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Preparation and Evaluation of Oral Dispersible Formulation of Amlodipine Beslate

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Abstract

The oral dispersible drug delivery system or fast dissolving drug delivery system are specially designed for the drugs which have extensive first pass metabolism and have low dose, for the enhancement of bioavailability. They undergo disintegration in the salivary fluids of the oral cavity within a minute, where they release the active pharmaceutical ingredient. The major amount of the active pharmaceutical ingredient is swallowed orally with the saliva where subsequent absorption takes place in the gastro-intestinal tract. The rapidly dissolving dosage forms are referred by various names by researchers like quick disintegrating, orally disintegrating, mouth dissolve or melt in mouth dosage forms Amlodipine belongs to the dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) which inhibits the Trans membrane influx of calcium ions into the vascular smooth muscle and cardiac muscle.

The contractile processes of the cardiac muscle and vascular smooth muscle are dependent on the movement of extracellular calcium ions into cells through specific ion channels. Amlodipine inhibits the calcium ion influx across cell membranes selectively, with the greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact. Salient Features of Oral Dispersible Drug Delivery System

- Ease of administration for patients who are mentally ill, disabled and uncooperative.
- No need of water to swallow the solid dosage form.
- Quick disintegration and dissolution of the dosage form.
- Drugs absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of the drug is increased
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.

Keywords: Dispersible, Hypertension, Dihydropyridine

Introduction

The oral route is the most preferred route by medical practitioners due to the highest acceptability of patients. About 60% of all dosage forms available comprise the oral solid dosage form. Fast-dissolving drug-delivery systems were initially developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experiences difficulties in swallowing oral solid-dosage forms as described by Siddiqui et al (2011).

The oral dispersible drug delivery system or fast dissolving drug delivery system are specially designed for the drugs which have extensive first pass metabolism and have low dose, for the enhancement of bioavailability as described by Battue et al (2007).

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They undergo disintegration in salivary fluids of oral mucosal cavity within a few minute, where active pharmaceutical ingredient is released. The major amount of active pharmaceutical ingredient is swallowed with the saliva orally where subsequent absorption takes place in gastro-intestinal tract as described by Sultana et al (2013).

The novel technology of rapid oral transmission methods is known to be fast-cutting, fast-cutting, fast-melting, and fast-spreading tablets described by Sabar et al (2013). By definition, it is a solid volume form that disperses or separates rapidly in the oral cavity, resulting in a solution or suspension without the need for water management, is defined as a volume form of rapid oral distribution as described by Rao et al (2013)

Fast Dissolving Oral Film

FDOFs is a form of solid volume that is well known for its flexibility and comfort. It improves drug performance by dissolving within a few minutes in the oral cavity after its contact with saliva without chewing and does not require water for its administration. It provides faster bioavailability and faster drug delivery due to higher blood flow and flexibility as described by Ratnaparkhi et al (2014). FDOFs are helpful for patients such as pediatric, geriatrics, bed rest, metabolic patients, diarrhea, sudden episodes of allergic attacks, or coughing in those who have an active lifestyle. Fast-acting oral films are based on transdermal bonding technology. Films are very similar to postage stamps in terms of their shape, size, and size as described by Arya et al (2010).

Fast dissolving oral tablets

Fast dissolving tablets are also called as mouth-dissolving tablets, oro-dispersible tablets, rapid melts, porous tablets, melt-in mouth tablets, quick dissolving etc. Fast dissolving tablets are basically those formulation which when put on tongue, disintegrates instantaneously by releasing the drug, that dissolve or disperses in the saliva. The faster the drug disperses into solution, quicker is the absorption and fast is the onset of clinical effect. Some of the drugs are absorbed from the pharynx, mouth esophagus and mouth as the saliva passes into the stomach. In these type of cases, the bio-availability of drug is significantly greater than that observed from conventional type of tablets dosage form as described by Ghosh et al (2005) and Masareddy et al (2008).Features of oral dispersible drug delivery system as described by Nagar et al (2011)Ease of administration for patients who are mentally ill, uncooperative and disabled and there is no need of water to swallow the solid dosage form, Quick dissolution and disintegration of the dosage form.An increase in bioavailability, mainly in cases of the hydrophobic and insoluble drugs due to rapid dissolution and disintegration of these tablets.The risk of suffocation or choking during oral administration of conventional formulation due to the physical obstruction is avoided, thus giving improved safety

Objectives

To perform identification and pre formulation studies on drug and to prepare the oral dispersible formulations of Amlodipine Besylate (Films and Tablets)

To evaluate the FDFs for surface pH, mechanical strength, thickness, folding endurance, tensile strength.

To evaluate FDTs for disintegration time, drug content, moisture contented.

To evaluate formulations with respect to drug estimation, in-vitro disintegration time of formulation and in-vitro dissolution rate studies.

To perform comparative in vitro drug release of prepared formulations of film and tablet with marketed tablet of Amlodipine Besylate.

Material and Methods

The various chemicals required for the formulations are given as follows:

Table 1: List of chemicals used in formulation

Sr.no.	Drug / Excipients	Manufacturer
1.	Amlodipine Besylate	Yarrow Chem
2.	Maltrodextrin	Hi Media
3.	HPMC 15 LV	Yarrow Chem
4.	MCC 102	Yarrow Chem
5.	Pectin	CDH
6.	Potassium Chloride	CDH
7.	PEG 6000	CDH
8.	Dichloromethane	CDH
9	Methyl Cellulose	Yarrow Chem
10	Fructose	Yarrow chem.
11	Aspartame	Yarrow chem..
12	Methanol (HPLC)	CDH

13	HPLC water	CDH
14.	Citric acid	CDH
15.	Glycerol	Hi Media

Equipments

The various chemicals required for the formulations are given as follows:

Table 2: List of equipment's used in formulation

Instrument/ Equipment	Manufacturer/ Supplier
UV spectrophotometer	Systronics, India
Dissolution Apparatus	Electro lab, India
Electronic balance	Dhona Instruments, India
Digital balance	Shimazdu, India
Digital type pH meter	Systronics, Ahemadabad, India
Melting point apparatus	Perfit, India
Mechanical stirrer	Electrolab, India
Water bath shaker	Electrolab, India
Hot air oven	NSW, New Delhi, India
Hardness tester	Electrolab, India
Friability apparatus	Electrolab, India
Disintegration apparatus	Electrolab, India
Franz diffusion cell	Electrolab, India

Methods

The present work was aimed to formulate different fast dissolving formulations i.e fast dissolving oral film (FDOFs) and fast dissolving tablets (FDTs) of drug Amlodipine Besylate.

Formulation: "The FDOFs or an oral dispersible film was prepared using different polymers i.e. HPMC E15, Pectin, HPMC 15 LV, HPMC 50 LV, out of these different formulations the batch prepared with Pectin shows the better result of disintegration". It was prepared by solvent casting method. Secondly, batches of FDTs or oral dispersible tablets was prepared by using different concentrations of MCC SANAQ BURST and using starch as binder in different ratios prepared by direct compression method.

Identification of Drug

Determination of meltingpoint: Melting point determination of drug was carried out by open capillary method. In this method an open end capillary tube was taken and it was closed from one end by fusion and the drug was filled from another end. Then the capillary tube was dipped in digital melting point apparatus and the temperature at which drug start to melt was noted Florey et al (2005).

Fourier Transform Infrared (FTIR) Spectroscopy Analysis

Fourier transform infra-red analysis was done for the determination of drug- polymer interaction. In this analysis the samples were mixed with KBr and a pressure of 300kg/cm was applied to get pellets. FTIR spectra of pure drug (AmlodipineBesylate) were recorded Kurkurni etal (2003).

Analytical Method

Preparation of media: Different media of 0.1 N HCl, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer were prepared.

Scanning of drug: "Accurately weighed 100 mg drug was dissolved in 100 ml of different media (distilled water, 0.1 N HCL, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer and methanol) to make a solution of concentration 1mg/ml". "Further suitable dilutions were made with different media and scanned within the range of 200- 400 nm with UV- Visible spectrophotometer to get absorption on maximum wavelength".

Preparation of standard Calibration Curve: Accurately weighed 100 mg of Amlodipine Besylate was dissolved in 100 ml of different media (distilled water, 0.1 N HCL, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer and methanol) to make a solution of 1mg/ml known as stock solution. From this different concentrations of drug from 5- 25 µ g/ml were prepared. Then the absorbance of each concentration at λmax was taken and slope, intercept and correlation coefficient were calculated.

Preformulation studies of drug: Pre formulation testing is the first step in the development of dosage forms of a drug substance. Pre formulation studies can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients as described byIshikava et al (2001).

Following pre formulation studies were carried out:

Determination of Solubility of drug: A small quantity (2 ml) of different media (distilled water, 0.1 N HCl, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer) was taken and drug was added to get a saturated solution. From the saturated solution 0.5 ml of solution was withdrawn and filtered. The filtered solution was diluted suitably and absorbance was taken. From the absorbance the concentration of soluble drug in different media was calculated from the regression equation of standard plot.

Determination of Partition Coefficient of drug: In 30 ml of pH 7.4 phosphate buffer drug was added to prepare a saturated solution and absorbance was taken after suitable dilution. After this the saturated solution was poured into a separating funnel and 30 ml of n-octanol was added into it. This mixture was shaken for 30 min and then was kept aside for 20 min to separate both the layers. Finally the aqueous layer was separated out and absorbance was taken and concentration was taken accordingly.

Bulk Density of powder blend (formulation): Bulk density (g/ml) is determined by pouring bulk drug into a graduated cylinder via a large funnel and measured the volume and weight. The ratio of mass (weight) to volume is known as the density of the material. This initial volume is called the bulk volume. Apparent bulk density (ρb) was determined by placing pre sieve drug excipients blend into a graduated cylinder and measuring the volume (Vb) and weight (M). Bulk density is calculated by using the formula.

$$\rho b = M/Vb$$

Tapped Density as described by Lachman et al (1990):Tapped density is determined by placing the graduated cylinder that contain a known mass of powder on a mechanical tapper apparatus, which operated fixed number of taps (~1000) until the powder bed volume reaches a minimum. "Using the weight of powder in cylinder and this minimum volume, the tapped density may be computed. The volume (V) occupied by powder in the cylinder was measured". The tapped density (ρt) was calculated using the formula:

$$\rho t = M / V$$

Angle of repose as described by Lachman et al(1990):The most extreme edge that can be gotten between the flat plane and the unattached surface of a powder load. The part power of free powder can be estimated by the point of rest (α). It is characteristic of the stream properties of the powder. The point of rest was controlled by the pipe technique. The mix was poured through the pipe that can be raised vertically until a greatest cone tallness (h) was gotten. The sweep of the pile was estimated. This is the edge ϕ as characterized by the condition.

$$\text{Tan } \theta = 2h/ D$$

Hausner's Ratio as described by Lachman et al(1990):Hausner's ratio is an index of ease of powder flow it is given by the formula:

$$\text{Hausner's ratio} = \rho t / \rho b$$

ρt= tapped density
ρb= untapped density

Film Formulation and its Optimization: "Polymers were taken in given quantity in 50 ml beaker in which 10 ml water is used as a solvent, glycerol is added and kept in magnetic stirrer for 1 hour until the clear solution is formed and is then kept aside for removal of bubble formed in the beaker. In another beaker drug and citric acid is dissolved in methanol and kept alongside in stirrer".

After clear solution is formed, tween 80 and fructose was added and kept in magnetic stirrer for 30 min. Both the solutions were mixed slowly and coloring, flavoring agent (q.s) is added and then kept in stirrer for 2 hour. After settling down of bubbles, the solution is then poured in petri plates and kept at room temperature for 24 hour. Then the petri plate was kept in oven at 55ºC for 10 hour. The dried film was cut in 2 X 2 cm2 area.

Table 3: Formulation code for optimization of FDOFs on the basis of polymers

INGREDIENT	F1	F2	F3	F4	F5	F6
HPMC 15 LV	250	-	-	-	-	-
HPMC 50 LV	-	250	-	-	-	-
HPMC E15	-	-	250	-	-	-
Pectin	-	-	-	250	-	-
HPMC K4 M	-	-	-	-	250	-
PVA+ PVPK30	-	-	-	-	-	250
Drug	10	10	10	10	10	10
Citric acid	25	25	25	25	25	25
Fructose	50	50	50	50	50	50
Tween 80	15	15	15	15	15	15
Glycerol	90	90	90	90	90	90
Coloring agent	q.s	q.s	q.s	q.s	q.s	q.s

Formulation: The best formulation was selected (Formulation with Pectin as Polymer) and was again optimized on the basis of quantity of sweetening agent used for masking the taste of Amlodipine Besylate.

Table 4: Formulation code for optimization of ODOFs on basis of sweetening agents.

Pectin	400	250	250	400
Drug	10	10	10	10
Fructose	600	200	600	200
Tween 80	15	15	15	15
Glycerol	90	90	90	90
Citric acid	25	25	25	25
Coloring agent	q.s	q.s	q.s	q.s

Characterization

Physical appearance and pH: "All the prepared Films were visually inspected for color, clarity, flexibility and smoothness. Also the film is checked for pH by dissolving it in distilled water and after 1 min solution is checked in pHmeter".

Thickness Uniformity: "The thickness of the formulated film was measured at 3 different places and average thickness of three readings was calculated".

Weight Uniformity: "For each formulation, three randomly selected films were used. For the weight variation test three films from each of the batches were weighed individually and average weight was calculated".

Folding endurance: It was measured manually for all the prepared films. A strip film (2X3 cm) was cut and repeatedly folded again at the same place until it brakes. The number of times the formulated film could be folded at the same place without any breaking/cracking gives the value of the folding endurance.

Percentage moisture absorption: "The thin films were weighed precisely and put in the desiccators containing 100ml of a soaked arrangement of potassium chloride, which keeps up 80-90% RH. Following three days, the movies were taken out and again gauged. The examination performed at room temperature". The level of dampness retention was determined utilizing the equation

$$Moisture absobtion \frac{Final weight - Initial weight}{Initial weight} \times 100$$

Drug content uniformity: "The thin films (1cm2) were sliced and added to a measuring utensil containing 100ml of phosphate-cushioned saline of pH 6.8. The medium was mixed with an attractive dot. The substance were separated utilizing Whatman channel paper and the filtrate was inspected for the medication content against the reference arrangement comprising of fake treatment films at 237 nm spectrophotometric ally". The analysis was rehashed to approve the outcome.

In vitro drug release studies: "20 ml of pH 6.8 phosphate cushion arrangement contained in the disintegration device, the turn speed of 50 rpm/min. At foreordained time stretches, 1 ml tests were pulled back utilizing a needle fitted with a channel. An equivalent volume of disintegration medium (additionally kept up at 37 ± 0.5ºC) was added to the measuring utencil so as to keep up a consistent volume of the disintegration medium". The pulled back examples were weakened reasonably, and the measure of medication discharged was resolved spectrophotometric ally at 237 nm

Permeation studies: "The in-vitro tranquilize discharge examines were directed utilizing Franz dissemination cells at 37±1°C with a receptor compartment containing 7.5 ml of cushion arrangement at pH 6.8. The movies were put on a cellophane layer and were mounted between the two compartments of the dissemination cell to such an extent that the support layer confronted the giver compartment and the glue film confronted the collector compartment and affixed with an O-ring. 1 ml tests were gathered intermittently through the inspecting port of the beneficiary cell at foreordained time spans (5, 10,15,20,25,30,35,40 min) and afterward supplanted with an equivalent volume of new receptor arrangement. The medication substance of the examples was dissected utilizing a spectrophotometer at a frequency of 237 nm". The entirety of the discharge tests were acted in triplicate, and the impacts of medication stacking and film thickness on the discharge profile were surveyed. The level of medication discharged was determined by partitioning the aggregate sum of discharged medication in the benefactor cell by the underlying measure of stacked medication in the film. (Patel et al, 2014)

Scanning Electron Microscopy (SEM) study: "SEM decides the surface morphology of the film as they uncovered as the best definition. The surface morphology of the enhanced definitions was seen with filtering electron magnifying lens. The examples were appended to the section surfaces with twofold sided cement tapes and the examining electron photomicrograph was taken at 200X, 500X, and 1000X amplification".

Drug scanning calorimetric: "The warm conduct of the unadulterated medication and medication with gelatin was recorded on differential examining calorimeter. Tests were precisely gauged and set in an aluminum dish and fixed with a top. Aluminum oxide was utilized as a kind of perspective. The warming pace of 10oC/min was applied at the scope of 50 to 300oC with a nitrogen cleanse of 0.2ml/min".

FDTs (fast dissolving tablets formulation):"Granulation: - Amlodipine Besylate, MCC Sanaq, Acacia, Starch, Mannitol was blended in blender to form hard mass and the resulting mass passed through 60# mesh size. The particles were retained on 60# are considered as granules.

Compression: "The required amount of granules was compressed in tablet punching machine to form tablet which was then optimized on basis of evaluation parameters".

Table 5: Formulation code for FDTs

Ingredients	Formulation code			
	FT1	FT2	FT3	FT4
Drug	10	10	10	10
MCC Sanaq Burst	120	100	80	70
Starch: Accacia(1:2)	30	30	30	30
Mannitol : Aspartame (1:2)	60	50	20	20
Talc	4	4	4	4
Citric acid	6	6	6	6

The best formulation was selected on the basis of disintegration time and drug release study which was further evaluated for all the evaluation parameters.

Weight variation test as described in Indian Pharmacopoeia (2010):"Loads of ten tablets separately and inside and out were taken". "At that point, the normal weight was determined from the all-out weight of the considerable number of tablets. The individual loads were then contrasted and the normal load of the tablet". The satisfactory rate contrast in the weight variety ought to be inside the cutoff points (± 5%).

Any variation in the weight of tablet (for any reason) leads to either under medication or over medication. So, every tablet in each batch should have a uniform weight. Deviation within the IP limits of 10 % is allowed as the tablet weighed 150mg.

Thickness

Thickness was determined of 10 tablets obtained by a digital vernier caliper (CD-6 CSX).

Hardness (Lachman et al, 1990):"Tablets require a specific measure of solidarity, to withstand the mechanical stun of dealing with in production, bundling, and transportation". The hardness of the tablet is characterized as the power applied over the width of the tablet so as to break the tablet. "The opposition of the tablet to scraped spot, chipping, or breakage under the state of capacity change and taking care of before use relies upon its hardness (kg/cm2)". The hardness of the tablet of every definition was resolved utilizing advanced hardness tester (EH 01P).

The **friability** of the tablets was resolved for twenty tablets taken arbitrarily from each group. "Subsequent to gauging, the tablets were set in the plastic office of the friability analyzer". The friability is assessed by the accompanying equation:

$$\text{Friability \%} = W1 - W2/W1 \times 100$$

Where

W1 is the heaviness of tablets before testing and W2 is the heaviness of tablets in the wake of testing.

Wetting time: "A conventional method was used to measure wetting time and capillarity of the Oral dispersible tablets. The tablet was placed in a Petridis of 5.5 cm in diameter, containing 10 ml of water at room temperature and the time for complete wetting was recorded. To check for reproducibility, the measurements were carried out three times and the mean value calculated".

In vitro disintegration Time as described by Lachman et al (1990)

"In-vitro breaking down time concentrate for FDTs was done in USP deterioration analyzer (ED 2AL) utilized 6 glass tubes that were three inches in length, open at the top, and held against a 10 – wreck screen at the base finish of the bushel rack get together". "To trial of breaking down time, one tablet was set in each cylinder. The bin rack was situated in a 1-liter measuring utencil of phosphate cradle (pH 6.8) at 37 ±0.5ºC. The time taken for the total breaking down of the readied tablet with no substantial mass staying in the crumbling mechanical assembly was estimated in a moment or two.

Content Uniformity: "Accurately weighed powder from each batch equivalent to 10 mg drug, was shaken with 100 ml of phosphate buffer pH 6.8 solution from which 10 ml was pipette out and then diluted up to 100 ml". Absorbance of appropriately diluted solution was measured at 285.5. (Indian Pharmacopoeia2010)

In vitro drug release studies of prepared FDTs as described in Indian Pharmacopeia (1996)

"In vitro dissolution study for fabricated FDTs was carried out in USP Dissolution Apparatus II paddle type (TDT -08L) at 50 rpm in 900 ml of 6.8 pH buffer as dissolution media, maintained at 37±0.5ºC. The study was carried for 30 min and at predetermined time intervals (0, 2, 5, 10, 15, 20, 25, 30 min) 5 ml aliquots were withdrawn, diluted, filtered and analyzed spectrophotometric ally at λmax 285.5 nm". An equal volume of fresh medium, which was pre- warmed at 37ºC, was replaced into the dissolution medium after each sampling. Dissolution study was performed in triplicate for each of the batch.

Drug scanning calorimetric: "The thermal behavior of the pure drug and drug with MCC SANAQ BURST was recorded on differential scanning calorimeter. Samples were accurately weighed and placed in aluminum pan and sealed with lid. Aluminum oxide was used as the reference". Heating rate of 10oC/min was applied at the range of 50 to 300oC with nitrogen purge of 0.2ml/min.

Comparative in-vitro drug release of FDFs, FDTs and marketed tablet of Amlodipine Besylate

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"In-vitro breaking down time concentrate for FDTs was done in USP deterioration analyzer (ED 2AL) utilized 6 glass tubes that were three inches in length, open at the top, and held against a 10 – wreck screen at the base finish of the bushel rack get together". To trial of breaking down time, one tablet was set in each cylinder. The bin rack was situated in a 1-liter measuring utencil of phosphate cradle (pH 6.8) at 37 ±0.5ºC. The time taken for the total breaking down of the readied tablet with no substantial mass staying in the crumbling mechanical assembly was estimated in a moment or two.

Results and Discussion

Identification of Drug

Determination of melting point

The melting point of Amlodipine Besylate was found to be 190◦C. The reported value of melting point is 195◦C- 204◦C (Indian Pharmacopoeia., 2010). From the result of melting point determination of drug, the drug was identified as Amlodipine Besylate.

Fourier Transforms Infrared (FTIR) Spectroscopy Analysis:

The reported characteristics peaks of Amlodipine Besylate were found to be retained in the FTIR spectra of given drug. Thus, the drug was identified as Amlodipine Besylate

Table 6: Major IR peaks of Amlodipine Besylate

Assignments	Reported Peaks (cm^{-1})	Observed Peaks (cm^{-1})
-OH	3180	3234
-N-H	3300	3369.7
-C-H	2958.5	2947.9
-C=O	1685.7	1688.8
-C=C	1434	1437

Analytical Studies

The λ_{max} of drug AmlodipineBesylate is shown in the Table 7 with their reported.

Table 7: Observed value of λ_{max} in different solvent

Medium	λ_{max}(nm)	
	Observed value	Reported value
Distilled water	237.8	238 (Kumar et al., 2013)
0.1 N HCl	236.8	236 (Joshi et al., 2011)
pH 6.8 phosphate buffer	237.5	238 (Kumar et al., 2013)
pH 7.4 phosphate buffer	236.7	237.5 (Joshi et al., 2011)
Methanol	237.8	237.5 (Joshi et al., 2011)

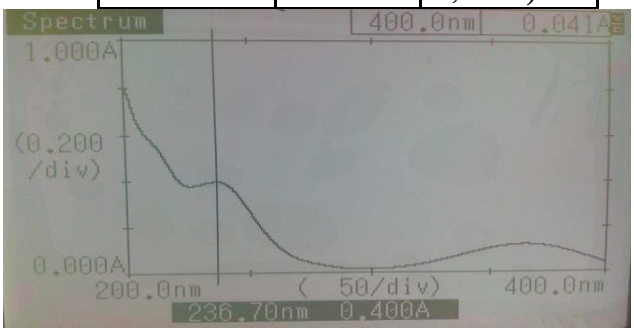

Fig 1: UV scans of Amlodipine Besylate in 7.4 phosphate buffer

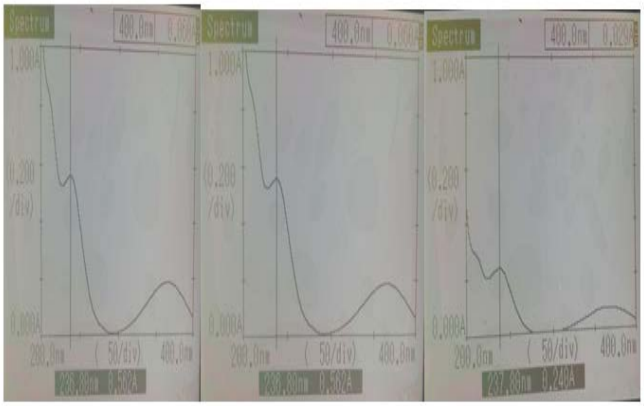

Fig 2: UV scans of AmlodipineBesylate in 6.8 phosphate buffer, 0.1 N HCl & methanol

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Preparation of Standard plot: The standard plot of AmlodipineBesylate was prepared in 0.1 N HCl, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer, distilled water and methanol. The absorbance is given in table 6.2, 6.3, 6.4, 6.5, 6.6 and standard plot in fig. 6.3, 6.4, 6.5, 6.6.

Table 8:Absorbance of Amlodipine Besylate in 0.1 N HCl

Concentration (µg/ml)	Absorbance			
	A1	A2	A3	Mean ± SD
5	0.152	0.154	0.153	0.153 ± 0.0010
10	0.348	0.349	0.349	0.349 ± 0.00057
15	0.523	0.524	0.523	0.523 ± 0.00057
20	0.699	0.695	0.697	0.697 ± 0.0020
25	0.854	0.855	0.854	0.854 ± 0.00057

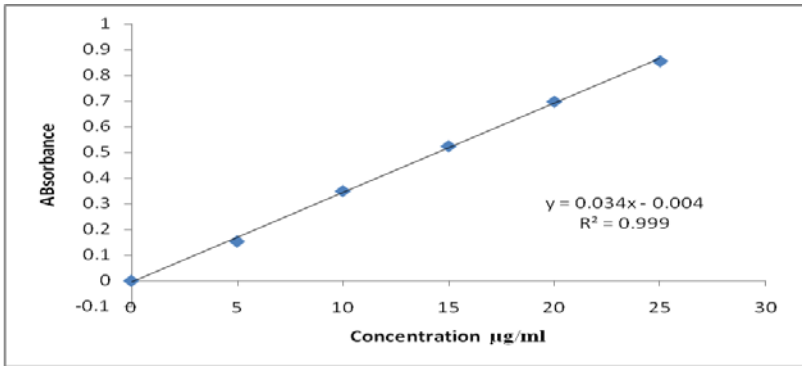

Fig 3: Calibration cure of Amlodipine Besylate in 0.1 N HCL

Table 9: Absorbance of AmlodipineBesylate in 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance			
	A1	A2	A3	Mean
5	0.218	0.217	0.216	0.217 ± 0.0010
10	0.401	0.406	0.404	0.404 ± 0.0025
15	0.610	0.611	0.610	0.610 ± 0.00057
20	0.805	0.804	0.804	0.804 ±0.0005
25	0.964	0.957	0.962	0.961 ± 0.0036

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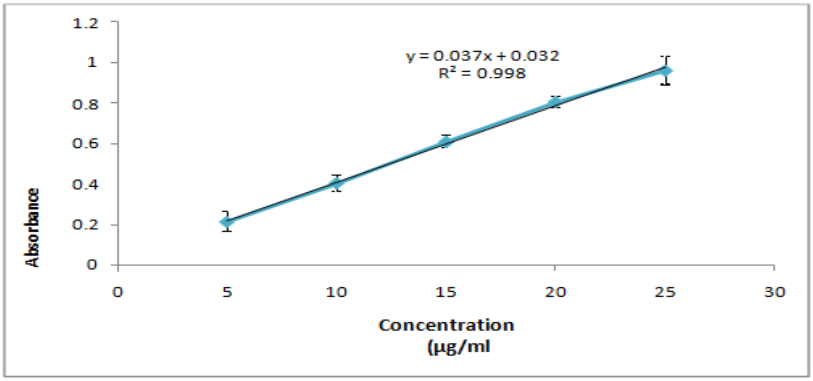

Fig. 4: Calibration curve of Amlodipine Besylate in 6.8 phosphate buffer

Table 10: Absorbance of Amlodipine Besylate in 7.4 phosphate buffer

Concentration (µg/ml)	Absorbance			
	A1	A2	A3	Mean ± SD
5	0.144	0.143	0.145	0.144 ±0.000471
10	0.272	0.271	0.168	0.270 ±0.00163
15	0.398	0.399	0.403	0.400± 0.002944
20	0.514	0.5.14	0.516	0.515 ±0.00163
25	0.654	0.655	0.654	0.654 ±0.001633

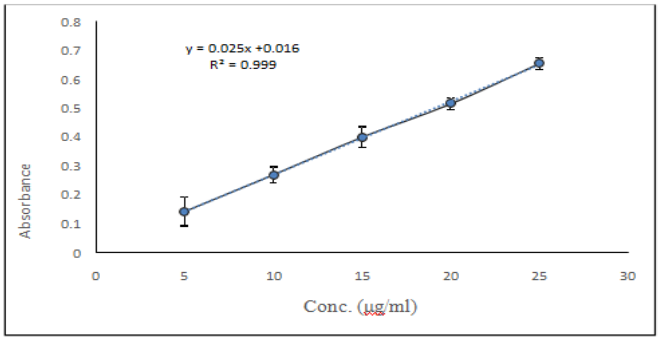

Fig. 5: Calibration curve of Amlodipine Besylate in 7.4 phosphate buffer

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Table 11: Absorbance table of Milli-Q- Water

Concentration (µg/ml)	Absorbance			
	A1	A2	A3	Mean ± S.D
5	0.201	0.203	0.205	0.203± 0.0016
10	0.390	0.396	0.392	0.392± 0.0028
15	0.588	0.588	0.589	0.589± 0.0040
20	0.771	0.773	0.772	0.771 ±0.00047
25	0.913	0.913	0.912	0.913 ±0.000943

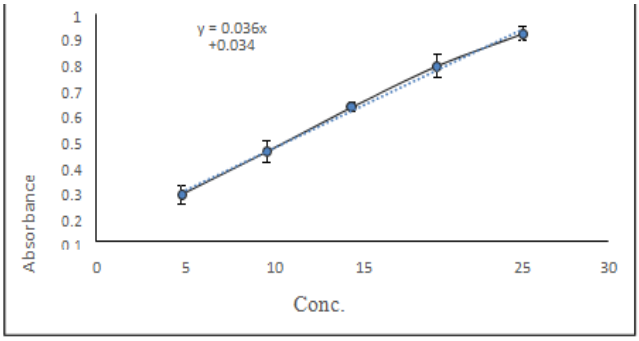

Fig. 6: Calibration curve of Amlodipine Besylate in distil water

Table 12: Absorbance of Amlodipine Besylate in methanol

Concentration (µg/ml)	Absorbance			
	A1	A2	A3	Mean ± SD
5	0.201	0.203	0.205	0.203 ± 0.045
10	0.390	0.396	0.392	0.392 ± 0.037
15	0.588	0.588	0.589	0.589 ± 0.038
20	0.771	0.773	0.772	0.771 ± 0.035
25	0.913	0.913	0.912	0.913 ± 0.047

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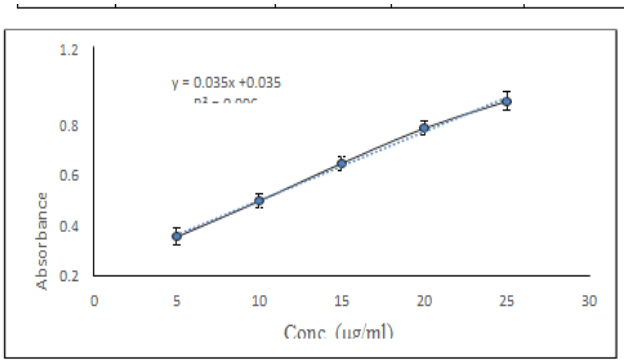

Fig. 7: Calibration curve of Amlodipine Besylate in methanol

Preformulation Studies:

Solubility of drug: Solubility of AmlodipineBesylate was determined in different media such as distilled water, 0.1 N HCl, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer and methanol. By the solubility study it was shown that the drug is highly soluble throughout the pH of GIT. Drug has highest solubility in 0.1 N HCl.

Table 13: Solubility profile of drug in different solvent

Solubility (mg/ml)		
Solvent	**Observed value ± S.D**	**Reported value**
Distilled water	8.43 ± 0.48	8.03
0.1 N HCL	11.35 ± 0.23	10.68
pH 6.8 phosphate buffer	3.64 ± 0.45	3.12
pH 7.4 phosphate buffer	1.43 ± 0.103	1.63
Methanol	12.22 ± 0.05	12.8

Partition coefficient: The partition coefficient of AmlodipineBesylate was found to be 4.2 and log P value was found to be0.621

Formulations of FDOFS of Amlodipine Besylate: Six formulations were designed varying the polymers in it and maintaining other ingredients in same ratio (Table 5.1). FDOFs were formulated and were evaluated in accordance with the results obtained.

Folding endurance- It indicates the film did not break and therefore would make their strength and integrity with mouth pH.

Disintegration time- It indicates the time taken to disintegrate completely in the buffer medium. The values are found in range 25 sec to 1 min 25 sec. The best disintegration time was seen of F4 formulation containing Pectin as polymer.

Table 14: Results for different formulation to be optimized with respect to different polymers

Formulation code	pH (n=2)	Weight (mg) ± SD (n=1)	Disintegration time ± SD (n=10) (sec)	Folding endurance (n=10)	Dissolution time (min.) (n=10)
F1	6.1 ± 0.1	40 ± 2.16	60 ± 2.26	100 ± 4.21	14 ± 2.12
F2	6.0 ± 0.17	35 ± 1.82	90 ± 2.10	150 ± 5.63	13 ± 1.03
F3	6.3 ± 0.17	38 ± 1.82	55 ± 6.32	200 ± 13.15	15 ± 2.09
F4	6.9 ± 0.1	38 ± 1.49	25 ± 2.16	250 ± 12.78	10 ±1.89
F5	6.1 ± 0.1	41 ± 1.88	60 ± 2.70	130 ± 14.75	13 ± 4.13
F6	6.4 ± 0.1	39 ± 1.49	40 ± 4.05	180 ± 3.43	12 ± 2.09

From the results obtained from six different formulations, the optimized formulation was found to be F4 that disintegrates in 25 ± 2.16 sec in mouth and shows dissolution within 10 ± 1.89min. As the prepared formulation of FDOFs of AmlodipineBesylate tastes bitter so masking was further done by changing the ratio of sweetening agent. A further study was carried out for optimization of formulation with respect to sweetening agent.

Appearance – all the prepared formulation was transparent visually, having pungent odor with no taste (identified by 10 volunteers).

Moisture content - it was found in range 2.06 to 2.46. The less moisture loss in formulation helps the films to remain stable and free from completedrying.

Drug content- the results for all of prepared formulations were uniformly dispersed range from 96.99 % to98.06%.

Table 15: Results for optimization of formulation with respect to sweetening agent of FDOFs

Formulation code	Odor (n=3)	Taste (n=10)	Texture (n=3)	Disintegration time (n=3)	Moisture content (n=10)	Drug content (n=10)
F7	Pungent	Tasteless	Viscous	60 sec	2.06 ±0.75	97.22± 0.19
F8	Pungent	Bitter	Smooth	1 min	2.46 ±0.43	96.99± 1.66
F9	Pungent	Tasteless	Smooth	25 sec	2.23 ±0.80	98.06± 1.10
F10	Pungent	Bitter	Smooth	45 sec	2.46± 0.83	97.06± 1.38

From the results obtained the best formulation found was F9 as the bitter taste was masked to tasteless by taking fructose approx 600 mg. Hence, all the evaluation parameters was further evaluated for formulationF9.

In vitro drug release profile ofFDOFs: In vitro drug release profile is an important tool that is employed to predict in advance how drug will behave in vivo. The release study is required for predicting the reproducibility of rate and release. In-vitro dissolution study was carried out in USP Dissolution Apparatus II paddle type (TDT - 08L) at 50 rpm in 900 ml of 6.8 pH buffer as dissolution media, maintained at 37±0.5ºC. The study was carried for 30 min and at predetermined time intervals (0,3,6,9,12, 15, 18, 21 min) 5 ml aliquots were withdrawn, diluted, filtered and analyzed spectrophotometrically at λmax 237.5 nm. An equal volume of fresh medium, which was pre- warmed at 37ºC, was replaced into the dissolution medium after each sampling. Dissolution study was performed in triplicate for each batch. The results of in vitro drug release studies for F9 formulation are tabulated below (table 6.12) and illustrated in

Table 16: *In vitro* drug release profile of F9 Formulation

Time (Min.)	Abs.	Conc. (µg/ml)	Drug in 5ml	Drug in 900ml	cf	Actual Amt. in 900 ml in mg	cumulative drug release	Cum % Drug Release
0	0	0	0	0	0	0	**0**	**0**
3	0.134	2.72973	13.648	2456.75	0	2.456	0.245	**24.567**
6	0.265	6.27027	31.351	5643.24	13.64	5.643	0.564	**56.432**
9	0.398	9.864865	49.324	8878.37	31.35	8.878	0.887	**88.783**
12	0.422	10.51351	52.567	9462.16	49.32	9.462	0.946	**94.621**

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15	0.424	10.56757	52.837	9510.81	52.56	9.510	0.951	**95.108**
18	0.424	10.56757	52.837	9510.81	52.83	9.510	0.951	**95.108**
21	0.424	10.56757	52.837	9510.81	52.83	9.510	0.951	**95.108**

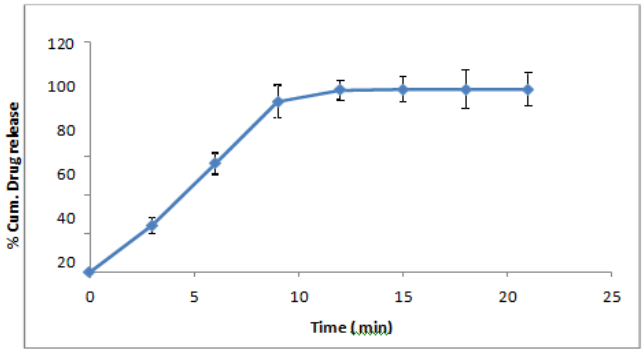

Fig. 8: Drug release profile of F9 formulation of FDOFs

Permeation studies of FDOFs: From the in vitro permeation study it was seen that approx 90.12% drug was permeated within 30 min. The % amount of drug permeated was plotted against time to obtain permeation time profile. It was observed that drug shows flux of 0.14 mg/cm2/hr. So it was seen that the formulated film was easily solubilized and absorbed from mouth.

Time (min)	Absorbance	Conc. (µg/ml)	Amount in µg/5 ml	Amount in 7.5 ml	correction factor	DM	S.DT	J=DM/DT
0	0	0	0	0	0	0	0	0
5	0.148	3.10	15.540	23.31	38.85	0.0388	0.166	0.23
10	0.209	4.75	23.783	35.6	59.45	0.0594	0.333	0.178
15	0.276	6.56	32.83	49.25	82.05	0.0820	0.5	0.16
20	0.356	8.72	43.64	65.47	109.12	0.109	0.666	0.16
25	0.375	9.24	46.21	69.32	115.54	0.115	0.83	0.13
30	0.405	10.05	50.270	75.40	125.67	0.125	1	0.12

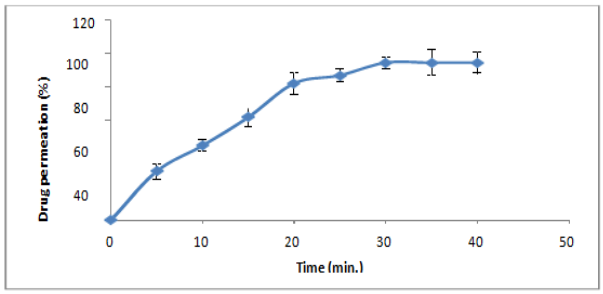

Fig. 9: Drug permeation profile of FDOFs of Amlodipine Besylate

Conclusion

Oral dissolving formulations have better patient compliance and may offer improved biopharmaceutical properties, improved efficacy and better safety compared with conventional oral dosage forms. The target population has expanded to those who want convenient dosing anywhere, anytime, without water within seconds.

The present study aims to formulate FDOFs by solvent casting method and FDTs by direct compression method and to study the comparative drug release profile with respect to marketed formulation .Amlodipine Besylate was selected as drug that belongs to BCS Class I

i.e. high solubility and high permeability. The identification and some of the analytical method development studies of Besylate were carried out. The melting point was 190ºC which lies in the range of accurate temperature (195-204ºC) reported for AmlodipineBesylate as described by Krushnan et al (2013), IP (2010). The standard calibration curves were prepared in 0.1 N HCl, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer, methanol and distilled water. The serial dilutions prepared from the stock solution of AmlodipineBesylate in 0.1 N HCl, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer, methanol and distilled water were scanned in a UV- visible double beam spectrophotometer. The λmax was 236.8 nm for 0.1 N HCl, 237.5 nm for pH 6.8 phosphate buffer, 236.7 nm for pH 7.4 phosphate buffer and 237.8 nm for distilled water which is very close to 238 nm for 0.1N HCl and 238 nm for pH 6.8 phosphate buffer, 237.5 nm for pH 7.4 phosphate buffer and 238 nm for distilled water as reported in literature. Standard deviation of absorbance ranged between 0.0005-0.002 with a regression value of 0.998 in HCl, 0.0005-0.003 with a regression value of 0.998 in pH 6.8 phosphate buffers, 0.0004-0.002 with a regression value of 0.999 in pH 6.8 phosphate buffer and 0.0005-0.005 with a regression value of 0.996 in distilled water. It was confirmed that the drug was pure.

Various formulations of FDOFs of AmlodipineBesylate was prepared with different polymers out of which formulation prepared with polymer pectin (F4) shows better disintegration time of 25 sec which was further optimized with respect to sweetening agent. These films was than evaluated for various parameters like thickness, drug content, folding endurance, disintegration time, drug uniformity, folding endurance, permeation studies. In vitro drug release data of F9 formulation showed 95% of drug release as evaluated.

Further, various formulations of FDTs was prepared using direct compression method. The use of super disintegrates for preparation of fast dissolving tablets was highly effective and commercially feasible which accelerate disintegration ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water was showing best results in breaking of tablets and hence faster disintegration. Disintegration was reported to have an effect on dissolution characteristics. The FDTs was prepared using MCC SANAQ BURST as a super disintegrating agent. Various evaluation parameters like hardness, pH, weight variation, drug content uniformity, thickness, disintegration, friability was done. The in vitro drug release showed F1 formulation with best result of82.54%

The drug release of both the formulations was compared with conventional Amlodipine tablets and was seen significant change in dissolution rate, as the prepared formulations FDOFs and FDTs dissolves drug fastly indicating the satisfactory of fast dissolving film formulation that can be used as an alternative to the oral conventional tablet. DSC and FTIR reveal no drug and polymer interaction. SEM studies shows that the formulated film was clear, transparent and had smooth surface.

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