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Research article

DEVELOPMENT AND CHARACTERIZATION OF MELT-IN-MOUTH TABLETS OF HALOPERIDOL BY SUBLIMATION TECHNIQUE

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ABSTRACT

The purpose of this investigation was to develop fast dissolving tablets of haloperidol using camphor as a subliming agent. Orodispersible tablets of haloperidol were prepared by wet granulation technique using camphor as subliming agent and sodium starch glycolate together with crosscarmellose sodium as superdisintegrants. Camphor was sublimed from the granules by exposing the granules to vacuum. The porous granules were then compressed in to tablets. Alternatively, tablets were first prepared and later exposed to vacuum. The formulations were evaluated for weight variation, hardness, friability, drug content, wetting time, *in vitro* and *in-vivo* dispersion, mouth feel and *in vitro* dissolution. All the formulations showed low weight variation with dispersion time less than 45 seconds and rapid *in vitro* dissolution. Sublimation of camphor from tablets resulted in superior tablets as compared with the tablets prepared from granules that were exposed to vacuum. The results revealed that the tablets containing subliming agent had a good dissolution profile. The drug content of all the formulations was within the acceptable limits of the United States Pharmacopoeia XXVII. The optimized formulation showed good release profile with maximum drug being released at all time intervals. It was concluded that fast dissolving tablets with improved haloperidol dissolution could be prepared by sublimation of tablets containing suitable subliming agent. This work helped in understanding the effect of formulation processing variables especially the subliming agent on the drug release profile. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Keywords: Mouth dissolving tablet, Haloperidol, Subliming agent, super disintegrant, Camphor.

INTRODUCTION

Difficulties with and resistance to tablet-taking are common in all patient groups and can exacerbate compliance problems and undermine treatment efficacy. Physical problems with

swallowing (dysphagia) can occur at any age but are particularly prevalent in the elderly and those with dementia, whereas refusal to swallow is often encountered in geriatric, pediatric, and psychiatric patients. Nonetheless, oral dosing remains the preferred mode of administration for many types of medication due to its simplicity, versatility, convenience, and patient acceptability. In recent years, rapid-dissolving oral drug formulations have been developed to overcome problems related to swallowing difficulties[1].

A melt-in-mouth tablets (MMT) can be defined as an oral solid dosage form which when placed on tongue, disintegrates rapidly, releasing the drug, which dissolves or disperses in the saliva and then swallowed. Some drugs are absorbed from the mouth, pharynx, and esophagus as the saliva passes down in to the stomach.

Poor compliance is a major concern in the treatment of depression. Between 30 and 68% of depressed patients, discontinue treatment within one month significantly increasing their risk of relapse. Poor compliance is promoted by many factors including aversion to antidepressant therapy. This aversion is mainly caused by the stigma associated with depression and drug related effects, including the slow onset of action observed with conventional antidepressants.

The problem of patient compliance in the administration of oral antipsychotic drugs can be overcome by development of an appropriate dosage form. MMT are best suited and have gained popularity in the recent years in oral antipsychotic drug therapy.

The fundamental principle used in the development of the fast-dissolving tablet is to maximize its pore structure. Researchers have evaluated spray dried materials[2] and plastic materials[3] for development of such tablets.Vacuum-drying[4-10] and freeze-drying[11-13] techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and yields a fragile and hygroscopic product. Therefore, a vacuum-drying technique was adopted in the present investigation after addition of a subliming agent to increase porosity of the tablets. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly.

Literature survey revealed haloperidol is a promising drug candidate to formulate MMT[14] therefore an attempt has been made to develop and characterize its feasibility for MMT. 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 haloperidol is well absorbed after oral dosing, there is a first pass metabolism leading to a reduced bioavailability of the drug (60-70%). Therefore, the present investigation is concerned with the development MMT of haloperidol and to investigate the effect of subliming agent on the release profile of the drug in the tablets.

MATERIALS AND METHODS

Materials

Haloperidol (Sun Pharmaceuticals Ltd, Mumbai, India), croscarmellose sodium, sodium starch glycolate, and microcrystalline cellulose (Maple Biotech Pvt Ltd., Pune, India), aspartame (Ranbaxy, New Delhi, India). Camphor, mannitol, polyvinyl pyrollidone (PVP), talc and magnesium stearate were purchased from S.D. Fine Chemicals, Mumbai, India.

Method

Formulation of mouth dissolving tablets of haloperidol

The orodispersible tablets of haloperidol were prepared using the subliming agent, camphor, sodium starch glycolate and crosscarmellose sodium as super disintegrates, 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 of the each batch shown in Table 1.

The raw materials were passed through a 100-mesh screen prior to mixing. The drug and other ingredients were mixed

Table 1: Composition of different batches of mouth dissolving tablets of haloperidol

Ingredients*	F1	F2	F3	F4	F5	F6
Haloperidol	10	10	10	10	10	10
Camphor	--	--	7.5	7.5	15	15
Aspartame	2.5	2.5	2.5	2.5	2.5	2.5
Crosscarmellose sodium	--	15	--	15	---	15
Sodium starch glycolate	15	--	15	--	15	---
Colloidal silicon dioxide	--	--	--	--	2.5	2.5
Mannitol q.s.	150	150	150	150	150	150

*All the quantities expressed in mg. All batches contained 10% polyvinylpyrrolidone in ethyl alcohol as a binder and 2% talc and 1% magnesium stearate. Camphor was sublimed from granules in Batches F1 to F5 and from tablets in Batch F6.

together, and a sufficient quantity of alcoholic solution of PVP (10%w/v) was added and mixed to form a coherent mass. The wet mass was granulated using sieve no. 12 and regranulated after drying through sieve no. 16. Granules of the formulations containing either of the superdisintegrants but without camphor (F1 or F2) were dried in a tray dryer (Tempo instruments and equipments, Mumbai) at 60^0C for 30 min. resulting in localized drying.

Other granular formulations (F3 to F5) 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. During drying, the camphor sublimed with the formation of a porous structure on the surface of the tablet. The dried granules were then blended with talc, magnesium stearate and compressed into tablets using flat face round tooling on a Rimek-I rotary tablet machine (Karnavati Eng. Pvt. Ltd, Ahmedabad). Sublimation was performed from tablets instead of granules at 60º C in selected batch (F6).

Evaluation of formulated tablets

Hardness [15]

The crushing strength of the tablets was measured using a Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India). Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability[15]

Ten tablets were weighed and placed in a Roche friabilator (Electrolab, India) .Twenty preweighed tablets were rotated at 25 rpm for 4 min. The tablets were then dedusted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets was measured as per the following formula,

Percentage friability =

$$\frac{\text{Initial weight - Final weight} \quad \text{x}\,100}{\text{Initial weight}}$$

Weight variation

Randomly, twenty tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±10.5% (USPXX).

Drug content

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 10 mg of haloperidol was dissolved in 100 ml of pH 6.8 phosphate buffer, filtered, diluted suitably and

analyzed for drug content at 248 nm using UV-Visible spectrophotometer (UV 1601- Shimadzu, Japan)

***In vitro* dispersion time**[16]

In vitro dispersion time was measured by dropping a tablet in a 10ml measuring cylinder containing 6ml of buffer solution simulating saliva fluid (pH6.8).

Dissolution study[17]

In-vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) [Electrolab (ETC-11L) Tablet Dissolution Tester] at 50 rpm. Phosphate buffer pH 6.8, 900 ml was used as dissolution medium which maintained at 37±0.5°C. Aliquot of dissolution medium (10 ml) was withdrawn at specific time intervals (2 min) and was filtered. The amount of drug dissolved was determined by UV spectrophotometer (Shimadzu, Japan) by measuring the absorbance of the sample at 248.0 nm.

Thickness

Thickness of tablet was determined by using dial caliper (Mitutoya, Model CD-6 CS, Japan).

Wetting time[18]

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (Internal Diameter=9cm) containing 9ml of buffer solution simulating saliva pH 6.8. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted.

RESULTS AND DISCUSSION

Water insoluble diluents such as microcrystalline cellulose and dicalcium phosphate were omitted from the study as they are expected to cause an unacceptable feeling of grittiness in the mouth. Among the soluble diluents, mannitol was selected as a diluent considering its advantages in terms of easy availability and negative heat of dissolution.

Table 2 shows that all the formulated tablets exhibited low weight variation. Addition of a subliming agent had no pronounced effect on hardness and increased friability of the tablets. The wetting time, *in vitro* dispersion time of the tablets were also considerably reduced in tablets containing camphor (Table 2). The drug content of all the formulations was found to be between 97.4 - 99.23% which was within the acceptable limits as per USP XXVII. The batches F3 and F5 were prepared using camphor at different concentrations to study its effect on disintegration time. The sublimation

time (0.5-8 hours) depended on the amount of camphor present initially (0%, 5%, or 10%). Batch F5, containing 10% camphor, showed the least disintegrating time. The results shown in Table 2 indicate that concentration-dependent disintegration was observed in batches prepared using camphor 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. It is worthwhile to note that as the concentration of camphor increased, the wetting decreased. Tablets with lower friability (0.5%) 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 colloidal silicon dioxide, extragranularly, at a level of 1% to decrease the friability of the tablets (batches F5 and F6). Addition of colloidal silicon dioxide resulted in appreciable decrease in friability and marginal decrease in disintegration time. Colloidal silicon dioxide helps to restore the bonding properties of the excipients.

Table 2. Evaluation of physicochemical parameters of mouth dissolving tablets of haloperidol

Formulation	Hardness (kg/cm^2) n = 6	Friability (%) n =10	Drug content (%) n = 4	*In vitro* dispersion time (s)	Wetting time (s)	Weight varriation (mg)	Thickness (mm)
F1	4.8±1.6	0.457	98.23±3.24	150	90±2.5	153±3	2.6± 0.019
F2	4.5±0.42	0.535	99.23± 2..68	140	73±2.0	152±1	2.6±0.07
F3	3.8±1.4	0.583	98. 6±3.23	110	41±1.5	155±2	2.8±0.05
F4	3.5±0.56	0.683	98.47± 1.26	85	31±1.4	154±3	2.6±0.02
F5	4±0.41	0.486	99.1± 2.32	70	22±1.2	149±1	2.5±0.01
F6	3.5±0.63	0.354	97.4±1.32	40	11± 1.3	149±1	2.5±0.05

In the first few attempts (F3-F5), sublimation of camphor was performed from granules prior to compression into tablets. Batches F1 to F5 showed good mechanical integrity, but the disintegration time was a little longer than the arbitrarily chosen value of less than 50 seconds. In Batch F6, sublimation was performed after compression rather than directly from granules. The results shown in Table 2 reveal that sublimation of camphor 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 F6 would be greater than batches F1 to F5. The granules required 4 hours of vacuum drying, whereas the tablets required 8 hours of vacuum drying. The longer drying time was required in the case of tablets probably because of the decreased surface area and porosity.

In vitro release studies were carried out using USP XXIII tablet dissolution test apparatus paddle method at 37±0.5 ^{o}C, taking 900 ml of simulated intestinal fluid (SIF) as dissolution medium. Speed of rotation of the paddle was set at 50 rpm. Aliquots of 10 ml were withdrawn after 2, 4, 6, 8, 10 min and analyzed spectrophotometrically at 248 nm. The *in vitro* dissolution profile (Fig.1) indicated faster and maximum drug release from formulation F6.

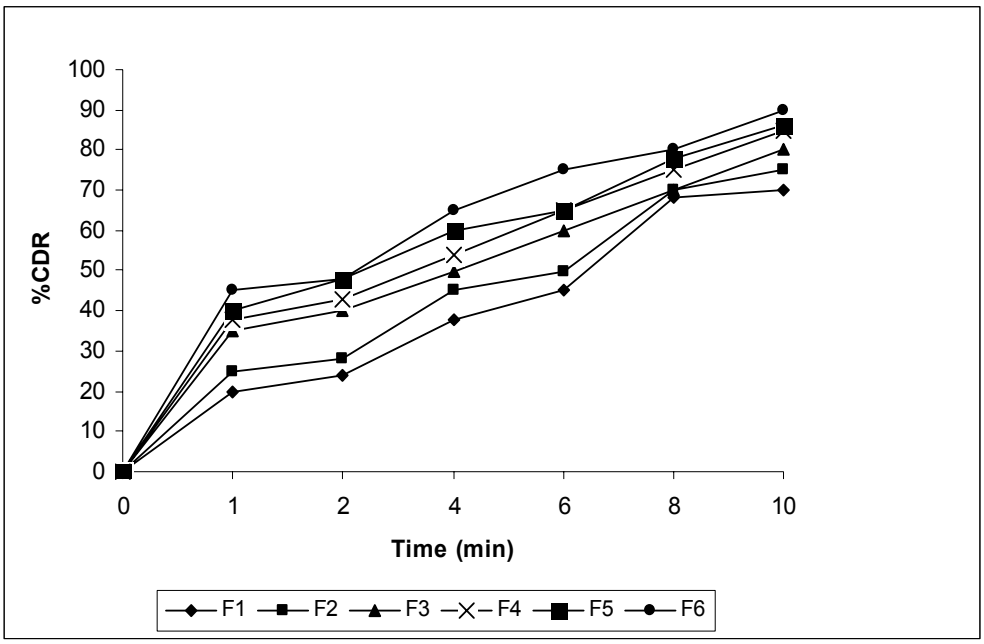

Fig. 1 : *In vitro* release profile of various haloperidol formulations

Formulation F6 prepared by direct sublimation of camphor from final tablets showed release 91.12% drug at the end of 10 min when compared to tablets prepared by sublimation of camphor from granules. 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.

CONCLUSION

Melt-in-mouth tablets (MMT) of haloperidol is successfully prepared by using sublimation method , Undoubtedly the availability of various technologies and the manifold advantages of MMT will surely enhance the patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effect, good stability, and its popularity in the near future. From the study, it can be concluded that sublimation method showed better disintegration and drug release. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the absorption leading to its increased bioavailability. Vacuum-drying technique would be an effective alternative approach compared with the use of more expensive adjuvants in the formulation of mouth dissolving tablets.

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