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Preparation and FT-IR Characterization of Amlodipine Fast Disintegrating Tablets

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A B S T R A C T

Amlodipine besylate is a long-acting calcium channel blocker used to treat 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. The rate of dissolution will increase by incorporating the drug in a fast dissolving dosage form. An attempt will be made to develop rapidly disintegrating oral tablets of Amlodipine Besylate by direct compression method. In this study, Fast Dissolving Tablet (FDT) was prepared using direct compression method using Crospovidone and Sodium starch glycolate as the super disintegrants. Amongst all formulations, formulation F3 prepared by a combination of both Crospovidone and Sodium starch glycolate showed least disintegrating time, and faster dissolution of 87%. Combination of super disintegrants were found to be better to formulate fast dissolving tablets of Amlodipine besylate.

Keywords: Fast Disintegrating tablet, Crospovidone, Sodium starch glycolate, Amlodipine Besylate.

A R T I C L E I N F O

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1. Introduction

Solid dosage forms are the most popular and widely preferred drug delivery system due to the advantages afforded both to the manufacturer and the patient (Abdelbary *et al.*, 2004, Banker, 2005). Many patients find difficulty in swallowing tablets and hard gelatin capsules; consequently fail to take medication as prescribed which results in high incidence of non-compliance and ineffective therapy (Shailendra *et al.*, 2012). Among the different types

of tablets, emerged the concept of Fast dissolving tablet with the desire to provide the patients with more convenient means of taking their medication. Fast dissolving technology offers some unique advantages over conventional drug delivery systems in that it offers quick disintegration and dissolution of tablets. The tablet dissolves or disintegrates in the oral cavity even without drinking water (Ved *et al.,* 2012). The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30–50 s after administration. The solutions containing the active ingredients are swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect (Dobetti *et al.,* 2001).

Target groups for oral FDTs are wide-ranging people of all ages who can have trouble in swallowing conventional tablets and capsules. This includes children and the elderly who either have trouble and cannot swallow or have not learned to swallow the conventional solid dosage forms. In addition, psychiatric patients as well as hospitalized or bedridden patients suffering from a variety of disorders such as stroke, thyroid disorders, Parkinson's disease and other neurological disorders such as multiple sclerosis and cerebral palsy (Sastry *et al.,* 2000) also find difficulty in swallowing tablets and require 'fast-melt' tablets because of their physical condition.

The convenience and ease of using FDTs is also important to normal consumers, with some adults preferring these dosage forms as they are easy to handle and swallow, can be taken without water and have a rapid onset of action (Ciper *et al.,* 2006, Jeong *et al.,* 2008). For example, patients and travellers with a limited access to water would also find such FDTs extremely beneficial (Sastry *et al.*,2000, Mizumoto *et al.,* 2005). Besides improving patient compliance, FDTs have been investigated for their potential in increasing the bioavailability of poorly water soluble drug through enhancing the dissolution profile of the drug (Ahmed *et al.,* 2007, Corveleyn *et al.,* 1998).

Fast dissolving tablets are prepared by various techniques, mainly direct compression (Bi *et al.,* 1996), lyophilization (Chandrasekhar *et al.,* 2009) and compression molding (Ford, 1986); thus, they exhibit different disintegration behaviour. The basic approach used in the development of the fast-dissolving tablets is the use of superdisintegrants. Sodium starch glycolate and crospovidone were screened in the present study. Another approach used in developing FDT is by maximizing the pore structure of the tablets.

Freeze-drying and vacuum-drying techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and it yields a fragile and hygroscopic product. Usually superdisintegrants are added to a drug formulation to ease the breakup or disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants (Abdelbary *et al.,* 2004).

Amlodipine besylate is a long-acting calcium channel blocker used in the treatment of chronic stable angina, vasospastic angina and hypertension (Brunton *et al.,* 2005). Amlodipine is a sparingly soluble orally administered drug and the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by incorporating the drug in a fast dissolving dosage form (Sinko, 2006).

The simplicity and cost effectiveness of the direct compression process have positioned this technique as an alternate to granulation technologies. In the present study we have developed an effective and stable FDT of Amlodipine besylate formulated by direct compression method with adequate hardness, low disintegration time and pleasant taste. Another purpose was to study the influence of superdisintegrants when used alone and in combination.

2. Materials and method

Materials

Amlodipine Besylate (ADB) and Microcrystalline Cellulose (MCC) were procured from Yarrow Pharmaceuticals, Mumbai, India. Magnesium Stearate, Lactose was procured from Vijlac Pharmaceuticals, Hyderabad, India. Crospovidone was purchased from DMV Fronterra excipients, Cuddalore, India. Talc and Sodium Saccharine was procured from Navdeep fine chemicals, Mumbai, India. All other chemicals and reagents used were of laboratory or analytical grade.

Methods

Preparation of Amlodipine fast disintegrating tablets

Fast disintegrating tablets containing 10 mg of amlodipine besylate were prepared by direct compression method and the various formula used in the studies are shown in (table 1). Solid dispersion equivalent to 10 mg of drug and colloidal silicone dioxide was mixed in a polyethylene cover. It was then mixed with Microcrystalline Cellulose, sodium starch glycolate, lactose and talc in another polyethylene cover. Vanilla flavour and sodium saccharin was added to the above material in geometrical dilution method. Magnesium Stearate was added to the above mixture and mixed well for not more than three minutes. Superdisintegrants like crospovidone and sodium starch Glycolate were used alone and finally the effect of combination of superdisintegrants was studied. The prepared solid dispersion was evaluated for various parameters like angle of repose, bulk density, and compressibility index and hausner ratio. After evaluation of the solid dispersion the tablets were compressed with single station punching machine (Cadmach TB-024) using 6 mm flat punches set.

Evaluation of Amlodipine Fast Disintegrating Tablets

Evaluation of Pre-compression parameters of powder

Prior to compression, powder were evaluated for their flow and compressibility parameters. Flow properties of powder were determined by angle of repose method. Compressibility index of powder were determined by Carr's index and Hauser ratio (Carter, 2004, Aulton, 2002).

Angle of repose

Angle of repose (θ) was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated.

$$\theta = \tan^{-1} h/r$$

Compressibility index

The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by % compressibility that is calculated as follows.

Carr's Index (%) = [(TBD-LBD) x100]/TBD

TBD= Total Bulk Density

LBD= Loose Bulk Density

Hausner's ratio: Hausner's ratio is an index of ease of powder flow; it is calculated by following formula.

Hausner's Ratio = TBD / LBD

TBD= Total Bulk Density

LBD= Loose Bulk Density

Evaluation of post-compression parameters of Tablets

Tablet Thickness

Dimension of the tablets was measured by using a screw gauge. Five tablets of each formulation were picked out randomly and its thickness was measured individually (Lachman et al., 2005).

Weight variation test

The procedure described in Indian Pharmacopoeia (IP, 2007) was employed to determine weight variation of tablets. Ten tablets were randomly selected from each batch and weighed on an electronic balance and mean weight was taken. Each tablet was then weighed individually and standard deviation in weight was calculated for each batch (Chowdhary et al., 1998).

Tablet Hardness

Five tablets were randomly selected from each batch and hardness of tablets was determined by using Monsanto Hardness Tester. The mean values and standard deviation for each batch were calculated (Lachman et al., 2005). The hardness was measured in terms of Kg/cm2.

Tablet Friability

Friability indicates the ability of a tablet to withstand mechanical shocks while handling. Friability of tablets were determined using Roche Friabilator and is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and placed into the friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions and then the tablets were weight again (W_{final}). The loss in tablet weight due to abrasion or fracture was the measure of tablet friability. Percent friability (f) was calculated by using the following formula (Lachman et al., 2005).

$$f = \frac{(W_{initial}) - (W_{final}) \times 100}{W_{Initial}}$$

% friability of less than 1 % is considered acceptable

Disintegration test

The disintegration time for all formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The phosphate buffer pH 7.2 was maintained at a temperature of 37°±2°C and time taken for the entire tablet to disintegrate completely was noted (Lachman et al., 2005).

Wetting time

The wetting time and capillarity of oral dispersible tablets were measured by a conventional method. Tablet was placed in a petridish containing 10 ml water at room temperature and the time for complete wetting of tablets were recorded (Lachman et al., 2005).

Uniformity of dispersion

This test is done for Dispersible tablets, and here the tablet is placed in a 200 ml beaker with about 100 ml of water in it. The system is stirred gently and allowed to pass through #22 size mesh. No particles or lumps should remain on the mesh.

Drug content

Twenty tablets were powdered and the blend equivalent to 10 mg of Amlodipine besylate was weighed and dissolved in suitable quantity of distilled water using ethanol as co solvent. The solution was filtered, suitably diluted and the drug content was analyzed colorimetrically at 414 nm. Each sample was analyzed in triplicate.

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Statistical analysis of data

Data were expressed as mean±S.D. Statistical evaluation was performed by one-way analysis of variance (ANOVA) at a significance level of $p<0.05$ by Dunnett's multiple comparison test using Graph Pad Prism software version 4.03.

3. Results and Discussion

Fast disintegrating tablets of Amlodipine were prepared by direct compression method employing crospovidone and sodium starch glycolate as super-disintegrants in different ratio. A total of three formulations were designed. The flow properties of the powder mixture are significant for the uniformity of mass of the tablets. The flow of the powder mixture were analyzed before compression to tablets. The values of pre-compression parameters evaluated were within prescribed limits and indicated a good free flowing property. Low Hausner`s ratio (≤1.25), compressibility index (≤20.16) and angle of repose (≤36.89) values indicated a fairly good flow ability of powder mixture (table 2).

(Table 3) depicts post-compression parameters of Amlodipine FDTs. As the tablet powder blend was free flowing, tablets produced were of uniform weight with acceptable weight variation in the range from 136 mg to 140 mg due to uniform die fill. Hardness (3.4-3.7 kg/cm^2) and friability loss (0.7-0.87 %) indicated that tablets had a fine mechanical resistance. Drug content was found to be high (≥97.6 %) in all the tablet formulations. Uniform distribution of the active agent was assessed by UV, the content of Amlodipine was found inside the 98.1% of the theoretical value.

The most important parameter that needs to be optimized in the development of fast disintegrating tablets is the disintegration time of tablets. In this present study, it was observed that the disintegration time of the tablets had a significant effect with the type of super-disintegrant. However, disintegration time decreased when the combination of disintegrants was used in the tablets. This indicates that combination of super disintegrants had a positive effect on the disintegration of the tablets, which may be due to its rapid capillary activity and hydration with little tendency to gel formation. Thus, these results suggest that the disintegration time can be increased by using single disintegrant.

Wetting time is an important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water and were found to be in the range of 26-28 seconds.

FTIR study

In order to further study whether Amlodipine undergoes a polymorphic change during preparation of FDTs and to test for possible intermolecular interactions between Amlodipine and excipients, FTIR was used. The FTIR spectra of pure Amlodipine, Amlodipine with urea and joint spectrum of Amlodipine and Amlodipine with urea (A, B and C) are depicted in (figure 1). All the principal IR peaks of Amlodipine were present in all formulations (F1, F2 and F3). This clearly indicates that there is no interaction between Amlodipine and excipients.

***In vitro* Drug Release Studies**

The dissolution profile of the formulations range from 77.84-87.55% (table 4). The dissolution rate was found to be comparatively less for the formulation containing sodium starch glycolate. The maximum increase in the dissolution rate was observed with the combination of crospovidone and sodium starch glycolate among the three formulations (figure 2). The order of the dissolution rate with various superdisintegrants was found to be combination of disintegrants > crospovidone > Sodium starch glycolate. Combination of superdisintegrants was found to be better than using alone and the formulation containing crospovidone and sodium starch glycolate was found to be showing the maximum dissolution after 30 minutes of dissolution study. Many factors contributed to faster release rate such as decrease in particle size, decrease in agglomeration of particles, increase wettability and decrease in crystallinity of the drug.

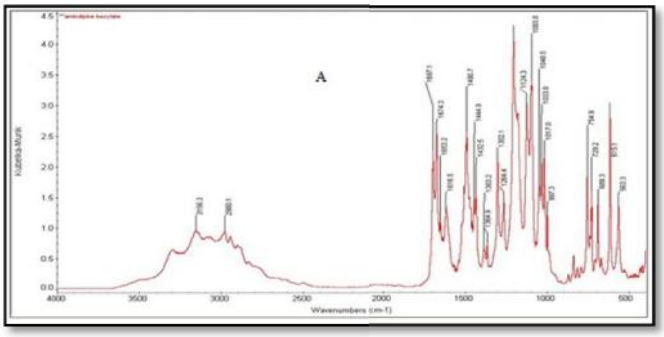

Figure 1

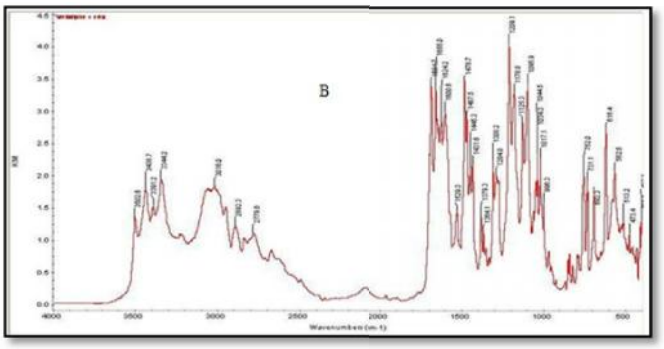

Figure 2

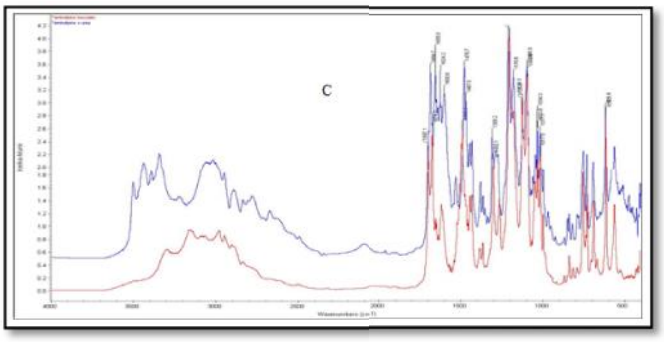

Figure 3

Table 1: Formulation of Fast Dissolving Tablets of Amlodipine Besylate

Sl.No	Ingredients	Weight in mg/tab		
		F1	**F2**	**F3**
1	Solid dispersion equivalent to 10 mg of drug	30	30	30
2	Microcrystalline Cellulose (MCC PH 101)	55	55	55
3	Lactose	41.75	44.30	37.3
4	Crospovidone	7.00	-----	7 .00
5	Sodium starch glycolate	-----	4.20	4.20
6	Colloidal Silicone dioxide	2.80	2.80	2.80
7	Vanilla flavour	1.00	1.00	1.00
8	Sodium saccharine	.75	1.00	1.00
9	Purified Talc	1.00	1.00	1.00
10	Magnesium Stearate	0.70	0.70	0.70
	Average weight	140mg	140mg	140mg

Table 2: Pre-Compression parameters of Amlodipine Fast Dissolving Tablets.

Formulations	Angle of repose (θ) ± SD (n=3)	Compressibility (%) ± SD (n=3)	Hausner's ratio (%) ± SD (n=3)
F1	36.37	20.15	1.32
F2	37.17	20.14	1.27
F3	36.14	20.16	1.25

Table 3: Post Compression Parameters of Amlodipine Fast Dissolving Tablets.

S. No	Parameters	Formulations		
		F1	**F2**	**F3**
1	Thickness (mm) **±SD** (n=6)	3.21 ± 0.05	3.37 ± 0.04	3.58 ± 0.04
2	Weight Variation **±SD** (n=10)	Pass	Pass	Pass
3	Hardness (kg/cm^2) **±SD** (n=3)	3.5 ± 0.08	3.4 ± 0.09	3.7 ± 0.07
4	Friability (%)**±SD** (n=3)	0.7088	0.8736	0.8191
5	*In vitro* dispersion time (sec) **±SD** (n=6)	28 ± 2.40	27.5 ± 2.30	26.2 ± 2.10
6	Disintegration Time (sec)**±SD** (n=6)	10.30 ± 1.20	10.16 ± 1.50	10.12 ± 1.30
7	Uniformity of dispersion	Pass	Pass	Pass

Table 4: Dissolution profile of Amlodipine Fast Dissolving Tablets.

S. No	Time in Minutes	FORMULATIONS		
		F1	**F2**	**F3**
1.	5	17.72	16.18	20.8
2.	10	28.62	27.59	30.98
3.	15	45.78	44.85	48.63
4.	20	69.21	66.15	472.69
5.	30	80.31	77.84	87.55

4. Conclusion

The present investigation of this study was undertaken with an aim to formulate and characterize fast disintegrating tablets of Amlodipine using direct compression method with the addition of super-disintegrating agents. FTIR study reveals that there is no drug-excipients interaction between Amlodipine and excipients. It is observed that the formulation F3 containing crospovidone and Sodium starch glycolate was found to be promising showing disintegration time of 10.12 second, wetting time of 26.2 second and highest dissolution rate (87.55%) in 30 min when compared to formulations (F1, F2). It was concluded that combination of superdisintegrants showed better disintegrating time, wetting time and dissolution property than the formulation of single disintegrant containing tablets.

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