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EVALUATION AND OPTIMIZATION OF GAS-GENERATING AGENTS IN FLOATING BILAYER TABLETS OF METFORMIN HYDROCHLORIDE AND CANAGLIFLOZIN

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Keywords:

Gastro-retentive systems, Floating tablets, Metformin hydrochloride, Canagliflozin, Sodium bicarbonate

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ABSTRACT: OBJECTIVE: The present study was designed to systematically evaluate and optimize gas generating agents for the development of a gastro retentive floating bilayer tablet containing metformin hydrochloride (sustained release layer) and canagliflozin (immediate release layer). **METHODS:** The investigation was carried out in two sequential stages. Initially, different gas generating agents sodium bicarbonate, sodium carbonate, potassium carbonate and calcium carbonate were screened at a fixed concentration of 7.5% w/w of the sustained release (SR) layer (batches C7–C10). Based on performance, sodium bicarbonate was selected for further optimization at varying concentrations of 5%, 7.5% and 10% w/w (batches C11, C7 and C12). Bilayer tablets were prepared using direct compression technique. Floating characteristics were assessed in simulated gastric fluid, while drug content and dissolution studies were performed using validated analytical methods. **RESULTS:** Among the tested agents, sodium bicarbonate demonstrated superior buoyancy characteristics. A concentration dependent reduction in floating lag time was observed. Batch C12, containing 10% w/w sodium bicarbonate (80 mg per 800 mg SR layer), exhibited the shortest floating lag time (65 ± 3 s) and remained buoyant for more than 12 h. The formulation also showed sustained release of metformin over 12 h and rapid release of canagliflozin within 30 min. All evaluated parameters complied with pharmacopeial specifications. **CONCLUSION:** Sodium bicarbonate at 10% w/w was identified as the optimal gas generating agent concentration for achieving rapid onset of buoyancy and prolonged gastric retention in the developed bilayer tablet system.

INTRODUCTION: Gastro-retentive drug delivery systems (GRDDS) are designed to enhance the residence time of dosage forms in the stomach, thereby improving drug absorption and bioavailability for drugs exhibiting a narrow absorption window in the upper gastrointestinal tract.

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Among various GRDDS approaches, floating drug delivery systems are widely explored due to their simplicity and effectiveness [1]. These systems rely on the generation of gas within the dosage form. Gas-generating agents react with gastric acid to liberate carbon dioxide, which becomes entrapped within the hydrated polymer matrix.

This entrapment reduces the overall density of the system, enabling it to float over gastric contents [2]. Different carbonate salts exhibit varying rates of reaction and gas generation. Sodium bicarbonate, in particular, reacts rapidly in acidic conditions, making it a preferred choice for achieving immediate buoyancy.

In contrast, other carbonates may show delayed or reduced gas generation. Hypromellose K100M (HPMC K100M) was selected as the matrix-forming polymer owing to its high viscosity, strong gel-forming capacity and ability to effectively entrap generated gas, thereby supporting both buoyancy and sustained drug release [3].

MATERIALS AND METHODS:

Materials: Metformin hydrochloride and canagliflozin were obtained from reliable pharmaceutical sources. HPMC K100M, microcrystalline cellulose (MCC pH 102), lactose, Kyron T-314, talc and magnesium stearate were used as excipients.

Methodology: The experimental design comprised two distinct phases:

1. Screening of different gas-generating agents at a fixed concentration of 7.5% w/w (C7–C10).
2. Optimization of sodium bicarbonate at 5%, 7.5% and 10% w/w (C11, C7, C12).

Preparation of Bilayer Tablets: All formulation components were passed through sieve #40 to ensure uniform particle size. The sustained-release blend was prepared by thoroughly mixing metformin hydrochloride, HPMC K100M, gas-generating agent and MCC for 20 minutes. Lubricants (talc and magnesium stearate), previously passed through sieve #80, were incorporated and blended for an additional 5 minutes [4].

The immediate-release blend was prepared separately using canagliflozin, lactose, MCC and super disintegrant. Bilayer tablets were compressed using a rotary compression machine equipped with 10 mm flat-faced punches.

The SR layer (800 mg) was initially compressed, followed by addition of the IR layer (150 mg), and final compression was carried out at a force range of 5–8 kg/cm². Formulation of batches C7-C10 were mentioned in **Table 1.**

TABLE 1: PRELIMINARY TRIAL BATCHES FOR USE OF GAS-GENERATING AGENTS

Ingredients (mg)	Batch Number			
	C7	C8	C9	C10
	Layer-SR			
Metformin HCl	500.0	500.0	500.0	500.0
Hypromellose K 100M	160.0	160.0	160.0	160.0
Sodium bi carbonate	60.0	-	-	-
Sodium carbonate	-	60.0	-	-
Potassium carbonate	-	-	60.0	-
Calcium carbonate	-	-	-	60.0
Microcrystalline cellulose pH 102	64.0	64.0	64.0	64.0
Magnesium stearate	8.0	8.0	8.0	8.0
Talc	8.0	8.0	8.0	8.0
Total wt. of SR layer (mg)	800.0	800.0	800.0	800.0
	Layer-IR			
Canagliflozin	50	50	50	50
Lactose	20.0	20.0	20.0	20.0
Microcrystalline cellulose pH 102	68	68	68	68
Kyron T-314	6.0	6.0	6.0	6.0
Talcum IP	2.0	2.0	2.0	2.0
Magnesium stearate IP	2.0	2.0	2.0	2.0
Iron oxide red	2.0	2.0	2.0	2.0
Total of IR layer (mg)	150.0	150.0	150.0	150.0
Total wt. of bilayer tablet (mg)	950.0	950.0	950.0	950.0

Composition of Batches

TABLE 2: GAS-GENERATING AGENT SCREENING (SR LAYER = 800 MG)

Batch	Agent	Amount (mg)	% w/w
C7	Sodium bicarbonate	60	7.5
C8	Sodium carbonate	60	7.5
C9	Potassium carbonate	60	7.5
C10	Calcium carbonate	60	7.5

TABLE 3: OPTIMIZATION OF SODIUM BICARBONATE

Batch	Amount (mg)	% w/w
C11	40	5
C7	60	7.5
C12	80	10

Evaluation of Powder Blend: Pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner ratio and angle of repose were determined to assess flow properties.

Post-Compression Evaluation: The prepared tablets were evaluated for: - Weight variation (n = 20) - Hardness using Monsanto hardness tester (n = 6) - Thickness using Vernier calipers (n = 10) - Friability using Roche friabilator (n = 10; acceptable limit ≤1%)

Floating Study: The time taken for dosage form to emerge on to the surface of medium is called Floating Lag Time (FLT) and the duration of time by which the dosage form constantly emerges on the surface of medium is called Total Floating Time (TFT).

One tablet from each formulation was placed in USP type II dissolution apparatus containing 900 mL of 0.1 N HCl (pH 1.2) using paddle at a rotational speed of 100 rpm. The temperature of dissolution media was maintained at 37 ± 0.5°C.[5]

Drug Content Analysis: Drug content for Canagliflozin: 10 tablets of each formulation were weighed and powdered. A quantity of powder equivalent to 50 mg of Canagliflozin taken into 100 ml volumetric flask.

The amount of drug present in a 50 mg equivalent amount of powder dissolved in and diluted with acetate buffer. Further 1ml of the above solution was diluted to 10 ml with acetate buffer and UV absorbance was measured at 233 nm. Drug concentration was determined from standard graph.

Drug content for metformin HCl in pH 6.8 Phosphate buffer: 10 tablets of each formulation of sustained release layers were weighed and powdered. A quantity of powder equivalent to 50mg of metformin HCl taken into 100 ml volumetric flask.

The amount of drug present in a 50mg equivalent amount of powder was determined by dissolving the powder mixture in Phosphate buffer pH 6.8 and suitably diluted with Phosphate buffer pH 6.8. Further 1ml of the above solution was diluted to 10ml with Phosphate buffer pH 6.8. UV absorbance was measured at 238 nm.

Drug concentration was determined from standard calibration curve. The method was validated for accuracy, precision and linearity. Acceptance criteria were set between 95% and 105% [6].

Dissolution Study: *In-vitro* dissolution studies were conducted using USP type II apparatus (paddle method) at 50 rpm in 900 mL of 0.1 N HCl at 37 ± 0.5°C. Samples were withdrawn at predetermined intervals for both SR and IR layers, filtered and analyzed using using HPLC under specified chromatographic conditions. An equal volume of fresh dissolution medium was replaced after each sampling to maintain sink conditions [7].

RESULTS AND DISCUSSION:

Physical Evaluation: All formulations complied with pharmacopeial specifications for weight variation, hardness and friability, indicating good mechanical strength and uniformity.

Physical Parameters:

Evaluation of Batches for Optimization of Sodium Bicarbonate Concentration:

TABLE 4: POWDER BLEND PROPERTIES OF TRAIL BATCHES C7, C11, C12

	Batch no	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of Repose (θ)	Carr's Index (%)	Hausner's ratio
Canagliflozin with Metformin HCl	C7	0.44±0.02	0.52±0.05	27.32±1.2	18.5±1.3	1.12±0.03
	C11	0.47±0.01	0.54±0.01	25.12±1.4	20.4±1.2	1.16±0.02
	C12	0.44±0.01	0.53±0.03	26.25±1.2	19.2±1.2	1.12±0.01

Mean ± SD, n=3

TABLE 5: PHYSICAL PARAMETERS OF TABLETS OF TRAIL BATCHES C7, C11, C12

	Batch No	Weight variation (mg)	Thickness (mm)	Friability (%w/w)	Hardness (kg/cm^2)
Canagliflozin with Metformin HCl	C7	948±0.53	6.8±0.02	0.58±0.16	5.1±0.13
	C11	951±0.631	6.6±0.01	0.60±0.12	5.4±0.16
	C12	952±0.54	6.7±0.03	0.53±0.17	5.3±0.14

Floating Behavior: Sodium bicarbonate demonstrated superior performance compared to other gas-generating agents. The reduction in floating lag time with increasing concentration confirms the role of CO_2 generation in enhancing buoyancy. Batch C12 showed optimal floating behavior due to higher gas generation and efficient entrapment within the polymer matrix.

TABLE 6: FLOATING PROPERTIES

Canagliflozin with Metformin HCl	Batch No	Floating lag time (sec)	Total floating time (h)
	C7	204 ± 5	7.2±0.2
	C11	129± 4	10.8±0.2
	C12	65± 3	12.4±0.2

Mean ± SD, n=3

Sodium bicarbonate exhibited superior performance due to rapid CO_2 generation. Increasing its concentration significantly reduced floating lag time.

TABLE 7: % DRUG CONTENT OF CANAGLIFLOZIN AND METFORMIN HCL

Batch no.	% Drug content	
	Canagliflozin	Metformin HCl
C7	99.74 ±0.14	99.42 ±0.14
C11	98.11±0.12	97.55±0.13
C12	98.96±0.13	98.89±0.17

Mean ± SD, n=3

According to the United States Pharmacopeia (USP) and British Pharmacopoeia (BP) monographs for Metformin Hydrochloride tablets, the acceptance criteria for assay (content) are typically:

Lower Limit: 95.0%

Upper Limit: 105.0%

Dissolution Studies: The sustained-release layer exhibited controlled drug release over 12 hours, which can be attributed to the gel-forming nature of HPMC K100M. The immediate-release layer demonstrated rapid drug release within 30 minutes, ensuring prompt therapeutic action. The bilayer system effectively combined immediate and prolonged drug release profiles.

TABLE 8: *IN-VITRO* DISSOLUTION PROFILE DATA OF FORMULATIONS C7, C11, C12

Batch no.	C7	C11	C12
Cumulative % drug release (Canagliflozin)			
5 min	58.13±0.22	60.76±0.31	54.17±0.23
10 min	89.32±0.33	83.96±0.13	89.14±0.15
15 min	93.21±0.12	90.41±0.12	94.53±0.43
20 min	96.71±0.24	95.65±0.15	96.32±0.11
30 min	98.42±0.12	99.02±0.13	99.84±0.24
Cumulative % drug release (Metformin HCl)			
0.5 h	19.69±0.11	23.22±0.21	24.19±0.21
1 h	25.11±0.29	30.53±0.13	36.65±0.15
2 h	38.73±0.12	33.14±0.18	42.21±0.11
3 h	46.76±0.24	48.34±0.12	47.22±0.23
4 h	54.82±0.22	53.82±0.15	50.61±0.16
6 h	69.51±0.17	59.15±0.12	54.75±0.14
8 h	84.23±0.21	68.98±0.22	72.50±0.11
10 h	89.69±0.11	82.24±0.17s	83.31±0.13
12 h	93.53±0.14	94.15±0.17	98.65±0.15

Mean ± SD, n=3

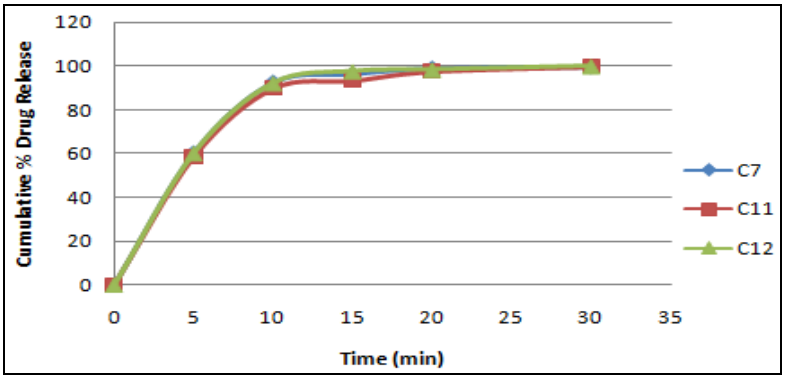

FIG. 1: *IN-VITRO* DISSOLUTION OF CANAGLIFLOZIN IR LAYER OF BATCHES C7, C11 AND C12

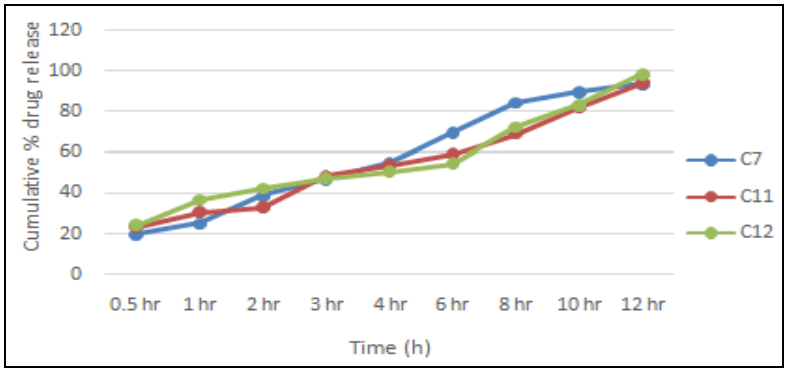

FIG. 2: *IN-VITRO* DISSOLUTION OF METFORMIN HCL SR LAYER OF C7, C11 AND C12

Fig. 1, 2 *in-vitro* Dissolution profile comparison for release of Canagliflozin IR layer and Metformin HCl SR layer Bilayer tablets using sodium bicarbonate. The SR layer demonstrated controlled release up to 12 h, while IR layer provided rapid drug release. The bilayer system ensured immediate and sustained therapeutic action.

CONCLUSION: The study successfully demonstrated that sodium bicarbonate is an effective gas-generating agent for floating drug delivery systems. Increasing its concentration significantly improved buoyancy characteristics by reducing floating lag time and extending floating duration. The optimized formulation (C12) exhibited desirable floating behavior along with appropriate drug release characteristics, making it a promising candidate for gastro-retentive drug delivery.

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CONFLICTS OF INTEREST: Nil

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