Fabriction and Evaluation of Spray Dried Solid Dispersion of Hesperidin Using Quality by Design Approach

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ABSTRACT:
the term solid dispersion refers to the dispersion of one or more active ingredients in a hydrophilic inert carrier matrix at molecular level. It is prepared by the melt (Fusion) method and solvent evaporation technique. However the process is individualized depending on the interaction between drug 4 carrier. Hesperidin is a plant-derived Flavonoid, abuntly present in the different citius species including lemon, orange, lime and groper Fruit. It possesses the diverse bilogical Potential of therapeutic significance, including antiinflammatory, anti-adipo-genic, antioxidant, insulin-sensitizing antimicrobial, neuroprotective and anticarcinogenic activities. the kinetic studies for drug release mechanism Inlere characterized through zero-order, First-order the optimized Formulation was Found to Follow the Higuchi model of the drug release kinetic With R² value OF 0.919.

I. INTRODUCTION:
Hesperidin is a plant chemical that is classified as a "bioflavonoid." It is most commonly found in citrus fruits. People use it as medicine. Hesperidin, alone or in combination with other citrus bioflavonoids (such as diosmin), is most commonly used for blood vessel conditions such as hemorrhoids, varicose veins, and poor circulation (venous stasis).

Hesperidin may help blood vessels function better. It may also reduce inflammation. Possibly Effective for Poor circulation that can cause the legs to swell (chronic venous insufficiency or CVI). Taking a particular product containing hesperidin methyl chalcone, butcher’s broom, and vitamin C by mouth seems to relieve the symptoms of poor circulation in the legs. Also, taking a different product containing hesperidin and diosmin by mouth for 2-6 months seems to improve CVI symptoms, although taking the drug Venoruton might be more effective for treating this condition. Hemorrhoids. Some research suggests that taking hesperidin and diosmin improves symptoms of anal hemorrhoids. It may also prevent hemorrhoids from coming back after they have healed and may help in an emergency worsening of hemorrhoids. Leg sores caused by weak blood circulation (venous leg ulcer). Taking a specific product containing hesperidin and diosmin by mouth for 2 months seems to improve the healing of small venous stasis ulcers when used along with compression dressings.

Hesperidin is extracted on a large scale from Citrus sinensis L. and Citrus unshiuMarcovitch [1-3]. It has also been recognized in a variety of plant species, including Cyclopia (Fabaceae), Carpinus (Betulaceae), Mentha (Lamiaceae), and Pterocarpus (Papilionaceae) species [4-7]. In addition, hesperidin has also been reported in the bark of
Zanthoxylum avicennae, Zanthoxylum cuspidatum, and roots of Acanthopanax setchuenensis Harmsex Diels [8, 9]. It was found to possess diverse biological actions of therapeutic significance, like insulin-sensitizing [10], anti-inflammatory, anti-carcinogenic activities [11], neuroprotective [12], type-2 diabetes [13], and metabolic syndrome [14], antioxidant and locomotor enhancing activities [15]. Chemically, it is (S)-7-(6-O-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranosyl)-oxy]-2,3-dihydro-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4H-1-Benzopyran-4-one, a colorless to a yellow crystalline powder having 260°C melting point. Solid dispersion is a method that increases the bioavailability of a drug by incorporating it into a polymer matrix, and nanoparticles are formulated to enhance the surface area of a drug [26]. The procedure was recorded for the preparation of the hesperidin drug. Solid dispersion is executed using natural polymer, i.e., Ocimum mucilage, through the melt extrusion method. The characterization of solid dispersion was performed using FTIR, DSC, and SEM [27]. The stable amorphous solid dissolution form of hesperidin is proved as the finest configuration with an enhanced dissolution rate. Amorphous pharmaceutical materials are thermodynamically metastable state and readily may convert into the more stable crystalline form. Quasi-equilibrium thermodynamic view of the amorphous form has higher solubility than crystalline form because it has a significantly higher free energy than the crystalline form (Lapuk et al., 2019a). It is illustrated that, amorphous materials are glassy nature and super cooled liquid and it can be achieved by rapid cooling.

II. AIM AND OBJECTIVE:

The objective of the present study was to enhance the dissolution characteristics of the model drug by increasing the solubility and release rate of hesperidin through solid dispersions using natural polymers by the hot-melt extrusion method.

The compatibility analysis was carried out through Fourier Transform-Infrared Spectroscopy (FT-IR) and Differential scanning calorimetry (DSC).

The kinetic studies for drug release mechanisms were characterized through zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models.

The dissolution analysis of solid dispersions showed exhibited more than 99% drug released. The optimized formulation was found to follow the Higuchi model of drug release kinetics with an R2 value of 0.919. Solid dispersions containing natural polymers prepared through the hot-melt extrusion method exhibited significant enhancement in the release profile compared to a pur.

III. PLAN OF WORK:

There are three fundamental steps involved in spray drying:

1) Atomization of a liquid feed into fine droplets.
2) Mixing of these spray droplets with a heated gas stream, allowing the liquid to evaporate and leave dried solids.
3) Dried powder is separated from the gas stream and collected.
DRUG PROFILE:
Name- Hesperidin
Hesperidin is a bioflavonoid found in a variety of nutritional supplements that is touted to have various beneficial effects on blood vessel disorders and various other conditions.

Generic Name: Hesperidin

Background: Hesperidin is a flavan-on glycoside found in citrus fruits.

Type: Small Molecule

Groups: Approved, Investigational Structure

Weight: Average: 610.560
Monoisotopic: 610.189770418

Chemical Formula: C28H34O15

Synonyms: Cirantin – Ciratin - Hesperetin - 7-O-rutinoside - Hesperidin - Hesperidina - Hesperidoside

Structure of Hesperidin

IV. MATERIALS AND METHODS

1. Drug and chemicals.

Hesperidin was obtained as a gift sample from Himachal Pradesh. The polymer Ocimum mucilage was prepared in the laboratory. All other chemicals like Mannitol, NaOH, Ethanol, HCl were procured from Nice chemical Pvt. Ltd. and were of analytical grade.

2. Pre-formulation studies.

2.1. Detection of melting point.

The melting point of the drug was detected by the digital melting point apparatus through the open capillary method.

2.2. UV spectroscopy of the drug and calibration curve preparation.

The determination of absorbance maxima (λmax) was carried out by scanning the hesperidin solution (in 0.1N NaOH, 0.1 N HCl, ethanol, and water) between 200-400 nm, and the calibration curve was prepared on UV-1800 Shimadzu UV spectrophotometer.


An excess quantity of the hesperidin was mixed separately with 20 mL of different solvents in conical flasks with continuous shaking and placed in a sonicator bath for 1 hour at 25°C. The sample solutions were filtered and, after appropriate dilutions, were characterized by a UV-visible spectrophotometer at 283 nm.

Molecular docking approaches:--
Monte Carlo approach. It creates a randomized conformation, translations, and rotation of a ligand in an active site. ...

-Matching approach. ...

-Ligand fit approach. ...

-Point complementarily approach. ...

-Fragment-based method. ...

-Distance geometry. ...

Inverse docking.

Molecular Docking Approaches

Numerous docking methods have been developed in the past for structural determination of protein-peptide complexes. Broadly, these methods can be classified into the following 3 categories;

i) protein-peptide docking,

ii) protein-protein docking and

iii) protein-small molecule docking

Methodologies for ASD:

Various preparation techniques were reported and captured in Fig. 2. Those techniques are melt fusion technique like hot melt extrusion, SCF cryogenic techniques, solvent evaporation technique including spray drying and solvent evaporation by rota evaporator, cyclodextrin-based inclusion complex techniques (co-evaporation, kneading, lyophilization/freeze-Drying technique, microwave irradiation method), electrostatic spinning, electrostatic blowing, electrospraying film casting. These techniques designed based on principles of molecular solubilizing mechanism such as micellar solubilization, complexation, increased porosity, or decreased particle size, and it should be deviated from polymer-based ASD (He and Ho, 2015). The different methods for preparing amorphous solid dispersion.
V. RESULTS AND DISCUSSION. 
Pre-formulation studies.
1. Melting point. The melting point of hesperidin was found to be 258° to 260°C, which is agreed with the existing literature.
2. UV Spectroscopy of the drug and calibration curve preparation.
The solution of hesperidin showed an absorption maximum ($\lambda_{\text{max}}$) at about 283 nm (Figure 1). The scanned graph was according to reported literature and hence confirmed that the obtained drug sample as hesperidin. The calibration curve was plotted between the concentration and absorbance (Figure 2). The straight-line equation was $y = 0.033x + 0.013$, and the regression coefficient ($R^2$) square (0.996, which shows a good correlation between concentration and absorbance.
3. Solubility of hesperidin in different solvents. The solubility of hesperidin was determined in four different solvents (including distilled water, 0.1 N NaOH, ethanol, and 0.1 N HCl) and depicted in Table 2.

The present study aimed to formulate solid dispersion of hesperidin using natural polymers to enhance the water solubility of hesperidin. The solubility of hesperidin was found high in basic medium (0.1N NaOH) and lower in acidic (0.1N HCl). The solid dispersion of hesperidin was prepared in Ocimum mucilage and mannitol by the hot-melt extrusion method and was characterized for drug content. Out of the five prepared solid dispersion formulations, F4 showed a marked increase in solubility compared to pure hesperidin. The FTIR confirmed no interaction between drug and polymer as characteristic peaks of hesperidin and polymers retained themselves.

REFERENCES
[7]. Pawłowska, L. Flavonoids in the leaves of Polish species of the genus Betula L. V.


