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Original Research Article

Eudragit E100 and Polysaccharide Polymer Blends as Matrices for Modified-Release Drug Delivery II: Swelling and Release Studies

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Abstract

Purpose: *To compare the effects of two states of polymer/polymer blending (dry and aqueous/lyophilized) of locust bean gum with Eudragit® E100 and sodium carboxymethylcellulose on swelling and drug (levodopa) release from their tablet matrices.*
Methods: *Sodium carboxymethylcellulose (SCMC), Eudragit® (E100) and locust bean (LB) were blended in their dry (as purchased) state or modified by aqueous blending and subsequent lyophilization prior to use as tablet matrices. The tablets were evaluated for swelling and in vitro drug release. Furthermore, in vivo absorption was predicted from the in vitro release data by convolution method.*
Results: *E100 matrices exhibited little or no swelling while the matrices of SCMC and LB and their blends exhibited a degree of swelling > 180 %. Aqueous blending and lyophilization modulated the rate of release from matrices formulated with LB, SCMC and their polymer/polymer blends. Drug release profiles of the lyophilized polymer/polymer blends matrices were dissimilar to those of the dry polymer/polymer blends. Formulations F1aq, F2aq and F3aq exhibited fairly uniform absorption in the first 8 h, indicating the possibility of producing a steady delivery of drug.*
Conclusion: *Polymer blending of LB, SCMC and E100, achieved by aqueous blending and lyophilization, enhances the performance of the matrices thereby exhibiting controlled levodopa release with no burst effect and the tablets retained their three-dimensional network.*

Keywords: *Controlled release, Drug delivery, Eudragit, Locust bean, Levodopa, Matrix, Polymer blend, Sodium carboxymethylcellulose*

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INTRODUCTION

Polymers form the integral aspect of drug delivery. They are used as drug carriers, having drug delivery properties that can be utilized for the administration of drugs. Prolonged delivery of drugs reduces frequency of dosing, prevents dose dumping which poses significant adverse effects, and enhances patient's adherence. Controlled release formulations over a prolonged period are paramount for drugs that are rapidly metabolized and eliminated from the body after administration [1].

A host of polymers are flexible and can be modified or tailored to achieve the desired effects. Xanthan gum [2,3], guar gum [4,5], gum Arabic [6,7], tragacanth [8], gellan gum [9,10], locust bean gum [11,12] are some of the natural polymers that have already been explored in the

pharmaceutical field for their role in drug delivery systems. The three main mechanisms that influence the release of drug from biodegradable natural polymeric systems are diffusion, swelling and erosion. Locust bean (LB) as purchased is a poor direct compressible polymer. When directly compressed, locust bean matrix disintegrates in a medium resulting in an initial burst release; and then, the particles are held together providing a controlled release subsequently.

Consequently, this study sought to prevent burst release by blending locust bean with two other polymers (Eudragit E100 and SCMC). In a prior study, the physicomechanical properties of the tablet matrices formulated with blends of LB, E100 and SCMC were evaluated, as these can influence release of incorporated drug. It was found that blending locust bean with other polymers provided harder, more resilient and denser matrices. It is envisaged that based on the modified physicomechanical properties, the swelling and drug release will also be modified. Therefore, the current study elucidates the use of polymer-polymer blending technique to modulate the release of drug, levodopa from locust bean gum and the outcome of dry and aqueous blending on the swelling and release properties of the polymer/polymer blends.

EXPERIMENTAL

Materials

Eudragit® E100 (Evonik Röhm GmbH & Co. KG, Darmstadt, Germany), sodium carboxymethylcellulose (SCMC, Fluka Biochemika, Medium viscosity) locust bean, barium sulphate, pullulan, levodopa (Sigma-Aldrich Inc., Steinheim, Germany), acetic acid glacial, hydrochloric acid (Rochelle Chemicals, Gauteng, South Africa), silica (Saarchem, Krugersdorp, South Africa), magnesium stearate (Merck Chemicals (PTY) LTD, Gauteng, South Africa).

Blending of polymers

The polymer/polymer blends were prepared as described in the prior study. Briefly, SCMC, Eudragit® (E100) and locust bean (LB) were employed individually as well as in combination of the three in dry and modified (aqueous blending and subsequent lyophilization) states. For aqueous blending method, 4.2 g of SCMC was dissolved under agitation in 50 mL of water and thereafter lyophilized. Aqueous/lyophilized states of E100 and LB were individually prepared using the same weight as that of SCMC and volume of water. The dry blend of the three polymers were obtained by uniformly mixing the polymers (SCMC, E100 and LB). The modified state of the tripolymer was achieved by first dissolving the polymers individually as described above. Thereafter, a solution of E100 was added into that of SCMC and was agitated using a magnetic stirrer for 2-3 h. Then LB was added and agitated for 15 min and subsequent lyophilisation was undertaken. The tripolymer blending was done in ratios 1:1:0.5; 1:0.5:1 and 1:1:1 of E100, LB and SCMC respectively. At the end of the lyophilisation process, the polymers/polymer blends were milled for subsequent formulation of tablet matrices by direct compression.

Formation of tablet matrices by direct compression

Formation of tablet matrices by direct compression was also undertaken as described also in prior study. Each tablet formulated comprised of levodopa (100 mg), pullulan as adhesive (100 mg), barium sulphate as a high density salt (234 mg), Magnesium stearate as lubricant (10 mg), silica as glidant (55 mg) and polymer/polymer blends (500 mg). These materials were mixed and compressed using a hydraulic tablet press (Carver Industries Inc. Wabash, In, USA) at 29.4 KN. With regards to the polymer/polymer blends, there were two batches: One batch employing the polymer/polymer blend in its dry state and the second batch with the polymer/polymer blend in its modified state.

Assessment of the degree of swelling of the tablet matrices and their blends

The degree of swelling was undertaken by gravimetric method. The matrices were weighed, and dropped into pre-weighed wired baskets. Thereafter, the baskets were submerged in 100 mL of 0.1 N HCl and placed in a shaker bath (Orbital Shaker incubator, LM-530, laboratory & scientific equipment Co. (PTY) LTD, Cape Town, South Africa) at 37 ^{o}C. Increase in weight was determined by weighing the tablets and the baskets at time intervals over 24 h after blotting out the medium (0.1 N HCl) each time. The degree of swelling was determined using Eq 1.

Degree of swelling = $(W_t-W_o)/W_o$ …… (1)

Where W_t is the weight of the tablet at time t, and W_o is the weight of tablet at time zero.

In vitro drug release studies of the tablet matrices of polymers and their blends

Levodopa release from the matrices was evaluated using USP apparatus II dissolution system (Erweka DT 700, Erweka GmbH, Heusenstamm, Germany) at 37 ± 0.5 °C and 50 rpm and the dissolution medium was 900 mL of 0.1 N HCl. Samples were withdrawn at pre-determined periods and the same volume withdrawn was replaced each time with fresh medium in order to retain sink conditions. Furthermore, the quantities of levodopa released were quantified using a spectrophotometer (LAMBDA 25 UV/Vis spectrophotometer, PerkinElmer, Massachusetts, USA) at 280 nm.

Data analysis

Basic statistics, such as standard deviation was used to analyze the results while mathematical models like zero and first order kinetics, Higuchi and Korsmeyer-Peppas equations as well as the difference factor f_1 and similarity factor f_2 were used to evaluate the drug release profiles using DD Solver. Microsoft Excel and PK Solver were used for computation of predicted *in vivo* absorption and determination of pharmacokinetic parameters respectively.

RESULTS

Degree of swelling of the tablet matrices of polymers/polymer blends

Figure 1 shows the various % degrees of swelling exhibited by the formulations. LBp exhibited the highest swelling, followed by F1p, while F2p exhibited the least swelling. After 'swellability' testing, the samples were left in the solvent for three months in a shaker incubator and tablets prepared with lyophilized polymers remained swollen and the three-dimensional network was retained, though traces of surface erosion were observed. However, although their three-dimensional network was sustained, they were very soft to touch.

In vitro drug release and prediction of in vivo absorption

E100p and E100aq did not modulate the release of levodopa from the tablet matrices and the total release of levodopa occurred within two hours. Tablets prepared with LBp released more than 50 % of levodopa in < 2 h, while those containing LBaq released only about 20 % (Figure 2a). At the 12th hour, tablets containing LBaq released 75 % while those containing LBp released 99.72 at the 7th hour. Furthermore, the tablets containing LBaq did not lose their three-dimensional network throughout the study. In addition, the rate of release from tablets of SCMCaq was also modulated. Tablets containing SCMCp, released over 90 % of drug by the 12th hour, while the tablets containing SCMCaq released about 58 % only, retaining its three-dimensional network. Drug release from the modified state polymer blends was also modulated in comparison to the dry blending of the polymers (Figure 2b). The polymer matrices were compared on the basis of time taken for 50 % release (T50), and for the single polymer matrices, the order was SCMCaq (9.72 h) > LBaq (6.17 h) > SCMCp (3.95 h) > LBp (0.69 h) > E100aq (0.63 h) > E100p (0.50 h). The T50 of the tripolymer blends was in the order F1aq (8.7 h) > F2aq (8.2 h) > F3aq (7.8 h) > F2p (5.3 h) > F1p (4.0 h) > F3p (3.9 h).

In order to predict the *in vivo* absorption of levodopa from the *in vitro* drug release data, the parameters – volume of distribution (1.6 L/Kg),

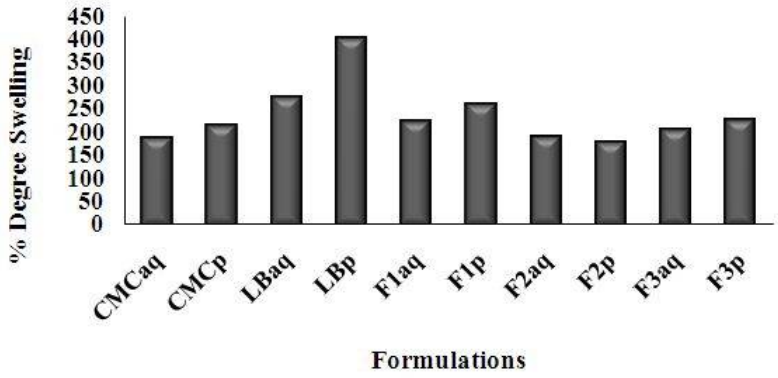

Figure 1: Percentage degree of swelling of the tablet matrices of polymers/polymer blends

half-life (1.5 h) and oral bioavailability (0.44) – were obtained from FDA published data [13]. We worked on the assumption that a carboxylase inhibitor such as carbidopa was co-administered with levodopa. Microsoft Excel was used for the computation to obtain plasma concentrations over time. Sigma plot was used to plot the concentration-time profiles while PK Solver was used to determine the pharmacokinetic parameters. Qureshi in his publication presented a simple and practical convolution technique, using Microsoft Excel which was used in this study to compute the plasma concentrations of the formulations [14]. Figures 2c and d depict the predicted plasma concentration-time profiles of the formulations of polymer/polymer blends.

Figure 3 shows samples of digital images of loss and retain of 3D network by the dry state and modified state polymers/polymer blends respectively.

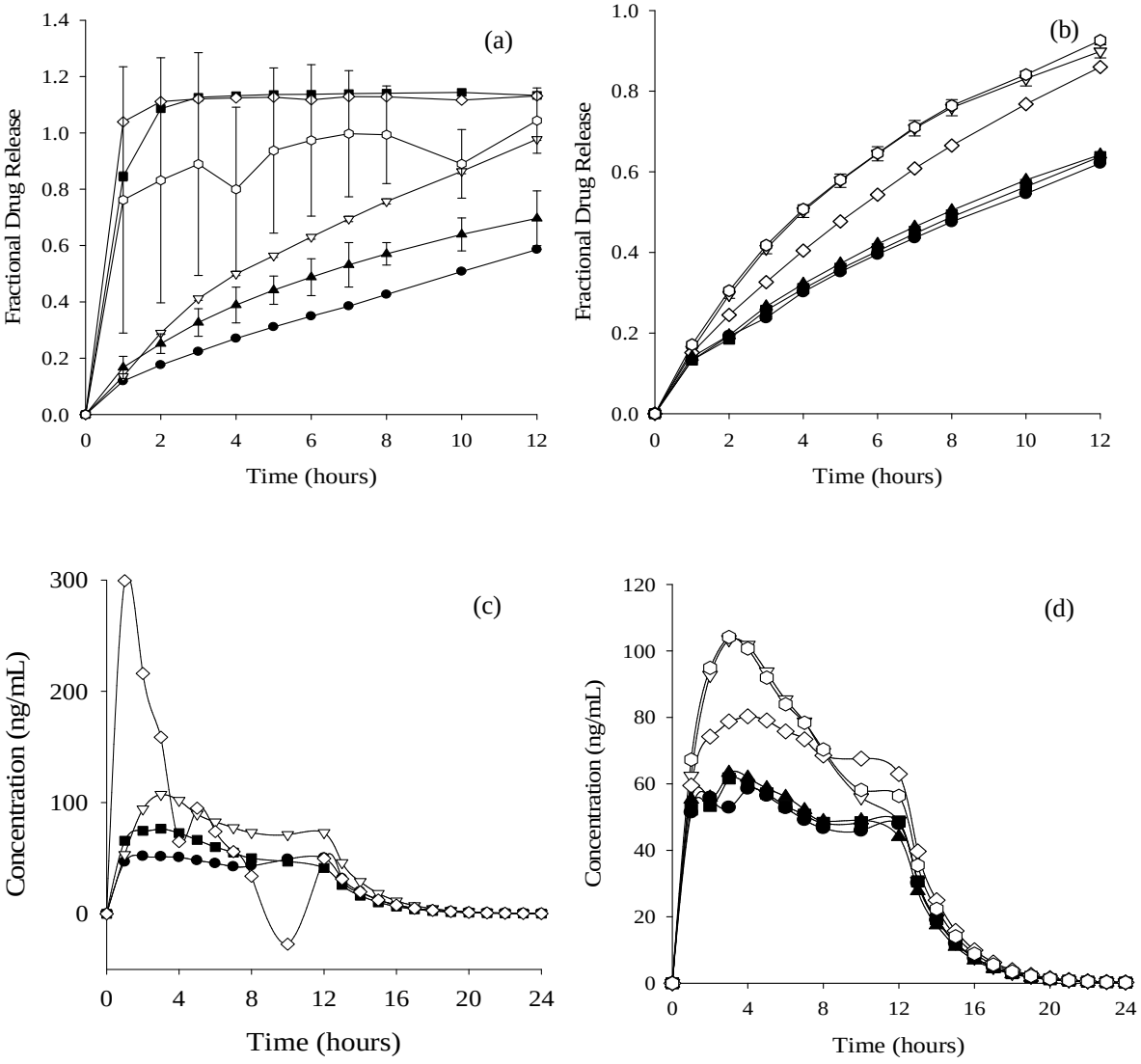

Figure 2: (a) In vitro drug release profiles tablet matrices of the native polymers in their dry and lyophilized states; Key: ● - SCMCaq; ▽ - SCMCp; ■ - E100aq; ◇ - E100p; ▲ - LBaq; ⬡ - LBp; (b) In vitro drug release profiles tablet matrices of the polymer blends in their dry and lyophilized states; Key: ● - F1aq; ▽ - F1p; ■ - F2aq; ◇ - F2p; ▲- F3aq; ⬡ - F3p; (c) Predicted plasma concentration-time profiles for the native polymers – CMC and LB - and their lyophilized; Key: ● - SCMCaq; ▽ - SCMCp; ■ - LBaq; ◇ - LBp and; (b) Predicted plasma concentration-time profiles for formulations of polymer blends and their lyophilized over 24 hours; and ● - F1aq; ▽ - F1p; ■ - F2aq; ◇ - F2p; ▲- F3aq; ⬡ - F3p

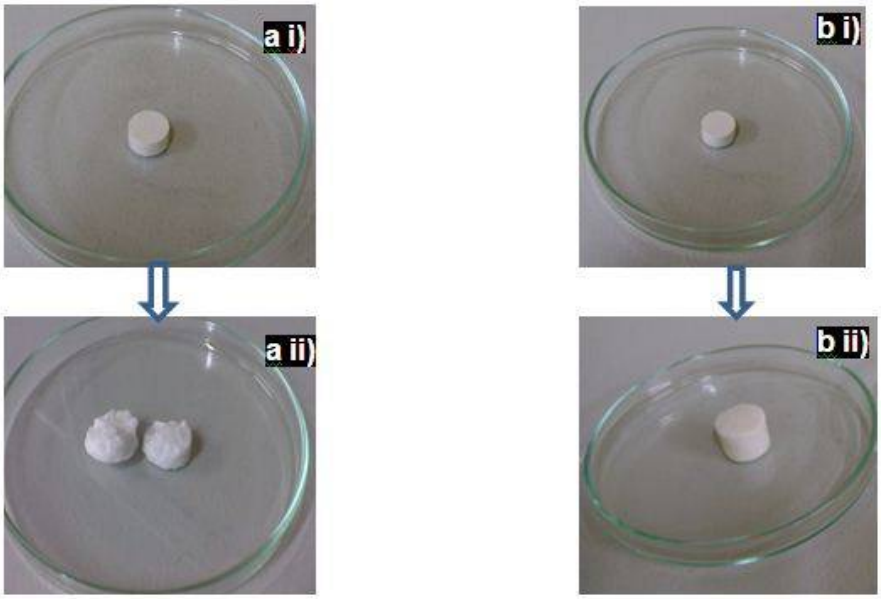

Figure 3: Digital images of (a) SCMCp after dissolution testing and; (b) F2aq after dissolution testing. The physical blends lost their 3D network while the wetted and lyophilized retained their 3D network

Table 1 reveals the predicted pharmacokinetic parameters and the half-life of levodopa. LBp has the highest value for C_{max}. Formulations of the modified state polymer/polymer blends produced lower C_{max}. However, the concentrations were still within optimal response.

Mathematical modeling of *in vitro* drug release profiles

In vitro drug release profiles of the native polymers and their blends were fitted into zero order, first order, Higuchi and Korsmeyer-Peppas to determine the best fit for each formulation. The best fit model for the formulations was Korsmeyer-Peppas model except for F1p and F3p matrices which followed first order pattern as indicated in Table 2. Kormeyer-Peppas equation is used to ascertain the possible drug release mechanisms from tablet matrices. Kormeyer-Peppas equation takes into account the structural and geometrical characteristics of the tablet matrix represented by K in equation 2:

$$Q_t/Q_\infty = K_t^n \quad \ldots\ldots\ldots (2)$$

n is the release exponent and can be obtained by plotting log of percentage released against log of time as in Eq 3.

$$\text{Log } [Q_t/Q_\infty] = \text{Log } K + n\text{Log } t \quad \ldots\ldots\ldots (3)$$

The pairwise procedures, difference factor f_1 and similarity factor f_2, were employed to compare the drug release profiles, using the dry state polymer/polymer blends as the reference products and the modified state polymer/polymer blends as the test products. The results are indicated in Table 3.

Table 1: Predicted pharmacokinetic parameters of the different formulations

PK parameters	Formulations									
	SCMCaq	**SCMCp**	**LBaq**	**LBp**	**F1aq**	**F1p**	**F2aq**	**F2p**	**F3aq**	**F3p**
C_{max} (ng/mL)	51.79	107.28	76.51	299.36	58.59	103.47	61.63	80.31	63.35	104.17
T_{max} (h)	2.00	3.00	3.00	1.00	4.00	3.00	3.00	4.00	3.00	3.00
$T_{1/2}$ (h)	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.5	1.50
AUC (ng/ml*h)	659.14	1090.58	770.85	1172.78	692.05	989.88	712.81	960.65	715.95	1023.23
MRT (h)	7.54	7.23	6.64	4.53	7.28	6.61	7.27	7.30	7.07	6.76
Vz/F ((mg)/(ng/ml))	0.33	0.20	0.28	0.18	0.31	0.22	0.03	0.23	0.30	0.21
Cl/F (mg)/(ng/ml)/h)	0.15	0.09	0.13	0.09	0.14	0.10	0.14	0.10	0.14	0.10

Table 2: Mathematical modelling of drug release profiles of the formulations

Formulation	First order (FO)		Zero order (ZO)		Higuchi (HI)		Korsmeyer-Peppas (KP)			Best fit Model
	K1	r2	*K0*	*r2*	*KH*	*r2*	*KKP (h-n)*	*r2*	*n*	
CMCaq	0.073	0.9712	5.373	0.8823	15.001	0.9425	10.458	0.9964	0.68	KP
CMCp	0.177	0.9787	9.337	0.8558	26.131	0.9470	18.952	0.9927	0.66	KP
E100aq	-	-	-	-	-	-	-	-	-	-
E100p	-	-	-	-	-	-	-	-	-	-
LBaq	0.112	0.9513	7.004	0.6650	19.833	0.9902	17.743	0.9980	0.56	KP
LBp	1.101	0.0905	12.316	-19.428	36.962	-4.9971	76.416	0.6762	0.11	KP
F1aq	0.084	0.9742	5.880	0.8458	16.473	0.9578	12.232	0.9986	0.65	KP
F1p	0.176	0.9989	9.122	0.7466	25.729	0.9643	21.220	0.9845	0.60	FO
F2aq	0.087	0.9796	6.036	0.8540	16.899	0.9558	12.400	0.9991	0.66	KP
F2p	0.138	0.9893	8.138	0.8933	22.702	0.9401	15.519	0.9992	0.69	KP
F3aq	0.091	0.9760	6.203	0.8241	17.406	0.9641	13.319	0.9987	0.64	KP
F3p	0.180	0.9956	9.253	0.7550	26.085	0.9702	21.461	0.9909	0.60	FO

Table 3: Pairwise comparison between the matrices of the dry state and modified state polymer/polymer blends

Reference vs test	Difference factor *f1*	Similarity factor *f2*	
CMCp vs CMCaq	42.44	28.40	Reject
LBp vs LBaq	50.63	16.25	Reject
F1p vs F1aq	39.19	32.36	Reject
F2p vs F2aq	25.08	42.42	Reject
F3p vs F3aq	33.45	33.85	Reject

DISCUSSION

Gravimetric determination of swelling without disturbing or removing the tablets was effective since the tablets remained fairly intact throughout the study. The use of basket made this possible as the tablets were weighed in the basket. However, SCMCp and the dry polymer blends underwent a measure of dissolution/erosion. This is due to the fact that E100 is not a swellable polymer, rather it dissolves in acidic medium and SCMC matrices also undergoes a bit of dissolution in aqueous medium. The tablets prepared with LBp disintegrated almost immediately it got in contact with the solvent, thereby losing their shapes. However, the particles were packed and swelling was measurable (403.15 %).

It is envisaged that the degree of swelling was higher for LBp due to increased surface area and porosity by disintegration of tablets which increased the rate of solvent penetration and hence rate of swelling. Furthermore, it is envisaged that the degree of swelling was less with modified state polymer/polymer blends due to the presence of bound water leading to less sites for water-polymer interactions during 'swellability' tests.

E100 is a non-viscous and non-swellable polymer which is also not suitable for controlled and prolonged release. This remained the case after aqueous blending and lyophilization. However, aqueous blending and lyophilization modulated the rate of release from LB and SCMC matrices (Fig. 2a and b). Lyophilization prevented burst release experienced with directly compressed tablets formulated with LBp (Fig. 2a). Consequently, LBaq exhibited an enhanced drug delivery property such that the rate of drug release from the polymer matrix is controlled and more linear, indicating that incorporated drugs can be delivered at a constant rate over a prolonged period. Wang *et al* [15] also observed that lyophilization eliminated burst release of bovine serum albumin from the microspheres as compared to the vacuum-dried microspheres. In addition, matrices of the modified state polymer/polymer blends were harder than dry state polymer/polymer blends (results not shown). Studies have explicated that the harder the tablets, the slower the drug release and vice versa [16,17]. Harder tablets have less voids and pores and so the rate of drug release is reduced due to reduced channels of transport across the tablet matrix. Less voids and pores decrease the rate of water ingress into the matrix, which decreases rate of solubility and diffusion of drug out of the matrix.

Prediction of *in vivo* absorption from *in vitro* drug release enables a product developer to have an insight of the possible liberation and absorption patterns of the product. The rate and extent of liberation of the drug from the matrix influences the rate of dissolution of drug and subsequent rate and extent of absorption of the drug into the systemic circulation. Dose dumping will lead to a

high concentration in the plasma at the period of release from the matrix.

A moderate rate of release from the matrix will lead to a moderate concentration of the drug in the plasma. This of course does not take into consideration drugs that are highly metabolized. Therefore, during products development, utilization of *in vitro* drug release data can assist the developer to determine if the rate of release, dissolution and subsequent absorption will attain the desired and safe therapeutic level. Furthermore, prediction will give insight into the completeness or incompleteness of absorption, erratic or stable absorption and the product developer may decide to move to the next step of development or re-formulate. Therefore, *in vitro-in vivo* correlation (IVIVC), does not only validates the *in vitro* drug release test but also affords some ethical and economic benefits such as reduction in the number of *in vivo* studies which in turn speeds up products development [14]. In this study, a convolution method was employed. This is a process of obtaining the drug concentration-time profile from the *in vitro* drug release data. However, the pharmacokinetics parameters, such as the volume of distribution, the half-life and the oral bio-availability of the drug are required. These parameters are characteristic to the drug and are not influenced by the product/dosage form.

The range (based on patients' variation) of mean plasma concentration to produce optimal response is 0.79-11.16 ng/mL (2.5–35.5 nmol/ml) [18]. The predicted concentrations over 12 h were over the above concentration range, indicating that the formulations may produce the therapeutic levels for at least 12 h (Fig. 2c and d). The challenge will be the gastric residence time which determines if levodopa being a narrow absorption window drug is made available at its site of absorption for at least 12 h. However, this is envisaged to have been tackled in the formulations as they were prepared to be gastroretentive – highly dense and swellable. The formulations F1aq, F2aq and F3aq exhibited a fairly uniform absorption in the first 8 h indicating the possibility of producing a constant delivery of levodopa.

In vitro drug release profiles of the native polymers and their blends were fitted into zero order, first order, Higuchi and Korsmeyer-Peppas, in order to assess the best fit for each formulation. For a cylindrical matric, if n = 0.45, the release mechanism is Fickian diffusion, non-Fickian release or anomalous transport if 0.45<n<0.89, case II transport or zero-order release if n = 0.89, and super case II transport if >0.89 [19]. The release exponent n, for all the formulations except LBp displayed non-Fickian release or anomalous transport, indicating that the patterns of release from the matrices were a combination of release mechanisms other than diffusion.

Although from Table 2A, it would imply that Kormeyer-Peppas is the best fit for LBp; however, it falls short in describing the mechanism of drug release from LBp matrices. This is due to the fact that n = 0.11 which is less than 0.45 implying that it falls out of specifications of Korsmeyer-Peppas drug release model. Furthermore, the further away correlation co-efficients (regression), r is from 1, the less perfect the utilized model is. While LBp matrices disintegrated on immediate contact with the dissolution medium releasing 76 % of the drug within the first hour, LBaq matrices released only 16.7 %. Hence, directly compressed LBp matrices cannot be considered as controlled release. The dose dumping can be modulated by using other techniques such as granulation or using its lyophilized form.

Two drug release profiles are stated to be similar, if f_1 values are lower than 15 (acceptable range of similarity is 0-15), and f_2 values are greater than 50 (acceptable range of similarity is 50-100) [20, 21]. From Table 2B, it can be observed that drug release profiles of the lyophilized polymer/polymer blends matrices were dissimilar to those of the dry polymer/polymer blends. Consequently, the products are bio-inequivalent and cannot be used interchangeably. Furthermore, it indicates that the modified state blending employed in this study, can modulate drug release. The modulation was significant such that the reference and test products may not exhibit similar rate and extent of absorption when administered orally as implied by the comparative analysis.

CONCLUSION

Native locust bean gum is a poor directly compressible agent. However, it is usually used in tablet formulation by wet granulation method or polymer-polymer blending. Modified state blending achieved by aqueous blending and lyophilization modified the gum, making it directly compressible and exhibiting controlled drug release with no burst effect with the tablets retaining their three-dimensional network. The matrices had a more controlled release of levodopa than those of the dry state polymer blends and retained their three-dimensional network.

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