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FORMULATION, DEVELOPMENT AND EVALUATION OF BILAYER TABLETS OF ANTIHYPERTENSIVE DRUGS

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ABSTRACT

Hypertension is a chronic, frequently asymptomatic medical condition characterised by increased systemic arterial blood pressure. The bi-layer tablet heralds a new era in the and with a variety of features to ensure effective medication delivery. Thus, this study aims at developing & evaluating bilayer tablet of antihypertensive drugs. The formulation & evaluation of bilayer tablet was performed according to standard method. The results of pre-compressional parameters of Hydrochlorothiazide instant release tablets suggested that all parameters are within the range. The drug content was found to be maximum for 99.45±0.32 % in IF7 formulation. The disintegration time was observed to be lowest for 43±2. Result of pre-compression properties of gastroretentive layer of Captopril tablets were also within the limits. Results of post compression properties of Captopril tablets varied suggested that the % drug content was observed to be maximum for F7 which is 99.45±0.19 % .The *In-vitro* drug release study of tablets suggest that the formulation F7 shows 99.12 % Cumulative Drug Release in 12 hours. Further IF7 formulation & F7 formulation was combined to produce a bilayer tablet. For this complete bilayer tablet the Hardness & friability was observed to be 6.5 kg/cm^2& 0.754% respectively. The thickness of tablet was calculated as 5.23mm. The weight variation test was also passed by this tablet successfully. Additionally the drug content of in house bi layer tablet was checked. The results revealed that the bilayer tablet contain 99.45 of Hydrochlorothiazide & 99.12 % of captopril. The Dissolution rate studies of bilayer tablets further clarified that at 12 hr the % Drug Release for captopril was found to be 99.45%. The Instant layer of Hydrochlorothiazide release approx 98.85 percent drug within 1.5 Hrs. Thus, from results it can be inferred that stable dosage form for Hydrochlorothiazide as immediate and captopril as sustained release via bilayered tablets can be produced.

Keywords: Hypertention, Antihypertensive drugs, Hydrochlorothiazide, Captopril, Bilayer tablet

INTRODUCTION

Cardiovascular diseases (CVDs) are a leading cause of disability and premature mortality, and as such, they are a serious public health concern. High blood pressure (BP), dubbed the "silent killer," is caused by a variety of reasons, including the interplay of genetic and environmental components, which causes BP regulation dysfunction. Hypertension (HTN) is the most prevalent risk factor in acute myocardial infarction, accounting for around 16.5% of deaths worldwide each year (Sowers *et al*., 2001; Gheorghe *et al*., 2018).

Hypertension is a chronic, frequently asymptomatic medical condition characterised by increased systemic arterial blood pressure. As a result, in order to transport blood to tissues, the heart is forced to work harder to combat the increased systemic pressure, putting strain on the heart and arteries. Over time, the added stress causes cardiovascular dysfunction and is a major contributor to congestive heart failure, myocardial infarction, pulmonary embolism, cerebral aneurysm, and renal failure. An individual can avoid and treat hypertension in a variety of methods, including changing their lifestyle by losing extra weight, increasing activity, and adopting healthy eating habit (Lionakis *et al*., 2012; Fuentes *et al*., 2000).

Although a variety of drugs are available to treat high blood pressure, including angiotensinogen converting enzyme (ACE) inhibitors, beta adrenergic blocking agents, angiotensin receptor blocking agents (ARB), and calcium-channel blockers. Many people have complained about headaches, dry mouth, nausea, vomiting, and sadness. Despite the availability of various pharmaceutical options, degrees of hypertension treatment and control vary, and hypertensive patients frequently require more than two medicines to achieve prescribed blood pressure levels; thus, other therapy options must be explored(Jackson and Bellamy, 2015).

The bi-layer tablet heralds a new era in the successful creation of controlled release formulations with a variety of features to ensure effective medication delivery. Bilayer layer tablets are made up of two layers: gradual release and instant release. In addition, improved useful technology is being developed to address the shortcomings of single layer tablets. Due to different incompatible active pharmaceutical ingredients (APIs) for each other, bilayer tablet formulations were required (Kitt *et al*., 2019; Rameshwar *et al*., 2014).

The pharmacokinetic benefit stems from the fact that drug release from the rapid releasing layer causes a sharp increase in blood concentration. However, once the drug is removed from the sustaining layer, the blood level remains constant. Multi-layer tablet dosage forms were developed for a variety of reasons, including the ability to control the delivery rate of either a single or two different active pharmaceutical ingredients (API), to separate incompatible APIs, to control the release of API from one layer by utilising the functional property of the other layer (such as osmotic property), and to modify the total surface area available for API layer by sandwiching with one or two inactive layer (Rao *et al*., 2019; Deshpande *et al*., 2011).

Captopril is used to treat essential or renovascular hypertension (typically in combination with other medications, mainly thiazide diuretics). In combination with other medications (e.g., cardiac glycosides, diuretics, -adrenergic blockers), it may be used to treat congestive heart failure. May enhance survival in patients with left ventricular dysfunction after a heart attack. It has the potential to be utilised to treat nephropathy, including diabetic nephropathy (Frohlich *et al*., 1994)

Also, Hydrochlorothiazide is used to treat edoema caused by congestive heart failure, hepatic cirrhosis, nephrotic syndrome, acute glomerulonephritis, chronic renal failure, and corticosteroid and oestrogen therapy, either

alone or in combination. Hydrochlorothiazide is also used to treat hypertension, either alone or in combination (Plosker and white, 2008). so, considering the advantages of bilayer tablets over conventional dosage form this study aims at developing & evaluating bilayer tablet of antihypertensive drugs.

MATERIALS AND METHODS

Chemicals & Reagents

Sodium Starch glycolate, Croscarmellose sodium, Crospovidone, Microcrystalline cellulose, Talc, Magnesium stearate were obtained from Loba Chemie Pvt Ltd Mumbai. All chemicals & reagents were of standard laboratory grade.

Preparation of instant layer of Hydrochlorothiazide (Phase-1)

Fast dissolving (Instant Layer) tablets of Hydrochlorothiazide were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone 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 Captopril were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablets weighing 350mg, were obtained.

Evaluation of Pre compression Parameter

Initially the bulk density & tapped density was checked. The bulk density was analysed by dividing mass of powder by volume of packing while the tapped bulk density was determined by dividing mass of powder by tapped volume of packing. The carr's index was estimated by dividing the difference between tapped & bulk density to that of tapped density. The Housner's ratio was simply calculated by dividing tapped bulk density by lose bulk density.

Evaluation of post compression parameter

The morphological evaluation, including shape & colour of tablet was evaluated at first place. Additionally the thickness of tablets was measured using dial-caliper. The Weight variation test was performed by selecting twenty tablets were randomly and average weight was determined. The hardness of tablet was measured by Pfizer hardness tester and results were expressed in $Kg/cm^{2.}$. The friability of tablets was analysed by using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The uniformity of drug content was estimated by randomly choosing ten tablets. They were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml 0.1 N HCl (Simulated gastric fluid of pH 1.2 without enzymes) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41.

From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 222nm for Hydrochlorothiazide

Method for preparation of Captopril Gastroretentive tablets

Direct compression was followed to manufacture the floating tablets of Captopril. 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. 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.

Evaluation of Pre-compression parameters

The procedure followed for evaluating pre compression parameter resembles with procedure already mentioned for evaluating pre compression parameters of Fast dissolving tablet.

Evaluation of post compression parameters

The organoleptic properties such as color, odor, taste, shape, were evaluated. Thickness and diameter of tablets were determined using Vernier caliper while the hardness was checked by using Monsanto hardness tester. The friability was measured by using friability test apparatus. The difference between initial weigh to that of weight obtained after processing in friability test apparatus gives out the percentage of weight loss. The Uniformity of weight was checked by using twenty tablets which were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated. For determining drug content 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.

Evaluation of bilayer 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 suchas color, odor, taste, shape, were evaluated. Appearance was judged visually .

Very good (+++), good (++), fair (+) poor (-), very poor (- -) (Shiyani. *et al*., 2010).

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.

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 (Remya *et al*., 2010).

Uniformity of weight

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

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 Captopril 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 drug at 264nm or Captopril and 222nm for Hydrochlorothiazide.

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 Captopril and Hydrochlorothiazide bilayer tablets using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch were tested.

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.

***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). 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 Captopril 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 264nm using spectroscopy.

Table 1: Composition of Hydrochlorothiazide fast dissolving tablets

Ingredients (mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Captopril	25	25	25	25	25	25	25	25	25
Sodium Starch glycolate	10	15	20	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	10	15	20	-	-	-
Crospovidone	-	-	-	-	-	-	10	15	20
Microcrystalline cellulose	50	45	40	50	45	40	50	45	40
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

Table 2: Various formulations of Captopril gastro retentive tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Captopril	25	25	25	25	25	25	25	25
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	105	75	105	75	100	75	105	75
Total Weight	250	250	250	250	245	250	250	250

Table 3: Results of pre-compressional parameters of Hydrochlorothiazide IR tablets

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
IF1	0.365	0.452	19.248	1.238
IF2	0.358	0.465	23.011	1.299
IF3	0.362	0.472	23.305	1.304
IF4	0.374	0.482	22.407	1.289
IF5	0.369	0.476	22.479	1.290
IF6	0.347	0.456	23.904	1.314
IF7	0.356	0.462	22.944	1.298
IF8	0.374	0.485	22.887	1.297
IF9	0.352	0.465	24.301	1.321

Table 4: Results of post-compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
IF1	3.5±0.2	0.685±0.058	102±5	1.9±2	98.45±0.32
IF2	3.6±0.1	0.745±0.032	103±3	1.8±1	97.15±0.25
IF3	3.7±0.3	0.852±0.025	102±2	1.9±5	98.74±0.25
IF4	3.2±0.2	0.658±0.012	98±4	1.9±3	98.85±0.32
IF5	3.5±0.2	0.882±0.015	100±5	1.8±2	96.65±0.14
IF6	3.6±0.1	0.782±0.023	101±6	1.7±4	98.78±0.22
IF7	3.5±0.2	0.812±0.018	99±4	1.9±5	99.45±0.32
IF8	3.8±0.2	0.845±0.014	103±3	1.8±3	98.74±0.15
IF9	3.4±0.1	0.832±0.022	104±2	1.8±2	98.65±0.36

Table 5: Results of Disintegration time of instant layer of Hydrochlorothiazide

Formulation code	Disintegration time (sec.) (n=3) Mean ± SD
IF1	100±8
IF2	80±5
IF3	75±4
IF4	80±6
IF5	74±2
IF6	68±4
IF7	43±2
IF8	55±3
IF9	51±6

Table 6: Result of pre-compression properties of Captopril tablets

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.385	0.478	19.456	1.242
F2	0.345	0.452	23.673	1.310
F3	0.365	0.473	22.833	1.296
F4	0.349	0.459	23.965	1.315
F5	0.365	0.472	22.669	1.293
F6	0.382	0.489	21.881	1.280
F7	0.374	0.483	22.567	1.291
F8	0.369	0.473	21.987	1.282

Table 7: Results of post compression properties of Captopril tablets

F. code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.4±4	5.4±0.2	255±4	0.858±0.045	97.45±0.32
F2	3.5±3	5.3±0.3	250±6	0.658±0.032	97.12±0.15
F3	3.4±2	5.7±0.2	254±5	0.489±0.025	98.65±0.25
F4	3.6±5	5.6±0.1	258±3	0.558±0.033	98.41±0.15
F5	3.5±6	5.4±0.1	248±2	0.658±0.015	96.85±0.14
F6	3.6±5	5.8±0.2	256±4	0.856±0.018	98.78±0.17
F7	3.5±4	5.7±0.2	254±3	0.658±0.016	99.45±0.19
F8	3.6±3	5.8±0.3	248±2	0.758±0.045	98.12±0.16

Table 8: *In-vitro* drug release study of tablets

Time	% Cumulative Drug Release							
(hr)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	55.56	45.54	43.23	40.23	38.89	35.56	33.21	30.12
1	75.56	58.89	55.56	52.32	45.65	42.23	40.23	38.89
1.5	85.56	88.89	80.25	75.65	68.89	65.65	60.32	55.65
2	99.89	98.29	89.98	85.65	78.38	73.25	71.12	65.65
3	-	-	98.89	92.25	85.56	80.32	78.89	70.23
4	-	-	-	98.65	90.23	86.69	82.23	78.32
6	-	-	-	-	99.52	92.23	89.98	85.56
8	-	-	-	-	-	99.85	95.59	90.23
12	-	-	-	-	-	-	99.12	93.32

Table 9: Post-compression parameters of optimized formulation

Formulation	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	6.5	0.754	Passes	5.23

Table 10: Results of Drug content analysis of bilayer tablets

Formulation	Hydrochlorothiazide (% Label Claim)	Captopril (% Label Claim)
In-house Bilayer tablet	99.45	99.12

Table 11: Results of dissolution rate studies of bilayer tablets

Time (Hour)	% Drug Release	
	Hydrochlorothiazide	Captopril
0.5	45.65	29.98
1	73.32	36.45
1.5	98.85	49.98
2	-	55.65
4	-	69.98
6	-	73.32
8	-	88.85
10	-	97.78
12	-	99.45

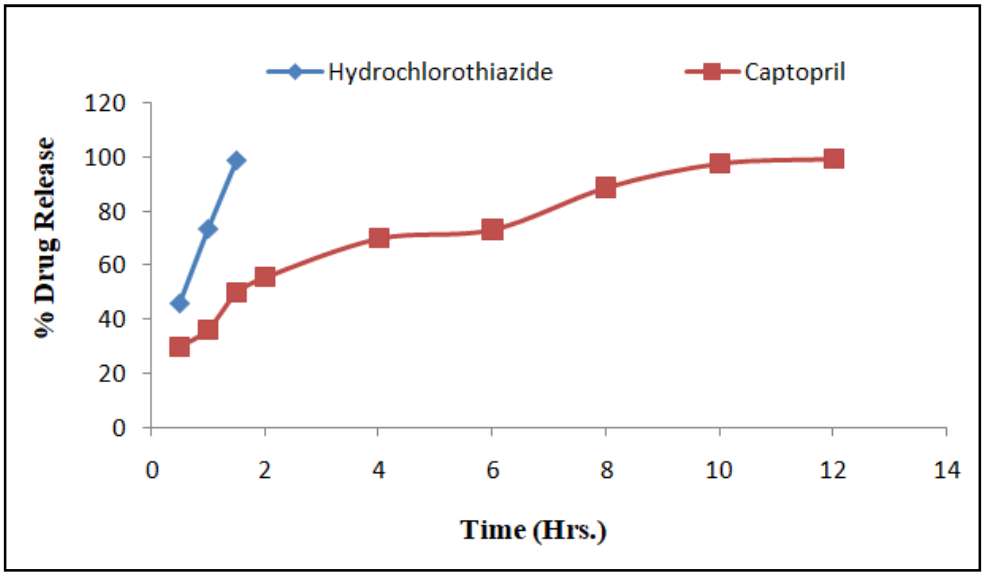

Figure 1: Graph of Release of Bilayer tablets

RESULTS AND DISCUSSION

The results of pre-compressional parameters of Hydrochlorothiazide instant release tablets suggest that bulk density for nine formulations ranged from 0.352 to 0.374. The tapped density varied from 0.452 to 0.485. The car's index value ranged between 19.248 to 24.301%. While the Hausner's Ratio lies between 1.238 to 1.321. Further the post compression parameters was evaluated. The hardness was found to be varied from 3.2±0.2 kg/cm^2 to 3.8±0.2 2 kg/cm^2. The drug content was found to be maximum for 99.45±0.32 % in IF7 formulation. The friability was found to be varied from 0.658±0.012 % to 0.882±0.015 %. The other parameters like weight variation & thickness was also checked. The thickness varied from 1.7±4mm to 1.9±5mm. The disintegration time was observed to be lowest for 43±2. Result of pre-compression properties of gastroretentive layer of Captopril tablets were also evaluated.

The bulk density for formulations F1 to F8 varied from 0.345 to 0.385gm/ml. The tapped density ranged 0.452 to 0.489 gm/ml. The compressibility & Hausner ratio were then calculated from tapped density & bulk density. The compressibility found to be maximum for F5 as 23.965 while minimum for F1 as 19.456. The Hausner ratio ranged from 1.242 to 1.315.

Results of post compression properties of Captopril tablets varied suggested that the % drug content was observed to be maximum for F7 which is 99.45±0.19. The thickness & hardness for F7 was estimated to be 3.5±4 mm & 5.7±0.2 kg/cm^2 . The weight variation & friability for F7 was noted as 254±3 mg & 0.658±0.016 %. The *In-vitro* drug release study of tablets suggest that the formulation F7 shows 99.12 % Cumulative Drug Release in 12 hours.

Further IF7 formulation & F7 formulation was combined to produced a bilayer tablet. For this complete bilayer tablet the Hardness & friability was observed to be 6.5 kg/cm^2& 0.754% respectively. The thickness of tablet was calculated as 5.23mm. The weight variation test was also paased by this tablet successfully.

Additionally the drug content of in house bi layer tablet was checked. The results revealed that the bilayer tablet contain 99.45 of Hydrochlorothiazide & 99.12 % of captopril.

The Dissolution rate studies of bilayer tablets further clarified that at 12 hr the % Drug Release for captopril was found to be 99.45%. The instant layer of Hydrochlorothiazide release approx 98.85 percent drug within 1.5 Hrs.

CONCLUSION

The experiment is concerned with the formulation and development of an oral pharmaceutical bilayer tablet of captopril for the administration of anti -hypertensive drug substance in order to achieve both a relatively fast or quick onset of therapeutic effect and the maintenance of a therapeutically active plasma concentration for a relatively long period of time. Experiment results show that bi-layer tablets are suitable for delivering the same drugs with different release patterns, such as one layer of drug as immediate release to provide quick pain relief and the second layer of drug as sustained release to provide drug effect for an extended period of time and reduce the frequency of dose.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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