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FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF AMLODIPINE BESYLATE

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ABSTRACT

The aim of present work was to prepare mouth dissolving tablets of Amlodipine besylate, used commonly for the treatment angina pectoris, commonly known as angina, is chest pain due to ischemia of the heart muscle, generally due to obstruction or spasm of the coronary arteries (the heart's blood vessels).The demand of fast disintegrating tablets has been growing, during the last decade especially for geriatric and pediatric patients because of swallowing difficulties. The objective of the present study is to prepare fast disintegrating tablets of Amlodipine Besylate by using different disintegrants for the potential emergency treatment of angina and hypertension. The superdisintegrant used in this study were crosspovidone, crosscarmelose sodium and Sodium Starch Glycolate in varying concentrations. . spray dried mannitol was used as diluent. Aspartame and lemon flavor were used to enhance organoleptic properties of the tablets. The formulated tablets were evaluated for weight variation, wetting time, hardness, friability and in vitro disintegration time, In vivo disintegration time and drug release characteristics. Results of *In vitro* disintegration time and *In vivo* disintegration time indicated that the tablets dispersed (or) disintegrate rapidly within 16 seconds, also the hardness, friability, dissolution rate and assay of prepared tablets were found to be acceptable according to standard limits.

Key words: Mouth dissolving tablets, Superdisintegrants, Amlodipine besylate, Direct compression.

INTRODUCTION

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. The various dosage forms administered orally, the tablet is one of the most Preferred dosage forms because of its ease of manufacturing, convenience in Administration, accurate dosing, stability compared with oral liquids, and because it is more tamperproof than capsules. The bioavailability of drug is dependent on *in vivo* disintegration, dissolution and various physiological factors. In recent years, scientists have focused their attention on the formulation of quickly disintegrating tablets[1]. The task of developing rapidly disintegrating tablets is accomplished by using a suitable diluents and superdisintegrant [1]. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market [2].

A major claim of some oral dispersible tablets is increased bioavailability compared to traditional tablets. Because some of the drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, the bioavailability of the drug is significantly increased over those observed in the conventional tablet dosage form [3].

Amlodipine besylate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl] -4-(2-chlorophenyl)-1, 4- dihydro -6-methyl-3, 5-pyridinedicarboxylate, mono benzenesulphonate monohydrate. Amlodipine besylate is a used in the treatment of chronic stable angina, vasospastic angina and hypertension. Amlodipine is a sparingly soluble orally administered drug and the rate of absorption is often controlled by the rate of dissolution [4].

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx

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across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure [5].

MATERIALS AND METHODS

Amlodipine Besylate was obtained from Wuhan Fortuna, china. Sodium starch glycol ate were obtained from Ascot Pharmachem Pvt Ltd, Gujarat, crospovidone were obtained from Crystal Pharma, USA. Croscarmellose sodium were obtained from Dmv Fonterra excipients, USA. Microcrystalline cellulose was obtained from Vijlak Pharma, Mumbai. Spray Dried Mannitol were obtained from KP Lalwuai & Co, India. Povidone were obtained from Nan hang Industries. Aspartames were obtained from the NutraSweet Company, USA. Magnesium Stearate was obtained from Amishi Drugs and Chemicals, Hyderabad.

Preparation of Oral Disintegrating Tablets of Amlodipine Besylate by Direct Compression Method

Amlodipine besylate, Spray dried mannitol, Microcrystalline celluolose, Povidone PVP K-30, disintegrant(Sodium starch glycolate, crospovidone, Croscarmellose), Aspartame and Lemon Flavour were passed through sieve no.40. Magnesium stearate was passed through sieve no.80 and was added to the above blend then it was mixed thoroughly in a poly bag. The resulting blend was compressed on a rotary compression machine using 7.0 mm punch.

Evaluation of Precompression Blend

Bulk density and Tapped density

An accurately weighed quantity of the granules (W), was carefully poured into the graduated cylinder and the volume (V_o) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus (bulk density apparatus). The density apparatus was set for 100 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the following formulas [4],

Bulk density = W / V_o, Tapped density = W / V_f

Where, W = Weight of the granules, VO = Initial volume, VF = Final volume [8].

Compressibility index

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30% is defined as the free flowing material [6].

$$\text{Compressibility Index} = \frac{100 (V_O - V_F)}{V_0}$$

Where, Vo – Untapped density, V_f – Tapped density

Hausner's Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner's Ratio = Tapped density/Bulk density

Evaluation of Orally Disintegrating Tablets

Weight Variation

This is an important in process quality control test to be checked frequently (every half an hour). Twenty tablets of each formulation were selected at random and weighed individually. The weight of individual tablet was noted. Average weight was calculated from the total weight of the tablets. The individual weight was compared with average weight. The weight of not more than two tablets should deviate from the average weight by more than the percentage deviation allowed and none should deviate by double the percentage deviation. The percentage deviation was calculated by using the formula [6].

$$\text{Percentage deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Thickness Variation

Ten tablets from each formulation were taken randomly and their thickness was measured with a digital vernier caliper. Average thickness and standard deviation were calculated.

Hardness

Hardness (diametral crushing strength) is the force required to break a tablet across the diameter. The tablet is placed across the diameter in between the spindle and anvil. The knob is adjusted to hold the tablet in position. The reading of the pointer is adjusted to zero. The pressure is increased slowly to break the tablet[13]. For each formulation, the hardness of 5 tablets was determined using a Monsanto hardness tester, mean and SD were calculated [7].

Friability

The friability of a sample of 20 orally disintegrating tablets was measured utilizing an Electro lab, Friability tester USP 23. Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, reweighed, and percentage weight loss (friability) was calculated.

$$\text{Friability} = \frac{(W_1 - W_2)}{W1} \times 100$$

Where, W_1= Initial weight of tablet and W_2= Final weight of tablet

Water Absorption Ratio (R)

The weight of the tablet prior to placement in the Petri dish was noted (Wb) utilizing a digital balance. The wetted tablet was removed and reweighed (Wa) [8]. Water absoption ratio, R, was then determined according to the following equation.

$$R = (Wa - Wb) / Wb$$

Where, W_b and Wa were tablet weights before and after water absorption, respectively [9].

Wetting Time

Five circular tissue papers were placed in a Petri dish of 10 cm diameter. Ten milliliters of water containing 0.5% nigrosine, a water-soluble dye, was added to the Petri dish. The dye solution was used to identify complete wetting of the tablet surface [10]. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicate of six. Wetting time was recorded using a stopwatch.

In-vitro disintegration time

In-vitro disintegration time of the ODTs was determined following the procedure described by Gohel et al. 10 ml water at 25^{o}C was placed in a petri dish of 10 cm diameter. The tablet was then carefully placed in the center of the Petri dish and the time required for the tablet to completely disintegrate into fine particles was noted. Observations were carried out in replicates (n=6) and mean±SD values were recorded [11].

Drug content

Ten tablets were randomly selected from each formulation and crushed into a fine powder. An accurately weighed aportion of the complex containing drug equivalent to a single dose (5mg) was transferred into a 100ml volumetric flask containing 0.1N HCl it was shaken by mechanical means for 1hour. Then it was filtered through a 0.45µ membrane filter and appropriate dilutions were made and absorbance was measured against blank at 237nm in a UV spectrophotometer [9].

In-vitro dissolution studies

In-vitro dissolution studies for orally disintegrating tablets is carried out by using USP II paddle method at 50 rpm in 900 ml of 0.1N HCl as dissolution media, maintained at 37±0.5ºC. Five ml aliquots were withdrawn at the specified time intervals (5, 10, 15, 20, 30, 40, and 50) filtered and analyzed spectrophotometrically against blank at 237nm in a UV spectrophotometer. An equal volume of fresh medium, which was prewarmed at 37ºC, is replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. Dissolution studies are performed in triplicate [12].

Stability Studies

The stability study of the tablets was carried out according to ICH guidelines by storing tablets in stability chamber at 40±20°C / 75±5% RH for 3 months. The effects of temperature and time on the physical characteristics of the tablet are evaluated for assessing the stability of the prepared formulations. The different parameters that are to be studied are disintegration time, hardness, friability, and drug content and dissolution rate [10].

RESULTS AND DISCUSSION

Amlodipine Besylate fast dissolving tablets of were pre-pared by direct compression method was carried out by using superdisintegrants like Crospovidone, Croscarmellose sodium and Sodium starch glycolate . In 5%, Bulk density and tapped density: range from 0.21 to 0.30g/ml) and 0.25 to 0.37 respectively. Compressibility index and Hausner ratio range from 11.1 to 15.31 and 1.12 to 1.23 respectively. The results for recompressed parameters are showed in Table 2.

Weight variation test range from 137.58mg to 143.27mg as per IP specification. Friability: range from less 0.73-0.80 as per IP specifications. Thickness: range from 3.55 mm to 3.57 mm; the results indicate that the tablets are suitable for packing. Content uniformity: was found in between 98.33% to 100.63%. Hardness of tablet was found to be between 3.6 to 4.2 kg/cm2. The results indicate that the tablets are mechanically strong and are in limit. Disintegration time: in between 16 to 39 second the results indicate that disintegration time of tablets is within 1minute. Wetting time: in between 29 to 44 second and water absorption ratio was found to be 0.63 to 1.36 the post compressed parameters are showed in Table 3.

In vitro dissolution test reveals the drug release. The maximum *in vitro* dissolution was found to be with formulation B6. The control formulation has the least *in vitro* dissolution (52.51 %) and the formulation B6 was found to contain maximum in vitro dissolution of 100.01%. It clearly shows due to the superdisintegrant – (crospovidone at 6%) and it seems to be the best. The reason is its highly porous structure and water wicking mechanism into porous network of tablet and hence increases in concentration of crospovidone accounts for rapid drug release (Table 4).

Table 1. Ingredients used in formulation of Orally Dispersible Tablet (Weight of each tablet is 140mg)
Magnesium stearate 1% in all formulations

Ingredients	**B_1 (mg)**	**B_2 (mg)**	**B_3 (mg)**	**B_4 (mg)**	**B_5 (mg)**	**B_6 (mg)**	**B_7 (mg)**	**B_8 (mg)**	**B_9 (mg)**
Amlodipine Besylate	10	10	10	10	10	10	10	10	10
Spray dried mannitol	102.2	99.4	96.6	102.2	99.4	96.6	102.2	99.4	96.6
Microcrystalline cellulose	18	18	18	18	18	18	18	18	18
Povidone (PVP K30)	4	4	4	4	4	4	4	4	4
Sodium starch glycolate	2.5	5.7	8.6	-	-	-	-	-	-
Crospovidone	-	-	-	2.5	5.7	8.6	-	-	-
Croscarmellose sodium	-	-	-	-	-	-	2.5	5.7	8.6
Aspartame	1	1	1	1	1	1	1	1	1
Lemon flavor	1	1	1	1	1	1	1	1	1

Table 2. Evaluation of Precompression Blend

Formulation	Bulk Density(g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hauser's Ratio
B_1	0.30±0.005	0.37±0.03	18.9±0.61	1.23±0.23
B_2	0.27±0.006	0.34±0.02	12.9±.0.35	1.17±0.004
B_3	0.24±0.002	0.25±0.002	16.0±0.20	1.15±0.002
B_4	0.21±0.003	0.25±0.01	16.0±0.19	1.19±0.02
B_5	0.27±0.007	0.30±0.002	15.6±0.15	1.20±0.01
B_6	0.23±0.004	0.27±0.002	11.1±0.20	1.12±0.02
B_7	0.21±0.003	0.26±0.003	16.0±0.34	1.15±0.04
B_8	0.27±0.005	0.33±0.01	14.6±0.11	1.20±0.01
B_9	0.22±0.002	0.25±0.02	12.0±0.66	1.134±0.06

*All the values are expressed as mean ±Standard deviation; n=3

The obtained values of compressibility index and Hausner's ratio for different formulations were found within the limits.

Table 3. Evaluation of Prepared Amlodipine Besylate Orally Disintegrating Tablets

Formulation	Wetting time (seconds)	Water Absorption Ratio (WAR)	In vitro Disintegration Time (seconds)
B_1	34±1.79	1.00±0.02	39±1.51
B_2	36±2.06	1.17±0.05	32±2.31
B_3	32±1.43	1.36±0.03	28±2.46
B_4	44±2.01	0.63±0.01	38±2.08
B_5	39±1.56	0.72±0.06	27±2.13
B_6	29±1.25	0.88±0.02	16±2.51
B_7	42±1.44	0.93±0.05	38±2.77
B_8	37±1.08	1.07±0.03	31±2.01
B_9	34±1.57	1.27±0.06	28±2.14

*All the values are expressed as mean ±Standard deviation; n=3

Table 4. Percent Cumulative drug release profiles for Amlodipine Besylate orally disintegrating formulations prepared by direct compression method

Time (mins)	B_1	B_2	B_3	B_4	B_5	B_6	B_7	B_8	B_9
5	19.34± 1.41	27.32± 1.23	34.56± 1.39	28.32± 1.46	39.43± 1.43	52.51± 1.25	26.23± 1.32	36.51± 1.43	45.12± 1.33
10	46.16± 1.38	53.43± 1.56	72.54± 1.42	56.43± 1.72	76.62± 1.12	101.21± 1.43	54.12± 1.43	77.53± 1.47	90.18± 1.44
15	67.34± 1.25	74.21± 1.31	97.22± 1.32	86.65± 1.56	98.26± 1.32	100.18± 1.52	88.32± 1.22	95.43± 1.64	99.81± 1.22
20	89.45± 1.41	98.52± 1.34	100.23± 1.43	99.81± 1.64	98.51± 1.22	100.13± 1.22	101.61± 1.34	98.51± 1.33	100.16± 1.43
30	101.18± 1.21	100.21± 1.54	99.91± 1.12	101.12± 1.33	100.23± 1.34	100.09± 1.43	100.43± 1.56	100.22± 1.42	99.99± 1.34
40	100.31± 1.52	99.96± 1.22	99.82± 1.43	100.08± 1.47	99.91± 1.52	100.02± 1.32	100.32± 1.32	100.14± 1.52	99.96± 1.22
50	99.88± 1.34	99.86± 1.25	99.78± 1.32	100.01± 1.53	99.84± 1.41	99.96± 1.45	99.86± 1.22	99.91± 1.46	99.87± 1.64

Figure 1. In-vitro drug release profiles of formulations prepared by direct compression at different concentrations of sodium starch glycolate

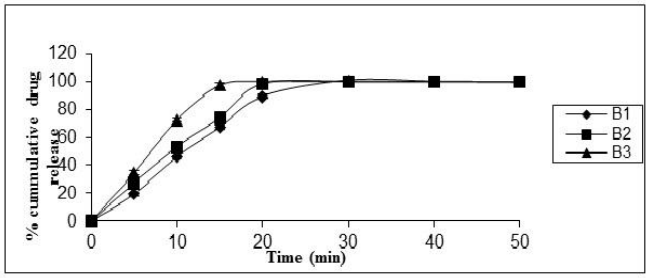


Figure 2. In-vitro drug release profiles of formulations prepared by direct compression at different concentrations of crospovidone

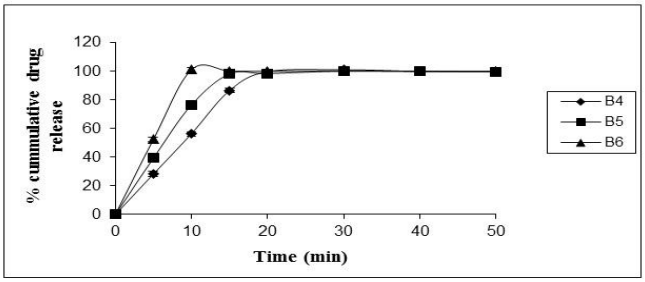
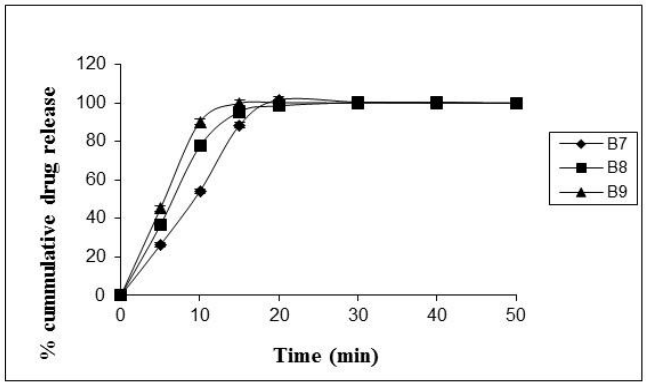


Figure 3. In-vitro drug release profiles of formulations prepared by direct compression at different concentrations of croscarmellose sodium



The optimized formulations B6 were kept for accelerated stability and monitored for appearance, hardness, friability, drug content, in vitro dispersion time, wetting time and dissolution profile study and found to stable for all the different parameters.

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