FORMULATION AND EVALUATION OF ATENOLOL AND INDAPAMIDE SR MATRIX TABLET FOR TREATMENT OF HYPERTENSION

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Abstract

In the present study we have formulated (f_1 to f_6) matrix tablets of Atenolol and Indapamide for the management of hypertension. As in simultaneous estimation of these drugs it was found that a confined release can be formulated. In the formulation of SR matrix tablet by using different concentration of delayed release agent DCP and pregelatinised starch as disintegrant we prepared tablets by wet granulation method. For sustained release action HPMC polymers were used for film coating. Preformulation studies were performed prior to compression. The compressed SR matrix tablets were evaluated for weight variation, hardness, friability, drug content, disintegration time and invitro drug release using USP dissolution apparatus type 2 (paddle). It was found that the optimized formulation showed 49.33%, 48.90%, 48.52%, 47.65%, 46.84% and 46.51% release for Atenolol in 12 hours respectively. However, Indapamide released 49.62%, 49.39%, 48.72%, 48.27%, 47.59% and 47.36% at the end of 12hrs. The IR spectrum study revealed that there is no disturbance in the principal peaks of pure drugs Atenolol and Indapamide. This confirms the integrity of pure drugs and no incompatibility of them with excipients. The stability studies were carried out for the optimized batch for one months and it showed satisfactory results. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug and release follows Zero order, Super case II transport.

Keywords: DCP, starch, HPMC, Atenolol, Indapamide, Zero order, simultaneous estimation.

Introduction

Combination therapy for treatment of various diseases and disorders require long term therapy such as hypertension and diabetes. Combination therapies have various advantages over monotherapy such as problem of dose dependent side effects minimized [1].

The sustained release matrix drug deliveries are to ensure safety and enhancement of efficacy of drug with improved patient compliance. Thus the use of these dosage forms is increasing in treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above minimum effective concentration and below the minimum toxic level for extended period of time [2]. Sustained release tablet allowing a twofold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form [3].A Tablet is a mixture of API and excipients usually in powder form, pressed or compacted in to solid.

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The excipient usually includes binders, disintegrants, sweeteners or flavours and pigments lubricants, glidents [4].Particles of drug are coated with matrix or entire product is matrix coated which along with its main function of sustained action, avoid exposure of unstable drug to the environment and render it stable [5].

Atenolol (Figure 1), [(4-2 – hydroxy-3 – isopropyl - aminopropoxy) phenylacetamide](Figure 1), is a cardioselective β-blocker. It is reported to lack intrinsic sympathomimetic activity and membrane-stabilising properties. It may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin and α-methyldopa [6]. Besides being one of the most widely used b-blockers clinically, it has often been used as a reference drug in randomized controlled trials of hypertension [7-10].The elimination half-life of atenolol is 6 to 7 hours and there is no alteration of kinetic profile of drug by chronic administration. Following intravenous administration peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5 to 10 fold) during the first 7 hours. Following oral doses of 50 mg or 100 mg both b-blocking and anti-hypertensive effects persist for at least 24 hours. The drug accumulates in patients with renal failure and dosage should be adjusted for patients whose creatinine clearance is less than 35 mL/min/1.73m2 [11].
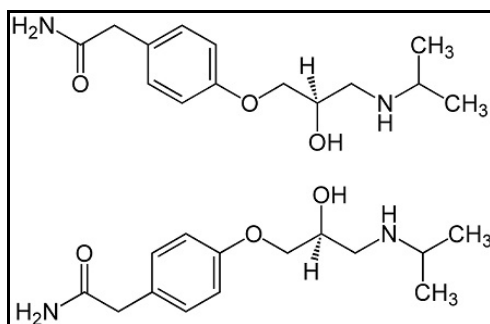

Figure 1: structure of Atenolol

Indapamide (thiazide-type diuretics) is indoline derivatives of chlorosulphonamide (4-Chloro-N-(2-methyl-1-indolinyl)-3-sulfamoylbenzamide) (Figure 2). It differs chemically from thiazides and contains only one sulphonamide group and no thiazide ring. Indapamide is an anti-hypertensive diuretic related to the thiazides. The anti-hypertensive effect is associated with an improvement in arterial compliance and a reduction in total and arteriolar peripheral resistance. Indapamide as a first step antihypertensive, has two properties beyond diuresis. First, there is added vasodilation [12]. A second unusual property is a high concentration class I and III antiarrhythmic effect [13]. Indapamide has a terminal half-life of 14 to 16 hours and effectively lowers the blood pressure over 24 hours. The initial dose is 1.25 mg once daily for 4 weeks, then if needed 2.5 mg daily. Indapamide appears to be more lipid neutral than other thiazides [14] but seems equally likely to cause other metabolic problems such as hypokalemia, hyperglycemia or hyperuricemia. Indapamide (2.5 mg daily) does not adversely affect serum triglycerides, LDL cholesterol, the LDL-HDL cholesterol ratio, or glucose tolerance.
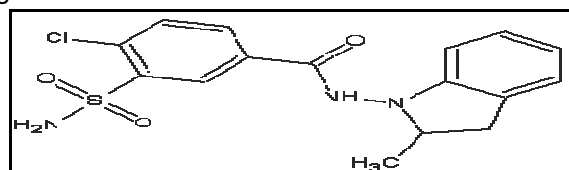

Figure 2: Structure of Indapamide

Materials and methods

List of material are shown in table 1.

TABLE 1: List of material.

List of materials	
Atenolol	Sodium starch glycolate
Indapamide	Cross carmelose sodium
Starch	Aerosil 101
Dibasic calcium phosphate	Magnesium stearate
Lactose	Talc
Polyvinyl pyrollidone k-30	Hydroxy propyl methyl cellulose
Isopropyl alcohol	Propyl ethylene glcolate 400

Preformulation Studies:
It is one of the important prerequisite in development of any drug delivery system. Preformulations studies were performed on the drug [4] (See table 2).

TABLE 2: List of pre-formulation parameters.

Pre-formulation parameters of powder	Evaluation of Pre-formulation parameters of granules
Organoleptic characteristics	Bulk Density and Tapped Density
Melting Point	Angle of repose
Solubility	Hausner's Ratio
Compatibility Studies	Compressibility index (Carr's Index)

Organoleptic characteristics [4]
The colour, odour, and taste of the drug were characterized and recorded. The results are shown in table 3.

TABLE 3: Evaluation of organoleptic properties of powder.

Excipients	Description	
	Appearance	Odour
Atenolol	White to off White crystalline powder	Odourless
Indapamide	White powder	Odourless
Starch	White to light yellow powder	Odourless
Dibasic calcium phosphate	White powder	Odourless
Lactose	White crystalline powder	Odourless
Polyvinyl pyrollidone k-30	Creamy white powder	Odourless

Excipients	Description	
	Appearance	**Odour**
Isopropyl alcohol	Colorless	Pleasant
Sodium starch glycolate	White powder	Odourless
Cross carmelose sodium	White powder	Odourless
Aerosil 101	White powder	Odourless
Magnesium stearate	Light white powder	Slight
Talc	Light to dark green, brown, white powder	Odourless

Determination of Melting Point [4]

Melting point of Atenolol and Indapamide was determined by capillary method. Fine powder of Atenolol and Indapamide was filled in capillary tube (previously sealed at one end). The capillary tube inserted in sample holder of melting point apparatus and a thermometer is also placed in the apparatus. The temperature at which powder melted was noticed (result shown in table 4).

Solubility

(Result show in table 4)

TABLE 4: Evaluation of pre-formulation parameters of powder

Excipients	Solubility	Melting point
Atenolol	Water (0.3 mg/mL), Ethanol(3.4 mg/mL) DMSO(18 mg/mL) Ether(Practically Insoluble)	152-155^{0}C
Indapamide	Water(Practically Insoluble)(75 mg/L) Alcohol(soluble) ethyl acetate(soluble) Acetonitrile(soluble)	161℃

Compatibility Studies (Drug-Excipients compatibility studies)

The pure drugs (Atenolol and Indapamide) along with formulation excipients and studies were carried out by mixing definite proportions of drug and excipients(ratio 1:1) and kept on glass vials which are stored at 40ºC ± 2ºC & 75±5% RH for one month [4, 19] (result shown in table 5).

TABLE 5: Drug-excipients compatibility studies

Excipients	Description	
	Starting of study (Initial)	**After one month (final)**
Active pharmaceutical ingredients(Atenolol + Indapamide)	White crystalline powder	White crystalline powder
API +Starch	White crystalline powder	White crystalline powder
API + Dibasic calcium phosphate	White crystalline powder	White crystalline powder
API + Lactose	White crystalline powder	White crystalline powder
API + Polyvinyl pyrollidone k-30	White crystalline powder	White crystalline powder

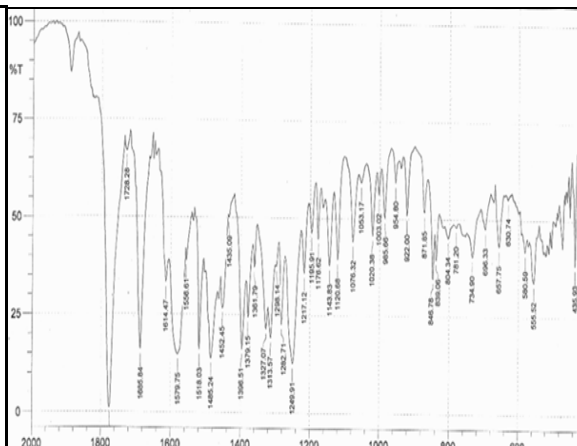| Excipients	Description	
	Starting of study (Initial)	After one month (final)
API + Sodium starch glycolate	White crystalline powder	White crystalline powder
API + Cross carmelose sodium	White crystalline powder	White crystalline powder
API + Aerosil 101	White crystalline powder	White crystalline powder
API + Magnesium stearate	White crystalline powder	White crystalline powder
API + Talc	White crystalline powder	White crystalline powder
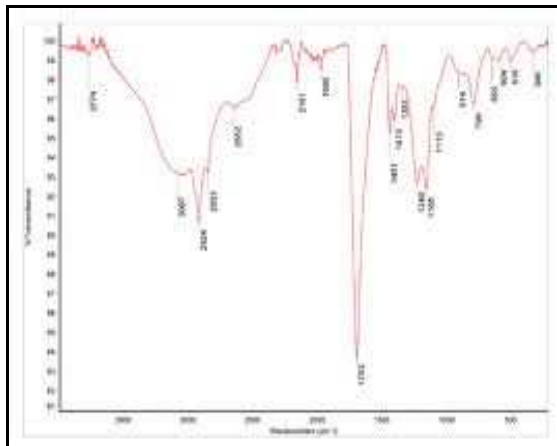
Figure 3: FTIR of Atenolol with excipients.   Figure 4: FTIR of Indapamide with excipients.

Evaluation of Pre-formulation parameters of granules [4,17,18]

Determination of Bulk Density and Tapped Density

20g of the mix blend (W) was introduced into a 100ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 Sec intervals. The tapping was continued until no further change in volume was noted (result shown in table 9). The bulk density, and tapped density was calculated using the following formulae.

> ➢ Bulk density=W/V_O
> ➢ Tapped density=W/V_F

Where,

W= weight of the granules,

V_O = initial volume of the granules.

V_F = final volume of the granules.

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation(shown limits in table 6).

$$\theta = \tan^{-1} h / r$$

Where, h and r are the height and radius of the powder cone respectively (result show in table 9).

TABLE 6: Angle of repose

SL.	Angle of repose(θ)	Type of flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

Hausner's Ratio

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density (shown limits in table 7)(result shown in Table 9)

Hausner's Ratio =Tapped density/Bulk density

TABLE 7: Hausner's ratio

Sr. No.	Hausner's Ratio	Property
1.	0-1.2	Free flowing
2.	1.2-1.6	Cohesive powder

Compressibility index (Carr's Index)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is (limits shown in table 8).

TABLE 8: Carr's index

Carr's Index	Properties
5-12	Free flowing
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

A material having values of less than 20% has good flow property (result shown in table 9).

$$C_I = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

TABLE 9: Evaluation of pre-formulation parameters of granules

Formula-ion	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
F1	0.486	0.567	14.28	1.16	21.30
F2	0.479	0.561	14.61	1.17	20.80
F3	0.487	0.558	12.72	1.14	21.80

Formula-ion	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
F4	0.478	0.563	15.09	1.15	24.22
F5	0.476	0.559	14.84	1.17	22.78
F6	0.482	0.570	15.43	1.18	22.29

Preparation of Standard Calibration Curve of Atenolol

ATL 50 mg was accurately weighed and dissolved in 50 ml methanol. From the above solutions 1 ml was diluted to 10 ml with methanol to produce 100 µg/ml of ATL. Suitable aliquot of this stock solution of ATL was diluted with methanol to obtain 6-30 µg/ml of ATL. Absorbance of the above dilution was determined at 225 nm absorbance (result shown in table 10). Calibration curve was plotted as concentration Vs absorbance. (Figure 5)

TABLE 10: Standard calibration curve of atenolol and indapamide

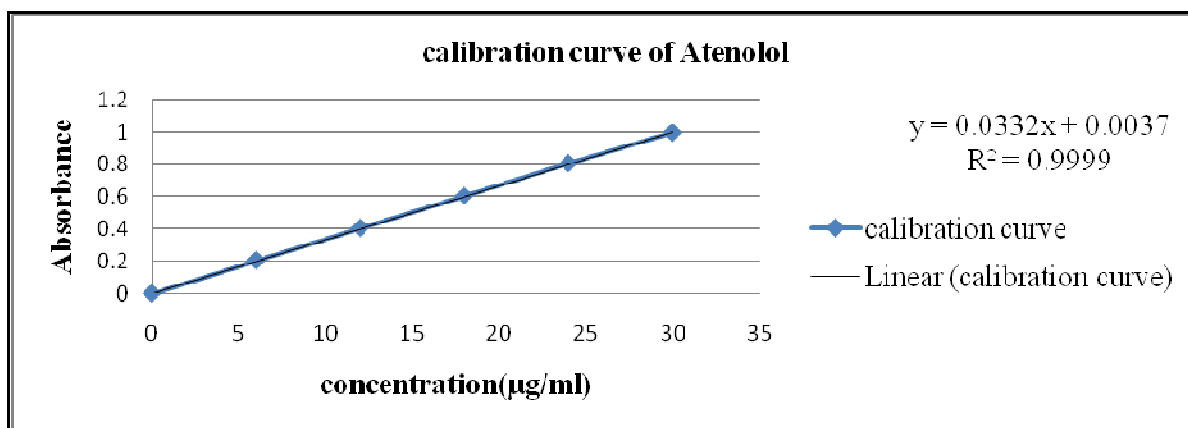| Atenolol		Indapamide	
Concentration	Absorbance	Concentration	Absorbance
0	0	0	0
6	0.2038	2	0.3158
12	0.4044	4	0.6356
18	0.6034	6	0.9716
24	0.8046	8	1.2830
30	0.9940	10	1.5868

Figure 5: Calibration curve of Atenolol

Preparation of Standard Calibration Curve of Indapamide

IND 50 mg was accurately weighed and dissolved in 50 ml methanol. From the above solutions 1 ml was diluted to 10 ml with methanol to produce 100 µg/ml of IND. Suitable aliquot of this stock solution of IND was diluted with methanol to obtain 0-10µg/ml IND separately. Absorbance of the above dilution was determined at 240 nm absorbance (result shown in table 10). Calibration curve was plotted as concentration Vs absorbance. (Figure 6)
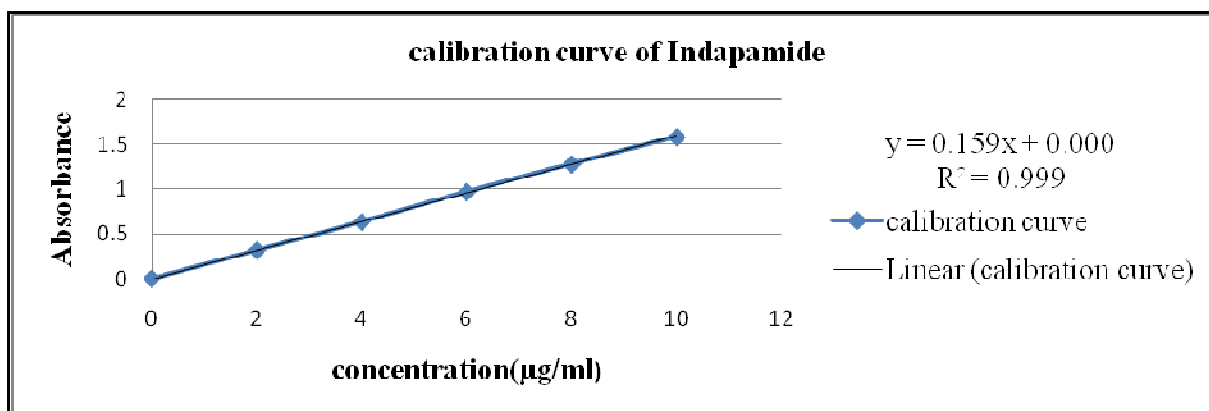
Figure 6: Calibration curve of Indapamide

Preparation of SR matrix tablets

Sustained release matrix tablet of Atenolol and Indapamide was manufactured by wet granulation technique. Atenolol, Indapamide and lactose for each batch was pre-blended for 5 minutes. Add DCP, starch and blended for additional 5 minutes in RMG. Finally paste (transparent homogenous solution) of pvp k-30 and IPA was added for binding and the formulation was mixed for further minutes to achieve an agglomerated mass. The granules were air dried for 5 min and then dried in FBD till moisture content achieved 1-2%. The dried granules were passed through the sieve (sieve no. 30#). Dried granules were lubricated with SSG, CCS, aerosil 101, magnesium sterate and talc for 5 minutes. Tablets were manufactured using a tablet compression machine and then compressed tablets were coated (sustained release film coating). (Table 11)

TABLE 11: Formulation chart

Ingredients	Formulation code					
	F1	F2	F3	F4	F5	F6
Atenolol(mg)	50	50	50	50	50	50
Indapamide(mg)	2.5	2.5	2.5	2.5	2.5	2.5
Starch(mg)	70	75	80	85	90	95
Dibasic calcium phosphate(mg)	30	27.5	25	22.5	20	17.5
Lactose(mg)	20	17.5	15	12.5	10	7.5
Polyvinyl pyrollidone k-30(mg)	3	3	3	3	3	3
Isopropyl alcohol(ml)	0.02	0.02	0.02	0.02	0.02	0.02
Sodium starch glycolate(mg)	5	5	5	5	5	5
Cross carmelose sodium(mg)	5	5	5	5	5	5
Aerosil 101(mg)	4.5	4.5	4.5	4.5	4.5	4.5

Ingredients	Formulation code					
	F1	F2	F3	F4	F5	F6
Magnesium stearate(mg)	5	5	5	5	5	5
Talc(mg)	5	5	5	5	5	5
Total weight	200.02	200.02	200.02	200.02	200.02	200.02

Analysis of laboratory mixture

Accurately weighed 50 mg of ATL and 2.5 mg of IND were transferred to 100 ml volumetric flask, dissolved in methanol and volume was adjusted up to the mark with same solvent. Appropriate aliquot 0.5 ml was transferred to 10 ml volumetric flask and volume was adjusted up to the mark with same solvent to obtained concentration 30 µg/ml of ATL and 1.5 µg/ml of IND. The absorbances of solutions were recorded at 225.0 nm and 240.0 nm against blank. Concentration of each drug was obtained by solving the simultaneous equation.

$$C1 = (A2ay1 – A1ay2) / (ax2ay1 - ax1ay2) \text{ ------------------- (1)}$$
$$C2 = (A1ax2 – A2ax1) / (ax2ay1 - ax1ay2) \text{ ------------------- (2)}$$
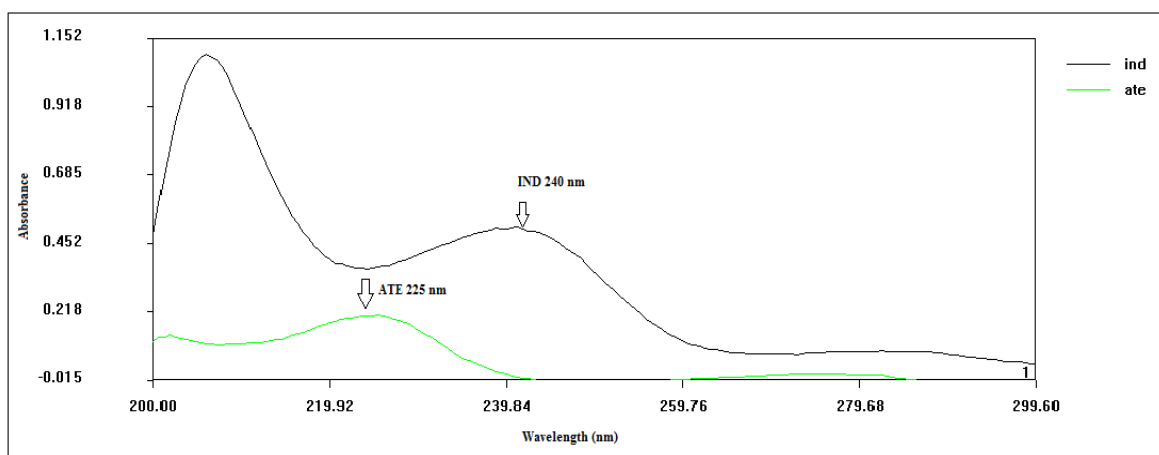

Figure 7: Simultaneous estimation of Atenolol and Indapamide SR matrix tablet

Evaluation parameter [4, 15]

General Appearance

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc [4].(result shown in table 12)

Size & Shape

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micrometer or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

Organoleptic properties

Colour distribution must be uniform with no mottling. For visual colour comparison compare the colour of sample against standard colour.

Weight variation

All prepared matrix tablets were evaluated for weight variation as per USP XXIV monograph. Twenty tablets of each batch were used to evaluate weight variation among tablets and standard deviation was calculated [4, 15]. (Result shown in table 12)

Friability

20 tablets were taken randomly and placed on a sieve. Loose dust was removed with the aid of a soft brush. Tablet samples were weighed accurately and placed in Roche friabilator. After the given number of rotations (100 rotations) loose dust was removed from the tablets as before and the finally tablets weight determined. The lost in weight indicate the ability of the tablets to withstand stress of handling and transportation [4, 15]. (Result shown in table 12)The percentage friability was determined by using following formula:

% friability = initial weight- final weight∕initial weight x 100

Hardness

The hardness of the tablets was determined by diametric compression using a Hardness testing apparatus (Monsanto tester). A tablet hardness of about 4-5 kg is considered adequate for mechanical stability. Determinations were made in triplicate [4, 15]. (Result shown in table 11)

Thickness

20 tablets were taken randomly for this purpose, the tablet thickness were determined individually with the aid of a vernier calliper [4, 15]. (Result shown in table 12)

Uniformity of content of active ingredient

Content uniformity

In this test, 30 tablet are randomly selected for the sample and at least 10 of them are assayed individually. Nine of the 10 tablet must contain not less than 85% and more than 115% of the label drug content. The 10 tablet may not less than 75% or more than 125% of the labelled content. If these condition not met. The tablet remaining from the 30 must be assayed individually, and none may fall outside of the 85% to 115% range. In evaluating a particular lot of tablet, several sample of tablet should be taken from various part of production run to satisfy statistical procedure [4, 15]. (Result shown in table 12)

Disintegration test

Sustained released matrix tablets are not expected to disintegrate like convectional tablets. Disintegration time was measured by using 6 tablets from each formulation, i.e. one tablet per disintegrating basket. Disintegration Apparatus was name of apparatus [4, 15].

TABLE 12: Post compression parameters.

Formulation	Weight variation	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Content uniformity (%)
F1	200	5.7	0.41	3.83	99.8

Formulation	Weight variation	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Content uniformity (%)
F2	200	5.5	0.62	3.85	99.5
F3	201	6.0	0.37	3.69	99.7
F4	200	6.0	0.29	3.67	99.9
F5	201	6.0	0.37	3.69	99.8
F6	200	5.9	0.41	3.85	99.6

Dissolution test (In-vitro dissolution study)

The release rate of Atenolol and Indapamide SR matrix tablet was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The in vitro release study was performed in 0.1 N HCL pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. At every interval 10 ml of the solution was withdrawn from the dissolution apparatus at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours and samples were replaced with fresh dissolution medium to maintain the constant volume. The samples were filtered through a filter and absorbance of these solutions was measured at 225.0 nm (Atenolol) and 240.0 nm (Indapamide) using Elico SL 210 UV/V is double beam spectrophotometer [4, 15]. (Result shown in table 13,14)

TABLE 13: In-vitro drug release of atenolol

Time(hrs)	Cumulative % drug release					
	Formulation					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	5.04	4.87	4.77	4.44	4.06	3.95
2	8.83	8.62	8.29	8.15	7.96	7.31
3	13.17	12.68	12.3	12.03	11.76	11.6
4	17.34	16.8	16.15	15.93	15.72	15.34
5	21.25	21.03	20.49	20.22	19.62	19.24
6	25.75	24.61	24.34	24.01	23.58	23.2
7	29.33	28.51	28.03	27.75	27.32	27.16
8	33.39	33.07	32.42	31.98	31.55	31.17
9	37.51	37.19	36.97	36.48	35.78	35.62
10	41.8	41.31	40.93	40.5	39.68	38.81
11	45.16	44.72	44.45	44.02	43.42	43.04
12	49.33	48.9	48.52	47.65	46.84	46.51

TABLE 14: In-vitro drug release of indapamide

Time(hrs)	Cumulative % drug release					
	Formulation					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	5.18	4.73	4.28	3.83	3.6	3.38
2	9.69	9.24	8.79	8.34	7.89	7.66

Time(hrs)	Cumulative % drug release					
	Formulation					
3	13.53	13.3	12.85	12.63	12.18	11.72
4	17.14	16.69	16.24	16.01	15.78	15.33
5	20.97	20.52	20.3	19.84	19.62	18.94
6	25.26	25.03	24.58	24.36	23.9	23.00
7	29.54	29.09	28.64	28.42	27.96	27.51
8	33.6	33.38	32.93	32.25	31.8	31.12
9	37.66	37.21	36.99	36.54	35.86	35.41
10	41.27	40.82	40.37	40.15	39.69	39.47
11	46.01	45.56	44.88	44.43	43.98	43.53
12	49.62	49.39	48.72	48.27	47.59	47.36

Drug release kinetics [5, 19, 20]
Zero-order kinetics [19]

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly can be represented by the following equation:

$A_0 + k_0t = A_t$,

where A_0 is the initial amount of drug in the solution, A_0 is the amount of drug in the solution at time t and k_0 is the zero order release constant.

First-order kinetics [19]

To study the first order release rate kinetics, the release rate data were fitted to the following equation.

$\ln c = \ln c_0 - kt$,

after converting to logarithms yields,

$\log c = \log c_0 - kt / 2.303$

where c represents the fraction of drug released in time t and kt is the first-order release constant.

Higuchi's model [20]

Higuchi developed a theortical model for studying the release of water-soluble and poorly soluble drugs from a variety of matrices, including semisolid and solids.

$Q_t = K_H t^{1/2}$

where Q_t represents the fraction of drug released in time t and K_H is the Higuchi dissolution constant.

Korsmeyer-Peppas model [5]

In order to understand the mode of release of drugs from polymer matrices, the data were fitted to the following power low equation.

$Mt/M = Kt^n$,

where Mt is the drug released at time t, M is the amount of drug released at infinite time, K is a kinetic constant, and n is the diffusion exponent related to the mechanism of the release.(Table 15).

TABLE 15: N- value limits for in-vitro drug release

Release exponent(n)			Drug transport mechanism
Slab	Cylinder	sphere	
0.5	0.45	0.43	Fickian diffusion
0.5 < n > 1.0	0.45 < n > 0.85	0.43 < n > 0.85	Anomalous transport (non Fickian)
1.0	0.85	0.85	Case-II transport
> 1.0	>>1.0	>1.0	Super case-II transport

Results and Discussion

The Prepared SR matrix tablets of Atenolol and Indapamide met the standard Pharmacopoeial requirements. In the present study Atenolol and Indapamide SR matrix tablets were prepared by wet granulation process by using ingredients shown in (table 1 and table 11). A total number of six formulations were prepared. The values of Preformulation parameters evaluated were within prescribed limit and indicated good fine flow property (table 3, 4, 5 and 6). The data of evaluated tablets such as weight variation, hardness, thickness, friability, content uniformity and In-vitro disintegration time are shown in (table 12). All the formulation showed very low drug release in 0.1 N HCL (pH 1.2) and complete drug release showed in phosphate buffer at pH 6.8. Thus it can be concluded that when pH rises above pKa, rapid increase in solubility occurs. The release of Atenolol and Indapamide from tablets was slow and sustained over longer period of time. The result of dissolution studies of formulations are shown in table 13, 14 and figures 8 to 13.
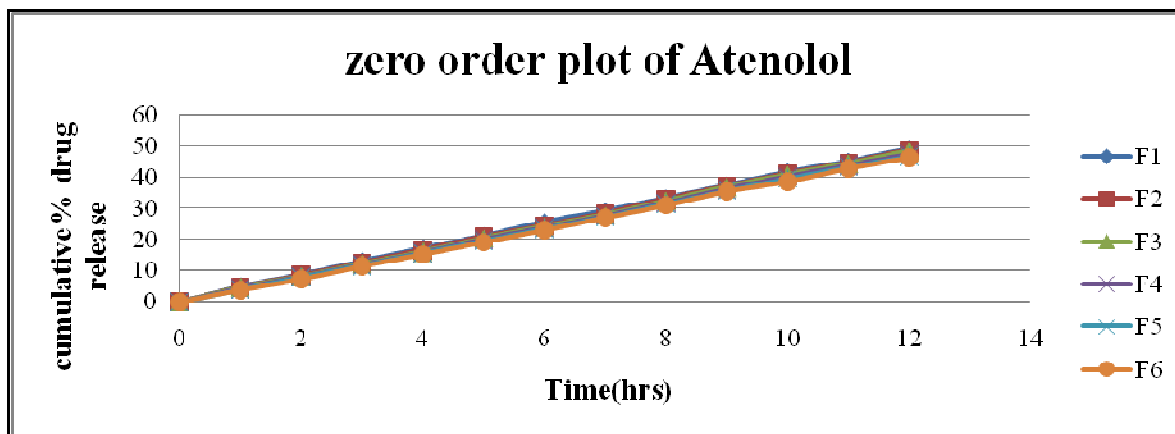

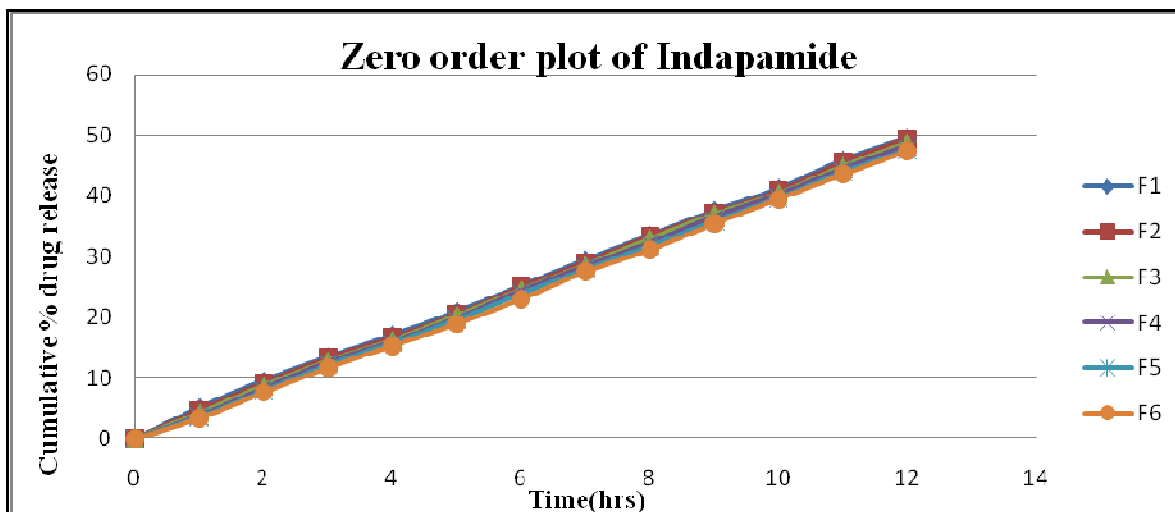Figure 8: Zero order plot of Atenolol
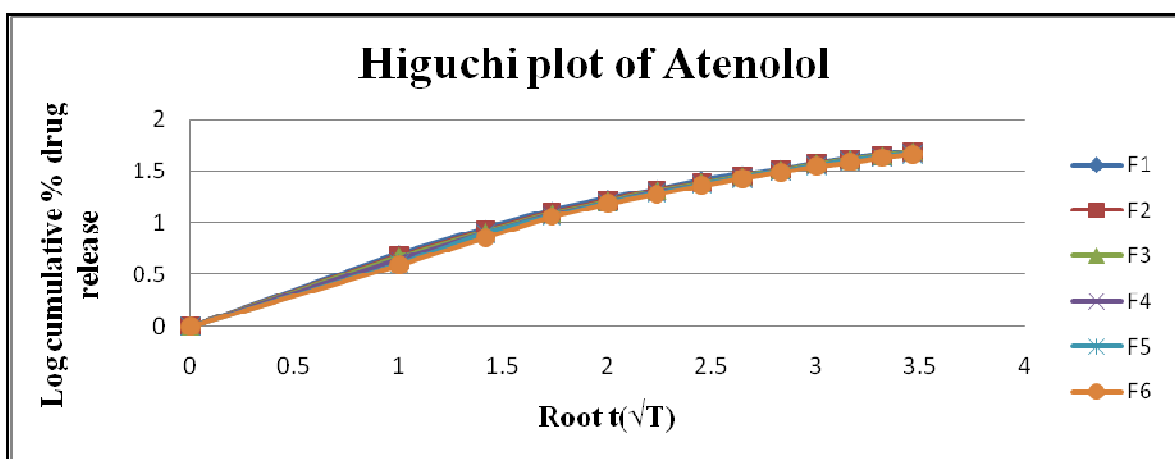
Figure 9: Zero order plot of Indapamide

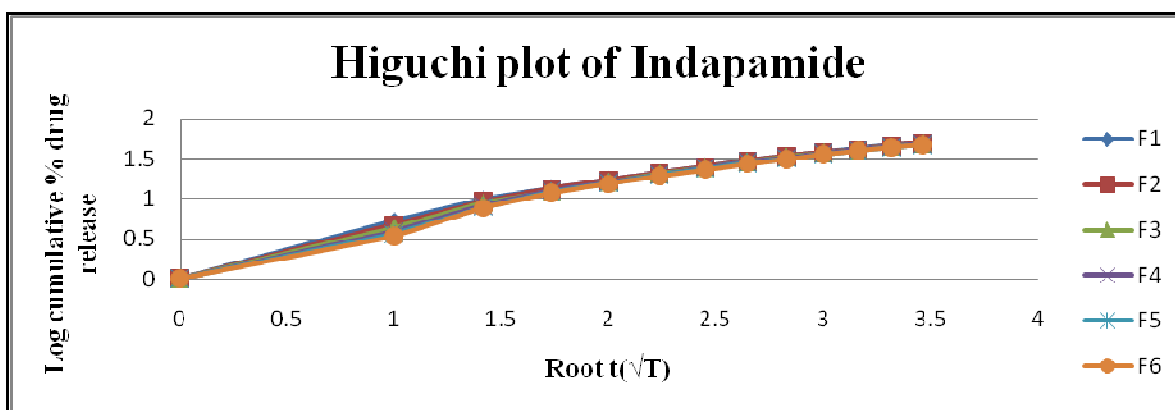Figure 10: Higuchi plot of Atenolol

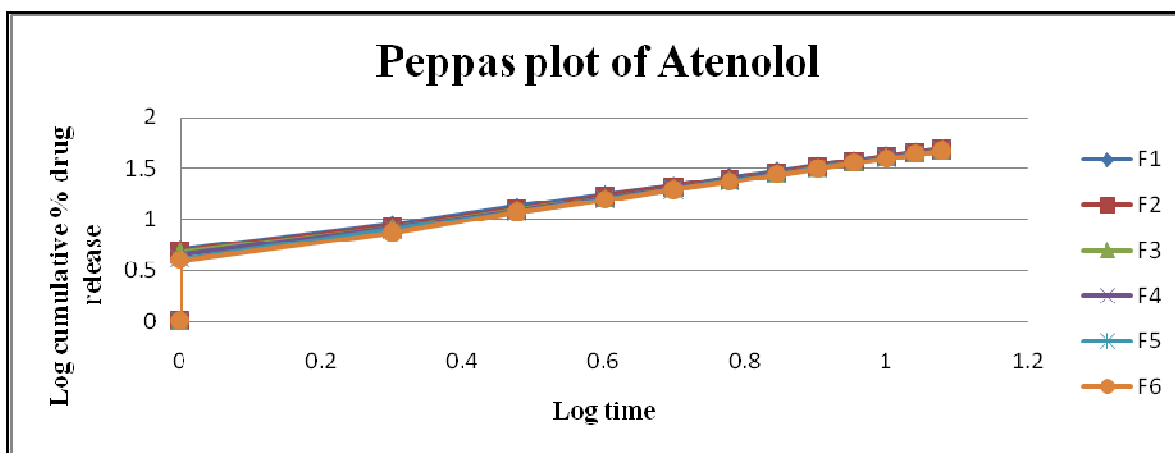Figure 11: Higuchi plot of Indapamide
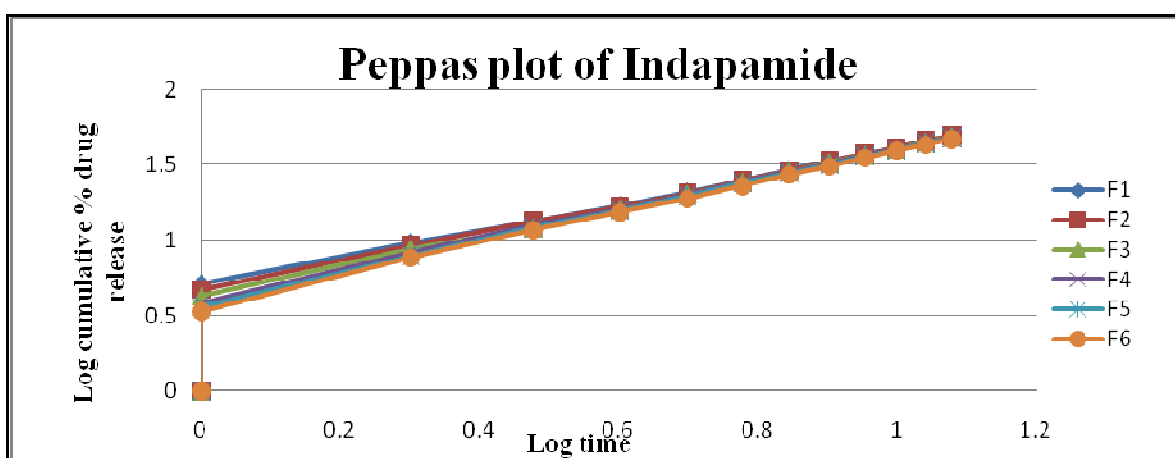
Figure 12: Peppas plot of Atenolol

Figure 13: Peppas plot of Indapamide

The drug release kinetics zero order, Higuchi, Peppas plot were constructed. For all the formulations zero order plots showed linearity with high regression coefficient values. According to 'n' values obtained from the Korsmayer Peppas plot, it may conclude that the drug release is by super case II transport. (Shown in table 16)

TABLE 16: Release kinetics results of formulations

Formula-tion	Zero order		Higuchi plot		Korsmayer Peppas plot			
	Atn	Ind	Atn	Ind	Atn	Ind	Atn	Ind
	R^2	R^2	R^2	R^2	n	R^2	n	R^2
F1	0.9995	0.9994	0.9585	0.9557	1.205	0.8877	1.1919	0.8794
F2	0.9997	0.9995	0.9626	0.9601	1.2089	0.8932	1.2087	0.8915
F3	0.9997	0.99997	0.9663	0.9659	1.2132	0.8982	1.2298	0.906
F4	0.9997	0.9998	0.9679	0.9658	1.222	0.9055	1.2466	0.9156
F5	0.9998	0.9999	0.9693	0.9680	1.2325	0.914	1.2575	0.9233
F6	0.9997	0.9997	0.9722	0.9709	1.241	0.9203	1.2673	0.9304
Zero order, Super case II transport								

Conclusion

The study was undertaken with the aim to formulate and evaluate combination therapy of Atenolol and Indapamide SR matrix tablet for treatment of hypertension using delay release agent (DCP), disintigrating agent (starch) and polymer HPMC for sustained release film coating as retarding agent.

From the above result and discussion, it is concluded that the formulation of SR matrix tablets show their slow, controlled and complete release of Atenolol and Indapamide over a period of 24 hours was obtained from SR matrix tablets of F_1 formulated and the drug was released by super case II transport.

Acknowledgements

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