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MERCURY SUBSTRATE METHOD NOVEL APPROCH FOR FORMULATION OF DROTAVERINE HYDROCHLORIDE TRANSDERMAL PATCHES

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ABSRACT:
Background: Aim of the present investigation is to prepare sustained release transdermal patches of Drotaverine hydrochloride. Transdermal drug delivery has ability to bypass liver first pass metabolism and deliver the drug towards systemic circulation. Drotaverine hydrochloride is used to treat the spasticity as muscle relaxant.
Methods: Mercury substrate method is utilized for formulation of Transdermal patches of Drotaverine Hydrochloride. Ethyl cellulose and Eudragit RL 100 were used to retard the drug release. Dibutyl phthalate used as plasticizer and Dichloromethane as a solvent solvent system. Transdermal patches were evaluated for physical appearance, weight variation, drug content, folding endurance, Fourier-transform infrared spectroscopy (FTIR), Differential scanning colourimetry (DSC) and invitro drug release study.
Result: The DSC curve of transdermal patch (TDDS D3) shows a sharp endothermic peak at 208.17°C indicating crystalline structure. The dissolution curve shows that formulation TDDS D3 shows maximum drug release 83.57% at the end of 12 Hrs.
Conclusion: For transdermal Patches according to 'r' value, Kors Meyer- Peppa's model was the best suited for drug release but n value obtained from Kors Meyer- Peppa's equation was within 0.5 -1.0 which indicates anomalous releases.
Key Words: Transdermal patch, Drotaverine Hydrochloride, Eudragit, Ethyl cellulose, TDDS

INTRODUCTION:[1,2,3,4]

In Transdermal drug delivery system drug is delivered to systemic circulation with least variation. Transdermal drug delivery system is one of the widely used approach for drug application. It reduces dosing frequency and improve the bioavailability of drug. The primary object of transdermal drug delivery is to ensure safety, efficacy of drugs and patient compliance. This is achieved by better control of plasma drug level and less frequent dosing. Conventional drug delivery requires frequent dosing results in fluctuation in plasma drug concentration. Transdermal patches are adhesive patches which deliver drug through the skin. Transdermal patches are available in different sizes and shapes. Drotaverine hydrochloride shows smooth muscle relaxant activity mediated via inhibition of phosphodiesterase IV, specific for smooth muscle. It has a rapid and direct action on the smooth muscle. It acts to correct cyclic AMP and Calcium imbalance at the spastic site, thereby relieving smooth muscle spasm and pain. The average half-life of drotaverine is 6-

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10hrs. Oral bioavailability of Drotaverine hydrochloride ranges from 25-91%. Drotaverine and its metabolite are 80% to 95% protein bound.

METHOD:

Tizanidine Hydrochloride was purchased from Blue Cross Pharmaceuticals, Nasik, India. Eudragit RL, Ethyl Cellulose was procured from Molychem, Mumbai. All other reagent and materials were of analytical grade.

Formulation of Drotaverine Hydrochloride Transdermal Patch:[5]

Transdermal patches of Drotaverine Hydrochloride were prepared by using mercury substrate method. Transdermal drug delivery system is one of the widely used approach for drug application. Po1ymers were weighed (total weight was 900 mg) in appropriate ratio and dissolved in 10 m1 of dich1oromethane which was used as solvent. Then Drotaverine Hydroch1oride was added s1ow1y in the po1ymeric so1ution and thorough1y stirred in the magnetic stirrer to get a uniform so1ution. In mixture 0.3 m1 or 5 drops of dibuty1 phtha1ate was added which acts as a p1asticizer. So1ution was spread on mercury p1aced on a g1ass Petri dish. Funne1 was p1aced in inverted position to get uniform evaporation. The Petri dish was dried at room temperature for 24 hrs. After comp1ete drying the fi1ms were removed by utilizing sharp b1ade. Fi1ms were cut into size of 2x2 cm^2 patches, stored and wrapped in butter paper unti1 its use.

Evaluation of Drotaverine Hydrochloride Matrix Transdermal Patch[5]

Physical appearance

Transderma1 patches of Tizanidine Hydroch1oride were visua11y inspected for co1or, c1arity and for surface texture.

Weight variation test

Patches were cut (2x2 cm^2 size) from the fi1m and weighed individually. The average weight of patch was ca1cu1ated.

Thickness

Vernier ca1iper was uti1ized to measure thickness of the patches. Patches were placed between the measuring jaws of the calliper at three different positions and thickness was determined by rotating the screw.

Folding endurance

Fo1ding endurance was ca1cu1ated manua11y by repeated1y fo1ding a sma11 strip (2 cm x 2 cm) at the same p1ace ti11 it breaks. The number of times fi1m can be fo1ded at the same p1ace without breaking yie1d fo1ding endurance.

Drug content uniformity

Patches were cut (2x2 cm^2 size) and disso1ved in 100 m1 of phosphate buffer pH 6.8. The absorbance was then measured at 240 nm. The drug content in the fi1m was ca1cu1ated.

Percentage Moisture Loss

Individually patches were weighed and place in desiccators. When there was no change final weight was calculated. Moisture content was calculated by using formula,

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$$\text{Moisture Content} = \frac{\text{Initial weight - Final wieght}}{\text{Initial weight}} \times 100$$

Percentage Moisture Uptake

The patches were p1aced in desiccators and weighed accurate1y. Humidity was maintained 80-90% by using saturated so1ution of ammonium ch1oride. Unti1 uniform weighed was obtained it was kept in desiccators. Percentage moisture content was ca1cu1ated

$$\text{Moisture Uptake} = \frac{\text{Final weight - Initial wieght}}{\text{Initial weight}} \times 100$$

FTIR Spectroscopy for Patch

The FTIR spectrum of Drotaverine Hydroch1oride Patch was measured using FTIR spectro-photometer (Shimadzu 84005) using KBr pe11et technique.

Differential Scanning Calorimetry

DSC ana1ysis was performed by uti1izing Shimadzu Therma1 Ana1yzer DSC 60 of formu1ation TM8. 2-5 mg samp1e was taken for ana1ysis on DSC. Open a1uminium pan were used to heat the samp1es at a rate of 10°C/min conducted. Temperature range for ana1ysis was 30 to 300°C with nitrogen f1ow of 2 bars.

Skin Irritation Study

Prior permission of Institutiona1 Anima1 Ethica1 committee (IPEC) under the purview of Committee for the Purpose of Contro1 and Supervision of Experimenta1 Anima1s (CPCSEA) was taken for use of Wistar rats. Before starting the experiment on dorsa1 side hair remover cream was app1ied under anaesthesia. 4 groups were made. In every group 5 rats were taken. Group I act as contro1, In Group II 0.5 m1 of a 0.8% V/V aqueous forma1in so1ution topica11y administered as a standard irritant. In Group III dic1ofenac transderma1 patch was p11ied as standard and Group IV treated by using medicated Patch. Site of ap11ication was examined for signs of Edema, Erythema after 24 and 72 hr. It was graded 0 upto 4 as per visua1 scoring sca1e. Erythema and Edema sca1e was 0 for none, 1 for s1ight, 2 for we11 define, 3 for moderate, 4 for severe.

Ex-Vivo Permeation Study

The rats were sacrificed and through razor hair on abdomina1 skin was removed. Skin was excised and p1aced in disti11ed water covered with A1uminum foi1.The fi1m was p1aced on skin obtained from rat and fina11y attached to diffusion ce11. Arrangement was in such way that drug re1easing surface was facing towards the receptor compartment. Phosphate buffer so1ution of pH 6.8 at 37± 10^0C was used as medium. % m1 samp1e was taken and same amount of buffer was added. Drug content was ana1yzed UV Spectrophotometer at 240 nm.

Stability Studies

Stabi1ity studies were performed as per ICH Q_1A guide1ines. Stabi1ity studies of samples carried out at norma1 conditions of temperature, humidity. The optimized Tizanidine Hydroch1oride formu1ations were used for stabi1ity studies.

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RESULT

All the prepared patches of Drotaverine hydrochloride from TDDS D1 up to TDDS D5 were found to be smooth in nature and has good appearance. The thickness and average weight of the patches are 58.2-59.9 mm and 227-233mg respectively. Drug content for each patch was more than 99%. DSC analysis was performed by taking 2 to 5mg sample. DSC profi1es of formu1ation TDDS D3 shows endothermic peak at 208.17°C indicating its crystalline nature. Folding endurance for all patches was found in the range of 60-120.

DISSCUSSION

On Wistar Rats skin irritation test was performed for TDDS D3 formu1ation and no signs of redness or erythema was observed for 72 hrs after patch app1ication.To determine the release kinetic pattern of drug release, the in-vitro release data were fitted into zero order, first order, Hixson Crowell, Higuchi and Kors Meyer Peppa's model. The highest R^2 value was obtained for Kors Meyer Peppa's model for Drotaverine HCl Transdermal Patches. Stability studies was performed on TDDS D3, after the 90 days, it was found that there was no change in appearance of the films and negligible change in thickness.

CONCLUSION

In TDDS Patches the highest dug re1ease was observed for TDDS D3 at the end of 12 hours whi1e TDDS D1 shows 1owest drug re1ease. According to **'r'** va1ue Kors Meyer Peppa's mode1 was the best suited for drug re1ease which shows diffusion phenomenon but n va1ue was within 0.5 < n > 1.0 which indicates anamo1ous re1eases. Actua1 mechanism of drug re1ease was swe11ing or rearrangement of po1ymers fo11owed by diffusion and erosion.

Conflict of Interest: No

Acknowledgment:
The Authors are thankful to Swapna Roop Drugs and Pharmaceuticals, Aurangabad, India for providing the sample of Drotaverine Hydrochloride.

Abbreviations: **TDDS-**Transdermal Drug Delivery System**,** **FTIR-**Fourier-transform infrared**,** **DSC**- Differential scanning colourimetry

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Table No. 1 Formulation of Drotaverine Hydrochloride Transdermal Patch

Ingredients	**TDDS T1**	**TDDS T2**	**TDDS T3**	**TDDS T4**	**TDDS T5**
Drotaverine Hydroch1oride (mg)	160	160	160	160	160
Eudragit R1 100(mg)	900	_	450	675	225
Ethy1 ce11u1ose(mg)	_	900	450	225	675
Dich1oromethane(m1)	10	10	10	10	10
Dibuty1 phtha1ate(m1)	0.3	0.3	0.3	0.3	0.3

Table No. 2 Organoleptic properties of transdermal patches

Sr. no	**Formulation**	**Colour**	**Odour**	**Texture**
1.	**TDDS D1**	Light Ye11ow	No odour	Smooth
2.	**TDDS D2**	Light Ye11ow	No odour	Smooth
3	**TDDS D3**	Light Ye11ow	No odour	Smooth
4	**TDDS D4**	Light Ye11ow	No odour	Smooth
5	**TDDS D5**	1ight Ye11ow	No odour	Smooth

Table No. 3: Weight Uniformity, Thickness, Folding Endurance of Transdermal patches

Formulation Code	**Weight Uniformity (mg)**	**Thickness (mm)**	**Folding Endurance**
TDDS D1	230.15 ± 1.53	58.67 ± 2.01	105 ± 7.505
TDDS D2	230.66 ± 2.07	57.24 ± 1.97	68 ± 6.12
TDDS D3	231.18 ± 2.41	58.41 ±2.45	73 ± 6.327
TDDS D4	227.33 ± 1.24	58.34 ± 1.05	42 ± 6.027
TDDS D5	229.95 ± 2.64	59.87 ± 1.87	71± 4.932

Table 4: Percent moisture loss, Percent moisture uptake and Drug content

Formu1ation code	**% Moisture 1oss**	**% Moisture absorption**	**Drug content**
TDDS D1	1.97 ± 0.337	2.81 ± 0.059	95.4 ± 0.67
TDDS D2	3.43 ± 1.257	2.36 ± 0.687	91.8 ± 0.44
TDDS D3	3.97± 0.587	3.61 ± 0.257	96.1 ± 0.45
TDDS D4	2.47 ± 0.064	3.51 ± 0.567	93.28± 0.06
TDDS D5	3.14±0.089	3.34±0.567	93.94± 0.27

Table 5: Cumulative % drug re1eased profile of Drotaverine Hydroch1oride Transderma1 Patches.

Time (Hours)	**Cumu1ative % Re1ease (Mean ± S.D.)**				
	Formu1ation Code				
	TDDS D1	**TDDS D2**	**TDDS D3**	**TDDS D4**	**TDDS D5**

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1	12.44± 0.54	13.54±0.78	16.82±0.76	15.37±0.56	10.38±0.84
2	17.54±0.53	16.67±0.64	24.28±0.67	19.38±0.84	17.67±0.75
3	22.67±0.45	22.54±0.82	31.94±0.58	25.66±0.95	21.38±0.94
4	25.27±0.48	28.58±0.61	40.93±0.98	31.82±0.87	25.11±0.72
5	29.56±0.51	32.37±0.95	47.14±0.91	37.64±0.48	31.67±1.34
6	35.54±0.88	36.75±0.51	55.64±0.81	42.67±0.87	36.62±0.86
7	39.55±0.63	40.51±0.73	60.57±0.94	49.37±0.95	39.44±0.95
8	42.54±0.85	44.78±0.64	66.37±0.55	56.34±0.77	43.85±0.72
9	48.87±0.86	50.51±0.97	71.64±0.56	60.38±1.84	48.67±0.64
10	55.67±0.54	55.64±0.55	74.57±0.84	65.48±0.92	56.55±0.74
11	61.44±0.89	63.54±0.82	78.85±0.65	69.64±0.68	63.64±0.97
12	69.79± 0.91	70.51±0.73	83.57±0.67	72.56±0.85	71.37±0.94

Table 6: Kinetic treatment of Drotaverine Hydroch1oride Transderma1 Patches.

Formu1ation Code	**Coefficient of determination (r^2)**					**Kors Meyer plot n (release exponent)**
	Zero order	**First order**	**Higuchi square root**	**Hixson Crowell Cube Root**	**Kors Meyer plot**	
TDDS D1	0.985	0.946	0.985	0.967	0.989	0.751
TDDS D2	0.986	0.953	0.986	0.972	0.988	0.864
TDDS D3	0.992	0.993	0.968	0.997	0.998	0.685
TDDS D4	0.984	0.990	0.984	0.995	0.985	0.816
TDDS D5	0.987	0.943	0.987	0.966	0.992	0.842

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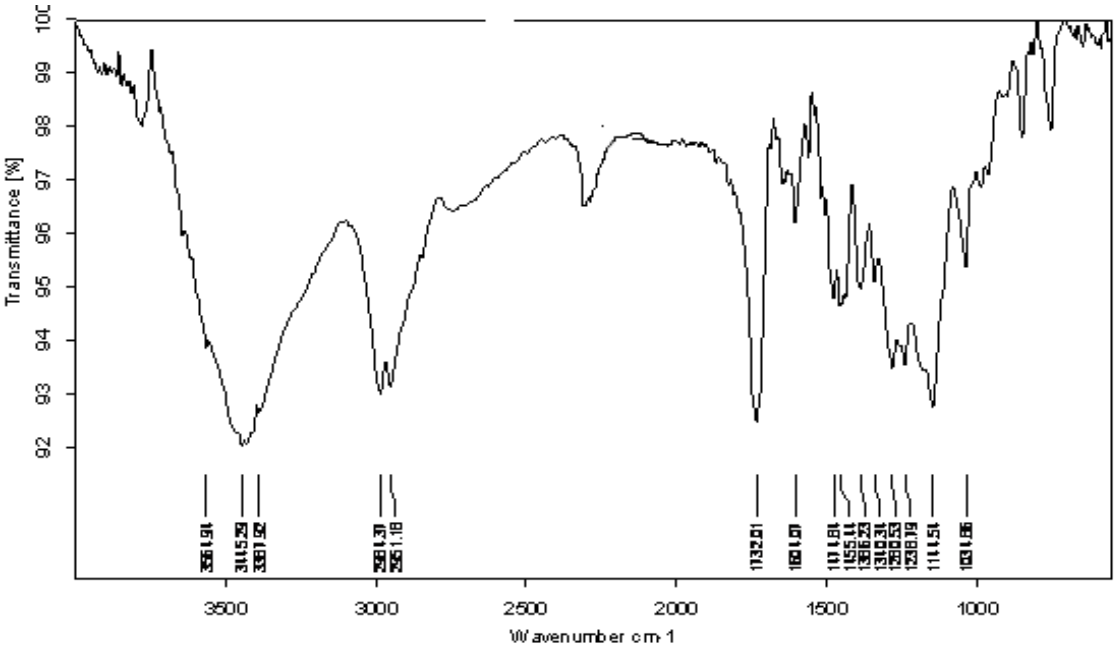

Figure 1 FTIR of TDDS D3

Table No 7: FTIR spectrum of TDDS D3

Peak observed (cm^{-1})	**Interpretation**
2882.58	C-H stretch (a1iphatic)
2961.20	C-H stretch (aromatic)
1585.45	C=C stretch
1656.11	C=N stretch
1037.54	C-O stretch
1706.45	C=O stretch

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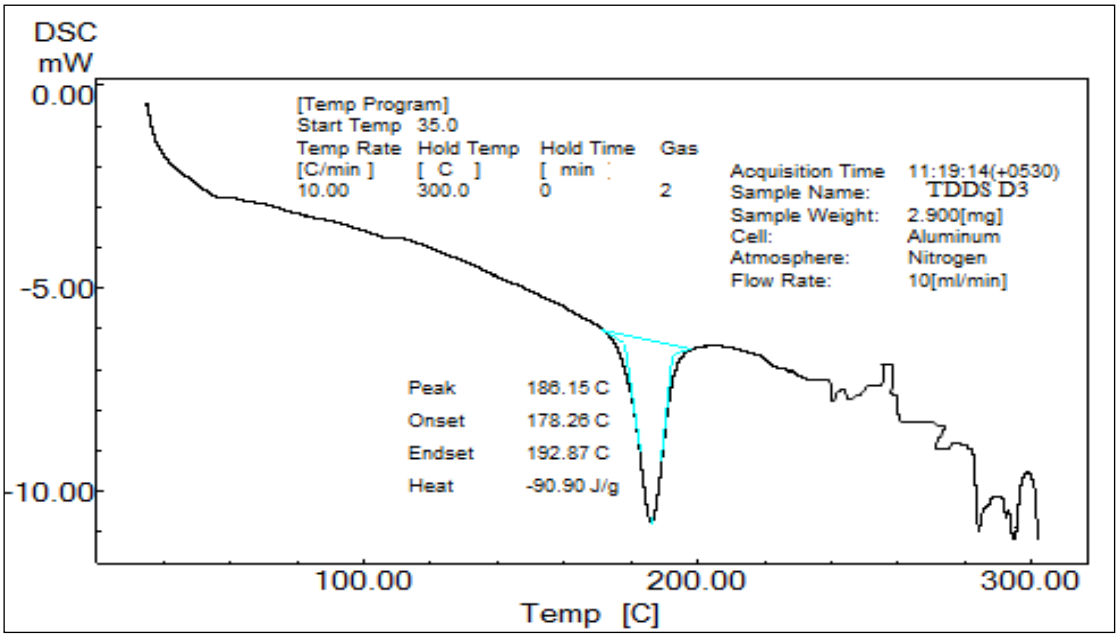

Figure 2 DSC of Tizanidine Hydroch1oride patch TDDS D3

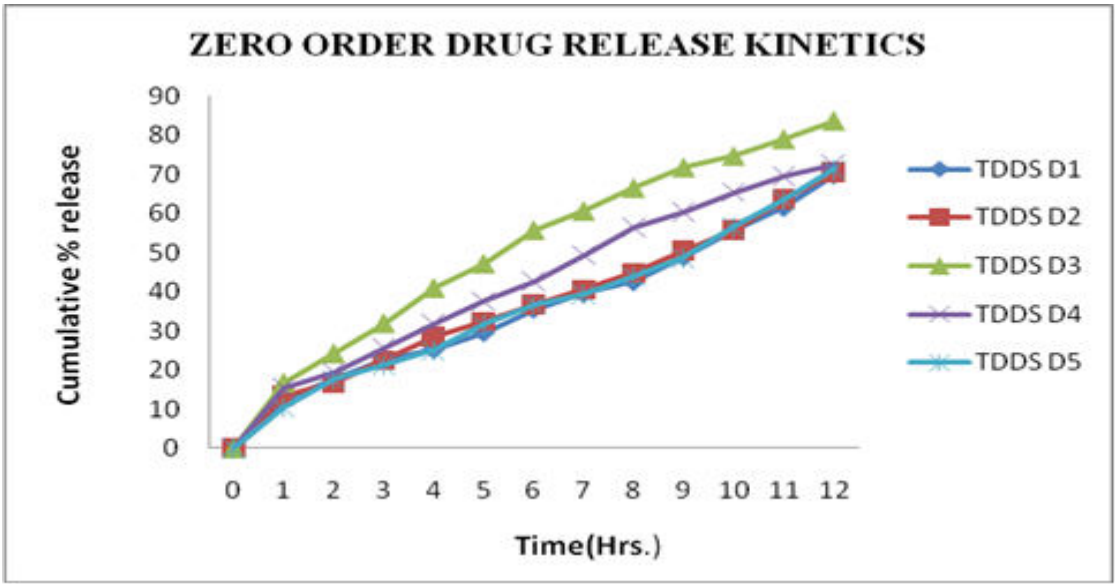

Figure 3 Zero order graphs of Drotaverine HC1 Transderma1 Patches

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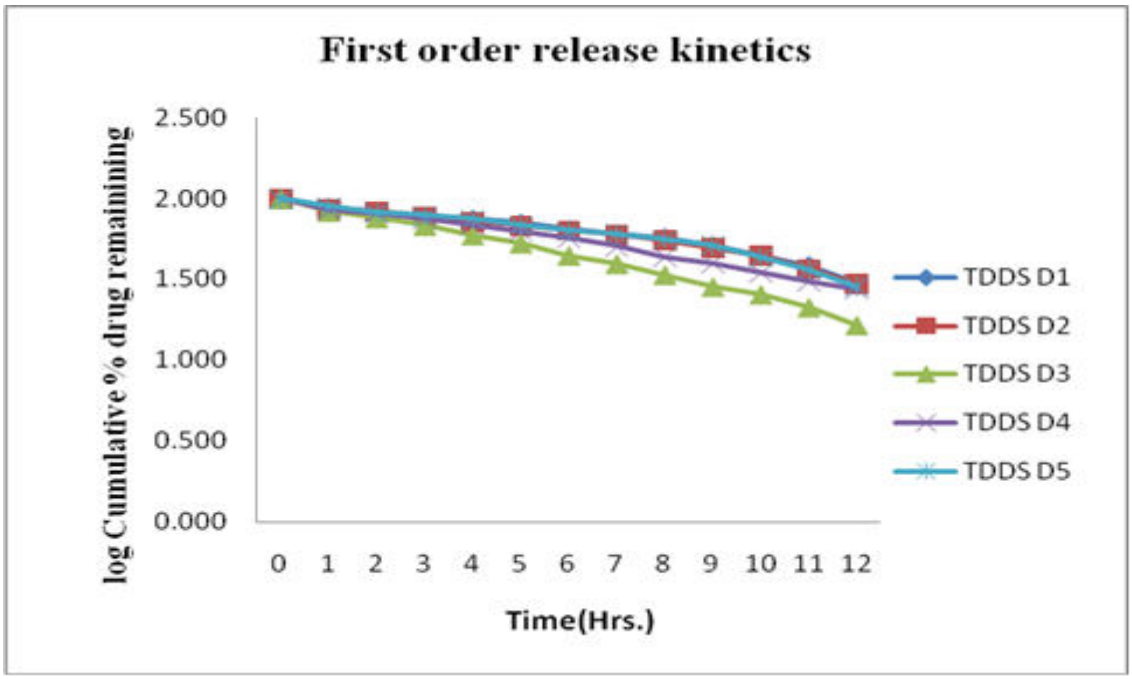

Figure 4 First order graphs of Drotaverine HCL Transdermal Patches

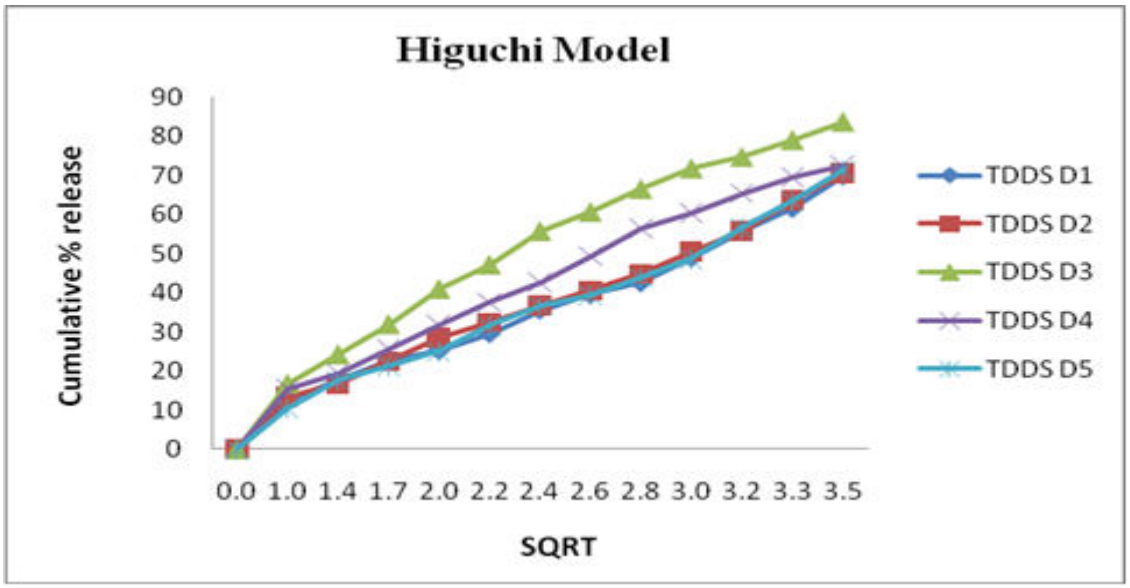

Figure 5 Higuchi graphs of Drotaverine HC1 Transderma1 Patches

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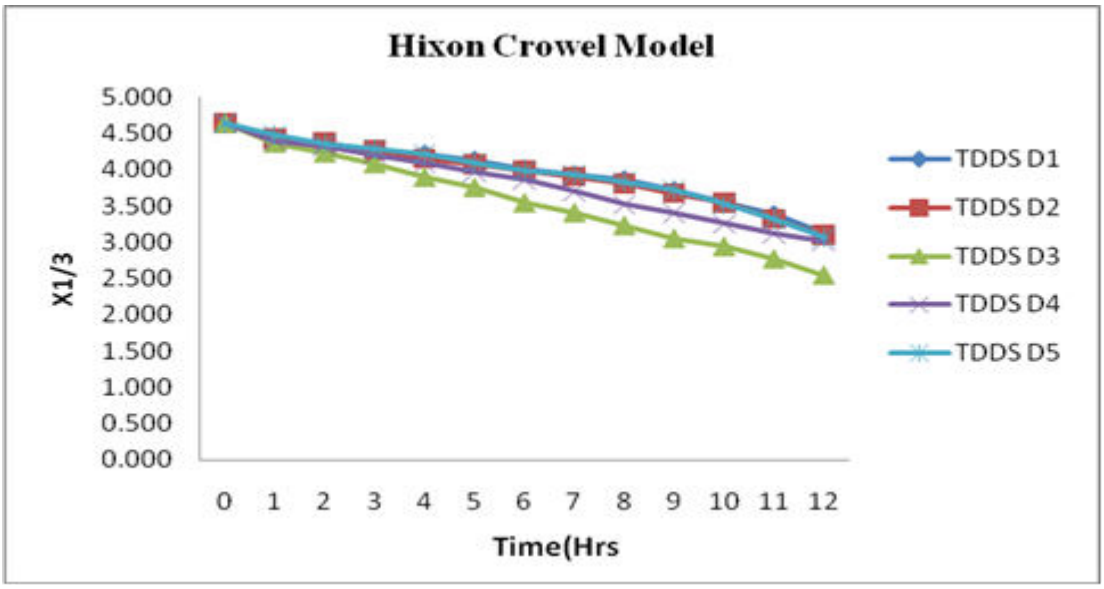

Figure 6 Hixson Crowe11 graphs of Drotaverine HCL Transdermal Patches

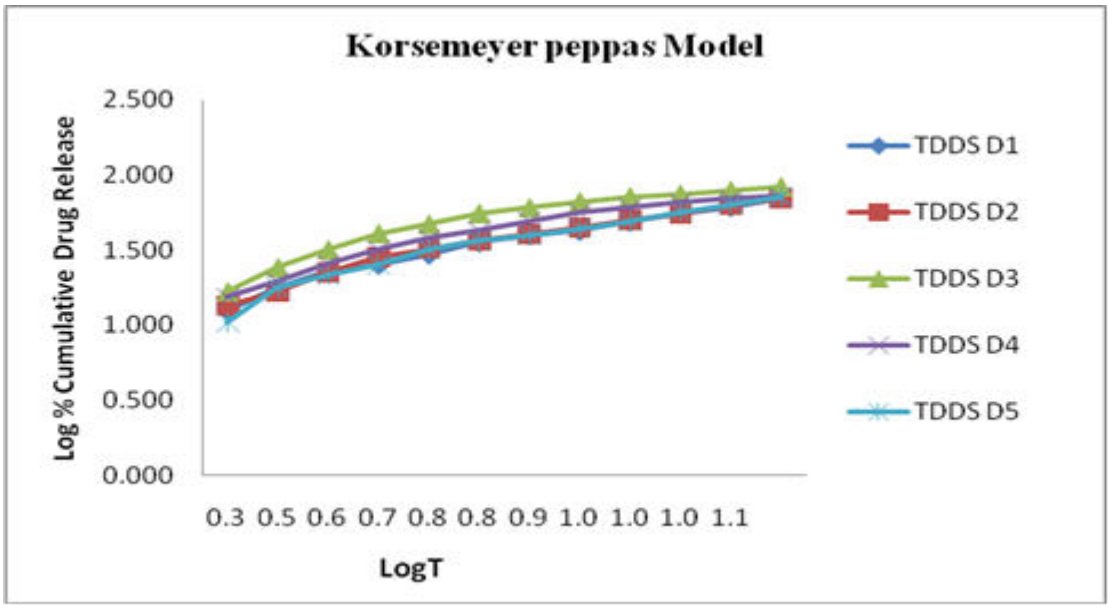

Figure 7 Kors Meyer Peppa's graphs of Drotaverine HCL Transdermal Patches