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FORMULATION AND EVALUATION OF DRY SYRUP

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ABSTRACT

The advantages of oral dosage form that are responsible for its popularity are itsease of Administration, patient compliance and stability of formulation. The most popular oral dosage Forms being'stablets and capsules, but one important drawback of the dosage forms however Is the difficulty to swallow especially when a dosage form is developed for pediatric and Geriatric patient. The modern scientific and technological advancement in the pharmaceutical Field had created bank of interest in reconstitutable oral suspension dosage form in the recent Year. The reconstituted system is the formulation of choice when the drugstability is a major Concern. Reconstitutable oral systems show the adequate chemical stability of the drug during Shelf life and also reduce the weight of the final product. Dry syrup form of the drug is also Useful in case of bioavailability as it has high bioavailability rather than tablets and capsules as it disintegrates in water outside of the oral cavity and directly the suspension is gone Through the gastrointestinal tract. So, the suspension easily absorbs in the GIT. The purpose of this research was to mask the intensely bitter taste of Ciprofloxacin is a broad-spectrum antibiotic. It is extremely bitter taste resulting in poor patient's compliance. The aim of present work was to prepare drug resin complex(DRC) using ion exchange resin (Kyron T114) for taste masking and formulate oral reconstituabledry syrup. Formulated ciprofloxacin reconstituable dry syrup has acceptable Drug Dissolution properties. In evaluating period of 7 days no significant change was observed in pH, sedimentation volume, specific gravity and drug content. From the results it concluded that effective taste masking of ciprofloxacin was achieve using Kyron T114 and successfully evaluated in reconstituable dry syrup. The present Review gives an account of the excipients used, methods of preparation of drysyrups along with their evaluations, their packaging, ICH guidelines.

Keywords: Dry Syrup, Patient Compliance, Antibiotic, Amoxicillin, Stability, Sedimentation Volume, Reconstituted Dry Syrup**.**

I. INTRODUCTION

Many antibiotic materials are unstable when maintained in solution for an appreciable length of time, and therefore, from a stability standpoint, Insoluble forms of the drug substances in aqueous suspensions or as dry Powder for reconstitution are attractive to manufacturers [1]. Since Decades among all the pharmaceutical products available, oral drug Delivery has gained a higher scope and popularity and has been widely Employed for the systemicdelivery of drugs. The positive aspect Regarding the oral dosage form which created its high levelof acceptance Was its ease of administration, patient compliance and stability of Formulation [2].The antibacterial oral suspensions include preparations of antibiotics substances (e.g., erythromycin derivatives, and Tetracyclines and its derivatives), sulfonamides (e.g., sulfamethoxazole and sulfisoxazole acetyl), other anti-infective agents (e.g., methenamine Mandelate and nitrofurantoin), or combinations of these (e.g., Sulfamethoxazole-trimethoprim). The antibiotic oral suspension, including those prepared by reconstitution, provide a convenient way to Administer dosages to infants and children and to adult patients who Prefer liquid preparations to solid ones. Although studies have Demonstrated that the dryoral suspension afterconstitution in a liquid Is stable for 24 h after preparation, reconstituted solution remains stable When stored in the refrigerator for the labelled period, usually 7 to 14 d, Depending on the preparation. This is a sufficient period for the patient to complete the regimen usually prescribed.However, in case the Medication remains after the patient completes the course of therapy, The patient should be instructed to discard the remaining portion, which Would be unfit for use at thelater time [3].

1.1 Dry Syrups:

"Dry pharmaceutical syrup may be defined as a Finely divided insoluble particle ranging from0.5-5 μ, which Is to be distributed in a suitable vehicle". Dry syrups are the solid dosage form that can be reconstituted by the

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addition of water to administer by the oral route. Mostly antibiotics, some moisture sensitive and pediatric Drugs are available in the form of dry syrup [4].

Many preparations like Amoxicillin trihydrate, Erythromycin Ethyl succinate, Dicloxacillin sodium etc. are available as dry Powder mixtures or granules that are intended to besuspended in water or some other vehicle before oral administration. The Reconstituted system isthe formulation of choice when the Drug stability is a major concern. The dry mix for oral Suspension contains the drug, colorants, flavors, sweeteners, stabilizing agents, suspending agentsand preserving agents That may be needed to enhance the stability of the formulation. Dry syrup form of drug shows improved bioavailability as Compared to tablets and capsules as it is in the dispersed state at the time of administration [5]. A reconstitubal suspension can Offer several advantages such as maintenance of the chemical Stability of the active compounds until reconstitution at the Start of treatment. The same suspension can be easily Administered to childrenof different ages by adjusting the Volume to swallow Dry syrups are oral pharmaceutical formulations particularly suitedfor use in pediatric medicine. As with other oral pharmaceutical formulations, the palatability of a dry syrup can havea profound impact on therapeutic outcome [6]. If the bitterness of an active pharmaceutical ingredient causes poor palatability, drug efficacy may be reduced due to non-compliance. The exploration of factors influencing the palatability of dry syrups may therefore lead to improvements in their pharmaceutical formulation [7].

Dry syrup are dry mixtures containing the drug and suitable suspending and dispersing agents to be diluted and agitated with a specific quantity of vehicle, most often purified water. Stability is defined as the capability of a drug substance or drug product to remain within the established specifications, to maintain its identity, strength, quality, and purity throughout theretest or until expiry date period.[8]

The reconstituted system is the formulation of choice when the drug stability is major concern. The medications are supplied in dry form because the product can be stored for a long time in dryform but becomes unstable and deteriorates in solution within a relatively short time. Such solutions are said to have a “short shelf life”. For example, reconstituted suspension of penicillin has a maximum shelf life of 14 days. The manufactured dry mixture, however, has a shelf life of at least 2 years. Augmentin dry powder has a shelf life of 24 months when stored below 25°C. andits reconstituted powder have a shelf life of 7 days when stored at2°C to 8°C. [9]

Another reason of prescribing antibiotics as dry syrup for infants and young children are children’s inability to swallow tablets or capsules; unavailability of certain antibiotics in a chewable tablet form; and the discomfort, expense and associated risk of antibiotic injection.[2] The process of reconstituting medications from powder to liquid form would be expected to causemore errors than dosing with ready-to- use liquid drugs. Errors could occur with regard to the reconstitution process, the volume and temperature of the reconstituted liquid, the medication shelflife, storage conditions and accurate dosing.[5] Stability studies have demonstrated that the dry oral suspension after constitution in a liquid is stable for 24h after preparation; reconstituted solution remains stable when stored in the refrigerator for the labeled period, usually 7 to 14 days,depending on the preparation. This is sufficient period for the patient to complete the regimen usually prescribed. However, in case the medication remains after the patient complete the courseoftherapy, the patient should be instructed to discard the remaining portion, which would be unfitfor use at the later time.[10].

The semantic differential (SD) method developed by Osgood et al. [7] is a method used toquantify an image. In a previous study, we have used the SD method in human taste testing studies to evaluate the palatability of total enteral nutrients [8]. In the present study, the SD method was used to explore the factors influencing the palatability of 20 dry syrups currently marketed in Japanand commonly used in pediatric medicine. The use of the artificial taste sensor for pharmaceuticalpurposes is an innovation which has reduced dependence on human gustatory sensation testing. The bitterness of active pharmaceutical ingredients in oral pharmaceutical formulations has previously been evaluated using the artificial taste sensor or “electronic tongue” [10]

There are several types of sensors which have different components of lipids and plasticizers andare sensitive to different materials: C00 is sensitive to acidic bitter materials such as diclofenac sodium, a non-steroidal anti-inflammatory drug [9]; AE1 is sensitive to astringent materials such as tannic acid; AC0 and AN0 are sensitive to basic materials such as solifenacin succinate [10] oramlodipine besilate [11] and BT0 is sensitive to hydrochloride salts, including quinine hydrochloride [13]. The bitterness of an active pharmaceutical ingredient in oral pharmaceutical formulations mixed with various foods or beverages has also been evaluated using a taste

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sensor [11].

- **Major application - paediatric therapy: taste masking (11):**

Oral Route of administration is the route of choice for administration of medicines in children. Theonly hurdle for dosage form designing for pediatric patients is the patient'sacceptance of the dosage form. Pediatric Patients tend to become uncooperative during the administration of oral medication; the most common reason being the taste of the oral formulationadministered among the children. Most of the drugs administered as granules for oral suspension under pediatric therapy are Antibiotics, which when administered orally as any other dosage formhave a bitter taste making it unpleasant for Children to consume the medication

Advantages of dry Syrup:

- There is accurate single dosing as the dose is packed in single dose sachets.
- Drug dose is comparatively independent of any physical factors like temperature, sedimentationrate and liquid flow properties.
- The packaging of the powder mixture is done in sachets making the formulation easy to carry. •The enhanced convenience of the single dosage regimen.
- Colored, flavored, sweetened formulation is advantageous for administration to the paediatricpopulation.
- Stable on storage and when reconstituted with an ingestible liquid for administration, the corresponding liquid suspension is stable for the duration for which the therapy is required.

Disadvantages of Dry Syrup:

- It is a bulk formulation, so there are chances of inaccuracy in single dosing.
- Drug dose depends on various physical factors of the dosage form such as the temperature ofstorage, sedimentation rate of the formulation, liquid flow properties

like viscosity, pourability, redispersion, flocculation and content uniformity.

- Stability of the liquid largely depends on the temperature of storage.
- Caking occurs upon storage.

II. LITERATURE REVIEW

1. Taste masking and development of palatable dosage forms of bitter drugs constitutes the objective of many a research project in the field of pharmaceutical technology. Taste is an important factor in the development of dosage form. The problem of bitter and obnoxious taste ofdrug in pediatric patient can create a bad psychological effect on mind. The purpose of this researchwas to mask the intensely bitter taste of Ciprofloxacin is a broad-spectrum antibiotic. It is extremelybitter taste resulting in poor patient's compliance. The aim of present work was to prepare drug resin complex (DRC) using ion exchange resin (Kyron T114) for taste masking and formulate oralreconstituable dry syrup. Formulated ciprofloxacin reconstituable dry syrup has acceptable Drug Dissolution properties. In evaluating period of 7 days no significant change was observed in pH, sedimentation volume, specific gravity and drug content. From the results it concluded that effectivetaste masking of ciprofloxacin was achieve using Kyron T114 and successfully evaluated in reconstituable dry syrup.[14]

2. Hydroxyurea (HU) is the drug of choice for the management of sickle cell disease but the available dosage form exists as a 500 mg capsule, which is not appropriate for pediatrics whose dosing requirements are 20 mg/kg. The current practice of compounding is prone to dose errors and contamination. Also, shortage of compounding laboratories in hospitals in the developing countries is a major issue. This study aimed at investigating the stability of HU in aqueous solutionfollowed by formulation and evaluation of its dry syrup. Stability of HU aqueous solution was investigated and subsequently dry syrups formulated. They were evaluated for flowability, assay,dissolution, moisture content, rheology and pH. The formulated dry syrups complied with the United States Pharmacopeia (USP) specifications for stability, angle of repose (24-25°), assay (90-110%), dissolution (more than 85% in the first 30 minutes), shear thinning and pH (7.3). HU dry syrup was successfully developed, optimized and found to comply with USP specifications [15].

3. The development of a capillary zone electrophoresis method with head-column field-amplifiedsample

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stacking injection for the determination of formoterol (FMTR) in a low dosage dry syrup form was described.To obtain the highest sensitivity, the sample solution was prepared by high content of organic solvent with the presence of a small amount of H+ (60-100 micro) and the capillary inlet end was dipped in water before electro injection. This method was fully validated interms of repeatability (RSDs for migration time, peak areaof FMTR and peak area ratio betweenFMTR and I.S. at 1 microg/ml of FMTR was 0.76, 1.10 and 0.55% respectively), reproducibility (RSDs from different capillaries, analytes, days and instruments were 1.52%, 1.04%, 1.16% and 1.93% respectively), linearity (y = 0.827x - 0.085, r = 0.9993 (n = 6) over the range of 0.25-2.0 microg/ml), limits of quantitation, ruggedness and robustness. The method was applied to the determination of the drug in commercial dry syrup preparation (recovery was 100.9%, RSD = 1.5%, n = 5) and proved to be fast and reliable for the quantitation analysis of FMTR in the pharmaceutical form [16].

4. Taste is an important factor in the development of dosage form. The problem of bitter and obnoxious tasteof drug in pediatric patient can create a bad psychological effect on mind. The purpose of this research was to mask the intensely bitter taste of Linezolid using ion exchange resin and to formulate the dry syrup of the taste masked drug. When suspension is swallowed thebitter taste of the drug may not be felt as ion exchange resin does not release the drug at salivary pH. When it comes in contact with acidic environment of stomach, the complex will be broken down releasing the drug which may then absorbed. Batch method was used for formation of drugresin complex. Various ion exchange resin like different grade of Kyron and indion 214 were usedfor masking the bitter taste. Optimization of drug loading was carried out. Indian 214 was selectedas an optimized resin with 84.47 % drug loading. Dry syrup was made using suspending agent likegellan gum, guar gum and CMC and evaluated for various parameters like color, odor, taste, viscosity, sedimentation volume, redispersibility, % drug content, drug release. By evaluating all the parameter, the batch formulation contained guar gum 3 % was the best one amongst all the other formulations [17].

5. Many patients with bronchiectasis suffer from two or more exacerbations per year. However, there are no approved therapies to reduce or delay exacerbations in this patient population. Ciprofloxacin Dry powder inhalation is in development as a long-term, intermittent therapy to reduce exacerbations in patients with non-cystic fibrosis (CF) bronchiectasis and evidence of respiratory pathogens. Ciprofloxacin DPI combines drug substance, dry powder manufacturing technology, and an efficient, pocket-sized, dry powder inhaler to deliver an effective antibiotic directly to the site of infection, with minimal systemic exposure and treatmentburden. Here we review the drug substance and particle engineering (PulmoSphere™) technology used, and key physical properties of Ciprofloxacin Inhalation Powder, including deposition, delivered dose uniformity, consistency, and stability. Design features of the T-326 Inhaler are described in relation to lung targeting, safety and tolerability of inhalation powders, as well as treatment burden and adherence. If approved, Ciprofloxacin DPI may provide a valuable treatmentoption for those with frequent exacerbations and respiratory pathogens [18].

6. Oral paediatric suspensions of antibiotics are mainly available as dry powders for reconstitution.Most of reconstituted antibiotic suspension is to be kept refrigerated in order to get the optimal therapeutic action from the drug. However, many patients do not keep to it to specified storage conditions for many reasons. Like no refrigeration and irregular power supply that may result in various degree of degradation of reconstituted antibiotics. Pharmacists are therefore challenged how to counsel patients when there is no refrigeration or erratic power supply.[1] Inappropriate use of antibiotics leads to economically and clinically preventable negative consequences including unnecessary adverse effects, increase mortality and morbidity from treatment failure, wasting healthcare resources, and increase the emergency of bacterial resistance.[2] Improper storage condition leads to physical instability, chemical instability, reduction in potency, or it may also leads to serious adverse effect on the patient's health **[**19].

7. Dry syrup form of the drug is also useful in case of bioavailability as it has high bioavailabilityrather than tablets and capsules as it disintegrates in water outside of the oral cavity and directly the suspension is gone through the gastrointestinal tract. These are dry mixtures containing the drug and suitable suspending and dispersing agents to be diluted and agitated with a specific quantity of vehicle, most often purified water. Drugs that are instable if maintained for extended periods in the presence of aqueous vehicle (e.g., many antibiotic drugs) are frequently supplied as dry powder mixtures for reconstitution at the time of dispensing. This type

of preparation is designated in the USP by atitle "for Oral Suspension". Thereconstituted system is the formulation of choice when the drug stability is a major concern. After reconstitution, these systems have a short but acceptable life if stored at refrigerator temperatures. Reconstitutable oral systems show the adequate chemical stability of the drug during shelf life, avoids the physical stability problemsrelated to solubility, pH and incompatibilities with other ingredients and also reduce the weight ofthe final product because the aqueous vehicle is absent and consequently the transportation expenses may be reduced [20].

8. The purpose of this study was to assess the bitterness intensity and pH of the solutions of clarithromycin dry syrup (CAM-DS), carbocisteine preparation (CC), and the concomitant use ofboth drugs. We conducted 6 types of human gustatory sensation tests with 6 healthy male volunteers. As a result, there was almost no difference in the bitterness intensity of CAM-DS between the branded (the latest and former preparations) and the generic formulations. The bitterness intensity of CAM-DS (the latest and former preparations of the branded as well as the generic formulations) was almost equally enhanced by mixing it with either the branded CC-DS or the branded and the generic carbocisteine granule (CC-Gr). On this occasion, the enhancing the bitterness of the branded CAM-DS (latest and former preparation) was nearly avoided safely by dosage form's changing CC-DS or CC-Gr to the branded CC-Sy. However, unlike the branded CC-Sy, some generic CC-Sy failed to suppress the bitterness. Furthermore, it was proven that somegeneric CAM-DS were shown to exhibit bitterness when mixed with even branded CC-Sy. In conclusion, it should be noted that the extent of bitterness of the mixture of CAM-DS and CC highly varies among the generic formulations [21].

9. The clinical efficacy was examined for the newly developed oral cephem antibiotic, cefpodoxime proxetil dry syrup, in the treatment of various acute infections in the field of pediatrics. dry syrup was administered at 10 mg/kg/day in 3-divided doses to 535 children at 21 institutions, including Tottori University Hospital and its related hospitals. The efficacy rate of this drug was determined to be 80.8%. Among isolates, Staphylococcus aureus and Streptococcussp. were highly susceptible to the drug, whereas Haemophilus influenzae showed relatively poor susceptibility. Side effects were observed in 2.80% of all of the patients, and abnormal laboratory findings were detected in 1.87%. The low incident of side effects demonstrated its high safety, and this drug was considered to be very useful for such pediatric infections as acute tonsillitis, acute pharyngitis and acute bronchitis [22].

III. MATERIALS AND METHODS

3.1 Materials

Amoxicillin was obtained as a gift sample from Cipla private Laboratories Ltd. Ion exchange resins(Kyron T114) obtained from Corel Pharma Limited as a gift sample. Preparation of standard curveof Amoxicillin HCl10 100 mg of Amoxicillin was dissolved in 0.1 N HCl in 100 ml of volumetricflask and the solution was made up to volume with 0.1 N HCl. The standard solution of Amoxicillinwas subsequently diluted with 0.1 N HCl to obtain a series of dilutions containing 1, 2, 3, 4 and 5µg of Amoxicillin in 1 ml solution. The absorbance of these solutions was measured at 276 nm using UV-VIS spectrophotometer (Electrolab, Model SL 1500) against blank.

Preparation of drug-resin complex.[23]

Drug resin complexes (DRC) were prepared by using batch process. Accurately weighed amountof Kyron T 114 dispersed in a beaker containing deionized water and allowed to swell for 45 minutes. Swelled resin slurry was filtered on what man filter paper. Then it was washed with deionized water. Drug resin complex (DRC) was prepared, by placing acid activated resin in a beaker containing deionized water. Accurately weighed amount of Ciprofloxacin was added slowly to the resin slurry and stirred for 3hours in magnetic stirrer. During stirring, pH of the drugresin slurry was measured frequently and adjusts to 6.5 by using 0.1 M KOH. After three hours ofstirring, the DRC was separated from dispersion by filtration and washed with deionized water. DRC was dried at 55°C until it was dry. The dried mass was powdered and sieved through 40- mesh sieve. Complex was evaluated for drug loading efficiency.

Evaluation of DRC :12 Effect of drug-resin ratio on complex formation

Ratio of the resin to drug can greatly impact the complex formation and ultimately affects the tastemasking ability. It was necessary to find out the optimum drug to resin ratio. In each case drug resin complexes (DRC) of Amoxicillin and Kyron T 114 were prepared in 1:1, 1:2 and 1:3 ratios.

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Drug loading efficiency for DRC

DRC equivalent to 100 mg of Ciprofloxacin was weighed accurately and was transferred into 100ml of volumetric flask. 100 ml of 0.1 N HCl was added to this volumetric flask and was stirred continuously **for** 1 hour on a magnetic stirrer. After stirring, this solution was filtered through whattman filter paper. Filtered sample solution was suitably diluted with 0.1 N HCl and the amountof drug dissolved were determined by UV spectrophotometer, by measuring the absorbance of thesample at 276 nm.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) thermo grams of the Amoxicillin, Resins and drug resincomplexes were recorded on NETZSCH DSC 204 (Germany). Samples (2-7 mg) were sealed intoaluminum pans and scanned at a heating rate of 10°C/min over a temperature range of 20-360°C under a nitrogen gas stream [24].

3.2 Preparation of Dry Mixture

Powder blends

Powder blends, sometimes called powder mixtures are prepared by mixing the excipients of the dry mixture in powder form. Excipients present in small quantities may require atwo-stage mixing operation. Such excipients can be mixed with a portion of a major excipient to aid in their dispersion. For example, milled sucrose provides a large surface areafor the adsorptionof the small quantities of flavor oils. The second stage comprises the mixing of the remaining excipients. The selection of the appropriate mixer involves several considerations, the most significant of which is that the mixer should rapidly and reliably produce a homogenous mixture.

Combination product

Powdered and granulated excipients can be combined to overcome some disadvantages of granulated products. Less energy and equipment for granulation may be requiredif the majority of the diluents can be added after granulation. Also, heat sensitive excipients suchas flavors can be added after drying of granulation to avoid exposure to elevated temperatures. Thegeneral method is first to granulate some of the excipients, then blend the remaining excipients with the dried granules before filling the container. The presence of the diluents helps to improveflow and reduces both segregation and dust formation.

Processing the dry mixture:

Use efficient mixing

- Determine an adequate duration of mixing time.
- Avoid accumulation of heat and moisture during mixing.
- Limit temperature/humidity variations. A general rule is 700 C at<40% relative humidity.
- The finished batch should be protected from moisture. Store in lined containers with silicadesiccant bags.
- The sample for batch uniformity. Test at the top, middle and bottom levels of the dry mixture**.**

Condition for manufacturing Dry Syrup:

For manufacturing of dry syrup following conditions shouldBemaintained.

- Relative humidity: Not more than 60%.
- Temperature: Below 25°C
- All relevant materials are removed
- Equipment is cleaned
- Balanced is calibrate

Table 3: Formulation of Amoxicillin dry syrup [25]

Ingredient	(mg/5 ml)	gm
Amoxicillin Teihydrateate	697.67	4.18602
Clavulanate Potassium	113.00	0.678
Xanthum Gum	3	0.018
Dextrose	12.50	0.075

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Silicon Dioxide	92.82	0.55704
Sodium Carboxymethylcellulose	30.00	0.18
Venilla	26.00	0.156

3.3 Preparation Of Dry Syrup

Bactericidal antimicrobials, such as amoxicillin, often are most effective in a "time-dependent" manner rather than a "concentration-dependent" manner. Time-dependent refers to the time that serum concentrations exceed the minimum-inhibitor-concentration (MIC) for the microorganism. Therefore, they are often dosed more frequently, rather than the concentration-dependent drugs, which can be dosed, for example, daily. The more "around-the-clock" dosing provides minor variation in peak and trough serum concentrations. Amoxicillin is an oral antimicrobial; whereas, ampicillin (which is structurally similar) can be given orally, intravenously, or intramuscularly. Amoxicillin comes in immediate-release or extended-release tablets. It also comes in a chewable tablet or a suspension. It may be mixed (after thoroughly shaking) and administered with formula, milk, water, fruit juice, ginger ale, or other cold drinks if given in suspension. The administration should take place immediately after mixing. Patients should not crush Extended-release tablets, and the administration should be within 1 hourafter finishing a meal. Amoxicillin is sometimes preferred over penicillin in children because of its taste.

3.4 Excipients used [26]:

Number of excipients should be minimum as more the number of excipients in the formulation, the greater is the possibility of problems, for example, the chances of compatibility Problems are increased as more excipients are used. More Processing is required to incorporate more excipients. For Reducing the number of excipients use an excipient that Performs more than one function. E.g., Sucrose can be used as a Diluents, sweetener and suspending agent. All excipients should disperse rapidly on reconstitution. This Criterion eliminates several suspending agents.

Granule disintegrant: It results in prevention of the particle Aggregation.

Granule binder: It helps to reduce the settling of particles in Suspensions. It is also used as a stabilizer for suspensions. Eg. High molecular weight povidone.

Suspending agents

Suspending agents should be easily dispersed during Reconstitution. These rules out several common suspending Agents because many require hydration, elevated temperatures or high shearmixing for adequate dispersion. Some of the Suspending agents that are recommended for use areAcacia, Carboxymethylcellulose sodium, Iota Carrageenan, Microcrystalline cellulose with Carboxymethylcellulose sodium, Silicon dioxide, Sodium Starch glycolate, Tragacanth, Xanthan gum. Xanthan gum is a common suspending agent in suspensions for reconstitution. Its solution viscosity is practically Independent of pH and temperature.

Sweeteners

Sweeteners can mask the unfavorable taste and enhance Patient acceptance in the pediatric population that uses this Product. The sweetener is a significant component of Suspensions for reconstitution. Drugs frequently have a bitter Taste and suspending agents, particularly clays, mayhave a Bland taste. e.g., Sucrose can perform both functions of sweetener and Suspending agent, and serve as a diluent in the dry mixture. Saccharin may become restricted by the Food and DrugAdministration because of its carcinogenic potential. Others Include Mannitol, Dextrose, Aspartame, Saccharin Sod.

Sucrose can perform both functions of sweetener and suspending agent and can serve as a diluentin the dry mixture. Aspartame has fair acid stability but poor heat stability. Saccharin may becomerestricted by the Food and Drug Administration because of its carcinogenic potential.[3]

Wetting agents

Many drugs in suspension are hydrophobic; they repel water and are not easily wetted. Must select the appropriate wetting Agent for optimum dispersion of the drug at the lowest Effective concentrations excess wetting agent can produce Foaming and impart an unpleasant taste. Eg. Polysorbate 80, Sodium lauryl sulfate. Polysorbate 80 is a common wetting agent. It is nonionic and is chemically compatible with both cationic and anionic excipients and drugs. It is used in concentrations lesser than or equal to 0.1%.Another common wetting

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agent is Sodium lauryl sulfate. This agent is anionic and may be incompatible with cationic drugs.[27].

Other excipients

The other excipients include buffers, preservatives, flavors and Colors. Buffers are used to maintain the optimal pH for all excipients. Suspension pH is often adjusted to ensure that the drug Remains in soluble.Eg. Sodium citrate Preservatives are required in most suspensions because the Suspending agents and sweetener are good media for growth of microorganisms. e.g.,Sorbic acid. Sucrose in sufficient Concentrations (60%w/w) can aid in the prevention of Microbial growth. Other common preservatives used are Sodium benzoate and Sodium propionate. Flavors enhance patient acceptability of product. Both natural and artificial flavors are used. Additional flavors used include Raspberry, pineapple etc. In some cases, refrigeration after Reconstitution is required for the stability of the flavoring Agent rather than for the stability of the drug. Colorantsare intended to provide a more aesthetic appearance to the final suspension. Anticaking agents such as amorphous silica gel have many Functions in suspensions for reconstitution. A common Problem in dry mixtures is poor powder flow and caking. This Is often caused by powder agglomeration due to moisture Uptake [28].

IV. EVALUATION PARAMETER OF DRY SYRUPCOLOR, ODOR AND APPEARANCE

All the developed batches of syrup were evaluated for Organoleptic properties such as color, odor and Appearance

Content:

Dry syrup equivalent to 100 mg of linezolid was taken in 100 ml volumetric flask and dissolved in 10 ml Methanol and volume was made up to 100 ml by Adding sufficient 0.1 N HCl. The solution was analyzed at 243.6 nm to found out drug content

Bulk density:

The powder (2 gm) filled in measuring cylinder called as bulk volume of powder and measure mass of that Powder. Bulk density is ratio of mass of powder to Bulk volume of powder. It is a measure used to Describe a packing of powder. The equation for Determining bulk density is Pb = m/ vbWhere, ρb= Bulk density m = Mass of powder vb= Volume of powder

Tapped density:

The pre-weighed powder (2gm) was filled in Measuring cylinder. Then it was tapped in bulk Density test apparatus. After 50 taps the volume is Measured andthe tapped density was measuredUsing following formula.

Pt = m/ vt

Where, ρt= Tapped density m = Mass of powder vt= Tapped volume

Carr's index (CI)[9,10)

Compressibility is indirectly related to the relative Flow rate, cohesiveness and particle size distribution of the powder. Powders with compressibility values Lesser than about 20%, has beenfound to exhibit good flow properties. Tapped (ρt) and Apparent (ρb) Bulk density measurements can be used to estimate the compressibility of a material

Carr's index (%) = (ρt – ρb) / ρt * 100 –Where, ρb= Bulk density ρt= Tapped density

PH -

The pH of the reconstituted suspension was determined using a pH Meter-Systronic μ pH system 361. A glass rod was dipped into a Suspension containing 100 mg of drug filled in a 50 ml of thebeaker.

Viscosity -

The rheologic parameters of the prepared suspensions, in terms of Viscosity, were determined byuse of the steady shear method, Measuring the "non-Newtonian viscosity". Rheology of all Suspensions was performed with a RVT Brookfield viscometer from Choksi Lab. (Indore, M. P.)All measurements were performed after Eliminating all thixotropy from the suspension.

Assay for Drug content

Sample solution:

Taken 3.45g of sample (Clarithromycin suspension) which is equivalent to 3.0 ml in 50 ml beaker,added 20 ml of

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mobile phase and stirred for 30 minutes to dissolve, transferred the content to 50 ml volumetric flasks and made up the volume with mobile phase, filtered with 0.2u filter paper and used the filtrate for further analysis. Chromatographic condition:

Mobile phase- Methanol: 0.2M KH2PO4 (35:65)

λmax-220nm

Temperature-50^0 C

Flow rate-- 1.0 ml/min

Stop time- - 15.0min

Sedimentation Volume

The sedimentation volumes were determined by keeping 50 ml of each suspension in stopper measuring cylinder and stored undisturbed at room temperature. The separation of clear liquid wasnoted at intervals of 1 day and up to 14 days. The sedimentation volume F was calculated using the formula F = Vu/Vo, where Vu is the volume of sediment and Vo is the original height of the sample. It is expressed as a percentage (Sateesha et.al, 2010).

Dry syrup sedimentation volume (%) (13)

The sedimentation volume was determined by keeping reconstituted dry syrup in 100 ml of measuring cylinder and kept aside for 7 days without any disturbance at room temperature. The separation of clear liquid was noticed on 1st and 7th day. The sedimentation volume (F %) was calculated using the formula F%=100Vu/Vo, where Vu is the volume of sediment and Vo is the original height of the sample.

PH and specific gravity measurements

Change in pH of the reconstituted syrup was measured using a digital pH meter on 1st and 7th day at 25oC. The specific gravity of the reconstituted syrup was determined on 1st and 7th day ina specific gravity bottle at 25oC by using following formula. Specific gravity = weight of the liquidsyrup formulation/weight of an equal volume of water.

Drug content determination from reconstituted syrup Reconstituted dry syrup

equivalent to 100 mg of Ciprofloxacin was measured accurately and was transferred into 100 ml of volumetric flask. 100 ml of 0.1 N HCl was added to this volumetric flask and was stirred continuously for 1 hour on a magnetic stirrer. After stirring, this solution was filtered through Whatman filter paper. Filtered sample solution was suitably diluted with 0.1 N HCl and the amount of drug dissolved was determined by UV spectrophotometer, by measuring the absorbance of thesample at 276 nm.

In vitro dissolution studies

An in vitro dissolution rate of Ciprofloxacin from its reconstituted syrup on 1st and 7th day was performed by using DISSO 2000, Lab India 8-Station Dissolution Rate Test Apparatus with a paddle stirrer (USP type II) at 50 rpm. 900 ml of 0.1 N HCl was used as dissolution medium whichwas maintained at 37±0.5oC. The reconstituted syrup equivalent to 100 mg of Ciprofloxacin wastransferred to each dissolution vessel. Aliquots of dissolution medium (5 ml) were withdrawn through 0.45 µ nylon disc filter at different time intervals of 5, 10, 15, 20, 25 and 30 minutes. Thesample of dissolution fluid withdrawn at each time was replaced with fresh dissolution fluid. Filtered sample solution was suitably diluted with 0.1 N HCl and the amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at 276 nm.

V. PACKAGING AND STORAGE

Dry powder for reconstitution packaged in wide mouth Container or in sachet in case of unit dosing.

- The dry powders for reconstitution should be packaged in Wide mouth container having sufficient air space above the liquid.
- The dry powders should be stored in tight container Protected from freezing, excessive heat and light.
- The label should contain the direction stating: “Shake Before Use” to ensure uniform distribution of solid Particles and thereby to obtain uniform and proper Dosage.
- The dry powders should be stored at room temperature.

- After reconstitution the suspension should be stored in the Refrigerator (freezing should beavoided to prevent Aggregation)
- For single dosage packing, sachets are used made up of 4 Layers of aluminum foil.

Labelling:

- That the contents are meant for preparation of an oral liquid.
- The directions for preparing the oral liquid including nature and quantity of liquid to be used
- The conditions under which the reconstituted solution should be Stored.
- The period during which the constituted oral liquid may be Expected to remain satisfactory for use when prepared and stored in Accordance with manufacturer's recommendations
- The strength in terms of active ingredients in a suitable dose Volume of reconstituted preparation.

VI. CONCLUSION

The aim of this present investigation was to develop taste masked Linezolid pediatric dry syrup. Ion exchange resin technique was selected to mask the bitter taste of Linezolidas complexation with ion exchange resin is a simple and cost-effective technique. Several ion exchange resins like kyron T104, kyron T- 134, kyron T-154, kyron T-314 and indion 214 were used to mask the taste. Complexation of Linezolid and resin was done by stirring them together for6-8 hours on magnetic stirrer. Taste masked dry syrup of Linezolid was prepared using indion 214as Linezolid had a maximum binding efficiency with indion 214 about 84. 47 %. So it was selected as a resin for final taste masked dry syrup. The resinate were evaluated for different parametersliketaste evaluation, micromeritic properties and % drug content. It was concluded that the taste was completely masked and acceptable for pediatric patients. The taste masked syrup was prepared using three different suspending agents namely gellan gum, guar gum and CMC. The final formulation contained three different concentrations of each suspending agents. Then it was evaluated for different parameters like colour, odour, % drug content, flow properties, sedimentation volume, pH, redispersibility, viscosity and in- vitro drug release. From the results it was concluded that the formulation with suspending agent guar gum with 3 % concentration showed highest sedimentation volume and better redispersibility which were very important parameter when once have to deal with suspension. The other parameters were also showed better results for the same suspending agent. So it was selected as an optimized suspendingagent amongst three. Even after studying the stability study of 18 days the results of parameters were matched with the initial once.

VII. REFERENCES

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