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Product, Process and Packaging Optimization for Development of Stable Oral Capsule Formulation of Second-line Anti- Tubercular drug

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Abstarct

Objectives: Cycloserine (CS) is a second-line anti-tubercular drug. It is an analog of d-alanine amino acid which directly interfere with peptidoglycan formation and bacterial cell wall synthesis in susceptible strains of *Mycobacterium tuberculosis*. Stability of CS and flowability of its final blend are the two major problems in formulation development of CS capsules. The main objective of the present investigation was to develop stable and commercially viable robust formulation of CS at affordable price.

Materials and Methods: For product formula finalization, selection of appropriate grade of diluent and quantitative optimization of glidant, anti-adherent, lubricant and alkalizer (s) was done. For process parameter optimization; processing environmental condition, slugging, filling process and packaging material optimization were done.

Results: Avicel® PH 200 was selected as a diluent due to its higher particle size, hence better flow property. Addition of magnesium oxide and sodium carbonate as an alkalizer mixture increased the micro-environmental pH of formulation and prevented auto-aminolysis of CS. Slugging (Dry Granulation) was the suitable technique of choice because CS is a moisture sensitive API. Flowability of blend was further augmented by sodium stearyl fumarate, purified talc and colloidal silicone dioxide. In packaging material study, it was concluded that capsules packed in fompack Alu-Alu blister displayed better performance as compared to HDPE bottle with CRC closure at 25°±2°C /60±5%RH and 30°±2°C /65±5%RH in long term stability study.

Conclusion: The formulation developed in our lab is stable and cost effective, which can be easily afforded by people of developing or least developed countries.

Key words

Tuberculosis; Cycloserin; Alkalize; Stability; Flow improvement; Dry Granulation; Slugging; Packaging; Alu-Alu blister

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Introduction

Tuberculosis (TB) is a chronic granulamatous infection caused by *Mycobacterium tuberculosis*. In Asian and African subcontinent, it is endemic due to its resistance to drugs and situation is worst if the patients suffering from AIDS. WHO estimates that the largest number of new TB cases in 2008 occurred in the South-East Asian Region, which accounted for 35% of incident globally. An estimated 1.7 million people succumb to death from TB in 2009. The highest number of causalities was reported in the Africa Region [1].

Cycloserine (CS) is D- 4-amino-3-isoxazolidinone, is a broad spectrum antibiotic i.e. bactriostatic to *Mycobacterium tuberculosis* at the clinically recommended dose. CS is an analog of d-alanine amino acid. It interferes with peptidoglycan formation and bacterial cell wall synthesis in susceptible strains of gram positive and gram negative bacteria (*Mycobacterium tuberculosis*). CS is indicated for the treatment of active pulmonary and extra pulmonary tuberculosis [2]. CS is a white to off-white crystalline hygroscopic powder, soluble in water. It is rapidly destroyed at neutral or acidic pH. Cycloserine has a pH between 5.5 to 6.5 in the form of solution having concentration of 100mg of CS per ml. In the very high and low pH range inactivation of cycloserine is independent of pH. The stability of cycloserine increases with increasing pH. It is least stable in acidic condition, while most stable in alkaline environment. It is inactivated mainly by two processes: pH based auto-aminolysis and moisture based hydrolysis. The major degradation occurs in dilute aqueous solution or upon exposure to moisture by opening of isoxazolidone ring due to the hydrolysis of CS as represented in Figure 1. β-aminoxy D-alanine is the product generated by this reaction, which undergoes further hydrolysis to serine and hydroxylamine [3].

One of the prominent government pharmaceutical research centre of India, CDRI (Central Drug Research Institute, India) director have expressed his opinion on TB as, "Diseases like tuberculosis and malaria do not attract multinational drug development

companies because the market for such diseases is not very large. Given the fact that the cost of development of a new drug is around two billion dollars, whereas the market for drugs of tuberculosis is expected to be around three hundred million dollars, the MNCs (Multi National Companies) are not very keen to work on such diseases [4]". If any anti-tubercular or anti malarial drug formulation is developed by any of MNCs, then they will try to keep that formula as a trade secret rather disclosed it as a patent. Despite the fact that there are several formulations of CS available in the market, surprisingly the authors could not find the formula of Cycloserine capsules in the literature, including patents. However in a monopolistic market, price is greater than marginal cost [5]. Because of this Research & Development (R&D) monopoly; the manufacturers are selling Cycloserine capsules at a very high price for e.g. The cost of Eli-lilly's Seromycin® capsules containing Cycloserine 250 mg at 7.53 USD/capsule [6], which is equivalent to more than 350/- Indian rupees. That is very high cost and even the average Indian earner whose per capita income is Rupees. 54,527 in 2010-11 (means Rs.150 per day); according to the Indian government data [7], so it is intricate to afford this life-saving medication. So keeping in view of the interest of atleast 70% population of India, the disclosed formulation will be very helpful in bringing the cost down to a reasonable value.

Materials and Methods

Materials

Cycloserine API was purchased from Dong- A Pharmaceuticals, Korea. Various grades of Microcrystalline cellulose (Avicel DG and Avicel® PH 102, Avicel® PH 112, Avicel® PH 200) were purchased from FMC Biopolymer, USA. Two different grades of Colloidal silicone dioxide –Fumed Silica (Aerosil®-200 and Aeroperl®-300) were acquired from Evonic industries, Germany. Purified Talc was procured from Luzenac Pharma. Two varieties of Magnesium oxide manufactured by Dead Sea Periclase were purchased from Signet, Mumbai. Sodium carbonate was procured from Fischer Scientific, India. Empty capsule shells were purchased from ACG World, Mumbai, India.

Experimental methods

During commercial production of capsules, it is desirable to have the blend with good flow characteristics for smooth operation and efficient production. If the blend is having poor flow characteristics, then weight variation problem may arise and hence content uniformity might be a critical matter. Ideally, the powders used for capsule filling should have good flow property; they should produce even packing density i.e. the particles of each component should have particle size and densities as close as possible to avoid segregation (de-mixing) and the powder should not be adhesive to the surface of either capsule body or any metal parts of capsule filling machine [8]. While CS is a hygroscopic, pH sensitive API, sticky in physical nature and hence having poor flow characteristics. Because of its sticky nature all the toolings have to be dissembled, cleaned and assembled again for continuous production.

So, the problems encountered in handling powder mixtures during mixing and filling operations were so diverse for example from poor flow, sticking to low density based improper filling problems. In order to develop a stable and commercial viable robust technology for CS capsules, one by one stepwise problems were undertaken to make stable, free flowing robust formulation of CS capsule as per scheme represented in Figure 2.

Product Optimization:

Optimization of Anti-adherant

Purified talc prevents sticking of blend to the metal parts (tamping tips and hopper) of capsule filling machine [9]. So, amount of Anti-adherent was optimized in F1 to F6 batch on the basis of sticking property of blend.

Optimization of Lubricant

Lubricant helps in dosing or tamping of required quantity of blend in the capsule body, as it facilitate easy ejection of dose from dosing tube or dosing disc to capsule body [9]. Sodium stearyl fumarate was selected as a lubricant and its level was optimized in batch F7 to F11 according to its lubrication property for blend to be filled.

Selection and optimization of Alkalizer(s):

In very high and very low pH range, inactivation of cycloserine is independent of the pH. Cycloserine is most stable under alkaline condition and least stable under acidic condition.

Sodium based alkalizer: Sodium Bicarbonate and sodium carbonate are the two major sodium based alkalizers. Among sodium carbonate and sodium bicarbonate; sodium carbonate was selected on the basis of its higher pH of 11.4 (0.1M aqueous solution at 25ºC) and lower incompatibility/ reactivity as compared to sodium bicarbonate towards acidic drugs [12].

Magnesium based alkalizer: Among Light and Heavy variety of Magnesium Oxide; heavy variety was selected owing to its higher bulk density of 0.25 gm/ml as compared to light variety (0.15 gm/ml) [13].

Combination of sodium based and magnesium based alkalizers:

When sodium carbonate and magnesium oxide are used in combination and its quantity was optimized as in F12 to F20, then pH of the final formulation could be achieved equal to 11.0 or above; which was a required alkaline micro-environmental pH for CS stable formulation.

Selection and Optimization of Glidant

As a Glidant, Colloidal silicone dioxide is generally used to promote flow of blend to the capsule body [9]. Colloidal silicone dioxide is available mainly in two different grades: Aerosil® -200 and Aeroperl®-300. Among these two grades, Aeroperl® 300 was selected due to its higher tapped density (250gm/ml) as compared to Aerosil® 200 (50 gm/ml), because excipients having higher density were preferred for suitable filling of blend in the capsule and then its quantity was optimized in F21 to F24 batch [11].

Selection and Optimization of Diluent

Keeping in view of physicochemical properties of CS, diluents/fillers are used to increase the bulk volume of a capsule [9]. By combining a diluent with the active pharmaceutical ingredient, the final product is given adequate weight and size to assist in production and handling. Microcrystalline cellulose is the appropriate choice due to its less hygroscopicity and good flowability. Among various available grades of Microcrystalline

cellulose such as Avicel® PH 102, Avicel® PH 112 and Avicel® PH 200; Avicel® PH 200 was selected on the basis of higher particle size (180 um), lowest moisture content (NMT 2%), high bulk density (~0.35gm/cc) and very good flow property as compared to other grades [10]. In formulation F25 to F27 quantity of Avicel® PH 200 was optimized. Table 1 records all trial developmental batches as well as optimized batch no. F27 of cycloserine formulation.

Process Optimization

Processing Environmental Condition

Due to temperature and moisture sensitivity of API; all the processing steps were carried out at 25°C±5°C temperature and 30±5% relative humidity by dehumidification.

Density related issues for suitable filling- Slugging

After the powder ingredients have been homogenously blended by mixing in double cone blender at 10±2 RPM for 15 minutes, the flow of the resultant mixture was adequate to ensure delivery of sufficient powder to the capsules at the time of filling. Particle sizes and powder densities should be matched as closely as possible to assist in the prevention of de-mixing and proper filling. But at the end of product (formulation) optimization; Tapped Density (TD) was 0.53g/ml; but the required TD was 0.70 gm/ml for filling of material in size 1 capsule as Seromycin® as per capsule size dosator chart [14].

Compression granulation is a valuable technique in situation where the effective dose of a drug is too high for direct compression, and the drug is sensitive to heat, moisture or both, which precludes wet granulation. Roller compaction and slugging are the two methods for dry granulation. Out of these two methods, slugging was preferred and efficient because it is a time saving method without setting too many parameters as in the case of roller compaction. i.e compaction under hydraulic pressure, auger speed, roller speed. When the material was subjected to compaction pressures, it strengthens the bonds that hold the particles together in the form of slugs [15]. The resultant granules also increase the fluidity of the powder mixtures, which by themselves do not flow well enough to fill the dosing tube or dosing disk in capsule filling machine, which ultimately solves the issue of accurate quantity of blend to be filled in capsule body. At R&D scale, compression granulation involved the compaction of the components of a formulation at 4 different hardness levels i.e. 2, 4, 5 and 6 kg/cm^{-1} by means of tablet press using large 20 mm flat base beveled edged punches. The compacted mass was called as "slugs" and the process was referred to as "Slugging". The slugs were then screened through 16# screen in oscillator granulator to produce granules, which flows more uniformly than the original powder mixture. Details of slugging process along with tooling, compaction hardness ranges and corresponding measured tapped densities are mentioned in Table 2.

After that processing, slugs were dried at 30°C at air flow of 50 ml/min in RETSCH® Fluidized Bed Drier (FBD) to achieve desired % Loss on Drying (LOD) of not more than 2.00%w/w. This material was immediately transferred to filling and packaging area.

Manual filling, packaging and stability:

Optimized formulation having desired TD of 0.70gm/ml was filled in Gelatin-PEG (as PEG create moisture barrier film within gelatin matrix) empty capsule shell through tamping principle by PAM® manual capsule filling machine, which were then packed in two different types of packaging material HDPE (High Density Poly Ethylene) bottle with child-resistant closure containing cotton and silica gel Alu-Alu 10's Blister. Final packed capsules were charged at different storage condition of temperature (°C) and relative humidity (%RH) for real time, intermediate and accelerated stability testing. After pre-decided time points samples were withdrawn from stability chamber and analyzed by UV-Visible spectroscopic assay (219nm) method as specified in International Pharmacopoeia, 4th edition [16].

Results and discussion

Product Optimization

CS is a hygroscopic, acidic pH sensitive drug with poor flow property. Based on number of formulation trials, it was finalized that blend containing Avicel® PH 200 as a diluent, sodium stearyl fumarate as a lubricant, talc as an anti-adherant, Aeroperl-300 as a glidant with combination of sodium carbonate and magnesium oxide makes the formulation having micro-environmental pH in higher alkaline range, which is flowable and non-sticky in its physical nature as stated with actual quantity in Table 3.

Process Optimization

The bulk and tapped density of optimized formulation was not suitable to fill the required dose in the capsule body of size 1 capsule by tamping principle. Thus, slugging process was involved, in which compaction pressure caused strengthening of the bonds between particles that ultimately increases density along with superior flow property as described in Table 4.

Filling method optimization and packaging material selection

(HDPE bottle vs Alu-Alu blister):

In Fompacked Alu-Alu Blister (cold formed foil: made up of 25 micron OPA(Oriented Poly Amide) Film /Adhesive/45 micron Aluminum foil/ Adhesive/60 micron PVC (Poly Vinyl Chloride) film overall with least void space and showing least permeability) with superior performance [17] that resist moisture, temperature, oxidation, all kinds of gases and light; formulation was stable at 25°±2°C /60±5%RH and 30°±2°C /65±5%RH; as compared to HDPE container (having higher void space and higher permeability to moisture and gases as compared to Alu-Alu blister) as per all results of physicochemical parametric evaluation as mentioned in Table 5 with desired ranges i.e. Assay between 95% to 102%, Related Substances (RS) below 0.5% with more than 70% drug released within 30 min in 6.8 pH phosphate buffer). Thus Alu-Alu blister packaging was preferred as an suitable packaging material in this case. Moreover this formulation should not be stored above 30°±2°C / 65±5%RH, because analytical results suggest remarkable degradation at higher temperature and higher relative humidity i.e. 40°±2°C/75±5%RH.

Conclusion

Two major problems were encountered during formulation development of Cycloserine capsules:-

(i) pH and moisture base instability of drug *per se*

(ii) Poor physical characteristics (stickiness and poor flow characteristics) of drug per se. This accounts as drug content was more than 70%w/w of the final formulation.

In present investigation, both these problems have been addressed carefully. Addition of magnesium oxide and sodium carbonate increased micro-environmental pH up to 11.0 that ultimately improved the stability of CS in capsules. Avicel® PH 200 was selected as a diluent due to its higher particle size improved the flow of the blend. Flowability of blend was further augmented by addition of optimized quantity of sodium stearyl fumarate, talc and colloidal silicone dioxide. In this situation, slugging of the blend by dry granulation was preferred method of granulation because CS is a moisture sensitive drug. Moreover, slugging played a major role in enhancing the density of the blend and imparted superior flow properties with concluding angle of repose 33º which comes under very good flow property range. This is an important aspect because 350 mg of blend has to be filled in size 1 capsule. By selection and optimization of packaging material study, it was concluded that fompacked Alu-Alu blister, with total thickness of 140 um having least void space and least permeability, showed better performance; in which packed formulation showed superior stability at 25°±2°C /60±5%RH and 30°±2°C /65±5%RH as compared to HDPE container (having higher void space and higher permeability to moisture and gases as compared to Alu-Alu blister. Thus, Alu-Alu blister packaging was preferred as an appropriate packaging material in this case. In brief, from overall results and discussion it can be concluded that developed free flowing, non-sticky stable, formulation of Cycloserine packed in Alu-Alu blister present a better alternative to costly market preparations of innovator. The formulation developed in our lab is robust, stable and cost effective which can be easily afforded by people of developing as well as least developed nations.

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Figure 1 Hydrolysis of D-Cycloserine into β-aminoxy D-alanine

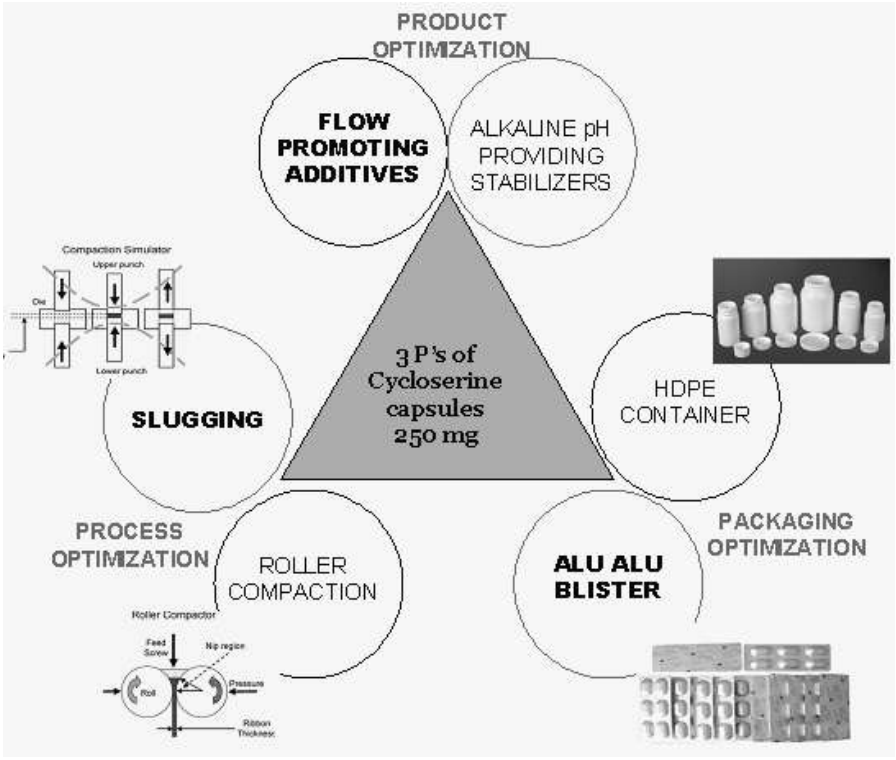

Figure 2 3 P's (i) Product (ii) Process and (iii) Packaging selection and optimization for development of stable Cycloserine capsule formulation.

Table 1 Selection and optimization of excipients for Cycloserine capsules

			OPTIMIZATION																											
SCREENING			F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24	F25	F26	F27
API	Therapeutic	CYCLOSERINE	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250
ANTI ADHERANT	To reduce powder adhesion to metal parts of filling machine.	Purified Talc	-	1.8	2.6	3.5	4.4	7	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
LUBRICANT	To reduce friction during ejection of slug from dosing disk to capsule body & improvement of flow properties	Na Stearyl fumc	-	-	-	-	-	-	1.8	2.6	3.5	4.4	7	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
		PEG 4000	-	-	-	-	-	-	1.8	2.6	3.5	4.4	7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		PEG 6000	-	-	-	-	-	-	1.8	2.6	3.5	4.4	7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Na BASED ALKALIZERS	As an Alkalizing agent for formulation stability	NaHCO3	-	-	-	-	-	-	-	-	-	-	-	3.5	7	11	14	-	-	-	-	-	-	-	-	-	-	-	-	-
		NaOH	-	-	-	-	-	-	-	-	-	-	-	3.5	7	11	14	-	-	-	-	-	-	-	-	-	-	-	-	-
		NaH2PO4	-	-	-	-	-	-	-	-	-	-	-	3.5	7	11	14	-	-	-	-	-	-	-	-	-	-	-	-	-
		Na2HPO4	-	-	-	-	-	-	-	-	-	-	-	3.5	7	11	14	-	-	-	-	-	-	-	-	-	-	-	-	-
		Na2CO3	-	-	-	-	-	-	-	-	-	-	-	3.5	7	11	14	14	14	14	14	14	14	14	14	14	14	14	14	14
Mg BASED ALKALIZERS	As an Alkalizing agent for formulation stability	Light MgO	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.5	7	11	14	18								
		Heavy MgO	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.5	7	11	14	18								
		MgCO3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.5	7	11	14	18	18	18	18	18	18	18	18	18
GLIDANT	For improvement of powder flow properties	Aerosil®	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.7	1.1	1.4	1.8				
		Aeropearl®	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.7	1.1	1.4	1.8	1.8	1.8	1.8	1.8
DILUENT	For improvement of plug formation & cohesiveness	Avicel® PH 102	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	20	40	60	
		Avicel® PH 112	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	20	40	60	
		Avicel® PH 200	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	20	40	60	
pH of formulation														9.2	9.7	10	10	10	10	11	11	11								

Table 2 Slugging process parameters

Sr No.	Compaction hardness	Tapped Density(TD) of 16# passed slugged dry granules
1	2 kg/cm^2	0.59 gm/cc
2	4 kg/cm^2	0.64 gm/cc
3	5 kg/cm^2	0.68 gm/cc
4	6 kg/cm^2	0.69 gm/cc

Table 3 Optimized formulation of Cycloserine capsules

S. No.	Category	Ingredient	mg/capsule
1	API	Cycloserine	250.00
2	Diluent	Avicel® PH 200	60.00
3	Na based alkalizer	Na_2CO_3	14.00
4	Mg based alkalizer	Heavy MgO	17.50
5	Glidant	Aeroperl®	1.75
6	Anti adherent	Purified Talc	3.50
7	Lubricant	Na Stearyl fumarate	4.37

Table 4 Physical analysis of optimized blend before and after slugging at 6 kg/cm^{-1}

S. No.	Physical Analysis	Before Slugging	After Slugging
1	Angle of Repose	46° (Poor flow)	33° (Good flow)
2	Bulk Density (gm/cc)	0.37 gm/cc	0.58 gm/cc
3	Tapped Density (gm/cc)	0.53 gm/cc	0.69 gm/cc
4	Hausner's ratio	1.43 (Poor flow)	1.18 (Good flow)
5	Carr's Index (in %)	30.18 % (Poor flow)	15.94 % (Good flow)

Table 5. Stability evaluation of Cycloserine capsules 250 mg for 3 months, packed in HDPE (High density poly ethylene) container with CRC (Child resistant container) closure containing cotton and silica gel as well as Alu-Alu 10's blister.

Note: Shaded area indicates failing in physicochemical parametric evaluation.

Storage Conditions → / Parameters ↓	Initial	25°±2°C /60±5%RH		30°±2°C/65±5%RH		40°±2°C /75±5%RH	
		HDPE	Alu-Alu	HDPE	Alu-Alu	HDPE	Alu-Alu
Total Impurities	**0.13**	0.68	0.35	4.37	0.42	13.23	5.20
Total Insoluble matter	**0.05**	4.95	0.07	20.33	0.70	18.47	11.19
%LOD(60°C/3hr Vacuum)	**0.51**	2.27	1.78	3.90	1.78	19.70	7.21
Assay (95% to 102%)	**99.3**	92.1	98.00%	71.4	97.10%	48.6	76.40%
pH of formulation(>10)	**10.9**	8.8	10.8	7.2	10.3	6.5	8.5
Disintegration time with disc	**<2 min**	<4 min	<2 min	<7 min	<3 min	<17 min	<8 min
Dissolution profile in 30 min in 6.8 pH PB	**94%**	71%	92%	59%	86%	28%	54%