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Research Article

Development and evaluation of haloperidol orally disintegrating tablets using novel co–processed superdisintegrants

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ABSTRACT

Orally disintegrating tablets are gaining popularity over conventional tablets due to their convenience in administration and suitability for patients. In the present work, fast dissolving tablets of Haloperidol were prepared using novel co-processed superdisintegrants consisting of crospovidone and primogel in the different ratios (1:1, 1:2 & 1:3) by direct compression technique. Evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content, disintegration time and in-vitro dissolution profile and found satisfactory. Among all, the formulation CP1 containing 4%w/w superdisintegrant (1:1 mixture of crospovidone and primogel) was considered to be best formulation, which release up to 99.21% in 12 min. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Keywords: Haloperidol; Orally disintegrating tablets; Co-processed superdisintegrants; Dissolution rate.

INTRODUCTION

Orally disintegrating tablets are gaining popularity over conventional tablets due to their convience in administration and suitability for patients (Kuchekar BS, 2003). Recently, useful dosage forms, such as rapidly disintegrating or dissolving tablets, have been developed and applied clinically. When such tablets are placed in the oral cavity, saliva quickly penetrates into the pores to cause rapid tablet disintegration (Koizumi K, 1997, Makino T, 1998).

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. The various dosage forms administered orally, the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids, and because it is more tamperproof than capsules. The bioavailability of drug is dependent on in vivo disintegration, dissolution, and various physiological factors. In recent years, scientists have focused their attention on the formulation of quickly disintegrating tablets. The task of developing rapidly disintegrating tablets is accomplished by using a suitable diluents and superdisintegrant (Mukesh CG, 2007).

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Coprocessing is defined as combining two or more established excipients by an appropriate process (Gohel MC, 2005). Coprocessing of Excipient could lead to formation of excipients with superior properties compared with the simple physical mixture of their components or with individual components. A large number of coprocessed diluents are commercially available. The representative examples are Ludipress, Cellactose, and Starlac (Gohel MC, 2005, Nachegari SK, 2004).

Haloperidol is widely used neuroleptic which is a butyrophenone. Chemically it is 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one. Though well absorbed after oral dosing, there is a first pass metabolism leading to a reduced bioavailability of the drug (60-70%) (Hardman JG, 2001). Therefore, the present investigation is concerned with the development orally disintegrating tablet of haloperidol and to investigate the effect of co–processed superdisintegrants on the release profile of the drug in the tablets.

Various techniques can be used to formulate orally disintegrating tablets. Direct compression one of the techniques requires the incorporation of a superdisintegrants into the formulation the use or highly water soluble excipients to achieve fast tablet disintegration (Indurwade NH, 2002). Direct compression dose not require the use of water or heat during the formulation procedure and is the ideal method for moisture and heat-labile medications.

The aim of purpose work was to formulate and characterization of haloperidol orally disintegrating tablets using novel co-processed superdisintegrants for rapid

Table 1: Formulation of haloperidol orally disintegrating tablets

Ingredients	FORMULATION CODE						
	CP0	PM1	PM2	PM3	CP1	CP2	CP3
Haloperidol	10	10	10	10	10	10	10
Superdisintegrants (CP+ primogel)	--	6	6	6	6	6	6
Mannitol	104	98	98	98	98	98	98
Microcrystalline cellulose	30	30	30	30	30	30	30
Aspartame	3	3	3	3	3	3	3
Sodium stearyl fumarate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium Sterate	1.5	1.5	1.5	1.5	1.5	1.5	1.5

PM - Physical Mixture of crospovidone and primogel in different ratios (1:1, 1:2, 1:3), CP- Co-processed Superdisintegrants of crospovidone and primogel in different ratios (1:1, 1:2, 1:3), CP0 - Control formulation (without superdisintegrants).

dissolution of drug and absorption, which may produce the rapid onset of action.

MATERIALS AND METHODS

Materials

Haloperidol was obtained from Stadmed Pvt. Ltd. Kolkata, India. Crospovidone, primogel and Microcrystalline cellulose were gift sample from Signet Chemical Corporation, Mumbai, India. All chemicals and reagents used were of analytical grade.

Methods

Preparation of co-processed superdisintegrants (Mukesh CG, 2007, Kuchekar BS, 2004**)**

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone and primogel (in the ratio of 1:1, 1:2 & 1:3) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was granulated through # 44 mesh sieve. The wet granules were dried in a hot air oven at 60º C for 20 minutes. The dried granules were sifted through # 44-mesh sieve and stored in airtight container till further use.

Preparation of orally disintegrating tablets by direct compression method (Bi YX, 1999**)**

Orally disintegrating tablets of haloperidol were prepared by direct compression. Compositions of various formulations are shown in Table 1. All the ingredients (except granular directly compressible excipients) were passed through # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 150mg using 8mm round flat punches using a Rimek tablet press machine. The total weight of the formulation was maintained 150mg.

Pre compression parameters

All the batches of coprocessed superdisintegrants or blend were evaluated for various parameters like angle of repose, bulk density, tapped density, carr's compressibility index and hausner ratio and results reported in Table 2 and Table 3.

Angle of repose

Angle of repose was determined using fixed funnel method. The coprocessed superdisintegrants or blend was poured through a 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 formula (Rockville MD, 2007).

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

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

Bulk Density

Apparent bulk density (ρb) was determined by pouring coprocessed superdisintegrants or blend into a graduated cylinder. The bulk volume (Vb) and weight of powder (M) was determined. The bulk density was calculated using the formula (Rockville MD, 2007, Liberman HA, 2005).

$$\rho b = M/Vb$$

Tapped Density

The measuring cylinder containing known mass of coprocessed superdisintegrants or blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight (M) of the coprocessed or blend as measured. The tapped density (ρt) was calculated using the formula (Rockville MD, 2007).

$$\rho t = M/Vt$$

Carr's compressibility index

The simplex way of measurement of the free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index of the granules was determined by Carr's compressibility index (I) which is calculated by using the following formula (Rockville MD, 2007).

Table 2: Pre-compression Parameters of Co-processed superdisintegrants and Physical Mixture of Superdisintegrants

Formulation code	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Compressibility index (%)
PM1	29.32	0.38	0.45	1.184	15.555
PM2	27.56	0.37	0.44	1.189	15.909
PM3	30.36	0.40	0.47	1.175	14.893
CP1	27.21	0.35	0.41	1.171	14.634
CP2	30.11	0.34	0.40	1.176	15.000
CP3	28.17	0.36	0.42	1.166	14.285

Table 3: Pre-compression Parameters 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 (%)
CP0	30.13	0.56	0.68	1.214	17.647
PM1	29.25	0.58	0.67	1.155	13.432
PM2	30.12	0.58	0.68	1.172	14.705
PM3	28.36	0.59	0.68	1.152	13.235
CP1	28.21	0.58	0.66	1.137	12.121
CP2	29.39	0.56	0.67	1.196	16.417
CP3	28.37	0.57	0.66	1.157	13.636

$$I = \{(Vo - Vt)/ Vo\} X 100$$

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula (Rockville MD, 2007).

$$\text{Hausner ratio} = \rho t/\rho b$$

Where ρt is tapped density and ρb is bulk density. Lower hausner ratio (< 1.25) indicate better flow properties than higher ones (>1.25).

Post compression parameters

All the batches of tablets were evaluated for various parameters like weight variation, friability, hardness, drug content, disintegration and dissolution and results reported in Table 4.

Weight variation test

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighting balance. The average weight of one tablet was determined from the collective weight (Rockville MD, 2007).

Hardness test

The hardness of the tablet was determined using Monsanto Hardness Tester (Rockville MD, 2007).

Friability test

Six tablets from each batch were examined for friability using Roche Fribilator (Tropical Equipment Pvt. Ltd. Mumbai, India) and the equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated (Rockville MD, 2007).

$$\%\text{Friability} = (\text{Loss in weight}/\text{Initial weight}) \times 100$$

Water absorption ratio

A piece of tissue paper folded twice was kept in a Petri dish (internal diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighted. Water absorption ratio, R was determined according to the following equation (Bandari S, 2008).

$$R = 100 (Wa - Wb)/Wb$$

Where Wb and Wb are the weight before and after water absorption, respectively.

Wetting time

A piece of tissue paper folded twice was kept in a Petri dish (inter diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then recorded (Mukesh P, 2009, Bandari S, 2008).

Content uniformity test

Five tablets were weighed and powdered, 10 mg of equivalent of haloperidol was weighed and dissolved in suitable quantity of methanol, the solution was filtered suitably diluted and the drug content was analyzed using UV spectrometer at 248 nm.

In vitro disintegration time

The disintegration test was performed using an USP disintegration apparatus, with distilled water at

Table 4: Evaluation data of the prepared haloperidol orally disintegrating tablets

Formulation code	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Disintegration time (sec.)	Water absorption ratio (%)	Wetting time (sec.)	% Drug release
CP0	3.69±0.02	0.35±0.03	97.22	110±0.31	63.49±0.54	121.21±1.34	31.56
PM1	3.93±0.12	0.34±0.05	98.83	39±0.46	59.31±0.25	27.31±1.23	84.15
PM2	3.71±0.31	0.36±0.07	99.29	44±0.52	61.26±0.41	31.26±0.32	82.39
PM3	3.51±0.25	0.35±0.02	97.79	41±0.62	60.41±0.45	29.62±0.37	83.24
CP1	3.36±0.13	0.26±0.03	99.21	15±0.26	59.26±0.39	17.21±1.42	99.21
CP2	3.59±0.23	0.29±0.06	99.23	29±0.54	60.36±0.52	24.31±1.11	97.91
CP3	3.72±0.37	0.28±0.04	98.91	26±0.59	58.24±0.36	26.32±1.25	96.86

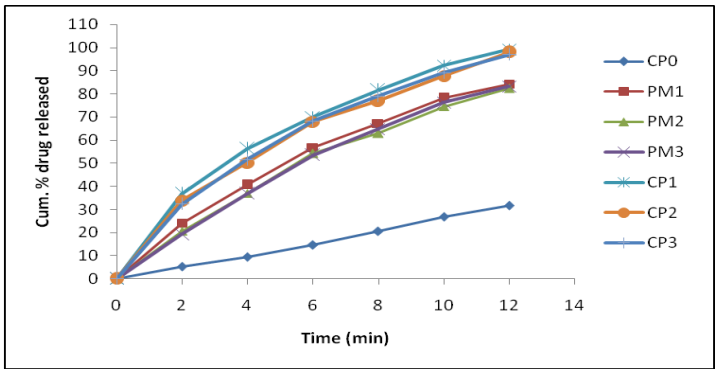

Figure 1: *In Vitro* release profile of haloperidol orally disintegrating tablets

24±0.5°C. The time reported to obtain complete disintegration of six tablets were recorded and average was reported (Rockville MD, 2007).

In vitro dissolution testing

Dissolution study was conducted for all the formulation using USP type-II apparatus (Electolab, Mumbai, India.). The dissolution test was performed using 900 ml of phosphate buffer (PH 6.8) was taken as the dissolution medium at 50 rpm and 37°C±0.5°C. Ten milliliters of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. (Rockville MD, 2007) The samples were analyzed spectrophotometrically at 248 nm.

RESULTS AND DISCUSSION

Co-processed superdisintegrants were prepared by solvent evaporation using crospovidone and primogel in different ratios (1:1, 1:2. & 1:3). The coprocessed superdisintegrants were evaluated for their flow and compression properties in comparison with physical mixture of superdisintegrants are shown in Table 2. The angle of repose of co-processed superdisintegrants and physical mixture of superdisintegrants was in the range of 27.21-30.36 indicating the good flow properties. Bulk density was found in the range of 0.34-0.40g/cm^3 and the tapped density between 0.40-0.47g/cm^3. Hausner's factor values which were in the range of 1.166-1.189 indicating good flowability. The compressibility index was found between 14.285-15.909. Hence the prepared co-processed superdisintegrants and physical mixture of superdisintegrants possessed good flow properties.

Orally disintegrating tablet of haloperidol was prepared using above co-processed superdisintegrants and physical mixture of superdisintegrants. The formulated powder blend evaluated and results are shown in Table 3. The angle of repose of powder blend was in the range of 28.21-30.13 indicating the good flow properties. Bulk density was found in the range of 0.56-0.59g/cm^3 and the tapped density between 0.66-0.68g/cm^3. The powder blends of all the formulations had Hausner's factor values which were in the range of 1.137-1.214 indicating good flowability. The compressibility index was found between 12.121-17.647. Hence the prepared blends possessed good flow properties and these can be used for tablet manufacture.

All batches of the tablets were preliminarily evaluated for various physical parameters such as hardness, friability, drug content, wetting time, water absorption ratio, disintegration and dissolution which were reported in Table 4. All above properties and value were near to boundary of standard limit. All the tablets maintained hardness in the range 3.36–3.93kg/cm^2. The loss in total weight of the tablets due to friability was in the range of 0.26-0.36%. The drug content in different formulation was highly uniform and in the range of 97.22-99.29%. The result in vitro disintegration were within the prescribe limit and comply with the criteria for orally disintegrating tablets, the value were with 15-44 sec indicating the efficacy of both the physical mixture of superdisintegrants as well as co-

processed superdisintegrant, when compared to control formulation (CP0) which shows 110 sec. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water. Wetting time is used as an indicator of the ease of tablet disintegration and found to be 17.21-31.26 sec. Water absorption ratio ranged from 58.24-61.26 and compared to CP0 which shows 121.21 sec and 63.49%. In-vitro dissolution studies on the promising formulation CP1, PM1 is formulation containing physical mixture of superdisintegrants in 1:1 ratio, and CP0 control formulations were carried out in pH 6.8 phosphate buffers. The cumulative % of drug release increased in 12 min are shown in Table 4 and Figure 1. This data reveals that among all the formulation CP1 shows nearly faster drug release. The formulations CP1 99.21 % of drug released in 12 min and CP0 control formulations 31.56 % of drug released in 12 min.

CONCLUSION

It was concluded that coprocessed superdisintegrant consisting of crospovidone and primogel exhibited good flow and compression characteristics. Haloperidol orally disintegrating tablet containing coprocessed superdisintegrant exhibited quick disintegration and improved drug dissolution. It was observed that to further increase the drug release from orally disintegrating tablets, solubility enhancement of haloperidol required and is under investigation.

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