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DEVELOPMENT AND *IN VITRO* ASSESSMENT OF GASTRO-RETENTIVE BILAYER FLOATING TABLET FOR MANAGING HYPERTENSION IN ACUTE CONDITIONS

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Background: *This study disseminates the formulation and in vitro assessment of bilayer floating tablets designed to be retained in the stomach, delivering a combination of amlodipine besylate and atenolol. The tablets aimed to swiftly release amlodipine besylate while ensuring the sustained release of atenolol. The immediate-release layer of the HPMC-based bilayer tablet contained crospovidone and sodium starch glycolate as super disintegrants, along with a combination of guar gum and xanthan gum as binding agents. The sustained release layer included $NaHCO_3$ and citric acid to facilitate floating.* ***Results:*** *The optimized formulation comprised 60% HPMC K15M, 16.5% Carbopol 934P, and 9% each of crospovidone and $NaHCO_3$ in the immediate release layer, along with 33.33% HPMC K15M, 10% $NaHCO_3$, 1.7% each of natural gums in the sustained release layer, all in w/w. Post-compression, characterisation and in vitro drug release tests were performed. On immersion in simulated gastric fluid (SGF), without enzymes, pH 1.2, at 37 ºC, the tablets floated and remained buoyant without disintegration for more than 20 h.In simulated gastric fluid (SGF), over 99% of amlodipine besylate was released from the immediate release layer within 75 mins, while 99.23% of atenolol was released from the delayed release layer within 12 hours.* ***Conclusion:*** *A comparison with a similar marketed product indicated the superior performance of the optimal batch in terms of in vitro drug release profile.*

Keywords: *Bilayer, Floating, Gastro-retentive, Immediate release, Sustained release*

INTRODUCTION

Crafting an oral drug formulation to float in the gastric environment under specific conditions demands adept manipulation. Over the last decade, there have been significant strides in developing single dosage forms that combine two or more active pharmaceutical agents (APIs), enhancing patient convenience and adherence[1]. Bilayer Tablets can be designed in such a way as to amend the discharge of drug/s as either of the layers can be kept as extended and immediate release layers[2]. Such Tablets have been developed to accomplish more or less controlled delivery of one of the drugs with a pre-determined release profile. They are suitable for the same drug as immediate release and sustained release layers, or two different drugs in two different layers to manage the required ailment of the patient[3]. Several works have been reported incorporating two different drugs in two different layers for rapid and prolonged release[4].

Lately, there has been a surge in endeavours aimed at enhancing drug bioavailability and therapeutic efficacy from oral dosage forms, achieved by promoting retention in the gastric environment[5]. Gastro-retentive bilayer Tablets[6] have contributed to a large extent in prolonging residence of the dosage form hence drug release in the stomach, of which floating drug delivery systems are quite common. For floating systems, a density lower than that of gastric fluids[7] is a

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requirement so that it remains buoyant in the gastric fluid for an elongated period.

Once patients with hypertension fail to attain control of their blood pressure, the strategies involve increasing the dose of mono-therapy (increases the risk of side effects) or using drug combinations with minimum side effects[8]. Thus, combination therapy with antihypertensive agents is a rational approach with reduced doses of drugs to lower the patient's blood pressure thereby minimize dose-dependent side effects and adverse reactions[9].

The current investigation revolves around formulating an indigenous bilayer floating tablet containing immediate release of amlodipine besylate and sustained-release of atenolol from respective layers. A rational study revealed a synergistic interplay between atenolol and amlodipine in mitigating blood pressure variability and augmenting baro reflex sensitivity, thus shielding against end-organ damage. The combined therapy exhibited superior effects compared to individual drugs, notably in curbing end-organ damage, especially in adults[10]. Moreover, the study underscored the potential advantages of utilizing half-dose combinations. This synergistic effect was consistent across various hypertension models, indicating broad relevance for hypertensive patients, especially those with coronary artery diseases or sympathetic nervous system over activity[11].

The immediate-release layer was formulated with crospovidone and sodium starch glycolate serving as super disintegrants[12]). So far, there have been no documented studies employing this specific combination of super-disintegrating agents in the immediate release layer. Sodium bicarbonate ($NaHCO_3$) and citric acid are incorporated into the sustained release layer to induce floating of the tablet. Additionally, HPMC K15M was introduced as a polymer for controlling the release rate[13] in both layers. Carbopol 934P was used to stabilise and control the release of active agents, overall. Guar gum and xanthan gum were used as binding polymers[14]

MATERIALS AND METHODS

Atenolol and amlodipine besylate were provided as complimentary samples by Cipla Ltd. Sikkim, India. HPMC K15M, xanthan gum, and guar gum were sourced from Balaji Drugs, while sodium bicarbonate, crospovidone, sodium starch glycolate, and citric acid were obtained from Merck Specialties Pvt. Ltd. Isopropyl alcohol was bought from EMPARTA®. Lactose was acquired from CDH (P) Ltd. Carbopol 934P was obtained from Stadmed Pvt. Ltd. Magnesium stearate and talc were obtained from Zacfa Chemicals. All the chemicals were of analytical grade and were used without further purification.

Electronic balance and moisture analyzer of Mettler Toledo, Switzerland; double beam UV Vis. spectrophotometer, Shimadzu, Japan; Fourier Transform Infrared Spectroscopy (FTIR), Bruker, Germany; dryer from Prism pharma; Tablet compression machine of Fluidpack, India; USP disintegration test apparatus and USP dissolution apparatus II of Electrolab, India; Monsanto hardness tester, friability tester, tap density tester were used for experimentation and analysis purpose.

Drug-excipient Compatibility Study

FTIR spectroscopy was done to check the compatibility of drugs with their respective excipients. The scanning was performed for both the drugs, amlodipine besylate[15] and atenolol[16]with a resolution of 1 cm^{-1} with a recording of KBr disc spectra in mid-IR regions. A plot of these scans was assessed for the presence of chief peaks of the drug alongside the shifting and masking of drug peaks and the appearance of new peaks due to drug-drug and or excipient interaction.

Formulation of Amlodipine Besylate Immediate (IR) Release Tablets

Amlodipine besylate immediate release Tablets were prepared using the direct compression method. Crospovidone, sodium starch glycolate, HPMC K15M and Carbopol 934P were weighed (ME55/A, Mettler Toledo, Switzerland) and mixed homogenously followed by the addition of magnesium stearate and talc. Then the blend was directed to compression where 80 mg of this mixture was fortified through flat-faced punches (8mm) (Rimek Mini Press I, Karnavati Engineering Pvt. Ltd. Mumbai, India), to result in the preferred Tablets according to the composition highlighted in **Table 1**.

Table 1: Composition of Amlodipine besylate Containing Immediate Release (IR).

Ingredients	Amlodipine besylate (mg)	Crospovidone (mg)	Sodium starch glycolate (mg)	HPMC K15M (mg)	Carbopol 934P (mg)	Talc (mg)	Total (mg)
A1	3.5	6.3	5	51.2	14	1.47	80
A2	3.5	6.3	-	56.2	14	1.465	80
A3	3.5	-	6.3	56.2	14	1.465	80
A4	3.5	6.3	6.3	50	14	1.465	80
A5	3.5	6.3	7	48	14	1.465	80
A6	3.5	2.2	12	48	13.2	1.5	80
A7	3.5	10.4	4	48	13.2	1.5	80
A8	3.5	14.4	-	48	13.2	1.5	80
A9	3.5	-	14.4	48	13.2	1.5	80
A10	3.5	12	2.2	48	13.2	1.5	80

Formulation of Atenolol Sustained Release (SR) Tablets

A prolonged release layer of atenolol was prepared by wet granulation technique with the proportion of ingredients indicated in **Table 2**. Atenolol and required quantities of polymer, sodium bicarbonate ($NaHCO_3$) and lactose were blended followed by the addition of sufficient amount of isopropyl alcohol and erythrosine red (1%) till a suitable (pink) wet mass for granulation was obtained, granulated and dried at 40 ℃ for 1 h. To this, citric acid, magnesium stearate and talc were added and allowed to mix well. According to **Table 2**, 120 mg of the respective mixture was fed into the die of a rotary Tablet machine, fortified through flat-faced punches (8 mm), resulting in preferred Tablets (F1-F10)[17].

Preparation of Bilayer Floating Tablets

Bilayer floating Tablets of amlodipine besylate and atenolol were formulated by direct compression and wet granulation techniques, correspondingly. The immediate release layer included Amlodipine besylate and the formulations were designated as A1 to A10 **(Table 1)**. The sustained release layer contained Atenolol, named F1 to F10 **(Table 2)**. Combination of both the layers produced bilayer Tablets, batches S1 to S6 **(Table 4)**.

According to **Table 1** and **Table 2**, tablets were compressed to result in an immediate release (IR) and sustained release (SR) layers that were used to formulate bilayer floating tablets of amlodipine besylate and atenolol. Accurately weighed 80 mg of immediate-release powder blend and 120 mg of sustained-release floating layer powder blend were punched simultaneously. Initially, SR powder composite was served physically into the dies of a rotary Tablet contrivance and compacted at low compression force. Consequently, the IR layer's powder blend of amlodipine besylate was added over the pre-compressed SR layer and compacted by a Tablet punching machine with an 8 mm flat-faced punch[18], wherein A1 through A10 was compressed with F1 through F10 to give S1 to S10 tablets.

Evaluation of Bilayer Tablets Physical Attributes

Physical features like the shape, size, hardness, friability, floating time, buoyancy, swelling index were checked and compared with existing standards in triplicate to minimize error.

Tablet Floating Behaviour

Tablets were placed in simulated gastric fluid (SGF) and the time when floating starts or the tablet becomes buoyant was noted. Briefly, tablets were checked for floating in a glass beaker containing 200 ml of simulated gastric fluid, without enzymes (pH 1.2) and placed in a water bath at 37 ± 0.5 °C [17], henceforth called as simulated gastric fluid (SGF). Total floating time (TFT) is the time duration for which the tablet remained buoyant in gastric fluid as noted in **Table 4**.

Table 2: Composition of Atenolol – SR layer.

Ingredient	Atenolol (mg)	HPMC K15M (mg)	Sodium bicarbonate (mg)	Xanthan gum (mg)	Guar gum (mg)	Lactose (mg)	IPA	Mg. stea-rate (mg)	Talc (mg)	Total (mg)
F1	25	40	12	2.4	2.4	30	q.s.	1.2	1	120
F2	25	40	12	-	-	34	q.s.	1.2	1	120
F3	25	-	12	2.4	2.4	70	q.s.	1.2	1	120
F4	25	40	12	4.8	-	30	q.s.	1.2	1	120
F5	25	40	12	-	4.8	30	q.s.	1.2	1	120
F6	25	40	25	2	2	18	q.s.	2	3	120
F7	25	40	25	4	2	18	q.s.	2	3	120
F8	25	30	25	2	4	25	q.s.	2	3	120
F9	25	40	25	6	-	17	q.s.	2	3	120
F10	25	40	25	-	6	17	q.s.	2	3	120

Table 3: Flow properties for evaluation of powders for pre-compression parameters analysis of Amlodipine besylate-IR, with glidant.

Formulation code	Angle of repose θ (^{0})	Bulk density (g/cm^3)	Tapped density (g/cm^3)	% Compressibility	Hausner's ratio
A1	32.00 (passable)	0.251	0.390	35.48 (very poor)	1.55 (poor)
A2	45.25 (very poor)	0.305	0.466	34.66 (poor)	1.53 (poor)
A3	48.94 (very poor)	0.301	0.523	42.44 (extremely poor)	1.73 (poor)
A4	47.43 (very poor)	0.392	0.604	35 (poor)	1.53 (poor)
A5	43.16 (very poor)	0.365	0.502	27.29 (poor)	1.37 (moderate)
A6	42.53 (very poor)	0.314	0.472	33.34 (poor)	1.5 (moderate)
A7	43.19 (very poor)	0.339	0.527	35.71 (very poor)	1.50 (moderate)
A8	43.40 (very poor)	0.374	0.584	36.00 (very poor)	1.56 (poor)
A9	43.32 (very poor)	0.331	0.464	28.57 (poor)	1.4 (moderate)
A10	42.66 (very poor)	0.380	0.593	36.00 (very poor)	1.56 (poor)

Table 4: Flow properties for evaluation of granules for pre-compression parameters analysis of Atenolol-SR, with glidants.

Formulation code	Angle of repose θ (^{0})	Bulk density (g/cm^3)	Tapped density (g/cm^3)	% Compressibility	Hausner's ratio
F1	33.10 (passable)	0.267	0.330	18.94 (fair)	1.23 (good)
F2	33.42 (passable)	0.267	0.334	20.00 (fair)	1.24 (good)
F3	23.74 (good)	0.502	0.711	29.39 (poor)	1.41 (moderate)
F4	31.21 (passable)	0.322	0.384	16.14 (good)	1.19 (good)
F5	33.58 (passable)	0.291	0.399	27.06 (poor)	1.37 (moderate)
F6	34.93 (passable)	0.359	0.431	16.67 (good)	1.20 (good)
F7	34.76 (passable)	0.318	0.439	27.49 (poor)	1.37 (moderate)
F8	32.68 (passable)	0.537	0.622	13.16 (good)	1.15 (good)
F9	32.72 (passable)	0.346	0.520	33.32 (poor)	1.49 (moderate)
F10	37.90 (passable)	0.344	0.569	39.54 (extremely poor)	1.65 (poor)

Degree of Swelling

Adequate swelling property for floating bilayer tablets was calculated before and after immersion in the SGF, without enzymes, following the equation as mentioned, and tabulated in **Table 4**.

$SI = \{(W_f - W_i)/W_i\} \times 100$

where SI is the swelling index, W_i is the initial weight of the tablet (before wetting) and W_f is the weight after absorption of SGF.

***In vitro* DrugRelease Study**

In vitro drug release study, the release of drugs from different batches of individual prepared Tablets of Amlodpinebesylate and Atenolol was studied using USP dissolution apparatus type II along with the final tablets prepared by taking the optimized individual formulations[19]. For the test, the dissolution medium used was 900 ml of 0.1 N HCl, pH 1.2, without enzymes for the first 75 min for the immediate release amlodipine besylate layer (IR layer), rotating speed of 50 rpm, and temperature maintained at 37 ± 0.5 °C. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 5 min. intervals till 75 min. and the samples were replaced with fresh dissolution medium, immediately. The collected samples were filtered through Whatman™ filter paper (# 41), appropriately diluted and absorbance measured simultaneously using UV Vis spectrophotometer[20]

To determine the percentage of atenolol being released from the sustained release layer, a dissolution study was carried out in a phosphate buffer (pH 6.8), without enzymes. Other parameters remained the same as those for amlodipine besylate. An aliquot (5 ml) of the solution was withdrawn from the dissolution apparatus at 1 h intervals for 12 h and the samples were replaced with fresh dissolution medium. The absorbance of the collected samples which were appropriately diluted was measured after passing through the Whatman™ filter paper (# 41). Simultaneous estimation of amlodipine besylate and atenolol was done using a UV Vis Spectrophotometer (UV 1800, Shimadzu, Japan). At 360.80 nm (λ_{max} of amlodipine besylate for simultaneous estimation) atenolol had zero absorbance, so amlodipine besylate was directly estimated at 360.80 nm, while, at 276 nm (λ_{max} of atenolol), atenolol was estimated[21], following the same grounds.

The results were calculated using the simultaneous equation method as given below:

$$Cx = \frac{A_2 ay_1 - A_1 ay_2}{ax_2 ay_1 - ax_1 ay_2},$$

$$Cy = \frac{A_1 ax_1 - A_2 ax_2}{ax_2 ay_1 - ax_1 ay_2},$$

Where, Cx and Cy are the concentrations of amlodipine besylate and atenolol, respectively; A_1 is absorbance value at wavelength λ_1; A_2 is absorbance value at wavelength λ_2; ax_1 is the absorptive value of amlodipine besylate at λ_1; ax_2 is the absorptive value of amlodipine besylate at λ_2; $ay_1$is absorptive value of atenolol at λ_1; $ay_2$is absorptive value of atenolol at λ_2.

In vitro drug release studies of bilayer tablets were carried out using USP dissolution apparatus type II in 900 ml of 0.1 N HCl (pH 1.2) for the first 75 minutes and in 900 ml of phosphate buffer (pH 6.8) up to 12 hours.

Stability Studies

A stability study was done following the ICH guidelines. Optimized bilayer Tablets were subjected to stability studies at 40 ± 2°C/75 % ± 5 % RH in a humidity chamber. The products were evaluated for their physical characteristics (like odour, color change, moisture content) and *in vitro* drug release profiles over a period of 3 and 6 months[22].

Kinetic Data Analysis

The drug release kinetics of amlodipine besylate in the IR layer and atenolol in the SR layer in the bilayer tablets were examined using the linear regression method. For instance, the kinetic model was verified by plotting the cumulative percentage of drugs released against time. The first-order kinetic model was checked for by plotting the logarithm of cumulative per cent drug remaining against time. Higuchi's model was studied by plotting the cumulative percentage of drugs released against the square root of time. Korsmeyer Peppas model was checked by plotting the logarithm of cumulative per cent drug released against the logarithm of time.

RESULTS AND DISCUSSION

Results

Bilayer Tablets were successfully prepared indigenously that contained amlodipine besylate in the immediate release layer and atenolol in the sustained release layer. Each of the tests were done in triplicate. The results of precompression tests, namely angle of repose, bulk density, tapped density, % compressibility and Hausner's ratio are indicated in **Table 3 and Table 4**. A6 and F6 respectively displayed better performance compared to other formulations. For all of the tests and analysis, formulations 1 through 5 were rejected since the floating attributes could not be complied at all, although the variation in weight and the thickness range was well acceptable, **Table 5**. Additionally, the swelling characteristics were also not as per the requirement of the swellable tablets. Hence, rest of the tests were limited to formulation 6 to 10 for both the layers, IR and SR, individually and in combination.

Compatibility Study of Drugs and Excipients

A compatibility check was done by conducting FTIR studies, delineated in **Fig. 1** Amlodipine besylate displayed characteristic peaks contributed by function groups were according to previous reports and did not overlap with each other as shown in **Fig. 1**.

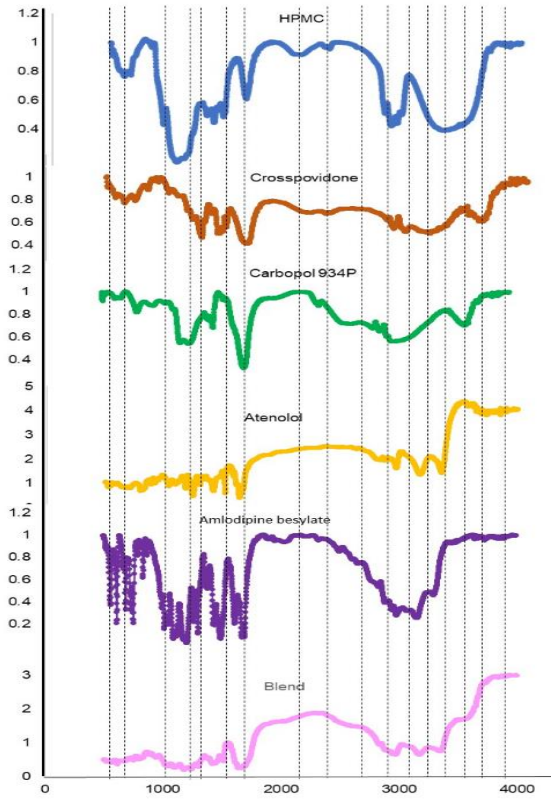

Fig. 1:FTIR spectrum of atenolol, Amlodipine besylate and bi-layered tablet.

Evaluation of Bilayer Tablet

For all the studies, experiments were conducted in triplicate to minimize error. The tablets so prepared were tested as per standard procedure for normal quality control tests. The hardness of the tablets of S1-S10 was found to be well within the limits, which is expectedto be favourable during *in vitro* drug release. However, S1 to S5 was rejected, later, for further studies since these batches could not pass the floating time requirements, as shown in Table 4. Loss during the friability study was less than 1% for all the batches.

Tablet Floating Behaviour and Buoyancy

Table 4 depicted that formulations S1 through S5 did not exhibit flotation behavior, due to less than optimum concentration of gas-generating sodium bicarbonate in the formulation. Hence, no further tests with the batches were carried out. Batches S6 to S10 with a 20% w/w concentration of $NaHCO_3$ and 5% w/w citric acid were found to float. Buoyancy lag time for S6-S10 was in the range of 4 to 58 seconds, without disintegration.

Degree of Swelling

The swelling aspect of xanthan gum is greater than that of HPMC K15M and formulations with a higher degree of swelling retard the release of drugs more than those with lower swelling degree. According to **Table 5**, the degree of swelling was appreciably high for the batches S6 through S10. S1 to S5 demonstrated extremely low % swelling in contrast to S6 through S10.

***In vitro* DrugRelease Study**

The prepared bilayer tablets were evaluated for drug release profiles. **Fig. 2** displayed the *in vitro* cumulative drug release profiles for each of the drugs from the corresponding individual layers of the bilayer Tablet formulation, S6 containing immediate release layer A6 and sustained release layer F6. Amlodipine besylate was present in the immediate release (IR) layer and atenolol in the sustained release (SR) of the bilayer Tablet. The release study for amlodipine besylate was done in phosphate buffer solution (PBS), pH 1.2 (without enzymes), 900 ml, maintained at 37 ± 2 ºC throughout the release study period. Release for amlodipine besylate from batches A6 through A10 has shown an IR profile between 82.27% and 99.47% within 75 min. A6 illustrated the highest drug release (99.47%) after 75 min. From the above data, Fig. 2, formulation A6 was chosen as the optimized batch for bilayer tablets as it reflected good physical attributes (Table 3) and F6 as seen from Table 4. Whereas, for the SR layer, atenolol demonstrated drug formulation A6 was selected to be merged with F6 so that S6 could be generated as the bilayered tablet, **Fig.3(a)**. It implied that the release of sustained release drug in the medium preferred for the immediate release layer was found to be negligible and thus showed no irregularities in the drug release of bilayer tablet and values are represented in **Fig. 3(a)**.

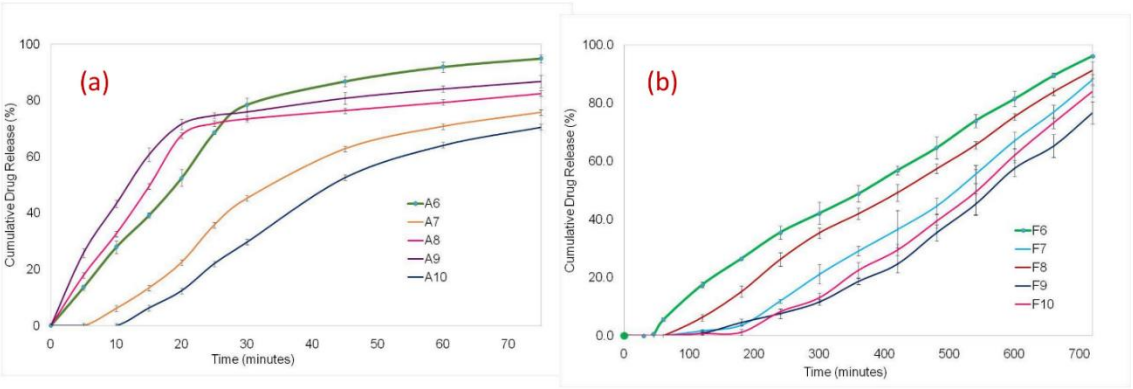

Fig. 2: Comparative Release Profiles for all accepted batches of (a) Amlodipine besylate (named A batches) from IR layer (b) Atenolol from SR layer, (named F batches).

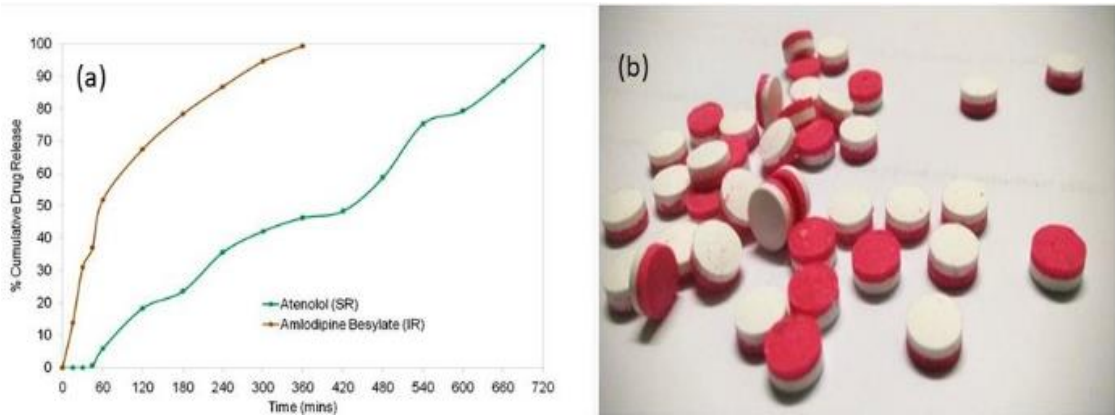

Fig.3: (a) Cumulative Drug Release of Amlodipine besylate and Atenolol from respective layers over the total length of time under study(b) Representative Batch of the Bilayered Tablets.

Stability Studies

As a part of the short-term stability studies, batches S6 to S10 were subjected to the test according to ICH guidelines. These batches were stored at 40 ± 2 °C / 75 ± 5 % relative humidity (RH) in closed high-density polyethylene bottles for 3 months and 6 months. No marked changes (organoleptic and physical features) were seen in any of the batches during and after the stability study period, indicating that they were stable until the study period and reported in **Table 5**

Drug Release Kinetic Data Analysis

The kinetic data for Amlodipine besylate from the immediate layer drug release is presented in **Table 6**. The analysis suggested that the cumulative release of the drug from the IR layer conforms best to the zero-order model, with a regression coefficient (R^2) of 0.9817. **Table 7** represents statistical analysis at 95% confidence level for marketed sample and prepared tablets.

Table 5: Physical Properties of Bilayered Tablets (*indicates that no floating was observed in S1-S5 even after 24 h).

Formulation code	Weight Variation (mg) ± SD	Thickness (mm) ± SD	Hardness (Kg/cm²)	Hardness (Kg/cm²) (after stability)	Friability	Floating lag time (s)	Total floating time (TFT) (h)	Degree of swelling (%)	Content Uniformity (%)	Color Changes (after stability)	Total floating time (TFT) (h) (after stability)
S1*	196±0.06	3.74±0.67	5.7	Not noticeable	0.151	-	-	52	94.47	Not noticeable	-
S2*	201±0.14	3.7.3±0.51	6.5	Not noticeable	0.251	-	-	38	93.56	Not noticeable	-
S3*	204±0.21	3.83±0.23	6.8	Not noticeable	0.322	-	-	61	90.89	Not noticeable	-
S4*	191±0.63	3.66±0.47	6.2	Not noticeable	0.102	-	-	44	92.01	Not noticeable	-
S5*	195±0.52	3.71±0.71	6.5	Not noticeable	0.198	-	-	59	91.61	Not noticeable	-
S6	199±0.08	3.90±0.52	5.5	Not noticeable	0.237	> 4	> 24	84	99.98	Not noticeable	> 24
S7	206±0.73	3.88±0.63	5.0	Not noticeable	0.194	> 7	> 24	82	99.81	Not noticeable	> 24
S8	201±0.07	3.93±0.18	6.0	Not noticeable	0.263	> 57	> 24	79	99.93	Not noticeable	> 24
S9	198±0.32	3.94±0.35	5.7	Not noticeable	0.218	> 17	> 24	88	98.77	Not noticeable	> 24
S10	204±0.09	3.88±0.83	5.2	Not noticeable	0.233	> 21	> 24	81	99.58	Not noticeable	> 24

Table 6: Kinetic data analysis of Amlodipine besylate (immediate release) layer and Atenolol (sustained release layer) in bilayer tablet.

Kinetics Model	*Amlodipine Besylate (Immediate Release Layer)*		*Atenolol (Sustained Release Layer)*	
	m (slope)	**R^2**	**m (slope)**	**R^2**
Zero Order	0.12597	0.9817	0.1395	0.9954
First Order	0.0182	0.8222	0.0013	0.9256
Higuchi	12.672	0.9385	3.9838	0.946
KP Model	0.6105	0.8986	1.267	0.828

Table 7: Understanding confidence intervals and statistical significance of Optimized Bilayer Tablets and Marketed Sample.

Parameters	Marketed Sample (Atenolol)	F6 (Atenolol)	Marketed Sample (Amlodipine besylate)	A6 (Amlodipine)
Upper Confidence Interval	48.633	59.986	61.562	84.31
Mean	32.996	41.408	40.641	62.215
Lower Confidence Interval	17.358	22.83	19.72	38.862

Discussion

There were ten batches of bilayer tablets prepared successfully; a representative batch of the prepared tablets is shown in **Fig. 3(b)**. The initial compatibility of the composition was checked by FTIR studies. Distinct peaks corresponding to the chemical bonds were studiedfor the components of the formulation in detail revealed that the same peaks were prominent in individual drugs, and physical mixtures of all the ingredients of the composition. such as phenyl ring substitution in the region 1400-1699 cm^{-1} and H bonded OH in the region 3200-3300 cm^{-1}. More specifically, the compound exhibited a small rise at 1405 cm^{-1} contributed by C=C. A sharp signal was noticed at 1586 cm^{-1} denoting absorption of the carbonyl group (C=O). A distinct spike at 1608 cm^{-1} was for C-H bending whereas another at 3234 cm^{-1} was contributed by O-H, and at 3354 cm^{-1} for N-H vibration.[23]

FTIR fingerprints for atenolol revealed an absorption band related to the C-O stretch of (Ar-O-R) at 1281 cm^{-1}. A peak close to 3383 cm^{-1} was observed for N-H bending. A spike centered at 2933 cm^{-1} was for the C-CH_3 bond. At 1592 cm^{-1}, a subtle peak was noticed for the presence of C=O. The presence of O-C=NH_2 could be located at 1490 cm^{-1}. This was further strengthened by the presence of the C=C (aromatic) bond of the molecule at 3034 cm^{-1}[24]. Identical peaks were detected in the crushed powder of the drug product, suggesting that no polymorphic transformations occurred in the drug substance during the tablet formulation process with excipients. Moreover, the fact that there were no shifts in the wave numbers of the FTIR peaks when comparing the solid dispersions to the physical mixture implied that there was no substantial interaction between the drugs and excipients at the molecular level, as depicted in **Fig. 1**.

No new peaks were observed, signifying that there were no traceable polymorphic changes in the drug substance during the preparation of the tablets. Also, the lack of shifts in the wave numbers of the FTIR peaks indicated the absence of pronounced interaction between the drugs and the other chief excipients at the molecular level. Thus, the FTIR studies indicated that there was no chemical interaction between the drugs and other components of the formulation.

The thickness and weight variation were clearly within the limits, **Table 5.** Hardness and friability reports were also in limits that affirm the easy transportation for tablet batches, S6 - S10, without impairing the tablet rigidity in addition to the content uniformity of the bilayer tablets[25].

The presence of a combination of natural polymers such as guar gum, xanthan gum and synthetic polymer, HPMC K15M were responsible for the desired performance of S6. An increase in the concentration of citric acid was found to cause a decrease in floating time as observed in **Table 5**. A similar observation was seen in a study, where HPMC-K100M,

HPMC-K4M, HPMC-E-15, and Carbopol 934 were used as gel-forming agents either alone or in combination[26].

Analysis of the kinetic data for the atenolol layer's drug release (SR layer) indicated that zero-order kinetics best describe this layer, with a regression coefficient (R^2) 0.9954 for the SR layer[27,28]. The outcome of their study was a tablet formulation that demonstrated a buoyancy lag time of 25 seconds and a total floatation time of 24 hours[29]

S6 through S10 exhibited effective swelling with the highest % swelling for S9 owing to the presence of the highest ratio of polymer: xanthan gum. The plausible reason for the delayed release of the drug in S6 could be the formation of a denser hydrogel network of HPMC K15M, xanthan gum and guar gum which offered more hindrance to the drug release[30].

F6 had no release of Atenolol up to 45 mins, only 5.85% release at the end of 1st hour followed by a steep rise in the drug release rate, **Fig. 3(a)**. After 12 h, 99.23% of drug release occurred from F6. An equal amount of guar gum and xanthan gum was probably responsible for the slow release of atenolol initially in F6. A sustained release layer containing 10% w/w of chitosan and 20% w/w of xanthan gum showed delayed release of atenolol up to 10 h in a comparable study[31]. On the contrary, the remaining formulations F7, F8, F9 and F10, showed no drug release at the end of an hour. After a duration of 12 h, each of F7, F8, F9, nd F10 delivered over 90% drug[32]. Nevertheless, considering the entire profile, F6 came up with superior performance comparing the cumulative drug release aspect.

S6 was named for bilayer tablet (A6 + F6), where A6 contained 2.75% w/w Crospovidone, 15% w/w sodium starch glycolate, 60% w/w HPMC K15M, 16.5% w/w Carbopol 934P in the IR layer, while F6, comprising of 33.33% w/w HPMC K15M, 20.83% w/w $NaHCO_3$, 1.67% w/w each of xanthan gum and guar gum in sustained release layer, displayed better result in this respect since the quantity of crospovidone was kept optimal. **Fig. 4** represents the *in vitro* dissolution study of bilayer floating tablets, which abides by the requirements of immediate and sustained release requirements for the dosage form.

An assessment of the prepared bilayer tablet, S6, was made with a similar product available in the drug stores, concerning the *in vitro* release of the drug for 12 h under identical conditions. The findings plotted in **Fig. 5(a)** rendered that the combined marketed tablet (of a similar combination of drugs) had practically released about 76 % Amlodipine besylate in the first 75 min, which was supposed to be the immediate release layer. In contrast, the indigenously prepared batch S6 (A6, for immediate release amlodipine besylate), demonstrated 99.4 % release of amlodipine besylate during similar time. Similarly, **Fig. 5(b)** presented practically no release of atenolol from S6, up to 1 h, followed by gradual release throughout the study period and a release of 99.23% at the end of 12 h. For the same drug, the marketed product released just above 82 % by the end of 12h.

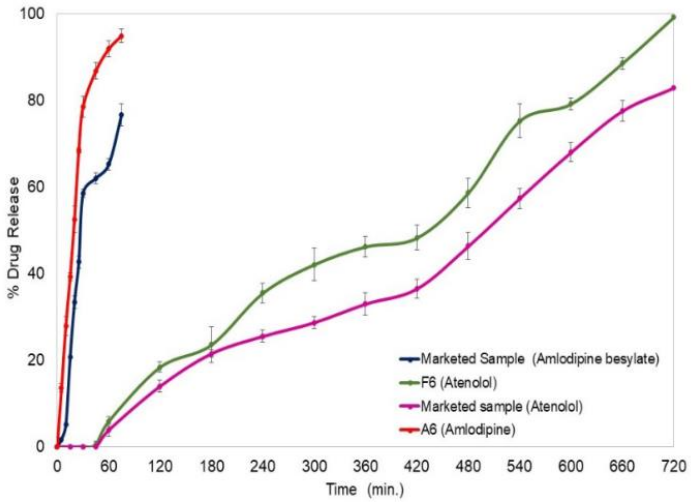

Fig. 4: *In vitro* dissolution study of the prepared bilayer floating tablets.

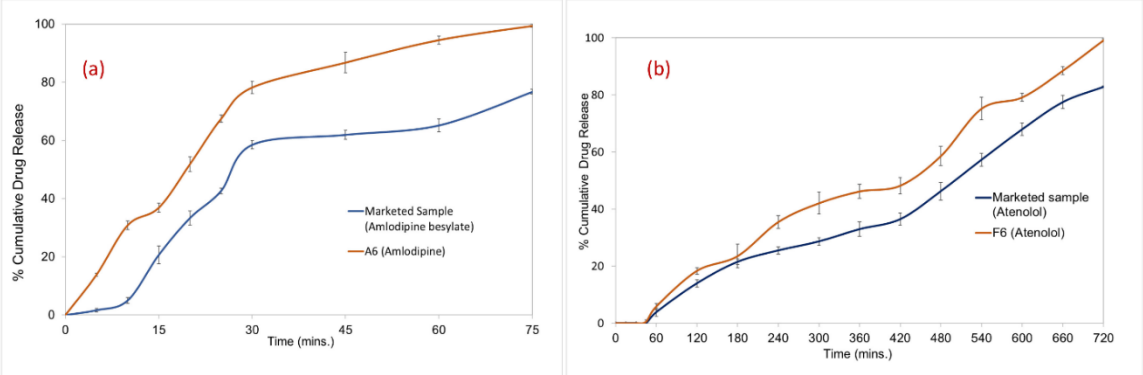

Fig. 5: Comparative Release Profiles of (a) Marketed sample (Amlodipine besylate) and Optimized Formulation S6 (b) Marketed sample (Atenolol) and Optimized Formulation S6.

The immediate release layer is to deliver the drug immediately after administration, which was not fulfilled by the marketed sample in contrast to the optimum batch, S6 (A6). A thorough analysis of the release pattern for both drugs from individual layers was matched with the appropriate kinetic model. The best-fit curve accorded with zero order kinetics from the IR and SR individually that was evident from **Table 6**. This was well in coherence with studies that were done on bilayered tablets[33]. Comparative drug release studies of S6 and marketed products revealed that S6 presented better release profiles of both the drugs from respective layers under identical conditions and hence may be regarded as superior to the existing marketed product. However, according to **Table 7**, a significant disparity in the confidence intervals for statistical analysis at the 95% confidence level between the marketed sample and the optimized batch highlights considerable uncertainty about the true population parameter.

Conclusions

In the current research, optimized bilayer tablets, with amlodipine besylate as immediate release and atenolol as sustained release layer were successfully formulated. All the formulation batches tested for physical parameters like weight variation, hardness, friability, swelling index, and floating time were found to be within the USP limits. The optimized formulations were found to be stable during the 3-month and 6-month study period. Further, a comparison of the release profile of this batch, with a commercial product with similar composition divulged better cumulative drug release in a simulated gastric environment, when studied for 12 hours and thus proposed for further *in vivo* and long-term stability tests. In conclusion, the formulation and evaluation of gastro-retentive bilayer floating tablets of amlodipine besylate and atenolol in the IR and SR layers respectively represent a promising strategy for optimizing combination drug therapy for hypertension. Future studies should focus on pharmacokinetic and pharmacodynamic evaluations to assess the clinical relevance and performance of these bilayer tablets *in vivo*, further advancing the field of controlled drug delivery systems for cardiovascular diseases.

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تطوير وتقييم القرص العائم ثنائي الطبقة المثبت في المعدة لعلاج ارتفاع ضغط الدم في الحالات الحادة : دراسة معملية

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الخلفية: تتناول هذه الدراسة تحضير وتقييمًا مختبريًا للأقراص العائمة ثنائية الطبقات المصممة للاحتفاظ بها في المعدة، والتي تحتوى مزيجًا من بيسيلات الأملوديبين والأتينولول. وتهدف الأقراص إلى إنطلاق بيسيلات أملوديبين بسرعة مع المحافظة على إنطلاق مستمر للأتينولول. وتحتوي الطبقة الثنائية سريعة الإنطلاق من القرص، المصنوعة من هيدروكسى بروبيل ميثيل السليلوز ، على كروسبوفيدون وجليكولات نشا الصوديوم كمواد سريعة التفكك ، بالإضافة إلى مزيج من صمغ الغوار وصمغ الزانثان كمواد رابطة.و تحتوى طبقة الإنطلاق المستمر على بيكربونات الصوديوم وحمض الستريك لتسهيل ظاهرة الطفو.

النتائج: تتكون التركيبة المحسنة من ٦٠% HPMC K15M، و١٦,٥% Carbopol 934P، و٩% لكل من كروسبوفيدون وNaHCO3 في طبقة الإنطلاق الفوري، إلى جانب ٣٣,٣٣% HPMC K15M، و١٠% NaHCO3، و١,٧% لكل من الصمغ الطبيعي في طبقة الإطلاق المستمر، كل ذلك بالوزن/الوزن. وأجريت اختبارات ما بعد ضغط الأقراص ، والتوصيف، وإنطلاق الدواء في المختبر. وعند غمر الأقراص في سائل يحاكى العصير المعوي (SGF)، بدون إنزيمات، بدرجة حموضة ١,٢، عند درجة حرارة ٣٧ درجة مئوية، طفت الأقراص وظلت طافية دون تفكك لأكثر من ٢٠ ساعة. وفي نفس السائل، تم إنطلاق أكثر من ٩٩% من بيسيلات الأملوديبين من طبقة الإنطلاق الفوري في غضون ٧٥ دقيقة، بينما تم إنطلاق ٩٩,٢٣% من الأتينولول من طبقة الإنطلاق المتأخر في غضون ١٢ ساعة.

النتيجة: أشارت المقارنة مع منتج مماثل يتم تسويقه إلى الأداء المتفوق للتركيبة المحسنة من حيث إنطلاق الدواء في المعمل.