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Formulate and evaluate once daily sustained release tablet of highly soluble drug of metformin Hcl

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ABSTRACT

The aim of this study was to style an oral sustained release matrix tablet of highly water soluble biguanide anti diabetic drug. The matrix tablets are prepared by melt granulation method using HPMC K 200M as hydrophilic drug release retarding polymer, and octadecanoic acid as melt able binder also as hydrophobic carrier. The drug and excipients compatibility was studied by FTIR. The formulated matrix tablets were characterized for physical parameters and *in vitro* dissolution profile. FTIR spectra revealed the absence of drug excipients interaction. The physical parameters of the tablets were found within the bounds. The drug release kinetics demonstrated that by increasing the concentration of hydrophilic polymer and hydrophobic carrier the drug release rate was retarded proportionally. Kinetic modelling of *in vitro* release profile revealing that the drug release from the matrix tablets following first order kinetics, and therefore the drug release mechanism of optimized (F7) formula following non fickian transport mechanism. Accelerated stability studies were performed consistent with ICH guide lines. Temperature $40 \pm 20^\circ\text{C}$ and ratio $75 \pm 5\%$ RH to review physical and chemical changes of formulation. No physical or chemical changes were observed after t accelerated stability studies.

Keywords: HPMC K 200M; hydrophilic polymer; Metformin Hcl; Matrix tables.

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INTRODUCTION

Sustained release dosage forms are dosage forms designed to release (liberate) a drug at a predetermined rate so as to take care of a continuing drug concentration for a selected period of your time with minimum side effect. The perfect drug delivery system have two things would be required first it might be one dose the duration of treatment whether it's for days or week, like lifetime of the patient as in hyper-

tension or diabetes. Second it should deliver the active entity on to the location of the action, thereby minimizing side effects.^[1]

Advantages of sustained release dosage forms:

1. Control of drug therapy is achieved
2. Rate and extent of drug absorption are often modified.
3. Frequency of drug administration is reduced.

Disadvantages of sustained release dosage forms:^[2]

1. It don't promote prompt termination of therapy
2. Less flexibility in dose adjustment

Oral route of administration is taken into account as widely accepted route thanks to ease inconvenience by self-administration, compactness, and simple manufacturing process. It had been observed that drugs administered by oral route produce 90% of systemic effects. Conventional dosage form produces the wide selection of fluctuation in drug concentration in bloodstream which results in a loss in drug effectiveness or increases the incidence of side effects with subsequent undesirable toxicity and poor efficiency. However, sustained or controlled drug delivery systems differ by conventional dosage forms thereby decreasing the frequency of the dosing and also increases effectiveness of the drug by localization at the site of action, reducing the dose required

and providing uniform drug delivery. Sustained release preparations are helpful to scale back the dosage frequency and side effects of medicines and improve patient's convenience. Sustained release matrix tablet is comparatively easy to fabricate by incorporating the drug in slowly dissolving or inert porous polymer materials.^[3]

Drug release through matrix system is set by water penetration, polymer swelling, drug dissolution, drug diffusion, and matrix erosion that lead to a rapid formation of external layer, allowing drug release modification. Hydrophilic matrices are becoming popular in controlling the discharge of soluble drugs from solid dosage forms. These systems appear to be one of the foremost attractive approaches from an economic also as from the tactic development points of view. The use of mixtures of polymers represents a possible way of achieving required release properties. Mixtures of varied non-ionic cellulose ethers are used to give different viscous efficiencies. The foremost widely used polymer for hydrophilic matrices is hydroxyl propyl methylcellulose (HPMC). This polymer is taken under consideration among the water-soluble polymers. Ethyl cellulose (EC) is taken under consideration as a water insoluble polymer because of the hydrophobic substituent's (ethyl-). This polymer has been used mainly to form films for the manufacture of oral extended release dosage forms like granules, pellets, microcapsules and film tablets. A second polymer like hydroxy propyl cellulose has been admixed to change the release properties by providing hydrated channels for drug release. Mixtures of varied proportions of polymers with different permeation characteristics could provide an honest range of release rates of a drug by changing the diffusivity of the drug through a polymer barrier.^[3]

DM, simply mentioned as diabetes, may be a group of metabolic diseases during which an individual has high level of blood glucose. The possible causative reason maybe that the body doesn't produce enough insulin, or cells don't answer the insulin that's produced by the pancreatic cells. Metformin hydrochloride is that the first-line drug of choice for the treatment of type II diabetes, especially, in overweight and obese people and people having normal kidney function. metformin helps to enhance hyperglycemia primarily by suppressing glucose production by the liver (hepatic gluconeogenesis). It does activate adenosine monophosphate-activated protein kinase, an enzyme that plays a crucial role in insulin signalling, maintains whole body energy balance, and thus metabolism of glucose and fats takes place. the traditional sort of Metformin tablets are found to possess many associated drawbacks like gastrointestinal upset, including diarrhoea, cramps, nausea, vomiting, and increased flatulence. So on reduce the above mentioned side-effects and to reinforce patient compliances, sustained release formulation of Metformin was developed.^[4]

Hence, within the present work an effort has been made, to formulate the sustained release matrix tablets of Metformin Hydrochloride and tested for controlled delivery of drug using hydroxyl propyl methyl cellulose (HPMC) as hydrophilic matrix polymer together with PVC which acts as hydrophobic polymer, leading to reduction in its dosing frequency of metformin and therefore the reby its related side effects and the release behaviour of the drug is evaluated.

Metformin is very soluble in water which may abruptly reduce the sugar level in blood thanks to rapid release when administered in normal tablets. generally, the utmost dosage of Metformin is 2,550 mg/day. it's administered 2-3 times/day at meals within the amount of 500 or 750 mg in tablet. However, this sort of administration may cause abrupt change within the blood concentration of the drug, which can end in adverse reactions and resistance to the drug. However, being a brief acting drug, Metformin requires twice-daily or three-times-a-day dosing.^[4]

A properly designed sustained release dosage sort of Metformin will minimize the fluctuation in blood concentration, decreasing the danger of side effects and can show uniform pharmacological response and reduce the frequency of administration. Therefore, the sustained-release dosage sort of Metformin may improve the standard of therapy in patients with non-insulin dependent DM.

The essential objective of any drug therapy is to realize steady state blood or tissue level for an extended period, which can be therapeutically effective & non-toxic. Recently, controlled release and sustained release drug delivery has become the standards within the modern pharmaceutical design and intensive research for achieving better drug product effectiveness, reliability and safety. Oral sustained release drug delivery system (OSRDD) will still account for the most important share (up to 80%) of drug delivery systems.^[5]

Hydrophilic polymer matrix systems are widely utilized in oral controlled drug delivery due to their flexibility to get a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. the power of the hydrophilic polymer matrices to release the entrapped drug in aqueous medium and to manage the discharge of such drug by control of swelling and cross linking makes them particularly suitable for controlled release application.

Oral administration has long been the foremost convenient & commonly employed route of drug delivery thanks to its simple administration, high patient compliance & flexibility within the design of dosage form. Hydrophilic polymers are getting very fashionable in formation of SR/CR tablets. These polymers absorb a big amount of water on coming in touch with either the dissolution media or biological fluids to make a gel. Because the dissolution medium

or biological fluids penetrate the matrix, polymer material swells & drug molecule begin to maneuver out of the system by diffusion at a rate determined by the character and composition of polymer. Due to their simple preparation, ability to accommodate great deal of drug & minimum influence exerted by the processing variables on their release rate, hydrophilic matrices are increasingly becoming popular for oral sustained / controlled drug delivery. During the last several years, hydrophilic polymers especially cellulose & its derivatives are studied as hydrophilic swellable matrices within the design of oral SR / CR systems. The water swellable cellulose ethers e.g., Hydroxy Propyl Methyl Cellulose (HPMC) and pH independent hydrophilic propenoic acid derivatives are mainly getting used for this purpose.^[6]

MATERIALS AND METHODS

Metformin HCl was obtained from Harman Finochem Ltd, Aurangabad India. Dicalcium phosphate anhydrous BP/Ph.Eur (granular) obtained from Rhodia Caers, Mumbai Pre gelatinized starch. BP/Ph.Eur, Hydroxy propyl methyl cellulose K200M BP/Ph.Eur, Stearic acid BP/Ph.Eur. Povidone BP/Ph.Eur (K90F) Colloidal anhydrous silica BP/Ph.Eur Magnesium stearate BP/Ph.Eur is obtained from DKSH India Pvt. Ltd, Chennai.

Study of physical interaction between drug and polymer

Infrared spectrum was taken by scanning the samples of pure drug and the polymers individually over a wave number range of 4000 to 400 cm^{-1} using Fourier transform infrared spectrophotometer (FT-IR, Shimadzu 8400S, Shimadzu, Japan). The change in spectra of the drug in the presence of polymer was investigated which indicates the physical interaction of drug molecule with the polymer.

Preparation of Metformin hydrochloride matrix tablets

All Materials are dispensed as per the approved work order Sift API through #20 mesh, Hypromellose K200M, Dicalcium phosphate anhydrous and PVP K 90 through #40 mesh and collect separately in polyethylene bag. Load the sifted materials in RMG and mix it for 10 minutes at impeller slow speed Add melt stearic acid with slow impeller speed and chopper off for 15 sec. Dissolve PVP K90 in the Water by the help of mechanical stirrer. Add the binder solution to the above mix at impeller medium speed for 5 minutes and continue with chopper medium speed for 3 minutes. Use additional quantity of purified water if required and continue mixing till proper consistency of wet mass is achieved. Dry the granules with inlet temperature 50°C to 55°C till the LOD limit in the range of 2-3% w/w. Sift the dried granules through #20mesh and mill the retentions through 2.0mm screen fitted to the Multimill and knives forward direction. Sift the milled granules through #20mesh. Prelubricate the sized granules with Aerosil-200

(sifted through #40 meshes) and Hypromellose K200M for 5 minutes and lubricate with magnesium stearate (sifted through #60 mesh) for 3 minutes in Octagonal blender. Tablets were compressed^[7]. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Pre formulation studies

The pure drug were evaluated for pre formulation studies like organoleptic properties in that colour, taste and odour then melting point determination, particle size distribution of pure drug, loss on drying, determination of λ max, flow properties of API like bulk density, tapped density, compressibility index, hausner's ratio and drug excipients compatibility study.

Evaluation of granules

The granules were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index and drug content. Angle of repose decided by funnel method. Bulk density and tapped density were determined by cylinder method, and Carr's index (CI) was calculated using the subsequent equation. $\text{Carr's Index} = \left(\frac{\text{TBD} - \text{LBD}}{\text{TBD}} \right) \times 100$. Hausner's ratio was associated with interparticle friction and will be wont to predict powder flow properties. Hausner's values of the prepared granules ranged from 1.12 to 1.25 was thought to point good flow properties

In vitro drug release studies

Drug release studies were conducted using USP- Type II apparatus, paddle type (Electrolab, Mumbai, India) at a rotational speed of 50 rpm at $37 \pm 0.5^\circ$. The dissolution media used were 1000 ml of 0.1 mol/l HCl for first 2 h followed by pH 6.8phosphate buffer solution for 12 h. Sink condition was maintained for the whole experiment. Samples (10 ml) were withdrawn at regular intervals and the same volume of pre-warmed ($37 \pm 0.5^\circ$) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45 μ membrane filter (Nunc, New Delhi, India) and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700) at 233 nm. The dissolution test was performed in triplicate. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve.

Kinetic Analysis of release data:

The release data obtained were treated consistent with zero-order ($R = K1t$), first-order ($R = K1t$), Higuchi ($R = K3\sqrt{t}$), Korsmeyer-Peppas ($\log R = \log K4 + n \log t$) equation, Hixson-Crowell equations $\left((UR)^{\frac{1}{3}} = K5t \right)$ to seek out the equation

Table 1: Compositions of different formulations

	S.no	Ingredients	F1	F2	F3	F4	F5	F6	F7
Intragranular materials	1	API	850	850	850	850	850	850	850
	2	Pregelatinized starch	40	40	40	40	40	40	40
	3	HPMC K200m	-	10	20	30	30	30	30
	4	DCP	20	95	70	45	30	15	
	5	Stearic acid	-	-	-	-	15	30	45
Binders	6	PVP K90	20	20	20	20	20	20	20
	7	Stearic acid (melt)	200	100	100	100	100	100	100
	8	Purified water	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Extra granular materials	9	HPMC K 200	-	15	30	45	45	45	45
	10	Aerosil	10	10	10	10	10	10	10
	11	Magnesium stearate	10	10	10	10	10	10	10
		Average weight	1150	1150	1150	1150	1150	1150	1150

with the simplest fit. Where R and UR are the released and unreleased percentages, respectively, at time (t); k₁, k₂, k₃, k₄, and k₅ are the speed constants of zero-order, first-order, Higuchi matrix, Peppas-Korsmeyer, and Hixon-Crowell model, respectively. so as to match the discharge profile of various formulas with possible difference in release mechanisms (n values), a mean dissolution time (MDT) was calculated using Equation. $MDT = \frac{(\frac{n}{n+1})K^{-1}}{n}$ Where n = release exponent and K= release rate constant.

Statistical Analysis

Moore and Flanner proposed a model independent mathematical approach was used for comparison of dissolution profile of selected formulation with marketed product. The dissolution profiles were compared by using two factors, F1 (Dissimilarity factor) and F2 (Similarity factor). When the 2 profiles are identical, F2=100. FDA has set a public standard of F2 value between 50-100 indicate similarity of two dissolution profiles, and ensures equivalence of the performances of the 2 products^[9]. F1 value above 15 to point dissimilarity.^[14]

RESULT AND DISCUSSION

In the preformulation studies color, taste and odor of pure drug was observed within the specifications (Table 2). Melting of active pharmaceutical ingredient was determined by using melting point apparatus, and the results are within the specifications. And the particle size of the pure drug of active pharmaceutical ingredient was found to be within the range of 180 – 250 microns. Loss on drying also of API was determined by digital moisture balance, the results are given in the following table. The actual quantity to be dispensed for trial batches was calculated base upon the assay (On dried basis) and loss on drying of API, The λ max of the sample was checked by using UV spectrophotometer and it was found at 233.3nm. Standard calibration curve was prepared by preparing different concentrations of active pharmaceutical ingredient in the range of 2 – 10 mcg/ml. then the absorbance of those solutions was scanned

at 232nm against blank No change in physical appearance was observed during compatibility studies with excipients^[12]. The results are given in the table below. (Table 3) The drug and exepients are compatible, and suitable to develop the formulation. Based on Preformulation data, Hypromellose K200M, Povidone K90 and Stearic acid was taken as drug release retardants for formulation of SR matrix tablets of a highly water soluble Class III drug. The tablets were formulated by wet granulation technology using the above mentioned polymers to match the drug release with that of marketed product.^[8-13]

Table 2: Preformulation studies of pure drug

Test	Specification	Observation
Color	White	White
Taste	Bitter	Bitter
Odor	Odorless	Odorless
Melting point	222 - 226°C	223°C
Loss on drying	Not more than 0.5%	0.10%

Figure 1: Calibration curve of API**Table 3: Absorbance of different concentrations of pure drug**

S.NO.	Conc.(mcg/ml)	Absorbance(nm)
1	2	0.201
2	4	0.375
3	6	0.558
4	8	0.758
5	10	0.95

Table 4: Blend flow properties of different formulation

S.no	Formulation Code	Bulk Density	Tapped Density	Hausner's Ratio	Compressibility Index	Angle of Repose	LOD (%)
1	F001	0.5	0.625	1.25	20	35 ± 0.65	2.42
2	F002	0.523	0.689	1.31	24	40 ± 0.72	2.33
3	F003	0.512	0.625	1.22	18	37 ± 0.77	2.46
4	F004	0.521	0.671	1.28	22	38 ± 0.29	2.1
5	F005	0.515	0.662	1.28	22	33 ± 0.81	3.2
6	F006	0.519	0.659	1.26	21	30 ± 0.72	2.74
7	F007	0.511	0.625	1.22	18	28 ± 0.29	2.82

Table 5: Physical parameters of tablets

Formulation Code	Average Weight (mg)	Thickness (in mm)	Hardness (kg/cm ²)	Drug content (%)	Friability (%) F = 100 (1- w ₀ /w _t)	Assay (%)
F1	1148.2±2.80	7.19±0.05	18±0.458	98.88±0.990	0.174%	98.2
F2	1150.35±2.8	7.12±0.04	19.6±0.519	99.81±1.206	0.18%	99.1
F3	1150.38±2.8	6.98±0.07	20.3±0.435	97.713±1.062	0.15%	98.6
F4	1151.06±3.4	7.20±0.02	21.3±0.65	100.45±2.458	0.14%	99.3
F5	1150.4±3.27	7.21±0.06	20.65±0.535	99.69±0.687	0.16%	99.1
F6	1151.99±4.1	6.89±0.09	19.95±0.5	99.497±0.529	0.19%	99.4
F7	1150.46±3.4	6.87±0.07	20.7±0.50	101.81±1.555	0.19%	98.21

n= 10, All the values are mentioned in average±SD

Table 6: Invitro release profile of different formulations

Time (hrs)	% Amount of drug released						
	F001	F002	F003	F004	F005	F006	F007
0	0	0	0	0	0	0	0
0.5	62.4	53.5	44.6	36.4	31.1	26.2	23.6
1	93.1	67.2	61.2	52.1	43.6	38.4	35.5
2	98	78.6	72.5	65.5	59.1	56.5	49.3
3	-	88.9	81.2	74.6	70.7	66.4	59.6
4	-	98.7	90.6	85.7	80.4	76.8	71.7
5	-	102.1	97.8	92.4	89.6	86.7	79.5
6	-	-	101.7	98.8	96.2	92.3	88.7
8	-	-	-	103.5	99.1	98.1	95.8
10	-	-	-	-	102	100.5	98.5

**All values are expressed as mean, n = 6*

Table 7: Regression values for various kinetic models of F7

F7	Zero order	First order	Higuchi	Peppas	n
R ²	0.6371	0.9746	0.985	0.991	0.4926

Table 8: Assessment of similarity and dissimilarity factors

Time (hours)	Reference Product	Test product	R – T	(R – T) ²
0	0	0	0	0
0.5	21.1	23.6	2.5	6.25
1	33.4	35.5	2.1	4.41
2	47.8	49.3	1.5	2.25
3	56.8	59.6	2.8	7.84
4	68.2	71.7	3.5	12.25
5	78.3	79.5	1.2	1.44
6	87.4	88.7	1.3	1.69
8	93.7	95.8	2.1	4.41
10	97.2	98.5	1.3	1.69
F ₁		3.1		
F ₂		81.16

Figure 2: IR Spectra of API

Figure 3: IR Spectra of physical mix

All the physico chemical properties of granules (bulk density, tapped density, angle of repose, Carr's index, and Hausner ratios) were determined. The results are summarized in the following (Table 4).

Compressibility index of all the formulations are measured and found to be 20%, 24%, 18%, 22%, 22%, 18% respectively for F1, F2, F3, F4, F5, F6, F7. From the observations F1, F3, and F7 having fair flow property, and F2, F4, F5 and F6 having passable flow property. The Hausner's ratios of all formulations are measured and results found to be almost within the fair to passable range.^[10] The angle of repose of all formulations are measured and found to be within the range of passable to good All the physical parameters of the compressed tablets (thickness, hardness, friability and weight variation) were measured and the results are summarized in the (Table 5).

Figure 4: Invitro release profile of different formulations

Figure 5: First order release kinetic profile of different formulations

Figure 6: Higuchi kinetic release profile of different formulations

Figure 7: Korsemeyer – peppas release profile of different formulations

Figure 8: Comparative dissolution profile of F7 and reference product

The matrix tablets of various batches formulated were evaluated for test such as uniformity of weight,

hardness, thickness, friability and drug content. The weight variation tests were performed according to as per procedure given in British pharmacopoeia. All formulations are found to be satisfactory. The thickness of the matrix tablet was found to be in the range of 6.7 to 7.2 mm. The hardness of all batches ranged from 17.0-22.0 KP. Another measure of tablet strength is friability. The friability of all formulation ranged from (0.17 % to 0.19%) which was below 1% limit as per the British pharmacopoeia indicating that the friability is within the specification limit.

The sustained release tablet was formulated to release the drug up to 10 hrs by varying polymer and Stearic acid concentration.

In formulation F1 melt stearic acid (hydrophobic agent) only used as drug release retarding agent without using of HPMC K200M. During dissolution studies fast release of drug was observed, 99% of drug released within 2 hours. So the release rate was not satisfactory

In formulation F2 3% HPMC K200M (was used along with melt Stearic acid. The drug release was retarded up to 5 hours, but the release rate profile was not satisfactory,

In formulation F3, F4, 6% and 9% HPMC was used along with melt Stearic acid, the drug release was controlled up to 8 hours, but the release rate was not matched with the reference product and also with IP specifications.

From formulation F4 to F7 1%, 2.5%, 4% Stearic acid was added intra granularly, the drug release was retarded up to 10 hours and the release profile of F7 was almost matched with the reference product. The similarity factor was observed 81.16%.

In vitro release study data indicates that duration of release of drug is dependent on the percentage of selected polymer and Stearic acid used in the formulations and, an increase in the polymer concentration not only causes increase in the viscosity of the gel but also leads to formation of gel layer with a longer diffusion path and the Stearic acid induces the hydrophobicity. This leads to a decrease in the diffusion of the drug and therefore a reduction in the drug release rate (Table 6).

Regression values for determined the various kinetic models of F7 (Table 7)

From the dissolution profiles, test product drug release found almost same as reference (Table 8)

Stability is an important parameter evaluated for the formulations to assess the stability of the drug in the formulation at the probable storage conditions.

The optimized formula Tablets were packed in PVC/PVDC clear Aluminium blisters and charged for stability as per ICH guidelines given in (Table 1) at 40° C/75%RH (1,2,3,6 month) Then the samples

were tested for assay, dissolution and related substances.

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REFERENCES

1. Modi Kushal, Modi Monali, Mishra Durgavathi, Panchal Mittal (2013) oral controlled release drug delivery system: an overview. International research Journal of Pharmacy. DOI: 10.7897/2230-8407.04312
2. Leon Shargel, Susanna Wu-Pong, Andrew B.C.Yu Applied Biopharmaceutics & Pharmacokinetics. Modified-Release Drug Products. 6th Edition, 2004:515-16.
3. Ratnaparkhi, M. P., & Gupta Jyoti, P. (2013). Sustained release oral drug delivery system-an overview. Terminology, 3(4).
4. Inoue S, Bian K, Okamura T, Okunishi H, Toda N. (1989) Mechanisms of action of eperisone on isolated dog saphenous arteries and veins Japanese journal of pharmacology, 50(3), 271-282. DOI: [10.1254/jip.50.271](https://doi.org/10.1254/jip.50.271)
5. Vamshidhar Reddy, D., & Rao, A. S. (2014). Formulation and evaluation of extended release tablets of Tapentadol hydrochloride using hydrophilic-hydrophobic polymer combinations. Journal of Pharmacy Research, 8(10), 1368-1374.
6. Jain, P., Jain, S., & Khan, M. A. (2019). Formulation and Evaluation of Extended Release Floating Matrix Tablet of Eperisone Hydrochloride by Direct Compression Method. Journal of Drug Delivery and Therapeutics, 9(3-s), 86-92. DOI [10.22270/jddt.v9i3-s.2798](https://doi.org/10.22270/jddt.v9i3-s.2798)
7. Alfred Martin, Physical Pharmacy-physiochemical principles in the pharmaceutical sciences. 4th ed. B.I Waverly Pvt. Ltd, New Delhi, 1996, pp 313-316.
8. Martin A, Micromeritics. In: Martin A, ed. Physical Pharmacy. Baltimores, MD: Lippincott Williams and Wilkins; 2001, pp 423-454.
9. Subramanyam CVS. Textbook of Physical Pharmaceutics, 2nd edition Vallabh Prakashan., 2001 pp 315.
10. Pharmacopoeia of India. New Delhi: Ministry of Health and Family Welfare, Government of India, Controller of Publications. 1996; 2:5 55-56.
11. Lachman Leon, Liberman H.A and Kanig J.L., "The Theory and Practice of Industrial Pharmacy" (3rd Edn) Varghese publishing House Bombay, 1991 pp. 430-456

12. Carstensen, J. T. (1996). Modeling and data treatment in the pharmaceutical sciences. CRC Press.
13. Ozturk, S. S., Palsson, B. O., Donohoe, B., & Dressman, J. B. (1988). Kinetics of release from enteric-coated tablets. *Pharmaceutical research*, 5(9), 550-565.
14. Dressman, J. B., Fleisher, D., & Amidon, G. L. (1984). Physicochemical model for dose-dependent drug absorption. *Journal of pharmaceutical sciences*, 73(9), 1274-1279.