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Development and Evaluation of Orally Disintegrating Tablet by Direct Compression Method

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Abstract: The aim and objective of orally disintegrating tablets by direct compression method was emerged from desired to provide patient with a conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. In the present work Ondansetron was chosen as a model drug. Ondansetron is a selective serotonin $5HT_3$ receptor antagonist. It is widely used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. It is also used for prevention and treatment of postoperative nausea and vomiting. Although it is commonly used drug but major problem is its bitterness. In the present work, taste masking of Ondansetron was carried out by adding trusil lemon lime ASV, peppermint powder as flavouring agent and aspartame as sweetening agent, using croscarmellose sodium, sodium starch glycolate, crospovidone as superdisintegrant while other formulation component kept constant. Nine formulations F1-F9 were prepared by varying the concentration of superdisintegrant and keeping other constant. The total weight of tablet was kept constant (100mg) and drug content was 4mg in case of all formulations. The Formulation containing Crospovidone (20%, 25% and 30%) showed lowest disintegration time, wetting time, dispersion time. All the formulation release more than 80% of drug within 10min which prove its fast dissolving action. Based on dissolution rate superdisintegrants can be ranked as Crospovidone > Sodium starch glycolate > Croscarmellose sodium. Among all the formulated tablets containing 25% crosspovidone showed good compressibility, flowablity and less friability, it also showed less disintegration, wetting time, dispersion time and percentage cumulative release of drug was 99.47% in 10min. It was concluded that ideal bitterless orally disintegrating Ondansetron tablet was prepared successfully with patient acceptabilility.

Key words: Ondansetron, Crospovidone, Sodium starch glycolate, Croscarmellose sodium, Trusil lemon lime ASV.

Introduction

For the past one decade, there has been an enhanced demand for more patient- friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost effective dosage forms[1].
Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy. The problem can be resolved by the creation of fast drug delivery system (FDDS), which do not require water to aid swallowing. The dosages forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way [2]. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients [3]. In order to allow fast disintegrating tablets to dissolve in the mouth, they are made of either very porous or soft molded matrices or compressed into tablets with very low compression force [4].
Fast dissolving tablets (FDTs) are the disintegrating tablets include sweeteners and flavors; however, these are not a sufficient means for taste masking many bitter drugs. Most of the FDDT technologies incorporate unique forms of taste masking as well [2].
Recent market studies indicate that more than half 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%)[1].
Ondasetron is serotonine receptor ($5HT_3$) antagonist. It is an antiemetic drug. It is widely used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. It is also used for the prevention and treatment of postoperative nausea and vomiting. Ondansetron is well absorbed from gastrointestinal track and undergo first pass metabolism [5]. It has a very bitter taste. Taste plays an important role in the patient acceptability as far as mouth dissolving/ dispersible tablet are concerned. Therefore bitter taste of drug i.e. Ondansetron was successfully masked by the use of peppermint powder, trusil lemon lime ASV and aspartame.

Materials and Methods

Materials used were Ondansetron USP gift sample from Medley Pharmaceuticals Ltd. Mumbai, Maharashtra, India, Croscamellose sodium (FMC Biopolymer, Mumbai, India), Crospovidone (BASF Corporation, Mumbai, India), Sodium starch glycolate (VASA Pharmachem Pvt Ltd., Mumbai, India), Mannitol (Signet Chemical Corporation Pvt. Ltd., Mumbai, India), Aspartame (Biocon Limited, Mumbai, India), Colloidal anhydrous silica (Cabot Sanmar Limited, Mumbai, India), Trusil lemon lime ASV (IFF Pvt. Ltd., Chennai, India), Peppermint powder (Bio-Organics Pvt Ltd. Mumbai, India), Quinoline yellow lake (Roha Dyechem Ltd. Mumbai, India), Magnesium stearate (S. Kant Health Care Ltd. Mumbai, India). Other materials used were purchased locally and was of analytical grade.

Experimental

Formulation of orally disintegrating tablets

The tablets were prepared by direct compression method, Ondansetron and various concentrations of superdisintegrating agents (crosscarmellose sodium, crosspovidone, sodium starch glycolate) were used. The excipients aspartame, mannitol and colloidal anhydrous silica were used for its sweetners, diluents and flow properties. The trusil lemon lime ASV, peppermint powder used as flavours and quinoline yellows used for its colouring property [6,7,8,9]. Average weight of tablet was kept constant i.e. 100mg with each tablet containing 4mg of Ondansetrone USP. Initially required quantity of ondansetron was weighed and sifted through sieve No. 24. Required quantity of superdisintgrating agent, mannitol were weighed and sifted through sieve No. 40. Mixed these ingredients geometrically with weighed quantity of Ondansetron. Required quantity of aspartame, colloidal anhydrous silica, lemon lime ASV and peppermint powder were weighed and sifted through sieve No. 40. Quinolline yellow lake was weighted and sifted through sieve No. 100. All these ingredients were mixed in polybag and finally mixed uniformly in planetary mixer for 10minutes. 1.6%w/w of magnesium stearate was sifted through sieve No. 60 and used as a lubricant for prepared blend in planetary mixer. The blend was then compressed by using MINI- II DT (Double Layer) machine by using 6.5 FFBE (flat face bevel edges) punch having break line on one

side (lower punch) and logo on other side (upper punch).
The details of formulations F1 to F9 are given in Table No. 01.

Evaluation of prepared tablets
The prepared tablets were evaluated for hardness, weight variation test, friability, content uniformity and thickness as per official procedures.
Standard physical parameters for orally disintegrating tablets are given in Table No. 02.

Evaluation of taste by panel (Mouth feel)
The taste evaluation was done by panel testing. For this purpose, 6 human volunteers were selected to taste all the formulation by keeping in the mouth till they disintegrated and ranked on a scale of perception ranging from 0-4[10]. 0- Good, 1- Tasteless, 2- Slightly bitter, 3-Bitter, 4-Very bitter .

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 [6].

Table No. 01: Formulation chart of Ondansetron orally disintegrating tablets

Formulation code/ Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ondansetron USP	4	4	4	4	4	4	4	4	4
Crosscarmellose sodium	20	25	30	--	--	--	--	--	--
Sodium starch glycolate	--	--	--	20	25	30	--	--	--
Crosspovidone	--	--	--	--	--	--	20	25	30
Mannitol	37.9	32.9	27.9	37.9	32.9	27.9	37.9	32.9	27.9
Aspartame	19	19	19	19	19	19	19	19	19
Colloidal Anhydrous silica	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Trusil lemon lime ASV	12	12	12	12	12	12	12	12	12
Peppermint powder	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Quinoline yellow lake	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Magnesium stearate	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Total Weight	100	100	100	100	100	100	100	100	100

Table No. 02: Standard physical parameters for orally disintegrating tablets

Formulation batches	Physical parameter*				
	Hardness (kg/cm^2)	Percent friability	Thickness (mm)	Content uniformity (%)	Wt. variation
F1	2.55±0.546	0.40±0.004	2.61±0.054	101.53±2.38%	Passes
F2	2.06±0.535	0.43±0.008	2.65±0.046	101.28±1.72%	Passes
F3	1.56±0.377	0.48±0.011	2.73±0.027	98.40±1.11%	Passes
F4	1.66±0.301	0.39±0.006	2.54±0.034	98.07±1.13%	Passes
F5	1.63±0.136	0.44±0.005	2.55±0.021	99.06±1.92%	Passes
F6	1.58±0.222	0.51±0.017	2.58±0.018	98.64±1.48%	Passes
F7	1.63±0.280	0.39±0.007	2.94±0.028	101.10±1.98%	Passes
F8	1.83±0.196	0.20±0.006	2.88±0.044	99.96±0.79%	Passes
F9	1.75±0.225	0.37±0.010	2.95±0.025	99.30±1.72%	Passes

*All the values represent mean ± Standard deviation (n=3)

***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 [11].

***In- vitro* disintegration time**
The *in-vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specification. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was determined and recorded [6,10].

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 [6].
In-vitro disintegration time, wetting time, dispersion time and mouth feel of the formulated tablets are given in Table No. 03.

***In-vitro* release profile of formulated tablets**
In-vitro drug release studies were carried out using IP type I Dissolution Testing Apparatus (1 vessel assemblies, Paddle type) at 50rpm. The dissolution medium consisted of 500ml of 0.1M HCl. Temperature was maintained at 37±0.1^{0}C. Aliquots of 1ml were withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots were filtered through whatman filter paper (No-41), diluted suitably using 0.1M HCl and analyzed spectrophotometrically at 310nm[12].
The plot of percentage cumulative drug release against time is given in Figure No. 01.
The plot of Percent cumulative drug released in 10 minutes of formulation F1-F9 is shown in Figure 02.

Stability studies
In any rationale design and evaluation of dosage forms, the stability of the active component must be major criteria in determining their acceptance or rejection. During the stability studies the product was exposed to normal conditions of temperature and humidity, however the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product was stored under extreme conditions of temperature. Optimized formulation F8 was subjected for stability study, the tablets were wrapped in aluminium foil and stored at temp 40^{0}C and RH 75% for three month. After thirty days each sample was withdrawn and evaluated for physical parameters, disintegration time, hardness, friability, content uniformity, wetting time and dissolution rate [7].
The plot of percent cumulative drug release of Formulation F8 before and after stability study is shown in Figure 03.
The plot of parameters studied on Formulations F8 before and after stability study is given in Figure 04.

Table No. 03: *In-vitro* disintegration time, wetting time, dispersion time and mouth feel of formulated tablet

Formulation batches	Parameters*			
	Disintegration time (sec.)	**Wetting time (sec.)**	**Dispersion time (sec.)**	**Mouth feel**
F1	73.33±0.577	178±2.645	186.33±1.154	Good
F2	68.66±1.154	158.33±2.516	173.66±2.886	Good
F3	63±1.00	153.33±3.055	167.66±2.081	Good
F4	63.33±1.527	188±2.645	176.33±2.886	Good
F5	55.66±0.577	170.66±3.511	156.66±2.516	Good
F6	49.66±0.577	167.33±2.516	143.33±2.081	Good
F7	19.33±0.577	48±1.00	94±2.00	Good
F8	17.66±0.577	45.66±0.577	83±1.732	Good
F9	21±1.00	68.66±1.527	87.66±2.081	Good

*All the values represent mean± Standard deviation (n=3)

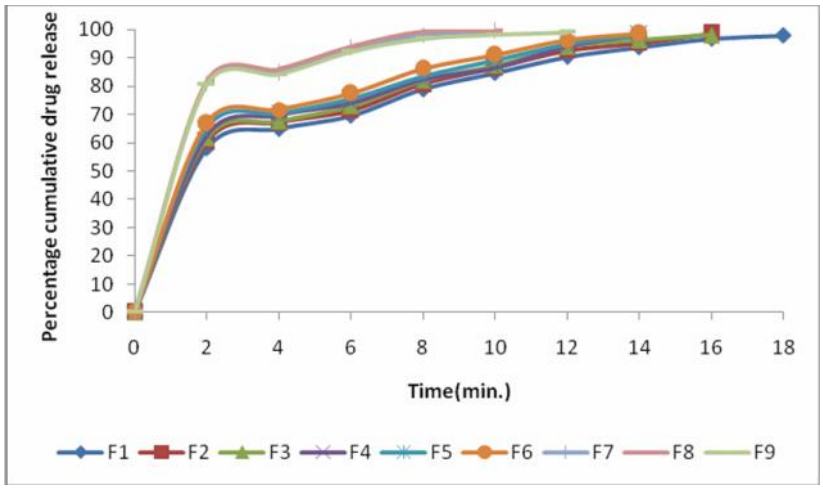

Figure 01: *In-vitro* drug release profile of formulation F1-F9

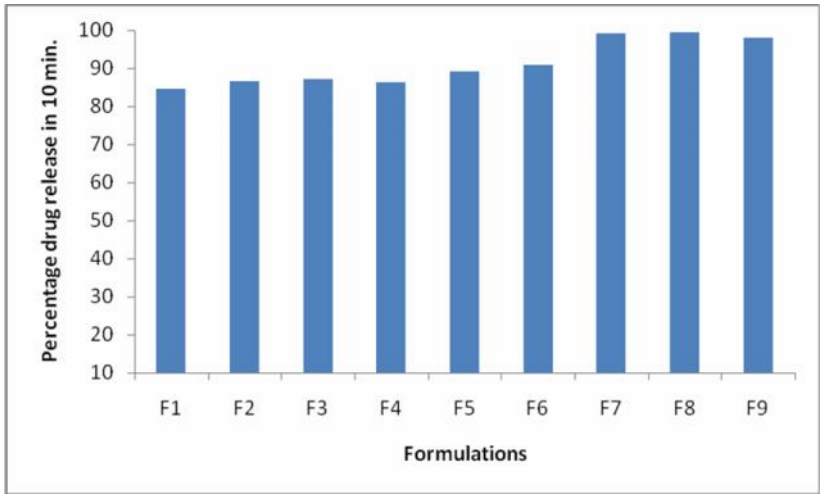

Figure 02: Percent cumulative drug released of formulation F1-F9 in 10 minutes

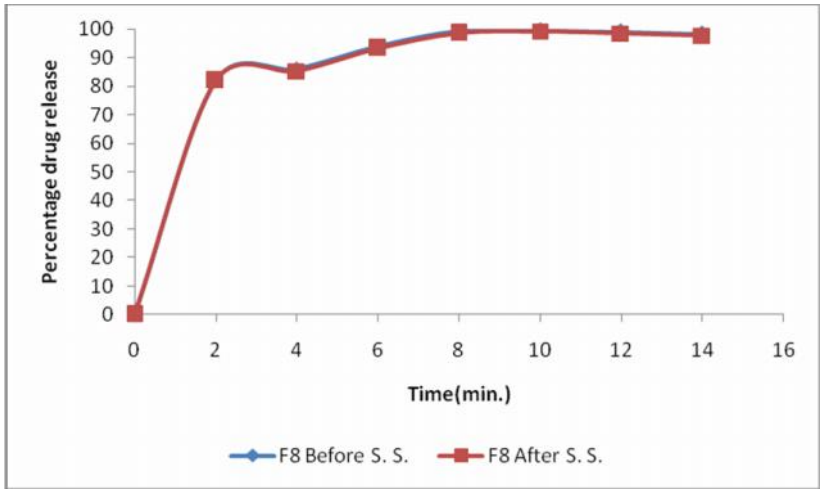

Figure 03: *In-vitro* drug release profile of formulation F8 before and after stability study

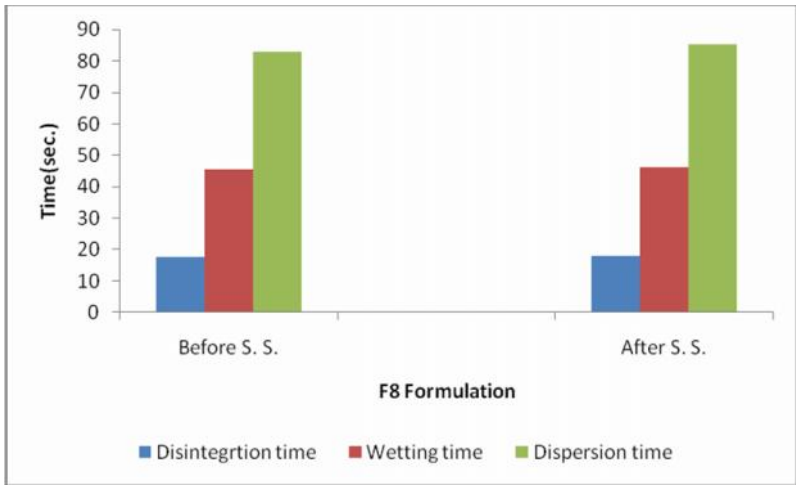

Figure 04: Disintegration time, wetting time, dispersion time of Formulation F8 before and after stability study

Result and Discussion

Ondasetron is serotonine receptor ($5HT_3$) antagonist. It is an antiemetic drug. It is widely used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. It is also used for the prevention and treatment of postoperative nausea and vomiting. Ondansetron is well absorbed from gastrointestinal track and undergo first pass metabolism. It has very bitter taste. Taste plays an important role in the patient acceptability as far as mouth dissolving/ dispersible tablet are concerned. Therefore bitter taste of drug i.e. Ondansetron was successfully masked by the use of peppermint powder, trusil lemon lime ASV and aspartame.

Mouth dissolving taste masked tablet were prepared using pearlitol 200SD (mannitol), aerosil (colloidal anhydrous silica), aspartame, trusil lemon lime ASV, peppermint powder and different superdisintegrants.

Nine formulations F1-F9 were prepared by varying the concentration of superdisintegrant and keeping other constant. The weight of tablet was 100mg and drug content was 4mg in case of all formulations.

The final blend of drug and excipients were evaluated for flow properties and compressibility. The blend for tablet formulation F1, F4, F7, F9 showed fair; F2, F3, F5, F6 showed passable and F8 showed good flow properties and compressibility.

Formulations F1, F2, F3 were prepared by using Croscarmellose sodium in 20%, 25%, 30% concentration. Formulation F4, F5 , F6 and F7, F8, F9 were prepared by using Sodium starch glycolate and Crospovidone in 20%, 25%, 30% and 20%, 25%, 30% concentration respectively.

All the tablet Formulation showed less than 1% friability and passes weight variation test. Also the hardness and thickness of all tablet Formulation was within acceptable range. Content uniformity of all tablet Formulation was between 90-110% and was in acceptable range as per I.P. specification.

The Formulation F7, F8 and F9 containing Crospovidone (20%, 25% and 30%) showed lowest disintegration time, wetting time, dispersion time. All the formulation release more than 80% of drug within 10min which prove its fast dissolving action. Based on dissolution rate superdisintegrants can be ranked as Crospovidone > Sodium starch glycolate > Croscarmellose sodium. Among all the formulated tablets F8 which is based on Ondansetron with 25% crosspovidone showed good compressibility, flowablity and less friability, it also showed less disintegration, wetting time, dispersion time and percentage cumulative release of drug was 99.47% in 10 min. Hence batch F8 chosen as optimized batch and selected for further studies.

The hardness, thickness, friability, Carr's index, Hausner's ratio, angle of repose, disintegration time, wetting time, dispersion time, content uniformity, dissolution of optimized formulation was found to be 1.83kg/cm^2, 2.88mm, 0.20%, 15.30%, 1.18, 34^o 74', 17.66sec., 45.66sec., 83sec., 99.96%, 99.47% respectively.

A stability study of optimized formulation was carried out at 40 ± 2^{0}C/75 ± 5 % RH for three months. Different parameter like colour, mouth feel, hardness, thickness, friability, disintegration time, wetting time, dispersion time, dissolution rate were evaluated. By observing the effect of storage

and temperature on colour, mouth feel, hardness, thickness, friability, disintegration time, wetting time, dispersion time, dissolution rate, it was confirmed that the formulated tablet posses good stability. Stability study result confirmed that all parameter of prepared formulation remain unchanged.

Conclusion

It was concluded that the method used for taste masking of bitter drug were found to be effective and the formulated mouth dissolving tablets posses all the pharmacopoeial standards. From above it was concluded that the successful formulation of mouth dissolving tablet of Ondansetron can be formulated by using crospovidone than croscarmellose sodium and sodium starch glycolate as a superdisintegrant. Thus an ideal bitterless oral dissolving/ disintegrating Ondansetron tablets were prepared with patient acceptabilility.

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