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Research Article

Development and Characterization of Rapidly DisintegratingTablets of Amlodipine Besylate

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ABSTRACT

Hypertension is one of the most important causes of premature death worldwide and the problem is growing; in 2025, an estimated 1.56 billion adults will be living with hypertension. Amlodipine besylate is a longacting calcium channel blocker used in the treatment of chronic stable angina, vasospastic angina and hypertension. Recent developments in the technology have prompted scientists to develop Rapidly Disintegrating Tablets (RDTs) with improved patient compliance and convenience. The present study aims to prepare and evaluate amlodipine besylate Rapidly Disintegrating Tablets using superdisintegrants by direct compression method. Amlodipine loaded-RDTs were characterized for weight variation, hardness, thickness, friability, wetting time and disintegration time. In vitro drug release study was performed using United States Pharmacopoeia (USP) II dissolution testing apparatus II (paddle method). The results revealed that Amlodipine loaded-RDTs were successfully formulated with good mouth feel, faster disintegration and better drug release.

INTRODUCTION

Hypertension, also known as high or raised blood pressure, is a condition in which the blood vessels have persistently raised pressure. Blood is carried from the heart to all parts of the body in the vessels. Each time the heart beats, it pumps blood into the vessels. Blood pressure is created by the force of blood pushing against the walls of blood vessels (arteries) as it is pumped by the heart. The higher the pressure the harder the heart has to pump [1].

Globally, nearly one billion people have high blood pressure (hypertension); of these, two-thirds are in developing countries. Hypertension is one of the most important causes of premature death worldwide and the problem is growing; in 2025, an estimated 1.56 billion adults will be living with hypertension. Hypertension kills nearly 8 million people every year, worldwide and nearly 1.5 million people each year in the South-East Asia (SEA) Region. Approximately one-third of the adult population in the SEA Region has high blood pressure [2].

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Amlodipine besylate, chemically described as 3-Ethy l-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1, 4-dihydro -6-methyl-3, 5-pyridinedicarboxylate monobenzene sulphonate [3, 4], is a long-acting dihydropyridine calcium channel blocker commonly used in the treatment of hypertension. Amlodipine selectively inhibits transmembrane influx of calcium ions into cardiac and vascular smooth muscle, leading to decreased vascular tone, reduced systemic vascular resistance, diminished after load and coronary vasodilation [5].

The term oral drug delivery, also known as peroral delivery, refers to taking a dosage form by mouth for local action or systemic absorption at any point along the gastrointestinal (GI) tract. Oral drug delivery is the most readily available and widely accepted route of delivery for medications. The most obvious challenge is that many drugs have a bad taste when placed in the mouth or exhibit foul odors, which must be resolved to be acceptable to patients. Apart from this, there are also many barriers and obstacles that inhibit drug absorption via the oral route. These include the acidic gastric environment, digestive enzymes, mucus layer diffusion and tight junctions between epithelial cells that prevent paracellular transport [6, 7]. Many

patients express difficulty in swallowing tablets and hard gelatin capsules, tending to non-compliance and ineffective therapy [8].

Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is rapidly disintegrating tablets [9-11]. Rapidly disintegrating tablets (RDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients [12]. The present study aims to prepare and evaluate amlodipine besylate rapidly disintegrating tablets using superdisintegrants by direct compression method.

MATERIALS AND METHODS

Materials

Amlodipine besylate was obtained as gift sample from Cipla Pharmaceuticals (Goa, India). Microcrystalline cellulose, Sodium starch glycolate and Aerosol were procured from Loba Chemie Pvt Ltd (Mumbai, India). Crosscarmellose sodium was obtained from Research Lab Fine-Chem (Mumbai, India). Other chemicals were of analytical grades.

Formulation of Rapidly Disintegrating Tablets of Amlodipine Besylate

Rapidly disintegrating tablets containing 5 mg of amlodipine besylate were prepared by direct compression method (Table 1). All the ingredients without magnesium stearate and talc were mixed uniformly followed by addition of magnesium stearate and talc. Superdisintegrants like Sodium Starch Glycolate, and Crosscarmellose sodium were used in different ratios and finally the effect of combination of superdisintegrants was studied. The prepared powder blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio.

Evaluation of Powder Blend Property

Bulk Density (BD) and Tapped Density (TD) [13, 14]

Accurately weighted amount of API was produced into a 100-ml measuring cylinder and tapped for 100 times from the height of 2.5 cm at 2-second intervals on tapped density apparatus. The tapping was continued until no further change in volume was noted. BD and TD were calculated using the following formula.

$$BD = \frac{\text{Weight of the powder}}{\text{Volume of the packing}}$$

$$TD = \frac{\text{Weight of the powder}}{\text{Tapped volume of packing}}$$

Percent Compressibility Index [14]

The compressibility property of the granules was determined by % compressibility Index.

$$\%C = \frac{(TD-BD)}{TD} \times 100$$

Hausner's Ratio (HR)

Hausner's Ratio was obtained by using formula;

$$HR = \frac{TD}{BD}$$

Evaluation of Tablet

Weight Variation [15]

Twenty tablets from each formulation were selected randomly and average weight was determined. Deviation of each tablet weight from average weight was determined. The specification used for the weight variation test was as per IP (not more than 2 of the individual masses deviate from the average mass by more than 5% and none deviate by more than 10%).

Hardness

The resistance of tablets to shipping or breakage under the conditions of storage, transportations and handling before usage depends on its hardness. The hardness of tablet was measured by Monsanto hardness tester. The hardness was measured in terms of Kg/cm^2.

Thickness

Thickness of the tablet is most important parameter for uniformity of the tablet size. It is measured by the Vernier calipers. This was measured during compression.

Friability

Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution.

Table 1: Formulation design of Amlodipine Besylate loaded Rapidly Disintegrating Tablets

Formulations/ Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Amlodipine besylate (mg)	5	5	5	5	5	5	5	5	5
Lactose (mg)	56.03	56.03	56.03	56.03	56.03	56.03	56.03	56.03	56.03
Microcrystalline cellulose (mg)	66.67	66.67	66.67	66.67	66.67	66.67	66.67	66.67	66.67
Crosscarmellose sodium (mg)	1	2	3	4	5	6	7	8	9
Sodium starch glycolate (mg)	10	9	8	7	6	5	4	3	2
Sodium saccharin (mg)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Vanilla flavor (mg)	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.83
Talc (mg)	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.83	0.83
Magnesium stearate (mg)	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62
Mannitol (mg)	7.77	7.77	7.77	7.77	7.77	7.77	7.77	7.77	7.77
Total	150	150	150	150	150	150	150	150	150

Tablets were then de-dusted using a soft muslin cloth and reweighed.

The friability (f) is given by the formula

$$\textbf{Friability (f) =} (1 - W0/ W) \times 100$$

Where'W0'is weight of the tablets before the test and 'W' is the weight of the tablet after the test.

Wetting Time [16]

Twice folded tissue paper was placed in a petri dish having an internal diameter of 6.5 cm to that 10 ml of purified water containing an eosin dye solution (0.05% w/v) was added to Petri dish. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for dye to reach the upper surface of the tablet and to completely wet was noted as the wetting time.

Disintegration Time

Disintegration time was calculated on the DT apparatus. 6 tablets were selected randomly and placed in to the basket. 3 discs were placed over the 3 tablets and machine was started. The time at which complete disintegration of the tablet takes place that was measured and recorded as disintegration time of that particular tablet.

IR Spectroscopy

IR spectroscopy was performed using shimadzu FTIR 83006 spectrophotometer and the spectrum was recorded in the wavelength region of 4000-400 cm^{-1} the procedure consisted of dispersing a sample in KBR and compressing in to discs by applying a pressure of 5t for 5 min in a hydraulic pressure. The pellet was placed in the light path and the spectrum was recorded.

***In Vitro* Drug Release Studies** [15]

The procedure was determined using United States Pharmacopoeia (USP) II dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl (pH-1.2) at 37 ± 0.5°C and 50 rpm. A sample of 5 ml of the solution was withdrawn from the dissolution apparatus at 5 minute interval with the replacement of fresh dissolution medium for 30 minute. The samples were passed through a 0.45-µm membrane filter and diluted to a suitable concentration with phosphate buffer. The absorbance of these solutions was measured at 241 nm using a Shimadzu UV-1601 UV/V is double beam spectrophotometer.

Drug Content Uniformity

Ten tablets were weighed and powdered and 10mg equivalent weight of Amlodipine besylate was accurately weighed and transferred in 100ml volumetric flask. It was dissolved and made up the volume with 0.1N HCl pH 1.2. Subsequently the solution was filtered and suitable dilution were made and analyzed at 241 nm using UV-Visible spectroscopy.

Stability Studies [17, 18]

In any rational design and evaluation of dosage form for drugs, the stability of the active component must be major criteria in determining their acceptance and rejection. During the stability study the product is exposed to normal conditions of humidity and temperature. However, the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions

of temperature. Tablets of batches F7 was subjected to stability studies.

Storage Conditions

The tablets were subjected to stability following some ICH guideline, as the following conditions.

1. 30° C / 75% RH (±2° C /±5% RH)
2. 40° C/ 75% RH (±2° C /±5% RH)

RESULTS AND DISCUSSION

Evaluation of Pre-Compression Parameters of In-Processed Materials of Amlodipine Besylate-Loaded Rapidly Disintegrating Tablets

Amlodipine Besylate-loaded rapidly disintegrating tablets were successfully formulated using different superdisintegrants by direct compression method. Evaluation parameters like bulk density, tapped density, Carr's compressibility index and Hausner's ratio of in-processed materials are shown in Table 2. The flow properties were within range and the physical mixture was compatible and stable for preparation of formulation.

Evaluation of Post Compression Parameters of Amlodipine Besylate Rapidly Disintegrating Tablets

Weight Variation

Ten tablets from each formulation were selected randomly and average weight was determined. Individual tablets were then weighed and was compared with average weight. All the batches of rapidly disintegrating tablets showed deviation below 7.5% as the allowable limit is 7.5%. The weight variation for all batches is given in Table 3. [15]

Thickness

The thickness for all batches is depicted in Table 3. The thickness of different batches of rapidly disintegrating tablets was found in the range of 2.80 – 3.00 mm.

Hardness test

The results are tabulated in Table 3. Hardness of rapidly disintegrating tablets varied from 2.4 to 3.0 kg/cm^2.

Friability [19, 20]

The values of friability test are given in Table 3. All the batches showed friability within the official limit i.e. less than 1%, thus all the batches passed the friability test.

Wetting time

Wetting time for all the formulations were found in range of 15 to 21 seconds. The batch containing superdisintegrants like sodium starch glycolate, crosscarmellose sodium in higher concentration shows the wetting time near to 20 seconds because it act by capillary action and time required to penetrate water into tablet is minimum as compared to other superdisintegrants. The results are given into the Table 3 and Fig.1

Figure 1: Wetting time of the optimized formulation

Disintegration Time

The most important parameter that is needed to be optimized during the development of rapidly disintegrating tablets is disintegration time of the tablets. The disintegration test of the tablet was conducted in purified water. The batch containing superdisintegrants like sodium starch glycolate, Crosscarmellose sodium in higher concentration shows the disintegration time below 25 seconds because it act by capillary action and having more disintegration power as compared to other superdisintegrants. Disintegration study for all batches is depicted in Table 3 and Fig. 2.

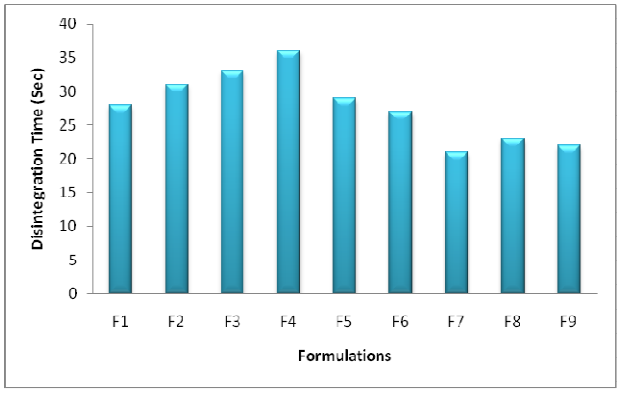

Figure 2: *In vitro* disintegration time of formulations

FTIR

The FTIR spectrum of Amlodipine Besylate rapidly disintegrating tablets formulation (F7) exhibited distinctive peaks at 1234.22 cm^{-1}due to C-N stretching, 1369.21 cm^{-1}due to C=C in aromatic ring, 3561.88 cm^{-1}due to NH stretching, and 2969.88 cm^{-1}C-H aromatic stretching.

Table 2: Evaluation of pre-compression parameters of Amlodipine Besylate rapidly disintegrating tablets

Formulations	Bulk Density (gm/ml)	Tapped density (gm/ml)	Carr's Index	Hausner's ratio
F1	0.522 ± 0.01	0.612 ± 0.005	14.04 ± 0.21	1.13 ± 0.004
F2	0.531 ± 0.03	0.623 ± 0.001	14.72 ± 0.34	1.15 ± 0.006
F3	0.511 ± 0.02	0.625 ± 0.003	14.94 ± 0.41	1.13 ± 0.003
F4	0.547 ± 0.01	0.641 ± 0.001	15.45 ± 0.20	1.16 ± 0.001
F5	0.551 ± 0.02	0.652 ± 0.002	15.97 ± 0.15	1.18 ± 0.003
F6	0.563 ± 0.012	0.659 ± 0.004	15.72 ± 0.25	1.14 ± 0.006
F7	0.576 ± 0.02	0.666 ± 0.002	14.24 ± 0.34	1.17 ± 0.005
F8	0.666 ± 0.002	0.671 ± 0.001	15.30 ± 0.41	1.16 ± 0.002
F9	0.573 ± 0.05	0.669 ± 0.004	16.42 ± 0.54	1.18 ± 0.007

Table 3: Evaluation of Post Compression Parameters of Amlodipine Besylate rapidly disintegrating Tablets

Formulation	Weight variation (%)	Thickness (mm)	Hardness kg/cm^2	% Friability	Wetting time (seconds)	*In vitro* disintegration time (seconds)
F1	1.72 ± 0.40	2.82 ± 0.01	2.8	0.41±0.165	21	28
F2	1.84 ± 0.43	2.86 ± 0.03	2.4	0.48±0.187	19	31
F3	1.92 ± 0.50	2.94 ± 0.01	2.4	0.56±0.178	17	33
F4	2.19 ± 0.72	2.98 ± 0.04	2.6	0.47±0.190	18	36
F5	1.52 ± 0.02	2.82 ± 0.01	2.8	0.59±0.160	16	29
F6	1.99 ± 0.51	3.00 ± 0.05	2.8	0.53±0.223	17	27
F7	1.71 ± 0.40	2.92 ± 0.02	2.8	0.40±0.256	15	21
F8	1.30 ± 0.06	2.88 ± 0.04	3.0	0.52±0.129	17	23
F9	1.89 ± 0.45	2.84 ± 0.03	2.6	0.63 ± 0.115	16	22

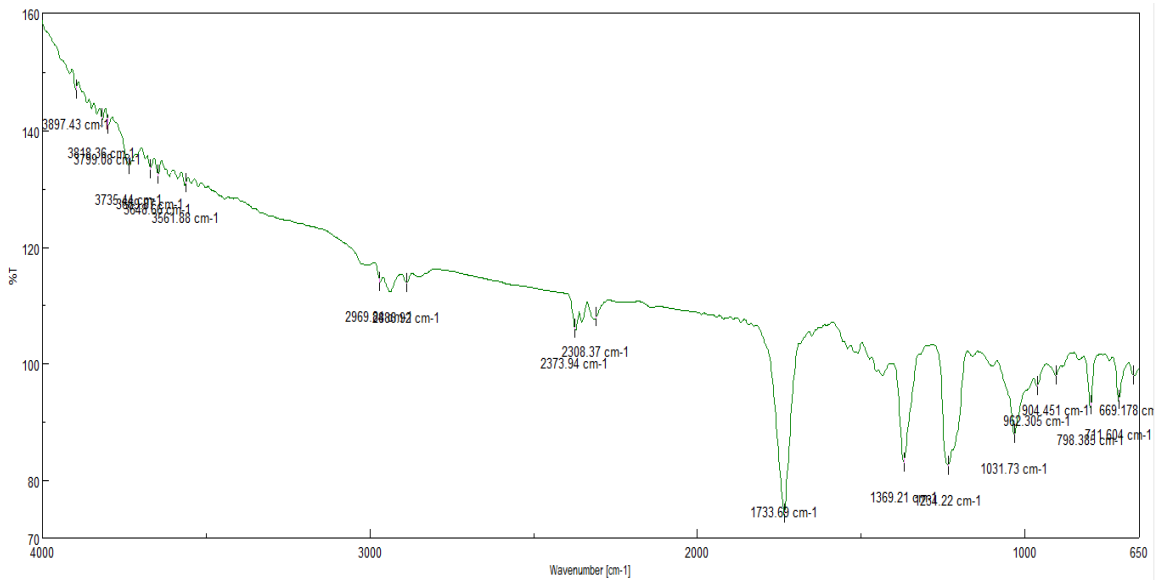

Figure 3: FTIR spectrum of Amlodipine besylate rapid disintegrating tablet formulation

In Vitro Drug Release [19]

The *in vitro* drug release of Amlodipine besylate was found to be in the range of 71.86% to 95.54%. As per IP standard (NLT 80% release within 10 minutes) all the batches of Amlodipine besylate passed the *in vitro* drug release test because there was no any effect of excipient seen on *in vitro* drug release. The *in vitro* study of all the batches is given in the Fig. 4.

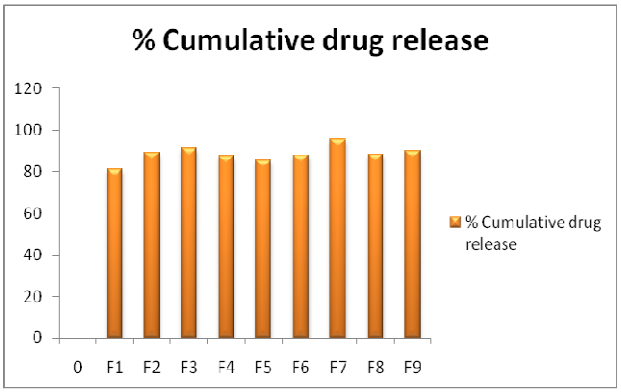

Figure 4: Cumulative drug release of formulations

Stability Study [17, 18]

Appearance

Tablets kept for stability studies were examined. The color of the formulation F7 was similar before and after stability studies. Surface texture of the formulations packed in Alu-Alu Blister packs does not show any significant change at 30°C/75%RH (±2°C/±5RH) and 40°C/75%RH (±2°C/±5RH) after 1 month. This indicated that the tablets not absorb moisture from the environment. The formulation F7 was taken as a stable formulation.

Drug Content

At the end of 1 month the drug content found in Formulation F7 was above 90%. This indicates that Amlodipine Besylate rapidly disintegrating tablets packed in vials was stable in presence of the excipients used, and stored at high temperature and in presence of high humidity.

Table 4: Drug content for the optimized batch for stability studies

Time interval		Drug Content in % w/w	Disintegration time in seconds
Initial		97.31	21
After 1 month	**30°C/75%RH**	97.11	22
	40°C/75%RH	96.73	22

CONCLUSION

We have successfully prepared and evaluated the amlodipine besylate-loaded rapidly disintegrating tablets using superdisintegrants by direct compression method. The results of all the pre-compressed and post-compressed parameters revealed that they are within the limits.

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