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Development of sustained release Ambroxol Hydrochloride by pelletization

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Abstract

The aim of the present study was to develop and characterize sustained release pellets of Ambroxol HCl using Ethyl cellulose 7cps and Ethyl cellulose 50cps.The pellets were prepared by Wurster process with EC 7cps in 0.5%w/w, 1%w/w and 1.5%w/w and EC 50cps at 2%w/w, 3.5%w/w and 5%w/w.Then the pellets were evaluated for bulk density, angle of repose and Carr's index. The pellets were characterized for particle size by sieving technology and particle surface, surface texture by SEM analysis. The in-vitro dissolution studies were carried out using 0.1N HCl foe first 2hrs followed by phosphate buffer of pH 6.8 up to 24hrs with USP-II dissolution apparatus. The mean dissolution time was found to be increased by increasing Ethyl cellulose levels. From one way ANOVA it was found that the ratio of binary polymer mixture had significant ($p < 0.05$) effect on drug release. The data were fitted to various kinetic models. The data fitted well in both Kosermayer ($r=0.98$) and Hixon-crowl model ($r=0.939$).The Kosermayer showed $n=0.992$, confirming the release by non-fickian super case-II kind of drug release.

Key Words: Ambroxol, Ethyl cellulose, Wurster process, Fluid bed coater, SR pellets.

INTRODUCTION

Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their Convenience of administration and their appropriateness for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules [1]. Pellets are gradually more being used as multiple unit dosage form. The pellets should contain as much as possible of the active ingredient t o keep the size of the final dosage form within reasonable limits. Pelletization involves the process of renovation of fine powder or granules of bulk drugs and the excipients into small, free flowing, spherical units in size between 0.5-1.5 mm, referred to as pellets [2,3] .The most widely used pelletization processes in the pharmaceutical industry are extrusion-spheronization, solution/suspension layering and

powder layering [4]. The techniques of solution, suspension and powder layering were reported by some of the authors using conventional coating pan or in fluid bed coater. In the current experiment drug containing cores were prepared by wurster process [5,6]. Pellets have some more advantages over conventional solid dosage forms. They are less susceptible to dose dumping, it reduces localized concentration of irritative drugs, and they offer reduced variation in gastric emptying rate and transit time [7]. Sparingly soluble Ambroxol hydrochloride was used in the experiment as a model drug. It is indicated in productive cough and 75 mg sustained release capsule is available in the market (Ambrolan by Launcher, Austria). The drug is chemically Trans-4-[(2-amino-3, 5-dibromobenzyl) amino] cyclohexanol hydrochloride with molecular weight of 414.6.

MATERIALS AND METHODS

Materials used in the experiment were Ambroxol hydrochloride (Alchymars ICM SM Pvt. Ltd., India), Ethyl cellulose (Ming Tai Chemical co. Ltd., Taiwan), Starch (Cerestar, Netherlands), HPMC 5 cps (ShinEtsu Chemical Company Ltd., Japan), and triethyl citrate (Morflex In c., USA). Other materials used were reagent grade.

Preparation of sustained release pellets

The nuclei containing Ambroxol Hydrochloride was manufactured using wurster process. In this process drug was coated on sugar pellets by using a binder solution (PVP K-90 and IPA).This process was carried out by using fluid bed coater (FBC).After that the drug loaded pellets were collected, dried and sieved. This stage was called as drug loading stage. After this stage SR polymer was coated on the drug loaded pellets as a solution form by using FBC. After this the SR pellets were dried and sieved. The pellets must be in 12≠ 16 mesh size [8]. The composition of SR pellets was given in Table 2.

Physical characterization of coated pellets

Physical characters like Angle of repose, bulk density, moisture content, sieve analysis was carried out [9,10] and values were mentioned in Table 3.

In vitro dissolution study

The dissolution of ambroxol hydrochloride sustained release pellets was studied by Eureka (Germany) dissolution tester USP (XXVIII) using USP apparatus 2 (Paddle method). Ambroxol hydrochloride sustained release pellets equivalent to 75 mg of Ambroxol hydrochloride was poured in 900 ml of 0.1 N HCl medium at $37^{o} \pm 0.5^{o}C$ with a rotation of 50 rpm for 1 hour. At the end of 1 hour the media was removed and drug content was determined spectrophotometrically at 244 nm. Then 900 ml of phosphate buffer pH 6.8 was placed in each vessel and rotated at 50 rpm at $37^{o} \pm 0.5^{o}C$ for 24 hours. 10 ml samples were drawn every one hour and replaced by fresh medium to maintain the volume constant and drug content was determined spectrophotometrically at 244 nm using UV-Visible Spectrophotometer [11,12](Shimadzu, Japan).

Release kinetics study

Release kinetic studies were done and results were reported in Table 7.

Scanning electron microscope (SEM) studies

The SEM photographs [13] were taken for the Ambroxol HCl SR pellets prepared by wurster process and depicted in figure 6.

Accelerated stability studies

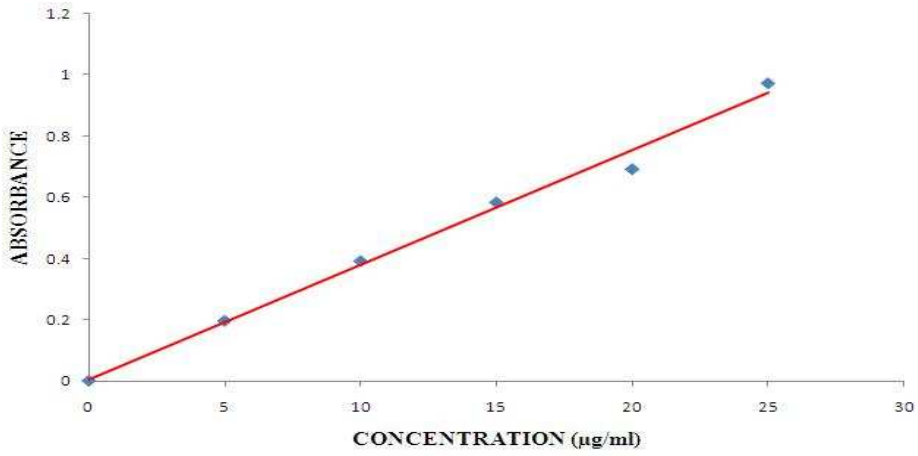
The formulations were stored at various temperature *viz.*25^{o}C/60%RH,30^{o}C/65%RH and 40^{o}C/75%RH as per ICH guidelines and various physicochemical parameters (appearance, percentage drug content and release profile) were monitored periodically for 3 months[14].

RESULTS AND DISCUSSION

Ambroxol HCl acts as a mucolytic agent, which acts by stimulation of serous cells of tonsils of bronchial tubes. The aim of the present study was to formulate and evaluate the SR pellets of Ambroxol HCl. When preformulation studies were carried out, the color of the drug loaded pellets was found almost white and round shape. FTIR studies showed no unaccountable extra peaks, which confirm the absence of chemical interaction between the drug and polymer (Fig 5).As the pellets were prepared by Wurster process only a little amount of moisture was expected. The loss on drying of pellets was determined as 2.5%w/w, which indicates that the layering processes as well as the raw materials were suitable to manufacture stable pellets having low moisture content (Table 3). Flow properties of pellets were estimated by angle of repose. All the formulations, except F5 showed angle of repose within the range of 25-30^{0}, indicates that they had good flow property (Table 3). The friability of nuclei was 0.26% which is very well within the requirement (below 1%).Tapped density of pellets was found in range of 0.75 – 0.9gm/ml (Table 3). These values were suitable to fill the pellets in empty hard gelatin capsule shell. Before coating the pellets size distribution was 710 - 850µ and after coating it was slightly increased (710 - 1250µ).For acceptable film coating, a narrow size distribution of pellets is a prerequisite. The size distribution effects the both the performance of the coating and release rate of the drug. SEM analysis was carried out and the photographs of pellets showed a uniform coating of SR polymer, the surface structure was appeared to be smooth (Fig 6).Thus the physical characteristics of the pellets prepared by wurster process were satisfactory and further studies were carried out with the sample.

The percentage drug content of drug was determined by extraction with methanol and analyzed by using UV-visible double beam spectrophotometer at 245nm after the proper dilution. All the formulations showed the percentage drug content of 100±5% (Table 4).

Fig.1 Standard Graph of Ambroxol HCl:



λ_{max} : 245; Medium : 6.8 pH Phosphate Buffer

Fig.2 Dissolution Profile of The Formulations:

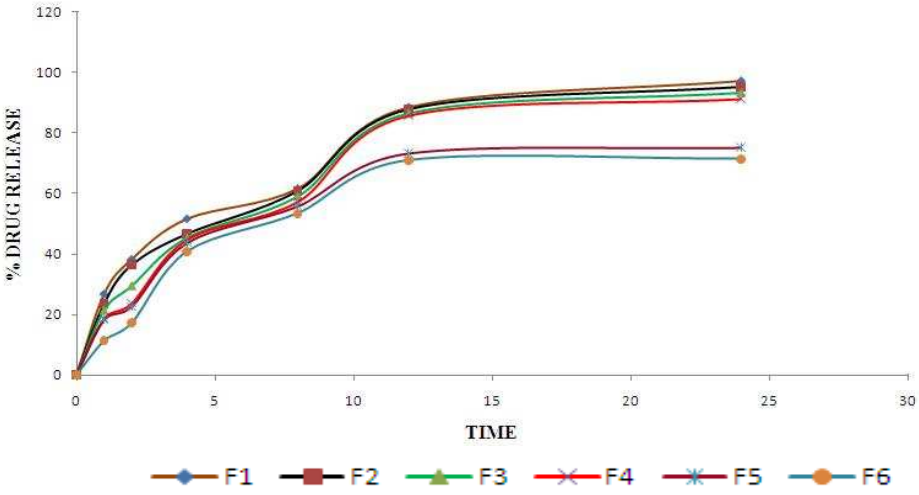


Fig.3 Curve fitting of Dissolution Study – Higuchi Model:

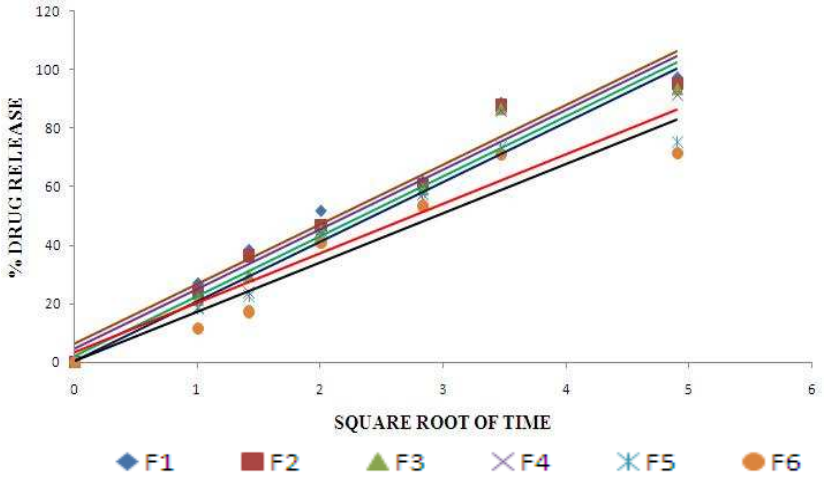


Fig.4 Curve fitting of Dissolution Study – Hixon crowl Model

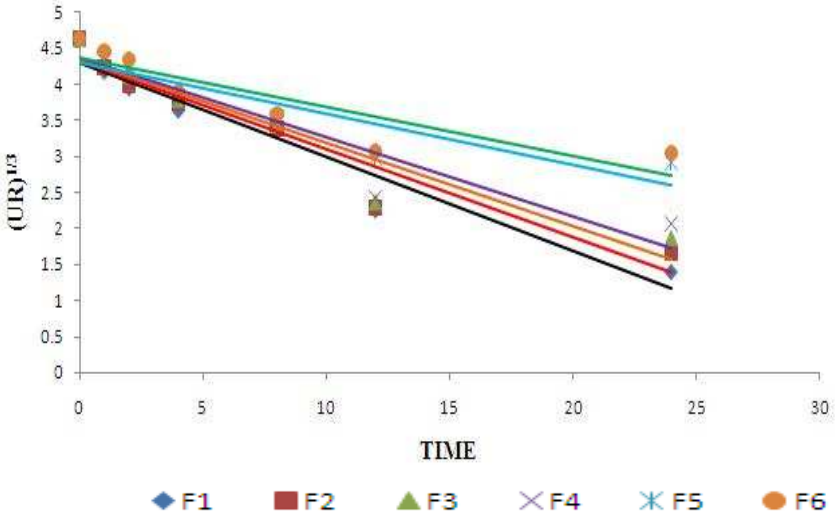


Fig.5 Drug Polymer Interaction Study (FTIR Studies):

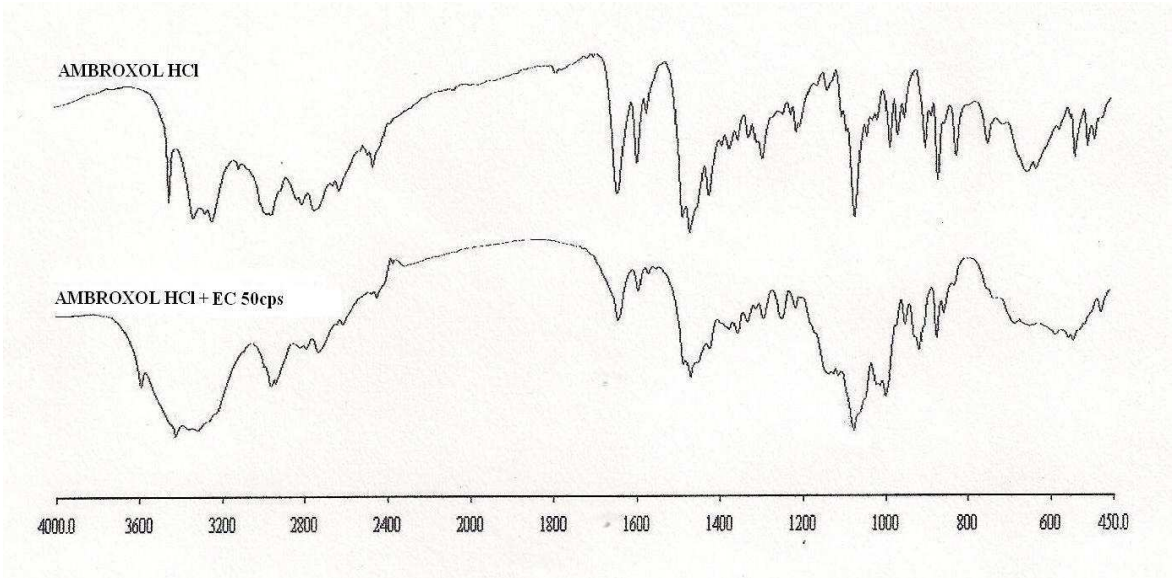
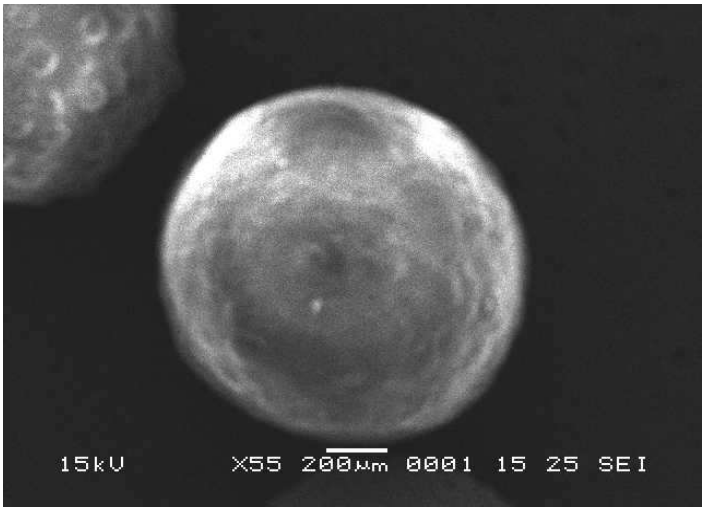
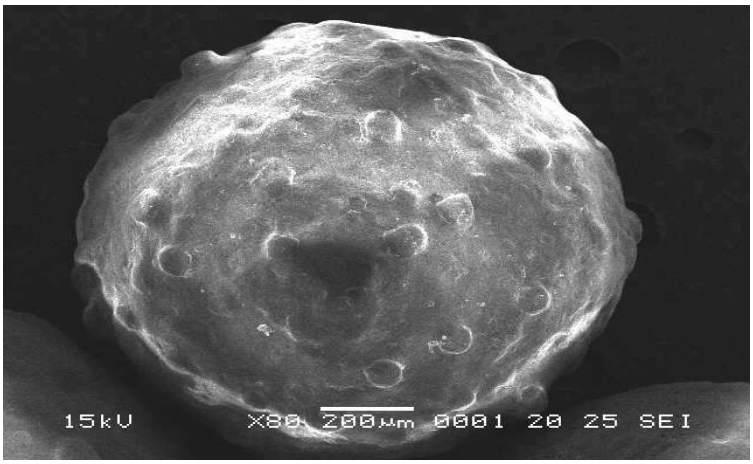


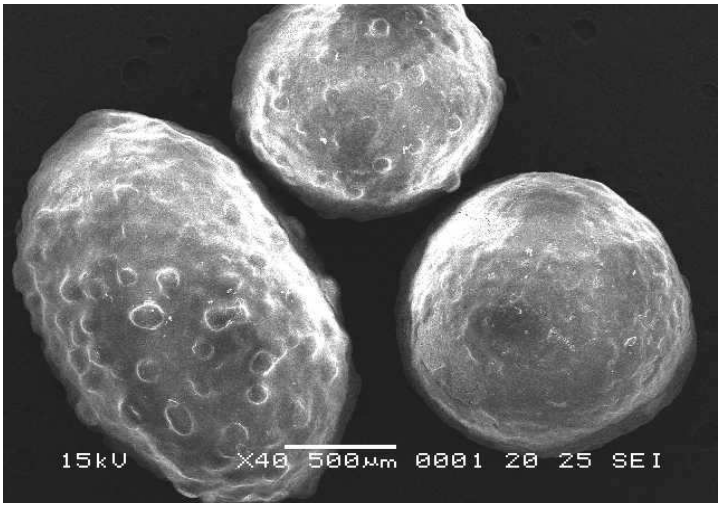
Fig.6 SEM Photographs



SEM Photograph of Formulation F5 at X55 Magnification



SEM Photograph of Formulation F5 at X80 Magnification



SEM Photograph of Formulation F5 at X40 Magnifications

Table.1 Preformulation Study of Active Pharmaceutical Ingredient:

S.No	Characteristics	Results
1	Physical appearance	A white (or) almost white powder, odorless.
2	Solubility	Sparingly soluble in water and soluble in Methanol, practically soluble in Methylene chloride.
3	Bulk density	0.75gm/ml
4	Tap density	0.89gm/ml
5	Compressibility index	15.73%
6	Melting point	235-240°C
7	Molecular weight	414.6.

Table.2 Formulations of Ambroxol HCl SR Pellets

S.No	Ingredients (gm)	F1	F2	F3	F4	F5	F6
	DRUG COATING:						
1	Ambroxol HCl	20	20	20	20	20	20
2	Starch	10	10	10	10	10	10
3	Sugar Pellets	18	18	18	18	18	18
4	PVP K90	1.2	1.2	1.2	1.2	1.2	1.2
5	IPA (ml)	30	30	30	30	30	30
	SR COATING:						
6	EC 7cps	0.22 **(0.5%)**	0.44 **(1%)**	0.66 **(1.5%)**	---	---	---
7	EC 50cps	---	---	---	0.98 **(2%)**	1.7 **(3.5%)**	2.46 **(5%)**
8	IPA (ml)	0.17	0.17	0.17	0.17	0.17	0.17
9	MDC (ml)	50	50	50	50	50	50
10	TEC (ml)	17	17	17	17	17	17

Table.3 Preformulation Characteristics

S.No	Formulations	Angle of Repose (°)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Moisture Content (%)
1	F1	25.7	0.74	0.86	13.95	2.2
2	F2	26.4	0.72	0.82	12.19	2.1
3	F3	28.9	0.69	0.87	20.68	2.2
4	F4	25.4	0.64	0.85	24.70	2.5
5	F5	24.3	0.75	0.89	15.73	2.5
6	F6	28.2	0.78	0.89	12.35	2.6

After 12th hour the percentage drug release from the formulations were 88.6%, 87.9%, 86.6%, 85.8%, 73.3%,70.9% for the formulations containing EC7cps 0.5%,1%,1.5% and EC50cps 2%,3.5% and 5% respectively (Table 5). The dissolution profile was shown in Fig 2 and mean dissolution time (MDT) of pellets were given in Table 6.The burst release of Ambroxol HCl from formulations with EC 50cps is comparatively lower than the one with EC 7cps, due to the fact that EC 50cps is more viscous and release retarding capacity is more when compared to EC 7cps.Formulation F4 was identified to be the best as it matches well with the innovator (f2 = 92). The release curve of best formulation fits better for First order kinetics (r^2 = 0.99), Higuchi (r^2 = 0.966) and Hixson crowl (r^2 = 0.975) model equations. The regression values are given in Table.9.It implies that the release kinetics follows a First order non-fickian super case-II diffusion process. As it obeys Hixson crowl model the drug release may also be due to erosion process. The drug release mechanism from pellets is following both diffusion and erosion phenomenon.

The statistical evaluation was performed by one way ANOVA and results were showed in Table.8.From the data it is evident that 'P' value is less than 0.05 in all formulations for 1hr, 2hr, 4hr, 8hr, 12hr, 24hr.Therefore it can be derived that the change in polymer ratio had significant effect on release of drug.

Table.4 Chemical Evaluation

Physical parameter	F1	F2	F3	F4	F5	F6
Assay% (w/w)	97.62	97.97	97.81	98.24	98.62	98.45

Table.5 Dissolution Studies

S.No	Dissolution Time(hr)	Percentage Drug Release (%)					
		F1	F2	F3	F4	F5	F6
1	1	26.8	23.6	21.4	**18.6**	18.2	11.3
2	2	38.3	36.4	29.5	**23.7**	22.6	17.2
3	4	51.7	46.7	45.4	**44.8**	43.7	40.8
4	8	62.7	60.9	59.1	**57.3**	55.8	53.4
5	12	88.6	87.9	86.6	**85.8**	73.3	70.9
6	24	97.3	95.3	93.4	**91.3**	85.2	81.4

Table.6 Mean Dissolution Time (MDT) Of the Formulations

S.No	Formulation	MDT (Hr)
1	F1	5.718
2	F2	5.774
3	F3	5.890
4	F4	5.906
5	F5	6.347
6	F6	6.448

Table.7 Correlation Coefficient of Drug Release

Formulation	Zero Order		Higuchi		Kosemayer plot			First Order		Hixon Crowl	
	r	k	r	k	r	n	k	r	k	r	k
F1	0.794	4.197	0.937	14.07	0.987	0.921	8.531	0.893	0.019	0.862	0.055
F2	0.829	4.801	0.957	15.14	0.986	0.939	7.943	0.904	0.021	0.881	0.060
F3	0.887	5.566	0.983	18.53	0.987	0.962	7.261	0.982	0.037	0.959	0.093
F4	0.893	6.577	0.972	20.41	0.980	0.992	6.546	0.954	0.044	0.939	0.107
F5	0.913	6.66	0.983	21.78	0.970	0.942	6.561	0.995	0.072	0.987	0.142
F6	0.887	5.774	0.968	18.32	0.960	1.018	5.152	0.955	0.030	0.936	0.081

Table.8 One Way ANOVA of Drug Release at Different Hours

HOUR	Source of Variation	SS	df	MS	F	P-value
1	Between Groups	426.14	5	85.229	18.712	0.000
	Within Groups	54.658	12	4.555		
	Total	480.80	17			
2	Between Groups	1029.5	5	205.90	45.206	0.000
	Within Groups	54.658	12	4.555		
	Total	1084.2	17			
4	Between Groups	197.13	5	39.425	8.656	0.001
	Within Groups	54.658	12	4.555		
	Total	251.78	17			
8	Between Groups	149.38	5	29.876	6.559	0.003
	Within Groups	54.658	12	4.555		
	Total	204.04	17			
12	Between Groups	938	5	187.60	41.187	0.000
	Within Groups	54.658	12	4.555		
	Total	992.66	17			
24	Between Groups	567.29	5	113.46	24.909	0.000
	Within Groups	54.658	12	4.555		
	Total	621.94	17			

SS – Sum of the squares; **MS** – Mean square; **df** – Degree of freedom

CONCLUSION

Ambroxol HCl pellets were prepared in this study by wurster process by using EC 7cps and EC 50 cps as SR polymers. Preformulation studies were carried out; all the results were within the limit. The drug release kinetics follows a First order non-fickian super case-II diffusion process. As it obeys Hixon crowl model the drug release may also be due to erosion process. Accordingly, it can be concluded that the F4 (2%w/w EC 50cps) is robust one and the performance is less likely to be affected by the various factors studied. The formulations were kept at stability studies according to ICH guidelines for 3 months, which showed that all the formulations were stable.

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