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(RESEARCH ARTICLE)

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Development and characterization of transdermal drug delivery system of ramosetron HCL using different polymers and their effect on *In-vitro* release

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Abstract

Transdermal Drug Delivery Systems (TDDS) offer a controlled and consistent release of medications, bypassing first-pass metabolism and minimizing side effects associated with traditional oral and intravenous therapies. This study focuses on the development and evaluation of Ramosetron HCl transdermal patches designed for sustained release to manage nausea and vomiting. Ramosetron HCl, a selective 5-HT_3 serotonin receptor antagonist, was incorporated into various formulations using different grades of Hydroxypropyl Methylcellulose (HPMC), Polyvinyl Pyrrolidone (PVP K30), and Polysorbate 80. The patches were prepared by solvent casting and evaluated for various parameters including thickness, weight variation, drug content, folding endurance, tensile strength, and in-vitro drug release. The calibration curve for Ramosetron HCl in 7.4 pH phosphate buffer was established with a λmax of 240 nm. Fourier Transform Infrared Spectroscopy (FTIR) was employed to ensure compatibility between the drug and excipients. Formulation F5 demonstrated optimal properties, including satisfactory drug release profiles and mechanical strength. Stability studies of F5 showed that the formulation maintained its release characteristics under accelerated storage conditions (40°C / 75% RH) for up to three months. This study confirms the potential of Ramosetron HCl transdermal patches as an effective alternative to oral dosage forms, providing sustained drug delivery and enhanced patient compliance.

Keywords: Transdermal Drug Delivery Systems; Ramosetron HCl; Hydroxypropyl Methylcellulose; Polyvinyl Pyrrolidone; Polysorbate 80; Solvent Casting; Drug Release; Stability Studies; Fourier Transform Infrared Spectroscopy; Patch Formulation

1. Introduction

Transdermal Drug Delivery Systems (TDDS) offer a controlled and consistent method of drug delivery, effectively bypassing hepatic first-pass metabolism and minimizing side effects associated with oral and intravenous therapies. TDDS is particularly suited for drugs with short biological half-lives and those requiring sustained, slow release. The stratum corneum, the outermost layer of the skin, presents a significant barrier that necessitates specific physicochemical properties in drugs for successful permeation. The efficacy of TDDS relies on pharmacokinetic parameters such as terminal half-life, area under the curve, volume of distribution, and steady-state concentration. Drug permeation through the skin, governed by Fick's laws of diffusion, depends on factors including drug concentration, permeability coefficient, and skin characteristics. Effective TDDS design includes various types, such as drug-in-adhesive, multi-laminate, reservoir, and matrix systems, each influencing drug release rates and overall effectiveness.

Ramosetron HCl ($C_{17}H_{17}N_3O$; molecular weight 279.34 g/mol) is a highly selective 5-HT_3 serotonin receptor antagonist, marketed as Ibset in India for the management of nausea, vomiting, and diarrhea-predominant irritable bowel syndrome. It demonstrates superior potency and extended antiemetic effects compared to first-generation 5-HT_3

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antagonists. While it is generally well-tolerated, Ramosetron HCl may cause side effects such as headache and constipation and is contraindicated in individuals with hypersensitivity to the drug.

To optimize the formulation of Ramosetron HCl in TDDS, excipients play a crucial role. Hypromellose ($C_{17}H_{17}N_3O$) is a fibrous powder used as a binder, coating agent, and viscosity enhancer, which forms a viscous solution in cold water, aiding in tablet binding, film coating, and thickening. Polyvinyl Pyrrolidone (PVP K-30), with a molecular weight of approximately 50,000 $(C_6H_9NO)_n$, functions as a binder, disintegrant, and solubilizer, enhancing drug dissolution and stabilizing suspensions. Polysorbate 80 (Tween 80), a viscous amber liquid with the molecular formula $C_{64}H_{124}O_{26}$, serves as an emulsifier and surfactant, stabilizing aqueous formulations and finding applications in both pharmaceuticals and cosmetics. Combining these excipients with Ramosetron HCl aims to improve the formulation's stability, release profile, and overall efficacy in TDDS.

2. Material and methods

2.1. Materials and equipment's

The materials used in this study include Ramosetron HCl obtained from Pharmatrain, Hyderabad, and various grades of HPMC (K15M, K100M, K200M), PVP K30, Tween 80, and Sorbitol, all sourced from S.D. Fine Chemicals, Mumbai. The equipment utilized comprises an Electronic Balance (AUW 2200) from Shimadzu Corporation, Japan; a pH Meter from Mettler Toledo, India; UV-Visible Spectrophotometers (UV-1601, UV-2550) from Shimadzu Corporation, Japan; Dissolution Apparatus TDT-08L and a Disintegration Tester (USP), both from Electro Lab, India; a Vernier Caliper from Mitutoyo Corp, Japan; a Hot Air Oven from Servewell Instruments; a Sonicator from Sidilusonicator; and a Gyratory Shaker from Lab India.

2.2. Method

2.2.1. Calibration Curve of Ramosetron HCl in 7.4 pH Phosphate Buffer

Preparation of 7.4 pH Phosphate Buffer

A 7.4 pH phosphate buffer was prepared by mixing 50 mL of 0.2 M potassium dihydrogen orthophosphate solution with 22.4 mL of 0.2 M sodium hydroxide in a 200 mL volumetric flask. The solution was diluted to the mark with distilled water and the pH was adjusted to 7.4 using dilute sodium hydroxide.

Preparation of Ramosetron HCl Standard Stock Solution (100 µg/mL)

A stock solution was prepared by dissolving 10 mg of Ramosetron HCl in 7.4 pH phosphate buffer to a final volume of 100 mL in a volumetric flask.

Determination of λmax

From the stock solution, a 10 µg/mL solution was prepared and scanned between 200 and 400 nm using a UV-Vis spectrophotometer. The λmax of Ramosetron HCl was determined to be 240 nm.

2.3. Calibration Curve

Aliquots of the stock solution were diluted to 1, 2, 3, 4, and 5 µg/mL in 10 mL volumetric flasks with 7.4 pH phosphate buffer. Absorbances were measured at 240 nm. The procedure was conducted in triplicate for accuracy.

2.3.1. Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectra of pure Ramosetron HCl, pure polymers, and their physical mixtures were recorded using the KBr pellet method in the range of 4000 cm^{-1} to 400 cm^{-1} to assess potential drug-polymer interactions.

2.3.2. Formulation of Ramosetron HCl Transdermal Patches

Transdermal patches were prepared via solvent casting. Ramosetron HCl was dissolved in a 1:1 ratio of dichloromethane (DCM) and ethanol. After sequential addition of other ingredients and continuous stirring, the solution was cast onto a 9 cm diameter glass petri dish and dried at 70°C to form peelable films. The films were then cut into 2.0 cm × 2.0 cm pieces, each with an area of 4.0 cm^2 and containing 10 mg of Ramosetron HCl.

Table 1 Formulation of Ramosetron Hcl Transdermal patches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ramosetron Hcl	10	10	10	10	10	10	10	10	10
HPMC K15M	40	40	40	-	-	-	-	-	-
HPMC K100M	-	-	-	40	40	40	-	-	-
HPMC K200M	-	-	-	-	-	-	40	40	40
PVP K30	20	40	60	20	40	60	20	40	60
Tween-80	10	10	10	10	10	10	10	10	10
sorbitol	60	40	20	60	40	20	60	40	20

2.4. Evaluation of Transdermal Patches

- Thickness: Measured at three different locations using a micrometer, with mean values calculated.
- Weight Variation: Assessed by weighing randomly selected patches individually. Each formulation was tested.
- Drug Content: Patches of 1 cm^2 were dissolved in 5 mL of dichloromethane, and the volume was made up to 10 mL with 7.4 pH phosphate buffer. The dichloromethane was evaporated using a rotary vacuum evaporator at 45°C. The solution was filtered through a 0.45 µm membrane, diluted as needed, and absorbance was measured at 240 nm using a UV-Vis spectrophotometer.
- Folding Endurance: Determined by repeatedly folding a film at the same place until it broke, with the number of folds before breaking recorded.
- Tensile Strength: Measured by gradually increasing the pulling force on the patch until it broke. Elongation and tensile strength were calculated using a pulley system and magnifying glass on graph paper.
- In-Vitro Skin Permeation Studies: Conducted using a Franz diffusion cell with a receptor compartment of 22.5 mL. Excised rat abdominal skin (Wistar albino) was mounted between donor and receptor compartments. The patches were placed over the skin, covered with paraffin film, and the receptor compartment was filled with 7.4 pH phosphate buffer. The solution was continuously stirred at 50 rpm, and the temperature was maintained at 32 ± 0.5°C. Samples were withdrawn at various time intervals, analyzed spectrophotometrically, and the cumulative percentage of drug permeated per square centimeter was plotted against time.
- Stability Studies: The objective of stability studies is to identify and manage factors that could compromise the stability of the active ingredient and ensure the formulation maintains its therapeutic efficacy and safety over time. Stability studies are essential to assess the long-term stability of the drug formulation, to select appropriate excipients, and to ensure no toxic degradation products are formed. Long-term stability studies are crucial for defining shelf life and expiration dates. Various stability conditions include:

Table 2 Stability Storage Conditions

Stability Storage Category	Testing schedule for Physical and Chemical attributes
LONG TERM 25°C ± 2°C / 60% ± 5% RH	3, 6, 9, 12, 18, 24 and annually till expiry and 6 Months hence after.
ACCELERATED 40°C ± 2°C / 75% ± 5% RH	1, 2, 3 & 6 Months
INTERMEDIATE 30°C ± 2°C / 60% ± 5% RH	3, 6, 9 & 12 Months
ZONE IV 30°C ± 2°C / 70% ± 5% RH	3, 6, 9, 12, 18, 24 and annually till expiry and 6 Months hence after.

3. Results and discussion

3.1. Calibration curve of Ramosetron Hcl in 7.4pH phosphate buffer solution:

Standard calibration curve of Ramosetron Hcl was drawn by plotting absorbance versus concentration. The λmax of Ramosetron Hcl in 7.4pH phosphate buffer solution was found to be 240nm.

Table 3 Calibration data of Ramosetron Hcl in 7.4pH phosphate buffer at 240nm

Concentration (µg/ml)	Absorbance
0	0
1	0.147
2	0.314
3	0.481
4	0.624
5	0.789

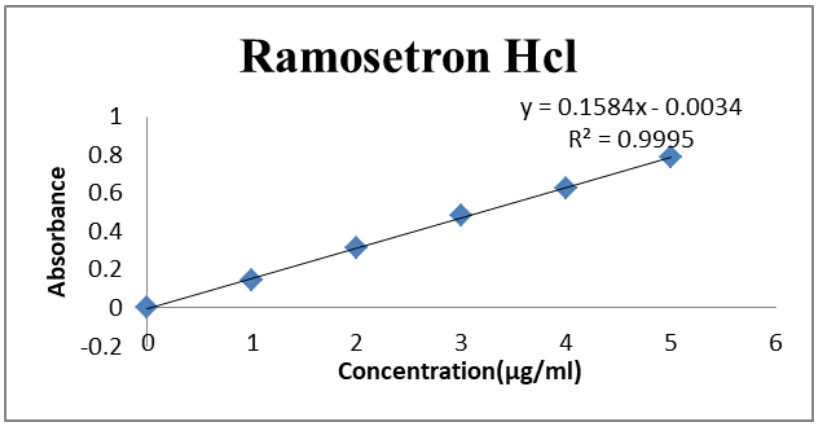

Figure 2 Standard calibration curve of Ramosetron Hcl in 7.4pH phosphate buffer solution

3.2. Compatibility study by FTIR

The compatibility of the drug with polymer was evaluated by performing FTIR analysis of standard drug and best formulation.

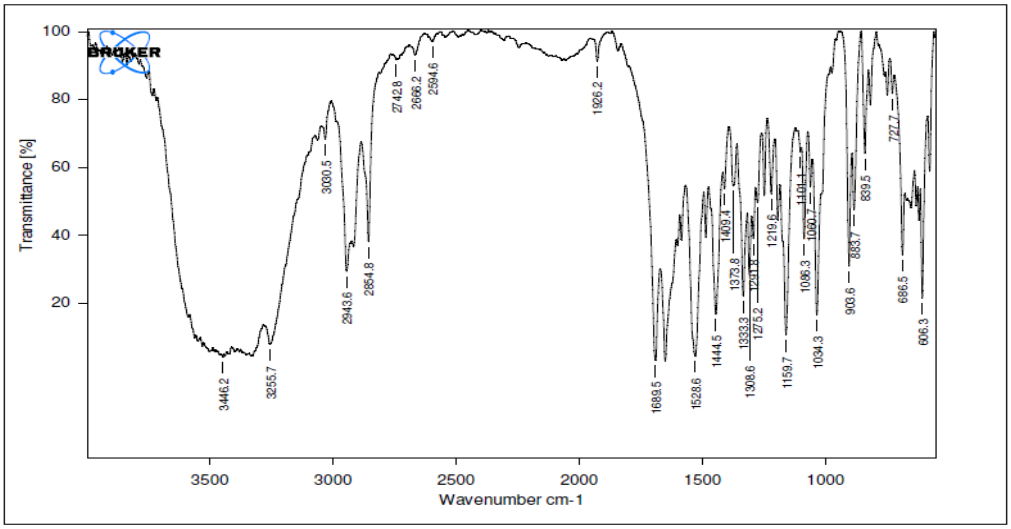

Figure 3 FTIR graph of Ramosetron Hcl pure drug

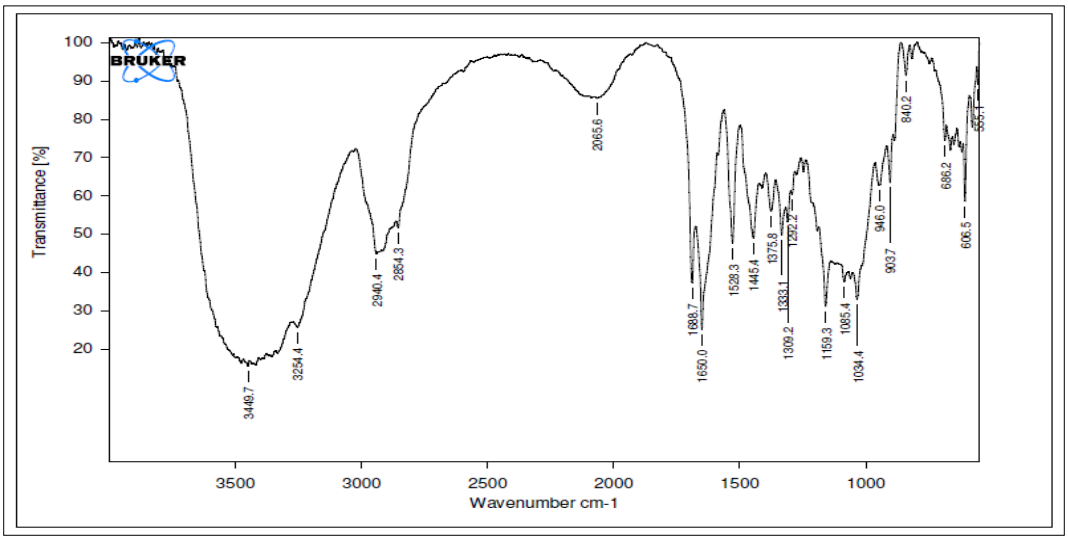

Figure 4 FTIR graph of Ramosetron Hcl best formulation

Table 4 Evaluation parameters of Ramosetron Hcl Transdermal patches

Formulation code	Thickness	Weight variation	Drug content	Folding endurance	Tensil strength
F1	162	Pass	98.23	201	2.74
F2	158	Pass	99.14	199	2.96
F3	153	Pass	99.67	212	3.12
F4	160	Pass	98.83	219	3.04
F5	157	Pass	99.37	210	2.83
F6	152	Pass	99.95	206	2.92
F7	147	Pass	99.67	218	3.15
F8	138	Pass	99.82	237	2.86
F9	156	Pass	99.37	204	2.46

Table *5* *In-vitro* drug release data for Transdermal patches

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	32	28	25	20	16	5	12	5	0
2	46	39	34	38	24	8	20	11	3
3	58	52	50	59	36	15	28	19	9
4	64	59	55	67	53	20	42	31	17
6	85	78	69	78	64	29	56	42	28
8	96	89	81	84	78	48	62	55	43
10	100	95	89	99	86	56	75	67	51
12	100	100	96	100	98	74	81	73	63

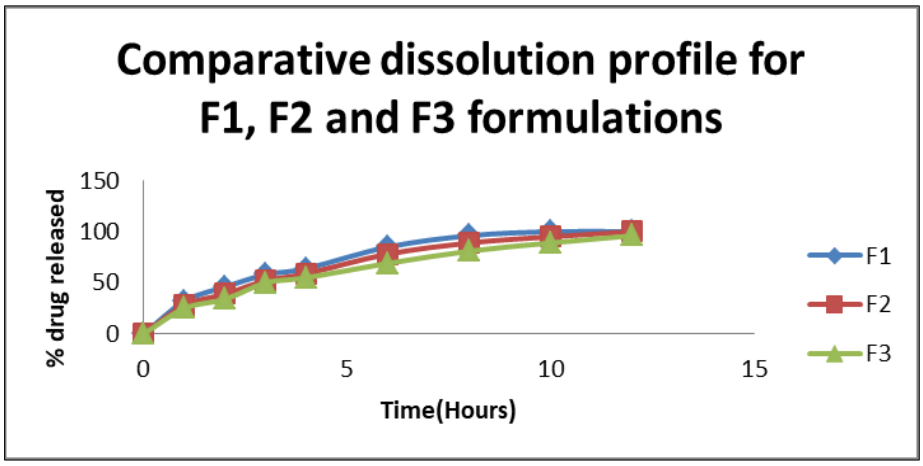

Figure 5 Comparative Dissolution profile for F1, F2 and F3 formulations

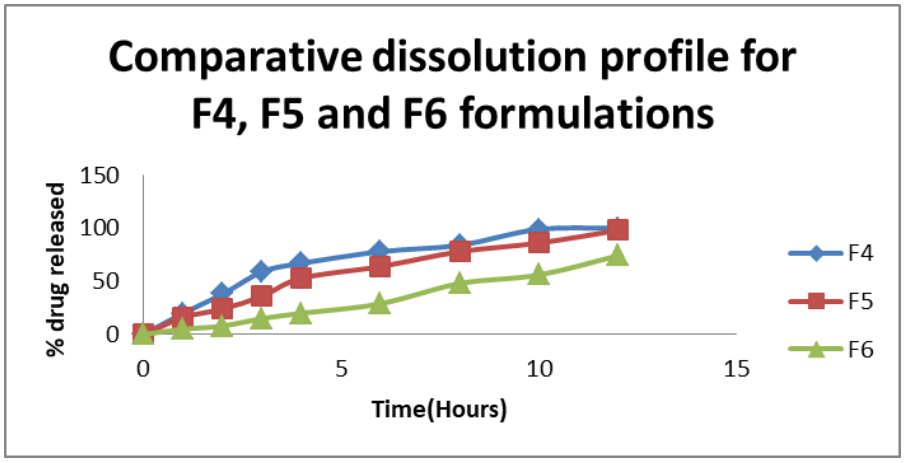

Figure 6 Comparative Dissolution profile for F4, F5 and F6 formulations

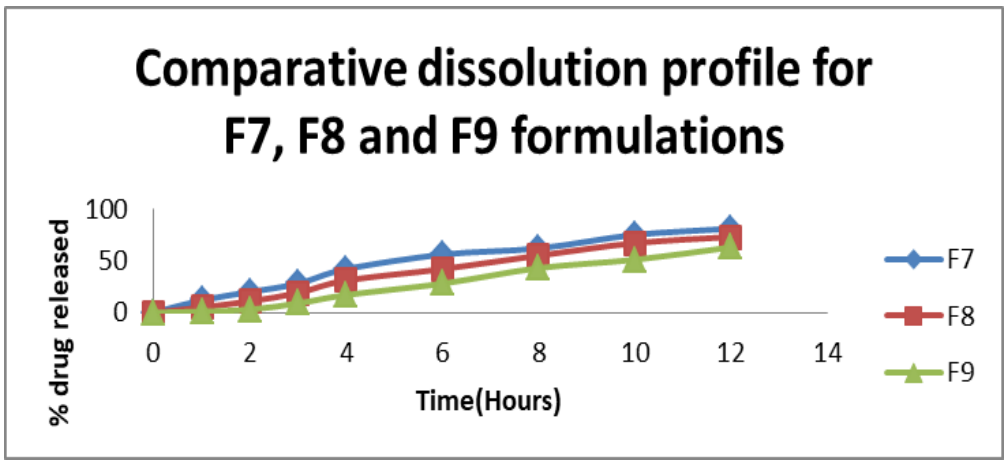

Figure 7 Comparative Dissolution profile for F7, F8 and F9 formulations

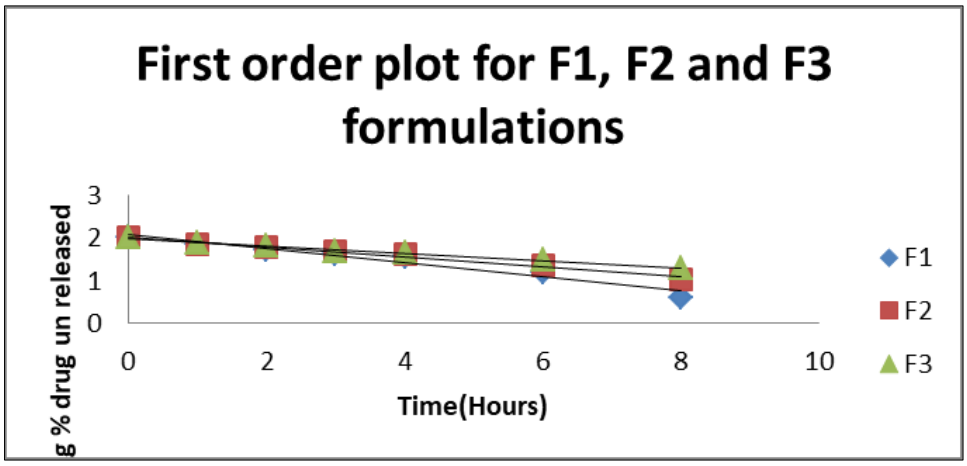

Figure 8 First order plot for F1, F2 and F3 formulations

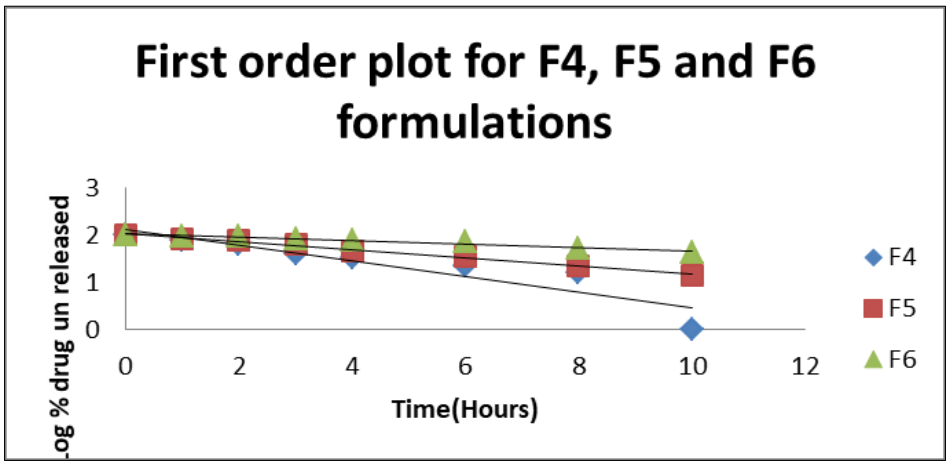

Figure 9 First order plot for F4, F5 and F6 formulations

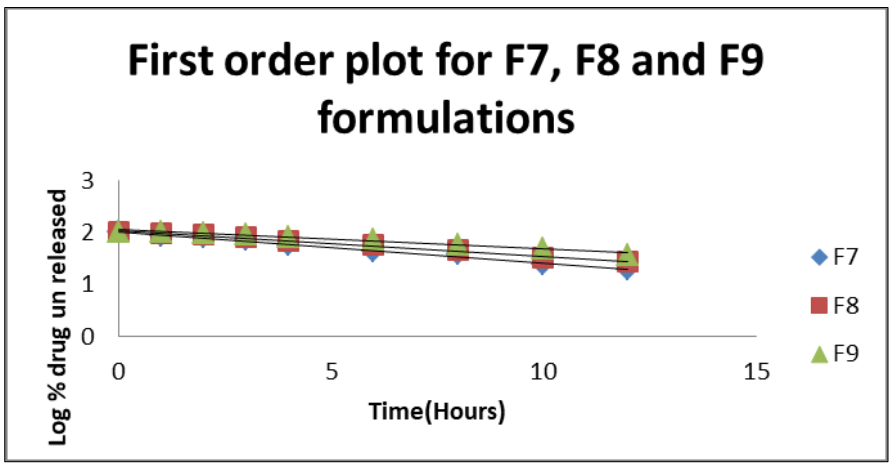

Figure 10 First order plot for F7, F8 and F9 formulations

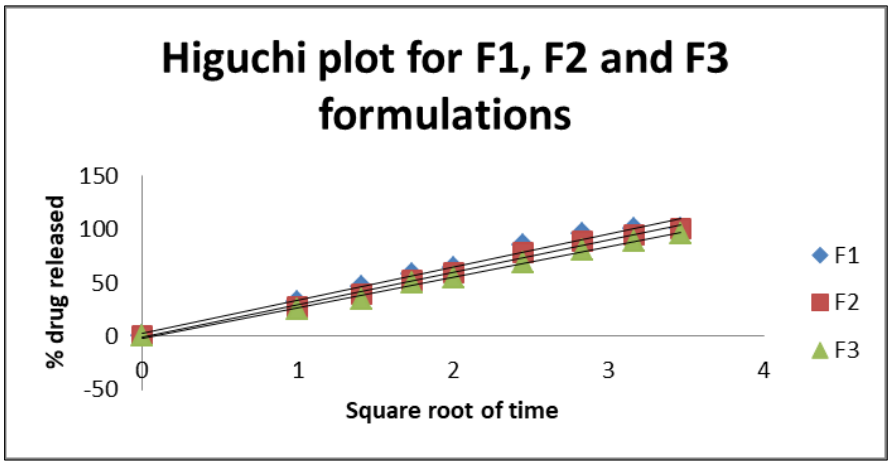

Figure 11 Higuchi plot for F1, F2 and F3 formulations

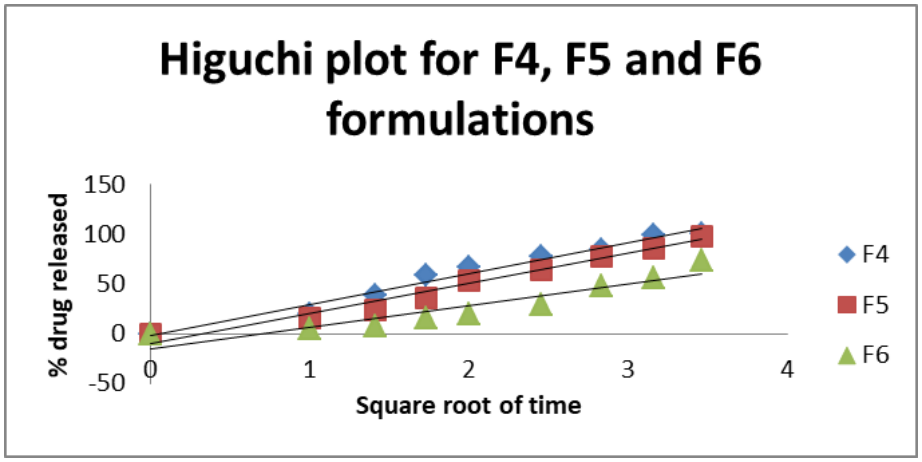

Figure 12 Higuchi plot for F4, F5 and F6 formulations

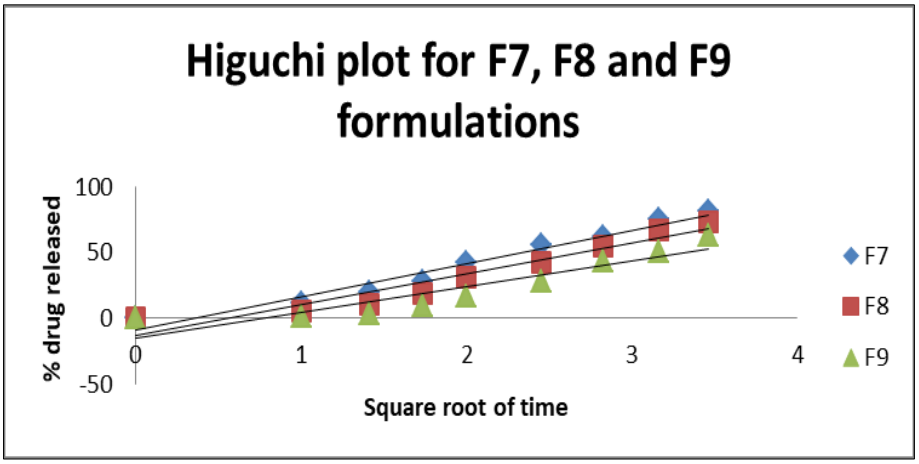

Figure 13 Higuchi plot for F7, F8 and F9 formulations

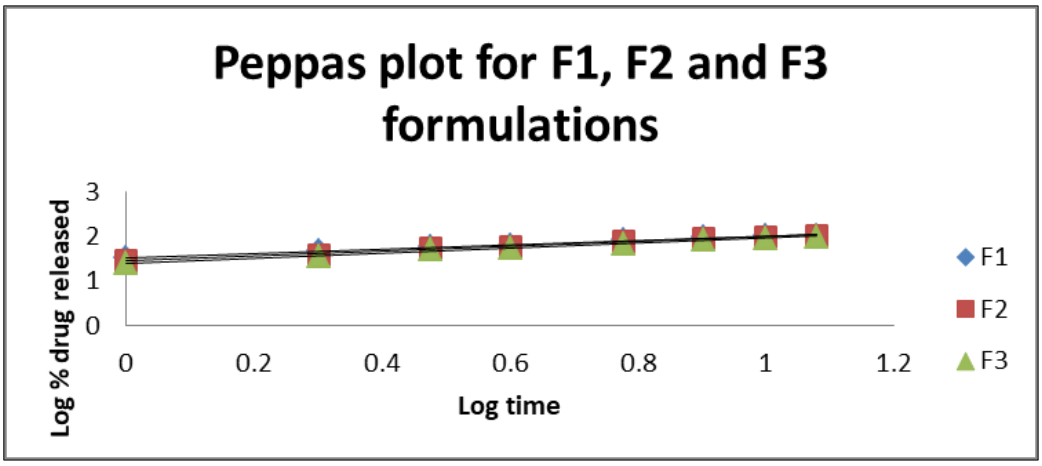

Figure 14 Peppas plot for F1, F2 and F3 formulations

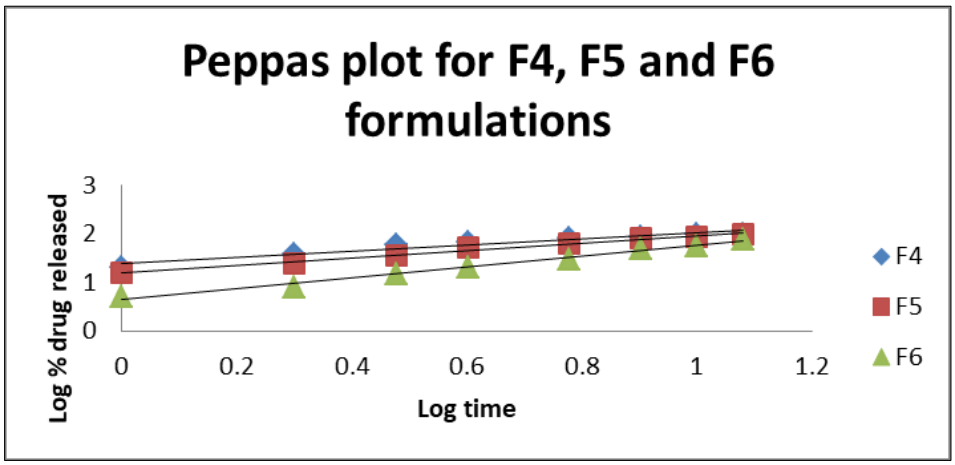

Figure 15 Peppas plot for F4, F5 and F6 formulations

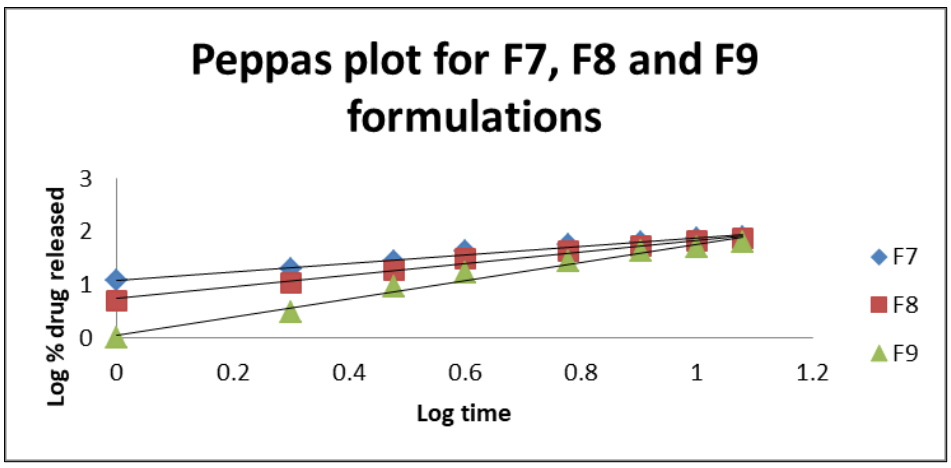

Figure 16 Peppas plot for F7, F8 and F9 formulations

Table 6 R^2 and 'n' result table

Formulation code	R^2 Values				N Value
	Zero order	First order	Higuchi	Peppas	
F1	0.852	0.951	0.98	0.982	0.483
F2	0.9	0.986	0.992	0.991	0.535
F3	0.918	0.992	0.995	0.99	0.556
F4	0.869	0.84	0.973	0.94	0.624
F5	0.96	0.991	0.971	0.984	0.753
F6	0.988	0.964	0.867	0.989	1.113
F5	0.963	0.992	0.966	0.987	0.793
F6	0.987	0.99	0.926	0.986	1.103
F7	0.987	0.969	0.858	0.979	1.709

3.3. Stability studies

Selected formulation F5 was stored at 40°C ± 2°C / 75% ± 5% RH or a period of 3 months. Samples were analyzed after storage for 1, 2 and 3 month and evaluated.

Table 7 In-vitro release profile of F5 during Stability studies (40°C ± 2°C / 75% ± 5% RH)

Time (Hrs)	Initial	Month 1	Month 2	Month 3
0	0	0	0	0
1	16	15	16	14
2	24	22	25	24
3	36	35	36	33
4	53	53	51	51
6	64	62	63	62
8	78	77	76	75
10	86	84	85	84
12	98	97	97	98

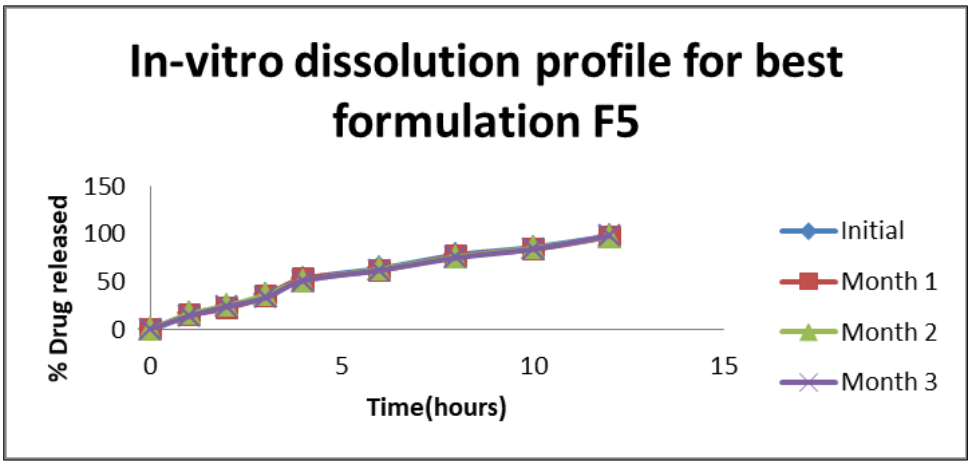

Figure 17 In-vitro release profile of F9 during Stability studies (40°C ± 2°C / 75% ± 5% RH)

4. Summary and Conclusion

- Ramosetron Hcl transdermal patches were successfully prepared with HPMC K15M and HPMC K100M and HPMC K 200M.
- The amount of plasticizer tween 80 was critical for patch formation and separation properties.
- Tween 80 was selected for solubility enhancer and plasticizer during shelf life period.
- It was concluded that formulations F-5 was found to be satisfactory batche and was optimized for the desirable properties.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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