RESEARCH ARTICLE

Solubility Enhancement and Formulation Development of an Oral Film of Ondansetron Hydrochloride Monohydrate using Mix-solvency Concept

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ABSTRACT

This research paper presents the formulation and evaluation of ondansetron hydrochloride monohydrate oral film using the mix-solvency concept. Ondansetron hydrochloride monohydrate a selective serotonin receptor antagonist is commonly prescribed to prevent chemotherapy or surgery-induced nausea and vomiting. The aim of the study was to enhance the solubility of ondansetron hydrochloride monohydrate which has been enhanced by the blend of varying aqueous solubilizers poly ethylene glycol, niacinamide, and caffeine. The oral film formulation was prepared using a solvent casting method, incorporating polymers, plasticizers and different solvents. Various formulation variables, including solvent type and concentration, polymer-to-plasticizer ratios, and drug loading, were optimized systematically the resulting oral film was investigated for various parameters such as thickness, drug content, disintegration time, folding endurance and surface pH. The % *in-vitro* release of drug of the best two formulations F3 and F5 was 99.70 and 96.62%, respectively.

Keywords: Solubility, Ondansetron hydrochloride, Mix-solvency.

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INTRODUCTION

Surfactants, cyclodextrin complexes, solid dispersions, micronization and non-ionisizing, permeation enhancers, supercritical technology gastro retentive, systems, nanosuspensions, dendrimers, carbon nanotubes, and most recently, lipid-based formulations have all been used to improve oral bioavailability in an effort to solve bioavailability issues.[1] Due to the rapid blood flow and 4 to 1000 times greater permeability of the oral mucosa than that of the skin, fast-dissolving oral films provide quick absorption and instant bioavailability of drugs.[2,3] In 70 to 80% of chemotherapy patients experience emesis within or after 24 hours of administration, and 10 to 44% of patients experience anticipatory emesis for a subsequent cycle of chemotherapy.[4] The solution of this problem is ondansetron hydrochloride monohydrate which has a low biological half-life (3–5 hours), which varies depending on the subject and a low bioavailability of about 60%.

Ondansetron hydrochloride monohydrate hydrochloride (ONH) is a 5-HT3 receptor antagonist that is typically prescribed as a first-line treatment for nausea and vomiting brought on by cancer chemotherapy, long-term medical conditions, gastroenteritis, and post-operative conditions.[5]

FDOFs was first of all defined in 1970 so that the drug will be used for disabled patient and also to create rapid DDS.[6,7] FDO films are one of the newer solid dosage forms used orally due to comfort.[8] OTFs have a shelf life of 203 years and are sensitive to moisture present in the environment.[9] The soluble oral film is available in doses of 4 and 8 mg is a new oral dosage form for ondansetron hydrochloride monohydrate proposed by Par Pharmaceutical, Inc. Ondansetron hydrochloride monohydrate has a better tolerability profile than metoclopramide and chlorpromazine in the context of chemotherapy and performs noticeably better. In comparison to placebo, droperidol, and metoclopramide, ondansetron hydrochloride monohydrate showed superior prophylactic antiemetic efficacy in children

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Table 1: Drug solubility in various solubilizers and their blends

S. No.	*Solubilizer blends*	*Solubilizer conc. in %w/v*	*Solubility in mg/mL*	*%Ration of solubility enhancement*
1	Demineralized water	-	0.072	-
2	PEG	15	0.033	0.458
		20	5.832	81
3	Glycerin	15	6.023	83.65
		20	8.753	121.56
4	PEG 400	15	12.658	175.80
5	PEG 600	15	10.356	143.83
6	PVP K 25	5	0.256	3.555
7	Urea	2	3.742	51.97
8	Caffeine	5	30.92	429.44
9	Niacinamide	5	0.32	4.444
10	Sodium caprylate	5	0.523	7.263
11	Cyclodextrin	5	2.232	31
12	Vanillin	1	0.896	12.44
13	PEG400: CAF	20:2	25.56	355
14	GLY: CAF	20:2	12.08	167.77
15	CYCLO: CAF	20:2	1.02	14.16
16	PEG600: CAF	20:2	20.89	290.1
17	UR: CAF	2:2	2.53	32.63
18	PG: CAF	20:2	2.75	38.19
19	NM: CAF	2:2	3.13	43.47
20	CAFF: SC	2:2	1.69	23.47
21	$PVPK_{25}$: CAF	2:2	0.49	6.805
22	CAF: NM	5:5	13.50	187.5
23	NM: PEG400: CAF	2:15:2	5.19	56.11
24	NM: PEG600: CAF	2:15:2	8.92	96.21
25	NM: PEG400: CAF	5:15:5	82.2	1141.66
26	NM: PEG600: CAF	5:15:5	70.25	975.69

Table 2: Properties of film of HPMC E-15

Polymer	*blend of solubilizers*	*Properties of film*		
		Appearance	*Pourability*	*Thickness (mm)*
HPMC E15 (6%)	B1	Translucent	Easy to pour	0.05
	B2	Transparent	Easy to pour	0.01
HPMC E15 (7%)	B1	Hazy	Slightly Difficult	0.09
	B2	Hazy	Slightly Difficult	0.09
HPMC E15 (7.5%)	B1	Translucent	Very Difficult to pour from vial	Whole solution was not incorporated in film
	B2	----	Non –pourable (Stuck inside vial)	

undergoing surgery. It also showed a low incidence of side effects.[10,11] The solvency process using solvents or soluble solids may be combined so that there will be an enhancement in the solubility of drug that are poorly water-soluble or else they may reduce the toxicity of individual solubilizers in the formulation.[12]

Table 3: Film properties in the presence of different concentration of PEG 600

Plasticizer concentration		*10% v/v*	*15% v/v*	*20% v/v*
Appearance	B1	Hazy	Translucent	Transparent
	B2	Hazy	Translucent	Transparent
Thickness (mm)	B1	0.1	0.08	0.4
	B2	0.12	0.09	0.2
Folding endurance	B1	174	220	186
	B2	182	226	188

Table 4: Formulation development of film

Batch of film	*F1*	*F2*	*F3*	*F4*	*F5*
Blend (8.5 mL)	B1	B1	B1	B2	B2
HPMC E15 (%w/v)	5.0	5.2	5.5	5.8	6.0
PEG600 (%v/v)	15	15	15	15	15
The drug used for 10 mL film solution (mg)	100	100	100	100	100

Table 5: Evaluation parameter of film

S. No.	*Coding*	*Folding Endurance ± S.D.*	*Disintegration Time (Sec) ± S.D.*	*Thickness (mm) ± S.D.*	*Surface pH*
1	F_1	150 ± 1 .01	58 ± 0.23	0.087 ± 0.13	6.72
2	F_2	153 ± 2.36	54 ± 1.63	0.097 ± 1.68	6.82
3	F_3	162 ± 1.25	50 ± 2.36	0.078 ± 0.54	6.80
4	F_4	151 ± 2.33	60 ± 0.89	0.123 ± 0.83	6.89
5	F_5	160 ± 1.92	49 ±1.05	0.075 ± 0.02	6.81

MATERIALS AND METHODS

Drug Procurement

Ondansetron hydrochloride monohydrate had been provided as a gift sample from Asoj soft Cap Pvt. Ltd, Vadodara, Gujarat. All excipients were of analytical grade obtained from Mandsaur University, Mandsaur, MP.

Solubility Studies

Solubility of the drug was determined in various solvents and %solubility was noted down (Table 1).[13]

Solvent Casting Method

Polymers that are water soluble were dissolved in the solvent and the drug + excipients was dissolved and was cast in petri plate and dried.[14]

Preparation of solubilizers and their blends in aqueous solution

For the selection of solubilizers, different concentrations and ratios of hydrophilic chemicals and plasticizers were used in (%w/v) such as caffeine, sodium citrate, niacinamide, β-cyclodextrin, propylene glycol, PEG 400, PEG 600, glycerin, PVP K 25 etc. The overall solute concentration in the prepared solution was kept ≤ 30% w/v conc. and the % solubility was noted down.

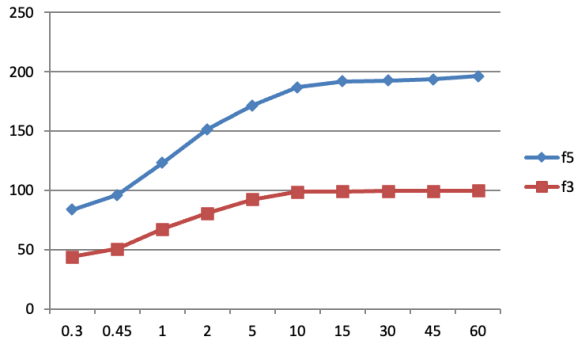

Figure 1: %Drug release of optimized batches

Table 6: Cumulative %drug release

Time (Second/Min)	*Cumulative %drug release*				
	F1	*F2*	*F3*	*F4*	*F5*
0.3	32.40	20.50	43.95	30.90	39.75
0.45	35.80	25.39	50.79	39.90	45.33
1	45.67	30.25	67.52	44.90	55.67
2	52.66	35.26	80.72	50.50	70.85
5	60.25	40.32	92.47	52.60	78.95
10	62.98	41.22	98.68	55.80	88.25
15	70.25	50.12	99.13	60.42	92.65
30	74.33	52.23	99.57	62.63	92.87
45	80.23	55.62	99.62	82.96	93.99
60	80.99	60.23	99.7	85.66	96.62

Solubilizer's blend selection

Based on the solubility enhancement of ondansetron hydrochloride monohydrate in different concentrations of individual solubilizers and their combinations, two best blends of solubilizers were selected of blend composition NM: PEG 400: CAF =5:15:5 (B1) and NM: PEG 600: CAF = 5:15:5(B2), for further studies.

Polymer concentration: optimization

Polymer i.e., HPMC E-15 having different conc. were used to form film and various properties were noted down (Table 2).

Selection of plasticizer

Taking HPMC E-15 as a polymer with different plasticizer concentrations (15% v/v) films were formulated and their different properties were observed (Table 3).

Preparation of oral film

The drug (100 mg) was taken and dissolved in a solubilizer and then PEG-600 & HPMC E-5 were added and the volume was made to 10 mL with DMW. It was dried at 40°C for 24 hours and then film was cut in the desired size. Table 4 represents the formulation development.

Table 7: Stability studies of final optimized batches F3 and F5

Stability at specific temperature	*Sampling duration (Days)*	*%Drug content (4 mg/ 4 cm^2)*		*pH*	
25 ± 2°C		Batch F3	Batch F5	Batch F3	Batch F5
	0	99.22	99.41	6.81	6.81
	7	98.33	98.08	6.82	6.83
	14	98.20	98.62	6.85	6.80
	21	97.18	98.25	6.84	6.85
	28	97.34	97.99	6.82	6.86
	35	96.69	97.82	6.85	6.84
	42	96.34	96.22	6.84	6.80
	49	96.34	96.59	6.67	6.56
	56	96.30	95.88	6.45	6.42
	63	96.25	95.63	6.92	6.90
	70	95.6	95.05	6.91	6.90
2–8°C	0	99.47	99.24	6.85	6.72
	7	98.67	98.23	6.81	6.77
	14	98.93	98.56	6.82	6.80
	21	97.02	98.33	6.80	6.82
	28	97.58	98.03	6.81	6.82
	35	96.44	96.62	6.67	6.52
	42	96.51	96.23	6.42	6.74
	45	95.55	96.31	6.65	6.82
	56	95.77	95.76	6.45	6.80
	63	94.32	95.11	6.90	6.65
	70	94.87	94.24	6.68	6.72

Evaluation Parameters

The prepared film was evaluated for DT, folding endurance, thickness, surface pH as per the standard method and the results are mentioned in Table 5.

Dissolution data of optimized batch F3 and F5

%DR of optimized batches were determined in the simulated salivary fluid was found to be 90.70 and 96.62%, respectively. The results are given in Table 6.

Drug content

In 10 films were taken to determine the %DC, weighed 100 mg and powdered, and was taken in 100 mL of VF. Phosphate buffer pH 6.8 was added and shaken for 6 to 8 hours. This was filtrated and filtrate was made to 100 mL with buffered and DC was determined at 232 nm. Results were given in Table 7.

RESULT AND DISCUSSION

The present research paper focuses on the formulation and evaluation of an oral film of ondansetron hydrochloride monohydrate using the innovative mix-solvency concept. Ondansetron hydrochloride monohydrate is a crucial drug used in preventing chemotherapy and surgery-induced nausea and vomiting. However, its low solubility and bioavailability have been major challenges. This study aimed to overcome these challenges and develop an effective oral dosage form. The mix-solvency concept, which involves combining water-soluble substances like polyethylene glycol, niacinamide, and caffeine was employed to enhance the solubility of ondansetron hydrochloride monohydrate. This concept not only improved solubility but also mitigated the individual toxicity of solubilizers in the formulation.

The formulation was prepared using a solvent casting method, incorporating polymers, plasticizers, and different solvents. A systematic optimization process was employed, considering various promising results, with % *in-vitro* drug release of 99.7 and 96.62, respectively (Figure 1). These formulations demonstrated fast disintegration without the need for water, making them suitable for rapid drug delivery.

The study also highlighted the Importance of selecting the right solubilizer and its blends, with the combination of niacinamide, PEG 400 and caffeine (blend B2) proving to be particularly effective. Additionally, HPMC E-15 was identified

as the optimal polymer and polyethylene glycol 600 was chosen as the plasticizer for the formulation.

Stability studies conducted at different temperatures (25 ± 2°C and 2–8°C) over a span of 70 days demonstrated that the final optimized formulations, F3 and F5 maintained acceptable drug content and pH levels. This indicates the potential for long-term stability and storage.

CONCLUSION

This research paper successfully developed and evaluated an oral film of ondansetron hydrochloride monohydrate using the mix-solvency concept. The optimized formulations F3 and F5 exhibit excellent drug release profiles and stability characteristics. These fast-dissolving films have the potential to provide a convenient and effective dosage form for patients experiencing nausea and vomiting due to chemotherapy or surgery, ultimately improving patient compliance and therapeutic outcomes.

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