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Evaluation of various HPMC grades on Microencapsulation Efficiency of Glimepiride

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ABSTRACT: Background: Glimepiride is an orally available sulfonylurea antidiabetic drug used for type II diabetes mellitus. **Aim:** The present study was aimed to evaluate the effect of various grades of Hydroxy Propyl Methyl Cellulose (HPMC) on designing of Glimepiride microcapsules. **Methods:** The Glimepiride microcapsules were prepared by ionic gelation method using various grades of HPMC (E5LV, K4M and K100M) in drug polymer ratios of 1:1 and 1:2. The drug polymer interaction was studied by FTIR. The prepared microcapsules were evaluated for yield, particle size, flow property, swelling index, moisture retention, moisture loss, drug content, surface drug content, encapsulation efficiency, *in vitro* drug release and kinetic studies. **Results:** The microcapsules were discrete, small and spherical with good free flowing. The FTIR study showed no such significant physical or chemical interaction was occurred between Glimepiride and HPMC. Almost all microcapsule formulations exhibited good surface properties and physicochemical properties. Glimepiride Microcapsule formulation F1 released only 29.8 % of drug in 5 h in more controlled and constant manner with excellent flow property, good drug content and encapsulation efficiency (75 %). **Conclusion:** The microcapsule formulation F1 (Glimepiride: HPMC E5LV 1:1) is the best optimized formulation, which could be successfully used for safe and effective management of type II diabetes mellitus.

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INTRODUCTIONS:

Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection and of controlling the release characteristics or availability of coated materials [1-5]. *Diabetes mellitus* (DM), commonly referred to as diabetes, is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period. Glimepiride is an orally available medium to long acting sulfonylurea antidiabetic drug used for type II diabetes mellitus [6]. The most problems

associated with conventional drug delivery system are less gastric emptying time, fluctuation in drug concentration in blood stream and sudden attainment of blood drug concentration near or above maximum safe concentration, which may result in persisting of various side effects as like in Glimepiride such are gastrointestinal tract (GI) disturbances, occasional allergic reactions, and rarely blood production disorders including thrombocytopenia, leukopenia, and hemolytic anemia. Thus need of a novel dosage form of Glimepiride which shall be able to overcome above mentioned side effects as much as possible [7,8]. Thus the objective of present study was to design, prepare and evaluate the microcapsules of Glimepiride using various grades of HPMC.

MATERIALS AND METHODS:

Glimepiride was procured from Macleod Pharm, Sikkim, as gift sample. HPMC E5LV, K4M and 100M were purchased from Himedia Lab., Mumbai. All other chemicals and reagent used in this Research work were of analytical grades and procured from authorized dealers.

Table 1. Formulation design of Pioglitazone loaded microcapsule formulations.

FC	Drug	HPMC E5LV	HPMC K4M	HPMC K100M
F1	50	50	-	-
F2	50	100	-	-
F3	50	-	50	-
F4	50	-	100	-
F5	50	-	-	50
F6	50	-	-	100

FC – Formulation code, HPMC – Hydroxy propyl methyl cellulose and SA – Sodium alginate. All values are expressed as mg.

Formulation Design and Preparation of Glimepiride Microcapsules:

Glimepiride Microcapsules were prepared by ionic gelation technique using various grades of Hydroxy Propyl Methyl Cellulose such are HPMC E5LV, K4M and K100M in the drug polymer ratios of 1:1 and 1:2. Sodium alginate (450 mg) and polymer (50 mg) were weighed individually and were dissolved in purified water (32 ml) to form a homogeneous polymer solution using Magnetic stirrer (1MLH Remi equipments, Pvt., Ltd., Mumbai). Core material, Glimepiride (50 mg) was added to the polymer solution and mixed thoroughly to form a smooth viscous dispersion. The resultant dispersion was extruded drop wise with the help of syringe and needle (Optimized gage 22) at optimized injection rate and height, in to 100 ml of (4 w/v %) aqueous calcium chloride solution and stirred at 100 rpm using magnetic stirrer. After stirring for 15 min, microcapsules were separated (Filtered), washed with distilled water and dried using Hot air oven (ACM-22066-1, ACMAS Technocracy Pvt., Ltd., New Delhi) at 50°C for 6 to 8 h. The different batches of microcapsules were prepared using same procedure [9,10].

Evaluations of Glimepiride microcapsule formulations:

Drug polymer interaction study:

The compatibility between drug and polymers was evaluated using Fourier Transform Infrared Radiation measurement (Bruker FTIR, U.S.A.) at ambient temperature using IR spectrophotometer. The fine physical mixture of about 2 mg of pure drug and polymers were measured separately in the range of 4000-400 cm^{-1} for 100 scans by Potassium bromide pressed pellet technique [11,12].

Yield:

The yield of various microcapsule formulations was calculated in considering to total amount of drug and polymer taken in weight in mg and total amount of microcapsules obtained in weight in mg, using following as given below [13].

$$\text{Yield (\%)} = [Wm/(Wd+Wp)]\times 100 \ldots. (1)$$

Whereas, Wm is weight of microcapsules in mg, Wd is weight of drug in mg and Wp weight of polymer in mg.

Microcapsules size measurement:

The microcapsules size (Diameter) was determined by using optical microscope (Olympus Pvt. Ltd., Mumbai) with a calibrated stage and eye piece micrometer, using following equation [14].

$$X_g = 10 \times [(n_i \times \log Xi) / N] \ldots\ldots\ldots (2)$$

Where, X_g is geometric mean diameter, n_i is number of particle in range, X_i is the midpoint of range and N is the total number of particles.

Flow Properties Study [15,16]:

The definite mass of drug was weighed using Electronic Digital balance (Sartorius AG BT2245, Sartorius Mechatonics India Pvt. Ltd., Bangalore). The volume of weighed powder drug was measured using measuring cylinder. The measured volume was treated as Bulk volume. The same weighed mass of drug was tapped using digital bulk density apparatus (HAMCO 124-A,

Hamko India) for 1000 taps in a cylinder and the changes in volume were measured. This volume was treated as tapped volume.

The Carr's index (CI) and Hausner's ratio of drug powder was calculated by using following equations;

$CI (\%) = [(\rho_t - \rho_v)/\rho_t]\times100$ ……(3)

Hausner Ratio = ρ_t/ρ_v …...…….(4)

Where, ρ_t and ρ_v are tapped and bulk densities in g/cc.

The Angle of repose was determined using falling funnel method. The microcapsules were poured through a vertically placed of height (h). Radius (r) of the heap was measured and the angle of repose (Q) was calculated by using the formula,

$\theta = \tan^{-1}(h/r)$ ……..(5)

Moisture loss study:

The microcapsules were weighed initially and kept in desiccator 24/29 (Thermo Fisher Scientific, U.S.A.) containing Calcium Carbonate as dessicant at 37°C for 24 h. The study was continued unless until no further reduction in weight of microcapsules was noted down. The moisture loss (ML) was calculated using following equation [15];

$ML (\%) = [(W_i-W_f)/W_i]\times100$..…(6)

Where, W_i and W_f are initial and final weight of microcapsules in mg.

Moisture absorption study:

The microcapsules were weighed initially and kept in desiccator containing saturated solution of Potassium Sulphate for 24 h, which will saturate the desiccator internal atmosphere with moisture of relative humidity of 98 %. The study was continued unless until no further increase in weight of microcapsules was noted down. The moisture absorption (MA) was calculated by using following equation [16];

$MA (\%) = [(W_f-W_i/W_i]\times100$ ……(7)

Swelling Index study:

The swelling Index parameter was studied by keeping predetermined definite weight of microcapsules in definite volume of Saline phosphate buffer of pH 7.4 for 24 h. The final weight of microcapsules was noted down after separating from medium. The Swelling Index (SI) was calculated using equation [16];

$SI (\%) = [(W_f-W_i/W_i]\times100$ …….. (8)

Drug Content study:

The drug loaded microcapsules (10 mg equivalent drug) were triturated in mortar, powdered and suspended in 100 ml Phosphate buffer solution of pH 7.4. The mixture was kept over Rotary shaker (Variable-Speed Orbital *Shaker* 6145, Thomas Scientific, U.S.A.). After 1 h, the solution was double filtered using Whatman Filter paper 4. The Glimepiride content in the filtrate was determined Spectrophotometrically using UV-Visible Spectrophotometer (Shimadzu UV-1800, Japan) at 228 nm [16,17].

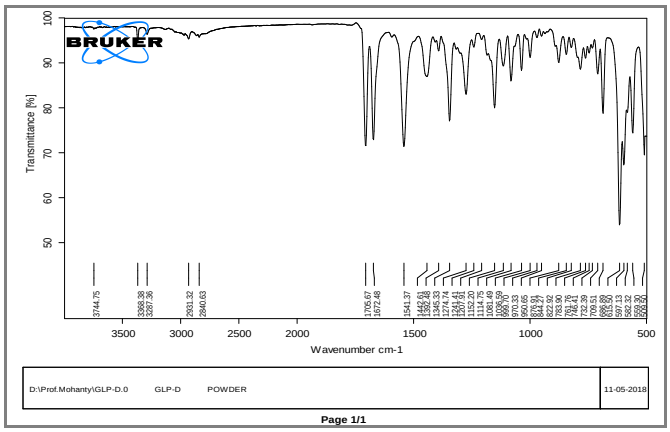

Fig 1. FTIR data of pure Glimepiride drug wave number range of 4000 to 500 cm^{-1}.

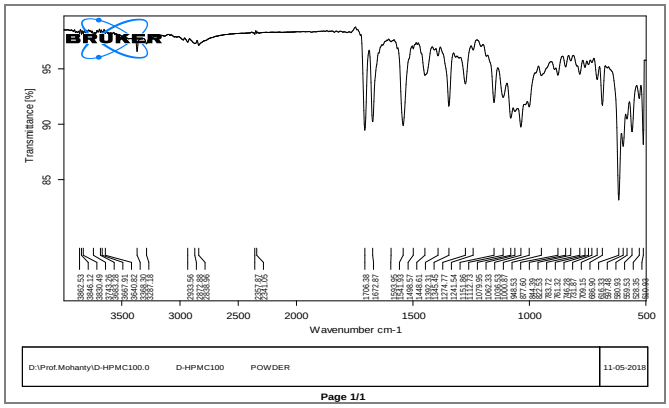

Fig 2. FTIR data of Glimepiride and HPMC physical mixture.

Surface drug content determination:

About definite weight of each microcapsule formulation was kept in specific vole of medium that is Phosphate buffer of pH 7.4 solution. After 2 to 3 min, with little shaking, the microcapsules was filtered by using Whatman Filter paper 4. The Glimepiride content in the filtrate was determined spectrophotometrically using UV-Visible Spectrophotometer at 228 nm [16,17].

Encapsulation efficiency (EE):

From the data of drug content and microcapsule outer surface drug content, the encapsulation efficiency in percentage was calculated by using equation [16,17];

$EE (\%) = [(PDC–SDC)/TDC]\times100$ … (9)

Where, PDC is practical drug content. SDC is surface drug content and TDC is theoretical drug content.

Drug release study:

In vitro drug release study was carried out in USP XXXI paddle type (II) dissolution test apparatus (Electro Lab, TDT-06P, Culcutta) using Phosphate buffer of pH 7.4 as dissolution medium of volume 900 ml and bath temperature was maintained at (37±1)°C throughout study. Paddle speed was adjusted to 75 rpm. An interval of 0.5 h, 5 ml of sample was withdrawn with replacement of 5 ml fresh medium. The dissolution study was continued for 5 h. The collected drug solutions were analyzed for Glimepiride content by using UV-Visible spectrophotometer at 228 nm. The same procedure was adopted for pure drug, microcapsule formulations and Glimepiride marketed tablet (Glimepex) [17,18].

Drug release Kinetic study:

In order to understand the mechanism and kinetics of drug release, the drug release data of the *In vitro* dissolution study of microcapsules were analyzed with various kinetic equations like zero order [19], first order [20], Higuchi equation [21] and Korsmeyer and Peppas equation [22].

Table 2. The particle Yield and size study of Glimepiride microcapsules.

FC	Size (d_{avg}) (µm)	Yield (%)
F1	734	100
F2	867	85
F3	924	133
F4	880	78
F5	1100	141
F6	1300	153

FC – Formulation code.

RESULTS AND DISCUSSIONS:

The FTIR data showed that the spectra were recorded over the wave number range of 3600 to 400 cm $^{-1}$. The drug shows different peaks at C-H = 3008, C=C = 1605, 1495, 1466, O-H = 3231, N=N = 1576 and Cl = 1200-1400cm $^{-1}$of benzene which confirms the purity of the drug. FT-IR spectrum of pure drug (Glimepiride) and physical mixture of drug and polymers are represented in Fig 1 and 2, which demonstrated that no such significant addition or deletion of major peak was observed in drug and polymers physical mixture. It signified that drug Glimepiride was compatible with HPMC, which would be safe and stable physically and chemically if formulated in suitable dosage forms or particulate forms.

The almost all microcapsule formulation exhibited satisfactory yield. The microcapsule yield was good for microcapsule formulation F1 and F2. The highest yield was obtained with formulation F2 (Table 2). The yield was beyond 100 % for the microcapsule formulations F3, F5 and F6, which might be due to retention of excessive moisture in the formulation.

Table 3. Flow properties data of Glimepiride microcapsule formulations.

FC	BD (g/cc)	TD (g/cc)	CI (%)	HR	AR (°)
F1	0.783	1.044	25	1.33	41
F2	0.75	0.80	2.5	1.07	21
F3	0.81	0.86	5.8	1.06	23
F4	0.74	0.78	6.3	1.07	20
F5	0.698	0.992	27	1.23	44
F6	0.779	1.032	26	1.28	45

FC – Formulation code, BD and TD – bulk and tapped density, CI – Carrs' Index, HR – Hausner ratio and AR – Angle of repose.

The microscopic study revealed that the prepared microcapsules outer surface morphology were more or less spherical except microcapsule formulation F5, which possessed irregular shape due to some tailing effect during manufacturing. The average size of microcapsules was ranged from 734 (F1) to 1300 µm (F6) as given in Table 2. Almost microcapsules were satisfactory average diameter. The bulk densities were found to be in ranges of 0.698 to 0.783 g/cc. The Table 3 showed that the tapped density was found to be in ranges of 1.044 to 0.78 g/cc. The compressibility index was found to be in ranges of 6.3 to 27 %. The Hausner ratio was found to be in ranges of 1.06 to 1.33. The angle of repose was found to be in ranges of 20 to 45°. When data were interpreted with specified value of US.P, the flow property was excellent except formulation F5 and F6, whose flow was passable as given in Table 4. The Table 5 represented that the moisture loss of all microcapsule formulation was ranged from 2 (F3) to 36 (F4) %. But almost all microcapsule formulations showed minimum moisture loss. The moisture absorption of all microcapsule formulation was ranged from 70 (F6) to 90 (F5) %. Almost all microcapsule formulations exhibited good swelling index. The Swelling Index of all microcapsule formulation was ranged from 80 (F6) to 106 (F5) %. The above data revealed that all polymers might be having good

mucoadhesion property. The total and surface drug content and encapsulation efficiency data of all microcapsule formulations are given in Table 5. The drug content of all microcapsule formulation was ranged from 65 (F5) to 86 (F2) %. But almost all microcapsule formulations showed satisfactory drug content. The surface drug content of all microcapsule formulation was ranged from 6.78 (F6) to 9.92 (F2) %. Almost all microcapsule formulation exhibited good Encapsulation Efficiency. The Encapsulation Efficiency of all microcapsule formulation was ranged from 58 (F5) to 76 (F2) %. Still the process of manufacturing of microcapsules has to be optimized to enhance Encapsulation Efficiency, which is an important quality parameter of microcapsules to make dosage form more economic.

Table 4. Moisture loss and absorption and Swelling Index data of Microcapsules.

FC	Flow comment	ML (%)	MA (%)	SI (%)
F1	Excellent	4	80	93
F2	Excellent	24	80	91
F3	Excellent	2	86	95
F4	Excellent	36	87	96
F5	Passable	24	90	106
F6	Passable	12	70	80

FC – Formulation code, ML – Moisture loss, MA – Moisture absorption and SI – Swelling Index.

Table 5. Drug content, surface drug content and encapsulation efficiency data of Microcapsule formulations.

FC	DC (%)	SDC (%)	EE (%)	CPDR (%)
F1	84	8.92	75	29.8
F2	86	9.92	76	31.4
F3	72	8.77	63	48.7
F4	78	9.91	68	73.6
F5	65	7.86	58	23.1
F6	76	6.78	69	54.5

FC – Formulation code, DC – Drug content, SDC – Surface drug content. EE – Encapsulation efficiency, CPDR – Cumulative percentage drug release.

The result of *in vitro* drug release is represented in Table 5 and Fig 2. The drug release data revealed that almost all microcapsule formulations released drug in sustained manner. The drug released from all Glimepiride microcapsule formulation was ranges from 23.1 (F5) to 71.6 % (F4). The total amount of drug released in less amount (50 % <) was shown by all Glimepiride microcapsule formulations except formulations F5 and F4. The fluctuation in drug released from Glimepiride microcapsule formulation was observed in microcapsule formulations F3 and F6. Glimepiride microcapsule formulation F1 exhibited drug release in more constant and controlled manner, as it released drug only 29.8 % in 5 h. The *in vitro* dissolution data of Glimepiride marketed tablet (Glimepex) which revealed that the Glimepiride tablet released 80.48 % of drug in only 35 min. This data demonstrated that the drug release profile of microcapsule formulations F1 was better than the marketed tablet, Glimepex.

Table 6. *In vitro* drug release kinetics data of various microcapsule formulations.

FC	ZOK	FOK	HK	KPK	
	Regression co-efficient (r^2)				n
F1	0.854	0.610	0.723	0.702	0.41
F2	0.375	0.406	0.512	0.622	0.36
F3	0.896	0.908	0.837	0.884	0.52
F4	0.759	0.610	0.717	0.798	0.32
F5	0.316	0.300	0.421	0.401	0.39
F6	0.072	0.005	0.068	0.066	0.44

FC – Formulation code, ZOK and FOK – Zero and First order kinetics and KPK – Korsmeyer Peppas kinetics.

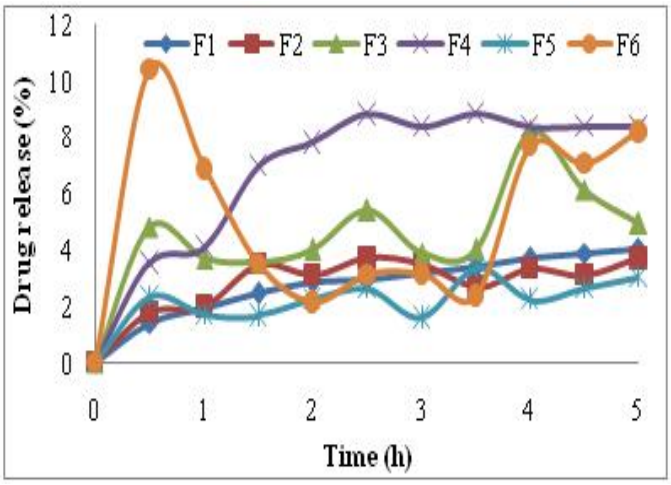

Fig 2. Percentage Drug release profile of Glimepiride microcapsule formulations (F1-F6).

The *in vitro* drug release kinetic result is given in Table 6. The Glimepiride microcapsule formulations F1, F4, F5 and F6 followed zero order drug release kinetic which demonstrated that rate of drug release is independent of drug concentration. Whereas the Glimepiride microcapsule formulations F2 and F3 followed First order drug release kinetic which demonstrated that rate of drug release is dependent of

drug concentration. The Glimepiride microcapsule formulations F1, F5 and F6 followed Higuchi kinetics, which signified that drug release mechanism follows diffusion process. Whereas Glimepiride microcapsule formulations F2, F3 and F4 followed Korsmeyer-Peppas drug release kinetics which signifies that the drug release followed polymer erosion mechanism. From the n value of Korsmeyer-Peppas equation, it was revealed that the all Glimepiride microcapsule formulations followed Fickian drug transport mechanism, whereas the formulations F3 followed Non-Fickian drug transport mechanism.

CONCLUSION:

It could be concluded that the microcapsule formulation containing glimiperide (Drug) and polymer (HPMC E5LV) in the ratio 1:1 is the best optimized Glimepiride Microcapsule formulation as it released only 29.8 % of drug in 5 h in more controlled and constant manner with good drug content, good encapsulation efficiency (75 %) and excellent flow properties, which could be successfully used for safe and effective management of type II diabetes mellitus to achieve the formulation merits to overcome the side effects of Glimepiride which being developed due to fluctuation of drug concentration in blood stream.

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