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Research Article

FORMULATION AND EVALUATION OF MOUTH DISPERSIBLE TABLETS OF AMLODIPINE BESYLATE

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ABSTRACT

An attempt has been made for the development of rapidly disintegrating oral tablets of Amlodipine Besylate by direct compression method. In this study, fast dissolving tablets of Amlodipine Besylate using different superdisintegrants were prepared by direct compression method. FDT's were evaluated for its physicochemical properties and in vitro dissolution. Effect of different superdisintegrants on disintegration behaviour of tablets was evaluated in phosphate buffer pH 7.2. All formulations were evaluated for pre-compression and post- compression parameters. Wetting time of formulations containing Crosscarmellose sodium was least and tablets showed fastest disintegration. FT-IR studies revealed that there was no physico-chemical interaction between amlodipine besylate and other excipients. Of the twelve formulations studied, F10 showed short dispersion time with maximum drug release in 30 minutes. Combinations of super disintegrants were found to be better in the formulation of fast dissolving tablets of Amlodipine besylate rather than using alone.

Keywords: Amlodipine Besylate, Fast dissolving tablets, In vitro

INTRODUCTION

Solid dosage forms are the most popular and preferred drug delivery system due to various advantages such as high patient compliance, stability, accuracy in dosing etc. Many patients (particularly pediatric and geriatric patients) find difficulty in swallowing tablets and hard gelatin capsules; consequently fail to take medication as prescribed. It is estimated that 50% of the population is affected by this problem which results in high incidence of non-compliance and ineffective therapy[1]. The concept of Fast dissolving drug delivery system emerged from 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[2]. Higher drug loading as well as pleasant feeling to the mouth are other advantages offered by the FDT's. Fast dissolving tablets when placed in mouth disintegrate instantaneously releasing the drug which dissolves or disperse in the saliva and can be swallowed as a liquid without the aid of water.

Moreover the dosage combines the advantage of both liquid and tablet formulation. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, the bioavailability of the drug is higher than from conventional tablet dosage form. Fast dissolving tablets are prepared by various techniques, mainly direct compression, lyophilization and moulding. The basic approach used in the development of the fast-dissolving tablets is the use of superdisintegrants. Croscarmellose sodium, 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 facilitate the break-up or disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants[3]. FDT will avoid missing out of dose even during traveling or other situations where there is no access to water.

Amlodipine besylate is a long-acting calcium channel blocker used in the treatment of chronic stable angina, vasospastic angina and hypertension[4]. 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[5]. Fast dissolving tablets of amlodipine besylate by sublimation method has been reported recently[6]. The simplicity and cost effectiveness of the direct compression process have positioned this technique as an attractive alternate to traditional granulation technologies. The present investigation deals with the development of an effective and stable FDT of Amlodipine besylate having adequate hardness, low disintegration time and pleasant taste. In this study, we are reporting the formulation of amlodipine besylate by direct compression method.

MATERIALS AND METHODS

Materials

Amlodipine Besylate was obtained as gift sample from Copella Laboratories Limited Hyderabad, India. Crospovidone, Croscarmellose sodium, Sodium starch glycolate, Aspartame, Lactose and Magnesium stearate was procured from S.D Fine Chemicals, Mumbai, India and all other chemicals / solvents used were of analytical grade.

Methods

Preparation of tablets

Fast dispersible tablets containing 10 mg of amlodipine besylate were prepared by direct compression method and the various formula used in the study are shown in [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, Crospovidone and Croscarmellose 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 ratio. After evaluation of powder blend the tablets were compressed with single station tablet punching machine (Rimek Mini Press1) using 6 mm flat punches set.

Post compression parameters

Tablet hardness[7]

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 Pfizer hardness tester. The hardness was measured in terms of Kg/cm2.

Weight variation[8]

Twenty tablets from each formulation were selected randomly and average weight was determined.

Individual tablets were then weighed and was compared with average weight.

Friability

Friability of the tablets was determined using Roshe 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. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions.

Tablets were then de- dusted using a soft muslin cloth and re-weighed. The friability (f) is given by the formula[8,9].

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

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

Wetting time and water absorption ratio[10, 11]

A piece of paper folded twice was kept in a Petri dish (internal diameter 5.5 cm) containing 6 ml of purified water. A tablet having a small amount of Rosaline dye powder on the upper surface was placed on the tissue paper. The time required to develop a red colour on the upper surface of the tablet was recorded as the wetting time. The same procedure without Rosaline dye powder was followed for determining the water absorption ratio R and it was determined using the following equation.

$$R = [(Wa – Wb)/Wb] \times 100$$

Where, Wb and Wa were the weights of the tablet before and after use.

In vitro disintegration time

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.

Dissolution studies[12, 13, 14]

The study has been carried out in type II apparatus at 75 rpm in 900 ml phosphate buffer pH 7.2 .Determine the amount of amlodipine besylate dissolved by employing UV absorption at about 259 nm on filtered portions of the solution under test in comparison with a Standard solution having a known concentration of amlodipine besylate RS prepared by dissolving an accurately weighed portion in a small volume of methanol and diluting quantitatively with Dissolution medium. An equal volume of fresh medium, which was pre warmed at 37^0 C was replaced into the dissolution medium after each Sampling to maintain the constant volume throughout the test. Dissolution studies were performed in triplicate.

Drug content[15]

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 calorimetrically at 414 nm. Each sample was analyzed in triplicate.

Characterization of Amlodipine besylate tablets

FTIR studies

The drug - excipients interaction were studied using FTIR. IR spectra for drug and powdered tablets were recorded in a Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets. The spectra were scanned over the 3600 to 400 cm-1 range.

Table 1: Formulation of fast dissolving tablets of amlodipine besylate

Ingredients (mg per tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Amlodipine besylate	10	10	10	10	10	10	10	10	10	10	10	10
Microcrystalline cellulose	80	80	80	80	80	80	80	80	80	80	80	80
Lactose	46.80	46.80	40.80	46.80	46.80	40.80	46.80	46.80	40.80	40.80	40.80	40.80
Cros carmellose sodium	6	9	12	----	----	----	----	----	----	6	-----	6
Sodium starch glycolate	---	----	----	6	9	12	-----	-----	-----	6	6	----
Croslinked PVP	-----	-----	-----	-----	----	-----	6	9	12	----	6	6
Sodium saccharin	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Vanilla flavor	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Talc	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Aerosil	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Magnesium stearate	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70
Total weight	150	150	150	150	150	150	150	150	150	150	150	150

RESULTS AND DISCUSSION

First nine formulations of amlodipine besylate were prepared with different concentration of three superdisintegrants namely Sodium Starch glycolate, Croscarmellose sodium, Crospovidone. Microcrystalline cellulose was used as the direct compressible vehicle. Talc and colloidal silicone dioxide are used as glidants to improve the flow property of the formulation. Magnesium stearate, which found to be having a deleterious effect on the dissolution, was used at very low concentration as anti-adherent. The formulation F1, F2, F3 having croscarmellose as superdisintegrants at a concentration of 4, 6, 8% respectively. F4, F5, F6 having SSG as disintegrant at a concentration of 4, 6, 8% respectively. F7, F8, F9 containing cros PVP as superdisintegrant at a concentration of 4, 6, 8% respectively. The last three formulations (F9-F12) were prepared by using combination of superdisintegrants. The bitter taste of the drug is masked by using sodium saccharin as sweetening agent. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters like angle of repose, bulk density, tapped density, hausner ratio and compressibility index. Using the bulk and tapped density data, Hausner's ratio and compressibility index was calculated. The powder blend of all the formulations had Hausner's ratio of 1.13 or less indicating good flowability. The compressibility index was found between 12.34 and 16.98 % and the compressibility flowability correlation data indicated a fairly good flowability of the blend. The good flowability of blend was also made evident with the angle of repose (range of 21 – 24°), which is below 40° indicating good flowability. Tablets were prepared using direct compression technique. Since the powder material was free flowing, tablets were obtained of uniform weight due to uniform die fill, with acceptable weight variations as per pharmaceutical specifications. The drug content was found in the range of 97.44– 101.54 % (acceptable limit) and the hardness of the tablets between 3.3 –3.9 kg/cm2 (Table 2 and 3). The hardness of

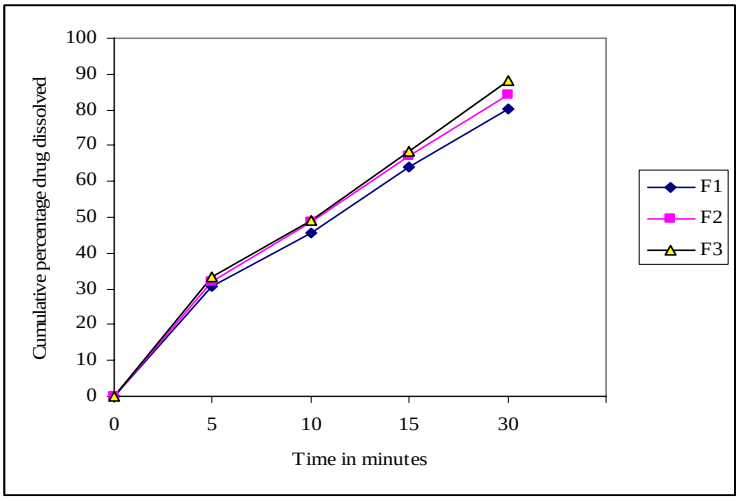

Fig. 1: Comparative dissolution profile of amlodipine besylate tablets containing different concentrations croscarmellose sodium as superdisintegrant f1, f2, f3

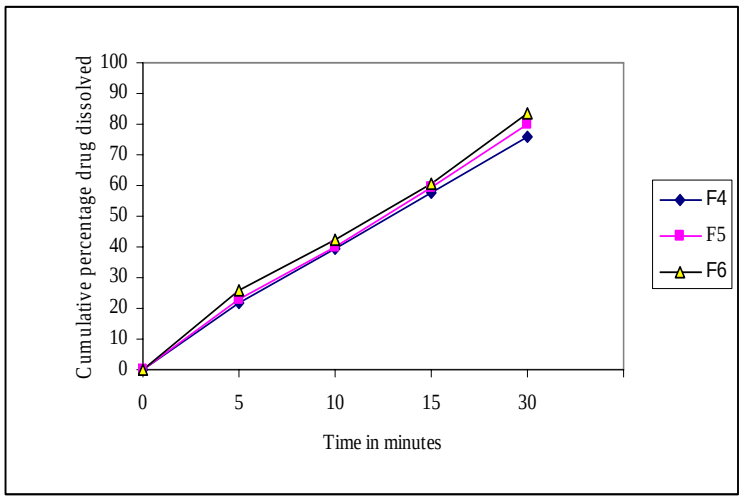

Fig. 2: Comparative dissolution profile of amlodipine besylate tablets containing different concentrations sodium starch glycolate as superdisintegrant f4, f5, f6

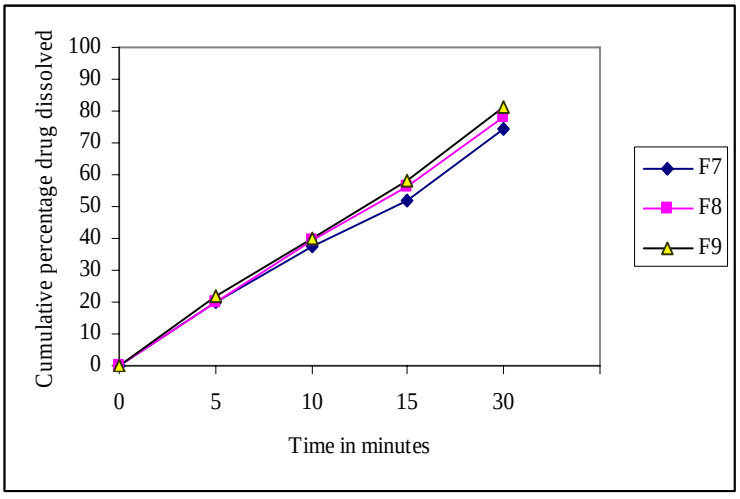

Fig. 3: Comparative dissolution profile of amlodipine besylate tablets containing different concentrations cros povidone as superdisintegrant f7, f8, f9

Table 2: Evaluation of fast dissolving tablets

Formulations	Average weight	Hardness Kg/cm2	Friability (%)	Wetting time(sec)	Water absorption ratio
F1	149.8±1.01	3.5±0.127	0.41±0.165	67±1.112	79±0.223
F2	148.7±1.04	3.6±0.132	0.49±0.171	65±1.012	88±0.612
F3	149.4±1.32	3.8±0.191	0.51±0.221	61±1.312	92±0.319
F4	151.5±1.43	3.6±0.134	0.48±0.187	69±1.041	72±0.169
F5	149.8±1.55	3.4±0.221	0.56±0.178	67±0.918	77±0.418
F6	147.7±1.34	3.3±0.329	0.59±0.160	65±1.513	81±0.513
F7	150.3±1.96	3.9±0.129	0.38±0.157	76±1.018	66±0.318
F8	148.6±1.22	3.6±0.162	0.47±0.190	73±0.810	69±0.610
F9	151.2±1.64	3.7±0.178	0.47±0.229	69±0.911	74±0.111
F10	152.5±0.99	3.9±0.174	0.40±0.256	55±1.810	97±0.210
F11	149±0.88	3.5±0.223	0.53±0.223	57±1.019	88±0.219
F12	150±0.76	3.5±0.241	0.52±0.129	59±1.314	94±0.314

Table 3: Evaluation of fast dissolving tablets

Formulations	Disintegration time(sec)	Drug content (%)	Percentage drug dissolved after 30 minutes
F1	32.8±0.761	98.12±1.222	80.23±0.519
F2	29.9±0.823	99.54±1.012	84.78±0.617
F3	26.5±0.789	101.54±1.111	88.98±0.692
F4	35.9±0.546	99.11±1.041	76.23±0.988
F5	32.5±0.678	97.44±0.818	80.87±0.478
F6	29.9±0.763	98.77±1.717	83.90±0.612
F7	46.4±0.890	101.88±1.112	74.33±0.991
F8	41.3±0.778	99.46±0.710	78.23±0.812
F9	38.5±0.729	98.67±0.611	81.70±0.332
F10	18.9±0.889	99.35±1.210	96.78±0.439
F11	24.8±0.760	97.67±1.019	89.67±0.789
F12	21.7±0.760	100.34±1.312	91.27±0.734

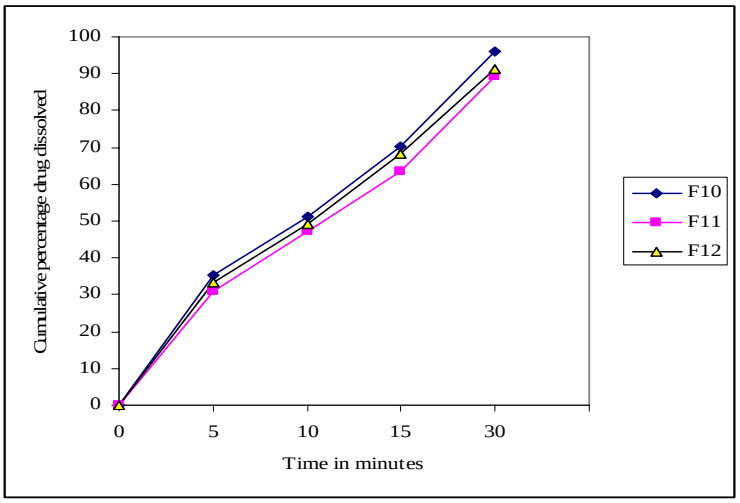

Fig. 4: Comparative dissolution profile of amlodipine besylate tablets containing combination of superdisintegrants f10, f11, f12

the tablet was found to be satisfactory so that the tablet will resist the mechanical shock during transportation and storage. Friability of the tablets was found below 1 % indicating good mechanical resistance of tablets. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tissue paper in a petri dish. Wetting time is closely related to the inner structure of the tablet. The results showed that wetting process was rapid in almost all formulations. The wetting time of formulations ranging from 55-67 minutes. The wetting time was found to be less for the formulations containing cross carmellose sodium as super disintegrant and it was found to be very less for the formulation containing combination of cros carmellose and sodium starch glycolate. The results (table 3) showed that tablet containing Croscarmellose sodium having low disintegration time as compared to other superdisintegrants.

The disintegration time of the formulation was ranging from 18.9-46.4 seconds. The disintegration time decreases as the concentration of superdisintegrants increases. The in vitro disintegration time of all formulated tablets was found to be less than 50 sec. The dissolution profile of the formulations ranges from 74.33-96.78%. The dissolution rate was found to be comparatively less for the formulation containing cross linked PVP. The maximum increase in the dissolution rate was observed with cros carmellose sodium amongst the three superdisintegrants. The order of enhancement of the dissolution rate with various superdisintegrants was found to be Croscarmellose> Sodium starch glycolate >

Crospovidone. Combination of superdisintegrants was found to better than using alone and the formulation containing croscarmellose and sodium starch glycolate was found to be showing the maximum dissolution after 30 minutes of dissolution study. Stability study shows no significant changes in values during one month study.

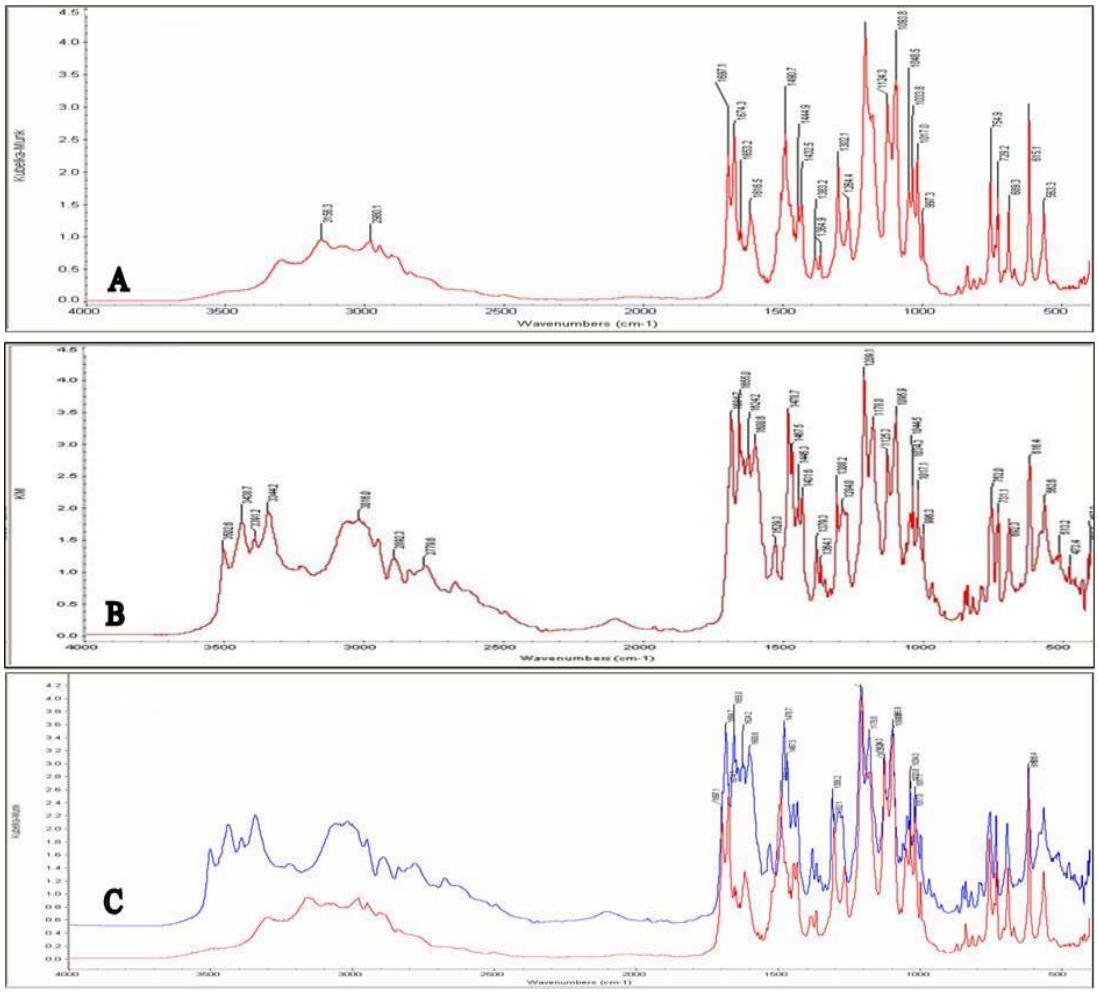

Fig. 5: FTIR spectra of pure drug (a), pure drug with formulation (b) and joint spectrum of pure drug and pure drug with the formulation (c)

CONCLUSION

The study shows that mouth dissolving tablets of amlodipine besylate can be successfully prepared by direct compression technique using selected superdisintegrants for better patient compliance and effective therapy.

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