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Bio Physics

Elixir Bio Phys. 78 (2015) 29790-29793

ISSN: 2229-712X

Formulation, evaluation & optimization of orally disintegrating tablet of cinnarizine using sublimation method

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ARTICLE INFO

Article history:

Received: 22 June 2011;

Received in revised form:

28 December 2014;

Accepted: 15 January 2015;

Keywords

Orally disintegrating tablet,

Disintegrating tablet,

Wetting time.

ABSTRACT

The present investigation was to develop and characterize orally disintegrating tablets (ODT) of cinnarizine using sublimation technique. ODT of cinnarizine were prepared using different subliming agents like camphor, thymol and different concentrations of menthol using direct compression method. Compatibility study between drug and excipients was done by DSC techniques, found compatible. The porous sublimed and non sublimed granular blends were examined for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, taste evaluation, mouth feel, wetting time, *in vitro* disintegration time, and *in vitro* dissolution studies. Tablets with menthol at 10.0% concentration have shown desired disintegrating features, i.e., within 20s. The dissolution study revealed that menthol at a concentration of 10.0 %W/W of the dosage form weight was able to improve the release of cinnarizine. The study concludes that sublimation technique is a useful to enhance the disintegrating and dissolution rate of poorly water-soluble drug like Cinnarizine.

Introduction

Paediatric and geriatric patients may have difficulties in swallowing or chewing pharmaceutical dosage forms for oral administration.

Tablets that rapidly dissolve upon contact with saliva in the buccal cavity could present a solution to those problems and so there is an increased interest in characterize orally disintegrating tablets dosage forms for buccal, sublingual and oral administration.

Orally dissolving/disintegrating tablet are perfect fit for these patients as these immediately release the active drug when placed on tongue by rapid disintegration/ dispersion, followed by dissolution of drug (Mishra et al, 2004 and Corveleyn S and Remon, 1998). ODT dosage form disintegrate in patient's mouth within few seconds without need of water, or chewing, providing best remedy for the patient suffering from dysphasia.

Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down the stomach. In such cases the bioavailability is greater than those observed for conventional dosage form.

The approach used in developing ODT are either use high percentage of super disintegrating agent or maximizing pore structure of the tablets. Freeze-drying (Corveleyn S and Remon, 1997 and 2000) and vacuum-drying (Heinemann and Rothe, 1975, Knistch et al 1979 and Roser and Blair 1998) 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.

Therefore, it was decided to adopt the vacuum-drying technique in the present investigation.

Vacuum drying was adopted after addition of a subliming agent to increase porosity and minimize disintegrating time of formulations. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly.

Experimental

Materials

Cinnarizine purchased from Rakshit Pharma (Mumbai, India), aspartame, peppermint oil, crospovidone, croscarmellose sodium, sodium starch glycolate, and sodium stearyl fumarate were obtained from (Welable healthcare, Mehsana, India). Colloidal silicon dioxide [Aerosil®] was purchased from Span Pharma Private Limited (Hyderabad, India); and nigrosine RM 247, a water soluble dye, was purchased from Hi Media Laboratories Private Limited. Camphor, menthol, and thymol were obtained S.D.Fine chemicals (Mumbai, India).

Method

The tablets were prepared by direct compression process using camphor, thymol, and different proportions of menthol. The raw materials were passed through a 100-mesh screen prior to mixing. The drug and other ingredients were mixed together and bounded with alcoholic solution of PVP (10%w/v) to form a coherent mass. The wet mass was granulated using sieve no. 10 and regranulated after drying through sieve no. 20. Granules of batch D4 without any subliming agents were dried in a tray dryer at 60^0C for 30 min. Other granular formulations (D1, D2 and D3) contained a subliming agent and were dried at room temperature, 20-22 ^{0}C for 8hrs. The final moisture content of the granules was found to be between 1-2%, which was determined using an IR moisture balance (Sartorius). During vacuum drying the menthol, camphor, and thymol were sublimed with the formation of a porous structure on the surface of the granules. Dried granular blends were evaluated for precompression properties. After evaluation of granule blend were then blended with talc, magnesium stearate, aerosil and compressed into tablets using flat face round tooling on a Rimek-I rotary tablet machine (Karnavati Eng. Pvt. Ltd, Ahmedabad, India). Sublimation was performed from tablets instead of granules at 60º C in selected batch (D6).

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Formulation of orally disintegrating tablets of cinnarizine

The orodispersible tablets of cinnarizine were prepared using the subliming agents viz; camphor, menthol and thymol. Crospovidone used as superdisintegrant, mannitol as a diluent, aspartame as sweetening agent, alcoholic solution of PVP (10%w/v) as binder and magnesium stearate with talc as a flow promoter. The composition was shown in Table 1.

All batches contained 10% polyvinylpyrrolidone in ethyl alcohol as a binder. Camphor/menthol/thymol was sublimed from granules in Batches D1 to D5 and Batch D6 sublimated after compression.

The granules required 3 hours of vacuum drying, whereas the tablets required 12 hours of vacuum drying.

Evaluation of Granule Blend

Pre-compression parameters

Angle of repose

Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, h, was obtained. Diameter of heap, D, was measured. The angle of repose, Ɵ, was calculated by formula.

$$\Theta = \tan^{-1}(h / r) \quad \text{……..(1)}$$

Where, Ɵ is the angle of repose, h is the height in cm and r is the radius.

Bulk Density

Apparent bulk density was determined by pouring presieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/ml and is given by

$$Db = M / V0 \quad \text{……..(2)}$$

Where, M is the mass of powder and V0 is the Bulk volume of the powder.

Tapped density

It was determined by placing a graduated cylinder, containing a known mass of drug- excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by

$$Dt = M / Vt \quad \text{……..(3)}$$

Where, M is the mass of powder and Vt is the tapped volume of the powder.

Powder flow properties

Carr's Index (I):

$$I = Dt - Db / Dt \quad \text{……..…….(4)}$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Hausner ratio (H)

$$H = Dt / Db \quad \text{…….(5)}$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Evaluation of tablet

General appearance

Five tablets from different batches were randomly selected and organoleptic properties such as colour, odour, shape, were evaluated.

Weight Variation

Twenty tablets from were randomly selected from each formulation and weighed using a Shimadzu digital balance. The mean SD values were calculated. [8]

Thickness Variation

Ten tablets from each formulation were taken randomly and their thickness was measured with a screw gauge micrometer. The mean SD values were calculated. (Indian Pharmacopoeia, 1996)

Hardness and Friability

Hardness or crushing strength of the tested orally disintegrating tablet formulations was measured using the dial hardness tester (Shivani Scientific India). The friability of a sample of 20 orally disintegrating tablets was measured utilizing a USP-type Roche friabilator (Camp-bell Electronics, Mumbai, India). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, reweighed, and percentage weight loss (friability) was calculated. (Lachman et al,m 1991)

$$\%Friability = \frac{W_0 - W}{W_0} \times 100 \quad \text{……..(6)}$$

W○= initial weight of 20 tablets, W= weight of 20 tablets after 100 revolutions.

Wetting Time

Five circular tissue papers were placed in a Petri dish of 10 cm diameter. Ten millilitres of water containing 0.5% nigrosine, a water-soluble dye, was added to the petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the petri dish at 25^{o}C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicate of six. Wetting time was recorded using a stopwatch. (Battu et al., 2007)

In Vitro Disintegration Time

In vitro disintegration time (DT) of the orally disintegrating tablets was determined following the procedure described by Gohel et al. 10 mL of water at 25^{o}C was placed in a petri dish of 10 cm diameter. The tablet was then carefully positioned in the centre of the petri dish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in replicates of six tablet (n=6) and mean SD values were recorded. (British pharmacopoeia, 2005)

***In Vitro* Release Studies**

In Vitro release studies of Cinnarizine from different formulations were performed according to USP XVIII apparatus II, paddle method (Electrolab, Mumbai, India). Paddle speed was maintained at 50 rpm and 900 mL of 0.1N HCl was used as the dissolution medium.

Samples (10 mL) were collected at predetermined time intervals (1, 2, 3, 5, 10 and 15, min) and replaced with equal volume of fresh medium, filtered through a 0.45 µm filter and analyzed with a UV—Visible spectrophotometer (Shimadzu, Japan) at λ= 254 nm. Drug concentration was calculated from a standard calibration plot and expressed as cumulative % drug dissolved. The release studies were performed in replicates of six. (British pharmacopoeia, 2005)

Assay

Orally disintegrating tablet formulations were assayed for drug content.

Ten tablets were randomly selected from each formulation and pulverized to a fine powder. Weighed aliquots containing an amount of powder equivalent to a single dose were taken in triplicate and assayed for the drug content utilizing a UV-VIS spectrophotometer (UV/Visible double beam Spectrophotometer, Shimadzu, Japan) at a wavelength of 254 nm. (Sunada et al. 1996)

Differential Scanning Calorimetric

DSC was used to characterize the thermal properties of the drug, bulking agent, physical mixture, and the compressed orally disintegrating tablet formulation. The DSC thermo grams were recorded using a differential scanning calorimeter (DSC-Shimadzu 60, Japan). Samples were analyzed in crimped aluminum pan and heated from 50–300°C at a linear heating rate of 10°C min^{-1}.

Results and Discussion

Evaluation of pre-compression properties

For each designed formulation, blend of drug and excipients was prepared and evaluated for pre-compression properties shown in table 2. Bulk density was found to be between 0.56±0.01 to 0.57±0.03gm/cm3 and tapped density between 0.69±0.01 to 0.72±0.03 gm/cm3 for all formulations. Carr's index was found to be between 17.39±0.04percent to 24.28±0.05 percent. Angle of repose was found to be in the range of 24.2±0.01 to 27.7±0.03. Hausner ratio was found below 1.21±0.05 to 1.35±0.04. All the formulation shows the fair to good flow properties.

Evaluation of post compression properties of orally disintegrating tablet

Tablets were obtained of uniform weight variations as per pharmacopoeial specifications (Table III). All the tablets were exhibit in whiter, odourless, convex in shape with smooth surface with zero defects. The drug content was found in the range of 97.12 – 100.12% and the hardness of the tablets between 2.9 – 3.07 kg/cm^2. Friability of the tablets was found below 1% indicating a sufficient mechanical resistance of tablets. Thickness of the formulations was varied from 2.8±0.03 to 3.1±0.01 mm and diameter from 5.9±0.01 to 6.1±0.03 mm.

***In vitro* disintegrating time and wetting time**

In vitro disintegrating time showed (Figure 1) the formulation D6 containing 10% menthol having least disintegrating time as compared to the other formulation due to the porous structure of the formulation facilitated the wicking action of the crospovidone. The result showed the effect of concentration of menthol on the disintegrating time. The formulation D4 did not having a sublimating agents resulted in higher disintegrating time. The result showed that as the concentration of menthol increases the wetting time of formulation decreased it showed the linear relationship between the concentrations with wetting time.

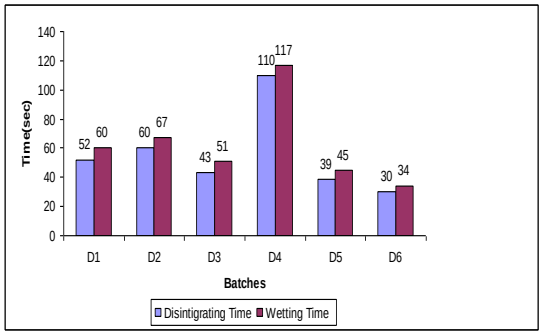

Figure I: comparative profile of *In vitro* disintegrating time and wetting time

***In vitro* drug release**

The *in vitro* dissolution profile indicated faster and maximum drug release from formulation D6 (Figure 2). Formulation D6 prepared by direct sublimation of menthol shown release 78% drug in 5 minutes which is fastest and desire for quick onset of action especially in vertigo. The rapid drug dissolution might be due to easy breakdown of particles due to porous structure formation after sublimation of camphor and rapid absorption of drugs into the dissolution medium, and slope values signify that the release rate follows first order kinetics.

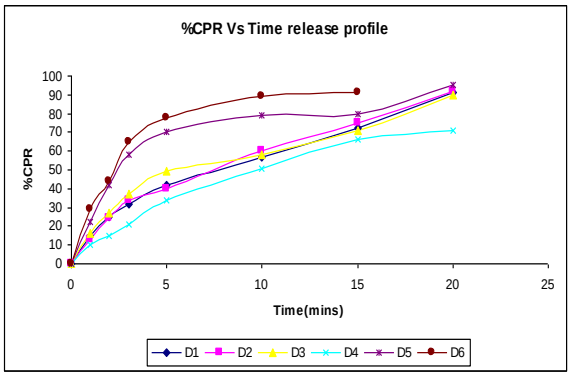

Figure II: Comparative dissolution profile of ODTs

Differential Scanning Calorimentry (DSC)

The DSC analysis of physical mixture of drug and excipients revealed no change in the melting point of cinnarizine in the presence excipients, indicating no modification or interaction between the drug and excipients (Figure 3).

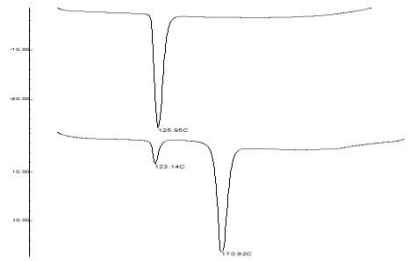

Figure III: DSC study of ODT formulation

Menthol containing tablets exhibited faster disintegration as compared with tablets containing camphor and thymol. Batch D5 containing 10.0 % menthol showed the least disintegrating time. The results shown indicate that concentration dependent disintegration was observed in batches prepared using menthol as a subliming agent. The porous structure is responsible for faster water uptake; hence it facilitates wicking action of crospovidone in bringing about faster disintegration. Tablets with lower friability (≤0.6%) may not break during handling on machines and/or shipping. The use of a sublimation agent resulted in increased friability probably due to increased porosity. It was decided to incorporate aerosil, extra granularly, at a level of 1% to decrease the friability of the tablets (batches D5 and D6). Addition of aerosil resulted in appreciable decrease in friability and marginal decrease in disintegration time. Aerosil helps to restore the bonding properties of the excipients. In the first few attempts (D1 to D5), sublimation of menthol was performed from granules prior to compression into tablets. In Batch D6, sublimation was performed after compression rather than directly from granules. The results shown in figure 1 reveal that sublimation of menthol from tablets resulted in faster disintegration. The compaction process might have caused breakage of porous granules and subsequent reduction in porosity. The low value of wetting time and disintegration time indicate that the porosity of tablets of batch D6 would be greater than batches D1 to D5. The granules required 3 hours of vacuum drying, whereas the tablets required 12 hours of vacuum drying. The longer drying time was required in the case of tablets probably because of the decreased surface area and porosity.

Conclusion

The prepared tablet gives benefit in terms of patient compliance, low dosing, and rapid onset of action, increased bio-availability, low side effect and good stability.

Acknowledgements

The authors would like to thank Welable healthcare, Mehsana, India for providing a gift sample.

Competing Interests

The authors declare no conflict of interest

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Table I: Composition of Cinnarizine Tablets (mg/tablet)

Ingredient	D1	D2	D3	D4	D5	D6
Cinnarizine	25	25	25	25	25	25
Camphor	5	-	-	-	-	-
Thymol	-	5	-	-	-	-
Menthol	-	-	5	0	10	10
Cross povidone	4	4	4	4	4	4
Aspartame	1	1	1	1	1	1
Peppermint flavour	1	1	1	1	1	1
Aerosil					1	1
Talc	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1
Mannitol q.s. to	100	100	100	100	100	100

Table II: Evaluation of pre-compression properties

Code	Angle of repose(θ)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Carr's index (%)	Hausner ratio (HR)
D1	27.0±0.03	0.56±0.02	0.70±0.01	20.0±0.04	1.25±0.01
D2	26.5±0.02	0.55±0.03	0.72±0.03	24.28±0.05	1.30±0.04
D3	27.0±0.01	0.56±0.02	0.69±0.01	18.84±0.05	1.23±0.03
D4	24.2±0.03	0.57±0.03	0.69±0.02	17.39±0.04	1.21±0.05
D5	26.2±0.02	0.57±0.02	0.71±0.02	19.71±0.03	1.24±0.04
D6	24.2±0.01	0.56±0.01	0.71±0.03	21.12±0.04	1.26±0.05

* In all evaluation n=3

Table III: Evaluation of post compression properties of orally disintegrating tablet

Code	Diameter (mm) (n=5)	Thickness (mm) (n=5)	Hardness (kg/cm^2) (n=5)	Friability (%) (n=20)	Drug Content (%)(n=10)	Weight variation (mg) (n=10)
D1	6.0±0.01	3.1±0.01	3.0±0.02	0.31±0.01	98.12±0.04	99±0.01
D2	6.1±0.03	3.1±0.02	3.0±0.04	0.44±0.01	98.56±0.02	98±0.03
D3	6.1±0.01	3.0±0.02	3.0±0.07	0.51±0.03	100.12±0.03	101±0.02
D4	5.9±0.01	2.9±0.02	3.0±0.05	0.55±0.01	97.12±0.04	98±0.01
D5	6.0±0.02	3.0±0.01	2.9±0.03	0.38±0.05	99.21±0.02	98±0.03
D6	6.0 ±0.01	2.8±0.03	3.0±0.05	0.29±0.01	98.32±0.03	97±0.03

* In all evaluation n=3