Formulation and Evaluation of Timolol Maleate Transdermal Patches Using Various Permeation Enhancers

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ABSTRACT

Objective: Our main aim was to formulating transdermal drug delivery systems of Timolol maleate of an anti-hypertensive drug using various polymer such as ethyl cellulose, eudragit RL100 and eudragit RS100.

Methods: The patches of Timolol was prepared by solvent casting method using ethyl cellulose (EC), eudragit RL100 (ERL100) and eudragit RS100 (ERS100)polymer were used in various ratio (EC:ERL100 or EC:ERS100). Polymeric solution was prepared by dissolving ethyl cellulose into the required volume of acetone with continuous stirring (Sol. A) Then Add of eudragitRL100 or eudragit RS100 into the Sol. A with continuous stirring for homogeneous mixing (Sol.B). Drug (0.75%) was dissolved in water and incorporated into the sol. B. To improve the patch performance and drug release different type of permeation enhancer like Tween 80 or Span 80 were added whereas glycerin was used as a plasticizer.

Results: The result of *In- Vitro* release kinetic for the optimized F5 formulation are represented in figure 4-7.It was observed that F5 follows the zero order R^2 value were 0.990 which are higher than other model.

Conclusion: It was concluded that this formulation follows zero order kinetics, which release drug in control manner and it is the ideal method of drug release to achieve pharmacological prolonged action.

Keywords: Transdermal drug delivery, Timolol maleate, permeation enhancer and zero order kineticsetc.

INTRODUCTION

Conventional systems of medication that require multi dose therapy are having many problems. The controlled drug delivery is a newer approach is to deliver

drug in to systemic circulation at a predetermined rate. Our system should duplicate continuous intravenous infusion, which not only by passes hepatic 'first pass' elimination but also maintains a constant, prolonged and therapeutically effective drug level in the body. This is made possible by using intact skin as a port of drug administration to provide continuous delivery of drug in to systemic circulation. Following skin permeation, the drugs first reach the systemic circulation. The drug molecules are then transported to the target site, which could be relatively remote from the site of administration, to produce therapeutic action[1-5].

Timolol maleate (TM) is a beta adrenoceptor-blocking agent, Fig. 1,Timolol Maleate has been proposed as an antihypertensive, anti-arrhythmic, anti-angina, and anti-glaucoma agent. It is also used in the treatment of migraine disorders and tremor[6-12].

Timolol is available in solution, drops and tablet forms. It is rapidly absorbed from gastrointestinal tract with peak plasma concentration of 5-10 mg/ml after 1 hr. and metabolized up to 80% in liver with a mean half-life of 2.0-2.5 hrs., thus required the frequent administration of larger doses to maintain therapeutic drug level[12-15]. So, Current work of formulating transdermal drug delivery systems of Timolol maleate of an anti-hypertensive drug using various polymer such as ethyl cellulose, eudragit RL100 and eudragit RS100, Fig. 2, in various ratio that provides controlled drug delivery without pre systemic metabolism, reduce toxic effects and enhances the bioavailability[16-17].

MATERIALS AND METHODS

Materials

Timolol Maleate was get a Gift sample from Albert David Limited Ghaziabad, U.P., Ethyl cellulose was

purchase from High purity Laboratory Chemicals Pvt. Ltd. Mumbai, Eudragit RL100and Eudragit RS100 from Evonik pharma polymer, Mumbai.

Method of preparation[16-20]

The patches of Timolol was prepared by solvent casting method using ethyl cellulose (EC), eudragit RL100 (ERL100) and eudragit RS100 (ERS100)polymer were used in various ratio (EC:ERL100 or EC:ERS100) which are reported in Table 1. Polymeric solution was prepared by dissolving ethyl cellulose into the required volume of acetone with continuous stirring (Sol. A) Then Add of eudragitRL100 or eudragitRS100 into the Sol. A with continuous stirring for homogeneous mixing (Sol. B). Drug (0.75%) was dissolved in water and incorporated into the sol. B. To improve the patch performance and drug release different type of permeation enhancer like Tween 80 or Span 80 were added whereas glycerin was used as a plasticizer.

For Casting of polymeric solution mercury was used as the substrate. In which Mercury was poured into the Petri dish. Them old was kept on the surface of mercury with smooth horizontal surface. Pour the polymeric solution in to the mould and allow to dry at room temperature for 48 hrs. After drying patch is removed and stored in desiccator.

Evaluation Studies of Transdermal Patches[21-24]

Thickness of patch

The thickness of the drug loaded patch is measured in different point by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

Uniformity of weight

Weight variation is studied by individually weighting randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination

An accurately weighted portion of film (about 100mg) is dissolve in 100 ml suitable solvent in which drug is soluble. The medium was stirred with a Teflon coated magnetic bead for five hr. The contents were filtered using what man filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films (containing no drug) by using spectrophotometry at 295nm.

Moisture content

The prepared film weighed individually and kept in a vacuum desiccators containing phosphorus pentoxide at room temperature for 24 h. The patches were weight again and again individually until they showed a constant weight. The percentages of moisture content were calculated as a difference between initial and final weight with respect to final weight.

$$\% \text{ of moisture content} = \frac{X - Y}{Y} \times 100 \text{ , where}$$
$$X = \text{initial weight}$$
$$Y = \text{final weight.}$$

Uptake moisture

The drug polymer film were weighed and then kept for drying up to a constant weight in vacuum desiccator at normal room temperature for 24 h exposed to 84% relative humidity (saturated solution of potassium chloride).

$$\% \text{ of moisture uptake} = \frac{Y - X}{X} \times 100$$

Where
$$X = \text{initial weight}$$
$$Y = \text{final weight}$$

Flatness

For flatness determination, one strip is cut from the center and two from each side of patch. The length of each stripe is measured and variation in length is measured by determining percent constriction. Zero persent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = \frac{L_1 - L_2}{L_2} \times 100 \text{ , Where}$$
$$L1 = \text{Initial length of each strip}$$
$$L2 = \text{Final length of each strip}$$

Folding Endurance

The patches were repeatedly folded at the same place till it broke. The number of times the patches could be folded at the same place without breaking gives the accurate value of folding endurance.

Swelling ability

The swelling behavior of a dosage form was measure using its weight gain or water uptake .The dimensional change could be measured in terms of the increase in patch diameter or thickness over time .water uptake was measured in terms of percentage weigh gain as given formula-

$$\% \text{ Swelling} = \frac{W_1 - W_0}{W_0} \times 100 \text{ , Where}$$
$$W1 = \text{Weight after time t}$$
$$Wo = \text{Initial weight}$$

Surface pH

Surface pH of the patch was determined by allowing them to swell in closed petridish at room temperature for 30 minutes in 0.1 ml of double distilled water. The swollen device were removed and placed under digital pH meter to determine.

In Vitro Permeation studies[25-27]

In vitro permeation studies were carried out using Franz diffusion cell. The dialysis sac was previously soaked for 12 h in phosphate buffer 6.8. The films were adhered to the barrier membrane (dialysis membrane) and the sac is tied firmly to the donor compartment of the Franz diffusion cell, the receptor compartment of which is filled with 50 ml phosphate buffer 6.8. The total setup was placed on a thermostatically controlled magnetic stirrer set at 37 ± 2°C. The content of the diffusion cell was stirred at a constant speed 100 rpm. Samples were withdrawn 1 ml at predetermined time intervals and replaced with same amount of distilled water to maintain the sink condition. The samples were analyzed for drug content using UV spectrophotometer at λmax 295 nm. The permeation study was carried out for 12 h.

In-Vitro drug release kinetics by using mathematical model

Various mathematical models were tested for investigate the model of release explaining the kinetics of drug release from TM patches. To analyze the mechanism of the drug release rate kinetics of the patches, the obtained data were fitted in to Zero-order, First –order, Higuchi's and Korsmeyer-pappas release model. Drug release rate kinetics of TM patches was calculated by using A Microsoft Excel Add-in. Stability studies were carried out as per ICH guidelines and formulations were found tobe Stable.

RESULTS AND DISCUSSION

Thickness of patch

Thickness of patch was found that all the patches have uniform thickness throughout the study. The formulation F7 had maximum0.32.064± 0.064 mm thickness and the formulation F1 shows low0.25±0.20 thickness, Table 2.

Uniformity of weight

In a weight variation test, the Pharmacopoeial limit for the percentage deviation of all the films of less than mg is ± 10%. The average percentage deviation of all formulations was found to be within the limit, Table 2.

Drug content determination

The drug content was analyzed using UV spectrophotometer at 295nm using placebo patch solution as a blank sample. The result are reported in the table 2.

Moisture content and moisture uptake

The results of .Moisture test for all formulation F1 to F7 are reported in Table 2.The result revealed that the moisture content and moisture uptake was found to increase with increasing concentration of hydrophilic polymers, Table 2 and 3.

Flatness

The results of the flatness study showed that none of the formulations had the differences in the strip length before and after their cuts. It indicates **100%** flatness observed in the formulated patches, Table 3. Thus, no amount of constriction was observed in the film of any formulation and it indicates smooth flat surface of the patches and thus they could maintain a smooth surface when applied on to the skin.

Folding Endurance

The recorded folding endurance of the patches was within 125 to 152 which

reflect the flexibility of patches this test ensure that prepare patches are suitable for large scale manufacture and continuous patches without breaking, Table 3.

Swelling index and surface pH

Swelling index test[28] was conducted for all formulation F1 to F7 as per IP. The results revealed that the moisture uptake was found to increase with increasing concentration of hydrophilic polymers and average surface pH of the prepared formulation was found out to be within 6.46 to 6.76, Table 3.

In-Vitro permeation study of the batches indicated F5 and F4 source 94.88% and 87.43% drug release using the permeation enhancer Span80 and Tween80 respectively. F6 and F7 source 78.29% and 92.69% drug release by using the permeation enhancer Tween80 and Span80 respectively[29], reported in Table 4 and Fig. 3.

In- Vitro Drug release kinetics

The *In- Vitro* Drug release kinetics should apply on best F5 formulation. Timolol maleate patches are evaluated by fitted the obtained *In- Vitro* release data into various kinetic model like zero order, First order and Haguchi equation. The drug release kinetic data of F5 Timolol maleate patches was shown in Table 5.

The result of *In- Vitro* release kinetic for the optimized F5 formulation are represented in figure 4-7. It was observed that F5 follows the zero order R^2 value were 0.990 which are higher than other model, So, it was concluded that this formulation follows zero order kinetics, which release drug in control manner and it is the ideal method of drug release to achieve pharmacological prolonged action.

CONCLUSION

From the evaluation of batches it was found that F4 and F5 shows good result in all physiochemical parameters. Flatness of the all formulation was 100% which is within the range and the% moisture content,% moisture uptake, and swallow ability was increase with increasing concentration of Hydrophilic polymer .The effect of non-ionic surfactants Tween80 and Span80 on drug permeation were studied. *In-Vitro* permeation study of the batches indicated F5 and F4 source 94.88% and 87.43% drug release using the permeation enhancer Span80 and Tween80 respectively. It was observed that F5 follows the zero order R^2 value were 0.990 respectively which are higher than other model. So, it was concluded that this formulation follows zero order kinetics, which release drug in control manner and it is the ideal method of drug release to achieve pharmacological prolonged action.

ACKNOWLEDGEMENT

REFERENCES

1. Praveen Tyle, Drug delivery device fundamental and biomedical application; Marcel Dekker: New York, 1988, 386-419.
2. Remington's Pharmaceutical Science, 17th ed., Mack Publishing Co., 1995, 1644-1661.
3. Bellantone N.H., Rim S., Rasadi B., Enhanced percutaneous absorption via Iontophoresis I. Evaluation of an in-vitro system & transport of model compound., *Int. J. Pharm*., 30, 1986, 63-72.

4. Gros L., Clark W.E., "The structure of skin" in " The tissue of the body" Le Gros& Clark W. E.(editors) edition VI, ELBS and Oxford University Press, London, 1980, 29-313.

5. Chien Y.W., "Systemic delivery of pharmacologically active molecules across skin" in "Targeted drug delivery" Radolph L., Juliano(Editor) Springer-Verlag, Berlin, 1991, 182-230.

6. Bernar B and John V.A. Pharmacokinetic characterization of Transdermal delivery systems. *Jour. Clinical pharmacokinetics* 1994, 26(2), 121-34.

7. Singh J, Tripathi K.T and Sakia T.R. Effect of penetration enhancers on the invitro transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations. *Drug Dev.ind.Pharm.* 1993, 19, 1623-1628.

8. Wade A, Wellar P.J. Handbook of pharmaceutical Excipients. Washington, DC; American pharmaceutical publishing Association; 1994, 362-366.

9. Raghuramreddy K, MuttalikS and Reddy S. Once-daily sustained release matrix tablets of nicorandil: formulation and invitro evaluations. AAPS Pharm Sci.Tech.2003; 4, 4.

10. Costa P, Ferrica DC, Morgado R, Soussa Lobo JM. Design and evaluation of a lorazepam transdermal delivery system, Drug Dev Ind Pharm 1997, 23, 939-944.

11. Shaila L., Pandey s and Udupa N. Design and evaluation of matrix controlledTransdermal drug delivery system of nicitin suitable for use in smoking cessation. *Indian Journ. Pharm. Sci.* 2006; 68, 179-184.

12. Wade A and wellar P.J. Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical publishing Association 1994, 362-366.

13. Sachan Richa, Bajpai Meenakshi, Transdermal drug delivery system a review, *Int. J. Resh. Pharm. Life sci.* 2013, 3, 48-65.

14. Jamakandi V.G., Mulla J.S., Vinay B.L., Formulation, characterization and evaluation of matrix type transdermal patches of a model antihypertensive drug. *Asian J. Pharm.*, 1, 2009, 59-65.

15. Murthy T.E.G.K., Ramana R.V., Kishore B.M., Influence of polymers on the release of Carvediol from transdermal films, Indian Drugs, 2008, 45(12), 970-974.

16. Wahid A., Sridhar B.K., Shiv Kumar S., Preparation and evaluation of transdermal delivery system of etoricoxib using modified chitosan, *Indian J. Pharm. Sci.*, 2008, 455- 460.

17. Murthy N.S., Hamsa V., Bhaskaran S., Comparative release studies of transdermal films of Terbutaline Sulphate across various diffusion barriers, *Indian J. Pharm. Sci,,* 58(4), 1996, 150-151.

18. Mishra A., Raghuvanshi R.S., Ganga S., Diwan M., Formulations of transdermal system for biphasic delivery of testosterone, *J. Controlled Rel.*, 1996, 39, 1-7.

19. Jain G.K., Sharma A.K., Agraval S.S., Transdermal controlled administration of Verapamil enhancement of skin permeability, *Int. J. Pharm.* 1996, 130(22), 169-177.

20. Lee Y. L., Chiang C. H., Chen J. L., In Vitro and In Vivo Percutaneous Absorption Studies of Ketotifen Patches, *Drug. Dev. Ind. Pharm.*, 1994, 20(19), 2965 – 2976.

21. Sharma Sanket,R.Yogendra and Bharti DR Devlopment of controlled release mucoadhesive buccal patches containing Timolol malaet using natural and synthetic polymers, *Int. J. Phar. Tech.Res.* 2013,5, 767-772.

22. Mahanthesha.M.K., NagrajaT.S. and DR. Bharti,R.Yogendra, Desing and evaluation of Timolol maleate buccal patches using Tween as Permiation enhancer, *Int. J. Uni. Phar. Bio. Sci,* 2013, 2(3), 71.

23. R.PannerSelvam, Sink Kumar Anoop T.Sivkumar, Transdermal drug delivery system for antihypertensive drug –A Review, *Int. J. Phar. Biomed Res.* 2010,1(1),1-8.

24. BhanjaSatyavrata,P.ellaiah,MarthaSujitkumar,SahuPratitKanchan,Tiwari,Sandip, Prasad,DasDevajyoti,Formulation and *in-vitro* evaluation muccoadhesive buccal tablet of Timolol malete, *int.J.pharm*.2010,1(4),129-134.

25. Pal Ranju, Shukla Ragini, Antihypertensive drug used for transdermal drug delivery A Review, *Asi. J.Pharm. Edu.Res*, 2012, 1, 31-52.

26. T. Esther Babita, Sd Umar Farook, V. Ravi Krishna, M.VamshiKrishna, D.Sudhirkumar, Devlopment of fast dissolving film Timolol maleate role of HydrophillicPolymer*, I.J.P.R.S*., 2014,3, 830.

27. Patel D Keyul, Patel j Himangi,Patel S Jitendra, Desmukh J Gajanan, Formulation and evaluation of transdermal drug delivery system of Timolol maleate as model drug, *A.J.Phar. Tech. Res*.,2015,845.

28. Anita G. Sullad, Lata S. Manjeshwar, Tejraj M. Aminabhavi and Praveen N. Naik, Microspheres of Poly (vinyl alcohol) and Methyl Cellulose for the Controlled Release of Losartan Potassium and ClopidogrelBisulphate, *American J. of Adv. Drug Delivery*., 2014, 2 (3), 407-423.

29. Vinay Rao, M.Kalyan Raj, S.Ravinder, K.Sowmya, K.Praveen Kumar, M.SudhakarEffect of Permeation Enhancers on Diffusionof Lamotrigine Drug through Cellophane Membrane, *American J. of Adv. Drug Delivery*, 2013, 1(4), 606-610.

Table 1. List of ingredients used in formulation of Timolol TDDS

S. No	Ingredient	F1	F2	F3	F4	F5	F6	F7
1.	Timolol(mg)	75	75	75	75	75	75	75
2.	Ethyl cellulose	2.5%	1%	1%	1%	1%	1%	1%
3.	Eudragit RS100	-	2%	-			2%	2%
4.	Eudragit RL100		-	2%	2%	2%	-	-
5.	Tween 80	-	-	--	0.5%	-	0.5%	-
6.	Span 80	-	-	-	-	0.5%	-	0.5%
7.	Acetone(ml)	10	10	10	10	10	10	10
8.	Water(ml)	1	1	1	1	1	1	1
9.	Glycerin	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%

Table 2. Evaluation of Transdermal patches

Formulation code	Thickness of patch(mm) ± SD	Uniformity of weight(mg) ± SD	Drug content determination ± SD	% moisture content ±SD
F1	0.25 ±0.206	256.24±0.046	86.053±0.066	1.02±1.13
F2	0.30±0.015	298.44±0.02	87.443±0.10	1.926±0.07
F3	0.31±0.068	300.62±0.082	88.127±0.13	1.64±0.12
F4	0.32±0.0126	310.42±0.016	89.343±0.05	2.267±1.04
F5	0.31±0.048	298.60±0.026	91.643±0.66	1.851±0.88
F6	0.31±0.081	308.24±0.048	87.84±0.03	2.62±0.24
F7	0.32±0.064	310.08±0.012	88.42±0.10	2.04±0.42

Table 3. Evaluation of Transdermal patches

Formulation code	Folding endurance±SD	Surface pH	Swelling index ±SD	%Moisture uptake±SD
F1	125±0.03	6.46	22.86±0.066	1.482±1.74
F2	147±0.015	6.68	36.45±0.10	1.566±0.34
F3	142±0.068	6.58	33.86±0.13	1.842±0.62
F4	150±0.0126	6.48	35.43±0.05	1.672±1.02
F5	153±0.048	6.68	34.63±0.66	1.70±0.82
F6	148±0.081	6.82	38.84±0.03	1.98±0.46
F7	152±0.064	6.76	37.42±0.10	1.97±1.02

Table 4. *In-Vitro* Permeation study

Time (hr)	F1	F2	F3	F4	F5	F6	F7
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	3.58±0.23	5.54±0.67	5.60±0.45	5.62±0.78	6.60±0.56	5.47±0.35	6.04±0.76
2	5.50±0.58	9.32±0.56	9.64±0.55	10.18±0.88	11.81±0.67	9.40±0.47	10.84±0.87
3	8.89±0.86	13.59±0.45	14.07±0.78	15.18±0.56	17.74±088	13.62±0.56	16.29±0.56
4	12.65±1.54	18.17±0.89	18.91±0.69	20.59±0.45	24.14±0.56	18.18±0.36	22.32±0.89
5	17.88±0.04	23.43±0.56	24.54±1.32	26.60±0.50	31.00±0.56	23.36±0.56	29.01±0.67
6	22.66±1.86	28.94±1.23	30.48±1.28	33.42±0.67	38.48±0.67	28.96±0.84	36.13±0.56
7	26.32±0.88	34.87±0.34	36.82±1.22	40.73±1.31	46.77±1.34	34.89±0.88	44.27±1.29
8	34.00±0.56	42.28±0.45	43.68±0.89	48.81±0.98	55.69±1.22	41.32±0.78	54.19±1.34
9	43.22±0.44	48.35±0.44	50.79±0.67	57.65±1.23	64.85±0.98	48.20±0.67	62.42±1.32
10	48.33±1.86	55.65±0.48	58.14±0.77	67.04±0.67	74.49±0.67	54.71±0.76	72.21±0.67
11	52.48±0.34	63.18±0.95	65.63±0.82	76.97±0.88	84.57±0.77	64.07±0.88	82.31±0.76
12	62.48±0.34	71.06±0.67	73.54±0.54	87.43±0.67	94.88±1.22	78.29±1.33	92.69±0.78

Table 5. Kinetics of F5 formulation

K- MODELS	R^2	F5 (result)
Zero order	R^2	0.990
First order	R^2	0.923
Korsmeyerpappas	R^2	0.989
Higuchi	R^2	0.87
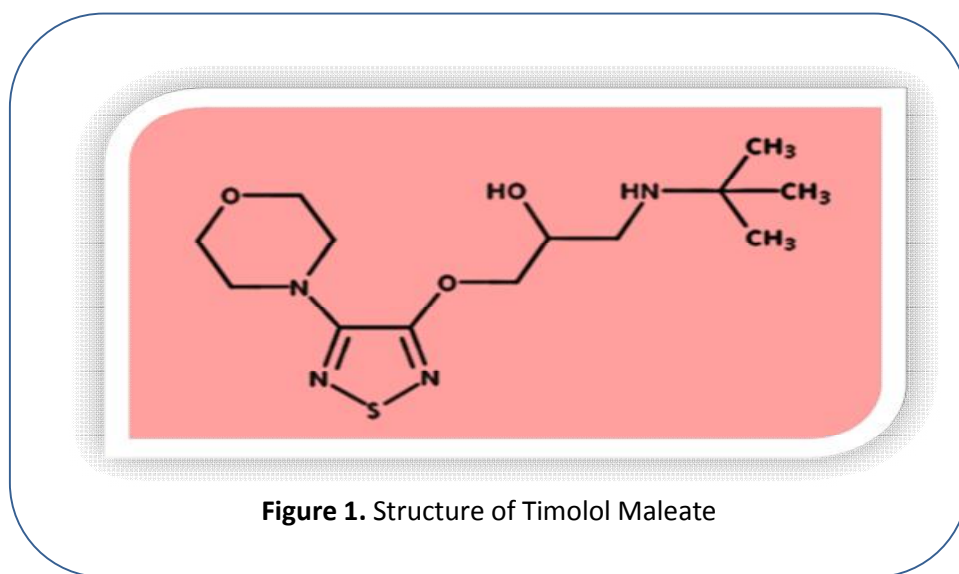
Figure 1. Structure of Timolol Maleate
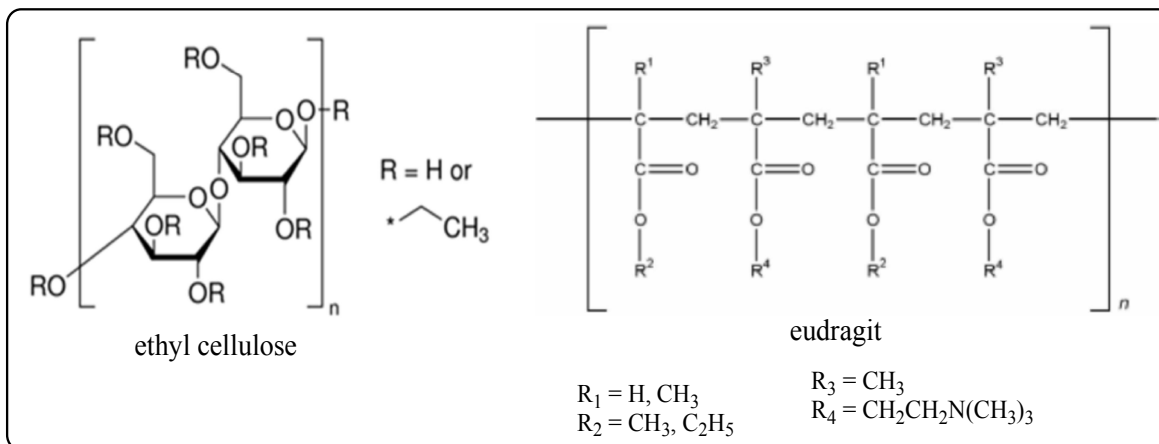
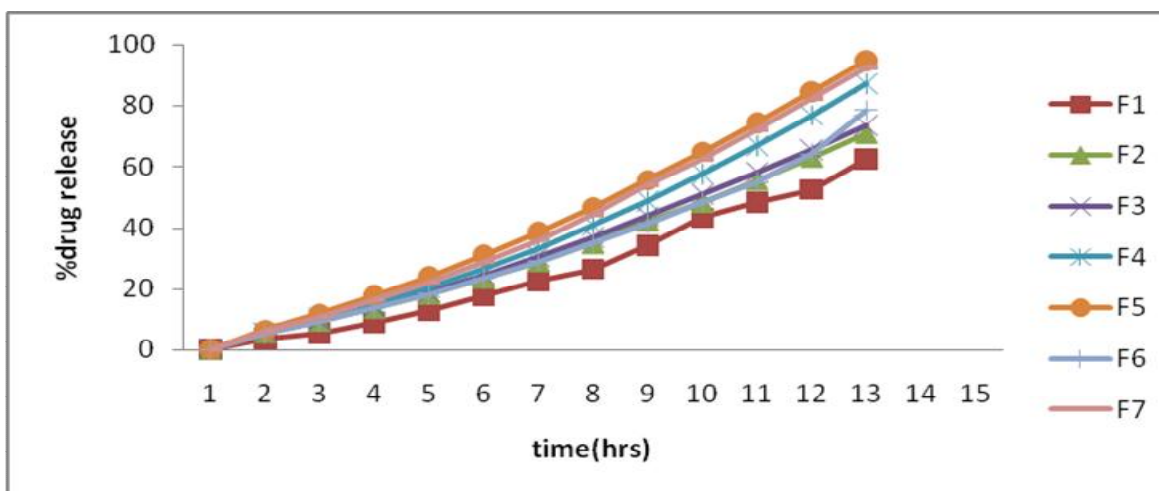**Figure 2.** Structure of ethyl cellulose and eudragit polymer

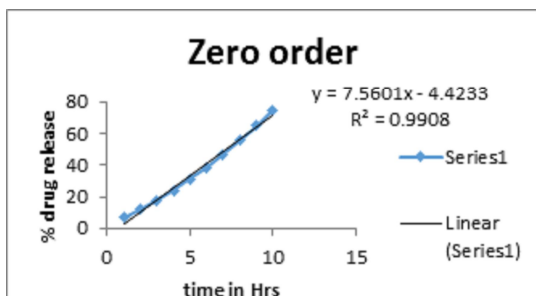**Figure 3.** *In-Vitro* % drug release (comparison between F1 to F7)

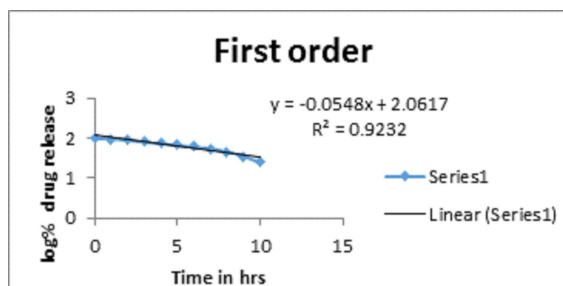**Figure 4:** Zero order kinetic of F5 formulation

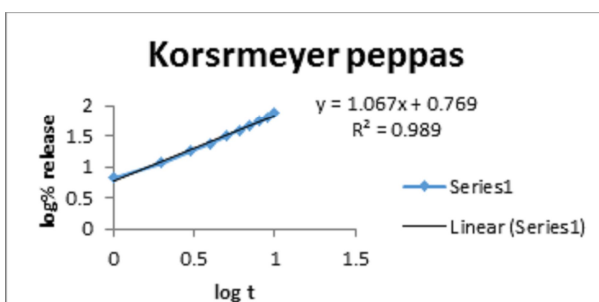**Figure 5:** First order kinetic of F5 formulation
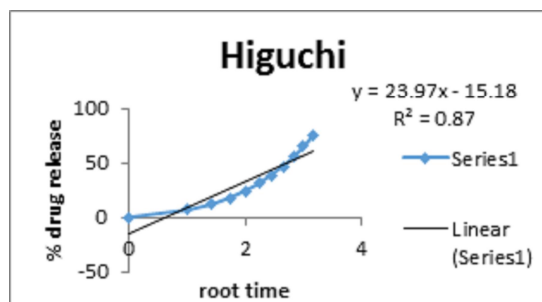

Figure 6: Korsmeyer pappas Kinetic of F5 formulation

Figure 7: Higuchi kinetics of F5 formulation