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Formulation and Evaluation of liquisolid compact of 6-gingerol loaded medicated lozenges for motion sickness

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ABSTRACT:

6-gingerol displays low and variable bioavailability because of its poor aqueous solubility and high log P-value. The present investigation was aimed to improve the dissolution profile of 6-gingerol by using a simple, scalable and cost-effective technique of liquisolid compact. The results of in-vitro dissolution test proved that liquisolid compacts have significantly higher dissolution rate than tablets containing pure drug. Locally-acting lozenges are among the most common types of solid dosage forms applied in the oral cavity. Since no guidance on the in vitro demonstration of local bioequivalence is available, we wanted to develop a new bio-predictive test method for dissolution of lozenges based on a set of physiological parameters relevant to lozenge dissolution in the oral cavity. An in vivo sucking study determining the impact of different lozenge (candy) bases and flavors on sucking times, saliva osmolality and salivaryflow rates was performed in 6 volunteers. In vivo sucking times were compared with in vitro dissolution times observed in experiments with official dissolution methods. In vitro dissolution times of all formulations were significantly longer than average in vivo sucking times (20–30 vs. <5 min) indicating that official test methods are not applicable for predicting in vivo dissolution of lozenges. Therefore, we developed and evaluated a novel test apparatus enabling the simulation of forces applied by tongue and hard palate during sucking. Results obtained in a first set of in vitro experiments came very close to those obtained in vivo. This novel in vitro approach is thus very promising in terms of predicting the bioequivalence of locally-acting lozenges.

I. INTRODUCTION:

People who get carsick, seasick or airsick are experiencing motion sickness. The condition causes cold sweats, nausea and vomiting. Women and children are more prone to motion sickness, but it can affect anyone. You can take steps while traveling to reduce your risk of getting sick. Medications like the lozenges can prevent nausea. Bioavailability of a drug depends upon the drug solubility in an aqueous environment and drug permeability through lipophilic membranes. Usually only solubilised drug molecules can be absorbed by the cellular membranes to subsequently reach the site of drug action. The dissolution properties of a drug and its release from a dosage form have a basic impact on its bio-availability. The poor dissolution characteristics of a water insoluble drugs are major challenge for pharmaceutical scientist.Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules Solubility is one of the important parameter to achieve desired concentration of drug present in systemic circulation .The dissolution rate is the rate limiting factor in drug absorption for class II (low solubility and high permeability) and class IV (low solubility and low permeability) drugs as defined in the Biopharmaceutics classification system(BCS)'. The selection of non-toxic hydrophilic solvent, carrier, coating excipients and its ratios are independent of the individual chemical entities and it leads to enhance the solubility and bioavailability. Lozenges are solid dosage forms that are intended to be dissolved or disintegrated slowly in the mouth. They contain one or more active ingredients and are flavoured and sweetened so as to be pleasant tasting. It is generally used for their topical effect, but may also have ingredients that produce a systemic effect. It is used to medicate the mouth and throat for the slow administration in digestion or cough remedies. Lozenges may contain an anaesthetic, a demulcent, or an antiseptic.Lozenges provide a pleasant dosage form for patients who are unable to swallow other types of solid dosage forms. Because lozenges are formulated to taste good, they must be kept out of

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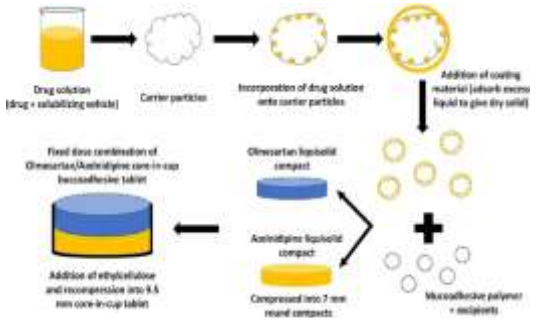
the reach of children, who may view them as candy. Types of lozenges can be ordered as hard candy, chewable gummy gel, and hand-rolled lozenges. Lozenges are produced mostly for the children.

II. METHODOLOGY:

6-gingeroldrug was obtained as a gift sample from Herbalcreation (Uttarakhand), Indiaand all other reagents used were of highest purity andanalyticalgrade.Doubledistilledwaterwasusedthroughoutthe experimentalwork.

SOLUBILITY STUDIES:

To Take 5 boiling test tube. Add pinch of drugs in each tube. Then add glycerol, water, propylene glycol, tween 80, PEG400 in separate test tubes and stir continuously, then sonicate for 15 mins. After that kept in shaker with temperature25℃for 48 hrs (REME,ISO 9001:2000, CIS-24BL). Then centrifuge for 30 mins and analysed in UV spectroscopy at the wavelength of 280nm.



To find out the best suitable carrier and coating material ratios.

LIQUISOLID TECHNIQUE:

The liquisolid formulation was obtained by mixing the drug with non-volatile solvent and then the drug solution was mixed with carrier excipients where coating of the drug molecule within film is formed .Theresultingliquid medication–carriersystemwasadsorbed on a coating agent to get a dry, free-flowing and non adherent powder that can be easily compacted into tablets. So screening of non-volatile solvents, carrier and coating material was essential.

Screening of non-volatile solvents:

For screening, various non-volatile solvents such as Tween 20, Tween 40, Tween 60, Tween 80, Tween 85,Polyethylene glycol 200, Polyethylene glycol 400, Polyethylene glycol 600 is selected and excess quantity of drug and inclusion complex were added into it. These suspensions were kept for 48 hrs. on an orbital shaker at room temperature and then filtered & analyzed for best non-volatile solvent .

Screening of carrier and coating materials:

Carrier & coating material selection were based on liquid load factor and flowable liquid retention potential. The flowable liquid retention potential (Φ- value) of a powder means maximum amount of a non- volatile liquid retained inside powder bulk to maintain adequate flowability. The liquid load factor (Lf) is the mass ratio of the liquid medication to the carrier powder in the liquisolid formulation (W/W). To calculate Lf, non-volatile solventwas dropwise added to 10 g carrier powder followed by blending for 1 min and carrier powder was evaluated for flowability . Lf and Φ-value were determined by,

Lf = Φ carrier + Φ coating (1/R) .

Φ value = weight of liquid medication / weight of powder mixing for a period of 10 to 20 minutes in a mortar. Then coating material (Aerosil 200) was added to the above mixture and mixed it thoroughly.

Then to the above mixture 5% disintegrant (sodium starch glycolate) and glidant (talc) were added and mixed. The final mixture was compressed into tablet by direct compression.

CHARACTERIZATIONOFFORMULATION:

Fourier transform infrared spectroscopy (FTIR)

FTIR spectroscopy helps in the determination of any kind of chemical interactions among drug and excipients used in the formulation. The optimized 6-gingerol formulation were obtained in the frequency range of 4000–500 cm^{-1} and resolution of 4 cm^{-1}.

Differential scanning calorimetry (DSC)

DSC is a method for the detection of any physicochemical interaction between drug and excipients. The optimized formulation to be subjected to thermal analysis using a differential scanning calorimeter for drug-excipient compatibility study over a temperature range of 0 °C–450 °C with a heating rate of 10 °C/min. The atmosphere around the sample cell was purged with nitrogen 200 mL/min. 4.0–6.0 mg sample amount

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was used for DSC testing. The instrument was calibrated by using indium and zinc as a standard and empty pan was used as a reference.

X-Ray diffraction (XRD)

For the identification of crystalline structure after complexation, the XRD study of the pure drug and 6-gingerol liquisolid compact inclusion complex was carried out as outside analysis with Cu- target X-ray tube and Xe-fill detector over a scope of 5–85 (2θ). The conditions were 40 kV voltage and 20 mA current

Drug entrapment studies

The entrapment efficacy of 6-gingerol loaded lozengs can be determined by using the cooling centrifuge machine. By diluting 1 part of preparation with 10 ml of solvent and afterward centrifuge -4˚C for 30 min with RPM equal to 18000. At this point the supernant solution will be collected and analyze UV/V spectroscopy to determine the quantity of free drug. The ultimate value of entrapment efficacy will be calculated by following formula

% entrapment=Total drug-Drug in supernatant liquid/Total drug X 100

Drug content The drug content can be determined by using UV Shimadzu spectrophotometer

III. MATERIALS & METHODOLOGY:

Preformulation study is the characterization of the physiochemical parameters of the drug substance by the application of biopharmaceutical principles with the goal of designing an optimum drug delivery system. The characterisation of drug and the drug-excipient compatibility information decides most of the subsequent events and approaches in development of the formulation. Preformulation study involves the physiochemical characterization of the drug, solubility determination of the drug. determination of the drug- excipient compatibility, development of the analytical methods and the stability studies. The prepared powder blend were subjected to evaluation as per the methods suggested in the Indian Pharmacopoeia like angle of repose, bulk density, tap density, compressibility index, Hausner's ratio.

A. Angle of repose

The angle of repose is the maximum angle which is formed between the surface of a pile of powder and horizontal surface. It is determined by the funnel method. A funnel was kept vertically at a specified height and the funnel bottom was closed. 10 gm of sample was filled inside the funnel. Then funnel was opened to release the powder to form a smooth conical heap which just touches the tip of the funnel. From the powder cone, the radius of the heap (b) were measured. The angle of repose is represented us and is calculated

B.Bulk density

The bulk densities of the samples were determined by transferring the accurately weighed sample ofpowderto the graduated 50 ml measuring cylinder .The initial volume (bulk volume)and weight was noted.

C. Tapped density

An accurately weighed powder sample was transferredto the graduated 50 ml measuring cylinder and wasplaced on the tap density apparatus. The apparatus was operated for a fixed number of taps. The final volume(tap volume) of thetapped mass. was noted.

D. Hausner's ratio:

Hausner's ratio is the ratio of the initial volume of thepowder mass to the final volume of the.

E.Compressibility:

The compressibility index is determined from the tap volume and bulk volume. The basic method used for the determination of compressibility index is to measure the bulk volume and the final tapped volume after a fixed number of tapping until no change in volume occurs. It is represented in percentage.

EVALUATION OF PHYSICOCHEMICAL CHARACTERISTICS OF OPTIMIZED 6-GINGEROL FORMULATION:

PRE & POST – COMPRESSION PARAMETERS

The pre-compression parameters of formulations such as tapped density ,bulk density, angle of repose , carr's index and Hausner's ratio were performed to check the feasibility of powdered complex for compression parameters of formulations such as weight variations , thickness, friability and content uniformity were carried out per standard methods of pharmacopeia of tablet powder com[plex.

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DISINTEGRATION TEST

The disintegration test was carried out in 6.8 pH phosphate buffer at 37°C ± 0.5°C and the time taken for the disintegration of tablets were noted. prepared Experiments were performed in triplicate.

DISSOLUTION STUDIES

USP dissolution test apparatus type II (Paddle) was used for dissolution studies. A dissolution test was carried out using 900 ml of phosphate buffer 6.8 pH at 37 ± 0.5°C temperature and 75 RPM. 5 ml sample solutions were collected at a precise time interval of 5, 10, 15, 20, 25, and 30 min and an equivalent volume of fresh solution was added to maintain the sink condition. The sample solution was analysed at 272 nm using a spectrophotometer against a suitable blank

HARDNESS- This is determined by Pfizer or Monsanto hardness tester.

DIAMETER AND THICKNESS- This is determined by Vernier caliper.

DRUG EXCIPIENT INTERACTION STUDIES- Determined by FTIR.

FRIABILITY - Determined by Roche Friabilator operated at 25rpm for 4min

WEIGHT VARIATION- 20 lozenges are weighed and average weight is determined. Individual weight is compared to the average weight.

IN-VITRO DRUG RELEASE- This is carried out in USP II paddle type dissolution apparatus

DRUG CONTENT- Appropriate number of lozenges are crushed and dissolved in an appropriate solvent and the absorbance of the solution is measured spectro photometrically

STABILITY STUDIES

The formulation was subjected to stability study at 40°± 2 °C and 75 ± 5% RH conditions for 1 month to evaluate storage condition. After 10, 20 and 30 days the formulation it is analysed for content uniformity and dissolution rate as per the procedures reported.

IV. CONCLUSION

The work done for solubility enhancement of 6-gingerol liquisolid compact techniques exhibited higher solubility and dissolution as compared to a pure drug of marketed formulation . Based on the results, it can be concluded that novel formulation will give immediate drug release with reduced dose frequency.

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