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Formulation and evaluation of fast dissolving sublingual tablets of amlodipine besylate

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ABSTRACT

The aim of this study was to prepare fast disintegrating sublingual tablets of amlodipine besylate by using different disintegrant for the potential emergency treatment of angina and hypertension. The sublingual tablets of amlodipine besylate were prepared by direct compression using Tulsion 671 and crospovidone as a superdisintegrants. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, Wetting time, water absorption ratio and in vitro disintegration time. All prepared tablets shows the disintegration time less than 1 minute which was within Pharmacopoeial limit. All the formulations were evaluated for hardness, friability, thickness and weight variation. The results revealed that the tablets had acceptable hardness 3.15 – 3.59 kg/cm^2 which further resulted into acceptable disintegration time 11-59 sec. It was found that the prepared formulations were also complying with the Pharmacopoeial standards for weight variation. Optimum formulation of Tulsion 671 and Crosspovidone in combination F-7 showed disintegration time of 11 seconds and 95.89 % of drug release.

Keywords: Amlodipine besylate, Tulsion 671, sublingual tablets, water absorption ratio.

INTRODUCTION

Sublingual meaning literally 'under the tongue' refers to a method of administering substances via the mouth in such a way that the substances are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract. The routes of absorption via the highly vascularised buccal mucosa allow the substance a more direct access to the blood circulation, thus providing direct systemic administration medically, sublingual drug administration is applied in the field of cardiovascular drugs, steroids, some barbiturates and enzymes. It has been a developing field in the administration of many vitamins and minerals which are found to be readily and thoroughly absorbed by this method.[1]

There is considerable evidence that most sublingual substances are absorbed by simple diffusion; the sublingual areas acting rather like litmus paper, readily soaking up the substance. However, not all substances are permeable and accessible to the buccal mucosa. The mucosa functions primarily as a barrier-similar to skin. But while it was once believed that the barrier of human skin was 'impenetrable' (e.g., Vitamins E and C creams, hormones, nicotine patches) and it is a growing field of endeavour. Similarly the buccal mucosa presents an ideal site for absorption.

The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes. The sublingual dosage form offers fast release of drug from the formulation and it reaches the systemic circulation directly, which bypasses the

metabolism of the Amlodipine in the liver and offers a fast relive form the anginal pain, hypertension which will be worth in such conditions. [2]

Amlodipine is a dihydropyridine calcium channel antagonist originally introduced for the treatment of hypertension, certain types of angina, and coronary heart failure. It is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Hence, the sublingual absorption of drugs is expected to be rapid thus eliciting a faster therapeutic so, there is a need to develop a sublingual tablet containing of Amlodipine with immediate response, escape from first pass metabolism, reduced manufacturing difficulties and cost effectiveness.[3]

MATERIALS AND METHODS

Amlodipine besylate and Tulsion 671 were obtained as gift sample by Glenmark Pvt Ltd, Nashik (Maharashtra) India. Crospovidone and Magnesium stearate were obtained as a gift sample from the Molychem Pvt Ltd, Mumbai, India. All other materials and solvents used were of analytical grade.

Preparation of sublingual tablets of amlodipine besylate:
Sublingual tablets of amlodipine besylate were prepared using the tulsion 671, crospovidone use as superdisintegrants, spray dried mannitol as diluents, sodium saccharin as sweetening agent, avicel-102 as the diluents. The amlodipine equivalent to 10 mg, mannitol, sodium saccharine and avicel PH-102 were mixed thoroughly in glass mortar using a pestle. Superdisintegrants were incorporated in the powder mixture according to each formulation in the tablet and finally magnesium stearate, talc was added as lubricant, and then passed through sieve no. 60. Tablets were prepared using 7 mm punch of the rotary tablet machine [Jaguar (JMD4-8)]. Compression force was kept constant for all formulations. Final formulation batches are shown in table no. 1.

Table no.1: Preparation of final formulation

Ingredients(Mg)	F1	F2	F3	F4	F5	F6	F7
Amlodipine besylate	10	10	10	10	10	10	10
Tulsion 671	----	-----	-----	4	6	8	4
Crospovidone	4	6	8	-----	-----	----	4
Avicel PH-102	24	22	20	24	22	20	20
Mannitol	50	50	50	50	50	50	50
Sodium saccharine	10	10	10	10	10	10	10
Talc	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1
Total wt. of tablets	100	100	100	100	100	100	100

Evaluation of tablet blend:
The prepared powder blend of all above mentioned formulations was performed for micromeritics properties which were discussed below:

Angle of repose:
Flowability of blend was determined by calculating angle of repose by fixed height method. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the stem of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured. Angle of repose was calculated from the average radius using the following formula. [4]

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

where, θ = angle of repose, h = height of the pile, r = average radius of the powder cone.

Bulk density:
Bulk density was determined by pouring gently 25 gm of sample through a glass funnel in to a 100 ml graduated cylinder. The volume occupied by the sample was recorded. Bulk density was calculated. [5]

$$\text{Bulk density (g/ml)} = \frac{\text{Weight of sample in gm}}{\text{Volume occupied by the Sample}}$$

Tapped Density:
25 gm sample (tablet blend) was poured gently through a glass funnel in to a 100ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after tapping were recorded and tapped density was calculated. [6]

$$\text{Tapped density (g/ml)} = \frac{\text{Weight of sample in gm}}{\text{Volume occupied by the sample}}$$

% Compressibility:
It was also one of the sample methods to evaluate flow property of a powder by comparing the bulk density and tapped density. A useful empirical guide was given by the Carr's compressibility. [7]

$$\text{Carr's index} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times 100$$

Hausner ratio:
It provides an indication of the degree of densification which could result from vibration of the feed hopper (USP, 2009).

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Lower Hausner ratio indicates better flowability while higher hausner ratio indicates poor flowability.

Post compressed evaluation of amlodipine sublingual tablets:
The prepared tablets of various formulations form F1-F7 were prepared and evaluated for various official as well as non-official test parameters which were discussed below:

Weight variation:
It was performed as per the method given in the Indian pharmacopoeia. Tablets were randomly checked to ensure the proper weight tablets were being made. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated. [8]

Friability:
The 20 tablets were weighed and placed in the roche friabilator test apparatus, the tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 revolutions the tablets were de-dusted and weighted again. The friability was determined as the percentage loss in weight of the tablet. [9]

$$\% \text{ Friability} = \frac{\text{Initial wt. of tablet - Final wt. of tablet}}{\text{Initial wt. of tablet}} \times 100$$

Hardness:
Hardness was measured using the Monsanto or Pfizer hardness tester. Measure the pressure required to break diametrically placed tablet, by a coiled spring. The result of weight variation was shown in table no.2. [10]

Dimensions:
The thickness and diameter of the tablets was determined using a micrometer screw gauge. Five tablets from each type of formulation were used and average values were calculated.

***In-vitro* disintegration studies:**
Initially the disintegration time for fast dissolving tablets was measured using the conventional test for tablets as described in the Pharmacopoeia. Tablets were placed in the disintegration tubes and time required for complete disintegration, that is without leaving any residues on the screen was recorded as disintegration time.

A modified method was also used to check the disintegration time. In about 3 tablets were tested from each formulation. In disintegration time study tablet was put into the 100 ml pH 7.4 phosphate buffer containing beaker at the 37±2°C. Tablet was placed in the cylinder and time required for the complete dispersion of tablet in the cylinder was recorded as the disintegration time [8]

Wetting time:
The method reported by Yunixia in 1999 was followed to measure tablet-wetting time. A piece of tissue paper folded twice was placed in a small petri dish (internal diameter =6.5 cm) containing 6 ml pH 7.4 phosphate buffer, a tablet was put on the paper containing amaranth powder on the upper surface of the tablet, and the time required for formation of pink colour was measured as wetting time. Three trials for each batch were performed and standard deviation was also determined. [11]

Water absorption ratio:
A piece of tissue paper folded twice was placed in a small petri dish containing 6ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wetted tablet was then weighed. Water absorption ratio R was determined using following equation. [12]

$$R = \frac{Wa - Wb}{Wb} \times 100$$

Where, Wa = Weight of the tablet after wetting.
Wb= Weight of the tablet before wetting.

Uniformity of Content:
Five tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 10 mg of amlodipine was weighed and dissolved in 100 ml of pH 7.4 phosphate buffer, This was the stock solution from which 1 ml sample was withdrawn and diluted to 10 ml with pH 7.4 phosphate buffer, The absorbance was measured at wavelength 239 nm using double beam UV-Visible spectrophotometer. [13]
Content uniformity was calculated using formula:

% Purity = 10 C (Au / As)

Where, C – concentration
Au and as – absorbance of unknown and standard respectively

***In-vitro* drug release study:**
Literature reveals that dissolution of sublingual tablets should be seen in pH 7.4. Dissolution studies were carried out for optimized formulation employing USP dissolution testing apparatus (TDT-08L, Electro lab, mumbai) type II paddle method. The dissolution medium (900 ml) at 50 rpm and 37 ± 0.5ºC. A 10 ml of sample was periodically withdrawn at 2, 4, 6, 8, 10, 12, 14 min. and volume replaced with equivalent amounts of same dissolution medium to maintained sink condition. The samples were analyzed spectrophotometrically at 239 nm by using pH 7.4 Phosphate buffer as a blank and drug content in dissolution sample were determined by using calibration curve. The UV visible spectrophotometer (UV 3000+ Labindia, mumbai) was used to measured absorbance. [14]

Compatibility study by FT-IR:
Drug- excipients compatibility was studied by using FT-IR spectral analysis. FT-IR instrument (Shimadzu, Japan) used for the drug-excipients interaction study. A preliminary study was carried out with formulation excipients to determine drug-excipients interaction or compatibility. Drug-excipients compatibility study included amlodipine, tulsion 671, crospovidone (CP), and avicel PH-102. Amlodipine was uniformly mixed in 1:1 ratio with the excipients and the mixture was placed in glass vials. Vials were sealed by carnauba wax were kept at room temperature and 40°C and 75 % RH. After 30 days sample were withdrawn and observed for change in colour and chemical change by recording FT- IR spectrums. The scanning range was 4000 to 400 cm^{-1}. [15]

Compatibility study by DSC:
Differential scanning colorimetry was performed on a Mettler DSC-6220, Japan instrument with a thermal analyzer. Under nitrogen flow of 20 ml/min, sample weights 2 mg for amlodipine besylate. 2 mg respectively for drug, drug-polymer mixture and crushed tablet were sealed in aluminium pan, and heated at a scanning rate of 10 ºC/min from 40 ºC to 300 ºC. An empty aluminium pan was used as reference. [15]

Accelerated stability study of optimum formulation:
Stability testing of optimized formulation batch F7 was carried out to determine the stability of drug and carrier and also to determine the physical stability of formulation under accelerated storage condition. The prepared tablets were placed in borosilicate screw capped glass containers. The samples were kept at condition of 45°C/75% RH and were analyzed at 0^{th}, $30^{th,}$ 60^{st}, 90^{th} days for their changes in.[16]

Precompression studies:

Precompression studies include the evaluation of tablet powder blend for the micromeritic properties like angle of repose, tapped density, bulk density, carr's index, hausner ratio. Their results were summarized in table no. 2.

Table no.2: Micromeritics properties of powder blend

Parameter / Batch	Angle of repose (^{0})	Bulk density (g / ml)	Tapped density (g / ml)	Carr's index (%)	Hausner's ratio
	Mean ± SD (n=3)				
F1	25.43 ± 0.50	0.57±0.31	0.63±0.40	11.67±0.73	1.10±0.10
F2	27.97 ± 0.34	0.59±0.22	0.69±0.22	14.87±0.60	1.17±0.08
F3	26.69 ± 0.55	0.58±0.18	0.64±0.20	13.72±0.27	1.09±0.03
F4	27.65 ± 0.93	0.55 ± 0.22	0.62±0.24	15.71±0.71	1.13±0.09
F5	24.32 ± 0.78	0.57 ± 0.25	0.67±0.51	15.31±0.99	1.18±0.14
F6	25.71 ± 0.59	0.54 ± 0.25	0.65±0.36	16.81±0.77	1.20±0.11
F7	26.93 ± 0.46	0.59 ± 0.24	0.66±0.32	12.96±0.49	1.13±0.09

The above results predict that, the Carr's index is in the range of 10-20% which is considered as excellent compression property. Angle of repose less than 30° gives the excellent flow property to the powder blend. Similarly, the bulk density and tapped density value was found to be less than one. Hence have good flow property so, all these results indicate that, the powder blend possess satisfactory flow and compressibility properties.

Post compressed evaluation of sublingual tablets of amlodipine besylate:

Physical evaluation of tablets:

All the tablet preparations were evaluated for various physical parameters and content uniformity before proceeding further table no.3 includes the values (mean ± SD) of weight variation, hardness, diameter and thickness of formulated batches prepared using different combinations of functional excipients. Tablet weights in all batches varied between 99.40 to 101.46, thickness between 2.86 mm to 2.95 mm and tablet hardness between 3.18 to 3.59 kg/ cm^2. Thus all the physical parameters of the manually compressed tablets were quite within control. The data of physical evaluation was showed in table no. 3

Table no.3: Physical evaluation of sublingual amlodipine tablets

Parameter / Batch	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	% Friability
	Mean ± SD (n=3)			
F1	2.91±0.045	3.59±0.31	99.54±0.43	0.70±0.21
F2	2.96±0.035	3.51±0.29	101.00±0.10	0.68±0.33
F3	2.93±0.040	3.40±0.56	100.50±0.50	1.03±0.30
F4	2.92±0.036	3.45±0.51	99.87±0.35	0.52±0.32
F5	2.89±0.080	3.35±0.37	99.90±0.81	0.67±0.64
F6	2.92±0.032	3.15±0.40	100.69±039	0.70 ±0.51
F7	2.90±0.075	3.35±0.49	101.01±0.10	0.55±0.36

The formulations containing low concentration of disintegrants have shown maximum hardness so they show less % friability. The lowest hardness was obtained in formulations containing high disintegrant concentration and shows % friability just near to the limit. All batches pass the test for % friability. The disintegration time was found 11 to 59 sec. The wetting time was found 20 to 33 sec. Drug contents of tablets from each batch showed uniformity of content as the concentration of drug in tablet was found in between 97.23% to 99.72%. All the results obtained were within the range. Result given in Table no.4.

Table no.4: Post compression evaluation parameter for sublingual tablet

Parameter / Batches	Disintegration time (sec.)	Wetting time (sec.)	Water absorption ratio (mg)	Uniform drug content
	Mean ± SD (n=3)			
F1	59 ± 0.33	23 ±.1.14	96.03 ± 0.04	99.72± 0.60
F2	36± 0.5	20 ±1.63	94.02± 0.04	97.23± 0.48
F3	22± 0.5	26 ± 2.00	91.91± 0.05	99.34± 0.62
F4	47± 0.2	25 ±1.48	94.95± 0.02	98.99±0.60
F5	25± 0.60	30 ± 1.50	97.94±0.03	98.72± 0.83
F6	16± 0.60	33 ± 1.51	91.95±0.02	98.59± 0.52
F7	11± 0.07	29 ±2.23	97.14±0.01	99.21± 0.52

***In-vitro* drug release study:**

The *in-vitro* dissolution studies of all formulations (i.e.F1 to F7) were carried out in pH 7.4 phosphate buffer. The release of drug is largely depends upon the disintegration of tablet i.e. faster the disintegration of tablets, better and faster will be the release of drug. The drug release was found above 20.90 % after 2 minutes. Formulation batch no. F1-F3 releases 88.85-92.90 % of drug after 14 minutes, containing crospovidone as a superdisintegrants (4 %, 6 %, 8 %) It was found that disintegration time lower when conc. of superdisintegrants increases, hence more drug release was observed form the fast disintegrating sublingual tablet of amlodipine besylate. while formulation batch no. F4-F6 containing tulsion 671 as a superdisintegrants (4 %, 6 %, and 8 %) released 90.25-93.72 % of drug after 14 minutes It was found that formulation containing tulsion 671 gives better and faster drug release than the crospovidone containing formulation. And batch F7 containing combination of tulsion 671(4 %) and crospovidone (4%) as a superdisintegrants which were release the 95.89 % drug release after 14 min. It was found that formulation was containing combination of superdisintegrants gives better and faster drug release than the crospovidone and tulsion 671 containing formulation. The graphical representation of drug release study was given in fig. no.1

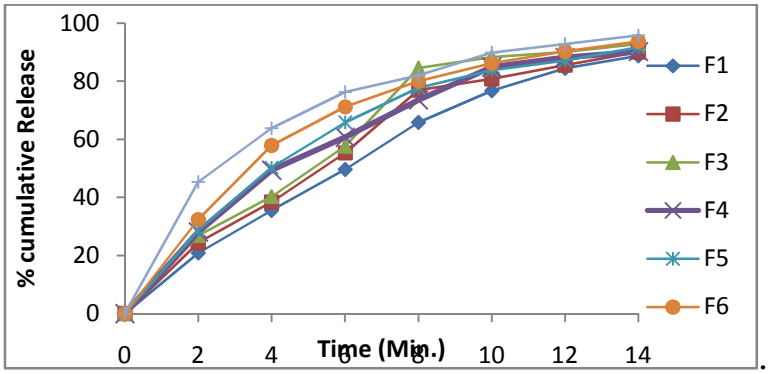

Fig. no.1: *in-vitro* drug release profile of formulation

Compatibility study by FT-IR:

The FT-IR spectra of the amlodipine, tulsion 671, crospovidone, avicel PH-102, drug-polymer mixture were recorded to check interaction between drug and polymers. The characteristic peaks of amlodipine were appeared in all the spectra and values were shifted slightly due to the formation of complex. This indicated that there was no chemical interaction between amlodipine and polymers. The fig.no.2-6 shows the results of compatibility study.

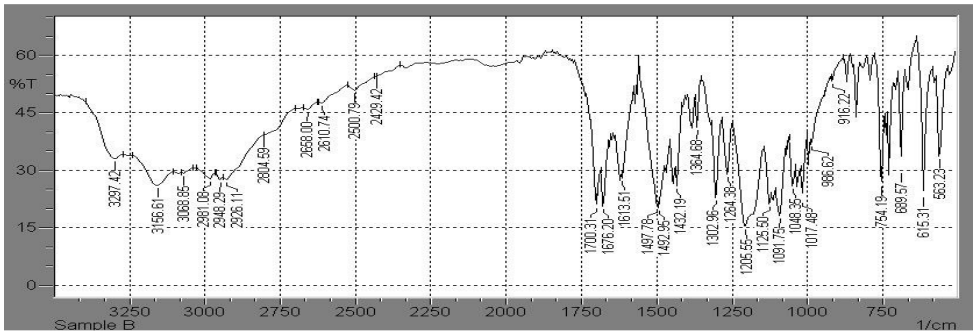

Figure no.2: FT-IR spectra of amlodipine besylate

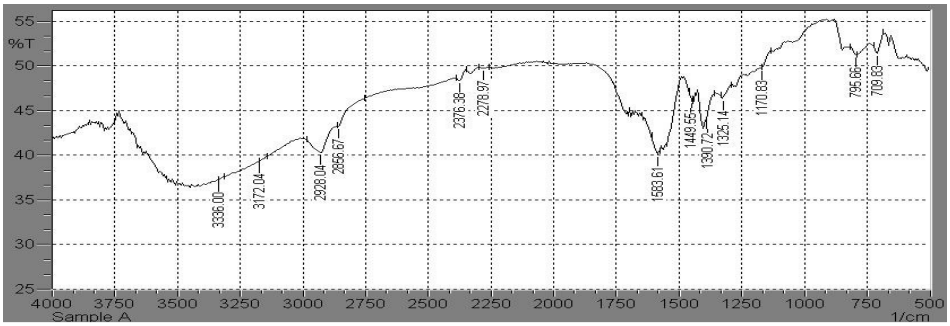

Figure no.3: FT-IR spectra of tulsion 671

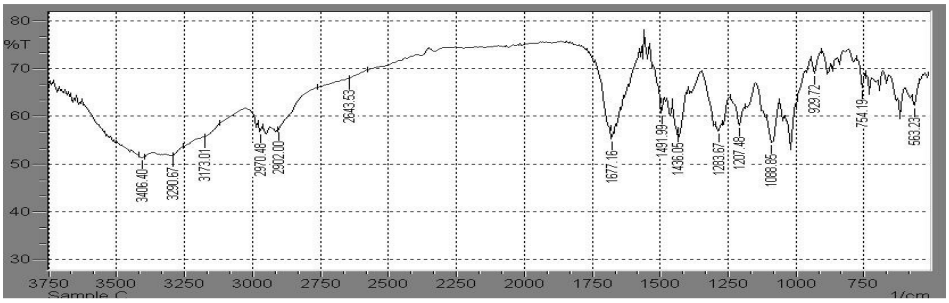

Figure no.4: FT-IR spectra of drug + crospovidone

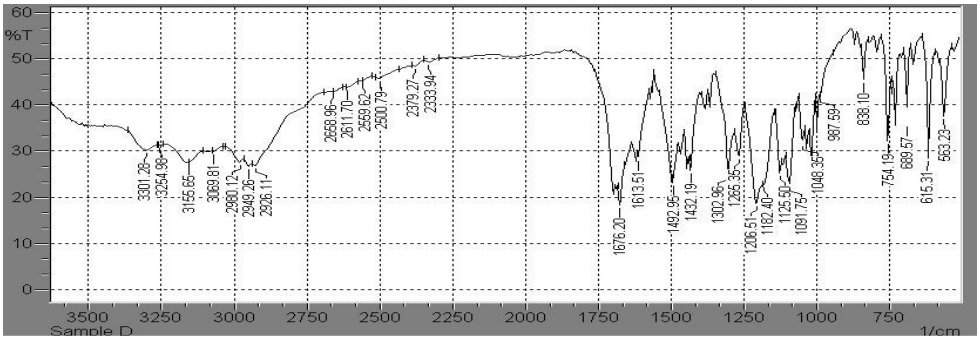

Figure no.5: FT-IR spectra of drug + tulsion + crospovidone

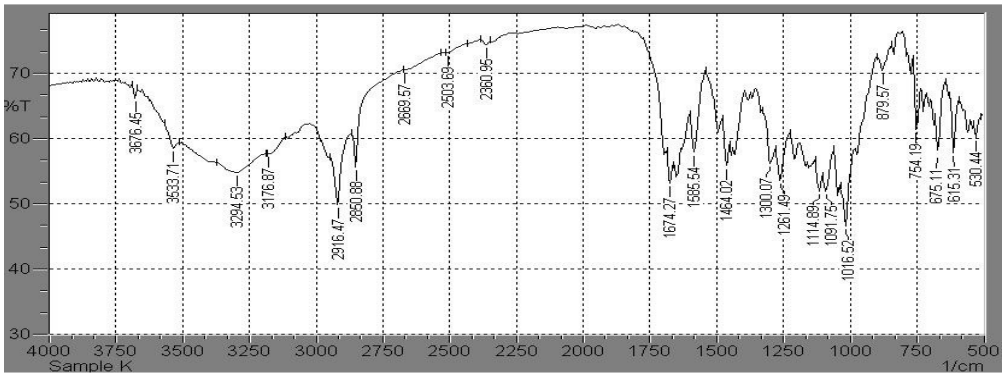

Figure no.6: FT-IR spectra of drug + tablet blend

Compatibility study by differential scanning colorimetry:

The differential scanning colorimetry of the amlodipine, and drug-polymer mixture was recorded as shown in fig no7-8. The DSC thermograms of physical mixture confirmed that there is no interaction between drug and polymers as shown in fig. no.8. It also showed a reduction in intensity of the peak and there was no new peaks found and endothermic to exothermic change not occur. Hence, it was confirmed that there was no interaction between drug and excipients.

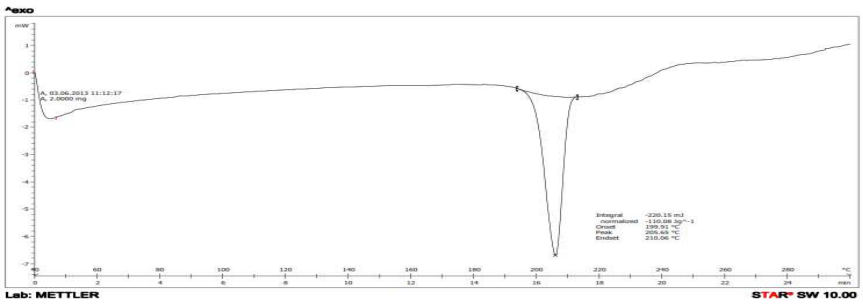

Figure no.7: DSC of amlodipine besylate

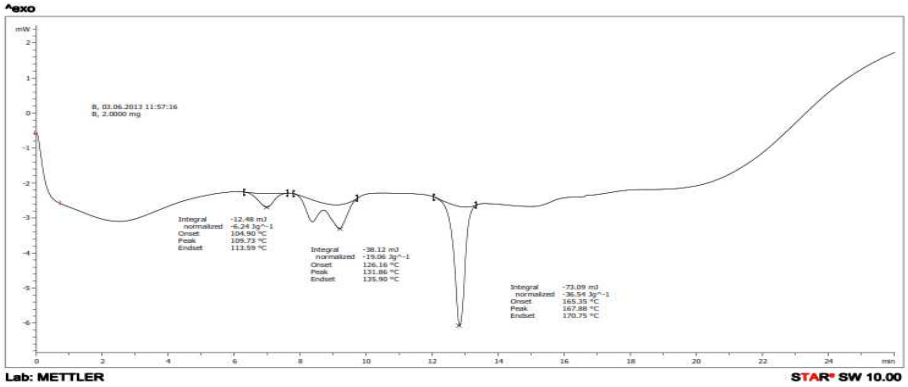

Figure no.8: DSC of drug + tablet blend

Accelerated stability study for optimum formulation:

An optimized batch F7 was carried for stability study due to its higher drug release, lower disintegration time, uniform content uniformity, so accelerated stability studies (AST) was carried for optimized batch F7 exposing it to 45°C/75% RH for 0,30,60 and 90 days. The sample was analyzed for Hardness, Drug Content, *In-vitro* disintegration time and *In-vitro* dissolution studies.Reults given in table no.5.

Table no.5: Accelerated stability study for F7

Parameter / Days	Hardness (kg/cm^2)	Drug content (%)	*In-vitro* disintegration time(sec)	*In-vitro* drug release study
	Mean ± SD (n=3)			
0	3.45±0.11	99.21± 0.87	11± 0.05	95.89±0.32
30	3.31 ± 0.14	99.20 ± 0.59	10.8± 0.39	94.90 ± 0.75
60	3.16 ±0.20	99.12 ± 0.35	11.2 ± 0.67	95.90 ± 0.39
90	3.05 ± 0.40	99.10 ± 0.74	12 ± 0.44	95.01± 0.47

CONCLUSION

The study conclusively demonstrated significant results for amlodipine fast dissolving sublingual tablet. The fast dissolving sublingual tablets of amlodipine was more palatable, and its mostly helpful to the patients for the management of cardiac failure, hypertension, cardiac angina. In this certain conditions patient leads to discomfort with or unwillingness to swallow the available oral tablet and associated water. Thus, the patient – friendly dosage form of drug, Hence, at the end of this investigation it can be cocluded that fast dissolving sublingual tablet of amlodipine was successfully prepared by direct compression technique using different superdisintegrants and the objectives of this study are achieved.

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REFERENCES

[1] Tanuja S., Meenu U., Shah. Ghamande A.R., Padma V., *J Pharm Pharmacol*; 46:192-5**. (1994)**
[2] Alai K, Thakare V.M, Tekade B.W, Patil V.R, , *World Journal of Pharmaceutical research*, Volume 1, Issue 3, 838-849 **(2012)**
[3] Laurence L Brunton, Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 10th Ed, McGraw-Hill, New York, 621-624 **(2001)**
[4] Patel K., Nibha., Pancholi S.S., *IJRPBS*,Vol. 3 (2),913-919**.(2012)**
[5] Sinko. P.J., 2006. In: Martin's, Physical Pharmacy and Pharmaceutical Sciences, fifth ed. Noida, B. I. publisher. pp. 550-560.
[6] Chaudhuray J., Maity S., Sa B., Bandyopadhyay A.K., *The East Pharm*; 37: 121-3. **(1994)**
[7] Lachman. L., Liberman. H., Kanig. J., third ed, The Theory and Practice of Industrial Pharmacy, Varghese Publication Bombay,296-306.**(1990)**
[8] United States of Pharmacopeia-National Formulary. USP 32 - NF 27. The United States Pharmacopoeial Convention, Rockville, MD., 53-54. **(2004)**
[9] Indian Pharmacopoeia,. Government of India, Ministry of Health and Family Welfare, Published by the Controller of Publication, New Delhi. II, pp. 442. **(2007)**

[10] Ansel, H.C., , Introduction to Pharmaceutical Dosage Form, fourth ed., K.M Varghese Company, Bombay, 146-158.**(2005)**
[11] Sreenivas, S.A., Gadad, A.P., *Indian Drugs*. 43, 1, 35-38 **(2006)**
[12] Chaudhari, P.D., Chaudhari, S.P., Lanke, S.D., Patel, N., *Indian. J. Pharm. Edu.* 41, 4, 319-27**. (2007)**
[13] Indian Pharmacopoeia. Government of India, Ministry of Health and Family Welfare, Published by the Controller of Publication, New Delhi. II, pp. 663-665**. (2007)**
[14] Bharadwaj V., Shukla V., Goyal N., Salim M.D., Sharma P.K., *Int J Pharmacy Pharm Sci*, Vol 2, Issue 3, 89-92.**(2002)**
[15] Chatwal, G.R., and Anand, S.K., Instrumental method of chemical analysis, Himalaya publication, Mumbai. 2, 44, 45**. (2007)**
[16] ICH Harmonised Tripartite Guideline, Stability Testing of New Drug Substances and Products Q1A (R_2), Current step. (4), 3-9**. (2003.)**