STABILITY STUDY OF AMBROXOL HYDROCHLORIDE SUSTAINED RELEASE PELLETS COATED WITH ACRYLIC POLYMER

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ABSTRACT

The aim of the present study is to perform stability study of Ambroxol Hydrochloride sustained release pellets stored in different storage conditions. The drug loaded beads were prepared by Extrusion-Spheronization technology then coated with ammonio methacrylate copolymer Type A (Eudragit RL 30 D) and ammonio methacrylate copolymer Type B (Eudragit RS 30 D) at a ratio of 2:3 (8% polymer by weight on dry basis) in Fluid Bed Coater (Wurster column). Stability study of pellets was performed as capsule dosage form in Aluminium-PVDC packaging mode at room temperature, 40°C, 40°C/75%RH & 30°C/70%RH for three months. After one month the shape & size of the pellets was changed in all conditions. The color of the pellets remains unchanged up to the 2nd month in all conditions except at 40°C/75%RH and in this case some pellets become brown. But after 3rd month, pellets become brownish in all conditions except at room temperature. At RT the color of pellets remains unchanged during the stability study. The mean drug content decreased gradually in all conditions. In acid media the initial drug release was 23% but after 1st month it was decreased to 13-15% in all conditions. In the buffer media (pH 6.8) the drug release was increased a little bit in all conditions except at 30°C/70%RH with the passes of storage time. Stability studies at 30°C/70%RH revealed consistent drug release (f_2>50) throughout the stability period. The physical properties of pellets as well as the *in vitro* release profile of the drug was found to be a function of the different storage conditions as well as the physico-chemical nature of the polymers.

Keywords: Ambroxol hydrochloride, pellets, acrylic polymer, aqueous coating, stability study.

INTRODUCTION

The pellet type of sustained-release preparation is often referred to as bead-type preparation. Pelletization process is applied for the preparation of solid oral controlled-release dosage forms (Shargel, 1941). A major advantage of pellet dosage form is that the pellets are less sensitive to the effect of stomach emptying. Because there are numerous pellets within a capsule, some pellets will gradually reach the small intestine and deliver the drug; where as a single tablet may be delayed in the stomach for a long time due to erratic stomach emptying (Shargel, 1941). The fluctuating drug concentrations in blood and tissues caused by conventional dosage forms lead to an insufficient influence on the mechanisms of disease and are related to the excessive use of a drug. Various oral dosage forms able to control the rate and extent of drug delivery into systemic circulation have been prepared and studied (Bidah, 1991). The production of the particles, which are regular in shape and size, can be achieved with the application of the proper polymer auxiliary materials and new pharmaceutical technological methods (extrusion, spheronization). Regularity in shape and size, attained by the optimization of several production parameters, can promote the coating procedure. Under optimal conditions, pellets having uniform size were prepared for coating in a high-shear mixer (Fekete *et al.*, 1998; Krogars *et al.*, 2000; Vergote *et al.*, 2001). Using a marketed microcrystalline cellulose (Avicel PH 101) excipient, optimum extrusion and spheronization conditions for less soluble drugs required more water, a longer wet mixing time, and prolonged spheronizing period (Hileman *et al.*, 1997). The successful spheronization of extrudates requires correct water content. This water content is different for the formulations as well as for the extruders. Pellet sphericity was also strongly dependent on the correct water content of the formulations (Thoma, 1998). The aim of the study was also to prove the importance of the raw materials composition, mixture and spheronization speed on pellet properties. Extrudates from mixtures of microcrystalline cellulose (Avicel PH 101), lactose and maize starch were prepared with a power-consumption-controlled extruder and spheronizer at different speeds. The spheronization speed had an influence on the size but not on porosity or surface tensile stress of the pellets (Kleinebudde *et al.*, 1999).

Aqueous film-coating dispersions generally consist of polymeric colloidal particles, a plasticizer, a pigment and an anti-adherent agent (Chuanbin, 2001). Poly-methacrylates are primarily used in oral capsule and tablet formulations as film coating agents (Lehmann 1973; Lehmann 1981; Okor 1990). Depending on the type of polymer used, films of different solubility characteristics can be produced. Eudragit RL 30 D and Eudragit RS 30 D

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are aqueous dispersion of copolymers of acrylic acid and methacrylic acid esters with a low content of quarternary ammonium groups (Kibbe 2000; Lehmann 1996; Rohm GmbH & Co., 2005). Eudragit RL 30 D is ammonio methacrylate copolymer Type A and Eudragit RS 30 D is ammonio methacrylate copolymer Type B polymer. The dispersions contain 30% polymer. The quarternary groups occur as salts and are responsible for the permeability of films made from these polymers (Lehmann 1996; Rohm GmbH & Co., 2005). Films prepared from Eudragit RL 30 D are readily permeable to water and to dissolve active substances, whereas films prepared from Eudragit RS 30 D are less permeable to water (Lehmann 1996; Lehmann *et al.,* 2001). Film coatings prepared from both polymers give pH-independent release of active substance. Plasticizers are usually added to improve film properties (Kibbe 2000). The most widely used aqueous polymer dispersions for sustained-release coating applications are either ethylcellulose-based (Aquacoat ECD, Surelease) or acrylate-based (Eudragit RL 30 D, Eudragit RS 30 D etc.) (Lin *et al.,* 2000). Because of ethylcellulose's relatively high glass-transition temperature (Tg) and pseudolatex nature, ethylcellulose aqueous dispersions require adequate plasticization, with the end product needing further curing steps. Although Eudragit products are true latex with low Tg's, particle coalescence at room temperature is still slow and incomplete, necessitating accelerated curing conditions and/or the incorporation of water-soluble additives (Lin *et al.,* 2000).

Ambroxol Hydrochloride has secretomotor with secretolytic effects. It stimulates serous cells of gland of bronchi mucous membranes, increases mucous secretion content by changing the structure of bronchial secretion. It clearly improves breathing and suppresses coughing to some extent. The aim of the present study was to prepare Ambroxol Hydrochloride sustained release pellets as well as to conduct the stability study in different storage conditions. Ambroxol Hydrochloride is used as a reference drug and Eudragit RL 30D & Eudragit RS 30D as release rate retarding acrylic polymers. Dissolution study was performed for studying the influence of pH of the dissolution medium on release rate of Ambroxol Hydrochloride from prepared pellets stored at different storage conditions.

MATERIALS AND METHODS

In this experiment materials used were Ambroxol Hydrochloride (Index Pharma, India), Maize Starch (Cerestar, Netherland), lactose (The Lactose Co. of Newzealand Ltd. Newzealand), Avicel PH 101 (Maple Biotech Pvt. Ltd. India), HPMC 6cps (Shin-etsu, Japan), purified talc (Asian Mineral, Thailand), titanium dioxide (Warner Jenkinson, Italy), triethyl citrate (Morflex Inc.USA), Eudragit RL 30 D & Eudragit RS 30 D (Rohm Pharma., Germany). All the other chemicals used were of analytical grade and were used as received.

Preparation of ambroxol hydrochloride sustained release pellets

Extrusion-Spheronization technology was used to prepare the Ambroxol Hydrochloride beads. A wet mass was prepared with Ambroxol Hydrochloride powder, lactose, maize starch, Avicel PH 101, HPMC 6 cps and purified water (table 1). Then the wet mass was passed through 1.00 mm aperture screen of the Screen type Extruder (Extruder 35, Caleva, UK) to prepare the extrudes. Then the extrudes were loaded on the specially designed pan of the Spheronizer (Spheronizer 500, Caleva, UK) and the pan was rotated at 550-570 RPM for 2-3 minutes to prepare the spherical beads. All beads were dried at 60^{o}C for 7 hours and various physical tests were performed (table 3). The desired size (18/24) of the drug loaded beads was used for coating (fig. 1).

Table 1: Core and coating formula of Ambroxol Hydrochloride sustained release pellets.

Formula	Qty (g)
Core materials	
Ambroxol hydrochloride	400.000
Maize Starch	66.000
Lactose	144.000
Avicel PH 101	446.000
HPMC 6cps	44.000
Water upto	440.000
**Coating materials*	
Eudragit RL 30 D	42.667
Eudragit RS 30 D	64.000
Purified Talc	4.725
Titanium Dioxide	3.150
Triethyl Citrate	6.300
Water upto	250.000

*400.00 g drug loaded beads used for coating

Sustained release coating suspension was prepared by mixing the required amount of Eudragit RL 30 D & Eudragit RS 30 D (8% polymer on dry basis with reference to 400.00g beads) (table 1). Paste was prepared by using purified talc, titanium dioxide & purified water. Triethyl Citrate was added, mixed well and diluted with purified water to make the final weight of suspension according to table 1. 400.00g drug loaded pellets was taken in the Bottom-spray Lab coater (Wurster Column) and coating suspension was sprayed according to table 2. After completion of spraying, the coated pellets were dried at 55^{o}C for 6 hours and various physical tests were performed (table 3). The desired size (18/24) of the coated pellets were used for subsequent analysis.

Table 2: Machine parameters set up during coating of Ambroxol Hydrochloride beads.

Machine	Fluid bed coater (Wurster), Umang Pharmatech Ltd. India
Batch Size	400.00 g
Inlet air temperature	60°C
Outlet air temperature	34°C
Product temperature	35°C
Chamber Humidity	56%
Air flow	100m^3/h
Nozzle Aperture	0.8mm
No. of spray gun	01
Spray direction	Bottom spray
Spray pressure	1 bar
Spray rate	2.0 g/min
Spray time	125 min
Peristaltic pump rpm	2
Secondary drying	50°C/5 min

After performing the relevant tests the coated pellets were encapsulated in Size 2 (Body-powder blue opaque & Cap-light blue opaque) shell (Associated co., India) using Automatic Encapsulation Machine (Sejong, Korea) at a fill weight of 249.917mg. Strips (using Aluminium & PVDC foils) were prepared by using Horn Noack Blister Machine (Germany) and set for stability study for next three months at RT, 40°C, 40°C/75%RH & 30°C/70%RH conditions in three different stability chambers (Thermolab -1000 L, India for 40°C; Memmert UFP 2016, Germany for 40°C/75%RH and Newtronic QCL 2016, India for 30°C/70%RH). After each month, dissolution test and other physical tests were performed as presented in figs. 2-5 and tables 3-4.

In vitro dissolution study

The dissolution of the prepared Ambroxol Hydrochloride sustained release pellets was studied by Erweka (Germany) dissolution tester USP (XXVIII) using USP apparatus II (Paddle method). Ambroxol Hydrochloride sustained release pellets equivalent to 75 mg of Ambroxol Hydrochloride was used in 900 ml of dissolution medium (0.1 N HCl) at 37°±0.5°C with 50 RPM for first 1 hour. At the end of 0.5 and 1 hour, drug content of the sample solution was determined spectrophotometrically at 244 nm by using UV-Visible Spectrophotometer (Shimadzu, Japan). After 1 hour acid media was replaced and 900 ml KH_2PO_4 buffer (pH 6.8) was added in each vessel then the test was continued for next 10 hours at 50 RPM. Samples were drawn at every one-hour interval and the drug content of the collected samples was determined spectrophotometrically at 244nm by using UV-Visible Spectrophotometer (Shimadzu, Japan).

Scanning electron microscope

Scanning Electron Microscope (SEM) was used to study the morphology of the prepared pellets without any coating. Scanning electron microscopy was performed using Hitachi (Model: S-3400 N, Japan) Scanning Electron Microscope at 5 KV having different magnifications. The scanning electron micrographs are presented in figs. 1A-1B.

RESULTS AND DISCUSSION

The ambroxol hydrochloride pellets was prepared by Extrusion-Spheronization technique then coated with polymers in the Fluid Bed Coater (Wurster Column). Then 3 months stability study was performed. The results of different tests were plotted in different fashions. It was revealed that the release kinetics of drug and physical parameters of the pellets were greatly influenced by the storage conditions.

Physical characterization

During beads preparation by Extrusion-Spheronization process total yield was found 89.42% due to some loss of

Table 3: Physical parameters of the ambroxol hydrochloride sustained release pellets.

Parameters		Core	Coating
Batch Size (g)		1100.00	400.00
% Yield		89.42	97.51
% LOD		2.04 ± 0.25	2.16 ± 0.78
% Potency		35.17 ± 0.29	30.01 ± 1.44
True density (g/cm^3)		1.15 ± 0.01	1.11 ± 0.02
Bulk density (g/cm^3)		0.91 ± 0.02	0.92 ± 0.01
Friability (%)		0.46 ± 0.02	0.31 ± 0.15
Sieve Test	30-40 mesh	1.43%± 0.61	2.59%± 0.14
	24-30 mesh	5.72%± 0.03	1.44%± 0.18
	18-24 mesh	88.56%± 1.17	92.75%± 0.75
	14-18 mesh	2.31%± 2.02	3.22%± 0.23
	14 mesh above	1.98%± 0.11	0.00%± 0.00

LOD: % Loss on drying. Three samples run for each trial

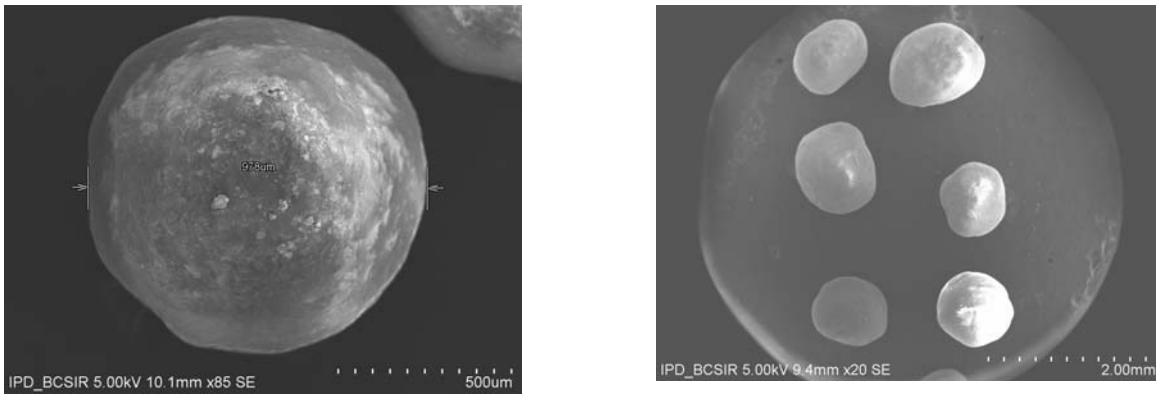
Table 4: Appearance of pellets at different time intervals during stability study.

Initial	After One month				After Two month				After Three month			
	RT	40°C	40°C/ 75%RH	30°C/ 70%RH	RT	40°C	40°C/ 75%RH	30°C/ 70%RH	RT	40°C	40°C/ 75%RH	30°C/ 70%RH
White to off-white spherical pellets	Color as initial but shape is not uniform	Color as initial but shape is not uniform	Color as initial but shape is not uniform	Color as initial but shape is not uniform	Color as initial but shape is not uniform	Color as initial but shape is not uniform	Some pellets become slightly brown	Color as initial but shape is not uniform	Color as initial but shape is not uniform	Pellets become brownish	Pellets become brownish	Pellets become brownish

Table 5: Difference factor (f_1) & Similarity factor (f_2) of dissolution profiles of drug at different time intervals during stability study.

Media	Time	f_1 value				f_2 value			
		RT	40°C	40°C/ 75%RH	30°C/ 70%RH	RT	40°C	40°C/ 75%RH	30°C/ 70%RH
0.1N HCl	1M	39	41	43	39	52	50	50	52
	2M	39	31	33	27	51	57	56	59
	3M	31	34	34	36	56	54	55	53
Phosphate buffer	1M	9	10	6	3	59	58	65	82
	2M	4	10	5	4	76	58	69	76
	3M	14	11	13	6	51	55	51	69

raw materials mainly from adhesion of wet mass to the machine surface that should be considered during manufacturing. But after performing sustained release coating 97.51% yield was found which indicates better coating efficiency with better tuning of machine's parameter setup. Initially the color of the coated pellets was white to off-white and the size was spherical (table 4, fig. 1A). After one month the color of the pellets stored in four conditions remained same but shape was not uniform (fig. 1B). After 2nd month at RT, 40°C and 30°C/70%RH the color & shape of the pellets were same as 1st month but at 40°C/75%RH some pellets become slightly brown. After 3rd month at RT, the color & shape of the pellets remained same as 1st & 2nd month but at the other conditions pellets become brownish (table 4). This data shows that with the increase in %RH the color & shape of the pellets changed this might be due to moisture absorption by the pellets and this result is also reflected by the moisture content (%LOD) data (fig. 2). Fig. 2 also shows that at 40°C the LOD value decreases with the passes of time whereas at RT, 40°C/75%RH and 30°C/70%RH this value increases sharply. No agglomeration or stickiness among the pellets or pellets with the capsule surface was observed during the stability period. Friability test of the drug loaded beads as well as coated pellets were performed for 10mins at 24rpm by using Electrolab EF-2 Friabilator (India) and the result showed that after coating the pellets become less friable (table 3) and that might be presence of few particles at the surface of the pellets (fig. 1A). Assay was done before and after coating and the results indicate that the manufacturing process was >92% efficient. Sieve test of the coated pellets also indicates that 92.75% pellets were with in 18/24 mesh size which reflects the uniform coating of the loaded beads (table 3). Data also reflect that minimum agglomeration and smaller granules (broken pellets) were formed during coating as only 3.22% and 4.03% pellets were found above 18 mesh and below 24 mesh respectively. After coating the friability of pellets was decreased to 0.31% where the friability of core pellets was 0.46% (table 3). In each testing parameter, the variation of the results found from three different samples was within the limit of ±5% and S.D. was found as little as 0.01 (table 3) which indicates that the values were much more closure to each other. During encapsulation the average fill weight per capsule was 249.917mg which contains 75mg Ambroxol Hydrochloride where weight variation & S.D. were found ±5% & ±1.02 respectively. The mean drug content of the pellets decreases along with time in all conditions which might be due to the drug-polymer interactions or sensitivity towards different stability conditions (fig. 3). At RT the mean drug content



A B

Fig. 1: Ambroxol Hydrochloride sustained release pellets (dried & sieved) having size 18/24mesh. [A). Pellets coated with Eudragit RL 30 D & Eudragit RS 30 D before encapsulation B). Deshaped pellets, after first month of stability study kept in Aluminium-PVDC strips].

decreased vigorously with time. So temperature and moisture might have greater influence on the stability of Ambroxol Hydrochloride. It can also be expressed that moisture might play the dominant role in this aspect which is reflected by fig. 2 where maximum LOD value was found in case of RT & 40°C/75%RH and drug content were found minimum.

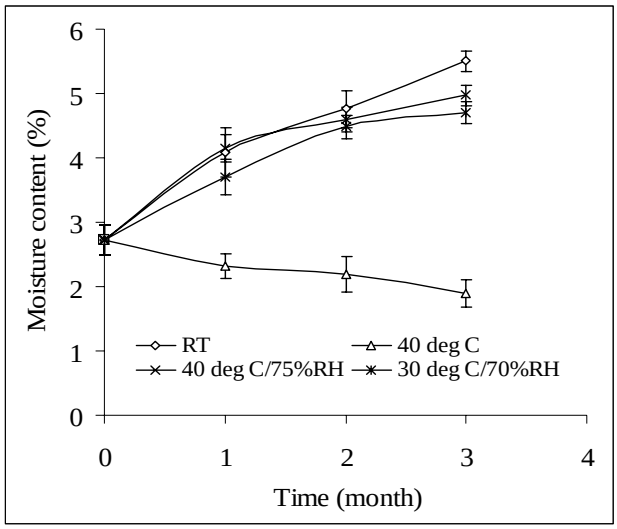


Fig. 2: Moisture content of Ambroxol Hydrochloride sustained release pellets during stability study at Room temperature (RT), 40°C, 40°C/75%RH and 30°C/70%RH.

Release kinetics study

In acid media about 24% drug was released at first hour which may be due to high permeability properties of Eudragit RL 30 D (Kibbe 2000) and low permeability properties as well as the presence of quaternary ammonium groups in the film of Eudragit RS 30 D (Kibbe 2000; Lehmann 1996). After 1st month the drug release was decreased to 15% in all conditions and this value remained same even at the end of 3rd month (fig. 4).

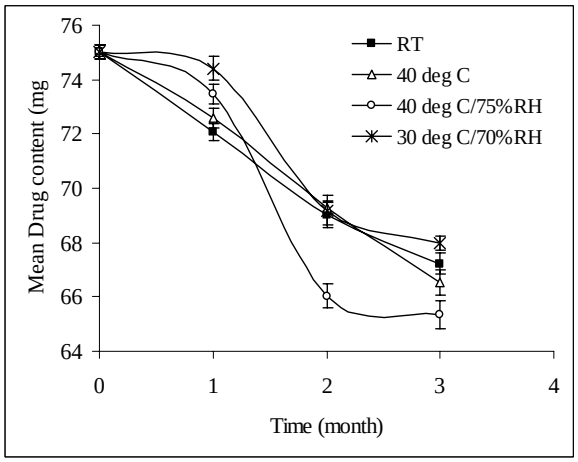


Fig. 3: Mean drug content of Ambroxol Hydrochloride in 250mg capsules during stability study at Room temperature (RT), 40°C, 40°C/75%RH and 30°C/70%RH.

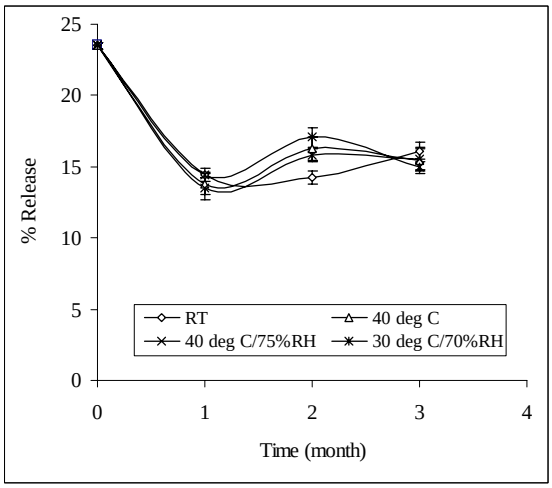


Fig. 4: Release of Ambroxol Hydrochloride from Eudragit RL 30 D & Eudragit RS 30 D coated pellets in 0.1N HCl during stability study at Room temperature (RT), 40°C, 40°C/75%RH and 30°C/70%RH.

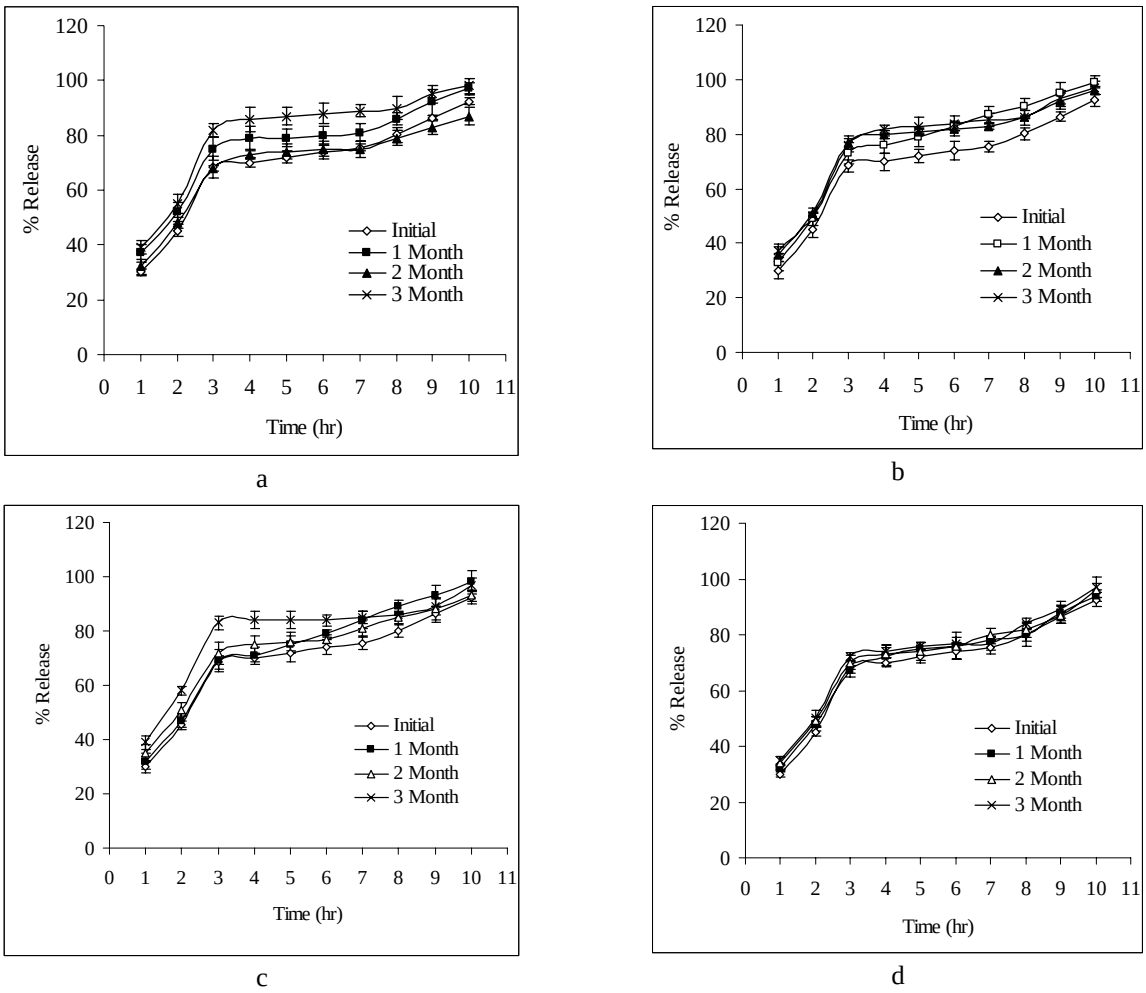


Fig. 5: Release of Ambroxol Hydrochloride from Eudragit RL 30 D & Eudragit RS 30 D coated pellets in phosphate buffer during stability study at four different conditions. [a) RT (Room temperature); b) 40°C; c) 40°C/75%RH; d) 30°C/70%RH]

So in acid media a difference in drug release was observed (f_1 value more than 15) in all conditions from initial release (table 4). These phenomena indicate that long time (15-20 hours at 50-80°C) curing is necessary (Zezhi *et al.,* 2002) after coating with acrylic polymers which will stabilize the drug release. When dissolution of the coated pellets was performed in the buffer media, it was revealed that about 30% of drug was released at first hour and about 70% drug was released at 3 hours whereas about 80% of drug was released within 8 hours (fig. 5a), which indicates the initial drug release rate was higher than that of the terminal drug release rate. This phenomenon of these two polymers can be attributed by the presence of hydrophilic groups within their structure which control the water absorption, the degree of swelling & the permeability of films. Both of these polymers are water-insoluble over the entire pH range but swell in the digestive fluids independently of pH. In the swollen state they are then permeable to water and dissolved actives. So more water permeability & more drug diffusive properties of Eudragit RL 30 D lead the drug to release faster than that of Eudragit RS 30 D (Lehmann *et al.,* 2001).

Stability study

When coated pellets stored at RT, after 1st month the drug release was increased and after 2nd month the drug release was decreased about to the initial value but after 3rd month again the drug release was increased (fig. 5a) in buffer media. When pellets stored at 40°C, from 1st month the drug release was increased gradually at the end of stability period (fig. 5b). At 40°C/75%RH, here an anomalous drug release profile was observed, after 1st month the drug release was increased whereas after 2nd month the drug release was increased up to 4th hr then from 5th hr the release increased and after 3rd month again the drug release was increased where about 85% drug was released within 3 hours (fig. 5c). So in buffer media no significant difference in the dissolution profile (f_1 value is

less than 15) was revealed after 1st, 2nd and 3rd month which indicates that during stability study the dissolution profiles at different time interval were similar as table 4 shows f_2 value is greater than 50 (Moore 1996; US FDA 1997). Also the release was found more consistent throughout the stability study for samples stored at 30°C/70%RH (fig. 5d). Such a change in dissolution profile is usually indicative of polymer structural relaxation (Ali 1970; Perez 1988; Struik 1978) necessitating a curing evaluation study. Increases in curing temperature resulted in continuous decreases in permeability as well as in dissolution, up to a temperature of as high as 80°C (Zezhi *et al.,* 2002). Whether the observed stability/curing phenomena are related to a selected drug candidate or a particular pellet system (layered nonpareil vs. extruded) remains to be elucidated. Kolter 2000 reported little curing effects on extruded pellet systems containing caffeine, propranolol, and theophylline. Dashevsky *et al.,* 2000 reported an increase in ibuprofen release following curing at 60°C for 24 hours.

CONCLUSION

The stability study of the sustained release pellets was performed in four different conditions in strips (Aluminium-PVDC) for three months. The color of the pellets found better at room temperature (RT) and at 30^0C/70%RH the drug release remains unchanged over the stability period. So 30^oC/70%RH condition denotes the suitable storage condition for Ambroxol Hydrochloride sustained release pellets. It was also observed that the shape and size of pellets were greatly influenced by mode of packaging as well as %RH of the stability chambers.

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