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Research Article

Formulation And Evaluation of Erythromycin Delayed Release Tablets

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ABSTRACT

The present study is to formulate and evaluate Erythromycin enteric coated tablets prepared by wet granulation method by using Povidone k30 as polymer, Tricetin as plasticizer ,titanium dioxide as opacifer ,aqueous coating Eudragit 100-55 as coating agent and opadry red as coloring agent .The physico - chemical incompatibity was studied by using Hplc and physical parameters of prepared enteric coated tablets were evaluated as pharmacopeia standards .The dissolution studies of prepared enteric coated tablets was evaluated as pharmacopeia standards .The dissolution studies were performed by using ph 4 acetate buffer for 2hrs and then transfer to phosphate buffer 6.8 for 1 hr. The release order kinetics was studied for the best formulation and was found zero order. The stability studies were performed as per ICH guidelines and results was found satisfactory.

INTRODUCTION

The ease of manufacturing, convenience in administration, accurate dosing, and stability compared to oral liquids, capsules and parental dosage forms, tablets are popular. Experts in the art of tableting are aware with the basic art of tableting by the three well-known methods, i.e. wet granulation, roller compaction and direct compression. The availability of new materials, new forms of old materials and the invention of new machinery has allowed the production of tablets by simplified and reliable methods.. The excipients can include glidants (flow aids), diluents, binders or granulating agents and lubricants to ensure efficient tableting; disintegrants to promote tablet break-up in the digestive tract; 3sweeteners or flavors to enhance taste and pigments to make the tablets visually attractive. A polymer coating is often applied to enhance the tablet's appearance or to make the tablet smoother and easier to swallow and to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life).

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TABLET COATING (3):

Tablet coating is one of the oldest pharmaceutical processes still in existence. Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form in order to confer specific benefits over uncoated variety. It involves application of a sugar or polymeric coat on the tablet. Coating can be applied to several kinds of solid dosage forms like tablets, pellets, pills, drug crystals, etc. The tablets are then allowed to dry and the film eventually forms a non-sticky dry surface. The coating technique involves parameters such as the spray pattern, drop size, and nozzle spacing (in addition to multiple other non-spray related parameters) which must all be precisely controlled in order to ensure uniform distribution of the coating material

Objectives of coating:

- To mask the disagreeable odor, color or taste of the tablet.
- To offer a physical and/or chemical protection to the drug.
- To control and sustain the release of the drug from the dosage form.
- To incorporate another drug which create incompatibility problems.
- To protect an acid-labile drug from the gastric environment.
- Increasing the mechanical strength of the dosage form.

TYPES OF COATING: Basically there are five major techniques for applying coatings to pharmaceutical solid dosage forms

- Sugar coating.
- Film coating.
- Enteric coating.
- Fluid bed or suspension coating.
- Compression coating.

ENTERIC COATING: The enteric-coated tablets deliver the drug almost locally at a predetermined rate and for a specified period of time with in the intestinal tract. This helps by either protecting drugs from the acidity of the stomach, the stomach from the detrimental effects of the drug, or to release the drug after the stomach (usually in the upper tract of the intestine). After contact with intestinal fluids, the coatings swell independent of pH and release the active ingredients by a diffusion controlled mechanism.[5] Reasons for putting such a coating on a tablet or capsule ingredient (6) : Protection of active pharmaceutical ingredients, from the acidic environment of the stomach (e.g. enzymes and certain antibiotics). To prevent gastric distress or nausea from a drug due to irritation (e.g. sodium salicylate). For the delivery of drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form. To provide a delayed-release component for repeat action. Required for minimizing first pass metabolism of drugs.

MATERIAS AND METHODS

MATERIALS: The following materials were used and supplied by the manufacturers are of pharmacopoeial or analytical grade.

S. No	Chemical Name	Supplied By
1.	Erythromycin	Hec Pharma co.ltd
2.	Pre gelatinanse starch	Universal starch-chem. allied ltd.
3.	Sodium starch glycol ate	Roquette Pharma
4.	Povidone k30	Quzhou jianhua nanhang industrial co., ltd
5.	Colloidal silicon dioxide (aerosol)	Evonik industries
6.	Magnesium Stearate	Nitika pharmaceutical pvt ltd
7.	Opadry sub coating (white)	Colorcon
8.	Opadry enteric coating (white)	Colorcon
9.	Opadry red film coating	Colorcon

PREPARATION OF CALIBRATION CURVE:

Preparation of drug in pH 6.8 phosphate buffer:

- Primary stock solution :Accurately weighed 100mg of API and transferred into clean dry 100ml of volumetric flask .To this add small quantity of pH 6.8 phosphate buffer ,shake well until contain get dissolved and make up to the mark with buffer solution. The resultant conc. of solution was 1mg/ml (1000 µg/ml).
- Secondary stock solution : From the above solution pipette 1ml and transferred into clean and dry 100ml of volumetric flask add little quantity of pH 6.8 phosphate buffer shake well until it uniformly distributed and make up to the mark with buffer solution . The resultant conc. of solution was 0.01mg/ml (10µg/ml). From the above solution pipette 2, 4, 6, 8, and 10ml transferred into clean and dry 10ml volumetric flask separately. .To this add small quantity of pH 6.8

S.No	Concentration (µg/ml)	Absorbance (nm)
1	2	0.056
2	4	0.104
3	6	0.161
4	8	0.215
5	10	0.262

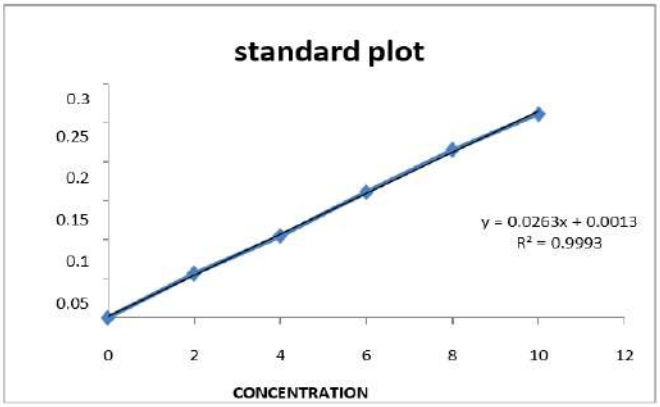


Fig: Standard curve of Erythromycin in pH 6.8 Phosphate Buffer

Pre-compression studies:

Bulk density

Tapped density:

Angle of repose:

Compressibility Index and Hausner's ratio:

Drug Excipient Compatibility Studies:

- **Formulation Development:**

The Erythromycin tablets were prepared using wet granulation technique. This method was selected due to good flow properties. The concentration of lubricant, binder and disintegrants were incorporated based upon trails. The prepared tabletswere subjected for sub coating, enteric coating and film coating.

FORMULATION DESIGN OF ERYTHROMYCIN ENTERIC COATING TABLETS						
Formulation Design of Core Tablet						
INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Erythromycin	250	250	250	250	250	250
Pre gelatinized starch	24.28	24.28	30.320	18.26	25.525	24.28
Sodium starch	13.56	9.79	13.56	6.02	10.35	13.56
Povidone	9.04	6.02	3.01	9.04	6.25	3.01
Colloidal silicon dioxide	3.01	6.78	3.01	10.54	5.175	3.01
Magnesium Stearate	1.50	4.52	1.5	7.53	4.14	7.53
Total (mg)	**301.75**	**301.39**	**301.4**	**301.39**	**301.4**	**301.39**
Formulation Design For Sub Coating Tablets						
Formulation	F2		F4	F5	F6	
Hypermellose	5.80		3.13	4.2	9.65	
Titanium dioxide	1.6		0.94	**1.2**	1.80	

Tricetin	0.8	0.45	**0.6**	0.60
Formulation Design For Enteric Coating Tablets				
Formulation	F2	F4	**F5**	F6
Eudragit L100 – 55	17.28 (5.73)	19.88 (6.59)	**16.09 (5.33)**	19.88 (6.59)
Sodium laurly sulfphate	4	7.23	**7.30**	7.23
Titanium dioxide	2.71	4.33	**3.51**	4.33
Tricetin	2.71	4.72	**3.1**	4.72
Formulation Design For Film Coating Tablets				
Formulation	F2	F4	**F5**	F6
Hypermellose	4.51	4.51	**4.51**	4.51
Sunset yellow FCF aluminum lake	0.9	0.9	**0.9**	0.9
Ponceau 4R lake	0,6	0,6	**0,6**	0,6
Tricetin	0.77	0.77	**0.77**	0.77

Procedure for Coating Solution:

- **Sub Coating Solution:**
  All components are ready mix available as opadry white YS-1-7027. Opadry white YS-1-7027 was added to purified water (10 % w/w) under continuous stirring, stir to get homogenous dispersion.
- **Enteric Coating Solution:**
  All components are ready mix available as acryclzee – 9301839 (Eudragit L 100- 55). Acryclzee white (9301839) was added to purified water (10% w/w) under continuous stirring to get a homogenous dispersion
- **Film coating solution:**
  All components are ready mix available as opadry red (03k55283) was added to purified water (10 % w/w) under continuous stirring to get homogenous dispersion.

❖ **Procedure for Formulation of Erythromycin Enteric Coated Tablets:**

- Weighed accurately required quantity of erythromycin, pregelatinize starch and sodium starch glycolate and passed through #40 mesh into clean and dried container, mixed for 15 mins to get uniformity
- The total mixture was transfer to rapid mix granulator and mixed for 10 mins. To this mixture required quantity of Povidone K30 (in solution form) was added and mixed thoroughly by using impeller 100 RPM until wet mass obtained.
- The obtained mass was subjected to kneading for 30sec by maintain impeller speed 100RPM and chopper speed 1200RPM.
- The obtained granules are dried at 45± 50 c in tray dryer, passed through sieve no #24 mesh ASTM mesh by using vibrosifter.
- To this required quantity colloidal silicon dioxide and Magnesium Stearate was added thoroughly blended by using octagonal blender for 10 mins.
- The above blend was transferred to hopper of compression machine and required strength of tablets was prepared.
- The compression tablets were subjected to sub coating by maintaining inlet temperature of 45 ± 5 0C, Outlet temperature of 40 ± 5 0C, Bed temperature of 40 ± 5 0C, atomization air was kept at 1.2 kg/Cm2, spray rpm was maintained in between 2-5 RPM at a spray rate of 1gm/min and Pan Rotation was maintained in between 8-25 RPM.

Inlet air temperature	45^0c ± 5
Tablet bed temperature	40^0c ± 5
Spray rate	2-5 g/min
Atomization ait pressure	1.2 bar
Air flow	33 m^3/hr
Pan speed	8-25 rpm

❖ **Evaluation of post compression tablets:**

There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

- **In Vitro Dissolution studies:**

In Vitro dissolution study was carried out using USP type-I apparatus (Rotating paddle apparatus). The drug release was carried out in 900 ml of pH 4.0 acetate buffer solution for 2 hours and replaced with pH 6.8 phosphate buffer and carried out for 1 hour. The temperature of the dissolution medium was kept at 37± 0.5oC and the rotating paddle was set at75 RPM. The drug was estimated by withdrawing samples for every time intervals and replacing fresh medium. the withdrawn sample filtered through Whatman filtered paper and necessary dilutions were made and drug content estimated by UV/Visible spectrophotometer.

❖ **Release Order Kinetics:**

- Zero-order equation (51)
- First Order Equation (52)
- Higuchi equation (53)
- Korsmeyer-Peppas equation (54)

❖ **Stability studies**

STUDY	STORAGE CONDITION	TIME PERIOD
Accelerated	40^0 C ± 2^0 C / 75 % ± 5% RH	6 months

RESULTS AND DISCUSSION

❖ **PRE-FORMULATION**

Physical Characterization of API

S.NO	Description	Result
1.	Appearance	White to off white crystalline powder
2.	Odour	Characteristic odour.
3.	Solubility	Practically insoluble in aqueous media, Soluble in ethanol.
4.	Moisture content	2.08 %

Drug Excipients compatibility studies

Ingredients	Initial	Final observation		Remarks
		40 ° c / 75 % RH		
		Initial	30 th day	
API (erythromycin)	White to Off white	White to off White	White to off White	Compatible
API+ Pregelatinized starch	White	No change	No change	Compatible
API + sodium starch glycolate	White	No change	No change	Compatible
API+ Povidone k30	White	No change	No change	Compatible
API+ colloidal silicon dioxide	White	No change	No change	Compatible
API+ MagnesiumStearate	White	No change	No change	Compatible
API+ Hypermellose	White	No change	No change	Compatible
API+ methacrylic acid	White	No change	No change	Compatible
API+ Triacetin	Unknown	No change	No change	Compatible
API+Titanium dioxide	White	No change	No change	Compatible
API+ Sunset yellow fcf aluminum lake	Orange-red	No change	No change	Compatible

FLOW PROPERTIES OF GRANULES

Formulations	Bulk Density	Tapped Density	Angle of repose	Compressibility Index	Hausner's Ratio
F1	0.34 ±0.06	0.47 ±0.03	47.4 ± 0.4	26 ± 0.04	1.36 ± 0.02
F2	0.41 ±0.02	0.47 ± 0.04	31.15 ± 0.3	14.63 ±0.03	1.14 ± 0.02
F3	0.42 ±0.01	0.57 ± 0.01	47.21 ±0.3	26.31 ±0.04	1.35 ± 0.05
F4	0.38 ±0.03	0.45± 0.01	33.15 ± 0.1	15.67 ± 0.02	1.18 ± 0 0.4
F5	0.41 ±0.06	0.48 ±0.02	34.16 ± 0.2	14.58 ± 0.01	1.17 ±0.01
F6	0.41 ±0.06	0.47± 0.04	33.14 ±0.5	12.7± 0.03	1.14 ± 0.02

Evaluation Tests for Coated Tablets

Formulation	Weight variation (mg)	Hardness (kg/cm^2	Thickness (mm)	Friability (%)	Disintegration (min)
F2	301.7 ± 0.52	8.5 ± 0.26	5.16 ±0.32	0.03 ± 0.2	2.40 ± 0.20
F4	302.1 ±0.46	8.7 ± 0.21	5.13 ± 0.31	0.04 ± 0.16	3.12 ± 0.22
F5	300.9 ± 0.69	8.1 ± 0.32	5.16 ± 029	0.06 ± 0.10	1 .45 ± 0.20
F6	301.7 ± 0.59	8.9 ± 0.22	5.14 ± 0.22	0.05 ± 0.12	2.53 ± 0.23

Dissolution studies of Erythromycin Enteric coated tablets

% Cumulative Drug Release					
Time	**F2**	**F4**	**F5**	**F6**	Innovator
pH 4.0 Acetate buffer as dissolution medium					
2hrs	-	-	-	-	-
pH 6.8 phosphate buffer as dissolution medium					
0	0	0	0	0	0
5	17± 0.65	12± 0.61	17±0.65	10±0.61	10±0.62
10	43±0.61	23±0.62	28±0.62	26±0.64	24±0.62
15	71±0.62	39± 0.64	48±0.64	43±0.67	53±0.65
20	75±0.64	48± 0.67	56±0.67	52±0.65	73±0.64
30	86± 0.67	65±0.64	68±0.65	64±0.64	86±0.62
45	91± 0.68	75±0.63	85±0.63	81± 0.63	92±0.64
60	93±0.65	84±0.67	99±0.70	94±0.62	98±0.63

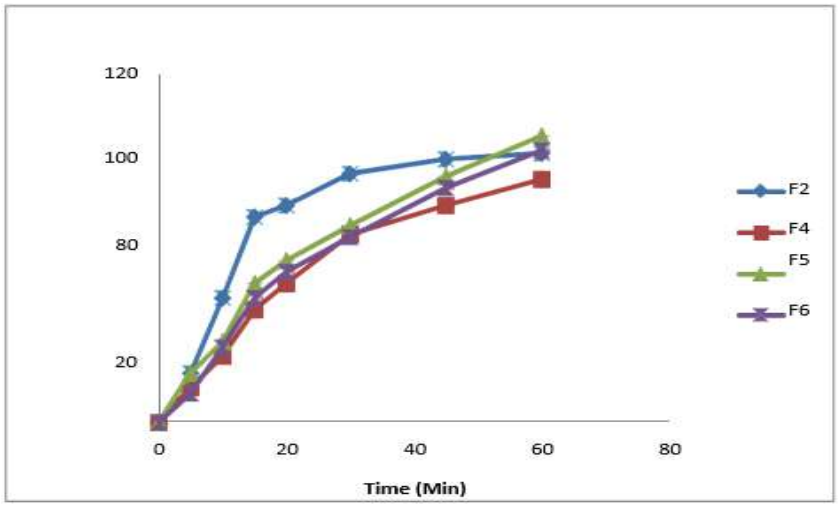


Fig: Comparative *in vitro* drug release profile of erythromycin tablets Formulated with different concentrations

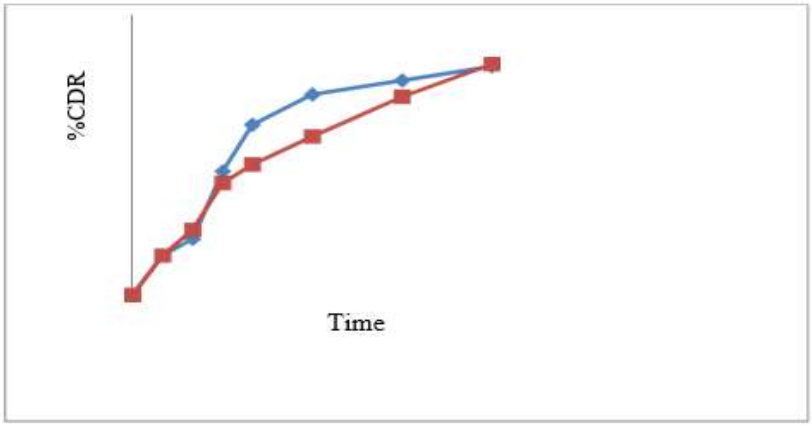


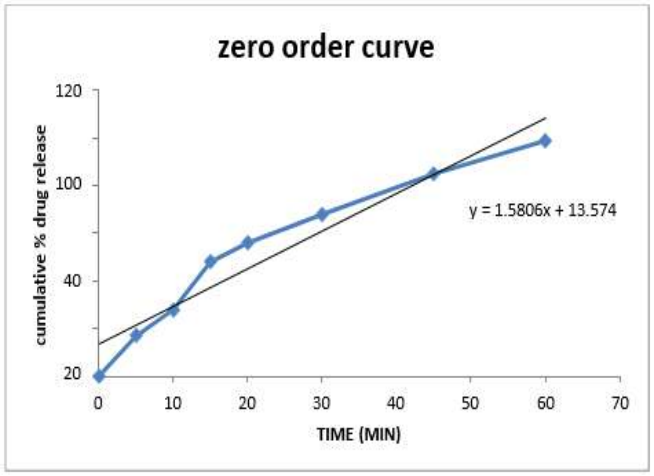
Fig: In Vitro **Dissolution Profile Of Market Formulation with Optimized Profile**

STABILITY STUDIES

S. NO	PARAMETERS	SPECIFICATIONS	Test condition			
			40^{o} c ± 2^{o} C / 75 ± 5 % RH (Accelerated)			
			INTIAL	1 MONTH	3 MONTHS	6 MONTHS
1	Description	Red colored round shaped enteric coated	Comply	Comply	Comply	Comply
2	Moisture content	Not more than 6%	4.2	4.1	4.2	4.04
3	Assay	NLT 90% & NMT 110% labeled amount of drug	98.3	97.8	97.3	97.1
4	Dissolution studyin pH 6.8 Phosphate buffer	NLT 80% of labeled amount of erythromycin dissolved in 60 min	95.8	94.8	95.8	93.6

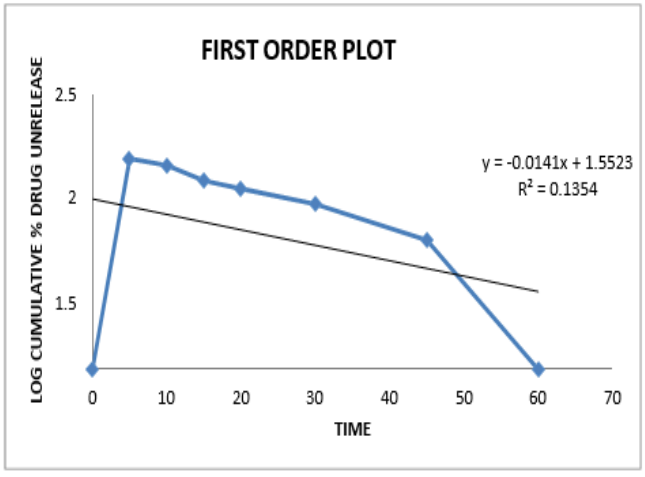
RELEASE ORDER KINETICS

- **Zero Order Kinetics**



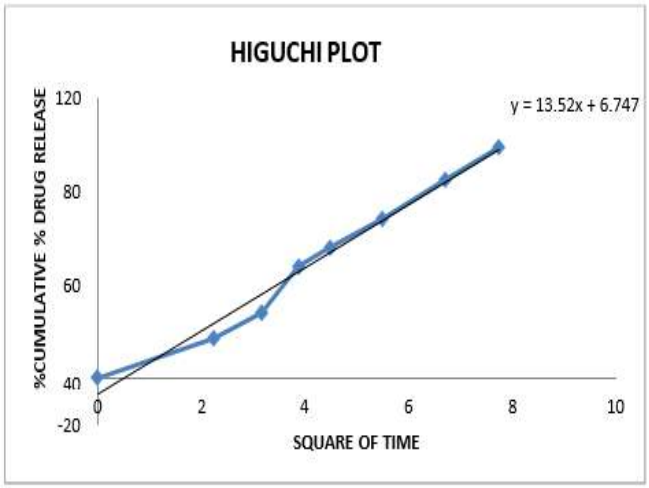
Zero Order drug release profile of Erythromycin from Enteric Coated Tablets

- **First Order kinetics**



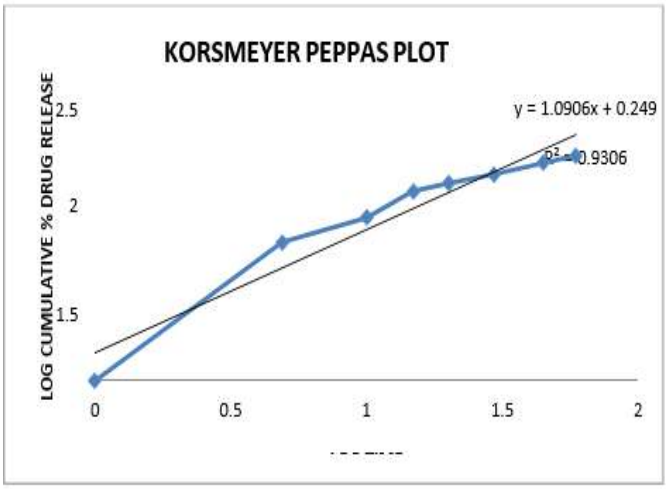
First Order drug release profile of Erythromycin from Enteric Coated Tablets

➢ **Higuchi Model**



Higuchi Plots drug release Erythromycin from Enteric Coated Tablet

➢ **Korsmeyer- Peppas Model**



Korsmeyer-peppas plot drug release of erythromycin enteric coated tablets

Release Order Kinetics

Formulation	Release order Kinetics				
	Zero Order(R^2)	First Order(R^2)	Higuchi plot(R^2)	Korsmeyer – Peppas	
				(R^2)	'n' values
F5	0.928	0.135	0.979	0.930	1.090

SUMMARY

From the prepared Erythromycin delayed release tablets, formulation F5 shown better micromeretic properties, pre- & post- compressional studies and % drug release of 99% in pH 6.8 phosphate buffer for 1 hr. When the in-vitro drug release data subjected to release order kinetics, it was conformed that the prepared Erythromycin delayed release tablets follows zero order release kinetics and super case –II transport mechanism. The stability study was performed for better obtained formulation as per ICH guidelines and it confirmed that the formulation was stable, with no physical change and also there was no significant reduction in drug release.

CONCLUSION

The Present Study concerns that the Development and Evaluation of enteric coated tablets of Erythromycin were prepared by wet granulation method. The formulation F5 has shown better release when compared to other formulations. The release order kinetics also states that the prepared formulation follows zero order release kinetics and Super Case –II Transport Mechanism. Further studies can be investigated for pharmacokinetic and pharmacodynamic parameters in animal model for preparing best formulation that reaches patient needs.

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