Stability Studies on a Cough Syrup in Plastic Containers

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Packaging of pharmaceuticals is a critical process. Plastics are unanimously used for solid dosage packaging. Due to their numerous advantages over glass, they are now being considered as an alternative to packaging of liquid dosage forms also. Cough syrups are preparations containing antitussive drugs, and are most commonly packaged in glass bottles. The interactive nature of plastics makes it essential that a detailed study be carried out before their use for any pharmaceutical packaging. The present work reports the stability and suitability of packaging antitussive syrup in plastic containers.

Key words: Interaction, plastic, stability, syrup

Packaging of pharmaceuticals is a critical process. It is an economical means of providing protection, presentation, information, identification, containment, administration, shelf-life and convenience for a product during carriage, storage, display and ultimate total use, paying due attention to any legal and environmental factors[1]. Plastics are a wide group of solid composite materials, which are largely organic, and can be cast, molded or polymerized directly into shape, usually through the application singly or together of heat and pressure[2]. They offer advantages in being light in weight, easy to process, break resistant, tamper proof, pilfer proof and corrosion resistant. Though plastics are being widely used in solid dosage packaging, their use in packaging liquid dosage forms is restricted. This is due to their drawbacks such as leaching, sorption, permeation, photodegradation and polymer modification. In spite of these drawbacks, the flexibility and versatility of plastics makes them an attractive alternate packaging material for packing liquid dosage forms, especially cough syrups.

Cough syrups are preparations containing antitussive drugs. They are formulated as concentrated aqueous preparations containing sugar or sugar substitute, with or without added flavoring agents. Cough syrups are most commonly packed in glass bottles. However, lately many cough syrups are being packed in plastic containers. Plastics being interactive in nature, it becomes essential to assess their suitability before using them for packaging. The present work reports the stability and suitability of packaging antitussive syrup in plastic containers.

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MATERIALS AND METHODS

HDPE containers were obtained as gift samples from Siddhi Enterprises, LDPE and Polypropylene containers from Deevesh Manufacturing India Limited, PET Amber and amber glass bottles from Emil Pharmaceuticals and PET Transparent from Pearl Polymers India Limited. Ammonium chloride AR was purchased from S. D. Fine Chemicals Limited and diphenhydramine hydrochloride was procured as a gift sample from Merind India Limited. All the other solvents and reagents used in the study were of AR grade and procured from S. D. Fine Chemicals Limited.

Formulation of cough syrup:
A cough syrup containing a combination of two antitussive drugs, namely ammonium chloride and diphenhydramine hydrochloride, was formulated in a syrup base and was suitably colored and flavored. The composition is shown in Table 1.

Physicochemical testing of plastic containers:
Five types of plastic containers were selected for the study, high density polyethylene (HDPE), low density polyethylene (LDPE), polypropylene, polyethylene terephthalate (PET) – amber and PET transparent. Amber glass bottles were used as control. All the plastic containers were subjected to physicochemical

TABLE 1: COMPOSITION OF COUGH SYRUP FORMULATION

Ingredients	Quantity % w/v
Ammonium chloride IP	2.76
Diphenhydramine hydrochloride IP	0.282
Refined sugar IP	50.0
Sodium saccharin IP	0.0506
Sodium citrate IP	1.14
Citric acid IP	0.134
Sodium methyl paraben	0.18
Sodium propyl paraben	0.02
Color sunset yellow	0.002
Color erythrosine	0.001
Color amaranth	0.0036
Menthol IP	0.0228
Propylene glycol IP	10.0
Flavor raspberry	0.04
Distilled water	q.s.100

tests and tests on extracts as per IP 1996[3]. In addition to the above tests, Water Vapor Permeation Test was carried out as per USP 23[4] on all plastics. PET containers were subjected to additional testing as per USP 23[5] namely tests for heavy metals, total terephthaloyl moieties and ethylene glycol.

Biological evaluation of plastic containers:

Biological evaluation of plastic containers was carried out as per IP 1996[6]. The protocol was approved by the institutional Animal Ethics Committee (CPCSEA-39). The systemic injection test was performed on albino mice of either sex weighing 17-23 g. Five animals were taken in a test group against the blank. Small strips (measuring 5×0.3 cm, equivalent to 60 cm^2 total surface area of all exposed areas) of the plastic containers were cut and cleaned thoroughly with sterile water for injection and dried in an oven at temperature not exceeding 50°. The extracts of the plastics were prepared by heating these clean and dried strips of plastic in autoclave at 121° for 1h with sodium chloride injection. Similarly, blank sodium chloride injection was prepared. All the extracts were cooled and stored aseptically and used within 24h of preparation. Dose of both the test and blank extract administered was 50 ml/kg body weight.

Stability studies:

The syrup prepared in the above manner was subjected to accelerated stability studies at room temperature, 37°, 45° and 60°. According to ICH guidelines, short term accelerated stability testing was carried out at 25°/60%RH, 30^0/60%RH and 40^0/75%RH. Sampling was carried out at 3, 6, 9, 12, 15 and 18 w for the samples stored at all the above conditions. Additional sampling was carried out at 21 and 24 w for room temperature, 37° and at the ICH conditions. All the samples were analyzed for color (appearance, clarity), flavor, pH, viscosity and drug content. Results are tabulated in Tables 2-5. The viscosity was determined on RVT 230V Brookfield Viscometer at 100 rpm using spindle no. 2.

Estimation of ammonium chloride:

An aliquot of syrup (5 ml) was taken in a conical flask; pipette was rinsed with 20 ml water. 50 ml water was added and pH adjusted to 7.0 with 0.1 M sodium hydroxide. 20 ml of previously neutralized 1:1 mixture of formaldehyde: water was added and solution titrated with 0.1 M sodium hydroxide using phenolphthalein as indicator till color of solution turned pink.

Estimation of diphenhydramine hydrochloride:

An aliquot of syrup (20 ml) was taken in a 50 ml volumetric flask, and made to volume with water. 20 ml of this solution was taken in a separating funnel and 20 ml benzene added followed by 20 ml 20% v/v sulphuric acid and 25 ml of cobalt thiocyanate reagent. Extraction was carried out till there was no blue color in the benzene layer. Volume was made up to 100 ml with benzene. Eight milligrams of diphenhydramine hydrochloride standard was weighed accurately and

TABLE 2: CHANGE OF COLOR IN COUGH SYRUP

Storage conditions	Glass	HDPE	LDPE	Polypropylene	PET amber	PET transparent
RT	No change	No change	No change	No change	No change	No change
37°	No change	No change	No change	No change	No change	No change
45°	Slightly brown (18 w)	Slightly brown (15 w)	Slightly brown (9 w)	Slightly brown (18 w)	Slightly brown (12 w)	Slightly brown (18 w)
60°	Dark brown (3 w)	Dark brown (3 w)	Dark brown (3 w)	Dark brown (3 w)	Dark brown (3 w)	Dark brown (3 w)
25°/60%RH	No change	No change	No change	No change	No change	No change
30°/60%RH	No change	No change	No change	No change	No change	No change
40°/75%RH	Slightly brown (21 w)	Slightly brown (18 w)	Slightly brown (12 w)	Slightly brown (21 w)	Slightly brown (15 w)	Slightly brown (21 w)

The color change of the cough syrup is compared against the initial color which is dark red.w is time in weeks.

TABLE 3: CHANGE OF FLAVOR IN COUGH SYRUP

Storage conditions	Glass	HDPE	LDPE	Polypropylene	PET amber	PET transparent
RT	No change	Off-flavor (18 w)	Off-flavor (3 w)	No change	Off-flavor (18 w)	No change
37°	No change	Off-flavor (18 w)	Off-flavor (3 w)	No change	Off-flavor (18 w)	No change
45°	Flavor reduced (21 w)	Off-flavor (9 w)	Off-flavor (3 w)	Off-flavor (12 w)	Off-flavor (9 w)	Off-flavor (12 w)
60°	Flavor lost (3 w)	Flavor lost (3 w)	Flavor lost (3 w)	Flavor lost (3 w)	Flavor lost (3 w)	Flavor lost (3 w)
25°/60%RH	No change	Off-flavor (21 w)	Off-flavor (3 w)	No change	Off-flavor (18 w)	No change
30°/60%RH	No change	Off-flavor (18 w)	Off-flavor (3 w)	No change	Off-flavor (18 w)	No change
40°/75%RH	No change	Off-flavor (9 w)	Off-flavor (3 w)	Off-flavor (12 w)	Off-flavor (9 w)	Off-flavor (12 w)

The change of flavor in the cough syrup is compared against the initial flavor which is raspberry flavor with sweet taste. w is time in weeks.

TABLE 4: CHANGE OF pH IN COUGH SYRUP

Storage conditions	Glass	HDPE	LDPE	Polypropylene	PET amber	PET transparent
RT	5.67 (24 w)	5.60 (24 w)	5.53 (24 w)	5.64 (24 w)	5.64 (24 w)	5.65 (24 w)
37°	5.59 (24 w)	5.51 (24 w)	5.47 (24 w)	5.58 (24 w)	5.56 (24 w)	5.57 (24 w)
45°	5.48 (18 w)	5.39 (18 w)	5.11 (18 w)	5.46 (18 w)	5.40 (18 w)	5.45 (18 w)
60°	4.25 (18 w)	3.25 (18 w)	3.18 (18 w)	3.67 (18 w)	3.59 (18 w)	3.62 (18 w)
25°/60%RH	5.68 (24 w)	5.63 (24 w)	5.61 (24 w)	5.67 (24 w)	5.66 (24 w)	5.67 (24 w)
30°/60%RH	5.64 (24 w)	5.60 (24 w)	5.56 (24 w)	5.63 (24 w)	5.62 (24 w)	5.64 (24 w)
40°/75%RH	5.52 (24 w)	5.41 (24 w)	5.39 (24 w)	5.51 (24 w)	5.46 (24 w)	5.51 (24 w)

The pH change of the cough syrup is compared against the initial pH which is 5.69. w is the time in weeks.

TABLE 5: CHANGE OF VISCOSITY IN COUGH SYRUP

Type of container	Viscosity in cps at		
	45°	60°	40°/75%RH
Glass	73.33 (18 w)	65.33 (18 w)	71.33 (24 w)
HDPE	69.67 (18 w)	61.33 (18 w)	66.67 (24 w)
LDPE	67.33 (18 w)	60.67 (18 w)	65.33 (24 w)
Polypropylene	71.33 (18 w)	61.33 (18 w)	70.67 (24 w)
PET amber	71.33 (18 w)	62.33 (18 w)	69.33 (24 w)
PET transparent	72.67 (18 w)	62.67 (18 w)	70.67 (24 w)

The change in viscosity is compared against the initial viscosity of the cough syrup which is 90-95 cps. Viscosity of cough syrup at room temperature, 37°, 25°/60%RH and 30°/60%RH shows no change and is 90-95 cps. w is the time in weeks.

made to 100 ml with water. 20 ml solution was transferred to separating funnel and similar treatment carried out as for sample solution. Blank was prepared similarly using 10 ml of water in place of sample. Absorbance of all solutions was measured at 605 nm using Shimadzu UV 160A spectrophotometer.

Determination of shelf life[7]:

Based on the drug content, plots of log percent drug remaining versus time in weeks was plotted for both the drugs in the respective glass and plastic containers at all the temperature conditions. From the slopes of the above graphs, the value of the rate constant (i.e. k) was obtained. Using these rate constants, an Arrhenius plot was constructed by plotting the logarithms of the rate constant (log k) vs. the reciprocal of the absolute temperature (1/T×1000) of 37°, 45° and 60°. From this Arrhenius plot, the value of log k for 25° was obtained by extrapolation. The antilog of this value was determined to get k. The time taken for the drug to fall to 90% of its initial concentration, i.e. the shelf life of the drug was calculated from the equation: $t_{10\%} = 0.10536 / k$.

RESULTS AND DISCUSSION

Physicochemical evaluation of plastics as per IP 1996 indicated that all the plastics complied with the whole container test, and tests on extractable, thus signifying negligible leaching from the containers. As per the systemic injection test included in the biological evaluation of plastics as per IP 96, no redness, erythema, or swelling was observed at the site of injection in any of the mice used for the study. None of the animals treated with the extract showed greater biological reactivity or dizziness than the animals treated with the blank immediately and 4, 24, 48 and 72 h after injection. This indicted that the containers were safe for use for packaging pharmaceutical products.

All the plastic containers showed permeation rate of not more than 100 mg/day/liter in 10 test containers at the end of the testing period (14 days), thus conforming to the water vapor permeation test, as per USP 23. PET containers complied additionally with heavy metals, total terephthaloyl moieties and ethylene glycol tests as per USP 23.

Initially, the syrup was a dark red colored clear liquid with a sweet raspberry flavor and odor. No color change was observed in the syrup stored at room temperature, 37^0, 25^0/60%RH and 30^0/60%RH in all the plastics during the entire test period. The color changed to slightly brown at 45^o and 40^o/75%RH in all plastics and glass containers. However, color deteriorated at higher temperature and gradually darkened over the period of study (Table 2). It turned to dark brown at 60^o at the end of only 3 w in all plastics as well as glass containers.

Flavor remained unaltered for the testing period in PET transparent and polypropylene containers. However, an off-flavor developed at a higher temperature in these containers. In the case of other plastics, an off-flavor developed much earlier under all the testing conditions at the time periods indicated in Table 3. Complete loss of flavor was observed at 60^o in all the containers, including glass, at the end of 3 w. The main sugars in raspberry are sucrose, glucose and fructose with citric as the major organic acid[8]. At least 200 volatile compounds have been identified in raspberry[9,10]. The off-flavor can be attributed to the difference in the permeability of the plastics, with LDPE being the most permeable and developing off-flavor within 3w at all the testing conditions. However, polypropylene and PET being less permeable offer good protection to the flavor and subsequently are able to maintain flavor for a longer period. The amber color in case of PET amber is a result of the charge transfer in the Fe-S chromophore between sulfide and ferric ions[11]. Probably these sulfide and ferric ions from the amber color leach out into the syrup resulting in off-flavor in PET amber containers.

Initial pH of the cough syrup was 5.69. As shown in Table 4, maximum change in pH was observed in the syrup that was stored in LDPE containers at all the testing conditions. The change in pH of the syrup stored in PET transparent and polypropylene containers was almost comparable to that in glass. The drop in pH was higher at 60^0 in all the containers (3.18 in case of LDPE). At ICH conditions, fall in pH was in the range 5.39-5.69 in 24 w in the containers.

Initial viscosity of the syrup was 90-95 cps. No significant change in viscosity was observed at room temperature, 37^0, 25^0/60%RH and 30^0/60%RH, viscosity remaining in the range of 90-95 cps in all the plastic containers throughout the entire testing period. However, viscosity decreased at higher temperature storage conditions (45^o, 60^o and 40^o/75%RH) as indicated by the results in Table 5.

The concentration of ammonium chloride fell down from initial concentration (100%) to 98.3, 97.2, 97.2, 98.1, 98.1 and 98.0%; while diphenhydramine hydrochloride concentration fell to 95.9, 95.7, 95.5, 95.6, 95.7 and 95.8% for glass, HDPE, LDPE, polypropylene, PET amber and PET transparent respectively at 60^0 at the end of 18 w (figs. 1-4).

The rate of degradation for the two drugs was found to increase with an increase in temperature. The coefficient of correlation r was above 0.99 at all temperature conditions in all the containers, thus suggesting that drug degradation followed first order kinetics. The shelf life of both the drugs was calculated using Arrhenius equation and is shown in Table 6. Comparing the shelf life of both the drugs in the five plastic containers with glass, it was observed that the drugs were most stable and comparable to glass only in PET transparent and PET amber containers. However, the organoleptic properties

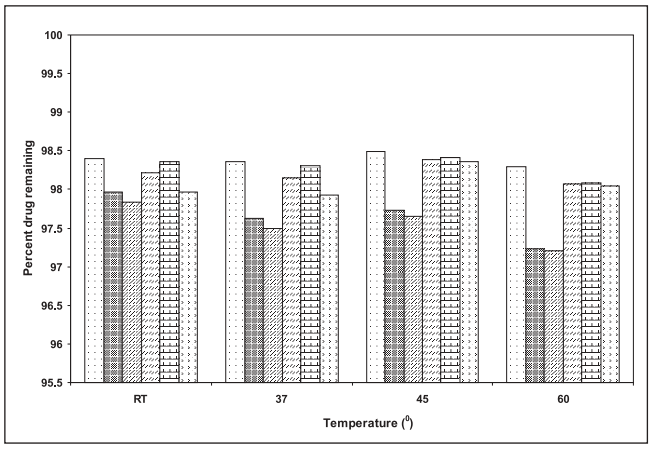

Fig. 1: Percent ammonium chloride in cough syrup stored at accelerated stability
Accelerated stability studies with cough syrup stored in containers made up of glass (□), HDPE (▦), LDPE (▨), polypropylene (▨), PET-amber (▤) and PET-transparent (▩)

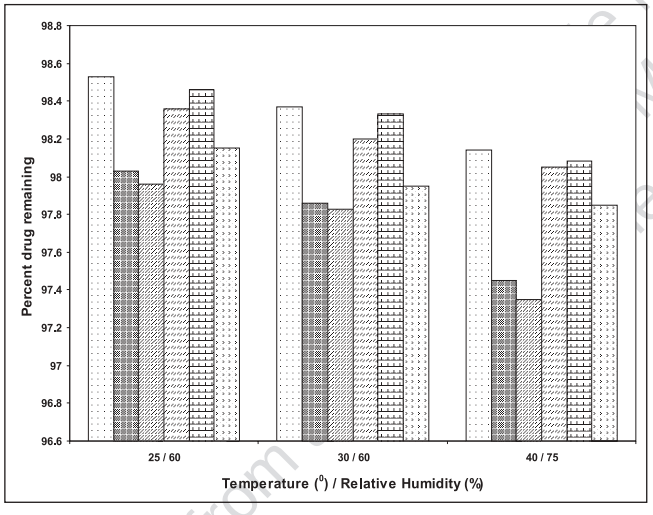

Fig. 2: Percent ammonium chloride in cough syrup stored at accelerated stability at ICH conditions
Accelerated stability studies with cough syrup stored in containers made up of glass (□), HDPE (▦), LDPE (▨), polypropylene (▨), PET-amber (▤) and PET-transparent (▩)

especially flavor of the syrup was better maintained in PET transparent containers as compared to PET amber containers. Therefore, PET transparent containers can be used as a suitable alternative to glass for packaging of cough syrup containing ammonium chloride and diphenhydramine hydrochloride.

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TABLE 6: SHELF LIFE OF COUGH SYRUP IN GLASS AND PLASTIC CONTAINERS

Type of container	Shelf life in years		
	Ammonium chloride	Diphenhydramine hydrochloride	Cough syrup
Glass	3.48	2.18	2.18
HDPE	2.40	1.88	1.88
LDPE	2.20	1.70	1.70
Polypropylene	2.94	1.84	1.84
PET amber	3.09	1.91	1.91
PET transparent	2.81	1.96	1.96

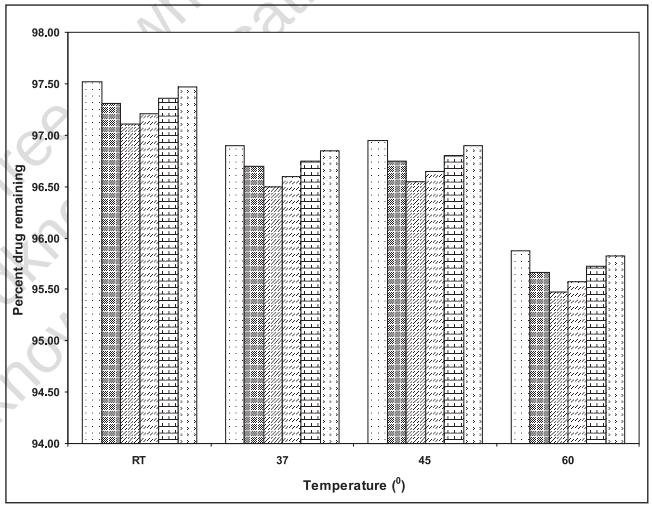

Fig. 3: Percent diphenhydramine hydrochloride in cough syrup stored at accelerated stability
Accelerated stability studies with cough syrup stored in containers made up of glass (□), HDPE (▦), LDPE (▨), polypropylene (▨), PET-amber (▤) and PET-transparent (▩)

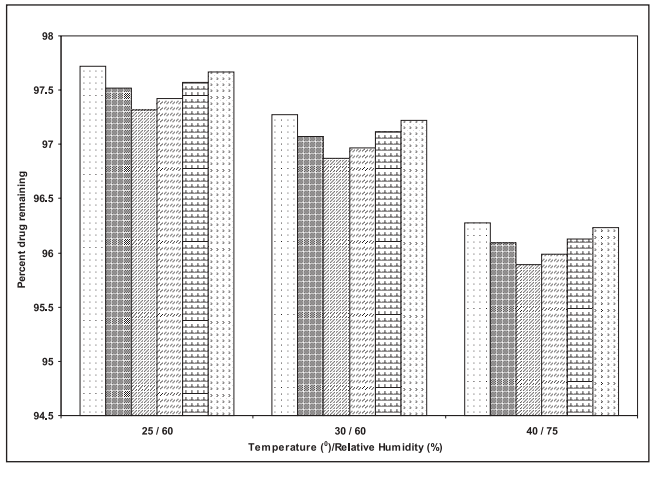

Fig. 4: Percent diphenhydramine hydrochloride in cough syrup stored at accelerated stability at ICH conditions
Accelerated stability studies with cough syrup stored in containers made up of glass (□), HDPE (▦), LDPE (▨), polypropylene (▨), PET-amber (▤) and PET-transparent (▩)

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