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Design and Development of Immediate Release Tablets Amlodipine Besylate by Employing Modified Superdisintegrants

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ABSTRACT

The aim and objective of the present work is to design and develop fast disintegrating tablets of Amlodipine Besylate to improve the patient compliance and desired bioavailability by selected delivery system by following immediate release mechanism. The drawbacks of the tablets can be overcome using methods involved in modified dissolving tablets, oral dissolving tablets (MDT) or orally disinter grating tablets (ODT) ; which started as an alternative oral dosage forms. To achieve successful delivery of drug , it needs to be protected from degradation, drug release to be improved and increase absorption. For this objective and to have the rapid uptake of drug in solution form by rapid disintegrating formulation to be expected to have better Therapeutic effect of both drugs in the gastrointestinal tract. The research objective of the present work understands the novel advancements that are made in oral fast disintegration preparations incorporated anti hypertensive drug like Amlodipine Besylate using combination of super disintegrants.

Keywords: Amlodipine Besylate, Disintegration, Anti - Hypertensive, Bioavailability.

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INTRODUCTION

A drug delivery system which dissolves fast, in extreme cases, is a solid tablet that dissolves or disintegrates in oral cavity without water or chewing". Many of fast-dissolving drug delivery system like films should include other excipients to mask the bad taste of the active compounds. All these are called as melt-in-mouth tablets, repi melts, porous tablets, oro-dispersible, quick dissolving or rapid disintegrating tablets[1] or immediate release tablets which makes to overcome the disadvantages of tablets like hand tremors, dysphasia occurrence in geriatric patients, the semi developed muscular systems in children and in case of bedridden, the problem of swallowing is very common phenomenon leads to very poor patient compliance[2]. Direct compression is selected as the technique where a group of ingredients can be blended, placed onto a tablet press, and made into a perfect tablet without any of the ingredients having to be changed. Powders that can be blended and com pressed are commonly referred to as *directly compressible* or as *direct-blend formulations.* The method selected is much suitable in development of solubility of poorly water soluble drugs and in improving the bioavailability of many drugs[3].

Amlodipine Besylate belongs to the dihydropyridine (DHP) class of calcium channel blockers (CCBs), the most widely used class of Calcium Channel Blockers. Amlodipine Besylate is slowly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached 6-12 hour following oral administration. Its estimated bioavailability is 64-90%. Absorption is not affected by food[4].

MATERIALS AND METHOD

Materials:

Amlodipine Besylate is purchased from Yarrow Chem Products, Mumbai. All the used other chemicals included are off to be Laboratory grade.

Formulation of Tablets using Co processed Super Disintegrants by Direct Compression Method

Tablets were prepared by using Direct Compression method consisting super disintegrants collected from different sieves co processed using different solvents in suitable concentration and ratios as shown in the given table. All the ingredients (except granular directly compressible excipients) were passed through # 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 150mg using 7 mm round flat punches on Single-station rotary tablet machine .

Table 1: Tablets prepared by Co processed Super Disintegrants

Ingredients (mgs)	Weight taken (mg)											
	FA1	FA2	FA3	FA4	FA5	FA6	FA7	FA8	FA9	FA10	FA11	FA12
Amlodipine Besylate	10	10	10	10	10	10	10	10	10	10	10	10
CCS:CP (1:1)(6%)	9	9	-	-	-	-	9	9	-	-	-	-
CP:SSG (1:1)(6%)	-	-	9	9	-	-	-	-	9	9	-	-
SSG:CCS (1:1)(6%)	-	-	-	-	9	9	-	-	-	-	9	9
MCC	93	93	93	93	93	93	93	93	93	93	93	93
Lactose	34	34	34	34	34	34	34	34	34	34	34	34
Talc	2	2	2	2	2	2	2	2	2	2	2	2
MgO	2	2	2	2	2	2	2	2	2	2	2	2

- FA1-FA6 consists of Super Disintegrants Co processed using Acetone as solvent.
- FA7-FA12 consists of Super Disintegrants Co processed using Ethanol as solvent
- FA1, FA3 ,FA5,FA7,FA9,FA11 – Co Processed Super Disintegrants collected from sieve no 24 where large amount retained
- FA2,FA4,FA6,FA8,FA10,FA12 - Co Processed Super Disintegrants collected from sieve no where large amount retained 66

Determination of Pre- Compression Characteristics[5-6]

The following Preformulation studies were performed for Amlodipine Besylate formulations:

Angle of Re pose:

For a burette stand a funnel was fixed upto a particular height. A graph sheet was placed under the funnel which was on the table. The powdered form of the drug was passed through funnel up to it forms a pile. The pile radius was noted . The Angle of repose of the material was calculated by using the formula.

Angle of repose $\theta = \tan^{-1} H/r$

Where, H = height of the pile, and r = radius of the pile.

Determination of Densities:

Apparent Bulk Density:

The bulk density, as a measure used to describe packing materials or granules, was determined by transferring the accurately weighed amount of powder sample to the graduated cylinder with the aid of a funnel. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated.

Tapped Density:

Weighed powder sample was transferred to a graduated cylinder and was placed on the tapped density test apparatus, was operated for a fixed number of taps (100). The tapped density was determined as the ratio of weight of sample to tapped volume.

Density = Mass/ Volume

Carr's Index (% Compressibility):

Based on the apparent bulk and tapped density, the percentage compressibility of the bulk drug was determined by using the following formula.

% compressibility = Tapped density – Bulk density/ Tapped density

Hausner's Ratio:

The ratio of tapped density to the bulk density of the powders is called the Hausner's ratio.

Dispersibility:

Weigh approximately about 1g of sample. the material was droped from a total height (610mm) on to a tarred watch glass(dia-120mm) through a hallow cylinder placed vertically 102mm above the watch glass. The cylinder was secured to a support-stand by using support rings above and below the cylinder. The drop point is approximately 178mm vertically above the top of cylinder. The material lanned within the watch glass is weighed. Any loss of powder during the fall was the result of dispersion. The percent dispersibility was caluculated using the formula

$$\text{Dispersibility}(\%) = \frac{weightofpowerinwatchglass}{initialweightofsample} \times 100$$

Porosity (€):

Porosity of the compound is determined by liquid dispersion method

$$(€) = \frac{bulkvolume - true\ volume}{bulk\ volume}$$

Evaluation tests[7-8]

All the formulations are subjected to evaluation for Hardness, Friability, Weight Variation Uniformity of Dispersion, Thickness, Disintegration Time, Wetting Time , Drug Content and *In-vitro* Drug Release.

Hardness:

Pfizer hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the plungers, and the handle was pressed, the force of the fracture was recorded.

Friability:

Two tablets were accurately weighed and placed in the friabilator (Electrolab. EF-2 Friabilator) and operated for 100 revolutions. The tablets were de-dusted and reweighed. The tablets that loose less than 1% weight were considered to be compliant.

Weight Variation:

10 tablets were selected randomly from the lot and weighed individually to check for weight variation.

Thickness and Diameter:

The thickness and diameter of 4 tablets were recorded during the process of compression using Vernier calipers.

Uniformity of dispersion:

2 tablets were placed in 100 ml water and stirred gently until completely dispersed. A smooth dispersion was obtained which passed through a sieve screen 710mcm (sieve number 22).

Wetting time:

A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5cm) containing 5 ml of distilled water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds.

Disintegration test:

Tablets were taken and introduced one tablet in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a 1-liter beaker and the time of disintegration was recorded. To discriminate between the formulations disintegration was done at room temperature and disk was not used for the study.

Drug Content:

Standard graph for Amlodipine Besylate:

Preparation of 0.1N Hcl

0.85ml concentrated hydrochloric acid was dissolved in 500ml of distilled water.

Instrument

Elico UV-Visible Spectrophotometer SL120.

Principle

Amlodipine Besylate showed maximum absorbance at 237 nm in 0.1N Hydrochloric acid and obeyed Beer's law.

Procedure

Stock solution

Weighed quantity of Amlodipine Besylate (50mg) was dissolved in 0.1 N HCl as buffer and the volume made up to 50ml with the same.

S.S I ⇒1000 mcg/ml.

10ml of Stock solution I was further diluted with 100ml of 0.1 N HCl as buffer to get a working standard

S.S I ⇒100mcg/ml

Aliquots of 10,20,30,40 & 50 µg/ml of stock solution were pipetted into 50ml volumetric flask and the volume was made upto 50ml with 0.1 N HCl. The absorbance was measured at 237 nm against reagent blank

Ten tablets from each formulation were taken, crushed and mixed. From the mixture 15 mg of Amlodipine Besylate equivalent of mixture was extracted thoroughly with 100 mL of 0.1N Hcl. The amount of drug present in each extract was determined using UV spectrophotometer at 237 nm. This procedure was repeated thrice and this average was chosen.

***In-Vitro* Drug Release studies of Amlodipine Besylate:**

The in vitro dissolution study was carried out in the USP dissolution test apparatus (EDISON-[ESI-06] Dissolution tester USP) type 2 (paddle). 900 ml of the dissolution medium 0.1 N Hcl (P^H 1.2) was taken in covered vessel and the temperature was maintained at 37 ± 0.5 ^{o}C. The speed of the paddle was set at 75 rpm. Sampling was done every one min interval. For each sample 5 ml of the dissolution medium was withdrawn and the same amount of dissolution medium at 37^{o}C was replenished to the dissolution medium. The % absorbance was determined.

For the best Formulations as per the FDA Dissolution criteria for medium.

The *In-vitro* dissolution study was carried out in USP dissolution test apparatus type 2 M (paddle)

Dissolution Medium : 900ml of

0.1N HCL, : To stimulate gastric environment

P^H 4.5 Acetate Buffer, : To stimulate drug release in the upper part of Duodenum

P^H 6.8 phosphate Buffer : To stimulate drug release in the intestinal Environment

Purified Water

Temperature : 37 ± 0.5 ^{o}C

RPM : 75

Tablets taken : 6 tablets were weighed & taken for study

Volume withdrawn &replaced : 5 ml every five minutes.

Lamda max : 237 nm

Stability Studies

Stability studies were performed with FA3 as per ICH guidelines for 3 months at 40°C ± 2°C / 75% RH ± 5%. Samples were withdrawn at regular intervals and evaluated for change in *in vitro* drug release pattern, hardness, and disintegration time.

***In-vivo* safety and pharmacokinetic study of Amlodipine Besylate Tablets**

Chromatographic system:

High pressure Liquid chromatography (Schemadzu HPLC Class VP series) and C-18 Column (250mm x 4.6 mm) particle size 5 µm . The HPLC system was equipped with the soft ware Class-VP series version 5.03.

Preparation of mobile phase for Amlodipine Besylate:

HPLC grade Water, Methanol and acetonitrile were filtered through 0.2m membrane filter and de aerated with the helium spurge for 15 minutes before use pumped through solvent reservoir to column at flow rate of 0.8ml/min yielded a column back pressure 200-225 kg/cm [74, 75]. The column temperature was maintained at 40^0C. The volume of 20µl was injected in to loop.

Extraction procedure and analytical method validation in rat plasma for pure drug

10 mg of drug was dissolved in methanol .The prepared serial dilutions (2, 4, 6, 8, 10 µL) were used to establish a calibration curve (RPHPLC) using blank plasma as a standard. The samples were evaluated for linearity statistically for its best fit [76].

Study design

The present study was agreed by the Institutional Animal Ethical Committee (IAEC) license no:(1032/AC/07/CPCSEA). Wistar rats weighing 150-200g and maintain normal temperature at 25^0C and three rats per cage and stabilized for one week. The rats were allowed to approach to water for 12hr before and during experiment.

Extraction of procedure and analytical method validation in rat plasma:

Rats were classified into Two groups with 6 rats in each group.

Group I: control was treated with distilled drinking water followed by normal saline daily by oral gavage.

Group II: Up to treatment with drug these were treated in a manner similar to Group I thereafter treated with Amlodipine Besylate tablets from the following time points:0, 2, 5, 7, 9, 11, 14, 16, 18, 21 and 24 h . Centrifuged the heparinized blood samples at 1000 *g* for 10 min in a cooling centrifuge, and the plasma separated and transferred to micro centrifuge tubes for storage at -20^0C.Frozen plasma samples were thawed. A sample 0.2mL was transferred into a glass tube lined with a Teflon cap, to it and add 0.2mL of methanol. The mixture was vortexed for10 min and

then centrifuged at 1000 g for 15min. Dry the supernatant under a stream of nitrogen and resuspended in 0.1mL mobile phase, vortexed for 3 min and centrifuged at 1000 *g* for 5 min; 0.02 mL of the subsequent supernatant was used to HPLC for analysis of Drugs as described below[80.81,82].

Pharmacokinetic Analysis:

Pharmacokinetic parameters were calculated by noncompartment analysis based on the statistical moment theory using PK1,PK2 MS excel function such as maximum plasma concentration(C_{max}) , and time of maximum concentration(T_{max}) were obtained directly from the Plasma concentration-time plots. Half life ($t_{1/2}$) ,Elimination rate constant (h^{-1}) , AUC $_{0-t}$, AUC $_{0-inf}$, AUMC $_{0-t,}$ AUMC $_{0-inf}$, and MRT mean residence time (MRT) was calculated as AUMC/AUC .All the results were expressed in mean ± SD.

Experimental Results:

Table 2 : Calibration curve of Amlodipine Besylate

Vol. made upto(ml)	Conc. (µg/ml)	Absorbance(nm) Mean (± SD), n=3
50	10	0.205 ± 0.002
50	20	0.358±0.021
50	30	0.551±0.034
50	40	0.734±0.041
50	50	0.943±0.056

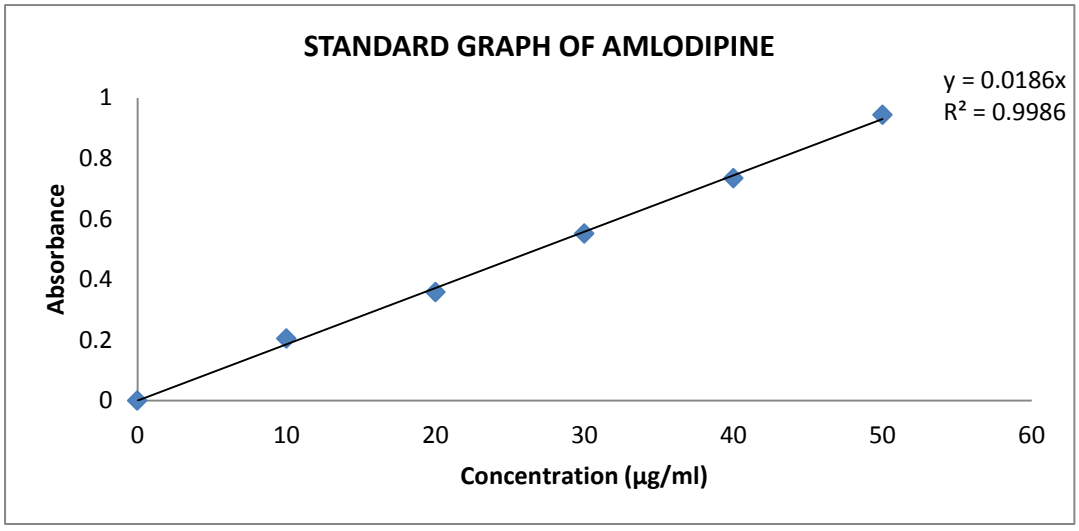

Figure 1 : Calibration Curve of Amlodipine Besylate

Table 3: Pre Compression Results for FA1 to FA12 (Formulations containing Co-Processed superdisintegrants in mixture and Compressed by Direct Compression Technique)

Parameters	Acetone Co- Processed Formulations						Ethanol Co- Processed Formulations					
	FA1	FA2	FA3	FA4	FA5	FA6	FA7	FA8	FA9	FA10	FA11	FA12
Angle of repose (degrees)	26.32 ±0.336	25.36 ±0.122	26.38 ±0.064	28.36 ±0.057	28.36 ±0.057	26.42 ±0.167	24.7 ±0.012	21.34 ±0.025	20.50 ±0.30	23.50 ±0.125	22.25 ±0.035	21.25 ±0.04
Bulk density (gm/cc)	0.39 ±0.39	0.36 ±0.065	0.41 ±0.086	0.33 ±0.008	0.32 ±0.004	0.38 ±0.0076	0.24 ±0.026	0.27 ±0.033	0.30 ±0.030	0.27 ±0.020	0.29 ±0.03	0.28 0.01
Tapped Density (gm/cc)	0.45 ±0.32	0.42 ±0.16	0.48 ±0.09	0.39 ±0.11	0.38 ±0.21	0.44 ±0.43	0.25 ±0.04	0.26 ±0.026	0.32 ±0.15	0.29 ±0.02	0.316 ±0.0202	0.29 ±0.017
Porosity(%)	21 ±0.577	32.33 ±0.666	28 ±0.288	35.66 ±0.141	35.3 ±0.230	25.33 ±0.342	6.6 ±0.05	6.6 ±0.070	4.7 ±0.015	6.2 ±0.015	6.6 ±0.32	3.0 ±0.45
Carr's index	1.15 ±0.45	1.16 ±0.66	1.17 ±0.38	1.14 ±0.54	1.14 ±0.65	1.15 ±0.017	1.07 ±0.01	1.07 ±0.01	1.06 ±0.030	1.07 ±0.02	1.06 ±0.01	1.03 ±0.021
Hausners Ratio	14.6 ±0.066	20.66 ±0.664	10.33 ±0.333	12 ±0.318	11.16 ±0.118	20.33 ±0.331	17.14 ±0.015	15.23 ±0.321	14.5 ±0.160	13.16 ±0.160	13.12 ±0.160	12.23 ±0.318
Dispersibility (%)	74.20 ±0.021	78.52 ±0.03	84.56 ±0.044	91.24 ±0.022	87.21 ±0.031	82.03 ±0.19	84.56 ±0.05	91.14 ±0.03	91.08 ±0.04	88.52 ±0.03	84.31 ±0.021	91.21 ±0.021

Table 4: Post Compression Results for FA1 to FA12 (Formulations containing Co-Processed superdisintegrants in mixture and Compressed by Direct Compression Technique)

Parameters	Acetone Co- Processed Formulations						Ethanol Co- Processed Formulations					
	FA1	FA2	FA3	FA4	FA5	FA6	FA7	FA8	FA9	FA10	FA11	FA12
Hardness(kg/cm^2) (±SD), n=3	3.8 ±0.107	3.7 ±0.091	4.2 ±0.224	4.42 ±0.224	4.3 ±0.235	4.9 ±0.455	3.5 ±0.0105	3.4 ±0.21	3.9 ±0.14	4.1 ±0.07	4.0 ±0.47	4.4 ±0.24
Friability (%) (±SD), n=3	0.89 ±0.065	0.92 ±0.108	0.87 ±0.063	0.93 ±0.167	0.94 ±0.118	0.98 ±0.40	0.91 ±0.20	0.93 ±0.54	0.89 ±0.47	0.92 ±0.05	0.95 ±0.402	0.72 ±0.71
Weight variation (mg) (±SD), n=20	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes
Uniformity of Dispersion	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes
Thickness (mm)	3.0	3.5	3.2	3.6	3.5	3.5	3.3	3.1	3.1	3.3	3.2	3.4

(±SD), n=4	±0.083	±0.083	±0.085	±0.090	±0.088	±0.089	±0.303	±0.021	±0.47	±0.49	±0.201	±0.28
Disintegration Time(sec)	20.3	23	21	27	22.6	28	25	27	26	26	24	25
	±1.45	±1.44	±1.15	±1.52	±1.57	±0.33	±0.54	±1.2	±0.75	±0.85	±0.58	±1.42
Wetting Time (Sec)	43	44	40	46	45	46	44	49	41	43	44	45
	±1.34	±1.63	±1.32	±1.37	±1.78	±1.32	±1.47	±1.65	±1.41	±1.32	±1.21	±1.14
Drug content (%)	97.38	99.3	98.3	99.6	98.5	98.9	99.5	98.3	99.4	98.7	98.3	98.8
	±1.64	±1.55	±1.39	±1.71	±1.65	±1.81	±1.49	±1.5	±1.78	±1.76	±1.12	±1.41

Table 5: Drug Release Studies for FA1 to FA12 in Water (Formulations containing Co processed superdisintegrants in mixture)

Time (min)	**Acetone co-processed formulations**						**Ethanol co-processed formulations**						**Market Formula (Amditor)**	**Similarity factor *f2***
	FA1	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**	**FA9**	**FA10**	**FA11**	**FA12**		
5	29.02 ±0.23	20.04 ±0.35	21.58 ±0.25	25.82 ±0.69	20.67 ±0.65	12.27 ±0.58	16.11 ±0.56	18.5 ±0.58	26.02 ±0.58	21.7 ±0.47	22.5 ±0.57	28.4 ±0.45	21.2 ±0.356	41.85
10	34.21 ±0.32	27.05 ±0.25	28.01 ±0.36	36.61 ±.87	21.48 ±0.47	25.03 ±0.54	29.35 ±0.74	25.7 ±0.25	34.3 ±0.14	25.3 ±0.41	26.4 ±0.47	31.4 ±0.23	28.34 ±0.369	
15	41.0 ±0.47	35.68 ±0.45	34.97 ±0.47	40.90 ±0.97	28.72 ±0.17	28.6 ±0.32	30.02 ±0.17	27.8 ±0.47	39.1 0±.14	31.7 ±0.74	31.3 ±0.14	34.3 ±0.21	37.20 ±0.569	
20	46.5 ±0.21	46.27 ±0.23	42.61 ±0.47	43.81 ±0.74	32.24 ±.72	38.9 ±0.41	32.4 ±0.47	34.1 0±.36	41.07 ±0.45	38.02 ±0.41	37.2 ±0.32	47.8 ±0.28	42.69 ±0.789	
25	53.23 ±0.23	47.04 ±0.21	47.20 ±0.47	46.13 ±0.25	37.35 ±0.38	40.3 ±0.47	36.28 ±0.87	35.6 ±0.54	44.5 ±0.32	40.6 ±0.74	44.8 ±0.58	49.5 ±0.45	46.23 ±0.654	
30	53.38 ±0.14	50.23 ±0.04	51.32 ±0.32	51.12 ±0.25	48.08 ±0.69	41.2 ±0.45	47.05 ±0.47	38.4 ±0.45	46.3 ±0.41	43.9 ±0.47	49 ±0.27	50.9 ±0.45	57.12 ±0.325	

Note : No Similarity exists between Market formula and Formulations

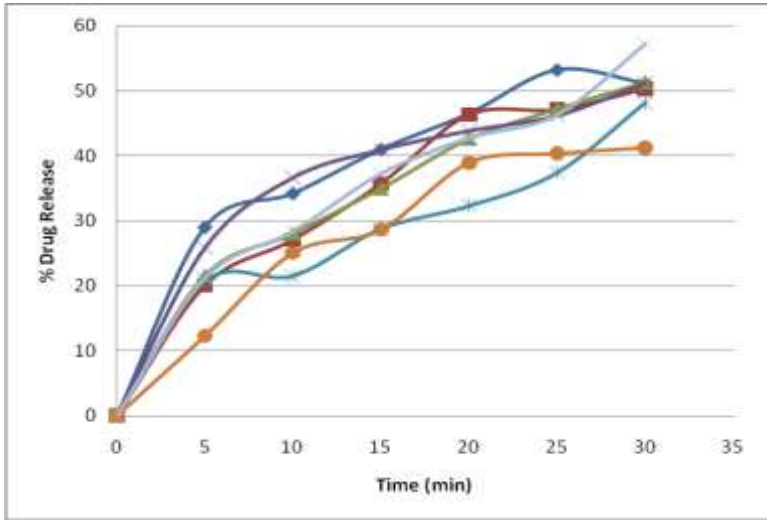

Figure 2: Drug Release Studies of FA1 to FA6 in water

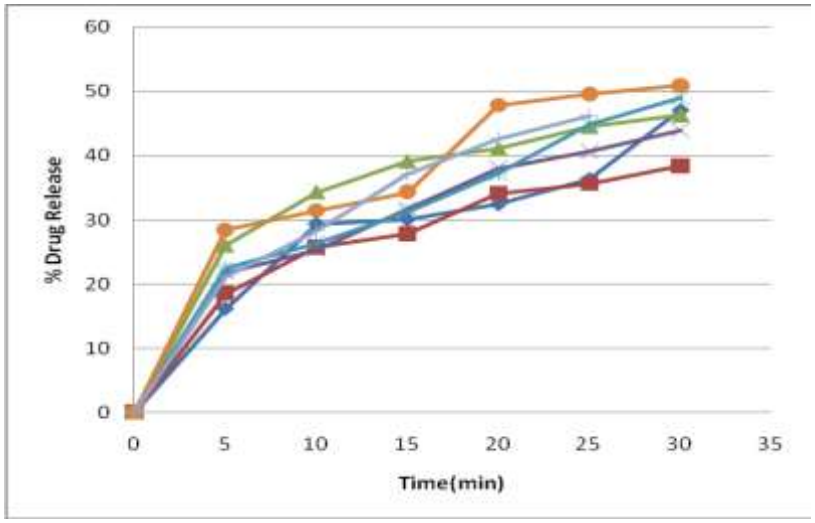

Figure 3: Drug Release Studies of FA7 to FA12 in water

Table 6: Drug Release Kinetics for FA1 to FA12 in Water (Formulations containing Co processed superdisintegrants in mixture)

	Acetone co-processed formulations						Ethanol co-processed formulations						Marketed Formula
Parameters	**FA1**	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**	**FA9**	**FA10**	**FA11**	**FA12**	
T50(min.sec)	28.23	29.41	29.54	29.68	31.3	38.7	35.6	41.2	33.4	41.3	31.4	29.65	27.99
T90(min.sec)	58.65	58.15	57.15	58.65	62.6	74.9	64.7	83.9	67.1	72.9	59.6	60.9	56.29
K µg/ml	2.303	1.84	2.7	1.01	1.84	9.5	0.23	0.59	0.32	2.98	1.01	1.28	1.32

Table 7: Drug Release Studies for FA1 to FA12 in 0.1 N Hcl (Formulations containing Co processed superdisintegrants in mixture)

Time (min)	Acetone co-processed formulations						Ethanol co-processed formulations						Marketed Formula Amditor	Similarity Factor *f2*
	FA1	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**	**FA9**	**FA10**	**FA11**	**FA12**		
5	51.21 ±0.21	37.04 ±0.25	28.58 ±0.14	34.63 ±0.47	36.74 ±0.44	35.27 ±0.36	36.11 ±0.63	31.36 ±047	44.82 ±0.32	49.10 ±0.41	39.28 ±0.45	49.7 ±0.99	68.4 ±0.356	
10	65.23 ±0.31	65.05 ±0.25	58.01 ±0.36	50.42 ±0.69	47.48 ±0.53	44.03 ±0.35	49.35 ±0.13	47.93 ±0.93	55.89 ±0.77	54.4 ±0.36	59.6 ±0.25	60.8 ±0.39	78.34 ±0.369	
15	88.38 ±0.41	78.68 ±0.36	67.97 ±0.29	66.55 ±0.49	59.50. ±0.33	53.92 ±0.69	51.49 ±0.92	51.97 ±0.44	64.95 ±0.39	59.30 ±0.26	75.6 ±0.69	69.9 ±0.11	89.2 ±0.569	100.32

20	91.5 ±0.69	84.27 ±0.92	78.6 ±0.61	75.94 ±0.25	79.24 ±0.65	56.82 ±0.36	65.93 ±0.19	61.26 ±0.81	75.68 ±0.36	64.8 ±0.22	84.6 ±0.91	82.6 ±0.33	90.69 ±0.789	
25	93.49 ±0.62	85.04 ±0.35	92.20 ±0.69	83.96 ±0.56	82.35 ±0.36	78.59 ±0.44	82.28 ±0.66	82.79 ±0.63	84.6 ±0.99	70.7 ±0.70	89.5 ±0.39	89.9 ±0.21	92.2 ±0.654	
30	94.9±0.25	96.81 ±0.36	99.58 ±0.69	97.2 ±0.36	96.02 ±0.15	91.3 ±0.63	93.34 ±0.75	96.48 ±0.39	97.3 ±0.24	97.2 ±0.31	97.9 ±0.33	98.5 ±0.99	96.4 ±0.325	

Note: Similarity exists between Market formula and Formulations

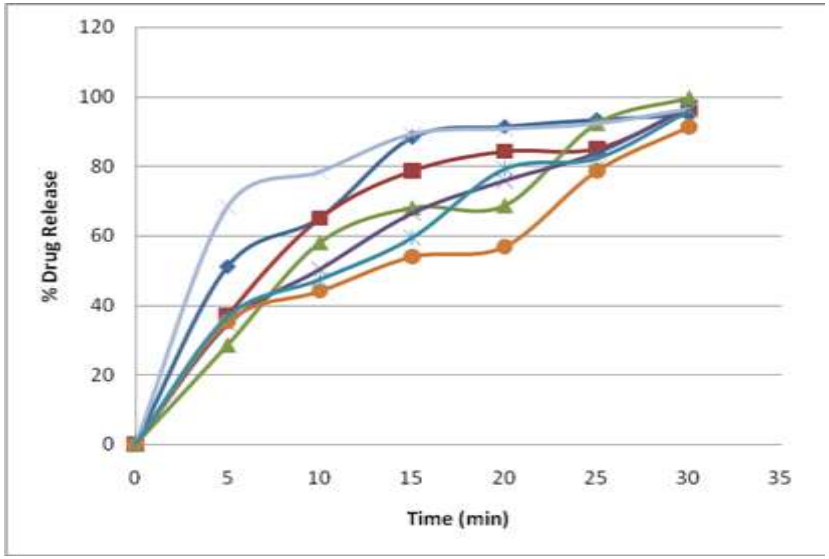

Figure 4: Drug Release Studies of FA1 to FA6 in 0.1N Hcl

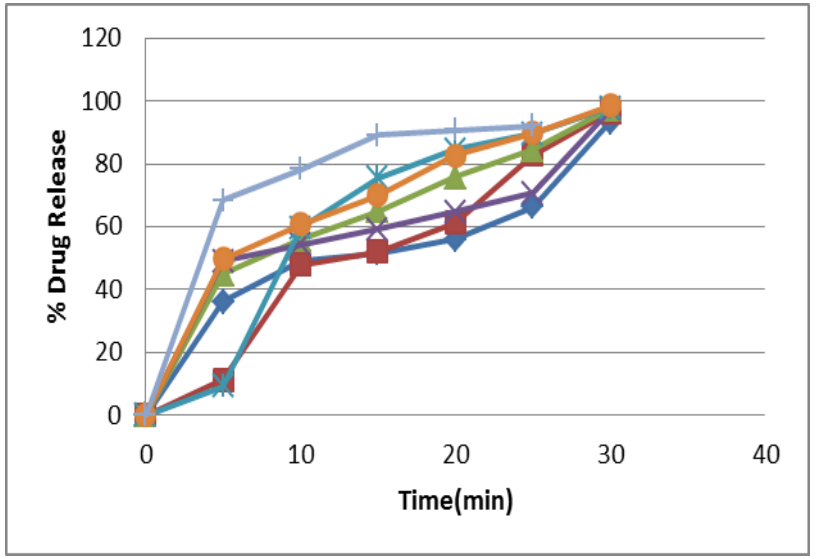

Figure 5: Drug Release Studies of FA7 to FA12 in 0.1N Hcl

Table 8: Drug Release Kinetics for FA1 to FA12 in 0.1 N Hcl (Formulations containing Co Processed superdisintegrants in mixture)

	Acetone co-processed formulation						Methanol co-processed formulations						Marketed formula
Parameters	**FA1**	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**	**FA9**	**FA10**	**FA11**	**FA12**	
T50(min.sec)	4.8	6.74	8.6	9.9	12.6	13.9	14.5	14.43	8.94	9.19	8.38	5.03	3.65
T90(min.sec)	19.6	28.7	21.6	28.8	29.1	28.8	29.4	29.1	28.4	29.3	25.1	25.0	19.13
K µg/ml	0.91	0.35	6.25	3.60	1.43	10.02	4.76	10.73	4.10	2.42	2.25	3.36	2.38

Table 9: Drug Release Studies for FA1 to FA12 in Acetate Buffer P^H 4.6 (Formulations containing Co Processed superdisintegrants in mixture)

Time (min)	**Acetone co-processed formulations**						**Methanol co-processed formulations**						**Marketed Formula Amditor**	**Similarity factor *f2***
	FA1	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**	**FA9**	**FA10**	**FA11**	**FA12**		
5	35.8 ±0.182	31.38 ±0.214	30.15 ±0.21	32.7 ±0.37	20.5 ±0.22	15.36 ±0.37	25.2 ±0.41	40.2 ±0.51	19.4 ±0.21	21.7 ±0.37	45.3 ±0.21	15.47 ±0.28	43.60 ±0.356	75.53
10	50.15 ±0.19	49.76 ±0.58	48.9 ±0.37	50.7 ±0.4	33.1 ±0.18	29.5 ±0.21	38.06 ±0.05	49.3 ±0.19	33.4 ±0.34	42.9 ±0.21	64.8 ±0.37	33.09 ±0.34	52.34 ±0.369	
15	55.92 ±0.25	58.25 ±0.45	64.86 ±0.24	56.0 ±0.21	50.9 ±0.11	48.3 ±0.12	49.5 ±0.21	64.9 ±0.23	66.02 ±0.78	49.3 ±0.58	79.9 ±0.24	40.7 ±0.27	79.24 ±0.569	
20	65.29 ±0.55	73.5 ±0.56	80.59 ±0.96	69.8 ±0.32	55.1 ±0.56	54.43 ±0.23	51.95 ±0.63	82.5 ±0.32	85.5 ±0.47	66.2 ±0.63	88.9 ±0.32	49.3 ±0.45	88.63 ±0.789	
25	79.7 ±0.21	86.28 ±0.32	97.43 ±0.35	84.9 ±0.88	85.5 ±0.85	73.02 ±0.12	84.5 ±0.85	93.8 ±0.63	98.9 ±0.45	89.5 ±0.52	98.7 0±.23	80.4 ±0.32	91.21 ±0.654	
30	98.5 ±0.32	96.2 ±0.32	98.93 ±0.12	94.8 ±0.55	95.4 ±0.14	87.8 ±0.66	94.7 ±0.44	95.5 ±0.47	96.3 ±.17	96.9 ±0.63	97.3 ±0.58	94.7 ±0.25	95.42 ±0.63	

Note: Similarity exists between Market formula and Formulations

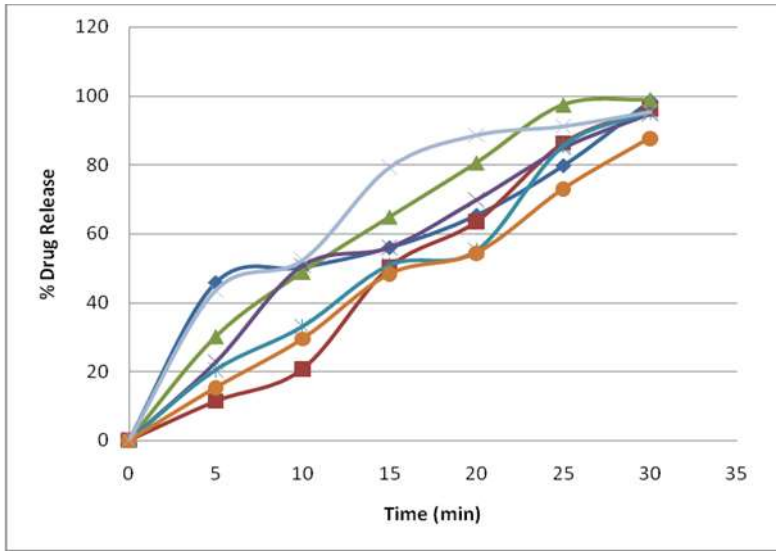

Figure 6: Drug Release Studies of FA1 to FA6 in Acetate Buffer P^H 4.6

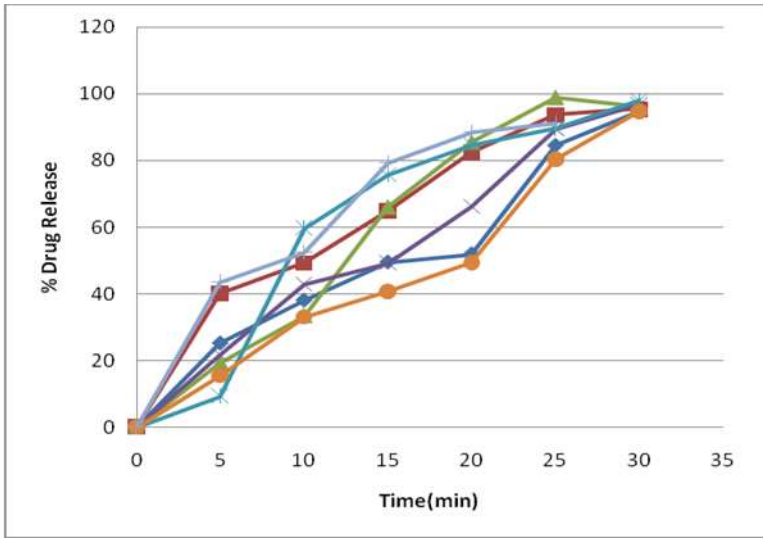

Figure 7: Drug Release Studies of FA7to FA12 in Acetate Buffer P^H 4.6

Table 10: Drug Release Kinetics for FA1 to FA12 in Acetate Buffer P^H 4.6 (Formulations containing Co Processed superdisintegrants in mixture)

	Acetone co-processed formulations						Methanol co-processed formulations						Marketed Formula
Parameters	**FA1**	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**	**FA9**	**FA10**	**FA11**	**FA12**	
T50(min.sec)	5.45	21.96	8.29	11.01	12.19	16.27	10.2	6.21	12.88	11.52	5.51	16.16	5.73
T90(min.sec)	28.23	26.07	23.09	26.50	26.3	30.8	23.75	23.98	26.75	25.13	25.7	27.98	24.67
K µg/ml	4.31	0.11	7.24	6.35	1.93	2.39	3.43	8.01	8.96	7.78	4.60	4.06	1.95

Table 11: Drug Release Studies for FA1 to FA12 in Phosphate Buffer P^H 6.8 (Formulations containing Co Processed superdisintegrants in mixture)

Time (min)	Acetone co-processed formulations						Methanol co-processed formulations						Marketed Formula Amditor	Similarity Factor
	FA1	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**	**FA9**	**FA10**	**FA11**	**FA12**		
5	37.24 ±0.25	28.71 ±0.15	33.83 ±0.14	22.08 ±0.58	14.14 ±0.36	25.47 ±0.25	18.3 ±0.36	24.2 ±0.58	13.9 ±0.69	23.23 ±0.45	15.52 ±0.36	16.9 ±0.58	34.6 ±0.356	54.36
10	43.25	39.56	45.3	37.57	23.8	48.57	28.3	31.7	29.7	36.74	30.39	33.3	42.34	

	±0.25	±0.89	±0.56	±0.45	±0.63	±0.96	±0.45	±0.36	±0.56	±0.85	±0.45	±0.58	±0.356
15	54.80 ±0.36	57.28 ±0.69	59.4 ±0.56	59.61 ±0.45	35.8 ±0.69	60.2 ±0.96	46.2 ±0.69	46.6 ±0.75	46.8 ±0.35	47.78 ±0.25	46.18 ±0.75	55.8 ±0.65	61.34 ±0.369
20	74.09 ±0.14	76.06 ±0.25	74.34 ±0.47	64.19 ±0.56	59.5 ±0.58	69.7 ±0.54	68.1 ±0.85	60.2 ±0.14	65.07 ±0.25	60.16 ±0.32	63.28 ±0.39	66.73 ±0.45	77.21 ±0.569
25	88.86 ±0.25	84.09 ±0.28	88.60 ±0.85	82.3 ±0.54	79.9 ±0.69	76.1 ±0.65	78.5 ±0.21	80.61 ±0.28	80.13 ±0.64	75.03 ±0.54	81.7 ±0.94	81.33 ±0.85	89.69 ±0.789
30	93.87 ±0.52	96.21 ±0.25	99.66 ±0.45	95.7 ±0.47	94.3 ±0.54	92.6 ±0.25	89.1 ±0.21	91.0 ±0.54	91.99 ±0.54	90.96 ±0.25	92.03 ±0.45	89.69 ±0.58	92.2 ±0.654

Similarity exists between Market formula and Formulations

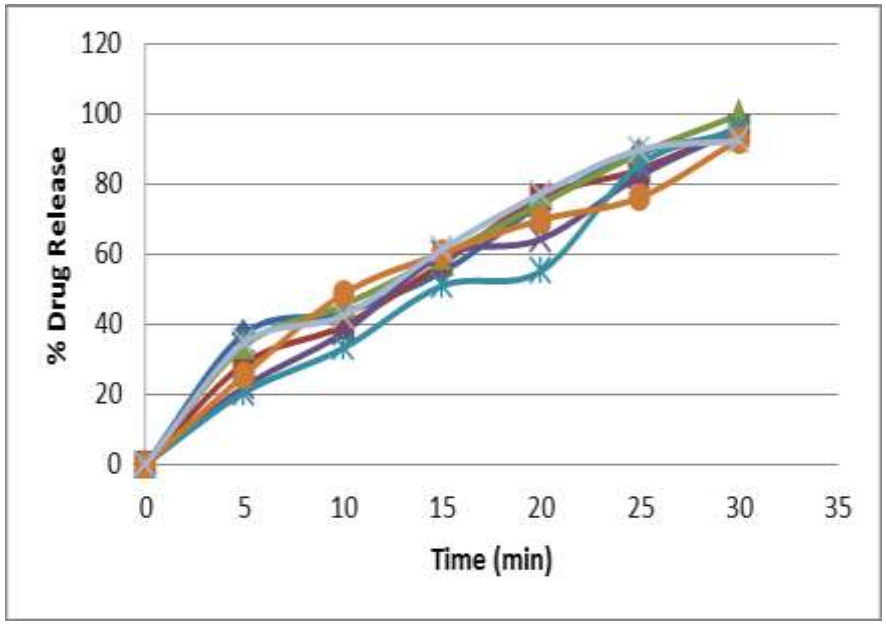

Figure 8: Drug Release Studies of FA1 to FA6 in phosphate Buffer P^H 6.8

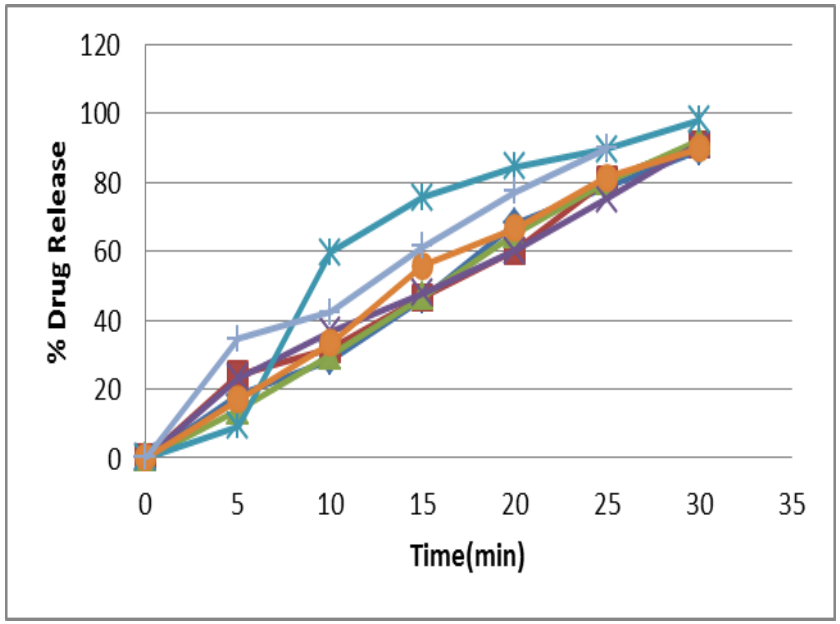

Figure 9: Drug Release Studies of FA7 to FA12 in phosphate Buffer P^H 6.8

Table 12: Drug Release Kinetics for FA1 to FA12 in Phosphate Buffer P^H 6.8 (Formulations containing Co Processed superdisintegrants in mixture)

	Acetone co-processed formulations						Methanol co-processed formulations						Marketed Formula
Parameters	**FA1**	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**	**FA9**	**FA10**	**FA11**	**FA12**	
T50(min.sec)	5.8	6.7	8.3	9.7	11.1	11.9	15.4	15.43	8.9	5.1	8.38	5.7	3.86
T90(min)	38.6	26.7	21.1	29.8	33.1	28.7	30.4	23.1	26.4	31.9	25.1	25	29.28
Kµg/ml	0.91	0.3	6.9	2.6	1.4	10.3	4.7	10.03	4.10	2.42	2.27	3.9	2.38

Stability Data:

Table 13 : Stability Data of Best Formulation after one month

S.NO	FA3
Colour and Appearance	No Change
Hardness (kg/cm^2)	4.2±0.03
Disintegration Time (sec)	40±0.4
IN Vitro Drug Release	99.5±0.012

Table 14 : Stability Data of Best Formulation after Two months

S.No	FA3
Colour and Appearance	NO CHANGE
Hardness (kg/cm^2)	4.2±0.01
Disintegration Time (sec)	40±0.2
IN Vitro Drug Release	99.4±0.01

Table 15 : Stability Data of Best Formulation after Three months

S.NO	FA3
Colour and Appearance	NO CHANGE
Hardness (kg/cm^2)	4.2±0.02
Disintegration Time (sec)	40±0.1
IN Vitro Drug Release	99.51±0.023

Establishment of Calibration curve of Amlodipine Besylate by HPLC in Rat Plasma:

Calibration curve was done by repeated five injection continued for three days repeated for three days, an average of fifteen injections. Concurrently stability of the plasma in sample was analyzed. Plasma was kept at -20 ^oC. 2 to 10µg/ml concentrations were used to develop the standard curve and was linear. The regression equation and correlation coefficient R^2 was obtained to be 0.997.

Table 16: Calibration curve data of Amlodipine Besylate in Rat Plasma

S.no	Concentration ug/ml	Peak area 1	Peak area 2	Peak area 3	Meanpeak area	Std. Deviatation	% RSD
1	0	0	0	0	0	0	0
2	2	10235	10240	10250	10239	10241±7.637	0.22
3	4	18450	18470	18460	18459	18460±10	0.16
4	6	26150	26145	26140	26144	26145±5	0.05
5	8	35220	35215	35225	35219	35220±5	0.04
6	10	44120	44130	44115	44114	44115±7.637	5.19

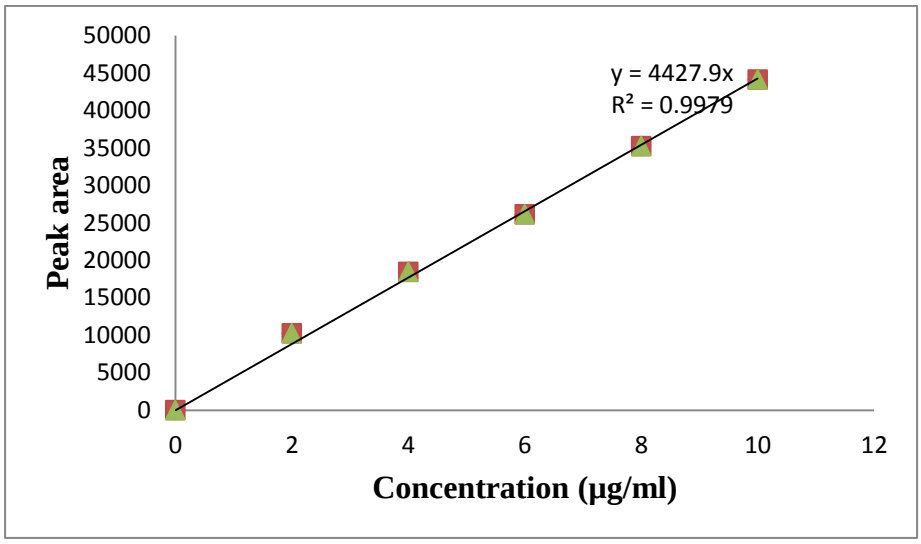

Figure 10: Calibration curve of Amlodipine Besylate by HPLC in Rat Plasma

Table 17 Concentration of drug and Peak area for Amlodipine Besylate in rat plasma

Parameter	Amlodipine Besylate
Linearity (µg/mL)	2-10 (µg/ mL)
Slope (m)	4432.3
Regression(r^2)	0.997
LOD (µg/ mL)	0.0021
LOQ (µg/ mL)	0.01101

Pharmacokinetic analysis

All the Pharmacokinetic required parameters were determined by using non compartment analysis based on the statistical moment theory using PK1, PK 2 excel function. The results was observed that C_{max} was (32 ± 0.5773) FA 3.

Statistical analysis : Difference in Pharmacokinetic parameters was analyzed using analysis of variance. Variation in mean PK Parameters of FA3 related to t-test and value of $P< 0.05$ was considered significant.

Table 18: Pharmacokinetic Parameter loaded with Amlodipine Besylate

S.no	**Pharmacokinetic parameters**	**FA3**
1	C_{max} (µ g/ml)	32 ± 0.5773
2	t_{max} (h rs)	10±0.2516
3	Elimination rate Constant(hr^{-1})	0.5493±0.0023
4	Half Life (hrs)	28.618±0.3477
5	AUC_{0-t}	60±0.5773
6	AUC_{0-inf} (µg. hr/ml)	90.909±0.528
7	$AUMC_{0-t}$ (µg.hr/ml)	5100±1
8	AUMC0-inf (µg. hr/ml)	161.8256±0.2779
9	MRT (days)	4.5±0.2

DISCUSSION OF RESULTS

General Discussion

A oral pharmaceutical Tablets has long been one of the most favorable dosage forms for all types of patients unable to tolerate parenteral dosage form .The Solid form is preferred because of ease of flexibility in the administration of dose, and importance in stability maintenance and economical. More therapeutic and commercial advantages ie,

1) High patient compliance, 2) Reduction in side effects 3) Non Invasive method

In this work a new method of system "Combinational effectt of coprocessed super disintegrants " were developed and leads to improved bioavailability, present work explain the mechanism of improved bioavailability. 1) incorporation of coprocessed superdisintegrants with various solvents, step 2) Effect of particle size on bioavailability 3) Release of drugs in different mediums.

Evaluation of powders :

Pre compression parameters:

All the powders and granules prepared as per the formulations required were subjected to evaluate the pre compression properties.The powders prepared with coprocessed superdisintegrants showed equal values as that of granules flow properties due to change in the shape and particle size by dissolving in solvents like acetone and methanol and passing through the sieves arranged in chronological order based on the size of the sieve or (sieve number). The powder changed to the form of granules made them specific to achieve good flow properties. The density of the materials have changed which maintained to regulate the granules in specific volume of die cavity of the punching machine. Compared to Amlodipine Besylate ,. All the results were tabulated in Table 3.

Post compression parameters:

All the results were tabulated in table 4. Fast disintegrating tablets are prepared in a single-station rotary compression mission shows the post-compressional parameters, hardness (3.4- 4.4 Kg/cm2), friability (≤ 0.75 %), weight variation (Passes) values of the tablets. It indicates that with the change in use of superdisintegrants mixture and concentration, the tablets obtained with thickness (3.28- 4.48 mm) , for all the prepared tablets and all the specified values are in acceptable range. All the formulations passed the uniformity of dispersion test. All the results were tabulated in table 4.

Disintegration time:

The most important parameter that is needed to be optimized during the development of a fast disintegrating tablets is disintegrating time of the tablets. The disintegration test of the tablets was

conducted in purified water. Disintegrating study showed that the disintegrating times of the tablets (from 21 sec to 28) with mixture of modified super disintegrants. The research work carried out selecting 6% concentration to be added in the mixture that is in the specified ratios. However, disintegration time of the tablets prepared with mixture of co processed superdisintegrants (1:1) are in the acceptable range with no much deviations due to combitional effect of superdisintegrant mixture. The results are in consistent with other results. Tablets prepared by direct compression technique showed better disintegration as the mechanism of hydration worked out here. Anhydrates are having much better capacity in absorbing water compared to hydrates. Comparatively, the disintegration times of the prepared tablets with coprocessed super disintegrants were much better and made the approach of fast disintegration and the objective was fulfilled and justified. The super disintegrants co-processed with the solvents acetone and ethanol made the drugs to change in the property of solubility and the effective selection of particle size which were retained on the sieve collected more made the selection of drug particles with uniform size and the basic literature showed that the decrease in particle size improved solubility was once again proved by the method developed for the decrease in disintegration time of the tablets along with decrease in wetting time of the tablets of both the drugs.

Wetting time:

As per the change in surface area by maintaining effective particle size with the modified process of coprocessing the superdisintegrants justified the decreased in wetting time. The coprocessing technique achieved the objective of faster disintegration which is prior depended on wetting capacity of the material in the particular solvent.

***In-vitro* release studies of Amlodipine Besylate :**

The dissolution data and kinetics of Amlodipine Besylate tablets prepared with various techniques and methods were shown in the table 6-12. From the results it is evident that the tablets prepared with the co processed superdisintegrant mixture in the ratio of (1:1) by direct compression technique showed good release of drug. Among the formulations prepared with mixture of super disintegrants the tablets containing 6% concentration of super However, T_{50}% and T_{90}% values are less for the formulations prepared by direct compression technique with 6% concentration of co processed super disintegrants compared with the all other prepared. While T_{50}% and T_{90}% values did not change with increase in the concentration of crospovidone. The rapid increase in dissolution of Amlodipine Besylate may be due to rapid swelling of Crosspovidone and sodium starch glycolate. The increase in the concentration of Crosspovidone and sodium starch glycolate

increased the swelling and disintegrating tablets rapidly into apparently primary particles. While tablets formulated with sodium starch glycolate, disintegrate by rapid uptake of water, followed by rapid and enormous swelling into primary particle but more fastly due to the change in viscous gel layer of sodium starch glycolate by crosspovidone. The study was carried out for the tablets prepared by co processing of super disintegrants using acetone and ethanol as solvents. The tablets prepared by selecting the materials retained more on the sieve no 24 gave the visionary and statistical evidence that the tablets were released the drug effectively and completely rather than the tablets prepared by ethanol coprocessed superdisintegrants and material retained less on the sieve no 44. The effective control of particle size and the solvation mechanism carried a way for enhancement of drug release and complete release (99.5%) proved that from all the formulations FA3 shown the better release with good kinetic values in all the mediums. The drug release tested in various mediums for the tablets as per the FDA dissolution acceptance criteria revealed that the drug has possible release in water and effective release through the entire length of GIT. The drug release was very effective in oral cavity pH and upper area of the stomach that is slightly acidic pH. The formulations drug release was compared with the market formulation (Amditor from sun pharmaceuticals- dose 10 mg). There exists similarity between market formulation and best formulation in the two mediums 0.1 N Hcl and phosphate buffer pH 6.8. All the evidences proved to be the techniques and methods adopted made the drug release effectively which intended to have good bioavailability.

Stability Studies:

The accelerated stability studies conducted for the best formulation as per the guidelines of ICH showed the consistent results for the period of three months. There are no changes in colour and appearance. The evaluated parameters like hardness, disintegration time and drug release was consistent in every month of study and even after 3 months. The studies showed FA3 were stable and effective in retaining their properties throughout their shelf life period.

Bioanalytical Study

Comparative pharmacokinetic study carried out using the previously developed HPLC method on wistar rats suggest that no reaction with the rat plasma, from the results it was shown that C_{max} was (32± 0.5773) for Amlodipine Besylate formulation FA3 and 26±0.5 The t_{max} values are like 10 min for FA3 The MRT was 4.5±0.5 (days) in the optimized FA3 formulations. Thus the formulation is best in release of the drug immediately.

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

The present investigation of this work "Design And Development Of Immediate Release Tablets By Employing Modified Superdisintegrants " were developed and leads to improvement of bioavailability, present work explain the mechanism of drug release from tablets using modified superdisintegrants

In this work tablets were prepared by using crosscarmellose , sodium starch glycolate and crosspovidone as superdisintegrants in various ratios and various methods . The influence of tablet compression technique on the manufacturing of tablets was evaluated. The physical modification of superdisintegrants using co processing technique and selection of processed material with particle size specificity made the drugs to possess required characteristics as fast dispersible. The pre compression and post compression properties are determined as per the procedure prescribed. The drug release studies and kinetics indicate that the prepared tablets with coprocessed superdisintegrants were best at its release in the entire tract of GIT due to their change in bio pharmaceutical property like dissolution. Optimized formulations were selected for stability concern and *in- vivo* performance.

The main aim of the work is to prepare, evaluate *in vivo* performance and safety study of Amlodipine Besylate tablets.

The optimized formulation of tablets were identical possess similarity between marketed formulation. *In-vivo* study was randomly designed to evaluating tablets of Amlodipine Besylate , best formulations, rat was chosen as animal models for *in-vivo* absorption study. Analytical method used was for pharmacokinetic profile. The pharmacokinetic parameters t_{max}, $t_{1/2}$, AUC, MRT were significant .

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