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ORALLY DISINTEGRATING TABLETS OF ONDANSETRON HYDROCHLORIDE FOR EMESIS THERAPY

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ABSTRACT

Out of all the dosage forms designed for the enhancement of medication, the orally disintegrating systems have been the favorite of product development scientists. Orally disintegrating tablets of ondansetron hydrochloride were developed by direct compression method using varying concentrations of different disintegrants like SSG and SCMC. Various physico-chemical properties and *in-vitro* dissolution characteristics of the formulations were analysed. Formulation F4 was found to have acceptable physic-chemical properties and the drug release was more than 80% within 10min. Which shows that the oral disintegrating tablets can be well utilized for emesis and other disease conditions also wherein the therapy requires patient compliance and in conditions which requires immediate release of the drug.

KEYWORDS

Oral distintegrating tablets, Ondansetron, Super disintegrants, SSG and SCMC.

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INTRODUCTION

Recent research in the Pharmaceutical field is mainly focussed on the development of novel oral dosage forms. Focus was laid in developing the novel drug delivery systems or increasing the patient compliance. There are different types of dosage forms utilized to improve the ease of medication, out of which, the orally disintegrating systems have been the favorite of product development scientists. In similar fashion the oral cavity is highly acceptable by patients also[1]. For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred

way of administration, owing to its several advantages and high patient compliance compared to many other routes[2]. However, many patient groups such as the elderly, children, and patients who are mentally challenged, not co-operating, having nausea and shortage of liquid-intake/diets have difficulties swallowing these dosage forms. Patients with continuous travel schedule and have only a very little accessibility to water are similarly affected[3-5]. To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as ODT, namely oral disintegrating tablets, that are able to disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take it water. The dissolution of the drug along with its absorption and the onset of the clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms[6-8].

Studies of the market positions in recent days show that about 50% of the patient population prefers ODTs to other dosage forms and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%)[9]. ODT products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia). ODTs could be developed using several approaches in the basic level by maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation[10]. Important desirable characteristics of these dosage forms include no water requirement for swallowing, provide pleasant feeling, compatible with taste masking, low sensitivity and high drug loading[11].

Velmurugan S and Sundar Vinushitha (2010) prepared oral disintagaration tablet by conventional technologies or patented technologies. ODTs are solid unit dosage forms which dissolve or disintegrate rapidly in the mouth without water or chewing. The several formulation aspects of ODT is explained along with details about the different superdisintegrants and technologies developed for ODT, along with various drugs explored, evaluation tests and marketed formulations in this field[12]. Bhupendra G Prajapati *et al*, (2010) prepared orally disintegrating tablets of piroxicam by using different super disintegrants and evaluated pre-compression and post-compression parameters. *In-vitro* dissolution profile revealed that 82.3% drug was released within 5 min[13].

Ondansetron hydrochloride is a selective serotonin 5-HT_3 receptor antagonist. The drug exhibits its anti-emetic effect by the inhibition of 5-HT_3 receptors present both centrally (modularly chemoreceptor zone) and peripherally (GI tract). The objective of the study is to determine the effect of different superdisintegrants like sodium starch glycolate (SSG) and sodium carboxymethyl cellulose (SCMC) on disintegration and dissolution properties of ODTs of Ondansetron HCl and to evaluate the feasibility of ODTs in emesis therapy.

MATERIAL AND METHODS

Ondansetron hydrochloride was received as gift sample from Sai Mirra Innopharm Pvt. Ltd, Chennai. Sodium starch glycolate, Sodium carboxy methyl Cellulose and Talc were obtained from Loba Chemie and Mannitol from SD fine chemicals, Mumbai.

PRE-FORMULATION STUDIES

Drug-Excipient compatibility study

The drug-excipient compatibility study was performed in 1:1 ratio of the drug and polymers. The sample was taken in the solid form, around 1/8" on a micro spatula and about 0.25-0.50mg of KBr was mixed thoroughly in a mortar with a pestle. Enough quantity of sample was placed just to cover the bottom in pellet die and pressed at 800-1000 psi pressed sample was carefully removed from the die and placed in the FTIR sample holder and the spectra was noted.

Standard Curve of Ondansetron HCL

Several dilutions of the pure drug were made with 0.1N HCl to obtain 50, 75, 100, 125, 150µg/ml

solutions. The absorbance of the solutions was estimated at 310nm by UV spectrophotometry.

Evaluation of Powder blend

Angle of repose

Funnel method is used to determine the Angle of repose. The blend was weighed accurately and put into the funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The blend of the drug and the excipient was passed through the funnel freely on to the surface. The cone formed by the powder was measured for its diameter and angle of repose is calculated using the following equation.

$$\tan \theta = h/r$$

Where, h and r are the height of cone and radius cone base respectively.

Bulk density

The determination of the apparent bulk density was done by passing a weighed quantity of blend into graduated cylinder and measuring the volume and weight. The calculation of the bulk density is done by using the formula:

Bulk density = powder weight / packing volume

Tapped density

It is determined by placing a graduated cylinder containing a known mass of drug-excipient blend. The cylinder was hit with the whole weight onto a hard surface from the height of 10 cm at 2 second intervals. The procedure was watched for no change in the volume and tapping is continued.The density of the tapped powder blend was calculated as follows:

Tapped Density = Powder Weight / tapped packing volume

Compressibility index

The compressibility index of the blends is determined by compressibility index. It can be calculated by using following formula:

Compressibility index (%) = [(td-bd) x 100] / td]

Hausner's ratio

The flow property of the powder is indicated by the similarity index and is defined by hausner's ratio using the following formula:

Hausner's ratio = (density of tapped powder x 100)/ (poured density)

Hausner's ratio <1.25 – good flow = 20% compressibility index

>1.25 – poor flow =33% compressibility index

Preparation of Oro dispersible Tablets

The orally disintegrant tablets of Ondansetron HCl were prepared by direct compression method. Required quantity of drug and mannitol were taken and mixed well. The mixture was passed through sieve no: 30. Then super disintegrant is taken separately and passed through sieve no: 45. Then the two mixtures were blended for about 40mins. Finally the blended powder is compressed to form a tablet as shown in Table No.1.

EVALUATION OF ONDANSETRON HCL ORAL DISPERSIBLE TABLETS[14]

General Appearance and Organoleptic Properties

The general appearance of the tablet is controlled by the measurement of a number of attributes such as a tablet's size, shape, color, presence or absence of an odor, consistency, flaws in appearance, texture of the surface, taste and legibility of any identifying markings.

Shape

Shape of the tablet was circular with flat shape.

Average Weight

20 Tablets from each batch were weighed accurately and the average weight was calculated using the formula:

$$\text{Average Weight} = \frac{\text{Weight of 20 tablets}}{20} \times 100$$

Weight Variation

Weight variation was calculated as per method descried in Indian Pharmacopoeia, 1996. 20 tablets were weighed individually and the average weight was calculated.

Thickness

Tablets were selected randomly and their thickness was measured using the calibrated vernier calipers.

Hardness

From every batch, five tablets were selected to measure the hardness using Monsanto hardness tester to find the average tablet hardness.

Friability

Batch wise random selection of 20 tablets was made and weighed. Friability testing for these tablets was done using Roche friabilator for 100 revolutions. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the % friability.

% F =1 (loss in weight/ initial weight) 100

Wetting time

The tablet was placed in a petridish of 6.5cm in diameter, containing 10ml of water at room temperature, and time for complete wetting was recorded. To check for reproducibility, the measurements were carried out 3 times and the mean value calculated.

***In- vitro* dispersion time**

Tablet was added to 10ml of phosphate buffer pH 6.8 and time required for complete dispersion was measured in seconds.

Disintegration Time

The determination of *in-vitro* disintegration time was done by using disintegration test apparatus. The six tubes were filled with one tablet and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass in the apparatus was measured in seconds.

Content uniformity

Tablet containing 4mg of drug is dissolved in 100ml of 0.1N HCl taken in volumetric flask. The solution was filtered, 1ml of filtrate was diluted with 0.1N HCl to 50ml in volumetric flask and analysed spectrophotometrically at 310nm. The concentration of Ondansetron hydrochloride in mg/ml was calculated by using standard calibration curve.

Dissolution Studies

The *In vitro* dissolution test was carried out using USP Type II dissolution test apparatus at 37±2°C and 50 rpm speed. The dissolution medium used was 500 ml of 0.1 N HCl. Aliquots equal to 10 ml was withdrawn at specific time intervals and amount of Ondansetron HCl released from tablet was determined by using UV – spectrophotometer at 310nm.

RESULTS AND DISCUSSION

Six formulations F1-F6 were prepared by varying the concentration of superdisintegrant and keeping other excipients as constant. The total weight of tablets was 200mg and drug content was 20mg in case of all formulations.

The evaluation of the flow properties and compressibility of drug and excipients blend was carried out. The blend for tablet formulations showed good flow properties and compressibility.

Formulations F1, F2, F3 were prepared by using sodium carboxy methyl cellulose with 5, 10, 15mg. Formulations F4, F5, F6 were prepared by using 5, 10, 15mg of sodium starch glycolate.

All the formulations showed less than 1% friability and passes weight variation test. Also the hardness and thickness of all the formulations was within acceptable range. Content uniformity of all formulation was between 91-98% and was in acceptable range as per I.P. specification.

The formulations F4, F5, F6 containing sodium starch glycolate showed lowest disintegration time, wetting time and dispersion time.

The formulation, F4 released more than 80% of drug within 10min which prove its fast dissolving action. Based on dissolution rate superdisintegrants can be ranked as sodium starch glycolate > sodium carboxy methyl cellulose. The formulation F4 was found to have good compressibility, flow ability and less friability, it also showed less disintegration, wetting time, dispersion time and percentage cumulative release of drug was 99.59% in 15 min. Hence batch F4 was chosen as the best batch.

Table No.1: Composition of Oral Dispersible tablet of Ondansetron HCl

S.No	Ingredients	F1	F2	F3	F4	F5	F6
1	Ondansetron HCl (mg)	20	20	20	20	20	20
2	SCMC (mg)	5	10	15	-	-	-
3	SSG (mg)	-	-	-	5	10	15
4	Mannitol (mg)	175	170	165	175	170	165
5	Talc (mg)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table No.2: Pre Compression Parameters of prepared ODTs

S.No	Formulation code	Angle of repose (θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Compressibility index	Hausner ratio
1	F1	32° 86 "	0.386 ± 44	0.468 ± 41	24.86 ± 76	0.1483 ± 21
2	F2	28° 64"	0.281 ± 25	0.389 ± 13	21.75 ± 91	0.54 ± 14
3	F3	26° 38"	0.520 ± 13	0.508 ± 14	11.88 ± 66	1.28 ± 96
4	F4	22° 89"	0.421 ± 48	0.404 ± 28	10.55 ± 22	1.08 ± 44
5	F5	25° 31"	0.494 ± 12	0.479 ± 13	12.42 ± 36	1.24 ± 63
6	F6	24° 99"	0.448 ± 46	0.463 ± 55	11.09 ± 13	1.20 ± 24

Table No.3: Post Compression Parameters of prepared ODTs

S.No	Formulation code	Weight Variation (mg)	Hardness (kg/cm^3)	Friability (%)	Wetting Time (sec)
1	F1	228 ± 2.3	3.5 ± 0.5	0.7	98 ±3
2	F2	230 ± 1.4	4.0 ± 0.5	0.8	109 ± 4
3	F3	225 ± 3.2	3.5 ± 0.5	0.7	120 ± 2
4	F4	224 ± 4.0	4.5 ± 0.5	0.6	40 ± 4
5	F5	226 ± 3.9	4.0 ± 0.5	0.6	64 ± 1
6	F6	229 ± 2.2	4.5 ± 0.5	0.7	76 ± 2

Table No.4: Post Compression Parameters of prepared ODTs

S.No	Formulation code	Dispersion time (sec)	Disintegration time (secs)	Drug content (%)
1	F1	104 ± 1	59 ± 3	96.08 ± 0.231
2	F2	115 ± 3	110 ± 1	92.38 ± 0.145
3	F3	130 ± 1	116 ± 5	95.47 ± 0.186
4	F4	48 ± 3	20 ± 2	98.88 ± 0.276
5	F5	70 ± 2	29 ± 1	91.28 ± 0.112
6	F6	82 ± 4	44 ± 3	95.32 ± 0.087

Table No.5: *In - Vitro* dissolution data of ODTs

Time (mins)	Cumulative % drug release					
	F1	F2	F3	F4	F5	F6
1	8.17 ± 0.127	7.21 ± 0.867	5.41 ± 0.132	13.65 ± 0.208	11.87 ± 0.876	10.45 ± 0.102
2	10.41 ± 0.045	9.35 ± 0.287	7.31 ± 0.276	20.58 ± 0.387	16.97 ± 0.324	12.47 ± 0.067
3	16.31 ± 0.654	15.46 ± 0.113	10.27 ± 0.386	26.65 ± 0.321	24.18 ± 0.675	18.74 ± 0.332
4	26.93 ± 0.934	20.71 ± 0.908	17.32 ± 0.398	36.60 ± 0.976	30.83 ± 0.221	25.56 ± 0.065
5	32.47 ± 0.121	29.35 ± 0.054	22.24 ± 0.476	45.41 ± 0.087	37.43 ± 0.165	36.98 ± 0.201
7	44.59 ± 0.861	35.42 ± 0.287	30.79 ± 0.123	53.87 ± 0.112	45.96 ± 0.342	40.54 ± 0.098
9	52.28 ± 0.075	43.62 ± 0.065	39.91 ± 0.088	65.65 ± 0.576	54.93 ± 0.132	55.32 ± 0.051
11	62.05 ± 0.134	50.43 ± 0.387	45.41 ± 0.186	80.65 ± 0.298	69.36 ± 0.265	68.25 ± 0.045
13	66.32 ± 0.198	55.67 ± 0.398	50.21 ± 0.658	98.75 ± 0.455	86.23 ± 0.481	79.52 ± 0.111
15	70.77 ± 0.188	60.23 ± 0.345	55.47 ± 0.468	99.59 ± 0.157	95.37± 0.005	92.85 ± 0.042

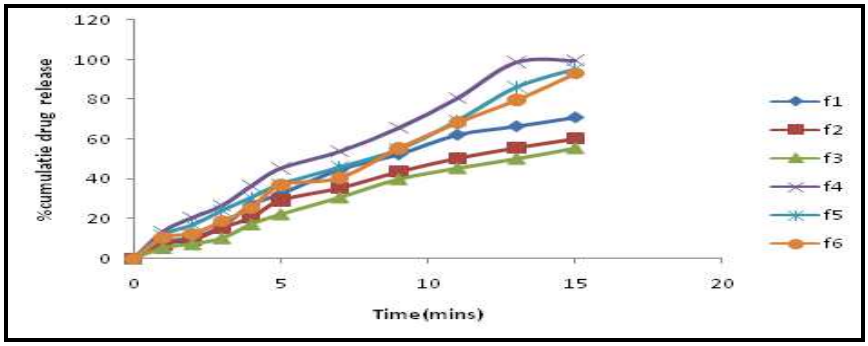

Figure No.1: Comparative *In- vitro* dissolution profile of ODT formulations

SUMMARY AND CONCLUSION

The present study concludes that the successful formulation of mouth dissolving tablet of Ondansetron HCl can be done by using sodium starch glycolate than sodium carboxy methyl cellulose as a super disintegrant. Thus an ideal bitter less oral dissolving/ disintegrating Ondansetron HCl tablets can be prepared for improving patient acceptabilility. The concept is suitable for other drugs of the same category also.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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