Larix Publications

Journal of Pharma Research

https://jprinfo.com/

Vol. 10, Issue 5 , 2021 ISSN: 2319-5622

USA CODEN: JPROK3

Review Article

A REVIEW TO FORMULATE A LIQUID DOSAGE FORM FOR TARGETING GLUCOSE ALTERED METABOLISM FOR COVID-19

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Received on: 01-06-2021; Revised and Accepted on: 08-10-2021

ABSTRACT

Over a decade, there is an amazing progress in research on 2-DG and its analog. Importantly, most of their mechanisms of action showed that virus infection induces glucose influx and glycolysis resulting in the selective of high accumulation fluorescent Glucose/ 2-DG analogue, 2- NBDG in these cells, many of which could have useful applications in various treatments. Subsequently, 2- DG reduces the virus multiplication and alleviates the cells from the infection induced cytopathic effect (CPE) and cell death. The drug developed by DRDO in collaboration with Hyderabad- based Dr Reddy's Laboratories was approved by the Drugs Controller General Of India (DGCI) for emergency use as an adjunct therapy in moderate to severe coronavirus patients having potential to become a game changer in the fight against the Covid pandemic. Clinical trials of 2-DG have demonstrated the challenges in its use in monotherapy due to poor drug-like characteristics, leading researchers to focus on improving bioavailability and achieving higher therapeutic concentrations. The liquid dosage for the pseudo glucose drug to be formulated and evaluated may show the immediate effect when comparing to 2- DG solid dosage forms. The formulated oral dosage form may also be more helpful for the diabetic patients as it excludes the sucrose ingredient.

Keywords: 2- DG, Covid, glycolysis, oral liquid dosage form, pseudo glucose

Introduction:

The present review is to conceptualize a liquid dosage form for targeting glucose altered metabolism for Covid-19. The present study relates to a process for the synthesis of 2-deoxy-D-glucose oral liquid dosage forms and also helps to understand the interactions between SARS-CoV-2 and the immune system. It also reviews the process to develop and evaluate an oral liquid dosage form which may be more palatable, efficient and cost friendly.

2-DG is a synthetic glucose analog, where the 2-hydroxyl group is replaced by hydrogen similarly to D-glucose thereby 2-DG is transported across the BBB and quickly taken up into cells mainly by glucose transporters (facilitated diffusion), in particular GLUT1 and GLUT4, although active transport via SGLT transporters. Once inside the cells, 2-DG is phosphorylated to 2-deoxy-d-glucose-6-phosphate (2-DG-6-P), a charged compound that is trapped inside the cell. However, because it is missing the 2-OH group, it is unable to undergo isomerization to fructose-6-P, leading to the intracellular accumulation of 2-DG-6-P and inhibition of glycolysis and glucose metabolism. As 2-DG is relatively non-

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DOI: https://doi.org/10.5281/zenodo.6473400

toxic and orally available, it is an attractive tool for potential anticancer therapy. Its diagnostic potential has been widely explored, but therapeutic applications have yet to be achieved. It seems that its most promising application may be as a synergistic agent in combination with cytotoxic therapies [1].

The antiviral effect of 2-DG has been recognized in previous studies. Inhibition of multiplication has been reported for some enveloped viruses such as an influenza virus, sindbis virus, semliki forest virus, herpes simplex virus, respiratory syncytial virus and the measles virus [2].

2-Deoxy-D-glucose is a glucose molecule with the 2-hydroxyl group substituted by hydrogen, preventing it from being glycolyzed further. As a result, it acts as a competitive inhibitor of glucose-6 phosphate production from glucose at the phosphor glucoisomerase stage. As a result, labeled types of 2-deoxyglucose are the useful markers for tissue glucose absorption and hexokinase function. 2-DG is taken up by the cell's glucose transporters. As a result, cells that take more glucose, such as tumor cells also may take in more 2-DG. Since 2-DG inhibits cell growth, it has been proposed as a tumor treatment, and 2 currently being tested in clinical trials [3, 4].

The drug has gone through the three phases of clinical trials. Published information for the trials is not yet available; however, as per the Ministry of Defense press release dated 8th May, 2021. Clinical trial results have shown that this molecule helps in faster recovery of hospitalized patients and reduces supplemental oxygen dependence. Higher the proportion of patients treated with 2-DG showed RT-PCR negative conversion in COVID patients [3].

2-DG competes with glucose and can competitively inhibit glucose transport. Oxygen deficiency is more common in the intratumoral environment, increasing the expression of glucose transporters and glycolytic enzymes, which increases 2-DG uptake in cancer cells as compared to normal cells in an aerobic environment. After entering the cell, 2-DG is phosphorylated by hexokinase II to 2-deoxy-d-glucose-6-phosphate (2-DG-6-P) unlike glucose. 2-DG-6-P cannot be further metabolized by phosphoglucose isomerase (PGI) to 5 carbon ring. This leads to the accumulation of 2-DG-6-P within the cell, allosteric and competitive inhibition of hexokinase, isomerase depletion of ATP, cell cycle arrest and the inhibition of cell growth, eventually, cell death [1, 5].

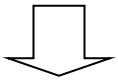
Therefore, if there is greater amount of the accumulated 2-DG-6-P, the greater will be the effect on glycolysis. Inhibition of glycolysis is more effective under hypoxic conditions, because cancer cells can continue to produce ATP using alternative sources, such as fatty acids or amino acids. In tumor cell as a consequence of their enhanced glucose uptake and dependence on glycolysis, are commonly used for cancer detection, staging, monitoring response to the treatment, and detection of recurrence in the several tumor types. Moreover, due to the ability of 2- DG to freely penetrate the BBB, it has been proposed for use in brain tumor diagnostics [6, 7].

Selection of materials used for development of oral liquid dosage form

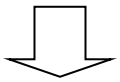
The following ingredients may be selected which can be used to formulate oral liquid dosage form [8, 9, 10].

S.NO	INGREDIENTS	CATEGORY
1	Pseudo glucose	Active pharmaceutical ingredient
2	Propylene glycol, glycerol, ethanol	Co-solvents
3	Sodium carboxy methyl cellulose (Cellulose derivatives)	To enhance the viscosity
4	Compound sodium cyclamates ,sorbitol, xylitol, mannitol, saccharin and aspartame	Low-calorie sweetener alternatives to sugar
5	Butylated hydroxyl toluene, sodium meta bisulphite, sodium sulphite, citric acid, ascorbic acid.	Antioxidants
6	Parabens, benzoates, sorbates	Preservatives
7	Carotenoids, chlorophylls, caramel, cochineal, saffron, peppermint, lemon & orange	Coloring & Flavoring agents
8	Lactic, citric , acetic acid or sodium salts	Buffering agents

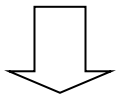
Steps involved in manufacturing of liquid dosage forms



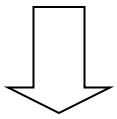
Drug (pseudo glucose) + Range of excipients include the vehicle (solvent) Purified water



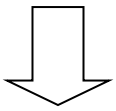
Co- solvents (To enhance the stability of therapeutic substance in the vehicle), preservatives (against microbial contamination)



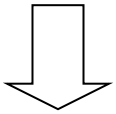
Viscosity modifiers (cellulose derivatives), Antioxidants (butylated hydroxyl toluene)



Coloring & Flavoring agents (oral only)



Buffering agents (to regulate the pH of the formulation)



2-DG oral liquid dosage form

Evaluation parameters for oral liquid dosage form

1. Microbial testing of the finished product

This test is mainly performed to check whether the finished product has any presence of the microorganism or not.

For this test two media were commonly employed namely,

1. Tryptone Soya Agar Medium (TSA) for bacteria.

2. Sabouraud Chloramphenicol Agar Medium (SCA) for yeast and mould.

Steps:

- TSA and SCA medium were prepared and autoclaved for 15 min at 121°C.
- 10 ml of the sample was added to the broth and mixed well.
- By using a micropipette, 1 ml from the broth was transferred to the two sterile petri dishes, one for the bacteria and the other for fungi.
- 20 ml of the TSA and SCA medium were poured into their respective plates.
- The plates were then rotated in clockwise and anti-clockwise directions for even spreading of the sample.
- The plates were allowed to solidify.
- TSA plate was incubated at 37°C for 48 hours in an inverted position.
- SCA plate was incubated at 20 -25°C for 5 days in an upright position

The colonies formed were counted and recorded.

Acceptable criteria

Bacteria: not more than 300 colonies per plate.

Fungi: not more than 100 colonies per plate

FORMULA (CFU/ML) =

$$\frac{\text{Number of colonies x Amount of sample taken}}{\text{Dilution factor}}$$

2. Uniformity of content

- This test is applicable to the single dose liquid in suspension form or liquid that contain less than 10 mg or less than 10% w/w of active ingredients (as per IP).
- The test for uniformity of content should be carried out only after the contents of active ingredient(s) in a pooled sample of the liquid has been shown to be within an accepted limits of the stated content.

Method

To determine the content of active ingredient(s), each of 10 dosage units were taken at random using the method given in the monograph or by any other suitable analytical method.

Acceptable criteria

- The preparation complies with the test if the individual values thus obtained are all between 85 to 115% of the average value.
- The preparation fails to comply with the test if more than one individual contents are outside the limits of 85 to 115% of the average value or if one individual contents are outside the limits of 75 to 125% of the average content.
- If one individual contents are outside the limits of 85 to 115% of the average content but within the limits of 75 to 125% repeat the determination using another 20 dosage units.

3. Uniformity of volume

- To ensure that the deliver volume of dosage form that is declared is on the label.
- Apply for both liquid preparations that is constituted from the solid upon addition a designated volume of specific diluents.
- Not for the single unit container when monograph include the test for uniformity of unit.

Method

- First determine the density of the liquid (if required)
- Select NLT 30 containers and proceed
- For oral solution and oral suspension: shake
- For powder: reconstitute as directed

4. Mass variation

- According to BP, accurately weigh the amount of liquid that is removed from each of 10 individual containers in conditions of normal use.
- If necessary compute the equivalent volume after determining the density.

Method

Calculate the active substance content in each container from the mass of the product removed from the individual the active substance content in each container from the mass of the product removed from the containers and the result of the assay

Calculate the acceptance value using the following formula:

$X1 = W1 . A / W$

Where, X1, X2……. .Xn = individual estimated contents of the dosage units tested,

W1, W2 …….W n = individual masses of the dosage units tested

A= content of active substance (percentage of label claim) obtained using an appropriate analytical method

W = mean of individual weights (W1, W2.....Wn)

Acceptance criteria

Unless otherwise specified consistent with BP the requirement is met if the acceptance value of 10 dosage units is less than or equal to 15 %

If acceptance value is greater than 15% test the next 20 dosage units and calculate the acceptance value

The requirements are met if the final acceptance value ofthe30 dosage units is less the dosage units is less than $(1-25 \times 0.01)M$ or more than $(1+25 \times 0.01)M$ in calculation of acceptance value under mass variation or content uniformity

5. Leakage test

To test the package integrity leakage test is employed. Package integrity reflects its ability to keep to keep potential contamination out

It is because the leakage occur when a discontinuity exists in the wall of a package that can allow the passage of gas under pressure or concentration differential existing across the wall

Method

- Leakage test can be done by the dye bath test the test container is immersed in a dye bath. Pressure and vacuum is applied for some time.
- From the dye bath the container is removed and washed.
- The container is then analyzed for the presence of dye either by means of UV-Spectroscopy or visually.
- The dye used may be of blue, yellowish-green, green color.
- To increase the capillary migration through the pores the dye test can be optimized by the use of a low viscosity fluid in the dye solution.
- The dye test is mostly accepted in industry and is approved in use of drug. The test is cheap and required no special equipment.
- For ampoules and vials this test is used.
- Discharge the containers contents into the suitable tared container (5s unit dosage, 10s multi dosage)
- Determine mass and determine volume using density deliverable volume content.
- Determine volume by pouring content into dry graduated.

Acceptable criteria

For multiple unit container: 10 unit

AVG: NLT 100 %

If an average volume is less than 100 % but contain of all 10 is more than 95 %

B average volume is NLT 100 % & volume of NMT container is less than 95 % but not less than 90 %

6. Uniformity of mass

According to BP this test is for the solutions or emulsions, single-dose powders and granules for syrups, oral solutions, oral suspensions and single-dose powders for oral drops

Method

- For this test weigh individually the contents of emptied as completely as possible and determine the average mass as stated by BP.
- For single-dose preparations that are solutions or emulsions for single dose powders and granules for syrups oral solutions, oral suspensions and single dose powders for oral drops according to BP not more than 2 of the individual masses deviate from the average mass by more than the percentage.

7. Consistency test

To evaluate the texture and homogeneity of the formulations the consistency of the formulations and presence of coarse particles were used [10, 11, and 12].

Summary

The principle of the study is cheat the cheater concept that is any virus once inside the body makes its own copies by cheating our human cells and takes their protein to multiply itself. For every doubling of the virus cell, it needs glucose for energy purpose and medicine is simply a pseudo glucose which the multiplying virus intakes but actually this glucose makes it neuter or unable to multiply thus cheating the cheater once the rapid multiplication of virus is halted, our own anti bodies can readily combat it and overpower within hours. The clinical trials established that a higher proportion of those administered with the DRDO-developed drug "improved symptomatically" by the third day of their treatment, as compared to those provided the standard treatment. The drug has developed 2- deoxy-D-glucose (2-DG) for emergency use, as additive therapy for moderate to severe covid-19 patients.

Conclusion

Liquid dosage forms are helpful for patients who have difficulty to take the tablets or capsules, as mighty be the case with the pediatric or geriatric patients and may have some hope on the oral liquid dosage form which can give a better result in the treatment of covid-19. The present review to formulate a liquid dosage of 2-DG is more helpful for diabetic patients because this formulation excludes the sucrose ingredient and be categorized as nutritive or simple syrup.

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Article Citation:

Authors Name. ASRA JABEEN. A REVIEW TO FORMULATE A LIQUID DOSAGE FORM FOR TARGETING GLUCOSE ALTERED METABOLISM FOR COVID-19 J Pharm Res, 2021; 10(5): 31-36
DOI: https://doi.org/10.5281/zenodo.6473400