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CAPTOPRIL-EXCIPIENT PREFORMULATION STUDIES FOR MOUTH DISSOLVING TABLETS DEVELOPMENT

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ABSTRACT

Captopril is a sulfhydryl-containing angiotensin-converting enzyme inhibitor which is the enzyme that converts angiotensin-I to angiotensin II and may also reduce the degradation of bradykinin. It is used in the management of hypertension, heart failure, myocardial infarction and in diabetic nephropathy. Therefore, it can be used as a model of mouth dissolving tablets MDTs as a more bioavailable form than conventional tablets. The main objective of the present study was to the preformulation studies were performed to know the development of formulation and evaluation of Captopril mouth dissolving tablets MDTs to improve the bioavailability of Captopril. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage. The drug-excipient compatibility studies were conducted to characterize the drug Captopril present in mouth dissolving tablets MDTs. Preformulation, formulation and evaluation of Captopril to avoid problems associated with conventional delivery system and one of the most recent antihypertensive agents. In the present study that the compatibility was assessed by, FTIR spectroscopy, and melting point apparatus, precompression parameters and powder flow properties. Results showed that physical mixtures physical mixtures of Captopril with different used excipients such as Microcrystalline cellulose, Mannitol, Maize starch and Lactose monohydrate as diluent, and

Croscarmellose sodium and Sodium starch glycolate as superdisintegrants were evaluated for preformulation studies parameters. It was concluded that the drug Captopril was found to be compatible with most Captopril MDTs formulations which were selected for the formulation development of the Captopril mouth dissolving tablets MDTs. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

KEYWORDS: Captopril, Compatibility, Excipients, Development, Preformulation, Formulation.

INTRODUCTION

Preformulation Studies[1-45]

Preformulation is essentials of pharmaceutical science that utilizes biopharmaceutical principles in the determination of physicochemical properties of the drug substance. Prior to the development of any dosage form new drug, it is essential that certain fundamental physical and chemical properties of drug powder are determined. This information may dictate many of subsequent event and approaches in formulation development. The safety, efficacy, quality and stability of a formulation are major concepts of any API development process. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

One of the objectives of this study is to development of drug delivery systems by building scientific pharmaceutical research information depend on formulation scientists to join the knowledge and experience as well as experimental and practical results of this study with regard to information in previous studies, and approved references. It was found to be that the most important concepts and basics of preformulation studies such as definitions, methods, conclusion, idea, and types of pharmaceutical analysis techniques using in evaluation of preformulation studies parameters, in this study that we focused on developing drug delivery systems and linking the formulation development to establish the basics of pharmaceutical research in studying the drug-excipient compatibility, dug with various excipients, which is

important for the safety, effectiveness, quality, formulation, stability, bioavailability, and pharmacokinetics of the drug etc.

Determination of physical chemical properties of API substance with the goal of developing a new drug which is safe stable and efficacious, each API, has intrinsic chemical and physical properties that were considered prior to the development of pharmaceutical formulation, the purpose of preformulation study is to generate useful information for the formulator in the development of stable and bioavailable dosage form, inappropriate preformulation study results in poor stability of active ingredients increase the overall cost of development and increased development time, preformulation studies help to fortify the pharmaceutical scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, enhance public safety standards, improve product quality, promote the implementation of new technologies, aids policy development and regulatory decision making and after compiling all data it is transferred to the development pharmacist and for the day work on formulation of dosage form.

Preformulation Study Objectives: To establish the Physico-chemical parameters of a new API entity, determine its kinetics and stability, establish its compatibility with common excipients, it provides insights into how drug products should be processed and stored to ensure their quality, estimate problem may arise during formulation that is stability problem poor *in-vivo* dissolution, poor bioavailability, to interpret BCS classification of drugs and its significance and develop optimal drug delivery system.

Drug-Excipient Compatibility Study: The primary objective of this investigation was to identify a stable storage condition for API in solid state and identification of compatible excipients for its formulation. Incompatibilities are major concerns in formulation development. Selection of the proper excipient during preformulation studies is of prime importance.

Dosage Forms: DF contain API and pharmaceutical excipients, which are intended to generate an ideal formulation and manufacturability of pharmaceutical products, thereby enabling a much safer and more effective administration. Pharmaceutical excipients are ideally inactive and have no impact on the stability or therapeutic effect of the active ingredient. On the other hand, there are studies that have presented that some pharmaceutical excipients are just allegedly described as inactive ingredient. Some pharmaceutical excipients

have the capacity to affect API, efficacy by affecting its pharmacokinetics. Excipients can affect the physical and chemical form of pharmaceuticals by several factors such as hydrogen bond interaction, polymorphic conversion, and others. Accordingly, drug-excipient compatibility should be conducted so as to determine any drug-excipient interactions that may obstruct the stability, bioavailability, and manufacturability of pharmaceutical dosage forms.

Importance of Drug-Excipient Compatibility

Studies of active pharmaceutical ingredient (API)-excipient compatibility represent an important study in the preformulation stage of the development of new dosage forms, stability of the dosage form can be maximized, any physical or chemical interaction between API, and excipient can affect bioavailability and stability of drug, it helps to avoid the surprise problem, by performing drug excipient compatibility studies (DECS) we can know the possible reaction before formulating final dosage form, DECS data is essential for IND (investigational new drug) submission, and now, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval.

The potential physical and chemical interactions between an API, and the excipients can affect the chemical nature, the stability and bioavailability of the former and, consequently, its therapeutic efficacy and safety, solid dosage forms are generally less stable than their API components and despite the importance of API-excipient compatibility testing, there is no universally accepted protocol to assess such interactions.

Pharmaceutical Excipients: Excipients are additive substances used to improve the bulkiness, disintegration, dissolution rate, and bioavailability of a formulation etc. Different dosage forms like powders, granules, capsules, tablets, oral liquids, injectable products, implants, eye products, nasal products, inhalers, topical creams, ointments, gels, transdermal patches and suppositories etc, contains different types of excipients. To make it acceptable and compatible various pharmaceutical excipients are added in pharmaceutical dosage form for their direct therapeutic action, manufacturing process, to protect, support or enhance stability, for bioavailability or patient compliance. These must be physiologically and chemically stable, must not have any incompatibility with the API, and must meet the standards of regulatory requirements.

Evaluation of Drug-Excipient Compatibility

The compatibility study of API and excipients is important to predict the stability of the API, in the final pharmaceutical product. It's the first time that API was compatible with excipients promoted physical and chemical compatibility studies was achieved by thermal and non-thermal methods. As a part of preformulation study, a compatibility study of API with the other excipients was carried out using physical blends in analytical techniques for the evaluation of drug-excipient interactions. The most commonly used pharmaceutical analytical techniques include, thermal techniques such as Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), Isothermal Microcalorimetry (IMC) and Hot stage microscopy (HSM) etc, and non-thermal techniques such as UV-Visible Spectrophotometric (UV), Infrared, Near-Infrared and Raman Spectroscopy (FT-IR), (NIR), Powder *X*-Ray Diffraction (PXRD), Solid-State Nuclear Magnetic Resonance Spectroscopy (ssNMR), Microscopic techniques: Scanning Electron Microscopy (SEM), Chromatographic techniques: Thin Layer Chromatography (TLC), and High-Performance Liquid Chromatography (HPLC) etc.

Preformulation Parameters: According to dosage form of API, mainly solid state, particle size, shape, pKa, pH determination, common ion effect, temperature, partition coefficient, solubility studies, dissolution rate, melting point, powder flow properties, crystallinity, polymorphism, hygroscopicity, stability study and drug-excipient compatibility etc. While other dosage forms according to important of preformulation parameters used in study before start in development of formulation.

Drug-excipient compatibility and formulation stability is not depended on API only but also its affected by excipient. Excipient play important role in dosage form but side by side it also increases compatibility problem so proper selection of excipient is very important in development of formulation. Incompatibility can be result mainly in any of following changes: Changes in organoleptic properties, changes in dissolution performance, decrease in potency, and increase in degradation rate etc.

Drug excipient physicochemical characterization is a systematic approach towards design of therapeutically active and stable dosage forms. The rapid advancements in novel drug delivery systems development have led to an interest by formulation scientists in the role and functionality of the excipients.

In the present study, it was proposed to Captopril -excipient compatibility studies of the safety, efficacy, quality and stability of a formulation are major concepts of any API development process. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage., with commonly different excipients using for formulation development of Captopril mouth dissolving tablets MDTs.

MATERIALS AND METHODS

Captopril (Wockhardt limited, India), Microcrystalline cellulose "Avicel PH101", Croscarmellose sodium "Ac-Di-Sol" (FMC co., Ireland), Aspartame (Asuka, Turkey), Lactose monohydrate, Disodium hydrogen phosphate, Potassium di-hydrogen ortho phosphate, Citric Acid, Maize Starch, Magnesium Stearate (E.Merk, Germany), Mannitol (Roqette, France), Sodium Starch glycolate "Explotab" (JRS pharma, Germany), Colloidal silicon dioxide "Aerosil 200" hydrophilic, Potassium chloride, Sodium chloride (Kirsh Pharma, Germany), Sodium hydroxide (Riedel-de Haen, Germany), FD & C blue dye no.1(Symrise, Germany), Methanol. Other solvent and chemicals are of analytical grades. Most of the previous materials were gift from (YEDCO Pharmaceutical Industry Company-Yemen).

Equipments: Tablet press, IOTA press (India). Spectrophotometer UV/Vis, (JASCO V- 550, Japan). Membrane filter 0.45µm, (Gelman, sciences Inc., Germany). PH meter (Sartorius, Germany). Hotplate magnetic stirrer (Stuart, U.K). Sensitive and electronic balance Sartorius, Germany). Sonicator (Elma, Germany). Sieves sizes (0.3, 0.5 and 1.4mm). Oven (Manesty PETRIE, U.K). Infrared spectrophotometer (Shimadzu FTIR8900, Japan).

Calibration Curve of Captopril in Phosphate Buffer pH 6.8[40,41]

Serial concentrations of Captopril in phosphate buffer pH6.8 containing 2,6,10,14,20 and 22µg/mL were prepared. The absorbance of the prepared solutions was measured spectrophotometrically at λ max 205nm against phosphate buffer pH 6.8 as a blank. The absorbance was plotted against the concentrations and the procedural constant (K) was calculated from the best fitting straight line using linear regression analysis as shown in Table 1 & Figure 1.

Table 1: Calibration Curve of Captopril in Phosphate Buffer PH6.8 at λmax 205nm.

Absorbance (nm)	Concentration(µg/ml)
0.28	2
0.41	6
0.55	10
0.68	14
0.84	18
0.98	22

R=0.9995266**, Slope=** 0.0351429**, Intercept=** 0.2016190**, K=** 28.5**.**

Formulation of Captopril MDTs by Different Methods[40,41]

The following excipients were used for the preparation of Captopril MDTs. Magnesium stearate and aerosil 200 as lubricants, lactose monohydrate, avicel PH101 and mannitol as diluents, croscarmellose sodium (Ac-Di-Sol) and sodium starch glycolate (Explotab) as disintegrants, aspartame as a sweetener, citric acid and sodium bicarbonate as effervescent agents, maize starch as binder. The calculated dose of the drug and other excipients listed in Table 2.

Table 2: Formulation of Captopril Mouth Dissolving Tablets.

Ingredients (%) Formulation Code	Captopril	Maize Starch	Avicel PH101	Lactose Mono-hydrate	Mannitol	Explotab (SSG)	Ac-Di-Sol (CCS)	Citric Acid	Sodium Bicarbonate	Aspartame	Aerosil200	Magnesium Stearate	Total
F1	13.9%	---	78.1%	---	---	5%	---	---	---	1%	1%	1%	**100%**
F2	13.9%	---	73.1%	---	---	10%	---	---	---	1%	1%	1%	**100%**
F3	13.9%	---	78.1%	---	---	---	5%	---	---	1%	1%	1%	**100%**
F4	13.9%	---	73.1%	---	---	---	10%	---	---	1%	1%	1%	**100%**
F5	13.9%	---	39.1%	---	39%	5%	---	---	---	1%	1%	1%	**100%**
F6	13.9%	---	26.1%	---	52%	5%	---	---	---	1%	1%	1%	**100%**
F7	13.9%	---	47.1%	31%	---	5%	---	---	---	1%	1%	1%	**100%**
F8	13.9%	---	44.1%	29%	---	10%	---	---	---	1%	1%	1%	**100%**
F9	13.9%	---	47.1%	31%	---	---	5%	---	---	1%	1%	1%	**100%**
F10	13.9%	---	44.1%	29%	---	---	10%	---	---	1%	1%	1%	**100%**
F11	13.9%	---	37.1%	---	37%	10%	---	---	---	1%	1%	1%	**100%**
F12	13.9%	---	24.1%	---	49%	10%	---	---	---	1%	1%	1%	**100%**
F13	13.9%	---	65.1%	---	---	---	---	8%	10%	1%	1%	1%	**100%**
F14	13.9%	9%	73.1%	---	---	5%	---	---	---	1%	1%	1%	**100%**
F15	13.9%	9%	68.1%	---	---	10%	---	---	---	1%	1%	1%	**100%**
F16	13.9%	---	78.1%	---	---	5%	---	---	---	1%	1%	1%	**100%**

Preparation of Captopril MDTs by Direct Compression Method

Formulae F1-F13 were prepared as the following: Accurately weighed quantities of Captopril, avicel PH101, aspartame and the superdisintegrant (Explotab or Ac-Di-Sol) or effervescence agents (as citric and sodium bicarbonate) were passed through a sieve mesh ≠60 and blended homogeneously. Then magnesium stearate and aerosil 200 were added to the mixture. The final mixture was converted into constant weight tablets by direct compression method using a single punch tableting machine (IOTA press, India) equipped with 8.5mm concave punch.

Preparation of Captopril MDTs by Indirect Compression (Wet Granulation Method)

Formulae F14-F16 were prepared as the following: Accurately weighed quantities of Captopril, avicel PH101, aspartame and the superdisintegrant were passed through 0.5 mm sieve and mixed in a glass mortar. The above blend was granulated with ethanol 95% as a non-aqueous granulating agent (with or without binder) and passed through a sieve (1.40 mm). The granules were air-dried, lubricated with magnesium stearate and aerosil 200 and compressed using a single punch tableting machine (IOTA press, India) equipped with 8.5 mm concave punch.

Drug-Excipient Compatibility Studies[15-56]

A physical mixture including Captopril and excipient was created in a 1:1 ratio, and it was subjected to analytical techniques such as FTIR spectroscopy. FTIR, of both pure drug and physical mixes were obtained, and the spectra of the both drug and mixture of excipient with drug were compared to look for any incompatibilities.

Samples equivalent to 2 to 3mg(previously prepared by finally powdering 3 tablets of each formula using mortar and pestle) were mixed with about 100mg of dry potassium bromide powder in micronized IR grade KBr powder using a mortar and pestle. The powder was compressed into discs under pressure of 10.000 to 15.000 pounds per square inch. The infrared spectra of the pure drug and fresh drug-excipient mixtures were recorded over a wave number range of 4000 cm-1 to 500cm-1.

Infrared Spectral Study of Samples in Room Condition

Compatibility studies were performed by preparing blend of Captopril MDTs formulations from different excipients with Captopril in room condition as shown in Table 3.

Table 3: Samples of Captopril and Different Excipients for Compatibility Studies of Formulation MDTs.

No	Component(s)	Amount
1	Captopril	2-3mg
2	F1	2-3mg
3	F2	2-3mg
4	F3	2-3mg
5	F4	2-3mg
6	F5	2-3mg
7	F6	2-3mg
8	F7	2-3mg
9	F8	2-3mg
10	F9	2-3mg
11	F10	2-3mg
12	F12	2-3mg
13	F13	2-3mg
14	F14	2-3mg
15	F15	2-3mg
16	F16	2-3mg

RESULTS AND DISCUSSION

Preformulation Studies

Characterization of Captopril by UV Spectroscopy

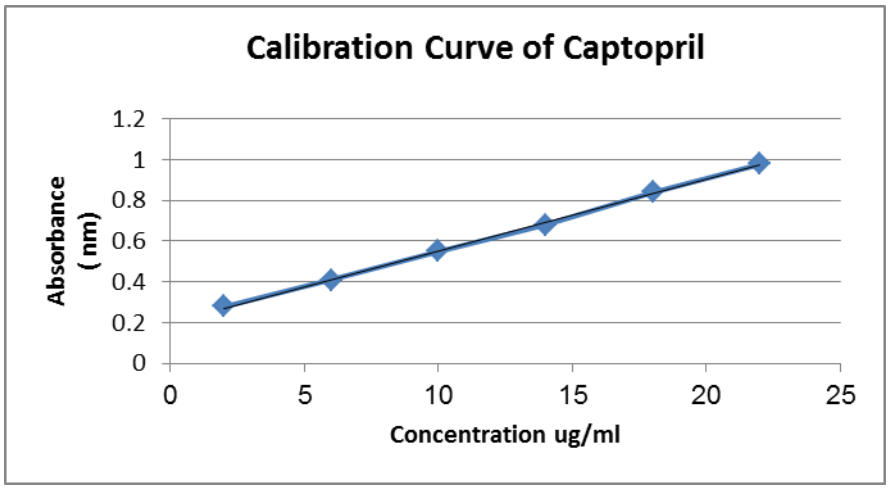

Fig. 1: Calibration Curve of Captopril in Phosphate Buffer pH6.8 at λmax 205nm.

The Results of Evaluation for Captopril

Table 1, illustrated the absorbance determined at λ_{max}205nm in phosphate buffer pH6.8 at λ_{max}205nm for serial concentrations of Captopril. Figure 1, illustrated that a linear relationship between the absorbance at the specified λ_{max} and the concentration was obtained

within the range of 2 to 22µg/mL. The procedural constant (K) was calculated and found to be 28.5 for phosphate buffer pH6.8.

Characterization of Captopril MDTs by FTIR

FTIR spectrum studies indicated that major functional groups present in Captopril MDTs show characteristic peaks in IR spectrum. Figures (2) to (18) show peaks observed at different wave numbers and the functional group associated with these peaks for drug and drug with different excipients. The major peaks are identical to functional group of Captopril. Hence, it was confirmed that there was compatibility between drug and various excipients, thus conforming that no interaction of drug occurred with the components of the formulation excipients.

Regarding infrared spectroscopy preformulation (Drug –excipient interaction), the characteristics peaks of Captopril MDTs formulations were observed at the normal range of functional groups for most Captopril MDTs formulations which were found to be identical with that of pure Captopril as shown in Figures 2-18.

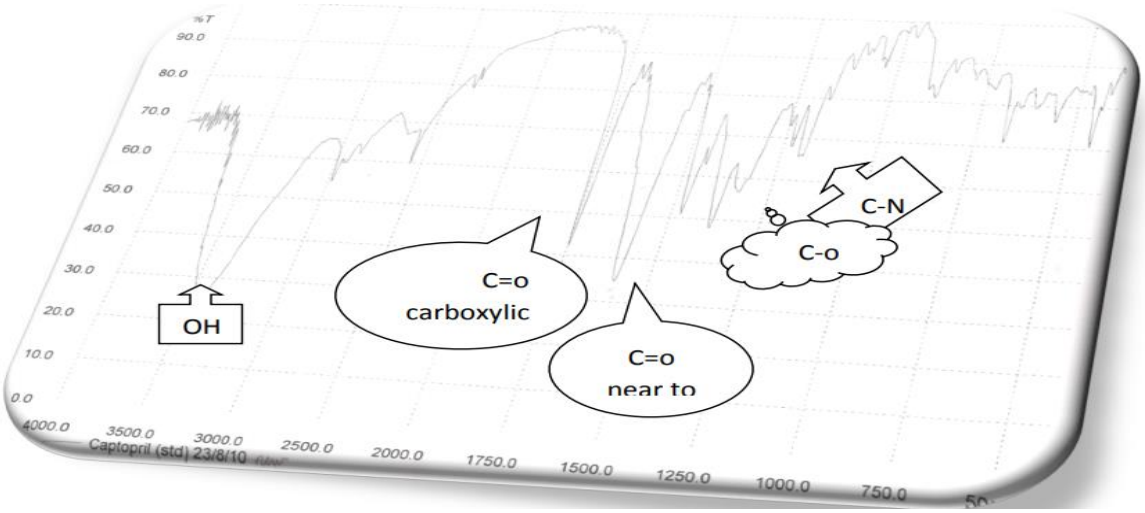

Fig. 2: FTIR Spectrum of Pure Captopril.

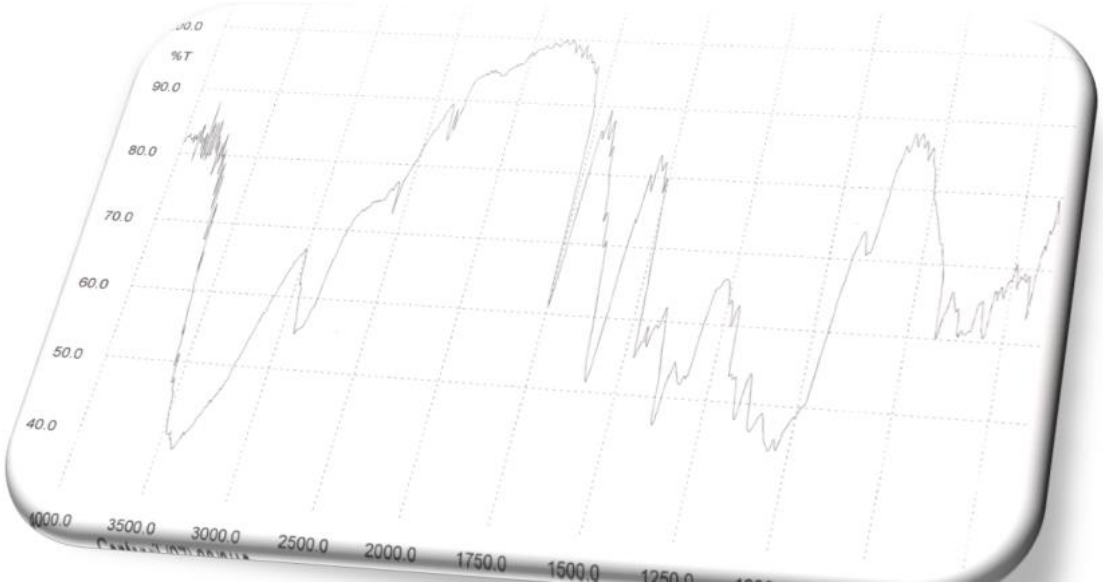

Fig. 3: FTIR Spectrum of Physical Mixture of F1.

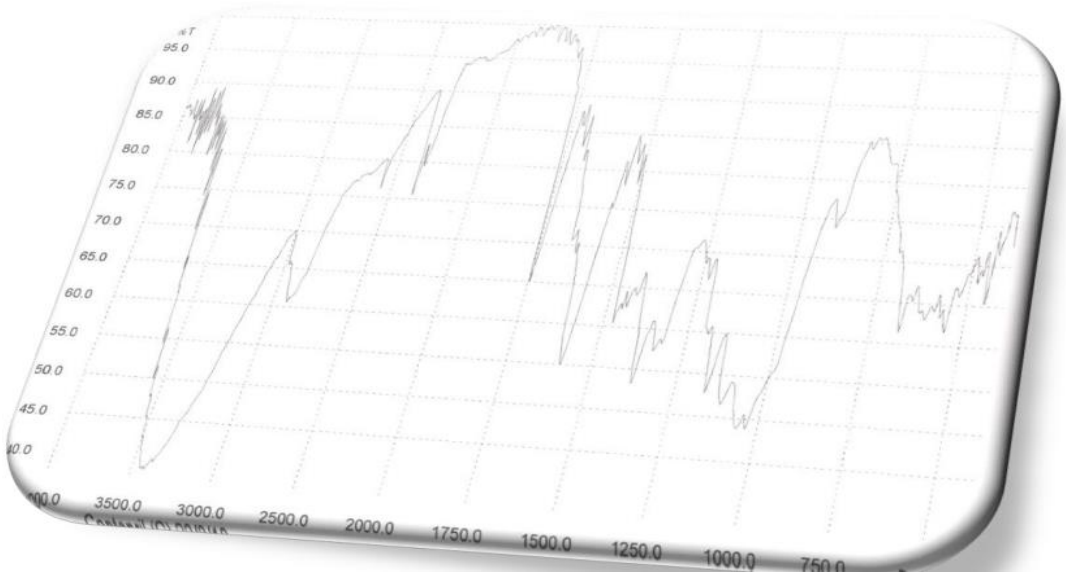

Fig. 4: FTIR Spectrum of Physical Mixture of F2.

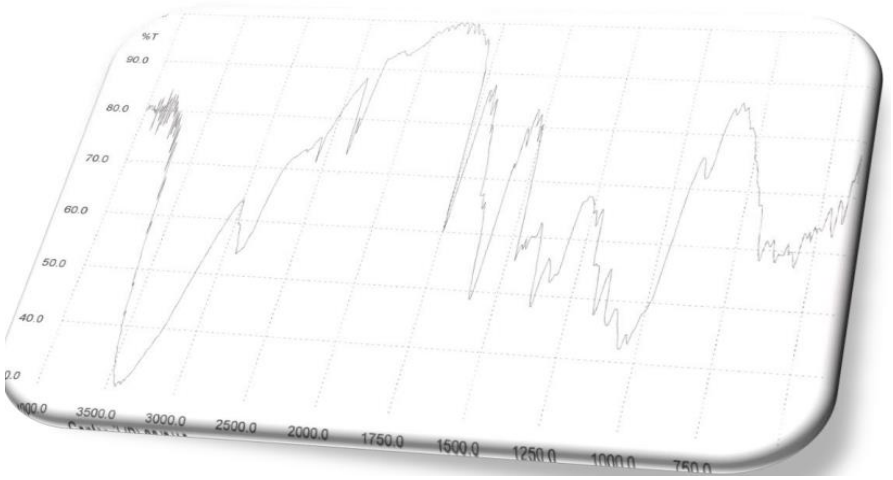

Fig. 5: FTIR Spectrum of Physical Mixture of F3.

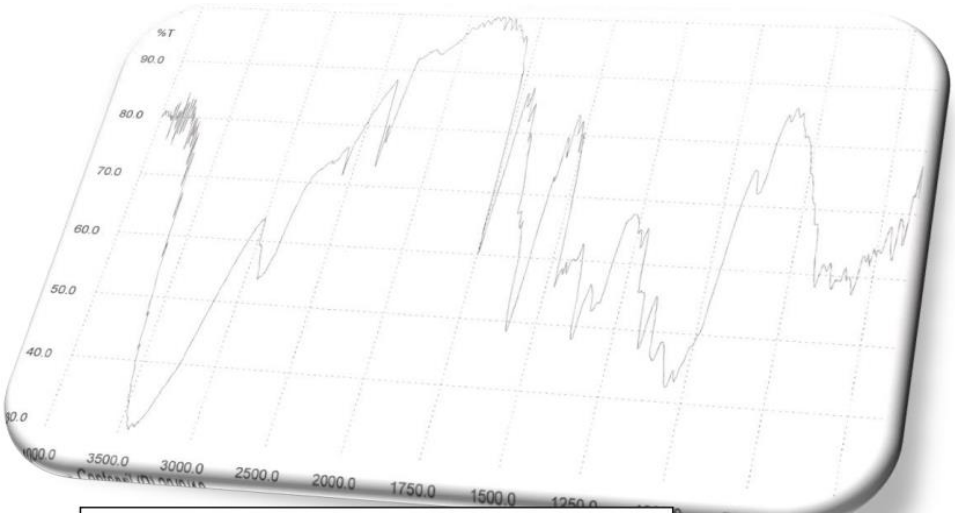

Fig. 6: FTIR Spectrum of Physical Mixture of F4.

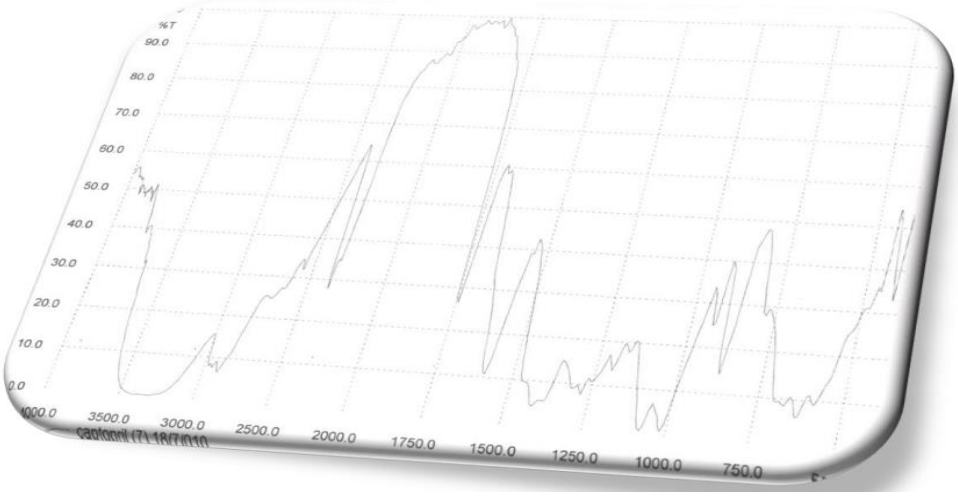

Fig. 7: FTIR Spectrum of Physical Mixture of F5.

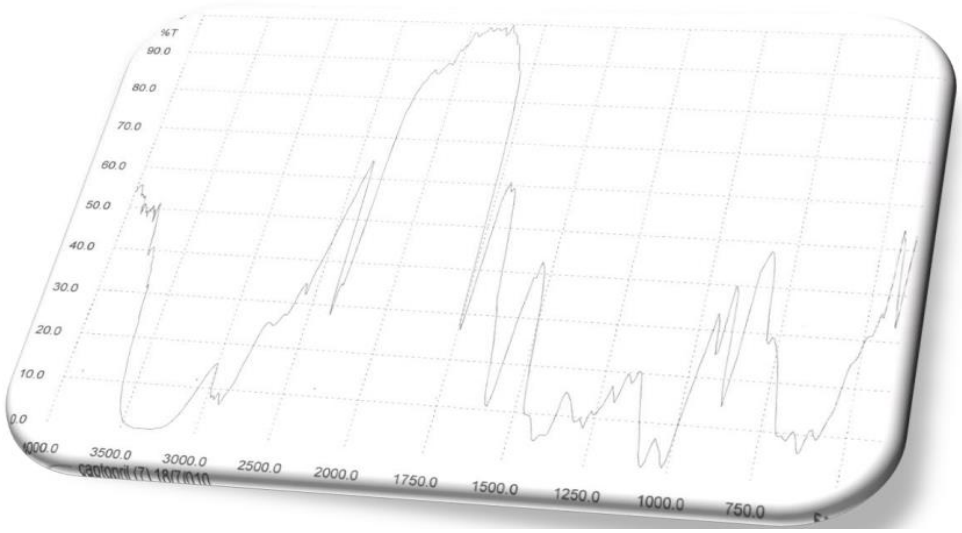

Fig. 8: FTIR Spectrum of Physical Mixture of F6.

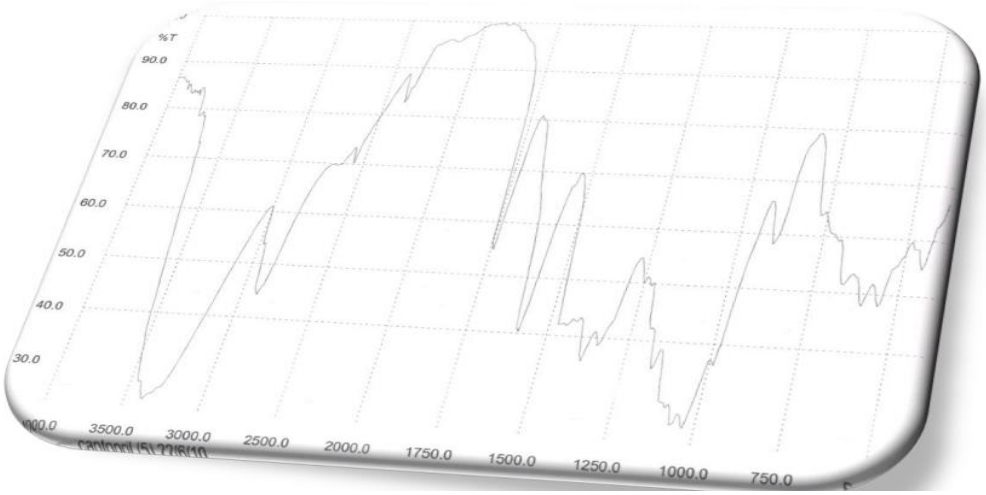

Fig. 9: FTIR Spectrum of Physical Mixture of F7.

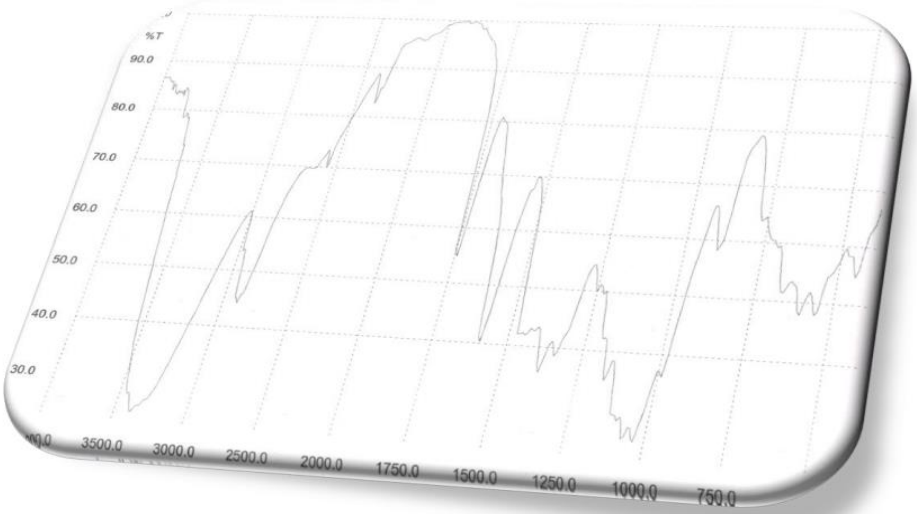

Fig. 10: FTIR Spectrum of Physical Mixture of F8.

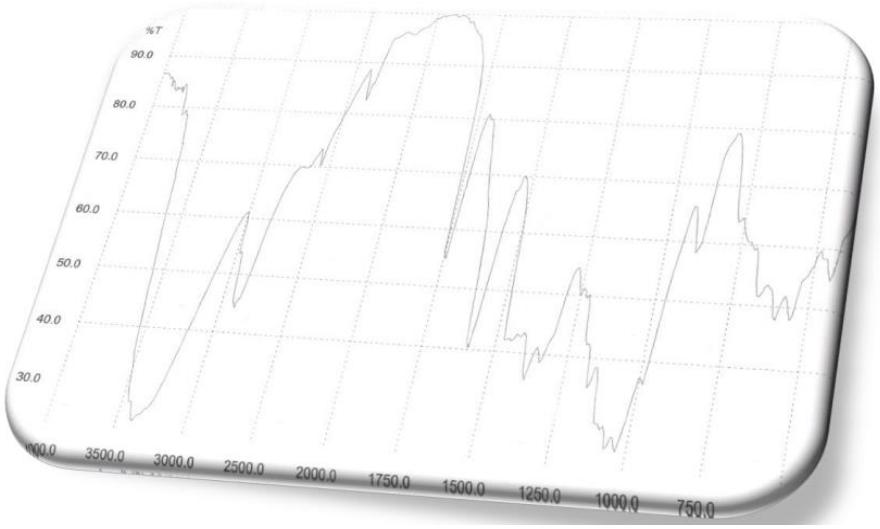

Fig. 11: FTIR Spectrum of Physical Mixture of F9.

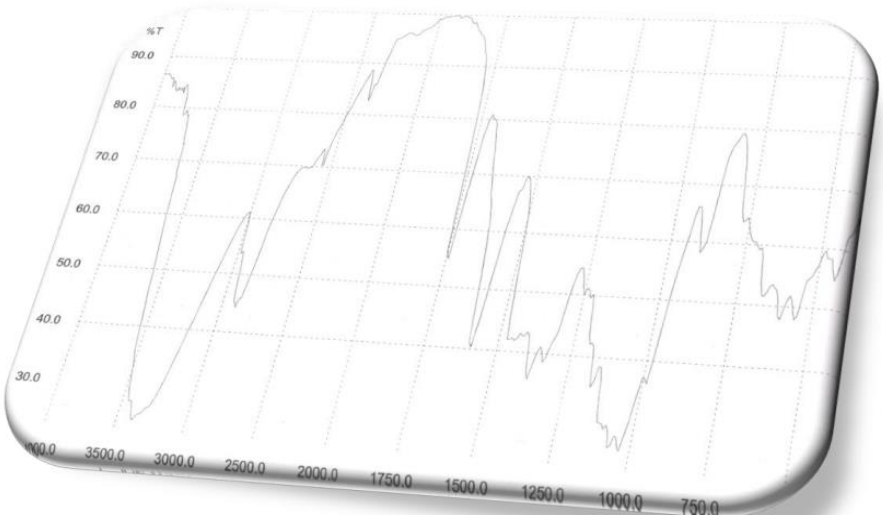

Fig. 12: FTIR Spectrum of Physical Mixture of F10.

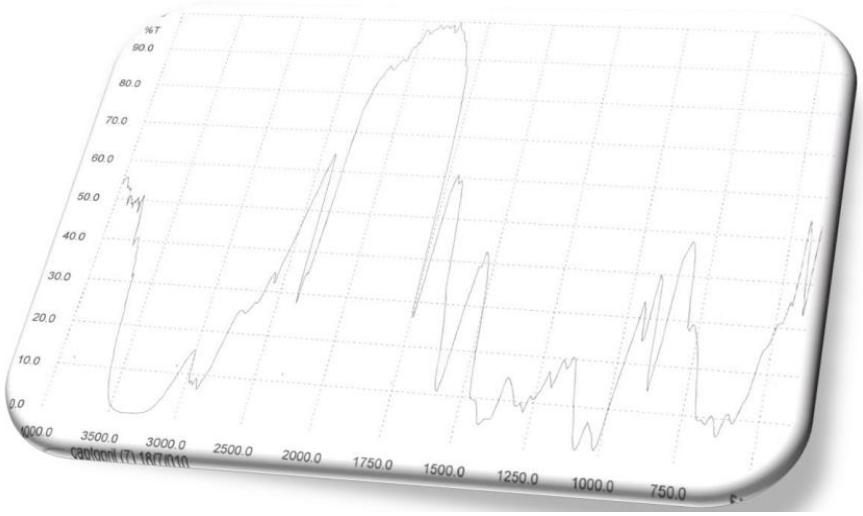

Fig. 13: FTIR Spectrum of Physical Mixture of F11.

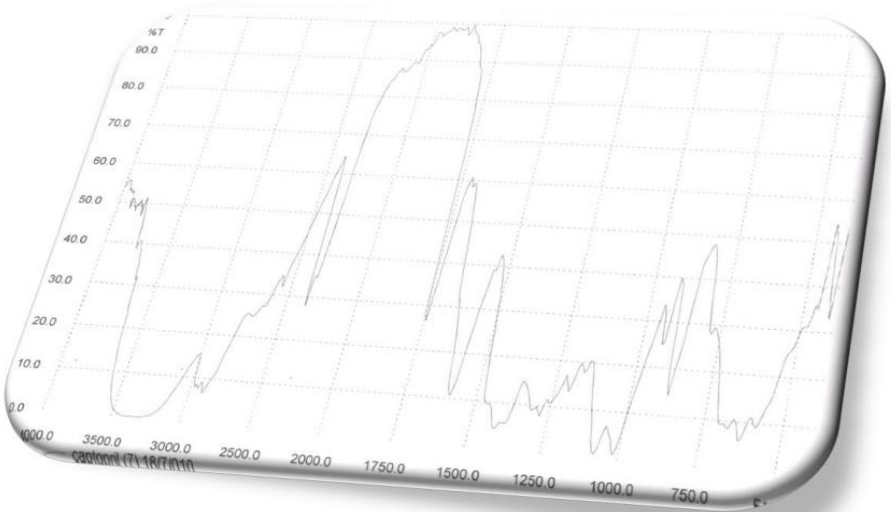

Fig. 14: FTIR Spectrum of Physical Mixture of F12.

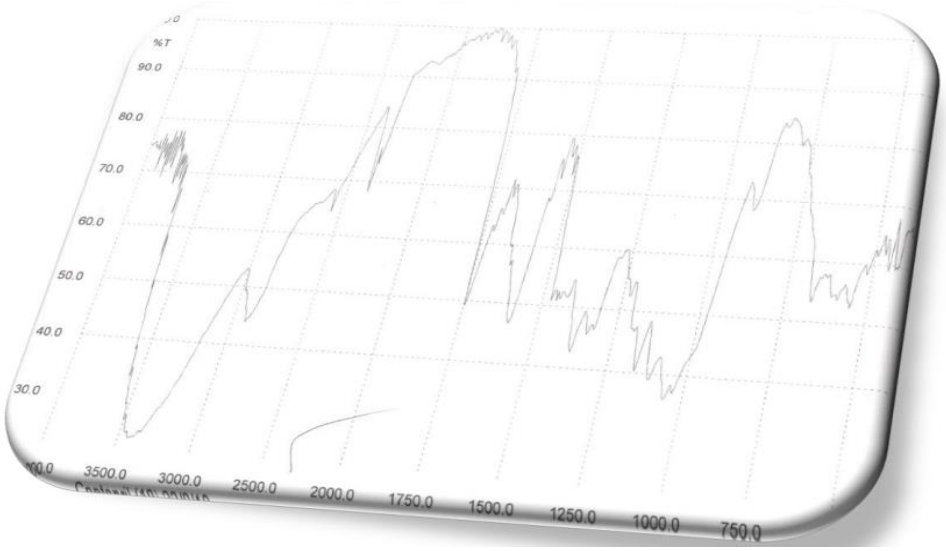

Fig. 15: FTIR Spectrum of Physical Mixture of F13.

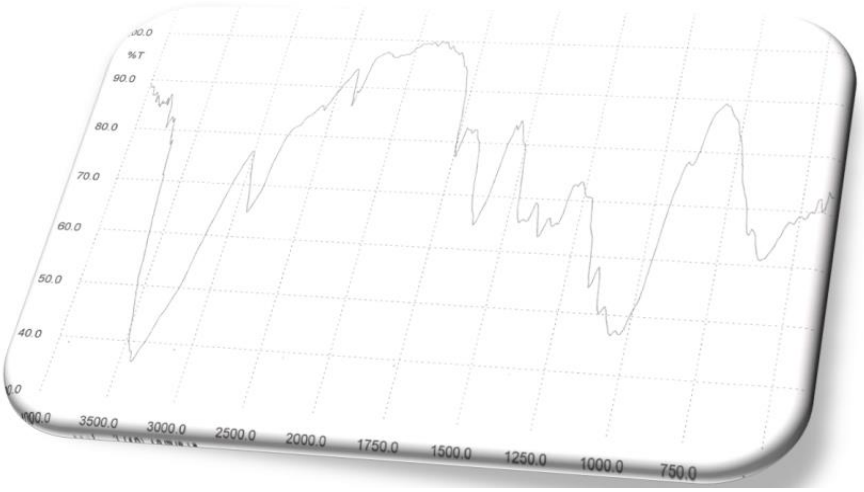

Fig. 16: FTIR Spectrum of Physical Mixture of F14.

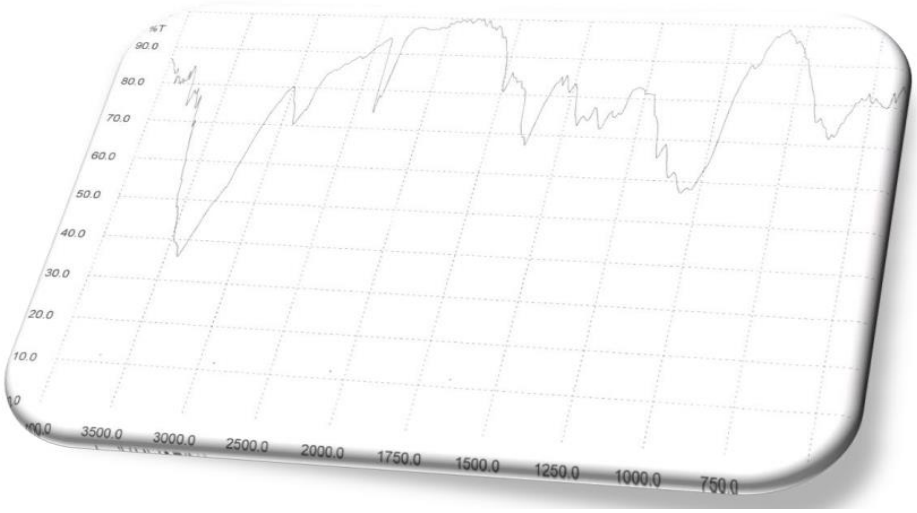

Fig. 17: FTIR Spectrum of Physical Mixture of F15.

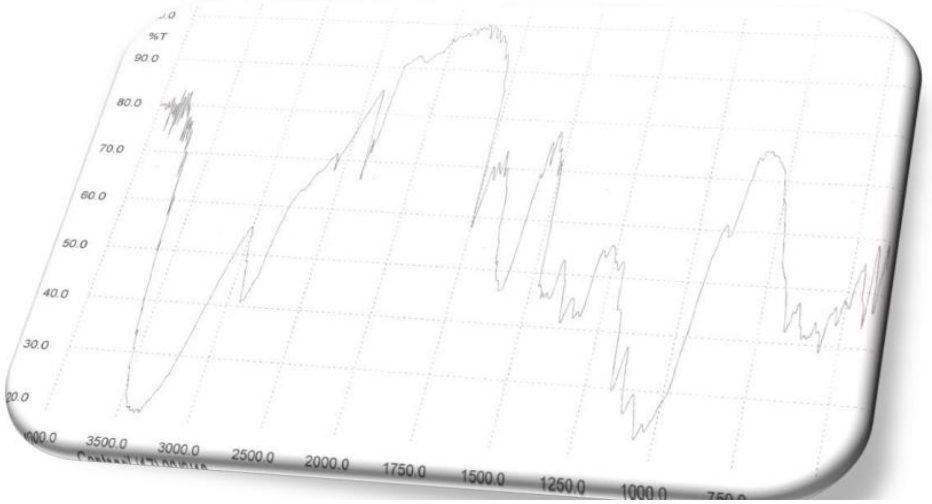

Fig. 18: FTIR Spectrum of Physical Mixture of F16.

CONCLUSION

The compatibility studies of physical mixtures of Captopril with different used excipients such as Microcrystalline cellulose, Mannitol, Maize starch and Lactose monohydrate as diluent, and Croscarmellose sodium and Sodium starch glycolate as superdisintegrants were investigated by FTIR it was detected that there was no variation or minor deviation in the characteristic peaks in FTIR spectroscopy. The Captopril formulations prepared were evaluated for precompression parameters and powder flow properties which were found to be within limits. It was concluded that the drug Captopril was found to be compatible with most Captopril MDTs formulations which were selected for the formulation development of the Captopril MDTs. Formulation scientist from his experience and knowledge have to

significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

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