International Journal of Trend in Innovative Research (IJTIIR)
Available Online @ www.ijtiir.com | ISSN: 2582-0354

Formulation, Characterization and Validation of Mucoadhesive Patches for Buccal Administration of Ondansetron

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Abstract: The aim of this thesis is to formulate stable mucoadhesive buccal patches of ondansetron hydrochloride with desired thickness and compare the effect of various concentrations of permeation enhancer on drug permeability. In this study, the statistical optimization on the formulation and carry out method development and validation of ondansetron hydrochloride by UV spectrophotometer according to ICH guidelines is carried out. The study confirmed the authenticity, strength and purity of the drug by means of melting point and characteristic FT-IR peaks. The method validation was done using UV spectrophotometer and the proposed method was found to be simple, accurate and precise. The solubility of the drug was found to decrease at higher pH. The polymers used were characterized by their organoleptic properties and FT-IR spectra.

Keywords*: Mucoadhesive, Buccal, Ondansetron, Buccal Route, Drug, Mucous, Cavity Lining.*

I. INTRODUCTION

Drug delivery via the oral route is the most desired and preferred route of drug administration due to its ease of administration, self-assistance, non-invasive and most importantly the patient compliance. However, there are several challenges such as first pass metabolism, poor gastric retention time, extensive pre- systemic elimination and drug degradation in gastrointestinal environment resulting into inadequate and erratic drug absorption and poor bioavailability. [1-3]To overcome the limitations of the oral route, attempts have been made to exploit the potential of newer routes such as the buccal route. The buccal route is useful in case of patients suffering from nausea or vomiting, who are unconscious or less co-operative and who have difficulty in swallowing. Buccal drug delivery is a mucoadhesive drug delivery system where in the dosage form comes in intimate contact with the mucous membrane of the buccal cavity lining the inside of the cheeks.[4][5] As drug directly enters systemic circulation via the buccal route it bypasses first pass metabolism and thus enhances its bioavailability. Ondansetron hydrochloride is a potent anti-emetic drug which is a highly selective serotonin 5-HT3 (5-hydroxytryptamine) antagonist. It is used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.[6] It is also used for the treatment of postoperative nausea and vomiting. It acts by blocking emetogenic impulses in the GIT as well as in the chemoreceptor trigger zone (CTZ) and nucleus tractus solitarius both centrally and peripherally. It is administered orally with a dose of 4 mg or 8 mg followed by 4 mg or 8 mg 12 h later and 32 mg intravenously 15 min prior to treatment.[7][8] It has a bioavailability of about 60% and t1/2 is 3 h for oral and parenteral doses. Drug reaches peak plasma concentration after 1.5 h and has 70-75% protein binding capacity. Hence, sustained release buccal patches can be prepared to enhance retention time of the drug in the buccal mucosa, reduce dose, increase bioavailability and overcome the limitations of the oral route.[9][10]

Challenges in the preparation of buccal patches include thickness of the patch and permeation of drug through the buccal mucosa. [4] Optimized concentrations of mucoadhesive polymer and permeation enhancer will provide desired thickness and permeability respectively and as well sustain the release of drug from the formulation. The aim of this thesis is to formulate stable mucoadhesive buccal patches of ondansetron hydrochloride with desired thickness and compare the effect of various concentrations of permeation enhancer on drug permeability. Then to carry out statistical optimization on the formulation and carry out method development and validation of ondansetron hydrochloride by UV spectrophotometer according to ICH guidelines.[11][12]

II. DRUG AND EXCIPIENT PROFILE

A. Rationale for selection of drug

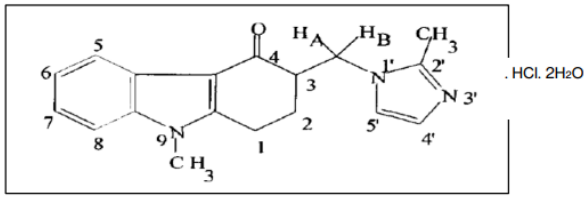
Ondansetron hydrochloride, 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1Himidazol-1-yl) methyl]-4H-carbazol-4-one is a highly selective serotonin 5-HT3antagonist, used in the treatment of nausea and vomiting associated with cancer chemotherapy, radiotherapy and surgery. It is also used in the prevention of postoperative nausea and vomiting. In order for a drug to be incorporated into buccal mucoadhesive drug delivery system, it should pass certain criteria. Mentioned below are such criteria along with profile of ondansetron hydrochloride suggesting its suitability for incorporation via the buccal route.

1. Ondansetron hydrochloride has potent pharmacological activity.
2. Buccal route is preferred for drugs undergoing hepatic first-pass metabolism leading to low bioavailability. Ondansetron hydrochloride has a bioavailability of about 60%.
3. The plasma elimination half-life of drug ondansetron hydrochloride is about 3 hours after oral or parenteral doses and about 6 hours after rectal use.
4. Ondansetron hydrochloride is a weak base and its pKa value is 7.4.
5. If partition coefficient log P>1 then buccal administration may offer advantages over oral administration. Log P value for ondansetron hydrochloride is 2.4.
6. The drug should be non-irritating, non-sensitizing to the buccal mucosa.

Also not much work has been carried out on buccal patches of the drug. Based on the above considerations, ondansetron hydrochloride has been selected as a model drug for administration via the buccal route.

B. Drug profile

ONDANSETRON HYDROCHLORIDE
Official in: IP
Structural Formula:



Chemical Name: 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-2yl) methyl]-4Hcarbazol-4-one, monohydrochloride, dihydrate.

III. EXPERIMENTAL WORK

A. List of materials and instruments

I) List of materials used:

1. Ondansetron hydrochloride (FDC Limited, Mumbai)
2. Polyvinyl alcohol (Central Drug House (P) Ltd., New Delhi)
3. Tamarind gum (Bhavna Gum Udhyog, Gujarat)
4. Chitosan (Central Institute of Fisheries Technology, Cochin, Kerala)
5. HPMC 15cps (S.D. Fine Chemicals Limited, Mumbai)
6. HPMC grades K4M, K15M and K100M (Colorcon Ltd., Goa)
7. Polyvinyl pyrrolidone K-30 (S.D. Fine Chemicals Limited, Mumbai)
8. Sodium alginate (S.D. Fine Chemicals Limited, Mumbai)
9. Carboxymethyl cellulose sodium (Central Drug House (P) Ltd., New Delhi)
10. Xanthan gum (S.D. Fine Chemicals Limited, Mumbai)
11. Dimethyl sulfoxide (S.D. Fine Chemicals Limited, Mumbai)
12. Propylene glycol (S.D. Fine Chemicals Limited, Mumbai)
13. Methanol AR grade (S.D. Fine Chemicals Limited, Mumbai)
14. Potassium bromide AR grade (S.D. Fine Chemicals Limited, Mumbai)

B. List of equipments used

1. Digital balance- Eureka, model EWT 100
2. Water bath shaker- Remi Ltd., model RSB-12
3. Dissolution test apparatus- Veego, model VDA-6DR
4. Disintegration test apparatus- Veego, model VTD-D
5. Digital pH meter- Elico, model LI 120
6. Sonicator- D4 Surgicals (India) Pvt. Ltd., model D-compact
7. Magnetic stirrer- Equiptronics, model EQ-770/ Remi equipments Pvt. Ltd., model BZMS-620
8. Franz diffusion cell
9. Hot air oven- Biotech India
10. IR Lamp- Literays Infrared lamp
11. Micrometer screw gauge- Aerospace

C. List of instruments used

1. UV/Vis double beam spectrophotometer- Jasco, model V-630
2. FT-IR spectrophotometer- Shimadzu, model IR Affinity 1 CE
3. Stability chamber- Bio-Technics India, model BTI-24

IV. PREFORMULATION

The drug is provided as a gift sample from the FDC mumbai for conducting the studies. Preformulation studies focus on the physicochemical properties of the drug molecule that could affect its performance and development of an efficacious dosage form. The main objective behind preformulation is the quantitation of the physicochemical properties that will assist in developing a stable, safe and effective formulation.

V. EXPERIMENTAL

1. Organoleptic properties of drug:

The drug sample of ondansetron hydrochloride obtained was examined for its appearance, colour and odour.

2. Authentication of drug:

a) Melting point:

The melting point was determined using melting point apparatus. The melting point was determined by introducing small amount of drug substance in the capillary attached to graduated thermometer and constant heat was applied to the assembly suspended in the paraffin bath. The point at which the drug melts was noted.

b) UV spectrum of drug ondansetron hydrochloride:

In pH 6.8 phosphate buffer:

10 mg of accurately weighed ondansetron hydrochloride was dissolved in 10 ml of methanol and volume was made upto 100 ml with pH 6.8 phosphate buffer. 1 ml of this solution (100 µg/ml) was further diluted to 10 ml with pH 6.8 phosphate buffer (10 µg/ml). This prepared solution (10 µg/ml) was scanned in the range of 200 - 400 nm using methanol and phosphate buffer (1:9) as blank in Jasco V-630 UV-Vis spectrophotometer to determine the wavelength of maximum absorbance i.e. λmax.67

c) Fourier transform infrared (FT-IR) spectroscopy:

The FT-IR spectra of drug sample was recorded by scanning the sample in potassium bromide (KBr) disc at a resolution of 4 cm-1 over a range of 4000 - 400 cm-1 and principle peaks were measured using Shimadzu IR affinity-1 CE (Japan) spectrophotometer. The drug was mixed with KBr in a mortar-pestle and was filled in the disc.

d) Solubility:

The solubility of ondansetron hydrochloride was determined by adding excess amount of drug in various solvents like water, ethanol, methanol, acetone, dichloromethane, chloroform, isopropyl alcohol, ethyl acetate and buffers of pH 1.2, 2, 4, 6, 6.8 and 7.4 and shaken for 48h until equilibrium in a water bath shaker at 37°C. The solubility was determined spectrophotometrically by suitably diluting 1 ml of the aliquot and measured at 210 nm.

3. Construction of calibration curve using UV-Vis spectroscopy:

A stock solution of 100 µg/ml was prepared by dissolving 10 mg of drug in 10 ml methanol and volume was made up to 100

ml with pH 6.8 phosphate buffer. Different concentrations were prepared in the range of 2 - 10 µg/ml by appropriately diluting the stock solution with pH 6.8 phosphate buffer. The absorbance values were measured at 210 nm and plotted against concentration to get a calibration curve. Values of slope, intercept and coefficient of correlation were calculated. These values were used for invitro drug release studies.70

4. Validation of spectrophotometric method:

The method was validated according to ICH Q2(R1) Guideline "Validation of Analytical Procedures Text & Methodology" in order to determine linearity, sensitivity, precision and accuracy.

5. Characterization of polymers:

a) Organoleptic properties of polymers: The different polymers were examined for their appearance, colour and odour.

b) Fourier transmission infrared (FT-IR) spectroscopy:

The FT-IR spectra of the polymers was recorded by scanning the sample in potassium bromide (KBr) disc at a resolution of 4 cm-1 over a range of 4000 - 400 cm-1 and principle peaks were measured using Shimadzu IR affinity-1 CE (Japan) spectrophotometer. The polymers were mixed separately with KBr in a mortar-pestle and were filled in the disc.

6. Drug excipient compatibility studies using FT-IR spectroscopy:

Resolution: 4 cm-1

Scanning range: 4000 - 400 cm-1

Procedure: The drug was mixed with the excipients and KBr in a mortar-pestle and was filled in the disc. The FT-IR spectra of the samples were recorded by scanning the samples over arrange of 4000-400 cm-1 using Shimadzu IR affinity-1 CE (Japan) spectrophotometer

VI. RESULTS AND DISCUSSION

The drug was procured as a gift sample from FDC Limited 142-48, S.V. Road Jogeswari (West) Mumbai-400102 Maharastra India. All the test performed by this sample are authenticated by the tests given below.

A. Organoleptic properties of drug

The organoleptic properties of the received sample of ondansetron hydrochloride shown in Table 1 were found to comply with that mentioned in literature.

Table 1: Organoleptic properties of drug

Properties	Observed Results	Reported Results
Appearance	Amorphous powder	Amorphous powder
Colour	White to almost off-white	White to almost off-white
Odour	Odourless	Odourles

B. Authentication of drug

a) Melting point:

The melting point of the drug was found to be 180°C. The reported value in the literature was 178.5-179.5°C that confirms the drug was pure.

b) UV spectrum of drug ondansetron hydrochloride In pH 6.8 phosphate buffer:

The solution of drug in pH 6.8 phosphate buffer was found to exhibit maximum absorbance at 210 nm after scanning in the range of 200 - 400 nm. The values are in close accordance with that reported in literature. Thus, the given sample complies with that of the standard.

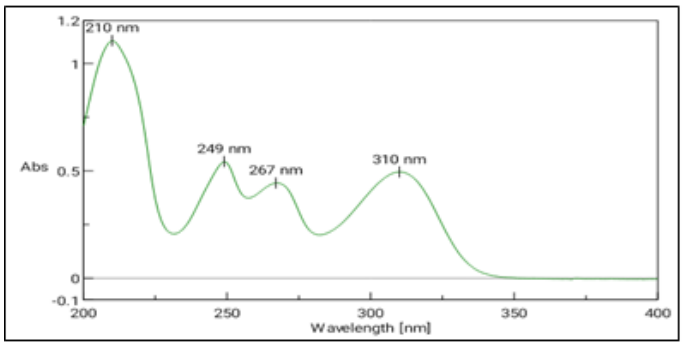


Fig 1: UV spectra of ondansetron hydrochloride in pH 6.8 phosphate buffer

The FT-IR spectra of the drug with various combinations of excipients are shown in Fig.2-13. The results of the peaks observed in the spectra of drug with the excipients are shown in Table 2. They showed no shift or change in the characteristics of the drug peak indicating no interaction between the drug and excipient.

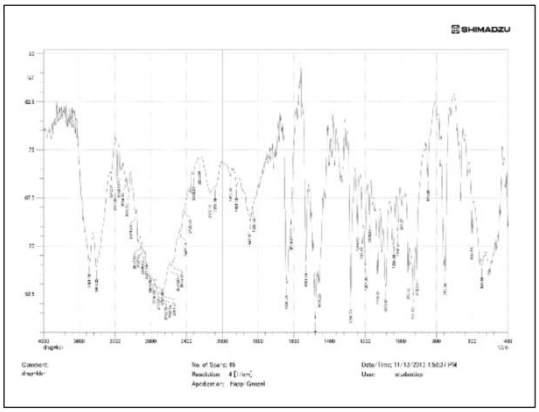


Fig 2: FT-IR spectra of Drug + PVA

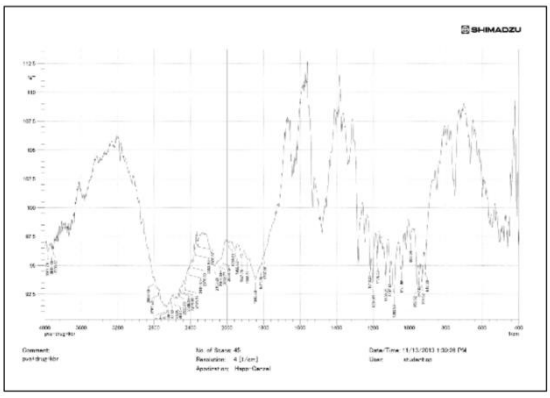


Fig 3: FT-IR spectra of Drug + PVA+ PVP K-30

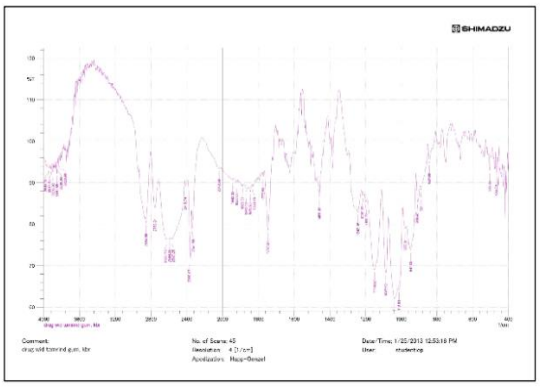


Fig 4: FT-IR spectra of Drug + Tamarind gum

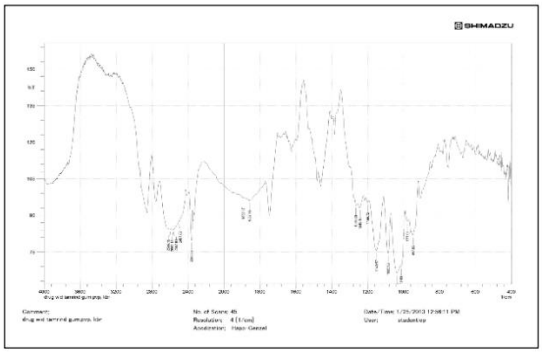


Fig 5: FT-IR spectra of Drug + Tamarind gum + PVP K-30

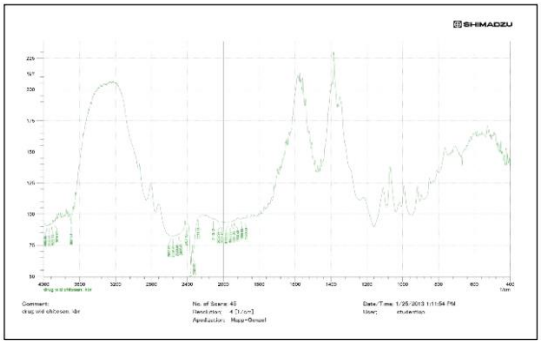


Fig 6: FT-IR spectra of Drug + Chitosan

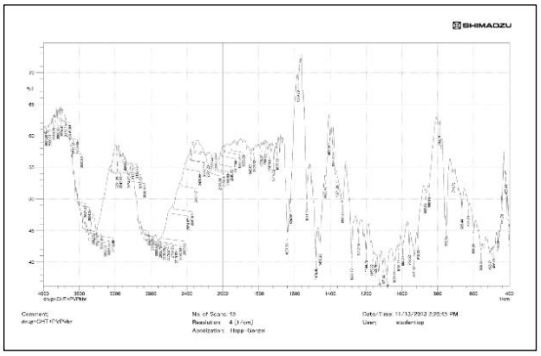


Fig 7: FT-IR spectra of Drug + Chitosan + PVP K-30

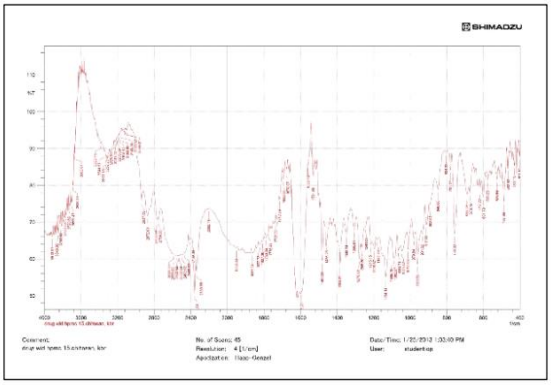


Fig 8: FT-IR spectra of Drug + Chitosan + HPMC 15 cps

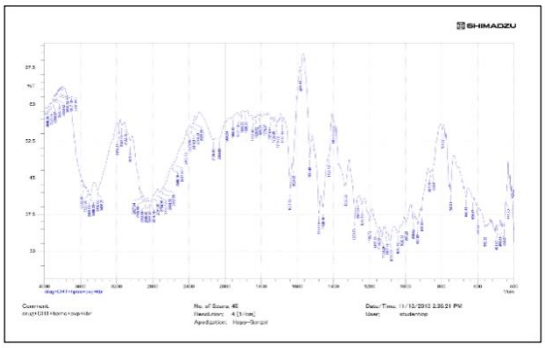


Fig 9: FT-IR spectra of Drug + Chitosan + HPMC 15 cps + PVP K-30

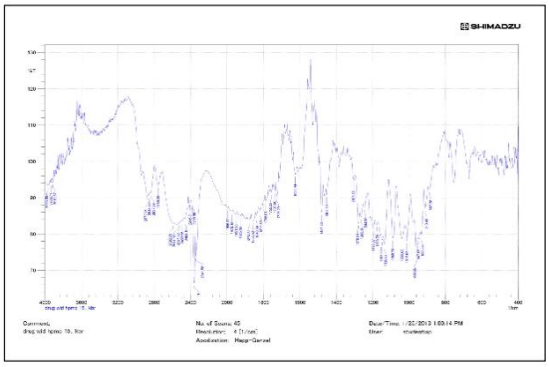


Fig 10: FT-IR spectra of Drug+ HPMC 15 cps

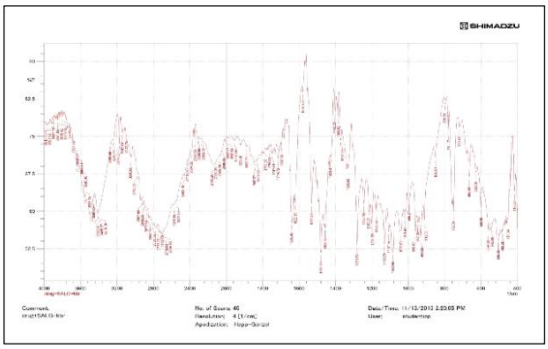


Fig 11: FT-IR spectra of Drug + Sodium alginate

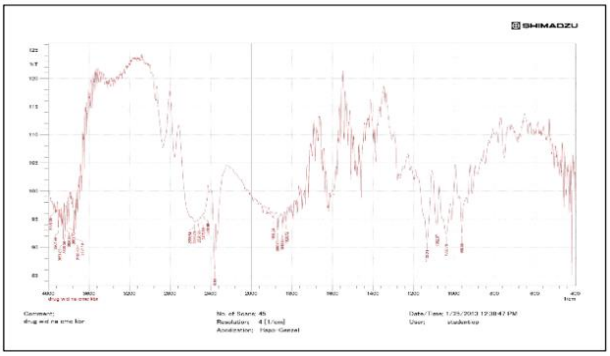


Fig 12: FT-IR spectra of Drug + Sodium CMC

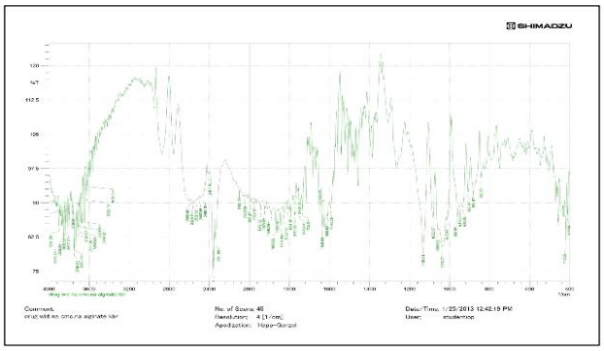


Fig 13: FT-IR spectra of Drug + Sodium alginate + Sodium CMC

Table 2: Peaks observed in the spectra of drug with the excipients

Sr. No.	FTIR Sample	Peaks observed(cm^{-1})	Drug-excipient compatibility
1	Drug+PVA	3390,1642,1529,1480,1450,1280,750; 3420, 2806.43,1700	
2	Drug+PVA+ PVP K-30	3419.79,1640,1529,1456.26,1265.3,748.38; 3481.51,2951.09,1716.65	✓
3	Drug+Tamarindgum	3400,1630,1520,1458.18,752; 3400,2854.65,1645,1039.63	✓
4	Drug +Tamarindgum +PVPK-30	3300,1625,1464,1265.3,756; 3500,2876,1037.7	✓
5	Drug+Chitosan	3400,1521,1480,748; 3697.54,2700,1420,1395,1100	✓
6	Drug +Chitosan +PVPK-30	3412.08,1637.56,1531.48,1479.4,1456.26, 1280.73,752.24; 3624.25,2927.94,2883.58,1579.7,1423.47, 1371.39,1083.99	✓
7	Drug +Chitosan +HPMC15cps	3383.14,1531.48,1481.33,1456.26,1278.81,758.02; 3668.61,2872.01,1593.2,1425, 1134.14; 2937.59,1593.2,1384.24,1089.78	✓
	Drug	3412.08,1637.56,1479.4,1458.18,	
8	+Chitosan +HPMC15cps +PVPK-30	1280.73,750.31; 3566.38,2927.94,2883.58,1425.4,1145.72; 2908.65,1577.77,1400.32,1083.99	✓
9	Drug+HPMC 15cps	3400,1625.99,1520,1481.33,1452.4,1278.81; 2873.94,1375, 1089.78	✓
10	Drug+Sodiumalginate	3410.15,1639.49,1531.48,1479.4,1456.26, 1280.73,752.24; 2927.94,1622.13,1423.47	✓
11	Drug+Sodium CMC	3400,1640,1530,1450,1279, 750; 2900,1625,1420,1037.7	✓
12	Drug+Sodiumalginate+ SodiumCMC	3400,1635.64,1525,1480,1279,752; 2920,1608.63; 3350,1420,1058.92	✓

The preformulation studies were carried out with an aim to study the physicochemical properties of the drug and to generate a data base for further formulation and evaluation procedures. The study confirmed the authenticity, strength and purity of the drug by means of melting point and characteristic FT-IR peaks. The maximum absorbance was found to beat a wavelength of 210 nm in pH 6.8 phosphate buffer. The equation for calibration curve was found to be y = 0.1196x + 0.011365 with a correlation coefficient of 0.9994. This equation was further used in drug release calculations. The method validation was done using UV spectrophotometer and the proposed method was found to be simple, accurate and precise. The solubility of the drug was found to decrease at higher pH. The polymers used were characterized by their organoleptic properties and FT-IR spectra. The excipients were found to be compatible with the drug from the FT-IR spectra obtained.

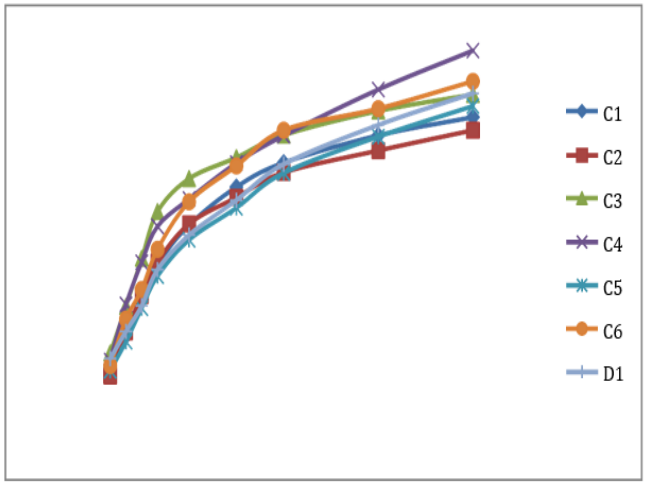


Fig 14: Swelling profiles of trial formulations C1-C6 and D1 containing different concentrations of Chitosan and HPMC

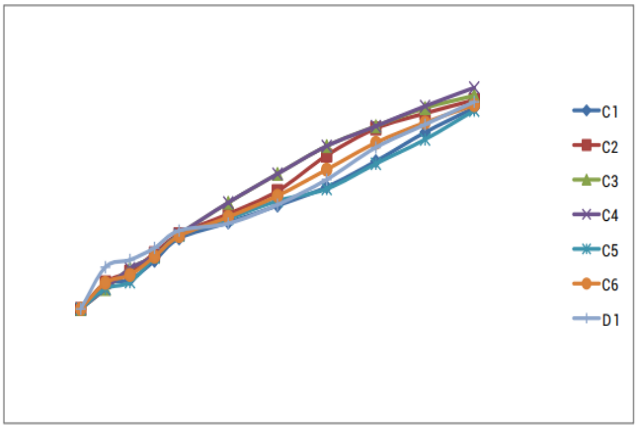


Fig 15: In vitro release profiles of trial formulations C1-C6 and D1 containing different
concentrations of Chitosan and HPMC

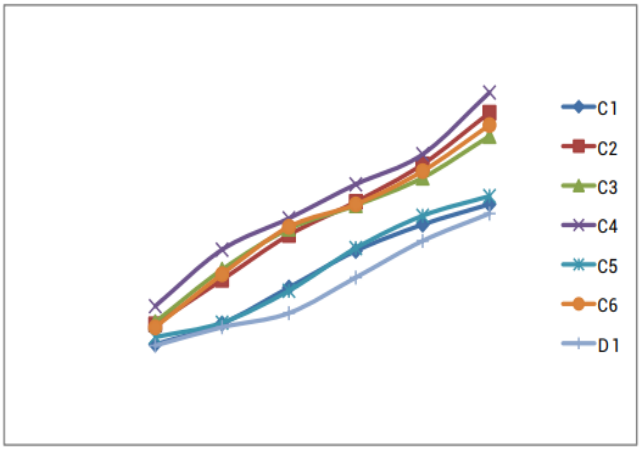


Fig 16: In vitro permeation profiles of trial formulations C1-C6 and D1 containing
different concentrations of Chitosan and HPMC

D1 exhibited precipitation of drug on the surface upon storage for prolonged period of time. The patches of all the other formulations showed good flexibility, strength and smooth surface and were found to be stable. The mucoadhesive polymer PVA showed good swelling characteristics, mucoadhesive property, drug permeation And in vitro drug release. It also showed a high in vitro residence time which indicates that it will remain in contact with the mucosal surface for a prolonged period of time. The formulation A4 showed good results in terms of drug permeation, in vitro release, swelling index and mucoadhesive strength. Hence, it was resolved that A4 can be considered for optimization experiments to optimize the eventual effective level of mucoadhesive polymer (PVA), hydrophilic polymer (PVP K-30) and permeation enhancer (DMSO) for optimal drug permeation and mucoadhesive strength.

VII. OPTIMIZATION BY STAT-EASE SOFTWARE

A. Optimisation

Formulation A4 from the trial formulations was considered for optimization using 23 full factorial design. The three factors were evaluated; each at 2 levels and experimental trials was performed on all 8 possible combinations by using Stat-Ease Design Expert software 8.0.7.1 trial version. The amounts of PVA (X1), PVP K-30 (X2) and DMSO (X3) were selected as independent. The responses % cumulative release (drug permeation) and mucoadhesive strength were selected as dep

B. Evaluation

The prepared optimized buccal patches were evaluated for different physical properties like weight uniformity, thickness, folding endurance, surface pH. Mechanical properties like invitro residence time, mucoadhesive strength of patches and other evaluation parameters like drug content, in vitro release study and ex vivo permeation study were performed.

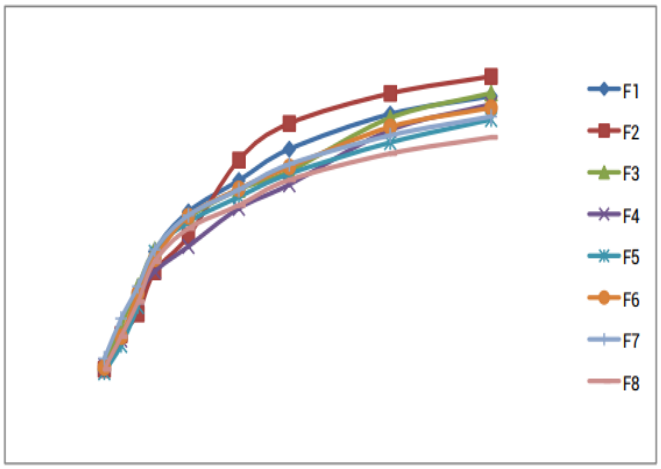


Fig 17: Swelling profiles of optimized formulations F1-F8

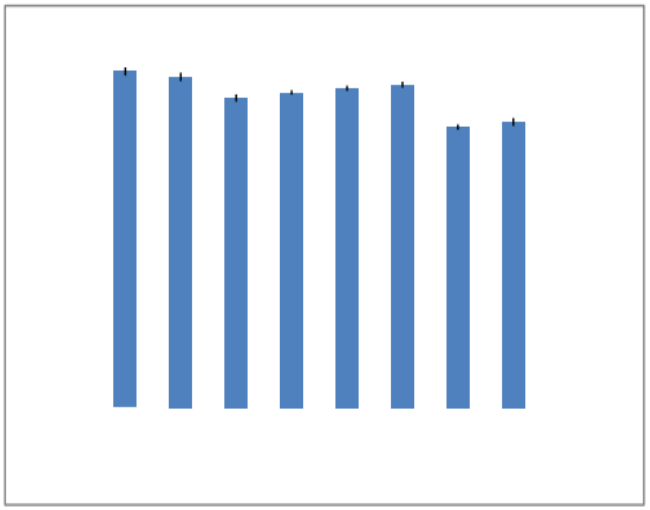


Fig 18: Graphical representation of mucoadhesive strength of optimized
formulations F1-F8

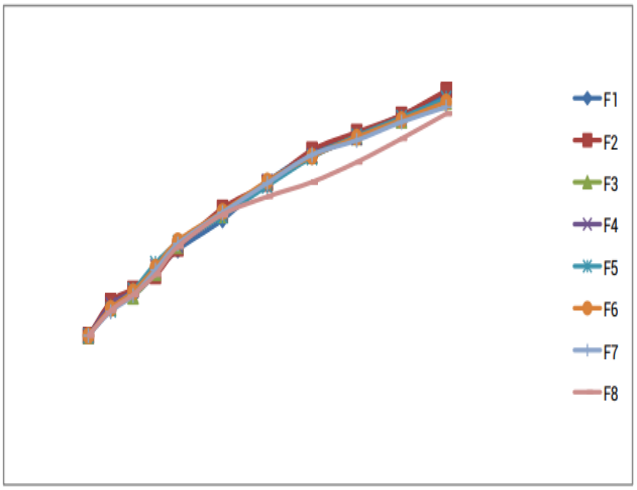


Fig 19: In vitro release profiles of optimized formulations F1-F8

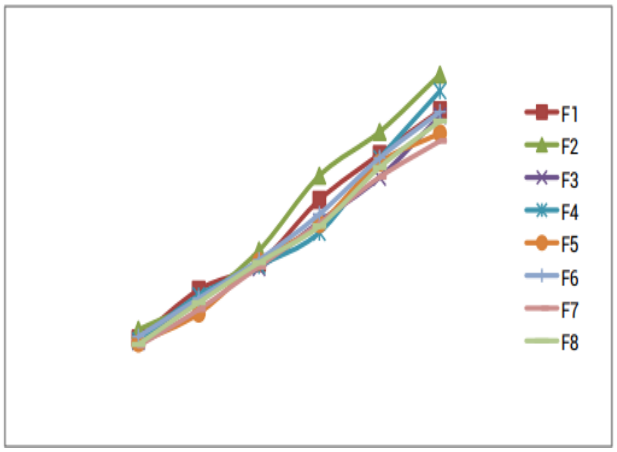


Fig 20: In vitro release profiles of optimized formulations F1-F8 (KINETIC ANALYSIS)

CONCLUSION

It may be concluded that mucoadhesive buccal patches would be a promising drug delivery system for systemic administration of ondansetron hydrochloride. The studies reveal that the drug ondansetron hydrochloride can be successfully delivered via the buccal route. The patches were of matrix type giving bi-directional release and were prepared by solvent- casting method. The mucoadhesive polymer PVA showed good mucoadhesive property and swelling characteristics. However, there was a need of a permeation enhancer to enhance the permeation of drug through the membrane. The statistical approach for optimization of formula is a useful tool, particularly when two or more variables are to be evaluated simultaneously. The results of optimization studies showed that mucoadhesive buccal patches containing 5.5% w/v PVA, 1.5% w/v PVP K-30 and 15% w/w DMSO were the most acceptable formulation and proved as a satisfactory carrier for buccal drug delivery of ondansetron hydrochloride. The optimized formulation showed good mucoadhesive strength, flexibility, tensile strength and was found to be smooth in appearance. The patches showed prolonged release for a period of 8 h.

References

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