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ABSTRACT

GEL BASED DRUG DELIVERY SYSTEM COMPRISING SELF EMULSIFYING FORMULATION

The present invention involves development of a drug delivery system comprising a matrix entrapping the pharmaceutically active ingredient dissolved in self emulsifying formulation for improved delivery of wide variety of pharmaceutical active ingredients for oral delivery. The drug delivery system is a gel composition including the gel forming matrix, self emulsifying oil formulation, cross-linking agent. The self emulsifying formulation contains different combination of lipophilic active pharmaceutical ingredient, hydrophilic surfactant, lipophilic surfactant and triglycerides. The composition of present invention can be used for improved delivery and remove instability of oil formulation with soft and hard gelatin capsule thus can increase the durability and stability of the formulation.

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We claim,

1. An oral drug delivery system comprising a lipophilic active pharmaceutical ingredient dissolved in a self emulsifying component and entrapped in a gel forming matrix, wherein, the self emulsifying component comprises a surfactant and a triglyceride and wherein the gel forming matrix comprises, a hydrogel forming agent, a swelling agent and a cross-linking agent.

2. The oral drug delivery system of claim 1 wherein, the lipophilic active pharmaceutical ingredient is a Class II drug as per Biopharmaceutical Classification System (BCS) Guidance.

3. The oral drug delivery system of claim 1 wherein, the surfactant is hydrophilic or hydrophobic.

4. The oral drug delivery system of claim 1 wherein, triglyceride is edible oil.

5. The oral drug delivery system of claims 1 and 4 wherein, the edible oil is castor oil, peanut oil or soybean oil.

6. The oral drug delivery system of claim 1 wherein, gel forming agent is sodium alginate

7. The oral drug delivery system of claim 1 wherein, the crosslinking agent is zinc chloride or calcium chloride.

8. The oral drug delivery system of claim 1 wherein, the swelling agent is hydroxy propyl methyl cellulose (HPMC).

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9. The oral drug delivery system of claims 1 and 8 wherein, the swelling agent aids in sustained release of the active pharmaceutical ingredient.

10. The oral drug delivery system of claims 1 and 6 wherein, gel forming agent is practically insoluble in gastric juice thereby preventing the release and degradation of the active pharmaceutical ingredient which is unstable in the gastric juice.

11. A method of making an oral drug delivery system comprising the steps of:

a. dissolving the active pharmaceutical ingredient in a surfactant and triglyceride mixture;

b. vortexing and equilibrating the mixture to make a persistent clear, mixture of a lipophilic active pharmaceutical ingredient and a self emulsifying component showing no phase separation;

c. preparing a solution of a gel forming agent and swelling agent by dissolving each in water;

d. adding the mixture of the lipophilic active pharmaceutical ingredient and the self emulsifying component to the solution of hydrogel forming agent and swelling agent to make a stable active pharmaceutical solution;

e. adding the said stable active pharmaceutical solution active pharmaceutical solution to a crosslinking agent to form hydrogel comprising of the active pharmaceutical ingredient trapped inside the hydrogel;

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f. collecting the hydrogel, and

g. packaging the hydrogel in a suitable dosage form.

12. The method as per claim 10, wherein the active pharmaceutical ingredient is dissolved in the surfactant and triglyceride mixture at 40 ^{0}C to 70 ^{0}C but preferably 60 ^{0}C.

13. The method as per claim 10 wherein, the vortexing and equilibrating of the mixture is done at a temperature of 30 ^{0}C to 50 ^{0}C but preferably 40 ^{0}C for at least 48 hours.

14. The method as per claim 10 wherein, the solution of the gel forming agent and the swelling agent is prepared at a temperature of 60 ^{0}C to 90 ^{0}C but preferably 70 ^{0}C to 80 ^{0}C and more preferably 40 ^{0}C at till the occurrence of complete dissolution of gel forming agent and the swelling agent.

15. The method as per claim 10 wherein the hydrogel comprising of the active pharmaceutical ingredient trapped inside the hydrogel, is of size 1.0 mm to 1.5 mm, but preferably 1.3 mm.

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FIELD OF INVENTION

[001] The present subject matter generally relates to a drug delivery system comprising a stabilized form of self emulsifying formulation. More particularly the subject matter relates to an oral drug delivery system comprising an active pharmaceutical ingredient dissolved in a self emulsifying formulation and entrapped in a matrix.

BACKGROUND

[002] Bioavailability of a pharmaceutical drug is the level to which the drug becomes available to the target tissue after being administered in the body. Low bioavailability is a result of the drug being poorly water-soluble i.e. hydrophobic or more soluble in lipids i.e. lipophilic. Such drugs are thrown away from the body before being absorbed in the human body, a compound has to be soluble in both water and fats (lipids). Poor bioavailability is a significant problem encountered in the development of many pharmaceutical formulations.

[003] Lipophilic drugs are a growing class of drugs with increasing applicability in a variety of therapeutic areas. These drugs suffer from a major drawback of having limited bioavailability hence their development as pharmaceuticals particularly in oral dosage form is a major obstacle hindering the development of these drugs. For example, hydrophobic pharmaceutically active ingredients such as Lovastatin, netaglinide,

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glyburide, and cyclosporine present delivery challenges because of their poor water solubility and slow dissolution rate.

[004] Patent number WO 2005014048 describes self-emulsifying and self-microemulsifying formulations for the oral administration of taxoids. EP 2601935 describes compositions comprising lipophilic active compounds and method for their preparation. US patent 5993858 describes method and formulation for increasing the bioavailability of poorly water-soluble drugs. WO 2001028524 describes sustained release microspheres. WO 2001037808 describes solid carriers for improved delivery of active ingredients in pharmaceutical compositions. US patent 6,375,968 describes encapsulated active material immobilized in hydrogel microhydrogel, wherein the microhydrogel suspended in solution are useful for delivering active material. US patent 6,576,258 describes a pharmaceutical formulation with controlled release of active substances that are unstable in acidic medium, when stored for longer periods of time in the presence of water and at the same time sensitive to heating. US patent 6,849,271 describes microcapsule matrix microspheres, absorption-enhancing pharmaceutical compositions and methods. US patent 7,879,362 describes oral pharmaceutical compositions with controlled release and prolonged absorption and prolonged/controlled release of the medicinal and/or nutritional active principle. US patent 8,273,375 describes a multiparticle pharmaceutical dosage form for a low-soluble active substances and method for producing said pharmaceutical

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dosage form containing a plurality of pellets, particles, granules or agglomerates. A method for producing the inventive multiparticle pharmaceutical dosage is also disclosed. US patent 8,445,023 describes anti-misuse microparticulate oral pharmaceutical form whose composition and structure make it possible to avoid misuse of the pharmaceutical active principle (AP) they contain. US patent 8,597,681 describes methods of producing stabilized solid dosage pharmaceutical compositions containing morphinans.

[005] As described in prior art, there are many approaches such as size reduction, emulsion, formulation, etc. to enhance bioavailability. These approaches suffer from several limitations. Size reduction (micronization, nanonization) presents processing and stability challenges, as well as dissolution limitations. Liquid formulations present drug precipitation and packaging challenges. Non solid formulations are more prone to chemical instability and capsule- shell incompatibility, leading to the possibility of leakage. Marketed, solid conventional formulations containing hydrophobic active pharmaceutical ingredient, such as tablets often exhibit slow and incomplete dissolution. Solid or gel based system comprising a stabilized form of self emulsifying formulation for the active pharmaceutical ingredient offer great advantage over micronized/nanonized, emulsion or nanoemulsion formulations. The above maintained problem of leakage and other disadvantage of liquid

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formulations can be avoided by solid or gel based system comprising a stabilized form of self emulsifying formulation.

OBJECTS

[006] Accordingly, the main object of the present invention is to provide a drug delivery system comprising a stabilized form of self emulsifying formulation. It is also an object of the present invention to provide an oral drug delivery system comprising an active pharmaceutical ingredient dissolved in a self emulsifying formulation and entrapped in a matrix.

SUMMARY OF THE INVENTION

[007] To meet the above objects and to overcome the problems existing in the prior art, the present subject matter describes an oral drug delivery system for administering a lipophilic active pharmaceutical ingredient to a patient. It is known that the lipophilic active pharmaceutical ingredients belong to Class II drugs as per Biopharmaceutics Classification System (BCS) Guidance. These pharmaceutical ingredients are less bioavailable. They are insoluble in water and need to be dissolved in a self emulsifying component. The self emulsifying component is made of two parts, a surfactant and a triglyceride. The surfactant is hydrophilic or hydrophobic and the triglyceride is edible oil, including any one of castor oil, peanut oil or soybean oil.

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[008] The lipophilic active pharmaceutical ingredient, solubilized in the self emulsifying component is further stabilized by entrapping in a gel forming matrix, made of a cross-linking agent, a hydrogel forming agent and a swelling agent. The cross-linking agent is zinc chloride or calcium chloride. The hydrogel forming agent is sodium alginate and the swelling agent, which aids in sustained release of the active pharmaceutical ingredient is hydroxy propyl methyl cellulose (HPMC).

[009] The invention also describes a method of making an oral drug delivery system. The method includes a step of dissolution of the active pharmaceutical ingredient in a surfactant and triglyceride mixture at a temperature of 40 ^{0}C to 70 ^{0}C but preferably 60 ^{0}C. In the next step, the mixture is vortexed and equilibrated at a temperature of 30 ^{0}C to 50 ^{0}C but preferably 40 ^{0}C for at least 48 hours to make a persistent clear mixture of the lipophilic active pharmaceutical ingredient and the self emulsifying component showing no phase separation.

[0010] In the next step, a solution of a hydrogel forming agent and swelling agent is prepared by dissolving each in water at a temperature of 60 ^{0}C to 90 ^{0}C but preferably 80 ^{0}C. Thereafter, the mixture of the lipophilic active pharmaceutical ingredient and the self emulsifying component is added to the solution of hydrogel forming agent and swelling agent. This mixture is added to a cross-linking agent to form hydrogel of size 1.0 mm to 1.5 mm, but preferably 1.3 mm comprising of

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the active pharmaceutical ingredient trapped inside the hydrogel. These hydrogels are collected and packaged in a suitable dosage form.

DETAILED DESCRIPTION OF THE INVENTION

[0011] According to one object, an oral drug delivery system for administering a lipophilic active pharmaceutical ingredient belonging to Class II drugs as per Biopharmaceutical Classification System (BCS) Guidance is described.

[0012] In one more form of the invention, the pharmaceutically active ingredients are less bioavailable as they are insoluble in water and are hence, dissolved in a self emulsifying component.

[0013] In yet another form of the invention, the self emulsifying component is made of two parts, a surfactant and a triglyceride and the surfactant is hydrophilic or hydrophobic and the triglyceride is edible oil, including any one of castor oil, peanut oil or soybean oil.

[0014] In another form of the invention, the lipophilic active pharmaceutical ingredient solubilized in the self emulsifying component is further stabilized by entrapping in a gel forming matrix, made of a cross-linking agent, a hydrogel forming agent and a swelling agent.

[0015] In a form of the invention, the hydrogel forming agent is sodium alginate.

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[0016] In yet another form of the invention, the cross-linking agent is zinc chloride or calcium chloride.

[0017] In one more form of the invention, the swelling agent is hydroxy propyl methyl cellulose (HPMC) which aids in sustained release of the active pharmaceutical ingredient.

[0018] In a form of the invention, a method of making an oral drug delivery system is described.

[0019] In yet another form of the invention, the method includes dissolution of the active pharmaceutical ingredient in a surfactant and triglyceride mixture at a temperature of 40 ^{0}C to 70 ^{0}C but preferably 60 ^{0}C and vortexing and equilibrating the mixture at a temperature of 30 ^{0}C to 50 ^{0}C but preferably 40 ^{0}C for at least 48 hours to make a persistent clear, mixture of the lipophilic active pharmaceutical ingredient and the self emulsifying component showing no phase separation.

[0020] In another form of the invention, a solution of swelling agent is prepared by dissolving in water separately at a temperature of 60 ^{0}C to 90 ^{0}C but preferably 70 ^{0}C to 80 ^{0}C and more preferably 40 ^{0}C at till complete dissolution.

[0021] In one more form of the invention, the mixture of the lipophilic active pharmaceutical ingredient and the self emulsifying

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component is added to the solution of hydrogel forming agent and swelling agent.

[0022] In yet another form of the invention, lipophilic active pharmaceutical ingredient and the self emulsifying component are mixed together and added to a mixture of hydrogel forming agent and swelling agent. The resultant mixture is added to a crosslinking agent to form hydrogel of size 1.0 mm to 1.5 mm, but preferably 1.3 mm.

[0023] In another form of the invention, the active pharmaceutical ingredient is trapped inside the hydrogel.

[0024] In one form of the invention, the gel forming agent is practically insoluble in gastric juice. This prevents the release and degradation of the active pharmaceutical ingredient, which has the property of being unstable in the intestinal fluid.

[0025] In yet another form of the invention, these hydrogel are collected and packaged in a suitable dosage form such as capsules.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] The subject matter shall now be described with reference to the accompanying figures, wherein:

[0027] FIG. 1 shows FESEM investigation of the formulation of present invention.

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[0028] FIG. 2 shows *in- vitro* dissolution/release as a function of time for the present invention and pure bulk drug.

[0029] FIG. 3 shows *in- vivo* absorption test in rat for pure bulk drug and drug from a formulation of present invention.

DETAILED DESCRIPTION OF THE SUBJECT MATTER WITH RESPECT TO DRAWINGS

[0030] Before the present subject matter is described in further detail, it is to be understood that the subject matter is not limited to the particular embodiments described, and as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0031] As per FIG. 1, all produced gels were spherical in shape (Fig.1 a). With increasing the magnification. Fig. 1 b, showed shape and size of a typical gel. There is obviously an incorporation of the self emulsifying formulation within the gel system which causes to produce smooth surface. It size was observed nearly 1.3 mm.

[0032] As per FIG. 2, the graph shows *in- vitro* dissolution/release as a function of time for according to the present invention and pure bulk drug.

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[0033] In the present invention, gel formulation is pH-responsive, exhibiting oscillatory contraction/swelling response under alternating pH step change between 1.2 and 7.8 demonstrating outstanding stability and repeatable response behavior. From the Fig 2, it can be observed that dissolution of gel formulation in acidic condition was low. But, sudden increased in dissolution of gel system was observed (more than 90%) in phosphate buffer which was nearly 4 times greater than pure lovastatin.

[0034] As per figure 3, the graph shows *in- vivo* absorption test in rat for pure bulk drug and drug from a formulation of invention.

[0035]. C_{max} of present invention was observed nearly 700 ng/ml while, C_{max} of pure lovastatin was observed nearly 360 ng/ml which was lesser than our present invention.

[0036] These results reveal that present invention can improve the bioavailability of drug. It can be envisaged that after oral administration, the formulation, developed in present invention get swelled and release the self emulsifying formulation witch further form o/w nano-emulsion spontaneously in the gastrointestinal fluid, with the active components entrapped in the oil droplets.

DETAILED DESCRIPTION OF THE SUBJECT MATTER WITH RESPECT TO EXAMPLES

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[0037] Preparation of different compositions of self emulsifying formulation: Compositions according to the present invention were prepared as follows. The specific components used are detailed in the example 1-5. A self emulsifying formulation was prepared by dissolving the desired amount of active pharmaceutical ingredient (Lovastatin) in the mixture of hydrophilic, lipophilic surfactant and oil (triglyceride) at 60 ^{0}C in an isothermal water bath. The final mixture was mixed by vortexing until a clear solution was obtained. The formulation was equilibrated at 40 ^{0}C in incubator shaker for at least 48 h and examined for signs of turbidity and phase separation.

[0038] Example 1:

Ingredient	% (w/w)
Oil of castor	40
Span- 80	20
Tween- 80	40

[0039] Example 2

Ingredient	% (w/w)
Oil of castor	40
span- 80	20
Labrasol	40

[0040] Example 3

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Ingredient	% (w/w)
peanut oil	40
span-80	20
cremophore EL	40

[0041] Example 4

Ingredient	% (w/w)
peanut oil	40
span-80	20
capmul MCM C-10	40

[0042] Example 5

Ingredient	% (w/w)
Soyabean oil	40
Capryol 90	20
Tween 80	40

[0043] Preparation of different gel formulation compositions comprising self emulsifying formulation

[0044] Gel formulation comprising self emulsifying formulations according to the present invention was prepared as follows. The specific components used are detailed in the example 6. In primary stage, a solution of HPMC and sodium alginate was prepared. For this purpose, HPMC was dissolved into a specific amount of water at 80 ^{0}C and leave it

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to cool up to 40 ^{0}C and dissolved sodium alginate into it. In second stage, a mixture was prepared by addition of self emulsifying formulation into above HPMC & sodium alginate, solution. Finally, in order to prepare gel formulation, this mixture was added dropwise into aqueous solution of $CaCl_2$ and $ZnCl_2$ in which round gel formulation comprising self emulsifying formulation was formed.

[0045] Example 6

Ingredient	% (w/v)
Sodium alginate	2.0
HPMC	0.4
Self Emulsifying formulation	14 % (v/v)
$Cacl_2$	1.0
$Zncl_2$	0.5

[0046] Example 7: **Comparative *in-vitro* dissolution study I**

[0047] The comparative *in-vitro* dissolution study was performed on two forms of active ingredient: gel formulation comprising self emulsifying formulation example 6 and the pure Lovastatin bulk drug. The dissolution study was performed by using fully calibrated six station USP type II dissolution test apparatus. For each two forms, material equivalent to 6mg of Lovastatin was used for each triplicate dissolution run in 500ml for two hours initially in 0.1 N HCl and in phosphate buffer pH 6.8 for the next one hour. The temperature of dissolution medium was maintained at 37±.05

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^{0}C and constantly stirred at a speed of 100 rpm. 5 ml of the dissolution media were pulled out at 15, 30, 60, 120, 180 minutes and replaced by fresh phosphate buffer to maintain the sink condition. The samples were passed through a 0.25 µ syringe filter immediately after the sampling and assayed on HPLC system.

[0048] The HPLC assay was performed on an YL9000 HPLC system by injecting 20 µl of the sample. The samples were separated on a C_{18} column by running the mobile phase of 20:80 v/v water (containing 0.1% orthophosphoric acid) / acetonitrile at a flow rate of 1ml/min, at ambient temperature. Lovastatin was detected by its UV absorption at 238 nm.

[0049] The result of the comparative dissolution study was expressed as the percent of Lovastatin was released by the gel formulation in the dissolution medium at the given time. The result is shown in **FIG. 1.** As the figure shows, gel based formulation comprising self emulsifying formulation of the present invention showed superior dissolution profile as compare to the pure bulk Lovastatin in the extent of Lovastatin in the dissolution medium.

[0050] Example 8: **Testing for the bioavailability**

[0051] Wistar rats are administered a 10mg/kg of dose of the Lovastatin in suspension. Samples of serum were collected at specific

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time intervals and analyzed by an YL9000 HPLC system equipped with UV- visible detector. In the table below, C_{max} and AUC (0-5hr) values are indicating the bioavailability of Lovastatin. The larger the AUC value, the greater the total amount of Lovastatin that accumulated in the plasma serum over the specific time period.

Sr. No	Indicator of bioavailability	Pure bulk Lovastatin	Formulation Example 6
1	C_{max}	180 min	240 min
2	AUC $_{(0\text{-}5\ hr)}$ µg-h /ml	75.746	23.205

[0052] The result in the above table show that our invention, gel based formulation comprising self emulsifying formulation exhibit enhance bioavailability over the pure bulk Lovastatin.

[0053] For the analysis of Lovastatin in the blood plasma, HPLC assay was performed on an YL9000 HPLC system by injecting 20 µl of the extracted sample. The samples were separated on a C_{18} column by running the mobile phase of 20:80 v/v water (containing .1% orthophosphoric acid) / acetonitrile at a flow rate of 1ml/min, at ambient temperature. Simvastatin was used as internal standard and both Simvastatin & Lovastatin was detected by its UV absorption at 238 nm.

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We claim,

1. An oral drug delivery system comprising a lipophilic active pharmaceutical ingredient dissolved in a self emulsifying component and entrapped in a gel forming matrix, wherein, the self emulsifying component comprises a surfactant and a triglyceride and wherein the gel forming matrix comprises, a hydrogel forming agent, a swelling agent and a cross-linking agent.

2. The oral drug delivery system of claim 1 wherein, the lipophilic active pharmaceutical ingredient is a Class II drug as per Biopharmaceutical Classification System (BCS) Guidance.

3. The oral drug delivery system of claim 1 wherein, the surfactant is hydrophilic or hydrophobic.

4. The oral drug delivery system of claim 1 wherein, triglyceride is edible oil.

5. The oral drug delivery system of claims 1 and 4 wherein, the edible oil is castor oil, peanut oil or soybean oil.

6. The oral drug delivery system of claim 1 wherein, gel forming agent is sodium alginate

7. The oral drug delivery system of claim 1 wherein, the crosslinking agent is zinc chloride or calcium chloride.

8. The oral drug delivery system of claim 1 wherein, the swelling agent is hydroxy propyl methyl cellulose (HPMC).

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9. The oral drug delivery system of claims 1 and 8 wherein, the swelling agent aids in sustained release of the active pharmaceutical ingredient.

10. The oral drug delivery system of claims 1 and 6 wherein, gel forming agent is practically insoluble in gastric juice thereby preventing the release and degradation of the active pharmaceutical ingredient which is unstable in the gastric juice.

11. A method of making an oral drug delivery system comprising the steps of:

a. dissolving the active pharmaceutical ingredient in a surfactant and triglyceride mixture;

b. vortexing and equilibrating the mixture to make a persistent clear, mixture of a lipophilic active pharmaceutical ingredient and a self emulsifying component showing no phase separation;

c. preparing a solution of a gel forming agent and swelling agent by dissolving each in water;

d. adding the mixture of the lipophilic active pharmaceutical ingredient and the self emulsifying component to the solution of hydrogel forming agent and swelling agent to make a stable active pharmaceutical solution;

e. adding the said stable active pharmaceutical solution active pharmaceutical solution to a crosslinking agent to form hydrogel comprising of the active pharmaceutical ingredient trapped inside the hydrogel;

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f. collecting the hydrogel, and

g. packaging the hydrogel in a suitable dosage form.

12. The method as per claim 10, wherein the active pharmaceutical ingredient is dissolved in the surfactant and triglyceride mixture at 40 ^{0}C to 70 ^{0}C but preferably 60 ^{0}C.

13. The method as per claim 10 wherein, the vortexing and equilibrating of the mixture is done at a temperature of 30 ^{0}C to 50 ^{0}C but preferably 40 ^{0}C for at least 48 hours.

14. The method as per claim 10 wherein, the solution of the gel forming agent and the swelling agent is prepared at a temperature of 60 ^{0}C to 90 ^{0}C but preferably 70 ^{0}C to 80 ^{0}C and more preferably 40 ^{0}C at till the occurrence of complete dissolution of gel forming agent and the swelling agent.

15. The method as per claim 10 wherein the hydrogel comprising of the active pharmaceutical ingredient trapped inside the hydrogel, is of size 1.0 mm to 1.5 mm, but preferably 1.3 mm.

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