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Research Article

FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLET CONTAINING AMLODIPINE BESYLATE

HARLALKA S. S*, CHAWARE V. J, DESHMANE S.V, BIYANI.K R

Department Of Pharmaceutics, Anuradha College of pharmacy, Chikhli-443201.(M.S.) India.

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ABSTRACT

Amlodipine besylate is a long-acting calcium channel blocker used in the treatment of chronic stable angina, vasospastic angina and hypertension. In the present study orodispersible tablet containing Amlodipine Besylate was prepared. The screening study of superdisintegrants was done using different concentration. The bitter taste of drug was masked by forming complex of drug with eudragit EPO polymer using precipitation method. The combination of crosspovidone, cross carmellose and sodium starch glycolate were screening with 9% concentration. The ODTs were prepared in consideration of varying concentration of diluents, MCC and mannitol. The formulation F8 was found optimized in consideration of disintegration and dissolution. Lastly, it conclude due to wide significance of an ODT, this drug delivery system may lead to better patient compliance and ultimate clinical output.

Keywords: Orodipersible tablet, Crosspovidone, Amlodipine Besylate, Drug-polumer complex.

INTRODUCTION: 1,2,3,4,5

It is observed that approximately one-third of the population has suffered from pill swallowing difficulties, mainly in the geriatric and pediatric patients. To overcome the problem associated with swallowing of conventional dosage form when water is not available the term, "orodispersible tablet (ODT)" has emerged as alternative oral dosage form. The production of ODT technology entered the market in the1980s, have grown steadily in demand, and their product pipelines are rapidly expanding.ODT are uncoated tablet intended to be place in the mouth where they disperse rapidly before being swallowed. ODT are also known as, fast dissolving tablet, mouth dissolving tablets, melt in mouth tablets, repimelts, or orodispersible tablets, quick dissolving or rapid disintegrating tablets" etc. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva in the oral cavity, results into solution without the need of water for administration. The faster the drug converts into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach[6].The basic approach used in the development of the orodispersible tablets is the use of superdisintegrants. Sodium starch glycolate and crospovidone were screened in the present study. Anotherapproach isto mask the taste of drug with eudragit EPO.

MATERIALS AND METHODS

Materials

Amlodipine besylate&Eudragitepo were procured from the pharmaceutical company. And all other ingredients were obtained from the college.

Methods

Preparation of drug-polymer complex (DPC):[6,7]

Amlodipine Besylate and Eudragit EPO complex was prepared using the precipitation method. Saturated solutions of Amlodipine besylate and Eudragit EPO were prepared in absolute ethanol in various ratios 1:1, 1:2, 1:3 Solutions were then injected into NaOH solution with pH11 with constant stirring at 500 rpm for 5 min. The foamy matrix obtained on the top of the solution was separated, dried at room temperature for 24 h under vacuum and then pulverized in order to obtain a fine powder. The optimized ratio was selected on the basis of drug release in simulated salivary fluid (SSF) pH 6.8 i.e*. In Vitro* taste evaluation (Table 1).

Characterization of DPCs: [6,7]

Drug Content

This was carried out to determine actual drug content per unit weight of the Drug polymer complex (DPC). About 100 mg of complex was stirred with 500ml of SSF on a magnetic stirrer at 500 rpm. The sampling was done at time interval of 10 minute. The amount of sample withdrawn was replaced with equivalent amount of fresh simulated fluid. The sampling was done until no further increase in concentration of the drug found in the solution. The withdrawn samples were analyzed spectrophotometrically at 237nm after doing sufficient dilution. The calculated drug content per 100mg of complex was determined (Table 2).

In Vitro taste evaluation of drug complexes

Drug complex equivalent to 10 mg of Amlodipine Besylate was taken in a 25ml volumetric flask. To this, 10ml of simulated salivary fluid (SSF) was added and was shaken for 60 seconds on mechanical shaker. The amount of drug released was analyzed spectrophotometrically at 237 nm.

Selections of superdisintegrants: [6]

Superdisintegrants play a most crucial role in the fast dissolving formulation. In the tablet formulation study, preliminary work was carried out for screening the better superdisintegrants among three namely; crosspovidone,crosscarmellose sodium, and sodium starch glycolate. For this study were prepared in various batches as shown in table 3.

Formulation and preparation of ODT

Ingriedients used in formulation of ODT are mentioned in table no.4. Total eight formulation (F1-F8) was prepared containing varying concentration of superdisintegrant and diluents. Direct compression method was used to compress powder blend using multitooking 12 station table press (cadmach, Ahmedabad)**.** The prepared ODT were subjected to various evaluation test.

Evaluation of ODTs Tablet:[8-13]

The General appearance of the tablet, includes tablets size, shape, colour, presence or absence of an odor, taste, surface texture were checked manually. In addition, thickness and diameter must be controlled to facilitate packaging. Thus thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter of three tablets of each batch was measured using micrometer. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester. The weight variation

test for each formulations were carried out as per the procedure given in Indian Pharmacopoeia. All the tablets were subjected to friability test using Roche Friabilator for 100 revolutions. Tablets were removed dedusted and weighed again.

Drug content

Ten tablets from each formulation were powdered. The powder equivalent to10 mg of amlodipine besylate was weighed and dissolved in phosphate buffer pH 6.8 in 100ml standard flasks.From this suitable dilution was prepared and thesolution was analyzed at 237 nm using UVdouble beam spectrophotometer (Elico SL164) using pH 6.8 as blank

Wetting Time

Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter. 10 mL of water-containing amaranth (a water soluble dye) is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

***In Vitro* Disintegration Test**

The process of breakdown of a tablet into smaller particles is called as disintegration. The *In Vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 phosphate buffer maintained at 37 ±2 °C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 phosphate buffer maintained at 37 ±2 °C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

***In-Vitro* Dispersion time**

One tablet was placed in a beaker containing 10 ml of distilled water at 37 ±0.5ºC and the time required for complete dispersion was determined.

***In Vitro* dissolution studies**

The dissolution study were carried out using USP paddle method at 50 rpm in 900 ml of 6.8 pH phosphate buffer as dissolution media, maintained at 37 ± 0.5º. 5 ml of samples, were withdrawn from the dissolution medium at the specified regular intervals, filtered through Whatmann filter paper and release of the drug was determined spectrophotometrically at 223nm.An equal volume of pre warmed (37ºC) fresh medium was replaced into thedissolution medium each sampling, to maintain the constant volume of the dissolution medium throughout the test.

Table 1: Evaluation of Drug Polymer complex by content

S. No.	Time (min)	Ratio	Drug content (%)
	10		68.45
1	20	1:1	81.99
	30		95.53
	40		98.38
	10		75.57
2	20	1:2	88.40
	30		99.10
	40		99.81
	10		65.59
3	20	1:3	82.01
	30		93.39
	40		98.38

Table 2: In- vitro taste evalution of drug complex

S. No.	Ratio	% Drug release
1	1:1	6.72
2	1:2	2.45
3	1:3	4.23

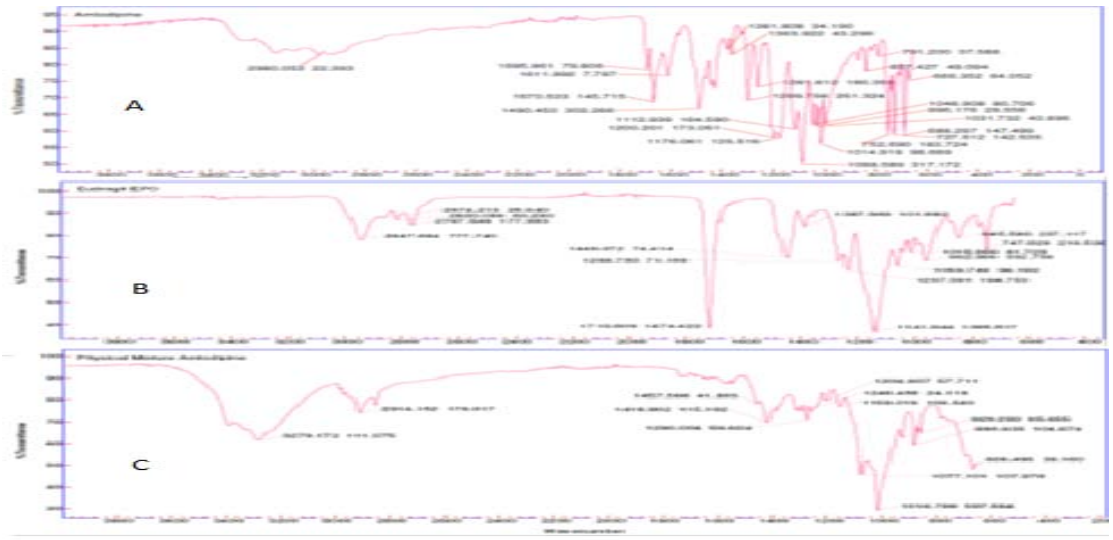

Fig. 1: IR-spectra of A-pure drug, B-eudragitepo, C-Combined of drug-polymer complex

Table 3: Screening of superdisintegrants

Batch	Disintegrant	Disintegrant (%w/w)	*Diluent (%w/w)	**Disintegration time(sec)
C1	-	-	100	84
C2	CRP	3	97	17
C3	CRP	6	94	12
C4	CRP	9	91	07
C5	CCS	3	97	18
C6	CCS	6	94	16
C7	CCS	9	91	14
C8	SSG	3	97	20
C9	SSG	6	94	15
C10	SSG	9	91	10

Table 4: Composition of orodispersibletablet of amlodipine besylate

Batches Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
DPC	10	10	10	10	10	10	10	10
Crosspovidone	9%	9%	-	-	-	--	3%	3%
Crosscarmellose sodium	-	-	9%	9%	-	-	3%	3%
Sodium starch glycolate	-	-	-	-	9%	9%	3%	3%
Micrcrystalline cellulose	70%	30%	70%	30%	70%	30%	70%	30%
Mannitol	30%	70%	30%	70%	30%	70%	30%	70%
Magnesium stearate	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%
Talc	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%

Table 5: Preliminary evaluation of orodipersibletablet

Formulations	Hardness ±SD (kg/cm^2)	Thickness ± SD	Diameter ± SD	WeightVariation ±SD (mg)
F1	3.4 ± 0.360	3.55 ± 0.251	8.1 ±0.00	204 ± 1.049
F2	3.96 ±0.152	3.69 ± 0.598	8.1±0.00	202 ± 1.024
F3	3.23 ±0.251	3.57 ± 0.304	8.1±0.00	200 ± 0.00
F4	3.13 ±0.152	2.88 ± 0.296	8.1± 0.00	201 ±0.152
F5	3.63 ±0.568	3.17 ± 0.168	8.1± 0.00	202 ± 0.942
F6	3.16 ±0.288	3.32 ±0.0381	8.1 ±0.00	200 ± 0.00
F7	4.03 ±0.162	3.33 ± 0.141	8.1± 0.00	200 ±0.00
F8	3.3 ±0.360	3.44 ±0.306	8.1± 0.00	200 ±0.00

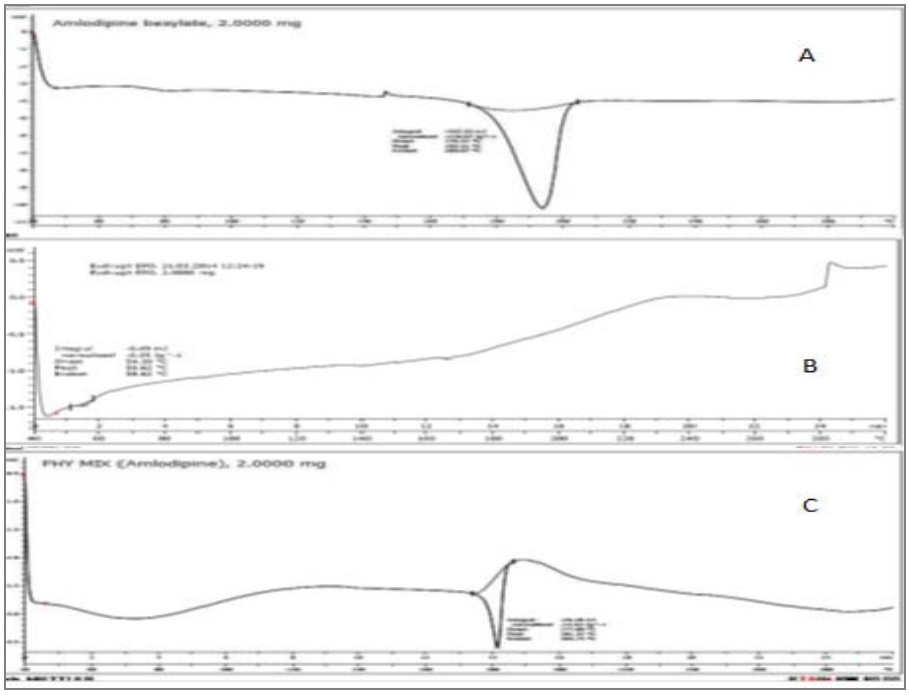

Fig. 2: DSC of A=Pure drug, B= eudragitepo, C=optimized batch F8

Table 6: Evaluation test of orodispersible tablet

Formulatins	Friability (%)	Disintegration Time (sec)	Wetting Time (sec.)	Drug content (%)
F1	0.65	87± 0.012	67±1.112	94.46
F2	0.67	21 ± 0.141	61±1.312	95.24
F3	0.46	138 ± 0.028	67±0.918	95.62
F4	0.40	34 ± 0.021	69±0.911	96.34
F5	0.69	70 ± 0.026	57±1.019	98.23
F6	0.93	62 ± 0.017	65±1.513	97.19
F7	0.37	32 ± 0.016	59±1.314	97.45
F8	0.33	20 ± 0.024	55±1.810	98.76

Table 7: *In Vitro* dispersion time

Formulations	F1	F2	F3	F4	F5	F6	F7	F8
In-Vitro Dispersion Time (sec)	29	28	25	27	29	28	27	31

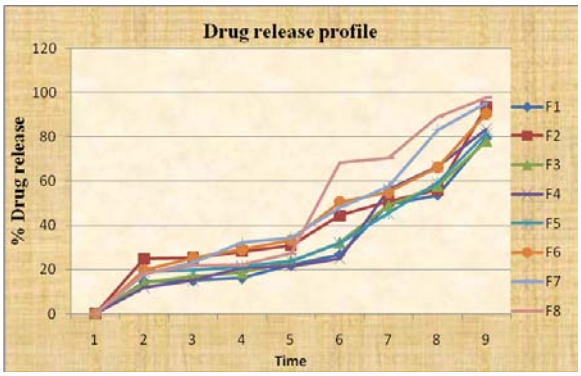

Fig. 3: Drug release profile

RESULTS AND DISCUSSION

FTIR and DSC study gives an idea about no chemical as well as physical incompatibility (Fig 1 and Fig 2). Tablets were evaluated for various tests like weight variation, hardness, friability, content uniformity, wetting time, water absorption ratio, in-vitro disintegration time, in-vitro dispersion time, & Dissolution.In all formulation thickness varies between 2.88 to 3.69 mm and hardness of the optimized batch was found to be 3.3 kg/cm^3. No variation in the hardness was found in the optimized batch which clearly indicates that the blending was uniform.Friability was less than 1% the entire batches. The entire tablet from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limit of ± 7.5 **%** of the weight (Table 5).The *in-vitro* disintegration time for all the formulations varied from20 to 138 sec. The rapid disintegration was seen in the formulation containing the combination of the three superdisintegrants(20 sec).the wetting time of ODTs are ranges between 55-69 sec. This is due to rapid uptake of the water from the medium, swelling and burst effect. It was also noticed that as the concentration of mannitol increases the time taken for disintegration get reduced & as the concentration of MCC increases the time taken for disintegration also get increased. It was found that the wetting time was rapid in the combination of the three(CPVP, CCS,SSG) followed by crossspovidone (Table 6). The Table 7 indicates the in-vitro dispersion time for all the batches ranges from 25 – 31 min. The drug release was found to be more than 85% after 45 min. From the all evaluation test carried for the each orodispersible tablet formulation of Amlodipine Besylate, the formulation F8, was found optimized batch in consideration of disintegration time, *In Vitro* dispersion time, wetting time, drug content uniformity, & % drug released over 1 min to 60 min (fig 3).

CONCLUSION

Orodispersible tablets(ODTs) of Amlodipine Besylate are successfully prepared by using direct compression method.Taste masked ODT will surely enhance the patient compliance, low dosing and rapid onset of action, increased bioavailability, low side effect, good stability and its popularity in near future.Due to this wide significance of an ODT, this drug delivery system may lead to better patient compliance and ultimate clinical output.Future might be witness of many more classes of drugs developed in the form of ODT.

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