



RESEARCH ARTICLE

FORMULATION AND IN-VITRO EVALUATION OF AMLODIPINE BESYLATE-HP- β -CD INCLUSION COMPLEX INCORPORATED MOUTH DISSOLVING TABLETS

Amaresh Prusty*

Department of Pharmaceutics, College of Pharmaceutical Science, Baliguali, Puri-752 002, Odisha, India

*E-mail: amareshprusty@gmail.com

Tel.: +91 9861184343.

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The objective of present study was to formulate and evaluate mouth dissolving tablets (MDTs) of poorly water soluble drug amlodipine by incorporating its inclusion complex with hydroxypropyl- β -cyclodextrin (HP- β -CD). The formulation of MDTs employed superdisintegrants croscopovidone and Ac-Di-Sol in different concentrations among which F3, consisting of 8 per cent of croscopovidone was found to be the best formulation, as it exhibited minimum disintegration time (15 sec) and better drug release profile as compared to other formulations.

Key words: Cyclodextrin inclusion complex, MDT, Amlodipine besylate, HP- β -CD.

INTRODUCTION

Tablets are most preferred solid dosage forms because of easy administration, compactness and flexibility in manufacturing. Because of changes in various physiological functions associated with aging, including difficulty in swallowing; administration of the intact tablet may lead to poor patient compliance and ineffective therapy. The pediatric and geriatric patients are of particular concern. To overcome this, dispersible tablets, mouth dissolving tablets or fast disintegrating tablets have been developed. Most commonly used methods to prepare these tablets are freeze-drying/lyophilization tablet molding and direct compression. The main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets. Therefore, direct-compression appears to be an attractive option for manufacturing the tablets. The mouth dissolving tablets prepared by the direct compression method, in general, are based on the action established by superdisintegrants such as croscarmellose sodium, croscopovidone, sodium starch glycolate. Moreover, preparation methods,

characterization, recent advancements and current status of orally disintegrating tablets (ODTs) and mouth dissolving tablets (MDTs) have been thoroughly reviewed in the literature (Bandari *et al* 2008; Hirani *et al* 2009; AlHusban *et al* 2010; Badgujar and Mundada, 2011; Bhatere *et al* 2012; Yadav *et al* 2014). The recent findings also witness formulation and evaluation of ODTs and MDTs without or with incorporation of inclusion complex of poorly soluble drugs with cyclodextrins using various techniques (Cirri *et al* 2005; 2009; Ajit Shankarrao *et al* 2010; Wang *et al* 2013; Zeng *et al* 2013; Desai and Prabhakar, 2014). So, in the present work, amlodipine mouth dissolving tablets were prepared using HP- β -CD complex using different superdisintegrants like croscopovidone and Ac-Di-Sol and evaluated for various parameters to establish the usefulness of inclusion complexation as well as direct compression technique.

MATERIALS AND METHODS

Materials

Amlodipine besylate obtained from matrix laboratories Bangalore. Hydroxypropyl- β -cyclo-

dextrin (HP- β -CD) from S.D. Fine chemicals, Mumbai. Other ingredients like crospovidone, Ac-di-sol (as superdisintegrants) and starch, talc, magnesium stearate were procured from S.D. Fine chemicals, Mumbai.

Methods

Phase solubility studies

Excess amount of different ratios of amlodipine besylate hydroxypropyl betacyclodextrin molar complexes were added to series of 100 ml conical flask containing 250 ml phosphate buffer pH 6.8. The complexes were shaken in rotator shaker for 24 h and then filtered through Whatttman's filter paper and assayed.

Preparation of complexes

Physical mixing method

Amlodipine besylate (AB) and hydroxypropyl betacyclodextrin (HP- β -CD) in the ratio (1:2) were taken and were mixed thoroughly with constant triturating and then passed through sieve no. 100 and stored in desiccators.

Kneading method

AB and HP- β -CD in the ratio (1:2) was taken in 10 ml methanol and mixed thoroughly with constant trituration till thick slurry was obtained and then, dried at 60°C and then passed through sieve no. 100 and stored in desiccator.

Drug content studies of complex

Complex (10 mg) was dissolved in phosphate buffer pH 6.8, one ml from which is diluted if necessary and subjected to quantitative estimation at 331 nm.

Preparation of mouth dissolving tablets

Tablets were prepared by direct compression technique. All the ingredients except magnesium stearate were blended in glass mortar pestle uniformly. After sufficient mixing, magnesium stearate was added and further mixed for 2-3 min. The tablets were compressed on a single stroke punching machine, the weights were kept constant for tablets of all batches (100 mg). The compositions of tablets are given in **Table 1**.

Table 1. Composition of mouth dissolving tablets

Ingredients (mg)	F1	F2	F3	F4	F5
AB and HP- β -CD complex	30	30	30	30	30
Crospovidone	4	6	8	-	-
Ac-Di-Sol	-	-	-	4	6
MCC	10	10	10	10	10
Talc	2	2	2	2	2
Magnesium stearate	2	2	2	2	2
Mannitol	52	50	48	52	50

Evaluation of mouth dissolving tablets

Micromeritics study of complex

Micromeritic parameters such as bulk and tapped density, angle of repose, Carr's compressibility index, Hausner's ratio were calculated.

Hardness and friability

Hardness was measured using Pfizer hardness tester. For each batch, 3 tablets were tested. Twenty tablets were weighed and placed in Roche Friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dedusted and weighed again. The percentage friability was measured using the formula:

$$\%F = [1 - (W / W_0)] \times 100$$

where %F = friability in percentage, W_0 = initial weight of tablet, W = weight of tablets after revolution

Weight variation test

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated and compared with pharmacopoeial standards.

Assay

Twenty tablets of each formulation were crushed, required concentration was obtained by suitable dilutions and drug content was measured by UV spectrophotometer at 331 nm.

Disintegration test

Disintegration test was carried out by Disintegration Test Apparatus. Tablets are placed individually in each tube of disintegration apparatus and disc was placed. Water bath was maintained at 37±0.5°C and the time taken for all tablets to disintegrate was noted. For MDT, the time should not exceed more than 3 min.

Moisture uptake studies

Ten tablets were taken from each formulation and weighed as W_i , which was kept at room temperature for 2 weeks. Then, it was put in desiccators for 1 day and final weight (W_f) was calculated.

$$\text{Moisture uptake \%} = (W_i - W_f) / W_f \times 100$$

Wetting time and water absorption ratio

One circular tissue paper of 10 cm diameter was placed in a petri dish with 10 cm diameter. Ten milliliter of water soluble dye eosin solution was added to petri dish. Tablet was placed on surface of tissue paper and time required for water to reach the upper surface of tablet was recorded as wetting time.

Water absorption ratio

Weight of tablet before keeping in petri dish was noted (W_b) and weights of tablets from petri dish (W_a) were reweighed.

$$\text{Ratio} = 100 (W_a - W_b) / W_b$$

Dissolution studies

Different MDTs were taken for dissolution study in USP II dissolution rate test apparatus set at 100 rpm using phosphate buffer pH 6.8 as the dissolution medium. Samples were

withdrawn at regular intervals for spectrophotometric analysis of drug content at 331 nm.

RESULTS AND DISCUSSION**Phase solubility studies**

Results of phase solubility studies suggested drug : polymer ratio of 1:2 (maximum drug solubility). The data of the studies are summarized in **Table 2**.

Table 2. Data of phase solubility studies

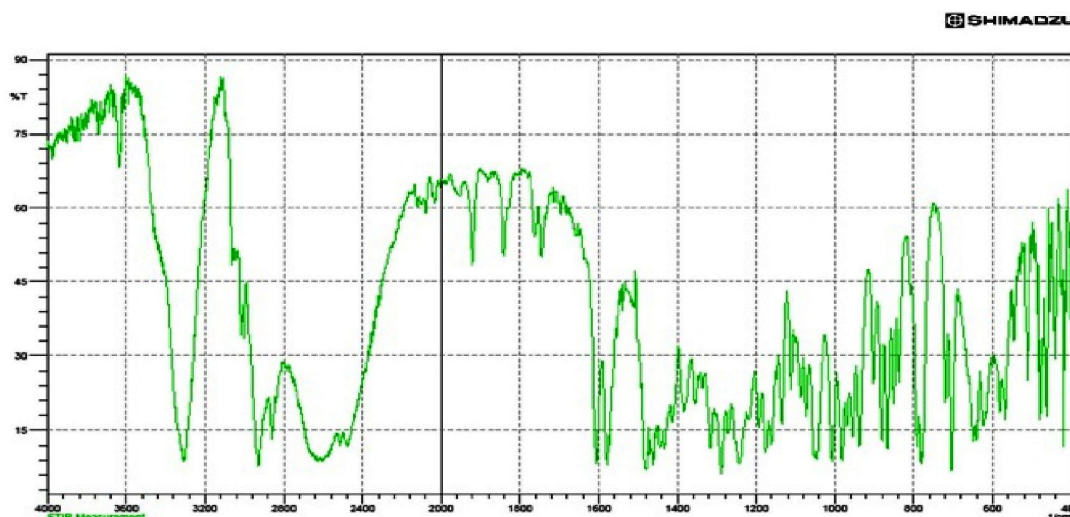
Sr. No.	Drug : HP- β -CD	Solubility (mg/ml)
1	0	0
2	1:0.5	1.00
3	1:1	0.98
4	1:1.5	1.09
5	1:2	2.20
6	1:2.5	2.18
7	1:3	2.15

Micromeritic parameters of complex were found to be improved as compared to pure drug (**Table 3**). Micromeritics study showed that the drug and HP- β -cyclodextrin complex showed good flow properties.

FTIR studies confirmed the purity of drug sample (**Figure 1**) whereas FTIR spectrum of complex was representative of presence of both drug and HP- β -CD indicating the intactness of complex (**Figure 2**).

Table 3. Comparative micromeritic parameters of complex and pure drug

Parameters	F3	Pure drug
Bulk density	0.52 g/ml	0.27 g/ml
Tapped Density	0.56 g/ml	0.63 g/ml
Compressibility Index	7.52%	57.69%
Angle of repose	25.97%	50.29%
Hausners ratio	1.07	2.31

**Fig. 1.** FTIR spectrum of Amlodipine besylate sample

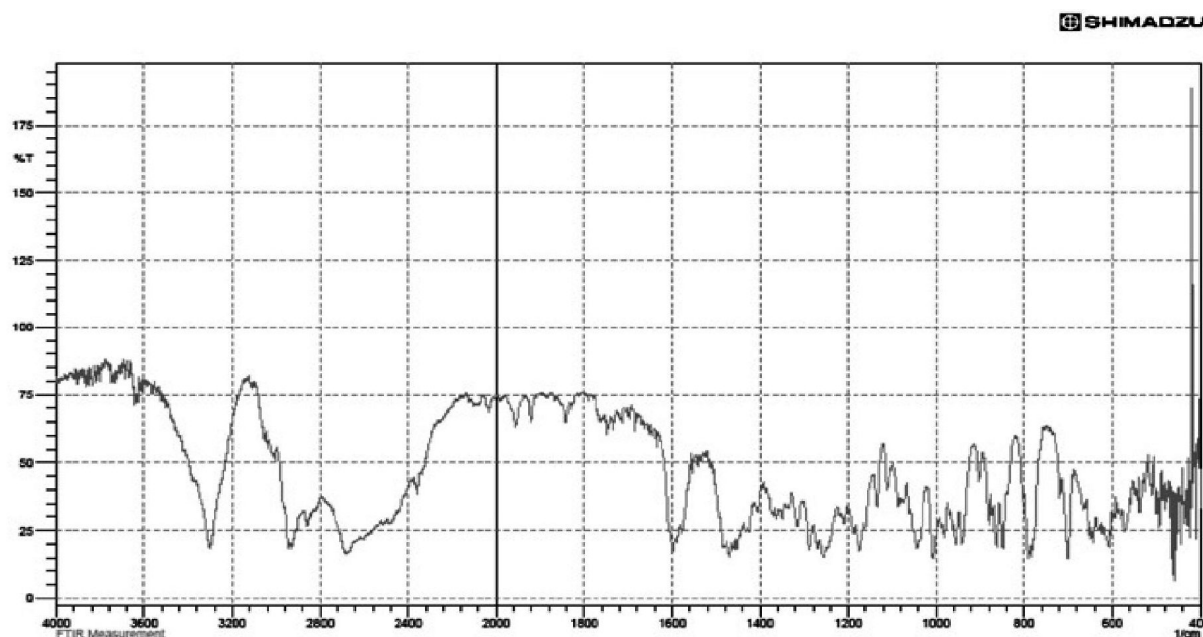


Fig 2. FTIR of Amlodipione Besylate-HP- β -cyclodextrin complex of formulation F3

Mouth dissolving tablets (MDT) of amlodipine-HP- β -cyclodextrin complex were prepared with different super disintegrants. The measured hardness of tablets of each batch ranged from 4 to 5 kg. The F3 formulation showed higher % of drug release in 15 min as compared to other

formulations. Hardness and friability of all formulations were within acceptable limits. Wetting time of all formulations varied in the range of 45 to 70 sec. Summary of results of mouth dissolving tablets parameters are given in **Table 4**.

Table 4. Summary of results of mouth dissolving tablets parameters

Formulation	% Friability	Wetting time (Sec)	Water absorption ratio	Disintegration time (sec)	Percent drug content	% Moisture uptake
F1	0.48	53 \pm 5	59.57	121	87.34	67.23
F2	0.62	50 \pm 5	54.78	70	98.00	55.78
F3	0.65	48 \pm 5	68.98	49	99.98	35.12
F4	0.58	68 \pm 5	42.12	145	96.53	46.07
F5	0.33	70 \pm 5	50.33	87	91.90	64.89

As per compendial standards, the batch passes the test for weight variation if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown and none deviate by more than twice the percentage shown in particular pharmacopoeia. Disintegration time is very important for MDT because rapid disintegration occurs due to uptake of water from the medium causing bursting effect (Dahiya *et al* 2011; Bhimavarapu *et al* 2012). Formulation F3 showed least disintegration time (less than 15 sec) as compared to other formulations (**Figure 3**).

CONCLUSION

Mouth dissolving tablets of the Amlodipine-HP- β -cyclodextrin complex were prepared successfully. Inclusion complexation was found

to be suitable technique for formulating complex incorporated mouth dissolving tablets as compared to that of poorly soluble drug alone.

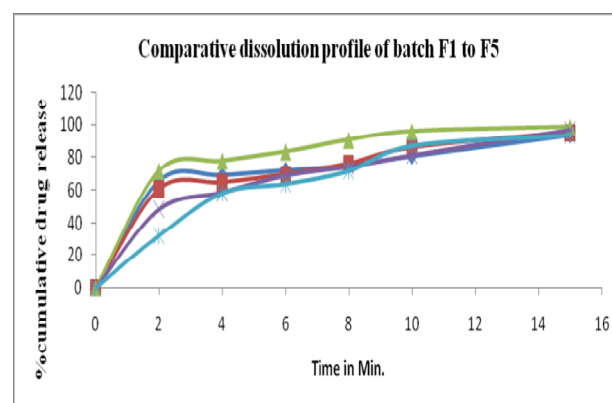


Fig. 3. *In vitro* dissolution studies of different formulations

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