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Formulation and Evaluation of Amlodipine besylate orally disintegrating tablet

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ABSTRACT

Amlodipine besylate is a recognized drug for hypertension therefore development of an ODT of Amlodipine besylate and to evaluate the effect of various superdisintegrants on its disintegration time and release profile was the prime objective of this research work. Tablets were prepared by direct compression technique using three different superdisintegrants. Sodium starch glycolate, Croscarmellose sodium and Crosspovidone XL-10 were used as superdisintegrants in combinations to achieve optimum release profile, disintegration time and hardness. Direct compression process was selected for this formulation of ODT tablets, because porous nature is more in direct compression blend than wet granulation blend, so it will give faster disintegration. Microcrystalline cellulose was used as diluent and mannitol, mint flavor and sodium saccharin were used to enhance the organoleptic properties of tablets. The tablets were evaluated for weight variation, hardness, friability, in-vitro disintegration time and drug release characteristics. Hardness and friability data indicated good mechanical strength around 3 kg/cm2 for all the batches. The results of in-vitro disintegration time indicated that the tablets dispersed rapidly in mouth within 60s. Dissolution study revealed release rate of drug from the tablets was comparable with marketed tablet formulation of Amlodipine besylate. It was concluded that superdisintegrants addition technique is a useful method for preparing orally disintegrating tablets by direct compression method.

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Introduction

Most of the oral pharmaceutical dosage forms like conventional tablets and capsules are formulated to be swallowed or chewed.[1] As a results children, bedridden patients and elderly patients have difficulty in swallowing these dosage forms. To overcome this drawback novel drug delivery systems like orally disintegrating tablets have been developed which disintegrate/dissolve/ disperse in saliva within few seconds without water.[2,3]

The major advantage of the ODT formulation is that it combines the advantages of both liquid and conventional tablet formulations. It provides the convenience of a tablet formulation, and also allowing the ease of swallowing provided by the liquid formulation.[4,5]

The various technologies used to prepare ODT's include direct compression, sublimation, tablet moulding, spray drying, and freeze drying and mass extrusion.[6] Direct compression is the most cost effective and simplest technique of all.[7]

Advantages of orally disintegrating tablets:[8,9]

1. Improved patient compliance.
2. Rapid onset of action and may offer an improved bioavailability.
3. Useful for pediatric, geriatric and psychiatric patients.
4. Suitable during traveling where water is may not be available.
5. No specific packaging required, can be packaged in push through blisters.
6. Smooth mouth feel and pleasant taste.
7. Conventional manufacturing equipment.
8. Cost effective.
9. Good chemical stability as conventional oral solid dosage form.

The fast disintegration and dissolution effect of orally disintegrating tablets mainly depends on the type of superdisintegrants used in the tablet formulation.[10] Most commonly used superdisintegrants include sodium starch glycolate, croscarmellose sodium (cross linked carboxymethylcellulose), crosspovidone (cross linked povidone).[11,12] Use of these superdisintegrants in combination mainly reduces the disintegration and dissolution time of ODT.

Amlodipine besylate is widely used for treatment of hypertension. Amlodipine besylate is chemically described as 3-Ethy l-5-methyl (±)- 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)- 1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is C20H25CIN2O5 • C6H6O3S, and its molecular weight of 567.1. Amlodipine besylate is a white crystalline powder slightly soluble in water and sparingly soluble in ethanol. 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. Peak plasma concentrations are attained within approximately 6-12 hour after oral administration. Although amlodipine besylate is well absorbed, its absolute bioavailability is approximately 64-90%7. The present investigation is concerned with the development ODT of amlodipine besylate and to investigate the effect of taste masking on the patient compliance and super disintegrating agent on the disintegration and release profile of the drug in the tablets.

Materials and Methods

Materials

The materials used were: Amlodipine besylate (obtained as a gift from Yashica Pharmaceuticals Pvt. Ltd., Maharashtra, India), Sodium Starch Glycolate (SSG) (NB Labortaries Pvt. Ltd., Nagpur, India), Patila and Das 77 Coscarmellose sodium (CCS) (NB Labortaries Pvt. Ltd., Nagpur, India), Crosspovidone XL-10 (CSP) (A. B. Enterprises, Maharashtra, India), Microcrystalline Cellulose (Avicel PH 102, Zeal

Medichem, Mumbai), Mannitol (A. B. Enterprises, Maharashtra, India), Sodium saccharin (Prakash Chemicals Agencies Pvt Ltd., Vadodara, Gujarat), Mint flavour (Bharat Aromatics, Maharashtra), Aerosil (S.D. Fine chemicals, Mumbai), Magnesium Stearate (S.D. Fine chemicals, Mumbai).

Methods

Direct compression technique was used to prepare the tablets. It is the simplest and most economical method for the manufacturing of tablets because it requires less processing steps than other techniques such as wet granulation and roller compaction. Required quantity of mannitol, sodium starch glycolate, croscarmellose sodium, crosspovidone XL-10 were passed through 60 # screen prior to mixing. Amlodipine besylate was mixed to this blend of powder. Thereafter, mint flavour, erosol and magnesium stearate were added and mixed.

The powder blends prepared for different batches were compressed into concave tablets; 150 mg in weight and 8.00 mm in diameter, by using rotary tableting machine (Rimek minipress-II MT). The composition of powder blends of 9 different batches is presented in Table 1.

Evaluation of tablets

Uniformity of weight (weight variation)

I.P. procedure for uniformity of weight was followed. Twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight. None of the tablets deviated from the average weight by more than ±5%.

$$\%\ \text{weight variation} = \frac{(\text{average weight} - \text{individual weight}) \times 100}{\text{average weight}}$$

Hardness

10 tablets were chosen randomly from composite samples and average value was determined. The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was determined using a Monsanto hardness tester.

Friability

Friability of tablets was measured by using Roche Friabilator. Friability was evaluated from the percentage weight loss of 20 tablets tumbled in a friabilator at 25 rpm for 4 min. The tablets were dedusted, and the loss in weight caused by fracture or abrasion was recorded as the percentage weight loss. Friability below 1% was considered acceptable.

$$\%\ \text{Friability} = \frac{\text{Initial weight} - \text{Final weight} \times 100}{\text{initial weight}}$$

In-vitro disintegration time

Disintegration time was determined using USP tablet disintegration apparatus (ED2L Electrolab, India) using 900 ml distilled water without disk at room temperature. A tablet was placed in each of the six tubes of the apparatus. The time taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

In-vitro dissolution study

In-vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) at 50rpm. 0.01 M HCl, 500ml was used as dissolution medium which maintained at 37±0.5°C 8. 10ml dissolution medium was withdrawn at specific time intervals. The amount of drug dissolved was determined by HPLC [Photodiode array detector (Waters 996)] by measuring the sample.

Assay

Amlodipine besylate content in the tablets was estimated by using UV spectrophotometric
method based on the measurement of absorbance at λ max 239nm in phosphate buffer 7.4.

Table 1.

Composition of Amlodipine besylate ODT. **Amount (mg/tablet)**

Sr. No.	Ingredients	ODT 1	ODT 2	ODT 3	ODT 4	ODT 5	ODT 6	ODT 7	ODT 8	ODT 9
1	Amlodipine besylate	10	10	10	10	10	10	10	10	10
2	Sodium starch glycolate	1	-	2	4	-	2	-	4	-
3	Croscarmellose sodium	-	1	2	2	-	-	2	-	4
4	Crosspovidone XL-10	-	-	-	-	1	2	2	2	2
5	Mannitol	20	20	20	20	20	20	20	20	20
6	Avicel PH-102	106.5	106.5	103.5	101.5	106.5	103.5	103.5	101.5	101.5
7	Sodium saccharin	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
8	Mint flavour	2	2	2	2	2	2	2	2	2
9	Aerosil	5	5	5	5	5	5	5	5	5
10	Magnesium stearate	5	5	5	5	5	5	5	5	5

Results and Discussion

The results for evaluation of different batches of Amlodipine besylate ODT's prepared by direct compression method are shown in Table 2. The most important parameter that needs to be optimized in the development of orally dispersible tablets is the disintegration time of tablets. In the present study tablets in all the batches disintegrated in _ 30 s fulfilling the official requirements (< 3 min) for dispersible tablets (European Pharmacopoeia, 2001). It was observed that the disintegration time for the batches (ODT 1, ODT 2, and ODT 5) containing a single superdisintegrant was nearly the same. In order to evaluate the effect of different combinations of superdisintegrants used in different ratios batches (ODT 3, ODT 4, ODT 6-ODT 9) were prepared. *In-vitro* disintegration time for different batches of ODT's was 8-22 s. The tablet formulations containing sodium starch glycolate, croscarmellose sodium and crosspovidone alone at low concentration (1 mg/tablet) showed higher values (20-22 s) for *in-vitro* disintegration time. The *in-vitro* disintegration time for tablet formulations containing low concentration of 1 mg/tablet for two superdisintegrants in combination was observed to be 8-18 s. similar results have been cited in reference (Avani et al., 2008). The tablet formulations containing each of 2 mg of sodium starch glycolate and croscarmellose sodium (ODT 3), each of 2 mg of sodium starch glycolate and crosspovidone (ODT 6), each of 2 mg of croscarmellose sodium and crosspovidone (ODT 7), showed 15, 16 and 18 s respectively. When the amount of sodium starch glycolate and croscarmellose sodium was increased to 4 mg in combination of other superdisintegrants in batch ODT 4, ODT 8, ODT 9 respectively the *in-vitro* disintegration time was reduced to in between 8-14 s. This result of *in-vitro* disintegration time indicates that the batch ODT 4

containing croscarmellose sodium and sodium starch glycolate combination in the ratio of 1:2 showed minimum time of 8 s to disintegrate *in-vitro.*

Table 2.
Evaluation parameters of ODT's of Amlodipine besylate.

Para-meters	ODT 1	ODT 2	ODT 3	ODT 4	ODT 5	ODT 6	ODT 7	ODT 8	ODT 9
Weight variation (%)	5.2±0.28	4.8±0.76	4.5±0.55	4.2±0.26	5.5±0.45	5.0±0.50	4.7±0.64	4.8±0.55	4.9±0.36
Hardness (kg/cm2)	3.3±0.32	3.2±0.39	3.0±0.76	3.0±0.28	3.0±0.59	3.0±0.30	3.0±0.54	3.0±0.94	3.0±0.69
Friability (%)	0.7±0.13	0.62±0.16	0.67±0.12	0.63±0.15	0.58±0.14	0.7±0.12	0.65±0.11	0.64±0.13	0.61±0.15
Assay	95.44±0.95	94.13±0.93	107.2±1.42	99.15±0.55	94.43±1.34	104.65±1.06	95.69±0.68	92.05±0.59	102.56±0.73
Disinte-gration time (s)	21 - 23	22 - 24	15 - 17	8 - 10	20 - 22	16 - 18	18 - 20	12 - 14	14 - 16

The cumulative percentage drug release of the tablets from the prepared batches along with the marketed tablet formulation is shown in Table 3. Batch ODT 4 gave better release profile of around 72% in 30 min as compared to other batches. For the batch ODT 4, in first 10 min 98% of the drug was released which was comparable to the release profile of marketed tablet formulation as shown in Figure 1. Its disintegration time was also found to be within 8-10 s so this batch was selected as optimized batch. Thus the disintegration time was reduced and also the release rate was improved by using two superdisintegrants (Croscarmellose sodium and Sodium starch glycolate in ratio of 1:2) in combination.

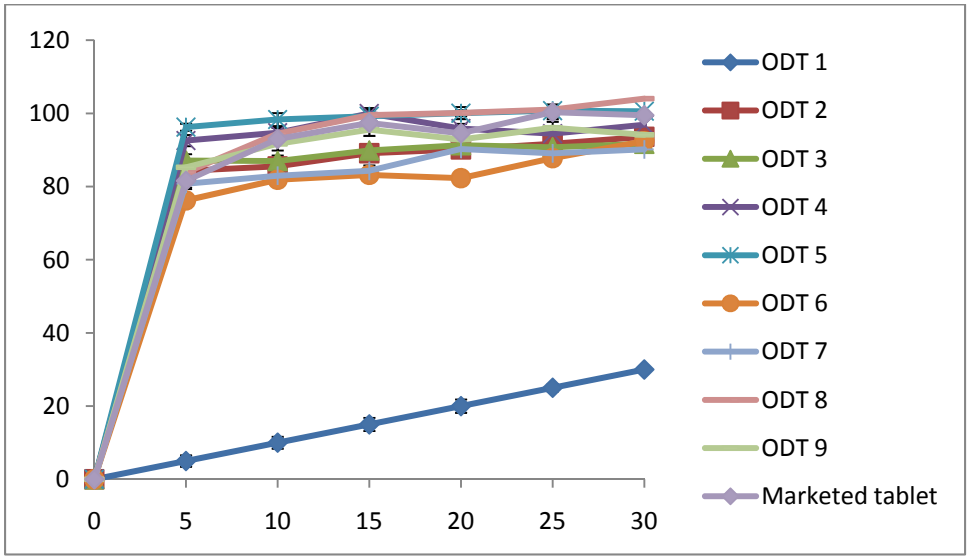
Further pharmacokinetic studies of the optimized batch were carried out to determine the release mechanism followed by the drug. It was found that the drug followed Korsmeyer model of drug release with a regression co-efficient (r2) value of 0.975. The value of diffusional co-efficient (n) was found to be 0.0211 which was less than 0.45 which indicates that the drug follows Fickian diffusion mechanism.

Table 3.
Dissolution profiles of ODT's of Amlodipine besylate.

	% Cumulative drug release*									
Time (min)	**ODT 1**	**ODT 2**	**ODT 3**	**ODT 4**	**ODT 5**	**ODT 6**	**ODT 7**	**ODT 8**	**ODT 9**	**Marketed tablet**
0	0	0	0	0	0	0	0	0	0	0
5	84.31 ±1.73	87.12 ±0.82	92.57 ±1.29	96.24 ±1.20	76.2 ±1.77	80.75 ±1.22	83.89 ±1.55	85.28 ±1.47	81.55 ±1.29	98.57 ±1.78
10	85.52 ±1.57	86.99 ±1.67	94.74 ±1.76	98.33 ±1.52	81.85 ±0.96	82.97 ±1.39	94.47 ±1.42	91.66 ±1.23	93.01 ±1.94	98.72 ±1.85
15	89.11 ±1.62	89.86 ±1.59	99.97 ±1.52	99.24 ±1.47	83.19 ±1.79	84.29 ±1.40	99.52 ±1.75	95.53 ±1.57	97.4 ±1.79	100.07 ±1.59
20	90.15 ±1.79	91.32 ±1.66	95.85 ±1.39	100.06 ±1.53	82.31 ±1.59	90.28 ±1.45	100.13 ±1.49	92.89 ±1.79	94.56 ±1.66	100.21 ±1.64
25	91.68 ±1.82	90.76 ±0.89	94.47 ±1.44	100.74 ±1.34	87.78 ±0.82	89.09 ±1.48	101.07 ±1.68	96.08 ±1.65	100.32 ±1.73	100.5 ±0.96
30	93.6 ±0.97	91.71 ±1.78	96.91 ±1.76	100.6 ±1.29	92.4 ±1.64	90.15 ±1.24	104.04 ±1.77	94.15 ±1.37	99.5 ±1.64	101.98 ±1.84

* The data are expressed as mean ± S.D. (n=3).

Figure 1.
Comparison of drug release profile of batches containing single super disintegrant with marketed formulation ODT 1 to ODT 9.



Conclusion

Orally disintegrating tablets of Amlodipine besylate were prepared by direct compression method using croscarmellose sodium and sodium starch glycolate as superdisintegrants in combination in the ratio of 1:2 (ODT4). The tablets had acceptable hardness of average 3 kg/ cm2 and approximately 0.67% friability. In-vitro disintegration time was reduced and *in-vitro* drug release was significantly improved. Hence it can be concluded that using a combination of superdisintegrants viz., croscarmellose sodium and sodium starch glycolate in the ratio of 1:2 in formulation of orally disintegrating tablets of Amlodipine besylate would be quite effective in providing fast onset of action without the need of water for swallowing.

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