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Factorial Design And Optimization Of Antiepileptic Drug: Lamotrigine Cocrystals Immediate Release Tablets

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Abstract

Objectives: The current study goal was to come up with an immediate release (IR) formulation for lamotrigine. Lamotrigine is a low soluble and high permeable biopharmaceutical classification class (BCS)-II drug. **Method:** 4-Hydroxy benzoic acid (4HBA), saccharin sodium (SAC), and methyl paraben (MP) were used as cocrystals formers to form IR tablets of lamotrigine. Variable amounts of L-Hydroxypropyl cellulose (L-HPC) and Croscarmellose sodium in different quantities using factorial design (22) by wet granulation. The amounts of the superdisintegrant (L-HPC and Croscarmellose sodium) X1 and X2 were chosen as independent variables to acquire drug release, respectively. The dependent variables were drug release, hardness, and disintegration time. **Results:** For each cocrystals formation, four formulations were created (4-HBA, SAC, MP), and a total of 12 formulations were tested utilizing pharmacopoeia limits. All of the factorial batches were found to be within the standard limits. All formulation dissolution characteristics were kinetically fitted, and numerous statistical parameters were established. For the dependent variables, polynomial equations were created and verified. Formulation F11, which contained 10 mg of HPC SSL and 3 mg of Croscarmellose sodium, was the most comparable (similarity factor (f2) =60.86, difference factor (f1) =8.36) to the commercial product (Lamictal). **Conclusion:** Fickian diffusion, and zero-order kinetics (n = 0.3479) are followed by the optimal formulation (F11). The F11 formulation is used to treat simple and complicated partial seizures as well as generalized tonic-clonic seizures that are resistant to multiple medication treatments. The best formulation shows good retention characteristics, which will ultimately improve the clinical response.

Key words: Factorial design, Fickian diffusion mechanism, Hydroxypropyl cellulose, Immediate release tablet, Lamotrigine, Zero order kinetics.

1. Introduction

The immediate-release dosage form should dissolve or disintegrate in the stomach within a short period of time. The advancements in increased oral protein delivery technologies, such as instant release tablets that may release pharmaceuticals at a faster rate, are particularly promising for the administration of poorly soluble drugs, such as high molecular weight proteins and peptides. Because of the low cost of therapy production and the convenience of administration, the oral route remains the best method for administering therapeutic agents. This results in high levels of patient compliance. [1-8]

According to the literature, the use of superdisintegrants is critical in the preparation of medicinal products. The development of a quickly dissolving tablet is made possible by the use of appropriate diluents and super disintegrants. [9]

A superdisintegrant is utilized to achieve the highest rate of disintegration and solubility for optimum bioavailability. Because of the high need for faster dissolving, a new innovation of "Superdisintegrants" has been developed in addition to the disintegrates [10]. Superdisintegrant is commonly used by formulation scientists to develop Fast Dissolving Tablets (FDTs) or to increase medication solubility [11]. The most commonly used superdisintegrants are crospovidone (XPVP), croscarmellose sodium (CCS), low-substituted hydroxyl propyl cellulose (L HPC), and sodium starch glycolate (SSG).

Among granulation techniques, wet granulation is the most widespread granulation technique used despite the fact that it involves multiple unit processes such as wet massing, drying, and screening, which are complex, time-consuming, and expensive, requiring large amounts of space and multiple parts of equipment. The current study focuses on the development of an IR formulation for lamotrigine. [12] Lamotrigine is an antiepileptic drug belonging to the phenyltriazine class. It is classified as biopharmaceutical class II. It's used to treat both epilepsy and bipolar illness, as well as a mood stabilizer. Lamotrigine works by selectively binding to the inactive sodium channel to block sodium currents. suppressing the release of the excitatory amino acid, glutamate. Lamotrigine is promptly and completely absorbed with minimal first-pass metabolism effects, with a bioavailability of 98%. Cmax is obtained between 1.4 to 4.8 hours' post-dose. Lamotrigine apparent volume of distribution (Vd/F) after oral dosing varies between 0.9 and 1.3 L/kg. Lamotrigine is thought to bind to approximately 55% of plasma proteins. It has an average elimination half-life of 14–59 hours. It is eliminated from the body primarily in urine (65%) and with only a small portion excreted in feces (2%). [13-15]

As a result, research was intended to prepare and assess IR tablets for Lamotrigine as a model medication, with the goal that the optimum formulation trial would exhibit the medicine's desired IR by means of an increased dissolving rate.

In the design and development of pharmaceutical products, response surface methodology (RSM) with a polynomial equation has been widely used. 22 factorial design, central composite design, and Box-Behnken design are examples of RSM variations. RSM is applied when only a few important factors are involved in the optimization process. This strategy has the benefit of requiring less testing and time, producing more effective outcomes, and being less expensive than classic experimental methods. [16-18]

As a result, in the current study, an attempt was made to prepare IR Lamotrigine tablets utilizing Hydroxy Propyl Cellulose (HPC) and Croscarmellose Sodium (CCS). To study the influence of formulation factors on release properties, a normal statistical technique called design of experiments was utilized instead of a heuristic method.

The influence of superdisintegrant on the drug release profile (effect of independent variables or factors), i.e., the quantity of HPC and CCS on the dependent variables (drug release, hardness, and disintegration time), was investigated using a 22 factorial design [19].

2. Materials

The resources utilized in the study came from a variety of places. Lamotrigine was a gift sample from A-Z pharmaceuticals at Chennai. Hydroxypropyl cellulose and Croscarmellose sodium were obtained from the Sigma-Aldrich chemical Pvt. Ltd, Microcrystalline cellulose lactose monohydrate, talc and magnesium stearate were purchased from Hi-media laboratories Pvt. Ltd.

Methods

2.1 IR Lamotrigine tablet formulation and development

Quantities needed for the HPC and CCS in IR Lamotrigine tablet preparation were selected as independent variables one of the goal of IR forms. To achieve quick medication release, superdisintegrants were used. Backward stepwise linear regression analysis chose drug release (Y1), hardness (Y2), and disintegration time (Y3) as dependent variables. [20,21]

The 2 levels of X1 (CCS) were 3 mg and 6 mg (weight with respect to per tablet). The 2 levels of X2 (HPC) were 4 mg and 10 mg (weight with respect to per tablet). Twelve IR Lamotrigine tablet formulations were created utilizing different combinations of three coformers cocrystals (HBA, SAC, and MP) with X1 and X2 being tested for the selection of the optimal composition needed to satisfy the study's primary goal.

2.2 IR Lamotrigine tablets preparation by wet granulation technology

The ingredients were procured and weighed accurately. For 10-15 minutes, they were blended equally in a polythene bag. The weighed quantity of Cocrystals with half the quantity of CCS, HPC, and lactose monohydrate all passed through screening (#40). Granulation with distilled water and drying at 55 ºC in a hot air oven for 2 hours. The prepared granules were transferred to a sieve (#30) and mixed for 10 minutes with the remaining amounts of CCS. The lubricant was then added, followed by thorough mixing and compression using a tablet compressor. The pharmacopoeia limitations were verified on the finished tablets. The tablets were kept in airtight containers that were well-sealed.

2.3 Design of an Experiment

The experimental design employed in this study was a 2^2 factorial design, with the quantity of CCS labeled X1 and the quantity of HPC labeled X2, and they are presented in Table 1. The 2 levels chosen for both X1 and X2, in the case of X1, were coded as -1=3 mg and +1=6 mg. X2 was coded as -1 = 4 mg and +1 = 10 mg. In Table 2, the factorial trail formulations are presented.

2.4 IR Lamotrigine Tablets Evaluation

2.4.1 Variation in weight

The weight variation test is used to confirm that the weight of tablets in a batch is consistent. The average was computed using the total weight of 20 tablets from each formulation. Individual tablet weights were also obtained with accuracy, and the weight variation was estimated. [22]

2.4.2 Hardness

A Monsanto hardness tester was used to carry out this test. The average hardness value is taken by measuring six tablets from each formulation.

2.4.3 Friability

This experiment was performed in a Roche friabilator. The original weight (W0) of 20 tablets was recorded, and they were then dedusted in a drum at 25 rpm for 4 minutes before being weighed (W). The following equation was used to compute percentage friability. The weight loss should not be more than 0.8%.

$$\%\text{Friability} = [(wo-w)/w] \times 100 \quad \text{Equation 1}$$

2.4.4 Assay

This experiment was carried out by pulverizing a set number of samples (20). The above-mentioned resulting combination powder was dissolved in 100 mL of solvent (6.8 buffer) and sonicated if necessary filtering. An ultraviolet (UV)-visible spectrophotometer set to 239 nm was used to test the absorbance of the resultant solution. [22]

2.4.5 Thickness

Vernier calipers were used to carry out this test. Six tablets from each formulation are measured to get the average thickness value.

2.4.6 Disintegration test

Six glass tubes "3 long, open at the top, and held against a 10" screen at the bottom end of the basket rack assembly" were used as the USP device to test disintegration. One tablet is inserted in each tube, and the basket rack is placed in a 1-liter beaker of distilled water at 37±2 ºC, with the tablets remaining below the surface of the liquid on their upward movement and descending no closer than 2.5cm from the bottom of the beaker [23].

2.4.7 In vitro dissolution

The USP Apparatus 2 was used to conduct the dissolution tests. Official techniques were followed, such as using 500 mL of pH 1.2 (0.1N HCl) buffer at 50 rpm and 37±0.5°C as the dissolving media. A pre-filter attached syringe was used to collect samples at pre-determined intervals, and new fluid was replaced at the same time. A Lab India UV-3200 UV-Visible spectrophotometer was used to assess the absorbance of samples at 239 nm (n=3) [23-25]

2.4.8 Drug release kinetic modeling

The kinetic data were statistically modeled using kinetics of zero order, first order, Higuchi, and Korsmeyer-Peppas. [26-29].

3. Results and Discussion

A 2^2factorial design was used to construct Lamotrigine IR tablets in order to determine the optimal composition of superdisintegrants (CCS and HPC) and get immediate drug release from the formulation. The layout for an experimental design is presented in Table 1. The quantity of CCS and HPC were designated as independent variables (X1, X2) in the formulation design, whereas drug release (Y1), hardness (Y2), and disintegration time (Y3) were chosen as dependent variables. Four formulations were

developed for each Cocrystals former (4-HBA, SAC, MP) and a total of twelve formulations were designed. All trials had 20 mg of Lamotrigine with conformer crystals as an IR tablet dosage form by wet granulation, represented in Table 2.

Table 1. Layout for an experimental design

Name of Ingredients	Experimental design											
	F 1	**F 2**	**F 3**	**F 4**	**F 5**	**F 6**	**F 7**	**F 8**	**F 9**	**F 10**	**F 11**	**F 12**
X-1 (CCS)	-1	1	-1	1	-1	1	-1	1	-1	1	-1	1
X-2 (HPC)	-1	1	1	-1	-1	1	1	-1	-1	1	1	-1

CCS- Croscarmellose Sodium, HPC- Hydroxy propyl Cellulose

Table 2. Formulation of IR Lamotrigine tablets

S.No	Ingredients' names	Amount of ingredients per tablet (mg/Tablet)											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	LTG+Cocrystal former	20	20	20	20	20	20	20	20	20	20	20	20
2	Croscarmellose Sodium (CCS)	3	6	3	6	3	6	3	6	3	6	3	6
3	Microcrystalline Cellulose	50	50	50	50	50	50	50	50	50	50	50	50
4	Hydroxy propyl Cellulose (HPC)	4	10	10	4	4	10	10	4	4	10	10	4
5	Lactose Monohydrate	120	111	120	111	120	111	120	111	120	111	120	111
6	Talc	1	1	1	1	1	1	1	1	1	1	1	1
7	Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
8	Total Weight	200	200	200	200	200	200	200	200	200	200	200	200

LTG-Lamotrigine, CCS- Croscarmellose Sodium, HPC- Hydroxy propyl Cellulose, F1-F4: LTG+ HBA Cocrystals, F5-F8: LTG+ MP Cocrystals, F9-F12: LTG+SAC Cocrystals

Various final product quality assurance tests were performed on all final batches, including weight variation, mean hardness, mean thickness, friability, and drug content [30-31]. Table 3 shows a summary of the findings.

Table 3. Parameters for ensuring the quality of the final product

Formulation Code	Weight Variation [a] (%)	Thickness [b] [mm]	Hardness [b] [kg/cm2]	Friability [c] [%]	Disintegration [b] [min]	Drug Content [b] (%)	CDR at 60 min [b] (%)
F1	197	3.15	5.9	0.64	19.3	97.4	89.05
F2	194	3.19	6.0	0.70	20	96.02	88.01
F3	198	3.0	5.8	0.62	19.2	98.2	90.25
F4	196	3.17	5.92	0.69	19.85	96.24	87.01
F5	199	2.89	4.9	0.56	17.58	98.2	99.25
F6	195.2	2.98	5.1	0.62	17.95	97.0	98.25
F7	199	2.8	4.8	0.54	17.5	99.8	100.01
F8	197	2.9	4.95	0.59	17.75	97.3	97.01
F9	199.9	2.75	4.35	0.46	14.28	99.4	99.25
F10	196.5	2.84	4.54	0.5	15	98.01	98.02
F11	200±0.12	2.65	4.25	0.42	14.2	100.4	100.2
F12	199	2.78	4.44	0.48	14.3	98.4	98.25

Mean a (n=20); b (n=6); c (n=10)

The hardness of the produced batches ranged from 4.25±0.3 to 6.0±0.5 kg/cm2. The thickness of the final batches ranged from 2.65±0.15 to 3.19±0.14 mm. The friability test yielded a result of less than 0.70 percent. The approval criterion for drug content in final batches was reached. For finished batches, drug release experiments were conducted using a pH 1.2 buffer under a standard set of settings of 50 rpm (paddle), 37±0.5°C.

Table 4. Drug release kinetic modeling

F.Code	Zero order		First order		Higuchi's		Peppa's		Release Mechanism
	%CDR Vs. Time		Log% Remaining Vs. Time		%CDR Vs. √T		Log% CDR Vs. Log T		
	K_0	r^2	K_1	r^2	K_H	r^2	n	r^2	
F1	1.594	0.922	0.036	0.991	9.915	0.739	0.458	0.978	Fickian
F2	1.568	0.926	0.034	0.990	9.785	0.747	0.460	0.976	Fickian
F3	1.625	0.913	0.038	0.991	10.110	0.733	0.438	0.984	Fickian
F4	1.547	0.929	0.033	0.989	9.681	0.754	0.468	0.974	Fickian
F5	1.712	0.896	0.066	0.807	10.79	0.737	0.374	0.986	Fickian
F6	1.695	0.901	0.057	0.868	10.660	0.739	0.388	0.989	Fickian
F7	1.732	0.895	0.062	0.850	10.870	0.731	0.375	0.990	Fickian
F8	1.674	0.905	0.050	0.906	10.550	0.744	0.394	0.988	Fickian
F9	1.719	0.887	0.067	0.823	10.83	0.729	0.354	0.983	Fickian
F10	1.689	0.888	0.055	0.877	10.61	0.727	0.356	0.984	Fickian
F11	1.741	0.999	0.644	0.866	11.04	0.736	0.349	0.996	Fickian
F12	1.682	0.894	0.056	0.852	10.57	0.732	0.366	0.981	Fickian

K_0-Zero order rate constant, r^2- Regression coefficient, K_1-First order rate constant, K_H-Higuchi's order rate constant, n-diffusion coefficient

The findings show that all formulation batches match zero-order kinetics the best, with r2 values ranging from 0.887 to 0.999. They also suit Peppas' kinetics, with r2 values ranging from 0.974 to 0.996. All batches follow a Fickian diffusion mechanism according to the Peppas kinetics (n values 0.348–0.468). Results are represented in Table 4.

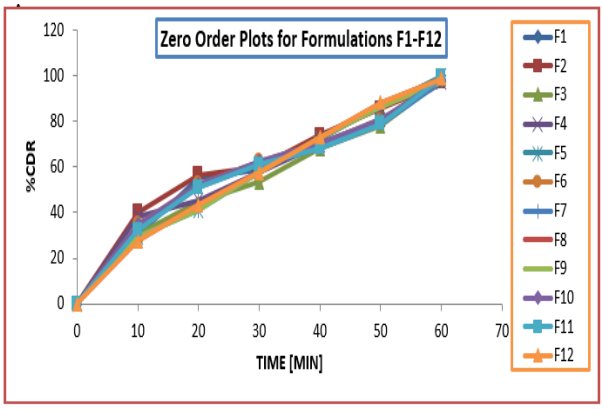

Figure 1. Zero-order graphs for comparison of F1-F12

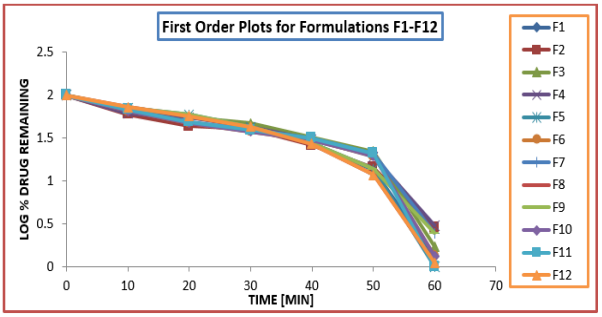

Figure 2. Comparative first order plots of F1-F12

The kinetic plots show the cumulative drug dissolution release shown in Figures 1-4, while Table 4 summarizes the statistical values. The percentage cumulative drug release for completed batches F1–F12 was 87.01–100.2 percent at the end of the 60th minute. The quantity of superdisintegrant was directly related to the rate of drug release, according to the findings.

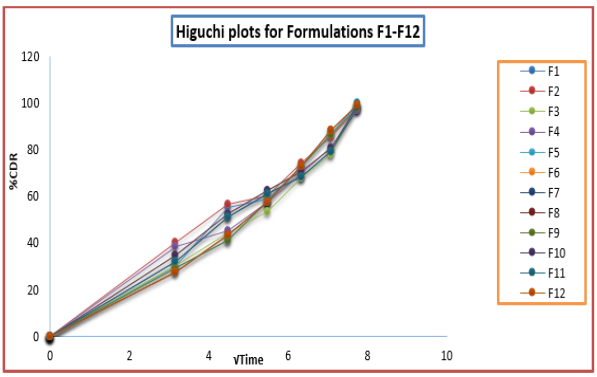

Figure 3. Higuchi plot for comparison of F1-F12

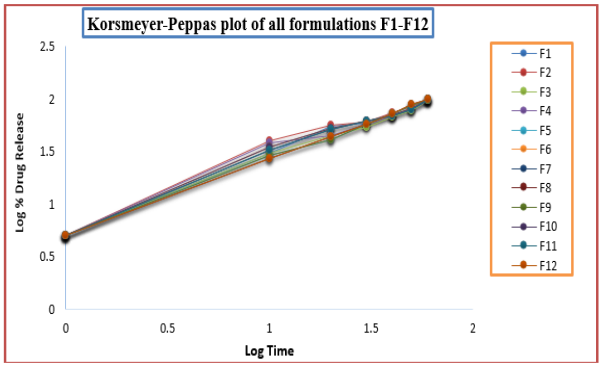

Figure 4. Comparative Korsmeyer-Peppas plots of F1-F12

The changes in the proportions of X1 and X2 caused a variation in dependent variables. The release characteristics of Formulation F11, which contained 3 mg of CCS and 10 mg of HPC, were satisfactory (100.2 percent at the end of the 60th minute), owing to variations in the superdisintegrant concentration.

An increase in superdisintegrant concentration causes a proportional increase in drug release (due to high disintegration). Kinetic modeling was used to examine the dissolving characteristics of IR Lamotrigine tablets. Table 4 and Figures 1-4 summarize the findings.

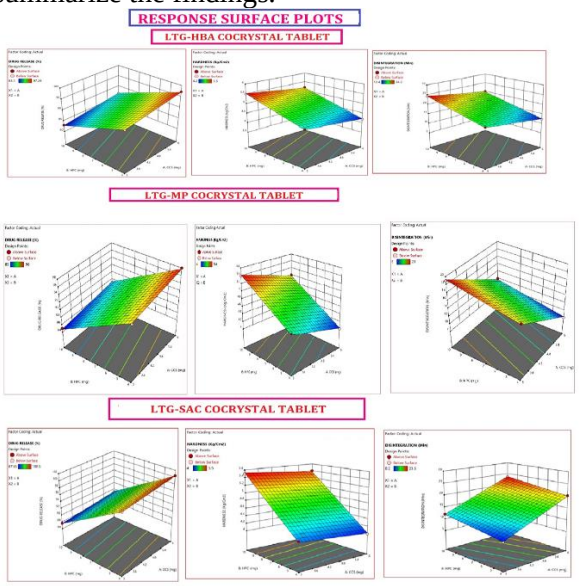

Figure 5. Response morphological plots

With the aid of PCP Disso software, polynomial equations were established for all dependent variables using linear stepwise backward regression analysis, and response morphological plots were created using design of experiment version 12.

Figures 5 show the response morphological plots for drug release (Y1), hardness (Y2), and disintegration time (Y3), with X1 and X2 on both axes to demonstrate the impacts of independent

factors on dependent variables. Table 4 shows the kinetic parameters for the trials (F1-F12).
For the 2^2full factorial designs, the polynomial equation was as follows:
Y=b0+b1 X1+b2 X2+b12 X1X2 Equation 2
Y- dependent variable, b0- mean response of 12 trials, b1- estimated coefficient for X1, b2 - estimated coefficient for X2, b12- interaction term
The dependent variable equations were derived as follows:
Y= 94+0.87 X1-5.56 X2-4.837 X1X2 (Drug Release) Equation 3
Y=4.78-0.075 X1 + 0.6750 X2-0.050 X1X2 (Hardness) Equation 4
Y= 16.02+ 5.87 X1 + 1.83 X2+ 10.742 X1X2 (Disintegration) Equation 5
The findings show that both X1 and X2 have an impact on drug release, hardness, and disintegration time. The findings suggest that increasing the amount of superdisintegrants increases the drug's release rate, and that the drug release rate may be adjusted by adjusting the amounts of X1 and X2 to appropriate levels. The created polynomial equation was valid, confirming the accuracy of the obtained equations. The effects of X1 and X2 on dependent variables were shown using response surface/surface morphological graphs. When compared to the marketed product(Lamictal), the final best (optimal, based on desirability factor over 0.999) formulation (F11) is an identical product with a similarity factor (f2) of 60.86, difference factor (f1) of 8.36, and a tcal is <0.05.

4. Conclusion

The current research work is aimed at the utility of superdisintegrants such as CCS and HPC in the formulation of IR tablets for Lamotrigine using a 2^2-factorial design. The results revealed that the amount of superdisintegrant was directly proportional to the rate of drug release from the formulation. Several patients require immediate onset of action in a specific therapeutic situation, necessitating fast release of the medication. This issue is expected to affect half of the population, leading to an increase in the prevalence of ineffective therapy [31]. As a result, pharmacists want to create superdisintegrants, which give the quick disintegration and dissolve rate necessary to ensure optimal bioavailability. Formulation F11 shows a Fickian diffusion mechanism and zero order release. This can be used to treat simple and complicated partial seizures as well as generalized tonic-clonic seizures that are resistant to multiple medication treatments. The best formulation shows good retention characteristics, which will ultimately improve the clinical response.

5. Acknowledgement:

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6. Ethical approval

The study did not require ethics committee approval or patient informed consent because it did not focus on any clinical parameters and did not utilize any humans or animals for the processing of work.

7. Conflicts of interest:

No conflict of interest was declared by the authors. The authors alone are responsible for the content and writing of the paper.

8. References

[1]. Leon Lachmann, Herbert A,Liberman, Joseph L.Kaing , The theory and practice of Industrial Pharmacy:293-303.
[2]. Ansel`s Pharmaceutical dosage forms & drug delivery systems, eighth edition, 227- 260
[3]. Aulton`s Pharmaceutics, The design & manufacture of medicines, Biopharmaceutics and pharmacokinetics, A Treatise, second edition, ValabhPrakashan, 315-384
[4]. Debjit Bhowmik, Chiranjib.B, Krishnakanth, Pankaj, R. Margret Chandira. Fast Dissolving Tablet: An Overview, Journal of Chemical and Pharmaceutical Research, 2009, 1(1): 163-177
[5]. Dali Shukla, Subhashis Chakraborty, Sanjay Singh, Brahmeshwar Mishra, Mouth Dissolving Tablets II:An Overview of Evaluation Techniques, www.scipharm.
[6]. SusijitSahoo, B. Mishra, P.IK. Biswal, Omprakash Panda, Satosh Kumar Mahapatra, Goutam Kumar Jana, Fast Disslving Tablet: As A Potential Drug Delivery System, Drug Invention Today 2010, (2), 130-133
[7]. A Gupta, AK Mishra, V Gupta, P Bansal, R Singh, AK Singh, Review Article, Recent Trends of Fast Dissolving Tablet - An Overview of Formulation Technology, International Journal of Pharmaceutical & Biological Archives2010; 1(1): 1 – 10

[8]. Shailesh S, Gurjeet S and Gupta AG: Formulation design and optimization of mouth dissolving tablets of Domperidone using the sublimation technique. International Journal of Pharmaceutical Sciences 2010; 1(1): 128-36

[9]. Bhowmik D, Chiranjib, Yadav J, Chandira RM and Sampath KKP: Emerging trends of disintegrants used in formulation of solid dosage form. Scholars Research Library 2010; 2(1): 495-04.

[10]. Patil CG and Majumdar SH: Comparative success of natural superdisintegrant over synthetic superdisintegrants in fast disintegrating tablets. Asian Journal of Biomedical and Pharmaceutical Sciences 2012; 2(12): 69-72.

[11]. Rhodes CT, Robinson JR. Sustained and controlled drug delivery system. Modern Pharmaceutics (4th ed). New York; Marcel Dekker Inc; 2003:503-505.

[12]. Goa KL, Ross SR, Chrisp P: Lamotrigine. A review of its pharmacological properties and clinical efficacy in epilepsy. Drugs. 1993 Jul;46(1):152-76. doi: 10.2165/00003495-199346010-00009.

[13]. Garnett WR: Lamotrigine: pharmacokinetics. J Child Neurol. 1997 Nov;12 Suppl1: S10-5. doi: 10.1177/088307389701200l041.

[14]. Rambeck B, Wolf P: Lamotrigine clinical pharmacokinetics. Clin Pharmacokinet. 1993 Dec;25(6):433-43. doi: 10.2165/00003088-199325060-00003.

[15]. Schwartz JB, O'Connor RE. Optimization techniques in pharmaceutical formulation and processing. Drug Pharm Sci.1996; 72:727-752.

[16]. Gunda RK, Kumar SJN. Formulation development and evaluation of zidovudine sustained release tablets using 3^2factorial design. DerPharmSin.2015,6:59-67.

[17]. Ramu Samineni, Jithendra Chimakurthy, Sathish Kumar Konidala, Udayaratna K, Devatulasi K, Ager Dengoc. Effect of Hydroxy propyl methyl cellulose and microcrystalline cellulose in design and optimization of Nebivolol Hydrochloride immediate release tablets by response surface methodology. International Journal of Research in Pharmaceutical Science.2021;12(3):1990-1998.

[18]. Ramu Samineni*, Jithendra Chimakurthy, Sathish Kumar Konidala, Venkateswarao Yamarthy. Development and Validation of Analytical Method for Estimation of Balofloxacin in Bulk and Pharmaceutical Dosage Form by RP-HPLC. Research J. Pharm. and Tech.2022;15(7):2992-2996.

[19]. Kharia AA, Hiremath SN, Singhai K, Omray K, Jain K. Design and optimization of floating drug delivery system of acyclovir. Indian JPharmSci.2010; 72:599-606.

[20]. Gunda RK, Manchineni PR, Dhachinamoorthi D. Design, development, and in vitro evaluation of sustained release tablet formulations of olmesartanm edoxomil.MOJDrug desDevelopTher.2018; 2:164-169.

[21]. Gunda RK, Manchineni PR, Thangavel V. A statistical study on the formulation development of sustained release tablets for valsartansodium. MOJDrugdesDevelopTher.2018; 2:217-222.

[22]. Kumar JNS, Gunda RK. Design, formulation and evaluation of pravastatin fast dissolving tablets. PharmMet.2018; 9:16-23.

[23]. Maurya SK, Bali V, Pathak K. Bilayered transmucosal drug delivery system of pravastatin sodium: statistical optimization, *in vitro*, *ex vivo*, *invivo* and stability assessment. Drug Delivery. 2012; 19:45-57.

[24]. RamuSamineni, Jithendra Chimakurthy, Sathish Kumar Konidala, Udayaratna K, Devatulasi K, Ager Dengoc.Effect of Hydroxy propyl methyl cellulose and microcrystalline cellulose in design and optimization of Nebivolol Hydrochloride immediate release tablets by response surface methodology. 2021;12(3):1990-1998.

[25]. Ramanathan A, Sreeja Sreekumar G. Development of chrono modulateddrug delivery system of pravastatin sodium for the treatment of hypercholesterolemia. DerPharmSin.2014; 5:36-41.

[26]. PuttegowdaVD, KarkiR,GoliD,JhaSK,MudagalMP. Formulation and pharmacokinetic evaluation of micro capsules containing pravastatin sodium using rats.Scientifica(Cairo).2016;7623193.

[27]. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. JPharmSci.1963; 51:1145-1149.

[28]. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. PharmActaHelv.1985; 60:110-111.

[29]. Ramu Samineni, Jithendra Chimakurthy. Effect of Coformers on Novel Co-Crystals of Gabapentin: An *In Vivo* Approach.Journal of Pharmaceutical Sciences and Research. 2020;12(5):639-648

[30]. Ramu Samineni, Jithendra Chimakurthy, K Sumalatha, G Dharani, J Rachana, K Manasa, P Anitha.Co-Crystals: A Review of Recent Trends in Co Crystallization of BCS

Class II Drugs.2019;12(7):3117-3124.
[31].Ramu Samineni, K Sumalatha, G Dharani, J Rachana, P Anitha, K Manasa. Formulation and Evaluation of Oral Disintegrating Tablets of Montelukast Sodium and Desloratidine. Research Journal of Pharmaceutical Dosage Forms and Technology.2019;11(3):152-158.