RESEARCH ARTICLE

DEVELOPMENT AND CHARACTERIZATION OF TRANSDERMAL PATCHES OF METOPROLOL TARTRATE

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Abstract: Transdermal drug delivery systems are polymeric patches containing dissolved or dispersed drugs that deliver therapeutic agents at a constant rate to the human body. Matrix type transdermal patches containing Metoprolol tartrate were prepared by solvent casting method employing a mercury substrate by using the combinations of EC-PVP and Eudragit RL100-PVP in different proportions. The transdermal patches were evaluated for their physicochemical properties like thickness, weight variation, flatness, tensile strength, hardness, folding endurance, drug content, swellability, surface pH, water vapour transmission, in vitro permeation and skin irritation studies. FTIR, DSC and UV studies indicated no interaction between drug and polymers. The permeability of Metoprolol tartrate was increased with increase in PVP content. The burst effect due to the incorporation of PVP was because of the rapid dissolution of the surface hydrophilic drug which results in the formation of pores and thus leads to the decrease of mean diffusional path length of the drug molecules to permeate into dissolution medium and higher permeation rates. The in vitro drug permeation followed higuchi kinetics as its coefficient of correlation values predominates over zero order and first order kinetics. Also the diffusion coefficient of release profiles (slope) had a value of nearly 0.5, which indicated fickian transport diffusion. The patches were found to be free of any skin irritation. Based on the above observations, it can be reasonably concluded that Eudragit RL100-PVP polymers are better suited than EC-PVP polymers for the development of transdermal patches of Metoprolol tartrate.

Keywords: Transdermal patches, metoprolol tartrate, *in vitro* permeation, ethylcellulose, polyvinylpyrrolidone, eudragit.

INTRODUCTION

The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs [1]. It offers many advantages over conventional administration such as enhanced efficacy, increased safety, greater convenience, improved patient compliance and absence of hepatic first pass metabolism [2]. It excludes the variables that affect drug absorption from the gastrointestinal tract such as pH, enzymatic activity and drug food interactions [3]. This approach of drug delivery is more pertinent in case of chronic disorders, such as hypertension, which require long term dosing to maintain therapeutic drug concentration [4].

Metoprolol tartrate is a cardio selective beta blocker. It is used in the management of hypertension, angina pectoris, cardiac arrhythmias and myocardial infraction [5]. It is almost completely absorbed after oral administration, although the systemic bioavailability varies widely owing to extensive presystemic metabolism. Peak plasma concentrations are achieved after 2-3 hours. The plasma half life is about four hours, which makes frequent dosing necessary to maintain the therapeutic blood levels of the drug for a long term treatment [6]. The transdermal route of administration is capable of avoiding the hepatic first pass effect, thus achieving higher systemic bioavailability of drugs. Matrix type transdermal patches were prepared by solvent casting technique employing a mercury substrate by using the combinations of ethylcellulose-polyvinylpyrrolidone and eudragit RL100-polyvinylpyrrolidone. The present work is aimed at developing a matrix dispersion type transdermal drug delivery of Metoprolol tartrate to ensure satisfactory drug release with the use of optimum polymer and thereby to avoid first pass metabolism and prolong duration of action.

MATERIALS AND METHODS

Materials

Metoprolol tartrate was obtained as a gift sample from Torrent Pharmaceuticals, Gandhinagar. Eudragit RL100 was obtained as a gift sample from Sun Pharma, Baroda. Ethyl cellulose, PVP K-30 (CDH (P) Ltd., New Delhi), Dibutyl Phthalate (S. D. Fine Chem. Ltd., Mumbai) were used. All other chemicals used were of analytical grade.

Methods

Drug polymer interaction studies

This was carried out to check the compatibility between drug and various polymers. It is therefore necessary to confirm that drug is not interacting with polymers under experimental conditions and shelf life.

UV analysis

The aqueous solutions of the pure drug and the patches containing Metoprolol tartrate were filtered through whatmann filter paper and scanned for UV absorption between 200 and 400nm.

FTIR analysis

Infra red spectroscopy was carried out on pure drug and physical mixtures of drug and polymer between 400 cm^{-1}- 4000cm^{-1}.

DSC Analysis

The DSC of the pure drug, polymers and the physical mixture of drug: polymer at 1:1 ratio was carried out.

Formulation of transdermal patches

Matrix type transdermal patches containing Metoprolol tartrate were prepared by solvent casting technique employing a mercury substrate [7]. A 10% w/v of polymer solution was prepared using chloroform as solvent. Dibutylphthalate was incorporated at a concentration of 40 % w/w of dry weight of polymers as plasticizer. Polymeric solutions were mixed thoroughly with the help of magnetic stirrer for 20 minutes and then were poured with in a glass bangle placed on the surface of mercury in a petridish. The rate of evaporation of the solvent was controlled by inverting the cut funnel over the petridish. The film formation was noted by observing the mercury surface after complete evaporation of the solvent. After drying at room temperature for 24 hours, membranes were taken out, cut into 3.14 cm^2, packed in aluminium foil and stored in dessicator until further use. The composition of transdermal patches is shown in Table 1.

Characterization of transdermal patches

The prepared transdermal patches were evaluated for uniformity of thickness, weight variation, percent flatness, tensile strength, hardness, folding endurance, drug content uniformity, swellability, surface pH, water vapour transmission, in vitro permeation and skin irritation studies.

Thickness

The thickness of transdermal patches was measured at three different places using a micrometer and the average values were calculated [8].

Weight variation

Weight variation was determined by weighing three patches individually, from each batch and the average weight was calculated [9].

Table 1. Composition of transdermal patches

Formulations	Polymers (10%w/v)	Polymer Ratio	Casting Solvent
A-1	Ethylcellulose + PVP	10 : 0	Chloroform
A-2	Ethylcellulose + PVP	9 : 1	Chloroform
A-3	Ethylcellulose + PVP	8 : 2	Chloroform
A-4	Ethylcellulose + PVP	6 : 4	Chloroform
A-5	Ethylcellulose + PVP	5 : 5	Chloroform
B-1	Eudragit RL100 + PVP	10 : 0	Chloroform
B-2	Eudragit RL100 + PVP	9 : 1	Chloroform
B-3	Eudragit RL100 + PVP	8 : 2	Chloroform
B-4	Eudragit RL100 + PVP	6 : 4	Chloroform
B-5	Eudragit RL100 + PVP	5 : 5	Chloroform

Plasticizer DBP (40 %) w/w of the polymer

Flatness

The constriction of patches cut out from a drug loaded matrix patch is an indicator of its flatness. Longitudinal strips were cut out from the prepared medicated patch, the lengths of each strip were measured and then variation in the lengths due to the non-uniformity in flatness was measured. Flatness was calculated by measuring construction of strips and a zero percent constriction is equal to a hundred percent flatness.

Constriction (%) = l_1-l_2/ l_2 x 100

Where l_1 = initial length of each strip, l_2 = final length of each strip [10]

Tensile strength

Mechanical properties of the polymeric patches were conveniently determined by measuring their tensile strength [11]. The tensile strength of the patches was determined by using a tensile strength instrument as described by Agarwal GP, et al. Average reading of three patches was taken as the tensile strength. The transdermal patch was fixed to the assembly, the weights required to break the patch was noted, and simultaneously elongation was measured with the help of a pointer mounted on the assembly and calculated the tensile strength of the patch using the following formula

T. S. = break force/ a.b (1+ΔL/L)

Where a, b and L are width, thickness and length of the patch respectively.

ΔL is the elongation of patch at break point.

Break force = Weight required to break the patch (Kg) [12]

Hardness

Hardness test was performed on three different patches individually from each batch by fabricated hardness instrument and the average was calculated. Hardness apparatus consists of a wooden stand of 8 cm in height, and a top area of 8 x 8 cm. A hole of 0.2 cm diameter was made in the centre of the wooden top. A small plastic pan was fixed horizontally on to one end of a 2 mm thick smooth iron rod, whose other end had been reduced to sharp point. This rod, having the pan on its upper end, was inserted into the hole of the wooden top and its lower sharp end was placed on a metal plate.

An electric circuit was made through a 3-volt battery in such a way that the bulb lighted up only when the circuit was completed through the contact of the metal plate and the sharp end of the rod. The sample patch was placed between the metal plate and the sharp end of the iron rod and weights were gradually added on to the pan and the total weight required to penetrate the patch, which was indicated by the lighted bulb, was noted [12].

Folding Endurance

The folding endurance was measured manually for the prepared patches. It is expressed as number of times the patch is folded at the same place either to break the patch or to develop visible cracks. This is important to check the ability of sample to withstand folding. This also gives an indication of brittleness [13].

This was determined by repeatedly folding one patch at the same place till it break. The number of times the patch could be folded at the same place without breaking/cracking gave the value of folding endurance [14].

Drug Content Uniformity

In order to ascertain the uniform distribution of the drug in the patches, the content uniformity test was carried out utilizing the pharmaceutical standard by means of a UV/Visible spectrophotometer. The transdermal patch of specified area (3.14 cm^2) was dissolved in 100 ml pH 7.4 phosphate buffer. This was then shaken in a mechanical shaker for 2 hour to get a homogeneous solution and filtered. A blank was performed using a drug free patch treated similarly. The drug content in each formulation was determined by measuring the absorbance at 223 nm after suitable dilution using a UV/visible spectrophotometer.

Swellability

The patches of 3.14 cm^2 was weighed and put in a petridish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed.

The degree of swelling (% S) was calculated using the formula

S (%) = $W_t - W_o/W_o$ x 100

Where S is percent swelling

W_t is the weight of patch at time t and W_o is the weight of patch at time zero [15].

Surface pH

Surface pH of the patches was determined by the method described by Bottenberg et al. The patches were allowed to swell by keeping them in contact with 0.5 ml of double distilled water for 1 hour in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 minute [16].

Water vapour transmission

The water vapour transmission is defined as the quantity of moisture transmitted through unit area of a patch in unit time. The water vapour transmission data through transdermal patches are important in knowing the permeation characteristics [17]. Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried to constant weight in an oven. About 1 gm of fused calcium chloride as a dessicant was taken in the vials and the polymeric patches were fixed over the brim with the help of an adhesive tape. These preweighed vials were stored in a humidity chamber at an RH of 80% with the temperature set to 30ºC for a period of 24 hours. The weight gain was determined every hour up to a period of 24 hours [18].

The water vapour transmission was calculated using the equation

Rate = WL/S

Where W is gm of water permeated / 24 hr.

L is thickness of the patch

S is exposed surface area of the patch[19].

***In vitro* permeation study**

The *in vitro* skin permeation from the prepared polymeric patches across the rat skin was studied using a modified Keshary Chien diffusion cell [20]. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. It was placed on a magnetic stirrer with a teflon bead placed inside for uniform distribution. The patches to be studied were placed in between the donor and the receptor compartment in such a way that the drug releasing surface faced toward the receptor compartment.

The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal [21].

The samples were analyzed spectrophotometrically at 223 nm taking phosphate buffer pH 7.4 as blank. The cumulative percent drug permeated at various time intervals were calculated and plotted against time.

Skin Irritation Study

The patches were tested for their potential to cause skin irritation /sensitization in rats. The rats were shaved carefully avoiding peripheral damage and the patch was applied onto the nude skin using an adhesive. The rats were divided into five groups. On the previous day of the experiment, the hair on the back side area of rat was removed. The

animals of groupI were served as normal without any treatment. One group of animals (Group II, control) was applied with marketed adhesive tape (official adhesive tape in USP). Transdermal systems (blank and drug loaded) were applied onto nude skin of animals of III and IV groups. A 0.8 % v/v aqueous solution of formalin was applied as a standard irritant (Group V). The animals were applied with new patch/formalin solution each day upto 7 days and finally the application sites were graded according to a scoring scale always by the same investigator [22] (Table 2). Ethical clearance for the handling of experimental animals was obtained from the institutional animal Ethical committee (IAEC) formed for this purpose.

Table 2. Draize scoring method [23]

S. No.	Skin Reaction		Score assigned
	(A) Erythema and Eschar formation	(B) Edema formation	
1.	No erythema	No edema	0
2.	Very slight erythema	Very slight edema	1
3.	Well defined erythema	Slight edema	2
4.	Moderate to severe erythema	Moderate edema	3
5.	Severe erythema	Severe edema	4

RESULTS AND DISCUSSION

Matrix type transdermal patches of metoprolol tartrate were prepared using ethyl cellulose, eudragit RL100 and PVP as film formers by solvent casting method. Incorporation of dibutyl phthalate at a concentration of 40% w/w of dry polymers yielded smooth and flexible patches. Decreasing or increasing the concentration of dibutyl phthalate from the above mentioned value resulted in the formation of brittle or soft patches respectively. There was no interaction between the drug and polymers. The physicochemical evaluation study reveals that all formulations measured weight and thickness with low standard deviation values. The results of flatness study showed that none of the formulations had the difference in the strip lengths before and after longitudinal cut, indicating 100% flatness, and thus they could maintain a smooth surface when applied onto the skin.

The folding endurance measures the ability of patch to withstand rupture. It was found to be satisfactory. The result indicated that the patches would not break and would maintain their integrity with general skin folding when used. The folding endurance of Eudragit patches is higher than patches containing Ethyl cellulose. The surface pH of all the formulations was in the range of 5.1-5.8, the pH range of skin and hence no skin irritation was expected. The tensile strength of the patches was found to vary with the nature of polymer and plasticizer. Polymer combination EC: PVP possessed high tensile strength than Eudragit RL100: PVP patches. Patches require certain amount of hardness to withstand the mechanical shocks in handling, packaging and at the time of application. The hardness of the patch varied from 228 gm. to 261 gm. Homogeneous uniform drug distribution is one of the important characteristics of a transdermal patch that ensures the uniform reproducible sustained release of the drug from the patch. Estimation of drug content indicated that the drug is uniformly distributed throughout the patches, evidenced by the low values of the SD.

The study of the hydration of polymers used in sustained release applications has been an area of interest because it is believed that it affects drug release from controlled release matrix. The consequence of water uptake could be the formation of empty spaces within the patch that could make its structure less resistant to mechanical stresses. The ERL 100: PVP patches showed more pronounced swelling as compared to EC: PVP patches. It varied between 16.97 to 38.59 %. The swellability varied with nature and composition of patches. Hydrophilic polymer showed considerable swelling, as it increased the surface wettability and consequently water penetration with in the matrix.

Eudragit RL100 patch showed good water vapour permeation than that of Ethyl cellulose patches. The enhancement of water vapour permeation with increase of PVP is due to the irregular arrangement of molecules in the amorphous state, which usually causes the molecules to be spaced further apart than in a crystal. Hence, the specific volume is increased and the density is decreased compared to that of crystal, which leads to the absorption of vapour into their interstices. All the formulations were permeable to water vapour.

Table 3. Characterization of transdermal patches

Code	Wt. variation (mg)	Thickness (mm)	Tensile strength (kg/ mm^2)	Folding Endurance	Surface pH	Hardness	Swellability (%)	Water vapour transmission (gmcm/cm^2.24h)	Flatness (%)	Drug Content (%)
A-1	160.2 ± 1.76	0.303 ± 0.0024	0.473 ± 0.0036	272 ± 4.34	5.5 ± 0.14	261± 2.78	16.97± 0.43	4.81*10^{-4}	100	98.87
A-2	153.1 ± 1.25	0.318 ± 0.0021	0.463 ± 0.0045	265 ± 3.11	5.6 ± 0.08	258 ± 4.21	18.32 ± 0.39	4.93*10^{-4}	100	97.92
A-3	176.3 ± 2.34	0.352 ± 0.0023	0.449 ± 0.0057	259 ± 5.23	5.3 ± 0.11	260 ± 3.54	19.18 ± 0.58	5.19*10^{-4}	100	97.11
A-4	157.0 ± 1.84	0.334 ± 0.0031	0.435 ± 0.0069	248 ± 3.88	5.8 ± 0.12	250 ± 3.09	22.42 ± 0.57	5.56*10^{-4}	100	98.92
A-5	168.9 ± 1.92	0.331± 0.0042	0.426 ± 0.0071	246 ± 4.61	5.7 ± 0.09	254 ± 4.16	23.43 ± 0.49	5.93*10^{-4}	100	98.40
B-1	165.3 ± 2.41	0.236 ± 0.0027	0.421± 0.0028	315 ± 4.12	5.3 ± 0.13	232 ± 3.66	28.63 ± 0.54	5.99*10^{-4}	100	96.87
B-2	168.7 ± 2.13	0.242 ± 0.0036	0.409 ± 0.0035	309 ± 3.86	5.2 ± 0.07	239 ± 4.22	30.13 ± 0.55	6.25*10^{-4}	100	97.32
B-3	158.4 ± 1.35	0.239 ± 0.0032	0.394 ± 0.0046	298 ± 5.02	5.4 ± 0.11	228 ± 5.48	32.87 ± 0.46	6.36*10^{-4}	100	98.67
B-4	173.9 ± 2.54	0.241± 0.0041	0.386 ± 0.0055	294 ± 5.11	5.1 ± 0.05	238 ± 4.43	35.48 ± 0.45	6.53*10^{-4}	100	98.77
B-5	166.2 ± 1.82	0.248 ± 0.0058	0.377 ± 0.0072	289 ± 4.51	5.2 ± 0.14	234 ± 4.03	38.59 ± 0.61	6.88*10^{-4}	100	98.55

Table 4. Various kinetic models for tdds of metoprolol tartrate

Code	Zero order			First order			Higuchi Model			Korsemeyer Model		
	Intercept	R^2	K (mg.hr^{-1})	Intercept	R^2	K (hr^{-1})	Intercept	R^2	K (mg hr$^{-1/2}$)	Intercept	R^2	n
A-1	7.1866	0.8450	1.1023	1.9689	0.8888	0.01335	0.6086	0.9951	6.0892	2.3207	0.9928	0.5087
A-2	7.6471	0.8419	1.1610	1.9669	0.8886	0.01427	0.7248	0.9953	6.4139	2.3244	0.9932	0.5072
A-3	7.8254	0.8636	1.2568	1.9666	0.9121	0.01566	0.3478	0.9974	6.9202	2.3111	0.9954	0.5059
A-4	8.3346	0.8705	1.3646	1.9648	0.9225	0.01750	0.2239	0.9972	7.5047	2.3066	0.9953	0.5056
A-5	8.7789	0.8874	1.5120	1.9639	0.9412	0.02003	0.1873	0.9954	8.2904	2.2966	0.9951	0.5033
B-1	8.7484	0.9123	1.6737	1.9660	0.9615	0.02303	1.1468	0.9801	9.1293	2.2716	0.9755	0.5057
B-2	9.0234	0.9169	1.7667	1.9656	0.9670	0.02487	1.4996	0.9829	9.6605	2.2668	0.9821	0.5086
B-3	9.5584	0.9188	1.8891	1.9646	0.9708	0.02740	1.6739	0.9802	10.318	2.2669	0.9788	0.5060
B-4	10.965	0.9074	2.0578	1.9601	0.9694	0.03132	1.1919	0.9808	11.228	2.2722	0.9730	0.5088
B-5	11.717	0.9071	2.1874	1.9589	0.9719	0.03477	1.1639	0.9801	11.921	2.2749	0.9769	0.5052

Release of the drug from transdermal patches is controlled by the chemical properties of the drug and delivery form, as well as physiological and physicochemical properties of the biological membrane. The process of drug release in most controlled release devices is governed by diffusion and the polymer matrix has strong influence on the diffusivity as the motion of a small molecule is restricted by the three-dimensional network of polymer chains. The cumulative percent drug permeation was higher in case of Eudragit containing polymer matrix. The cumulative percent of drug permeated from formulations of A series was 29.825, 31.403, 34.145, 37.124 and 41.225 respectively from A-1, A-2, A-3, A-4 and A-5 and from B series was 45.721, 48.021, 51.345, 56.314 and 60.052 respectively from B-1, B-2, B-

3, B-4 and B-5. The reason for high release from Eudragit RL100 polymer could be explained by the hydrophilic nature of this polymer and the existence of the quaternary ammonium groups which could affect the release from the patches because of the hydration and swelling of the patches. Eudragit (Polymethyl methacrylate) is known to have larger cavity size in its polymeric network and thus it may involve a faster mode of diffusion of Metoprolol tartrate from the Eudragit RL100: PVP formulations as compared to the EC: PVP formulations. The addition of Eudragit RL100 in the drug polymer matrix was also driven by the fact that Eudragits produce crystallization free polymeric patches leading to higher skin permeation (Table 3).

The increase of release with increase of PVP content in the patch may be due to the leaching of PVP and pore formation. This leads to an increase in the external film area exposed to the solvent, increased internal porosity and decreased the tortuosity. Also PVP has antinucleating effect that converts crystalline drug into high energy amorphous state with improved solubility. The enhancement in solubility of drug increases thermodynamic activity that facilitates permeation of drug across the skin.

The other possible mechanism of enhancement of skin flux with increase of PVP in the patches may be due to its coenhancing property in aqueous vehicle system. The initial burst effect due to the incorporation of PVP was because of the rapid dissolution of the surface hydrophilic drug. The rapid leaching of hydrophilic fraction of polymers resulted in the formation of pores and thus leads to the decrease of mean diffusional path length of the drug molecules to permeate into dissolution medium.

The patch coded A-1 {EC: PVP (10:0)} showed the slowest permeation. This could be attributed to the hydrophobic nature of this polymer which helps to retain the drug in the matrix system by reducing the penetration of solvent molecules into the patch, in contrast to Eudragit RL100: PVP system.

The *in vitro* permeation data were fit to different equations and kinetic models to explain permeation profiles (Table 4, Figure 1, 2, 3, 4). The coefficient of correlation of each of the kinetics was calculated and compared. The *in vitro* permeation profiles of all the different formulations of transdermal patches did not fit to zero order behavior truly and they could be best expressed by Higuchi's equation for the release of drug from a homogeneous polymer matrix type delivery system that depends mostly on diffusion characteristic. The data was further treated as per Korsmeyer's equation. The slope (n) values obtained by this equation indicated that the drug released by Fickian diffusion predominated with all formulations. The skin irritation study indicated that neither the polymer nor the drug caused any noticeable irritation or inflammation on or around the patch area, either during the period of study or after removal of the patch.

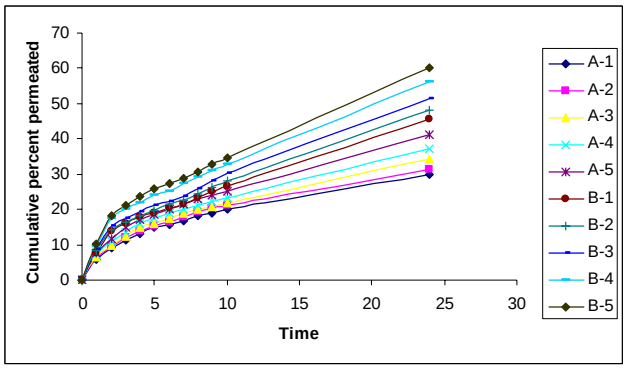

Figure 1. Zero order plot for different formulations

From the evaluation studies of the transdermal patches, it may be concluded that transdermal drug delivery system of metoprolol tartrate can be formulated, which provides better compliance than conventional drug delivery system.

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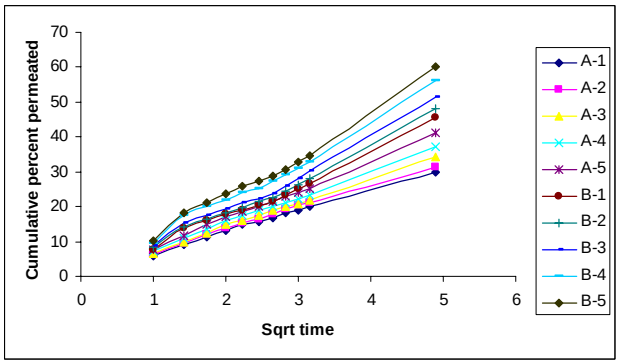

Figure 2. Higuchi plot for different formulations

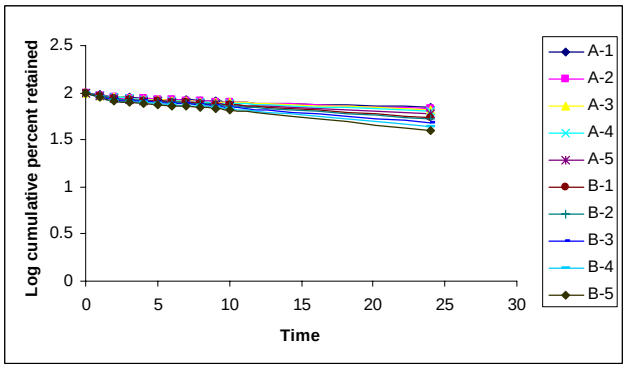

Figure 3. First order plot for different formulations

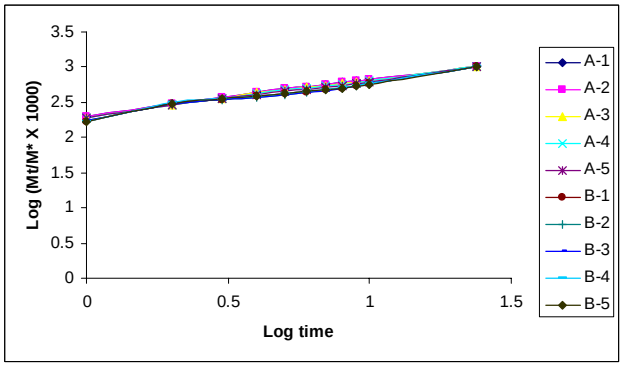

Figure 4. Korsemeyer Peppas plot for different formulations

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