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Formulation and Evaluation of Amlodipine Fast Dissolving Tablets

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ABSTRACT

Fast dissolving tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. In the present study, an attempt was made to design and evaluate fast dissolving tablets of Amlodipine besylate, which is used commonly for the treatment of angina pectoris. The tablets were prepared by direct compression method followed by sublimation method using super disintegrants sodium starch glycolate, crosspovidone and croscarmellose sodium. The prepared powder blends were evaluated for preformulation parameters. The tablets were evaluated for thickness, hardness, weight variation, drug content uniformity, friability and in vitro drug release studies. In vitro drug release studies were performed by using USP type II apparatus (paddle method) at 50 rpm in 900 ml of 0.1N HCl as dissolution medium for 30 minutes at 37±0.5°C. The formulation F9 containing Croscarmellose sodium (7%) showed better disintegration and dissolution up to 30 minutes. Hence, formulation F9 was considered as optimized formulation which showed the best drug release profile up to 30 minutes. The results of mathematical model fitting of data obtained indicated that, the best fit model in all the cases the release was found to be by diffusion and fickian release. The results of FTIR analysis showed that there was no physical and chemical interaction between drug and other excipients. The study indicates that the fast dissolving tablets of Amlodipine besylate can effectively reduce the adverse effects and frequency of administration of the drug.

KEYWORDS: *Amlodipine besylate; Superdisintegrants; Crospovidone; Sodium starch glycolate; Cross carmellose sodium; Direct compression; Sublimation method; FDT; Evaluation parameters.*

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INRODUCTION

Tablet is still most popular conventional dosage forms existing today because of ease of self administration, compact in nature, easy to manufacture and it can be deliver in accurate dose. One important drawback of conventional dosage forms is the difficulty in swallowing (dysphagia) or chewing in some patients particularly pediatric and geriatric patients. United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue." Fast dissolving tablets are also known as mouth-dissolving tablets, melt-in mouth tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet. Fast dissolving tablets dissolve or disintegrate in the oral cavity without the need of water[1]. Most fast dissolving tablets must include substances to mask the bitter taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients. It has been concluded that faster the dissolution, faster the absorption (only the unionized form of drug) and onset of action. Some drugs are absorbed from the oral cavity, pharynx and esophagus as the saliva passes down into the stomach. Thus the bioavailability of drug is significantly more than those observed from conventional tablets dosage form. The time for disintegration of fast disintegrating tablets is generally considered to be less than one minute. The fast dissolving solid dosage form turns into a soft paste or liquid form for easy swallowing, and thus it is free of risk of choking[2].

Angina pectoris, commonly known as angina, is chest pain due to ischemia of the heart muscle. Amlodipine besylate is a calcium channel blocker, chemically it is 3-Ethyl-5-methyl (±) -2-[(2-aminoethoxy) methyl] -4-(2-chlorophenyl) -1,4 dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzene sulphonate[3]. Amlodipine besylate is a white crystalline powder with a molecular weight of 567.1. Its empirical formula is $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$. Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Like other calcium channel blockers, amlodipine acts by relaxing the smooth muscle in the arterial wall, decreasing total peripheral resistance and hence reducing blood pressure; in angina it increases blood flow to the heart muscle[4].

The basic approach in development of FDT is the use of super disintegrants like cross povidone (2-5%), sodium starch glycolate (2-8%), crosscarmellose sodium which provide instantaneous disintegration of tablet after putting on tongue their by release the drug in saliva[5].

The other ingredients are micro crystalline cellulose as tablet disintegrant, mannitol as diluent, talc and magnesium stearate as lubricant, and camphor as sublimating agent which increases the porosity of the tablet[6]. Direct compression was used for the preparation of FDT[7]. The technologies used for manufacturing fast dissolving tablets are freeze-drying, spray-drying, tablet moulding, sublimation, sugar-based excipients, tablet compression, and disintegration addition[8].

MATERIALS AND METHODS

Materials

Amlodipine Besylate was purchased from Yarrowchem Products, Mumbai, India. Crosspovidone, Sodium starch glycolate, Crosscarmellose sodium, Mannitol, Micro crystalline cellulose, Camphor, Magnesium stearate and talc all of them are purchased from Yarrowchem Products, Mumbai, India. All the excipient and reagents used are analytical grade.

Methods

Preparation of FDT of Amlodipine besylate

Amlodipine besylate FDTs were prepared by direct compression method followed by sublimation method. The superdisintegrants such as Crosspovidone,Sodium starch glycolate,Cros carmellose sodium used in varying concentrations (3,5,7%). In this study camphor is used as a sublimating agent. All the ingredients were passed through the sieve no 60. The drug/polymer mixture was prepared by homogeneously mixing the Croscarmellose sodium, crospovidone, sodium starch glycolate, microcrystalline cellulose, mannitol and Amlodipine. All the ingredients of the fast dissolving tablet of amlodipine were weighed, sifted and mixed in mortar with the help of pestel, and finally magnesium stearate and talc were added as lubricating agent and camphor were added as sublimating agent. The 150 mg mixture was then compressed using an 8 mm punch in a single stroke on single punch tablet machine. Each tablet weighed 150 mg. The force of compression was adjusted so that hardness of all the prepared tablets ranges from 2-4 kg/cm^2. Camphor was sublimated in vacuum at 80°c for 30 minutes after preparation of tablets (Fig: 1).

EVALUATION OF FAST DISSOLVING TABLET

General Appearance

The general appearance of a tablet, its visual identity and overall elegance, is essential for consumer acceptance. The control of the general appearance of a tablet includes the measurements of a number of attributes such as a tablets size, shape, colour, presence or absence of an odour, taste, of any identifying markings. The prepared tablet was evaluated for its colour, shape, odor, taste, surface etc.

Thickness[9]

The thickness of a tablet is the only dimensional variable related to the process. At a constant compressive load, tablet thickness varies with change in die fill, with particle size distribution and packing of the particle mix being compressed, and with tablet weight, while with a constant die fill, thickness varies with variations in compressive load. Tablet thickness should be controlled within ± 5 % variation of a standard value. Any variation in tablet thickness within a particular lot of tablets or between manufacture's lots should not be apparent to the unaided eye of consumer acceptance of the product. In addition, thickness must be controlled to facilitate packing. Thickness of tablets indicates the strength to withstand compression force applied during manufacturing process. Thickness of tablets was measured by verniercalliper. It is expressed in millimetre.

Weight variation[10]

With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made is routinely measured to ensure that a tablet contains the proper amount of drug. The weight variation test is done by weighing 10 tablets individually and calculating the average weight, and comparing the individual tablet's weight to the average. The limits for weight variation are given in the table 1.

S1. No	Average Weight	Maximum percentage difference allowed
1	130 or less	10
2	130-324	7.5
3	More than 324	5

Table1: Weight variation range

Hardness/Crushing strength[11]

Tablet requires a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness can be tested using Monsanto hardness tester or Pfizer. Here Monsanto was used. The tablet to be tested was held between a fixed and a moving jaw of Monsanto Hardness Tester. The force applied to the edge of the tablet was gradually increased by moving the screw knob forward until the tablet breaks. The reading was noted from the scale which indicates the pressure required to break the tablet. The hardness of a tablet depends on the weight of the material used, space between the upper and lower punches at the time of compression and pressure applied during compression. The hardness also depends on the nature and quantity of recipients used during formulation. If the finished tablet is too hard, it may not disintegrate in the required period of time and if the tablet is too soft it may not withstand the handing during packing and transporting.

Friability[9]

Tablet's hardness is not an absolute indicator of strength since in some formulations, when compressed into very hard tablets, tend to cap on attrition, losing their crown portions. Friability test can be performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. The Friabulator consists of a plastic chamber divided into two parts and revolves at 25 rpm. A fixed number of tablets are weighed, placed in the tumbling chamber and rotated for four minutes of 100 revolutions. During each revolution the tablets fall from a distance of six inches to undergo shock. After 100 revolutions the tablets are again weighed. The loss in weight indicates the friability. The acceptable limits of weight loss should not be more than 0.8% t.

The friability (f) is given by

$$f = 1 - \frac{wo}{w} X\ 100$$

Where,
w_o = initial weight of the sample before friability test
w = weight of the samples after friability test

Drug content[9]

The potency of tablet is expressed in terms of grams, milligrams or micrograms of drug per tablet and is given as the label strength of the product. So to evaluate the tablet's potency, the amount of drug per tablet needs to be monitored from tablet to tablet, and batch to batch. For the drug content uniformity test ten tablets were weighed and pulverised to a fine powder.A quantity of powder equivalent to 5 mg of amlodipine was taken and dissolved in suitable quantity of pH 1.2 solutions and liquid was filtered using whatman filter paper and diluted. The amlodipine content was determined by measuring the absorbance at 239 nm using UV spectrophotometer.

Wetting Time[12]

The wetting time of the tablets can be measured by using five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. 10 mL of water-containing amaranth a water soluble dye is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Water Absorption Ratio[12]

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using following equation.

$$R = 100 \times W_a - W_b/W_a$$

Where, W_a = Weight of tablet after water absorption
W_b = Weight of tablet before water absorption.

Disintegration[9]

A generally accepted fact is that for a drug to be readily available in the body it must be in solution form. For most tablets, the first important step towards dissolution is the breakdown of tablet into smaller particles or granules. This process is known as disintegration. Disintegration is still be used as a tool of quality control of tablets and capsules.

Procedure

The test was carried out on 6 tablets using Tablet disintegration tester. Distilled water at 37°C ± 2°C was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

Dissolution[13]

Dissolution is a physiochemical process by which a solid substance enters the solvent phase to yield a solution. Dissolution (release of drug from the dosage form) is a key prerequisite for any orally administered drug to be systemically effective .In case of oral drug products, the release properties are mainly influenced by disintegration of the solid dosage form into granules, deaggregation of granules to yield fine particles and dissolution of drug from the fine particles into solution.

Drug dissolution is a multistep process involving heterogenous reactions at solid-liquid phase boundaries. The heterogenous reactions that constitute the overall mass transfer process are considered to take place in two steps

1. Convective transport of the soluble solid through hydrodynamic boundary layers surrounding solid-liquid interphase to the bulk phase
2. A reaction at the solid –liquid interphase(Interfacial transport)

Procedure

Apparatus	: USP Type 2 (paddle)
Agitation speed (rpm)	: 50
Medium	: 0.1 N HCl
Temperature	: 37 ± 0.5° C
Time	: 5, 10, 15, 20, 25, 30 minutes
Wavelength	: 239 nm

Steps

900 ml of 0.1 N HCl was taken in the basket. Temperature was maintained at 37 ± 5° C. One tablet was placed in the basket. The basket was rotated at 50 rpm. 1 ml of sample from each basket was withdrawn at the intervals of 5, 10, 15, 20, 25, 30 minutes. Replace the basket with equal volume of 0.1 N HCl .The samples withdrawn was filtered and diluted to 10 ml with 0.1 N HCl. The absorbance of these solutions is measured at 239 nm. The amount and percentage of drug release can be calculated from the given formula.

$$Amount\ of\ drug\ release = \frac{Concentration \times Bath\ volume \times Dilution\ factor}{1000}$$

$$\%\ of\ Drug\ release = \frac{Amount\ of\ drug\ release}{Drug\ loaded} \times 100$$

Kinetic study[14]

Dissolution profile modeling

There are several linear and non-linear kinetic models to describe release mechanisms and to compare test and reference dissolution profiles are as follows:

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:

$$W_0 - W_t = K_0 t$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage form at time t and k is proportionality constant.

Dividing this equation by W_0 and simplifying:

$$f_t = k_0 t$$

Where $f_t = 1 - (W_t / W_0)$ and ft represents the fraction of drug dissolved in time t and k_0 the apparent dissolution rate constant or zero order release constant

First order kinetics

This type of model to analyze drug dissolution study was first proposed by Gibaldi and Feldman and later by Wagner. The relation expressing this model:

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 t/2.303$$

Where Q_t is the amount of drug released in time t, Q_0 is initial amount of drug in the solution and K_1 is the first order release rate constant.

Korsmeyer Peppas model

Korsmeyer developed a simple semi empirical model, relating exponentially the drug release to the elapsed time (t).

$$Q_t/Q_\alpha = K_k t^n$$

Where K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism as shown in the table 2:

Table2: Drug transport mechanism

Sl. No	Release exponent(n)	Drug transport mechanism	Rate as a function of time
1	0.5	Fickian diffusion	$t^{-.0.5}$
2	0.5 <n < 1.0	Anomalous transport	t^{n-1}
3	1.0	Case II transport	Zero order release
4	Higher than 1.0	Super case II transport	t^{n-1}

The Release exponent can be obtained from the slope and the Constant (K_k) obtained from the intercept of the graphical relation between logarithmic versions of left side of the equation versus log t.

Higuchi Model

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

Where Q_t = the amount of drug released at time t and

K_H = the Higuchi release rate;

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship with the square root of time versus the concentration indicates that the drug release follows strict Fickian diffusion.

RESULTS AND DISCUSSION

The powder blend for all formulation containing various concentration of Crossspovidone (3,5,7%), Sodium starch glycolate (3,5,7%) and cross carmellose sodium (3,5,7%) as superdisintegrant was prepared shown in the Table 3, and then the FTIR studies were carried out on the basis of as the method specified(Fig.7-10), FTIR spectrum of drug shows the prominent peaks with respect to the functional groups. The FTIR spectrum of physical mixture of drug with polymer and drug with excipient concludes that there is no significant interaction between the drug, polymer and excipients. In the spectrum of drug-polymer mixture, the characteristic peak of drug was not altered. The soluble diluents, such as mannitol and microcrystalline cellulose were selected as diluents considering its advantages in terms of easy availability and negative heat of dissolution. Post formulation studies of the formulated batches are shown in the Table 5 and 6. From the physical evaluation of all the batches formulated shown in Table 4, it was concluded that the tablets of all the batches had desirable physical properties. Hardness varies from 2.8 -3.7 Kg/cm^2. The thickness varies from 2.9-3.3 mm. The friability was varies from 0.40 -0.72 %, which indicates that all the batches had sufficient mechanical strength to withstand mechanical abrasion. All batches of formulation passes the weight variation test as per the limits prescribed in IP. The wetting time (Fig: 2) of all the batches were also considerably reduced in tablets. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time. It is clear that the wetting time varies depend on the concentration of the superdisintegrants used for the study. The drug content uniformity of all the batches was in the limit of 95 - 98 %. The water absorption ratio of all the batches were tested by the method it is clear that the order of swelling observed in these polymers could indicate the rates at which the preparation are able to absorbed water and swell. Maximum liquid uptake and swelling polymers were achieved after 2 -8 minutes. The swelling index was calculated with respect to time .As the time increases, the swelling index was increased because weight gain by the tablet was increased proportionally with rate of hydration. Later it decreased due to the dissolution of outer most gelled layer of tablet into dissolution medium. Batches F1 to F9 showed good mechanical integrity, but the disintegration time was in the range of 15 to 40 seconds. The results shown that sublimation of camphor from tablets resulted in faster disintegration. *In vitro* release studies were carried out using USP Type 2 tablet dissolution test apparatus paddle method at 37±0.5 °C, taking 900 ml of pH-1.2 dissolution medium. Speed of rotation of the paddle was set at 50 rpm. Aliquots of 1 ml were withdrawn after 5, 10, 15, 20, 25, 30 min and analyzed spectrophotometrically at 239 nm. The percentage drug release of formulations F_1-F_3 formulated with different concentrations of same superdisintegrant crosspovidone showed the drug release 79.09 %, 81.90 % and 82.09 % respectively at the end of 30 minutes(Fig:3). From formulations F_4-F_6 with another superdisintegrant sodium starch glycolate were showed 82.29 %, 83.60 % and 86.29 % respectively at the end of 30 minutes(Fig:4). From formulations F_7- F_9 formulated with superdisintegrant croscarmellose sodium were showed the results as 89.10 %, 91.19 % and 92.29 % respectively at the end of 30 minutes(Fig:5). F_9 shows the percentage drug release of 92.29 % at the end of 30 minutes. So F_9 selected as the optimized formulation in this study.

The dissolution profile of most satisfactory formulation F_9 was fitted to zero order, first order, Higuchi model, Korsmeyer-Peppas model and Hixson-Crowell model to ascertain the kinetic modeling of the drug release(Fig:6). The kinetic treatment of the drug release data of F_9 followed first order drug release and Korsmeyer-Peppas profile with R^2 values 0.989 and 0.993 respectively(Table:7&8). It indicated that drug release was dissolution controlled and directly proportional to log cumulative percentage drug release.

Fig:1: Fast dissolving tablets of Amlodipine.

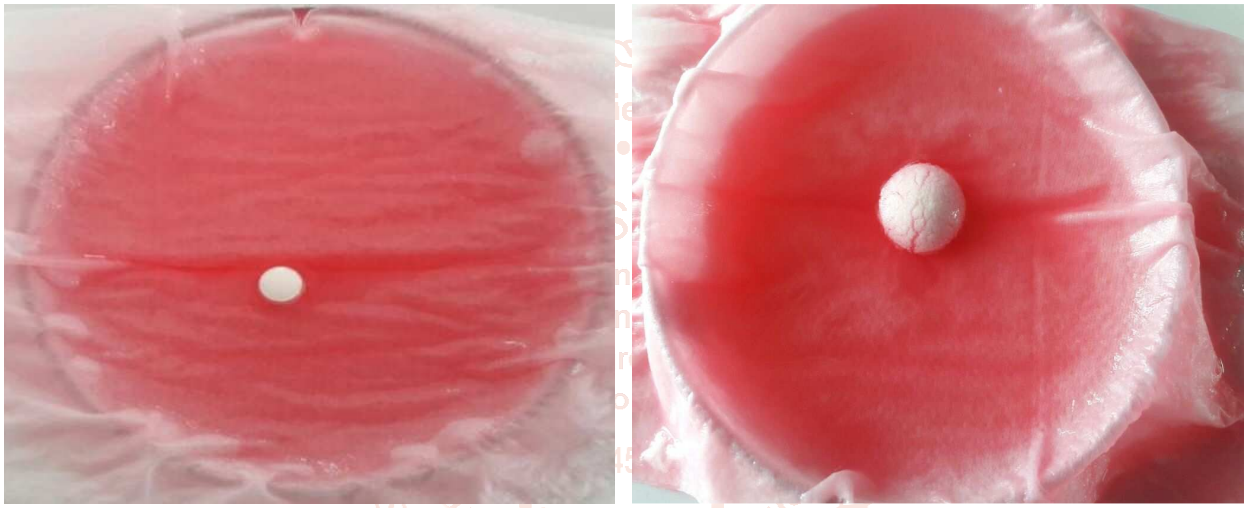


Fig:2: Before and after wetting time of FDTs

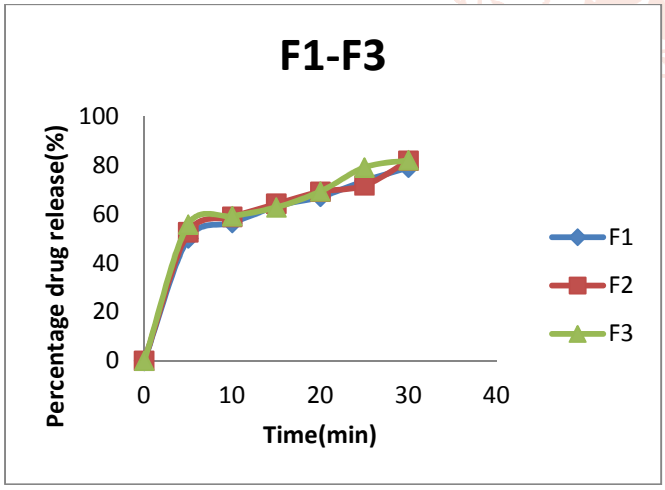


Fig: 3: Dissolution profile of Formulations F1-F3.

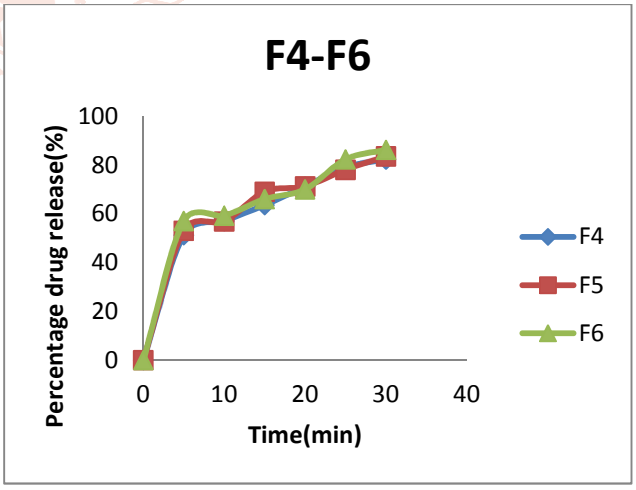


Fig: 4: Dissolution profile of Formulations F4-F6.

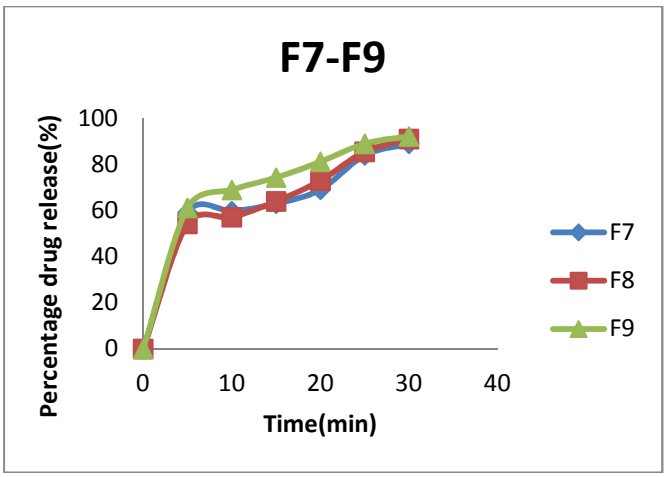
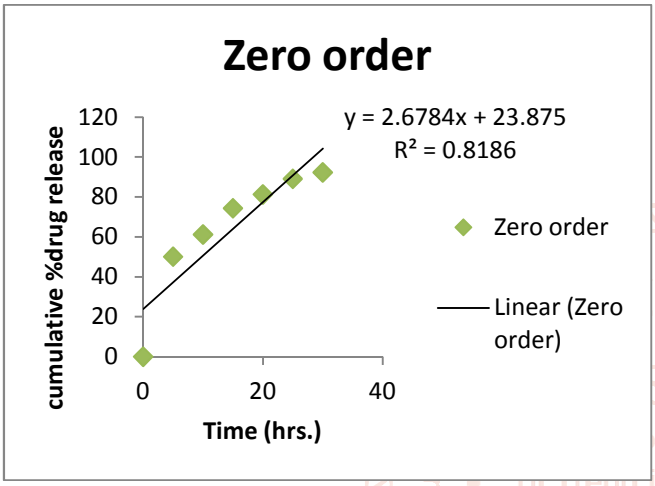
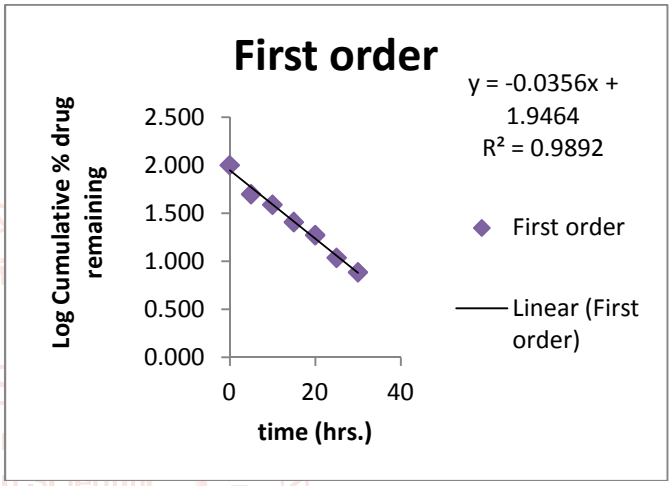
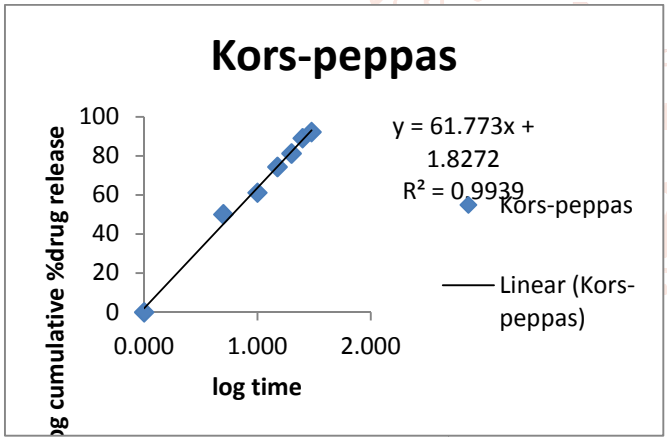
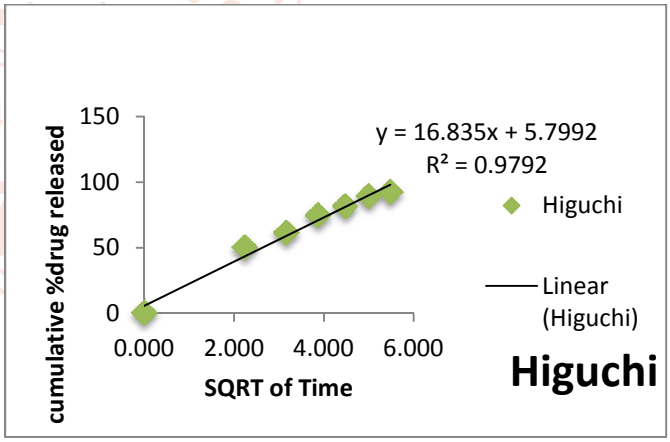


Fig: 5: Dissolution profile of Formulations F7-F9.









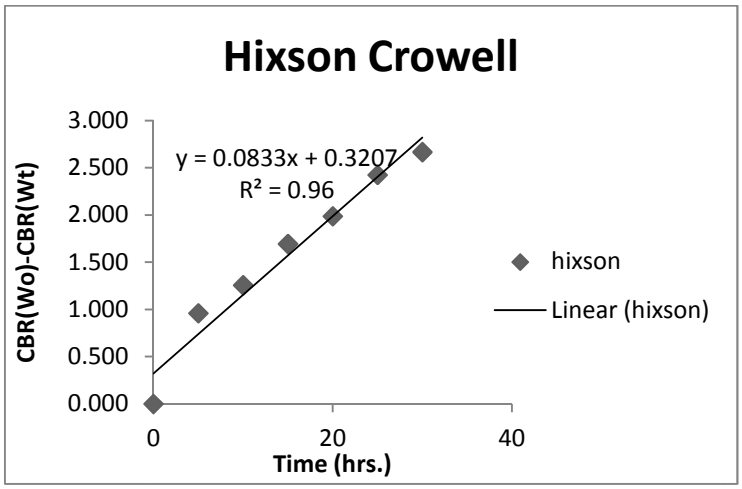


Fig: 6: Kinetic study of formulation F9

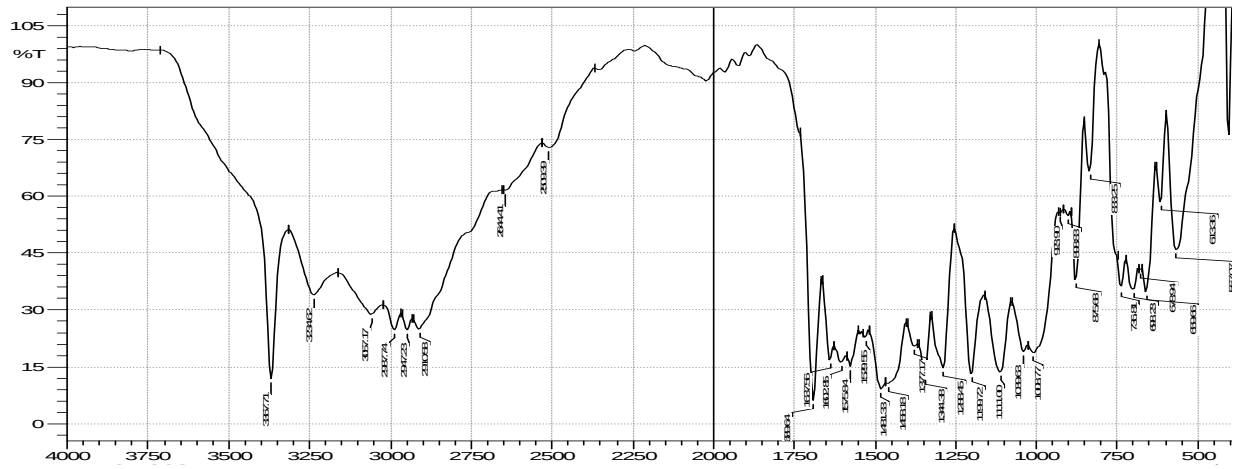


Fig:7: FTIR of Amlodipine +Croscarmellose sodium

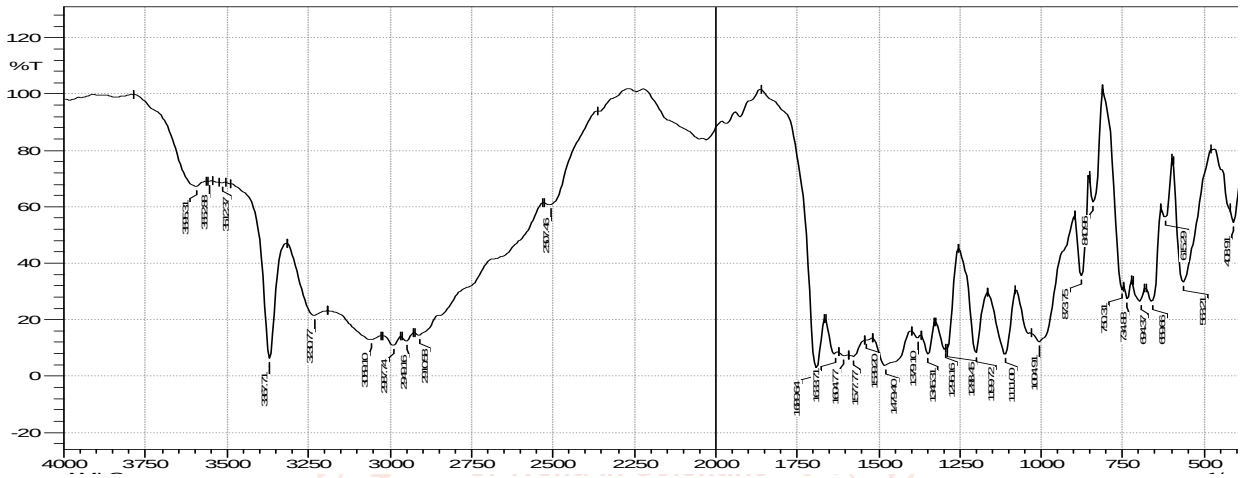


Fig:8 FTIR of Amlodipine +Crosspovidone

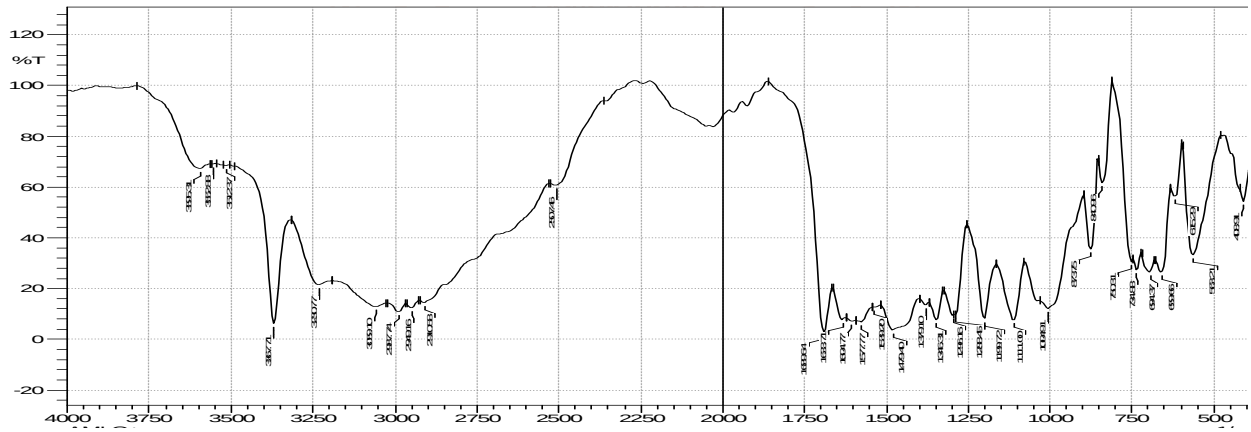


Fig:9: FTIR of Amlodipine +Sodium starch glycolate

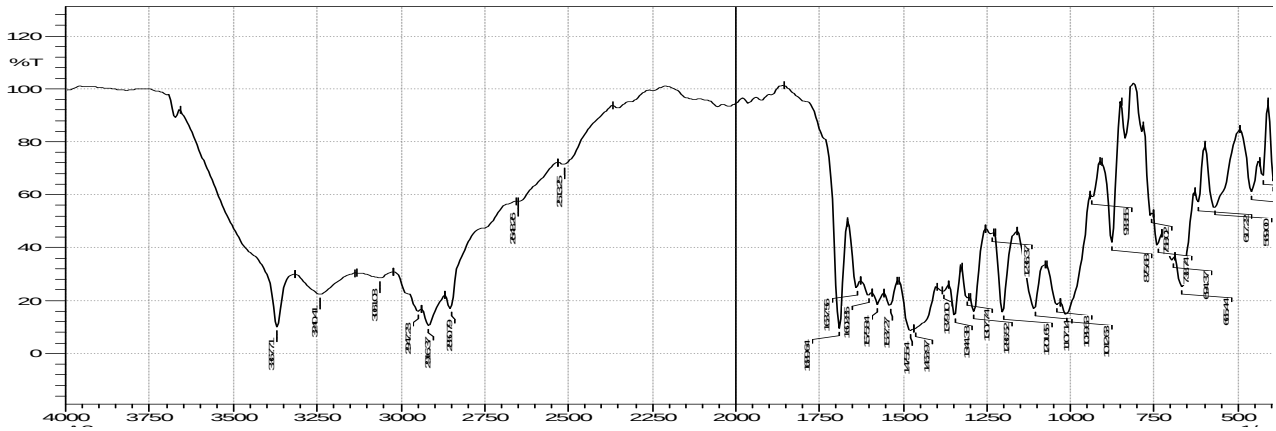


Fig:10: FTIR of Drug + Excipients

Composition of Fast dissolving tablet

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Amlodipine besylate	10	10	10	10	10	10	10	10	10
Crosspovidone	3	5	7	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	3	5	7	-	-	-
Cross carmellose sodium	-	-	-	-	-	-	3	5	7
Mannitol	100	100	100	100	100	100	100	100	100
Microcrystalline cellulose	25	23	21	25	23	21	25	23	21
Camphor	10	10	10	10	10	10	10	10	10
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Total weight(mg)	150	150	150	150	150	150	150	150	150

Table: 3 Formulation ingredients

Physical evaluation

Sl. No	Formulation	Weight variation (mg)	Thickness (mm)*	Hardness (Kg/cm^2)*	Friability (%)*
1	F_1	149±0.042	3.2±0.042	3.5±0.021	0.46±0.021
2	F_2	149±0.034	2.95±0.015	3.2±0.042	0.48±0.042
3	F_3	151±0.042	3.1±0.041	2.8±0.031	0.66±0.026
4	F_4	149±0.026	3.0±0.036	3.6±0.052	0.67±0.042
5	F_5	151±0.029	3.3±0.021	2.9±0.012	0.58±0.042
6	F_6	152±0.021	3.1±0.042	3.3±0.030	0.72±0.034
7	F_7	149±0.036	2.9±0.052	3.1±0.016	0.51±0.036
8	F_8	148±0.042	3.0±0.021	3.5±0.040	0.40±0.021
9	F_9	151±0.021	3.15±0.034	3.7±0.038	0.65±0.029

Table4: Physical evaluation of tablet

*Average of three determinations

Sl. No	Formulation	Wetting Time (Sec)	Drug content (%)	Disintegration Time(sec)
1	F_1	20	96.28	27
2	F_2	19	97.41	23
3	F_3	23	96.85	19
4	F_4	18	97.12	33
5	F_5	17	96.30	25
6	F_6	20	96.78	28
7	F_7	21	97.14	19
8	F_8	18	97.12	18
9	F_9	15	97.88	15

Table5: Wetting time, drug content and disintegration time of tablets

Sl. No	Formulation	% swelling (Time in Min)			
		2	4	6	8
1	F_1	92.06	94.52	95.56	93.61
2	F_2	65.28	73.75	84.26	83.40
3	F_3	67.58	75.89	94.56	92.43
4	F_4	67.19	76.05	99.65	93.42
5	F_5	69.12	87.79	108.32	103.85
6	F_6	75.89	98.34	101.65	95.41
7	F_7	75.98	89.31	109.36	105.45
8	F_8	97.15	104.67	112.26	105.28
9	F_9	96.06	101.45	107.35	102.19

Table6: Water absorption study of tablet

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remainining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug RemainingWt	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
5	50.09	49.91	2.236	1.698	0.699	1.700	50.09	3.682	0.960
10	61.20	38.8	3.162	1.589	1.000	1.787	11.11	3.385	1.257
15	74.39	25.61	3.873	1.408	1.176	1.872	13.19	2.948	1.694
20	81.29	18.71	4.472	1.272	1.301	1.910	6.9	2.655	1.987
25	89.10	10.9	5.000	1.037	1.398	1.950	7.81	2.217	2.425
30	92.29	7.71	5.477	0.887	1.477	1.965	3.19	1.976	2.666

Table 7: Kinetic analysis data of F_9

FORMULATION	Kinetic Models				
F9	Zero order	First order	Kors Peppas Plot	Hixon crowell	Higuchi
R^2 value	0.818	0.989	0.993	0.960	0.979

Table8: Regression values of kinetic models

CONCLUSION

Fast dissolving tablets of Amlodipine besylate was prepared by direct compression and followed by sublimation method using three different superdisintegrants such as Croscarmellose Sodium, Crospovidone and Sodium Starch Glycolate with other standard excipients. FTIR studies showed that there was no marked interaction between fast dissolving tablets and superdisintegrants. *In vitro* drug release from the tablets shows significantly improved drug dissolution. Optimized formulation F_9 showed a drug release of 92.29 % and showed the minimum disintegration time was 15 seconds.

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