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Design, development and evaluation of fast release bilayer tablets of Antihypertensive drug (Amlodipine besylate and Losartan potassium)

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Abstract

Amlodipine besylate and Losartan Potassium is Cardio vascular agent, calcium channel blocker Amlodipine belongs to the dihydropyridine (DHP) class of calcium channel blockers (CCBs), the most widely used class of CCBs. There are at least five different types of calcium channels in Homo sapiens: L-, N-, P/Q-, R- and T-type. And Losartan is a selective, competitive angiotensin II receptor type 1 (AT_1) receptor antagonist, reducing the end organ responses to angiotensin II. Losartan administration results in a decrease in total peripheral resistance (afterload) and cardiac venous retum (preload) All of the physiological effects of angiotensin II, including stimulation of release of aldosterone, are antagonized in the presence of losartan. Fast dissolving tablets are solid dosage form that contains medicinal substances and that disintegrate and dissolve rapidly without water (within seconds) when placed on the tongue. Fast dissolving tablets of Amlodipins and Losartan Potassium were prepared by direct compression method using Sodium Starch Glycolate, Ac-Di-Sol, as a super disintegrants, and controlled tablets without any super disintegrant and evaluated for hardness, friability, disintegration time, dissolution time, water absorption ratio and content uniformity. All tablets containing super disintegrates shows release of drug more than 95% within 10 minutes

Key-words: Fast release, Bilayer tablets, Antihypertensive drug

Introduction

Oral drug delivery system is considered to be one of the most convenient and commonly employed drug delivery system as it possesses some specific advantageous characteristics, such as ease of administration, least aseptic constraints and flexibility in the design of the dosage form. Another revolution towards the oral drug delivery is the modified release dosage forms which have huge advantages over immediate release formulations of the same drug. There are different methods for the designing of this modified dosage form, some of them are film coated pellets, tablets, capsules or more sophisticated and complicated delivery systems such as osmotically driven systems, systems controlled by ion exchange mechanism, systems using three dimensional printing technology and systems using electrostatic deposition technology[1-5]. The release of highly water soluble drug inherently follows near first-order diffusion with an initially high release rate.

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The enhanced release rate observed at the beginning within a short period of time and it is known as burst effect, sometimes it is undesirable as it can have some negative therapeutic impact (i.e. toxicity due to increase of the concentration of the delivered substance beyond maximum therapeutic concentration).After this burst effect, hydration and consequent swelling and/or erosion of retard polymer occurs. These phenomena control the release process but sometimes this result in a progressively slow release rate as due the increasing of the diffusion path-length, as a result of which ultimately a saturation effect is attained[6-11].

A number of factors that are used to overcome this undesirable behavior and release pattern of drug from polymeric matrix include physicochemical properties of drug (solubility, viscosity, etc.), content of drugs and polymers in matrices, drug/polymer weight ratio, route of administration, and manufacturing process[12-15].

The another new drug delivery concept is the control release of drug form the dosage form where the drug is released from the dosage form in a constant

manner in respect to time but without depending upon the initial concentration of the drug and hence the release of drug from this type of dosage form follows zero order release kinetics. This drug delivery system has been widely used as drug delivery system for the drugs having low therapeutic index to reduce the dose dumping. To alter the kinetics of drug release from inherent non-linear behavior to linear include the use of geometry factors (solid units having spherical, cylindrical, conical, biconcave, biconvex, donut shapes, hemisphere with cavity, core in cup, circular sectioned cylinder, rings, oval bi-dose divisible tablets etc.), films, erosion/dissolution controlled and swelling controlled mechanisms, non-uniform drug loading and matrix-membrane combination. A linear release profile is achieved by combining a time-dependent control of the hydration rate of the device with the reduction of tablet surface exposed to the dissolution medium. It is also possible to obtain various dissolution patterns such as multi modal, pulsatile or delayed delivery, extended release (characterized by reasonably constant rate) for different drugs by varying the formulations of layers. The major criterion for all of this application is the multi-layered system should swell gel and finally erode completely, leaving negligible residue in the gastro-intestinal tract[16-20]. The system overcomes the major disadvantage of non-linear release associated with most diffusion controlled matrix devices. Beside the above, this system also has the advantage of being compatible with conventional manufacturing methods. From the word 'Bilayer Tablet' indicates that it is a solid oral dosage form, usually round, spherical, oval or biconcave in shape and consist of one or more than one medicaments designed in a two layers system which can be suitable for combination therapy and biphasic release therapy[21-25].

Material and Methods

Calibration curve of Amlodipine Besylate:

100 mg of Amlodipine besylate was accurately weighed and dissolved in 25 ml of methanol in 100ml volumetric flask and the volume was made up to the mark using methanol, to make (1000 µg/ml) standard stock solution . Then 1 ml stock solution was taken in another 100 ml volumetric flask and further diluted in 100 ml of methanol to make (10 µg/ml) standard stock solution, then final concentrations were prepared with 0.1N HCL.The absorbance of standard solution was determined using UV/VIS spectrophotometer at 237nm.

Calibration Curve of Losartan Potassium

Accurately weighed 100mg Losartan Potassium was transferred into 100ml volumetric flask and dissolved in Small quantity of Methanol and the volume was made up with phosphate buffer pH **6.8** to give a stock solution of concentration of 1mg/ml. Further dilutions were made in the range of 2-20mcg/ml with phosphate buffer pH 6.8 and absorbance was measured at 235nm**.**

Manufacturing process of Losartan Potassium and Amlodipine Besylate Bilayer Tablets:

Losartan Part:

Sifting:

Sift the weighed quantities of Losartan Potassium, Microcrystalline cellulose plain, starch plain and Polyplasdone XL10 through Mesh 30#.

Dry Mix and Granulation:

Transfer the sifted materials and Binder solution to Granulation area. Load the sifted material into the main bowl of rapid mixer and mix it for 15 minutes

Initial Drying, Sifting and Milling:

Transfer the sifted materials into FBD main bowl. Dry the granules at 50 degrees Celsius. Sift the Semi-Dried granules through Mesh 20# and pass the retained granules through Multi-Mill fitted with 1.0 mm screen using knives forward medium speed.

Final drying and shifting:

Transfer the semidried sifted and milled granules into FBD bowl. Dry the semidried sifted granules at 50 degrees Celsius till the required LOD is achieved. Check the LOD of the granules (Limit: Between 2.0-4.0% w/w at 105 C)

Lubrication:

Sift the following materials Pregelatinised Starch, and Polyplasdone XL10 through Mesh 30#.Load the sifted dried granules along with the above sifted materials into blender and blend it for 10 minutes. Finally sift Magnesium Stearate through Mesh 60#and mix for 5 minutes.

Amlodipine Part:

Sifting:

Sift the weighed quantities of Amlodipine Besylate, Dicalcium Phosphate Anhydrous, Microcrystalline cellulose pH 102, starch 1500, sodium starch glycolate, colloidal silicon dioxide and pass through Mesh30#. Ponceau 4R Lake was passed through Mesh100# and added to the above blend.

Dry Mixing:

Load the sifted materials such as Amlodipine Besylate, Dicalcium Phosphate Anhydrous, Microcrystalline cellulose pH 102, Starch 1500, Sodium Starch
glycolate, colloidal silicon dioxide and Ponceau 4R Lake in Hexagonal blender and mix for 15 minutes

Lubrication:
Sift Magnesium Stearate through Mesh60# and add to the above mixture in the blender and mix for another 5 minutes.

Compression of Bilayer tablets
The quantity of granules for the immediate-release layer was compressed lightly using 27 stationary double rotary compression machine (Cad mach, India) using 13/32 inch circular standard plain punches. Over this compressed layer, required quantity of the other immediate release layer was placed and compressed to obtain hardness in the range of 8-12 kg/cm² to form a bilayer tablet of Immediate release of Losartan potassium and Immediate release of Amlodipine besylate. Then the compressed bilayer tablets were evaluated.

Evaluation of Granules

Bulk density
Bulk density is the ratio of the weight of the powder to the bulk volume it occupies. it is expressed in gm/ml. A weighed quantity of powder blend previously shaken to break any agglomerates formed, was introduced in to a measuring cylinder and the volume was noted.
powder blend**.**

Tapped density
A weighed quantity of powder blend previously shaken to break any agglomerates formed, was introduced in to a measuring cylinder and the volume was noted. The cylinder was placed in the tapped density apparatus and allowed to fall under its own weight on to a hard surface (USP-II), that provides fixed a drop of 3mm(±10%) at a nominal rate of 250 drops per minute is used. Tapping was continued until no further change in volume was noted.

Carr's Index
Carrs Index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 is defined as the free flowing material.

Hausner's ratio
It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density

Angle of repose
Angle of Repose is an indication of the frictional forces existing between granule particles. The maximum angle possible between the surface of the pile of granules and the horizontal plane gives the angle of repose:

Moisture content
Initially 5 g of weighed granules were taken and kept for drying at 105^0 C for a required time in a oven. Then removed and again reweighed and noted as final weight. The difference in weight was noted as moisture content.

Evaluation of tablets:

Evaluation of physical characteristics
The formulated tablets were evaluated for the following physical parameters,

Thickness
Thickness depends on die filling, physical properties of material to be compressed. There is possibility of small variation in the thickness of individual tablet in a batch. But it should not be apparent to the unaided eye. The thickness and diameter can be measured by vernier calipers.

Hardness
Tablet must possess sufficient strength or hardness and can be measured by Monsanto hardness tester. Ten tablets were randomly picked from each formulation and were evaluated for hardness and can be expressed in Kg/cm^2.

Friability
Friability can be performed in Roche friabilator, Preweighed ten tablets were introduced in the friabilator. Then the machine was operated for 100 revolutions. Tablets were dropping from a distance of six inches with each revolution. Tablets were then dusted and reweighed.

Weight variation test
Twenty tablets were selected randomly and weighed individually. Calculate average weight and compare the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in table and none deviate by more than twice the percentage.

Results and Discussion
The present research was carried out to develop a Immediate Release Bilayer tablet of Amlodipine Besylate and Losartan Potassium. Combination of Amlodipine Besylate and Losartan Potassium are indicated for the successful treatment and relief of hypertension. Prepared bilayer tablets were film coated in a conventional coating pan. Formulation characteristics such as content uniformity, hardness, friability were found to be satisfactory.
In vitro dissolution studies of bilayer tablets were conducted for 30 minutes. Samples were analyzed by HPLC. The formulation (F-8) showed acceptable pharmacotechnical properties and complied with the internal specification for weight variation, thickness,

hardness, friability, drug content and *in vitro* drug release. Reproducibility was checked by intra batch variability study and found no pronounced variation was observed.

Accelerated stability profile of bilayer tablets were found to be satisfactory. No sign of degradation was observed in HPLC analysis. Hence, it is finally concluded that, the Bilayer tablet technology can be successfully applied for Immediate-release of Amlodipine Besylate and Losartan Potassium.

Table 1: Calibration Curve of Amlodipine Besylate

Calibration Curve of Amlodipine Besylate		
S.NO	**Concentration(mcg/ml)**	**Absorbance**
1	2	0.072
2	4	0.149
3	6	0.211
4	8	0.270
5	10	0.346
6	12	0.410
7	14	0.466
8	16	0.523
9	18	0.597
10	20	0.647

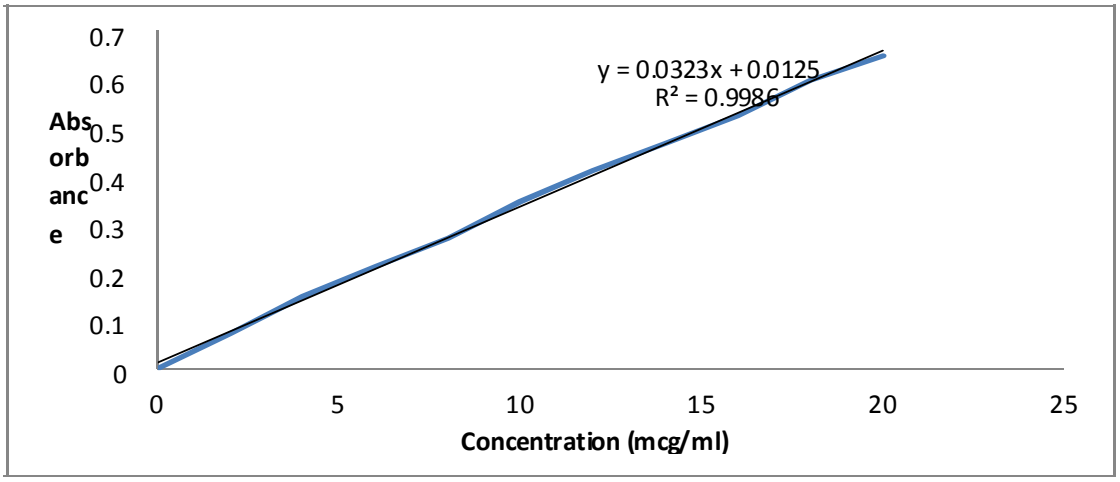

Figure 1: Calibration Curve of Amlodipine Besylate

Table 2: Calibration Curve of Losartan Potassium

Calibration Curve of Losartan Potassium		
S.NO	**Concentration (Mcg/ml)**	**Absorbance**
1.	2	0.122
2.	4	0.209
3.	6	0.341
4.	8	0.483
5.	10	0.555
6.	12	0.625
7.	14	0.751
8.	16	0.814
9.	18	0.888
10.	20	0.960

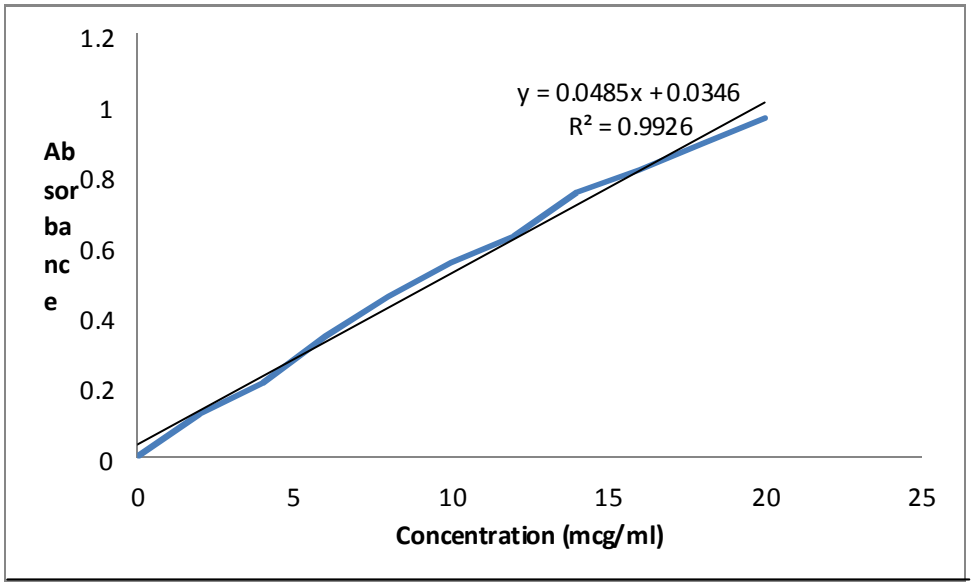

Figure 2: Calibration Curve of Losartan Potassium

Table 3: Precompression parameters for Amlodipine layer blend

FORMULATION	BULK DENSITY (g/ml)	TAPPED DENSITY (g/ml)	HAUSNER'S RATIO	CARR'S INDEX (%)	ANGLE OF REPOSE (θ)
A1	0.634±0.002	0.740±0.001	1.16±0.01	14.32±0.65	26.3º±0.98
A2	0.623±0.001	0.754±0.003	1.21±0.01	17.37±0.87	29.8 º±1.17
A3	0.578±0.002	0.722±0.004	1.25±0.03	19.94±1.11	28.8 º±0.75
A4	0.595±0.004	0.758±0.002	1.27±0.01	21.20±0.87	28.6 º±0.88
A5	0.589±0.001	0.737±0.002	1.25±0.02	20.08±0.45	28.4 º±1.24
A6	0.613±0.003	0.766±0.003	1.24±0.02	19.73±0.72	29.4 º±1.32

Table 4: Precompression parameters for Losartan layer blend

FORMULATION	BULK DENSITY (g/ml)	TAPPED DENSITY (g/ml)	HAUSNER'S RATIO	CARR'S INDEX (%)	ANGLE OF REPOSE (θ)	MOISTURE CONTENT (%)
L1	0.488±0.002	0.605±0.002	1.17±0.01	19.39±0.89	30.4 º±1.40	4.3±0.2
L2	0.479±0.003	0.604±0.006	1.25±0.01	20.60±1.12	31.7 º±1.23	4.4±0.2
L3	0.491±0.001	0.617±0.001	1.26±0.03	20.89±1.45	32.5 º±0.95	4.5±0.1
L4	0.487±0.002	0.612±0.002	1.25±0.01	20.41±1.23	31.8 º±0.89	4.2±0.2
L5	0.490±0.007	0.599±0.002	1.09±0.02	18.19±1.16	26.2 º±1.15	4.5±0.1
L6	0.479±0.008	0.605±0.001	1.26±0.01	20.82±1.31	29.9 º±1.63	4.1±0.2
L7	0.486±0.009	0.609±0.003	1.25±0.02	20.32±0.93	29.4 º±1.34	4.3±0.1
L8	0.477±0.005	0.600±0.004	1.25±0.02	20.51±0.96	30.3 º±0.90	4.2±0.1

Table 5: Post compression parameters for core bilayer tablets.

BATCH	THICKNESS (mm)	HARDNESS (kg/cm^2)	FRIABILITY %	DISENTEGRATION TIME(MINUTES)
F-1	4.09±0.011	6.4±0.57	0.22	11m 53s
F-2	4.21±0.015	7.3±0.73	0.19	9m 14s
F-3	4.32±0.014	7.8±0.34	0.13	7m 40s

F-4	4.28±0.012	8.9±0.69	0.09	7m 47s
F-5	4.24±0.011	8.5±0.76	0.15	6m 18s
F-6	4.35±0.010	6.4±0.43	0.22	6m 41s
F-7	4.26±0.011	7.9±0.67	0.18	6m 25s
F-8	4.19±0.013	8.8±0.82	0.17	5m 30s

Table 6: Post compression parameters for coated tablets.

BATCH	THICKNESS (mm)	DISENTEGRATION TIME(Minutes)	ASSAY%
F-1	4.21±0.011	10m 35s	(A)-92.32
			(L)-97.34
F-2	4.30±0.012	10m 28s	(A)-91.66
			(L)-98.15
F-3	4.43±0.015	8m 57s	(A)-90.78
			(L)-97.56
F-4	4.39±0.014	8m 42s	(A)-94.98
			(L)-96.87
F-5	4.34±0.017	7m 25s	(A)-93.71
			(L)-97.87
F-6	4.46±0.012	7m 32s	(A)-92.45
			(L)-94.79
F-7	4.37±0.011	6m 44s	(A)-94.06
			(L)-95.50
F-8	4.31±0.014	6m 45s	(A)-94.70
			(L)-96.87

Table 7: Weight Variation Test

BATCH	F1	F2	F3	F4	F5	F6	F7	F8
AVG WT (20 TAB)	362±0.71	371±0.84	364±0.71	369±0.78	358±0.63	365±0.82	370±0.68	363±0.69
% max positive deviation	+1.98	+3.23	+2.76	+1.98	+2.41	+3.14	+2.23	+2.65
% min negative deviation	-1.34	-2.75	-1.87	-2.75	-2.63	-2.25	-1.87	-1.98

Table 8: In vitro dissolution profile of Bilayer tablet F-8

Immediate Release Layer of Amlodipine Besylate			
S.NO	Time (Mins)	Amount of Drug Release (mg)	Cumulative Drug Release (%)
1.	5	3.43±0.06	73.12
2.	10	3.72±0.08	79.54
3.	15	3.84±0.14	82.17
4.	20	3.90±0.12	83.21
5.	25	3.92±0.11	83.64
6.	30	3.93±0.15	84.02
Immediate Release Layer of Losartan Potas sium			
S.NO	Time (Mins)	Amount of Drug Release (mg)	Cumulative Drug Release (%)
1.	5	37.66±0.55	77.67
2.	10	40.50±0.48	83.82
3.	15	41.22±0.37	85.05
4.	20	42.71±0.71	88.12
5.	25	43.55±0.68	89.85
6.	30	43.65±0.42	90.08

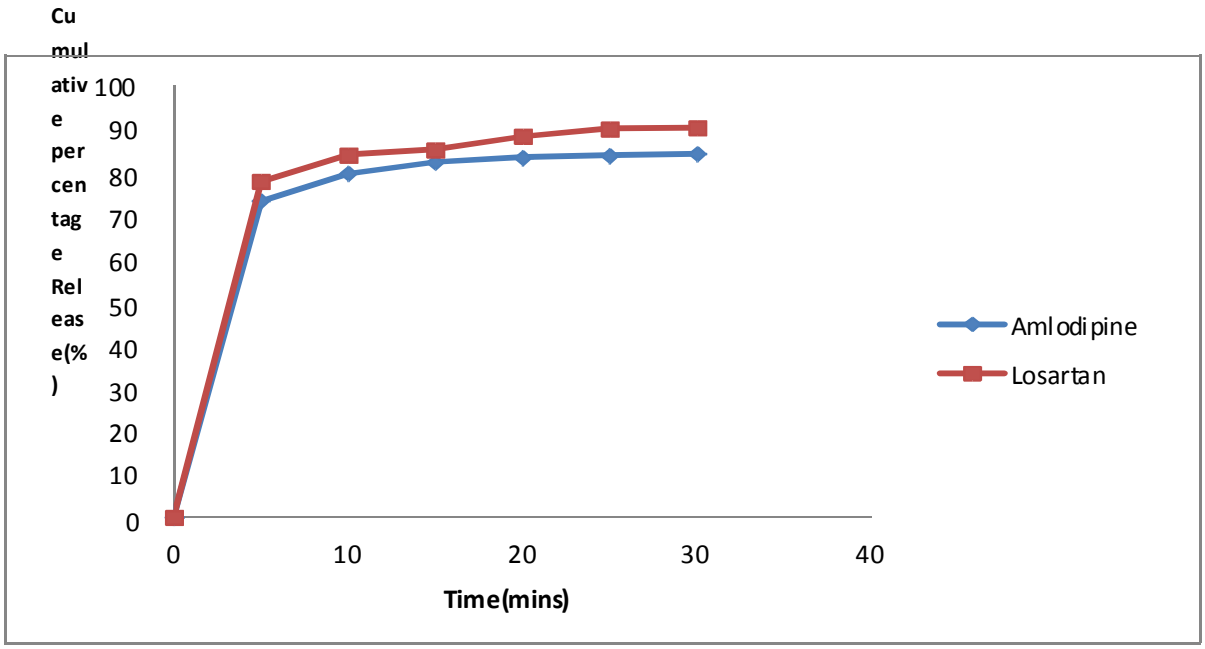

Figure 3 *In vitro* Dissolution Profile of Formulation F 8 -

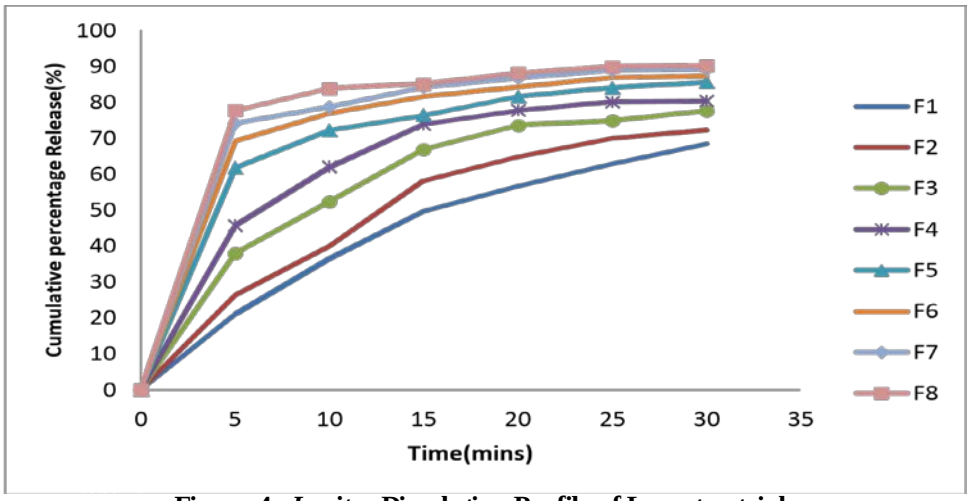

Figure 4 *In vitro* Dissolution Profile of Losartan trials

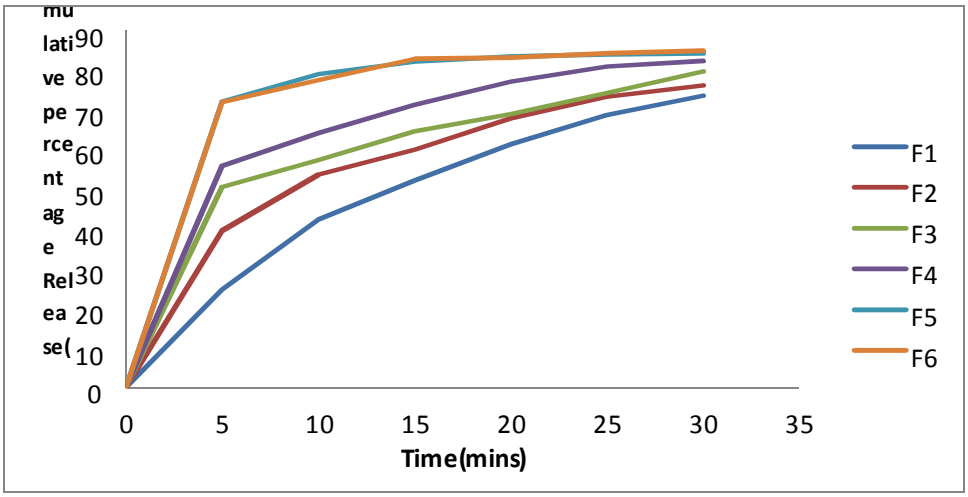

Figure 5: *In vitro* Dissolution Profile of Amlodipine trials

Table 9: Optimized Formulation Parameters- F8

S.NO	Test	Optimized Formulation (F8)
1.	Description	Yellow colour, circular, slightly, biconvex, plain, film Coated
2.	Average Weight(Mg)	363±4
3.	Identification Test Amlodipine Besylate Losartan Potassium	 Complies Complies
4.	Thickness(mm)	4.31±0.014
5.	Assay Amlodipine Besylate Losartan Potassium	 94.70% 96.87%

6.	Dissolution Amlodipine Besylate Losartan Potassium	 84.02% 90.08%

Table 10: Stability Studies

S.No	Parameters	Conditions				
		Initial	**40°C& 75% RH**	**40°C& 75% RH**	**40°C& 75% RH**	**40°C& 75% RH**
		0 Day	**1 month**	**2 month**	**3 month**	**6 month**
1	Average weight	363±5mg	363±5mg	363±5mg	363±5mg	363±5mg
2	Thickness(mm)	4.31±0.014	4.31±0.014	4.31±0.014	4.31±0.014	4.31±0.014
3	Disintegration time	6min45sec	7min17sec	7min23sec	7min20sec	7min 55 sec
4	Assay(%)	A-94.70	A-94.66	A-94.49	A-94.45	A-94.21
		L-96.87	L-96.81	L-96.74	L-96.72	L-96.50
5	Dissolution (30min)	A-84.02	A-83.98	A-83.89	A-83.86	A-83.53
		L-90.08	L-89.91	L-89.88	L-89.85	L-89.71

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