A STUDY ON FORMULATION AND CHARACTERIZATION OF NOVEL BILAYER TABLET OF ANTIHYPERTENSIVE DRUG.

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ABSTRACT

Hypertension or high blood pressure occurs when the high cardiac output exerts pressure on the arterial wall as the blood flow increases. Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, either as second dose or in an extended release manner. Bi-layered tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs.

Keywords: Hypertension, Bi-layered tablet, Isosorbide nitrate, Immediate release and Sustained release.

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INTRODUCTION

Oral Drug Delivery System

The oral drug delivery market is the largest segment of the drug delivery market and there's no sign that it is slowing down. Oral route of drug administration have wide acceptance up to 50-60% of total dosage form and is the most convenient and preferred route for systemic

effect due to its ease ofdosing administration, pain avoidance, accurate dosage, patient compliance and flexibility in formulation. The major aim of controlled drug delivery is to reduce dosing frequency. The design of modified release drug product are to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval and provide better patient compliance and patient convenience. Over 90% of the formulations manufactured today are ingested orally.

Types of Tablet

A) Oral Tablets for Ingestion

1. Standard compressed tablets
2. Multiple compressed tablets

a. Layered tablets
b. Compression coated tablets
c. Inlay tablets

3. Modified release tablets
4. Delayed action tablets
5. Targeted tablets

a. Floating tablets
b. Colon targeted tablets

6. Chewable tablets

B) Tablets used in the Oral Cavity

1. Buccal tablets
2. Sublingual tablets
3. Troches and lozenges
4. Dental cones

C) Tablets administered by other Routes

1. Implantation tablets
2. Vaginal tablets

D) Tablets used to prepare Solution

1. Effervescent tablets
2. Dispersible tablets
3. Hypodermic tablets
4. Tablet triturates
5.

Figure 1.1(a): Single layer tablet

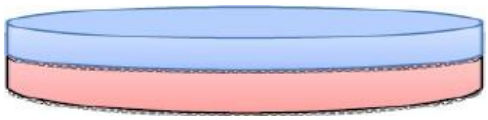


Figure 1.1(b): Bilayer tablet

Introduction to Bilayer (Multi component or Dual component) Tablet[1]

Bilayer tablet is the new era for the successful development of controlled release formulation. It is also called Dual or Multi component tablet. Bilayer tablet is better than the traditionally used dosage form. It is suitable for sequential release of two drugs in combination. It also capable of separating two types of incompatible substances and also for sustain release tablet in which one layer is immediate release as initial dose and second one is maintenance dose. Bilayer tablet contain immediate and sustained release layers is sustained release (maintenance dose) layer releases drug in sustained or prolonged time period.

Figure 1.2 shows picture of bi-layer tablet.

Figure 1.2: Bilayer tablet

Table 1.1: Examples of Superdisintegrants and its mechanism of action

MATERIALSANDMETHODS

Isosorbide nitrate (IN; M/s Cadilla Pharmaceuticals Chem Pvt. LTD. India), and Hydralazine from Torrent Pharma pvt ltd ss a Gift Sample, HPMCK-100 (Colorcon asia pvt ltd..) and Carbopol 940 (LobaChemie Pvt., Mumbai-400002,India), Ethyl cellulose from Colorcon asia pvt ltd. All other ingredients used invarious studies were of analytical grade and were employed as such as procured. Double distilled water was used during the experiment.

Preparation of 0.1N HCl

0.1N HCl was prepared by diluting 8.5 ml of concentrated Hydrochloric acid to 1000 ml distilled water. Final pH of above solution was then measured with pH meter and adjusted to

pH 1.2.

HPLC Assay Method for Determination of Drug

Standard preparation

Take about 10 mg of Standard Isosorbide dinitrate (25% Diluted) and about 10 mg Standard of Hydralazine HCl transfer into a clean and dry 25 ml volumetric flask, addabout 15 ml of mobile phase mix to dissolve it and make up 25 ml volume with mobilephase and mix.

Test preparation

Take about 10 mg of Standard Isosorbide dinitrate (25% Diluted) and about 10 mg Standard of Hydralazine HCl transfer into a clean and dry 25 ml volumetric flask, addabout 15 ml of mobile phase mix to dissolve it and make up25 ml volume with mobilephase and mix.

Preparation of Standard Calibration Curve of Hydralazine HCl

The construction of standard calibration curve of Hydralazine HCl was prepared by using mix volume of methanol and distilled water 1000ml containing 0.1ml TEA each(60:40). From the stock solution, take 50, 75, 100, 125, 150 µg/ml solutions were prepared respectively. Take the absorbance of above samples at $\lambda_{max.}$ 215 nm.

Preparation of Standard Calibration Curve of Isosorbide Dinitrate

The construction of standard calibration curve of Isosorbide Dinitrate was prepared byusing mix volume of methanol and distilled water 1000ml containing 0.1ml TEA each(60:40). From the stock solution, take 50, 75, 100, 125, 150 µg/ml solutions were prepared respectively. Take the absorbance of above samples at $\lambda_{max.}$ 215nm.

Identification of Hydralazine HCl and Isosorbide Dinitrate by FT-IR Infrared (IR) spectroscopy was conducted using a FT-IR Spectrophotometer (Shimadzu8400S) and the spectrum was recorded in the wavelength region of 4000 to 600 cm^{-1}.The procedure consisted of dispersing a drug in KBr and compressed into discs byapplying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed inthe light path and the spectrum was obtained.

Drug and Excipients Compatibility Study by FT-IR

The Fourier transform infrared spectrum of moisture free powdered sample of 1:1 ratioof Hydralazine HCl and Isosorbide Dinitrate with excipients was recorded on IR spectrophotometer by potassium bromide (KBr) pellet methodat Accuprec Research lab.

Physical Compatibility Study

A Pre-formulation study was carried out with potential formulation excipients to determine

drug-excipients interaction/compatibility.

Protocol for drug-excipients compatibility study

(a) Drug: Excipients Ratio

Drug and excipients were taken in different ratios

(b) Pack details

USP type I Clear transparent glass vials with bromo butyl rubber stopper and aluminumseal.

(c) Storage condition

40°C/75 % RH for (Open and Close)

(d) Test to be performed

Organoleptic Characteristics of Hydralazine HCl and Isosorbide Dinitrate This includes recording of color, odor and taste of drug using descriptive terminology.Record of color of early batches is very useful in establishing appropriate specificationsfor later production. Drugs generally have a characteristic odor and taste.

Flow Properties of Drugs and Excipients

Bulk Density

Weigh accurately 10 gm of drug, which was previously passed through 30# sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting and read the unsettled apparent volume (V_o). Calculate the apparent bulk density in gm/ml by the following equation.

Tapped Density

Weigh accurately 10 gm of drug, which was previously passed through 30# sieve and transferred in 100 ml graduated cylinder. Then mechanically tap the cylinder containingthe sample.

Angle of Repose

The angle of repose of API powder will be carried out by funnel method. Accurately weighed powder blend is taken in a funnel. Height of the funnel is adjusted in such ways that tip of the funnel just touches the apex of the powder blend. The powder blendis allowed to flow through the funnel freely onto the surface

Formulation Development

Immediate release layer of Hydralazine HCl

The development of the immediate release layer containing hydralazine hydrochloride 25 byselecting ingredients in the appropriate amount and the super-disintegrants optimized thereafter. The immediate release layer of hydralazine hydrochloride was prepared by the

direct compression method. Sodium starch glycolate, croscarmellose sodium, and ac-di-sol® were used in varying amounts as shown in table 1.

Table 6.6: Preliminary screening of super disintegrating agent for immediate release layer of Hydralazine HCl

Ingredients(mg)	**Qty. (mg/tab)**									
	H1	**H2**	**H3**	**H4**	**H5**	**H6**	**H7**	**H8**	**H9**	**H10**
Hydralazine HCl	25	25	25	25	25	25	25	25	25	25
MCC PH102	51	50	48	51	50	49	51	50	49	48
Tablattose	20	20	20	20	20	20	20	20	20	20
Sodium starch glycolate	2	3	5	0	0	0	0	0	0	0
Croscamellose sodium	0	0	0	2	3	4	0	0	0	0
Ac-Di-Sol®	0	0	0	0	0	0	2	3	4	5
Magnesiumstearate	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1
Total	**100 mg/tab**									

Formulation of Optimized Bilayer tablets

Table 6.12: Evaluation Parameters of Optimized Formulation

HDID	
Ingredients (mg)	**Qty. (mg)**
Hydralazine HCl	25
MCC PH102	45
Tablattose	20
Sodium starch glycolate	3.99
Ac-Di-Sol®	4
Magnesium Stearate	1
Talc	1.01
	100mg

Isosorbide Dinitrate	40
MCCPH102	60.86
HPMC K100M	70
Polyox^{tm} wsr303	77.94
Quinoline yellow	0.2
Magnesium stearate	1
	250mg
Total = 350mg	

Evaluation Parameters of Bilayer Tablet

Prepared powder blend were evaluated for the following parameters.

Weight variation Test or Uniformity of Weight

It was performed as per the method given in the Indian pharmacopoeia. Tablets were randomly checked to ensure that uniform weight tablets were being made. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated.

Table 6.13: IP standards for uniformity of weight

Sr. No.	Average weight of tablet(mg)	% of deviation
1	80mg or less	10%
2	80-250mg	7.5%
3	250mg or more	5%

Thickness

Tablet was selected at random from individual formulations and thickness was measured using vernier caliper scale, which permits accurate measurement. Tablet thickness should be controlled within ± 0.5% variation of standard value.

Hardness

Hardness of the tablet was tested by placing the tablet longitudinally in between the two plungers of the Monsanto tablet hardness .

Friability Test

The friability of the tablets was determined by Roche Friabilator in which the tablets were subjected to the combined effect of abrasions and shock in a plastic chamber revolving at

25RPM and dropping the tablets at a height of 6 inches in each revolution.

Drug Content for Hydralazine HCl

The drug content was carried out by weighing 10 tablets form each batch and calculatedthe average weight. Then the tablets were triturated to get fine powder. From the resulting triturate, powder was weighted accurately which was equivalent to 100 mg Hydralazine HCl and dissolve in 100 ml volumetric flask containing 100 ml of 0.1N HCl and volume was made to 100 ml with solvent. The volumetric flask was shaken using sonicator for 1 hr. and after suitable dilution with 0.1N HCl the drug content wasdetermined using HPLC at 215nm.

Drug Content for Isosorbide dinitrate

The drug content was carried out by weighing 10 tablets form each batch and calculated the average weight. Then the tablets were triturated to get fine powder. From the resulting triturate, powder was weighted accurately which was equivalent to 100 mg Isosorbide dinitrate and dissolve in 100 ml volumetric flask containing 100 ml of 0.1NHCl and volume was made to 100 ml with solvent. The volumetric flask was shaken using sonicator for 1 hr. and after suitable dilution with 0.1N HCl the drug content wasdetermined using HPLC at 215 nm.

Disintegration Test

It is determined by using USP device which consist of 6 glass tubes that are 3 inches long, open at one end and held against 10 mesh screen at the bottom end of basket rackassembly. To test for disintegration time, one tablet is placed in each tube and the basket arch is positioned ina1liter beaker of water at 37°C ± 2°C., all tablets must disintegrate and all particles must pass through the 10 mesh in the time specified.

***In-vitro* Drug Release Study for Hydralazine HCl**

In-vitro drug release of bilayer tablets was determined using a USP type -II dissolution test apparatus at 100 rpm. The dissolution was studied using 900 ml of simulated gastric fluid 0.1N HCl (without enzyme, pH 1.2) for the first 2 hr and half dissolution model was followed for the sustained release layer for 12 hr. Filter through whatman filter paper and replaced by an equal volume of dissolution medium sample were suitably diluted and analyzed by HPLC at 215 nm.

***In-vitro* Drug Release Study for Isosorbide Dinitrate**

In-vitro release of bilayer tablets was determined using a USP type -II dissolution test apparatus at 100 rpm. The dissolution was studied using 900 ml of simulated gastric fluid 0.1N HCl (without enzyme, pH 1.2) for the first 2 hr and followed by a simulated intestinal

fluid (without enzyme, pH 6.8) for the remaining 10 hr. The temperature wasmaintained at 37 ± 0.5 ^{0}C. 5 ml sample was taken at different time intervals up to 12 hr.Filter through whatman filter paper and replaced by an equal volume of dissolution medium sample were suitably diluted and analyzed by HPLC at 215 nm.

Table 6.15: Summary of Dissolution Study

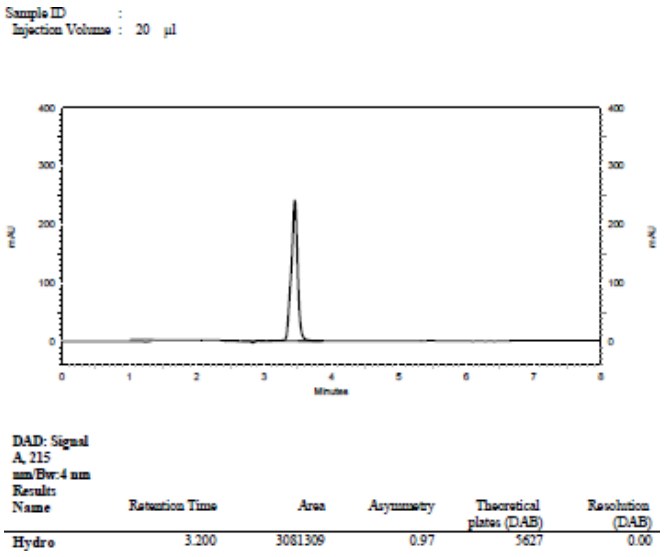
Condition	**For Hydralazine HCl Immediate release tablet**	**For Isosorbide dinitrate Sustainedrelease tablet**
USP Dissolution apparatus	Type II (Paddle)	Type II (Paddle)
Media	0.1 N HCl	Phosphate Buffer pH 6.8
Volume of diss. Medium	900ml	900ml
Speed of paddle rotation	100RPM	100RPM
Temperature	$37^0 \pm 0.5^0$C	$37^0 \pm 0.5^0$C
Sampling point	5,10,15,30,45,60 min	0.5,1,2,4,6,8, 10 hr

RESULTS AND DISCUSSION

Determination of Hydralazine HCl

Take about 10 mg of Standard Hydralazine HCl (25% Diluted) transfer into a clean anddry 25 ml volumetric flask, add about 15 ml of mobile phase mix to dissolve it and make up 25 ml volume with mobile phase and mix. Inject equal volume (20 µl) of the standard preparation of the five replicate injections of standard and find out following suitability and two injection of test solution. Record the chromatogram and measure thepercentage.

Figure 6.1: HPLC Chromatogram at 215nm of Hydralazine HCl



Determination of Isosorbide Dinitrate

Take about 10 mg of Standard Isosorbide dinitrate (25% Diluted) transfer into a clean and dry 25 ml volumetric flask, add about 15 ml of mobile phase mix to dissolve it andmake up 25 ml volume with mobile phase and mix. Inject equal volume (20 µl) of the standard preparation of the five replicate injections of standard and find out following suitability and two injection of test solution. Record the chromatogram and measure the ercentage.

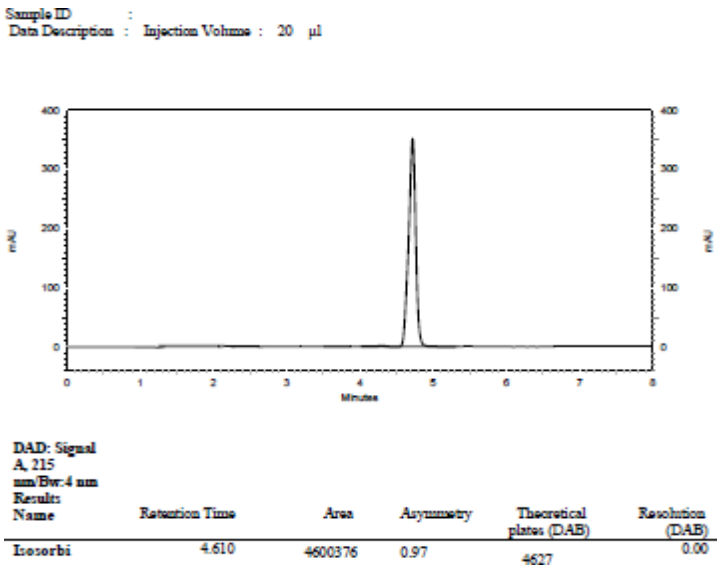
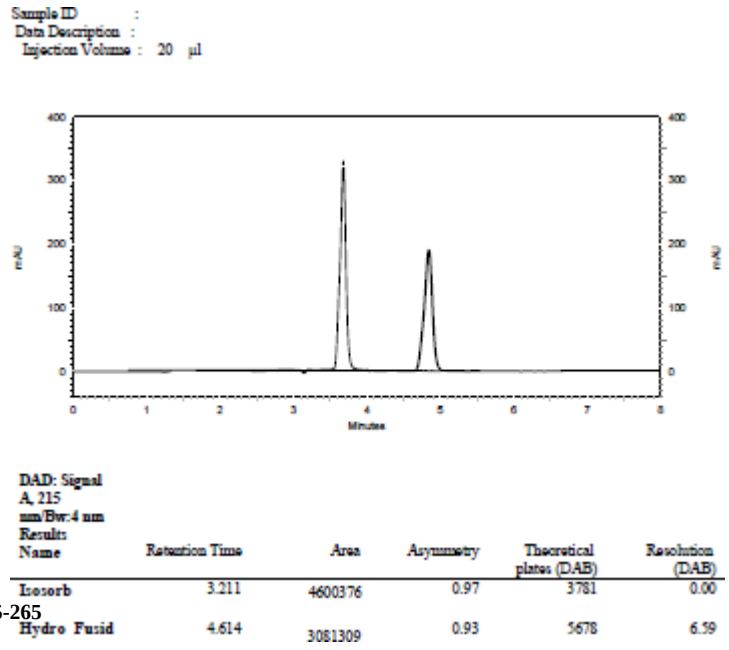


Figure 7.2: HPLC Chromatogram at 215nm of Isosorbide Dinitrate

Determine Combination of Hydralazine HCl and Isosorbide dinitrate byHPLC

Take about 10 mg of Standard Isosorbide dinitrate (25% Diluted) and about 10 mg Standard of Hydralazine HCl transfer into a clean and dry 25 ml volumetric flask, add about 15 ml of mobile phase mix to dissolve it and make up 25 ml volume with mobilephase and mix.

Figure 7.3: HPLC Chromatogram at 215nm Combination of Hydralazine HCl &Isosorbide dinitrate



Determination of Calibration Curve

Calibration Curve of Hydralazine HCl by HPLC

The standard calibration curve of Hydralazine HCl was obtained by plotting Area vs. concentration. Peak area of different concentrations were listed in below Table. The standard calibration curve of Hydralazine HCl was developed at λ_{max} 215nm. The calibration curve was linear between 50-150 µg/ml concentration ranges. R^2 value was obtained 0.999, it indicates the linearity of the curve.

Table 6.1: Area of different concentration of Hydralazine HCl

Concentration (µg/mL)	Peak Area
0	0
50	3355658
75	4976495
100	6593596
125	8210407
150	9843493

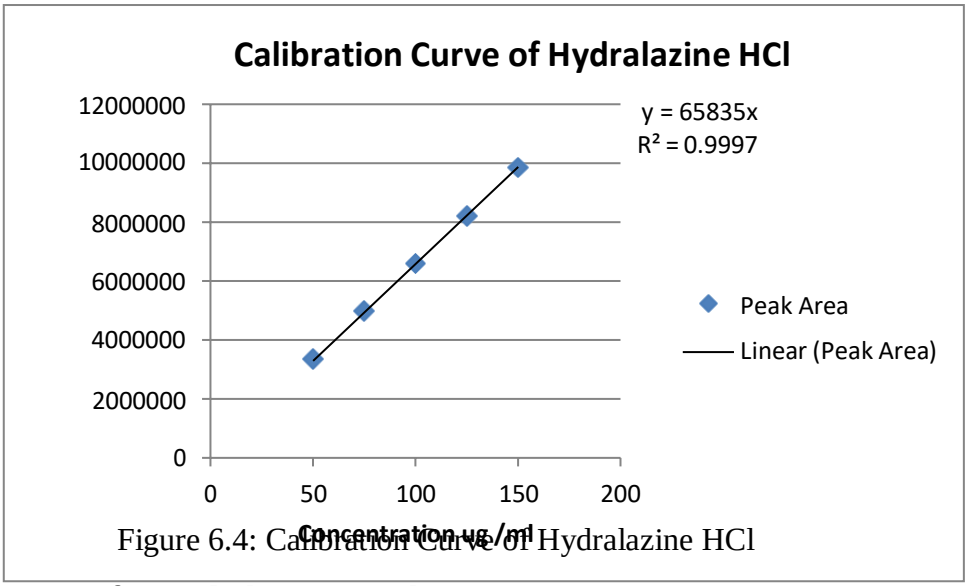


Figure 6.4: Calibration Curve of Hydralazine HCl

Calibration Curve of Isosorbide Dinitrate by HPLC

The standard calibration curve of Isosorbide Dinitratewas obtained by plotting Area vs. concentration. Peak area of different concentrations were listed in below Table. The standard calibration curve of Isosorbide Dinitrate was developed at λ_{max} 215nm. The calibration curve was linear between 50-150 µg/ml concentration ranges. R^2 value was obtained 0.999, it indicates the linearity of the curve.

Table 6.2: Area of different concentration of Isosorbide Dinitrate

Concentration (µg/mL)	Peak Area
0	0
0	6254635
75	9629461
100	12700701
125	15965898
150	18934406

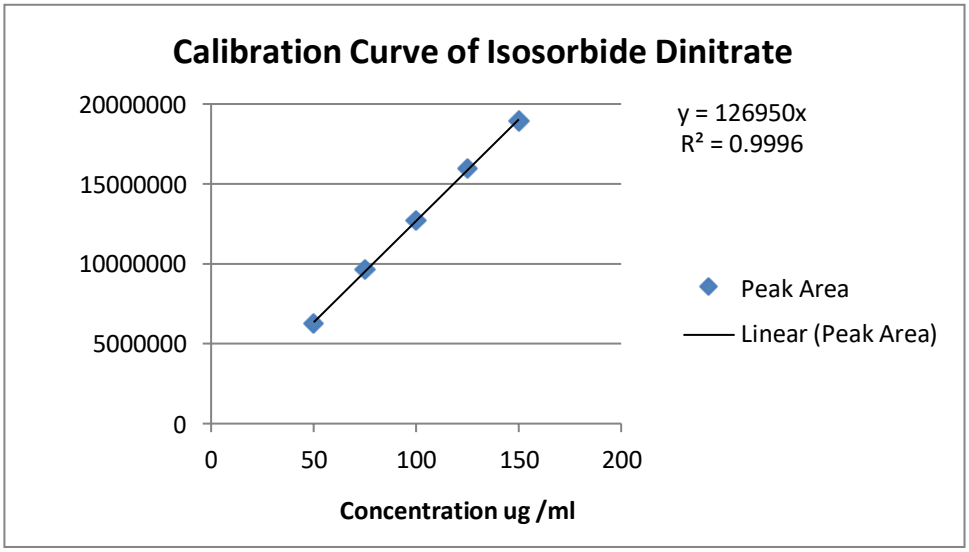


Figure 7.5: Calibration Curve of Isosorbide Dinitrate

Identification of Isosorbide Dinitrate by FT-IR

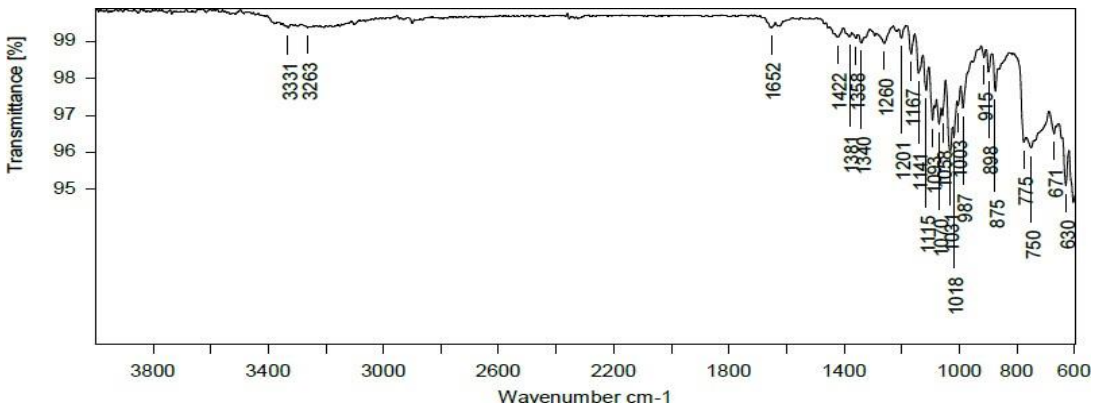


Figure 7.8: FT-IR Spectra of Isosorbide Dinitrate

Physical Characterization of Hydralazine HCl and Isosorbide Dinitrate

Organoleptic Characteristics[62]

Table 7.9: Organoleptic Characteristic of API

Properties	Hydralazine HCl	Isosorbide Dinitrate
Description	White crystalline powder	White crystalline powder
Color	White	White
Odor	Odorless	Odorless
Taste	Bitter	Bitter

Solubility

Table 7.10: Solubility of API in Different media

Media	Solubility of Hydralazine HCl (mg/ml)	Solubility of Isosorbide Dinitrate(mg/ml)
Water	Soluble	Very slightly Soluble
0.1N HCl	Soluble	Slightly soluble
Buffer PH 6.8	Very soluble	Soluble
Alcohol	Slightly soluble	Very soluble

Melting Point[58, 60]

Melting point of Hydralazine HCl and Isosorbide Dinitrate was carried out by capillarymelting point apparatus and the melting point was found to be 170 to 173°C and 70°Crespectively.

Flow Properties of Drug and Excipients

From the Table 6.9, it was concluded that Hydralazine HCl, Isosorbide Dinitrate, Sodium Starch Glycolate, Acdisol, Crospovidone, MCC PH102, Tablattose, HPMCK100, PolyoxWSR303, Ethyl cellulose, Magnesium Stearate have excellent flow property based on angle of repose because they all have angle of repose value between 19.52 ± 2.41 to 28.22 ± 2.73.

Table 7.11: Flow Properties of Drug and Excipients

Ingredients	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
HydralazineHCl	0.57 ± 0.003	0.65 ± 0.002	12.30 ± 0.4	1.14 ± 0.5	26.6 ± 0.64

Isosorbide Dinitrate	0.512 ± 0.02	0.598 ± 0.4	14.38 ± 0.3	1.16 ± 0.1	25.35 ± 2.73
Sodium Starch Glycolate	0.54 ± 0.01	0.63 ± 0.3	14.28 ± 0.3	1.16 ± 0.2	25.2 ± 2.94
Acdisol	0.51 ± 0.03	0.60 ± 0.3	15.0 ± 0.2	1.17 ± 0.3	23.34 ± 2.75
Crospovidone	0.56 ± 0.02	0.64 ± 0.2	12.5 ± 0.3	1.14 ± 0.3	27.21 ± 2.65
Tablattose	0.56 ± 0.03	0.62 ± 0.3	9.6 ± 0 .2	1.10 ± 0.3	26.31 ± 2.83
HPMC K100	0.57 ± 0.02	0.64 ± 0.3	10.9 ± 0.3	1.12 ± 0.2	28.22 ± 2.73
Ethyl Cellulose	0.62 ± 0.05	0.70 ± 0.03	11.1 ± 0.2	1.23 ± 0.3	25.20 ± 2.25
Polyox^{tm}wsr303	0.64 ± 0.01	0.70 ± 0.05	12.0 ± 0.3	1.20 ± 0.2	20.21 ± 2.65
MCC PH102	0.45 ± 0.04	0.52 ± 0.03	11.2 ± 0.3	1.18 ± 0.3	19.52 ± 2.41
Magnesium stearate	0.68 ± 0.02	0.75 ± 0.03	12.5 ± 0.2	1.21 ± 0.4	21.56 ± 2.41

Table 7.21: Formulation and evaluation of check point batches

Evaluation Parameters of Isosorbide Dinitrate

re-compression Evaluations of Granules of Preliminary Batches

Table 6.22: Pre-Compression Evaluations of Preliminary Batches

Batch Code	**Bulk density (gm/cm^3)**	**Tapped density (gm/cm^3)**	**% Carr'sindex**	**Hausner'sratio**	**Angle ofrepose (Ɵ)**
I1	0.27 ± 0.002	0.31 ± 0.002	12.73 ± 0.075	1.15 ± 0.0059	23.52 ± 0.01
I2	0.28 ± 0.003	0.32 ± 0.003	12.76 ± 0.076	1.15 ± 0.0061	23.54 ± 0.02
I3	0.28 ± 0.002	0.33 ± 0.002	12.21 ± 0.075	1.15 ± 0.0054	22.55 ± 0.05
I4	0.29 ± 0.002	0.32 ± 0.002	11.62 ± 0.076	1.11 ± 0.0045	22.06 ± 0.05
I5	0.27 ± 0.003	0.31 ± 0.002	12.73 ± 0.076	1.15 ± 0.0051	22.96 ± 0.04
I6	0.29 ±0.003	0.33 ± 0.003	11.94 ±0.076	1.14 ±0.0051	22.36 ± 0.09

All values are expressed as mean ± standard deviation, n=3

Post Compression Evaluation of Preliminary Batches

Table 7.23: Post-Compression Evaluation Parameters of Preliminary Batches

Batch Code	**Weight variation**	**Thickness (mm)**	**Hardness (kg/cm^2)**	**% Friability**	**% Drug Content**
I1	Pass	4.57 ± 0.047	3.30 ± 0.08	0.40 ± 0.02	99.8 ± 0.14
I2	Pass	4.67 ± 0.037	3.22 ± 0.06	0.42 ± 0.05	99.5 ± 0.75
I3	Pass	4.54 ± 0.015	3.18 ± 0.03	0.48 ± 0.03	100.1 ± 0.37
I4	Pass	4.51 ± 0.054	3.26 ± 0.02	0.46 ± 0.05	99.7 ± 0.18
I5	Pass	4.56 ± 0.075	3.35 ± 0.04	0.42 ± 0.04	99.6 ± 0.43
I6	Pass	4.58 ± 0.047	3.28 ± 0.01	0.44 ± 0.07	99.4 ± 0.23

All values are expressed as mean ± standard deviation, n=6

All the tablets were evaluated for various physical parameters before proceeding further. Table 6.23 includes the values (mean ± SD) of weight variation, hardness, thickness, friability, % drug content and *in-vitro* drug release of batches I1 to I6 prepared using different combinations of functional excipients. Tablet weights in all the 6 batches varied between 249.82 mg to 251.19 mg.

***In-vitro* Drug Release of Preliminary Batches I1 to I6**

Table 7.24: % CDR of Preliminary Batches

Time(Min)	**I1**	**I2**	**I3**	**I4**	**I5**	**I6**
0	0	0	0	0	0	0
0.5	12.2 ±1.15	18.7 ±2.53	8.10 ±3.53	18.2 ±2.45	25.4 ±2.89	10.3 ±1.51
1	51.09 ±2.35	46.03 ±2.85	43.09 ±2.35	38.30 ±2.85	35.20 ±1.38	32.70 ±2.67

2	90.80 ±1.57	85.60 ±2.47	80.80 ±1.57	75.60 ±2.47	74.05 ±2.48	70.08 ±1.41
4	98.80 ±1.57	97.20 ±1.51	96.08 ±1.57	96.07 ±2.32	93.01 ±1.79	90.07 ±1.81
6	99.90 ±1.89	98.60 ±2.15	98.09 ±1.89	98.18 ±1.65	98.58 ±2.38	99.08 ±1.34

Table 6.25: Pre-Compression Evaluations of Batches ID1 to ID9

Batch Code	**Bulk density (gm/cm^3)**	**Tapped density (gm/cm^3)**	**% Carr'sindex**	**Hausner'sratio**	**Angle of repose(Ɵ)**
ID1	0.579 ± 0.002	0.668 ± 0.003	12.72 ± 0.027	1.15 ± 0.035	23.54 ± 0.02
ID2	0.612 ± 0.001	0.698 ± 0.005	11.92 ± 0.028	1.14 ± 0.015	22.36 ± 0.09
ID3	0.632 ± 0.005	0.726 ± 0.004	11.94 ± 0.026	1.14 ± 0.057	22.38 ± 0.09
ID4	0.559 ± 0.002	0.654 ± 0.005	12.92 ± 0.027	1.16 ± 0.05	23.82±0.07
ID5	0.654 ± 0.007	0.773 ± 0.003	13.39 ± 0.025	1.18 ± 0.07	25.38 ± 0.06
ID6	0.513 ± 0.001	0.602 ± 0.007	13.18 ± 0.034	1.17 ± 0.071	24.80 ± 0.05
ID7	0.007 ± 0.394	0.696 ± 0.008	12.94 ± 0.031	1.16 ± 0.025	23.81 ± 0.03
ID8	0.008 ± 0.32	0.639 ± 0.008	12.94 ± 0.018	1.16 ± 0.025	23.86 ± 0.31
ID9	0.603 ± 0.009	0.708 ± 0.008	13.13 ± 0.085	1.17 ± 0.011	24.85 ± 0.07

All values are expressed as mean ± standard deviation, n=3

Drug Release Kinetic

In order to examine the kinetic of drug release from prepared sustained release tablets, the dissolution data of optimized formulation HDID was fitted into different kinetic models i.e. Zero order, First order, Higuchi model, Hixson- Crowell and Korsemeyer- Peppas model. The criteria for the selection of most suitable model were value of regression coefficient (R^2) nearer to 1, smallest values of Residual sum of squares (SSR) and Akaike Information Criteria (AIC). Table 6.32 shows the data obtained.

Table 7.32: Fitting of Release Profile of Optimized Formulation to Kinetic Models

Batch	**Model**	**Parameters Used**				
		R^2	**R**	**K**	**SSR**	**AIC**
	Zero-order	0.7429	0.9494	12.177	2381.0501	64.2024

ID9	**First-order**	0.9773	0.9902	0.342	210.0399	44.7784
	Higuchi	0.9922	0.9963	33.388	72.0347	36.2172
	Korsemeyer – Peppas	0.9935	0.9968	35.104 n=0.472	60.4890	36.8197
	HixsonCrowell	0.9616	0.9882	0.090	355.4174	48.9863

CONCLUSIONS

The present study was undertaken with an aim formulation and evaluation of Bilayer Tablets containing Hydralazine HCl and Isosorbide Dinitrate by Direct compression technology was to formulate a stable, safe and convenience dosage form for the better management of most common cardiovascular disorders or blood pressure. The formulations of bilayer tablets showed good results in case of Hydralazine HCl immediate release layer physicochemical parameters and prepared using concentration of superdisintegrant sodium starch glycolate and ac-di-sol® for the fast release layer and sustained release layer of isosorbide dinitrate containing HPMC K100 M and polyox^{tm} WSR 303 for the delay the drug release up to 10-12 hrs. The FTIR and DSC analysis indicates that there were no drug-drug and drug-excipients interactions. Pre compression and post compression parameters were found to be within the satisfactory limits and hence suitable to formulate Bilayer tablets. Formulation batch HDID was finally optimize in which HD9 (Hydralazine HCl) batch is selected as immediate release layer and ID9 (Isosorbide Dinitrate) batch is selected as sustained release layer as final selected formulation.

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