Asian Journal of Pharmaceutical Education and Research
Vol -13, Issue-3, July- September 2024
ISSN:2278 7496

RESEARCH ARTICLE Impact Factor: 7.014

FORMULATION AND CHARACTERIZATION OF BILAYER TABLETS OF ANTIHYPERTENSIVE DRUGS QUINAPRIL AND HYDROCHLOROTHIAZIDE

Sahil Siraj Makhani*, C. R. Doijad, Sachin B Dudhe
Maharashtra Institute of Pharmacy, Betala, Bramhapuri, Maharashtra

*Corresponding Author's E mail: sahilmakhani76@gmail.com
Received 11 June. 2024; Revised 18 June. 2024; Accepted 22 June. 2024, Available online 10 July. 2024

Cite this article as: Makhani SS, Doijad CR and Dudhe SB. Formulation and Characterization of Bilayer Tablets of Antihypertensive Drugs Quinapril and Hydrochlorothiazide. Asian Journal of Pharmaceutical Education and Research. 2024; 13(3): 330-340.

https://dx.doi.org/10.38164/AJPER/13.3.2024.330-340

ABSTRACT

This study investigates the formulation, quality attributes, and performance characteristics of Hydrochlorothiazide and Quinapril tablets, with a focus on bilayer formulations. Pre-compression and post-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio, hardness, friability, weight variation, thickness, and drug content were comprehensively analyzed. Dissolution rate studies provided insights into the release kinetics of the active pharmaceutical ingredients, highlighting formulation optimization strategies. Formulation F7, identified as the optimized control layer, exhibited superior drug release kinetics and mechanical integrity in bilayer tablets, ensuring dose accuracy and therapeutic efficacy.

Keywords: Hydrochlorothiazide, Quinapril, tablets, Pre-compression parameters, Post-compression parameters, Dissolution rate, Bilayer tablets, Formulation optimization.

INTRODUCTION

Hypertension, a prevalent cardiovascular condition, necessitates effective management through combination therapy with multiple antihypertensive agents to achieve optimal blood pressure control and reduce associated risks such as cardiovascular diseases and stroke [1, 2]. Among these agents, Quinapril, an angiotensin-converting enzyme (ACE) inhibitor, and Hydrochlorothiazide, a thiazide diuretic, are commonly prescribed due to their complementary mechanisms of action and synergistic effects in lowering blood pressure [3, 4].

Traditional dosage forms often present challenges such as variable drug release profiles and dosing frequencies, impacting patient compliance and therapeutic efficacy [5]. Bilayer tablets, comprising two distinct layers designed for immediate and sustained drug release, offer a promising solution to enhance drug delivery efficiency and patient adherence in antihypertensive therapy [6,7]. By formulating Quinapril and Hydrochlorothiazide into bilayer tablets, synchronized release profiles can be achieved, optimizing pharmacokinetics and potentially improving therapeutic outcomes.

This research paper aims to explore the formulation and characterization of bilayer tablets containing Quinapril and Hydrochlorothiazide. It will investigate formulation strategies to achieve desired release kinetics, evaluate the physical and chemical properties of the bilayer tablets, and assess their in vitro and potentially in vivo performance. The study seeks to contribute valuable insights into the development of innovative dosage forms for optimized antihypertensive therapy, emphasizing the potential clinical benefits and practical applications of bilayer tablets in pharmaceutical practice.

MATERIAL AND METHODS

Preparation of instant layer of Hydrochlorothiazide (Phase-1)

Instant release (Instant Layer) tablets of Hydrochlorothiazide were prepared by direct compression method after incorporating different natural disintegrants such as, Guar Gum, Gum Karaya, Gellan Gum and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60. Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio. The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Nine different formulations of Quinapril were prepared and each formulation contained one of the three disintegrant in different concentration [8]. Each tablets weighing 350mg, were obtained. Composition of tablets is mentioned in Table 7.1.

Table 1: Composition of Hydrochlorothiazide instant release tablets

Ingredients (mg)	Formulation code								
	IF1	IF2	IF3	IF4	IF5	IF6	IF7	IF8	IF9
Hydrochlorothiazide	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Guar Gum	10	15	20	-	-	-	-	-	-
Gum Karaya	-	-	-	10	15	20	-	-	-
Gellan Gum	-	-	-	-	-	-	10	15	20
Microcrystalline cellulose	57.5	52.5	62.5	57.5	52.5	62.5	57.5	52.5	57.5
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	10	10	10	10	10	10	10	10	10
Total weight	100	100	100	100	100	100	100	100	100

Method for preparation of Quinapril gastroretentive tablets

Direct compression was followed to manufacture the floating tablets of Quinapril. Eight different formulations (F1, F2, F3, F4, F5, F6, F7, & F8) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation [9]. The amount and ratio of drug and polymers were weighed as per given in table No. 2 and all the formulation were used for further evaluations parameters.

Table 2: Various formulations of gastro retentive tablets of Quinapril

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Quinapril	20	20	20	20	20	20	20	20
HPMC K4	90	120	-	-	-	-	30	40
HPMC K15	-	-	90	120	-	-	30	40
Xanthan gum	-	-	-	-	90	120	30	40
PVP K30	15	15	15	15	15	15	15	15
Talc	5	5	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10	10	10
Lactose	110	80	110	80	110	80	110	80
Total Weight	250	250	250	250	250	250	250	250

Evaluation of tablets

All the tablets were evaluated for following different parameters which includes;

General Appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated [10].

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and reacts with dye and analyzed for drug content by UV spectrophotometer at a λ_{max} of 264nm using of 0.1 N HCl as blank [11].

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated [12].

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated[13].

In vitro drug release study of gastro retentive tablet

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type) [14]. The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50ºc and rpm of 75. One Quinapril tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37^0C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCl and take the absorbance at 222nm using spectroscopy.

Formulation development of bilayer tablet

Optimized formulation IF-3 of Instant release layer and optimized formulation of F-7 for control release used for formulation of Bi-layer tablet[15].

Evaluation of bilayer tablets

All the tablets were evaluated for following different parameters which includes;

7.6.1 General Appearance

Five tablets from different batches were randomly selected and organoleptic properties suchas color, odor, taste, shape, were evaluated. Appearance was judged visually [16].

Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated[17].

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach) [18].

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated [19].

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of Quinapril was transferred to 10ml standard flask. The powder was dissolved in 10 ml of 0.1 N HCl and made up to volume with 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was further diluted 0.2 ml to 10 ml suitably 10 ppm solutions of and determines the Conc. of Hydrochlorothiazide at 264nm or Quinapril at 222nm.

Dissolution rate studies

In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 12 hrs period for Quinapril and Hydrochlorothiazide bilayer tablets using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch were tested [20]. The media used was 0.1N HCl at a pH 1.2 and a volume of 900 ml was maintained at 37±0.5◦C. Test sample (1ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using U.V. (Labindia 3000 plus) spectrophotometer.

RESULTS AND DISCUSSION

Table 3 and Table 6 showed the post-compression parameters, including hardness, friability, weight variation, thickness, and drug content, were assessed across different formulations (IF1 to IF9 for Hydrochlorothiazide layer and F1 to F8 for Quinapril layer). Overall, the tablets exhibited consistent hardness values ranging between 3.2 to 3.6 kg/cm² for Hydrochlorothiazide layers and 5.4 to 5.8 kg/cm² for Quinapril layers. Friability remained low across formulations, indicating good mechanical resistance, with values typically below 1%. Weight variation and thickness measurements showed acceptable uniformity across formulations, ensuring consistent dosing. Drug content analysis revealed high percentages, reflecting uniform distribution of active ingredients within the tablets.

Table 4 showed the disintegration time of the instant layer of Hydrochlorothiazide (IF1 to IF9) varied between formulations, with times ranging from 43 seconds to 88 seconds. Formulation IF3

demonstrated the shortest disintegration time of 43 seconds, suggesting rapid release characteristics suitable for immediate drug action.

Table 5 showed bulk density, tapped density, compressibility index, and Hausner ratio were evaluated for Quinapril tablets (F1 to F8). These properties influence the flowability and compactibility of the powder blend prior to compression. The values indicated good flow properties, with compressibility index ranging from 23.568 to 27.752%, indicating moderately compressible powders suitable for tablet manufacturing.

Table 7 and 10 showed the in-vitro drug release studies demonstrated sustained release profiles for both Hydrochlorothiazide and Quinapril layers over different time intervals (0.5 to 12 hours). Formulations exhibited gradual release kinetics, with significant drug release achieved by the end of 12 hours. The optimized bilayer tablet formulation showed controlled release characteristics, maintaining therapeutic drug levels over an extended period.

Table 8 and Table 9 showed the optimized bilayer tablet formulation (from Table 8) exhibited enhanced hardness, minimal friability, consistent weight variation, and appropriate thickness, meeting pharmaceutical quality standards. Drug content analysis (Table 9) confirmed high percentages of Hydrochlorothiazide (99.85%) and Quinapril (99.25%), indicating precise dosing accuracy and uniform drug distribution within the tablets.

Table 10 showed dissolution rate studies further elucidated the release profiles of Hydrochlorothiazide and Quinapril from the bilayer tablets over different time intervals. The formulations showed gradual and sustained release patterns, crucial for maintaining therapeutic efficacy throughout the dosing interval.

The comprehensive evaluation of these parameters underscores the meticulous formulation development process aimed at optimizing the bi-layer tablets of Quinapril and Hydrochlorothiazide. The results indicate that the formulations achieved desired characteristics such as controlled drug release, mechanical strength, and uniform drug content. The choice and integration of excipients played a crucial role in achieving these outcomes, ensuring both immediate and sustained drug release profiles suitable for hypertension management. Further optimization based on these findings could potentially enhance the therapeutic effectiveness and patient compliance of the bi-layer tablet formulation.

Table 3: Results of post-compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
IF1	3.2±0.2	0.558±0.023	98±2	1.6±0.2	97.74±0.12
IF2	3.5±0.3	0.625±0.035	95±4	1.7±0.1	98.65±0.15
IF3	3.4±0.2	0.664±0.041	102±2	1.8±0.3	99.74±0.32
IF4	3.5±0.1	0.638±0.032	99±3	1.6±0.2	97.74±0.14
IF5	3.4±0.3	0.748±0.022	104±4	1.7±0.3	96.65±0.32
IF6	3.3±0.4	0.632±0.015	102±2	1.5±0.2	98.74±0.25
IF7	3.4±0.3	0.752±0.013	98±5	1.6±0.2	97.45±0.20
IF8	3.6±0.4	0.732±0.014	99±2	1.8±0.4	98.65±0.32
IF9	3.4±0.2	0.658±0.022	102±6	1.7±0.3	98.74±0.22

Table 4: Results of Disintegration time of instant layer of Hydrochlorothiazide

Formulation code	Disintegration time (sec.) (n=3) Mean ± SD
IF1	85±3
IF2	69±2
IF3	43±4
IF4	75±5
IF5	68±3
IF6	55±4
IF7	88±2
IF8	76±5
IF9	63±2

Table 5: Result of pre-compression properties of Quinapril tablets

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.315	0.436	27.752	1.384
F2	0.325	0.442	26.471	1.360
F3	0.341	0.456	25.219	1.337
F4	0.326	0.436	25.229	1.337
F5	0.322	0.438	26.484	1.360
F6	0.347	0.454	23.568	1.308
F7	0.342	0.463	26.134	1.354
F8	0.322	0.438	26.484	1.360

Table 6: Results of post compression properties of gastro retentive tablets of Quinapril

F. code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.5±0.2	5.6±0.2	250±5	0.745±0.023	96.65±0.45
F2	3.6±0.3	5.8±0.3	255±2	0.658±0.025	98.78±0.36
F3	3.5±0.2	5.7±0.2	256±4	0.732±0.014	98.85±0.41
F4	3.4±0.4	5.4±0.1	248±3	0.748±0.023	97.44±0.25
F5	3.5±0.3	5.6±0.3	250±2	0.658±0.015	96.85±0.36
F6	3.7±0.2	5.6±0.4	253±3	0.745±0.036	97.74±0.39
F7	3.6±0.3	5.7±0.5	254±4	0.669±0.022	99.85±0.32
F8	3.5±0.4	5.8±0.3	249±5	0.742±0.011	97.12±0.71

Table 7: *In-vitro* drug release study of all formulations

Time	% Cumulative Drug Release							
(hr)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	49.98	46.65	45.65	45.65	43.32	36.65	26.65	22.32
1	63.32	60.32	56.63	59.98	55.45	49.98	38.85	35.65
1.5	78.85	74.65	63.32	73.32	69.98	64.45	49.98	42.12
2	88.96	85.65	75.65	84.45	76.65	73.25	56.65	54.65
3	98.74	95.65	86.65	94.45	89.98	82.23	69.98	68.85
4	-	99.12	96.65	99.41	94.45	92.23	78.85	73.32
6	-	-	99.45	-	98.85	97.74	86.65	84.45
8	-	-	-	-	-	99.25	94.45	92.56
12	-	-	-	-	-	-	99.74	94.65

Table 8: Post-compression parameters of optimized formulation of Bilayer tablets

Formulation	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	6.5	0.658	Passes	4.85

Table 9: Results of Drug content analysis of bilayer tablets

Formulation	Hydrochlorothiazide (% Label Claim)	Quinapril (% Label Claim)
In-house Bilayer tablet	99.85	99.25

Table 10: Results of Dissolution rate studies of bilayer tablets

Time (Hour)	% Drug Release	
	Hydrochlorothiazide	Quinapril
0.5	85.65	24.65
1	98.85	31.45
1.5	99.65	42.32
2	-	56.68
4	-	63.32
6	-	75.65
8	-	86.65
10	-	93.32
12	-	99.15

CONCLUSION

The formulation development of bi-layer tablets containing Quinapril and Hydrochlorothiazide has resulted in tablets with robust mechanical properties and uniform drug content. Post-compression parameters such as hardness, friability, weight variation, and thickness consistently met quality standards, indicating good tablet integrity and dose uniformity. Disintegration studies showed rapid disintegration times for immediate drug release. Pre-compression properties demonstrated favorable powder flow characteristics essential for efficient manufacturing. In-vitro drug release profiles confirmed sustained release over extended periods, supporting their efficacy in managing hypertension. Overall, the study validates the formulation's potential for effective therapeutic delivery and sets the stage for further optimization and clinical application.

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