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Formulation and evaluation of cap-in-cap technology for biphasic drug delivery of glimepiride

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ABSTRACT

In the present research work, a novel capsule-in-capsule technology for biphasic delivery of Glimepiride was developed for the Diabetic patient to the best of our knowledge very less information is available on this type of formulations. The advantages of fast releasing liquid-filled-capsules and slow release tablet-filled-capsule were combined to meet the optimized requirements of our biphasic drug delivery system. Glimepiride slow releasing tablet were prepared by direct compression method and were filled into a smaller capsule. Glimepiride fast releasing liquid was prepared using olive oil and drug. This fast releasing liquid and slow releasing tablet-filled-capsule was further inserted into a bigger capsule body and closed with the cap. The various formulation batches were subjected to physicochemical studies. Drug content, in vitro drug release and stability studies. Interaction studies reveal that there was no interaction between drug and excipient employed in this study. The optimized capsule-in-capsule formulation released 21.01% of drug at the end 30min and 97.23% of drug at the end of 12hr. The drug release profile of Glimepiride capsule-in-capsule formulation fits well with higuchi model followed by zero order, First order and korsmeyer- Peppas model analysis. The stability study results indicate that the various parameters of our optimized formulation are not affected on storage at 45^0c/75%RH upto 6 month.

Key words: Cap-in-Cap**,** Duo Cap, Dual Component, Capsule-in-Capsule.

INTRODUCTION

Solid dosage forms can be divided into two main categories: immediate release dosage forms, where disintegration and subsequent drug release and dissolution occurs in stomach, and the (nonimmediate) modified-release technologies, which utilize polymers to alter the site or time of drug release within gastrointestinal tract. Thus, in recent years a growing interest has developed in designing drug delivery systems that include an immediate release (IR) component to extended release (ER) dosages. Conditions (Thus in certain Diabetes, hypertension), drug treatment may be advantageous to be delivered in biphasic manner rather than conventional or single phase. Release preparation. In the first phase of drug release, the immediate release dose fraction (also called “loading dose”) reaches therapeutic drug level in the blood plasma quickly after administration, while the second extended release phase called the “maintenance dose”)provides the dose fraction, required to maintain an effective therapeutic level for a prolonged period[1].

Biphasic Drug Delivery System

Biphasic delivery systems are designed to release a drug at two different rates or in two different periods of time: they are either quick/slow or slow/quick[2,3].

Capsule-in-Capsule Drug Delivery System

Capsule in Capsule - The dual capsule system available to the pharmaceutical industry which can facilitate the delivery of combination products or the release of a single active from the two compartment system with different release profiles or at different locations within the GI tract[4].

Fig.1- Cap-in Cap Formulation

MATERIALS AND METHODS

MATERIALS:-

Glimepiride was obtained as a gift sample from IPCA Pvt .ltd, Mumbai. HPMC, MCCTalc, Magnesium stearate from Research-Lab, Fine Chem Industry, Mumbai. Starch from Loba Chemie, Mumbai. Olive oil purchased from Figaro Pvt. Ltd, Spain. Empty hard gelatin capsules (size00 and size 1)were obtained as a gift sample from Manga Capsules Ltd, Nashik. All other materials used were of analytical grade.

Drug-Excipients Compatibility Study

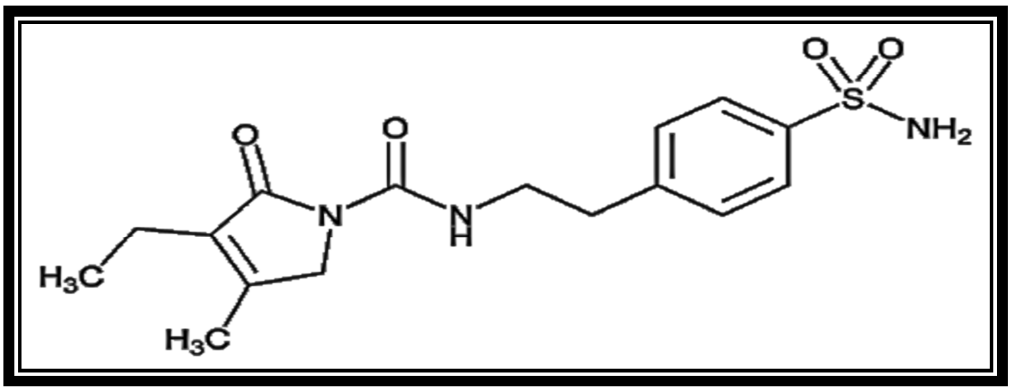

Fig. 2: Structure of Glimepiride

Table 1: FTIR of mixture of MCC, HPMC, Talc, Magnesium stearate and Starch with Glimepiride

Sr. No	Functional group	Observed Ranges (cm^{-1})	Standard Ranges (cm^{-1})
1.	S=O SULFONE	1338.64	1350-1300
2.	CH_2& CH_3	1454	1470-1450
3.	NH_2 Plane bend	1573	1640-1560
4.	C=O stretch	1643	1720-1635
6.	CH stretch	2850.88	3000-2850
7.	CH stretch broad dimer	2912.61	3400-2800

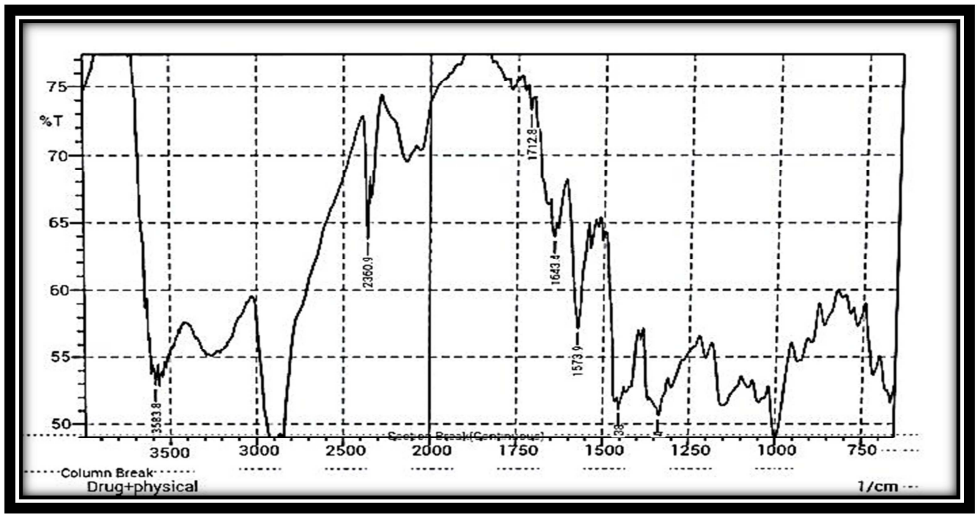

Fig. 3: FTIR of mixture of MCC, HPMC, Talc, Magnesium stearate and Starch with Glimepiride

FTIR spectra of glimepiride and olive oil mixture

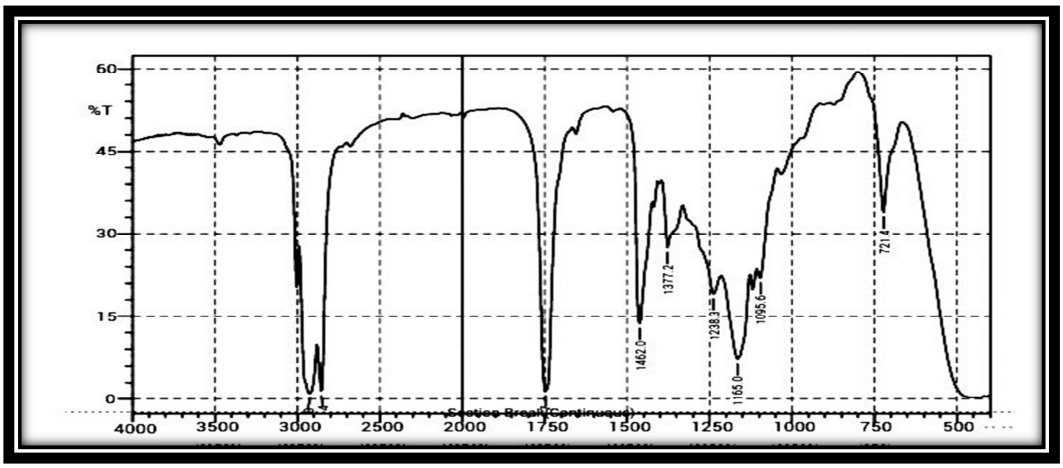

Fig.4: FTIR of mixture of Olive oil+ Glimepiride

METHODS

Preparation of Cap-in-Cap Formulation

Cap-in-Cap formulation containing two phases i.e immediate release phase and sustained release phase both of Glimepiride. For sustained release tablet various batches were prepared using Direct Compression method as per table 1. Using Karnawati Mini press in 6 mm punch; (various precompression evaluation like bulk density, tapped density, angle of repose etc).

Table 2- Ranges of Independent Variables Used In the 3^2 Full Factorial Designs Preparation of tablet mass:

Sr.No	Formulation Code	X1	X2	MCC(mg) X1	HPMC(mg) X2
1	TFC-1	-1	-1	20	20
2	TFC-2	-1	0	20	38
3	TFC-3	-1	+1	20	55
4	TFC-4	0	-1	25	20
5	TFC-5	0	0	25	38
6	TFC-6	0	+1	25	55
7	TFC-7	+1	-1	30	20
8	TFC-8	+1	0	30	38
9	TFC-9	+1	+1	30	55

Table 3: Composition of Cap- in-Cap formulation (4 mg) As per 3^2 full factorial design

Ingredients	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sustained Release Tablet									
Glimepiride (mg)	3	3	3	3	3	3	3	3	3
MCC (mg)	20	20	20	25	25	25	30	30	30
HPMC (mg)	20	38	55	20	38	55	20	38	55
Talc (mg)	5	5	5	5	5	5	5	5	5
Magnesium stearate(mg)	5	5	5	5	5	5	5	5	5
Starch (mg)	47	29	12	42	24	7	37	19	2
Immediate Release liquid phase									
Glimepiride (mg)	1	1	1	1	1	1	1	1	1
Olive oil (ml)	1	1	1	1	1	1	1	1	1

EVALUATION OF TABLET FORMULATION:

Thickness:

The thickness of the tablets was determined using Vernier Caliper. 5 tablets from each batch were used and the mean value were calculated[6].

Hardness:

The Hardness of the tablets was determined using Monsanto tablet Hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and analysed for hardness. The average and standard deviation values were also calculated

Friability Test:

As weight of tablet was less than 650 mg so tablets corresponding to 6.5 gm were taken for the test. All tablets were dedusted carefully and weighing accurately the required number of tablets were placed in the drum and rotated about 100 times. Tablets were removed from the drum and loose dust was removed from the tablets, weighed accurately. The percentage weight loss should not be more than 1% of the total weight.

Uniformity of Weight

20 tablet of each formulation were weighted using an electronic balance and the test was performed as per the official procedure [7].

Drug content uniformity

Units were selected at random and drug content was determined as specified in monograph. The tablet preparation complies with the test, only if each individual content lies between 85 to 115% of the average content.[8].

In-vitro Dissolution studies

Dissolution studies were carried out using USP dissolution test apparatus II basket type (Electrolab TDL-08L) at a rotation speed of 75rpm and at 37 ± 0.5°C using 900 ml of 0.1N HCl for two hours and from 3-12 in pH 7.8 phosphate buffer. A 5 ml sample was withdrawn at 30min time intervals and replaced by an equal volume of pre-warmed 0.1N HCl and methanolic phosphate buffer pH 7.8, respectively. Samples withdrawn were filtered through whatmann filter paper (0.45 micron). The amount of glimepiride released was analyzed at 210nm and 226nm for samples tested in 0.1N HCl and the phosphate buffer pH 7.8 respectively, using a Jasco V630 UV-spectrophotometer. The studies were carried out in triplicate and the mean values plotted verses time with standard error of mean[9,10].

EVALUATION OF CAPSULE-IN-CAPSULE FORMULATIONS:

Special leak proof capsules for both smaller and bigger size were used in this formulation. To prepare a novel capsule-in-capsule technology the prepared optimized sustained release tablet equivalent to 3 mg of Glimepiride were filled in size 1 hard gelatin capsule. This prepared sustained release smaller capsule was filled into a bigger capsule body size 00 which was further filled with the liquid of Glimepiride equivalent to 1mg as loading dose using medicine droppers. The filled capsules were stored at room temperature until testing.

In-vitro release studies of Capsule-in-Capsule.
Dissolution studies were carried out using USP dissolution test apparatus II basket type (Electrolab TDL-08L) at a rotation speed of 75rpm and at 37 ± 0.5°C using 900 ml of 0.1N HCl for two hours and from 3-12 in pH 7.8 phosphate buffer. A 5 ml sample was withdrawn at 30min time intervals and replaced by an equal volume of pre-warmed 0.1NHCl and methanolic phosphate buffer pH 7.8, respectively. Samples withdrawn were filtered through whatmann filter paper (0.45 micron). The amount of glimepiride released was analyzed at 210nm and 226nm for samples tested in 0.1N HCl and the phosphatebuffer pH 7.8 respectively, using a Jasco V630 UV-spectrophotometer. The studies were carried out in triplicate and the mean values plotted verses time with standard error of mean[11].

Release kinetics studies:
The analysis of a drug release mechanism from a pharmaceutical dosage form is an Importantbut complicated process and is practically evident in the case of matrix systems.

To study the release kinetics in vitro release data was applied to kinetic models such as zero-order, firstorder, Higuchi and Korsemeyer-Peppas.

Comparison with Marketed Tablet Formulation
The Present Formulation of Glimepiride was compared with marketed tablet formulation i.e Glimuline. The % CDR of batch F7 was compared.

Stability studies:
Stability studies were carried out as per ICH Q_1A guidelines. Packaging material- The were wrapped in aluminum foils. During the stability studies, the product is exposed to normal conditions of temperature and humidity. The optimized formulation capsules were stored in glass bottles and subjected to accelerated stability studies as per ICH Q1A (R2)guidelines i.e. 40°C ± 2°C /75 % RH ± 5% RH. Sampling was done at predetermined time intervals of 6 month. Capsules were evaluated for the drug content and in vitro release profile. It was also noted that no leakage or visible change in appearance was apparent during the time of storage under ambient temperature.

RESULTS AND DISCUSSION

Characterization of Bulk Prepared For Tablet: Angle of Repose. Bulk Density, Tapped Density, Hausner Ratio & Carr's Index.

Table.4: Pre Compression Parameters

Sr. no.	Batch code	Angle of repose (θ ± SD)	Bulk density (gm/ml) ± S.D.	Tapped density (gm/ml) ± S.D.	Hausner's ratio ± S.D.	Carr's index ± S.D
1	TFC-1	22.29±0.360	0.64±0.96	0.69±0.007	1.09±0.028	15.69±0.56
2	TFC-2	24.78±0.586	0.62±1.10	0.65±0.058	1.08±0.014	14.89±0.08
3	TFC-3	23.76±0.113	0.59±0.73	0.62±0.019	1.07±0.012	13.62±0.82
4	TFC-4	22.78±0.78	0.63±0.98	0.67±0.009	1.10±0.042	15.80±0.21
5	TFC-5	23.26±1.025	0.61±0.65	0.64±0.009	1.08±0.028	14.65±0.73
6	TFC-6	23.74±1.301	0.58±0.79	0.61±0.004	1.04±0.035	12.39±0.48
7	TFC-7	24.70±0.544	0.65±0.88	0.70±0.098	1.10±0.033	15.99±0.27
8	TFC-8	23.74±0.388	0.60±0.32	0.63±0.007	1.05±0.014	14.95±0.5
9	TFC-9	22.92±0.007	0.57±0.14	0.60±0.007	1.10±0.014	12.12±0.87

Many types of Bulk properties have been employed to assess flow ability, of these; angle of repose is the most relevant. Angle of repose of the powder was investigated. The value of Angle of repose (θ°) decreased after the addition of lubricant. Angle of repose (θ°) is an indicative parameter of powder flow ability from hopper to die cavity. The angles of repose of all the formulations were within the range of 22°–24° indicative of excellent flow ability. Bulk density may influence compressibility, tablet porosity, dissolution and other properties and depends on the particle size, shape and tendency of particles to adhere together. The bulk density of powder was found to be between 0.57-0.65 gm/cm^3.The values indicates good packing capacity of Powder. The tap density of the granules of factorial design batches were found in the range of 0.60-0.70gm/cm^3. The bulk density and tap density was used to calculate the percent compressibility of the powder.

The compressibility index of the Powder was observed in range of 12-16, indicating good compressibility of the Powder. The values of the Hausner's ratio were found to be in the range of 1.08 to 1.10 indicating good and fair flow ability.

Table.5: Post Compression Parameters:

Batch Code	Drug content (%) ± S.D	Friabiliy (%) ± S.D	Hardness ($kg/cm^{2)}$ ± S.D	Thikness (mm) ± S.D	Uniformity of weight (mg)± S.D	% Variation
TFC-1	99.20± 0.187	0.35± 0.098	2.9± 0.217	2.1± 0.1524	98±0.54	0.30
TFC-2	97.88± 0.191	0.36± 0.187	3.0± 0.243	1.9± 0.1256	97±0.60	0.20
TFC-3	95.96± 0.185	0.46±0.288	3.2± 0.249	1.6± 0.1112	97.5±0.70	0.25
TFC-4	98.71± 0.1906	0.30± 0.048	2.9± 0.369	2.0± 0.1569	98±0.58	0.37
TFC-5	97.46± 0.183	0.35± 0.098	3.1± 0.278	1.8± 0.2358	96.2±0.65	0.40
TFC-6	95.62± 0.192	0.48± 0.268	3.2± 0.258	1.7± 0.896	98.5±0.73	0.29
TFC-7	99.80± 0.182	0.2± 0.0622	2.9± 0.025	2.2± 0.1458	99.5±0.40	0.22
TFC-8	96.63± 0.189	0.18± 0.049	3.1± 0.168	1.9± 0.1788	97.3±0.68	0.31
TFC-9	95.05± 0.190	0.15± 0.06	3.3± 0.149	1.6± 0.1598	95.8±0.78	0.35

Hardness of tablets varied between 2.9±0.10kg/cm^2 and 3.3±0.14 kg/cm^2 indicating good binding and satisfactory strength of tablets. The % friability was found in the range of 0.15 -0.48 %.The drug content of formulations F1 to F9 were found to be in between 95.05% to 99.80 %.

From above data it is confirmed that weight variation, hardness, thickness, friability and drug content of uncoated tablets was found within the range.

In-vitro Drug Release studies:

The dissolution of sustained release tablet was carried out. The results are shown in Table.5

Table.6: In-vitro Release of Tablet Filled in Capsule (Drug-3mg: HPMC- 20mg, MCC- 30mg,talc-5 mg, Mg stearate-5mg,starch-37 mg)

Time (hrs)	%CDR ± S.D
1	0.00±0.00
2	0.010±0.0001
3	28.15±0.015
4	38.10±0.0113
5	49.29±0.015
6	55.60±0.0183
7	67.40±0.0112
8	72.10±0.009
9	83.00±0.010
10	89.20±0.015
11	95.32±0.0111
12	98.10±0.0128

Sustained release tablet filled in capsule do not release drug for first 2 hrs.It showed 98.00 % of drug at 12 hr. on the basis of In-vitro dissolution study. This also confirms that S.R. Tablet did not dissolved in acidic media.

EVALUATION OF LIQUID FILLED CAPSULES:

Drug content Uniformity:

The drug content of liquid filled capsules is given the Table.7.

Table.7: Drug content of liquid filled capsules

Sr.no.	Batch code	Drug content (%)± S.D
1	LIF	98.68±0.064

In-vitro Release of Liquid Filled Capsule

Table.8: In-vitro Release of Liquid Filled Capsule (Drug-1mg: 1ml Olive Oil)

Time (min)	%CDR ± S.D
10	5.299±0.012
20	11.18±0.0153
30	17.55±0.0231
40	24.06±0.0123
50	31.07±0.0142
60	34.68±0.0220
70	42.97±0.0115
80	51.78±0.0181
90	69.45±0.0131
100	80.12±0.0321
110	88.69±0.0330
120	97.64±0.0150

Liquid filled capsule releases 97.64 % of drug within 2 hrs. on the basis of In-vitro dissolution study.

EVALUATION OF CAP-IN-CAP FORMULATION
Drug content of Cap-in-Cap Formulation

Table.9: Drug content of Cap-in-Cap Formulation

Sr.no.	Batch code	Drug content (%)± S.D
1	BFC-1	98.68±0.064
2	BFC-2	98.73±0.016
3	BFC-3	97.46±0.021
4	BFC-4	98.99±0.038
5	BFC-5	96.99±0.077
6	BFC-6	97.00±0.015
7	BFC-7	99.80±0.064
8	BFC-8	97.23±0.044
9	BFC-9	98.22±0.013

In-vitro release studies of Capsule-in-Capsule
Cap-in Cap Formulation were subjected to In-vitro drug release studies in simulated gastric and intestinal fluid. Dissolution study was performed in 0.1 N HCl for 2 hrs and for remaining 10 hrs.In Phosphate buffer pH 7.8, obtained result summarized in (Table 8.19).Hence, it was evidence that increase in concentration of MCC the drug release from the system found to be decreased, but drug release was also decreased after increase in the concentration of release retardant (HPMC).

The drug release at the end of two hours was found to be 19.61±0.10% and 98.30 ±0.15% at the end of 12 hours.

Table.10: In-vitro Drug release

Time (Min/Hr)	%Cumulative Drug Release ± S.D								
	TFC-1	TFC-2	TFC-3	TFC-4	TFC-5	TFC-6	TFC-7	TFC-8	TFC-9
0	0	0	0	0	0	0	0	0	0
30	5.98 ±0.13	6.06 ±0.41	9.54 ±0.46	7.85 ±0.15	6.79 ±0.19	8.44 ±0.11	9.20 ±0.35	7.19 ±0.24	8.89 ±0.28
60	10.36±0.14	9.24±0.63	15.73±0.68	10.03±0.12	10.28±0.41	13.09±0.23	15.88±0.57	12.54±0.53	14.70 ±0.42
2	19.35±0.25	15.33±0.54	18.99±0.24	14.88±0.34	16.55±0.23	15.02±0.35	19.61±0.10	17.23±0.77	18.66 ±0.29
3	28.42±0.37	26.39±0.12	26.02±0.62	28.12±0.45	25.62±0.13	25.88±0.37	28.66±0.65	25.92±0.15	25.30 ±0.31
4	41.07±0.21	34.02±0.36	33.50±0.31	40.51±0.30	32.85±0.28	32.81±0.43	39.12±0.44	32.26±0.63	30.80 ±0.26
5	63.93±0.30	42.40±0.32	40.55±0.44	49.12±0.23	40.40±0.37	41.02±0.54	48.31±0.65	39.89±0.21	37.35 ±0.11
6	76.71±0.19	51.05±0.27	47.00±0.41	61.30±0.10	48.31±0.34	47.00±0.21	56.62±0.23	47.87±0.20	43.41 ±0.10
7	89.05±0.17	59.90±0.20	54.32±0.32	72.02±0.56	56.12±0.32	53.85±0.34	67.20±0.40	55.88±0.62	50.22 ±0.54
8	95.55±0.16	67.12±0.24	61.03±0.24	81.77±0.26	65..2±0.14	62.71±0.56	75.01±0.31	64.74±0.51	58.16±0.23
9	98.02±0.27	75.23±0.14	69.03±0.29	92.32±0.32	73.85±0.25	69.82±0.48	83.00±0.23	71.80±0.65	66.36 ±0.42
10	98.06±0.29	83.02±0.10	76.15±0.25	98.10±0.11	81.05±0.41	75.90±0.20	89.25±0.26	78.51±0.30	72.12 ±0.46
11	98.13±0.13	88.13±0.23	81.12±0.19	98.12±0.41	86.02±0.43	80.00±0.41	95.34±0.45	85.12±0.34	78.30 ±0.32
12	98.15±0.17	92.33±0.34	87.85±0.11	98.5 ±0.26	90.21±0.54	84.85±0.36	98.30 ±0.15	89.63±0.20	81.23 ±0.22

The result showed that with decrease in concentration of MCC and decreasing the concentration of HPMC the release rates gradually increases. The results showed that the Cap-in-Cap Formulation has the ability to release 1 mg drug upto 2 hrs from external liquid phase and rest of the extended release was found from tablet matrix formulation filled in internal capsule shell extend the release of glimepiride for the duration of about 12 hrs. on the basis of In–vitro drug release profile the optimum formulation was selected.

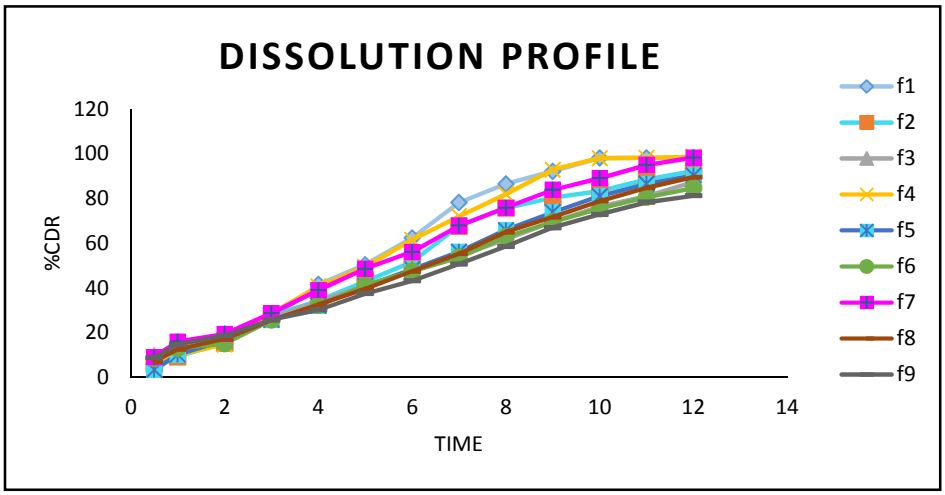

Fig. 5 Dissolution profile of various batches of Tablet

Release kinetics studies

The drug release from capsule-in-a-capsule formulation fits well with Korsemeyer Peppas model which is generally used to analyze the release mechanism when more than one type of release phenomenon is operational. Good linearity was observed with high 'R^2' value – 0.9910. The value of release exponent 'n' is an indicative of release mechanism. The value of 'n' obtained for the optimized formulation was found to be 1.158 suggesting probable release by non-Fickanian or anamolous diffusion.

Table.11: Coefficient of Determination (R2)

Formulation Code	Zero Order	First Order	Higuchi Square root	Korsmeyer Plot	Korsmeyer 'n' (release exponent)
F1	0.9068	0.9111	0.9024	0.9897	1.233
F2	0.9851	0.9632	0.8132	0.9901	1.1829
F3	0.9842	0.9563	0.9732	0.9907	0.9409
F4	0.9851	0.9973	0.9325	0.9899	1.281
F5	0.9750	0.9511	0.9732	0.9896	1.1083
F6	0.9896	0.9631	0.9740	0.9905	1.038
F7	0.9906	0.9496	0.9613	0.9910	1.158
F8	0.9876	0.9689	0.9531	0.9900	1.037
F9	0.9769	0.9567	0.9653	0.9898	0.9548

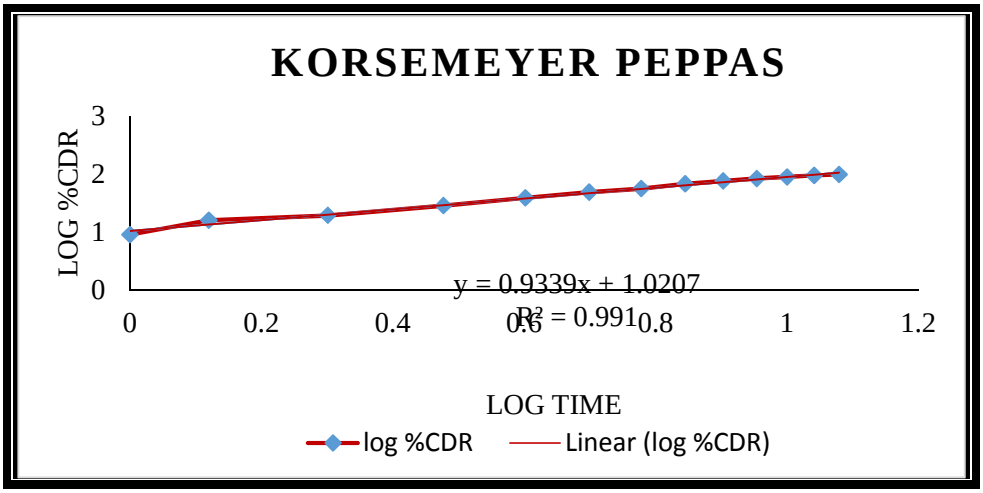

Fig. 6 Korsemeyer peppas mode

Optimization:

Design Summary for Glimepiride Tablet

Percentage Drug Release

Table.11: ANOVA for Response Surface Linear Model

Analysis of variance table [Partial sum of squares - Type III]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F value**	**P Value Prob > F**	**Significant/not Significant**
Model	291.35	2	145.68	68.67	<0.0001	Significant
A-MCC	277.03	1	277.03	130.59	<0.0001	
B-HPMC	14.32	1	14.32	6.75	0.0408	

Std. Dev.	Mean	R-Squared	C.V. %	PRESS	Adeq Precision	Pred R-Squared	Adj R-Squared
1.46	91.20	0.9581	1.60	38.78	19.836	0.8725	0.9442

The Linear model obtained from the regression analysis used to build a 3-D graph's in which the responses were represented by linear surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots.

Final Equation in Terms of Actual Factors:

%CDR=(+113.48-0.38829)* HPMC(+0.30900)* MCC

The response surface plot was generated using Design Expert 7.0.0 software presented in (Figure 31). To observe the effects of independent variables on the response studied % drug release. From response surface 3 level factorial designs was chosen using Qadratic design mode. The range was set in percent from minimum 81.23 to maximum 98.30. The 9 run was performed for the response % drug release and model was found to be linear.

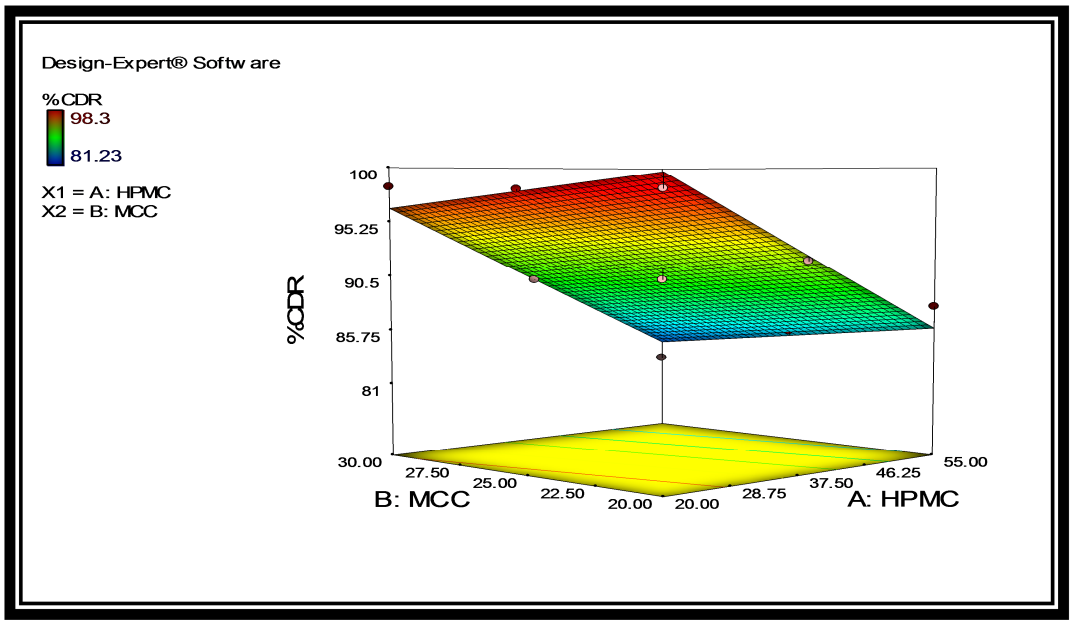

Fig 7: Surface Response plot showing effect of HPMC and MCC on drug release

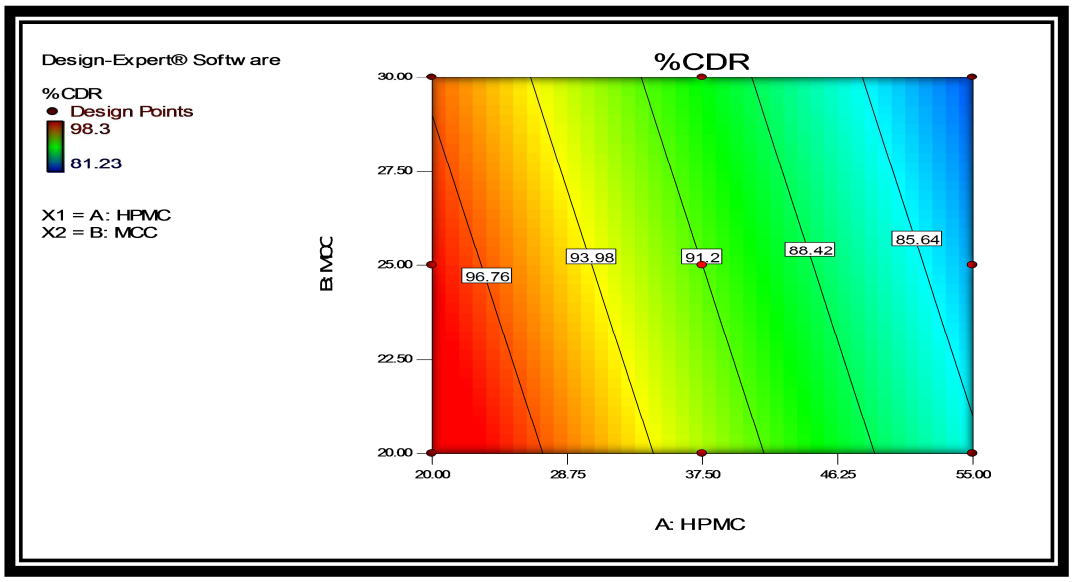

Fig.8: Contour plot showing effect of HPMC and MCC on drug release

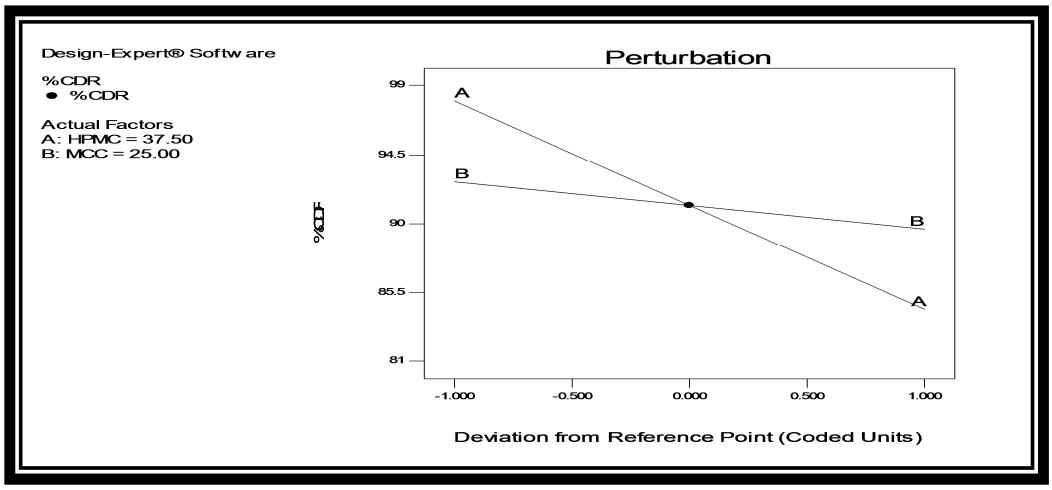

Fig.9: Perturbation Plot

Design summary:
Design summary and Response summary is shown in Table no.12

Table.12: Design summary

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
HPMC	Is in range	20	55	1	1	3
MCC	Is in range	20	30	1	1	3
%CDR	Maximize	81.23	98.30	1	1	3

From Design expert version 7.0.0 solutions were found in which optimum batch (HPMC) 20 mg and (MCC) 30mg with was found to be optimum. From this data F7 batch was selected as optimum formulation.

Comparison of optimized formulation with Marketed Formulation (Glimulin)

Table.13: Comparison with Marketed Formulation (Glimulin)

Time (min/hr)	Marketed Formulation (Glimulin) %CDR±S.D	F7 %CDR ±S.D
30	15.42±0.12	9.20 ±0.35
60	20.01±0.09	15.88±0.57
2	23.32±0.18	19.61±0.10
3	35.18±0.16	28.66±0.65
4	42.81±0.15	39.12±0.44
5	44.85±0.17	48.31±0.65
6	47.32±0.10	56.62±0.23
7	55.46±0.21	67.20±0.40
8	60.32±0.19	75.01±0.31
9	62.51±0.23	83.00±0.23
10	70.81±0.20	89.25±0.26
11	77.81±0.21	95.34±0.45
12	80.88±0.15	98.30 ±0.15

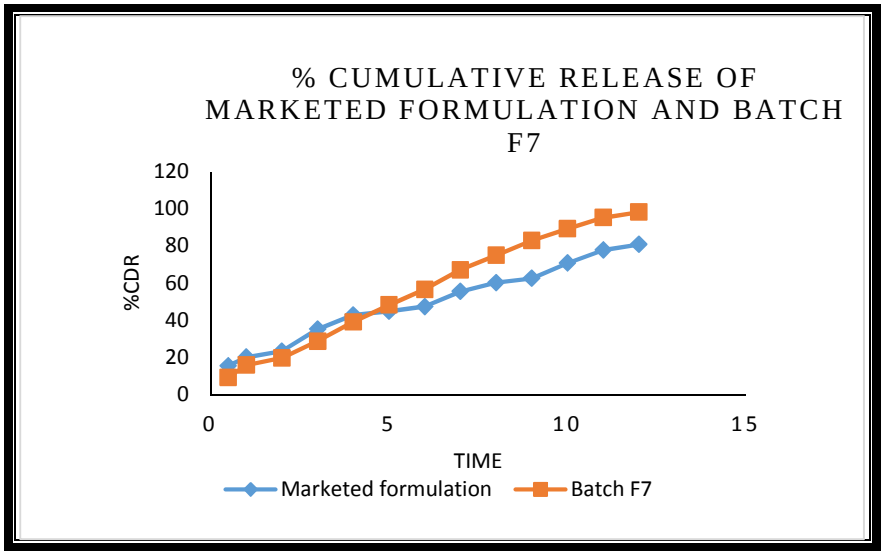

Fig.10: Cumulative Release of Marketed Formulation and Batch F7

From the above in-vitro study data it can be concluded that, Cap-in-Cap formulations i.e optimized F7 batch show significant drug release i.e.98.30% i.e upto 12 hrs as compared to marketed Glimulin formulation.

STABILITY STUDIES:

The optimized formulation capsules were stored in glass bottles and subjected to accelerated stability studies as per ICH Q1A (R2) guidelines i.e. 40°C ± 2°C /75 % RH ± 5% RH was found to be stable upto 6 month. There was no significant change in drug content, cumulative drug release.

Table.14: Results of stability studies

Parameters	Initial Sample of Optimized formulation	After storage at 40±^{0}C 75 % RH ± 5% RH
	F7	F7
Colour	White	White
Drug Content	99.80	99.78
% Drug Released after 12 hr.	98.30	98.29

CONCLUSION

A novel biphasic delivery system was successfully developed by filling smaller liquid Tablet filled capsule into a bigger liquid filled capsule body. The bigger capsule body was sealed with 15% (w/w) warm gelatin solution. The immediate releasing liquid and sustained releasing tablet (TFC-7) of Glimepiride were selected through in-vitro dissolution studies. The result shown that with decrease in concentration of MCC and decrease in concentration of HPMC the release rate gradually increase. Optimized capsule-in-a-capsule formulation released 19.61±0.10 of drug at the end of 2 hr. and 98.30±0.15 % of drug at the end of 12hr.These release pattern suggested the release of about 1mg drug as loading dose in outer capsule shell and about 3mg drug as maintenance dose in inner capsule shell containing matrix tablet. In the present study the cap-in-cap formulation of Glimepiride was compared with marketed formulation Glimuline. The %CDR for Glimuline was 80.88±0.15 and for cap-in-cap formulation %CDR was 98.30±0.16. It was also found to be stable at 40°C/75% RH for a period of 3 month.

Acknowledgement

This effort in my academic pursuit would not have been a reality, but for the constant support, guidance and encouragement rendered by a number of people whose help I specially recognize throughout this study.

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