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Original Research Article

To Formulate A Hyperlipidemia Dry Powder for Oral Solution Consisting of Cholestyramine Resin (without sucrose)

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Abstract:

The pharmaceutical industry has played a crucial role in improving patient health, but the rising costs of medications have led to concerns about sustainability. Governments worldwide are implementing measures to contain healthcare spending, with a focus on curbing pharmaceutical expenses Dosage forms, especially for oral administration, are vital in drug delivery. Among them, dry powder for oral suspension stands out as a favorable option. This formulation consists of an active pharmaceutical ingredient (API) and excipients in powder form. Dry suspensions offer advantages such as accuracy, uniformity, oral administration, stability, patient acceptability, and cost-effectiveness. They are particularly suitable for populations like pediatrics and geriatrics who may have difficulty swallowing tablets. The formulation of dry powder for oral suspension involves selecting appropriate suspending agents, sweeteners, wetting agents, buffers, preservatives, flavors, and colorants. The choice of these ingredients is crucial for improving powder flow, preventing caking, and enhancing patient acceptance. The inclusion of sweeteners like sucrose helps mask the bitter taste of drugs, while wetting agents aid in the dispersion of hydrophobic drugs. This study delves into the reformulation of cholestyramine resin for oral suspension, focusing on physicochemical properties affecting drug performance. The API undergoes thorough physical characterization, identification, and assay, ensuring compliance with quality standards. The formulation development involves selecting the optimal method (powder blends), optimizing the formula, and addressing factors like pH, sedimentation behavior, and flavor to match the innovator product. Evaluation of the optimized formulation includes pH determination, powder flow characteristics, sieve analysis, sedimentation pattern observation, viscosity determination, assay, and in vitro bile acid binding studies. The results

indicate the optimized formulation's stability, comparable hygroscopic nature to the API, and bioequivalence in bile acid binding with the innovator product.In conclusion, the study provides insights into the formulation and optimization of dry powder for oral suspension, showcasing the importance of selecting suitable ingredients and ensuring bioequivalence. The optimized cholestyramine resin formulation presents a stable and viable alternative for patient use.
Keywords: *cholesterol-lowering dry powder, oral suspension, cholestyramine resin, bioequivalence in bile acid binding*

Introduction

Pharmaceuticals have significantly improved patient health, but their rapid expenditure outpaces economic growth. Governments are implementing cost-containment measures to slow healthcare spending, focusing on pharmaceutical spending. Generics, marketed at lower prices, are becoming attractive options for healthcare providers and governments[1]. The global generics market continues to grow, with sales slowing in mature markets like the US. However, as governments curb healthcare spending, pro-generic legislation will see less mature markets. Manufacturers are now looking elsewhere, targeting markets in countries like France, Italy, Spain, and Japan. The US, the world's largest generic market, is attractive for foreign investors due to its free pricing rules and pro-generic environment. However, competition is putting a brake on growth, driving consolidation and global expansion.[2]

Dosage forms are the physical forms of medication that deliver drugs to their sites of action within the body. The oral route of drug administration is the most popular and successful, with almost 90% of drugs used to produce systemic effects being administered by oral route. There are various dosage forms available for oral administrations, including powder, elixir, solution, suspension, emulsion, tablet, and capsule[3].

Dry powder for oral suspension is a mixture of active pharmaceutical ingredient (A.P.I.) and excipients, usually in powder form. Advantages of dry suspension include accuracy, uniformity, can be administered orally, stability, patient acceptability, lower cost of production, and maintenance of chemical stability until reconstitution. Dry suspensions are most suitable for pediatrics and geriatric populations who cannot swallow tablets[3,4.5].

Formulating suspensions for reconstitution is common due to inadequate chemical stability, physical stability problems, reduced weight of final product, and transportation expenses. Suspending agents used in dry powder for oral suspension should easily disperse during vigorous hand shaking during reconstitution. Some suitable suspending agents include acacia, carboxymethylcellulose sodium, iota carrageenan, microcrystalline cellulose with -ve, propylene glycol alginate, silica dioxide, colloidal 0, sodium starch glycolate, tragacanth, and xanthan gum[6,7].

Ionic charges of agents should be considered to avoid chemical incompatibilities with other ingredients. Natural gums, such as acacia and tragacanth, are used for suspending dense particles, while Xanthan gum is a common suspending agent due to its batch-to-batch uniformity and few microbial problems.[8]

Sucrose is a common sweetener used in suspensions for reconstitution, as it can mask the bitter taste of drugs and aid in suspending drug particles. Other sweeteners include mannitol, dextrose, aspartame, and

sodium saccharin. Wetting agents, such as polysorbate 80 and sodium lauryl sulfate, are used to aid in the dispersion of hydrophobic drugs. The formulator selects the appropriate wetting agent for optimum dispersion[9].

Other ingredients in suspensions include buffers, preservatives, flavor, and color. Flocculating agents are not commonly used in suspensions for reconstitution, as they are often redispersed frequently enough to prevent caking. Buffers maintain the optimum pH for all ingredients, while preservatives are required to prevent microorganism growth. Flavors enhance patient acceptability, and both natural and artificial flavors are used. Colorants provide an aesthetic appearance but may be chemically incompatible with other ingredients. Anticaking agents, such as amorphous silica gel, remove moisture from the dry mixture, prevent caking, and separate dry particles. In summary, suspensions for reconstitution use sweeteners, wetting agents, buffers, preservatives, flavors, and colorants to improve powder flow, prevent caking, and enhance patient acceptance. Powder blends are prepared by mixing dry ingredients in powder form, requiring less capital equipment and energy, and avoiding chemical and stability problems[9,10]. They have advantages such as low moisture content and a lower risk of homogeneity problems. However, they are prone to homogeneity problems and systematic loss of active ingredients during mixing. Granulated products are produced through wet granulation, which involves massing and screening solid ingredients with granulating fluid[19,11]. They have advantages such as improved appearance, flow characteristics, less segregation problems, and less dust generation during filling operations. However, they require more capital equipment and energy, and the residual fluid may reduce product stability. Combination products combine powdered and granulated ingredients to overcome some disadvantages. They require less energy and equipment for granulation and can be combined with heat-sensitive ingredients. The general method involves some ingredients being first granulated and then remaining ingredients blended with dried granules before filling the container. The presence of diluents helps improve flow and reduce segregation and dust formation. Granules can be made by spray coating or microencapsulation. Disadvantages include increased risk of non-uniformity, physical uniformity, and batch-to-batch variation. To achieve uniform potency during processing, bulk storage, and packaging, particle sizes of the various fractions should be carefully controlled[12,13].

II.Objective: The present study aims to formulate a cholesterol-lowering dry powder for oral suspension of cholestyramine resin that is bioequivalent to an FDA-approved innovative product.

III. Materials and Methods

3.1. Reformulation study

The reformulation studies should focus on those physicochemical properties of the new compounds that could affect drug performance and development of an efficacious dosage form. A thorough understanding of these properties may ultimately provide a rationale for formulation design, the reformulation studies like physical characterization of drug sample including description, identification, pH and solubility, loss on drying, hygroscopicity study and assay were performed[14-16].

3.2.1 Physical characterization of API

Cholestyramine resin (API) was characterized for its identification and authenticity. The drug was physically characterized for description, colour, odour

and then the results were compared with the official books, observations mentioned in table 3.1.

3.2.2 Identification of API

Procedure : Quantity of cholestyramine for oral suspension, equivalent to about 500 mg of dried cholestyramine resin was transferred to a suitable flask, to it 100 ml of 0.1N HCl acid was added, then stirred to suspend the solid and heated on a steam bath for 10 minutes. Solution was then filtered and residue was washed with three 50-ml portions of water, and dried at dried 70°C and at a pressure not exceeding 50 mm of mercury for 16 hours, the IR absorption spectrum of a potassium bromide dispersion of the residue so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of USP cholestyramine resin RS[17].

Infra-Red Spectrum

IR of the drug sample was obtained using Shimadzu FTIR-IR Prestige-21. One mg of the treated API as per procedure was mixed with 100mg of KBr in a mortar by trituration and the mixture was compressed into a pellet by pellet maker and the sample was scanned at 4000– 400 cm^{-1}. The IR spectrum obtained was compared with the IR spectrum of a similar preparation of USP cholestyramine resin RS[17].

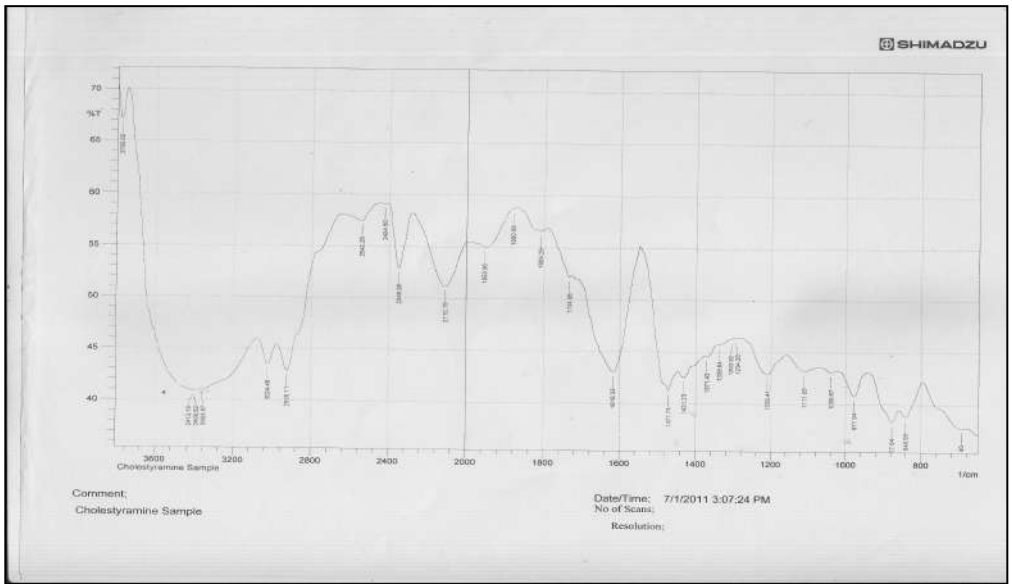


Fig 3.1IR spectrum of given cholestyramine resin API

3.2.3 Assay of cholestyramine resin (sodium glycocholate exchange capacity – HPLC method) [16,17]

Note: In this procedure, a secondary cholestyramine standard is used, this secondary standard is cross-referenced to a certified USP reference standard. Both sample and reference are dried in a vaccum oven at 70°C for a minimum of 16 hours, i.e. 'overnight', prior to this determination[21]..

3.3 Formulation development

Development of cholesterol lowering dry powder for oral suspension is divided into following phases

3.3.1 Selection of method

Dry powder can be prepared by three methods 1) powder blends 2) granulated products 3) combination products, but from the results obtained by sieve analysis in innovator characterization it can be

concluded that innovator is complete #80 mesh passed, so used method is powder blend.

3.3.2 Optimization of formula

The proposed formula as per the innovator product was optimized by taking different trail batches on formulation and error basis so as to match physical parameters, and then final formula is optimized by varying the concentration of one excipient at a time. The quantity of drug and other excipients were kept constant.

3.3.2.1 Optimization of concentration of anhydrous citric acid to match pH with innovator product

Batches were planned by taking different concentrations viz. 0.17% (0.01g in 5.7g), 0.35% (0.02g in 5.7 g), 0.52% (0.03g in 5.7g), 0.70% (0.04g in 5.7g), 0.87% (0.05g in 5.7g), 1.05% (0.06g in 5.7g) of anhydrous citric acid (as shown in table 3.4) .Concentration of all other ingredients were kept constant so as to observe impact of concentration of citric acid on pH of suspension and to choose best possible concentration so as to match pH of test product to innovator product. Impacts of citric acid concentration on pH in different formulations were shown in table 3.5.

Table 3.4 Formulation batches for optimization of concentration of anhydrous citric acid

Sr.No	Ingredients (gm/sachet)	A1 0.17% (0.01g in 5.7g)	A2 0.35% (0.02g in 5.7g)	A3 0.52% (0.03g in 5.7g)	A4 0.70% (0.04g in 5.7g)	A5 0.87% (0.05g in 57.7g)	A6 1.05% (0.06g in 5.7g)
1	API	4	4	4	4	4	4
2	**Citric acid**	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**	**0.06**
3	Aspartame	0.03	0.03	0.03	0.03	0.03	0.03
4	FD&C Yellow No. 10	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004
5	FD&C Yellow No. 6	0.006	0.006	0.006	0.006	0.006	0.006
6	Propy. Glycol Alginate	0.4	0.4	0.4	0.4	0.4	0.4
7	Aerosil 200	0.079	0.079	0.079	0.079	0.079	0.079
8	Xanthun Gum	0.007	0.007	0.007	0.007	0.007	0.007
9	Fructose	0.440	0.420	0.410	0.400	0.390	0.380
10	Mannitol	0.230	0.230	0.230	0.230	0.230	0.230
11	Pectin	0.20	0.20	0.20	0.20	0.20	0.20
12	Sorbitol	0.30	0.30	0.30	0.30	0.30	0.30
13	Orange flavour	0.01	0.01	0.01	0.01	0.01	0.01
	TOTAL	**5.7 g**	**5.7 g**	**5.7 g**	**5.7 g**	**5.7 g**	**5.7 g**

IV.RESULT AND DISCUSSION

41 Preformulation study

The present investigation was carried out to develop dry powder of cholestyramine resin for oral suspension; different excipients were selected in reference of combination used by innovator.

5.1.1API Characterization study[8-17].

Physical characterization

The drug was physically characterized for description, colour, odour and results obtained comply with official books.

Identification of API

Infra-red spectrum of cholestyramine API was determined as per the procedure and compared with the IR spectrum of a similar preparation of *USP cholestyramine resin RS*, and found to show absorption maxima on same wavelengths as shown by reference standard, IR spectrum of API is shown in Fig. 4.1.

Assay (sodium glycocholate exchange capacity)

Sodium glycocholate exchange capacity was determined as per USP procedure, and found to be 2.17g/g of resin, i.e. comply with the limit (USP) that each gram of resin can exchanges not less than 1.8g and not more than 2.2g of sodium glycocholate, calculated on dried basis.

Solubility study

Solubility of cholestyramine API was checked in water, ethanol, chloroform, ether, and found to be insoluble thus comply with the USP specifications.

Loss on drying

LOD at 105°C was found to be 6.63% MC, i.e. as per specification.

pH of aqueous solution

pH of aqueous solution (1 in 100) of API was found to be 5.21, i.e. as per proposed specification between 4.0 and 6.0 in a slurry (1 in 100).

5.1.2 Drug excipients compatibility study

Drug excipients compatability study was performed and from fig 4.2 it may concluded that drug and excipients are found to be compatible.

4.1.3 Hygroscopicity study

Hygroscopicity study was performed as per the procedure mentioned in section 3.2.8 for four weeks, and from the observations obtained API can be concluded as hygroscopic in nature and thus complies with the USP specification. Four week hygroscopic study is done so as to compare water gaining ability of finally optimized formulation and API, as well as on the basis of ability to gain moisture package for the dispensing of final formulation was decided.

4.2 Optimization of formulation

Different formulation batches were planned by varying concentration of citric acid (so as to match pH), concentration of propylene glycol alginate and xanthun gum, pectin (so as to match sedimentation behavior), concentration of orange flavor (so as to match physical appearance) ultimately to match physical parameters with the innovator product.

Finally optimized formula was shown in table 3.10.

4.3 Evaluation of optimized formula[8,16,17]

Determination of pH

pH of the final formulation was found to be 3.130 (on 60 ml dilution) and 3.081 (on 180 ml dilution).

Powder flow characteristics

From the parameters obtained (Table 3.11 & 3.12), it may concluded that optimized formulation have passable flow properties, and in comparison to innovator, flow of test formulation is better, so probably cannot produce any problem during filling operation, in large batch.

Sieve analysis

Based on observations obtained (table 4.6), it may concluded that average particle size for innovator cholestyramine powder is 106.64 µm and that for the test (optimized formulation) cholestyramine powder is 83.04 µm.

Sedimentation pattern

From the observations, obtained from the study (table 4.7 & table 4.8) it may conclude that innovator and test formulations show similar sedimentation pattern.

Viscosity determination

Viscosity of innovator as well as test formulation was determined as per procedure, by using spindle no SC4-18 rotating at 30 and 150 rpm, at 25°C, and from the observations (table 4.9) obtained it may concluded that both have similar viscosity.

Assay

Assay of optimized test formulation was performed as per USP procedure (refer. Section 3.3.8) and from the study, amount of dried cholestyramine resin was found to be 99.20%, i.e. as per specification of USP between limit not less than 85% and not

more than 115% of the labeled amount of dried cholestyramine resin.

***In vitro* bile acid binding study**

Equilibrium and kinetic *in vitro* bile acid salts binding studies are recommended to document bioequivalence between generic (test) and innovator (Reference) formulations of cholestyramine. Equiliribium study with and without acid pretreatment was conducted as per procedure mentioned in section III B of *Interim Guidance*, and on the basis of observations reported. Total percent of bile acid salts bound as well as total mM of bile salts bound was reported (table 4.12 & 4.15).

<u>In-vitro Equiliribium Study :</u>

Following are the result for Study of Invitro Equiliribium Binding of Bile Acid salts:

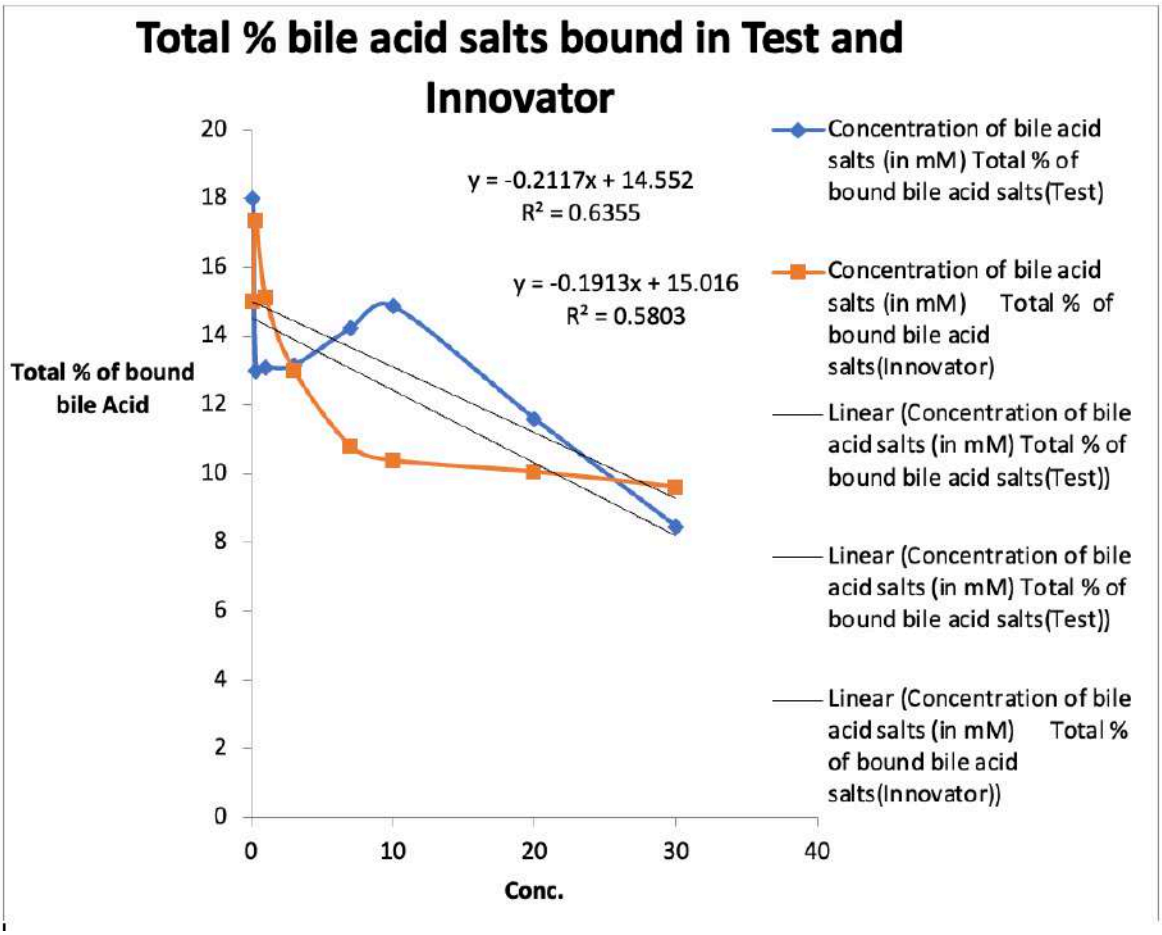


Fig 4.1 Percent of bile salts bound of Test and Innovator at different mM concentration of bile acid salts to resin in SIF without acid pre-treatment :

K_1 (Reference) =0.0145, K_1 (Test) = 0.0127
K_2 (Reference) =4.723, K_2 (Test) =5.227
R^2 (Reference) =0.6355, R^2(Test) =0.5803

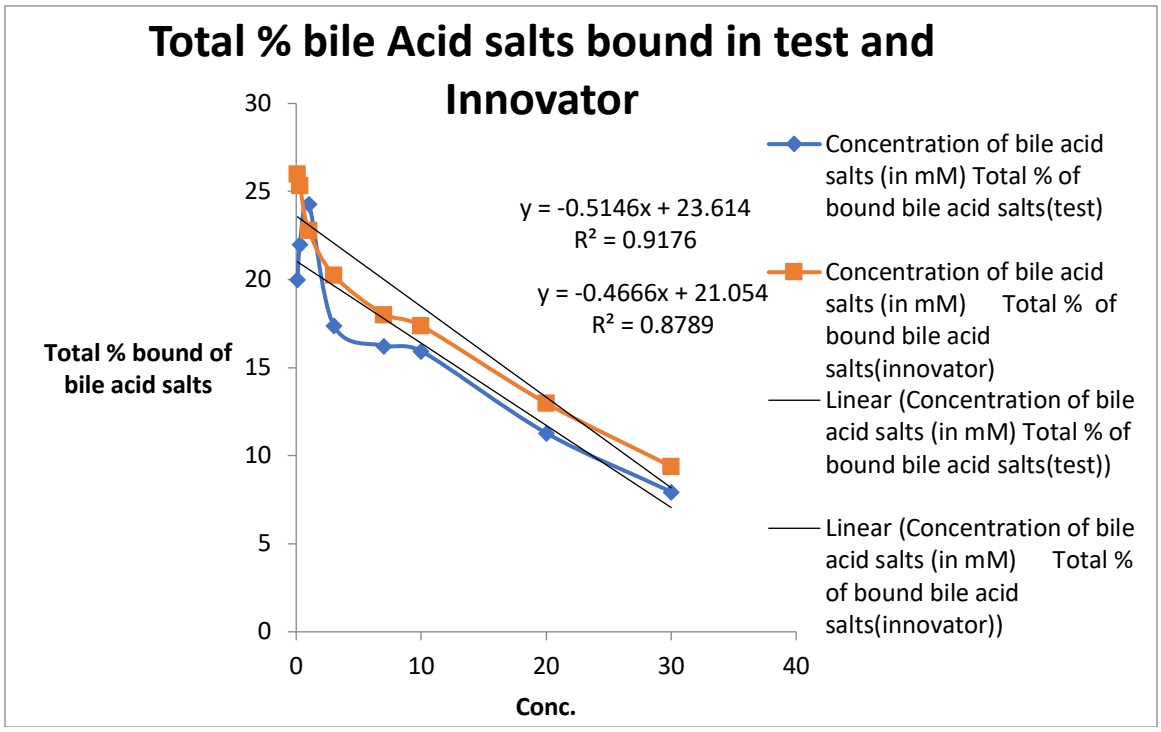


Fig 5.2 Percent of bile salts bound of Test and innovator at different total mM concentration of bile acid salts to resin in SIF with acid pre-treatment:

K_1 (Reference) =0.0217, K_1 (Test) = 0.0221
K_2 (Reference) =1.943, K_2 (Test) =2.143
R^2 (Reference) =0.9176, R^2(Test) =0.8789

In-vitro kinetic Study :[14,17]

A) Following are the result for Study of kinetics of Binding of Bile Acid salts in 0.3mM in the presence of Added Sodium Chloride(0.1) :

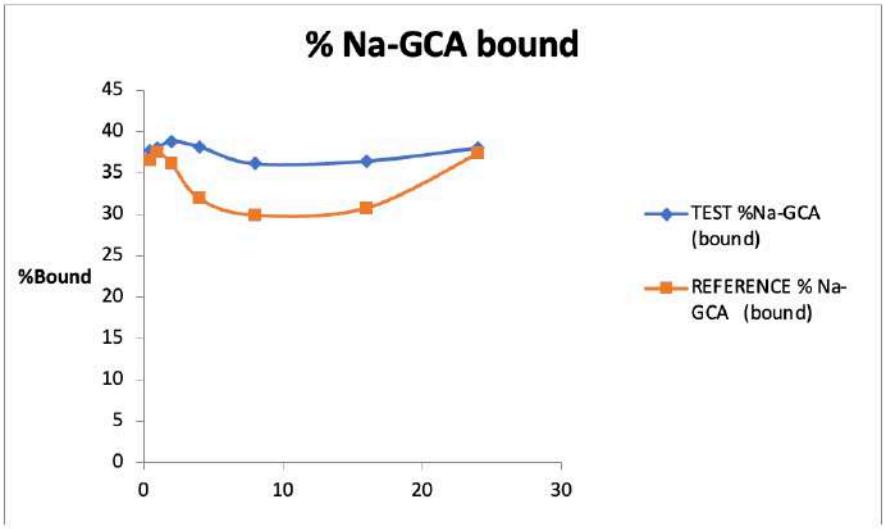


Fig 4.3 Percent of Na-Glycocholic Acid bound of Test and Innovator (Reference) at different time interval at total 0.3mM concentration of bile acid salts.

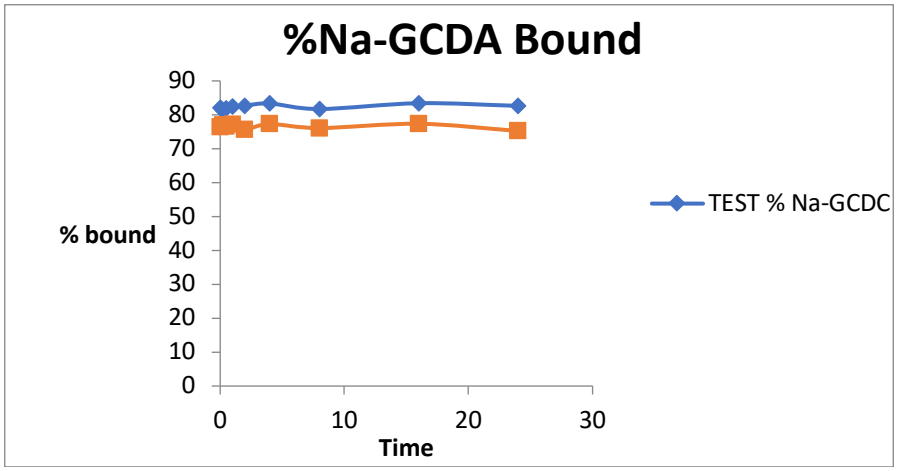


Fig 4.5 Percent of Na- Taurodeoxycholic acid bound of Test and Innovator (Reference) at different time interval at total 0.3mM concentration of bile acid salts.

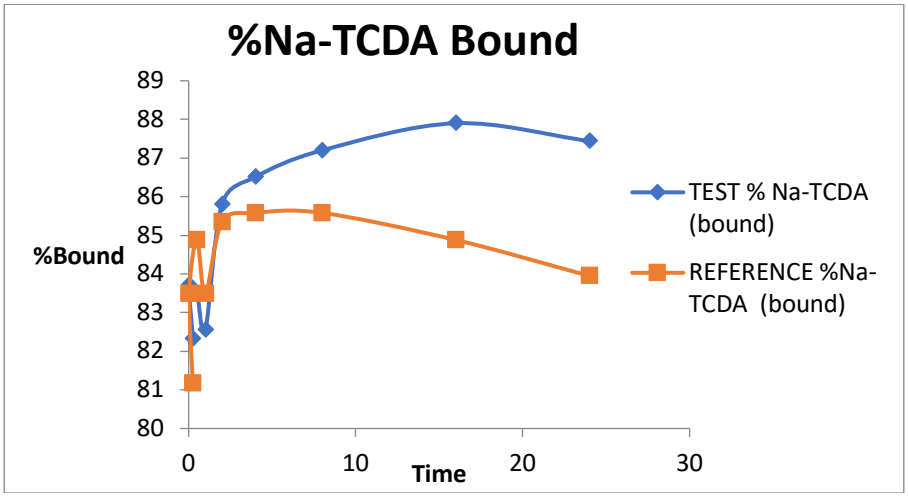
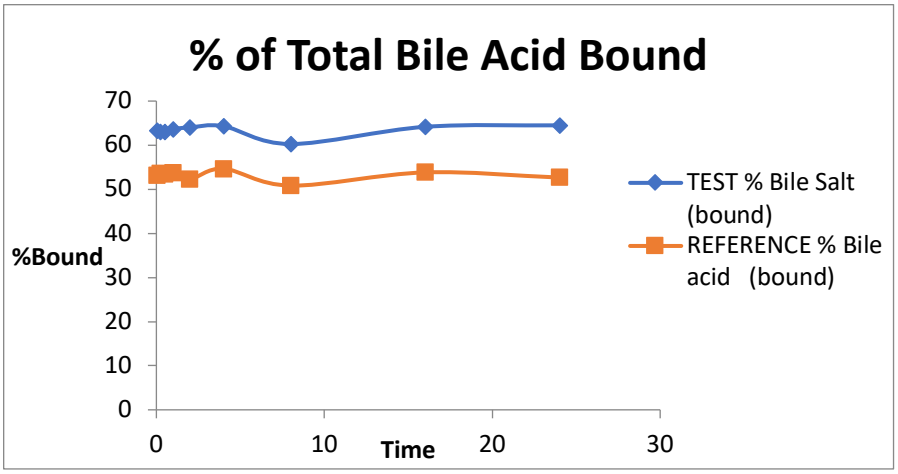


Fig 4.6 Percent of Total bile salts bound of Test and Innovator (Reference) at different time interval at total 0.3mM concentration of bile acid salts.



B) Following are the result for Study of kinetics of Binding of Bile Acid salts in 3mM in the presence of Added Sodium Chloride(0.1) :

Fig 5.7 Percent of Na-Glycocholic Acid bound of Test and Innovator (Reference) at different time interval at total 3mM concentration of bile acid salts.

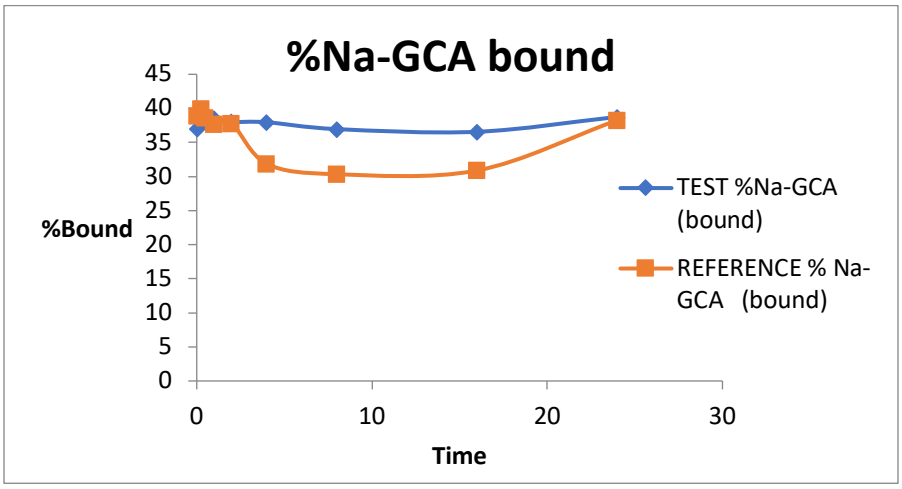


Fig 4.8 Percent of Na- glycochenodeoxycholic acid Acid bound of Test and Innovator (Reference) at different time interval at total 3mM concentration of bile acid salts.

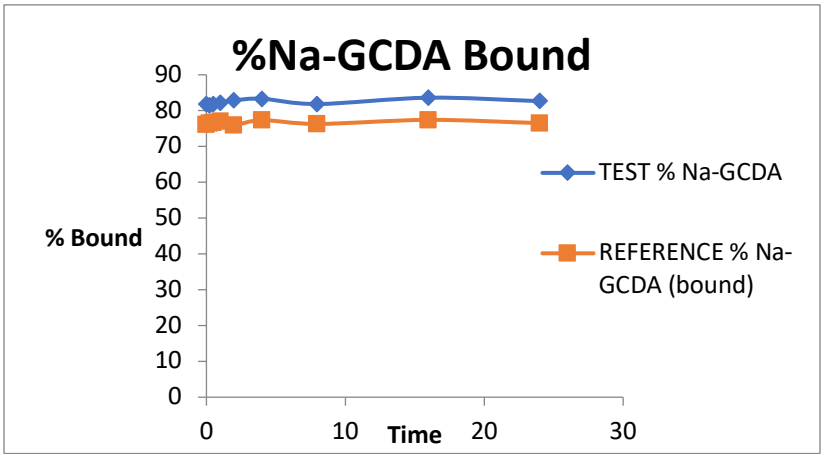


Fig 5.9 Percent of Na-Taurodeoxycholic Acid bound of Test and Innovator (Reference) at different time interval at total 3mM concentration of bile acid salts

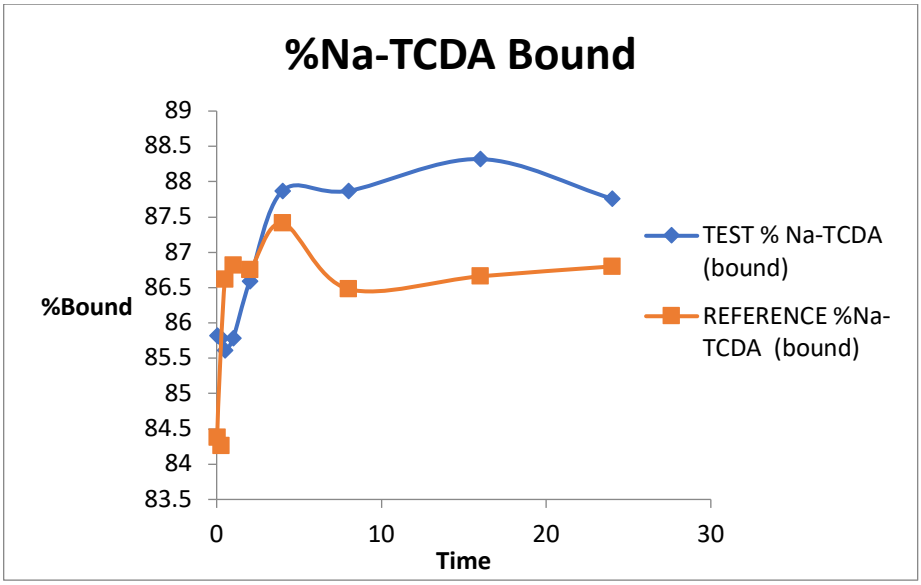
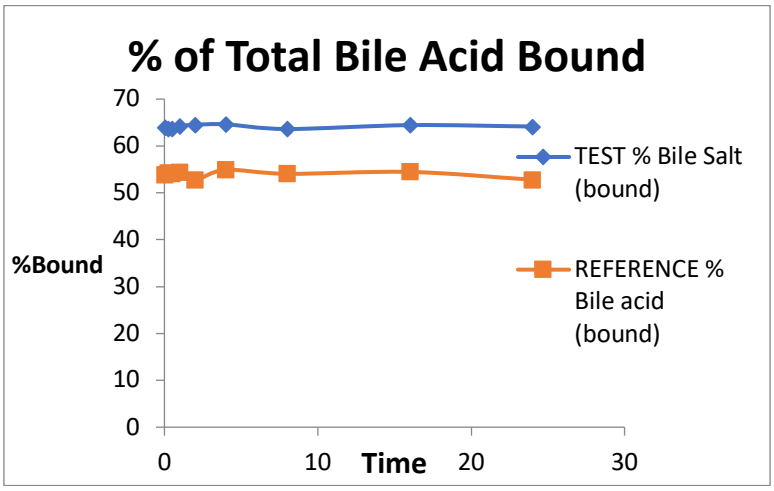


Fig 4.10 Percent of Total Bile Acid bound of Test and Innovator (Reference) at different time interval at total 3mM concentration of bile acid salts.



So from the observations obtained in this study, it may concluded that ability to bound bile acid salts of test and innovator is similar, so results complies with the bioequivalence requirements. For more optimized results, study should be repeated for six times and through the mean value final conclusion should be drawn.

Hygroscopicity study[14,17].

Hygroscopicity study for finally optimized cholestyramine formulation (i.e. test) was done as per procedure mentioned in section 3.2.8.

Objective of this study on final formulation is to compare the hygroscopic tendency of cholestyramine resin API and cholestyramine powder (i.e. final formulation), and to decide the RH condition suitable for manufacturing of product because it is department to decide the packaging material for the product

Stability Study

From the stability study it was concluded that, at 80°C the assay of drug increased due to more water loss as compared to other conditions, at this condition pH was also found to be increased. At 40˚C/75% RH and at 30°C/75% RH the assay of drug was slightly increased, but at 25˚C/60%RH there was no more changes in assay of drug in comparison of initial value.One month stability data reveals that formulation is stable and shows parameters as per specifications, for further conclusion *in vitro* bile salts binding study should be done with formulation stored in each of condition. But from the data obtained it may concluded that the 25˚C/60%RH condition is more suitable for storage of formulation.

CONCLUSION

From the observations obtained, it may concluded that finally optimized test cholestyramine formulation have similar (or slightly less) hygroscopic nature as that of the API.Low RH condition is suitable for processing operations during manufacturing of large batch, though it may be finalized latter on. As it is a ready to use product, so supplied in pouches, pouch material should be such as easy to tear and have sufficient strength to avoid the moisture entry into the product, on the basis of the data obtained in hygroscopic study as well as on evaluation of innovator pack, packaging material proposed was plain laminate, having structure as paper/extrusion/foil/extrusion having total GSM in between .

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