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DEVELOPMENT AND EVALUATION OF FAST DISSOLVING AMLODIPINE BESYLATE TABLETS

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ABSTRACT

Fast dissolving drug dosage form is a better way for the treatment of paediatric, geriatric, nauseous, bedridden and noncompliant patients. It is also better for those who have difficulty in swallowing the solid unit dosage form and best suitable for those patients also who have fear of chocking due to tablet engulfing. Amlodipine Besylate is the besylate salt of amlodipine, a synthetic dihydropyridine with antihypertensive and antianginal effects. Amlodipine inhibits the influx of extracellular calcium ions into myocardial and peripheral vascular smooth muscle cells, thereby preventing vascular and myocardial contraction. Mouth dissolving tablet of Amlodipne besylate is formulated by two method i.e. direct compression and sublimation method. Amlodipne besylate is identified with the help of FTIR And standardization through UV/VIS spectroscopy. Drug excipient compatibility is checked by the IR spectral analysis of formulations. The blended powder is then inspected for micromeritic properties like bulk density, tapped density, compressibility index, hausner ratio and angle of repose. The value obtained is within the prescribed limit and show good flow properties. When blended powder is compressed into tablets then these tabets are evaluated for post compression parameter. The amalgamation of superdisintegrant (cross povidone) and subliming agent (camphor) is best shown in the formulation SX6 and SX9 in ratio of 20:15 and 20:20. In the sublimation method the in-vitro dispersion and in-vitro disintegration time is good. About 99.80% drug was released within 6 sec by sublimation method. In drug kinetics the Peppas and Korsmeyer kinetics ispassed.

KEYWORDS: Fast dissolving, Amlodipne besylate.

INTRODUCTION

Fast dissolving tablet is a better way for the treatment of paediatric, geriatric, nauseous, bedridden and noncompliant patients.[1-3] It is also better for those who have difficulty in swallowing the solid unit dosage form and best suitable for those patients also who have fear of chocking [4]due to tablet engulfing. Mouth dissolving tablet are also better because wastage of drug due to first pass metabolism is avoided by this drug delivery system. The rate of release of mouth dissolving/disintegrating tablet is increased with the help of superdisintegrant.[4] Therefore, the bioavailability of mouth dissolving tablet increased withby the help ofsuperdisintegrants.

Mouth dissolving tablet disintegrate in the mouth instantaneously. This drug is released dissolve or dispersed in the mouth therefore it is engulfed without the help of water.[5] This drug can also be easily administered to the patient at the place where water is not available. Therefore, we can say that this drug offer a advantage of solid and liquid both dosage form. when saliva mixed drug is swallowed some drug is absorbed from buccal cavity therefore the bioavalability of drug is increased. This drug can be administered at any time, at any place whenever needed because water is not required for swallowing the drug. It reduces the possibility of non compliance. Now a days these drugs become a popular choice of dosage form due to the benefits of.

a. Patientadaptability,
b. Instantaction,
c. The fraction of drug released in the systemic circulationincreased
d. long viability.

To conquer such issues, researchers have created unique medication methodolgy known as Fast dissolving/disintegrating tablets.[6]

Mouth dissolving tablets breaks into the buccal cavity without need of water or biting within minute. This dosage form is really helpful in the medication of infants and old age patients.[3] Patients suffering from mental disorder, heart disease, pain, allergy and erectile dysfunction[4] get instant relief with the help of mouth dissolving tablets. MDTs are formulated fundamentally by two methodology.

1. First by the use of superdisintegrant.

2. Second is by improving pore structureby.

a. freezedrying

b. vacuumdrying.

Fast dissolving drug framework rose up out of the longing to give understanding progressively regular methods for administration of dosageform.

Patient suffered with motion sickness and the condition where water is not available, gulping of traditional oral tablets might be troublesome. Pediatric and old age patients experience mostly this problem. Mouth dissolving tablet is a better alternative for this type of issues. At the point when tablet is put over the tongue, Fast dissolving tablet disintegrate instantly and dissolve in buccal cavity.

Tablet comprises of multiple active pharmaceutical ingredients as well as number of different excipients utilized in the formulation of a dosage form. Oral dosage forms are utilized chiefly for systemic circulation yet additionally for particular medication activity. Tablet can be formulated for local activity of medications in the mouth or GIT, or can be utilized to increment incidentally the PH of the stomach.

MATERIALS AND METHODS

Materials

Amlodipine besylate was gifted from Orchid pharmaceuticals, Camphor, Cross povidone, MCC, Mg. Stearate, Mannitol, Dextrose, Talc were also used. All other materials used were of Analyticalgrade.

Methods

Formulation of mouth dissolving tablets of Amlodipne besylate

Amlodipne besylate fast dissolving tablets were manufactured by direct compression according to the formula in **Table 1**. Eight formulations were created in all. All materials were passed through a 60-mesh filter separately and collected, before being compressed into tablets with talc (2%) and magnesium stearate (1%) using an 8.5mm flat bevelled edged punch set on a 16 station Rotatory Tablet Compressing Machine. Tablets were squeezed uniformly. **Table 1** summarises themakeup.

Prior to tablet manufacturing, the mixture blend was submitted to compatibility tests (IR) utilising a Shimadzu FTIR spectrophotometer and pre-compression characteristics such as

angle of repose, compressibility index, bulk density, tapered density, and Hausner ratio. Post-compression parameters such as thickness uniformity, hardness, friability, weight variation, drug content uniformity, wetting time, and in vitro disintegration time were determined on the manufactured Amlodipne besylate mouth dissolvingtablet.

Evaluation Parameter[7-11]

Bulk density

Bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the blend (M) was determined. The bulk density is expressed in gm/ml and is givenby.

Bulk density = M /Vb Where,

M = mass of powder taken

V_b = Bulk volue of the powder.

Tapped density

It tested measuring cylinder was tapped about several times and later its true volume was measured and true density was measured by using the following formula.

True density = {weight of the powder (mg)/ true volume of the powder (without void spaces) (ml)}.

Carr's index (compressibility index)

It was determined by using the above determined bulk density and true densities using the following formula,

Carr's index (%) = {(tapped density-bulk density)/tapped density} × 100.

Hausner's ratio

It was also determined by using the above tapped and bulk density values using the following formula.

Hausner's ratio = {tapped density / bulk density}.

Angle of repose: Angle of repose (θ) was determined using funnel method. The blend test sample powder was passed through a funnel that can be elevated perpendicularly until a maximum pinecone height (h) was obtained. The radius of the pile (r) was measured and angle of repose was calculated.

(θ) = tan-1(h/r).

***In-vitro* Dissolution studies Amlodipne besylate Dissolution system**

Apparatus : Dissolution apparatus USP standard Type II (basket) Medium : 900 ml PBS (pH6.8)

Speed : 50 rpm Temperature : 37^0C $\pm 0.5^0$C

Time : 30min.

2.7 Kinetics of drug release[19]

Kinetics of drug release is studied by plotting the data obtained from *in vitro* release in various kineticmodels.

Zero order equation

The graph was plotted as % drug released Vs time in hours.

$C=K_0t$

Where,

K_0 – Zero order constant in concentration/time

t – Time in hours

The graph would yield a straight line with a slope equal to K_0 and intercept the origin of the axis. The results were tabulated and graph was shown.

First order equation

The graph was plotted as log % cumulative drug remaining Vs Time in hours.

$\text{Log } C = \log C_0 - Kt/2.303$

Where,

C_0 - Initial concentration of drug. K- First order constant.

t- Time in hours

Higuchi kinetics

The chart was plotted as % Cumulative drug released Vs square root of time.

$Q = Kt^{½}$

Where,

K – Constant reflecting design variable system. t - Time in hours

Thus drug release rate is relative to the complementary of square root of time. On the off chance that the plot yields a straight line, and the slope is one, at that point the specific dosage form is considered to pursue Higuchi plot of drug release. The results weretabulated.

RESULTS AND DISCUSSION

Table 1: Composition of different batches of Mouth dissolving tablet of Miloxicam.

Formulations Code by factorial design									
Ingredients (mg)	**SX1**	**SX2**	**SX3**	**SX4**	**SX5**	**SX6**	**SX7**	**SX8**	**SX9**
Amlodipine besylate	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
Camphor	8mg	15mg	20mg	8 mg	15 mg	20 mg	8 mg	15 mg	20 mg mg mg
Crospovidone	8 mg	8 mg	8 mg	15 mg	15 mg	15 mg	20 mg	20 mg	20 mg
MCC	125 mg	118mg	110 mg	125 mg	118 mg	110 mg	125 mg	118 mg	110mg
Dextrose	16.5 mg	16.5 mg	16.5mg	16.5 mg	16.5mg	16.5mg	16.5mg	16.5mg	16.5mg
Mannitol	135 mg	135 mg	135 mg	135 mg	135mg	135 mg	135 mg	135 mg	135mg
Magnesium Stearate	10.2 mg	10.2mg	10.2mg	10.2 mg	10.2mg	10.2mg	10.2mg	10.2mg	10.2mg
Talc	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Total weight	317 mg	317mg	314mg	324mg	324mg	321mg	329mg	329mg	326mg

Evaluation Parameter

Table 2: Pre-compression studies of Amlodipne besylate MDTs.

Formulation	Bulk density (g/cm^2)	Tapped density ($g/cm^{2)}$	Carr's index (%)	Hausner's Ratio	Angle of Repose
SX1	0.30±0.24	0.35±0.18	14.28±0.13	1.16±0.14	28.90±0.21
SX2	0.35±0.28	0.40±0.20	12.50±0.14	1.14±0.15	29.56±0.23
SX3	0.43±0.28	0.51±0.21	15.68±0.16	1.18±0.18	28.10±0.24
SX4	0.32±0.26	0.38±0.25	15.78±0.15	1.18±0.20	30.67±0.26
SX5	0.45±0.28	0.52±0.24	13.46±0.14	1.15±0.22	30.21±0.23
SX6	0.44±0.29	0.52±0.26	15.38±0.18	1.18±0.24	28.00±0.25
SX7	0.43±0.27	0.50±0.28	14.00±0.19	1.16±0.16	27.42±0.24
SX8	0.48±0.23	0.56±0.29	14.28±0.21	1.16±0.18	29.39±0.21
SX9	0.47±0.24	0.54±0.26	12.96±0.22	1.14±0.19	30.56±0.20

Table 3: Evaluation of Post-compression studies of Mouth dissolving tablet of Miloxicam.

Formulation	Hardness[a] (kg/cm^2)	Friability[b] (%)	Weight[c] (mg)+D	Thickness[a] (mm)	Drug content[d] (%)
SX1	2.8±0.22	0.25±0.36	2.4±0.59	3.7±0.4	96.20
SX2	3.1±0.24	0.28±0.38	2.8±0.63	4.2±0.2	97.72
SX3	3.2±0.31	0.29±0.35	3.3±0.45	3.6±0.3	98.40
SX4	3.5±0.28	0.29±0.24	3.5±0.88	3.1±0.2	97.00
SX5	2.9±0.35	0.35±0.25	3.8±0.56	3.8±0.1	98.44
SX6	3.5±0.23	0.32±0.30	2.9±0.74	3.7±0.2	99.80
SX7	3.2±0.28	0.28±0.32	4.0±0.67	3.5±0.3	97.20
SX8	3.0±0.35	0.29±0.28	2.9±0.77	3.6±0.2	98.40
SX9	3.1±0.23	0.24±0.35	2.8±0.86	4.1±0.1	99.32

Where, D=standard deviation, a = 6 tablets, b = 33, c = 20, d=10

Table 4: Evaluation of MDT for formulations (SX1 – SX9)

Formulation	Disintegration time (sec)	Wetting time(sec)	Waterabsorption ratio[a](%)
SX1	8±0.54	15±0.23	80±0.42
SX2	6±0.63	12±0.47	85±0.47
SX3	4±0.68	14±0.16	86±0.32
SX4	7±0.57	10±0.32	88±0.13
SX5	4±0.72	14±0.49	82±0.27
SX6	6±0.43	15±0.25	80±0.47
SX7	7±0.41	16±0.28	88±0.17
SX8	8±0.48	11±0.35	87±0.78
SX9	7±0.60	10±0.51	82±0.92

Table 5: *In-vitro* drug release study of formulation marketed formulation.

Time (min)	Absorbance	Concentration (µg/ml)	Dilution factor	amount of drug in 900ml	% drug release
2	0.330	4.73	2	8.51	34.05
4	0.465	6.68	2	12.02	48.07
6	0.599	8.62	2	15.52	62.06
8	0.726	10.47	2	18.84	75.35
10	0.867	12.51	2	22.53	90.1
12	0.931	13.43	2	24.18	96.72
14	0.960	13.86	2	24.95	99.8

Table 6: comparative % drug release vs. time.

Time	SX1	SX2	SX3	SX4	SX5	SX6	SX7	SX8	SX9	Marketed
0	0	0	0	0	0	0	0	0	0	0
2	17.32	16.04	18.77	18.52	20.158	20.3	19.03	27.21	24.82	26.6
4	27.05	26.42	28.07	29.64	28.809	29.6	33.19	38.32	35.94	37.3
6	36.45	35.22	37.09	41.87	42.341	41.7	46.7	51.55	48.57	49.9
8	45.32	43.06	46.12	53.92	54.358	54.2	58.2	64.63	60.92	61.7
10	53.03	50.09	55.58	65.09	66.606	67.2	68.33	76.95	73.62	72.5
12	60.33	56.59	63.82	75.15	77.732	78.2	78.22	87.65	84.59	83
14	66.49	62.71	71.32	84.14	88.24	88.8	87.63	98.22	95.54	93.8

Table 7: Comparative % drug release vs. time of SX8, SX9 and Marketed.

Time	SX8	SX9	Marketed
0	0	0	0
2	27.207	24.815	26.578
4	38.323	35.944	37.321
6	51.553	48.565	49.935
8	64.632	60.919	61.662
10	76.945	73.622	72.514
12	87.645	84.586	82.995
14	98.218	95.541	93.837

Table 8: Calculation of drug kinetics.

Formulation Code	Zero order		First order		Higuchi		Hixon Crowell		Peppas		Best fit Model
	R	K	R	K	R	K	R	K	R	K	
Marketed	0.9744	7.1967	0.9449	- 0.1563	0.9827	22.8012	0.9848	- 0.0384	0.9959	15.9032 N=0.65	PEPPAS
SX1	0.9732	6.0372	0.9971	- 0.0998	0.9840	19.1389	0.9984	- 0.0277	0.9997	12.2980 N=0.69	PEPPAS
SX2	0.9693	5.7092	0.9990	- 0.0899	0.9861	18.1229	0.9966	- 0.0255	0.9997	11.6690 N=0.69	PEPPAS
SX3	0.9739	6.1963	0.9927	- 0.1055	0.9836	19.6376	0.9976	- 0.0290	0.9984	13.2770 N=0.67	PEPPAS
SX4	0.9913	6.3731	0.9783	- 0.1148	0.9668	20.0277	0.9947	- 0.0308	0.9988	10.3200 N=0.79	PEPPAS
SX5	0.9934	6.5690	0.9593	- 0.1256	0.9613	20.6008	0.9865	- 0.0328	0.9939	10.7707 N=0.78	PEPPAS
SX6	0.9936	6.6031	0.9560	- 0.1277	0.9607	20.7031	0.9849	- 0.0331	0.9943	10.8834 N=0.78	PEPPAS
SX7	0.9857	6.7238	0.9763	- 0.1283	0.9738	21.2000	0.9955	- 0.0335	0.9997	11.1675 N=0.78	PEPPAS
SX8	0.9776	7.5542	0.8863	- 0.1989	0.9805	23.9043	0.9678	- 0.0440	0.9956	16.0245 N=0.67	PEPPAS
SX9	0.9838	7.2517	0.9242	- 0.1664	0.9753	22.8849	0.9772	- 0.0398	0.9960	14.3213 N=0.70	PEPPAS

Table 9: Stability Studies.

Parameters	Initials	At 40°C and 75 % RH
Shape	Round	Round
Colour	White	White
Weight variation	0.600±0.12	0.590±0.05
Thickness (mm)	3.12±0.05	3.12±0.13
Hardness (kg/cm^2)	3.72±0.20	3.73±0.10
Friability (%w/w)	0.28±0.21	0.29±0.05
Disintegration time (sec)	6.0±0.12	6.2±0.10
Wetting time (sec)	11.8±0.30	12.1±0.28
Water absorption ratio (%)	83.50±0.22	83.56±0.20
Invitro dispersion time (sec)	18±0.12	18.2±0.12
% Drug content	101±0.10	102±0.12
% CDR	96.8	96.8

The purpose of this study was to determine the influence of several superdisintegrants on the dissolution profile and other characteristics of Amlodipne besylate mouth dissolving tablets. Nine formulations of Amlodipne besylate with varying amounts of superdisintegrants, Ac-di-sol (croscarmellose sodium), Polyplasdone XL-10, and Microcrystalline cellulose pH 1.02 were produced. Each suggested formulation was made as a powdered mixture of medication and excipient and analysed for various pre-compression parameters. There was no evidence of peaks appearing or disappearing in the polymer-drug mixture, indicating that there was no chemical interaction between the medication and polymers. The pre-compression parameters suggested a high capacity for flow. The following are thefindings.

Disintegration Time: The disintegration time was found in the range 12-14 seconds for all batches. The batch SX8 and SX9 showed fastest disintegration.

In-vitro Release studies

The comparative examination of each formulation was conducted using in-vitro kinetic parameters that provided insight into the formulation's release profile. For comparative interpretation of superdisintegrants, the time required for 80 percent drug release was used. The weight variation, hardness, friability, drug content, and T80 percent of the tablet were all assessed. The results indicate that the Amlodipne besylate mouth dissolving tablet formulation was stable under the conditionstested.

DISCUSSIONS

Oral dispersible tablet of Amlodipine besylate were formulate by sublimation method. Formulation was developed with the help of different superdisintegrants and optimizes the concentration and hardness of the tablet to give the least time to drug release. Taste and odour was acceptable for geriatric and paediatric patient. Amlodipine besylate drug was used as an antihypertensive drug because of best relief in the pain of hypertension.

The standard curve obtained was straight line. The curve was obtained in 6.8 pH phosphate buffer at the maximum wavelength of 239nm. The slope, intercept and regression coefficient were obtained from the graph. Drug contents and *in-vitro* drug release calculation is based on the standard calibration curve. The micromeritics properties of the powder mixture was calculated before compression of tablets.

The result of angle of repose was (28.00º to 30.67º) and the percentage of compressibility index (%) ranged from (12.50% to 15.78%).Bulk density was found in the range of (0.30 to 0.48) and tapped density ranged from (0.35 to 0.56). Hausner ratio in the range of 1.14 to 1.18. The results of these micromeritics parameters show the good flow properties of blend of powder.

Compatibility studies of Amlodipine besylate with different polymers were carried out prior to the preparation of tablets. All the significant peaks of Amlodipine besylate were present in all the spectrum obtained between drug and excipients. It shows no notable variation in compatibility.

Hardness varied from 2.8 to 3.5 kg/cm^2. It indicates good strength of formulation. The thickness was found to be in the range of 3.1 to 4.2 mm.

The friability percentage loss was found in the percentage of (0.24 - 0.35%) which is lessthan 1% and show good mechanicalstability.

The maximum percentage deviation was ±0.88 %. No formulations showed more than ±5% (USP limit) deviation. Thus formulation complies with the USP requirement of weight variation.

The uniform drug content is found in the different MDT tablet formulations which is in the range of 96.2 to 99.8. The maximum percentage drug content found was 99.80%. It is in the limit mention under Indian pharmacopoeia.

The wetting time obtained from the sublimation method 10-16sec. these result shows that the in-vitro disintegration time obtained from the sublimation method was good.

The water absorption ratio obtained from the sublimation method 80-88%. In this method shows the water absorption ratio within the limit.

In-vitro disintegration time by sublimation method, the 99.80% drug was released within 6 sec. Therefore the formulation no. SX6 and SX9 showed better in-vitro disintegration time within 6 sec.

CONCLUSION

The objective of this experimental approach was to develop and inspected fast dissolving tablet of Amlodipine besylate as an antihypertensive drug. The sublimation technique was used for the development of oral dispersible tablets of Amlodipine besylate. The mouth dissolving tablet is beneficial for geriatric and paediatric patient. The camphor and cross povidone showsbestcombinationinformulationSX6andSX9inratioof20:15and20:20.Inthe

sublimation method the in-vitro dispersion and in-vitro disintegration time is good. About 99.80% drug was released within 6sec by sublimation method. In drug kinetics the Peppas and Korsmeyer kinetics ispassed.

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