RESEARCH ARTICLE

Improving the Drug Loading of Ondansetron Mouth Dissolving Film by the Use of Mix-Solvency Concept and *In-vitro* Evaluation

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ABSTRACT

The ondansetron oral solution film was successfully prepared by the solvent casting method. The combination of HPMC E16 as a film former with honey as a film modifier and PEG400 as a plasticizer produced a uniform, transparent, hard and easy to peel film. The design of experiments has proven to be a very useful tool for understanding the effect of excipients on film properties. The recipe kit powered by Stat Ease Inc. uses Design Expert 11 software trial version. The R1 formulation was found to be the best optimized group with a disintegration time of 68.0 ± 2.16 seconds and a drug release of 104.49 ± 1.06% Hanger 9 minutes.

Keywords: Co-solvency, Mouth Dissolving, Ondansetron.

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INTRODUCTION

The term "water solubility" has been used to describe the water solubility of various poorly water-soluble compounds, the water solubility of which is increased by the presence of large amounts of excipients. Concentrated aqueous solutions of urea, niacinamide, sodium benzoate, sodium salicylate, sodium acetate, and sodium citrate have been observed to increase the aqueous solubility of many sparingly soluble drugs. 'water. Drug solubility, aqueous solubility and synergistic solubility of mixed forms of aqueous solvents. Rather than using a single solvent at a given concentration, lower concentrations of multiple solvents are used to produce a concentrated solution that synergistically increases or increases solubility.[1-4]

This hybrid solution concept makes combining the concentrations of different water-soluble additives (sodium benzoate, sodium citrate, niacinamide) of the so-called water-soluble classes possible. urea), co-solvents (glycerin, propylene glycol, PEG-200, PEG-400, PEG-400, PEG-600), water-soluble solids (PEG-4000 and PEG-6000), low and safe concentrations of hydrochloride for low solubility in the water. Tropical solutions (solid solvents), co-solvents, and mixtures of solvents have been used to measure the solubility of poorly water-soluble model drugs.[5-7]

Hydrotropes, solvents and mixed solvent solutions (40% w/v) were used for solubility studies. Equilibrium solubility measurements used to select appropriate hydrotropes, co-solvents, and solvent mixtures for several poorly water-soluble model drugs.[8]

EXPERIMENTAL

Drug and Excipient Compatibility Study using DSC for Ondansetron Formulation

Excipient compatibility studies were performed on dry formulations of ondansetron MDF by DSC. This study was performed using a V4SA TA Universal Differential Scanning Calorimeter (DSC) from Asian Labs Mumbai. Record thermograms of drugs and drugs with polymers at a test price of 1°C per step per minute in a nitrogen atmosphere at temperatures ranging from 100 to 400°C.[9]

Check recorded thermogram for unusual changes in appearance and changes in elevation.

Drug Excipient Compatibility Study using FTIR Spectroscopy for Ondansetron Formulation

To test drug-excipient compatibility, a 1:20 mixture of neat drug to KBr was prepared using the same ratios of agate and KBr as the dry formulation. to use. These mixtures were then used to make granules in an IR granulator. The prepared particles were then scanned in the 4000–400/cm spectral range. Compare the drug substance and product spectra for unusual peak shifts oror appearances.[10]

Solubility Determination

Add sufficient excesses of indomethacin, aceclofenac, and zaltoprofen to 10 mL amber screw-cap glass bottles containing distilled water and solvent solutions (various mixtures), respectively. Shake the bottle on a mechanical shaker for

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12 hours at room temperature. Allow the solution to equilibrate over the next 24 hours, then centrifuge at 2000 rpm for 6 minutes.

$$\text{Solubility enhancement ratio} = \frac{\text{Solubility in the mixed solvent system}}{\text{Solubility in distilled water}}$$

The Gibbs unfastened strength of switch (AG°tr) of a drug from natural water to aqueous answers of solubilizers has calculated the use of the subsequent equation

$$(AG°tr) = - 2.404RT \text{ Log } [Sc/ S0]$$

In which Sc is the molar solubility of the drug inside the aqueous blended solvent device and S0 is the solubility of the drug in herbal water. The trade-in Gibbs unfastened electricity suggests the system of drug switch from several aqueous water solubilities to aqueous blended solvents. The Gibbs loose strength (AG°tr) of the drug transfer from natural water to combined solvent systems highlights the effectiveness of solubilization.[12]

RESULT AND DISCUSSION

Analytical Methods for Ondansetron Spectrophotometric Determination of Ondansetron in Phosphate-buffer, pH 6.8

Spectra were measured in the UV of a solution of ondansetron drug at a concentration of 10 µg/mL in phosphate buffered saline at pH 6.8. A 248 nm (UV1800) spectrophotometer scan from 200 to 400 nm showed maximum absorption, so 248 nm was chosen as the wavelength of maximum absorption. H. λ_{max}, acquisition.[13-15]

Construct a standard calibration curve for drug evaluation using concentrations ranging from 2 to 22 µg/mL. Determine the triplicate readings' mean absorbance value and standard deviation (SD). The slope is 0.046 and the regression coefficient is 0.999.

Compatibility study of medicinal excipients for the formulation of ondansetron validated by the DSC method (Figures 1 and 2).

The pure drug DSC curve has an endothermic peak at 228.66°C, and the drug-assisted combination has an endothermic peak at 241.66°C. The endothermic peak is slightly shifted due to the presence of the polymer. Miscibility of drug and excipients was ruled out as there was no significant change in the endothermic peak.

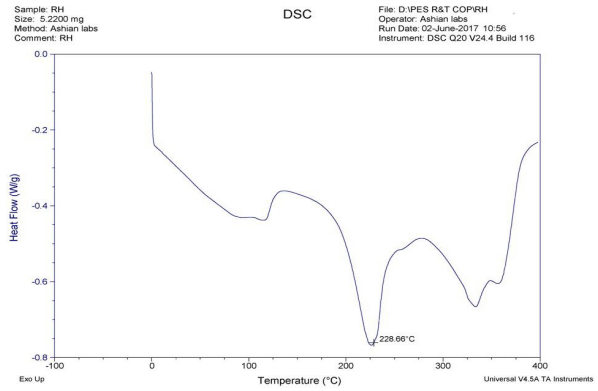

Figure 1: DSC thermogram of ondansetron pure drug

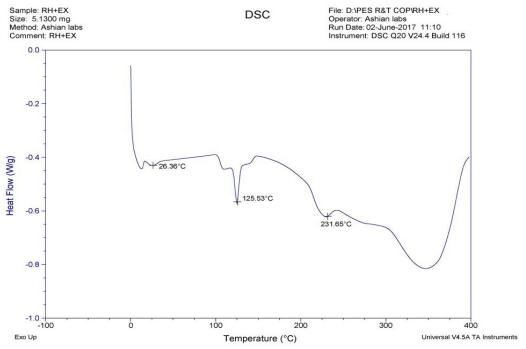

Figure 2: DSC Thermogram of Ondansetron Drug with Excipients

Fourier Transform Infra-red Spectroscopy study for Drug-excipient Compatibility of Ondansetron Formulation

FTIR-recorded IR spectra of the pure drug ondansetron and the drug excipient combination) are shown below (Figures 3 and 4). Characteristic peaks for the drug were identified, as shown in Table 1, representing functional groups in the drug-excipient combination. Spectra of pure drug and drug-excipient combinations were compared. Due to the absence of spectral shifts or peaks, it can be concluded that there is no drug-

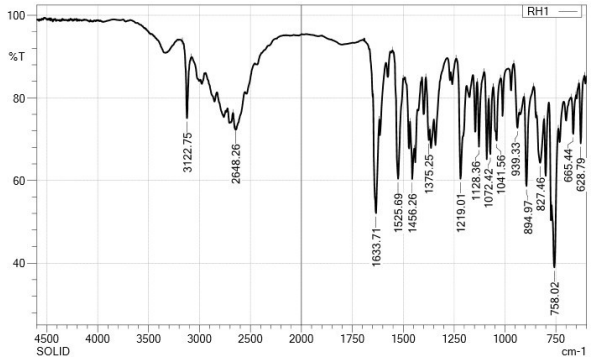

Figure 3: Infra red spectra of ondansetron

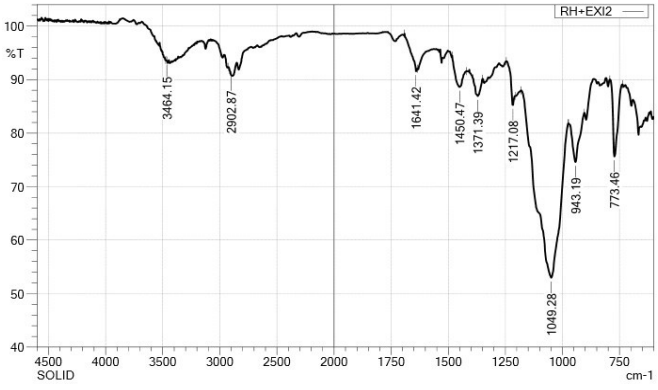

Figure 4: IR spectra of a combination of ondansetron and excipients

excipient interaction in the film formulation of ondansetron in oral solution.[16-20]

The solubility of ondansetron in distilled water was found to be 0.046 mg/mL.

The results show that the solubility of ondansetron in 40% sodium benzoate solution is the highest, the solubility increase rate is 666.021, and the solubility increase rate is arranged from large to small as SB > N > UR > SC > PEGST > PEGFT. PEG 600 solution has the highest solubility, the solubility increase rate is 42.801, and the solubility increase rate from large to small is PEFSH > PEGFH > GLY > PEGTF1 > PG. A maximum solubility enhancement ratio of 188 was found for ondansetron.

Table 1: Interpretation of IR spectra for drug excipient compatibility

Sr no	*Functional groups*	*Ondansetron (Drug)Frequency in cm^{-1}*	*Ondansetron + Excipients Frequency in cm^{-1}*
1	N-H stretch	4411.00	4464.16
2	C-H aromatic	4122.86	4120.0
4	C-H aliphatic stretch	2648.2	2902.8
4	C=O carbonyl	1644.8	1641.4
6	C=C Benzene ring	1466.2	1460
6	Cl Stretch	868.02	884.46

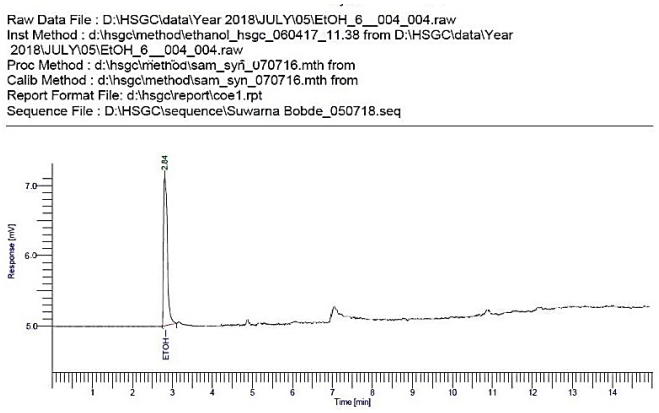

Figure 6: Chromatogram of Standard-2 4 µg/mL Concentration using HSGC

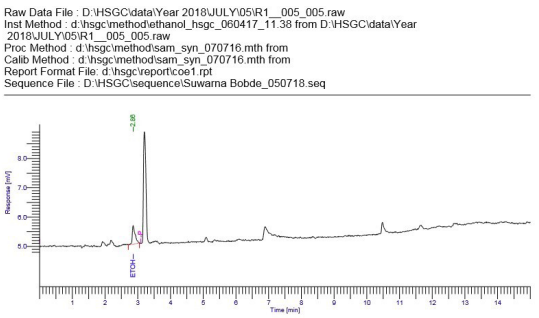

Figure 7: Chromatogram of standard-4 6 µg/mL concentration using HSGC

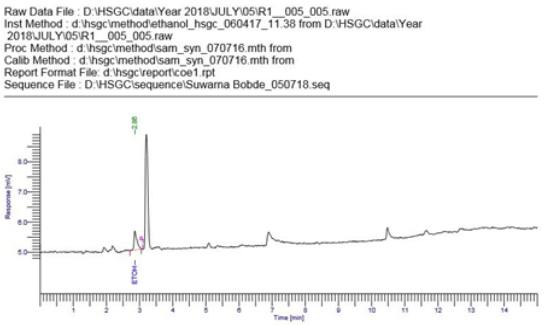

Figure 8: Chromatogram of sample R1 using HSGC

Table 3: Physicochemical evaluation of ondansetron MDF

Code	*DT (s)*	*T.S (g/cm^2)*	*DR at 9 minutes*
R1	69.0 ± 2.01	86.66 ± 2.48	108.42 ± 1.66
R2	66.66 ± 2.61	82.48 ± 2.91	104.49 ± 1.68
R4	84.00 ± 2.64	91.09 ± 1.44	90.44 ± 2.06
R4	80.0 ± 4.06	86.68 ± 1.64	89.08 ± 4.88
R6	88.0 ± 2.64	94.44 ± 4.81	89.02 ± 2.66
R6	89.44 ± 4.61	100.84 ± 0.84	84.89 ± 2.64
R8	90.44 ± 2.61	96.68 ± 1.64	84.84 ± 1.89
R8	94.66 ± 4.60	104.68 ± 1.49	89.88 ± 4.60
R9	110.98 ± 4.60	114.08 ± 2.46	62.62 ± 4.08

DT= Disintegration-time, TS= Tensile-strength, DR= Drug-release

Results are presented as mean ± SD (n=4)

Table 2: Physicochemical evaluation of ondansetron MDF

Code	*W (mg)*	*T (mm)*	*FE*	*Surface pH*	*Assay (%)*
R1	44.64 ± 2.08	0.096 ± 0.006	846.44 ± 4.61	6.66 ± 0.01	100.84 ± 1.08
R2	64.0 ± 4.60	0.10 ± 0.01	864.44 ± 4.06	6.80 ± 0.01	100.62 ± 0.86
R4	86.0 ± 2.64	0.114 ± 0.006	806.44 ± 4.06	6.80 ± 0.01	102.18 ± 1.22
R4	68.44 ± 4.08	0.114 ± 0.006	814.00 ± 4.60	6.86 ± 0.01	100.16 ± 1.41
R6	64.44 ± 2.08	0.110 ± 0.01	822.66 ± 2.61	6.88 ± 0.01	100.86 ± 1.08
R6	84.0 ± 1.0	0.124 ± 0.006	849 ± 4.60	6.86 ± 0.01	101.86 ± 1.84
R8	81.0 ± 4.60	0.144 ± 0.006	868 ± 4.00	6.88 ± 0.01	98.06 ± 1.68
R8	82.44 ± 2.61	0.126 ± 0.006	889 ± 4.60	6.89 ± 0.01	101.68 ± 0.46
R9	80.0 ± 1.0	0.146 ± 0.006	946.44 ± 2.61	6.84 ± 0.02	99.62 ± 0.68

W= weight, T= Thickness, FE= Folding Endurance

Results are presented as mean ± SD (n=4)

Table 4: Comparative *in-vitro* drug release study of ondansetron MDF

Time/ (min) Code	*R-1*	*R-2*	*R-4*	*R-4*	*R-6*	*R-6*	*R-8*	*R-8*	*R-9*
4	64.94 ± 1.90	48.16 ± 1.64	48.02 ± 1.88	48.06 ± 1.96	40.02 ± 1.28	24.88 ± 1.09	41.26 ± 1.04	20.96 ± 2.48	26.88 ± 2.89
6	94.84 ± 1.48	68.44 ± 1.69	68.48 ± 0.82	86.41 ± 2.12	69.66 ± 1.48	66.60 ± 1.00	64.18 ± 1.16	60.86 ± 1.01	49.18 ± 1.68
9	108.42 ± 2.46	104.49 ± 1.44	90.44 ± 2.20	89.08 ± 2.48	89.02 ± 1.44	84.89 ± 1.60	84.84 ± 1.89	89.88 ± 0.66	62.62 ± 1.44
12	-		101.98 ± 1.46	98.82 ± 2.49	86.01 ± 1.49	89.01 ± 1.66	91.90 ± 1.66	82.04 ± 2.48	81.68 ± 1.98
16	-		-	104.90 ± 1.44	92.81 ± 2.46	98.89 ± 1.64	100.62 ± 1.88	96.06 ± 2.26	96.06 ± 1.26
18	-	-	-	-	101.48 ± 1.64	102.24 ± 1.24	-	104.00 ± 0.98	101.99 ± 1.10
21	-	-	-	-	-	-	-	-	-

The Results are represented as mean ± SD (n=4)

Table 5: Summary for ANOVA and regression analysis for disintegration time

Outputs	*DF*	*SS*	*M S*	*F*	*p-value Prob > F*
Model	2	2064.16	1026.68	91.00	< 0.0001
HPMC E16	1	486.64	486.64	44.06	0.0006
Honey	1	1668.62	1668.62	148.96	< 0.0001
Residual	6	68.68	11.28	-	-
Total	8	2120.84	-	-	Significant

Response	*p-value*	R^2	*Adjusted-R^2*	*Predicted-R^2*	*Adequateprecision*	*SD*	*CV%*
Y_1	< 0.0001	0. 9681	0. 9684	0. 9224	26. 9499	4. 46	4. 14

Reduced Model equation: $Y_1 = 81.14 + 9.0\ X_1 + 16.16\ X_2$

Table 6: Calibration curve data for solvent ethanol in distilled water

Sample name	*The concentration of EtOH (µg/mL)*	*Area from chromatogram*
EtOH-1	1.0421	2016.84
EtOH-4	4.0964	8214.64
EtOH-6	6.1926	14948.42
R1	1.8 (from graph)	4866.62
Regression equation	Y=2299x-186.88	
Regression coefficient R^2	0.998	
Slope	2299.0 Intercept	-186.8

% (w/w) ethanol= (4866.62+186.8) / 2299 X 60/240 X104.21/1000= 0.049%

For the three fixed-ratio solvent combinations, a magnification of 44 times was obtained when combined with the SB+N+SC mixture. These results of the solubility study show that the combination of solvents has a harmonious effect on the solubility of a poorly water-soluble drug, namely ondansetron. Further, adjust the ratio of each solubilizer to achieve maximum solubility.

In the combined mixture SB + UR + SC, the maximum solubility improvement ratio of ondansetron in the combination of the three solvents in different ratios was more than 204.094 times. The results of these solubility studies reflect that the combination of solvents has a synergistic effect on low water solubility. Water-soluble substances include the drug ondansetron. Observations indicated that different combinations of the three solvents had no major effect on drug solubility. Only high concentrations of sodium benzoate and nicotinamide had a synergistic effect on solubility, with a maximum ratio of solubility enhancement of 204.094 found the SB:UR:SC combination at a ratio of 20:10:10, which was the greatest improvement in drug solubility. It's a relationship. There are 268.46 combinations of different proportions of the four combinations. For all combinations of four-solvent aqueous systems, the total concentration of all solvents is 40% w/v.

The results showed increased solubility of ondansetron in various mixtures of solubilizers. The maximum solubility ratio of SB+N^UR+SC was found to be 14:12:8:6, indicating a 268.46 fold increase in solubility. The maximum parental solubility improvement ratio of ondansetron in each combination of the six combined solutions was 440.24 times and again 440.

24 times, probably due to the additive/synergistic effects of the combined solvents. In all aqueous mixed solvent configurations (combinations of 6–8 solvents), the total energy of all solvents becomes 46 and 4% w/v. The results showed that the solubility of ondansetron in the combined solvents was prolonged. Blend IB was found to have a maximum solubility of 14 and a solubility improvement factor of 440.24.

Optimization of Ondansetron Mouth Dissolving Film using 4^2 Factorial Design[20-23]

The results of the evaluation of nine ondansetron oral dispersible film formulations prepared using the experimental design are shown in the table. Film weights ranged from 44.44 ± 2.08 mg to 80.00 ± 1.0 mg. The film thickness was found to be between 0.096 ± 0.006 mm and 0.146 ± 0.006 mm. The wrinkle resistance of the films was found to range from 846.44 ± 4.61 to 946.44 ± 2.

The physicochemical evaluation of ondansetron MDF for different parameters is described in Tables 2 and 3.

Table 7: Stability results of optimized formulation R1

Evaluation parameters	*40 days*	*60 days*	*90days*
Physical observation	Transparent film	Transparent film	Transparent film
Weight (mg)	46.0 ± 0.86	44.66 ± 1.16	44.6 ± 2.62
Thickness (in mm)	0.1 ± 0.001	0.1 ± 0.002	0.1 ± 0.004
Folding capacity/endurance	840 ± 6.0	846 ± 4.0	844 ± 4.0
Surface pH	6.66 ± 0.02	6.88 ± 0.01	6.8 ± 0.02
In-vitro disintegration time (s)	68.0 ± 2.16	66.0 ± 4.06	68 .0 ± 2.62
% Drug release at 9 minutes	104.49 ± 1.06	104.66 ± 2.62	104.21 ± 1.16
Assay (%)	100.82 ± 1.16	100.04 ± 1.00	100.24 ± 2.62

Results are represented as mean ± SD (n=4)

Whereas a comparative *in-vitro* drug release study of ondansetron MDF is shown in Table 4.

Study of Effect of Formulation Variable on Disintegration Time[24-26]

Data from 42 factorial designs showed the best linear model for the Y1 response. Cooldown was reasonable. A summary of the regression analysis and ANOVA is shown in Table 5. The p-value was found < 0.0001, the model was classified as significant. Predicted R2 values were in acceptable compromise with adjusted R2 values of 0.9224 and 0.9684, respectively. The difference was less than 0.2. A reasonable measurement accuracy for the S/N ratio was found to be 26.960. Model *F*-value 91.

Stability Study[27]

The optimized formulation did not show any visual change in appearance and the results of the entire test conducted, which are described in Table were found to be within limits which indicates the stability of the formulation. Various chromatograms are shown in Figures 5-7. Calibration Curve Data for Solvent Ethanol in Distilled Water mention in Table 6.

RESULT

Ethanol is a class 4 residual solvent. The class 4 solvent limit per USP40 NF 46/ICH Guideline Q4C (R6) is no more than 60 mg per day, which equates to 6000 ppm or 0.6%. Ondansetron MDF can be considered safe for administration to cancer patients as the amount of solvent is well below the specified limits.

Stability Study[28]

A stability study of ondansetron MDF was performed on optimized lot R1 for 90 days at room temperature and ambient humidity, results are shown in Table 7.

CONCLUSION

The experimental layout is a useful tool for understanding the effect of excipients on average film properties. The set of plugins is efficiently optimized using Stat Ease Inc.'s Layout Software, Trial Version 11.0. The R1 system is the largest optimized group with a fallback time of 68.0 ± 2.16 seconds, 104.49 ± 1.06% drug release after 9 minutes.

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