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Development and Evaluation of Mesalamine—Glutamine Cocrystal Tablets for Colon Specific Delivery

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ABSTRACT

The objective of the work was to develop the co-crystal formulation of mesalamine with glutamine. It was done to enhance dissolution rate, solubility and physicochemical properties to be used in pharmaceutical composition (tablet) for colon targeting. Co-crystal preparation was carried out by liquid assisted grinding method using glutamine as a co-crystal former (1:1 stoichiometric ratio) and acetonitrile as a solvent giving maximum solubility and dissolution rate. The formation of the co-crystals was confirmed by Fourier Transform – Infra Red spectrometry, Differential Scanning Calorimetry and Powder X-Ray Diffraction. Pre-compression studies included measurement of bulk density, tapped density, angle of repose, Hausner's ratio and compressibility index. The tablets were prepared by direct compression. Post compression parameters for uncoated tablets included hardness, size and thickness, friability and weight variation. Enteric-coated tablets were prepared by dip-coating process using Eudragit RSPO, Triethyl citrate and isopropyl alcohol mixture as coating solution. The coated tablets were further evaluated for disintegration and dissolution testing. All the results were found to be under specified limits. Finally, co-crystal tablets were compared with marketed formulation. *In vitro* dissolution rate of optimized mesalamine co-crystal tablet was comparatively higher than marketed formulation, which reflects improvement in solubility. Glutamine has good anti-inflammatory property. Formulation with glutamine as co-crystal added more efficacies to mesalamine for treatment in colon related inflammatory diseases. It was concluded that stable co-crystals of mesalamine -glutamine having better anti-inflammatory property, increased solubility and improved *in vitro* dissolution of mesalamine can be successfully prepared.

KEYWORDS: Mesalamine; Co-crystal; Colon targeting; Enteric coating; Glutamine.

Introduction

During the last decade many investigations have been carried out with the aim of discovering an ideal formulation for colon-specific drug delivery. Many approaches have been demonstrated (Bauer and Kesselhut, 1995). Treatment might be more effective, if the drug substances were targeted directly on the site of action in the colon (Marvola et al., 1999; Yang et al., 2002). The colon may be the best site for drug delivery because of the long residence time and the low digestive enzymatic activities this may be useful for prolonged drug delivery (Nykanen et. al., 1999; Valentine, 2006). Colon specific drug delivery systems have gained increasing attention for the treatment of diseases such as Crohn's disease, ulcerative colitis and irritable bowel syndrome (Patel et al., 2005).

Co-crystal is a crystalline structure composed of at least two components, where the components may be atoms, ions or molecul*es* (Stahly, 2009). A more inclusive definition is that co-crystals consist of two or more components that form a unique crystalline structure having unique properties (Stahly, 2007). The components interact via non-covalent interactions such as hydrogen bonding, ionic interactions, Vander Waals interactions and Π-interactions. The intermolecular interactions and resulting crystal structures can generate physical and chemical properties that differ from the properties of the individual components (Braga et al., 2009).

Pharmaceutical co-crystals are defined as hydrogen bonded complexes between an active pharmaceutical ingredient (API) and a co-former (benign partner molecule), usually having a fixed API: co-crystal formers stoichiometry. The co-crystal formers can be selected from the group consisting of phenolics, flavonoids, monoterpenes, aminoacids, alkaloids, vitamins, nutraceuticals, which works synergistically along with active pharmaceutical ingredient (API).These co-crystals have utility in imparting desirable physical properties and stability, which are otherwise not achievable for the pure active agent or in combination as a simple formulation using the excipients incorporated with the active agent. (Rambabu et al., 2012)

Currently, salt formation is one of the primary solid-state approaches used to modify the physical properties of APIs (Datta and Grant, 2004). However, a major limitation within this approach is that the API must possess a suitable (basic or acidic) ionizable site. In comparison, co-crystals (multi-component assemblies held together by freely reversible, non-covalent interactions) offer a different pathway, where any API regardless of acidic, basic, or ionizable groups, could potentially be co-crystallized. This aspect complements existing methods by reintroducing molecules that had limited pharmaceutical profiles based on their non-ionizable functional groups. In addition, the number of potential nontoxic co-crystal formers (or Co-formers) that can be incorporated into a co-crystalline reaction is numerous (Bowkar et al., 2000).

Mesalamine (5-amino salicylic ccid) is an anti-inflammatory drug used to treat Crohn's disease and ulcerative colitis (Badhana et al., 2013). It acts by reducing inflammation of colon topically by preventing production of substances involved in inflammatory process, such as arachidonic acid (Figure 1). Glutamine is an amino acid that affects the processes of growth and function of cells in the stomach and intestines (Figure 2). The objective of the work was to develop the co-crystal formulation of mesalamine with glutamine. It was done to enhance dissolution rate, solubility and physicochemical properties to be used in pharmaceutical composition (tablet) for colon targeting.

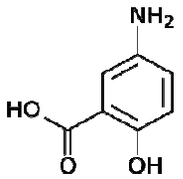

Fig.1. Structure of mesalamine.

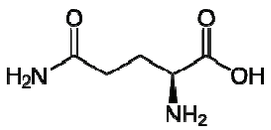

Fig. 2. Structure of glutamine.

Materials and Methods

Materials

Mesalamine drug & Eudragit RSPO was gift sample by Aurobindo pharmaceutical company Ltd, Hyderabad. Micro crystalline cellulose, talc, magnesium stearate, methanol, triethyl citrate, isopropyl alcohol, concentrated hydrochloric acid, sodium hydroxide, potassium dihydrogen orthophosphate, lactose monohydrate, sodium starch glycolate & povidone were procured from SD Fine-Chem Ltd, Mumbai and glutamine from Chemika- Biochemika-reagents, Mumbai. All the reagents and solvents were of analytical grade.

Spectrophotometric Method

Determination of λ_{max}: Standard stock solution was prepared by dissolving accurately weighed quantity of mesalamine in suitable volume of 0.1N HCl and pH 7.2 phosphate buffer. Dilutions were made to get 10 μg/mL and scanned in the range 200-400 nm against 0.1 N HCl and pH 7.2 phosphate buffer as blank respectively. Wavelength of maximum absorbance was determined for the drug.

Preparation of standard solutions and calibration curve of mesalamine: Accurately weighed 10 mg of drug was dissolved in 100 mL each of 0.1N HCl and Phosphate buffer (pH 7.2) which gives stock solution of 100 μg/mL. From this stock solution, dilutions were made and absorbance's of the resulting solutions were measured at respective λ_{max} using UV spectrophotometer against respective parent solvent as blank. The standard curve was obtained by plotting Absorbance v/s Concentration in μg/mL.

Preparation of mesalamine co-crystal with glutamine: Mesalamine and glutamine at 1:1 stoichiometric ratio were ground in acetonitrile or methanol for 10 minutes using a mortar and pestle and left it for solvent evaporation to obtain free flowing co-crystal solid.

Characterisation: The formation of these co-crystals was confirmed by Fourier Transform– Infra Red spectrometry (FT-IR), Differential Scanning Calorimetry (DSC) and Powder X Ray Diffraction (PXRD).

FT-IR analysis: FTIR spectra of Mesalamine and co-crystals were obtained on a FTIR-8400S (Shimadzu, Model-8400S) using the Potassium bromide (KBr) disk method. The scanning range was 4000–500 cm^{-1}. Approximately 0.1 to 1.0 % sample was well mixed into 200 to 250 mg fine alkali halide powder and then finely pulverized and put into a pellet-forming die. A force of approximately 8 tons was applied under a vacuum of several mm Hg for several minutes to form transparent pellets.

DSC (Differential scanning calorimetry): DSC of Mesalamine co-crystal was done (Shimadzu DSC TA-60) at a heating rate of 10 ºC/ min between 50 to 300 ºC in the nitrogen atmosphere. Method of melting and boiling points in DSC is based on enthalpy. The enthalpy was calculated by integrating the area of the DSC peak on a time basis. A sharp well defined melting peak corresponds to well define crystal structure. Changes in melting temperature and energy gives information about, for instance, content of amorphous material. Thus, the melting endotherm can be used for determination of purity of the sample.

PXRD (Powder X-ray diffraction): X-ray diffractogram of Mesalamine co-crystal was obtained using a Schimadzu 7000. A scanning rate of 0.04 2θ s^{-1} over then range of 10-600 2θ by using CuK∝ as tube anode having wavelength 1.5418Aº was used to record each spectrum. (Patil et al., 2011).

Formulation of mesalamine-glutamine co-crystal tablets: Composition for the formulation of Mesalamine-glutamine co-crystal tablets are represented in Table 1.

TABLE 1

Composition of mesalamine tablet.

Ingredient	Quantity per tablet (mg)
Mesalamine co-crystal	400.0
Lactose monohydrate	76.4
Povidone	8.7
Sodium Starch Glycolate	18.3
Magnesium Stearate	6.2
Talc	10.4
Total weight	520 mg

Pre-Compression Study

Bulk density: Bulk Density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density was determined by placing powder mix into a graduated cylinder via a large funnel and measuring its volume and weight.

Bulk density = weight of powder mixed/Bulk volume of powder mixed

Tapped density: Tapped density was determined by placing a graduated cylinder containing a known mass of powder mix and by mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.

Tapped density = weight of powder mixed / tapped volume of powder mixed

Angle of repose: The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The method used to find the angle of repose is to pour the powder through a conical funnel on a level, flat surface and measure the included angle with the horizontal.

$$\text{Tan } \theta = h/r$$

Where,

h = Height of the heap,

r = radius of the heap.

Hausner's ratio: It indicates the flow properties of the powder and ratio of Tapped density to the bulk density of the powder.

Hausner's ratio = Tapped density of powder mixed/ Bulk density of powder mixed

Compressibility index: Compressibility index was measured using the values of bulk density and tapped density. The following equation was used to find the Compressibility index.

$$\text{Carr's index} = (TD - BD) \times 100/\text{Tapped density}$$

Where,

TD = Tapped density,

BD = Bulk density.

Direct compression: The accurately weighed ingredients were mixed and were directly compressed to form tablets. Tablets were weighed and checked for the requirements on the tablet mass uniformity. For this purpose, average weight of the tablets was calculated and the relative deviation of the tablets was found out from this average.

Post Compression Parameters of Uncoated Tablets

Physical appearance: The general appearance of the tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of the tablet involves measurement of number of attributes such as Tablet size, Shape, Color, Presence or Absence of odor, taste, surface texture and consistency of any identification marks.

Hardness: This is the force required to break a tablet in a diametric compression (Mamatha et al., 2015). Hardness of the tablet was determined by Monsanto hardness tester. The tablet hardness of the 5 kg is considered as suitable for handing the tablets.

Tablet size and thickness: Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity.

The thickness of the tablet was measured by vernier calipers scale. The thickness of the tablet is related to the tablet hardness and can be used as an initial control parameter. Tablet thickness should be controlled within ± 5% range.

Friability: The test was performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting (Mamatha et al., 2015). Initial weight of 20 tablets was taken and these were placed in the friabilator, rotating at 25 rpm for 4 min. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

$$\% \text{ Friability} = (W_1 - W_2)/W_1 \times 100$$

Where,

W_1 = Weight of tablets before test,

W_2 = Weight of tablets after test

Weight variation: It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits.

20 tablets were taken randomly and weighed accurately. The average weight was calculated by using formula,

Average weight = Weight of 20 tablets/20

Percentage deviation was calculated by comparing with average weight.

Dip Coating

Preparation of mesalamine enteric coated tablet: In dip-coating process, coating solution containing Eudragit RSPO, Triethyl citrate, Isopropyl alcohol was prepared by mixing them (Table 2) and then tablets were dipped into it. Coating thickness generally increases with faster withdrawal speed. The applied coating may remain wet for several minutes until the solvent evaporates. Once the layer is cured, another three to four layers were applied on top of it with another dip-coating process. In this way, multi-layered tablets were produced.

TABLE 2

Enteric coating composition.

Ingredients	Quantity
Eudragit RSPO	1000 mg
Triethyl citrate	0.5 ml
Isopropyl alcohol	10 ml

Post compression parameters of coated tablets: The important parameter in the evaluation of tablets can be divided into physical and chemical parameter.

Disintegration test: For most of the tablets, first important step towards the solution is the breakdown of the tablet into smaller particle or granules, a process known as disintegration. The USP device used to test

disintegration contains six glass tubes that are 3 inches long, open at the top and held against a 10- mesh screen at the bottom end of the basket rack assembly.

Disintegration test for mesalamine - glutamine co-crystal tablets in 0.1N HCl: To test disintegration, one tablet is placed in each of the six tubes of the basket rack assembly. It was positioned in a one liter beaker of 0.1N HCl, (simulated gastric fluid) maintained at 37 ± 2 ºC. A standard motor drive device was used to move the basket assembly containing the tablets up and down through the distance of 5-6cm at a frequency of 28 to 32 cycles/min. After 3min of operation in simulated gastric fluid, the tablets were observed. The tablets should show no evidence of disintegration, cracking or softening. The apparatus was operated for the time specified.

Disintegration test for mesalamine - glutamine co-crystal tablets in pH 7.2 phosphate buffer: To test disintegration, one tablet was placed in each of the six tubes of the basket rack assembly which was kept in a one liter beaker of pH 7.2 phosphate buffer, simulated intestinal fluid maintained at 37±2ºC.

Dissolution test: *In vitro* dissolution test for mesalamine - glutamine co-crystal tablets was performed by various methods using different test conditions but always under "sink" conditions. In present study the drug dissolution study was carried out in 900 mL of pH 7.2 buffer at 37 ± 0.5 °C, using United States Pharmacopoeia (USP) Paddle method at a stirring speed of 50 rpm. At regular time intervals of 15, 30, 45, 60, 90, 120 min, 5 mL of samples were withdrawn and immediately replaced with an equal volume of fresh dissolution medium. Dissolution profiles were compared with that of a reference product.

Results and Discussion

λ_{max} and Linearity of Mesalamine in 0.1N HCl

The λ_{max} (maximum absorbance) was found to be at 303.27 nm (Figure 3). The absorbances of mesalamine drug solutions were estimated at 303.27 nm to get linearity and standard calibration graph. (Figure 4).

The λ_{max} of mesalamine in pH 7.2 phosphate buffer was found to be at 330.14 nm (Figure 5). Absorbance's of the drug solutions were estimated at 330.14 nm to obtain linearity and standard calibration graphs (Figure 6).

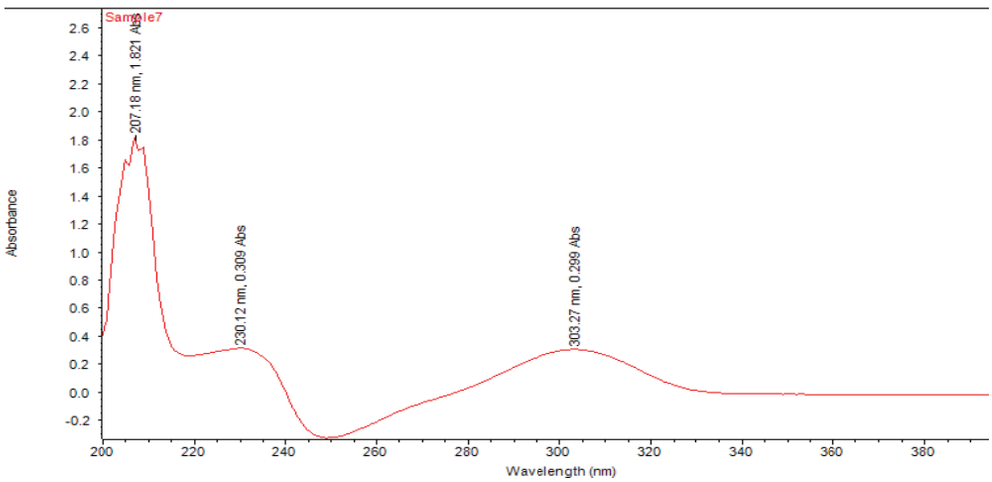

Fig. 3. λ_{max} of mesalamine in 0.1N HCl.

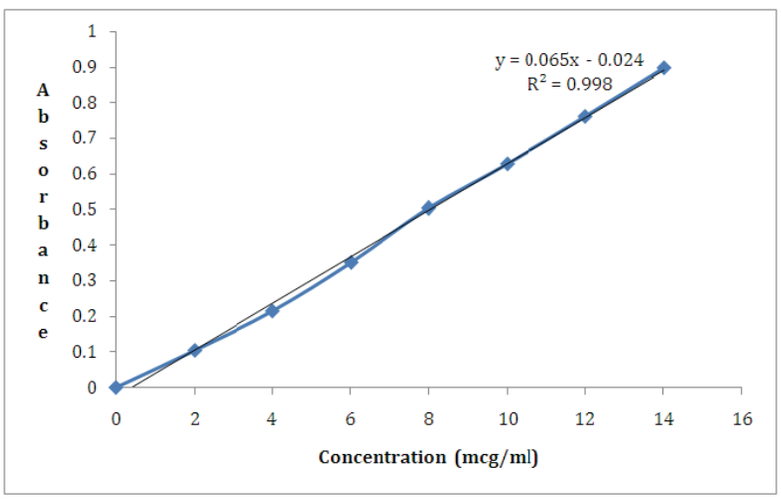

Fig. 4. Standard calibration curve of esalamine in 0.1N HCl.

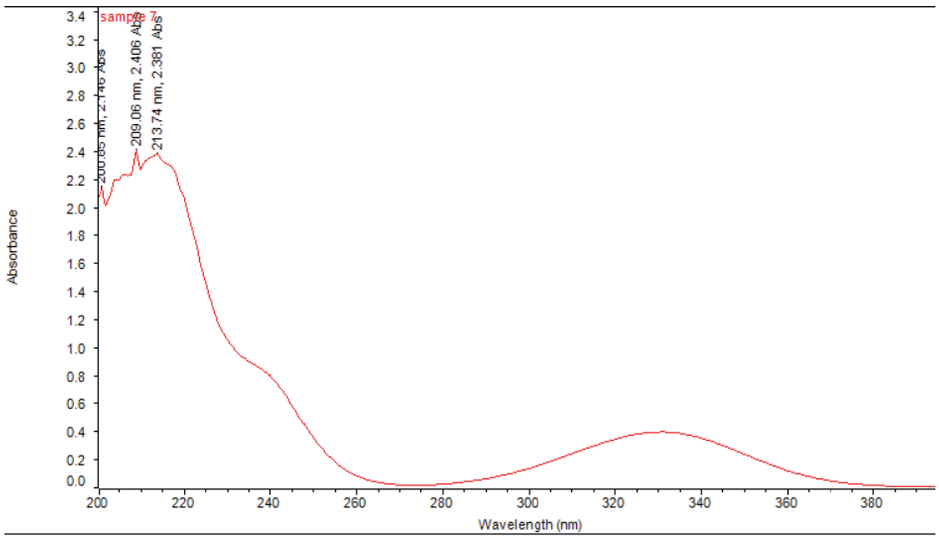

Fig. 5. λ_{max} of mesalamine in pH 7.2 phosphate buffer.

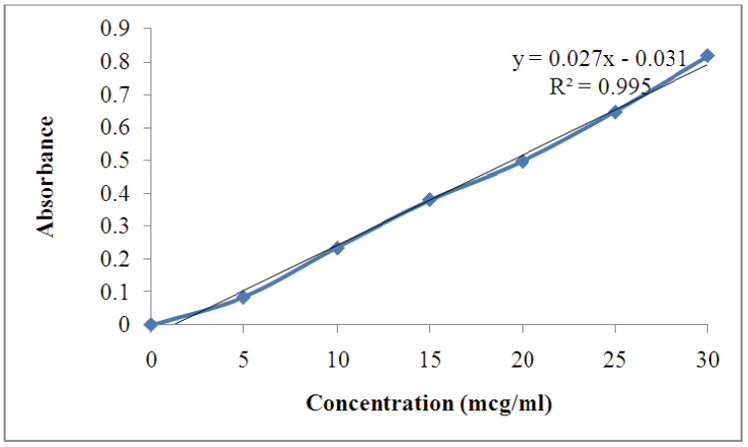

Fig. 6. Standard Calibration curve of mesalamine in pH 7.2 phosphate buffer.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis of mesalamine, glutamine and mesalamine glutamine co-crystal was done to know the interaction between mesalamine and glutamine. By comparing the FTIR spectra of mesalamine (Figure 7), glutamine (Figure 8) and co-crystal of mesalamine and glutamine (Figure 9) hydrogen bond formation between amino group of mesalamine and carboxyl group of glutamine can be observed. As N-H Stretching can be found in range of 3300-3600 cm^{-1} peaks (Figure 9).

Differential Scanning Calorimetry (DSC)

Thermogram of mesalamine co-crystal is shown in Figure 10. The melting point of pure mesalamine is 283 °C and of glutamine is 185 °C but in thermogram of co-crystal it was found that there is shift towards left, decrease in melting point was observed. The endotherm was observed at 193.67 °C along with a short endotherm at 244.28 °C, indicating interaction between mesalamine and glutamine. This interaction results in the formation of co-crystal.

PXRD Results

The reduced peak intensities in X-ray pattern clearly shows that the mesalamine appears amorphous. (Figure 11).

Pre-compression parameters: All the pre-compression parameters were found to be in specified limits. Bulk density and tapped density were found to be 0.490 ± 0.020 g/mL and 0.65 ± 0.025 g/mL respectively. Angle of repose was good i.e., in the range of 25 – 30. Compressibility index (Carr's index) and Hausner's ratio showed passable flow ability (24.61 ± 1.5 & 1.32 ± 0.10 respectively).

Post-compression parameters: All the post-compression parameters were found to be in specified limits which included weight variation along with average thickness (5.01 ± 0.02 mm), average hardness (8.01 ± 1.2) and friability (0.0303 ± 0.002).

Dissolution profile of mesalamine – glutamine co-crystal tablet: Dissolution profile of mesalamine – glutamine co-crystal tablet is represented in Figure 12. The formulated tablet showed better dissolution in comparison to marketed formulation.

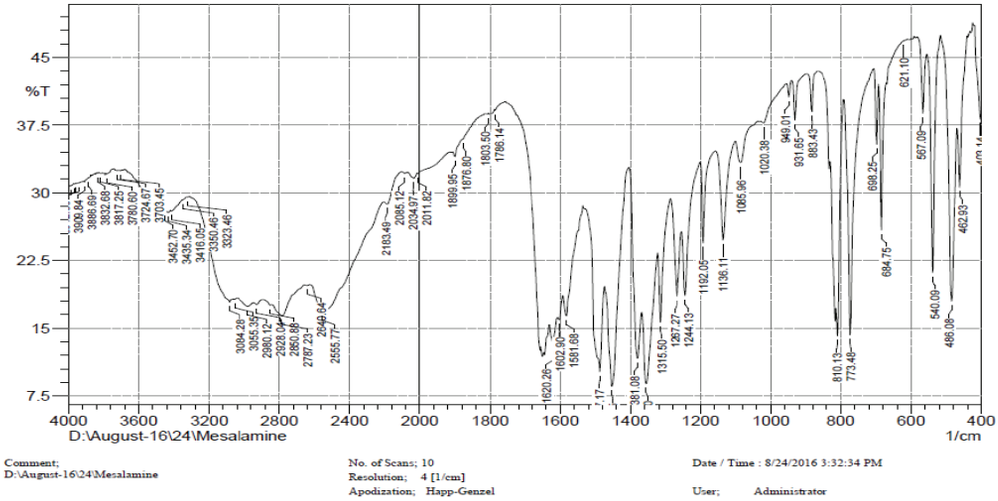

Fig. 7. FT-IR Spectra of mesalamine.

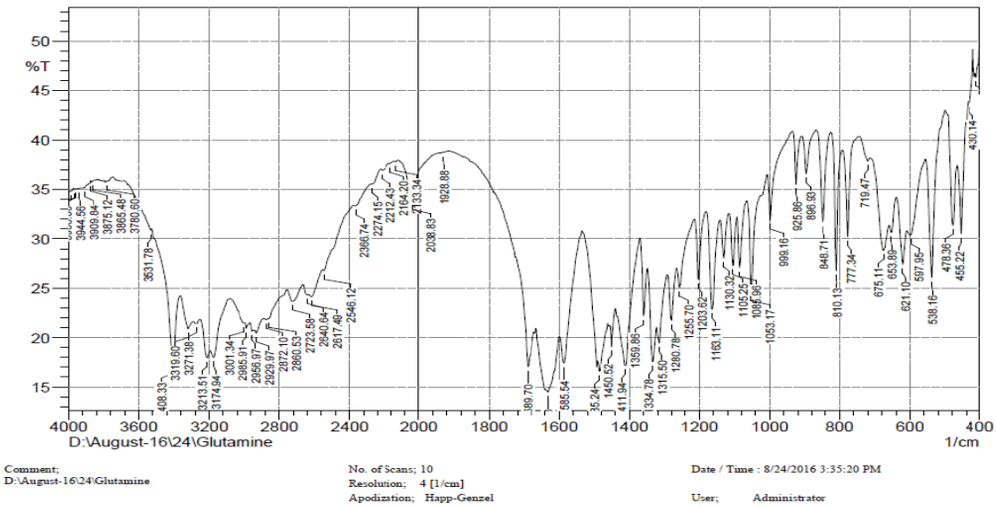

Fig. 8. FT-IR spectra of glutamine.

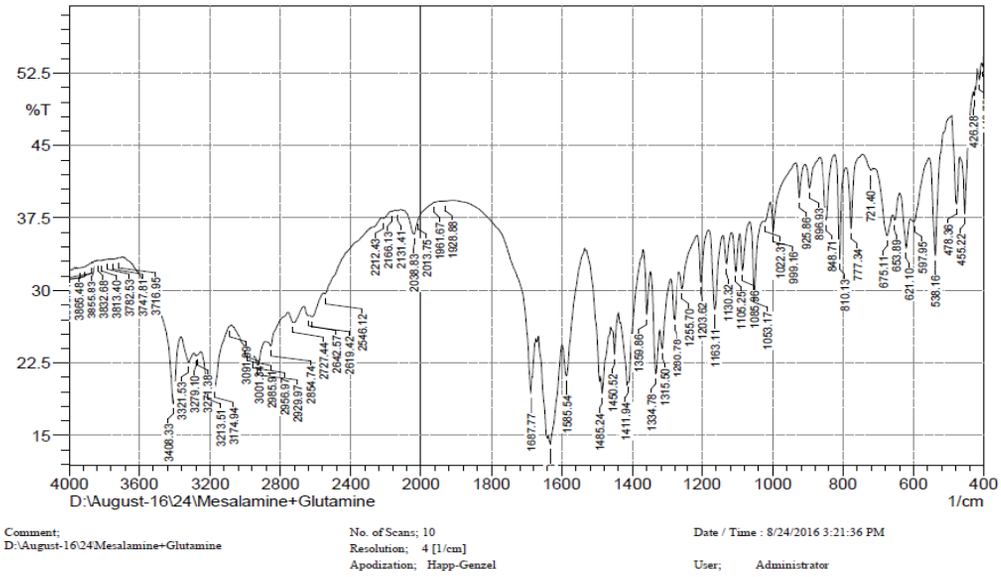

Fig. 9. FT-IR Spectra of mesalamine with glutamine.

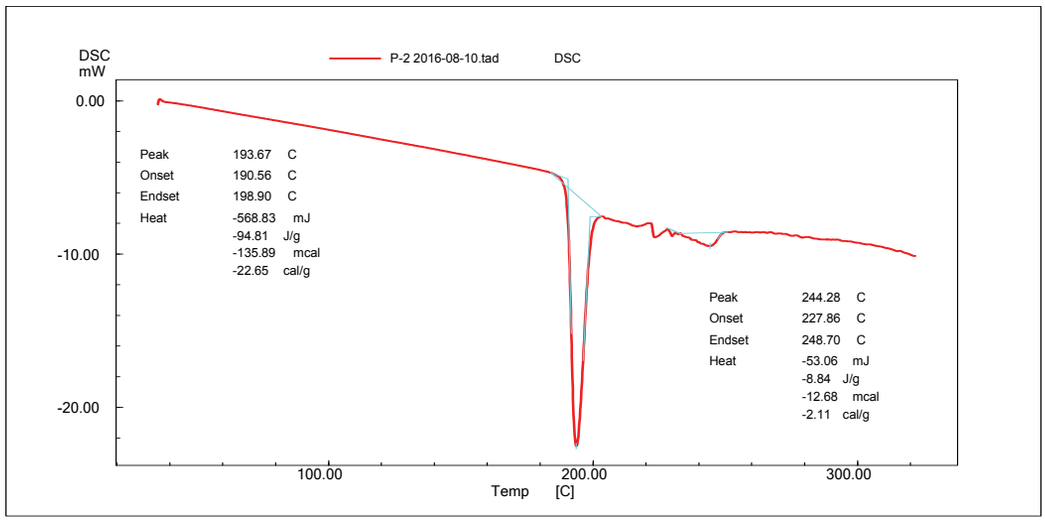

Fig. 10. DSC of Mesalamine with glutamine.

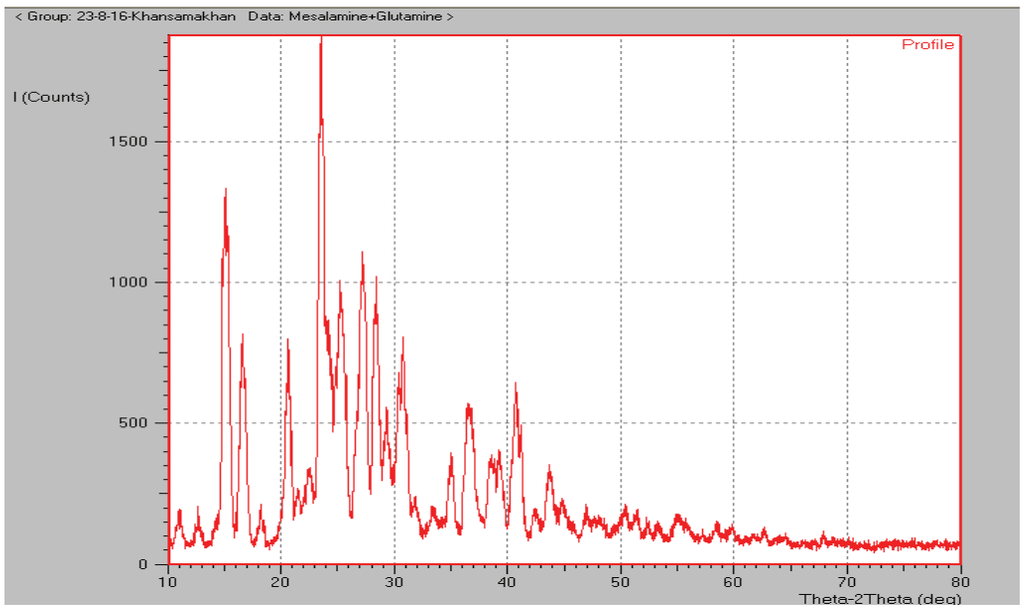

Fig. 11. PXRD of Mesalamine co-crystal.

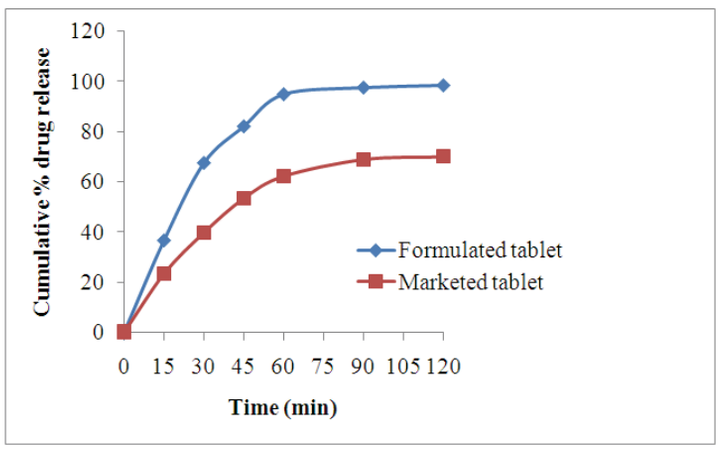

Fig. 12. Graph showing % drug release of mesalamine tablet v/s marketed formulation.

According to biopharmaceutical classification system (BCS), mesalamine is classified as a low solubility and high permeability drug (class II). The major problem related with mesalamine is its low solubility and there by highly variable bioavailability after oral administration. The T_{max} of mesalamine is about 1-2 h after oral administration. Rapid solubilization is necessary to provide rapid absorption of drug. Therefore, it is necessary to enhance the solubility and dissolution rate of mesalamine to obtain faster onset of action. In order to minimize the variability in absorption and improve its overall oral bioavailability, mesalamine was formulated as co-crystals along with glutamine. Glutamine is showing synergistic action along with main API i.e, mesalamine. Both the drugs are together aiding in the treatment of colon related diseases. Co-crystals were prepared by liquid assisted grinding method by using glutamine and acetonitrile as a solvent giving maximum solubility and dissolution rate.

Infrared spectroscopy can be a very powerful tool in detecting co-crystal formation, especially when a carboxylic acid is used as a co-former and/or when a neutral O–H···N hydrogen bond is formed between an acid and a base which is the main principle of present work. Hydrogen bond formation was seen between amine group (NH_2) of mesalamine and carboxyl group (COOH) of glutamine which is helping in the improvement of solubility profile of mesalamine. From the above discussion it is clear that improvement in solubility and dissolution rate of mesalamine can be achieved by co-crystals.

Glutamine (encoded by the codons CAA and CAG) is an α-amino acid that is used in the biosynthesis of proteins. It has anti-inflammatory properties, which is useful in colon related diseases. Glutamine is a medical food product that is used to supplement dietary sources of glutamine. One of the well-established roles of glutamine in human health is its contribution to the integrity of the intestinal mucosa. This role is partly related to the fact that glutamine is a critical nitrogen source for rapidly dividing cells, such as those that line the gastro-intestinal tract. Glutamine is also considered important for the maintenance of the renal tubules, contributing to the healthy function of the kidneys. L-glutamine benefits ulcerative colitis and inflammatory bowel disease. (Fujita and Sakurai, 1995).

The said co-crystal improves the bioavailability of mesalamine and increases the amount of mesalamine available at the colon with the help of glutamine. As L-glutamine has the tendency to accumulate in the colon. Further, the other side effects of mesalmine viz, flatulence will be mitigated as L-glutamine has the acid - base stabilization effect in the gastrointestinal fluids.

Hence, Effectiveness in action of mesalamine was further enhanced when it was used in combination with glutamine. *In vitro* dissolution of optimized Mesalamine - glutamine co-crystal tablet was comparatively higher than pure drug and marketed formulation, which reflected its improvement in solubility.

Conclusions

Mesalamine is a BCS class II drug. In order to increase its solubility, it was formulated along with glutamine as co-crystal. The co-crystals were evaluated for pre compression and post compression parameters. They were directly compressed to form tablets, which were, then dip coated. All the parameters were found to be within specified limits. The co-crystal tablets showed better dissolution profile in comparison to marketed formulation. From the work carried out it was concluded that stable co-crystals of mesalamine - glutamine with increased solubility, better anti-inflammatory property and improved *in vitro* dissolution could be successfully prepared.

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