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Research Article

FORMULATION AND EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM FOR IBUPROFEN

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Abstract

In the present study the transdermal patch of Ibuprofen was formulated. . The drug is usually administered as the racemic compound, but preparations containing only the S (þ)-enantiomers (dexibuprofen) are available in some countries. Ibuprofen is usually given as the free acid but various salts, esters, and other complexes are also used. The pKa of ibuprofen is in the range of 4.5–4.6. Ibuprofen is well absorbed throughout the gastrointestinal tract and is therefore suitable as a model drug in relation to study of colon-specific formulations. The elimination half-life of ibuprofen is about 2 hours. Therapeutic concentrations in plasma range from 5 to 50 mg/l.

Keywords: Transdermal patch, Ibuprofen, prostaglandin synthetase inhibitor, NSAIDs etc

Introduction

Ibuprofen is derived from propanoic acid derivative and widely used non- steroidal anti-inflammatory drug (NSAID). Its chemical name is (RS)-2-(4-Isobutyl- phenyl) propionic acid. Ibuprofen is Prostaglandin synthetase inhibitor. Its molecular formula is $C_{13}H_{18}O_2$ and molecular weight is 206.28.

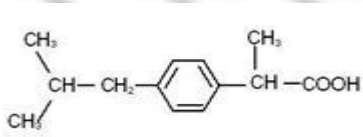


Figure 1: Structure of Ibuprofen

It was a white colored powder drug having melting point 74-77°C. Ibuprofen is very slightly soluble in water (< 1 mg/ml) and readily soluble in organic solvents such as ethanol and acetone. Ibuprofen possesses analgesic and antipyretic activities. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition. In clinical studies in patients with rheumatoid arthritis and osteoarthritis, Ibuprofen have been shown to be comparable to aspirin in controlling pain and inflammation and to be associated with a statistically significant reduction in the milder gastrointestinal side gastroscopy studies at varying doses show an increased tendency toward gastric irritation at higher doses. The drug is usually administered as the racemic compound, but preparations containing only the S (þ)-enantiomers (dexibuprofen) are available in some countries. Ibuprofen is usually given as the free acid but various salts, esters, and other complexes are also used. Ibuprofen is regarded one of the safest NSAIDs available. Ibuprofen is almost insoluble in water. The pKa of ibuprofen is in the range of 4.5–4.6. Ibuprofen is well absorbed throughout the gastrointestinal tract and is therefore suitable as a model drug in relation to study of colon-specific formulations. The elimination half-life of ibuprofen is about 2 hours. Therapeutic concentrations in plasma range from 5 to 50 mg/l.

Table 1: Pharmacokinetics of Ibuprofen

Bioavailability	t_{max} is 1 to 2 hrs. Bioavailability is less than 80 %.
Plasma Half Life	Plasma t ½ is 1.8 to 2 hrs. 45 % to 79 % is eliminated through the urine. Clearance is 30 to 35 L/h.
Plasma Protein Binding	15- 20%
Peak Plasma Conc. (C_{max})	1- 2 hours
Excretion	Renal Excretion (45-79%) Metabolic Excretion (21-55%)
Renal Clearance	500-583 ml/min
Drug Interaction	**ACE inhibitors**: Antihypertensive effect of ACE inhibitors may be diminished. **Aspirin:** Protein binding of ibuprofen may be reduced; in addition, the risk of gastric erosion and bleeding may be increased. **Beta-blockers:** Antihypertensive effect may be decreased. **Digoxin:** Ibuprofen may increase digoxin serum levels. **Diuretics:** Diuretic effects may be decreased. **Lithium**: May increase lithium levels. **Methotrexate:** May increase methotrexate levels. **Warfarin**: May increase risk of gastric erosion and bleeding.
Contraindications	Treatment of pre-operative pain in the setting of coronary artery bypass graft surgery; patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs; hypersensitivity to any component of the product.
Theraputic efficacy	**Osteoarthritis** In patients with osteoarthritis of the knee, Ibuprofen decreases the pain, reduces disease severity and improves the functional capacity of the affected joints. **Rheumatoid arthritis** The drug was found to reduce base line joints inflammation, pain intensity and the duration of morning stiffness with improvement in hand grip strength. **Ankylosing spondylitis** The duration of morning stiffness and pain intensity are reduced and spinal mobility was improved with ibuprofen administration. **Other uses include analgesic efficacy in** Dental pain Low back pain Sprains and strains Post traumatic pain Pain associated with minor surgical procedures

Adverse effects of Ibuprofen	**Cardiovascular:** Edema, fluid retention (greater than 1 % and less than 3 %). **CNS:** Dizziness (3 % to 9 %); headache, nervousness (greater than 1 % and less than 3 %). **Dermatologic:** Rash including maculopapular (3 % to 9 %); purritus (greater than 1 % and less than 3 %). **ENT:** Tinnitus (greater than 1 % and less than 3 %). **GI:** Epigastric pain, heartburn, nausea (3 % to 9 %); abdominal cramps or pain, abdominal distress, constipation, diarrhea, fullness of GI tract (bloating, flatulence), indigestion, nausea and vomiting (greater than 1 % and less than 3 %). **Metabolic-Nutritional**: Decreased appetite (greater than 1 % and less than 3 %).

Materials and Methods

Ibuprofen was received as a gift sample from Sky Lab Pvt Ltd, Rohtak. Ethyl cellulose, polyvinyl pyrrolidone, polyethylene glycol 400 and propylene glycol were received as a gift samples from Loba Chemicals, India. Aluminium foil was used as a backing membrane. Toluene and Ethanol were received from Rankem Pvt Ltd, New Delhi. All the other solvents and chemicals were of analytical grade.

Preparation of formulation with aluminium backed adhesive film method

1.Weighed quantity of ethylcellulose (630, 720, 540, 810mg), PVP (270, 180, 360, 90mg) were dissolved in ethanol (4ml) and kept for swelling upto 15 minutes.

2.The ibuprofen was dissolved in toluene (16ml) and was added to polymeric solution.

3.To the above PEG was added

4.The contents were mixed for about 10 minute and sonicated to evolve the entrapped air

5.The above solution was poured into petridish with aluminium foil and allowed to evaporate the solvent for about 8 to 12 hours at room temperature.

6.Ibuprofen possesses analgesic and antipyretic activities. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition. In clinical studies in patients with rheumatoid arthritis and osteoarthritis, Ibuprofen have been shown to be comparable to aspirin in controlling pain and inflammation and to be associated with a statistically significant reduction in the milder gastrointestinal side Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. To avoid gastric irritation transdermal drug delivery route is adopted.

Table 2: Preparation of trial batches with different polymers with different concentration

Patch No.	Patch A	Patch B	Patch C	Patch D
Ingredients	**mg/patch**	**mg/patch**	**mg/patch**	**mg/patch**
Ibuprofen	100	100	100	100
Ethyl cellulose : PVP	900 (7:3) (630:270)	900 (8:2) (720:180)	900 (6:4) (540:360)	900 (9:1) (810:90)
Toluene : ethanol	20 ml (8:2) (16 ml:4 ml)	20 ml (8:2) (16 ml:4 ml)	20 ml (8:2) (16 ml:4 ml)	20 ml (8:2) (16 ml:4 ml)
Polyethylene glycol	0.3 ml	0.3 ml	0.3 ml	0.3 ml
Backing membrane (Aluminium foil)				

Evaluation of Transdermal Patch

Weight Variation

The patches were weighed individually and the average weight was calculated.

Table 3: Weight variation

Formulation	Weight in gram	Average Weight
Patch-A	1.10	1.10 gm
Patch-B	1.09	
Patch-C	1.08	
Patch-D	1.12	

Hardness

The patch was folded several times at a same place until it breaks the hardness was calculated in the number of folds.

Table 4: Hardness

Formulation	Crushing force
Patch-A	Patches was broken in 3 times folding given at the same place
Patch-B	Patches was broken in 4 times folding given at the same place
Patch-C	Patches was broken in 3 times folding given at the same place
Patch-D	Patches was broken in 4 times folding given at the same place

Thickness

Ten patches were taken and their thickness was measured by using screw guage and the average was calculated.

Table 5: Thickness

Formulation	Thickness (µm)
Patch-A	44.4
Patch-B	42.6
Patch-C	44.1
Patch-D	42.7

Diffusion study

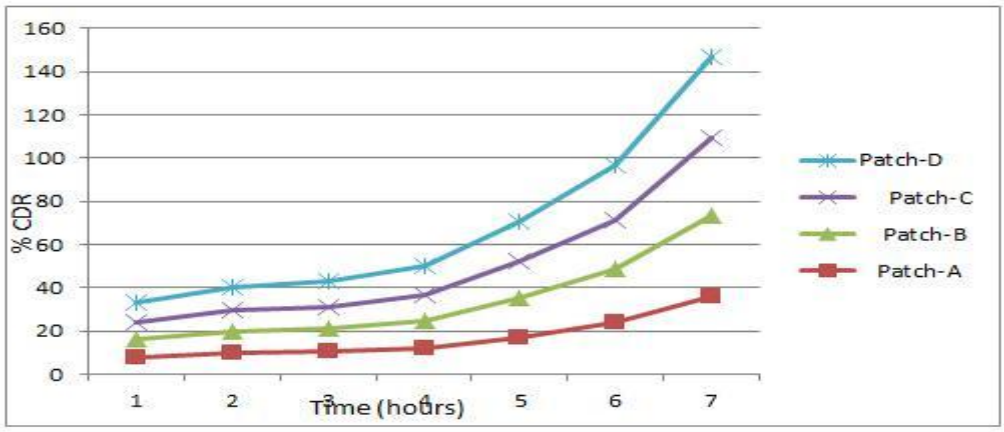
- The patch was taken and sandwiched between two dialysis membranes and further it was placed in between two compartment of diffusion cell.
- Phosphate buffer of pH 7.2 was taken in receptor compartment.
- Entire assembly was placed on magnetic stirrer and the experiment was carried out for 24hrs at 37°C.
- 5ml of sample was collected at each interval replaced it with the same amount of buffer.
- The concentration in the sample was measured by using UV double beam at 272 nm.
- The amount of drug diffused was calculated from the standard graph of ibuprofen.
- Cumulative amount of drug was calculated and then plot a graph taking time on x-axis and cumulative amount on y-axis.

Results of drug diffusion studies in Phosphate buffer saline

Table 6: Percentage release of Ibuprofen in Phosphate buffer saline

Time (hrs)	Patch-A	Patch-B	Patch-C	Patch-D
0.5	8.16	8.3	7.92	8.64
1.0	9.83	10.32	9.6	10.68
1.5	10.44	11.04	9.8	11.64
2	12	12.6	11.88	13.44
3	17.16	18	16.8	18.84
4	23.88	24.6	23.04	25.44
6	36.24	37.08	35.76	37.8

Figure 2: Percentage release of Ibuprofen in Phosphate buffer saline



Study of Release Kinetics of all the Patches

The data obtained from *in vitro* diffusion studies were fitted in different models to determine the mechanism of drug release.

- Zero-Order Kinetics
- First-Order Kinetics
- Higuchi Kinetics
- Hixon-Crowell`s Kinetics
- Korsmeyer-Peppas Kinetics

Various kinetic models of all the formulations are shown in following figures.

Study of Release Kinetics of Patch A

Table 7: *In vitro* drug release parameters for Patch A

Time (hours)	% CDR	Log % CDR	Cube root of % drug remaining	Log % cumulative drug remaining	Square root time	Log time
0.5	8.16	0.9116	774632.34	1.9630	0.25	-0.3010
1.0	9.83	0.9925	733138.80	1.9550	1	0
1.5	10.44	1.0187	718360.18	1.9521	2.25	0.1760
2	12	1.0791	681472	1.9444	4	0.3010
3	17.16	1.2345	568486.65	1.9182	9	0.4771
4	23.88	1.3780	441058.64	1.8814	16	0.6020
6	36.24	1.5591	259205.92	1.8045	36	0.7781

Figure 3: Ibuprofen diffusion kinetics of Patch A according to Zero order kinetics.

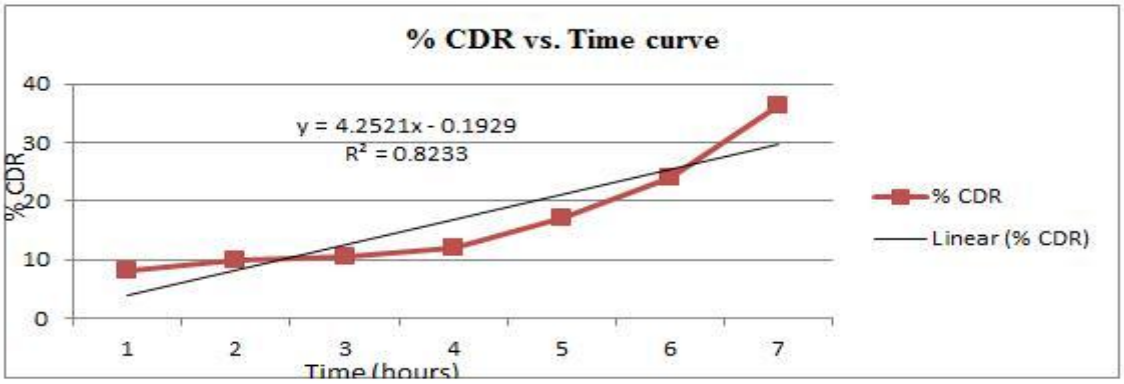


Figure 4: Ibuprofen release kinetics of Patch A according to First order kinetics.

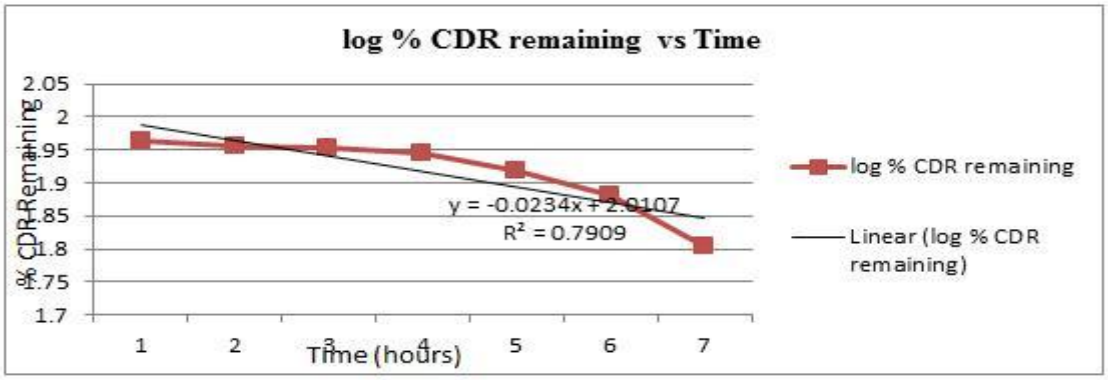


Figure 5: Ibuprofen diffusion kinetics of Patch A according to Hixon-Crowell's kinetics.

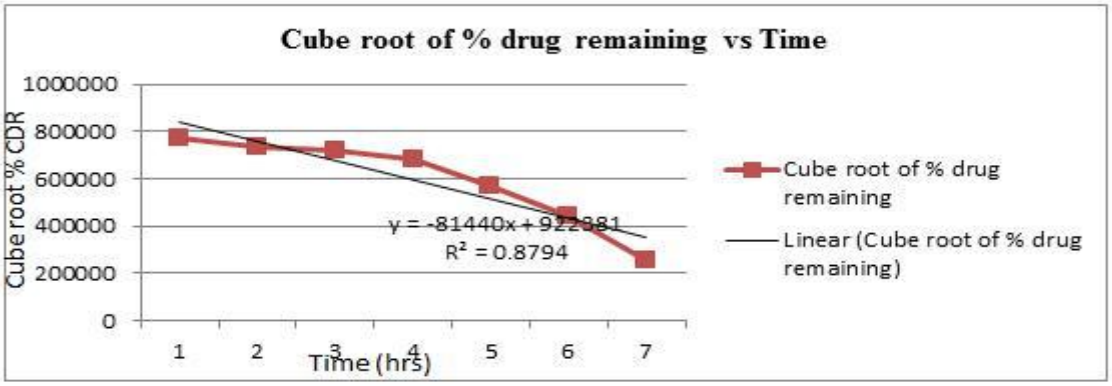


Figure 6: Ibuprofen diffusion kinetics of Patch A according to Higuchi kinetics.

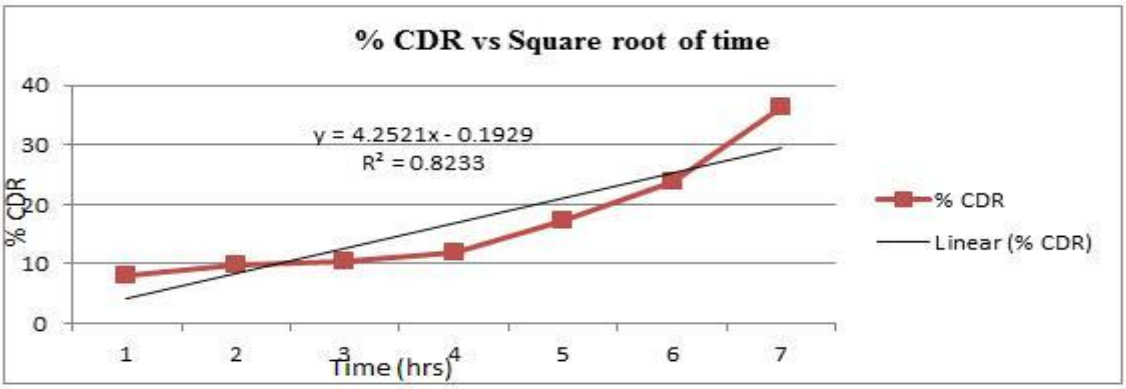
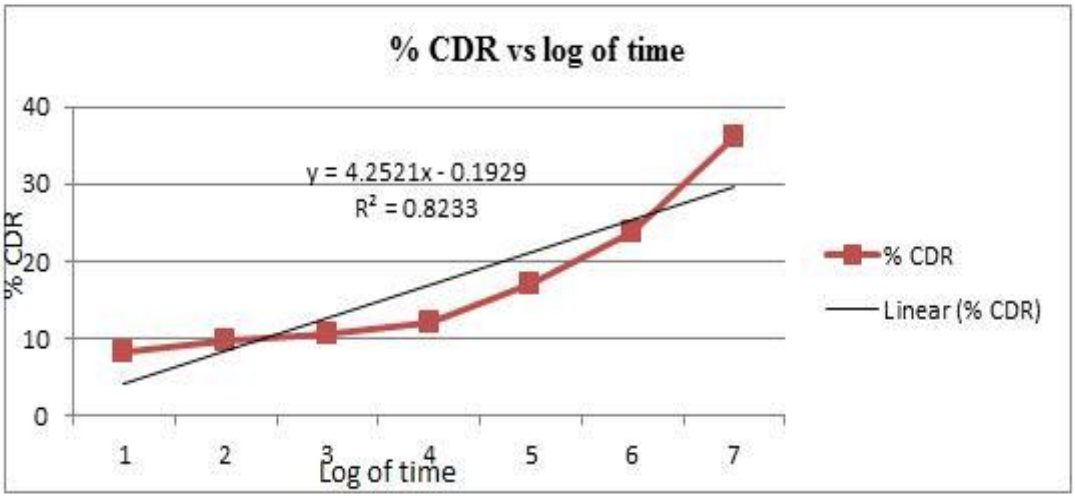


Figure 7: Ibuprofen diffusion kinetics of Patch A according to Korsmeyer- Peppas kinetics.



The statistical kinetics value for the Patch A is represented in Table 8.

Table 8: Statistical kinetics values of Patch A

Kinetic models	R^2	Slope
Zero- order	0.823	4.252
First-order	0.790	-0.023
Higuchi kinetics	0.823	4.252
Hixon-Crowell	0.879	-81440
Korsmeyer- Peppas	0.823	4.252

Among the entire kinetic model studied for the Patch (A), it was found that the batch followed **Hixon-Crowell kinetics** because of having maximum R^2 value of 0.879 (closest to 1.0).

Study of Release Kinetics of Patch B

Table 9: *In vitro* drug release parameters for Patch B

Time (hours)	% CDR	Log % CDR	Cube root of % drug remaining	Log % cumulative drug remaining	Square root time	Log time
0.5	8.3	0.9190	771095.21	1.9623	0.25	-0.3010
1.0	10.32	1.0136	721251.61	1.9526	1	0
1.5	11.04	1.0429	704018.90	1.9491	2.25	0.1760
2	12.6	1.1003	667627.62	1.9415	4	0.3010
3	18	1.2552	551368	1.9138	9	0.4771
4	24.6	1.3909	428661.06	1.8773	16	0.6020
6	37.08	1.5691	249095.64	1.7987	36	0.7781

Figure 8: Ibuprofen diffusion kinetics of Patch B according to Zero order kinetics.

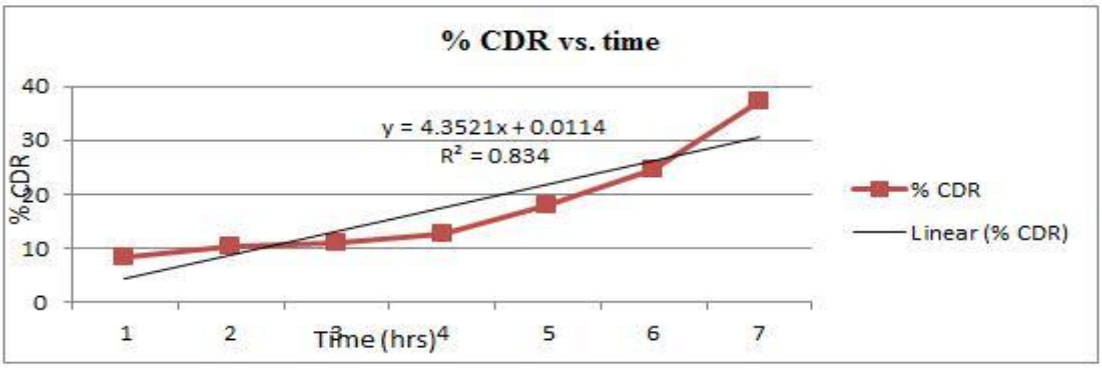


Figure 9: Ibuprofen release kinetics of Patch B according to First order kinetics.

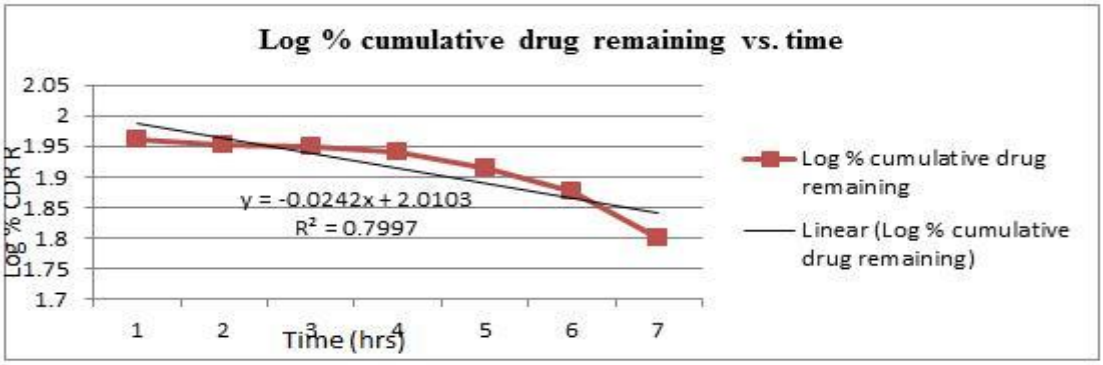


Figure 10: Ibuprofen diffusion kinetics of Patch B according to Hixon-Crowell's kinetics.

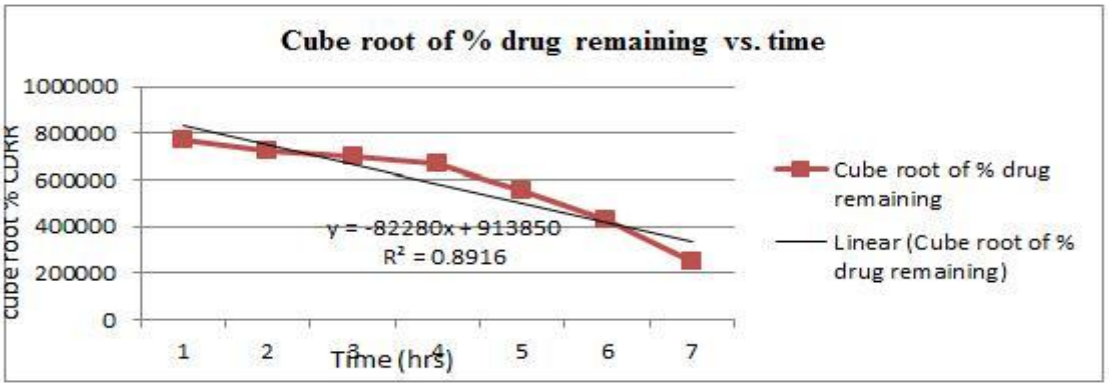


Fig 11: Ibuprofen diffusion kinetics of Patch B according to Higuchi kinetics.

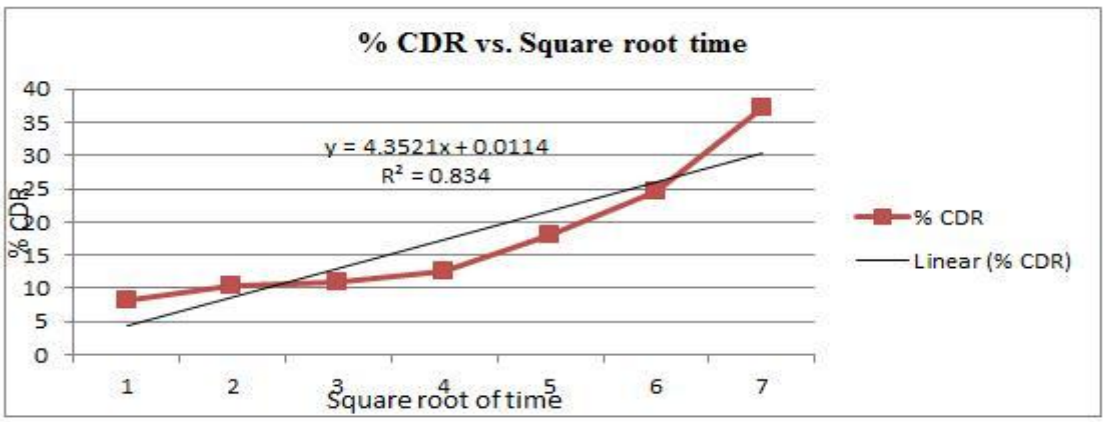
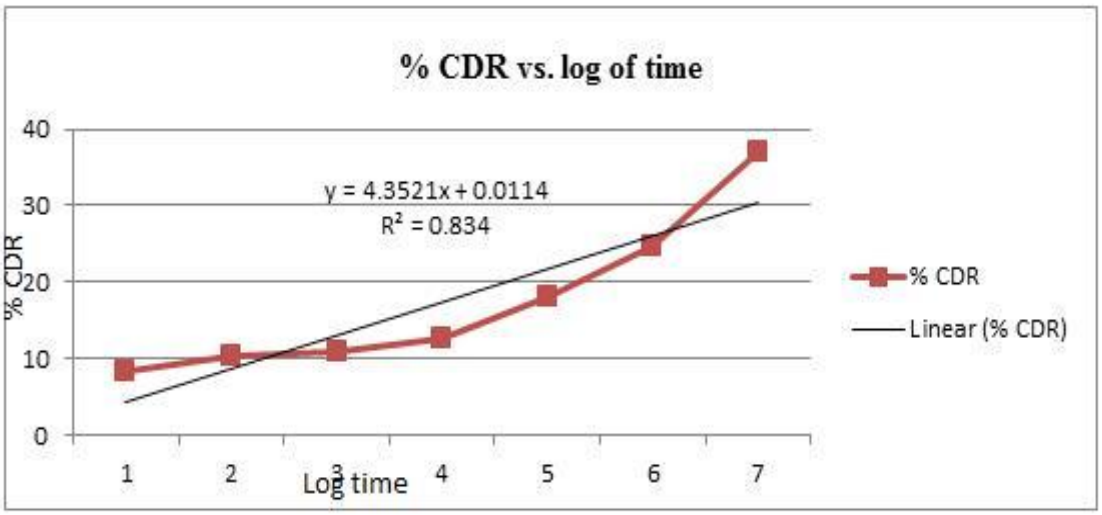


Figure 12: Ibuprofen diffusion kinetics of Patch B according to Korsmeyer- Peppas kinetics.



The statistical kinetics values for the Patch B is represented in Table 10

Table 10: Statistical kinetics values of Patch B

Kinetic models	R^2	Slope
Zero- order	0.834	4.352
First-order	0.799	-0.024
Higuchi kinetics	0.834	4.352
Hixon-Crowell	0.891	-82.280
Korsmeyer- Peppas	0.834	4.352

Among the entire kinetic model studied for the Patch (B), it was found that the batch followed **Hixon-Crowell kinetics** because of having maximum R^2 value of 0.891 (closest to 1.0).

Study of Release Kinetics of Patch C

Table 11: *In vitro* drug release parameters for Patch C

Time (hours)	% CDR	Log % CDR	Cube root of % drug remaining	Log % cumulative drug remaining	Square root time	Log time
0.5	7.92	0.8987	780721.12	1.9641	0.25	-0.3010
1.0	9.6	0.9822	738763.26	1.9561	1	0
1.5	9.8	0.9912	733870.80	1.9552	2.25	0.1760
2	11.88	1.0748	684263.64	1.9450	4	0.3010
3	16.8	1.2253	575930.36	1.9201	9	0.4771
4	23.04	1.3624	455821.88	1.8862	16	0.6020
6	35.76	1.5533	265104.19	1.8078	36	0.7781

Figure 13: Ibuprofen diffusion kinetics of Patch C according to Zero order kinetics.

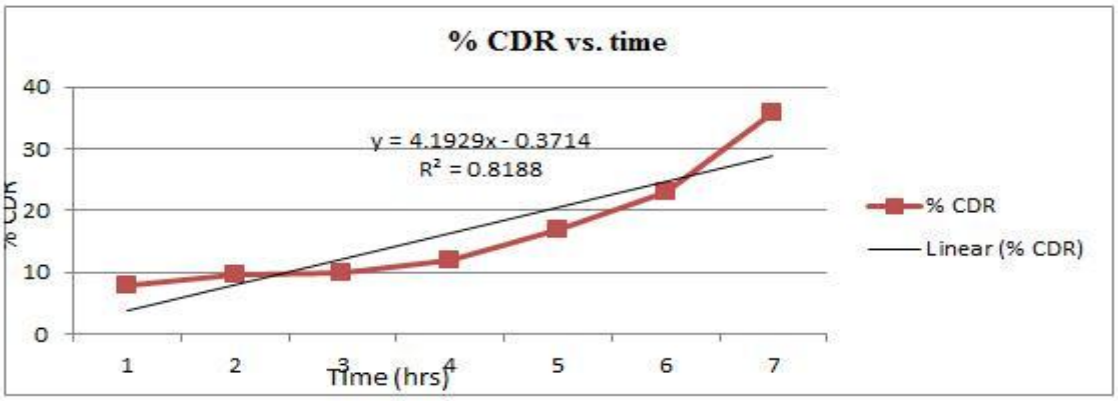


Figure 14: Ibuprofen release kinetics of Patch C according to First order kinetics.

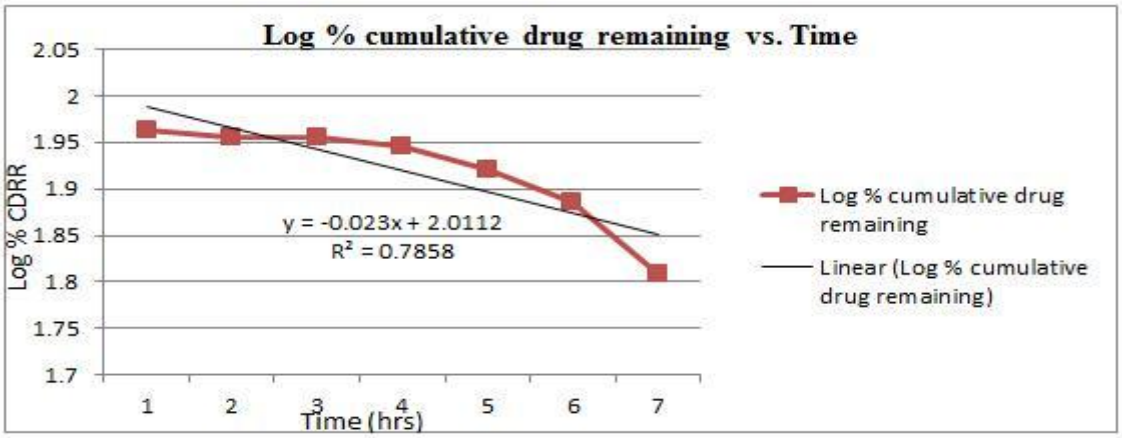


Figure 15: Ibuprofen diffusion kinetics of Patch C according to Hixon-Crowell's kinetics.

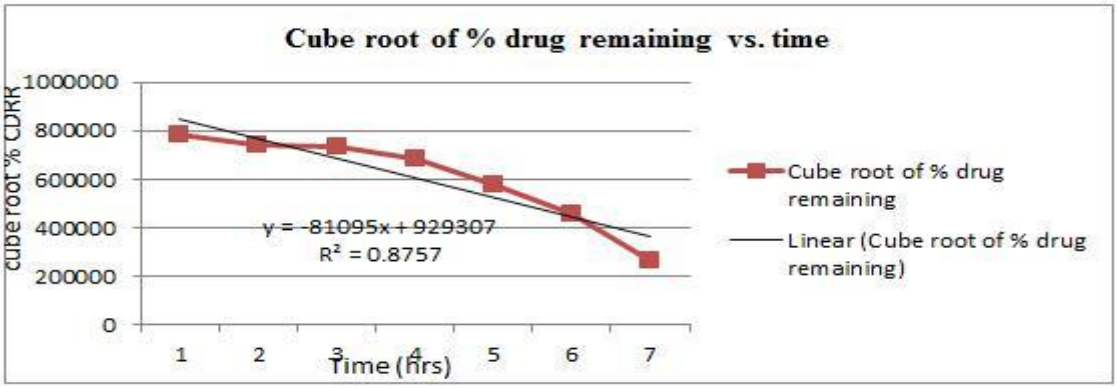


Figure 16: Ibuprofen diffusion kinetics of Patch C according to Higuchi kinetics.

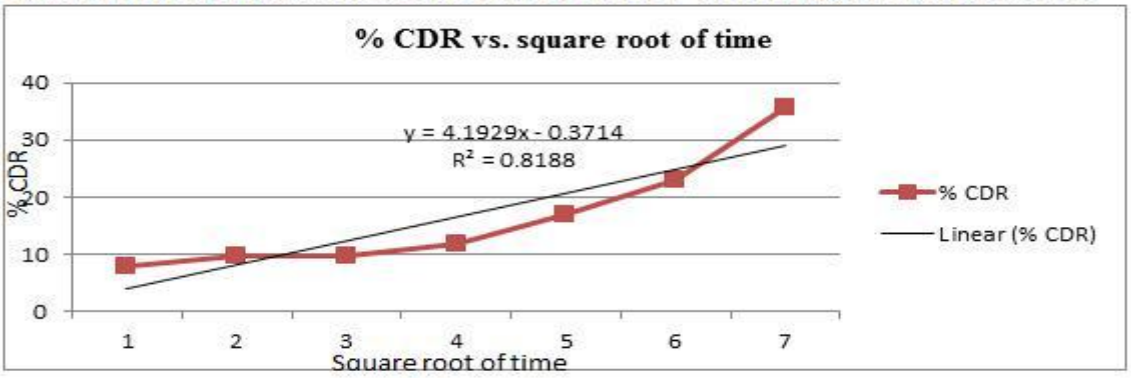
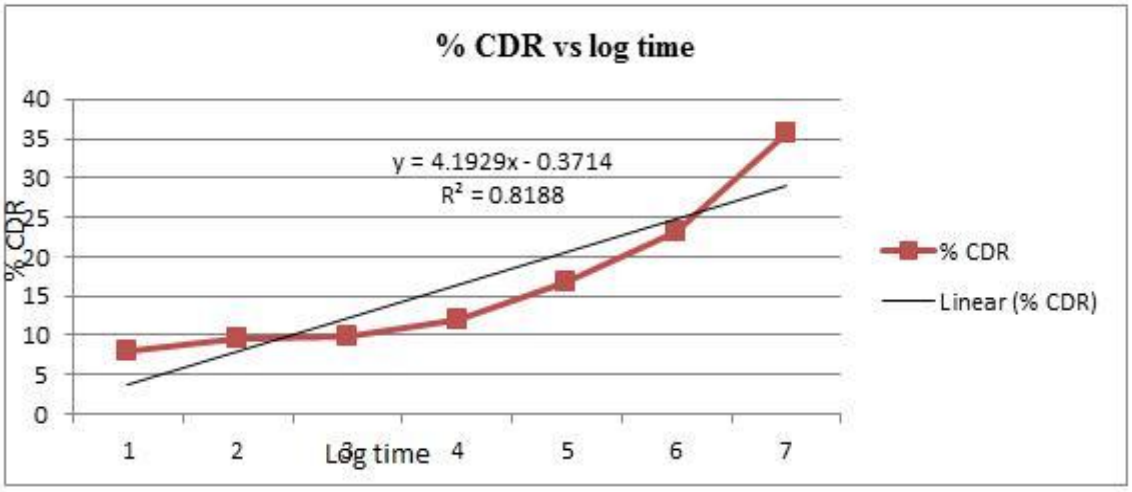


Figure 17: Ibuprofen diffusion kinetics of Patch C according to Korsmeyer- Peppas kinetics.



The statistical kinetics values for the Patch C is represented in Table 12

Table 12: Statistical kinetics values of Patch C

Kinetic models	R^2	Slope
Zero- order	0.818	4.192
First-order	0.785	-0.023
Higuchi kinetics	0.818	4.192
Hixon-Crowell	0.875	-81095
Korsmeyer- Peppas	0.818	4.192

Among the entire kinetic model studied for the Patch (C), it was found that the batch followed **Hixon-Crowell kinetics** because of having maximum R^2 value of 0.875 (closest to 1.0).

Study of Release Kinetics of Patch D

Table 13: *In vitro* drug release parameters for Patch D

Time (hours)	% CDR	Log % CDR	Cube root of % drug remaining	Log % cumulative drug remaining	Square root time	Log time
0.5	8.64	0.9365	762549.90	1.9607	0.25	-0.3010
1.0	10.68	1.0285	712600.53	1.9509	1	0
1.5	11.64	1.0659	689869.78	1.9462	2.25	0.1760
2	13.44	1.1283	648562.36	1.9373	4	0.3010
3	18.84	1.2750	534596.50	1.9093	9	0.4771
4	25.44	1.4055	414493.47	1.8725	16	0.6020
6	37.8	1.5774	240641.84	1.7937	36	0.7781

Figure 18: Ibuprofen diffusion kinetics of Patch D according to Zero order kinetics.

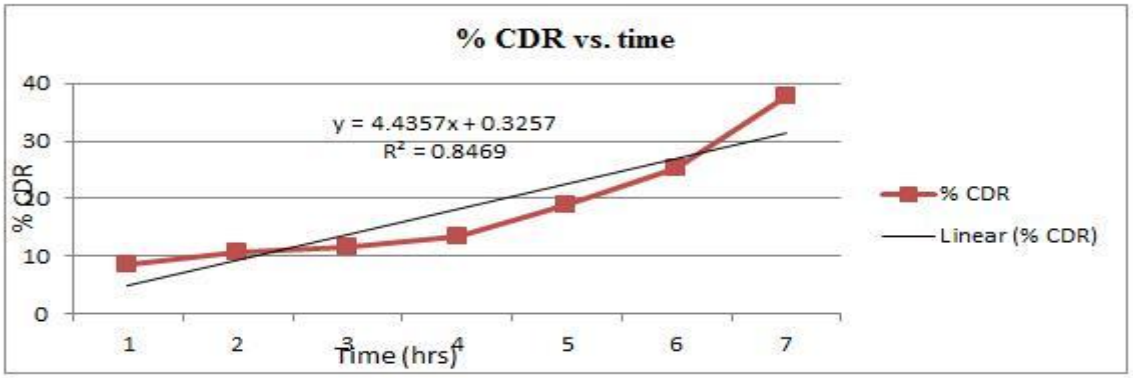


Figure 19: Ibuprofen release kinetics of Patch D according to First order kinetics.

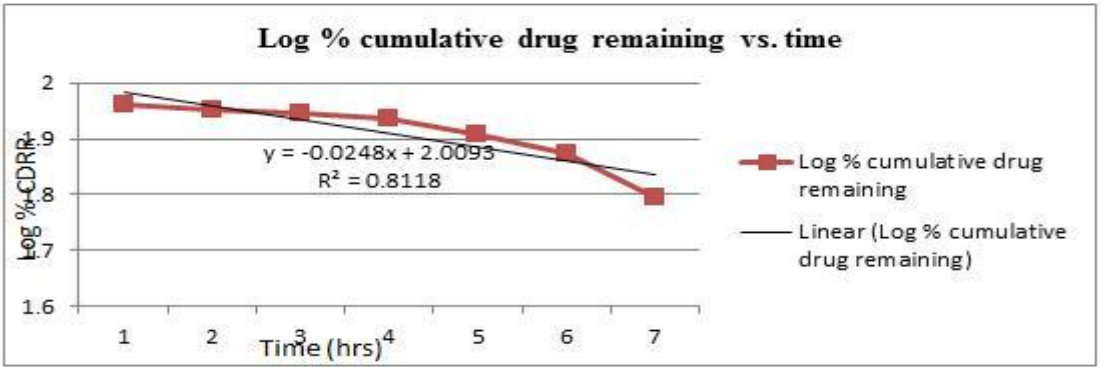


Figure 20: Ibuprofen diffusion kinetics of Patch D according to Hixon-Crowell's kinetics.

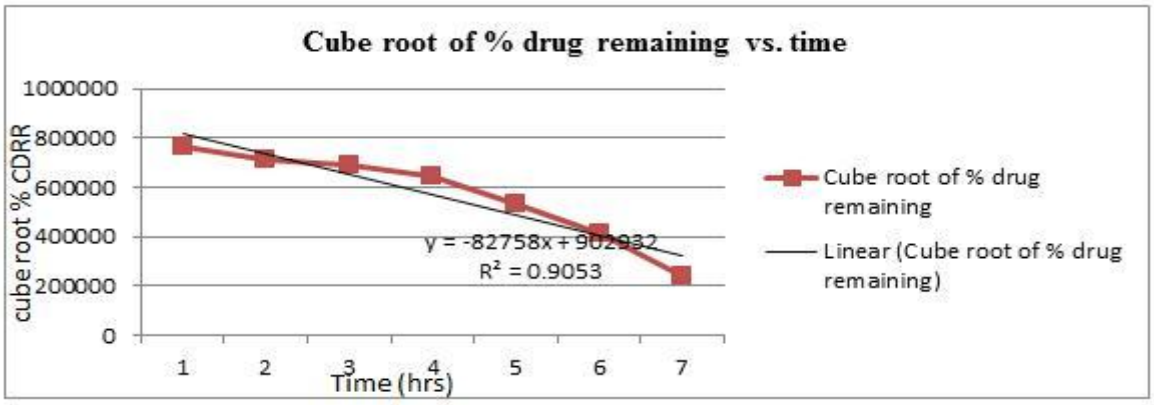


Figure 21: Ibuprofen diffusion kinetics of Patch D according to Higuchi kinetics.

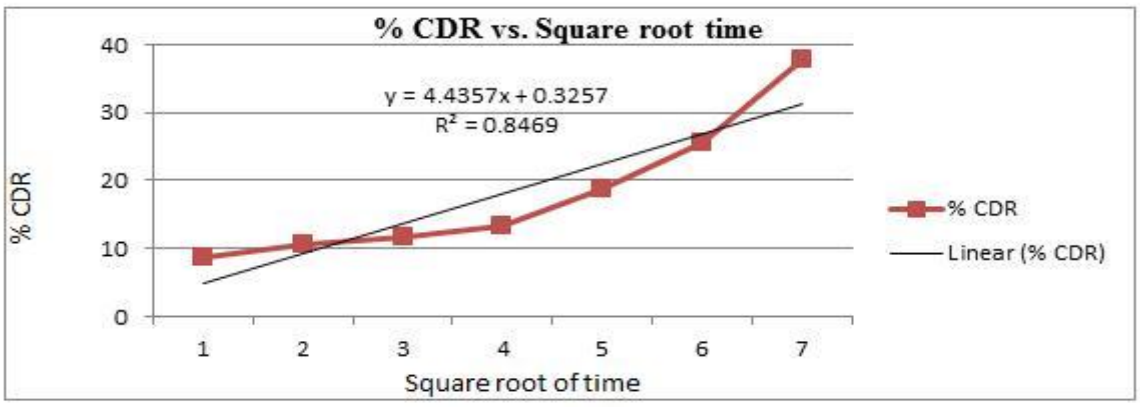
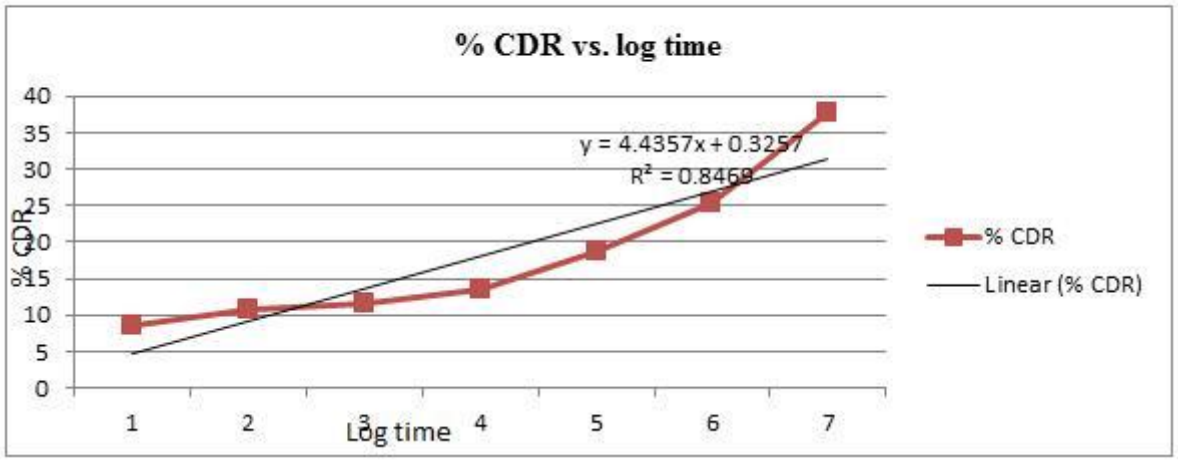


Figure 22: Ibuprofen diffusion kinetics of Patch D according to Korsmeyer- Peppas kinetics.



The statistical kinetics values for the Patch D is represented in Table 14

Table 14: Statistical kinetics values of Patch D

Kinetic models	R^2	Slope
Zero- order	0.846	4.435
First-order	0.811	-0.024
Higuchi kinetics	0.846	4.435
Hixon-Crowell	0.905	-82758
Korsmeyer- Peppas	0.846	4.435

Among the entire kinetic model studied for the Patch (D), it was found that the batch followed **Hixon-Crowell kinetics** because of having maximum R^2 value of 0.905 (closest to 1.0).

Discussion

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Four batches of transdermal patches were made using ethyl cellulose and Polyvinylpyrollidine (PVP) in their maximum and minimum concentrations. Various effects of both ethyl cellulose and PVP on the drug release were noted. Results show that when ethyl cellulose was used in its maximum concentration of 9:1 ratio with PVP in patch D, the patch give maximum release or diffusion. Out of four batches of different concentration, the patch D shows maximum release because in patch D, the concentration of ethylcellulose is 9:1 ratio. In patch A the ratio of ethylcellulose: PVP is 7:3, in patch B the ratio of ethylcellulose: PVP is 8:2, in patch C the ratio is 6:4 and in patch D the ratio is 9:1. The patch was taken and sandwiched between to dialysis membranes and further it was placed in between two compartments of a. diffusion cell. Phosphate buffer of pH 7.4 was taken in receptor compartment. Entire assembly was placed on magnetic stirrer and the experiment was carried out for 24 hours at 37 °C. 5 ml of sample was collected in each interval and replaced it with the same amount of buffer. The concentration in the sample was measured by using UV double beam spectrophotometer at 272 nm. The amount of drug diffused was calculated from the standard graph of ibuprofen. The cumulative amount of drug was calculated and then plot a graph by taking time on x – axis and cumulative amount on y – axis.

Conclusion

Four patches were prepared of ibuprofen and checked the effect of different concentration of the polymers like ethylcellulose and PVP. If the concentration of the ethylcellulose was increased then the release was increased. After all the physicochemical test when the diffusion kinetics was determined of all the patches then Among the entire kinetic model studied for the Patch (A,

B, C and D), it was found that the batches followed **Hixon-Crowell kinetics** because of having maximum R^2 value of 0.879, 0.891, 0.875, and 0.905 respectively (closest to 1.0). This shows that patch D give the best release out of these four patches.

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