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DEVELOPMENT AND CHARACTERIZATION OF TRANSDERMAL PATCH OF ONDANSETRON MICROSPONGE TO TREAT CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

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ABSTRACT

The present study aims to develop ondansetron microsponge loaded transdermal patch for the management of Chemotherapy-induced nausea vomiting (CINV). **Method and results**: Microsponges were prepared by using the quasi-emulsion solvent diffusion method, optimized the formulations by selecting suitable retardant material (Ethyl cellulose and Eudragit L 100), type of internal phase, volume of internal and external phase, concentration of surfactants and process variables such as stirring conditions like speed and time. F10 showed the highest entrapment efficiency (94.99%) and 95.12% in vitro drug release. This optimized formulation was further incorporation into a patch base, Optimized Microsponge loaded transdermal patch (M-LTP) was compared with Ondansetron loaded transdermal patch (O-LTP). The M-LTP showed highest drug release compared to O-LTP and M-LTP demonstrated a consistent and sustained drug release over 11 hours. The stability studies demonstrated that the prepared microsponge (F10) And M-LTP has good stability after one months, with no considerable changes. **Conclusion:** The optimized microsponges showed the desired drug release profiles and physical characteristics. M-LTP of ondansetron can be a promising system for the transdermal for effective treatment for chemotherapy induced nausea vomiting (CINV).

KEYWORDS: Ondansetron, Microsponges, Quasi emulsion solvent diffusion, Ethyl cellulose, Eudragit L 100, O-LTP, M-LTP.

1. INTRODUCTION

Chemotherapy-induced nausea vomiting (CINV) is one of the most distressing side effects of chemotherapy; approximately 70 % of patients who receive chemotherapy will experience some level of CINV. CINV can cause significant discomfort and anxiety, dehydration, electrolyte imbalances, affect normal physical and mental function, and decrease quality of life. Hence, some patients may choose to give up the beneficial chemotherapy in the end due to its side effects, CINV still remains as an important issue.[1]

Microsponges are polymeric drug delivery system composed of porous microspheres having a particle size of 5-300µm with an average pore size of 0.25 µm, which is lesser than most of the size ranges of the microorganisms, as a result, preventing their penetration. This is why microsponges are called as self sterilizing and they do not need any kind of excipients for the stability of microsponges, Additionally they have capability to entrap a wide range of active ingredients. They can deliver the drug efficiently at a minimum dose with enhanced stability, reduced side effects and modified drugs release profile.[2]

Use of antiemetic medications is very common in clinical practice. Ondansetron, a member of the serotonin (5-hydroxytryptamine) subtype 3 (5-HT3) group of receptor antagonists, can effectively act on chemoreceptor trigger zone of postrema to control nausea and vomiting. As Ondansetron does not inhibit dopamine subtype-2 receptors, it does not cause side effects such as extrapyramidal reactions. Although Ondansetron is a potent antiemetic, including for patients receiving highly emetogenic agents, oral administration is only effective in patients who can swallow medications after chemotherapy.

Several disadvantages with oral, intravenous and rectal administration include extensive liver metabolism, low bioavailability, vomiting before drug absorption, rapid onset that may result in undesirable side effects, high clearance, short half-life, and low patient compliance. A patch containing drug-loaded microsponge offers several advantages, i.e. microsponges can control drug release, reduce initial burst effects, and improve drug kinetics, can increase solubility, permeability, and lead to better bioavailability. microsponges can carry high drug payloads, reducing the need for multiple patches.[3]

Microsponge-based patches can be designed to deliver drugs at varying durations, and doses. These patches can provide sustained release, reducing the need for frequent dosing. By incorporating drug-loaded microsponges into patches, drug delivery becomes more efficient, comfortable, and effective, leading to better patient outcomes.

Our research focused on the successful development and optimization of Ondansetron - loaded microsponges using the quasi-emulsion solvent diffusion method, followed by their evaluation and incorporation into transdermal patch prepared with film forming polymers. The study demonstrated that by optimizing various formulation parameters, such as the concentration of polymers and surfactants, type of internal phase, volume of internal and external phase, and process variables such as stirring conditions like speed and time, the desired drug release profiles and physical characteristics of microsponges could be achieved.

2. MATERIALS AND METHOD

2.1 MATERIALS

The formulation of Ondansetron-microsponges loaded transdermal patch utilized various chemicals and excipients. Ondansetron was provided by Shilpa Medicare Limited (SML). Ethyl cellulose and Eudragit L 100 were sourced by SD fine chemicals, Mumbai. Methanol, ethanol were sourced from Qualigens Fine Chemicals, Mumbai. Dichloromethane sourced from Karnataka Fine Chem, Bangaluru. Acetic acid and Propylene glycol obtained from Nice Chemicals Pvt. Ltd. HPMC K100M and Xanthan gum wers supplied from Essel Fine Chem. Mumbai.

2.2 METHODOLOGY

PRE-FORMULATION STUDIES

Pre-formulation testing is the initial stage in developing dosage forms for a drug substance, examining its physical and chemical properties alone and when combined with excipients, with the aim of generating useful information for mass-produced dosage forms.

2.2.1 Calibration curve of Ondansetron

2.2.1.1 Preparation of Phosphate buffer (pH6.8)

Accurately weighed 28.8gm of potassium dihydrogen phosphate and 11.45gm disodium hydrogen phosphate was dissolved in water in a 1000ml volumetric flask and the volume was made up to the mark with distilled water.

2.2.1.2 Determination of λmax of Ondansetron

To determine the wavelength of maximum absorption (λmax), Ondansetron solution (10µgm/ml) was prepared using phosphate buffer of pH 6.8 and scanned in UV wavelength 200-400nm using the buffer solution as blank solution.

2.2.1.3 Preparation of solutions for calibration curve

- **Stock-1**

Solution of concentration 1000µgm/ml was prepared using ethanol as solvent.

- **Stock-2**

Solution of concentration 100µgm/ml was prepared using phosphate buffer (6.8) pH.

Serial dilution

Serial dilutions were made using phosphate buffer to get the concentration ranging from 2-16 µgm/ml. Stock solutions of desired concentrations were prepared and the absorbance was measured at 310nm using UV visible spectrophotometer.

2.2.2 Compatibility studies

The compatibility of the drugs with excipient was determined. Any change in the chemical composition of the drug after combining it with the polymer was investigated with I.R. spectral analysis.

A weighed amount of drugs with excipient were mixed with IR grade KBr (1:10) and compressed under 10- ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by FT-IR Spectrophotometer over a range of 4000 cm^{-1} to 400cm^{-1} range.

2.2.3 Method of preparation of microsponge

Quasi- emulsion solvent diffusion method

The procedure involves the preparation of two phases, the internal phase contains the drug and polymers in a suitable solvents and external phase contains water and the surfactant, the internal phase is slowly added to the external phase under stirring, further the mixture is filtered to separate the microsponges and dried in the hot air oven at 40^0C for 12h and weighed to determine the yield.[4]

Table 1: Composition of Ondansetron loaded Microsponge.

Batch	Drug: Polymer ratio	Type of internal phase	Volume of internal phase (ml)	Volume of External phase (ml)	Surfactant Conc. (%)	Stirring speed (RP)	Stirring time (min)
INFLUENCE OF TYPE AND CONCENTRATION OF RETARDENT MATERIAL							
F1	(EC) 1:7.5	Ethanol:DCM	10	100	0.5	1500	120
F2	1:10	Ethanol:DCM	10	100	0.5	1500	120
F3	1:12.5	Ethanol:DCM	10	100	0.5	1500	120
F4	(Eud) 1:7.5	Ethanol:DCM	10	100	0.5	1500	120
F5	1:10	Ethanol:DCM	10	100	0.5	1500	120
F6	1:12.5	Ethanol:DCM	10	100	0.5	1500	120
INFLUENCE OF DRUG: POLYMER RATIO							
F6	1:12.5	Ethanol:DCM	10	100	0.5	1500	120
F7	2:12.5	Ethanol:DCM	10	100	0.5	1500	120
F8	3:12.5	Ethanol:DCM	10	100	0.5	1500	120
INFLUENCE OF TYPE OF INTERNAL PHASE							
F8	3:12.5	Ethanol:DCM	10	100	0.5	1500	120
F9	3:12.5	Methanol:DCM	10	100	0.5	1500	120
INFLUENCE OF INTERNAL PHASE VOLUME							
F8	3:12.5	Ethanol:DCM	10	100	0.5	1500	120
F10	3:12.5	Ethanol:DCM	15	100	0.5	1500	120
F11	3:12.5	Ethanol:DCM	20	100	0.5	1500	120
INFLUENCE OF SURFACTANT CONCENTRATION							
F10	3:12.5	Ethanol:DCM	15	100	0.5	1500	120
F12	3:12.5	Ethanol:DCM	15	100	0.75	1500	120
INFLUENCE OF EXTERNAL PHASE VOLUME							
F10	3:12.5	Ethanol:DCM	15	100	0.5	1500	120
F13	3:12.5	Ethanol:DCM	15	150	0.5	1500	120
INFLUENCE OF STIRRING SPEED AND TIME							
F10	3:12.5	Ethanol:DCM	15	100	0.5	1500	120
F14	3:12.5	Ethanol:DCM	15	100	0.5	1000	60

2.2.3 EVALAUATION OF MICROSPONGES

2.2.3.1 Determination of production yield

The production yield of the microsponges was determined by calculating accurately the initial weight of the raw materials and the final weight of the microsponges obtained.

Production yield = Practical mass of microsponges / Theoritical mass × 100

2.2.3.2 Drug content

The various batches of the Microsponges were subjected for drug content analysis. Accurately weighed Microsponge samples were powdered. The powdered Microsponge were dissolved in adequate quantity of phosphate buffer pH 6.8 and then filtered. The UV

absorbance of the filtrate was measured using a UV spectrometer at 310 nm, keeping phosphate buffer as blank.

2.2.3.3 Entrapment efficiency

Microsponge containing equivalent to 10 mg of drug was allowed to equilibrate in 100 ml of phosphate buffer pH 6.8 for 24 h. The solution was filtered using Whatman filter paper. The resulting solution was analyzed using a UV spectrophotometric method at 310 nm, using phosphate buffer as blank.[5]

% Drug entrapment = Calculated drug concentration / Theoretical drug concentration × 100

2.2.3.4 Particle size distribution

Measurement of the particle size distribution and mean diameter of microsponges was carried out with an optical microscope. Stage micrometer was used to calibrate the eye piece micrometer. 10 deviation of stage micrometer was matched with the deviation of eye piece micrometer and calibration factor was calculated. The particle size was calculated by multiplying the number of the deviation of the eye piece micrometer occupied by the particle with calibration factor. 30 randomly chosen microsponges taken to measure their individual size.

2.2.3.5 Surface morphology studies

SEM analysis was done on the optimized aquasomes exterior morphology. The powders were imaged by a scanning electron microscope (SEM) run at an accelerating voltage of 10kV using ZEISS EVO 18 SEM. The powder in few µg were fixed on to the stub by a double sided sticky carbon tape and subjected to sputter coating then kept inside the SEM chamber and analysed at different magnification to obtain better clarity on the particle morphology/topology.[6]

2.2.3.6 Zeta potential determination

10mg of the prepared Microsponges diluted with 10ml of double distilled water. Then the samples were transferred into the cuvette which contains electrodes and kept inside the instrument. Then the laser scanning light was passed through the cuvette tube and analysed the zeta potential using Horiba scientific (Nanoparticle) SZ-100.

2.2.3.7 Invitro drug release study

In vitro drug release pattern of microsponges was carried out in dissolution apparatus USP Type-I (basket type dissolution apparatus) using phosphate buffer pH 6.8 as dissolution

medium with a basket consisted of 5µm of stainless-steel mesh. Microsponges equivalent to 8 mg of drug was taken in the basket. The speed of the rotation was maintained at 50 rpm and temperature of 37± 0.5°C. At fixed intervals, aliquots 5 ml sample were withdrawn periodically and were replaced by fresh buffer. The samples were assayed by UV spectrophotometer at 310 nm using phosphate buffer pH 6.8 as blank and % CDR was calculated and plotted against time.

2.2.4 PREPARATION OF TRANSDERMAL PATCH BY SOLVENT EVAPORATION TECHNIQUE

Required quantity of drug and polymeric solution was stirred for 30-60 min in a magnetic stirrer till the polymer dissolves completely and Propylene glycol was used as a Plastisizer.

The mixture was poured into a petri plate with casting area 63.60cm^2 and air bubbles was removed by keeping aside overnight ,then it was dried using hot air oven at 40°C.

The patch obtained was carefully peeled off and evaluated. Then each patch was cut into 2cm^2.[7]

Table 2: Composition of microsponge loaded transdermal patch (M-LTP) and ondansetron loaded transdermal patch (O-LTP).

Formulation	Microsponge	Drug	HPMC K100M	Propylene glycol	Water	1% Acetic acid
F1	Equivalent to 254.4mg of drug	-	954mg	10%	20ml	-
F2	-	254.4mg	954mg	10%	-	20ml

2.2.5 Evaluation of M-LTP and O-LTP

2.2.5.1 Visual appearance

The patch was physically inspected for color, clarity, uniformity, flexibility and smoothness.

2.2.5.2 Thickness of patch

Vernier calipers were used to determine the thickness of randomly selected patches. The patch was measured at different points and the average of three readings was taken.[8]

2.2.5.3 Folding endurance

Folding endurance of patch was measured manually by folding the patch at one place a number of times till it breaks. This gives a value of folding endurance.[9]

2.2.5.4 Weight variation

Weight variation was studied by individually weighing 3 randomly selected patches. The mean value was calculated.

2.2.5.5 Drug Content

The patch is tested for content uniformity. Films of $2cm^2$ was cut, placed in 100 ml volumetric flask and dissolved in 6.8pH buffer, volume was made upto 100ml. Solution was suitably diluted. The absorbance of the solution was measured at 310 nm.[10]

2.2.5.6 Tensile strength

The design of the instrument was constructed in the lab such that, it had one wooden frame that was horizontally placed having fixed scale. On top of the frame two clips were attached to hold patches under study. From two clips one of the clips was fixed and the other was movable. Instrument also has a pulley to hold the weight, weight is applied to one end of the pulley and the other end is attached to a fixed clip. During the test the wooden platform should not dislocate from the original place so the base was fixed carefully on the table. Patches used for the study were cut in the size of $2cm^2$ sizes. Thickness of the patches were noted. Rate of stress change was maintained constant with the addition of 50 gm per minute. The elongation was observed and the total weights taken were used for the calculation.

Formula for tensile strength is

Tensile strength = s = P/a

Where,

S is the tensile strength

P is the force required to break (kg)

A is the cross-sectional area (mm^2)

2.2.5.7 *In-vitro* diffusion studies

In-vitro diffusion study was carried out in a Franz diffusion cell using dialysis membrane which is soaked overnight in pH 6.8 phosphate buffer. The membrane was tied to the donor compartment and mounted on the reservoir compartment of Franz diffusion cell containing 135 ml of pH 6.8 phosphate buffer. circular patchs of $2cm^2$ diameter equivalent to 8mg of ondensetron was placed over the dialysis membrane of donor compartment. Whole set was placed on the magnetic stirrer. Samples were withdrawn from the sampling port of reservoir

compartment at regular intervals and same volume was replaced absorbance was measured using spectrophotometer at 310nm as withdrawn sample.

2.2.5.8 Stability Study

a) Procedure for optimized microsponge

Stability studies were performed according to ICH guidelines. The optimized formulations were selected for stability studies. They were subjected to short-term stability studies. Formulation was divided into 2 sets of samples and stored at 5±3°C in the refrigerator and stored at room temperature(30°±2°C, 65%±5% RH), and their % Drug content and *Invitro* drug release were determined after 30 days.

b) Procedure for microsponge loaded transdermal patch

The patch was covered in aluminium foil and stored in a desiccator with saturated sodium chloride (NaCl) solution at a temperature of 25°±2°C and 70±5% RH for 1 months. The samples were collected at 1 months and evaluated for drug content and % cumulative drug relese upto 24 hours.

3 RESULTS AND DISCUSSION

3.1 PREFORMULATION STUDIES

Preformulation studies were carried out and the results for the experiment conducted areas follows

3.1.1 Determination of λmax of Ondansetron

The λmax of Ondansetron was found to be 310nm

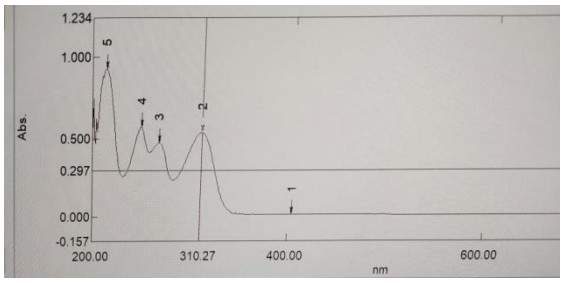

Figure 1: λmax of Ondansetron.

3.1.2 Standard Calibration Curve of Ondansetron

Stock solutions of desired concentrations were prepared and the absorbance was measured at 310nm using UV visible spectrophotometer.

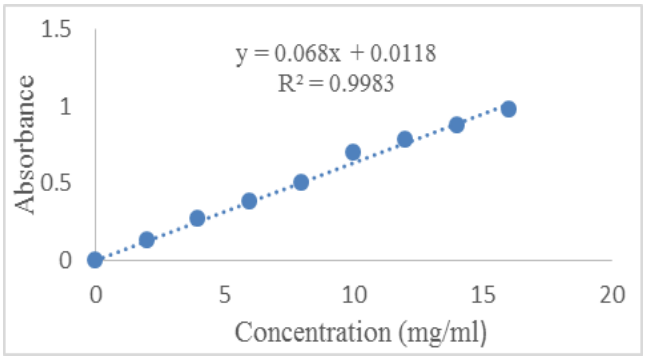

Figure 2: Calibration Curve of Ondansetron in PBS 6.8.

Phosphate buffer pH 6.8

Working stocks: 4,8,12,16,20 µg/ml

λmax: 310nm

Beer's Lambert's range: 2-16 µg/ml

Straight line equation: y=0.068x+0.0118

Regression coefficient: 0.9944

3.1.3 Compatibility studies by FTIR spectrophotometer

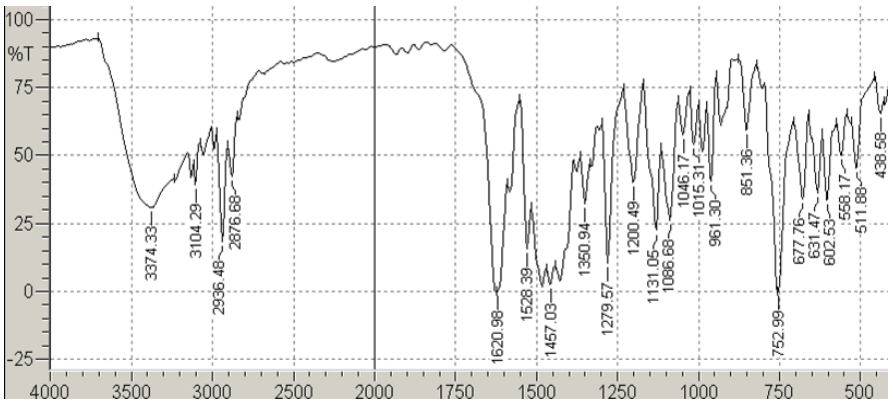

Figure 3: FTIR Spectra of Pure drug (Ondansetron).

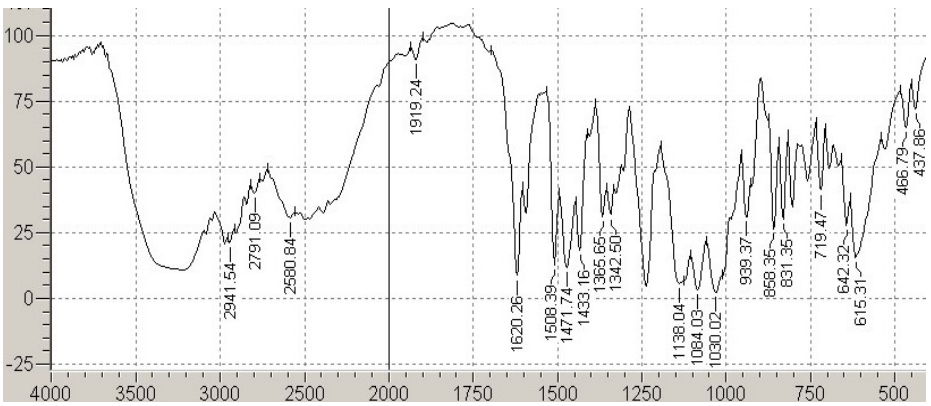

Figure 4: FTIR spectra of drug with excipients.

Table 3: Interpretation of FT -IR spectra.

Vibrations	Range (cm-1)	Pure drug	Wave number (cm-1) of drug with excipients
N-H stretching	3000-3700	3374.33	3200
C-H stretching	2700-3300	2936.48	2941.54
C=O	1600-1900	1620.98	1620.26
C-H bending	1300-1500	1350.94	1365.65
C-C	1200-800	1131.05	1138.04

➢ CHARACTERIZATION OF MICROSPONGE

The ondensetron loaded microsponges are prepared by quasi emulsion solvent diffusion method. Then, the formulated microsponges are evaluated by the following parameters.

- **Scanning electron microscopy of microsponge**

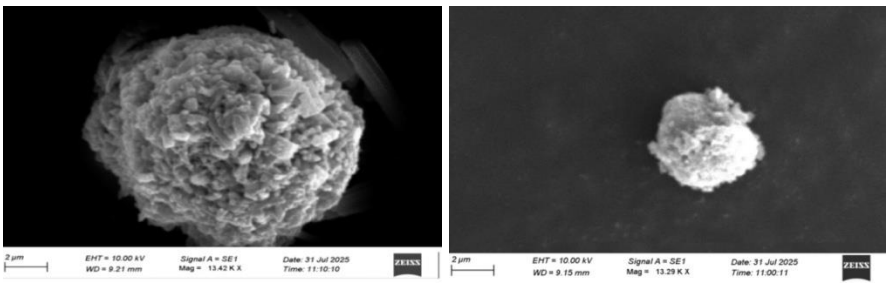

Figure 5: SEM images of optimized formulation.

The captured SEM images of microsponges are shown in figure 5 it reflected that the microsponges formed were porous and spherical. the pores were induced by the diffusion of the solvent from the surface of the microparticles. The appearance of particles was such that they were termed microsponges.

- **Zeta potential**

The zeta potential indicates important role in stability. It measures the surface charge of the particle in the microsponge. when zeta potential either more +ve or more –ve the particle repel each other leading to increase the stability of microsponge'

- **Influence Of Type And Concentration Of Retardent Material**

Table 4: Results of Influence Of Type And Concentration Of Retardent Material.

Batch	% Yield	Average particle size (µm)	% Drug content	% Loading efficiency	Zeta potential	% Drug release
F1	32.64	59.3	70.21	51	-11.8	86.19
F2	36.83	60.20	62	60.90	-5.6	77.75
F3	38.58	63.23	52.56	62.76	-11.3	72.1

F4	34.82	34.8	84.09	68.81	-22.7	93.1
F5	38.71	48.12	75.46	87.80	-11.5	85.53
F6	40.28	54.3	74.90	89.01	-11.0	83.87

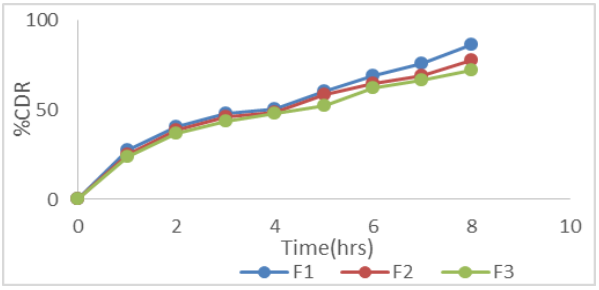

Figure 6: Graphical representation of % CDR on an Influence of type and concentration of retardant material (ethyl cellulose).

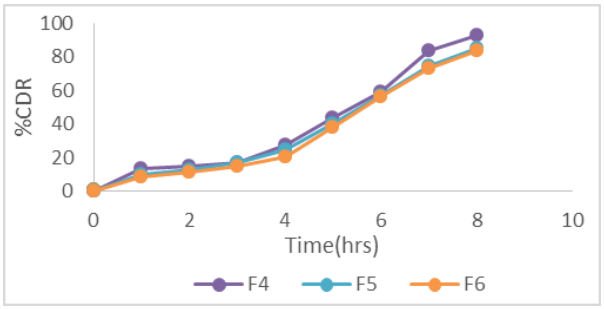

Figure 7: Graphical representation of % CDR on an Influence of type and concentration of retardant material (Eudragit L 100).

At constant drug level when the polymer concentration is increased, the drug content is decreased due to dilution of solution. However entrapment efficiency increases as amount of polymer to hold the drug increased. Increased particle size with increase in polymer concentration has resulted in reducing effective surface area to decrease the drug release, also increase in concentration of retardant polymer could increase the diffusion pathlength.

Based on the results eudragit L 100 at 1:12.5 was considerd as retardant polymer for further studies.[11][12]

- **Influence Of Drug: Polymer Ratio**

Table 5: Results Of Influence Of Drug: Polymer Ratio.

Batch	% Yield	Average particle size (µm)	% Drug content	% Loading efficiency	Zeta potential	% Drug release
F6	40.28	54.3	74.90	89.01	-11.0	83.87
F7	43.71	47.41	75.45	91.07	-14.2	87.64
F8	46.46	38.18	78.76	92.17	-14.2	92.62

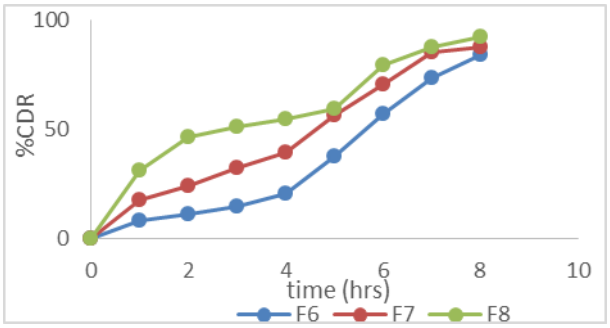

Figure 8: Graphical representation of % CDR on an effect of drug to polymer ratio.

An increase in the drug to polymer ratio from 1:12.5 to 3:12.5, has resulted in increased drug content, entrapment efficiency and % cumulative drug release. This could be due to increase in the concentration of drug. When the drug to polymer ratio is increased, the mean particle size falls, this might be due to increased viscosity of internal phase leading to smaller microsponge. As the amount of drug increased, the drug content, entrapment efficiency, %Yield and % Drug release gradually increased. This might be due to increased viscosity and faster diffusion of internal phase of the emulsion system. The 3:12.5 ratio (F8) is likely represents the optimal balance and considered for further studies.[13]

- **Influence Of Type Of Internal Phase**

Table 6: Results Of Influence Of Type Of Internal Phase.

Batch	% Yield	Average particle size (µm)	% Drug content	% Loading efficiency	Zeta potential	% Drug release
F8	46.46	38.18	78.76	92.17	-14.2	92.62
F9	37.44	40.09	66.06	61.33	-14.3	67.08

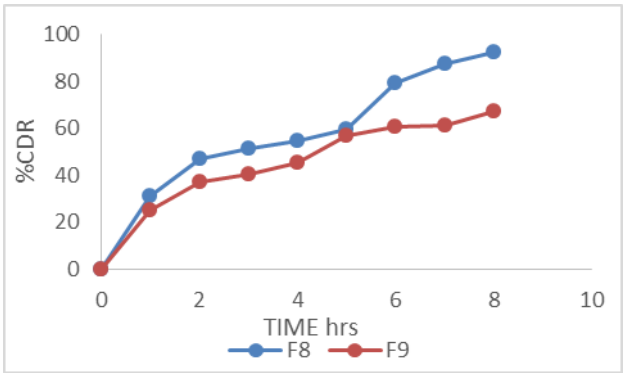

Figure 9: Graphical representation of % CDR on an type of Influence of internal phase.

Internal phase system with DCM:Ethanol showed good results as compaired to DCM:Methanol this may be due to, Ethanol likely improves ondansetron solubility in the DCM:ethanol mixture, ensuring more drug remains dissolved during emulsification and is

incorporated into the Eudragit L 100 matrix. Methanol's higher polarity and greater miscibility with water (used in the external aqueous phase, typically containing PVA) may cause ondansetron to partition prematurely into the aqueous phase during emulsification. This reduces entrapment efficiency and drug content, as some drug is lost to the external phase before the microsponge structure fully forms.[14]

- **Influence Of Internal Phase Volume**

Table 7: Results Of Influence Of Internal Phase Volume.

Batch	% Yield	Average particle size (µm)	% Drug content	% Loading efficiency	Zeta potential	% Drug release
F8	46.46	38.18	78.76	92.17	-14.2	92.62
F10	31.28	37.4	83.48	94.99	-27.4	95.12
F11	41.22	35.75	54.20	52.43	-12.4	80.46

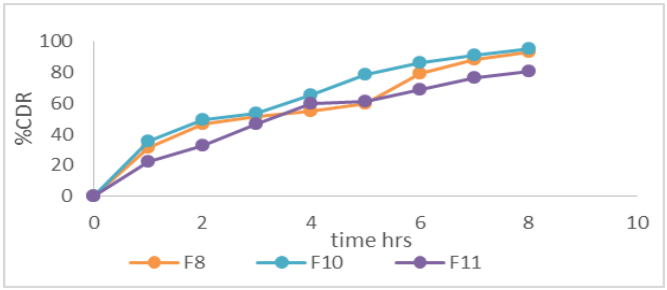

Figure 10: Graphical representation of % CDR on an Influence of Internal phase volume.

At 15 ml, the internal phase volume likely achieves an optimal balance with the external phase volume, resulting in a stable, uniform emulsion droplets. this results in higher production yield due to stable emulsion and reduced material loss. Higher the drug content and entrapment efficiency is due to the uniform droplet formation ensures more drug is encapsulated within the polymer matrix before solvent diffusion completes. The higher the % drug release is may be due to the optimal porosity. The mean particle size decreases as internal phase volume increases. It could be due to greater viscosity of the internal phase with increased volume.[15]

- **Influence Of Surfactant Concentration**

Table 8: Results Of Influence Of Surfactant Concentration.

Batch	% Yield	Average particle size (µm)	% Drug content	% Loading efficiency	Zeta potential	% Drug release
F10	31.28	37.4	83.48	94.99	-27.4	95.12
F12	30.64	34.4	78.10	81.37	-16.7	80.46

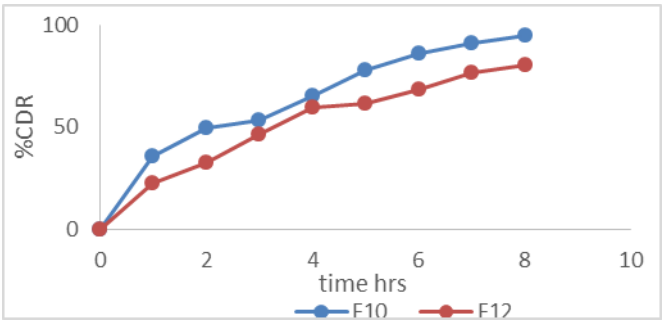

Figure 11: Graphical representation of % CDR on an Influence of surfactant concentration.

The surfactant concentration plays an important role in the formation of microsponge. Increasing the PVA concentration from 0.50% to 0.75% likely reduces production yield, entrapment efficiency, particle size and drug content due to increased external phase viscosity. The reduced particle size is due to reduced interfacial tension between the globules and external phase. Increase in amount of PVA, the drug release went on decreasing because as a concentration of PVA increases, the polymer matrix takes more time to swell completely and thus drug release decreases. The 0.50% PVA concentration appears as a optimal balance for stable emulsion formation and microsponge preparation.[16]

- **Influence Of External Phase Volume**

Table 9: Results Of Influence Of External Phase Volume.

Batch	% Yield	Average particle size (µm)	% Drug content	% Loading efficiency	Zeta potential	% Drug release
F10	31.28	37.4	83.48	94.99	-27.4	95.12
F13	36.99	41.45	60.93	92.99	-11.5	77.92

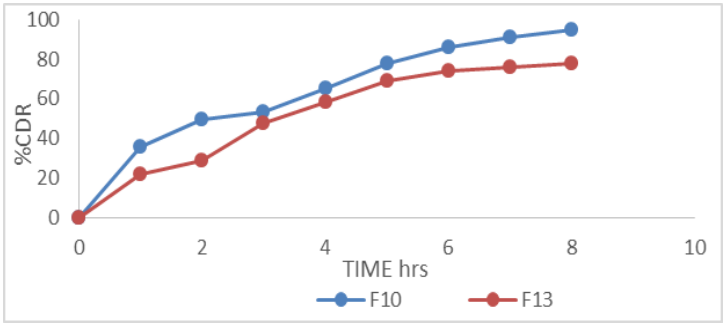

Figure 12: Graphical representation of % CDR on an Influence of External phase volume.

The volume of external phase is critical for the development of microsponges as they lower the free drug concentration. It also affects drug content, %EE, particle size and drug release.

An increase in the volume of the external phase liquid there is an increase in the particle size, due to greater viscosity of internal phase globules. Increased volume of external phase results in development of microsponges with lesser drug content and also entrapment efficiency. This is because the drug is more is exposed to aqueous environment of external phase, which results in less effective entrapment in microsponges and reduced % drug release.[17]

- **Influence Of Stirring Speed And Time**

Table 10: Results Of Influence Of Stirring Speed And Time.

Batch	% Yield	Average particle size (µm)	% Drug content	% Loading efficiency	Zeta potential	% Drug release
F10	31.28	37.4	83.48	94.99	-27.4	95.12
F14	40.16	60.4	73.03	71.54	-13.3	86.83

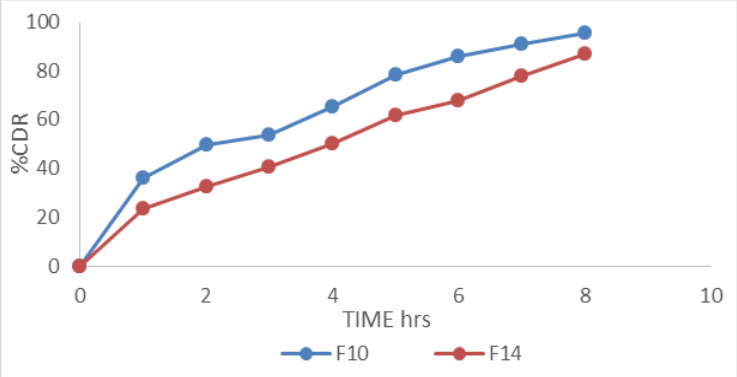

Figure 13: Graphical representation of % CDR on an Influence of stirring speed and time.

The stirring speed and time play a crucial role in the development of microsponges, mainly effects on the particle size, the stirring had same effect on the % EE and drug content. Stirring speed of 1500RPM and time 120 minutes was considered as an optimal speed and time for preparation of microsponges. The production yield was increased by decreasing the stirring speed and time. The Decreasing stirring speed and time reduces mechanical stress and shear forces, minimizing particle breakdown and loss during production. The weak mechanical shear by decreasing the stirring speed and time produce the larger droplets which increase the mean particle size. Decrease in the stirring speed and time decreases the % EE and drug content due to less solubility of drug. Lower stirring speed and time reduce agitation, leading to a thicker matrix layer and slower mass transfer, which decreases % drug release.[18]

Stability studies of optimized microsponge

Table 11: Stability studies of optimized microsponge formulation.

Temperature (ºC)	% Drug content
Control (F10)	83.48
5°±3°C (Refrigerated)	82.70
37ºC±5ºC/65%RH	80.46

Table 12: Comparison of % Cumulative Drug Release of optimized formulation stored at 5º± 0.3ºC and 37º± 5ºC/65% RH before and after 30 days.

Time in hrs	% Cumulative Drug Release		
	At zero month	After 30 days	
	F10	Refrigerated (5ºC±0.3ºC)	Room condition (30ºC±2ºC/65%RH)
0	0	0	0
1	35.76	23.84	21.65
2	49.54	38.41	34.72
3	53.54	45.62	43.53
4	65.23	56.18	55.58
5	77.99	64.89	62.76
6	85.93	72.89	71.03
7	90.9	79.59	76.81
8	95.12	94.23	91.58

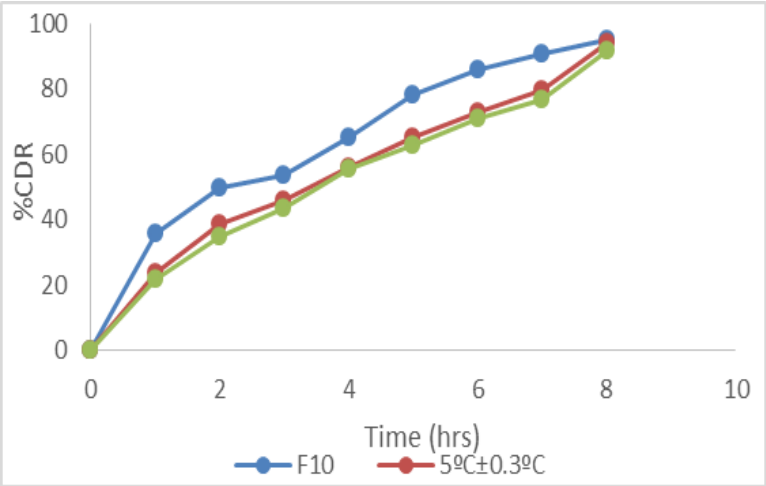

Figure 14: Comparison of % Cumulative Drug Release of optimized formulation stored at 5º± 0.3ºC and 37º± 5ºC/65% RH.

- **Evaluation of the microsponge loaded transdermal patch (M-LTP) and Ondansetron loaded transdermal patch (O-LTP)**

Table 11: Results of evaluated M-LTP and O-LTP

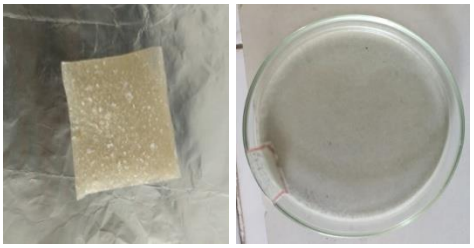

Figure 15: Images of the prepared microsponge loaded transdermal patch (M-LTP) and Ondansetron loaded transdermal patch (O-LTP)

Table 13: Comparative *In-vitro* diffusion studies between M-LTP and O-LTP.

Time (hr)	M-LTP	O-LTP
	%CDR	%CDR
0	0	0
1	9.12	25.67
2	12.45	39.56
3	18.62	54.52
4	24.56	67.45
5	32.67	80.32
6	38.48	89.98
7	57.35	82.34
8	74.69	
9	81.76	
10	88.45	
11	92.61	
12	92.61	
24	70.40	

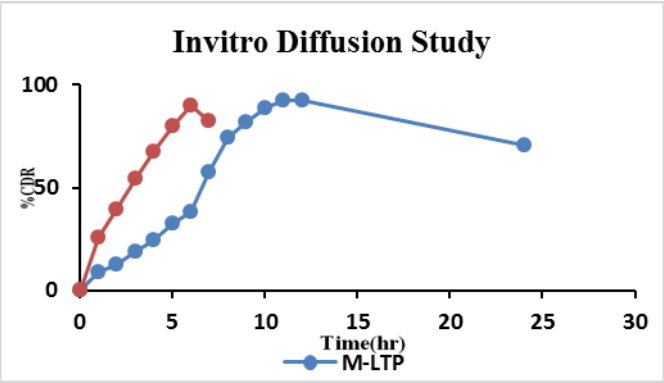

Figure 16: Comparision of M-LTP and O-LTP.

The microsponge loaded transdermal patch showed slow release pattern than ondensetron loaded transdermal patch as shown in table 12, it is due to dual resistance from microsponge and the patch.

Stability Studies Of M-LTP

Table 14: Results Of Stability Studies.

M-LTP	Drug content (mg)	Weight variation (mg)
Initial	95.34	0.096±0.2
30 days	93.4	0.093±0.019

Table 15: % Cumulative Drug Release of M-LTP.

Time (hr)	At zero month	After 30 days
0	0	0
1	9.12	8.95
2	12.45	10.74
3	18.62	17.07
4	24.56	22.53
5	32.67	31.74
6	38.48	35.78
7	57.35	56.12
8	74.69	73.13
9	81.76	80.67
10	88.45	84.44
11	92.61	90.86
12	92.61	87.04
24	70.40	67.37

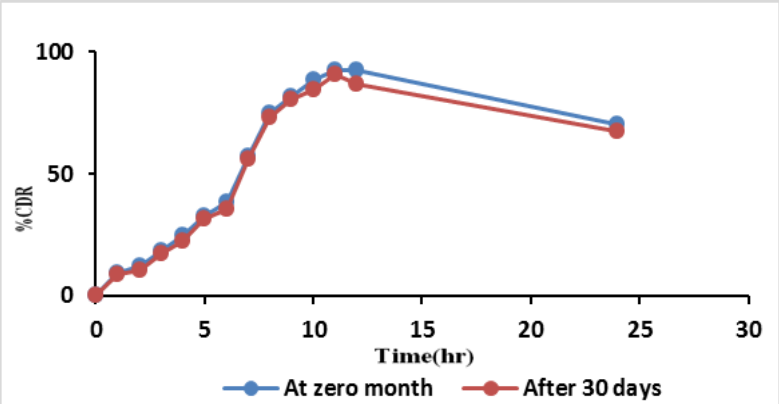

Figure 17: % Cumulative Drug Release of M-LTP.

Table 13 and Table 14 displays the results of an accelerated stability investigation. All values for drug content, weight variation and %drug release showed minimal variation. There are no significant changes in drug content, and Weight variation observed and statistically significant, which indicated that there was no susceptibility to stability problems during storage. The drug content, weight variation were shown in table 13 and %CDR of microsponge loaded transdermal patch were shown in table 14.

CONCLUSION

Our research focused on the successful development and optimization of Ondansetron - loaded microsponges using the quasi-emulsion solvent diffusion method, followed by their evaluation and incorporation into transdermal patch prepared with film forming polymers.

The study demonstrated that by optimizing various formulation parameters, such as the concentration of polymers and surfactants, type of internal phase, volume of internal and external phase, and process variables such as stirring conditions like speed and time, the desired drug release profiles and physical characteristics of microsponges could be achieved. Upon incorporation into transdermal patch, the Ondansetron loaded microsponges retained their efficacy thus, M-LTP of ondansetron can be a promising system for the transdermal for effective treatment for chemotherapy induced nausea vomiting (CINV).

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