

RESEARCH ARTICLE

STUDY OF VARIOUS PARAMETERS EFFECTING IN FORMULATION OF WATER SOLUBLE METFORMIN HYDROCHLORIDE ETHYL-CELLULOSE MICRO-PARTICLES

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ABSTRACT

Water soluble Metformin hydrochloride microparticles was being prepared by ethyl-cellulose in liquid paraffin medium with variable rotating speed, different drug polymer ratio and different concentration of the surface-active agent. Percentage yield, bulk density, tapped density, Carr's compressibility index, Hausner ratio, Angle of repose of prepared microparticles was determined. The release study of the water soluble Metformin hydrochloride microparticles also performed. From the findings of the present investigations, it was evident that the selected materials and sustained release property offering very promising area in the field of research.

Key words: Metformin hydrochloride, Ethyl-cellulose, Micro-particles, *In-vitro* drug release study, Bioavailability.

INTRODUCTION

Metformin hydrochloride is a biguanide antihyperglycemic drug, which is orally used in the management of noninsulin-dependent diabetes mellitus (NIDDM or Type II diabetes mellitus) alone or in combination with other hypoglycemic agents. Its antihyperglycemic effect is due to the metabolic activities at several sites (biophase), including liver, intestinal cells, and adipocytes^{1,2,3}. It has a short biological half-life of 1.5–1.6 h and the daily requirement of it is 1.5–3 g/day. Therefore, the marketed immediate release product needs to be administered 2–3 times daily to maintain effective plasma concentration⁴. So that, there being high incidence of gastrointestinal side effects and toxicity. These drawbacks can be overcome by designing suitable sustained release Metformin hydrochloride formulations. Administration of a sustained Metformin hydrochloride release dosage form could reduce the dosing frequency and improve the patient compliance¹.

Among various oral sustained drug delivery systems, polymeric microparticles are one of the options and have been studied in past few decades in order to deliver drug molecules to the target site with specificity with several advantages like better oral bioavailability of drugs, reduction in side effects, decreased dosing frequency, and hence, improved patient compliance^{5,6,7}.

Microparticles are solid, approximately spherical particles ranging in size from 1 to 1000 μm . They are made up of polymeric substances, in which the drug molecules are dispersed, entrapped, or adsorbed in the polymeric matrix. Microparticles are sometimes referred to as microspheres, and other synonymous words are micro beads, beads and microcapsules⁸.

The objective of present investigation is to prepare sustained release water soluble microparticles of Metformin hydrochloride using different drug polymer ratio and different concentration of the surface-active agent in the liquid paraffin medium applying a variable rotating speed of the electrical stirrer, evaluation of the prepared microparticles and also the comparison of drug release in *in-vitro* condition from the different batches of prepared microparticles.

MATERIALS AND METHODS

Drugs & Chemicals: Metformin hydrochloride was received from Zydus Cadila Health Care Ltd; Ahmedabad, Ethyl cellulose (S.D. Fine-Chem. Ltd., Mumbai), Methanol (Finar Chemical Ltd., Ahmedabad), Acetone (Merck Specialities Pvt. Ltd., India), Liquid Paraffin (Merck Specialities Pvt. Ltd., India), Span 80 (Ranbaxy Fine Chemicals Ltd., India), Petroleum ether (Merck Specialities Pvt. Ltd., India). All the chemicals were of analytical grade, obtained commercially and were used without further purification.

Instruments used: UV-VIS Spectrophotometer (Model No. UV-1700 Pharmaspec, SHIMADZU, Japan), Single stage Dissolution Apparatus (Electrolab), Single pan Electronic Balance (Model No.160D, Dhona Instruments Pvt. Ltd. Kolkata), Digital Stirrer (Remi Motors and Equipments), Hot air Oven (Sisco, Thane East, Maharashtra) Digital P^H Meter (Model No. MK-VI, Systronics, Ahmedabad).

Preparation of microparticles¹: Ethyl cellulose microparticles containing Metformin hydrochloride were prepared by emulsification- solvent evaporation technique

varying various formulation variables. Briefly, the drug, Metformin hydrochloride was mixed in methanol and ethyl cellulose was mixed in acetone at various drug-polymer ratios. Then, these two were mixed properly, and the slurry was slowly introduced into 50mL of liquid paraffin containing Span 80 (variable percentage) as stabilizer and

stirred (600 to 900 rpm) by a mechanical stirrer equipped with a three bladed propeller at room temperature for 2hr to allow the solvent to evaporate completely and the formed microparticles were collected by filtration. The microparticles were washed repeatedly with petroleum ether (40–60 °C) until free from oil.

Table 1: Formulation parameters used in the preparation of microparticles

FORMULATION CODE	DRUG:POLYMER RATIO	STIRRER SPEED (RPM)	SURFACTANT (SPAN80) CONC. (%)
F-1	1:2	600- 900	4 %
F-2	1:3	600- 900	4%
F-3	1:4	600- 900	4%
F-4	1:5	600- 900	4%
F-5	1:5	600- 900	2%

Evaluation of prepared microparticles^{8, 9, 10, 11}:

(A) Bulk density: A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume V_o , to the nearest graduated unit. Calculate the bulk density, in gm per ml, by the formula m / V_o .

(B) Tapped density: Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. Cylinder dropping distance 14 ± 2 mm at a normal rate of 300 drops / minute. Unless otherwise specified, tap the cylinder 500 times initially and measure the tapped volume, V_a , to the nearest graduated unit. Repeat the tapping an additional 750 times and measure the tapped volume, V_b , to the nearest graduated unit. Tapped Density = M/V .

(C) Carr's Compressibility Index: The Carr's index (also: Carr's index or Carr's Compressibility Index) is an indication of the compressibility of a powder. It is named after the pharmacologist Charles Jelleff Carr (1910–2005). The Carr index is calculated by the formula, $C = 100 \times (V_B - V_T) / V_B$; where, V_B is the freely settled volume of a given mass of powder, and V_T is the tapped volume of the same mass of powder. It can also be expressed as $C = 100 \times (1 - \rho_B / \rho_T)$, where, ρ_B is the freely settled bulk density of the powder, and ρ_T is the tapped bulk density of the powder. The Carr index is frequently used in pharmaceuticals as an indication of the flowability of a powder. A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

(D) Hausner ratio: The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is named for the engineer Henry H. Hausner (1900–1995). The Hausner ratio is calculated by the formula, $H = \rho_T / \rho_B$; where ρ_B is the freely settled bulk density of the powder, and ρ_T is the tapped bulk density of the powder. The Hausner ratio is not an absolute property of a material; its value can vary depending on the methodology used to determine it.

(E) Angle of Repose: The angle of repose or more precisely the critical angle of repose of a granular material is the steepest angle of descent or dip of the slope relative to the horizontal plane when material on the slope face is on the verge of sliding. This angle is in the range 0° – 90° . When bulk granular materials are poured onto a horizontal surface, a conical pile will form. The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose and is related to the density, surface area and shapes of the particles, and the coefficient of friction of the material. Generally 25 – 30° exhibits good flow property.

(F) Determination of percentage Yield: Microcapsules dried in vacuum dessicator were then weighed and yield of microcapsules was calculated using following formula:

Percent yield = The amount of microcapsules obtained/The theoretical amount $\times 100$.

(G) Entrapment Studies: Drug entrapment efficiency of Metformin HCl microparticles was performed by accurately weighing 50 mg of microparticles and suspended in 100ml of PBS of pH7.4 and it was kept aside for 24 hours. Then, it was stirred for 15 mins and filtered. After suitable dilution, Metformin HCl content in the filtrate was analyzed spectrophotometrically at 232 nm using U.V. spectrophotometer.

Percent yield = Estimated drug content/ Theoretical Drug content $\times 100$.

(H) In-vitro drug release studies: Release of Metformin HCl from separate formulations was studied by taking phosphate buffer (pH-7.4) solution as dissolution media. Dissolution assays for each batch for separate drugs were carried out in triplicate to get reproducible results and the assay procedure was carried out till the drug release was almost constant from the prepared devices. The tests were performed into an apparatus as described in USP. The sample holder consisting of 100mg of microcapsules containing plain Metformin HCl. The Agitation speed was maintained at 100 rpm. At prefixed time (15 min, 30min,

60min, 90min, 120min and then at 1hrs. interval onwards), 5ml of solution were withdrawn and replenished with dissolution medium kept at constant temperature of 37°C and the solutions were filtered by using 0.45µ membrane filter and spectrophotometrically assayed for the Metformin HCl content in the various formulations (at, λ = 232 nm). The drug release rates were plotted as a function of time (in hours) versus percent (%) release.

Preparation of calibration curve of Metformin hydrochloride

At first 100 mg of Metformin HCl was weighed out in a 100ml volumetric flask and to this flask, 100ml phosphate buffer (6.8 pH) was added and then from this stock solution of prepared concentration of 1mg/ml, taken 1ml of solution in a volumetric flask of 100ml capacity and diluted the solution to 100ml which gave a concentration of 10 µg/ml and this process was repeated to obtain concentration of 20 µg/ml, 30 µg/ml, 40 µg/ml and 50 µg/ml by taking respectively 2ml, 3ml, 4ml and 5ml from the stock solution. Thus the absorbance of the prepared solutions was measured in a UV-VIS spectrophotometer.

RESULTS AND DISCUSSION

(A) Table 2: Bulk density.

FORMULATION CODE	BULK DENSITY (g/cm ³)
F-1	0.324
F-2	0.49
F-3	0.82
F-4	0.632
F-5	0.51

(B) Table 3: Tapped density.

FORMULATION CODE	TAPPED DENSITY (g/cm ³)
F-1	0.54
F-2	0.552
F-3	0.93
F-4	0.665
F-5	0.55

(C) Table 4: Carr's Compressibility Index.

FORMULATION CODE	CARR'S COMPRESSIBILITY INDEX (%)
F-1	40.7
F-2	11.27
F-3	11.82
F-4	4.87
F-5	7.27

(D) Table 5: Hausner ratio.

FORMULATION CODE	HAUSNER RATIO
F-1	1.687
F-2	1.12
F-3	1.13
F-4	1.05
F-5	1.07

(E) Table 6: Angle of Repose.

FORMULATION CODE	ANGLE OF REPOSE (°)
F-1	43°53'
F-2	41°98'
F-3	36°86'
F-4	32°12'
F-5	32°02'

(F) Table 7: Determination of percentage yield.

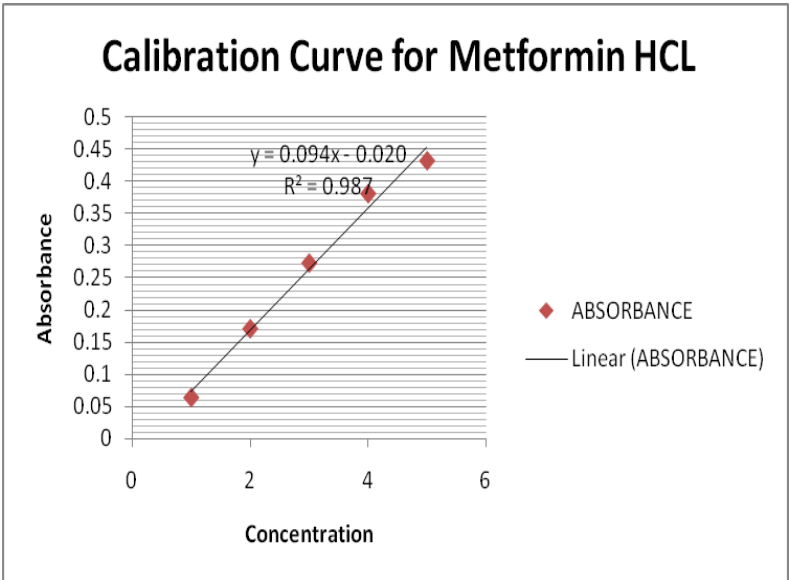
FORMULATION CODE	PERCENTAGE YIELD (%)
F-1	59.66
F-2	61.25
F-3	62.12
F-4	41.2
F-5	68.58

(G) Table 8: Drug Entrapment Studies.

FORMULATION CODE	PERCENTAGE ENTRAPMENT (%)
F-1	65.56
F-2	62.55
F-3	51.04
F-4	41.40
F-5	68.92

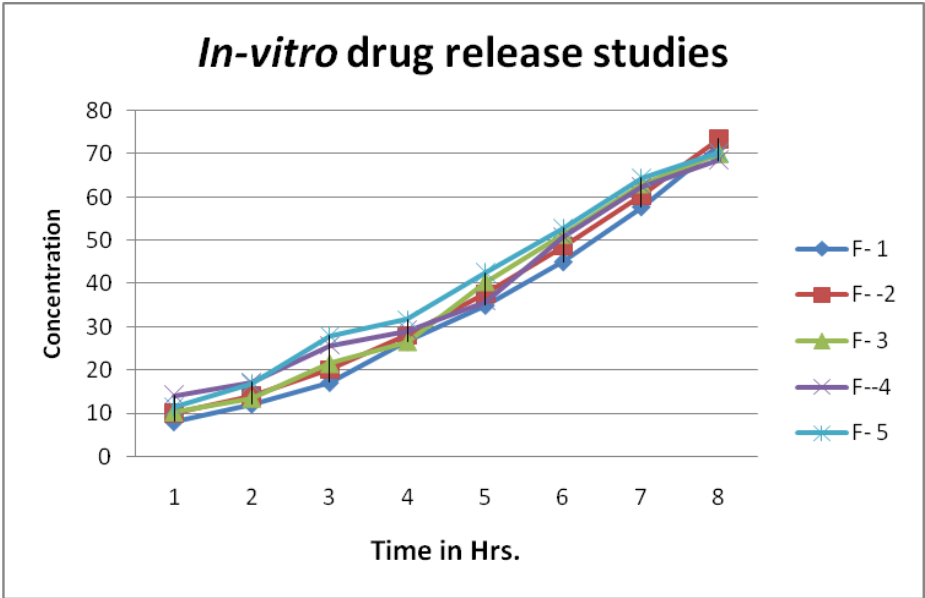
(H) Table 9: Calibration Curve for Metformin HCL.

CONC (µg/ml)	ABSORBANCE
10 µg/ml	0.063
20 µg/ml	0.170
30 µg/ml	0.272
40 µg/ml	0.380
50 µg/ml	0.431



(I) Table 10: *In-vitro* drug release studies.

S. NO	TIME IN HRS	F- 1	F- 2	F- 3	F- 4	F- 5
1	1	8.103	10.105	10.232	14.106	11.452
2	2	12.192	14.109	13.482	17.178	16.819
3	3	17.185	20.190	21.456	25.627	27.879
4	4	26.654	28.104	26.543	29.105	31.764
5	5	35.012	37.687	40.432	35.912	42.564
6	6	45.074	48.670	51.453	50.876	52.789
7	7	57.798	60.321	63.145	62.389	64.456
8	8	72.102	73.452	70.145	68.568	70.342



Water soluble Metformin hydrochloride was being prepared by ethylcellulose in liquid paraffin medium with variable rotating speed, drug polymer ratio and different ratio of the surfactant. Percentage yield been found between 57 to 73% and the percentage entrapment is found between 41.2 to 68.58% .The bulk density been found between 0.324 to 0.82 (g/cm³), tapped density between

0.54 to 0.93 (g/cm³), The Carr's compressibility between 4.87 to 40.7 %. Hausner ratio came between 1.05 to 1.68. Angle of repose noted between 32°2' to 43°53'. In release study it was seen that the water soluble Metformin HCL microspheres are giving good sustained effect as the release after 8 hours are noted near about 70% in maximum cases. Here it was observed that when the

amount of polymer is increased and the concentration of the surfacting agent been decreased the microparticles are coming in good spherical shape with a standard particle size.

CONCLUSIONS

From the above findings of the present investigations, it was evident that the selected materials and sustained release property offering very promising area in the field of research. This field is wide open for the researchers to work on this material on designing of drug delivery

devices. This will lead to a new application of the specified drug (Metformin HCl) in the field of controlled drug delivery system.

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