IGBINEDION UNIVERSITY OKADA
JOURNAL OF PHARMACEUTICAL SCIENCES

https://pharmacy-journal.iuokada.edu.ng/ Volume 3, no. 2, pp. 018-027 (2024)

ISSN (online): 2992-5746 **ISSN (print): 2992-5339**

RESEARCH ARTICLE

EVALUATION OF CO-POLYMER BASED GRANULATED METFORMIN HYDROCHLORIDE FOR ENCAPSULATION IN HARD GELATIN CAPSULE: AN *IN VITRO* STUDY

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ABSTRACT

Background and aim: This study explores copolymer combination with the sole aim of improving the release profile of encapsulated metformin hydrochloride.

Methods: Varied ratios (1:1, 2:1, and 1:2) of hydroxypropyl methyl cellulose (HPMC) and guar gum were used as copolymer matrix to encapsulate granulated metformin. Thereafter the final granules were manually filled in a hard gelatine capsule size 00. Evaluation such as thermal behaviour using differential scanning calorimeter (DSC), drug entrapment efficacy (DEE) using dialysis membrane, and flow properties using cone-funnel methods were carried out.

Results: The DSC shows a transient, but no obvious peak due to heat of absorption, and there was no obvious peak of the polymers noted. This is a possible indication of no incompatibility. The DEE result showed good granule entrapment of > 97.46 %. Micromeritics analysis showed Carrs' indices 8.55 – 23.08 %, Hausner ratio 1.094 – 1.300 and angle of repose 27.54 – 41.54^{o}, all these are indication of good flow properties. The capsules showed passable disintegration of < 9.10 min, with correlation-coefficient in the range of 0.91-0.97. The mechanism of release was found to be Korsemeyer-Peppas with n-value release exponent of > 1.0 for super case II diffusion.

Conclusion: The drug release properties of encapsulated metformin in HPMC and guar gum was found to be highest in the formulation consisting of 2.0 % HPMC and 4.0 % guar gum.

Keywords: Entrapment, correlation-coefficient, release n-value, super case II diffusion

INTRODUCTION

Dosage form performance is influenced by excipient materials, formulation, process and environmental factors [1,2,3]. Optimising excipient choices and formulation processes can modify drug release from dosage forms. Lipid excipients such as polyethylene glycol and other fatty acid esters, vegetable oil and surfactants have been shown to impact drug properties [4,5]. Lipid based formulations (LBF) may transform drug active particles, improve drug stability, shield drug from some gastric environment, prevent first-pass effect of drug, and control drug bioavailability [6]. LBF designs, such as solid self-emulsifying drug delivery systems (SEDDS), have been used to improve drug stability and permeability [7]. Ternary solid dispersion of lyophilized drugs in carriers have been used to produce advanced third generation drug dispersion with improved release properties [8,9]. The lipid carrier acts as a bridge between drug and copolymer, increasing surface area, improving drug stability and permeability, and preventing re-crystallization. Process factors such as the method of incorporating a drug-carrier with polymer blend can affect the formulation process and dosage properties. Matrix technology for blending drug-carrier-polymer has gained acceptance because of its efficacy, simplicity, stability, and ease of processing ease and validation [10]. Matrices from different polymers such as guar gum and hydroxypropyl methylcellulose (HPMC) and polymer blends have varied functionalities, customised properties, and applications in drug delivery [2, 11].

Guar gum is a natural polysaccharide from *Cyamopsis tetragonoloba* plant that is stable to wide pH ranges and can retard gastric digestion [12, 13, 14]. Guar gum is soluble in cold and hot water and has binding, emulsifying and stabilising properties. Guar gum slurry has eight times the thickening properties of starch, hydrates without heating and can form paste without gelling. Guar gum has been applied as a versatile excipient in pharmaceutical industries as binder, disintegrant, and as base material for controlled release formulation [12, 13, 14, 15, 16].

Hydroxypropyl-methylcellulose (HPMC) is a non-ionic hydrophilic polymer with high gelling, swelling capacities and film-forming properties. Hydrophobic polymer components of the matrix serve as the continuous base to shield, channel, and control the interaction of the hydrophilic polymer – drug with surrounding solvent. HPMC has been used as a porous carrier for a modulated drug delivery system [17].

Inclusion of co-processed guar gum and HPMC excipients in coating materials have shown promise in enhancing and modifying drug release. Film coating material with 80 % guar gum and 20% HPMC resulted in colon delivery [18]. Hashem *et al.* [18] showed that, as coating material, HPMC below 20 % increased release rate, while HPMC above 30 % reduced drug release from prednisolone tablets. Co-processed guar gum and HPMC polymers with essential oil have been used as orally disintegrating film coating for tablets [16].

In this study, lyophilized metformin was dispersed in HPMC -guar gum copolymer matrix. The goal of this study is to investigate drug release of metformin capsules containing dispersion of solid emulsified drug active in HPMC-guar gum copolymer. Metformin is an anti-hyperglycaemic drug mostly administered as an extended release formulation once daily in management of type-2 diabetes mellitus. Metformin causes taste and gastric disturbances such nausea, diarrhoea, and stomach upset. A metformin formulation that masks tastes, moderate gastric release and extended drug release in the colon will be of benefit to patient care.

MATERIALS AND METHODS

Materials: Guar gum (Sigma-Aldrich Brazil), Polyethylene glycol (Shandong Longze Chem., Shandong, China), Hydroxypropyl methylcellulose (Sigma-Aldrich Brazil) and Metformin Hydrochloride (Harman Finochem, Maharashtra, India) were gifted by Ulticare-Lyka Pharmaceuticals (Nigeria). All other chemicals were of analytical grades and were used as such without any further purification.

Preparation of metformin granules: A 280 g metformin powder, 12 g HPMC, 12 g guar gum, and 20 g lactose powders were separately weighed, pulverised, sifted through a sieve of size #40 mesh, and appropriately labelled. Using a 2^3 factorial design, 8 combinations of HPMC, guar gum and propylene glycol were used in formulating batches MF1 – MF8 of metformin granules formula as shown in Table 1. For each of the batch, HPMC, guar gum and metformin were weighed out and mixed properly in a Labomix rapid mixer granulator (Prism Pharma Machinery, Ahmedabad-India) for 5 min at 100 rpm to achieve uniform blend of the polymers and metformin. This was followed by addition of propylene glycol and mixed until a gum mucilage was formed, in accordance with earlier method of Yahaya *et al*. [19]. The mixture was removed, placed in a beaker and heated to 60 ^{o} C in a hot plate stirrer (Model TK43, Kartell, Italy) at 1700 rpm operated for 15 min. A 10 ml distilled water was heated to 60 ^{o} C, and was added gradually into the beaker, and blended to achieve complete mix. The mixture was allowed to cool. Thereafter, starch was added and mixed thoroughly. The blended polymer mixed with starch was sieved, and dried in an oven at 45 ^{o} C for 4 hr. Finally, the sieved granules were blended with talc and magnesium stearate, and stored in a desiccator for further study.

Evaluation of compatibility behaviour of granules: Compatibility behaviour of the excipients with the drug active was determined from differential scanning calorimetry (DSC) thermal analysis. The DSC thermal analysis was carried out on the pure drug, polymer excipients, and the lyophilized dispersion using a PerkinElmer Differential Scanning Calorimeter (Model DSC 800, PerkinElmer Private Limited, India). Adapting the method of Talik *et al*. [20] for the DSC analysis, a 5.2 mg sample was placed in an aluminium pan and heated to 10 ^{o}C / min, with indium in the reference pan, at a temperature range of 60 - 300 ^{o}C. The thermogram of each test sample was read from an attached computer monitor and printed for interpretation.

Determination of drug entrapment efficacy: A 600 mg granules from a batch was transferred into a 100 ml volumetric flask, and made to volume with acidified methanol. The contents were dispersed using a probe sonicator (PCI Analytics, Mumbai, India) for 120 sec, and filtered. The filtrate was analysed for metformin content using a UV-visible spectrophotometer (Model 23D, Uniscope, England) at 233 nm wavelength (λmax).

The drug entrapment efficacy was calculated from equation 1 below;

$$\text{Drug entrapment efficacy} = \frac{actual\ drug\ in\ granules}{theoretical\ drug\ in\ load} \quad \text{.....1}$$

Evaluation of granules flow characteristics: The flow characteristics of the granules were determined from the Carrs' index, Hausner ratio and angle of repose properties of the granules and interpreted using Table 2.

Table 1: Formula for producing 50 metformin (500 mg) capsules

Component	Batches							
	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8
Metformin	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
HPMC	1.2	1.2	1.2	0.6	0.6	0.6	0.6	1.2
Guar gum	1.2	1.2	0.6	0.6	1.2	1.2	0.6	0.6
Propylene	2.0	1.0	1.0	1.0	2.0	1.0	2.0	2.0
Starch	0.4	1.4	2.0	2.6	1.0	2.0	1.6	1.0
Talc	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Mg stearate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Total	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0

NB: Each capsule of 500 mg metformin weighs 600 mg,HPMC= Hydroxypropyl methylcellulose

Table 2: Flow character interpretation of powder in relation to micromeritics properties

Carrs' Index (%)	Hausner's ratio	Angle of repose (^{o})	Flow character
5-11	1.00-1.11	25-30	Excellent (free flowing granules)
12-16	1.12-1.18	31-35	Good (free flowing granules)
18-21	1.19-1.25	36-40	Fair (powdered granules)
23-28	1.26-1.34	41-45	Poor. Passable. May hang
28-35	1.35-1.45	46- 55	Very poor. Fluid cohesive powder. Agitate and vibrate to flow
> 40	1.46-1.59	56-65	Very poor (Cohesive powder)
	> 1.60	> 66	Extremely poor (non-flowing powder)

Carrs' index and Hausner ratio: Granules (10 g) were weighed into a measuring cylinder. The volume occupied by the granules was read and the bulk density was calculated using equation 2. The cylinder and its granules content was tapped 100 times. The tapped volume was read and the tapped density was calculated using equation 3. The bulk and tapped densities were also used to calculate the Carrs' index and Hausner ratio using equations 4 and 5 respectively.

$$\text{Bulk density} = \frac{Weight\ of\ Granules}{Bulk\ Volume} \text{ ---------equation 2}$$

$$\text{Tapped density} = \frac{Weight\ of\ Granules}{Tapped\ Volume} \text{---- -- equation 3}$$

$$\text{Carrs' index} = \frac{(tapped\ density - bulk\ density)}{tapped\ density} \text{x100 eq4}$$

$$\text{Hausner's ratio} = \frac{tapped\ density}{bulk\ density} \text{----------equation 5}$$

Angle of Repose: A funnel was clamped to a retort stand at a height of 30 cm from flat table base. Granules (25 g) were weighed and poured through the funnel onto a paper on the table base. The base and the height of the heap formed was measured and recorded. Angle of repose (Θ) was calculated using equation 6.

$$\Theta = \tan^{-1}\frac{h}{r} \text{ ----------equation 6}$$

Where r is the radius of the granules base, h is the height of the granules heap.

Filling of granules into hard gelatin capsules: A 600 mg of 0.71-0.8 g/ml granules, equivalent to 750 - 900 ml volume, would require capsule size 00 with capsule cubage of 950ml. The 600 mg metformin dispersion, containing 500 mg metformin drug active, was filled into an opened size 00 hard gelatin capsule shell. The filled capsule was covered and sealed tight, and stored in an appropriately labelled dry bottle container.

Capsule disintegration time test: A disintegration tester (MK4, Manesty Machine Limited, England) was used to determine the disintegration time of six randomly selected capsules. Each of the capsules were placed in one of the six-opened cylindrical transparent tubes of the basket-rack assembly of the tester containing 1000 ml of 0.1 N HCl disintegration medium, and operated at operated at 30 cycle/ mm at a temperature of 37 ℃ and observed over 30 min. The test was done in triplicate, and the average disintegration time of the capsules recorded.

Capsule dissolution studies: A single phase dissolution experiment was conducted at 37±0.5 °C using a 1000 L beaker containing 900 ml of 0.1 N HCl solution (pH 1.2) placed on a magnetic stirrer (Model TK23, Kartell, Italy). A randomly selected capsule from a batch was placed inside a dialysis bag (Himedia Dialysis Membrane-60, Mumbai, India), and the two ends of the bag were bound tightly with cotton threads. The bound bag was hung to an extended stand that lowered into the 1000 L beaker, and the stirrer operated at 50 rpm 37±0.5 °C for 120 min. Thereafter the beaker was replaced with another 1 L beaker containing 900 ml phosphate buffer pH 6.8 and operated under the same condition for the remaining 180 min. At 15, 30, 45, 60, 90, 120, 150 and 180 min intervals during the 3 h dissolution test operation, aliquots of 5 ml of the dissolution medium were withdrawn and replaced with 5 ml corresponding fresh dissolution medium to maintain sink condition. The absorbance readings of the diluted aliquots were taken at 233 nm wavelength in a UV-spectrophotometer (Model 23D, Uniscope, England). The tests were repeated in triplicate and the mean and standard deviations calculated. The percentage of drugs released from the capsule was calculated and recorded.

Capsule release kinetics studies: Drug release data from the dissolution test were correlated with different mathematical model equations (equations 7 -10) to understand the drug release kinetics.

$C_0 - C_t = K_0t$ (Zero order equation……7

where C_0 = initial amount of drug at time o.
C_t = amount of drug released at time t.

Zero order kinetics was derived from plot of cumulative % drug release vs. time

$DC/dt = K_1C$……equation 8

$Log\ C = Log\ C_0 - K_1t/2.303$ (First order equation)

where C_0 = initial concentration of drug.
C = percent of drug remaining at time t.

First order kinetics was derived from a plot of log cumulative % drug remaining vs. time.

$Q = K_H * t^{1/2}$ (Higuchi equation)……...…….9

where Q = drug release in time per unit area.
K_H = Higuchi dissolution constant.
$t^{1/2}$ = time to dissolve half of the drug.

Higuchi kinetics is derived from plot of cumulative % drug release vs. square root of time

$M_t / M_\varphi = kt^n$ (Korsemeyer-Peppas equation)… 10

where M_t / M_φ = fractional release of drug,

t = release time; k = constant incorporating structural and geometric characteristics of the dosage; and n = release exponent indicative of mechanism of release obtained from the slope of graph plot of log (M_t / M_φ) vs. log (t).

The kinetics of the plot with highest correlation coefficient (R) is interpreted to have significant effect on the drug release.

The value of the release exponent (n) from the Korsemeyer-Peppas plot is used to indicate the mechanism of release where n=0.5 is Fickian diffusion; 0.5<n> is Anomalous diffusion; n=1.0 is Case II transport; and n>1.0 is Super case II diffusion.

RESULTS

Drug entrapment efficacy and DSC analysis: The drug entrapment efficacy of the granules was 97.46 – 98.7 %**.** DSC thermograms revealed endothermic peaks at 87.37, 87.27, 82.28 and 92.18 ^oC for guar gum, HPMC, Metformin and metformin dispersion. While the guar gum and HPMC had near similar endothermic melting peaks, the melting peak of metformin dispersion was increased in comparison to its constituent. The remaining enthalpy curve of metformin was retained in the metformin dispersion as seen in Figure 1.

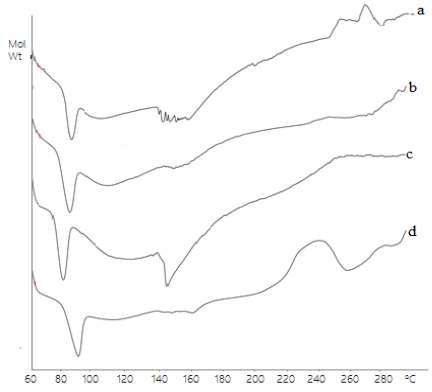

Figure 1: DSC Thermogram of (a) Metformin, (b) Guar gum, (c) HPMC and dispersion of Metformin-Guar gum - HPMC

Flow Character: The results of flow character determination of the granules are in physicochemical properties of granules and capsules in Table 3. The ranges of Carrs' indices 8.55 – 23.08 %, Hausner ratio 1.094 – 1.300 and angle of repose 27.54 – 41.54^o was observed.

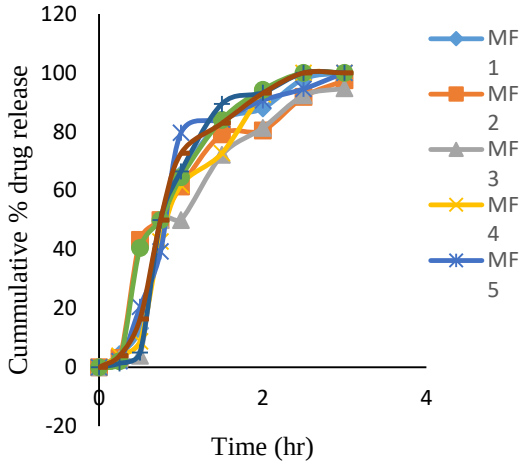

Figure 2: Zero order kinetic release of metformin

The correlation coefficient from plots of different dissolution mathematical models is presented in Table 4. The highest correlation coefficient ranges of 0.91-0.97 of the dissolution mathematical model was observed for the first order plot, and the n-value release exponent of the Korsemeyer-Peppas plot was > 1.0. The plot of the best fit first order release model is presented in Figure 3.

Statistical analysis

The results were given mean±standard error mean (SEM). The significant difference was tested using one-way analysis of variance (ANOVA). A difference of $p < 0.05$ was considered significant.

Table 3: Physicochemical properties of granules and capsules

Batch	Granules			Capsules	
	Carrs' Index (%)	Hausner's ratio	Angle of repose (°)	Drug entrapment efficacy (%)	Disintegration time (min)
MF1	13.94	1.162	28.32±1.03	97.76±1.22	5.43±0.12
MF2	19.68	1.245	27.54±0.66	97.98±0.98	5.41±0.34
MF3	10.75	1.121	29.35±0.21	97.46±0.76	7.28±1.05
MF4	08.55	1.094	28.53±0.09	98.71±0.14	7.17±1.14
MF5	17.53	1.213	41.54±1.18	98.32±0.19	9.51±1.32
MF6	17.53	1.213	31.77±0.27	97.76±0.37	9.13±1.06
MF7	23.08	1.300	32.87±0.24	98.13±0.07	9.04±0.88
MF8	20.00	1.250	32.34±1.11	97.67±0.11	7.76±0.57

Table 4: Correlation Coefficient (r^2) and K-P Release Exponent (n) of the Dissolution Studies.

	Zero	FIRST	HIGUCHI	K-P	n
MF1	0.8627	0.9155	0.9042	0.8149	1.233
MF2	0.8492	0.957	0.934	0.6809	1.1241
MF3	0.8821	0.977	0.8889	0.7507	1.5077
MF4	0.897	0.9353	0.9048	0.8065	1.34
MF5	0.8244	0.9517	0.8798	0.7713	1.39
MF6	0.8539	0.9641	0.9306	0.6894	1.286
MF7	0.8302	0.9627	0.8652	0.7679	1.7451
MF8	0.8451	0.9594	0.8995	0.7902	1.241

K-P = Korsemeyer-Peppas

DISCUSSION

The higher endothermic melting point from the DSC thermogram of metformin dispersion is an indication of hydrogen bonding of excipients with metformin. Ashames *et al*. [21] had demonstrated that high molecular weight guar gum forms weak van der waals interaction and bonding with no complex chemical reaction in aqueous interaction. Hashem *et al*. [18] and Ashames *et al*. [21] demonstrated that high molecular weight guar gum, and copolymer of guar gum and HPMC form weak Van der Waals interactions and bonding with no complex chemical reactions in aqueous interaction with drug actives. This is an indication that no new chemical entity nor complex reaction was created in metformin dispersion.

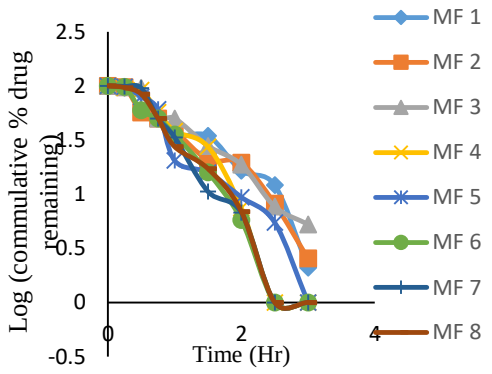

Figure 3: First-order kinetic release of metformin

The DEE result is indicative of good drug entrapment. Flow character result indicated passable flow that may require vibration and agitation to fill the capsule uniformly. The disintegration time range of 5.41 – 9.51 min is within the 15 min official set time for hard gelatin capsule disintegration. This shows that the formulation did not affect hard gelatin capsule breakdown.

Significant dissolution started after 15 min. Batch MF6 with 2.0 % HMPC and 4.0 % guar gum optimised the first order release. This can be attributed to lesser concentration of HPMC in the copolymer matrix. Hashem *et al.* [18] had explained that at higher concentration of HPMC, compressed HPMC and guar gum tablet compact remain intact in the stomach after 1.5 h and completely disintegrated only in the colon after 8 hr [18]. The dissolution and kinetic release studies indicate first order release model and super case II diffusion from capsules. First order release and super case II diffusion mechanism is indicative concentration dependent release by sorption from the boundary of a severely modified unpenetrated matrix. Danyuo *et al*. [22] explained that in a super case II transport system, a defined outer swollen shell boundary exists at equilibrium penetrant concentration from the unpenetrated matrix. As the polymer comes in contact with water and swells, the swelling stress induces relaxation of the boundary resulting in diffusion and time-dependent viscous flow of the penetrant away from the unpenetrated polymer. The diffusibility and viscous flow rate of the penetrant concentration determine the rate of drug release [23]. From the characteristics of the polymers, HPMC-guar gum copolymer formed an unpenetrated matrix that swells to relax its boundary with penetrant metformin which is released for dissolution. As explained in Hashen *et al*. [18], guar gum interaction with HPMC served as a dissolution enhancing surfactant in metformin - polyethylene glycol micellar conjugate. Predhan *et al*. [24] have earlier recorded first order reactions of metformin and vanadium through outer sphere electron transfer pathway of metformin-n-oxide in aqueous acidic and micellar medium. Predhan *et al*. [24] had shown that metformin release has been improved by surfactant.

CONCLUSION

The drug release properties of lyophilized metformin-HPMC-guar gum copolymer infer presence of unpenetrated polymer. It can be deduced that guar gum is complexed with HPMC to form an unpenetrated swelling copolymer matrix that borders penetrant lyophilized metformin. This matrix attracts water and upon swelling creates stress induced relaxation and release of its border lyophilized metformin penetrant into the dissolution medium. The formulation with 2.0 % HPMC and 4.0 % guar gum optimised the release of metformin after 15 min. There is need for in-vivo research to ascertain the stability and permeability of this lyophilized metformin in the body.

Conflict of interest

Authors declare no conflict of interest.

Acknowledgment

The authors are grateful to the management of Ulticare-Lyka Pharmaceuticals (Nigeria) for the materials donated, and to the laboratory staff of Department of Pharmaceutics and Pharmaceutical Technology, Igbinedion University for their assistance during the research work.

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