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(54) Title: RESINATES OF TOFACITINIB FOR TASTE MASKING

(57) Abstract: The present invention relates to resinates of Tofacitinib. The invention also relates to taste masked, stable and readily dispersible resinates of Tofacitinib, rapidly disintegrating and or quick release taste masked pharmaceutical compositions comprising the said resinates and process for the preparation of resinates and compositions. In order to form the resinate, the resin is selected from copolymers of methacrylic acid and divinylbenzene, cross linked polymer of methacrylic acid and divinylbenzene, sulphonated copolymers of styrene and divinylbenzene. In order to form the resinate, Ion exchange resin is contacted with the solution of Tofacitinib prepared in nonaromatic solvent. The resinate is useful to formulate different pharmaceutical dosage forms such as Tablets, Capsule, drysyrups.



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RESINATES OF TOFACITINIB FOR TASTE MASKING

FIELD OF INVENTION

The present invention relates to resinates of Tofacitinib, fast disintegrating and or quick release pharmaceutical compositions comprising the said resinates and process for the preparation of resinates and compositions.

BACKGROUND OF THE INVENTION

Oral dosage forms containing Tofacitinib have bitter taste. Therefore these are provided in coated form, preferably film coated. Bitter taste of Tofacitinib does not support its use without coating. Fast disintegrating and or quick release taste masked oral dosage forms of Tofacitinib are not available. Therefore there is a need to provide fast disintegrating and or quick release taste masked oral dosage forms containing Tofacitinib.

Conventional means to mask the taste is to sugar coat it or film coat it. But such tablets are not readily dispersible in the mouth and have to be swallowed with water. Swallowing with water as method of administration of drugs has several disadvantages.

Taste masking is also done by various other means such as formation of new salt, various types of coatings, resinates and inclusion complexes. Rapid melt, Fast melt or quick disintegrating techniques also enable oral dispersion of compositions. Each of these methods is associated with peculiar disadvantages which are method specific.

Selecting the appropriate resin to form resinate is a difficult task. The resin has to be drug compatible. It has to be drug specific otherwise desirable drug release profile may not be achieved. Formulating a stable composition is an important aspect in drug development. Composition in which an improper resin is used can jeopardize drug stability and or drug availability for absorption. Therefore formation of appropriate resinate is a problematic, complicated and challenging process.

A taste masked composition of a bitter tasting drug in combination with two enteric polymers comprising, a methacrylic acid copolymer and a phthalate polymer is taught by US 6565877. In preparing the taste masked composition, it alarms against the use of cation-exchange resins such as polysulfonic acid and polycarboxylic acid polymers for adsorbing amine drugs.

Loading active substances onto an ion exchange resin is also disclosed by US 2990332 and is told to be dependent upon several factors such as equilibrium constant, temperature, the rate of diffusion and the presence of other ions.

IN 225628 teaches resinate complexes of Cetirizine, levocetirizine, its enantiomers salts and the compositions thereof.

IN 207068 teaches a manufacturing process for the preparation of mouth dispersible tablets using active pharmaceutical substance Alprazolam.

IN 206560 teaches a novel method for the preparation of mouth dispersible tablet of active pharmaceutical substance Ondansetron using Betacyclodextrin.

5 US 5188825 teaches freeze-dried dosage forms prepared by bonding or complexing a water-soluble active agent to or with an ion exchange resin to form a substantially water insoluble complex.

US 5219563 teach use of synthetic cation exchange resins such as copolymers of styrene and divinylbenzene which are sulphonated and copolymers of methacrylic acid and divinylbenzene
10 for masking the bitter taste of ranitidine.

Patent application number 2842/MUM/2015 which is not published on the date of application refers to orally disintegrating tablets of Tofacitinib but is silent on resinate formation or resinates of Tofacitinib.

Prior art does not teach the resinate of Tofacitinib, rapidly disintegrating and or quick release
15 taste masked pharmaceutical compositions comprising the said resinates and process for the preparation of resinates and compositions.

There are quite a few papers describing Fast dissolving tablets. The Publication “Critical Reviews™ in Therapeutic Drug Carrier Systems, 21(6):433–475 (2004)” by Yourong Fu, Shicheng Yang, Seong Hoon Jeong, Susumu Kimura, & Kinam Park provides insight to
20 many technologies such as Freeze drying, molding, Sublimation, effervescent, humidity treatment to produce fast disintegrating tablets. It enlists the drawbacks associated with each of the technologies.

Tablets produced by Freeze drying technology have high cost of production, besides sensitive to humidity. Their soft, fragile nature renders them unsuitable for conventional
25 blister packing. Useful only for low dose water soluble drugs, poor stability at higher temperature and humidity and very poor physical resistance are additional disadvantages. Claritin, Reditab, Dimetapp, Zofran, Lorazepam, Loperamide and few more products are available based on Zydis Tecnology, freeze drying technology.

Tablets produced by Molding, lack mechanical strength. These often get eroded and
30 damaged during handling or opening the blister pack. Increasing hardness results into undesirable effect on disintegration. Improvement of mechanical strength and disintegration is possible but with huge investments.

Orally disintegrating or fast dissolving tablets produced by other technologies necessitate use of robotic techniques such as robotic pick and pack type of packaging systems which are costly.

5 Dysphagia, or difficulty in swallowing, is common among all age groups and is more pronounced in infants, small age and geriatric populations. It is also prominent in physically challenged, elderly institutionalized individuals. Swallowing with water is a difficult task for them.

10 Size, form, surface and taste of tablets accentuate problem of swallowing. Geriatric and pediatric patients and traveling patients may not have ready access to water. These and such other difficulties jeopardize patient compliance. These facts emphasize the need for a new dosage form of Tofacitinib that can improve patient compliance.

Solid dosage forms that can be dissolved in water or suspended in the mouth, promote easy swallowing and are highly desirable for the pediatric, geriatric population and for other patients who prefer the convenience.

15 Orally disintegrating tablets have added advantage that bioavailability of drugs is enhanced due to absorption from mouth, pharynx and oesophagus, besides rapid or fast onset of therapeutic action. Orally dispersible tablets have other advantages such as cost effective and simple packaging if appropriate method is selected to produce and pack it. Enhanced palatability, ease of administration and hence patient compliance are its pronounced advantages.

20 Resinate of Tofacitinib and or the fast release or quick release compositions such as orally disintegrating tablets, dry syrups and such other dosage forms made from such resins are not reported as yet.

25 There is an urgent and unfulfilled need to provide resins of Tofacitinib in which bitter taste is masked and their compositions that rapidly disintegrate and or provide quick release, optionally containing other actives.

30 Further in view of safety issues and in view of providing a better composition, it is always desirable to prepare such compositions without the use of aromatic solvents. Tofacitinib orally dispersible compositions comprising the resins of Tofacitinib, without the use of aromatic solvents are not known. The invention discloses use of non aromatic solvents to prepare resinate of Tofacitinib or its pharmaceutical salts such as Tofacitinib Citrate.

There is a need to invent and provide the process which does not require the use of costly and sophisticated packaging machinery.

OBJECTS OF THE INVENTION

The main object of the invention is to provide resinsates of Tofacitinib, rapid disintegrating and or quick release taste masked pharmaceutical compositions comprising the said resinsates and process for the preparation of resinsates and compositions.

5 Another object of the invention is to prepare stable resinsates of Tofacitinib, rapid disintegrating and or quick release taste masked pharmaceutical compositions comprising the said resinsates and process for the preparation of resinsates and compositions.

Yet another object of the invention is to provide easily dispersible resinsates of Tofacitinib, rapid disintegrating and or quick release taste masked pharmaceutical compositions
10 comprising the said resinsates and process for the preparation of resinsates and compositions.

Yet another aspect of the invention is to provide resinsates of Tofacitinib, a rapidly disintegrating and or quick release taste masked pharmaceutical compositions of Tofacitinib without the use of aromatic solvents and without the use of sophisticated
15 packaging machinery.

Yet another object of the invention to provide taste masked rapidly disintegrating and or quick release composition of Tofacitinib with at least one more active ingredient.

SUMMARY OF INVENTION

20 The present invention relates to resinsates of Tofacitinib. The invention also relates to taste masked, stable and readily dispersible resinsates of Tofacitinib, rapidly disintegrating and or quick release taste masked pharmaceutical compositions comprising the said resinsates and process for the preparation of resinsates and compositions. Further the invention relates to the preparation of resinsates and the compositions comprising the resinsates without the
25 use of aromatic solvents and without the use of sophisticated packaging machinery.

The process for preparation of resinsates comprises steps:

- 1) Contacting solution of Tofacitinib with ion exchange resin,
- 2) Separating the resinate and optionally washing and drying it at temperatures below 110°C.

30 The process of preparation of taste masked resinsates of Tofacitinib and compositions comprising these resinsates comprises steps of:

- a) Dissolving Tofacitinib in an appropriate solvent to prepare the solution of Tofacitinib;
- b) Contacting ion exchange resin with the solution of Tofacitinib obtained in step a) to obtain the resinate;

- c) Optionally washing the resinate obtained in step b) with solvent to obtain washed resinate
- d) Optionally drying the washed resinate obtained in step c);
- e) Processing the resinate obtained in step b) or c) or d) with at least one pharmaceutical excipient to obtain rapidly disintegrating and or quick release compositions with or without other actives.

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Resinates prepared by the above process are stable resinates. These resinates and the compositions are prepared without the use of aromatic solvents and without the use of sophisticated packaging machinery.

10 DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to resinates of Tofacitinib. The invention also relates to compositions comprising tofacitinib resinates. The invention also relates to process to prepare the resinates and the compositions comprising the resinates.

The process for preparation of resinates comprises steps:

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- 1) Contacting solution of Tofacitinib with ion exchange resin,
- 2) Separating the resinate and optionally washing and drying it at temperatures below 110°C.

The process of preparation of taste masked resinates of Tofacitinib and compositions comprising these resinates comprises steps of:

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- a) Dissolving Tofacitinib in a non-aromatic solvent to prepare the solution of Tofacitinib;
- b) Contacting ion exchange resin with the solution obtained in step a) to obtain the resinate;
- c) Optionally washing the resinate obtained in step b) with solvent to obtain washed resinate
- d) Optionally drying the washed resinate obtained in step c);
- e) Processing the resinate obtained in step b) or c) or d) with at least one pharmaceutical

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excipient to obtain rapidly disintegrating and or quick release compositions with or without other actives.

Resinate formation takes place when ion exchange resin is contacted with drug solution. Thereafter depending upon the dosage form to be produced it may be washed and it may be dried or it may be washed and dried. When the resinate is incorporated into dosage forms, it should be free from non aqueous solvents used in preparing and or washing. The content of solvents should conform to ICH guidelines and the applicable pharmacopoeia. This can be achieved by drying alone, or by washing with water and then drying. The resinate obtained when incorporated into suitable liquid base with the processes known in the art, it gives taste masked liquid suspension of Tofacitinib.

30

If solid dosage forms are to be prepared, it is advisable to dry the resinate before it is incorporated into solid dosage forms. The process of preparation of solid dosage form compositions with the resinates of Tofacitinib comprises steps of:

- f) Taking suitable quantity of resinate, preferably dried resinate,
- 5 g) Incorporating it with other pharmaceutically acceptable excipients in order to formulate a desired pharmaceutical composition.

The dried resinate is processed to obtain fast disintegrating and or quick release compositions. Fast disintegrating and or quick release compositions of resinate are prepared as illustrated in the exmaples.

- 10 Spray drying in which fluidized bed processor is also an efficient process to form the resinates. Dried free flowing resinates in powder form are produced which are useful in designing the solid dosage forms.

The resinate of Tofacitinib has a versatile use. It is processed to obtain several oral dosage compositions such as granules for dispersion either in sachet pack or as a dry syrup, or such
15 granules dispersed into flavored syrupy base to obtain liquid suspension, quick dispersing tablets. Incorporation of resinate into chewing gum base gives chewing gum composition or dispersed into lozenge base to have a lozenge. The resinate when used with cooked glucose or similar base, gives a lollypop. Resinate can be incorporated into a wafer base or a soluble film base to have medicated wafer or soluble film.

- 20 As illustrated by exmaples, desired composition is prepared by incorporating the resinate with other pharmaceutically acceptable excipients.

The cation exchange resin used for resinate formation is selected from Methacrylic acid polymer with divinylbenzene and Acrylic acid Potassium salt or Methacrylic acid polymer with divinylbenzene and Potassium salt, Methacrylic acid polymer with divinylbenzene and Acrylic
25 acid, sulphonated copolymers of styrene and divinylbenzene, cross linked polymer of methacrylic acid and divinylbenzene. These resins are commercially available including those available as Indion resins, Tulsion resins, Dowex resins, Amberlite IRP resins and their equivalents in the form of salt with alkali metals or in acid form. Resinate formation takes place even when ratio of resin to Tofacitinib is 0.5:1. It was observed that resinate formation
30 takes place when the ratio of resin to Tofacitinib in the range of 9:1 to 0.5:1 is acceptable. However for effective and better taste masking it is advisable to take more quantity of resin. As the ratio of resin to Tofacitinib increases we get better taste masked resinates. Therefore preferable ratios of resin to Tofacitinib are 9:1 to 5:1.

Non aromatic solvent can be used singularly or in presence of another non aromatic solvent i.e. co-solvent. Non aromatic solvent and or co-solvent is selected from ethanol, isopropyl alcohol, water, Dichloromethane, organic polar and non-polar solvents, glycerin, propylene glycol and their suitable mixtures.

- 5 Solubility of Tofacitinib in water is very poor. Very large quantities of water are required. Therefore it is better to use other solvents which can be removed after resinate formation.

Non aromatic solvents as per the present invention includes open chain aliphatic solvents and mixtures thereof. These solvents are selected from compounds having carbon atoms ranging from C1 – C6. It includes solvents such as ethers, esters, aldehydes, Ketones, alcohols, chlorinated solvents, water miscible and water immiscible solvents. Alcohols includes
10 acohols having carbon atoms C1 to C6. Aldehydes and ketones having carbon atoms from C1 to C6. Ethers, alcohols and esters having carbon atoms C1 to C6 are covered by present invention. Chlorinated solvents having carbon atoms from C1 to C6 are included in the present invention. Preferred alcohols are methanol, ethanol, straight and branched propyl
15 alcohol and mixtures thereof. Preferred ketone being acetone and preferred aldehyde being acetaldehyde. Preferred chlorinated solvents include dichloromethane or methylelne dichloride.

Preferred solvent is one in which the Tofacitinib is soluble, which can be removed to conform to GMP and or ICH standards and which is physiologically acceptable.

- 20 Resinate is dried in one embodiment by heating in hot air oven. In another embodiment it is air dried at room or slightly elevated temperatures. Evaporation, vacuum evaporation, tray drying, microwave drying, spray drying, drum and belt film drying are other effective drying techniques. Centrifuging and optionally followed by drying is yet another methtdod of removing the solvent. Drying method is selected depending on solvent to be removed.

- 25 Resinate is dried at a temperature less than 110°C. It is advisable to carry out drying at temperature range of above 20°C to about 110°C. Suitable temperature is selected to ensure removal of solvent from the resinate. Preferable range for drying is 30°C to 105°C, more preferable range being 40°C to 90°C, most preferable range being 50°C to 80°C. The resinates were found to be stable in the temperature range of 40°C to 70°C when exposed for 30 minutes
30 duration. There was no impact on taste masking ability.

Active ingredient is Tofacitinib. The process of forming resinate as illustrated by the invention provides sufficient motivation to form resinates of acid addition salts of Tofacitinib and hence other pharmaceutically acceptable acid addition salts are covered by the invention.

The content of active ingredient in the resinate is in the range of about 11% to about 67%w/w, preferably from about 11% to about 16.66% w/w which is approximately equal to 17% w/w. Content of active in the resinate in the preferred range is useful for orally disintegrating tablets or orally disintegrating compositions. Content of active ingredient can be adjusted in the range
5 of about 18% to 50% w/w or from 51% to 67% w/w of that of resinate by taking lesser quantity of resin. 67% of active content would mean resin to Tofacitinib ratio of 1:2. It is advisable to keep the resin quantity more to get better taste masked resinate. Additional taste masking agent when used with resinate containing higher active content, in the composition, provide better compositions.

10 Resinate wherein active content is in the range of 25% to about 67% can be conveniently filled into empty hard gelatin capsules with or without other excipients. In case of dry syrups or granules ready for suspension, additional sweetening agents such as aspartame, sucralose or flavors such as Peppermint, strawberry, mint, orange flavours also enable incorporation of resinate with higher content of active. Similar granular preparation can be
15 prepared by known methods which is to be taken directly from the container without dilution with any solvent such as water. These are powders to be taken orally.

The resinate is processed with pharmaceutically acceptable excipients to obtain rapidly disintegrating or fast disintegrating and or quick release compositions such as quick dispersing tablets, granules for dispersion to prepare suspension just before consumption or as a dry
20 syrup. The resinate when dispersed into flavored syrupy base gives a liquid suspension. When mixed with chewing gum base, gives chewing gum composition. When dispersed into lozenge base, gives a lozenge. When the resinate is incorporated into cooked glucose or similar base, gives a lollypop. It can be incorporated into a wafer base or a soluble film base to obtain wafer or medicated soluble film by the known processes. Resinate with suitable active content is
25 conveniently filled into empty hard gelatin capsules with or without other excipients. Capsule filling can be done either manually on hand filling machines or by mechanized means on automatic or semiautomatic machines.

Taste masked pharmaceutical compositions of Tofacitinib intended by this application / invention encompass all aforesaid compositions and dosage forms.

30 It is possible to vary the content of the resinate in the composition in various dosage forms. Resinate can be easily incorporated into various dosage forms in various percentages weight by weight. Resinate content from 0.1 %w/w to 99%w/w of the weight of composition provides suitable Tasteless, rapidly disintegrating and quick release dosage form. The percentage of the resinate in the composition is also decided by the quantity and extent of other ingredients used

and other desired attributes. Although 0.1% w/w or such lower concentrations of resinate can be incorporated to form a composition, use of 0.1% w/w or such lower concentrations of resinate in the composition would make the composition bulky or voluminous and hence not desirable. It is preferable to keep content of the resinate in the composition from 10% w/w to 5 90% w/w. Preferred resinate percentage in the composition is in the range of about 25% w/w to about 90% w/w. Resinate along with additional one or more active pharmaceutical ingredient provides fixed dose combination dosage form.

Additional sweetening agents that can be employed for preparation of Tofacitinib resinate compositions can be selected from sugars such as Mannitol, Sucrose, Maltitol, Fructose, Sorbitol, 10 Sucralose, Dextrose; Aspartame; Saccharin Sodium, Acesulfame Potassium and the like pharmaceutically acceptable sweeteners. The resinate was given to 8 volunteers for testing palatability and substantial reduction in bitter taste was noticed which is otherwise associated with Tofacitinib. The compositions comprising resinate were given to 8 volunteers for testing palatability, mouth-feel, and taste. The compositions were found to be substantially free from 15 the bitter taste, otherwise associated with Tofacitinib, were found to be palatable and had acceptable mouth feel. Use of taste enhancing agents improves the taste further. The disintegration time of the tablet in the oral cavity was about well below 2 minutes. In some compositions it was 30 - 45 seconds.

Quickly disintegrating or fast release compositions mean disintegration in oral cavity within 2 20 minutes. Thus the invention provides resinates of Tofacitinib and the process to prepare the same. So prepared resinates are found to be stable at drying temperatures mentioned hereinabove. These are also easily dispersible. These resinates and the compositions comprising the resinates are prepared without the use of aromatic solvents and without the use of sophisticated packaging machinery.

25 Orally disintegrating, quick release compositions with improved palatability, mouth-feel, and taste eliminate the use of the water and support patient compliance.

As these resinates are stable, it is easy to incorporate them with another active ingredient, to provide fixed dose combination dosage form comprising multiple active pharmaceutical ingredients in addition to Tofacitinib.

30 Although no specific example is given of incorporation of other active, use of resinate in fixed dose combination composition would bring fixed dose combination within the purview of this invention and application.

Fixed dose combination dosage forms including fast disintegrating or quick release compositions, are rendered stable by using techniques known the prior art including but not

limited to multi-layered tablets, tablets in capsules, compressed coating, capsule in capsule and so on. Such dosage forms comprising active pharmaceutical ingredients in addition to resinsates of Tofacitinib are covered by this invention. In this manner it is possible to combine other active ingredients which are used to treat rheumatoid arthritis, or auto-immune diseases and the other indications on which Tofacitinib is useful, with the resinsates of Tofacitinib.

Resinsates and the compositions such as rapid disintegrating and or quick release taste masked pharmaceutical compositions comprising the said resinsates and process for the preparation of resinsates and compositions is described by non-limiting examples.

10 Examples:

Example 1: Process to prepare the resinates of Tofacitinib base

Name of the Resin	INDION		
	234	294	204
(Ethanol Absolute : DCM) (ml)	30:30	30:30	30:30
API (gms)	1	1	1
Resin (gms)	5	6	8
% of active	16.66%	14.29%	11.11%

1. Approximately 30:30 ml of Ethanol and Di-chloro Methane (DCM) were taken in three different containers and 1 gm of Tofacitinib Base was dissolved into each, under continuous stirring till clear solution formed.
2. 1 gm Resin of different grade was added slowly and stirred for 45 minutes. 1gm of incremental resin was added and stirred for further period of 45 minutes. This was carried out till satisfactory taste masking effect was observed.
3. These solutions were kept under stationary mode till cake formation was seen.
4. Supernatant solution was decanted. Cake dried at room temperature for 4 hours.
5. Dried cake was tasted.

The bitter taste was masked to different degree in case of different resins used and cake had acceptable taste and was not bitter like Tofacitinib base.

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Example 2: Rapid disintegrating taste masked tablet composition of resinates of Tofacitinib with Indion 294. [Resinate content = 26.72%w/w]

Component	Quantity/ Tablet (mg)
Tofacitinib Base: (Indion 294) (1:7)	40.078 (8.078 Equivalent API)
Pearlitol SD200	81.022

Microcrystalline cellulose (Avicel PH 112)	20.000
Crospovidone (Polyplastdone XL 10)	5.000
Aspartame	1.000
Peppermint Flavour	0.400
Magnesium stearate	2.000
Tablet Core Total	150.000

Example 3: Rapid disintegrating taste masked tablet composition of resinate of Tofacitinib with Indion 234. [Resinate content = 33.39%w/w]

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Component	Quantity/ Tablet (mg)
Tofacitinib Base: (Indion 234) (1:6)	50.078 (8.078 Equivalent API)
Pearlitol SD200	71.022
Microcrystalline cellulose (Avicel PH 112)	20.000
Crospovidone (Polyplastdone XL 10)	5.000
Aspartame	1.000
Peppermint Flavour	0.400
Magnesium stearate	2.000
Tablet Core Total	150.000

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Example 4: Rapid disintegrating taste masked tablet composition of resinate of Tofacitinib with Indion 204. [Resinate content = 46.72%w/w]

Component	Quantity/ Tablet (mg)
Tofacitinib Base: (Indion 204) (1:9)	70.078 (8.078 Equivalent API)
Pearlitol SD200	51.022
Microcrystalline cellulose (Avicel PH 112)	20.000
Crospovidone (Polyplastdone XL 10)	5.000
Aspartame	1.000
Peppermint Flavour	0.400
Magnesium stearate	2.000
Tablet Core Total	150.000

15 **Example 5: Manufacturing Process for Example 2, 3 and 4.**

Formulae represent unit composition. Input materials taken in multiples depending upon available equipments to produce 10 tablets.

1. Passed the resinate through 40# and collect in a polybag of suitable size.
- 5 2. Transferred MCC into the polybag containing resinate and mix for 5 min.
3. Co-sifted step 2 blend with half quantity of Pearlitol SD200 through mesh 40 #.
4. Sifted Crospovidone, Aspartame , Peppermint Flavour & Colloidal anhydrous silica through mesh 40 #.
5. Rinsed polybag with remaining quantity of Pearlitol SD200 & sifted through mesh 40 #.
- 10 6. Transferred sifted blends in 500cc HDPE bottle and mixed for 15 min at 16 rpm by attaching HDPE bottle with blender.
7. Sifted magnesium stearate through mesh 40 and mixed with step 6 blend for 3 min.
8. Compressed the tablet on compression machine. Hardness was 40-45N & Friability of 0.8% for 100 revolutions. Tablets disintegrated rapidly in the mouth.

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Example 6: Dry syrup composition comprising resinate of Tofacitinib. [Resinate w/w % is 80.16%.]

Ingredient	Qty / 5ml (mg)
Tofacitinib resinate (Indion 294) (mg)	40.078
Sodium CMC(mg)	7.000
Sucrose(mg)	1.592
Propyl Paraben(mg)	1.330
Water to (ml)	5

- Tofacitinib resinate 40.078 mgs in 5 ml is equal to 5mg of Tofacitinib base or 8.078mg of Tofacitinib citrate per 5ml. Tofacitinib resinate, Sodium CMC, Sucrose and Propyl Paraben were mixed. Water was added to make volume to 5 ml. Similarly in another experiment 500 ml were prepared without sugar. The compositions were studied for 7 days. Subjective evaluation testing was done during and after 7 days. Composition with sugar had acceptable taste. Bitter taste was adequately masked. The composition without sugar had acceptable taste taste even after 7 days.
- 25 The suspensions remain easily re-dispersible at the end of 7 days and were palatable.
- When the same composition is prepared without sugar, % of resinate in the composition is 82.8% or approximately 83% w/w of dry solids.

Example 7: Dry syrup composition comprising resinate of Tofacitinib resinate (Indion 234) [Resinate w/w % is 83.46%]

Ingredient	Qty / 5ml (mg)
Tofacitinib resinate (Indion 234) (mg)	50.078
Sodium CMC(mg)	7.000
Sucrose(mg)	1.592
Propyl Paraben(mg)	1.330
Water to (ml)	5

Tofacitinib resinate 50.078 mgs in 5 ml is equal to 5mg of Tofacitinib base per 5ml. Tofacitinib resinate, Sodium CMC, Sucrose and Propyl Paraben were mixed in mixer. Water was added to make volume to 5 ml. Similarly in another experiment 500 ml were prepared without sugar. The compositions were studied for 7 days. Subjective evaluation testing was done during and after 7 days. Composition with had acceptable taste. Bitter taste was adequately masked. The composition without sugar had acceptable taste taste even after 7 days. The suspensions remain easily re-dispersible at the end of 7 days and were palatable.

When the same composition is prepared without sugar, % of resinate in the composition is 85.8% or approximately 86% w/w of dry solids.

Example 8: Dry syrup composition comprising resinate of Tofacitinib resinate (Indion 204) [Resinate w/w % is 87.6%.]

Ingredient	Qty / 5ml (mg)
Tofacitinib Citrate resinate (Indion 204) (mg)	70.078
Sodium CMC(mg)	7.000
Sucrose(mg)	1.592
Propyl Paraben(mg)	1.330
Water to (ml)	5

Tofacitinib resinate 70.078 mgs in 5 ml is equal to 5mg of Tofacitinib base per 5ml. Tofacitinib resinate, Sodium CMC, Sucrose and Propyl Paraben were mixed in mixer. Water was added to make volume to 5 ml. Similarly in another experiment 500 ml were prepared without sugar. The compositions were studied for 7 days. Subjective evaluation testing was done during and after 7 days. Composition with sugar had acceptable taste. Bitter taste was adequately masked. The

composition without sugar had acceptable taste even after 7 days. The suspensions remain easily re-dispersible at the end of 7 days and were palatable.

When the same composition is prepared without sugar, % of resinate in the composition is 89.4% or approximately 90% w/w of dry solids.

5 **Example 9:**

Dry Syrup compositions as listed above were prepared without sugar. The composition without sugar had acceptable taste. Bitter taste was adequately masked.

Example 10: Stability of resinates of Tofacitinib at 70°C with respect to taste.

- 10 Resinates when kept at 40°C, 50°C, 60°C and 70°C in hot air oven for 30 minutes, did not show any change with respect to its taste masking ability. It was substantially free from bitter taste associated with drug.

CLAIMS

We Claim:

- 1) A resinate of Tofacitinib.
- 2) A resinate as claimed in claim 1, wherein the resin is selected from copolymers of methacrylic acid and divinylbenzene, cross linked polymer of methacrylic acid and divinylbenzene, sulphonated copolymers of styrene and divinylbenzene.
- 3) A resinate as claimed in claims 1 and 2, wherein the resin is used in its free acid form or in the form of alkali metal salt.
- 4) A resinate as claimed in claims 1-3, wherein Tofacitinib is present upto 67%w/w.
- 5) A resinate as claimed in claims 1-4, wherein Tofacitinib is present in the range of 11% to 17%w/w.
- 6) A resinate as claimed in claims 1-4, wherein Tofacitinib is present in the range of 18% to 50%w/w.
- 7) A resinate as claimed in claims 1-4, wherein Tofacitinib is present in the range of 51% to 67%w/w.
- 8) A resinate as claimed in claims 1-4, wherein the ratio of resin to Tofacitinib is in the range of 9:1 to 0.5:1, preferable being 9:1 to 5:1.
- 9) A process of preparation of resinate of Tofacitinib, comprises steps of:
 - a) Dissolving Tofacitinib in an non-aromatic solvent to obtain solution;
 - b) Contacting ion exchange resin with the solution obtained in step a) to obtain the resinate;
 - c) Optionally washing the resinate obtained in step b) with solvent to obtain washed resinate and
 - d) Optionally drying the washed resinate obtained in step c);
 - e) Optionally processing the resinate obtained in step b) or c) or d) with at least one pharmaceutical excipient to obtain rapidly disintegrating and or quick release compositions with or without other actives.
- 10) A process as claimed in claim 9, wherein the resin is used in its free acid form or

in the form of alkali metal salt.

- 11) A process as claimed in claim 9-10, wherein the resin is selected from copolymers of methacrylic acid and divinylbenzene, cross linked polymer of methacrylic acid and divinylbenzene, sulphonated copolymers of styrene and divinylbenzene.
- 12) A process as claimed in claims 9, wherein Tofacitinib is present upto 67%w/w.
- 13) A process as claimed in claims 9, wherein Tofacitinib is present in the range of 11% to 17%w/w
- 14) A process as claimed in claims 9, wherein Tofacitinib is present in the range of 18% to 50%w/w.
- 15) A process as claimed in claims 9, wherein Tofacitinib is present in the range of 51% to 67%w/w.
- 16) A process, as claimed in claim 9, wherein solvent used is selected from water, alcohol, dichloromethane, isopropyl alcohol, glycerin, propylene glycol, pharmaceutically acceptable organic or inorganic solvents, non aromatic solvent selected from ethers, esters, aldehydes, Ketones, alcohols, chlorinated solvents, water miscible and water immiscible solvents or their mixtures.
- 17) The process as claimed in claim 9 where the preferred solvent is mixture of Ethanol and Di-chloro Methane.
- 18) A process, as claimed in claims 9, wherein the ratio of resin to Tofacitinib is in the range of 9:1 to 0.5:1, preferable being 9:1 to 5:1.
- 19) A process, as claimed in claim 9, wherein drying is carried out at temperature range of 20°C to 110°C, preferable range being 30°C to 105°C, more preferable range being 40°C to 90°C, most preferable range being 50°C to 80°C.
- 20) A composition, comprising Tofacitinib resinate content from 0.1 %w/w to 99%w/w of the weight of composition, preferable being 10% w/w to 90% w/w.
- 21) A fast disintegrating tablet comprising a resinate of Tofacitinib wherein the resinate content is 0.1 %w/w to 100%w/w of the weight of composition, preferable being 10% w/w to 90% w/w.

- 22) A composition as claimed in claims 20 - 21, comprising pharmaceutically acceptable excipients optionally with one or more additional active ingredients.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2016/055490

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A61K 9/20; C07D 211/56; C07D 487/04 (2016.01)
 CPC - A61K 9/0053; A61K 9/0056; A61K 9/4891; A61K 31/519; C07D 211/56; C07D 487/04 (2016.11)
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC(8) - A61K 9/20; C07D 211/56; C07D 487/04 (2016.01)
 CPC - A61K 9/0053; A61K 9/0056; A61K 9/4891; A61K 31/519; C07D 211/56; C07D 487/04 (2016.11)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 USPC - 424/78.1; 424/465; 514/249; IPC(8) - A61K 9/20; C07D 211/56; C07D 487/04; CPC - A61K 9/0053; A61K 9/0056; A61K 9/4891; A61K 31/519; C07D 211/56; C07D 487/04 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 Orblt, Google Patents, Google Scholar, Google
 Search terms used: Tofacitinib, Xeljanz, Jakvinus, tasocitinib, ion exchange, taste, methacrylic, divinylbenzene, sulphonated, sulfonated, sulfonic, sulphonic, disintegrating, rapid, quick, citrate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2013/0344149 A1 (RATIOPHARM GMBH) 26 December 2013 (26.12.2013) entire document	1, 2, 9, 10, 12-16, 18 ----- 17, 19-21
Y	US 2015/0336961 A1 (GLENMARK PHARMACEUTICALS LIMITED) 26 November 2015 (26.11.2015) entire document	17
Y	US 2008/0095842 A1 (ANTARKAR et al) 24 April 2008 (24.04.2008) entire document	19-21

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 30 December 2016	Date of mailing of the international search report 19 JAN 2017
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Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2016/055490

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

- 2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

- 3. Claims Nos.: 3-8, 11, 22
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
- 2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
- 3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

- 4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - No protest accompanied the payment of additional search fees.