International Journal of Drug Delivery 4 (2012) 125-133

http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

# Development and In Vitro Evaluation of Matrix Type Transdermal Delivery of Ondansetron Hydrochloride.

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## Abstract

Release and permeation studies were carried out with the objective of developing transdermaltherapeutic systems with Ondansetron Hydrochloride (OS).The patches were prepared with Eudragit RSPO/RLPO as polymer and dibutylsebacate (DBS) and triethyl citrate (TEC) as the plasticizer in different compositions. Thickness, tensile strength, drug content, moisture content and water absorption studies of the patches were measured. In vitro release/permeation of OS was studied by using a Franz diffusion cell. Chemical enhancers like eugenol and Virgin linseed oil were added to compare the release pattern of the drug. All the formulations are developed and passed the mechanical as well as physiochemical properties, while in the case of release profile, the patch containing DBS had better percentage cumulative release compared to those with TEC containing patches. Eugenol acted as a good chemical enhancer as it increased percentage of permeation compared to linseed oil significantly. The ratio of Eudragit RSPO/RLPO (1:1) with combination of using 25% DBS as plasticizer and 3% eugenol as chemical enhancer favourable release profile. The selected formulations may be used for further pharmacokinetic and pharmacodynamic studies in suitable animal models.

Keywords: Ondansetron Hydrochloride; dibutylsebacate; triethyl citrate; eugenol; linseed oil

## Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect encountered by cancer patients during chemotherapy treatment. Ondansetron is a serotonin subtype 3 (5-$HT_3$) receptor antagonist used in CINV management. Ondansetron hydrochloride (OS) is commercially available in oral and injectable forms. Orally administered OS undergoes extensive hepatic first-pass metabolism, which accounts for its low bioavailability and short half-life [1-3]. It tends to be vomited before being absorbed and has limited use in patients with difficulty swallowing after chemotherapy [4]. As for intravenous administration, pain at injection site is the main limitation and onset of action is too rapid thus causing undesirable side effects such as headache, dizziness, and constipation [5]. Therefore, a new drug delivery system should be developed to improve OS therapeutic efficacy and patient's compliance.

Transdermal drug delivery system (TDDS) is a topically administered medicament which delivers controlled amount of drug through the skin over certain period of time [6]. Polymers act as the backbone of systems for transdermal delivery and promote drug release in a pre-designed manner. Plasticiser is added to improve flexibility besides reducing patch brittleness [7-9]. Transdermal delivery of OS should be considered for use in CINV treatment since it promotes better patient compliance and unwanted side effects can be terminated by removing the patch from application site [10].

Gwak*et al.*,(2004) investigated the effects of vehicles on *in vitro* permeation of OS solution formulations across mouse skins and found that ethanol and water were the most effective vehicles [5]. However, they do not mix well with pressure-sensitive adhesive (PSA) so a further study was done using different vehicles to develop OS transdermal PSA matrix formulations [1]. Krishnaiah*et al.*,(2008) prepared hydroxypropyl cellulose gel drug reservoir formulations of OS and evaluated the effect of menthol (a penetration enhancer) on drug permeation across rat epidermis [10]. Pattnaik*et al.*, (2011) [11] reported that chloroform was a preferred casting solvent for OS in transdermal films [5]. OS matrix type transdermal patches were prepared by using different

ratios of ethyl cellulose (EC) and polyvinylpyrrolidone (PVP) polymers [12] results showed that increased amount of PVP enhanced drug permeation. However, the flux achieved was significantly lower than the desired flux for effective transdermal delivery of OS and the need for permeation enhancement techniques was indicated [12].

In the present study, OS transdermal matrix patches were developed by using Eudragit RSPO/RLPO as the polymer matrix with different percentages of dibutylsebacate (DBS) and triethyl citrate (TEC) as plasticisers. Eugenoland linseed oil were incorporated as chemical enhancer to increase drug permeability across the skin. Physicochemical properties, mechanical properties, *in vitro* drug release and permeation of OS matrix patches were studied. OS patch formulations were optimised based on experimental data, findings, and statistical analysis.

## Materials and Methods

### Materials

Ondansetron hydrochloride (OS) was a gift from Aurobindo Chemicals, India. Eudragit RSPO and Eudragit RLPO were purchased from Evonik Rohm GmbH Pharma Polymers, Germany. Dibutylsebacate(DBS) and triethyl citrate (TEC) were purchased from Merck Chemicals. Virgin linseed oil B.P/EP grade was a gift sample from John L Seatons& Co Limited, UK. Eugenol was purchased Spectrum Chemical Mfg. Corp., USA.All other chemicals used in the study were of analytic reagent grade.

### Preparation of the patches

For preparation of the patches, 500mg or 700mg of various ratios of Eudragit RSPO/RLPO were dissolved in a suitable solvent followed by slow magnetic stirring. Then the plasticizer (TEC or DBS, the amount of 15-25% the total polymer weight) and 16mg of drug (OS) were added to the solution and stirred for 15 to 20 minutes. Finally the required amount of chemical enhancers such as linseed oil and eugenol (3% of the total weight of polymers) was added into selected patches and again stirred for 30 minutes[13]. Next the total mass was slowly poured into the centre of stainless steel rings having a backing layer of aluminium foil. The total mass was dried at room temperature for 48 hours. The dried patches were kept in sealed plastic pouches and stored in desiccators until use (Table 1).

### Determination of patch thickness

Thickness was measured using a digital micrometer.An average of three readings was obtained. The results are reported as an average of six readings (Table 2).

### Determination of tensile strength

The tensile strength of the patches was evaluated using Instron 4204 Tensile tester, with a 50KN load cell (Instron, UK). Six samples of each formulation were tested at an extension speed of 5mm/min [American Society for Testing Materials (ASTM); method D 882- 75D]. The test was carried out at 25±2 C and 56± 2% RH. The tensile strength was calculated as follows:

$= L_{max} / A_i$

Where is the tensile strength; $L_{max}$ is the maximum load and $A_i$ is the initial cross sectional area of the sample. The results are reported as an average of six readings (Table 2) [13].

### Drug content

A known area of each patch was weighed accurately and dissolved in 2mL chloroform followed by dilution with distilled water and then filtered. Drug content was analysed by UV spectrophotometer (PerkinElmer, USA) at 249nm. A drug-free film was used as a control [13]. An average of three readings was recorded. The results are reported as an average of six readings (Table 2).

### Moisture content

Each patch was weighed and kept in a desiccator containing fused calcium chloride at 40 C for 24 hours. Patches were reweighed until a constant weight was obtained. An average of three readings was taken[13]. The results are reported as an average of six readings (Table 3).

### Water absorption studies

Each patch was weighed and kept at room temperature for 24 hours with exposure to two relative humidities of 75% (containing saturated sodium chloride solution) and 93% (containing saturated ammonium hydrogen phosphate solution) in different desiccators. Patches were reweighed until a constant weight was obtained [13]. An average of three readings was recorded. The results are reported as an average of six readings (Table 3).

### In vitro release studies

*In vitro* release studies were carried out in a Franz diffusion cell (PermeGear, USA). A piece of circular matrix patch was mounted on receptor compartment, which was filled with freshly prepared phosphate buffered saline having pH 7.4. Temperature was maintained at 32 ± 0.5 C. Sample (0.5mL) was withdrawn every hour for 8 hours and being replaced immediately with same volume of saline solution [14]. Samples were then diluted and analysed by UV spectrophotometer at 249nm. An average of three readings was recorded (Table 4).

### In vitro permeation studies

A matrix patch was bound intimately with a section of freshly excised albino mouse abdominal skin on the receptor compartment. The skin's dermal side was kept in contact with the receptor liquid at all times to ensure continuous drug permeation. All other analysis conditions were similar to *in vitro* release studies [14]. An average of three readings was recorded (Table 4).

### Statistical analysis

The results obtained were treated statistically using one-way analysis of variance (ANOVA). Post-hoc Tukey-HSD (Honestly Significant Difference) test was performed when there was a statistically significant difference, which was considered at p 0.05.

## Results and Discussion



## Thickness, tensile strength and drug content

The formulation composition and results from these studies are presented in Tables 1& 2. Initially the patch was prepared by using total 500mg amount of blended RSPO/RLPO polymer and then examined its mechanical properties and showed the tensile strength about 5MPa with lesser thickness. However, we decided to enhance the tensile strength value above 5MPa, hence increased the blended amount up to 700mg of matrix patches (Table 1).

Tensile testing of the patch allows analysis of mechanical properties, such as stress strain curves and stress at failure (strength). These properties are important since the patch must remain intact during storage or use.In this study one hydrophobic plasticizer, DBS and another hydrophilic plasticizer, TEC were added to determine if there were difference, in physiochemical and mechanical properties and in release profile prepared from this blended matrix patches. Table 1 shows that the patches containing TEC (0.09-0.18 mm) were thicker then patches using DBS as plasticizer (0.07-0.17 mm). Patches which were thinner were more favourable, for not affecting quality of life of patients and giving feel of bulkiness.[5] For the tensile strength, patches containing TEC or DBS (4.93-8.25 MPA) passed the studies as their tensile strength all over 4 MPa, which is the value means the object is elastic in nature and not cracking or breaking easily [15]. Drug content of all formulation (425.78-427.81µgm/cm$^2$) exceeded 99% of calculated drug content (423.59 µgm/cm$^2$). For physiochemical properties studies, patches containing TEC showed significant higher readings compared with those containing DBS, due to hydrophilic nature of TEC [16].

The ultimate tensile strength value increases with increasing the blended ratio of RSPO grade. Table 1 shows clearly that there is no significant difference in mechanical properties between these two plasticizers. However, while increasing the percentage of from 15% – 25% of the both the plasticizers the tensile strength also increases considerably. Though DBS containing patches are slightly superior thanTEC containing patches in terms of tensile strength, thickness and physical appearance. This may be due to a higher miscibility of DBS plasticizer with the blended polymer matrix and OS. In Table 2 shows that the average drug content of all the patches is more than 99% of the intended amount and the most of the patches were elastic and flexible with an average tensile strength greater than 5MPa. Literature [17]and mechanical engineering handbooks show that materials that have an average tensile strength of more than 4.0 MPa are elastic in nature.

## Moisture content &water absorption studies

The results of these studies are presented in Table 3. Water absorption and moisture content studies show that the storage and handling of such transdermal patches would be difficult if they did not have suitable properties. Table 3shows that the moisture content and water absorption capacities of the matrix patches are purely dependent on the concentration of plasticizer as well as amount of blended grades (either RSPO or RLPO) used in the study. The patches with lesser amount of hydrophobic RSPO grades containing combinations (15 to 25% :T1 –T 16), have higher moisture contents and water absorption compared to the higher amount of RLPO grades (D1-D16).

Similarly the water absorption at both RH conditions was also higher at higher amount of RLPO grades with TEC containing patches, because this excipient allows the water to more easily diffuse into the patch which leads to higher uptake of moisture and water absorption [18]. The relatively more hydrophobic DBS & RSPO grade containing patches are more difficult to hydrate during the moisture content and water absorption studies, especially at 15%. From Table 3 it is clear that the water uptake and capacity of both types of patches remain intact when fully hydrated.

## In vitro release studies

The percentage cumulative release and release rate after 8 hrs from different plasticized OS matrix patches are shown in Table 4. The cumulative release of drug on a percentage basis from the matrix patch with and without enhancers was plotted against time ($t^{1/2}$) in Fig. 1 and Fig. 2. Plots which are having Higuchi pattern & optimum release formulations are only presented.Figure 1 & 2 plots represent cumulative percentage release of OS from the patches which contain DBS and TEC plasticizer respectively. From the figure 1, the release pattern from the DBS contained patches D 5 – D 12, it is observed that they follow Fick's law of diffusion, it is also clear that the release of the drug from the patches followed the diffusion controlled matrix model in which the total percentage of drug released is proportional to square root of time.

In the case of TEC contained patches, the cumulative percent release of drug from the range of 4% - 30% after 8 hrs. It may be due to plasticizing effect of TEC is lesser to that of DBS. It may be due to three main reasons (i). hydrophilic TEC leaches from the patch, resulting in decreasing plasticizer content and thus decreasing diffusivity [15]. (ii). greater degree of coalescence of the methacrylate polymer particles into a patch for a given set of processing conditions with increasing plasticizer level [19]. (iii). during the release studies, the patch is in contact with the release medium, hence water-filled cavities/channels are created, and drug transport also occurs via diffusion through these domains.

## Release profile with enhancers

Each formulation was added 3% linseed oil and 3% eugenol respectively. The percentage cumulative releases with chemical enhancer containing matrix patches are shown in Table 5.

It can be seen that as the percentage release increases with eugenol significantly higher permeation (DE 9, DE 10 and DE 13: 62% – 84%) than for the corresponding without enhancer patch (D 9, D 10 and D13: 42% – 54%). In the case of linseed oil containing patches having lesser cumulative percent release than eugenol it may be either linseed oil blocks the pores or acts as a secondary plasticizer to prevent drug diffusional pathor hydrophobic nature of the linseed oil does not allow the drug easily into the phosphate buffer saline solution. Statistical findings showed there was significant different to the effect of adding chemical enhancer (p=0.07-0.11).



## Ex vivo Permeation Studies

After review of all the factors including mechanical and physiochemical properties, percent release, release rate, patch quality before and after release by visual examination, surface smoothness and the effect of permeation enhancers, from DBS contained patches (D1, D3, D5, D9, DL10, DL13, DE9, DE10, DE13) were selectedfor skin permeation studies. Each selected formulation was evaluated using the mouse skin model, and the average of three determinations reported. The cumulative percent permeation after 8 hrs through RSPO/RLPO matrix patches and mouse skin are shown in Table 6.

From this data, it can be seen that the DE 9, DL 10 and DL 13 matrix patches have the highest permeation, 47%, 55% and 58% respectively. Henceboth linseed oil and eugenolare more suitable enhancerswith RSPO/RLPO; Eugenolprobably modify the solvent nature of the stratum corneum, improving drug partioninginto the tissue and it may also modify drug diffusivity through the membrane and bring about a reduction of the lag time for permeation, indicating an increase in the diffusivity of the drug through the skin membrane [20]. In the case of linseed oil the cumulative percent release of OS highest compare to all the formulations such as 55% and 58% (DL 10 and DL 13) respectively. Permeation of linseed oil into the lipid layers of the skin may lead to the change in the lipid barrier properties. Further disruption of the stratum corneum barrier by the abrading agent might enhance the permeation by removing the upper dead stratum corneum.This may be probably because the primary pathway of transdermally delivered drugs is paracellular, i.e. around the cells than through the elastin. Elastin is composed of collagen and hyaluronic acid and other lipids, which occupies the interstices between the cells of the top-most layer of the skin (i.e. the epidermis, including, e.g. stratum corneum, lucidum, granulosum, spinosus) and must be dissolved and/or disrupted in order for the drug to be able to transverse through the viable skin to the subcutaneous tissues where the cutaneous plexi of the capillary net can be reached [21].

The cumulative percent permeation and permeation rate from patches without any enhancers (D 1, D 3, D 5and D 9) was lower compare to others.The *in vitro* drug release and skin permeation studies showed that the skin is the rate-limiting factor because the *in vitro* release of the drug was greater from each type of the matrix patch compared with the respective *in vitro* drug permeation rate. Thecumulative drug permeation as a percentage from all the patches was plotted against the permeation time in hours (t) in figure 3. In each plot, the rate of drug permeation is fairly constant over time and the permeation profiles exhibit the concentration dependent first-order kinetics.

## Conclusion

The percentage release and permeation from the Eudragit RSPO/RLPO blended matrix patch formulations plasticized with DBS and containing either 3% eugenol or linseed oil 80 are higher than for thecorresponding TEC containing formulations.Patch thickness was lower and tensile strength was higher compared to TEC containing patches. From the above observations, it may be concluded that the blended ratios of the eudragit RSPO/RLPO (50:50 or 60:40), the plasticizer DBS(20-25%) and addition of 3% eugenol as well as linseed oil as chemical enhancersto be needed for better release percentages of ondansetron hydrochloride. The patch formulations DE9, DL 10 and DL 13 were the best TD matrix patch compositions in thispresent study for the uniform and continuous release/permeation of OS 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.

## Acknowledgements

The authors wish to express sincere gratitude to Research Laboratory of International Medical University for providing financial and lab facilities for the studies. We would also like to thank Aurobindo Chemicals, India and EvonikRöhmGmbH Pharma Polymers, Germany for the gifts of Ondansetron Hydrochloride and Eudragit RSPO/RLPO respectively. We also offer sincere thanks to the Emeritus Professor Dr. S.Pal, Ex Director of the School of Bioscience and Engineering, Jadavpur University, Kolkata, India for providing facilities for the mechanical studies of transdermal patches.

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**Table 1. Patch composition and formulations**

| Sr. no. | Patch Composition | | Total Polymer Weight (mg) | Patch Code | | | |
|---|---|---|---|---|---|---|---|
| | RSPO | : RLPO | | % Plasticizer | | % Plasticizer | |
| **1** | 50 | : 50 | 500 | 15% TEC | T1 | 15% DBS | D1 |
| **2** | 60 | : 40 | 500 | | T2 | | D2 |
| **3** | 70 | : 30 | 500 | | T3 | | D3 |
| **4** | 80 | : 20 | 500 | | T4 | | D4 |
| **5** | 50 | : 50 | 700 | 15% TEC | T5 | 15% DBS | D5 |
| **6** | 60 | : 40 | 700 | | T6 | | D6 |
| **7** | 70 | : 30 | 700 | | T7 | | D7 |
| **8** | 80 | : 20 | 700 | | T8 | | D8 |



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **9** | 50 | : 50 | 700 | 20% TEC | T9 | 20% DBS | D9 |
| **10** | 60 | : 40 | 700 | | T10 | | D10 |
| **11** | 70 | : 30 | 700 | | T11 | | D11 |
| **12** | 80 | : 20 | 700 | | T12 | | D12 |
| | | | | | | | |
| **13** | 50 | : 50 | 700 | 25% TEC | T13 | 25% DBS | D13 |
| **14** | 60 | : 40 | 700 | | T14 | | D14 |
| **15** | 70 | : 30 | 700 | | T15 | | D15 |
| **16** | 80 | : 20 | 700 | | T16 | | D16 |

*RSPO: Eudragit® RSPO RLPO: Eudragit® RLPO, polymer used for matrix-based transdermal formulations. TEC: Tri-ethyl citrate, DBS: Di-butyl sebacate, both are plasticizers added into patch formulations.

**Table 2.Mechanical properties of patch formulations.**

| Patch Code | | Average Thickness (mm) | | Average Tensile strength (MPa) | | Average Drug content (µgm/cm2) | |
|---|---|---|---|---|---|---|---|
| **TEC** | DBS | TEC | DBS | TEC | DBS | TEC | DBS |
| **T1** | D1 | 0.10 | 0.08 | 4.93 ± 0.9 | 5.34 ± 0.2 | 426.45 | 426.98 |
| **T2** | H2 | 0.10 | 0.08 | 5.82 ± 0.8 | 6.07 ± 0.5 | 426.57 | 426.70 |
| **T3** | H3 | 0.09 | 0.07 | 5.93 ± 0.5 | 6.65 ± 0.3 | 426.15 | 427.01 |
| **T4** | H4 | 0.09 | 0.07 | 5.73 ± 0.4 | 6.83 ± 0.9 | 426.38 | 427.10 |
| **T5** | D5 | 0.15 | 0.124 | 5.83 ± 0.5 | 6.63 ± 0.6 | 426.71 | 426.89 |
| **T6** | D6 | 0.15 | 0.13 | 6.12 ± 0.7 | 7.24 ± 0.7 | 426.52 | 427.57 |
| **T7** | D7 | 0.14 | 0.13 | 6.67 ± 0.6 | 7.46 ± 0.4 | 426.87 | 427.09 |
| **T8** | D8 | 0.13 | 0.12 | 7.18 ± 0.4 | 7.97 ± 0.2 | 426.79 | 427.64 |
| **T9** | D9 | 0.18 | 0.16 | 6.15 ± 0.5 | 6.94 ± 0.4 | 426.03 | 427.06 |
| **T10** | D10 | 0.17 | 0.16 | 6.53 ± 0.7 | 7.78 ± 0.6 | 426.08 | 427.10 |
| **T11** | D11 | 0.17 | 0.16 | 7.18 ± 0.4 | 7.94 ± 0.1 | 426.19 | 427.64 |
| **T12** | D12 | 0.16 | 0.15 | 7. 74± 0.6 | 8.25 ± 0.4 | 426.51 | 427.81 |
| **T13** | D13 | 0.18 | 0.17 | 5.95 ± 0.5 | 6.97 ± 0.3 | 425.78 | 426.97 |
| **T14** | D14 | 0.17 | 0.17 | 6.41 ± 0.2 | 7.25 ± 0.5 | 425.83 | 427.08 |
| **T15** | D15 | 0.18 | 0.16 | 6.72 ± 0.4 | 7.37 ± 0.6 | 426.08 | 427.19 |
| **T16** | D16 | 0.18 | 0.16 | 6.97 ± 0.9 | 7.58 ± 0.7 | 426.47 | 427.67 |



**Table 3.Moisture content and water absorption studies.**

| Patch Code | | % Plasticizer | | Moisture content (wt %) | | Water absorption (wt %) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | TEC | | DBS | |
| **T1** | D1 | 15 | 15 | 1.43 | 1.06 | 2.92 | 5.08 | 1.89 | 2.67 |
| **T2** | D2 | 15 | 15 | 1.31 | 1.01 | 2.73 | 4.82 | 1.61 | 2.48 |
| **T3** | D3 | 15 | 15 | 1.20 | 0.92 | 2.59 | 4.67 | 1.48 | 2.31 |
| **T4** | D4 | 15 | 15 | 1.09 | 0.89 | 2.41 | 4.57 | 1.09 | 2.07 |
| **T5** | D5 | 15 | 15 | 1.91 | 1.20 | 3.09 | 4.91 | 2.08 | 3.08 |
| **T6** | D6 | 15 | 15 | 1.84 | 1.10 | 2.83 | 4.8 | 1.73 | 2.79 |
| **T7** | D7 | 15 | 15 | 1.67 | 1.01 | 2.67 | 4.59 | 1.51 | 2.51 |
| **T8** | D8 | 15 | 15 | 1.46 | 0.94 | 2.58 | 4.43 | 1.38 | 2.28 |
| **T9** | D9 | 20 | 20 | 2.09 | 1.15 | 2.09 | 4.09 | 1.7 | 3.02 |
| **T10** | D10 | 20 | 20 | 1.90 | 1.08 | 1.87 | 3.91 | 1.51 | 2.72 |
| **T11** | D11 | 20 | 20 | 1.82 | 0.96 | 1.64 | 3.52 | 1.37 | 2.58 |
| **T12** | D12 | 20 | 20 | 1.64 | 0.91 | 1.52 | 3.19 | 1.27 | 2.40 |
| **T13** | D13 | 25 | 25 | 2.13 | 1.07 | 2.20 | 4.16 | 1.51 | 2.92 |
| **T14** | D14 | 25 | 25 | 2.03 | 0.97 | 2.07 | 3.95 | 1.38 | 2.57 |
| **T15** | D15 | 25 | 25 | 1.93 | 0.86 | 1.82 | 3.82 | 1.21 | 2.34 |
| **T16** | D16 | 25 | 25 | 1.68 | 0.74 | 1.67 | 3.57 | 1.16 | 2.08 |

**Table 4.Cumulative percentage release and release rate after 8 hours with permeation enhancer.**

| Patch Code | | Percentage of diffusion (%) | | Diffusion rate (µgm/cm$^2$/hr) | |
|---|---|---|---|---|---|
| **T1** | D1 | 4.752 | 53.912 | 0.174 | 9.983 |
| **T2** | D2 | 24.357 | 43.239 | 32.11 | 5.752 |
| **T3** | D3 | 14.176 | 53.364 | 0.079 | 29.98 |
| **T4** | D4 | 9.033 | 44.797 | 3.194 | 2.411 |
| **T5** | D5 | 9.169 | 50.346 | 8.354 | 9.443 |
| **T6** | D6 | 9.446 | 45.141 | 16.87 | 17.48 |
| **T7** | D7 | 3.740 | 40.092 | 0.370 | 1.392 |
| **T8** | D8 | 3.529 | 29.637 | 0.033 | 4.256 |
| **T9** | D9 | 21.627 | 54.581 | 4.355 | 2.024 |
| **T10** | D10 | 26.206 | 45.116 | 8.473 | 0.171 |
| **T11** | D11 | 21.957 | 28.451 | 0.053 | 1.320 |
| **T12** | D12 | 24.870 | 23.158 | 31.91 | 0.172 |
| **T13** | D13 | 24.284 | 42.851 | 3.623 | 0.996 |
| **T14** | D14 | 28.763 | 23.555 | 5.985 | 1.010 |
| **T15** | D15 | 30.379 | 29.242 | 7.932 | 0.970 |
| **T16** | D16 | 22.409 | 29.279 | 6.143 | 2.890 |



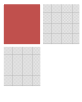

**Table 5.Cumulative percentage release after 8 hours with permeation enhancer**

| | Patch code for formulations with chemical enhancers | | | |
|---|---|---|---|---|
| Patch Code | 3% Linseed oil | Percentage of release (%) | 3% Eugenol | Percentage of release(%) |
| D 9 | DL 9 | 37.75 | DE 9 | 62.08 |
| D 10 | DL 10 | 51.43 | DE 10 | 78.67 |
| D 13 | DL 13 | 57.34 | DE 13 | 84.82 |

**Table 6.**Cumulative percentage permeation and rate after 8 hours.

| Patch Code | Cumulative Percent of permeation (%) | permeation rate (µgm/cm$^2$/hr) |
|---|---|---|
| **D1** | 23.537 | 8.64 |
| **D3** | 23.286 | 12.57 |
| **D5** | 24.102 | 16.14 |
| **D9** | 26.847 | 21.04 |
| **DL10** | 27.686 | 22.14 |
| **DL13** | 42.648 | 25.47 |
| **DE9** | 47.746 | 20.49 |
| **DE10** | 55.437 | 22.14 |
| **DE13** | 58.380 | 26.37 |

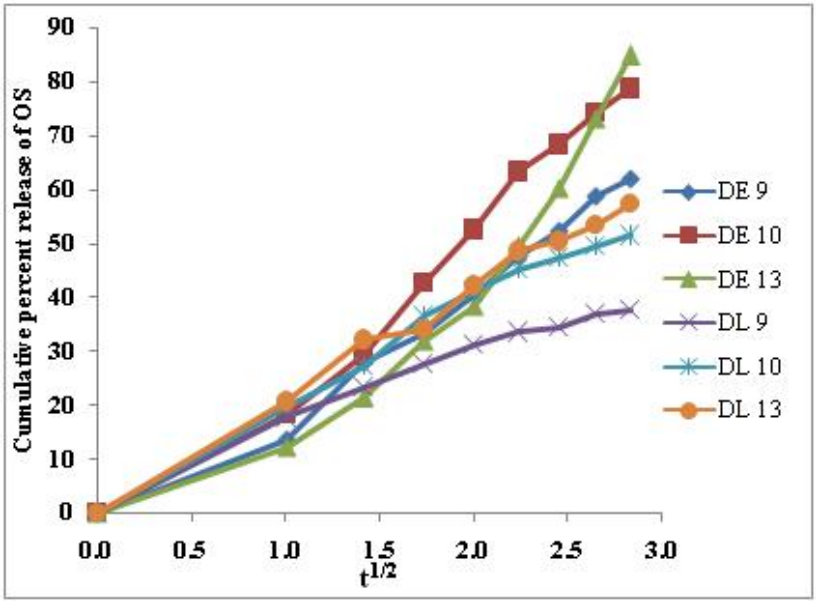


Figure 1 Release profile of OS

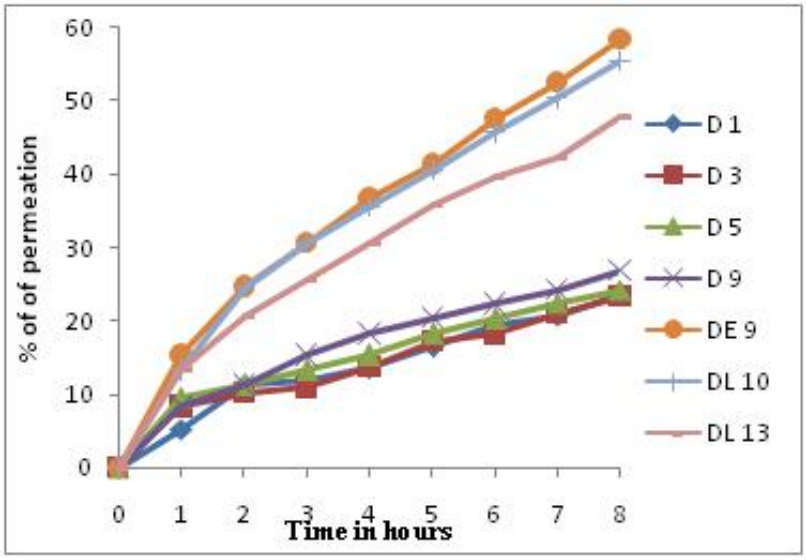


**Figure 2 Release profile of OS**