

Formulation and *In Vitro* Evaluation of Ondansetron Hydrochloride Matrix Transdermal Systems Using Ethyl Cellulose/Polyvinyl Pyrrolidone Polymer Blends

Rajan Rajabalaya, Li-Qun Tor, and Sheba David

Abstract—Transdermal delivery of ondansetron hydrochloride (OdHCl) can prevent the problems encountered with oral ondansetron. In previously conducted studies, effect of amount of polyvinyl pyrrolidone, permeation enhancer and casting solvent on the physicochemical properties on OdHCl were investigated. It is feasible to develop ondansetron transdermal patch by using ethyl cellulose and polyvinyl pyrrolidone with dibutyl phthalate as plasticizer, however, the desired flux is not achieved. The primary aim of this study is to use dimethyl succinate (DMS) and propylene glycol that are not incorporated in previous studies to determine their effect on the physicochemical properties of an OdHCl transdermal patch using ethyl cellulose and polyvinyl pyrrolidone. This study also investigates the effect of permeation enhancer (eugenol and phosphatidylcholine) on the release of OdHCl. The results showed that propylene glycol is a more suitable plasticizer compared to DMS in the fabrication of OdHCl transdermal patch using ethyl cellulose and polyvinyl pyrrolidone as polymers. Propylene glycol containing patch has optimum drug content, thickness, moisture content and water absorption, tensile strength, and a better release profile than DMS. Eugenol and phosphatidylcholine can increase release of OdHCl from the patches. From the physicochemical result and permeation profile, a combination of 350mg of ethyl cellulose, 150mg polyvinyl pyrrolidone, 3% of total polymer weight of eugenol, and 40% of total polymer weight of propylene glycol is the most suitable formulation to develop an OdHCl patch. OdHCl release did not increase with increasing the percentage of plasticizer. DMS 4, PG 4, DMS 9, PG 9, DMS 14, and PG 14 gave better release profiles where using 300mg: 0mg, 300mg: 100mg, and 350mg: 150mg of EC: PVP. Thus, 40% of PG or DMS appeared to be the optimum amount of plasticizer when the above combination where EC: PVP was used. It was concluded from the study that a patch formulation containing 350mg EC, 150mg PVP, 40% PG and 3% eugenol is the best transdermal matrix patch compositions for the uniform and continuous release/permeation of OdHCl over an extended period. This patch design can be used for further pharmacokinetic and pharmacodynamic studies in suitable animal models.

Keywords—Ondansetron hydrochloride; dimethyl succinate; eugenol.

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I. INTRODUCTION

CHEMOTHERAPY induced nausea and vomiting (CINV) was rated as the most distressing symptoms by patients receiving chemotherapy [1]. In spite of the achievement in controlling acute CINV, delayed CINV remains a problem. It occurs after 24 hours of chemotherapy. It is proven that 5-HT₃ receptor plays a major role in delayed CINV. Oral ondansetron, which is a 5-HT₃ antagonist, fails to prevent delayed CINV though it is effective to prevent acute CINV [1]. This is because its short half-life of 3-3.5 hours. In addition, its use is restricted in patients receiving high emetogenic anticancer drugs. Besides that, it loses its effect in patients who are CYP3D4 extensive metabolizers because it is metabolized extensively in the liver [2].

Currently, OdHCl is available in oral and injectable form in the market. Injectable ondansetron hydrochloride gives rapid effect however it leads to undesirable side effects sometimes. Transdermal patch OdHCl avoids the problems encountered by oral and injectable ondansetron. Transdermal OdHCl gives prolonged OdHCl effect, reduces frequency of dosing, minimises interpatient and inpatient variability, and its administration can be terminated by peeling off [2]. It is possible to incorporate OdHCl into transdermal patch because of its low bioavailability of 60%, its low molecular weight of 293.4, low dose of 16mg/day, and partition coefficient of 1.87. All these characteristics fulfil the criteria of a drug if it is to be incorporated into transdermal patch [3]. In the fabrication of previously done OdHCl patch, the desired flux of OdHCl was not achieved [4]. However, in another study, the optimum formulation with incorporation of chemical enhancer was known by setting the desired flux of OdHCl in Design Expert (DE) software. The formulation optimized by DE software gave desirable flux. The aim of this study is to investigate physicochemical properties of an OdHCl transdermal patch by using DMS or propylene glycol as plasticizer without using any software. Based on the physicochemical result, optimum formulation can be known. In addition, this study investigates the effect of eugenol and phosphatidylcholine on release of OdHCl.

II. MATERIALS AND METHODS

A. Materials

Ondansetron hydrochloride was obtained as a gift from Aurobindo Chemicals, India. Ethyl cellulose (EC; ethoxy content 48.0-49.5%, viscosity 18 to 22mPa) was received from Dow Chemical, Germany. Polyvinyl pyrrolidone (PVP) was obtained as a gift from BASF chemical company, Germany. DMS and propylene glycol (PG) were purchased from Merck Chemicals, Germany. Eugenol was purchased from Spectrum Chemical mfg. Corp., US. Phosphatidylcholine was purchased from Lipoid GmbH, Germany. All other chemical were of analytical grade.

B. Preparation of Matrix Patch

Required amount of polymers (EC and PVP) were dissolved in 5ml chloroform. DMS or PG was added then. This is followed by 16 mg of OdHCl. Finally, eugenol or phosphatidylcholine was added to the solution at 3% of the total polymer weight. The addition of each material was done at 15 minutes interval. Once EC was added to the chloroform, the solution was stirred slowly by magnetic stirrer until all of the materials dissolved. After that, the mixture was slowly poured into the stainless steel ring having a backing layer of aluminium foil. It was then dried at room temperature for 24-48 hours to form transdermal patch. The dried patches were kept in sealed plastic pouches until further use.

C. Determination of Patch Thickness

Patch thickness was determined by using digital micrometer (Mitutoyo, Japan) [5].

D. Determination of Tensile Strength

It was measured using tensilemeter (Instron, UK) with a mounted load of 50 KN. Three samples of each formulation were tested with an appropriate extension speed of 5 mm/min as mentioned in method D 882-75D in America Society for Testing Materials. The test was carried out at $25 \pm 2^\circ\text{C}$ and $56\% \pm 2\%$ relative humidity [5]. The tensile strength was calculated by

$$\tau = L_{\max}/A_i$$

(τ : tensile strength; L_{\max} : maximum load and A_i : initial cross-sectional area of the sample).

E. Determination of Drug Content

1cm² of each patch was weighed and dissolved in appropriate amount of chloroform. Then, the solution was filtered and diluted with distilled water. Drug content in each formulation was determined by UV spectrophotometer at 249nm. A control was performed by using a drug-free film [5].

F. Determination of Moisture Content

The patch was weighed individually and kept in a desiccator containing fused calcium chloride at 40⁰c for 24 hours. The patch was reweighed until a constant weight was obtained [5].

G. Determination of Water Absorption Studies

Weighed patch was kept in two different desiccators with different relative humidity of 75% and 93% for 24 hours. Humidity of 75% was created by putting saturated solution of sodium chloride whereas 93% by placing saturated solution of ammonium hydrogen phosphate in desiccators. The patches were weighed periodically to gain constant weight [5].

H. In Vitro Release and Ex Vivo Permeation Studies

The *in vitro* release study was carried out in Franz diffusion cell (Perme Gear, US). A piece of circular matrix patch was mounted on the receptor compartment with backing membrane facing donor compartment. For permeation study, albino mouse abdominal skin was put between receptor compartment and patch. The receptor compartment was filled with freshly prepared phosphate buffered saline of pH7.4. 32⁰c of water from a constant temperature water bath was flowing continuously into the jacket of diffusion cell. 0.5ml of sample was withdrawn each hour for 8 hours and the volume of the cell was replaced immediately with 0.5ml of saline. The sample was analyzed by UV spectrophotometer at 249nm after dilution to determine its drug concentration [5].

III. RESULTS AND DISCUSSION

TABLE I
PATCH FORMULATIONS AND ITS COMPOSITIONS

S. No	Patch composition (mg)	Patch code		Percentage of plasticizer		
		EC : PVP	DMS	PG	DMS	PG
1	300 : 000		DMS 1	PG 1	10	10
2	300 : 000		DMS 2	PG 2	20	20
3	300 : 000		DMS 3	PG 3	30	30
4	300 : 000		DMS 4	PG 4	40	40
5	300 : 000		DMS 5	PG 5	50	50
6	300 : 100		DMS 6	PG 6	10	10
7	300 : 100		DMS 7	PG 7	20	20
8	300 : 100		DMS 8	PG 8	30	30
9	300 : 100		DMS 9	PG 9	40	40
10	300 : 100		DMS 10	PG 10	50	50
11	350 : 150		DMS 11	PG 11	10	10
12	350 : 150		DMS 12	PG 12	20	20
13	350 : 150		DMS 13	PG 13	30	30
14	350 : 150		DMS 14	PG 14	40	40
15	350 : 150		DMS 15	PG 15	50	50
16	350 : 200		DMS 16	PG 16	10	10
17	350 : 200		DMS 17	PG 17	20	20
18	350 : 200		DMS 18	PG 18	30	30
19	350 : 200		DMS 19	PG 19	40	40
20	350 : 200		DMS 20	PG 20	50	50
21	350 : 250		DMS 21	PG 21	10	10
22	350 : 250		DMS 22	PG 22	20	20
23	350 : 250		DMS 23	PG 23	30	30
24	350 : 250		DMS 24	PG 24	40	40
25	350 : 250		DMS 25	PG 25	50	50

Table I showed that with the increase of the amount of plasticizer, patches become more flexible. However, 50% containing plasticizer leads to sticky patches.

A. Patch Thickness

Though PG containing patches were thicker than DMS, they were still considered to have optimum thickness. PG is

more hydrophilic compared to DMS and absorbs more moisture that leads to thickness of the patches (Table II).

TABLE II
AVERAGE THICKNESS IN DMS OR PG CONTAINING PATCHES

Patch code		Thickness (mm)	
DMS	PG	DMS	PG
DMS 3	PG 3	0.150 ± 0.03	0.164 ± 0.01
DMS 4	PG 4	0.156 ± 0.01	0.169 ± 0.03
DMS 5	PG 5	0.159 ± 0.02	Sticky
DMS 8	PG 8	0.189 ± 0.01	0.206 ± 0.04
DMS 9	PG 9	0.193 ± 0.04	0.209 ± 0.05
DMS 10	PG 10	0.197 ± 0.03	Sticky
DMS 13	PG 13	0.205 ± 0.04	0.218 ± 0.02
DMS 14	PG 14	0.209 ± 0.06	0.223 ± 0.01
DMS 18	PG 18	0.211 ± 0.05	sticky
DMS 23	PG 23	0.219 ± 0.02	sticky

Tensile Strength

Tensile strength is important because optimum tensile strength prevents patch from tearing when it is applied on the skin [6]. From the mechanical engineering handbook, material with tensile strength of more than 4MPa is elastic [5]. However, there was no significant difference between DMS and PG containing patches in tensile strength in Fig. 1 ($P > 0.05$).

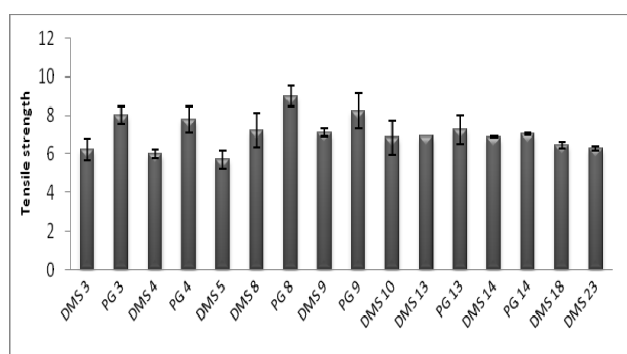


Fig. 1 Tensile strength in DMS and PG containing patches

B. Drug Content

In the Fig. 2 showed that distribution of OdHCl was not affected by the amount of PG and DMS. This means PG and DMS does not affect the good distribution characteristic of EC/PVP proven by Kalpana et. al [4]. Another reason for uniform drug distribution may due to PG or DMS does not interact with chloroform. It is a suitable casting solvent for OdHCl because it prevents crystallization of OdHCl. Salt form of drug favours less polar solvent [7].

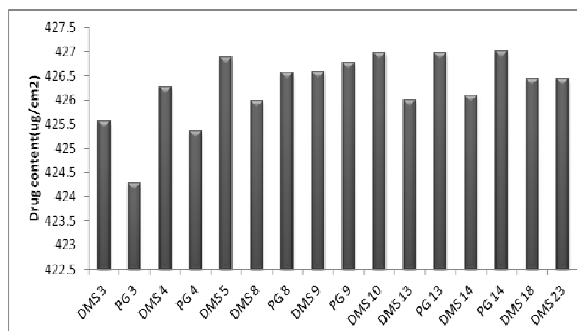


Fig. 2 Drug content in DMS and PG containing patches

TABLE III
AVERAGE MOISTURE CONTENT AND WATER ABSORPTION

Patch code		Moisture content (%)		Water absorption (%)			
DMS	PG	DMS	PG	DMS		PG	
DMS	PG	DMS	PG	75%RH	93%RH	75%RH	93%RH
DMS 3	PG 3	1.01	1.35	1.58	1.65	1.93	2.98
DMS 4	PG 4	1.05	1.38	1.62	1.70	1.98	3.19
DMS 5	PG 5	1.09	S	1.65	1.76	2.04	S
DMS 8	PG 8	1.12	1.56	1.89	2.05	2.11	4.02
DMS 9	PG 9	1.15	1.59	1.94	2.11	2.14	4.11
DMS 10	PG 10	1.19	S	1.98	2.16	2.18	S
DMS 13	PG 13	1.25	1.69	2.06	2.18	2.21	4.20
DMS 14	PG 14	1.26	1.72	2.09	2.19	2.38	4.56
DMS 18	PG 18	1.38	S	2.10	2.21	2.36	S
DMS 23	PG 23	1.41	S	2.15	2.26	2.45	S

S- Sticky

C. Moisture Content and Water Absorption

Moisture content in a patch can neither be too low nor too high. If the moisture content is too high, the patch is either susceptible to microbial growth or increase in bulkiness that brings inconvenience in transportation. However, the patch is brittle when the moisture content is too low [4]. From Table III, when the amount of plasticizer increased, moisture content and water absorption in the patch increased. This is due to the hydrophilic nature of both DMS and PG. When the amount of hydrophobic DBP increased, the patch was more difficult to hydrate compared to hydrophilic and hygroscopic PG. From this study and previous study done by Rajan et. al., it can be concluded that nature of plasticizer affects moisture content and water absorption of a patch [5]

D. In Vitro Release without Enhancer

From Table IV, OdHCl did not increase in release with the increase of the percentage of plasticiser. DMS 4, PG 4, DMS 9, PG 9, DMS 14, and PG 14 had better release profile in the batch of using 300mg: 0mg, 300mg: 100mg, and 350mg: 150mg of EC: PVP. Thus, it is concluded that 40% of PG or DMS appear to be the optimum amount of plasticiser when the above combination of EC: PVP was used. From Table IV, PG containing patches had higher OdHCl release at 8th hour compared to DMS. This was explained by swelling of EC in the presence of hydrophilic PG which resulted in greater distance in polymer matrix for drug to release. PG is a more

suitable plasticizer to make OdHCl patch (Table IV) [5].

From the data, r^2 of zero order, first order, Korsmeyer peppas and Higuchi model was shown. Obeying Higuchi release means release of OdHCl from transdermal patch is

TABLE IV
PERCENTAGE OF DRUG RELEASE AT 8TH HOUR

Patch Code		Percentage of drug release (%)	
DMS	PG	DMS	PG
DMS 3	PG 3	17.10	40.92
DMS 4	PG 4	29.45	64.09
DMS 5	PG 5	28.14	sticky
DMS 8	PG 8	21.61	74.99
DMS 9	PG 9	32.21	77.89
DMS 10	PG 10	30.08	sticky
DMS 13	PG 13	32.07	32.10
DMS 14	PG 14	35.33	38.71
DMS 18	PG 18	37.80	sticky
DMS 23	PG 23	38.32	sticky

proportionally to square root of time, confirming diffusion controlled system. Zero order means the drug release is proportional to time and concentration independent. First order indicates the drug release is concentration dependent. Korsmeyer peppas developed a model to describe mechanism of drug release based on 'n' of the equation $M_0/M_\infty = ktn$. N value of 0.45, 0.45-0.89, and 0.89 indicate Fickian diffusion-controlled drug release, anomalous transport, and case II relaxational release transport respectively. Anomalous transport is combination of both diffusion and erosion controlled release [8]. PG is more suitable to be used than DMS because more PG containing patches followed anomalous transport which is desirable in transdermal patch.

E. Effect of Eugenol and Phosphatidylcholine on Release

To investigate effect of eugenol or phosphatidylcholine on drug release, they are added to patches DMS 4, DMS 9, DMS 18, DMS 23 and PG 14. They were added because they have low release and were the better formulations in batch of using 300mg: 0mg, 300mg: 100mg, and 350mg: 150mg of EC: PVP. PG 4, PG 9, DMS 14 has either more than 50% of release or fluctuated release. So, they were not added enhancers. Fig. 3 showed that eugenol and phosphatidylcholine can increase OdHCl release at 8th hour in certain patches ($P < 0.05$). Mechanism of phosphatidylcholine was believed due to its miscibility with EC/PVP that leads to increased spacing in polymer chains [9]. Drug can release faster from patch if there is increase of spacing in polymers. Further studies using scanning electron microscopic or Fourier transform infrared spectroscopy to check any structural changes in matrix EC/PVP after adding eugenol or phosphatidylcholine can be done in the future because internal structure of polymer affects drug release [2].

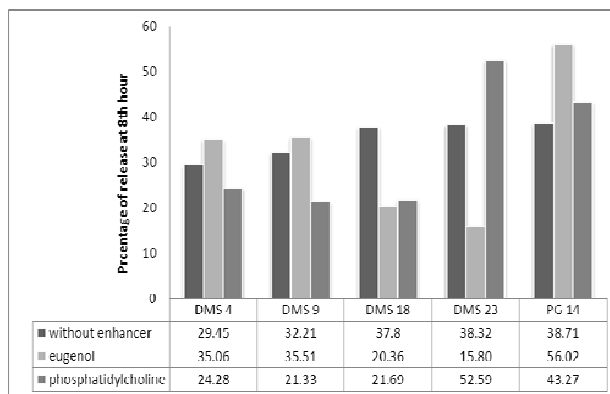


Fig. 3 Comparison of drug release between with/without enhancer

F. Ex Vivo Permeation Studies

To find out optimum formulation, percentage of permeated OdHCl is important because it ensures that sufficient amount of OdHCl can cross the stratum corneum. Patch having 50% of release underwent permeation studies. From Fig. 4, PG 14(E) had the highest permeation profile and followed by PG 9. PG 14(E) had good permeation profile in which OdHCl permeated across skin gradually and almost reached plateau after 3rd hour which confirmed controlled release manner. The remaining formulations in the graph had low percentage of permeated OdHCl thereby they are unsuitable to be formulated into patch.

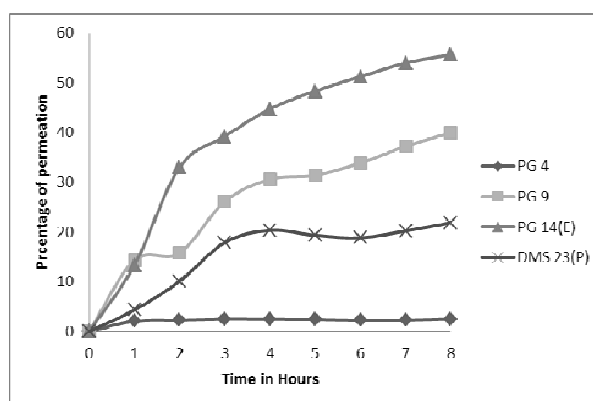


Fig. 4 Permeation profile in DMS or PG containing patches

IV. CONCLUSION

The patch formulation PG 14(E) containing 350mg EC, 150mg PVP, 40% PG and 3% eugenol is the best TD matrix patch compositions in this present study for the uniform and continuous release/permeation of OdHCl over an extended period, and to maintain a sustained therapeutic level of the drug in plasma. These selected formulations may be used for further pharmacokinetic and pharmacodynamic studies in suitable animal models.

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