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Development and Evaluation of Fast Dissolving Tablets of Ondansetron HCl Using Vacuum-Drying Approach

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Abstract

The aim of present investigation was to design 'Traveler Friendly Drug Delivery System' of Ondansetron HCl. Conventional tablet of Ondansetron HCl are not capable of rapid action and water is also needed. Tablets were formulated by direct compression using mannitol, superdisintegrants and camphor, whereby camphor, a subliming material, is removed by sublimation from compressed tablets. Tablets prepared with camphor (20%) and Ac-Di-Sol (6%) exhibited disintegration time (21 s) and friability (0.49%). Further to decrease the disintegration time and friability aerosol (0.5%) is used as lubricant, which gives least disintegration time (19 s) and friability (0.32 %).

Keywords: Vacuum-drying technique, camphor, mannitol, fast dissolving tablet, Ac-Di-Sol.

Introduction

The tablet is the most widely used dosages form because of its convenience in terms of self administration, compactness, and ease of manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient's compliance. We often experience inconvenience in swallowing conventional tablets when water is not available. To overcome this weakness, scientists have developed innovative drug delivery system known as fast dissolving tablets (FDT). This is a novel technology in which the dosages form is placed in the mouth and disintegrate in the oral cavity with in 60 s or less without the need of water. The benefits in terms of patient's compliance, rapid onset of action, increased bioavailability and good suitability makes these tablets popular as a dosages form of choice in the current market (Bi et al., 1996, Change et al. 2000). The basic approach used in the development of the fast dissolving tablet is the use of superdisintegrants. Another approach used in the development of FDT is maximizing pore structure of the tablets. Freeze-drying (Corveleyen et al. 1997). Technique has been tried by researchers to maximize the pore structure of tablet matrix. Freeze- drying method require specific machine for production and packaging and its yield a fragile and hygroscopic material. The compressed tablets prepared with crystalline cellulose and low- substituted hydroxypropylcellulose (L-HPC) rapidly disintegrate in saliva (or a small amount of water) in the mouth of human (Watanabe et al. 1995). However, patients sometimes feel rough texture in their mouth due to incomplete solubilization of this type of tablet in saliva.

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To eliminate the rough texture in the mouth, we attempt to use a water soluble material Mannitol and Ac-Di-Sol instead of crystalline cellulose and L-HPC, in the preparation of this type of tablet. The compressed tablets prepared using mannitol did not rapidly dissolve in saliva since it is difficult for water to penetrate into the tablet due to its low porosity. We therefore investigated a new convenient method of preparing compressed tablets with high porosity, which dissolve rapidly in the mouth, using mannitol and Ac-Di-Sol with a subliming material. We chose camphor as a subliming material since it can be used as a medicinal drug.

Ondansetron HCl is a potent ant emetic drug (Aurora et al. 2005), indicated for the treatment and/or prophylaxis of postoperative or chemotherapy- or radiotherapy-induced emesis and also used in the early onset of alcoholism (Johanson et al. 2000). In general, emesis is preceded with nausea and in such condition it is difficult to administer drug with a glass of water; hence it is beneficial to administer such drugs as FDTs.

Conventional tablets of Ondansetron HCl are incapable of the rapid action required for faster onset of drug effect and immediate relief from nausea and vomiting. Thus, the present study aims to develop FDT of Ondansetron HCl able to rapidly dissolve in saliva and ensure immediate relief from nausea and vomiting, serving dual purpose of increasing patient compliance, particularly for pediatric and geriatric patients, and providing immediate relief.

Material and Methods

Material

Ondansetron HCl was obtained as a gift sample from Cadila Pharmaceutical limited, Ahmedabad. Cross carmellose sodium (Ac-Di-Sol), Crosspovidone, and sodium starch glycolate were received as a gift sample from Torrent Research Center Ahmedabad, Camphor were obtained from a local ayurvedic pharmacy. Mannitol and magnesium stearate were purchased from S.D. Fine Chemicals, Mumbai. All other chemicals used in the study were of analytical reagent grade.

Methods

Selection of camphor concentration for formulation of tablets

Before formulation of tablets, the best concentration of camphor was screened out. Tablets were prepared in various batches containing different concentration of camphor with mannitol (Table 2). Camphor was mixed with mannitol in different concentration, and tablets were compressed. Tablets were subjected to Vacuum-drying using vacuum oven (Erection Engineering Pvt. Ltd., Ahmedabad, India) for 3-4 h at temperature ranging from 50-60 ^{0} C and at a pressure of 300 mm Hg. The concentration of camphor screened was used for the final formulation of tablet (Table 1).

Preparation of tablets

Tablets were prepared by direct compression. All the raw materials were passed through # 60 sieves prior to mixing. Ondansetron HCl, and the superdisintegrants (Cross povidone /Ac-Di-Sol / Sodium starch glycolate), camphor (20%), and mannitol (as much as required) were blended. The powder blend was lubricated with magnesium stearate (1%) and aerosil (0.5%). The powder blend was compressed on a 10 station mini press tablet machine (CPMD 3-10, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad, India.) equipped with 9 mm concave punch. The tablets were dried in a vacuum oven for 4 h at a temperature of 60 ^{0} C and at a pressure of 300 mm Hg.

Table 1. Tablet formulations

Formulation	S1	S2	S3	S4	S5	S6	S7	S8	S9
Ondansetron HCl	10	10	10	10	10	10	10	10	10
Camphor	40	40	40	40	40	40	40	40	-
Mannitol	139.5	135.5	139.5	135.5	131.5	139.5	135.5	136.75	175.5
Cross povidone	8	12	-	-		-	-	-	-
Ac-Di-Sol	-	-	8	12	16	-	-	12	12
Sodium starch glycolate	-	-	-	-	-	8	12	-	-
Mag-stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	-	2.5
Aerosil	-	-	-	-	-	-	-	1.25	-

Evaluation of tablet properties

The hardness of tablets was measured using Pfizer hardness tester. Tablet Friability was measured using Roche Friabilator according to specification given in IP 1996. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm for 4 min. The tablets were dedusted, and the loss in weight caused by the fracture and abrasion was recorded as the % weight loss. Friability below 1% was considered acceptable.

$$F\% = \left(1 - \frac{W}{Wo}\right) X100$$

Where, W_0 is initial weight of the tablets before the test and W is the weight of the tablets after test.

The wetting time of the tablets was measured using a piece of tissue paper folded twice was kept in a culture dish (internal diameter 5.5 cm) containing ~6 mL of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time (Kuchekar et al. 2004).

Disintegration of fast dissolving tablets is achieved by saliva in the mouth, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate *in vivo* condition. The disintegration time was measured using a modified disintegration method. According to this method, a Petri dish of 10 cm diameter was filled with 10 ml of distilled water, the tablet was carefully places at the center of the Petri dish, and the time necessary for the complete disintegration of the tablet in to fine particles was noted as disintegration time.

The optimized tablet was also observed by scanning electron microscope (ESEM TMP with EDAX , Philips, Holland). Pictures were taken at an excitation voltage of 30 kv and a magnification of 120 X

In-vitro drug release

Tablet test condition for the dissolution rate studies were used according USP specification using USP 24, type I apparatus. The dissolution medium was 900 ml of Phosphate buffer (pH 6.8). The temperature of the dissolution medium and the rate of agitation were maintained at 37± 0.5^0 C and 100 rpm respectively. Aliquots of 10 ml of dissolution medium were withdrawn at specific time interval and the volume replaced by fresh dissolution medium, pre warmed to 37± 0.5^0 C. The drug concentration was determined spectrophotometrically at 249 nm using UV spectrophotometer (Shimadzu S 1700, Japan).

Stability Study

Stability study for Representative samples (S4, and S8) were carried out at 25± 2^0 C/60± 5% RH, and 40± 2^0 C/75± 5% RH for 6 month. The effect on various tablet properties such as disintegration time, Friability and hardness was measured. A value of $P< 0.05$ was considered as significant.

Result and Discussion

Selection of camphor concentration for formulation of tablets

In first experiment weight before and after sublimation of camphor was carried out (Table 3). The decrease in the mean weight corresponded to the weight of camphor added to the tablets. We concluded that almost all camphor had sublimated from the tablets. Based on the agreement between the weight of camphor added and the weight decrease observed. As shown in (Table 2), there were no pre-camphor sublimation difference in hardness among the tablets prepared using various concentration of camphor. The pre-camphor sublimation hardness of tablets prepared using various concentration of camphor was in range of 6.3-6.8 kg/cm^2. Unfortunately, the hardness of these tablets after sublimation of camphor decreased and consequently tablets with 40% camphor concentration did not remain compressed. However tablets prepared with camphor concentration of less than 30% remain compressed. The tablets prepared using camphor concentration of 20% have sufficient strength for practical use, and rapidly disintegrated in 31 s. Rapidly disintegration of tablets may be related to an improvement in the ability of water to penetrate in to tablet due to high porosity obtained by the increase in the number of pores after sublimation of camphor. The result showed that the disintegration time was significantly affected by the camphor concentration, with the camphor concentration increasing with the decrease in the disintegration time. From the result obtained camphor 20% was screened out for the final formulation of tablets.

Table 2. Hardness and Disintegration time of batches containing different amount of camphor

Conc. of camphor	Hardness (kg/cm^2) before sublimation	Hardness (kg/cm^2) after sublimation	Disintegration time (s)
0	6.8	-	> 130
10	6.5	4.2	38±2.01
20	6.5	3.5	31±3.10
30	6.4	1.5	8±1.82
40	6.3	Very fragile	-

*values given as mean ± standard deviation (n=3)

Table 3. Tablet weight (mg) before and after sublimation

Camphor (mg)	Before sublimation	After sublimation
0	198±2.67	198±1.12
20	201±3.12	181±2.01
40	203±2.71	180±2.19
60	198±2.10	138±1.43

*values given as mean ± standard deviation (n=3)

Evaluation of tablet properties

Tablets were evaluated for various physical parameters such as hardness, friability, disintegration time and wetting time (Table 4). Hardness of all batches was found in range of 3.4-3.6 kg/cm^2. Friability of all batches was less then 1%, which is regarded to be good mechanical resistance. It is worthwhile to note, however, that the addition of camphor also resulted in increased friability, probably due to generation of porous structure in the tablet matrix. So, in order to decrease the tablet's friability, colloidal silicon dioxide (aerosil) was added in batch S8, because aerosol helps to restore the bonding properties of excipients (Shiyousaku et al. 1999). The addition of aerosol resulted in an appreciable decrease in the percent of friability from 0.49% in batch S4 to 0.32% in batch S8 and a marginal decrease in disintegration time from 21 s in batch S4 to 19 s in batch S8.

Table 4. Tablet properties of fast dissolving tablets

Formulation	Hardness (kg/cm^2)	Friability (%)	Disintegration time (s)	Wetting time (s)
S1	3.5±0.15	0.50±0.10	27±2.23	24±1.10
S2	3.4±0.05	0.51±0.21	26±2.10	22±1.13
S3	3.4±0.73	0.49±0.02	23±1.80	20±1.12
S4	3.4±0.19	0.49±0.10	21±1.17	18±1.03
S5	3.4±0.03	0.50±0.19	26±1.91	23±1.31
S6	3.6±0.09	0.48±0.03	29±2.30	25±1.23
S7	3.5±0.17	0.47±0.07	28±2.01	23±1.19
S8	3.5±0.10	0.32±0.11	19±1.25	14±1.03
S9	3.5±1.13	0.40±0.31	35±1.57	31±1.01

*values given as mean ± standard deviation (n=3)

The disintegration time of the FDT showed wide variation, thus indicating that the type of superdisintegrants and camphor concentration had an effect on disintegration time. In corporation of cross carmellose sodium (Ac-Di-Sol) (6%) with camphor showed quick disintegration time 21s followed by Crosspovidone and sodium starch glycolate, while tablet prepared with Ac-Di-Sol alone disintegrated in 35 s. The porous structure induced in the tablet matrix due to sublimation of camphor was responsible for faster water uptake. Thus, facilitating the swelling action of Ac-Di-Sol and allowing faster disintegration which has been reported in the literature (Koizumi et al. 1997, Shimizu et al. 2003).

Figure 1. SEM micrograph of the cross sectional view of a high porosity fast dissolving tablet after sublimation of camphor.

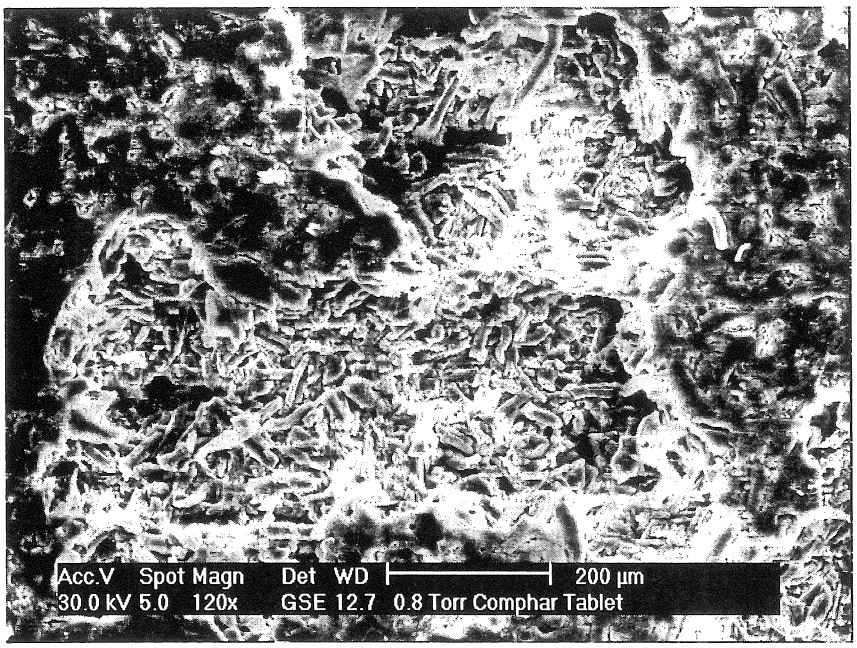

Figure 1 shows a micrograph of the cross section of a high porosity fast dissolving tablet. It was found that many porous cavities in the tablet were formed due to the sublimation of camphor. The probable reason of delayed disintegration with Crosspovidone and sodium starch glycolate might be due to their tendency to gel more than Ac-Di-Sol. Opposite result was observed at with fraction higher than 6% of Ac-Di-Sol. Ac-Di-Sol is a superdisintegrant of excellent disintegration ability. It swells to a large extent when in contact with water. However, Ac-Di-Sol is made by crosslinking of sodium carboxymethylcellulose which greatly reduce its water solubility, while permeating the material to swell and absorb water in amounts of several times its own mass without losing its fibrous structure. Such hydration makes Ac-Di-Sol more viscous and adhesive, when added in higher concentration (Bi et al. 1999). This can be the possible reason for increasing of wetting and disintegration time of the tablet containing more than 6% of Ac-Di-Sol. Tablet containing sodium starch glycolate with camphor having disintegration time higher than Ac-Di-Sol and Crosspovidone. The 'superdisintegrant' action of sodium starch glycolate is governed by extensive swelling, contact of water with sodium starch glycolate leads to the formation of viscous plugs (Augsburger et al. 2001). Due to increase in the viscosity, further uptake of water may be retarded; and the tablets break in to large floccules instead of disintegrating in to smaller particles. This might be the reason for increased disintegration time with increase amount of sodium starch glycolate.

Drug release profiles for different formulations are shown in Figure 2. Tablets prepared with crosspovidone, Ac-Di-Sol and sodium starch glycolate in combination with 20% camphor released about 100% with in (6-7 min), (2-3 min) and (8 min) respectively, while tablets prepared without camphor released 100% drug with in 10 min . The overall release rate of

Ondansetron HCl from the tablets containing 6% Ac-Di-Sol (S4 and S8) with 20% camphor was highest. Erosion of tablets is probably an important mechanism of drug release, since very rapid disintegration was noticed with these tablets by visual inspection during dissolution and disintegrations studies. The tablet containing more than 6% Ac-Di-Sol took more time for complete release of Ondansetron HCl. This might be due to higher viscosity and adhesiveness in cases where Ac-Di-Sol is added in higher fractions. Tablets prepared with sodium starch glycolate showed slower release. These tablets showed rapid ability to hydrate with the formation of a swollen sponge like arrangement, which might create a barrier for drug dissolution.

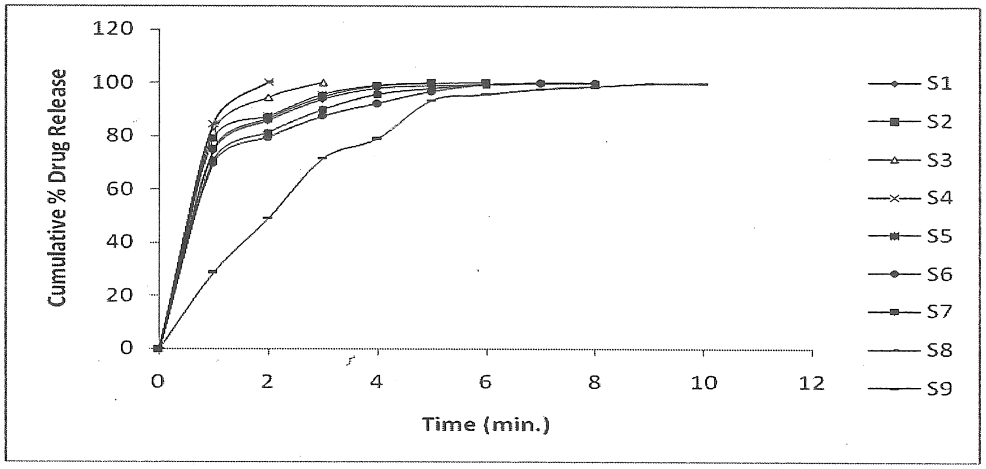

Figure 2. Drug release profile of different formulations

The result of stability testing indicate that there is no significant change in disintegration time, friability and hardness at 25± 2^0 C/60± 5% RH, and 40± 2^0 C/75± 5% RH was observed.

Summary

The results of different formulations revealed that Ac-Di-Sol (6%) was the most effective superdisintegrant among those employed in the study, but the use of superdisintegrants alone was not able to fulfill the requirements of an FDT, and so it was accompanied by a vacuum-drying technique using camphor as a subliming agent. Camphor was able to generate porous structure in the tablet matrix, decreasing the disintegration time below 30 s by acting synergistically with superdisintegrants. Thus it is concluded that by adopting a systemic formulation approach, FDTs of Ondansetron HCl could be formulated using superdisintegrants in combination with a vacuum-drying technique.

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