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FORMULATION OF EFAVIRENZ NANOPARTICLES BY USING SPRAY DRYING AND HIGH PRESSURE HOMOGENIZATION TECHNIQUE: A COMPARATIVE STUDY FOR TASTE MASKING AND SOLUBILITY ENHANCEMENT

1. EXPERIMENTAL DESIGN

During the development of the efavirenz nanoparticles number of initial trials were conducted to improve the solubility of efavirenz. The preliminary experiments include the change in efavirenz, PVPk30 concentration ratio and amount of HPβCD. We found that these selected independent variables had great influence on the encapsulation efficiency (EE) as well as drug release (DR) and hence selected as an independent variable. A 3-level 2- factor design was used to derive a second order polynomial equation and constructed 3D surface graph to predict responses. The independent variables selected were the amount of PVPk 30 A[mg], amount of HPβCD B (mg). Encapsulation efficiency (EE) and drug release (DR) were selected as dependent factors. The transformed values of the independent variables and the dependent variable were subjected to multiple regressions to establish a full-model second-order polynomial equation [1,2].

2.1. SPRAY DRYING

Efavirenz nanoparticles were prepared by spray drying technique. The efavirenz and PVPk 30 were first dissolved in ethanol at room temperature. It was sonicated for 10 minutes. HPβCD and citric acid dissolved in distilled water and added into the drug loaded PVPk30 solution by using syringe and stirred for 30 minutes. The formed feed was then stirred for further 1 hour and then spray dried using spray dryer (Spray-Mate, JISL, PVT LTD, Mumbai, India by keeping inlet temperature at $85^{o}C \pm 1^{0}C$ corresponding to an outlet air temperature of $45^{o}C \pm 1^{0}$ C, depending upon the solid composition of the feed. The feed rate was 10 ml/min and aspirator pressure was 2 kg/cm^2 with aspirator speed 1400 rpm [3,4,5,]. The prepared nanoparticles were collected in the collection chamber.

2.2. HIGH PRESSURE HOMOGENIZATION TECHNIQUE

The batches from the spray drying technique having high EE were selected for high pressure homogenization technique under the same parameters. The efavirenz and PVPk 30 were first dissolved in ethanol at room temperature. It was then sonicated for 10 minutes. HPβCD and citric acid dissolved in distilled water and added into the drug PVPk30 solution by using syringe and stirred for 30 minutes then the suspension was passed through the high pressure homogenizer (Panda Plus, GeaNiroSoavi, Italy) at a pressure of 300 to 500 bars for three cycles at room temperature. The solution obtained was collected in a glass beaker and kept on lab

stirrer at room temperature until the evaporation of organic solvent, rinsed with n-Hexane and freeze dried subjected to lyophilizer (Labosene, Scanvac Coolsafe, Denmark) for 48 hr. The recovered nanoparticles were used for further study [6, 7].

2. RESULTS AND DISCUSSION

In this study, attempt was made to mask bitter taste of efavirenz with the sufficiently high encapsulation efficiency by spray dryer method and high pressure homogenization technique. Particles in nanometer size help to increase in bioavailability and permeability because efavirenz is BCS class II drug, whereas the lowest particle size was obtained at 600nm.

Statistical Analysis of Encapsulation Efficiency (EE)

Encapsulation efficiency calculated by using following formula

$$\%\text{Encapsulation efficiency} = \frac{\text{Practical drug loading}}{\text{Therotical drug loading}} \times 100$$

3-level factorial design with two independent variables PVPk 30 and HPβCD at three different levels (-1, 0, 1) was used to study the effects on the dependent variables (Encapsulation efficiency, Drug Release). From the results, the encapsulation efficiency was found to be in the range of 58.43 to 74.21 %. Formulation batches 3, 6, 9, 11 and 13 had good encapsulation efficiency.

The polynomial equation obtained for EE was given by [5].

EE =+52.34389+0.031942 * PVPK 30+2.43889E-003* HPβCD Eq.(1)

The value of correlation coefficient [R^2] was found to be 0.9614, indicating good fit, The result showed that EE affected by the independent variables like PVPk 30 and HPβCD. In regression equation, the main effects of A and B represents the average results of changing one variable at a time from its low level to high level. The negative coefficients of the independent variables indicate an unfavorable effect on the EE while the positive coefficients of the independent variables indicate favorable effect on the EE. the model F value of 22.95 implies the model is significant. The Model F-value of 108.23 implies the model is significant.

There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of" Prob>F" less than 0.0500 indicate model terms are significant.In this case A are significant model terms.Values greater than 0.1000 indicate the model terms are not significant.If there are many insignificant model terms (not counting those required to support hierarchy), the effects of PVPk 30 and HPβCD with their interaction on the EE.The maximum EE could be obtained at highest ratio of HPβCD and PVPk 30. From this, it was clear that as

polymer concentration increases EE increases. We concluded that when polymer concentration was maintained at highest level % EE was found to be 61.76 to 74.21% which was least compared to other levels. The effect of polymer concentration on the EE was found to be significant (P=0.0001). The model P value should be less than 0.05 indicate the significance of the model and terms [8].

3.1 Particle Size

The average particle size of the efavirenz nanoparticles were determined by Particle Size Analyzer (ZetasizerVer System; Serial Number: MAL 1051945; Malvern Instruments Ltd, Malvern, UK) Count Rate (kcps): 557.2, duration used: 40s, cell Description: Disposable sizing cuvette at Attenuator. The particle size of the nanoparticles was obtained in the range of 600-900 nm [9].

3.2Surface Morphology Study

The surface morphology of efavirenz loaded nanoparticles was analyzed by scanning electron microscopy. The nanoparticles were discrete and free flowing in nature. The surface of the nanoparticles was smooth and regular without any erosion and cracking this could be the reason for the taste masking of the drug. No pores were spotted on the surface of the nanoparticles. Due to the lack of pores and cracks there would have been less chances of the drug to leach out from the polymeric coat of the PVPk 30 and HPβCD[10] .

3.3 XRD

XRD patterns of pure Efavirenz showed sharp peaks at 2θ-scattered angles of 5, 13, 20, 24, and 33these peaks are indicating the crystalline nature of drug. These crystalline peaks were decreased in the efavirenz nanoparticles, indicates amorphous nature of the drug after entrapment. Intensities of drug peaks were also decreased in the formulation. This reduced intensity indicates the decreased crystallinity of efavirenz.

4.4 Fourier Transforms Infrared (FTIR) Spectroscopy Study

IR spectra were generally similar in terms of overlapping bands of EFV and PVP K-30, with a predominance of EFV, indicating no interaction between these**.** The FTIR spectra revealed that there was no such interaction between efavirenz, PVPk 30 and HPβCD. Characteristic band of efavirenz were observed at 3314 cm−1 of EFV was present relative to the N–H primary stretching vibration. C-C triple bond stretching at 2250 cm−1, C-O stretching at 1749 cm−1. For PVPk 30 stretching vibration of the carbonyl group that would typically appear around 1689.53 cm–1. 3000–3700 cm−1 due to O-H stretching vibrations of absorbed water. The IR spectrum of pure HPβCD is characterized by prominent peaks at 3412cm^{-1} (O–H), 2929.13cm^{-}

^{1} (C–H), 1645.73cm^{-1} (H–O–H bending), 1032.28cm^{-1} (C–O–C). The identical peaks were also appeared in the spectra of efavirenz nanoparticles [11].

4.5 Taste Masking Ability

In vitro evaluation of the taste masking efficiency of efavirenz nanoparticles was performed in order to determine effective bitterness inhibition. The taste masking ability of prepared nanoparticles was checked by in vitro methods where a delayed drug release from the spherical coating in early 5 min. was considered as main in vitro parameter for successful taste masking. There are several methods reported that have been used for taste masking evaluation of pharmaceutical products, where formulation efavirenz were suspended in the prescribed vehicle for making test sample followed by taste masking intensity rating [14].Efavirenz nanoparticles, equivalent to 10 mg of efavirenz were accurately weighed and dissolved in a volumetric flask containing 25 ml phosphate buffer pH 6.8 and stirred for 5 min. The mixture was filtered and the filtrate was analyzed for efavirenz concentration at 252 nm by UV spectrophotometer [18].Efavirenz release in the phosphate buffer pH 6.8(simulated saliva) was compared to the threshold bitterness concentration of efavirenz. The concentration of drug in the simulated saliva was less than the bitterness threshold of efavirenz, the formulation was considered taste masked. In vitro taste assessment of all the prepared batches was carried out to determine the releases of efavirenz at 5 min in phosphate buffer at pH 6.8

4.6 Phase Solubility Studies

Efavirenz nanoparticles equivalent to 10 mg of efavirenz were accurately weighed 10 mL of aqueous solution, each containing increasing concentrations of each carrier (i.e., 0.01%, 0.05%, 0.1%, 0.3%, 0.5%, 0.7% and 1%) (w/v), with the exception of HPβCD, for which the concentrations tested were 0.01%, 0.05%, 0.1% and 0.3% (w/v), owing to its high viscosity. The samples were sealed in triplicate and shaken in an incubator shaker thermostatically controlled at 25^{0}C for 48hours, and then filtered through a 0.22 µm cellulose membrane filter. The filtrate was suitably diluted and analyzed spectrophotometrically at 252 nm[13].

4.7 Drug Release (DR):

The value of correlation coefficient [R^2] was found to be 0.9558, indicating good fit. The DR values measured for all the batches showed wide variation from minimum 73.12% to 93.72%. The Model F-value of 124.50 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob>F" less than 0.0500 indicate model terms are significant. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.The relationship between the

dependent and independent variables was further elucidated by constructing the 3D surface graph. The polynomial equation obtained for DR was given by[14].

DR= + 66.96521 + 0.019050 * PVPK30 + 0.019811 * HPβCD Eq.(2)

5. Conclusion:

The present study reports the formulation of efavirenz nanoparticles by using spray drying and high-pressure homogenization technique 3level 2 factorial design with the percentage EE of 58.43to74.21%. The release of efavirenz nanoparticles were remarkably faster than pure drug and solubility also increased compared to pure drug. Pure efavirenz was successfully developed and converted into nanoparticles. Thus, use of spray drying and high pressure homogenization technique offers good methods for preparing taste masked substrates of efavirenz. From the present study it was concluded that nanoparticles of efavirenz could be developed and it would bring a reduction in dose and possible side effects of the efavirenz.

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Lyophilized excipient base: a technique for taste masking of oral disintegrating tablet of ranitidine

1. INTRODUCTION

The aim of this study was to formulate ODTs with sufficient mechanical integrity and to achieve faster disintegration in the oral cavity without water. To achieve this goal, lyophilised excipient base was used for the formulation of tablets [1]. Attempts were made to enhance dissolution rate alongwith faster disintegration using to assess the suitability of lyophilised excipient base in the formulation of ODT of ranitidine. Super disintegrants (such as sodium starch glycolate, cross caramellose sodium, avicel), diluents (mannitol) alongwith sweetening agent (aspartame) were used in formulation of tablets. Model drug ranitidine with good aqueous was selected for the studies. H2 receptor antagonist, ranitidine occurs as a white to pale-yellow granular substance with a bitter taste and a sulfur-like odor. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis. The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily. The effective treatment of erosive esophagitis requires administration of 150 mg of ranitidine 4 times a day [2, 3].

Materials

Ranitidine was kindly gifted by Dr. Reddy's Laboratories unit 5, Nalgonda, India. Mannitol, aspartame, Magnesium stearate, Sodium starch glycolate, and HPLC Grade distilled water were purchased from Himedia Laboratories, PVT. Ltd., Mumbai, India. Avicel- PH 101 was purchased from Sigma Aldrich, USA. Cross caramellose sodium was kindly gifted by cellulose pharma. Chem. Jalgaon, India. Sodium hydroxide was purchased from RFCL, Mumbai, India. Potassium dihydrogen phosphate was purchased from MERCK specialties Pvt. Ltd. Mumbai, India. All other solvents and reagents of analytical grade and used as provided.

2. Experimental Design

During the development of the oral disintegrating tablet of ranitidine numbers of initial trials were conducted to mask the bitter taste of ranitidine and disintegration time. The preliminary experiments include the change in avicel, SSG and amount of CCS. We found that these selected independent variables had great influence on the disintegration time as well as taste masking and hence selected as an independent variable. A 3-level 2- factor design was used to derive a second order polynomial equation and constructed 3D surface graph to predict responses. The independent variables selected were the amount of avicel (mg), SSG (mg) and amount of CCS (mg). The transformed values of the independent variables and the dependent

variable were subjected to multiple regressions to establish a full-model second-order polynomial equation. Dependent and independent variables along with different levels are presented [4]. Formulation of tablets by following two methods (i) Direct compression and (ii) Lyophilisation

2.2 Direct Compression

Directly compressible Avicel PH-101, Mannitol, and superdisintegrants like Sodium starch glycolate, cross caramellose sodium were mixed uniformly after passing through sieve no. 120. Ranitidine was added to the above mixture with aspartame and magnesium stearate (0.1%) respectively and compressed into tablets using Kbr press (Technosearch instruments Pvt. Ltd. Thane, India) [5].

2.3 Lyophilisation

Mannitol was dissolved in water using sonicator and requisite quantity of other ingredients viz. Avicel PH-101, SSG, CCS and aspartame (0.1%) were added resulting in formation of a suspension. The suspension was kept in lyophiliser to obtain solid mass of excipient base which was passed through sieve #120. The drug was added to lyophilised excipient bases and after that Magnesium stearate (0.1%) was added as lubricant. Then obtained feed compressed into tablets by using Kbr press to produce tablets weighing 150 mg each [6].

3. RESULTS AND DISCUSSION

Flow properties of the powder can be judged from the angle of repose. The angle of repose < 30° indicates free flowing material and > 40° with poor flow properties. A value for angle of repose for lyophilised excipient base was found in the range of 25.24^{o} to 29.43° showing that the base was free flowing and can be used for direct compression method. The angle of repose for the three different super disintegrants was observed in the order sodium starch glycolate, cross caramellose sodium, Avicel and the lyophilised excipient base showed lower angle of repose (better flow properties) than the excipient alone, which is probably due to increased sphericity of lyophilised dried excipient base which was further supported by scanning electron micrographs. The prepared tablets were evaluated for physical parameters such as weight variation, hardness and friability.

Percent weight variation was observed between 2.4 and 3.2; well within the acceptable limit for uncoated tablets as per USP. Since mechanical integrity is of paramount importance in successful formulation of ODTs, hence the hardness of tablets was determined and were found to be in the range of 2.9—3.7 kg. Friability was observed between 0.71—0.79%, which were below 1% indicating the sufficient mechanical integrity and strength of the prepared

tablets. It was observed that lyophilised excipient base formulations had higher water absorption ratio and take more time for wetting of tablets. Wetting is closely related to the inner structure of the tablets and the hydrophilicity of the excipients. SSG shows its disintegrant effect by the mechanism of "swelling". Increased porosity provides pathways for the penetration of fluids into tablets resulting in "wicking" through capillary action causing faster disintegration of tablets. Using direct direct compression Formulations, showed less wetting time and water absorption ratio (59.64 to 51.32) Ranitidine is hydrophilic drug shows higher absorption ratio and less wetting time.

As the DT is of much importance in the formulation of ODTs, it was tried to keep the DT less than 1 min. The disintegration time (DT) was found in the range of 27 to 36s for the tablets with lyophilised excipient base (L1 to L15) and 27to 36 s for the tablets prepared by direct compression (D1 to D15). The tablets made by direct compression took more time to disintegrate than the tablets made with lyophilised method. It was also observed that tablets with the least wetting time (observed with the tablets made with lyophilised excipient base) also had the minimum disintegration time showing a strong correlation between disintegration time and wetting time. The tablets made from lyophilised excipient base showed the maximum encapsulation efficiency of ranitidine i.e. 89.75% and the tablets made by direct compression showed the minimum encapsulation efficiency (79.28 to 89.55) using the same excipients. In comparison to direct compression tablets containing the same ingredients, a faster drug release was observed from the tablets made from lyophilised excipient base which might be attributed to increased porosity in the lyophilised dried excipient base. The effects of Avicel, SSG, CCS and HPβCD with their interaction on the EE and DT.

3.1 Field Emission Scanning Electron Microscope (FE-SEM)

The surface morphology of ranitidine and ODT tablets were analyzed by scanning electron microscopy. The tablets were discrete and free flowing in nature. Increased sphericity of lyophilised excipient base this could be the reason for the better flow properties. No pores were spotted on the surface of the nanoparticles [7].

3.2 Fourier Transforms Infrared (FTIR) Spectroscopy Study

IR spectra were generally similar in terms of overlapping bands of ranitidine Avicel-101, CCS, and formulation with a predominance of ranitidine, indicating no interaction between these**.** The FTIR spectra revealed that there was no such interaction between ranitidine, avicel-101, and CCS, IR spectrum of Ranitidine hydrochloride showed characteristic bands at 3257.77cm-1, 3192.19 cm-1 and 3095.75 cm-1 (N–H bond), 3014.74cm-1 (C–H furane bond), 2995.45cm-1, 2974.23cm-1, 2945.3cm-1, and 2910.58cm-1 (C–H aliphatic bond). Based on this study we can

state that there is no interaction between ranitidine and CCS used in this study, as there is no change or shift in the characteristic peak of drug [8].

3.3 Taste Masking Ability

In vitro evaluation of the taste masking efficiency of ranitidine ODT tablets were performed in order to determine effective bitterness inhibition. The taste masking ability of prepared tablets was checked by in vitro methods where a delayed drug release from the spherical coating in early 5 min. was considered as main in vitro parameter for successful taste masking. There are several methods reported that have been used for taste masking evaluation of pharmaceutical products, where formulation ranitidine were suspended in the prescribed vehicle for making test sample followed by taste masking intensity rating. Ranitidine tablets dissolved in a volumetric flask containing 25 ml phosphate buffer pH 6.8 and stirred for 5 min. The mixture was filtered and the filtrate was analyzed for ranitidine concentration at 315 nm by UV spectrophotometer. Ranitidine release in the phosphate buffer pH 6.8(simulated saliva) was compared to the threshold bitterness concentration of ranitidine. The concentration of drug in the simulated saliva was less than the bitterness threshold of ranitidine, the formulation was considered taste masked. In vitro taste assessment of all the prepared batches was carried out to determine the releases of ranitidine at 5 min in phosphate buffer ph 6.8 [9].

4. CONCLUSIONS

Taste masked orally disintegrating ranitidine tablets were formulated for more palatable and compliance disintegration in oral cavity. It was concluded that lyophilised excipient base was a better technique for the formulation of orally disintegrating tablets, due to better flow property and enhanced disintegration in comparison to the tablets made by direct compression method. Thus use of lyophilised excipient base offers good method for preparing taste masked substrates of ranitidine.

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Development of reconstituted Powder for oral suspension (PFOS) of taste masked drug - Cyclodextrin Inclusion complex

1. INTRODUCTION:

Ulcers are sores which form in the lining of the stomach (called gastric ulcers), just below the stomach at the beginning of the small intestine in the duodenum (called as duodenal ulcers) or less commonly in the esophagus (called as esophageal ulcers). Ulcers in the stomach and duodenum are referred to as peptic ulcers. A peptic ulcer is an area of the gastrointestinal tract that is usually acidic and thus extremely painful [1-3]. Though the reason for ulceration is varied, as many as 80% of ulcers are associated with *Helicobacter pylori*, a spiral- shaped bacterium that lives in the acidic environment of the stomach.

Famotidine, (An antiulcer drug) has bitter taste act as a competitive inhibitor of histamine H_2-receptors. The primary clinically important pharmacologic activity of famotidine is inhibition of gastric secretion, which in turns reduces irritation of the stomach lining and allows an ulcer to heal. Both the acid concentration and volume of gastric secretion are suppressed by famotidine. Hence histamine H_2 –receptors antagonists like Famotidine, in combination with other drugs are an effective means of treating ulcers [4-6]. Histamine H_2 – receptors antagonists are administered by various means in combination with the other drugs in the body includes liquids, capsules, tablets and sustained release dosage forms, suspensions either readymade or made by dry powder for reconstitution [7].

Advantage of the suspensions made by using dry powder for reconstitution as it reduces the weight the final product because the aqueous vehicle is absent, reducing transportation expenses, its physical stability is less prone to microbial contamination. However, they offer disadvantage of inadequate chemical and physical stability of the drug in an aqueous vehicle resulting very short half life and uneven dosage due to pH changes from chemical degradation, incompatibility of ingredients, viscosity changes, conversion of polymorphic form, crystal growth and caking [8-10].

It is therefore necessary to prepare a formulation that is offered to the patient in form or a powder for oral suspension (PFOS) which is easily bio-available offers immediate effect, has a longer shelf life, permanently stable physical stability, is not susceptible to pH changes from chemical degradation, viscosity changes, conversion of polymeric form and crystal growth, caking and has no incompatible ingredients and is acceptable for pediatrics and elderly patients

2. TASTE MASKING OF FAMOTIDINE

2.1 Drug profile of Famotidine

Category: Antiulcer **Solubility:** Water insoluble

Half life: 2-3 Hr. **Dose:** 20-40 mg

2.2 Experimental work

A) Analytical Method Development of Famotidine: 10 ppm solution of Famotidine was scanned in UV from 200-400nm. Maximum absorption wavelength was found to be 265 nm.

B) Calibration curve of Famotidine in Phosphate buffer (pH 4.5)

C) Phase solubility studies: Solubility studies were performed according to the method described by Higuchi and Connors.

D) Preparation of the Inclusion Complex: By lyophilization technique

2.3 Characterization of Inclusion complex

- Encapsulation efficiency
- FTIR
- XRD
- Particle size distribution

3. Development of reconstituted Powder for oral suspension (PFOS):

The present invention describes a pharmaceutical composition for oral administration in powder form; where in taste of the active pharmaceutical ingredient is masked by Lyophilization technique. The pharmaceutical composition comprising the 2-Hydroxy propyl) –β-Cyclodextrin and Polyvinyl pyrrolidone K-30, which is used as taste masking agent for the unpleasant drug. The composition contains taste masked active pharmaceutical ingredients (Famotidine), Xanthan gum and other pharmaceutically acceptable ingredients and the said pharmaceutical composition is homogeneously distributed for extended period of when dispersed in suitable suspending agent.

3.2 Experimental methods:

- **Excipients used in the PFOS**

a. Active Pharmaceutical Ingredient in the form of taste masked drug: Cyclodextrin Inclusion complex
b. Preservative: Sodium benzoate
c. Sweetener: Sucrose
d. Suspending agent: Xantham gum
e. Flavor: Vanilla

f. Anticaking agent: Silica

3.3 Formulation of PFOS

Formulation of PFOS of taste masked drug: Cyclodextrin Inclusion complex is carried out by using powder blend method. All ingredients are weighed accurately. With the help of the mortar and pestle large sized ingredients are triturated in such a way that they all passed through the required sieve mesh number. After sieving all the ingredients are mixed with geometric mixing. Further mixing is carried out in a polythene bag or suitable blender for sufficient time. The final powder blend of PFOS is weighed and stored in suitable airtight container for further study and use.

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Development and characterization of Fast Dissolving Film of Chitosan embedded Famotidine Using 3^2 Full Factorial Design Approach

Abstract

The aim of the present study was to develop a fast dissolving film (FDF) of taste masked inclusion complex of Famotidine (FMT) using film forming polymer. FDFs were prepared by solvent casting method applying 3^2 full factorial design. Response surface methodology (RSM) was used to optimize the independent variables like chitosan as a film forming polymer and PEG-400 as a plasticizer for dependent variable i.e. *in vitro* drug release (DR).The developed FDFs were characterized for film thickness, disintegration time, FTIR, DSC, XRD, and FESEM analysis.The developed FDFs of FMT were transparent, elegant, smooth and homogenous. Physicochemical characterization of FDFs showed no interaction between the drug and film forming polymer. The drug content was found in the range of 96.05 to 102% and disintegration time was found in pharmacopeial limit, which was less than 1 min. *In vitro* drug release study showed that approximately 82% drug release within 5 min.

1. Introduction

On the basis of Biopharmaceutical Classification System (*BCS*), poorly water soluble drugs can be considered as class II or Class IV drugs. Drug having low water solubility and low bioavailability have been categorized under BCS Class II drugs, once these drugs are dissolved, they rapidly absorbed over the biological membrane such as the gastrointestinal tract. After oral administration these drugs having slow dissolution rate in gastrointestinal tract result in low oral bioavailability due to the poor aqueous solubility [1-4]. Therefore increasing the solubility or dissolution rate of class II drugs can improve the oral bioavailability [5-7].

Famotidine (FMT) is H_2-receptor antagonist, potent histamine having low oral bioavailability and bitter taste. FMT is used for the treatment of ulcers like peptic ulcer and to treat, prevent heartburn due to acid indigestion and sour stomach caused by eating or drinking certain foods or drinks [8-10]. Some of the patients groups, particularly paediatrics and elderly patients may have swallowing problems of the conventional solid dosage form such as tablets and capsules. This leads to the prolonged duration of action and patient's non-compliance, which can be solved through the development of orally disintegrating dosage forms that disintegrate in the saliva and are swallowed without water [11-14].The main objective of this work was to develop fast dissolving film of taste masked inclusion complex of Famotidine using chitosan (CH), biodegradable, film forming polymer. Chitosan is the best known natural polymer used for its versatile applications in pharmaceutical industry. Along with general applications as binder, diluents, wetting agent, disintegrant, preparation of hydrogels, and improvement of dissolution

of poorly soluble drug substances. Chitosan has been used to develop fast mouth dissolving film due to its superdisintegrant property [15, 16].

2. Materials

Famotidine and chitosan were obtained as a gift sample from Lupin Ltd., Pune, India and India Sea Foods, Kochi respectively. Polyvinyl pyrrolidone K-30 (PVP K-30) and Cross carmellose Sodium (CCS) were obtained as a gift sample from Nanhang Industrial, P.R. China and Cellulose Pharma Chem., Jalgaon, India, respectively. (2-Hydroxy propyl) –β-Cyclodextrin (HP-β-CyD), Aspartame and citric acid were purchased from HIMEDIA® laboratories Pvt. Ltd. (Mumbai, India). All other chemicals and reagents were of analytical grade and used as provided.

3. Formulation of Fast Dissolving Film

Fast Dissolving Film (FDFs) of FMT was prepared by solvent casting method [20], Solution – I was prepared by dissolving CH and PEG-400 in 2% aqueous solution of acetic acid and was allowed to stirred for 2 hours. After 2 hours, for removal of the entrapped air bubbles solution was kept for 1 hour at room temperature in crescent condition Solution-II was prepared by dissolving the specific proportion of Complex (equivalent to 10 mg dose), Aspartame as a sweetening agent, and CCS as a superdisintegrant, citric acid, tween-80 and vanilla flavor in distilled water. Solution-I and solution-II were mixed and stirred for 2 hours. Then the solution was casted on mercury and dried for 12 hours. The film was removed from the casting material and cut according to the size required for testing (1cm ×1cm area).

4. Results and discussions

Physicochemical Characterisation of FDFs

Drug polymer interactions were studied by using a FTIR spectrophotometer (Shimadzu, FTIR-8400). X-ray diffraction analysis of samples was carried out by X-ray diffractometer (D8 Advance, Bruker) with Cu Kα radiation (λ=1.54060 A°). Thermal behavior of the sample was determined by Differential Scanning Calorimetry (DSC-60, Shimadzu & 821, Mettler Toledo). Surface morphology of the film was analyzed by Field Emission Scanning Electron Microscope (Hitachi, Model-S4800, Type -II). FDFs was also characterized for Thickness, *in vitro* disintegration time, Drug content uniformity and for *In- Vitro* drug release studies. The *in vitro* disintegration time was carried out in phosphate buffer (pH=6.8). Drug release studies of the FDFs were carried out in a 900 ml dissolution medium of phosphate buffer pH 4.5 and in salivary pH 6.8 by using Tablet Dissolution Tester Apparatus, Type-II (Paddle method, Electrolab, TDT 06) at 37±0.5º C and at paddles speed of 50 rpm. 5 ml sample was withdrawn from the dissolution apparatus at different time intervals (1, 5, 10, 15, 20, 30, 60 min) and

filtered through a membrane filter. The withdrawn sample was replenished with 5mL of fresh media to maintain the sink condition. The drug content was determined at 265 nm by double beam ultraviolet spectrophotometer (Hitachi, U-2900).

5.1 FTIR and XRD Analysis

FTIR spectra and XRD patterns of FMT, CH, CYD, PVP, FL (FDF) and COMPLEX of optimized formulation. Famotidine consists of guanidine, thiazole, thioether and sulfamoyl parts. The spectral position of NH2 groups in guanidine and sulfamoyl depends upon bonded atom or groups to NH2 group. However, its stretching vibrations generally give rise to bands in the region 3550–3250 cm-1, which is disappeared from the spectrum of the inclusion complex. The band observed at 1491 cm-1 is assigned to the C=N stretching vibration of thiazole ring. Further, a shift in the position of the C = N stretching bands in the region of 1528-1636 cm-1 is observed in the IR spectrum of the complex. These spectral changes may have resulted from the inclusion of famotidine within the cavity of HP-β-CyD and the dissociation of the intermolecular hydrogen bonds of famotidine between the guanidine nitrogen and thiazole nitrogen through this complexation. There is no major interaction was found between the drug and polymer in the complex and film. XRD patterns of pure FMT shows the intense peak of crystallinity, whereas decrease in the peak intensity in complex shows amorphous nature of the drug. Intense peak of crystallinity was found in the XRD pattern of chitosan, whereas XRD pattern of film show some intense peak with semi crystalline nature in comparison to pure FMT, which indicates that FMT completely embedded in the chitosan. Slightly amorphous nature of the FMT in film is also responsible for the faster dissolution rate, which leads to the increase in bioavailability of FMT

5.2 DSC and Surface Morphology

DSC thermo grams of FMT, CH and chitosan embedded film (FL). DSC scan of FMT shows Sharp endothermic peak at 163.5 ºC, which is corresponding to the melting point of FMT. Thermogram of film shows sharp single endothermic peak with low intensity, which indicate the homogeneity of the film with the polymer and other film components. The melting point of the FMT in the chitosan film was shifted slightly below the 163.5 ºC due to the physical interaction of FMT and CH, which interrupt the rearrangement of polymer chain due to intermolecular forces. FESEM study revealed that the pure FMT was in crystalline form. Chitosan film of FMT shows uniform distribution of drug in film with porous nature. The pores on the surface of the film are responsible for the fast release of the drug from film. Thickness of the film was found in the range of 8±0.42µm to 10±0.78µm and drug content ranges from 96.05 to 102%, which was in specified limit. Disintegration time of the FDFs was found 14 sec and completely disappeared in 1.5 minute in salivary pH.

5.3 In Vitro drug release study

From the *in-vitro* drug release, it was found that inclusion complex can mask the bitter taste of FMT by retarding the release of FMT in salivary pH=6.8 [17]. The *in vitro* drug released study of optimized film formulation (Run 9) in phosphate buffer pH 4.5 showed approximately 82% drug released within 5 min and 98.57 % in 20 min. This might be due of the fact that Run 9

contained 60% CH, 0.25% PEG and 2% CCS. Chitosan along with CCS reduce the wetting time of the film, which leads to the fast disintegration of film in oral cavity, which is responsible for the faster drug released from the film. From the dissolution profiles of taste masked FDFs as well as of control (pure drug), it was observed that the cumulative percentage drug released in phosphate buffer pH 6.8 was 0.42% in 1 min. while 2.9% in 5 min from FDFs of taste masked preparation. Whereas FDFs prepared with pure drug gives 6.12% in 1 min and 16.32 % in 5 min. This value is more than the FDFs of taste masked complex. This suggests that sufficient taste masking has been achieved and that the bitter taste of the drug will not be perceived while the film was in the mouth after oral intake**.**

Conclusion

In the present work, an approach was used for incorporating the inclusion complex of the poorly water soluble drug into fast dissolving film with the goal of faster dissolution rate. *In vitro* drug released study showed that approximately 82% drug released within 5 min in comparison to the pure drug. Effects of independent variables on dependent variables were screened out by applying response surface methodology. FTIR and DSC studies of the film confirmed the good compatibility between the drug and polymer. FESEM images confirm the uniform distribution of drug in the film with porous nature. These pores are responsible for the fast release of FMT from the film. From the study we can conclude that FDFs formulation could be an alternative approach for the delivery of various drugs for the paediatrics as well as elderly patients which having swallowing problems.

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TASTE MASKING OF EFAVIRENZ BY SPRAY DRYING TECHNIQUE USING ION EXCHANGE RESIN

ABSTRACT

We have prepared fast dissolving tablet of developed complex by direct compression method. Tulsion-335 and amount of Solvent were selected as independent variables while encapsulation efficiency was selected as dependent variable. A 3^2 full factorial design was employed to evaluate the responses. The produced drug resin complex (DRC) was characterized for encapsulation efficiency, X-ray diffraction (X-RD), particle size distribution, Fourier transform infrared (FTIR) spectroscopy, surface morphology by FESEM and in vitro dissolution study. The encapsulation efficiency was found to be 37.98-84.67%. The compressed tablets were evaluated for the hardness, Friability, wetting time, disintegration time and *in vitro* drug release studies. We can conclude that the complexation of drug with ion Exchange resin can effectively mask the bitter taste of drug in combination with the fast dissolving tablets.

Keywords: Efavirenz, Ion-Exchange Resin, Drug-resin complex, Taste masking, Spray drying.

3.INTRODUCTION

Taste of the active pharmaceutical ingredient(API) plays an important role in the suitability/ palatability in its pharmaceutical formulation of oral drug delivery and resulting in compliance issues of patients especially in geriatrics or pediatrics liable for the commercial success of medicament [1-2]. Hence, the general thought to succeed this specific obstruction of a bitter taste at the time of delivering API to patients i.e. taste-masking [3].

Efavirenz, a nucleoside reverse transcriptase inhibitor (NRTI) has bitter taste and low oral bioavailability, one of the most promising antiretroviral drug. The oral dose is 600 mg/day and its bioavailability is 40% [4]. Thus, in present work EFV was selected as a model drug for taste masking study.

One of the popular approaches in the taste masking of the bitter drugs is based on the ion exchange resin (IER). Ion exchange resins are poorly water soluble or insoluble cross-linked polymers that contain acidic or basic functional groups at repeating positions on the polymer chain [5-6]. Depending upon the nature of the exchangeable ion of the resin like cation or anion, they are classified as cationic and anionic exchange resins respectively [7]. The degree of cross-linking and particle size of the resin substantially modifies its properties and

applications. Apart from the taste masking properties, ion exchange resins can also be used to enhance the solubility of poorly water-soluble drugs, deliquescence, and poor dissolution of the drugs. Due to their swelling properties, resins are used as superdisintegrants in tablet dosage form [8-9]. Weak acid cation exchange resin, Tulsion-335 (crosslinked polyacrylic copolymer backbone) containing carboxylic group have been used as a taste masking agent and to develop fast release dosage form. Ion exchange reaction takes place during the formation of DRC. The drug is released from the DRC by exchanging the ions in gastric fluid [10]

Generally, two methods are used for the loading of drugs into ion exchange resins i.e. column method and batch method [11]. In the present study batch method was used followed by spray drying. Spray drying is one of the widely-used process in pharmaceutical and biochemical fields as well as in the food industry because of the potential utilization of moderate conditions and easy automation to create crude medication or excipients. It is a one-stepprocess to move from a liquid feed into a dry product [12-14].

2. MATERIALSAND METHOD

2.1 Materials

Efavirenz and PVP K-30 was obtained as a gift sample from Cipla Limited, Mumbai, India and Nanhang Industrial, P.R. China respectively. Commercially available cation exchange resin (Tulsion-335) containing crosslinked polyacrylic backbone was used as a taste masking agent. Avicel 101 and Silicon dioxide amorphous (Silica, fumed) were purchased from Sigma-Aldrich. Magnesium stearate and Aspartame were purchased from HIMEDIA® laboratories Pvt. Ltd. Mumbai, India. Double distilled water was used throughout the experiment. All other chemicals and reagents were of analytical grade and used as provided.

2.2 Methods

2.2.1 Experimental Design

During the development of the DRC, a number of initial trials were conducted to improve the encapsulation efficiency of efavirenz. The preliminary experiments included the change in concentration of Tulsion and solvent concentration ratio. We found that these selected independent variables had great influence on the encapsulation efficiency (EE) and hence selected as the independent variable. To optimize the formulation variables, a 3^2 full factorial design was applied for the development of taste masked DRC complex of Efavirenz using Design-Expert® Software (Stat-Ease Inc., Minneapolis,) which allows evaluation by nine experiments in order to limit the number of experiments. Response surface methodology (RSM) was used for the analysis of results. The effect of two independent variables was studied

such as concentration of Tulsion (A, w/v %) and Solvent (B, ml) with respect to drug. These statistical models were used to evaluate the effect of independent variables on the dependent variables like encapsulation efficiency (Y_1, %). The significance of the model was determined by the comparisons of statistical parameters, and the best model (suggested) was decided based on reasonable agreement between adjusted R^2 and predicted R^2 ; higher values of adjusted R^2 , predicted R^2; model p value (should be less than 0.05) and small PRESS value of the model. PRESS is a measure of the fit of the model to data points in the design. The PRESS for the chosen model should be small relative to the other models under consideration. Three-dimensional (3D) response plots and two-dimensional (2D) contour plots resulting from the equations were constructed using Design-Expert® software [15-17].

2.2.2 Purification of Ion Exchange Resin

Tulsion-335 was washed with distilled water. The wet resin was activated by 500 ml of 0.1 M HCl followed by washing with distilled water and dried in hot air oven at 50°C overnight. The dried resin was stored in an air tight container [10, 18].

2.2.3 Preparation of Taste masked DRC of Efavirenz

In order to prepare Taste masked DRC of EFV with Tulsion spray drying technique was employed [19]. At first, accurately weighed quantity of EFVwas dissolved in distilled water and ethanol (1:3) to get a clear solution according to the design.

Subsequently, Tulsion was dispersed into clear solution of EFV and stirred at 1200 rpm on magnetic stirrer for 24h at room temperature. Finally, spray drying was performed according to the parameters by using programmable spray dryer (Spray Mate, Make JISL, and Mumbai). The product obtained was kept in desicator over silica gel till further study. Spray drying yields micro/nano particle of narrow size distribution with proper selection of atomizer and operating conditions and characterized by high encapsulation efficiency [20].

2.2.4 Formulation of Tablets

Fast Dissolving Tablets (FDTs) of DRC and conventional tablets of pure drug with excipients were prepared by direct compression method with a theoretical weight of 500 mg of each tablet [18]. Each tablet of different batches contain 400 mg of the DRC (equivalent to 100 mg of EFV), lubricant (1% Magnesium stearate), sweetening agent (1% Aspartame), flavor (0.5% Mint) and superdisintegrants (1-3% Cross carmellose sodium)**.** Anhydrous lactose was used as a diluent and Avicel pH 101 as directly compressible material. Finally, 500 mg of each blend was weighed and compressed manually in KBr press with 13 mm flat, round, single punch. The maximum compaction load was 400-500 KN.

3. EVALUATION OF TASTE MASKED DRUG RESIN COMPLEX

3.1 Determination of Efavirenz in DRC by HPLC

The amount of EFV was analyzed using a reversed-phase HPLC system (YL-9300) assembled with UV-detector (YL9120 UVD). EFV was separated at room temperature on ODS Hypersil C-18 column (4.6mm×250mm, 5µ) (Thermo Scientific, USA) keeping the flow rate at 1ml/min and analyzed at 252 nm. The mobile phase consists of 70 % v/v of acetonitrile and 30% v/v of aqueous solution containing 0.86 % Amonium dihydrogen phosphate. The pH of aqueous mobile phase was maintained at 3.5±0.1. An external calibration curve was constructed by plotting the EFV peak areas versus the known concentrations (2-10 ppm) of the drug with regression coefficient (R^2) 0.999 [21].

3.2 Encapsulation efficiency (%EE)

The amount of EFV encapsulated into the DRC was determined by HPLC. An accurately weighed 10 mg equivalent of DRC was stirred with 100 ml of ethanol and water (3:1) to dissolve the drug, sonicated for 10 minute and extracted in phosphate buffer solution (pH 4.5). Stirring was continued for 30 min to facilitate the evaporation of organic solvent. The dispersion was filtered, and residue was washed with phosphate buffer solution. The % EE was determined in the filtrate after appropriate dilution with phosphate buffer solution at 252 nm using HPLC. The encapsulation efficiencywas calculated using the following equations [22].

$$\%\text{EE} = \frac{\text{weight of drug in DRC}}{\text{theoretical weight of drug}} x\ 100 \qquad \textbf{I}$$

3.3 Particle Size and Zeta Potential

Particle size and Zeta Potential was determined by Particle size analyzer (Zetasizer, Malvern ZS 200). DRC and Pure EFV were dispersed in distilled water and analyzed by particle size analyzer at room temperature [23].

3.4 Field Emission Scanning Electron Microscope (FESEM)

The morphology of DRC and pure EFV was investigated by field emission scanning electron microscope (FESEM-S 4800, Hitachi, Japan) at a working distance of 8.6–8.7mm and accelerating voltage of 1.0 kV. The samples were gold-coated prior to imaging. The Samples were mounted on metal stub using double sided adhesive tape and images were captured at different resolutions [21].

3.5 Fourier Transforms Infrared (FTIR) Spectroscopy Study

Functional group analysis was studied using FTIR spectrophotometer (Shimadzu, FTIR-8400). FTIR analysis of the pure drug, DRC, and Tulsion was carried out by KBr pellet

method. Sample (2 mg) was mixed with KBr (100mg) and compressed into disc in a manual press. The spectrum was scanned from 4000 to 400 cm^{-1}[21].

3.6 X-Ray Diffraction Analysis

In order to confirm the formation of new solid state; crystalline or amorphous nature of the EFV in TMC, pattern of XRD of pure EFV, GLY, PVPK-30 were obtained by X-ray diffractometer (D8 advance, Bruker,) with Cu Kα radiation (λ=1.54060 A°). Data collection was performed using Cu anode at monochromatorvoltage of 40 kV. The deflection pattern was determined in the area $2^0 < 2\theta < 80^0$, using continuous scanning rate of 10°/min [21].

3.7 Evaluation of taste by *in vitro* drug release study

In-vitro drug release test could be a good substitute for taste assessment especially for this type of formulation where drug release is prevented or delayed in the oral cavity by encapsulating the drug in polymer. Bitterness of drug release medium was calculated by measuring drug release and comparing it with bitterness threshold concentration. *In vitro drug* release from DRC in the phosphate buffer pH 6.8(simulated saliva) was compared to the threshold bitterness concentration of pure drug. If the concentration of drug in the phosphate buffer pH6.8 (simulated saliva) was less than the bitterness threshold of efavirenz (pure drug), then the formulation was considered as taste masked [24-25].

According to FIP/AAPS (Federation International Pharmaceutique/American Association of Pharmaceutical Sciences) guidelines, dissolution values of an early time point (e.g.≤5 min) can be used to establish the approximate baseline of taste [26].

3.8*In Vitro* Dissolution Studies

Drug release studies were performed in fully calibrated eight station dissolution test apparatus (USP type II) assembled with auto sampler (Eletrolab, Mumbai India) at 37±0.5 ^{0}C and at paddles speed of 75 rpm. DRC and pure EFV were placed into dissolution bowl and test was performed for 1h in 0.5% SLS in 900ml distilled water.

Total 10 ml of aliquots from each bowl (2ml for rinse and 8ml for analysis) were pulled out at predetermined time intervals (5, 10, 15, 20, 30 and 60 min.) and replenished with the same amount of fresh dissolution media to maintain the sink condition. The samples were filtered through 0.22 μ (PVDF, 25mm) syringe filter and directly injected into the HPLC system for the analysis. The EFV concentration in each unknown sample was calculated using a pre-estimated calibration curve at 252nm.

3.9 Physiochemical evaluation of FDTs of EFV

The prepared FDTs were characterized for hardness, weight variation, friability, wetting time, drug content and disintegration time. Tablet hardness was obtained using Monsanto hardness tester. Friability was determined on Roche friabilator (Adinath industries, Mumbai, India) at a speed of 100 rpm for 4 min. Disintegration time was determined by using tablet disintegration test apparatus (Veego, VTD-2, Mumbai, India).

3.10 Wetting Time and water absorption ratio of FDTs

A piece of tissue paper (10.75 cm × 12 cm) folded twice was placed in a petridish of 9 cm internal diameter containing 6 mL of simulated saliva (pH 6.8). A weighed tablet was placed on the upper surface of the tissue paper and the time for complete wetting was measured. The wetted tablet was again weighed. Wetting time of each batch was calculated in triplicate. Water absorption ratio (R) was determined by using following equation [27]:

$$R = 100 \times (W_a - W_b)/ W_b \ldots\ldots \quad (2)$$

Where, W_a= Weight of tablet before wetting

W_b= Weight of tablet after wetting

4. RESULTS AND DISCUSSION

In this study, attempt was made to mask the bitter taste of efavirenz by ion exchange resin, Tulsion-335, with the sufficiently high encapsulation efficiency by spray drying.

4.1 Statistical Analysis of Data

Using 3^2 factorial design, total nine runs were carried out for the preparation of DRC and investigated the effects of two independent variables on the dependent variable (response) using factorial design [28]. The Quadratic mathematical model (suggested) generated by 3^2 factorial design was used to evaluate the response(%EE):

$$Y = \beta_0 + \beta_1 A_1 + \beta_2 B_2 + \beta_3 A_1 B_2 + \beta_4 A_1^2 + \beta_5 B_2^2 \quad (VI)$$

Where, β_0 is the intercept; β_1 to β_5 are the estimated coefficient obtained from the observed experimental values of *Y*; *A* and *B* are the coded levels of the factor. A study showed that the formulation parameters had an influence on the encapsulation efficiency. The Quadratic model describing the correlation between the formulation variables and the response can be represented by the following equation-

$$Y = 71.94 + 14.89A - 3.06B + 0.19AB - 4.13A^2 - 12.12B^2 \quad (VII)$$

The equation represents the quantitative effects of factor (A and B) upon the response (Y). The sign of the coefficient shows how the factor influences the response. If the coefficient is positive, the response has increased (synergistic effect) as the factor moves from low level (−1) to high level (+1); the contrary is obtained (inverse relationship/antagonist

effect) if the coefficient is negative. Linear, cross-product contribution (2FI), quadratic and cubic models were generated for the responses by the software. The Quadratic model (**p-value=0.0019)** showed a best fit for the response %EE.

P-values and ANOVA of each factor for the measured responses. Significant values indicated in bold faces. Significant factors affecting the response Yis A (amount of Tulsion (mg), **p-value = 0.0003**) and B (amount of Solvent (ml), **p-value = 0.0317**). To validate the model, all the points were selected and observed their experimental and predicted value for the responses.

The prediction point of experimental and predicted values for the responses. Therefore, it can be concluded that the model is best suitable because of the difference between experimental and predicted value is very low [29],[22].

*Percent prediction error = (Experimental value − predicted value)/experimental value×100

3D response surface and 2D contour plots was constructed to visualize the effect of independent variables on response. 3D response surface plot gives the idea about interaction effects of the independent variables whereas visual representation of the values of responses was given by 2D contour plots. Effect of tulsion and solvent on %EE is shown in. From the3D response surface plot and 2D contour plotit was observed that %EE was increases with increase in amount of tulsion concentration and decreases with increase in amount of solvent.This might be due to the swelling of resin containing carboxylic group. As the concentration of solvent increases, leaching of drug takes place from the DRC due to the dilution of the complex. %EE of the EFV in complex ranges from 37.98% - 84.67 % of all the experimental runs.

4.3 Particle Size and Zeta potential

The particle size of pure drug and DRC. It was found that particle size of the pure drug ranges in between 458.7 (d.nm) to (712.4 d.nm). While after preparation of DRC of EFV with the resin, bi-phases particles were observed. The average particle size of DRC was found to be 164.2 nm. One phase of particle size ranges from 141.8 nm to 255 nm while second phase particle size ranges from 615.1(d.nm) to 955.4(d.nm). By comparing DRC particle size with the particle size of pure EFV, it could be concluded that amount of EFV which was not formed complex due to the increase in concentration of solution by mixing with resin, which resulted in bigger particle size but at less/negligible amount. Thus reduction in particle size of the pure drug increases surface area. The zeta potential of the optimized batch of DRC was found to be -20.9mV resulted stability of DRC [30].

8.3.4 Surface Morphology Study and FTIR study

The surface morphology of DRC and EFV was analyzed by scanning electron microscopy. It was observed that DRC prepared by spray drying technique was spherical in shape, discrete and free flowing in nature. The surface of the particles of DRC was smooth and regular without any erosion and cracking. This could be the reason for the taste masking of the drug. No pores were spotted on the surface of the nanoparticles. Due to the lack of pores and cracks there would have been less chances of the drug to leach out from the DRC.

FTIR spectra were generally similar in terms of overlapping bands of EFV and Tulsion with a predominance of EFV, indicating no interaction between these**.** The FTIR spectra revealed that there was no such interaction between efavirenz and Tulsion. Characteristic band of efavirenz were observed at 3314 cm^{-1} of EFV was present relative to the N–H primary stretching vibration. C-C triple bond stretching at 2250 cm−1, C-O stretching at 1749 cm−1. The identical peaks were also appeared in the spectra of DRC [31].

4.5X-Ray Diffraction

The X-ray diffraction pattern of pure EFV, DRC and Tulsion. XRD patterns of pure Efavirenz showed sharp peaks, indicating the crystalline nature of drug.

These crystalline peaks were decreased in the DRC, indicates amorphous nature of the drug after complexation. This reduced intensity indicates the decreased crystallinity of efavirenz. As the change in nature of EFV in DRC from crystalline to amorphous, also support the masking of bitter taste of EFV by ion exchange resin complexation approach [32].

4.6Taste Masking Ability

In vitro evaluation of the taste masking efficiency of DRC was performed in order to determine effective bitterness inhibition. The taste masking ability of prepared DRC was checked by *in vitro* methods where delayed drug release from the DRC in early 5 min was considered as main in vitro parameter for successful taste masking. There are several methods reported that have been used for taste masking evaluation of pharmaceutical products, where formulation of efavirenz was suspended in the prescribed vehicle for making test sample followed by taste masking intensity rating. DRC and pure EFV equivalent to 10 mg of efavirenz were accurately weighed and dissolved in a volumetric flask containing 25 ml phosphate buffer pH 6.8 and stirred for 5 min. The mixture was filtered and the filtrate was analyzed for efavirenz concentration at 252 nm by UV spectrophotometer [33].

Efavirenz release in the phosphate buffer pH 6.8(simulated saliva) was compared to the threshold bitterness concentration of efavirenz. The concentration of drug in the simulated saliva was less than the bitterness threshold of efavirenz, then the formulation was considered

taste masked. *In vitro* taste assessment of the optimized batch was carried out to determine the releases of efavirenz at 5 min in phosphate buffer pH 6.8. [24, 34].

4.7Evaluation of FDTs of EFV

All the tablet formulations showed acceptable physicochemical properties and met the pharmacopoeial requirement of hardness, thickness, weight variation and drug content. *Invitro* wetting time of all the formulations were found to be within the acceptable limits (less than 1 min) of FDTs. The Batch F_3 having maximum concentration of Crosscarmellose sodium (CCS)shows the minimum disintegration time of 16.74 sec. This might be due to the fast swelling capability of CCS in contact with water.

In vitro drug release profile of prepared FDT and conventional tablet of EFV in phosphate buffer pH=4.5**.** Drug releasefromprepared FDT and conventional tablet of EFV was found to be more than 80% and 35% respectively within 5 min. After comparing drug release behaviour, it can be concluded that dissolution rate of the FDT of EFV was nearly 2 fold higher than conventional tablet of EFV.

5. CONCLUSIONS

- The present study reports the formulation of taste masked DRC of efavirenz by using spray drying.
- Efficient taste masking was achieved with encapsulation efficiency more than 80% and that can be formulated as fast dissolving tablets dosage form for better patient compliance.
- The zeta potential of the DRC was found to be -20.9 mV, resulted stability of the DRC.
- Statistical analysis of data suggested quadratic model.
- Dissolution study confirmed that FDT shows better dissolution profile of EFV as compare to conventional tablets.
- Disintegration time of FDT was found to be less than 1 min.
- All the tablet formulations showed acceptable physicochemical properties and met the Pharmacopoeial limits.

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Solubility Enhancement of Olanzapine by Spray Drying Technique Using Screening Design

Abstract

The Aim of the present study was to prepare olanzapine (OLZ) solid dispersion (SD) by spray drying technique to enhance the solubility of OLZ. Olanzapine is a psychotropic agent having low water solubility hence, slow dissolution rate and oral bioavailability. To increase the water solubility and dissolution rate of the OLZ, solvent evaporation method was used for the preparation of solid dispersion of OLZ using spray drying technique. Plackett–Burman screening design (PBD)was used to optimize the independent variables like polyvinylpyrrolidone K-30 (PVP K-30) and mono amino glycyrrhyzinate pentahydrate respectively, for dependent variables like Encapsulation efficiency (%EE) and solubility (mg/ml) by using Design Expert software.Prepared SD was characterized for solubility, %EE, X- ray diffraction (X-RD), Fourier transform infrared spectroscopy (FTIR). Result of XRD confirmed the successful incorporation of drug in the SD. Solubility of OLZ in SD (11.51 mg/ml) was found nearly 11 fold higher than pure OLZ (0.983 mg/ml) while %EE was found 64 to 90%.Statistical analysis of the data (ANOVA) indicates an adequate model fitting predicting the effect of process parameters affecting the solubility and %EE. In conclusion, spray dried solid dispersion can effectively increases the solubility as well as dissolution rate of the OLZ.

1.Introduction

According to the Biopharmaceutical Classification System (BCS) many new drugs can be considered as class II or Class IV drugs. BCS Class II drugs are poorly water soluble but once these drugs are dissolved, they rapidly absorbed over the biological membranes such as the gastrointestinal tract. After oral administration due to the poor aqueous solubility these drugs having a slow dissolution rate in gastrointestinal tract result in low oral bioavailability [1-2]. Solubility is the key factor in determining the rate and extent of absorption of BCS class II drugs. Therefore increasing the solubility or dissolution rate of class II drugs can improve the oral bioavailability [3-4]. Several techniques are used to increase the solubility of poorly water-soluble drugs and thus improve its bioavailability such as (a) particle size reduction to increase surface area, (b) complexation with cyclodextrin, (c) salt formation, (d) use of Prodrugs, (e) pH adjustment, (f) self- emulsifying formulations, (g) use of surfactants and change in solid form such as nanocrystals, preparation of liposome and solid dispersion. Solid dispersion is

one of the approaches to increase the dissolution rate of poorly water soluble drugs. Solid dispersion may be defined as dispersion of active ingredients within an inert carrier in solid state [5-7].

The improvement of solubility and dissolution rate of drugs from solid dispersions is based on mainly three different mechanisms include increased wettability of drug due to direct contact with hydrophilic carrier, the reduction in particle size results increased surface area, and the conversion of crystalline state to more soluble amorphous state. Solid dispersion is a viable and economic method to enhance bioavailability of poorly water-soluble drugs and also overcomes the limitations of the previous approaches [8-9]. Numbers of strategies are used for the preparation of nano sized drug particles, which are classified as bottom- up, top-down, combination approaches and chemical synthesis. Most of the top-down process requires high energy input where the drug particles are broken down into smaller size by the use of high pressure homogenization, pearl milling and wet ball milling. Disadvantage of the top-down process is the requirement of high energy for the reduction of particle size, chemical degradation by milling and more possibility of the contamination by grinding media. On the other hand Bottom-up processes are basically precipitation processes, where drug is dissolved in an organic solvent and the precipitation of the drug particles occur by the addition of antisolvent in the presence of stabilizer from the supersaturated solution of drug. Various adaptations which increase the precipitation such as solvent- evaporation, reduction in temperature or by addition of antisolvent [10-11]. Drug crystal size cannot be controlled in this process which is the disadvantage of most currently applied bottom-up processes, therefore, amorphous solid dispersion was prepared to overcome these disadvantages [12-13].

Olanzapine is a relatively new benzodiazepine a typical antipsychotic medication, which belongs to the class of the thienobenzodiazepines and has proven efficacy against the positive and negative symptoms of schizophrenia other forms of psychosis. It exhibits poor water solubility and belongs to biopharmaceutical classification system (*BCS*) class II of drugs having low solubility and high permeability, highly bound to plasma protein about 93% [14-15]. Thus, in the present study SD of OLZ with the polyvinylpyrrolidone K-30 (PVP K-30) and mono amino glycyrrhyzinate pentahydrate was prepared by bottom-up process based upon spray drying.

2. Materials and Method

2.1 Materials

Olanzapine was obtained from SP Pharmaceuticals, Jalgaon, India as a gift sample. PVP K-30 and Mono amino glycyrrhyzinate pentahydrate (GLY) were donated as a gift sample

by Nanhang Industrial, P.R. China and Sami Labs, (Bangalore, India) respectively. Silicon dioxide amorphous (Silica, fumed) were purchased from Sigma-Aldrich. Double distilled water was used throughout the experiment. All other chemicals and reagents were of analytical grade and used as provided.

2.2 Design of Experiment

In order to screen the factors, Plackett–Burman design (PBD) was employed using Design-Expert® Software (Stat-Ease Inc., Minneapolis, MN) which allows the evaluation by total 12 experiments. The purpose of PBD is to evaluate the effect of the processing variables and identify the key one influencing the responses like solubility and encapsulation efficiency. The amount of GLY (A, mmol), PVP K -30 (B, w/v %), Nozzle diameter (C, mm), Flow rate (D, ml/min), Aspiration speed (E, rpm), Inlet temperature (F, ºC) &solvent (G, ml), were selected as independent variables and solubility (Y_1, mg/mL) and encapsulation efficiency (Y_2, %EE) were dependent (Response) variables. The significance of the PBD design was determined by the comparisons of statistical parameters and on the basis of higher values of R^2. Two-dimensional (2D) contour plots and three-dimensional (3D) response plots obtained from the equations were fabricated using Design-Expert® software. Following polynomial model is used to correlate the dependent and independent variables [16-17].

$$Y=A_0 + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_4 + A_5X_5 + \ldots + A_nX_n \quad (1)$$

(Where Y is the response, A_0 the constant and A_1-A_n are the coefficients of the response values)

2.3 Preparation of Solid dispersion of olanzapine (OSD)

In order to prepare OSD with PVP K-30 and GLY spray drying technique was employed [4]. At first, accurately weighed quantity of PVP K-30 and GLY were dissolved in distilled water and ethanol (1:3) to get a clear solution according to the design. Subsequently, OLZ was dispersed into clear solution of PVP K-30 and GLY and stirred for 30 minutes at room temperature. Secondly, immediate after stirring, Silicon dioxide (300 mg) was added into the dispersion of OLZ. Finally, spray drying was performed according to the parameters by using programmable spray dryer (Spray Mate, Make JISL, and Mumbai). The product obtained was kept in desiccator over silica gel till further study.

3. Physical characterization of solid dispersion

3.1 Saturation solubility studies

Solubility studies of OLZ were performed according to the method described by Higuchi and Connors [18]. Excess amount of OLZ was added into water containing different concentration of GLY (mmol), PVP K -30 (%) respectively. Initially, samples were sonicated at room temperature for 5 min using water bath sonicator (Leela Electronics, Leelasonic 60).

Subsequently by using incubator shaker (Remi Instrument, Mumbai) shaking was performed for 48 hrs. at 27 ± 2 °C.5 ml aliquots were withdrawn at equilibrium condition and passed through syringe filter (PVDF) 0.22μm. The amount of OLZ dissolved was analyzed spectrophotometrically (UV/Visible Spectrophotometer, U-2900, Hitachi, Japan) at 256 nm.

3.2 Encapsulation efficiency (%EE)

The amount of OLZ encapsulated into the OSD was determined by UV. An accurately weighed quantity of OSD equivalent to 10 mg OLZ was stirred with 10 ml of ethanol and extracted in phosphate buffer solution (pH 6.8). Stirring continued for 30 min to facilitate the evaporation of organic solvent. The dispersion was filtered and residue was washed with phosphate buffer solution. The %EE was determined in the filtrate after appropriate dilution with phosphate buffer solution at 256 nm using UV/Visible Spectrophotometer. The encapsulation efficiency (%EE) was calculated using the following equations:

$$\%\text{EE} = \frac{\text{weight of drug in OSD}}{\text{theoretical weight of drug}}\ x\ 100 \qquad \textbf{I}$$

3.3 Fourier transforms infrared spectroscopy (FTIR)

Functional group analysis was studied by using a FTIR spectrophotometer (Shimadzu, FTIR-8400). FTIR analysis of the OLZ, OSD GLY, and PVP K-30 was carried out by KBr pellet method. Sample (2 mg) was mixed with KBr and compressed into a disc in a manual press. The spectrum was scanned from 4000 to 400 $cm^{-1.}$

3.4 X- ray diffraction analysis

In order to confirm the formation of new solid state; crystalline or amorphous nature of the OLZ in OSD, pattern of XRD of pure OLZ, GLY, PVPK-30 were obtained by X-ray diffract meter (D8 advance, Bruker,)with Cu Kα radiation (λ=1.54060 A°). Data collection was performed using Cu anode at monochromator voltage of 40 kV. The deflection pattern was determined in the area $2^0 < 2\theta < 80^0$, using continuous scanning rate of 10°/min.

3.5 *In-Vitro* drug release studies

Drug release studies were performed in fully calibrated eight station dissolution test apparatus (USP type II) assembled with auto sampler (Eletrolab, Mumbai India) at 37±0.5 ^{0}C and at paddles speed of 50 rpm. OSD and pure OLZ were placed into dissolution bowl and test was performed for 1h in 0.1 N HCl (pH 1.2).

Total 10 ml of aliquots from each bowl (2ml for rinse and 8ml for analysis) were pulled out at predetermined time intervals (5, 10, 15, 20, 30 and 60 min.) and replenished with the same amount of fresh dissolution media to maintain the sink condition. The samples were

filtered through 0.22 μ (PVDF, 25mm) syringe filter and OLZ concentration in each unknown sample was calculated using a pre-estimated calibration curve at 256 nm.

4. RESULTS AND DISCUSSION

4.1 Statistical Analysis of Data

In a multivariable system PBD is powerful and useful mathematical tool for the determination of key factors on a particular response generated by conducting a smaller number of experimental trials, but this method does not determines the exact quantity, it provides some essential evidence about each factor by performing comparatively few experiments [19].

In the present study, each variable was investigated at two levels namely high level (+1) and low level (−1). The effects of 7 independent variables on dependent variables (response) were investigated by 12 runs of experiments. The factors under investigation as well as the level of each factor used in the experimental design. The factor ranges were selected based on prior knowledge from the initial trial experiments. The polynomial equations were generated for each response which describes the correlation between the formulation process variables, solubility and encapsulation efficiency. The polynomial equations for the responses are represented as follows-

$$\mathbf{Y_1=3.43+1.44A+0.95B-1C+1.12D+0.069E+1.31F-0.85G-0.69J-0.77L} \quad \mathbf{(3)}$$

$$\mathbf{Y_2=79.32+2.15A+0.79B-4.11C+6.10D-1.40E+1.83F-1.07G+2.38H+0.84J} \quad \mathbf{(4)}$$

These equations represented the quantitative effects of independent variables on the responses (Y_1 and Y_2). Both signs of the coefficient show how the factors influenced the response. If the coefficient is positive, the response is increased (synergistic effect) as the factor moves from low level (−1) to high level (+1) and vice-versa (inverse relationship/antagonist effect) if the coefficient is negative[4, 19].

From above equation **(3)**, it can be observed that the solubility (Y_1) was influenced by the factors like A, B, C, D, F, G, dummy factor J and L. Likewise from the equation **(4)**, factors A, C, D, F and dummy factor H show the significant effect on the % EE (Y_2). Dummy factor is the unknown factor which affects the solubility and % EE during the formulation process. Results of analysis of variance (ANOVA), p- value, F-value, mean square are the solubility and % EE respectively. Correlation coefficient (R^2) value for the solubility and % EE are found to be $R^2 = 0.9956$and $R^2 = 0.9968$respectively.

4.2 Characterization of the solid dispersion (OSD)

4.2.1 Solubility (Y_1, mg/ml) and Encapsulation efficiency (Y_2, %EE)

It was observed that solubility of the OLZ in OSD increases with increase in concentration of PVP K-30 and GLY whereas %EE was increases with increase in amount of PVP K-30 and decreases with increase in amount of GLY [20]. This might be due to the more time taken for the precipitation of GLY, which was in higher amount. Solubility OLZ in OSD ranges from 1.44 mg/ml to11.51 mg/ml. The enhancement of drug solubility in the hydrophilic carrier could also be equally well explained by co-solvency effect of the carrier. It was also suggested that the hydrophilic carriers may interact with the drug molecules by electrostatic bonds and other types of bonding such as Van der Waals forces, and this was the likely cause for the formation of weakly soluble complexes [21].

The %EE decreases with an increase in the amount of GLY due leaching of drug from the OSD. The percent encapsulation efficiency of the OSD of OLZ was ranged from 64 to 90 % of all the experimental runs.

4.2.2 Fourier transforms infrared spectroscopy (FTIR)

FTIR analysis was conducted to study the change in the structure before and after the drug loading due to the change in bonding between functional groups. Pure OLZ showed characteristic absorptions at 3239 cm^{-1} (NH and OH stretching), 2929 cm^{-1} (C–H stretching), 1587 cm^{-1} (C=C stretching), 1421 cm^{-1} (C=N stretching) and 1287 cm^{-1}(C–N stretching). The characteristic peaks of pure OLZ were found to be present in the spectra of solid dispersions. This finding reveals the lack of interaction between the drug and the carrier in the samples. It was also noticed that the significant peaks of pure drug at specific wave number (3239 cm–1) was found to be in reduced form, with less sharpness and more broadness as the amount of hydrophilic carrier was increased in the OSD [22].

4.2.3 XRD

The XRD patterns of the drug-loaded samples were recorded to determine whether a crystalline OLZ phase could be detected. The diffraction pattern of pure OLZ was highly crystalline in nature as indicated by the numerous peaks were visible.

Less distinctive peaks was observed in OSD indicates the amorphous nature. However, no crystalline OLZ was detected in OSD. It is known that the absence of distinctive peaks indicates that the OLZ loaded into the PVPK-30 and GLY solid dispersion was in an amorphous state [23]. The absence of OLZ peaks in OSD may be largely attributed to the hydrogen bonding of the amine- groups to the carboxyl groups of OLZ leading to disordering of the encapsulated OLZ as well as encapsulation of OLZ [24-25]. Change in the physical state

from crystalline to the amorphous state largely attributed to the formation of amorphous solid dispersion of olanzapine. Hence conversion of crystalline to amorphous nature of the OLZ in OSD is responsible for higher solubility and dissolution rate as compared to pure drug.

4.2.4 *In vitro* drug release study

The % cumulative release of pure OLZ was found to be 40 % in 1 h while solid dispersions showed a significant increase in dissolution rate of OLZ in solid dispersion. The percentage of drug release from OSD was nearly 90% in 1 h. As the amount of hydrophilic carrier in solid dispersion was increased, dissolution rate of OLZ also increased. This is due to the formation hydrophilic diffusion layer around the drug particles by hydrophilic carrier PVP K 30. Results change in hydrophobic nature and increased wettability of drug within the dissolution medium. The factors like amorphous nature, prevention of aggregation and agglomeration of the drug by the carrier are also responsible for the enhanced dissolution rate from the solid dispersions [6].

5. Conclusion

In this study, solid dispersion of OLZ was successfully prepared by spray drying technique and the effects of independent variables on dependent variables have been screened out by employing Plackett–Burman design. Also, it has met great success in regards to solubility, dissolution rate and encapsulation efficiency of drug. Encapsulation efficiency and solubility study revealed that both are dependent on concentration of PVPK-30 and GLY. Solubility of OLZ in OSD (11.51 mg/ml) was found nearly 11 fold higher than pure OLZ (0.983 mg/ml) while %EE was found 64 to 90%of all the experimental runs. Change in Physical state of OLZ from crystalline to amorphous nature attributed to the improvement of the dissolution rate of OLZ in OSD, which is also responsible for the solubility enhancement of OLZ, which is confirmed by the XRD analysis. Dissolution study confirmed that solid dispersion shows better dissolution profile of OLZ as compare to OLZ. While, analytical study such as FTIR confirmed the compatibility of OLZ with various ingredient as major deviation in peaks of OLZ in solid dispersion were observed. Hence, it can be concluded from the study that the combination of hydrophilic polymers could be successfully employed for the development of amorphous solid dispersion along with improved solubility and dissolution rate.

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Development and evaluation orally (ODTs) disintegrating tablets containing taste masked ibuprofen microparticles prepared by spray drying and freeze drying method for taste masking and solubility enhancement.

1.Abstract

In the current study, Ibuprofen was encapsulated in methacrylate copolymer (Eudrajit L-100) to formulate taste masked microparticles prepared by spray drying and freeze-drying method. The microparticles were developed by varying the ratio of Eudrajit L-100, PVP k30 and β-cyclodextrin while a direct compression method was used to compress the ODTs under various compaction forces to optimize tablet hardness and robustness. The properties of the microparticles and ODTs which included surface morphology, Particle size, XRD, FTIR, hardness, friability and disintegration study, encapsulation efficiency and phase solubility study were further evaluated and compared with marketed ODTs. The taste assessment of prepared ODTs was done by in vitro method based on drug release.

2.Introduction

The development of oral disintegrating tablets (ODTs) has received increased interest among researchers and pharmaceutical industries over the last decade. The ODTs are designed to disintegrate or dissolve rapidly on contact with saliva, in the absence of additional water, compared to the traditional tablet forms. ODTs provide several advantages as they combine the properties of both liquid and conventional tablet formulations [1,2]. ODTs are quickly ingested upon introduction on the tongue, thus eliminating the need to chew the tablet, swallow an intact tablet, or take the tablet with water. Furthermore, administration of ODTs is favourable to paediatric and geriatric patients or people who find swallowing difficult and for the treatment of patients where compliance is difficult. However, as a result of the rapid ODT disintegration, the active substance comes in contact with the taste buds and the need for a pleasant taste becomes a key aspect for patient palatability. Thus the taste-masking of bitter active substances is a critical hurdle to overcome for the successful development of ODT formulations.[3] In general, oral administration of bitter active substances through ODT formulations should provide an improved degree of palatability, increased patient compliance and a concomitantly beneficial therapeutic effect. In the past, the methods of taste-masking in fast dissolving/disintegrating tablets included sweeteners and flavors. Nevertheless, these additives were not a sufficient means for complete taste-masking[4,5]. The aim of this twofold study was to increase ibuprofen dissolution rate and to incorporate the taste masked granules produced into robust ODT formulations. ibuprofen is a well-known and widely used nonsteroidal anti-inflammatory drug (NSAID) with 3.7 mg/ml water solubility. At the present, ibuprofen's over-

the-counter ODTs are marketed as Nurofen® (Meltlets) to treat migraine, headache and rheumatic/muscular pain[6]. Here we report the development of an orally disintegrating tablet developed spray drying and freeze-drying method of ibuprofen – methacrylic pH-sensitive copolymer (Eudrajit L-100) mixtures and the evaluation of the ODTs produced.

3.Materials

Ibuprofen was kindly gifted by SP pharmaceuticals, Jalgaon, India. PVP k30, β-cyclodextrin, polyvinyl alcohol(PVA) and Potassium dihydrogen phosphate were purchased from Himedia Laboratories India. Eudrajit L-100 Dichloromethane(DCM) was purchased from MERCK specialties Pvt. Ltd. Mumbai, India. Sodium hydroxide was purchased from RFCL, Mumbai, India. All other solvents and reagents of analytical grade and used as provided.

4.Methods

During the development of the ibuprofen microparticles number of initial trials were conducted to mask the taste and increase the solubility of ibuprofen. The preliminary experiments include the change in Eudrajit L-100, PVP k30 and β-cyclodextrin. We found that these selected independent variables had great influence on the encapsulation efficiency (EE) as well as disintegration time (DT)and hence selected as independent variables[7,8]. A 3-level 2- factor design was used to derive a second order polynomial equation and construct a 3D surface graph to predict responses. The independent variables selected were the amount of PVP k30 A [mg], amount of β-cyclodextrin B (mg) and amount of Eudrajit L-100[C]. Encapsulation efficiency (EE) and disintegration time(DT) were selected as dependent factors. The transformed values of the independent variables and the dependent variable were subjected to multiple regressions to establish a full-model second-order polynomial equation [9].

Spray drying

Ibuprofen microparticles prepared by spray drying technique. Eudrajit L-100, PVP k30 and β-cyclodextrin was dissolved in DCM (solution A). PVA was used as a surfactant and dissolved in the aqueous phase (solution B). Solution A was dropwise added into solution B by using a syringe and stirred for 30 minutes. The formed feed was then stirred for further 1 hour and then spray dried using spray dryer (Spray-Mate, JISL, PVT LTD, Mumbai) India by keeping inlet temperature at 85^{o}C ±10^{o}C corresponding to an outlet air temperature of 45^{o}C ± 10^{o}C, depending upon the solid composition of the feed. The feed rate was 10 ml/min and aspirator pressure was 2 kg/cm2 with aspirator speed 1400 rpm [5, 6]. The prepared nanoparticles were collected in the collection chamber.

Freeze drying

Eudrajit L-100, PVP k30 and β-cyclodextrin was dissolved in DCM (solution A). PVA was used as a surfactant and dissolved in the aqueous phase (solution B). Solution A was dropwise added into solution B by using a syringe and stirred for 30 minutes [7]. The formed feed was then stirred for further 1 hour and then Immediately after stirring, Freeze drying was performed by using a programmable freeze dryer (Lyophilizer, Make M/s Labogen Aps,Denmark)[8].

5.Characterization

1.EVALUATION OF NANOPARTICLES

Particle Size

Particle size was determined by Particle size analyzer (Malvern ZS 200 UK). Nanoparticles were dispersed in distilled water and analyzed by particle size analyzer at room temperature (Patil et al. 2015). Particle size was obtained in the range of 122.2-190.1nm [9].

2.Field Emission Scanning Electron Microscope (FE-SEM)

The morphology of nanoparticles was investigated by field emission scanning electron microscope (FESEM-S 4800, Hitachi, Japan) at a working distance of 8.6–8.7mm and accelerating voltage of 1.0 kV. The particles were examined for size, shape, and surface morphology. The nanoparticles were mounted on metal stub using double sided adhesive tape and coated with gold under vacuum. Ibuprofen was in crystalline. The ibuprofen loaded microparticles were analyzed by scanning electron microscopy. The nanoparticles were discrete and free flowing in nature. The surface of the nanoparticles was smooth and regular without any erosion and cracking [10].

3.Fourier Transforms Infrared (FTIR) Spectroscopy Study

The infrared spectra of ibuprofen, PVP k30, β-cyclodextrin and tablets were scanned under FTIR spectrophotometer (Perkin-Elmer Pvt. Ltd. Singapore) by the potassium bromide pellet method. Sample (1mg) was mixed with potassium bromide (40 mg) and formed into the transparent disc in KBr press. The scan range of 4000–500 cm-1 was used to record spectra [11].

4.X-Ray Diffraction Analysis

In order to confirm the amorphous or crystalline nature of the sample, pattern of XRD of ibuprofen, PVP k30, β-cyclodextrin and nanoparticles(C)were characterized by X-ray diffractometer (Bruker, D-8 advance, Germany). Cu anode was used for data collection and a voltage of the monochromator was at 40 kV. The diffraction pattern was determined in area $2^0 < 2\theta < 80^0$, using continuous scan[12]. XRD patterns of pure ibuprofen shows the intense peak of crystallinity, whereas decrease in the peak intensity in batches shows amorphous nature of

the drug. Intense peak of crystallinity was found in the XRD pattern of ibuprofen, whereas XRD pattern of batch show some intense peak with semi crystalline nature in comparison to pure ibuprofen, which indicates that ibuprofen completely embedded in the Eudrajit L-100. amorphous nature of the ibuprofen in tablet is also responsible for the faster disintegration rate,This reduced intensity indicates the decreased crystallinity of ibuprofen.

Phase Solubility Studies

The water solubility of ibuprofen was 3.7 mg/mL indicating that it is insoluble in water. PVP k30 and β-cyclodextrin influenced ibuprofen water solubility in different ways. The linearity of the curves plotted for PVP k30 and β-cyclodextrin were analyzed in order to detect the tendency for drug solubility to increase in relation to the increase in PVP k30 and β-cyclodextrin concentration, as well as the maximum solubilization percentage for the drug. These results were evaluated using the coefficient of determination R^2 for each curve and the drug dissolved at the tested concentrations. This showed that not all carriers provided an increase in linear solubility with random variations for the different concentrations. The solutions that demonstrated a more predictable and linear behavior were those with the PVP k30 and β-cyclodextrin [13,14]. This clearly shows a positive influence of the polymers on ibuprofen nanoparticles. The higher slope value indicates the increase in aqueous solubility.

Disintegration Studies and encapsulation Efficiency

3-level factorial design with two independent variables PVPk 30 and HPβCD at three different levels (-1, 0, 1) was used to study the effects on the dependent variables Tablet disintegration time was measured in vitro method using distilled water at 37 ± 2 C. Six tablets were randomly chosen for disintegration testing using a disintegration tester (Tablet Disintegration Test Apparatus, Veego Instruments Co., Ltd., India). A disintegration time that was less than 30 s was considered acceptable [15].

5. *In- Vitro* Drug Release Study

Drug release profiles were evaluated *in-vitro* using a dissolution test apparatus (USP type-II Paddle TDT 08L, Electrolab Mumbai, Maharashtra, India). The test for all the formulations was carried out in 900 mL water with 0.5 N % sodium lauryl sulfate (SLS) (900 mL) at 37 ± 0.5◦C. Withdrawing 5 mL samples at preselected time intervals up to 8 hrs. Same volume (5 mL) of dissolution medium was replenished after each sampling. The samples were filtered and solutions were analyzed for ibuprofen by UV-absorbance at 233nm using a spectrophotometer (HITACHI U-2900). The mean of three determinations were considered for UV-absorbance. The dissolution studies were performed for the pure drug and all formulations.

Conclusion

The present study reports the Formulation of ibuprofen ODT by using spray drying and Lyophilization technique 3level 2 factorial design with the percentage EE of8 94.33to85.77%. The release of ibuprofen was remarkably faster than pure drug and solubility also increased compared to pure drug. Pure efavirenz was successfully developed and converted ODT. From the present study it was concluded that ibuprofen ODT could be developed, and it would bring a reduction in dose and possible side effects of the ibuprofen.

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