0.1N HCl has been used as a dissolving medium that was agitated at 100 RPM. To estimate the release of Sitagliptin, 10 ml samples were taken at 5, 10, 15, 20, 30, 40, and 60 minutes for 1 hour. To estimate the release of Metformin, samples were taken at 1, 2, 4, 6, 8, 10, and 12 hours each hour. The dissolving media was replenished at regular intervals with the same volume, and samples were filtered using whatman filter paper no. 41. By using UV Spectrophotometry with their respective λ max values of 233 nm and 267 nm, the samples were examined for Metformin HCl

& Sitagliptin.

After the first hour, the samples were examined for Sitagliptin concentration at 267 nm using a UV spectrophotometer. To avoid interference, the solution containing the Metformin HCl formulation was kept as a blank. Using a UV spectrophotometer, we measured the concentration of Metformin HCl at 233 nm in samples taken between 1 and 12 hours. To avoid interference, we kept the solution containing the Sitagliptin formulation as a blank. [11,12]

Results and Discussion

Table 1: Results of average weight, hardness, thickness, friability and drug content

Formulation	Average Weight mg (n=20) (± SD)	Hardness Kg/cm^2 (n=3) (± SD)	Thickness mm (n=3) (± SD)	Friability % (n=20) (± SD)	Drug content (n=3)	
					Metformin HCl	Sitagliptin
Bi Layer Tablet (F7 + S9)	945.07 ±1.38	6.7 ± 0.5	6.5 ± 0.63	0.75	99.67± 0.42	99.63 ± 0.7

a) Shape and description of the tablets

The tablets were examined physically and found to be bi-layered with a capsule shape. One side of the tablets had a split. The two layers were clearly differentiated, with the Metformin HCl layer being colorless and the sitagliptin layer having a faint red tint.

b) Tablet dimensions

The tablets exhibited a consistent thickness of 6.5 ± 0.63 mm across the whole batch.

c) Hardness

The tablets were determined to have a hardness of 6.7 ± 0.5 kg/cm^2, which was adequate for their handling for the whole shelf life.

d) Friability

Percentage weight loss, often known as %, is a measure of the amount of weight that has been lost in relation to the initial weight. The friability was assessed and determined to be within the range of 0.75%, which falls under the pharmacopeial limit of less than 1% (F<1%).

e) Weight Variation Test

The tablets from the batch successfully passed the weight variation assessment according to the restrictions set by the United States Pharmacopeia (USP), as they exhibited a deviation of less than 5% from their designated weight.

f) Drug Content Uniformity

The bilayer tablet was found to contain Metformin HCl & Sitagliptin at concentrations of 99.67 ±0.42 and 99.63 ±0.7, respectively. Both medications were found to contain drug contents that were within the specified limits according to the Indian Pharmacopoeia (I.P) and International Council for Harmonization (ICH) recommendations. Additionally, they exhibited satisfactory content uniformity.

Conclusion

The formulated bilayer tablet of Metformin HCl and Sitagliptin successfully provides immediate release of Sitagliptin and extended release of Metformin HCl, enhancing the management of T2DM. The bilayer tablet format not only improves patient compliance by reducing the pill burden but also ensures effective glycemic control through synchronized drug release. The tablets were examined physically and found to be bi-layered with a capsule shape.

One side of the tablets had a split. The tablets exhibited a consistent thickness of 6.5 ± 0.63 mm across the whole batch. The tablets were determined to have a hardness of 6.7 ± 0.5 kg/cm^2. The friability was assessed and determined to be within the range of 0.75%. The bilayer tablet was found to contain Metformin HCl & Sitagliptin at concentrations of 99.67 ±0.42 and 99.63 ±0.7. The research shown that the preparation of bilayer tablets may lead to a reduction in the overall dose, dosage frequency, and dose-related adverse effects of Metformin. However, more clinical investigations are required to evaluate the efficacy of this technique.

Table 2: *In Vitro* Drug Release Profile of the Bi - Layered Tablet (S9 – F7)

S. no	Time intervals (min.)	Cumulative % drug release	
		Sitagliptin IR S9	Metformin HCl F7
1	**0**	0.00	0
2	5	37.85	0.53
3	10	72.05	2.36
4	15	88.64	5.42
5	20	97.20	8.37
6	30	99.15	13.56
7	40	100.10	19.34
8	60	-	21.56
9	120	-	33.75
10	240	-	52.40
11	360	-	71.02
12	480	-	81.31
13	600	-	92.20
14	720	-	97.65

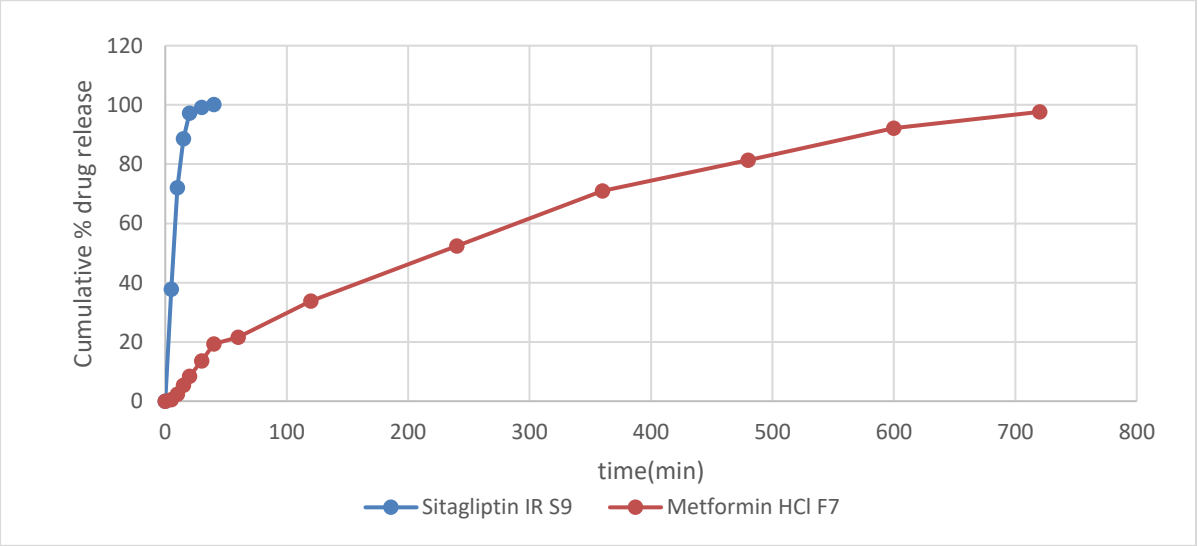

Figure 1: *In-vitro* Drug Release Profile of the Bilayer Tablet (S9+F7)

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