Research Article

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Formulation Development and Evaluation of Mouth Melting Film of Ondansetron.

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The present study deals with formulation of an edible film forming polymers based mouth melting thin film formulation of an antiemetic drug, Ondansetron, which can offer higher patient compliance and excellent effectiveness of the drug. Low viscosity grade of hydroxylpropyl methylcellulose (HPMC E 15) and Maltodextrin were used as excipient. due to their excellent film forming property and palatable taste. Glycerol and carragenan were used as a plasticizers and stabilizing agent, respectively. Increasing maltodextrin concentration in the formulation resulted in a brittle film formation as compared to lower concentration of the same. Higher concentration of HPMC E 15 was resulted in sticky film formation. Concentration of glycerol was optimized during preliminary studies. Formulation containing HPMC E 15 (20%w/w), Maltodextrin (25%w/w) and glycerol (2% w/w) showed optimum performance against all other prepared formulations.. The formulation was found to show a significant improvement in terms of the drug release as compared to mouth dissolving tablet. Thus, mouth melting thin film formulation of Ondansetron was successfully developed.

Key Words: Mouth Melting Film, Ondansetron, HPMC E 15.

INTRODUCTION

Some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms[8]. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking[5].

Ondansetron (OND) is a potent, highly selective $5HT_3$ receptor-antagonist. Many times they are given intravenously about 30 minutes before beginning therapy. OND is not highly protein bound (70-76%) and is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. The 5-HT_3 receptor antagonists are the primary drugs used to treat and prevent chemotherapy-induced nausea and vomiting (CINV). Following oral administration of OND, absorption is rapid with maximum peak plasma concentrations of about 30ng/ml being attained and achieved in approximately 1.5 hours after an 8 mg dose.

HPMC (E-15) is the low viscosity grade of the HPMC series of polymers. It is widely used as a film coating material for the tablets. It is a good film forming agent with both water and alcohol solubility. Maltodextrin is classified as a complex carbohydrate, but acts like a simple carbohydrate in the body. Maltodextrin will not supply long-lasting energy provided by most complex carbohydrates because of this particular structure, maltodextrin can be classified as a complex carbohydrate, as opposed to a simple carbohydrate like glucose[9]. Maltodextrin must first be enzymatically altered by the body before its benefits are realized in the form of energy[3].

The main objectives of the present study were to prepare and evaluate the mouth melting thin film of OND and to study the various formulation variables that affect the drug release.

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MATERIALS AND METHODS

Materials

OND hydrochloride BP was received as gift samples from Cadila pharmaceuticals Ltd., Ahmedabad, India. Maltodextrin and Carragenan were received as generous gift from Gujrat Ambuja export Ltd., INDIA Hydroxypropyl methyl cellulose (E-15) was procured from The Dow chemicals, China. Glycerol, Neotam, Sodium benzoate, Flavor Bitter-mask, Flavor Spearmint and Color

Table 1: Formulation of mouth melting film of OND batch S1-S11

Ingredients	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11
Ondansetron HCL	2.66	2.66	2.66	2.66	2.66	2.66	2.66	2.66	2.66	2.66	2.66
Maltodextrin	15	20	25	30	35	40	25	25	25	25	25
HPMC(E-15)	15	15	15	15	15	15	20	25	30	35	40
Carragenan	3	3	3	3	3	3	3	3	3	3	3
Glycerol	2	2	2	2	2	2	2	2	2	2	2
Neotame	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Flav. Bittermask	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Flav. Spearmint	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sodium benzoate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Colr. Brilliant blue supra	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Distilled waret	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s

* All quantities are in mg.

Brilliant-blue supra were supplied by Linclon Pharmaceuticals Ltd., Ahmedabad, INDIA. All other reagents and chemicals were of analytical grade.

Figure 1: DSC curve of Ondansetron (A), Maltodextrin (B), HPMC (C) and ONDA + MALTO + HPMC (D)

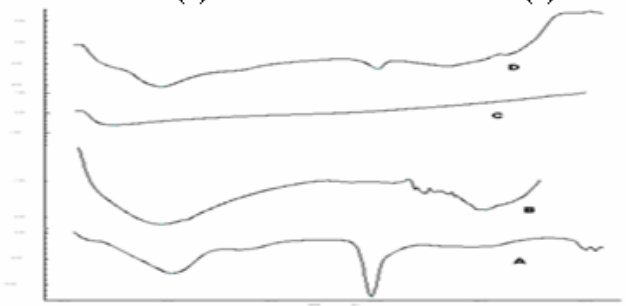
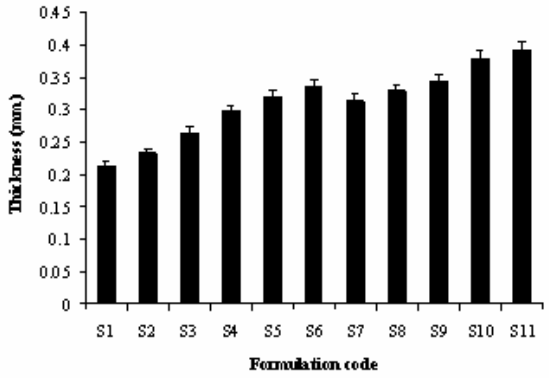


Figure 2: Comparison study of thickness of mouth melting film of OND batch S1-S11



Methods

The mouth melting thin films were prepared by using solvent casting method. Maltodextrin and HPMC-E-15 were solubilized in minimum amount of water. Accurately weighed quantity of carragenan and OND was added in the solution. Sodium benzoate, neotame, flavors and color were added and homogenous solution was prepared. The thick viscous solution was degassed to remove air entrapment by using ultrasonicator. The solution was poured in the suitable moulds and kept at room temperature at about 15 minuets. The moulds were kept in the hot air oven at 75º to 80º for the final drying for about 30 minuets. The moulds were allowed to equilibrate to the room temperature and the films were cut in to desired size and finally were pilled off from the moulds. The films were stored airtight plastic container and kept for further studies. Table shows the formulation and optimization of the films of the films.

Various concentrations of maltodextrin and HPMC-E-15 were used to formulate the films. First the HPMC (E-15) concentration was fixed and amount of maltodextrin was varied for optimization. Then the optimized amount of maltodextrin was fixed and HPMC-(E-15) concentration was optimized. All the batches containing different amount of polymers were evaluated further.

Table 2: Drug content of mouth melting film of OND batch S1-S11

Sr.No.	Formulation code	Drug content			
		Trial 1	Trial 2	Trial	Average
1	S1	99.88	99.89	99.89	99.89
2	S2	99.88	99.90	99.89	99.88
3	S3	99.84	99.84	99.85	99.84
4	S4	99.83	99.83	99.83	99.83
5	S5	99.90	99.89	99.88	99.89
6	S6	99.87	99.87	99.86	99.87
7	S7	99.87	99.87	99.87	99.87
8	S8	99.85	99.83	99.84	99.84
9	S9	99.87	99.88	99.87	99.88
10	S10	99.92	99.93	99.93	99.93
11	S11	99.88	99.87	99.88	99.88

Evaluation

Drug-Excipients Interaction studies

Assessment of possible Incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of solid dosage form. Differential Scanning Calorimeter (DSC) allows the fast Evaluation of possible incompatibilities, because it shows changes in the appearance, Shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug, other excipients and final tablet were recorded. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10^0C/min over a temperature range of 50^0C to 300^0C.DSC study was performed for the OND, maltodextrin, HPMC (E-15) and physical mixture of all three[2].

Drug content: Total drug content per film was calculated by random sampling of the all

batches. The drug content assay was carried out using HPLC method. All the batches found satisfactory for the assay. All the batches contain more than 90% ondansetron hydrochloride of the label claim [7].

Uniformity of drug content: The same procedure was followed to calculate the uniformity of drug content. 1cm^2 pieces were cut from two places and the drug content was calculated using HPLC method as described earlier [7].

Thickness: All the batches were evaluated for thickness by using calibrated digital vernier calipers. Three samples from all the batches was withdrawn and evaluated for thickness [1].

Folding endurance: The folding endurance was measured manually for the prepared films. A strip of film was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance[4].

Palatability study: Palatability study was conducted on a group of 5 volunteers. The mouth melting thin films were rated on the basis of taste, after bitterness and physical appearance. All the batches rated A, B and C grades as per criteria. When the formulation scores at least one A grade, formulation was considered as average. When the formulation scores two A grade then it would be considered as good and one with all three A grade it would be the very good formulation.

Grades: A= very good, B=good, C= poor

Disintegration test: Disintegration test was performed in the USP disintegration time testing apparatus. Simulated salivary fluid (PH 6.8) was used as medium. The films were placed in the tubes of the container and the disks were placed over it. All the batches were disintegrated within 10 seconds.

Figure 3: Comparison study of folding endurance of mouth melting film of OND batch S1-S11

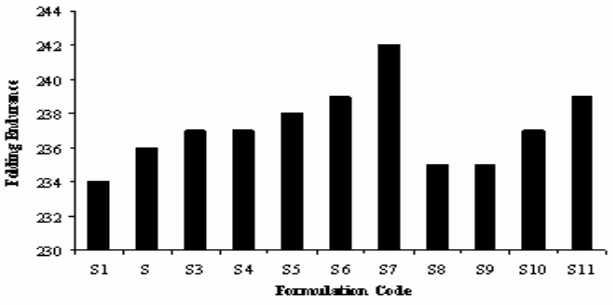


Table 6: Kinetic study of mouth melting film of OND batch S1-S11

Batch code	Zero order	First order
S1	0.96	0.935
S2	0.908	0.872
S3	0.984	0.923
S4	0.948	0.889
S5	0.983	0.951
S6	0.961	0.908
S7	0.907	0.814
S8	0.97	0.898
S9	0.972	0.901
S10	0.984	0.921
S11	0.977	0.892

***In-vitro* dissolution studies:** Dissolution study was carried out in USP basket type apparatus using the stimulated salivary fluid (Ph 6.8) as a dissolution medium at 50 rotations per minute. 10ml aliquots were withdrawn at the interval of 1 minute and same amount of fresh dissolution medium was added. The aliquots were assayed for drug content by HPLC method. Comparative dissolution studies were performed with the marketed mouth dissolving formulation (onden) and similarity factor (f_2) was calculated for the same. The obtained data was treated for zero order and first order of reaction.

Kinetics modeling of drug dissolution profiles

The dissolution profile of all the batches was fitted to Zero order, First order [6,11] to ascertain the kinetic modeling of the drug release.

Zero order

In many of the modified release dosage forms, particularly sustained or controlled release dosage forms (those dosage forms that release the drug in planned, predictable and slower than the normal manner), is zero-order kinetic.

$$m = k * t \qquad (1)$$

Where, k is zero-order constant, m is the % drug unreleased and t is the time. The plot of % drug unreleased (released) versus time is the linear.

First order

Most conventional dosage forms exhibits this dissolution mechanism. Some modified release preparation, particularly prolonged release formulations, adheres to this type of dissolution pattern.

$$m = ea * e\text{-}bt \qquad (2)$$

Where a is the intercept and b is the slop. It assumes that the drug molecules, diffuses out

through a gel like layer formed around the drug during the dissolution process. A plot of log % drug release versus time is the linear.

Stability study: 3 months stability study was carried out for all the batches at 65% relative humidity and 35ºc temperature in the humidity chamber. After 3 months the films were evaluated for the drug content, disintegration time and physical appearance observation [10].

Table 3: Drug content uniformity of mouth melting film of OND batch S1-S11

Sr.No.	Formulation code	Drug content uniformity			
		Trial 1	Trial 2	Trial 3	Average
1	S1	0.1532	0.153	0.1535	0.1535
2	S2	0.1535	0.1532	0.153	0.1532
3	S3	0.153	0.153	0.1532	0.153
4	S4	0.1532	0.153	0.153	0.153
5	S5	0.1535	0.1535	0.1532	0.1535
6	S6	0.1532	0.1532	0.1535	0.1532
7	S7	0.153	0.153	0.1535	0.1532
8	S8	0.1532	0.153	0.1532	0.153
9	S9	0.153	0.1532	0.153	0.1532
10	S10	0.1532	0.153	0.1532	0.1536
11	S11	0.153	0.1532	0.153	0.1532

RESULTS AND DISCUSSION

Differential Scanning Calorimetric (DSC) Study: DSC study was performed for the OND, maltodextrin, HPMC (E-15) and physical mixture of all three. From the DSC curves, the drug was found compatible with the polymers (Figure 1).

Drug content: Total drug content of all the batches were estimated by prior mentioned HPLC method. All the batches were found satisfactory as per given in the table 2.

Uniformity of drug content: Uniformity of drug content was estimated for all the batches. The thin film was cut in 1cm^2 area from two sides and the cut parts were evaluated for drug content using the prior mentioned HPLC method. All the batches were found satisfactory in uniformity of drug. All the films were found about 0.153 mg/cm^2. Results are given in the table 3.

Thickness: All the batches were evaluated for thickness using digital vernier calipers. As all the formulations contain different amount of polymers, hence the thickness was gradually increases with the amount of polymers. All the batches were found to have thickness in the range of 0.2 mm to 0.45 mm. Results are given in the table. Figure 2 shows gradual increase in the thickness.

Table 4: Palatability test of mouth melting film of OND batch S1-S11

Sr.No.	Formulation code	Palatability test			
		Taste	After bitterness	Physical Appearance	Remarks
1	S1	C	C	B	POOR
2	S2	C	C	B	POOR
3	S3	B	C	B	AVERAGE
4	S4	B	B	C	AVERAGE
5	S5	A	B	C	GOOD
6	S6	A	B	C	GOOD
7	S7	A	A	A	VERY GOOD
8	S8	B	B	A	GOOD
9	S9	A	A	C	GOOD
10	S10	A	A	C	GOOD
11	S11	A	A	C	GOOD

Table 5: Stability study of mouth melting film of OND batch S1-S11

Batch code	Drug content (% Of label claim)	Disintegration time (Seconds)	Physical appearance
S1	97.29	5	Sticky
S2	98.51	5	Sticky
S3	98.17	6	Good
S4	98.40	6	Good
S5	97.38	6	Good
S6	98.19	6	Good
S7	98.41	5	Good
S8	98.13	5	Good
S9	98.18	6	Brittle
S10	98.23	7	Brittle
S11	98.28	7	Brittle

Folding endurance: The folding endurance was measured manually for the prepared films. A film was repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. Figure 3 shows the results for all the batches. Initial batches with lower amount of maltodextrin were found having folding endurance between 234 and 236 as the concentration of maltodextrin was increased the folding endurance was improved in later batches. Batches with higher amount of HPMC (E-15) scored lower folding endurance than the higher ones. Batch S7 containing 25% maltodextrin and 20% HPMC (E-15) had scored highest folding endurance (Figure 3).

Palatability study: All the batches were evaluated for the palatability among the group of 5 volunteers. The mouth melting thin films were rated on the basis of taste, after bitterness and physical appearance. Results are given in the table.

A= very good, B=good, C= poor

Formulation S1 and S2 were failed in taste and after bitterness and had average physical appearance. As the concentration of maltodextrin increased the taste of films improved. As the concentration of HPMC (E-15) increased the taste improves but also spoiled the physical appearance of the film. Formulation

S7 was found having a good taste, no after bitterness and good physical appearance as per table 4.

Figure 4: Release profile of mouth melting film of OND batch S1-S6

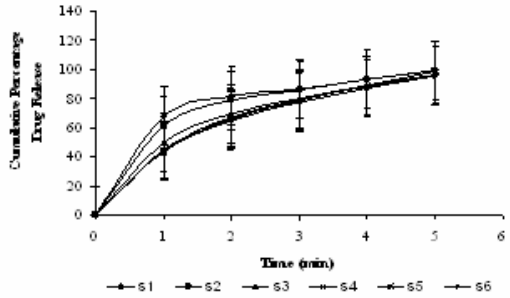
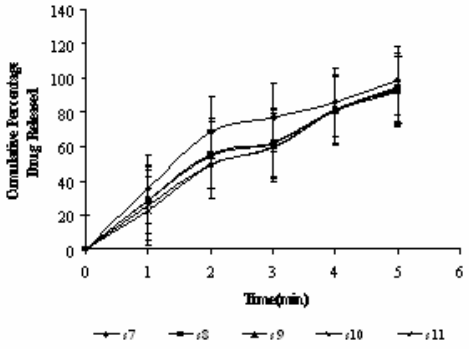


Figure 5: Release profile of mouth melting film of OND batch S7-S11



Disintegration time: Disintegration test was performed for all the batches and all the batches found to disintegrating within 10 seconds. Batches with higher amount of polymers had comparatively high disintegration time as per table 5.

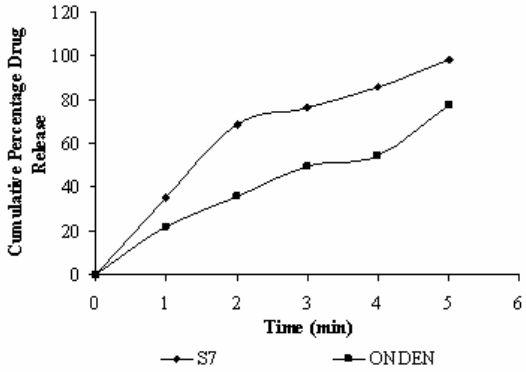
***In-vitro* dissolution studies:** *In-vitro* dissolution study was carried out using USP basket type apparatus and the 500 ml stimulated salivary fluid (pH 6.8) as a dissolution medium at 50 rotations per minute. 10 ml aliquots were withdrawn at the interval of 1 minute and same amount of fresh dissolution medium was replaced immediately. The aliquots were assayed for drug content by HPLC method. Results are shown in the fig. Results showed all the batches release more than 90% of drug within 5 minuets. But the S7 batch releases drug in the linear manner than the other batches. Higher amount of maltodextrin and HPMC-E-15 resulted in release of drug at the slower rate. In first 6 batches the amount of maltodextrin is increasing constantly. Dissolution data of first 6 batches suggests that higher the amount of maltodextrin slower the drug release from the thin films. Figure 4 shows the comparative dissolution profile of first 6 batches.

Later batches i.e. S7 to S11 containing optimum amount of maltodextrin and various amount of HPMC (E-15) showed slower drug release as compared to first six batches (Figure 5). The formulation containing 25% maltodextrin and 20% HPMC (E-15) showed uniform release than other formulations.

Table showing R^2 values for zero order release and first order release. The values for zero order were closer to 1 than those for first order. So, it was assumed that all the formulations followed zero order kinetics. The release is found concentration independent.

The optimized batch S7 was tested against the marketed mouth dissolving formulation (Onden) of OND. The marketed formulation released about 80% of drug in 5 minutes, and S7 released about 99% of drug. Figure 6 shows the comparison between S7 and marketed formulation. Similarity Factor (f_2) was calculated for S7 and marketed formulation and it was found 59.14, which indicates similarity between the two formulations.

Figure 6: Comparison between the release profiles of mouth melting film of OND batch S7 and the marketed preparation



Stability studies: Stability study was carried out for all the batches at 65% relative humidity and 35 ºC temperature in the humidity chamber for the three months. After 3 months the films were evaluated for the drug content, disintegration time and physical appearance observation. After the stability period first two batches that containing lower amount of maltodextrin were physically not compliances with the desired criteria. They lack the physical strength. On the other side the batch with highest amount of

maltodextrin become brittle and it fails in disintegration time test.

CONCLUSION

The mouth melting thin films of Ondansetron is rational in all the aspects of mouth dissolving dosage form. DSC studies show compatibility of drug with the polymers. Optimized formulation passed entire evaluation tests and scores better convenience than the marketed mouth dissolving tablets of Ondansetron. This formulation was also stable at the accelerated conditions. The mouth melting thin films was found superior in palatability and patient convenience than the tablets. It is suitable for pediatrics and elderly patients due to is convenience.

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