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Original Article

Formulation, Evaluation and Optimization of Enteric Coated Tablets of Erythromycin Stearate by Multivariate Anova Method

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ABSTRACT

The present investigation concerns with the development, optimization and evaluation of an enteric coated tablets of Erythromycin stearate. Tablets were prepared by wet granulation method. Enteric coating of Erythromycin stearate tablets were done using two hydrophilic polymers like ethyl cellulose and pectin by multivariate ANOVA method by alternating the 2 variables X and Y in rows and columns. Polyethylene glycol was used as a plasticizer while Isopropyl alcohol & water was incorporated as a solvent. The effects of polymers and Isopropyl alcohol as a binder on drug release profile, gastro-resistant properties and matrix integrity of tablet were investigated. Developed formulations were evaluated for their physical characteristics, drug content, disintegration time, friability, hardness, thickness, swelling index, weight variation, *In vitro* drug release profile etc. On the basis of various physical characteristics parameters, it was found that all the formulations shows good result. On comparative kinetic modeling study such as (Zero order, First order, Higuchi model and Korsmeyer-Peppas) it was found that all the formulations follow Higuchi model and correlation coefficient (R^2) values were nearer to unity. Among those formulations, F4 showed R^2 value of Higuchi model more near as compared to the other formulation.

Keywords: Erythromycin stearate, Ethyl cellulose, Pectin, Polyethylene glycol, Isopropyl alcohol.

INTRODUCTION

Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation.[1,2] Drugs with short half-lives and drugs that easily

absorbed from gastrointestinal tract (GIT) are eliminated quickly from the systemic circulation. For these types of drugs the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time.[3,2] The basic goal of any drug delivery systems is to provide a therapeutic amount of drug to the proper site of body to achieve therapeutic level promptly and then maintain the desired drug concentration in systemic circulations.[4] The most important objectives of these new drug delivery systems are: First, it would be single dose, which releases the active ingredient over an extended period of time. Second, it should deliver the active entity directly to the site of action, thus, minimizing or eliminating side effects. To overcome the limitations of conventional drug delivery system, enteric coated tablets have been developed. An enteric coating is a barrier that controls the location of oral medication in the digestive system where it is absorbed. The word "enteric" indicates small intestine; therefore enteric coatings prevent release of medication before it reaches the small intestine. The enteric coated polymers remain unionise at low pH, and therefore remain insoluble. But as the pH increases in the GIT, the acidic functional groups are capable of ionisation, and the polymer swells or becomes soluble in the intestinal fluid.

Erythromycin base is selected for enteric coating as it is destroyed by gastric acid in the stomach. Acidic media degrades erythromycin rapidly to form derivates with little antimicrobial activity. Erythromycin is only slightly absorbed from the stomach. In man, absorption occurs mainly in the duodenum.[5,6] Erythromycin's oral availability is affected by food in different ways depending upon the formulation used (i.e. decreased with the base forms and increased with the estolate form). The half life of Erythromycin stearate is about 1-1.5 hrs. A short half-life (1-1.5h) means dosing four times daily is generally required and well absorbed in small intestine.

MATERIALS AND METHODS

Materials

Erythromycin stearate was selected as a model drug which was obtained from Kwality pharmaceuticals Pvt. Ltd. as a gift sample. The reagents used were pectin, ethyl cellulose, lactose, isopropyl alcohol, polyethylene glycol, magnesium stearate, talcum powder, sodium hydroxide and potassium dihydrogen orthophosphate. Tablets were prepared by wet granulation method.

Wet granulation is the most widely used process of granulation in the pharmaceutical industry. It involves addition of a liquid solution (with or without binder) to powders, to form a wet mass or it forms granules by adding the powder together with an adhesive, instead of by compaction. The wet mass is dried and then sized to obtained granules. The liquid added binds the moist powder particles by a combination of capillary and viscous forces in the wet state.[7] More permanent bonds are formed during subsequent drying which leads to the formation of agglomerates.[8]

Preparation of core tablets[9]

Granules were prepared using wet granulation method. Erythromycin and other excipients were passed through sieve no. 80 and add sufficient quantity of binding agent slowly to get dough mass. The mass was sieved through sieve no. 8 and dried at 45ºC for about 1 hrs. And these granules were passed through sieve no. 20 and lubricated with magnesium stearate. Mixed blend was compressed into tablets on single punch

tablet compression machine to a weight of 250 mg each with desired hardness, thickness, diameter, shape and size.

Coating of Erythromycin core tablets

Preparation of enteric coating solution

The formula for preparing coating solution was prepared by using Multivariate ANOVA method showed in Table no. 2. Weighed amount of pectin was dissolved in 50 ml of water and ethyl cellulose was dissolved in 50 ml of isopropyl alcohol. The two solutions were then mixed well to form a homogeneous solution and PEG-6000 was added as a plasticizer.

Coating of core tablets

Tablets were taken and were coated in a pan coater at 50 rpm at a temperature of 50ºC and at a flow rate of 10 ml/min. Coating was carried out with spraying method and dried.

Formulation of erythromycin tablets

Preparation of coating solution

The coating solution was prepared by using Multivariate ANOVA method.

Where,

1st column = alternate every other (2^o) row
2nd column = alternate every 2 (2^1) row
3rd column = alternate every 4th (2^2) row and
X, Y is two variables

Where,

X = 1.5 gm, Y = 2 gm, so that means, (see table 1.1)

Evaluation Parameters

Standard calibration curve of erythromycin stearate in 0.2 (M) Phosphate buffer pH 6.8 was prepared

This standard graph is shown below in Fig. 1.

Evaluation of Erythromycin Granules

The following evaluation parameters of granules were determined such as Angle of repose, Loose Bulk density, Tapped Bulk density, Compressibility index, Hausner's ratio. The results are shown below in Table no. 5.

Evaluation of Erythromycin Tablets

The following evaluation parameters of erythromycin tablets were determined thoroughly during my research work i.e General appearance, Diameter, Thickness, Hardness, Weight variation, Friability, Drug Content, Disintegration time and Swelling index. The results of these various parameters are listed below in Table no. 6.

In-vitro dissolution study

In vitro drug release studies for the prepared enteric coated tablets of erythromycin stearate were conducted for a period of 12 hrs by using USP XXIV type-I (Basket) dissolution apparatus. The dissolution rate was studied in 900 ml of 0.1 N HCl (pH 1.2) maintained at a temperature of 37±1ºC with a speed of 100 rpm for first two hours followed by phosphate buffer (pH 6.8) for further ten hours. Samples of 5 ml were withdrawn after every hour, filtered (through 0.45 µm) and replaced with 5ml of fresh dissolution medium to maintain the sink condition. After filtration and appropriate dilution, the samples were analyzed by UV spectrophotometer at 285 nm. Then the release kinetics of the drug erythromycin stearate was studied with the help of percentage cumulative drug release by using the models of release kinetics; such as Zero order release kinetics, first order release kinetics, Higuchi model and Korsmeyer-Peppas model.

Stability studies

Definition

Stability is defined as "the capacity of the drug product to remain within specifications established to ensure its identity, strength, quality and purity" (FDA1987). In other words the stability of a drug is its ability to resist deterioration.

Need for stability studies

Objective and Purpose

- It is important that the point of view of the safety of patients, it is important that the patient receive a uniform dose of a drug throughout the whole of shelf life.
- Consideration must be taken to the relevant legal requirements concerned with the identity, strength, purity, and quality of the drug.
- Such a study is important to prevent economic repercussion of marketing an unstable product.
- Deterioration of drug may take several forms arising from changes in the chemical, physical and microbiological properties .These changes may affect therapeutic value of dosage form or increases toxicity.

The International Conference of Harmonization (ICH) Guidelines titled, "stability testing of new drug substance and products" describes the stability test requirements for drug registration application in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions.

Note

The analyst can select any one of the three study conditions. Stability study was carried out at 40^0C / 75% RH for the optimized formulations.

The procedure was divided into two parts,

Part I

Achieving of 60% RH

26.66 gm. of sodium hydroxide was weighed and dissolved in 100 ml of distilled water to get 26.66% sodium hydroxide solution. The solution was placed in the desiccator over which a wire mesh was placed, over which the dosage form was placed and the desiccator was sealed. The desiccator was placed in room temperature at 25^0C to create the Relative Humidity of 60%.

Achieving of 75% RH

Saturated solution of sodium chloride was prepared and placed in the desiccators over which a wire mesh was placed, over which the dosage form was placed and the desiccator was sealed. The desiccator was kept in oven maintained at 40^0C to create the relative humidity of 75%.

Part II

The sealed formulation were placed in ambered colored bottles, tightly plugged with cotton and capped. They were then stored at 25^0C /60% RH and 40^0C / 75% RH for two months and evaluated for their physical appearance and drug content.

In this research, we studied the accelerated stability testing of best formulation.

RESULTS AND DISCUSSION

Standard plot of erythromycin stearate in 0.2 (M) Phosphate buffer solutions

Evaluation of Granules

Evaluation parameters of granules are listed below in Table no. 5:

Evaluation of tablets

Evaluation parameters of tablet are listed below in Table no. 6:

In vitro Drug Release Studies

In-vitro Dissolution Profile of Formulation F1 to F8 in 0.1 N HCl for (2 hrs) and Phosphate buffer pH 6.8 I.P for (10 hrs). (See table 7-9)

In-vitro Dissolution Profile of Formulation F1 to F8 in 0.1 N HCl for (2 hrs) and Phosphate buffer PH 6.8 I.P for (10 hrs). (See figure 2-5)

Stability studies

Among all the formulation F1, F3, F5 & F6 follow all necessary parameters efficient for tablet formulation within the specified range. Out of these F4 formulation showed R^2 value of Higuchi model nearer to unity. Hence this optimized formulation F4 was charged on accelerated stability study at 30, 60 and 90 days. The stability study reveals no significant variation in physicochemical parameter. Stability studies for F4 formulation at 40 ± 2^0C & 75 ± 5% RH test condition were shown in the Table no. 11.

DISCUSSION

From the above studies it was concluded that among all the formulations, F4 is the best formulation because it will show no significant changes during all the evaluation parameters such as bulk density, tapped density, angle of repose, hardness, thickness, disintegration time and other parameter. The F4 formulation also show very good release kinetics as compared to other formulation. The drug release data were fitted to models representing Zero order (cumulative percentage of drug released vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time), First order (log percentage of drug remained vs. time) and Korsmeyer's equation (log cumulative percentage of drug released vs. log time) kinetics to know the release mechanisms. Among all the formulations F4 showed R^2 value of Higuchi model value nearer to unity as compared to the other formulations. Hence F4 is the optimized formulation from this project studies.

CONCLUSION

Enteric coated tablets of Erythromycin stearate were prepared using two hydrophilic polymers like ethyl cellulose and pectin by multivariate ANOVA method by alternating the 2 variables X and Y in rows and columns. Eight formulations were prepared. All those formulations showed good acceptable Pharmacotechnical characteristics but F4 showed very excellent result as compared to the other formulations and able to survive the stability testing. Formulations like F4 showed higher stability as well as more steady state drug release profile. On comparative kinetic modeling study (such as Zero order, Higuchi model, First order and Korsmeyer-Peppas model) it was found that all the formulations follow Higuchi model and correlation coefficient (R^2) values were near to unity. Among those formulations, F4 showed R^2 value of Higuchi model more near as compared to the other formulations.

The research entitled and result obtained reveals that the combine effect of enteric coated agent in different ratio was suitable for long protection of active pharmaceutical ingredients, from the acidic environment of the stomach and to provide a delayed-release component for repeat action thus minimizing the first pass metabolism of drugs.

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Formulation of erythromycin tablets

Table 1. Composition details of erythromycin tablets

Material	Quantity
Erythromycin stearate	250 mg
Lactose	147 mg
Talc	2 mg
Magnesium stearate	1 mg
Isopropyl alcohol	q.s.
Total dosage form	400 mg

Table 1.1. Preparation of coating solution

Formulation Code	Pectin (gm)	Ethyl cellulose (gm)	Polyethylene glycol (gm)	Water (ml)	Isopropyl alcohol (ml)
F1	X	X	X	50 ml	50 ml
F2	Y	X	X	50 ml	50 ml
F3	X	Y	X	50 ml	50 ml
F4	Y	Y	X	50 ml	50 ml
F5	X	X	Y	50 ml	50 ml
F6	Y	X	Y	50 ml	50 ml
F7	X	Y	Y	50 ml	50 ml
F8	Y	Y	Y	50 ml	50 ml

Table 2. Composition details of enteric coating solution

Formulation Code	Pectin (gm)	Ethyl cellulose (gm)	Polyethylene glycol (gm)	Water (ml)	Isopropyl alcohol (ml)
F1	1.5	1.5	1.5	50 ml	50 ml
F2	2	1.5	1.5	50 ml	50 ml
F3	1.5	2	1.5	50 ml	50 ml
F4	2	2	1.5	50 ml	50 ml
F5	1.5	1.5	2	50 ml	50 ml
F6	2	1.5	2	50 ml	50 ml
F7	1.5	2	2	50 ml	50 ml
F8	2	2	2	50 ml	50 ml

Table 3. ICH guidelines for stability study

Study	Storage Condition		Minimum time
	Temperature	Relative humidity (%)	
Long term	25ºC ± 2ºC	60% ± 5% RH	12 Months
Intermediate	30ºC ± 2ºC	65% ± 5% RH	6 Months
Accelerated	40ºC ± 2ºC	75% ± 5% RH	6 Months

Table 4. Absorbance of standard Erythromycin solution

Conc. (µg/ml)	Absorbance	Equation	Slope	R^2 value
0	0	Y = 0.006x + 0.001	0.006	0.998
10	0.064			
20	0.129			
30	0.197			
40	0.246			
50	0.321			

Table 5. Shows various evaluation parameters of granules

Formulation Code	Loose Bulk Density (g/cc) ± sd, n=3	Tapped Bulk Density (g/cc) ±sd, n=3	Angle of Repose (°degree) ±sd, n=3	Compressibility Index (%) ± sd, n=3	Hausner's Ratio ± sd, n=3
F1	0.588 ± 0.20	0.75 ± 8.85	29.41 ±0.4761	21.6 ± 0.549	1.28 ± 0.169
F2	0.6 ±0.0017	0.756 ± 0.02	27.28 ± 0.631	20.6 ± 0.207	1.26 ± 0.372
F3	0.435 ±0.015	0.44 ± 0.016	26.133 ±0.507	1.14 ± 0.677	1.01 ± 0.008
F4	0.25 ±0.0020	0.266 ±0.0020	26.31 ±0.843	6.01 ±0.282	1.06 ± 0.0163
F5	0.152 ± 2.05	0.164±0.00163	23.22 ± 1.077	7.3 ± 0.658	1.08 ± 0.016
F6	0.25 ± 0.016	0.282 ± 1.632	29.60 ± 0.656	11.34 ±0.449	1.13 ± 0.016
F7	0.3415 ± 0.81	0.377 ± 0.0016	27.23 ± 0.471	9.4 ±0.711	1.10 ± 0.002
F8	0.316 ± 0.141	0.333 ± 1.632	29.06 ± 0.610	5.11 ±0.744	1.05 ± 0.002

Table 6. Shows various evaluation parameters of tablets

Formulation code	Weight Variation (mg)	Diameter (cm)	Thickness (cm)	Hardness (kg/cm^2)	Friability (%)	Drug (%) content 6.8pH	Disintegration Time (mins)		Swelling index
							0.1N HCL (min)	6.8pH (min)	
F1	100.4±4.4	8.00±0.017	3.05±0.064	2.63±0.124	0.8±0.008	96.4	-------	50	56
F2	105.6±5.0	799±0.006	3.22±0.085	3.03±0.124	0.56±0.016	92.4	100	-------	65
F3	99.36±2.9	7.96±0.001	3.17±0.110	3.23±0.205	0.91±0.028	91.6	-------	35	68
F4	101.6±3.0	7.99±0.019	2.95±0.056	4.7±0.163	0.35±0.001	98	-------	55	90
F5	97.33±3.0	7.99±0.016	3.13±0.067	3.16±0.205	0.81±0.016	95	90	15	68
F6	101.4±3.9	7.98±0.039	3.02±0.124	4.1±0.163	0.68±0.008	97.2	-------	40	62
F7	96.8±3.2	7.97±0.017	3.02±0.124	3.2±0.163	0.80±0.005	96.6	110	-------	77
F8	105.4±3.1	7.96±0.049	2.99±0.085	4.3±0.163	0.5±0.008	97.6	100	30	82

Table 7. Zero order plot & Higuchi release kinetics

Time (hrs)	√Time	% CAR F1	% CAR F2	% CAR F3	% CAR F4	% CAR F5	% CAR F6	% CAR F7	% CAR F8
0	0	0	0	0	0	0	0	0	0
1	1	8.713693	13.14935	3.438865	20.5102	16.57895	27.62346	3.10559	39.34426
2	1.414214	21.21024	16.63149	39.15666	22.46088	19.82895	32.40655	35.57626	48.78415
3	1.732051	22.83541	33.69589	42.46634	37.47109	29.63596	32.12363	39.79382	61.43784
4	2	31.86895	38.82305	41.33734	53.01361	34.74298	37.83179	39.35041	68.57753
5	2.236068	60.54979	51.83802	45.91612	63.20153	49.13947	47.74005	41.98758	70.92213
6	2.44949	61.33126	66.35823	50.36299	69.68622	51.27193	59.83196	48.05814	72.01076
7	2.645751	64.44675	77.96447	55.13646	74.6199	53.49386	63.75686	52.28433	72.93887
8	2.828427	68.19848	81.59993	64.33315	78.01446	55.55877	77.51286	61.93496	73.71243
9	3	77.86653	85.02886	76.99327	82.93112	58.25439	82.37311	63.0754	74.79252
10	3.162278	78.38693	89.10624	80.66594	89.23384	59.37456	85.64043	86.37336	76.02801
11	3.316625	79.78994	90.26515	81.83224	92.32993	60.80175	87.51029	93.17978	76.64959
12	3.464102	79.95332	92.38185	82.82114	94.03061	62.70439	89.98971	94.14855	77.11407

Table 8. First order plot

Time (hrs)	Log % drug remaining	Log % drug remaining	Log % drug remaining	Log % drug remaining	Log % drug remaining	Log % drug remaining	Log % drug remaining	Log % drug remaining
0	2	2	2	2	2	2	2	2
1	1.960406	1.938773	1.984802	1.900311	1.921276	1.859598	1.986299	1.782872
2	1.89647	1.921002	1.784213	1.889521	1.904018	1.829905	1.809046	1.709404
3	1.887418	1.82154	1.759922	1.796081	1.847351	1.831719	1.779641	1.586161
4	1.833345	1.786588	1.768362	1.671972	1.814627	1.793568	1.782828	1.49724
5	1.596049	1.682704	1.733068	1.56583	1.706381	1.718169	1.763521	1.463563
6	1.58736	1.526879	1.695806	1.48164	1.687779	1.603881	1.715517	1.446991
7	1.550879	1.343124	1.651894	1.404493	1.66751	1.559226	1.678661	1.432346
8	1.502448	1.26482	1.552265	1.342137	1.647786	1.351934	1.580526	1.41975
9	1.34505	1.175255	1.361855	1.232205	1.620611	1.246176	1.567316	1.401529
10	1.334716	1.037178	1.286323	1.032061	1.608798	1.157141	1.134389	1.379704
11	1.305568	0.988329	1.259301	0.884799	1.593267	1.096552	0.833798	1.368295
12	1.302042	0.881849	1.234994	0.77593	1.571658	1.000447	0.767263	1.359569

Table 9. Korsmeyer and peppas

Log time	Log %car	Log %car	Log %car	Log %car	Log %car	Log %car	Log %car	Log %car
0	0	0	0	0	0	0	0	0
0	0.940202	1.118904	0.536415	1.31197	1.219557	1.441278	0.492144	1.594881
0.30103	1.326545	1.220931	1.592806	1.351427	1.2973	1.510633	1.55116	1.688279
0.477121	1.358609	1.527577	1.628045	1.573696	1.471819	1.506825	1.599816	1.788436
0.60206	1.503368	1.58909	1.616342	1.724387	1.540867	1.577857	1.594949	1.836182
0.69897	1.782113	1.714648	1.661965	1.800728	1.691431	1.678883	1.623121	1.850782
0.778151	1.787682	1.821895	1.702112	1.843147	1.70988	1.776933	1.681767	1.857397
0.845098	1.809201	1.891897	1.741439	1.872855	1.728304	1.804527	1.718372	1.862959
0.90309	1.833775	1.91169	1.808435	1.892175	1.744753	1.889374	1.791936	1.867541
0.954243	1.891351	1.929566	1.886453	1.918718	1.765329	1.915785	1.79986	1.873858
1	1.894244	1.949908	1.90669	1.95053	1.7736	1.932679	1.93638	1.880974
1.041393	1.901948	1.95552	1.912924	1.965343	1.783916	1.942059	1.969322	1.88451
1.079181	1.902836	1.965587	1.918141	1.973269	1.797298	1.954193	1.973814	1.887134

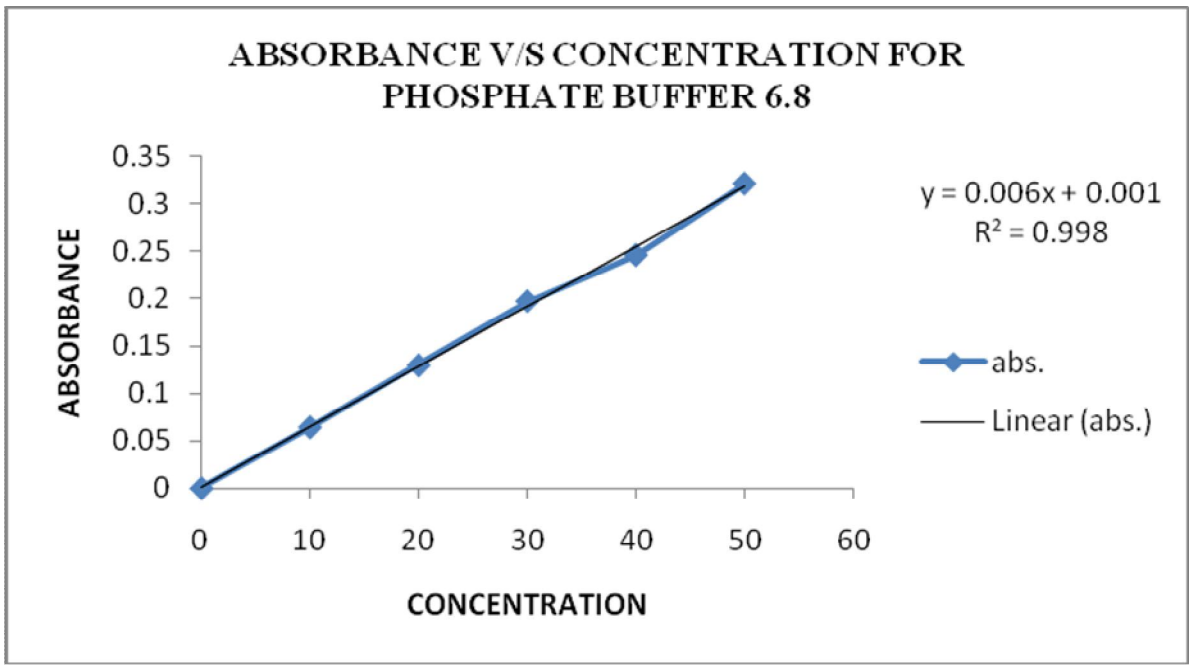

Figure 1. Standard calibration curve of Erythromycin stearate in phosphate buffer pH 6.8

Zero order plot

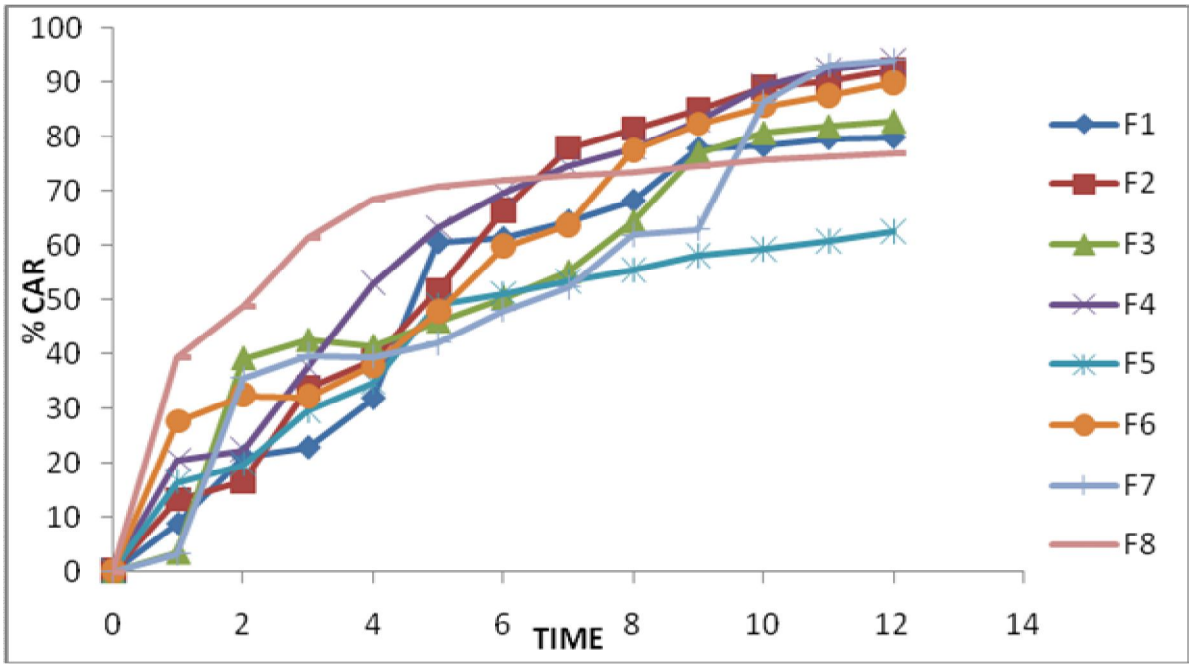

Figure 2. Comparative study on *In-vitro* Dissolution profile of batch F1-F8

Higuchi release kinetics

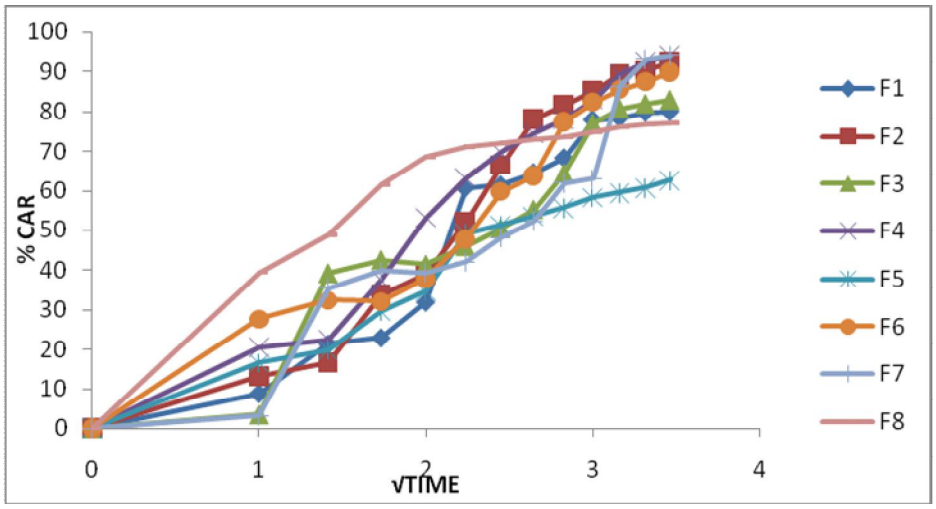

Figure 3. Comparative study on *In-vitro* Dissolution profile of batch F1-F8

First order plot

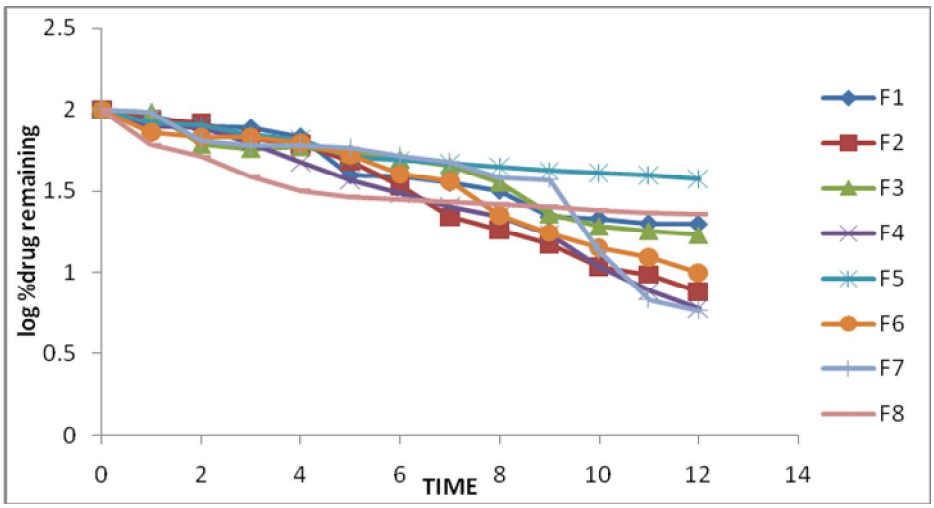

Figure 4. Comparative study on *In-vitro* Dissolution profile of batch F1-F8

Korsmeyer and peppas release kinetics

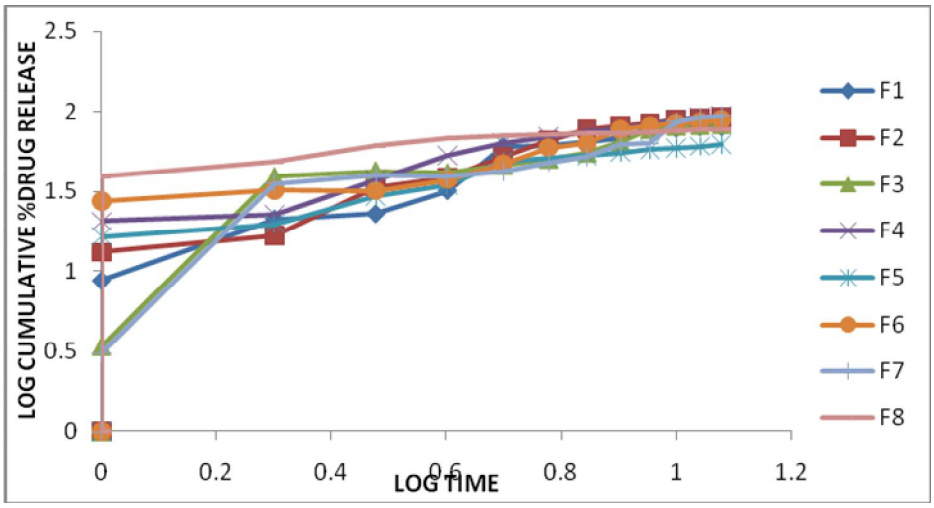

Figure 5. Comparative study on *In-vitro* Dissolution profile of batch F1-F8