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FORMULATION AND IN-VITRO EVALUATION OF GLIBENCLAMIDE DRY EMULSION IN VEGETARIAN CAPSULES

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Abstract:

The purpose of this study is to improve the bioavailability and dissolution of Glibenclamide in the preparation of a dried emulsion. This dry emulsion formulation is filled in HPMC capsules as it is of vegetarian source but not gelatin because of several drawbacks. The animal source of gelatin may be a problem for some consumers, such as vegetarian and religious groups or ethical groups, since unmodified gelatin is subjected to cross linking in contact with aldehydes, solubility problems can be expected with certain fill formulations. Dry emulsions are prepared by the drying of liquid emulsions in which there is a solid form in the aqueous phase. The solid support provides the dry and bulk emulsions. In this preparation the emulsion was dried, sesame oil in which the drug is soluble, hydroxyl propyl methyl cellulose as the organic filler and Tween 80 as the surfactant is used. The dried emulsion was evaluated for the drug content, determination of the globular size and surface characterization, in vitro release of the drug in dry emulsion was studied by a type II USP-type paddle dissolving apparatus. This study revealed that the solid dry emulsion technique proved to be promising and useful for improving dissolution.

Key Words: *Glibenclamide, Dry Emulsion, HPMC capsules, Sesame oil*

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INTRODUCTION:

The formulation of the dry emulsion is intended to improve the bioavailability [1, 2] of the drug substances and to reduce their side effects. Dry emulsions are attractive because they are physically and microbiologically stable formulations. They represent a potential system for the administration of oral medicines for lipophilic and sparingly soluble pharmacological substances. The dry emulsions [3] are prepared by techniques such as freeze drying, spray drying and rotary evaporation. For the preparation of dry emulsions, the organic fillers used are lactose, mannitol and malto-dextrin. Co-solvents commonly used are polyethylene glycol, propylene glycol, glycerol, and the like. The thickeners used are natural and synthetic gums, cellulose derivatives and colloidal silica. The sweetening agents used are glucose, aspartame, sucrose and the like. For the preparation of oil-in-water emulsions, medium-chain triglycerides are generally used as the lipid phase, the preferred oils being sesame oil [4], olive oil and peppermint oil. Glibenclamide [5] is a second generation sulphonylurea anti diabetic agent with very low solubility in biological fluids. Therefore, in order to improve the bioavailability and stability of the drug, it is formulated as a dry emulsion.

Hard shell capsules [6], which are normally used for dry powdered ingredients or miniature pellets. The cases are produced using fluid arrangements of gelling operators, for example, creature proteins, predominantly gelatin and non-gelatin, for example, vegetable polysaccharides or subsidiaries thereof, for example, carrageenans or changed types of starch and cellulose. Regardless of the considerable favourable circumstances of gelatin containers, gelatin has a few disadvantages that breaking points its utilization for cases. The animal source of gelatin may be a problem for some consumers, such as vegetarian and religious groups or ethical groups, since unmodified gelatin is cross linked upon contact with aldehydes, solubility problems may be encountered with certain formulations filling. Vegetarian capsules [7] consist of starch, HPMC, PVA and alginate.

MATERIALS AND METHODS:

Materials: Glibenclamide was obtained as a gift sample from Hetero Drugs Pvt. Ltd. (Hyderabad, India). The sesame oil came from the Empire Scientific Company. Polyethylene glycol was donated by SD fine chemicals; Tween 80 and Span 80 were donated by Gattefosse (Mumbai, India). HPMC K4M obtained from Ontop Pharmaceuticals. HPMC capsules were administered by natural capsules pvt Ltd, India.

Method of preparation of dry emulsion: The drug is thoroughly mixed with polyethylene glycol using a magnetic stirrer. In another beaker, an aqueous phase was taken and to this gum, organic filler was added and a surfactant added and well stirred until a homogeneous solution was obtained. Subsequently, the polyethylene glycol with the drug was added to this solution and thoroughly mixed. The above mixture was maintained on a magnetic stirrer and the oily phase was added drop wise. Stirring was continued until a milky-white emulsion with a desired droplet size was obtained. Now drying this emulsion, the samples were subjected to freeze-drying (lyophilization) [8-10]. The emulsion was carefully dried and the emulsion powder was collected and dried and stored in a sealed vessel. The stability of the emulsion is verified by keeping it for 48 hours.

Preparation of the solution for the calibration curve: Solutions of 2 to 10 µg / ml were prepared from the standard working solution (100 µg / ml) and the calibration curve was plotted at concentrations of 2, 4, 6, 8 and 10 µg / ml. The standard calibration curve of Glibenclamide in 0.1 N HCl at 339.6 nm was plotted taking absorbance on the Y axis and concentration on the X-axis and following the beer's law.

Pre-formulation Studies:

Studies of compatibility with excipients: Before formulating the pharmacological substances in dosage form, it is essential that they are chemically and physically characterized [11, 12]. The preformulation studies provide the information necessary to define the nature of the drug substance and provide a framework for the combination of drugs with pharmaceutical excipients in the manufacture of a dosage form. In this compatibility study, one of the requirements for the selection of polymers or vehicles suitable for the pharmaceutical formulation is their compatibility.

FTIR studies: FTIR studies were carried out using the potassium bromide pallet method.

Melting point determination: The melting point of the Glibenclamide was determined by capillary method.

Solubility: The solubility of Glibenclamide was determined by adding the excess amount of drug but measured in a 100 ml volumetric flask containing 0.1 N HCl and maintained under stirred conditions at 370 ° C ± 0.5 in a stirrer water bath for 2 hours. The dispersions were filtered on Whatmann filter paper and analyzed for the amount of dissolved drug.

Glibenclamide pure drug analysis: The absorbance of the prepared solutions was checked using a UV spectrophotometer at 339.6 nm. 0.1N HCl was used as the blank.

Evaluation Studies [13-15] for the Formulated Dry Emulsion:

Dry emulsion is subjected to the following evaluation tests.

Drug entrapment:

The drug entrapment of the prepared dry emulsion should be in the range of 98.772 to 101% w/w.

***In-vitro* dissolution studies [16, 17]:**

In vitro drug release studies from dry emulsions were performed using a USP type 2 dissolution apparatus (paddle apparatus) at 25 rpm. A dry emulsion preparation equivalent to 5 mg of Glibenclamide was taken. The dissolution medium consisted of 900 ml of distilled water maintained at 37 ± 0.5 ° C. At predetermined time intervals 5 ml of aliquot were removed and an equivalent volume of fresh solution medium was immediately added. The amount of drug released was estimated by measuring the absorbance at 339.6 nm using a spectrophotometer. A cumulative percentage of drug release was observed over a time interval of five minutes. The dissolution profiles of the pure drug and dry emulsion were compared on the basis of the time required to release the maximum drug.

Particle size analysis:

The particle sizes of the charged formulations were measured using an optical microscope equipped with an ocular micrometer and on stage and the particle size distribution was calculated.

For this, the Olympus model (SZX-12) was used with a resolution of 30 x. The instrument was calibrated in an eyepiece unit. The micrometer was equal to 1/30 mm (33.33 µm). In all measurements, at least 100 particles were examined in five different domains.

Each experiment was carried out in triplicate. The dried emulsions were diluted to 100 ml with distilled water. The droplet size distributions and the poly dispersibility index of the resulting dry emulsions were determined using a particle size analyzer.

Globule size determination [18]:
Microscopic examination of the emulsion was observed before and after reconstitution, the minimum size of the oil globule in the micron range is important since the reduction of the surface leads to an improvement in the solubility and dissolution rate of an emulsion.

Estimation of drug content:
The percentage of the drug content of the dry emulsion formulations was estimated by dissolving the appropriate amount of dry emulsion equivalent to 100 mg in water. The samples were thoroughly mixed to dissolve the drug in water. The samples were sonicated by ultrasound for 15 minutes and analyzed using a UV spectrophotometer and recorded absorbance.

Table 1: Formulation Table with selected excipients

Ingredients	F1	F2	F3	F4
Glibenclamide	5mg	5mg	5mg	5mg
Sesame oil	100mg	200mg	100mg	300mg
Tween 80	720mg	640mg	-	200mg
Span 80	-	-	180mg	500mg
PEG400	180mg	160mg	720mg	-
HPMC K4M	2g	2g	2g	2g
Purified water	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml

Table 2: Drug Content and Drug Entrapment Efficiency Data of Dry emulsions

Formulation code	Drug content	Drug entrapment efficiency
F1	95.933±0.611	95.04±0.311
F2	97.473±0.351	98.831±0.314
F3	72.966±0.568	70.333±0.709
F4	68.62±0.655	64.933±0.450

All values are expressed as mean ± standard deviation, (n=3)

Table 3: Globule Size Distribution of Dry Emulsion before and after Reconstitution

S.No	Range in micrometer	No. of Globules Before Reconstitution				No. of Globules After Reconstitution			
		F1	F2	F3	F4	F1	F2	F3	F4
1	1-14	325	338	472	512	318	332	439	498
2	15-28	59	36	68	75	54	43	59	67
3	29-42	23	17	32	37	21	22	28	32
4	43-56	18	3	24	20	14	5	21	19

Table 4: cumulative %release of pure drug and formulations

Time	Cumulative % drug release				
	pure drug	F1	F2	F3	F4
5	11.412	51.786	61.146	22.682	25.684
10	13.868	53.352	62.856	23.547	26.981
15	15.226	56.232	63.234	25.874	28.549
30	16.07	57.148	65.852	26.521	30.267
45	17.112	57.956	67.012	27.254	31.584
60	19.064	58.658	67.39	27.851	32.158
75	20.216	58.838	67.678	28.734	32.874
90	20.404	59.378	68.416	29.287	33.291

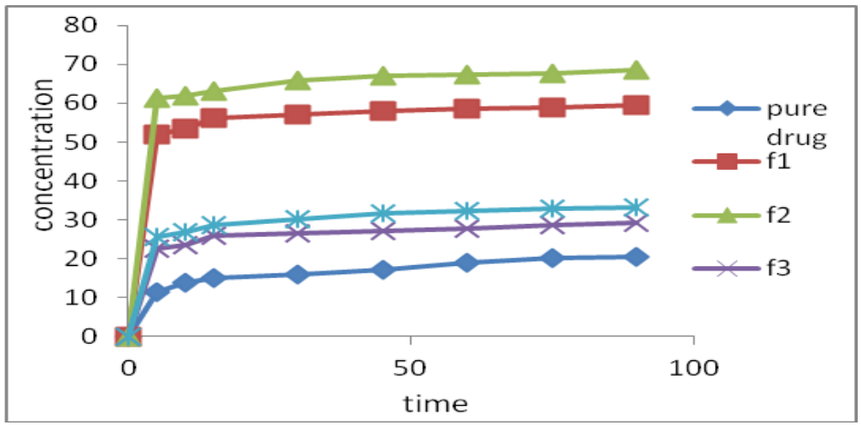

Fig1: Plot of Cumulative % Drug Releaseof dry emulsion formulations

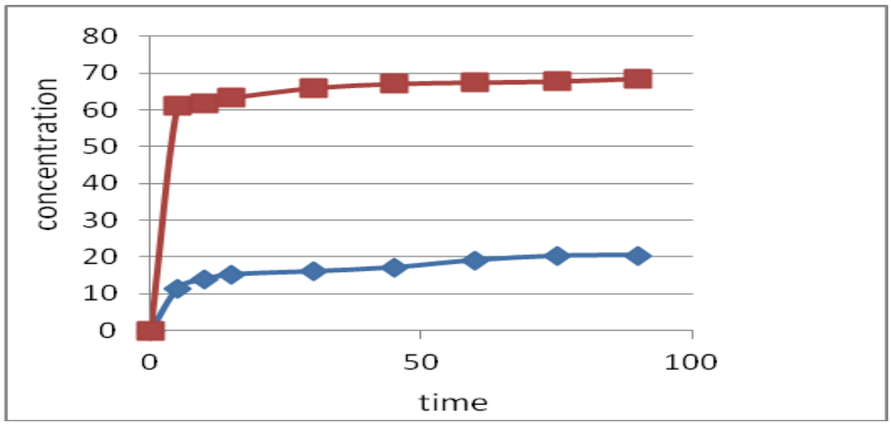

Fig 2: Comparison of In-vitro drug release of pure drug and dry emulsion formulation

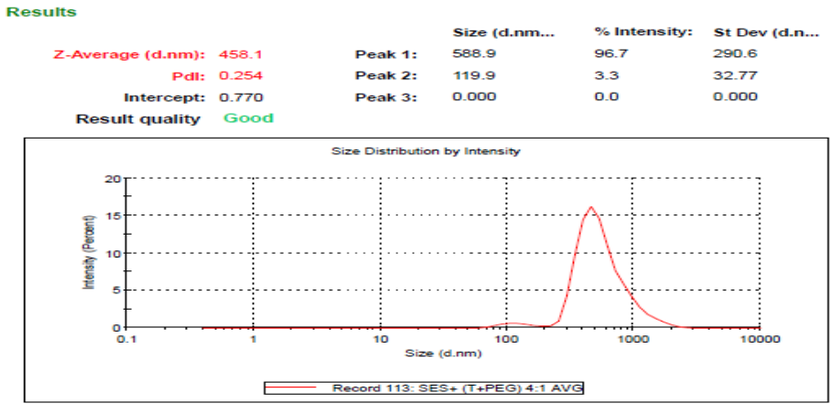

Fig 3: Droplet size distribution of dry emulsion after reconstitution

RESULTS AND DISCUSSION:

Melting point determination:

The melting point of the Glibenclamide was determined by the capillary method. The melting point was 172 ^{0}C.

Evaluation Studies for the Dry Emulsion formulation

The formulated Dry emulsion was subjected to the following evaluation tests.

Drug Entrapment Efficiency:

The drug entrapment of the prepared dry emulsions was found to be in the range of 95.04-98.831 and the values are shown in the Table 2.

Globule size determination:

The size distribution of the globules was analyzed and calculated. Prior to reconstitution, it suggests that the globule size has been reduced, which contributes to the high dissolution rate of the dry emulsion and subsequent reconstitution suggests that the size of the globules remains almost identical, and also suggests the stability of the emulsion, after reconstitution.

Drug Content Estimation:

The drug content for the prepared formulations F1, F2, F3 and F4 was found to be 95.933, 97473, 72.966 and 68.62% respectively.

***In-vitro* Drug release studies:**

From in vitro drug release profile it was found that the % drug release from dry emulsions in HPMC capsules was higher than that of pure drug. The cumulative % drug release for formulations F1, F2, F3 and F4 at the end of 90min was 59.378, 68.416, 29.287 and 33.291% respectively, where as pure drug showed 20.404% drug release in 90minutes. At the end of 90min, formulation F2 showed maximum

cumulative % drug release of 68.416%. Stability studies were conducted for a period of 3 months. The cumulative % drug release for formulations and pure drug at the end of 90 min was shown in Table 4.

CONCLUSION:

By formulating Glibenclamide in the form of a dry emulsion, its solubility and dissolution rate have been improved. The dry emulsion formulation was analyzed for stability studies [19, 20] for 3 months at 45 ° C with 75 ± 5% RH. The emulsion was analyzed by drug trapping and cumulative % drug release over a 3-months period without variation in results. After three months, the dry emulsion was reconstituted and the emulsion formed was stable with the desired consistency and viscosity and without any sign of instability. Compared to the dissolution rate of the Glibenclamide formulations, it was found that pure Glibenclamide <Dry Emulsion. From the previous study, it can be concluded that the dry emulsion formulation (F2) showed immediate release of the drug relative to pure Glibenclamide.

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