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Research Article

FORMULATION AND EVALUTION OF MOUTH DISSOLVING TABLETS OF AMITRIPTYLINE HYDROCHLORIDE BY DIRECT COMPRESSION TECHNIQUE

MOHSIN A.A *[1], NIMBALAKR N.E, SANAULLAH S, AEJAZ A

[1]Department of Pharmaceutics, Luqman College of pharmacy, Gulbarga, 585102. Karnataka, India

ABSTRACT

Fast dissolving drug delivery system offers a solution for those patients having difficulty in swallowing tablet. In the present study, an attempt has been made to prepare fast dissolving tablets of the drug Amitriptyline hydrochloride using superdisintegrants such as Croscarmellose sodium (Ac-Di-Sol), Sodium starch glycolate (Explotab) and Crospovidone by direct compression technique. The prepared tablets were evaluated for hardness, friability, wetting time, weight variation, *in vitro* disintegration time and *in vitro* dissolution study. The hardness of the tablets was in the range of 2.0 - 4.0 Kg/cm^2. The percentage friability of the tablets was less than one. Weight variation test results showed that the tablets were deviating from the average weight within the permissible limits of ±7.5 %. Drug content uniformity study results showed that uniform dispersion of the drug throughout the formulation i.e. 98.54% to 101.23%. Tablets containing Crospovidone (DC9) showed better disintegrating character along with the rapid release (99.83% drug within 7 minutes). No appreciable difference was found between the formulations containing other two superdisintegrants. Crospovidone was found to be better suited for the formulation of mouth dissolving tablet of Amitriptyline hydrochloride compared to other superdisintegrarnts used in the study.

Keywords: Fast-dissolving tablets, Amitriptyline Hydrochloride, Superdisintegrants.

INTRODUCTION

Solid dosage forms and capsules are most popular and preferred drug delivery system because of they have a high patient compliance. Many patient find difficulty to swallow tablet and hard gelatin capsule, consequently they do not take medication as prescribed. It is estimated that 50% of the population is affected by this problem which result high incidence of non-compliance and ineffective therapy[1].

The difficulty is experienced in particular by pediatric and geriatric patients, but it is applicable to people who are ill in bed and those active working patients who are busy or traveling, mentally ill, developmentally disable and patients who are uncooperative. To overcome this problem fast dissolving tablet is prepared[2].

Amitriptyline HCl inhibits the reuptake of norepinephiren and serotonin almost equally. These actions help in Amitriptyline HCl as an antidepressant and antipsychotic drug[3].

With the view to all the above information, an attempt had been made to develop a rapidly disintegrating Amitriptyline HCl mouth dissolving tablets of which disintegrate in the oral cavity without the need of water within a matter of seconds. This will lead to the formation of suspension / solution form which can be easily swallowed, thereby improving dissolution rate and bioavailability of drug and onset of pharmacological action.

MATERIALS AND METHODS

Materials

Amitriptyline HCl was obtained as gift sample from Vasudha Pharma Chem Ltd., Hyderabad,India, Crospovidone, Croscarmellose sodium, Sodium starch glycolate and aspartame were gifted sample from Cipla, Kurkumbh,India, Lactose, Magnesium stearate was procured from S.D Fine Chemicals, Mumbai, India, were used and all other

chemicals/solvents used were analytical grade.

Method

Formulation of mouth dissolving tablets of Amitriptyline Hydrochloride

Tablet each containing 25 mg Amitriptyline Hydrochloride were prepared as per composition given in Table1. The drug and excipients were passed through sieve (#80) to ensure the better mixing. Microcrystalline Cellulose was used as a direct compressible vehicle. Super disintigrants like Sodium Starch Glycolate, Crospovidone and Croscarmellose Sodium were used in different ratios. The powder was compressed using Rimek compression machine equipped with 8 mm round punch by direct compression technique. A minimum of 50 tablets was prepared for each batch.

Pre Compression Parameters

Angle of Repose

Angle of repose was determined using funnel method[4]. The blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using the formula

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

Where, θ is the angle of repose, h is height of pile; r is radius of the base of pile.

Bulk Density

Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder[4]. The bulk volume (V_b) and weight of powder (M) was determined. The bulk density was calculated using the formula

$$\rho_b = \frac{M}{V_t}$$

Tapped Density

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and weight (M) of the blend was measured. The tapped density (ρ_b) [4] was calculated using the following formula

$$\rho_t = \frac{M}{V_t}$$

Carr's Compressibility Index

The simplest way of measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility. The compressibility index of the granules was determined by Carr's compressibility index[4] (I), which is calculated by using the following formula

$$I = \frac{V_0 - V_t}{V_o} \times 100$$

Hausner Ratio

Hausner ratio[5] is an indirect index of ease of powder flow. It is calculated by the following formula

$$\text{Hausner ratio} = \frac{\rho_t}{\rho_d}$$

Where ρ_t is tapped density and ρ_d is bulk density. Lower Hausner ratio (< 1.25) indicates better flow properties than higher ones[6] (>1.25).

Post compression parameter

Hardness

The hardness of the tablet from each formulation was determined using Pfizer hardness tester[4].

Weight Variation

Twenty tablets from each formulation were selected at a random and average weight was determined. Then individual tablets were weighed and was compared with average weight [4].

Friability

Friability of the tablets[4] was determined using Veego 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 to100 revolutions. Tablets were de dusted using a soft muslin cloth and re weighed. The friability (f) is given by the formula.

$$\text{Friability (f)} = \left(1 - \frac{W_0}{W}\right) \times 100$$

Where W_0 is weight of the tablets before the test and W is the weight of the tablet after the test

***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 water was maintained at a temperature of 37°±2°C and time taken for the entire tablet to disintegrate completely was noted[7].

Drug content

Five tablets were powdered and the blend equivalent to 100 mg of Amitriptyline hydrochloride was weighed and dissolved in suitable quantity of distilled water. The solution was filtered, suitably diluted and the drug content was analyzed spectrophotometrically at 239nm. Each sample was analyzed in triplicate[8].

***In vitro* Dissolution studies**[9]

In vitro dissolution studies for all the fabricated tablets was carried out by using USP Type II apparatus (USP XXIII Dissolution Test Apparatus) at 50 rmp in 900 ml of phosphate buffer pH 6.8, maintained at 37±0.5ºC. 5 ml aliquot was withdrawn at the specified time intervals, filtered through whatmann filter paper and assayed spectrophotometrically at 239nm using Shimadzu 1700 spectrophotometer. 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.

Stability study[10, 11]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light and enables recommended storage conditions, re-test periods and shelf lives to be established.

ICH specifies the length of study and storage conditions:

- Long term testing 25°C ± 2°C / 60 % RH ± 5 % for 12 months

- Accelerated testing 40°C ±2 °C / 75 % RH ± 5 % for 6 months

In the present study, stability studies were carried out at 25°C ± 2°C / 60 % RH ± 5 % and 40°C ±2 °C / 75 % RH ± 5 % for a specific time period up to 30 days for the selected formulations. Tablets were evaluated for hardness, weight variation, friability, content uniformity, disintegration and drug release.

Table 1: Composition of different batches of mouth dissolving tablets of Amitriptyline Hydrocholride

Ingredients (mg)	DC_0	DC_1	DC_2	DC_3	DC_4	DC_5	DC_6	DC_7	DC_8	DC_9
Amitriptyline Hydrocholride	25	25	25	25	25	25	25	25	25	25
Lactose (DC)	103	99	97	95	99	97	95	99	97	95
Sodium starch glycolate (Explotab)	--	4	6	8	--	--	--	--	--	--
Croscarmellose sodium (AC-Di-Sol)	--	--	--	--	4	6	8	--	--	--
Crospovidone (Polyplasdone)	--	--	--	--	--	--	--	4	6	8
Microcrystalline cellulose	50	50	50	50	50	50	50	50	50	50
Aspartame	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Talc	10	10	10	10	10	10	10	10	10	10
Total weight	200	200	200	200	200	200	200	200	200	200

Table 2: Evaluation of Mixed Blend of Drug and Excipients

Formulation code	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Compressibility index (%)
DC_0	25.11	0.454	0.522	1.14	13.03
DC_1	23.42	0.451	0.542	1.201	17.01
DC_2	24.14	0.459	0.539	1.173	14.18
DC_3	24.30	0.438	0.523	1.194	16.28
DC_4	25.01	0.447	0.539	1.205	17.01
DC_5	26.56	0.473	0.565	1.194	16.31
DC_6	25.76	0.46	0.553	1.202	16.79
DC_7	25.17	0.427	0.508	1.189	15.93
DC_8	25.11	0.478	0.567	1.186	15.72
DC_9	26.56	0.442	0.537	1.21	17.68

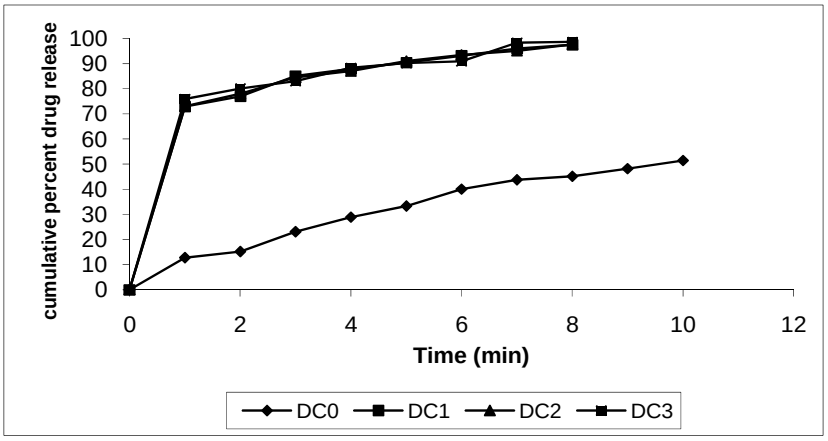

Fig. 1: **Comparative dissolution profile of Amitriptyline hydrochloride tablets containing different superdisintegrants DC_0, DC_1, DC_2 & DC_3**

Table 3: Evaluation of tablets

Formulation Code	Weight Variation (mg)	Hardness Kg/ cm² ± SD	Thickness (mm) ± SD	Friability (%)	Drug content (%) ± SD	In vitro disintegration time (sec) ± SD	Water absorption ratio (Sec)	Wetting time (Sec)	% Drug release
DC_0	199 – 205 (within the IP limit of ±7.5 %)	4.1±0.311	3.71±0.010	0.42	99.18±0.72	242±0.73	83.01±0.26	61 ± 0.263	97.13
DC_1		3.4±0.401	3.70±0.030	0.52	99.81±1.07	39±0.90	72.3±0.31	25 ± 0.201	97.60
DC_2		3.1±0.209	3.73±0.012	0.56	98.54±0.50	23±0.68	77.64±0.54	12 ± 0.324	97.72
DC_3		3.2±0.216	3.73±0.040	0.67	99.12±0.72	20±0.64	75.15±0.11	17 ± 0.496	98.78
DC_4		3.6±0.513	3.70±0.011	0.71	99.30±027	24±0.71	68.15±0.31	19 ± 0.406	99.01
DC_5		3.2±0.291	3.71±0.035	0.63	101.23±0.39	22±0.27	68.77±0.45	17 ± 0.496	98.90
DC_6		3.4±0.316	3.71±0.053	0.60	101.03±0.73	31±0.55	59.25±0.78	12 ± 0.324	99.12
DC_7		3.5±0.263	3.73±0.025	0.68	98.63±0.44	23±0.94	70.17±0.70	10 ± 0.201	99.56
DC_8		3.9±0.315	3.70±0.013	0.42	99.50±0.34	18±0.57	68.79±0.32	14 ± 0.263	99.01
DC_9		3.7±0.277	3.70±0.033	0.47	99.96±0.77	13±0.76	57.77±0.55	9 ± 0.413	99.83

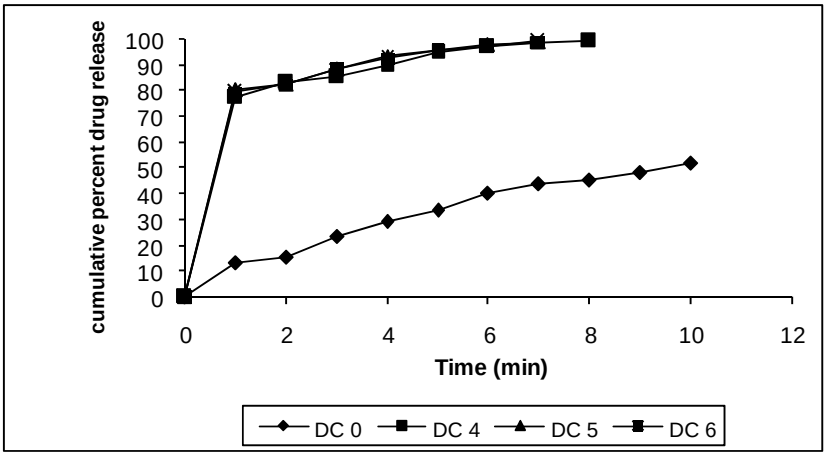

Fig. 2: **Comparative dissolution profile of Amitriptyline hydrochloride tablets containing different superdisintegrants DC_0, DC_4, DC_5 & DC_6**

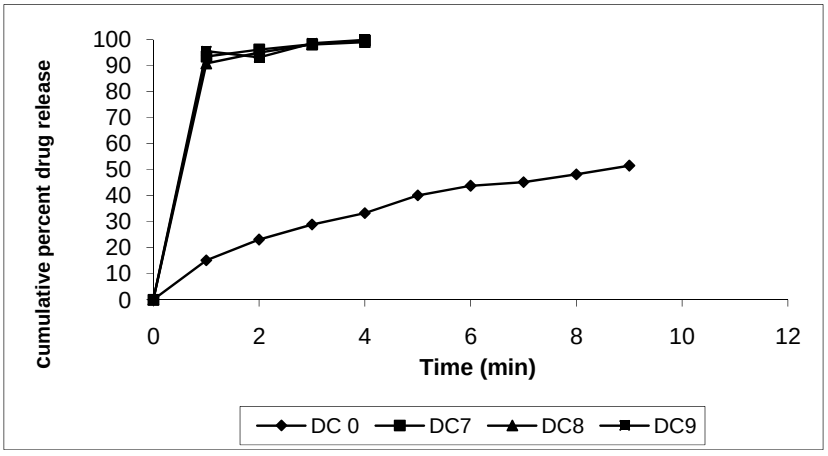

Fig. 3: Comparative dissolution profile of Amitriptyline hydrochloride tablets containing different superdisintegrants DC_0, DC_7, DC_8 & DC_9

RESULTS AND DISCUSSION

Nine formulations of Amitriptyline Hydrochloride were prepared with concentration of three superdisintegrants: Sodium Starch glycolate, Croscarmellose sodium, Crospovidone and microcrystalline cellulose were used as a direct compressible vehicle. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using direct compression technique. Bulk density was found in the range of 0.427-0.478 g/cm^3 and the tapped density between 0.508-0.567 g/cm^3 (Table II). Using these two density data Hausner's ratio and compressibility index was calculated. The powder blend of all the formulations had Hausner's ratio of 1.2 or less indicating good flowability. The compressibility index was found between 13.03 and 17.68 % and the compressibility - flowability correlation data[12] indicated a fairly good flowability of the blend. The good flowability of blend was also evidenced with angle of repose (range of 23 – 27 ^{0}), which is below 40 ^{0} indicating good flowability.

Tablets were prepared using direct compression technique. Thickness of the tablets was measured by screw gauge by picking tablets randomly from all the batches. The mean thickness was (n=3) almost uniform in all the formulations and values ranged from 3.70 ± 0.013 mm to 3.73 ± 0.040 mm. The standard deviation values indicated that all the formulations were within the range. 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 98.54 – 101.23 % (acceptable limit) and the hardness of the tablets between 3.0 – 4.0 kg/cm^2 (Table III). Friability of the tablets was found below 1 % indicating a good mechanical resistance of tablets. Wetting time is closely related to the inner structure of the tablet. This showed that wetting process was very rapid in almost all formulations. This may be due to ability of swelling and also capacity of water absorption and causes swelling. The *in-vitro* dispersion time is measured by the time taken to undergo uniform dispersion. Rapid dispersion within few minutes was observed in all the formulations. The results showed that tablet containing Crospovidone having low dispersion time as compare to other superdisintegrants. The dispersion time increases as the concentration of superdisintegrants increases. The in vitro disintegration time of the tablets was found to be less than 60 sec. All the formulations showed enhanced dissolution rate as compared to Amitriptyline hydrochloride with out superdisintegrants. The maximum increase in the dissolution rate was observed with crospovidone amongst the three superdisintegrants. The order of enhancement of the dissolution rate with various superdisintegrants found to be Crospovidone >Cross carmellose>Sodium starch glycolate.

Stability study shows no significant changes in values during one-month study.

CONCLUSION

It was concluded that mouth-dissolving tablets of Amitriptyline hydrochloride can be successfully prepared by direct compression technique using selected superdisintegrants for the better patient compliance and effective therapy.

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