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RELEASE KINETIC STUDY OF NOVEL TRANSDERMAL PATCH OF ANALGESIC DRUG CONTAINING PERMEATION ENHANCER

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ABSTRACT

Transdermal drug delivery system (TDDS) represents one of the most rapidly advancing areas of novel drug delivery. TDDS are designed for controlled release of drug through the skin into systemic circulation maintaining consistent efficacy and reducing dose of the drug and its related side effects. Present study was conducted to prepare transdermal patch of Mefenemic acid with permeation enhancer to reduce extra side effects and to provide sustain drug delivery. The optimized formulations were examined by various kinetic models such as Zero-order, First-order, Higuchi equation, Korsemeyer–Pappas equation and Hixson–Crowell equation. The study showed synergistic effects of PEG 400 and Eucalyptus oil with sustained drug delivery.

Key words: *Release Kinetics, Permeation enhancer, NSAID*

I. INTRODUCTION

Transdermal drug delivery system (TDDS) represents one of the most rapidly advancing areas of novel drug delivery. Statistics reveal a market of $ 12.7 billion in the year 2005 which is expected to increase by $ 21.5 billion in the year 2010 and $ 31.5 billion in the year 2015.These are designed for controlled release of drug through the skin into systemic circulation maintaining consistent efficacy and reducing dose of the drug and its related side effects. (Samad*et al*, 2009).One challenge in designing TDD is to overcome the natural transport barrier of the skin. Chemicals offer tremendous potential in overcoming the skin barrier to enhance transport of drug molecules. Individual chemicals are however limited in their efficacy in disrupting the skin barrier at low concentrations and usually cause skin irritation at high concentrations.(Mitragotri*et al*, 2009).

Conventional drugs and dosage forms like tablet, capsule, injection, liquids like- solution and syrup are common which cure disease state. This therapy required fixed dosage form at a regular intervals of time, after the administration of one dose, the concentration raise to high initially shown in figure 1 with the passage of time the concentration diminishes owing to natural metabolic processes and a second dose must be administered to prevent the concentration from dropping below the minimum effective levels. Due to high dose greater chances of adverse side effects and the therapy is insufficient and costly since large amount of dose lost by metabolic processes in our body, and sufficient amount of drug not reach to target organ.TDD is a "Self-contained, discrete dosage forms which when applied to intact skin, deliver the drugs through the skin, at a controlled rate to the systemic circulation takes place" (Jain, 2004). To overcome the skin barrier chemical and physical enhancers are used to facilitate drug transport across the skin. (Swarbrick and Boylan, 2007).

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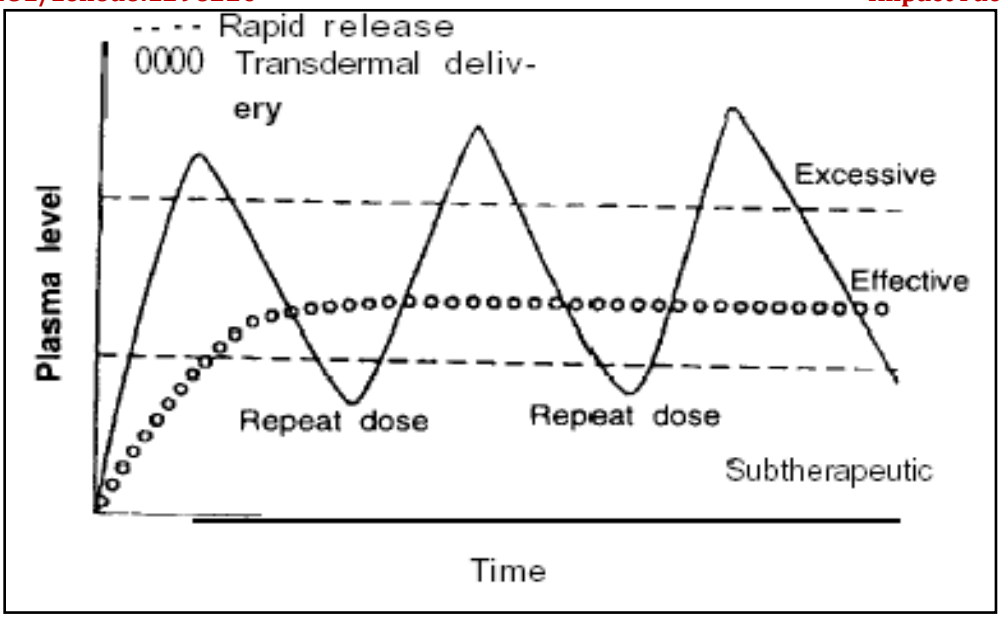

Figure 1 Release profile of TDDS (adopted from Punchgulla R, 2005)

Advantages of Transdermal Drug Delivery System (Chien, 1992)

- This system by pass first passmetabolim so that reduce the formation of metabolite that cause side effects.
- This system provides near zero order drug release at prolonged period of time.
- It is safe and convenient.
- This system provides predictable and extended duration of activity.
- It improves physiological and pharmacological response.
- It reduces inter and intra patient variation.
- Avoiding the fluctuation in drug level.
- Needle free drug delivery so that improve patient compliance.
- Predictable and extended duration of activity.
- Drug which have to be administered for a long period of time or which cause adverse effects to non target tissues can also be formulated for transdermal delivery (Jain, 2004).

Anatomy of Skin

The skin is the main site for TDD. An average adult body covers a surface area of approximately 2 m^2 and received one third of the blood circulating through the body. It is elastic, rugged and under normal physiological conditions, self-regenerating. Skin thickness of only few millimeters (2.97 mm), it separates underlying blood circulation network and viable organs from the outside environment. It serves as a barrier against physical and chemical attacks and shield the body from invasion by microorganism (Chien, 1992).Microscopically, the skin is a multilayered organ composed of many layers but generally described by three tissue layers- the epidermis, the dermis, and the subcutaneous fat tissue as shown in figure 1.2. The stratum corneum is the outermost layer of the epidermis and has a thickness of 10–15 mm. It is the principal barrier for the transport of most solutes (except for very lipophilic compounds) across the skin.The epidermis outer most layer of the skin is composed of stratified squamous epithelial cells. The epithelial cells are held together mainly by highly convoluted interlocking bridges, which are responsible for the unique integrity of the skin. Microscopic sections of the epidermis show two main parts. The stratum corneumand stratumgerminativum. The stratum corneum forms the outermost layer of the epidermis and consists of many layers of compacted, flattened, dehydrated, keratinized cells in stratified layers. Dermis is made up of a network of robust collagen fibers of fairly uniform thickness with regularly spaced cross-striations.Beneath the dermis fat containing subcutaneous tissues are present (Chien, 1992).There are three routes of penetration as shown in figure 2,which are sweat pore, stratum corneum and hair follicle.The stratum corneum is responsible for the

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barrier function of the skin. For the permeation of skin so many permeation enhancer used which generated pores and carry the drug molecule to the systemic circulation.

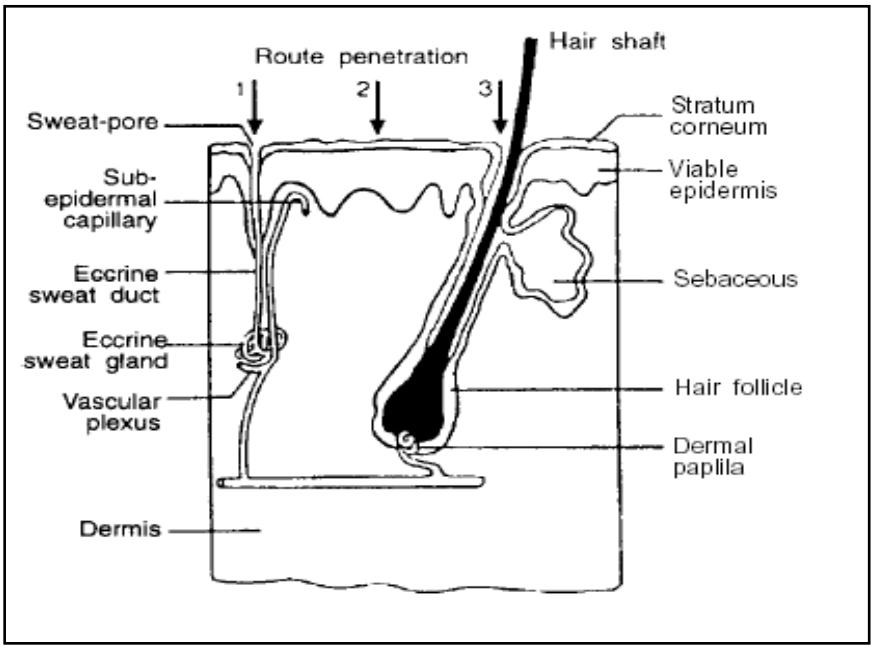

Figure 2 Microscopy of skin (adopted from Punchgulla R, 2005)

II. MATERIALS AND METHOD

Method of Preparation of Transdermal patch of NSAID

Transdermal patch of drug was prepared by solvent evaporation method.Firstly, solution A was prepared by adding ethyl cellulose and drug in ethanol.Solution B was prepared by adding weighed quantity of Poly Vinyl Alcohol and water and melted at temperature 60-80°C.After melting solution A was poured into B.Different concentration of permeation enhancer was added, after cooling, rapid shaking perform to homogeneous mixing of all components.Poured into moulds and kept at room temperature for drying.Placed inverted funnel was placed on it to prevent rapid evaporation of solvent so that the patch remains wrinkle free and smooth.After drying films were stretch from mould and wrapped in suitable aluminum foil for further study.This is the polymeric film consist of polymer, drug, solvents and permeation enhancer in a define concentration. Liner and backing membrane were fixed after drying. For storage of film, film were wrapped in aluminum foil and kept in refrigerator 2-8 ^{o}C.

Table 1 Formula for transdermal patch with permeation enhancer

FC*	(EC :PVA)	PEG -400 (mg)	EU (mg)	PG(mg)	T-80 (mg)	PEG-400 + PG (mg)	EU + PEG-400 (mg)	PG + EU (mg)	PEG-400 + T-80 (mg)	Blank (mg)	Drug (mg)	Ethanol (mL)	Water (mL)
MF1	1:4	5	-	-	-	-	-	-	-	-	20	5	q.s
MF2	1:4	-	5	-	-	-	-	-	-	-	20	5	q.s
MF3	1:4	-	-	5	-	-	-	-	-	-	20	5	q.s
MF4	1:4	-	-	-	5	-	-	-	-	-	20	5	q.s
MF5	1:4	-	-	-	-	1:1	-	-	-	-	20	5	q.s

MF6	1:4	-	-	-	-	-	1:1	-	-	-	20	5	q.s
MF7	1:4	-	-	-	-	-	-	1:1	-	-	20	5	q.s
MF8	1:4	-	-	-	-	-	-	-	1:1	-	20	5	q.s
MF9	1:4	-	-	-	-	-	-	-	-	-	20	5	q.s

Where, EC= ethyl cellulose, FC*= Formulation code, T-80= Tween 80,EU= Eucalyptus oil, PG= propylene glycol, q.s. = quantity sufficient

The factorial design 3^2 was best suited where three level (low, medium, high) of polymer was fixed and 2 factors like moisture content and percent cumulative drug release was fixed. The ratio 1:4 (EC:PVA) was found to be optimal for moisture content and percentage cumulative drug release. The transdermal preparation solvent evaporation method was most prominent method to obtain clear, smooth and transdermal patch with superior thickness.

Release Mechanism of Optimized Formulation

In order to examine the release mechanism of drug sample from the prepared transdermal patch of the optimized formulation (MF6), the results of the percent cumulative drug release was examined in accordance to the kinetic models such as Zero-order, First-order, Higuchi equation, Korsemeyer–Pappas equation and Hixson–Crowell equation. The regression coefficient R^2 value nearer to 1 indicated the model fitting of the release mechanism.

Zero-Order Model (Chien, 1992)

In many of the modified release dosage forms particularly controlled or sustained release dosage forms (those dosage forms that release the drug in planned, predictable and slower than normal manner) is Zero-order kinetics.

$$\mathbf{Q = K_o t}$$

Where-Q is the amount of drug release at time t and $K_o$is the release rate constant. The plot of cumulative percentage drug released versus time is linear.

First-order Model

Most conventional dosage forms exhibit this dissolution mechanism. Some modified release preparations, particularly prolonged release formulations, adhere to this type of dissolution pattern.

$$\mathbf{Log\ Q = K_1 t}$$

Where- Q is the percent of drug release at time t and K_1 is the release rate constant. It assumes that the drug molecules diffuse out through a gel like layer formed around the drug during the dissolution process. A plot of log cumulative percentage drug remained versus time is linear.

Higuchi Model (Chien, 1992)

A large number of modified release dosage forms contain some sort of matrix system. In such instances, the drug dissolves from this matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled) and thus the following relationship applies:

$$\mathbf{Q = K_2 t^{1/2}}$$

Where-Q is the percentage of drug release at time t and K_2 is the diffusion rate constant. In Higuchi model, a plot of cumulative percentage drug released versus square root of time is linear.

Hixon-Crowell Model (Chien, 1992)

Some specialized dosage forms contain many drug particles of the same size and shape of their agglomerates that dissolve evenly. In such instances the cube-root law can express the dissolution process. If the dissolution pattern of the drug is dictated by the actual dissolution of drug molecules, then the following relationship applies:

$$\mathbf{(100-Q)^{1/3} = 100^{1/3} - K_3 t}$$

Where-Q is the amount of drug release at time t and k is Hixon Crowell Constant. In this model the cube root of cumulative percent drug retained versus time is linear.

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Korsmeyer and Pappas Model (Chien, 1992)

If n=1, the release is zero-order, and if n=0.5, the release is best explained by Fickinian diffusion, and if 0.5 < n < 1 then the release is through anomalous diffusion or case II diffusion.

$$Q = Kt^n$$

Where,Q is the fraction of drug release at time t and K is the diffusion rate constant and n is diffusional exponent. In this model, a plot of log cumulative percent drug released versus log time is linear.

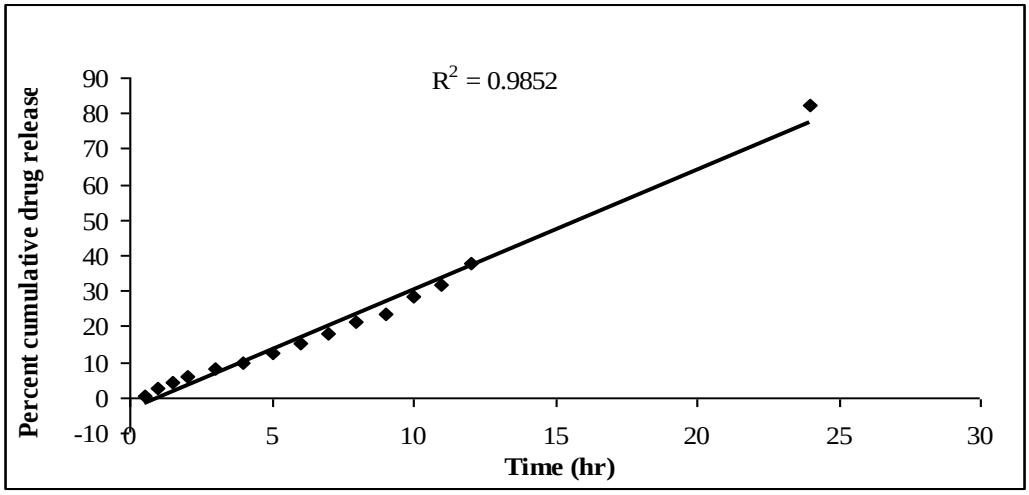

Figure 3: Zero-order drug release of optimized formulation

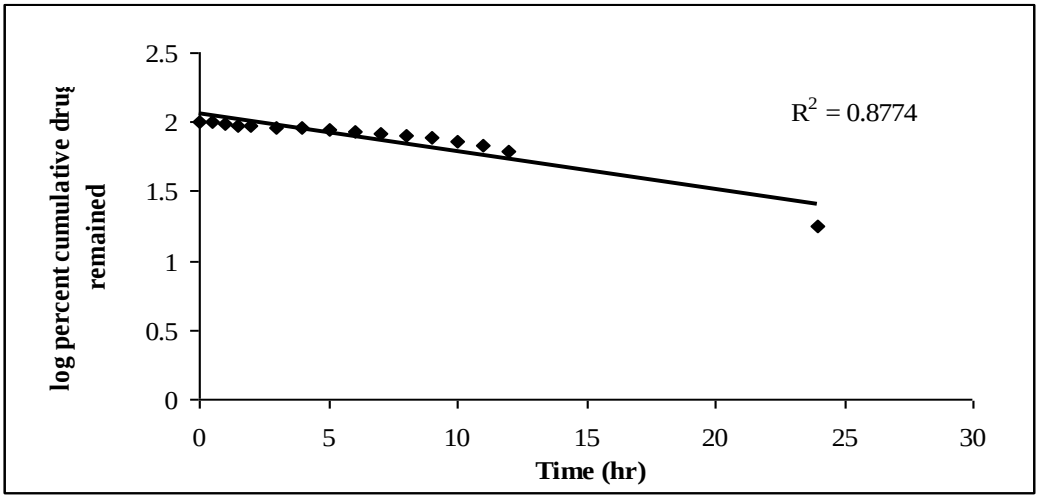

Figure 4: First order drug release model of optimized formulation

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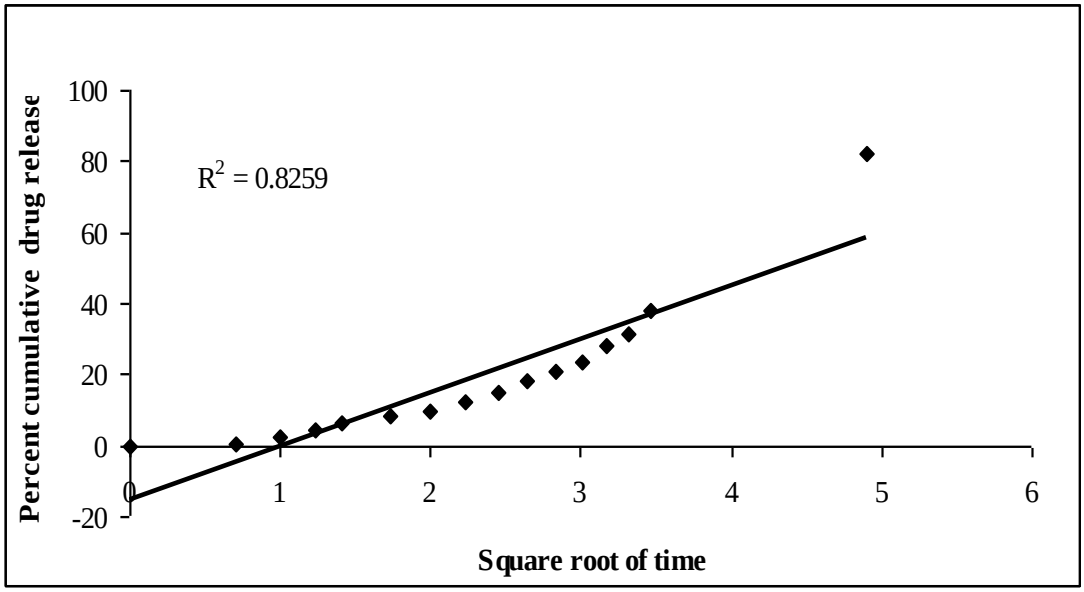

Figure 5: Higuchi model of optimized formulation

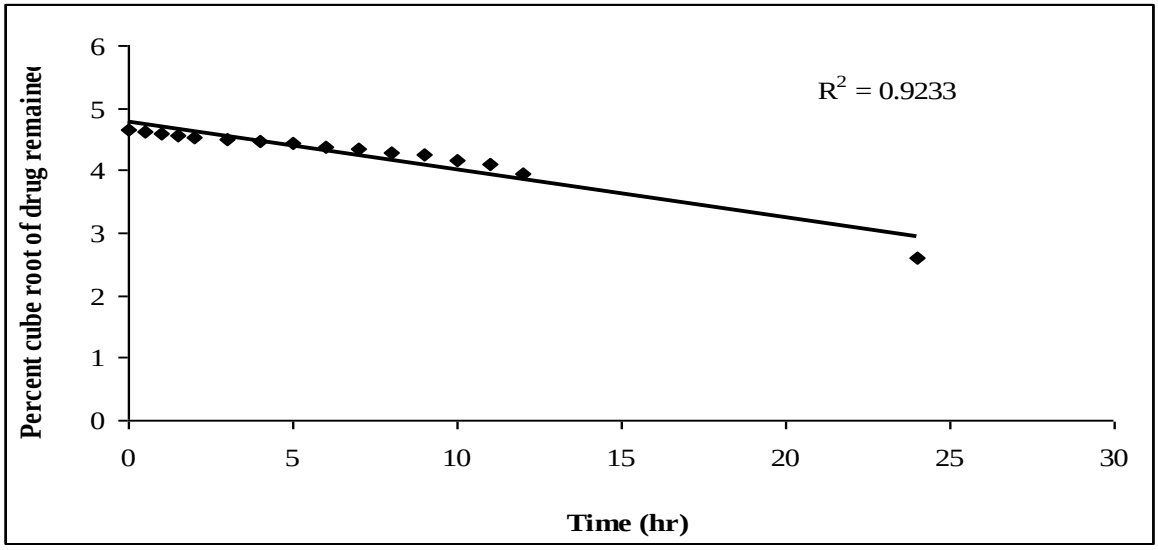

Figure 6 : Hixon-Crowell model of optimized formulation

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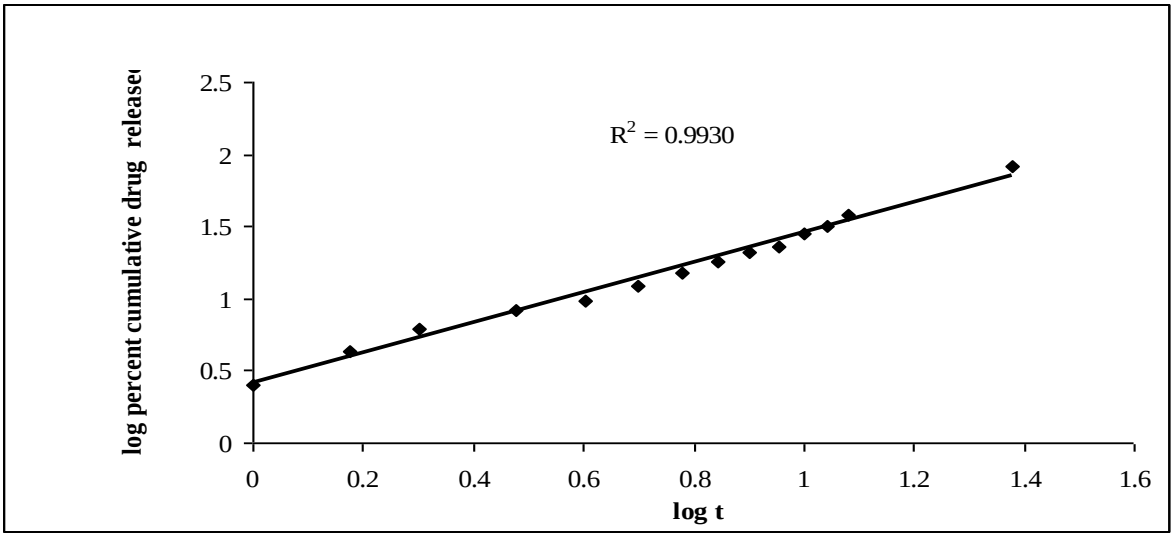

Figure 7: Korsmeyer and Peppas model of optimized formulation

Table2: Models and their R^2 values of optimized formulation

S. No.	Model	R^2
1	Zero order	0.986
2	First order	0.877
3	Higuchi	0.826
4	Hixen-Crowell	0.923
5	Korsmeyer and Peppas	0.993

III. RESULT AND DISCUSSION

The best formulation was found to be MF6 in which concentration of (PEG400+eucalyptus oil) in optimum quantity were mixed and show good result as compared to all formulations. When used in combination it gives synergistic action with (PEG 400+ EU). The results of the percent cumulative drug release was examined in accordance to the kinetic models such as Zero-order, First-order, Higuchi equation, Korsemeyer–Pappas equation and Hixson–Crowell equation.In Zero order, graph was plotted between cumulative percentage drug released versus time was found be linear and the value of regression coefficient was R^2= 0.985.In First order, graph was plotted between log percent cumulative drug remained versus time was found be linear and the value of regression coefficient was R^2= 0.877. In Higuchi model graph was plotted between cumulative percentage drug released versus square root of time was found be linear and the value of regression coefficient was R^2= 0.825.In Hixon-Crowell model, graph was plotted between cube root of percent drug remained versus time was found be linear and the value of regression coefficient was R^2= 0.923.

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IV. CONCLUSION

In Korsmeyer and Pappas model, graph was plotted between log percent cumulative drug released versus log time was found be linear and the value of regression coefficient was R^2= 0.993. The optimized formulation follows the Korsmeyer and Pappas model

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