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Research Article

FORMULATION AND EVALUATION OF FAST DISINTEGRATING SUBLINGUAL TABLETS OF AMLODIPINE BESYLATE USING DIFFERENT SUPERDISINTEGRANTS

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ABSTRACT

The demand of fast disintigrating tablets has been growing, during the last decade especially for geriatric and paediatric patients because of swallowing difficulties, the characteristics of fast-disintegrating sublingual tablets for the potential emergency treatment. The aim of this study was to prepare fast disintegrating tablets of Amlodipine Besylate by using different disintegrants and to evaluate the effect of increasing Amlodipine Besylate load on the characteristics of fast-disintegrating sublingual tablets for the potential emergency treatment of angina and hypertension. The superdisintegrant used in this study were Kollidon CL, Ac-Di-Sol and Sodium Starch Glycolate in varying concentrations (2%, 4%, 6%). The tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution study. Using the same excipients, the tablets were prepared by direct compression and were evaluated in the similar way. From the results obtained, it can be concluded that the tablet formulation prepared with Ac-Di-Sol showed average disintegration time of 16 seconds in vitro that is faster than the other superdisintegrants used in the study. Also the hardness, friability, dissolution rate and assay of prepared tablets were found to be acceptable according to standard limits. The stability studies were performed as per ICH guidelines. The Optimized formulation (F9) showed no significant variations for the tablets parameters and it was stable for the specified time period.

Keywords: Fast disintegrating tablet, Sublingual, Angina, ICH guidelines.

INTRODUCTION

The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes. A fast dissolving tablet system can be defined as a dosage form for oral administration, which when placed in mouth, rapidly dispersed or dissolved and can be swallowed in form of liquid. Recently fast dissolving formulation is popular as NDDS because they are easy to administer and lead to better patient compliance. Paediatric and geriatric patient have difficulty in swallowing the conventional dosage forms these dosage forms dissolve or disintegrate in the oral cavity within a minute without the need of water or chewing. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract[1-3].

Amlodipine Besylate is a drug that is used for treating high blood pressure, certain types of angina, and coronary heart failure. The drug works by slowing down the rate at which calcium moves to your heart and blood vessel walls, allowing better blood flow. Amlodipine Besylate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol. It is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Amlodipine Besylate is a dihydropyridine calcium antagonist (calcium ion antagonist or slow channel blocker) that inhibits the Trans-membrane influx of calcium ions into vascular smooth muscle and cardiac muscle[4].

Water wicking and swelling are the two most important mechanisms of disintegrant action for Ac-Di-Sol[5]. Water wicking is the ability to draw water into the tablet matrix. Both the extent of water uptake and the rate of water uptake are critically important. Exposure to water can cause ingredients to swell and exert pressure against surrounding tablet or capsule ingredients, causing existing bonds between particles to break. The fibrous nature of Ac-Di-Sol provides many sites for fluid uptake and gives it excellent water wicking capabilities. The cross-linked chemical structure of Ac-Di-Sol creates an insoluble, hydrophilic, and highly absorbent excipient that results in exceptional swelling properties. The solubility of Kollidon CL[6] varies considerably from one solvent to another. Sodium starch glycolate[7] is a commonly used super disintegrant employed to promote rapid disintegration and dissolution of solid dosage forms. It is manufactured by chemical modification of starch, i.e., carboxymethylation to enhance hydrophilicity and cross-linking to reduce solubility.

MATERIALS AND METHODS

Amlodipine Besylate is procured from Pfizar Labs, Kollidon CL, Ac-Di-Sol, Sodium starch glycolate are gifted by Signet chemical corporation Mumbai, Mannitol, Sodiam saccharin, Talc, Magnesium Stearate are procured by Loba Chemie, Cochine.

Preparation

The superdisintegrants (Kollidon-CL, Ac-di-sol, Sodium starch glycolate) in varying concentration (02 %, 04% & 06 %) used to develop the tablets. All the ingredients (shown in Table 1) were passed through mesh # 60. All the ingredients were mixed in a pestle motor for 5 min. The mixed blend of excipients was compressed using cadmech tablet punching machine weighing 100 mg each, with diameter of 8.0 mm[8].

Evaluation

Fourier Transform Infrared Spectroscopy

FTIR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrometer (1600 series, Perkin-Elmer Inc, Norwalk, CT). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}.

Hardness (H)

The H or the crushing tolerance of tablets was measured using an Electrolab hardness tester model EL 500.

Uniformity of weight[9]

The weights were determined to within ±1mg by using Sartorious balance (Model CP- 224 S). Weight control is based on a sample of 20 tablets. Determinations were made in triplicate

Tablet friability[10]

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight or a sample of 20 tablets are de-dusted in a drum for a fixed time (100 revolutions) and weighed again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

Friability = [(Initial weight- Final weight) / (initial weight)] x 100%

Disintegration time (DT)[11]

A relatively simple method with rigorous conditions was developed to evaluate the DT of rapidly disintegrating tablets. Each individual tablet was dropped into 10-mL glass test tube (1.5-cm diameter) containing 2 ml distilled water, and the time required for complete tablet disintegration was observed visually and recorded using a stopwatch. The visual inspection was enhanced by gently rotating the test tube at a 45° angle, without agitation, to distribute any tablet particles that might mask any remaining non disintegrated portion of the tablets.

Table 1: Formulation composition for tablets prepared by using superdisintegrants direct compression

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Amlodipine besylate	10	10	10	10	10	10	10	10	10
Kollidon CL	2	4	6	-	-	-	-	-	-
SSG	-	-	-	2	4	6	-	-	-
Ac-di-sol	-	-	-	-	-	-	2	4	6
Mannitol	50	50	50	50	50	50	50	50	50
Avicel	26	24	22	26	24	22	26	24	22
Sodium Saccharine	10	10	10	10	10	10	10	10	10
Mg. Stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Total Wt. Of Tablet	100	100	100	100	100	100	100	100	100

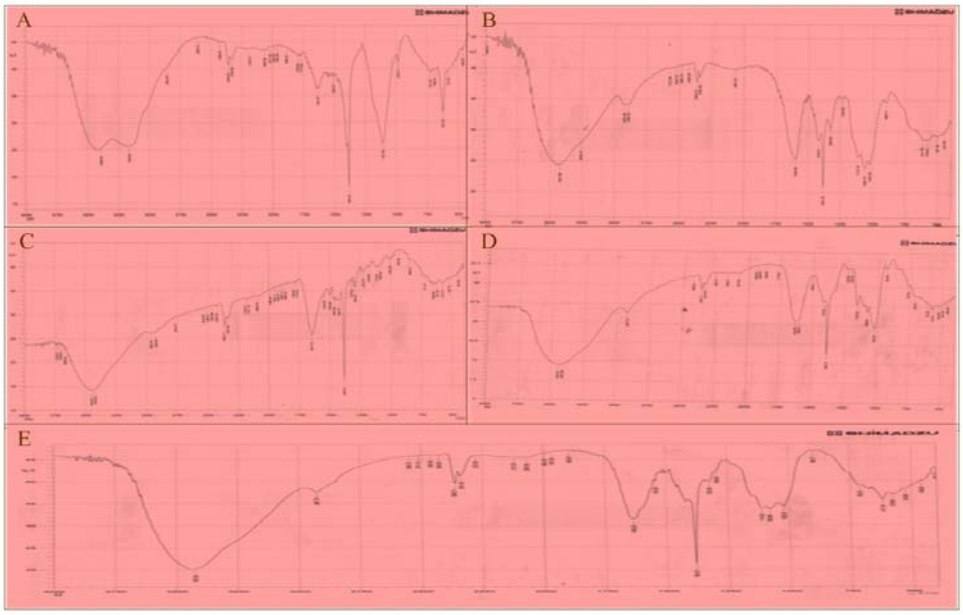

Fig. 1: FTIR spectra of Amlodipine Besylate (A), Ac di sol (B), Sodium starch glycolate (C), Kollidon CL (D), Mixture (E)

Fig. 2: State of Tablet while measuring Wetting Time (A) Initial stage, (B) Intermediate, (C) Completely Wetted Tablet

Wetting time (WT)[11]

Tablet WT was measured by a procedure modified from that reported by Bi et al. The tablet was placed at the centre of 2 layers of absorbent paper fitted into a dish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch.

Water absorption ratio[11]

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using following equation.

$R = 100 \times Wa - Wb/Wa$

Where, Wa = Weight of tablet after water absorption

Wb = W

In-vitro dissolution study

The release rate Amlodipine Besylate from fast dissolving tablets was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of buffer (pH=7.4), at 37± 0.5^{0}C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 2, 4, 6, 8, 10, 12 and 14 min. The samples were replaced with fresh dissolution medium of same quantity. Absorbance of these solutions was measured at 239 nm using a Shimadzu UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Accelerated stability study[12,13,14]

In order to determine the change in in-vitro release profile on storage, stability study of batch F9 was carried out at 40 ^{o}C in a humidity chamber having 75% RH. Sample were withdrawn at various intervals the study was conducted for 60 days interval and evaluated for change in in-vitro drug release pattern, hardness, wetting time, percent drug content and disintegration time.

RESULTS AND DISCUSSION

The powder blend for all formulation containing various concentration of Kollidon-CL (2,4,6%), Ac-Di-Sol (2,4,6%) and sodium starch glycolate (2,4,6 %) as superdisintegrant was prepared and then the FTIR studies were done that suggests incompatibility (Fig. 1), the study suggests that the drug and excipients are compatible to each other. The tablets were prepared by direct compression using cadmech tablet punching machine. These tablets were evaluated for weight variation test, hardness, friability, water absorption ratio, disintegration time and In-vitro dissolution rate. It was observed that all the tablets pass the test for weight variation as shown in Table 2. Hardness of all tablets was between 2.3-3.7 kg/cm^2 while friability below 1% showed that all the tablets have good mechanical strength. Out of all formulation tablets containing Ac-Di-Sol as superdisintegrant showed highest water absorption ratio than all other formulation with single use of superdisintegrant (Table 2). Disintegration time of all tablets was observed within fraction of second. It was found that as concentration of Kollidon-CL and Ac-Di-Sol increases the disintegration time decrease for sodium starch glycolate, as concentration in tablet increases disintegration time not decreased significantly, the formulation containing 6% Ac-Di-Sol as superdisintegrant showed faster dissolution rate and disintegration rate as compared to other superdisintegrants. The water absorption ratio and the wetting time increased as the concentration of superdisintegrant increased The dissolution studies of respective formulation batches shows good dissolution behaviour (Fig.3), the formulation containing 6% Ac-Di-Sol showed 99.15% drug release within 2-6 minutes while that for tablet containing Kollidon-CL showed 98.54% drug release within 2-8 minutes. Tablet containing SSG showed 98.62% drug release within 2-10 minutes (Fig.3). It suggests that increase in concentration of superdisintegrant disintegration time decreases in the order of Ac-Di-Sol < Kollidon-CL < Sodium salt glycolate.

Table 2: Evaluation of Fast Disintegrating Sublingual Tablets

Formulation	Weight variation	Hardness (Kg/cm^2)	Friability (%)	Wetting time (Sec.)	Water absorption ratio	Disintegration time (Sec.)
F1	2.2±0.51	2.3±0.14	0.43±0.29	10±0.9	20.91±2.1	37±2.1
F2	3.1±0.29	2.6±0.11	0.52±0.13	21±1.1	33.30±1.9	23±2.8
F3	4.2±0.28	3.2±0.15	0.74±0.32	30±1.7	50.69±1.7	26±2.0
F4	1.1±0.35	3.1±0.14	0.33±0.16	23±1.9	31.23±1.4	43±2.2
F5	3.6±0.12	3.2±0.27	0.47±0.25	37±1.2	48.11±1.2	36±2.3
F6	2.4±0.46	3.5±0.26	0.69±0.27	55±1.7	49.89±1.4	42±1.0
F7	3.3±0.23	2.8±0.30	0.37±0.16	13±0.9	22.92±1.9	17±2.0
F8	2.8±0.15	3.2±0.13	0.52±0.32	24±1.0	34.47±2.2	21±2.5
F9	1.4±0.33	3.7±0.22	0.75±0.33	32±0.8	51.73±2.4	16±2.2

Table 3: Physical characteristics of Amlodipine Besylate fast disintegrating tablet of optimised batch F 9 at temperature (40^{o}C ± 2^{o}C / 75% RH ± 5%)

Physical Parameter	Batch F9			
	0 days	15 Days	30 Days	60 Days
Weight gain (mg)	100	100	103	103
Percent drug content (%)	99.8	99.2	98.65	97.23
Hardness (Kg/cm^2)	3.7	3.7	3.6	3.6
Disintegration time (Sec)	16	16	16	17
Wetting time (Sec)	32	32	35	35

Table 4: Drug release % at 40^{o}C ± 2^{o}C/75% RH ± 5%

S. no.	Time (Days)	40^{o}C / 75% RH
1	0	99.8
2	30	97.2
3	60	96.8

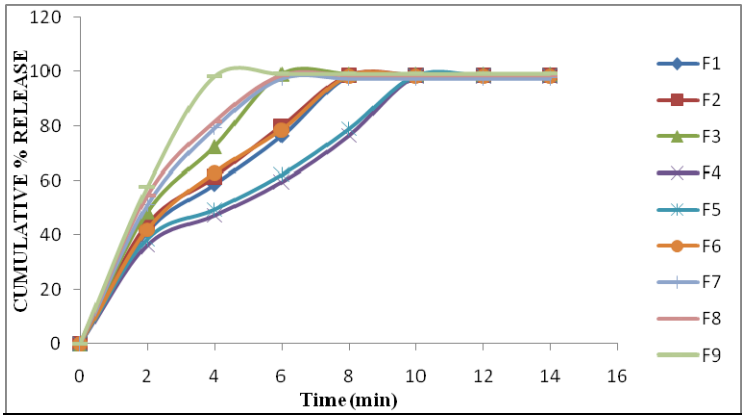

Fig. 3: In vitro Dissolution Curve between Cumulative % Release Vs Time

The tablets prepared by using superdisintegrant (F9) showed rapid dissolution as increase the concentration of superdisintegrants that is due to the result of rapid disintegration. The optimised batch is selected on the bases of faster disintegration time and dissolution studies on that bases batch F9 was selected on that bases accelerated stability studies was conducted at 40°C/ 75% RH that suggests that after sixty days tablets has no significant change in physical properties that is indicated in Table 3 and the dissolution profile is given in Table 4 of batch F9 that shows after 96.80 % release after the 60 days of studies.

CONCLUSION

The use of superdisintegrants for preparation of fast disintegrating sublingual tablets is highly effective and commercially feasible. These superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore faster disintegration. This disintegration is reported to have an effect on dissolution characteristics as well. Prepared fast disintegrating tablet gets dispersed in the mouth quickly and releases the drug fast. Fig. 3 show the cumulative percentage of Amlodipine Besylate released from formulated tablet with different concentration of Kollidon- CL, Sodium Starch Glycolate and Ac-Di-Sol. It is clear that the dissolution and disintegration of Amlodipine Besylate has improved considerably in batch F9 as compared to rest of formulations, Batch F9 tablet showed good dissolution efficiency and rapid dissolution. The study shows that the dissolution rate of Amlodipine Besylate can be enhanced to a great extent by direct compression technique with the addition of superdisintegrants and no extreme changes in formulation F9 during stability studies.

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REFERENCES

1. Berner B, Birudaraj R, Shen S, Li X. Buccal permeation of buspirone: mechanistic studies on transport pathways. J Pharm Sci. 2005; 94: 70-78.
2. Ishikawa T, Koizumi N, Mukai B. Pharmacokinetics of acetaminophen from rapidly disintegrating compressed tablet prepared using microcrystalline cellulose (PH-M-06) and spherical sugar granules. Chem Pharm Bull (Tokyo). 2001; 49: 230-32.
3. Price TM, Blauer KL, Hansen M, Stanczyk F, Lobo R, Bates GW. Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 beta-estradiol. Obstet Gynecol. 1997; 89: 340- 45.
4. Ohmori M, Arakawa M, Takasali H, Hifumi S, Fujimura A. Stereoselective pharmacokinetics of amlodipinebesylate in elderly hypertensive. Am J Ther. 2003; 10: 29-31.
5. Weller PJ. Croscarmellose Sodium. Ainely Wade and Paul (London). 1994; 2: 141-142.
6. Masareddy RS, Kadia RV, Manvi FV. Development of mouth dissolving tablets of clozapine using two different techniques, Indian journal of pharmaceutical sciences. 2008; 4: 526-528.
7. Banker GS. Sodium Starch Glycolate. 2nd edn. Ainely Wade and Paul, London. 1994.
8. Sharma S, Gupta GD, Formulation and characterization of fast dissolving tablets of Promethazine theoclate. Asian Journal of Pharmaceutics. 2008; 70-72.
9. Indian Pharmacopoeia. Ministry of Health and Family Welfare, Govt. of India. The controller of publications. New Delhi. 1996.
10. Lachman L, Lieberman A, Kinig JL. The Theory and Practice of Industrial Pharmacy. 2nd edn. Varghese Publishing House, Bombay. 1991.
11. Bi Y, Sunada H, Yonezawa Y, Danjo K, Otsuka A, Iida K. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem Pharm Bull (Tokyo). 1996; 44: 2121-127.
12. Swamy PA, Areefulla SH, Shrisand SB, Gandra S, Prashanth B. Orodispersible tablets of meloxicam using superdisintegrant blends for improved efficiency. Ind J Pharm Sci. 2007; 69: 836-40.
13. Malke S, Shidhaye S, Kadam VJ. Formulation and evaluation of oxcarbazepine fast dissolving tablets. Ind J Pharm Sci. 2007; 69: 211-14.
14. Patel MM, Patel DM. Fast dissolving valdecoxib tablets containing solid dispersion of valdecoxib. Ind J Pharm Sci. 2006; 68: 222-26.