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FORMULATION AND *IN - VITRO* EVALUATION OF SUBLINGUAL TABLETS OF AMLODIPINE BESYLATEUSING CO-PROCESSED EXCIPIENTS

Vinayraj Paramshetty[1], D. Nagendra Kumar[1], N. M. Vageesh*[2], Anuradha[1]

[1]S.V.E.T's College of Pharmacy, Humnabad, Dist.-Bidar, Karnataka
[2]St. Johns college of Pharmaceutical Sciences, Yerrakota, Yemmiganur, Kurnool, A.P

*Corresponding author E-mail: vageesh.swamy@gmail.com

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ABSTRACT

The aim of the present study was to develop and optimize oral sublingual tablets of model drug (AMD) to give quick onset of action by rapidly disintegrating in a few seconds without the need of water with better patient compliance. In such cases, bioavailability of drug is significantly greater and adverse event is reduced than those observed from conventional tablet dosage form. By performing compatibility studies by IR spectrophotometer, no interaction was confirmed. Oral disintegrating tablets were formulated by direct compression method and suitable analytical method based on UV-Visible spectrophotometer was developed for the model drug. Prior to compression, the blend of drug and excipients were evaluated for flow properties. All the formulations showed good flow properties. Sublingual tablets of Amlodipine can be successfully prepared by direct compression method using selected superdisintegrants with Crosspovidone 1.5%, 3%, 6%, Crosscarmellose 1.5%, 3%, 6% and Sodium starch glycolate 1.5%, 3%, 6%, for the better patient compliance and effective therapy the relative efficiency of these superdisintegrant to improve the disintegration and dissolution rate of tablets were found in order. Post compression evaluations of prepared sublingual tablets were carried out with the help of different pharmacopoeial and non pharmacopoeial (industry specified) tests. The disintegration of F1, F2, F3 with 1.5%, 3%, 6% Crosspovidone formulations to be as 8, 6, 5secs respectively and is almost better than F4, F5, F6, F7, F8, F9 formulations. Formulation F3, In-vitro Dissolution studies 10 minutes almost total amount of the drug is released 6% crosspovidone (i.e. 96.96%). Crosspovidone shows good result as compare to other superdisintegrants. Crosspovidone > crosscarmellose sodium > sodium starch glycolate

INTRODUCTION

Development of a formulation involves a great deal of study and experimental work to get optimum results. While doing so we have to keep in mind various factors are considered like choice of excipients, drug bioavailability, drug stability in required dosage form, cost effectiveness, manufacturing aspects. Now a day's formulation research is breaking barriers of conventional methods. Present day's drugs can be delivered with a convenience manner, performance and bioavailability[1]. Drugs have been applied to the mucosa for topical application for many years. However, recently there has been interest in exploiting the oral cavity as a portal for delivering drugs to the systemic circulation[2]. Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream through the ventral surface of the tongue and bottom of the mouth[3]. The sublingual route usually produces a faster onset of action than the orally ingested tablets and the portion absorbed through the sublingual blood vessels

bypasses the hepatic first-pass metabolic processes[4]

Oral Mucosa*:* The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of the mouth. The lining of the oral cavity is referred to as the oral mucosa, and includes the buckle, sublingual, gingival, palatal and labial mucosa. The oral mucosa top quarter to one-third is made up of closely compacted epithelial cells. The main role of the oral epithelium is to protect fluid loss and underlying tissue against potential harmful agents in the oral environment. The lining mucosa is found in the outer oral vestibule (the buckle mucosa) and the sublingual region (floor of the mouth). The specialized mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (the upper surface of the mouth) and the gingiva (gums). The superficial cells of the masticatory mucosa are keratinized, and a thick lamina propia tightly binds the mucosa to underlying periosteum. The mucosa of the dorsum of the tongue is specialized gustatory mucosa's, which has a well papillae surface; which are both keratinized and some non-keratinized[5]. The oral mucosal cavity, delivery of drugs is classified into three categories**:**

Sublingual delivery: Which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth?

Buccal delivery: which is drug administration through the mucosal membranes lining the cheeks (buckle mucosa),

Local delivery: which is drug delivery into the oral cavity[7?]

Sublingual Dosage Forms: Drugs administered by this route rapid produce systemic/ local effects. In general, absorption form this route is observed because of the thin mucous membrane and rich blood supply.

Sublingual Tablets: Sublingual tablets are intended to be placed beneath the tongue and held until Absorption has taken place. They must dissolve or disintegrate quickly, allowing the medicament to be rapidly absorbed.

Formulation of sublingual tablets:

The formulation of sublingual tablets involves the selection of suitable excipients of bland taste that shall ultimately resulting in a rapid disintegrating tablet their by enhancing the dissolution of active ingredient. There are two different types of sublingual Tablets[13,14].

Objectives of the study: In the present work, studies will be carried out on the development and evaluation of sublingual tablets of Amlodipine in the management of hypertension with respect to: To maximize drug utilization and improve therapy, to increase the bioavailability of drug and make shortest treatment for patient. To reduce fluctuation in steady-state level of drug for better control of disease condition. To achieve the greater therapeutic efficacy. To reduce intensity of local or systemic side effects etc.

Methodology:

FORMULATION OF DIFFERENT BATCHES

The main aim of the present study was to formulate different batches using three various superdisintegrants and other ingredients in varying concentrations. According to that F1, F2, F3 (with Crosspovidone 1.5%, 3%, 6%), F4, F5, F6 (with Crosscarmellose 1.5%, 3%, 6%) and F7, F8, F9 (with Sodium starch glycol late 1.5%, 3%, 6%). The slight bitter taste of the drug was masked using aspartame (2.5% to 6%) as the sweetening agent.

Method of formulation

1. Direct compression method: The model drug is thoroughly mixed with the superdisintegrants, and then other excipients are added to the mixer and passed through the sieve (#:40). Collect the powder mixer, blend with magnesium stearate (pre sieved), and subject the blend for tablet compression.

Representation of Direct Compression Technique for design of Sublingual Tablets

The drug and the excipients were passed through sieve no: 40 except lubricant. The blend was further lubricated with Magnesium stearate (#:60) and the powder blend is subjected to drying for removal of moisture content and was compressed by direct compression method by using flat faced punches in CADMACH 16 punches tablet punching machine. Round punches measuring 8.7mm diameter were used for compression.

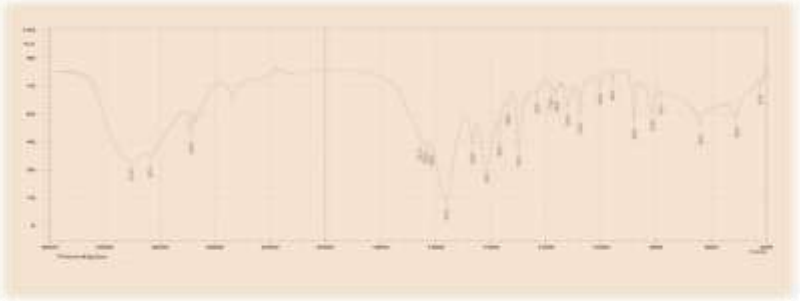

Fig.2. FTIR studies of Pure Amlodopine

Table No. 1: Formulations of different batches

	Formulation Code								
Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Amlodipine	30	30	30	30	30	30	30	30	30
Crosspovidone	3	6	12	-	-	-	-	-	-
Crosscarmellose sodium	-	-	-	3	6	12	-	-	-
SSG	-	-	-	-	-	-	3	6	12
MCC 102	66	64	58	66	64	58	66	64	58
Aspartame	10	10	10	10	10	10	10	10	10
Mannitol	80	80	80	80	80	80	80	80	80
Magnesium stearate	6	6	6	6	6	6	6	6	6
Talc	4	4	4	4	4	4	4	4	4

Pre-compression studies: Table No. 2: Evaluation of tablet blend for formulations (F1-F9)

Formulation	Bulk Density (g/cc)	Tapped Density(g/cc)	Hausner's ratio	Compressibility index (%)	Angle of repose
F1	0.464	0.574	1.23	19.1	29.47
F2	0.423	0.501	1.16	15.5	27.63
F3	0.456	0.542	1.22	15.8	25.54
F4	0.467	0.559	1.25	16.4	26.23
F5	0.485	0.593	1.10	18.2	27.21
F6	0.460	0.556	1.21	17.2	30.38
F7	0.478	0.575	1.24	16.8	28.46
F8	0.450	0.554	1.28	18.7	25.71
F9	0.442	0.537	1.27	17.6	31.82

Post compression studies: **Table No. 3: Evaluation of sublingual tablets for formulations (F1 – F9)**

Formulation	Hardness (kg/cm2)	Friability (%)	Weight (mg)	Thickness (mm)	Drug content (%)
F1	3.0±0.17	0.25	201±0.59	3.9±0.05	97.2
F2	2.8±0.20	0.23	198±0.63	4±0.02	97.72
F3	3.1±0.18	0.26	201±0.45	3.7±0.07	98.4
F4	2.9±0.15	0.24	202±0.88	3.8±0.10	97
F5	3.2±0.16	0.28	204±0.56	3.9±0.03	98.44
F6	2.8±0.22	0.32	198±0.74	3.9±0.06	100.8
F7	3.2±0.24	0.27	201±0.67	3.8±0.15	97.2
F8	2.9±0.22	0.29	201±0.77	3.9±0.03	98.4
F9	2.8±0.16	0.24	203±0.86	4±0.01	95.32

Evaluation of tablets:

Table No. 04: Evaluation of Sublingual tablets for formulations (F1 – F9)

Formulation	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio (%)	*In vitro* dispersion time (sec)
F1	8	20	19.42	8
F2	6	15	22.47	5
F3	5	12	19.78	5
F4	10	16	16.13	15
F5	9	14	17.27	11
F6	8	19	12.17	9
F7	18	27	15.32	14
F8	10	20	12.047	12
F9	9	20	13.92	8

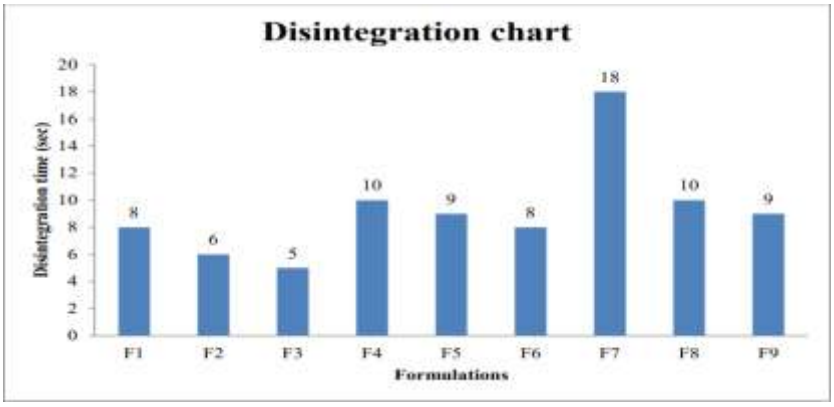

Figure No. 03: Bar graph comparison between DT for formulations (F1- F9)

Table No. 05: Cumulative % drug release for formulations (F1 – F9)

Cumulative % drug release									
Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
2 Min	55.15	58.9	65.5	48.07	51.5	62.7	45.93	50.54	57.9
4 Min	68.6	72.1	74.9	57.29	61.5	71.1	55.97	61.7	61.07
6 Min	71.12	80	82.64	72.93	76.55	81.16	71.44	73.2	77.2
8 Min	81.9	87.08	89.06	79.68	84.61	86.5	76.05	81.8	84.12
10 Min	91.17	94.82	96.96	88.4	93.3	94.1	85.2	87.07	89.2

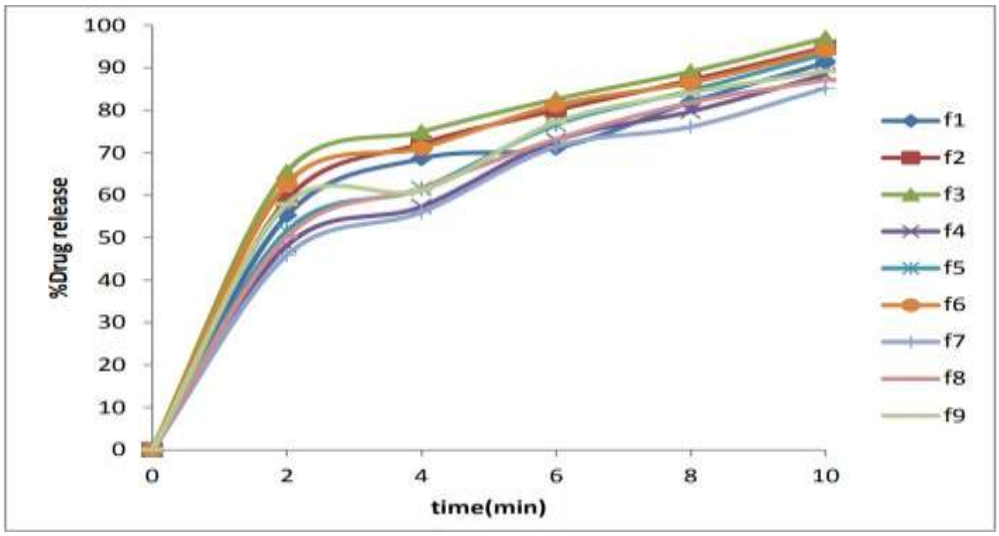

Figure No. 04: Comparison between cumulative % drug releases for formulations (F1- F9)

Table No.06: Drug release kinetics: Correlation coefficient (r) & rate constant (k) Values of Amlodipin sublingual tablets containing Crospovidone, cross carmellose sodium,sodium starch glycolate.

Kinetic model		**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Zero order	R	0.9436	0.9391	0.9179	0.9364	0.9318	0.9151	0.9424	0.8383	0.8979
	K	17.15	18.25	18.72	14.32	15.37	17.77	13.99	15.42	15.42
Higuchi	R	0.9945	0.9913	0.9646	0.9943	0.9737	0.9833	0.9953	0.9927	0.9797
	K	35.17	37.09	39.09	29.63	31.80	37.17	28.82	31.76	32.71
First order	R	0.9963	0.9939	0.9991	0.9981	0.9994	0.9903	0.9989	0.9991	0.9822
	K	0.2697	0.3192	0.3456	0.2127	0.2466	0.3104	0.2057	0.241	0.24
Peppas	R	0.9796	0.9995	0.9985	0.9892	0.9914	0.9125	0.9914	0.9971	0.9615
	K	0.294	0.2894	0.2387	0.3878	0.3758	0.2511	0.3894	0.3489	0.2882
Hixson-crowell	R	0.9659	0.9704	0.9626	0.9816	0.9855	0.859	0.9761	0.9741	0.9602
	k	0.3717	0.4022	0.4284	0.2865	0.3162	0.3932	0.2776	0.3177	0.3177
DE10		44.73	47.48	51.48	38.36	41.13	49.13	36.96	40.47	44.38
DE30		58.96	63.64	66.89	54.53	57.96	64.55	52.84	56.59	59.72
T 50		1.81	1.70	1.53	2.42	1.94	1.59	2.81	1.98	1.73
T 90		9.75	8.75	8.24	0	9.28	8.92	0	0	0

Stability Study: Table No. 07: Comparison of Various Parameters for Stability Study

Evaluation Parameter	**Initial**	**1 month**	**2 month**	**3 month**
Hardness(kg/cm^2)	3.1 ± 0.18	3.2 ± 0.36	3.3 ± 0.05	3.3 ± 0.90
% Friability	0.26	0.25	0.24	0.24
Disintegration Time (sec)	5	7	8	9
Drug Content	98.4	99.6	99.2	99.80

Tablet of 200mg was prepared by adjusting hardness and volume screw of compression machine properly.

Evaluation of tablets

Hardness test: Using a Monsanto hardness tester the rigidity (hardness) of the tablet was determined[14].

Friability: The friability of a sample of 20 tablets was measured using a Roche friabilator. 20 previously weighed tablets were rotated at 25 rpm for 4 min. The weight loss of the tablets before and after.[15.] Measurement was calculated using the following formula

Percentage friability = Initial weight – Final weight/ Initial weight x 100.

Weight Variation: It was performed as per the method given in the united state pharmacopoeia. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated.

Tablet thickness: Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the identical thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded Vernier calipers using micrometer.

Drug Content Uniformity: Selected twenty tablets randomly and powdered. A quantity of this powder corresponding to 200mg of model drug was dissolved in 100 ml of 6.8pH phosphate buffer, stirred for 15 min and filtered. The 1ml of filtrate was diluted with 100 ml with 6.8pH phosphate buffer. Absorbance of this solution was measured at 250nm using 6.8pH phosphate buffer as blank and content of drug was estimated[16].

***In- vitro* Disintegration Time:** Disintegration times for sublingual tablets were determined using USP tablet disintegration apparatus with saline phosphate buffer of pH 6.8 as medium. Maintained the medium temp at 37±2°. The time in minute taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured.

Wetting Time: A piece of tissue paper folded twice was placed in a small Petri dish (ID = 6.5 cm) containing 6 mL of simulated saliva pH, a tablet was put on the amaranth powder containing paper the time required for upper surface of the tablet for formation of pink color was measured.

Water absorption ratio: For measuring water absorption ratio, the weight of the tablet before keeping in the petri dish is noted (W_b). The wetted form of tablet was taken from petridish and reweighed (W_a). The water absorption ratio (R) can be the determined according to the following equation.

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

***In vitro* dispersion time**: *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of pH 6.8 (simulated saliva fluid) .Tablets from each formulation were randomly selected and in vitro dispersion time is expressed in seconds.

***In-vitro* Dissolution studies**: Dissolution of the tablet of each batch was carried out using USP XXIII dissolution type II apparatus (ELECTRO LAB) using paddles at 50 rpm. As per the official recommendation of IP 900ml of 6.8 pH of phosphate buffer used as dissolution medium and the temperature of the medium was set at 37 ± 0.5 0C. 5 ml of sample was withdrawn at predetermined time interval of 2 .,4., 6., 8 and 10 min. And same volume of fresh medium was replaced. The withdrawn samples were analyzed by an UV spectrophotometer at 243 nm using buffer solution as blank solution. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm. The USP 1 (basket) apparatus may have certain applications for sublingual but is used less frequently due to specific physical properties of tablets[17].

Drug release kinetics:

As a model independent approach, comparison of time taken for the given proportion of the active drug to be dissolved in the dissolution medium and figures such as T_{50} and T_{90} were calculated by taking the time points of 50% and 90% of the drug dissolved and another parameter dissolution efficiency (DE) suggested by Khan were employed. DE is defined as the area under the dissolution curve up tothe time t expressed as a percentage of the area of the

rectangle described by 100% dissolution in the same time. Dissolution efficiency can have a range of values depending on the time interval chosen. In any case, constant time intervals should be chosen for comparison. For example, the index DE30 would relate to the dissolution of the drug from a particular formulation after 30 minutes could only be compared with DE30 of other formulations. As a model dependent approach, for describing the mechanism and also the release kinetics, dissolution data were fitted to popular release models such as Zero order kinetics, First order kinetics, Hixon-crowell cubth root model, Higuchi model, Korsmeyer-peppas model.

Stability Studies: Stability studies were carried out at $40^0C \pm 2^0C$ /75% RH ± 5% for all the formulations for a period of 3 months. The selected formulations were closely packed in aluminium foils and then stored at 40^0 C ± 2^0 C /75% RH ± 5% in stability chamber for 3 months and evaluated for their physical appearance, drug content and *in-vitro* drug release studies at intervals of 1month. The shelf life period of the prepared buccal tablets is determined by using similarity factor.

FT-IR Pure Amlodopine showed principal absorption peaks at 782.17 cm^{-1} (C-H aromatic bending), 1369.52cm^{-1} (NO_2stretching), 1465.96 cm^{-1}(C=C aromatic stretching), 1626.06 cm^{-1} (N-H bending), 2973.40 cm^{-1} (C-H stretching) and 3411.26cm^{-1} (O-H stretching). Theidentical peaks ofC-H aromatic bending, NO_2 stretching, C=C aromatic stretching, N- H bending, C-H stretching and O-H stretching, vibrations were also noticed in the spectra of physical mixtures which contains drug and excipients. FT-IR spectra revealed that there was no interaction between the drug and the excipients used for fast dissolving tablets preparation. The angle of repose less than 32, which reveals good flow property it shown in for formulations F1 – F9. The loose bulk density and tapped bulk density for all formulation (F1 – F9) varied from 0.442 gm/cm^3 to 0.467 gm/cm^3 and 0.501 gm/cm^3 to 0.574 gm/cm^3respectively.The results of carr's consolidate index or % compressibility index for the entire formulation (F1 – F9) blend range from 15 to 19 shows fair flow properties. The hardness values ranged from 2.8±0.16$kg/cm^2$to 3.2±0.24 kg/cm^2 for formulation (F1-F9) and were almost same. The friability values were found to be within the limit(0.5 - 1%). The above evaluation parameter showed no significant difference between F1, F2, F3, F4, F5, F6, F7, F8, F9 formulations. The entire tablet passes weight variation test as the average % weight variation was within the Pharmacopeia limit of 7.5%. It was found to be 198±0.63 mg to 204±0.56 mg. The weight of all the tablets was found to be uniform with less deviation. The maximum concentration among all the formulations was found to be 100.8% and minimum % drug content from all formulation was found to be 95.32%. The results of drug content of all batches are shown in Table 03. Disintegration test carried out in modified dissolution apparatus, it shows the formulations with1.5%, 3%, 6% SSG showed high value for disintegrating time as 18, 10, 8 secs. The results showed that the disintegration time of F1, F2, F3 with 1.5%, 3%, 6% CP formulations to be as 8, 6, 5 secs respectively and is almost better than F4, F5, F6, F7, F8, F9 formulations and comparative profile.

Wetting time is closely related to the inner structure of tablet. The experiment mimics the action of saliva in contact with the tablet to illustrate the water uptake and subsequent wetting of tablet. This shows the wetting process was very rapid in almost all formulations. This may be due to the ability of swelling followed by breaking and also capacity of water absorption and causes swelling. It was found to be in the range of 14 secs to 27secs.It shows crosspovidone formulations F1, F2, F3 (1.5 – 6%) have better wetting time comparing with that of cross carmellose sodium starch glycolate, and comparative profile result was shown in table no:15. Water absorption ratio which is important criteria for understanding the capacity of disintegrants to swell in the presence of little amount of water, was calculated. It was found to be in the range of 12.17 to 22.47% . This shows that all the formulations have good water absorption capacity result was shown in table no:15. The in vitro dispersion time is measured by time taken to uniform dispersion, the rapid dispersion. It was found to be in the range of 5secs to 15secs (Graph). The result showed that the in vitro dispersion time of F1, F2, and F3 formulations is almost equal and better than F4,

F5, F6, F7, F8, F9 formulations and comparative ***In vitro*** **dissolution studies:** Dissolution is carried out in USP-2 type apparatus at 50rpm in the volume of 500 ml dissolution media (phosphate buffer pH 6.8) for 10 minutes. At the end of 10 minutes almost total amount of the drug is released (i.e. 96.96%), from the formulation prepared by the direct compression method with 6% crosspovidone result was shown in table no: 16. The drug release profiles of Amlodipin sublingual tablets were fitted to various kinetic models such as Zero order, First order, Higuchi, Peppasand Hixson Crowell. The dissolution parameters such as dissolution efficiency (DE) at10 and 30 minutes were increased proportionately. Half-life of drug i.e., T50 was found to be 1.81, 1.70, 1.53, 2.42, 1.94, 1.59, 2.81, 1.98 and 1.73 min for F1, F2, F3, F4, F5, F6, F7, F8 and F9 formulations respectively. Shelf-life of the drug i.e., T90 was found to be 9.75, 8.75, 8.24, 9.28 and 8.92 minutes for F1, F2, F3, F5and F6 formulations respectively. The drug release data of Amlodipin fast dissolving tablets have treated with different kinetic models are shown in Table No. 06. The drug release patterns of Amlodipin fast dissolving tablets had followed the first order kinetic model. This release patterns are evident with the correlation coefficient 'r' values which are nearer to 1. The optimized formulation F3 is kept for stability studies. Accelerated stability studies were carried out at 40^0C/75%RH for 3 months. The tablets were then evaluated for hardness, friability, disintegration and drug content at 1st month, 2nd month and 3rd month. The results indicated that there was no significant change in evaluation of the tablets. The results were tabulated in Table No: 18. The optimized formulation F3 is evaluated for *in-vitro* drug release studies after keeping the tablets at accelerated stability conditions (40^0C/75%RH) for 3 months. It is evaluated initially, 1st month, 2nd month and 3rd month. *In-vitro* drug release studies were performed in phosphate buffer pH 6.8 by using USP dissolutiontest apparatus-Type II, Rotating Paddle method. The results indicated that there was no significant change in i*n-vitro* drug release studies.

profile result was shown in Table No:15.

CONCLUSION:

Sublingual tablets of Amlodipin can be successfully prepared by direct compression method using selected superdisintegrants with Crosspovidone 1.5%, 3%, 6%, Crosscarmellose 1.5%, 3%, 6% and Sodium starch glycolate 1.5%, 3%, 6%, for the better patient compliance and effective therapy the relative efficiency of these superdisintegrant to improve the disintegration and dissolution rate of tablets were found in order, The disintegration of F1, F2, F3 with 1.5%, 3%, 6% Crosspovidone formulations to be as 8, 6, 5secs respectively and is almost better than F4, F5, F6, F7, F8, F9formulations, Formulation F3 In-vitro Dissolution studies 10 minutes almost total amount of the drug is released 6% crosspovidone (i.e. 96.96%). Crosspovidone shows good result as compare to other superdisintegrants. Crosspovidone > crosscarmellose sodium > sodium starch glycolate.

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