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COMPARATIVE *IN VITRO* DRUG RELEASE STUDIES OF GLIMEPIRIDE SOLID DISPERSIONS & METFORMIN MICROCAPSULES

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Glimepiride, Extended release, immediate release, Metformin hydrochloride, Hypoglycemic agents, Synergic effect

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ABSTRACT: The study was undertaken to compare the efficacy and safety of Glimepiride and Metformin in the management of patients with type 2 DM. The present invention is directed to a pharmaceutical composition in the form of a capsule with increased bioavailability as well as the process for obtaining said composition. The tablet of the present invention comprises two active ingredients comprising two oral hypoglycemic agents: one phase with a sulphonylurea, such as immediate release Glimepiride and second phase with a biguanide, such as extended release Metformin hydrochloride (Metformin HCL). This composition of capsule, which can include over 500mg of Metformin HCL (i.e. up to daily requirements of each patient), is to be orally administered once or twice a day. The combination of these hypoglycemic agents has a synergic effect. Finally we can explain that the availability of Metformin-Glimepiride combination can minimize the effects of diabetic conditions. From the complete work we assume that these hypoglycemic agents have a synergistic effect and therefore a greater effectiveness in controlling the blood glucose level in patients with type II diabetes mellitus.

INTRODUCTION: Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications.

The lifestyle modification, diet and exercise of moderate intensity are used to improve insulin sensitivity and are recommended as an integral part of treatment of Type 2 diabetes.

When all these are failed to maintain the adequate glycogenic control, oral hypoglycemic agents are introduced as a treatment approach.

Oral Hypoglycemic Agents (OHAs) can be used either alone or in combination with other OHAs or insulin. The incidence of symptomatic hypoglycemia was higher in the combination therapy than monotherapy¹.

Combination of Glimepiride and Metformin hydrochloride, two antihyperglycemic agents with complementary mechanisms of action, to improve glycemic control in patients with type 2 diabetes.

Glimepiride is one of the third generation sulphonylurea, antidiabetic drug which stimulates insulin release².

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The drug shows low, pH dependent solubility. In acidic and neutral aqueous media, Glimepiride exhibits very poor solubility at 37°C (<0.004 mg/ml). In media pH>7, solubility of drug is slightly increased to 0.02 mg/ml. This poor solubility may cause poor dissolution and unpredicted bioavailability^{2,3}.

Glimepiride is rapidly absorbed by the liver after oral administration. It undergoes extensive first pass metabolism in the liver. It is practically insoluble in water and other aqueous media. The very poor aqueous solubility and wettability of Glimepiride give rise to difficulties in the design of pharmaceutical formulations and led to variable oral bioavailability. A few reports are available on the enhancement of solubility, dissolution rate of Glimepiride. Rate of absorption and/or extent of bioavailability for such insoluble drug are controlled by rate of dissolution in gastrointestinal fluids. The peak plasma concentration (C_{max}) and the (t_{max}) depend upon extent and rate of dissolution of drug respectively. Hence, the present investigation was aimed to increase the rate of dissolution of Glimepiride.

Metformin hydrochloride is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. It decreases hepatic glucose production, intestinal absorption of glucose, improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin is the only oral antihyperglycemic agent that is not associated with weight gain⁴.

In spite of its favorable clinical response and lack of significant drawbacks, chronic therapy with Metformin hydrochloride suffers from certain specific problems of which, the most prominent being the high dose (1.5-2.0 g/day), low bioavailability (60%) and high incidence of GI side effects (30% cases).

Therefore, there are continued efforts to improve the pharmaceutical formulation of Metformin hydrochloride in order to achieve an optimal therapy. These efforts mainly focus on controlled/slow release of the drug. The situation is complicated further with decrease in absorption of the drug with food that delays t_{max} by up to 35 mins⁵.

Bioavailability of the drug has been found to be reduced further with CR dosage forms, probably due to the fact that passage of the CR single unit dosage forms from absorption region to large intestine and most of the drug released at the colon where Metformin hydrochloride is poorly absorbed^{6,7}.

Sustain release formulation suitable for Metformin hydrochloride, therefore, should be a *micro-encapsulation* dosage form, which releases the drug slowly in the stomach for gradual absorption in the intestines. The slow but complete drug release in the stomach is expected to *increase bioavailability* of the drug as well its complete utilization which may results to, lower dose and GI side effects. Multi-unit dosage forms are considered to release the drug at a controlled rate and remain in the stomach for a prolonged period with much less chance of dose dumping. Furthermore they are supposed to cause less gastric adverse reactions and are insensitive to concomitant food intake, thereby reducing inter and intra-patient variability and increasing the predictability of the dosage form.

Objective: The present work is carried out to prepare a dosage form consists of both immediate and controlled release thereby improving the treatment for type – II diabetes. The capsule of the present invention comprises two active ingredients comprising two oral hypoglycemic agents: one phase with a sulfonyl urea, such as immediate release Glimepiride and a second phase with a biguanide such as extended release Metformin HCl.

The combination of these hypoglycemic agents has a *synergistic* effect and therefore a greater effectiveness in controlling the blood glucose level in patients with *type II diabetes mellitus*. Solid dispersions is the one of the most successful strategies to improve the solubility, drug release of poorly soluble drugs and microencapsulation is the successful technique for site specific sustained drug release.

Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with *low gastrointestinal solubility and high permeability*. By improving the drug release profile of these drugs, it is possible to enhance their *bioavailability* and reduce their side effects.

Solid dispersions are one of the most successful strategies to improve the drug release of poorly soluble drugs. The advantage of solid dispersions over other approaches is that many of the carriers that can be applied are already extensively used in the pharmaceutical industry as excipients, so additional toxicity studies above and beyond what is required for the drug itself should not be required. The possibility of combining several carriers to produce an optimized product further extends the range of possibilities for formulation.

MATERIALS AND METHODS: Metformin hydrochloride and Glimepiride were obtained as a gift samples from Aurobindo Pharma Pvt. Ltd, Hyderabad. Calcium chloride, Urea, Sodium alginate, Sodium hydroxide, Hydrochloric acid, and Potassium dihydrogen phosphate were obtained from Royal Madhu Enterprises, Kurnool, and A.P.

Preparation of solid dispersion of Glimepiride:

Solid dispersions of Glimepiride were prepared with carrier's mannitol in 1:0.5, 1:1 and 1:2 weight ratios by fusion method. A weighed quantity of carriers (urea) and Glimepiride were mixed thoroughly and the mixture was subjected to thermal fusion with constant stirring. Then the melt was shock cooled on an ice cooled ceramic tile. The solid mass formed was powdered and kept in desiccators for 48 hours. It was then passed through sieve (No: 100) and stored in airtight container for further studies.

Process optimization: Various concentration of solid dispersion was formulated to study the influence of process variable such as concentration of polymer employed on entrapment efficiency on drug release rate.

Preparation of Microspheres: Microspheres containing metformin were prepared through ionic Gelation process using sodium alginate as a polymer.

Ionic Gelation process: Polymer is dispersed in required amount of distilled water to form a homogenous polymer mixture. The active ingredient Metformin was added to the polymer dispersion and mixed thoroughly with a magnetic stirrer to form a viscous homogenous dispersion. The resulting dispersion was then added manually drop wise into calcium chloride (10%w/v) solution

(40 ml) through a syringe with a needle of size no.20. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce spherical rigid microcapsules having a different coat: core ratio (1:1). Similarly microcapsules with various ratios of polymer were prepared. The obtained beads were filtered using filter paper, washed thrice with distilled water and dried at room temperature for 24 hrs.

Process optimization: Various microcapsules were formulated to study the influence of process variable such as concentration of polymer employed on entrapment efficiency on drug release rate.

Evaluation of solid dispersion and microspheres: The microspheres prepared were evaluated for the following parameters:

1. Angle of Repose
2. Bulk Density & Tapped Density
3. Carr's Index
4. Hausner's Ratio
5. Drug Entrapment Efficiency, Drug Content
6. *In vitro* Drug Release Study

Angle of Repose^{8,9}: Angle of repose is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The flow characteristics of different microcapsules were studied by measuring the angle of repose employing fixed funnel method. The angle of repose was calculated by using the following formula.

$$\tan \theta = h / r$$

$$\theta = \tan^{-1} (h / r)$$

Where, h = height of pile, r = radius of the base of
 θ = angle of repose.

The angle of repose values of Glimepiride solid dispersions and metformin microcapsules were tabulated in **table 1 and 3**.

Bulk Density & Tapped Density^{8, 9}: Bulk density and tapped density were measured by using 10 ml of graduated cylinder. The pre weighed sample was placed in a cylinder; its initial volume was recorded (bulk volume) and subjected to tapings for 100 times. Then the final volume (tapped volume) was noted down. The values of Glimepiride solid dispersions and metformin microcapsules were tabulated in table 1 and 3. Bulk density and tapped density were calculated from the following formulae.

$$\text{Bulk density} = \frac{\text{Mass of Microspheres}}{\text{Bulk volume}}$$

$$\text{Tapped density} = \frac{\text{Mass of Microspheres}}{\text{Tapped volume}}$$

Carr's Index^{8, 9}: Compressibility index (CI) or Carr's index value of micro particles was computed according to the following equation:

TABLE 1: MICROMERITIC PROPERTIES OF GLIMEPIRIDE SOLID DISPERSION

| Drug: carrier | Angle of repose | Bulk density (g/ml) | Tapped density (g/ml) | Compressibility index (%) | Hausner's ratio |
|---------------|-------------------------------------|---------------------|-----------------------|---------------------------|-----------------|
| 1:1 | 23 ^{0.3} ± 32 ⁰ | 0.7 ± 0.002 | 0.5 ± 0.009 | 50 ± 0.112 | 0.66 ± 0.005 |
| 1:2 | 34 ^{0.4} ± 24 ⁰ | 0.4 ± 0.006 | 0.7 ± 0.006 | 46 ± 0.232 | 1.87 ± 0.003 |

Drug Content analysis of Microcapsules: Microcapsules containing equivalent to 100 mg of Metformin were crushed to fine powder in a motor and transferred into 100ml volumetric flask. The contents was dissolved by using 0.1M hydrochloric acidic solution and made up to 100 ml with acidic buffer containing. It was filtered; 5ml of the filtrate was diluted to 50ml using the 0.1NHCl solution. The absorbance of the resulting solution was measured at 300nm.

In vitro drug release studies of Solid Dispersion: Accurately weighed amount of solid dispersion was taken for dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 226nm using phosphate buffer pH 6.8 as dissolution medium. The volume withdrawn at each time intervals were replaced with same quantity of fresh medium.

In vitro drug release studies of Microcapsules: The *in-vitro* drug release studies of Metformin microcapsules were conducted, using the USP type

Carr's Index (%) =

$$[(\text{Tapped density} - \text{Bulk Density}) / \text{Tapped Density}] \times 100$$

The obtained values of Glimepiride solid dispersions and metformin microcapsules were tabulated in table 1 and 3.

Hausner's Ratio^{8, 9}: Hausner's ratio of microspheres was determined by comparing the tapped density to the bulk density using the equation:

$$\text{Hausner's Ratio} = \text{Tapped density} / \text{Bulk Density}$$

The obtained values of Glimepiride solid dispersions and metformin microcapsules were tabulated in **table 1 and 3**.

2 *in vitro* dissolution rate apparatus. The test was performed using 900ml of dissolution medium (0.1NHCl acidic buffer) and a sample equivalent to 500 mg Metformin was subjected to dissolution studies. The paddle was maintained to a speed of 75 rpm and temperature was kept at 37 ± 5 °C. Five ml of the sample was withdrawn at regular intervals of time (0.5 hr) until 12 hrs and replenished with 5ml of fresh dissolution medium. The samples were filtered, suitably diluted and analyzed at 265 nm by using Shimadzu UV-1700 double beam spectrophotometer.

RESULTS AND DISCUSSION:

Studies on Solid Dispersion formulated with Glimepiride: This study is aimed at improving the dissolution of poorly water-soluble drug (Glimepiride). It is insoluble in water and hence orally administered drug is less bioavailable. In order to enhance the bioavailability it is necessary to improve its solubility, hence the solid dispersion technique was adopted to enhance solubility. The solid dispersions were prepared in different

proportions using hydrophilic carriers like Urea. The dissolution rate studies were performed in both simulated gastric fluid and simulated intestinal fluid. It is observed that the dissolution was affected by the concentration of the carrier. Solid dispersions gave faster dissolution rate when compared to corresponding pure drug. The resulting solid dispersions were evaluated for the drug content and the corresponding dissolution data is showed in **Table 3 & 2**. The drug release data

observed from these solid dispersions is showed in **Fig. 1**.

Comparative drug release studies of the Glimepiride Solid Dispersion and the marketed formulation: To compare the drug release profile of Glimepiride solid dispersion formulated with the various concentrations of the carrier (urea) and the marketed formulation was subjected to *in vitro* release studies, that comparative release profile were shown in Table 2, Fig. 1.

TABLE 2: DISSOLUTION DATA OF GLIMEPIRIDE SOLID DISPERSION

| Time (min) | %Drug Release | | | | |
|------------|---------------|----------------|----------------|----------------|----------------|
| | Marketed | F ₁ | F ₂ | F ₃ | F ₄ |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 5 | 23.86 | 94.06 | 58.8 | 26.48 | 24 |
| 10 | 33.06 | 40.76 | 14.84 | 15.64 | 15.95 |
| 15 | 60.44 | 94.06 | 12.81 | 14.64 | 14.34 |
| 20 | 78.91 | 94.06 | 14.71 | 14.14 | 0.34 |
| 25 | 82.37 | 94.06 | 16.13 | 16.8 | 17.17 |

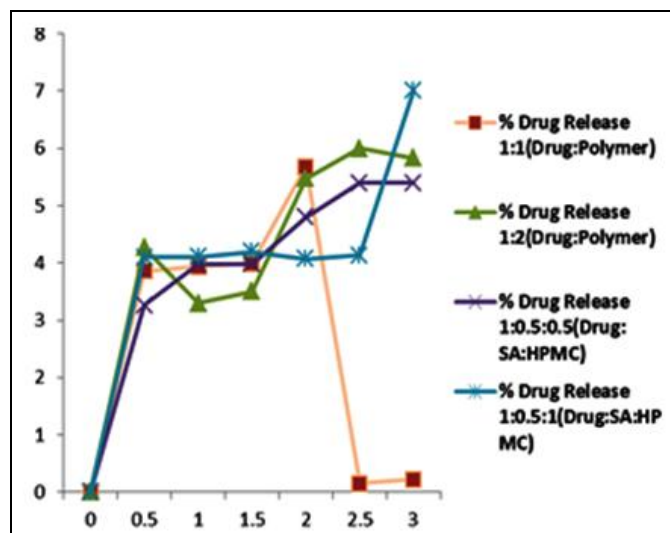


FIG. 1: IN VITRO RELEASE PROFILE OF GLIMEPIRIDE SOLID DISPERSION

Studies on microcapsules formulated with Metformin: Sustained Release is way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug. Micro fabricated system is having potential advantages over conventional drug delivery systems. Microspheres and microcapsules are established as unique carrier systems for many drugs, they can be tailored to adhere to targeted tissue systems. Microcapsules and microspheres can be used not only for controlled release but also for targeted delivery of drugs to a specific site in the body. It is having significant advances in the release of drugs. The micromeritic properties of the microcapsules formulated using sodium alginate are reported in Table 3.

TABLE 3: MICROCAPSULES FORMULATED WITH SODIUM ALGINATE ALONG WITH HPMC

| Drug : polymer | Angle of repose (°) | Bulk density (g/ml) | Tapped density (g/ml) | Compressibility index (%) | Hausner's ratio | Drug content |
|----------------|-----------------------|---------------------|-----------------------|---------------------------|-----------------|--------------|
| 1:1 | 11 ^{0.6} ±21 | 0.89 ±0.01 | 1.19 ±0.003 | 0.002 ±0.26 | 1.3± 0.04 | 4.9 ± 0.1 |
| 1:2 | 12 ^{0.5} ±13 | 0.76±0.005 | 1.53 ±0.004 | 0.005 ±0.19 | 2 ±0.006 | 4.1 ±0.2 |
| 1:0.5:0.5 | 16 ^{0.2} ±33 | 0.31±0.003 | 0.46 ±0.005 | 0.008 ±0.31 | 1.4± 0.01 | 3.1 ±0.05 |
| 1:0.5:1 | 10 ^{0.9} ±27 | 3.12±0.006 | 6.24 ±0.004 | 0.005 ±0.21 | 2 ±0.002 | 2.2 ±0.1 |

Factors influencing Encapsulation:

- Solubility of polymer in the organic solvent
- Solubility of organic solvent in water
- Concentration of the polymer

- Ratio of dispersed phase to continuous phase
- Rate of solvent removal
- Interaction between drug and polymer
- Solubility of drug in continuous phase
- Molecular weight of the polymer

The process optimization studies of metformin microcapsules were carried out to select the concentration of (Sodium alginate) polymer employed and the entrapment efficiency and drug release.

Drug release studies on Metformin Microcapsules formulated with different concentrations of Sodium alginate: The drug release from the microcapsules formulated with core coat ratio 1:0.5 offered high drug release of the microcapsules were not formed properly in this core coat ratio, the drug was not released completely from these microcapsules. So to improve the extent of drug release and to achieve the desired drug release rate, the different polymer concentrations were employed in the formation of microcapsules. The resulting microcapsules were evaluated from the drug content, entrapment efficiency and the corresponding dissolution data is showed in **Table 3 and 4**.

TABLE 4: DISSOLUTION DATA OF METFORMINE MICROCAPSULES

| Time (hr) | % Drug Release | | | |
|-----------|------------------------|------------------------|-------------------------------|-----------------------------|
| | 1:1 (Drug: Polymer) | 1:2 (Drug: Polymer) | 1:0.5:0.5 (Drug: SA: HPMC) | 1:0.5:1 (Drug: SA: HPMC) |
| 0 | 0 | 0 | 0 | 0 |
| 0.5 | 3.86 | 4.27 | 3.26 | 4.1 |
| 1 | 3.94 | 3.301 | 3.97 | 4.11 |
| 1.5 | 3.99 | 3.50 | 3.98 | 4.2 |
| 2 | 5.68 | 5.48 | 4.8 | 4.07 |
| 2.5 | 0.15 | 6.00 | 5.40 | 4.13 |
| 3 | 0.22 | 5.83 | 5.40 | 7.01 |

The drug release data observed from these microcapsules is showed in **Fig. 2**. The drug release follows zero order kinetics. The drug release rate was found to be depended on the concentration of the polymer employed in the preparation of microcapsules. Based on suitability for sustained release rate, the polymer concentration can be ranked as 1:2>1:1. It may be because of the polymer concentration employed in the formulation.

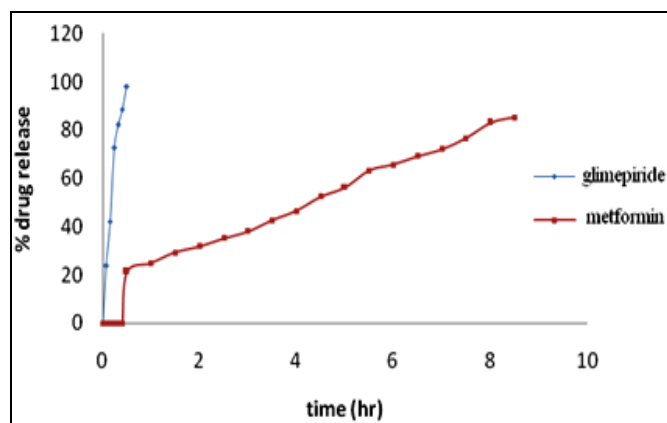


FIG. 2: %DRUG RELEASE PROFILES OF GLIMEPIRIDE SOLID DISPERSION AND METFORMIN MICROCAPSULE

CONCLUSION: The present investigation comprises of Glimepiride of immediate release as solid dispersion and Metformin of sustained release as mucoadhesive microcapsules. The results of the above study confirm that the Glimepiride solid dispersions has greater influence on the rate of dissolution. Based on the above results it can be concluded that solid dispersion form of Glimepiride can be formulated with high dissolution rate, faster onset of action and improved bioavailability.

From investigation it was concluded that microcapsules formulated with HPMC in combination with sodium alginate (SA) could be used for better mucoadhesive action and SA could be used for better sustained action over an extended period of time. Release retardation depends not only on coat material percentage but also on mucoadhesive polymer selected and optimization of mucoadhesive polymer is needed to get formulations with desired quality. The microcapsules exhibit good mucoadhesive property.

Metformin release from these mucoadhesive microcapsules was slow and extended over longer period of time. These mucoadhesive microcapsules are thus suitable for oral control release of Metformin and better bioavailability.

From the assumption described in results, the present study concludes that the both combination of Metformin-Glimepiride has shown the continuous availability of the oral hypoglycemic agents, so that improved glycemic controlled can be achieved. From the complete work, we assume that these hypoglycemic agents have a synergistic effect and therefore a greater effectiveness in controlling the blood glucose level in patients with type II diabetes mellitus can be achieved.

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